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Clinical trial: dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive oesophagitis

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SUMMARY

Background
Dexlansoprazole MR heals all grades of erosive oesophagitis (EO).

Aim
To assess efficacy and safety of dexlansoprazole MR in maintaining healed EO and heartburn relief.

Methods
In this randomized, double-blind trial, 445 patients with healed EO received dexlansoprazole MR 30 mg or 60 mg or placebo once daily for 6 months. This trial assessed maintenance of endoscopic healing (primary endpoint) and continued symptom relief based on daily diaries (secondary endpoints).

Results
Dexlansoprazole MR 30 mg and 60 mg were superior to placebo for maintaining healed EO ($P < 0.0025$; Hochberg's). By life-table analysis, maintenance rates were 75%, 83% and 27% for dexlansoprazole MR 30 mg, 60 mg and placebo respectively. Crude maintenance rates were 66% for both dexlansoprazole MR doses and 14% for placebo. Dexlansoprazole MR controlled heartburn (medians of 91–96% for 24-h heartburn-free days, 96–99% for heartburn-free nights). The only more common adverse event occurring at a significantly higher rate in dexlansoprazole MR groups than placebo when analysed per patient-months of exposure was upper respiratory tract infection.

Conclusions
Dexlansoprazole MR effectively maintained EO healing and symptom relief; most patients were heartburn-free for >90% of days. Both doses were well tolerated.

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INTRODUCTION

Erosive oesophagitis (EO) is a common manifestation of gastro-oesophageal reflux disease (GERD).[1–3] Most patients whose EO is initially healed with proton pump inhibitor (PPI) treatment will relapse within 6–12 months if therapy is discontinued.[4–7]

Long-term treatment with a PPI is recommended in patients with healed EO to maintain healing, control symptoms and preserve the quality-of-life (QOL) improvements achieved with initial treatment.[4, 7–9] Although some have suggested that maintenance therapy be stepped down from the dose given for EO healing,[4, 7] lower doses are less effective in maintaining long-term remission, as documented in a Cochrane review of randomized controlled trials of EO maintenance therapy in nearly 6000 patients.[9] Even when continuing the initial healing dose, 17.5% of patients relapse on therapy.[9] In patients with more severe baseline EO [Los Angeles (LA) Grades C or D], relapse rates are higher (24–41%) in those who are maintained on lower doses.[10]

Dexlansoprazole MR (TAK-390MR, Takeda Global Research & Development Center, Inc., Deerfield, IL, USA) is a modified-release formulation of dexlansoprazole, an enantiomer of lansoprazole, which employs a novel dual delayed-release technology designed to prolong the plasma concentration-time profile of dexlansoprazole and provide extended duration of acid suppression. To prolong drug exposure with a single daily dose, dexlansoprazole MR releases drug in two distinct phases in the gastrointestinal tract and therefore incorporates higher doses than conventional PPIs. In a phase 1 study, dexlansoprazole MR 60 mg and 90 mg administered once daily (QD) produced a dual-peaked pharmacokinetic profile and maintained intragastric pH >4 for 71% ($P < 0.01$) and 70% ($P < 0.05$) of the 24-h postdose period respectively compared with 60% for lansoprazole 30 mg QD.[11]

In two identically designed, randomized controlled trials in EO healing evaluating dexlansoprazole MR 60 mg and 90 mg with lansoprazole 30 mg (ClinicalTrials.gov NCT00251693 and NCT00251719), dexlansoprazole MR produced consistently high healing rates in all grades of EO by both life table (92–95%) and crude rate (85–89%) analyses.[12] Differences between dexlansoprazole MR and lansoprazole were not statistically significant in the life table analysis. In the crude rate analysis, dexlansoprazole MR 60 mg was superior to lansoprazole in 1 study (85% vs. 79% respectively, $P = 0.004$) and dexlansoprazole MR 90 mg was superior to lansoprazole in both studies (86% vs. 79%, $P = 0.001$ and 89% vs. 85%, $P = 0.019$). Patients with healed EO following 4–8 weeks of treatment in either of these trials were eligible to enter 1 of 2 EO maintenance trials.

This trial assessed the efficacy and safety of maintenance treatment with dexlansoprazole MR 30 and 60 mg compared with placebo for patients whose EO had been healed with dexlansoprazole MR or lansoprazole in either healing trial. Placebo is a standard comparator used in EO maintenance trials.[9, 13, 14]

METHODS

Study design

This was a phase 3, randomized, double-blind, multicentre, placebo-controlled, 6-month trial (ClinicalTrials.gov identifier NCT00321737) of dexlansoprazole MR 30 mg and 60 mg QD in maintaining healed EO and symptom relief.

The final visit of the EO healing trials was considered Day-1 of this trial. Patients returned for study visits after 1, 3 and 6 months of treatment and underwent endoscopy, physical examination including vital signs, safety laboratory evaluations (including serum gastrin and, in all women, serum pregnancy test), collection and/or dispensing of study drug, assessment of concomitant medications and assessment of adverse events (AEs). Serum gastrin values were measured at baseline (defined as last measurement prior to treatment with dexlansoprazole MR or lansoprazole in the previous EO healing studies), Day-1 (final visit of previous EO healing studies), month 1 (only if it was the final visit), month 3 and month 6. Gastric biopsies (two tissue samples each from the antrum and fundus/body) were collected during the month 6/final visit.

The study protocol was approved by central and local Institutional Review Boards and was within the ethical principles stated in the 1989 Declaration of Helsinki. All patients gave written informed consent and completed any Health Insurance Portability and Accountability Act authorization forms (US sites only) before any study-related procedure was initiated.

Patients

Investigators at 94 centres (75 US and 19 non-US sites) enrolled patients; the trial was conducted from May 2006 to May 2007. Adult men and women

(aged ≥18 years) who had participated in 1 of 2 EO healing trials and had endoscopically proven healed EO were eligible to participate. Positive *Helicobacter pylori* status was an exclusion criterion for the two EO healing trials; status was determined primarily by serology in North America and CLOtest Rapid Urease Test (Kimberly–Clark/Ballard Medical Products, Roswell, GA, USA) elsewhere.

Patients were instructed that lifestyle or behaviour should not be altered to treat their GERD symptoms. Women of child-bearing potential were required to use a double-barrier method of birth control.

Patients were excluded for any condition that may have required surgery during the course of the study; use of prescription or nonprescription PPIs, histamine$_2$-receptor antagonists or sucralfate; long-term use (>12 doses per mo) of nonsteroidal anti-inflammatory drugs including cyclooxygenase-2 inhibitors (aspirin ≤325 mg daily was permitted); use of antacids [except study-supplied Gelusil (US sites) or a similar equivalent approved antacid (non-US sites)]; use of misoprostol or prokinetics; need for continuous anticoagulant therapy; or evidence of uncontrolled systemic disease.

Treatment assignment/masking

On Day-1, patients meeting the admission criteria were randomized 1:1:1 using a central telephone system (ClinPhone, Inc., Northbrook, IL, USA) to receive dexlansoprazole MR 30 mg, dexlansoprazole MR 60 mg or placebo. During the 6-month treatment period, patients self-administered the study drug once daily 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). Study drug for all three treatments was provided in size 0 gray opaque capsules to make the treatments indistinguishable.

Open-label Gelusil (US sites) or an approved antacid with similar components (non-US sites) was provided as rescue medication (up to 6 tablets per day).

Efficacy endpoints

The primary efficacy endpoint was the percentage of patients who maintained healed EO for 6 months as assessed by endoscopy. The secondary efficacy endpoints, which were assessed in sequential order, were the percentage of days without daytime or nighttime heartburn during treatment as assessed by daily diary and the percentage of nights without heartburn during treatment as assessed by daily diary. Additional efficacy endpoints included mean severity of heartburn, percentage of days without rescue medication use, severity of GERD symptoms as assessed by the investigator and patient-reported QOL and symptom severity using validated questionnaires.

Efficacy assessments

Endoscopy was performed at months 1, 3 and 6 to document the presence or absence of EO. Starting at Day-1, patients were asked to document the presence and maximum severity of daytime and nighttime heartburn and use of rescue medication daily throughout the trial. This was performed every morning upon waking and every evening at bedtime in either electronic or paper diaries. Patients rated the severity of their daytime and nighttime heartburn according to the following 5-point scale for symptom severity that has been used in previous studies: none (0) = no heartburn; mild (1) = occasional heartburn that could be ignored and did not influence daily routine or sleep; moderate (2) = heartburn that could not be ignored and/or occasionally influenced daily routine or sleep; severe (3) = heartburn that was present most of the day and/or regularly influenced daily routine or sleep; very severe (4) = heartburn that was constant and/or markedly influenced daily routine or sleep;[15] a similar scale has been used in other trials.[16–18] Investigators assessed symptoms on Day-1 and at months 1, 3 and 6 (or final visit) to evaluate the maximum severity of heartburn, acid regurgitation, dysphagia, belching and epigastric pain as none, mild, moderate, severe or very severe during the 7 days before the patient's study visit.

Patient-reported outcomes were assessed at the same visits using two validated, self-administered questionnaires. The Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life (PAGI-QOL) Index 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).[19] The Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity (PAGI-SYM) Index is a brief symptom severity instrument (subscales: nausea/vomiting,

fullness/early satiety/bloating, upper and lower abdominal pain and heartburn/regurgitation).[20]

Safety assessments

All AEs observed by the investigator, elicited during study visits, or spontaneously reported by the patient were collected from the day of signing the informed consent form until 30 days after the last day study drug was administered. Investigators evaluated event severity and whether the event(s) may have been related to study drug therapy. Any clinically significant change in a laboratory parameter was to be reported by the investigator as an AE. Routine laboratory evaluations (haematology, chemistry, and urinalysis), serum pregnancy tests and fasting serum gastrin levels were conducted by Covance Central Laboratory Services (Indianapolis, IN, USA), a certified clinical laboratory.

Gastric biopsies were evaluated for reactive gastropathy, chronic gastritis, *H. pylori*, intestinal metaplasia with or without dysplasia, neuroendocrine cell proliferation and adenocarcinoma. All gastric biopsies were analysed at the Cleveland Clinic Foundation (Cleveland, OH, USA).

Statistical analyses

For the primary endpoint of percentage of patients with maintenance of healed EO, a sample size of 120 patients (allowing for 20% dropout from 150 patients) per treatment group provided at least 95% power at the 0.00125 level of significance to detect a 45% difference between a dexlansoprazole MR dose (70%) and placebo (25%). The use of 0.00125 in the power calculation was conservative to ensure power even if only 1 of the doses was effective. The overall level of significance was 0.0025 for efficacy variables and 0.05 for demographic and safety variables. For all efficacy analyses, Hochberg's method was used to ensure that the overall 0.0025 level of significance was maintained for the pairwise comparisons between the dexlansoprazole MR groups and placebo.[21]

The SAS/STAT Version 8.2 (SAS Institute, Inc., Cary, NC, USA) software for the UNIX operating system was used to perform all statistical analyses. Demographic and baseline variables were summarized for all patients according to the treatment they received in the maintenance study. Comparisons were performed among all treatment groups with a one-way analysis of variance (ANOVA) for continuous demographic variables and chi-squared tests for categorical demographic variables.

The efficacy analyses were performed on modifications of the intent-to-treat (ITT) population, defined as all randomized patients who were documented with healed EO before the maintenance trial, had no gap >7 days between the healing and maintenance trials and who received ≥1 dose of study drug in the maintenance trial.

For the analysis of the primary efficacy endpoint, the life-table method was pre-specified as the primary analysis method and the crude rate analysis as an additional analysis method. Crude rate estimates are, in general, more conservative than the life-table estimates; both analyses are presented here.

The life table analysis was performed on all ITT patients because those without endoscopy were censored according to the life-table method. For each treatment group, life-table methods were used to estimate the percentage of patients who maintained healed EO at each of months 1, 3 and 6 using the intervals of days 2–35, 36–105 and 106–195 respectively. Patients who prematurely discontinued without evidence of recurrence were censored based on the day of their last endoscopy. Pairwise comparisons between treatment groups were made using log-rank tests.

The crude rate analysis was performed on all ITT patients who also had ≥1 endoscopy in this study. The crude percentage of patients who maintained healed EO for months 1, 3 and 6 was calculated for each treatment group using the same intervals as for the life-table methods. Patients whose EO recurred any time in an interval were considered as having had a recurrence for the visit. Patients who did not have a recurrence and who did not complete the study were included in the analysis as having recurred based on the day of their last endoscopy. Pairwise comparisons between treatment groups were made with Fisher's exact tests.

Subgroup analyses of maintenance of healed EO rates included stratifying by baseline LA grade of EO and also by treatment administered in the healing trial. For the subgroup analyses, pairwise comparisons were made using the log-rank test with subgroup levels as the strata for the life table analyses and using Cochran-Mantel-Haenszel (CMH) tests with the subgroup levels as strata for the crude rates.

For each of the secondary efficacy endpoint analyses, separate ITT populations were defined as all patients who were in the ITT population and who completed ≥1 of the appropriate heartburn yes/no questions during treatment. Comparisons between each dexlansoprazole MR dose and placebo were performed for the first secondary endpoint for each dexlansoprazole MR dose that was found to be superior to placebo for the primary efficacy variable. The analysis proceeded to the second secondary endpoint for each dexlansoprazole MR dose that was superior to placebo for the first secondary endpoint.

The secondary efficacy endpoints were summarized by treatment group. Pairwise comparisons between each dexlansoprazole MR dose and placebo for each endpoint were made with Wilcoxon rank sum tests. The mean severity of 24-h heartburn and nighttime heartburn during the entire treatment period, also assessed by patient diary, was compared among treatment groups using Wilcoxon rank sum tests.

Results for the two patient questionnaires (each subscale and total scores of the PAGI-SYM and PAGI-QOL) were summarized by treatment group. At each visit, pairwise comparisons for the change from Day-1 values were made using a one-way analysis of covariance model with Day-1 values as covariates and treatment group as a factor. Results of the GERD symptoms investigator assessment were summarized by treatment group and Day-1 severity. At each visit, severity was compared between treatment groups using a CMH test for ordered responses using Day-1 severity as the stratification variable.

Treatment-emergent AEs were summarized by treatment group; pairwise comparison between treatment groups was made using Fisher's exact test. AEs were also summarized in *post hoc* analyses per 100 patient-months (PM) of exposure to account for the imbalance in study drug exposure between treatment groups; pairwise comparisons between treatment groups were made using conditional exact tests. Laboratory values, including gastrin, were summarized by treatment group. For each visit, pairwise comparisons of the mean change from baseline and Day-1 between the treatment groups were made using contrasts within ANOVA with treatment group as the factor. For each visit, pairwise comparisons of the treatment groups for the percentage of patients with abnormal laboratory values that were potentially clinically important and shifts in laboratory values outside the limits of the normal range were conducted using Fisher's exact tests. Findings for gastric biopsy samples were also summarized and compared between the treatment groups using Fisher's exact tests.

RESULTS

Participant flow and follow-up

The first subject was enrolled on May 18, 2006 and the last subject visit took place on May 3, 2007. A total of 445 patients (previously healed on dexlansoprazole MR 60 mg, $n = 145$; healed on dexlansoprazole MR 90 mg, $n = 162$; and healed on lansoprazole 30 mg, $n = 138$) were randomized and received ≥1 dose of study drug: dexlansoprazole MR 30 mg ($n = 140$), dexlansoprazole MR 60 mg ($n = 158$) or placebo ($n = 147$) (Figure 1). Of these, 224 discontinued prematurely, primarily because of relapse of EO before month 6. Withdrawal rates were 83% for placebo and 34% for each dexlansoprazole MR treatment group ($P < 0.001$ for pairwise comparison of each dexlansoprazole MR group vs. placebo). Of the patients who did not relapse, eight withdrew from the placebo group, two from the dexlansoprazole MR 30-mg group and six from the dexlansoprazole MR 60-mg group because of AEs. Ten patients were not included in the ITT population (3, 5, and 2 patients in the dexlansoprazole MR 30 mg, 60 mg, and placebo groups, respectively) because they had a gap in dosing of >7 days between the healing and maintenance trials. There were no statistically significant differences in demographics among treatment groups at baseline or in the proportion of patients in each group healed by the different EO healing treatments (Table 1).

Maintenance of healed erosive oesophagitis

The cumulative rate of maintaining healed EO over 6 months using the ITT population and time-to-event (life-table) analysis was 74.9% and 82.5% in the dexlansoprazole MR 30- and 60-mg groups respectively compared with 27.2% in the placebo group ($P < 0.00001$) (Figure 2). By crude rate analysis using all ITT patients who also had ≥1 endoscopy during the maintenance trial, dexlansoprazole MR 30 mg and 60 mg QD each maintained healing in 66.4% of patients at month 6 compared with 14.3% for placebo ($P < 0.00001$).

The therapeutic gains (differences in maintenance rates) for both dexlansoprazole MR doses over placebo

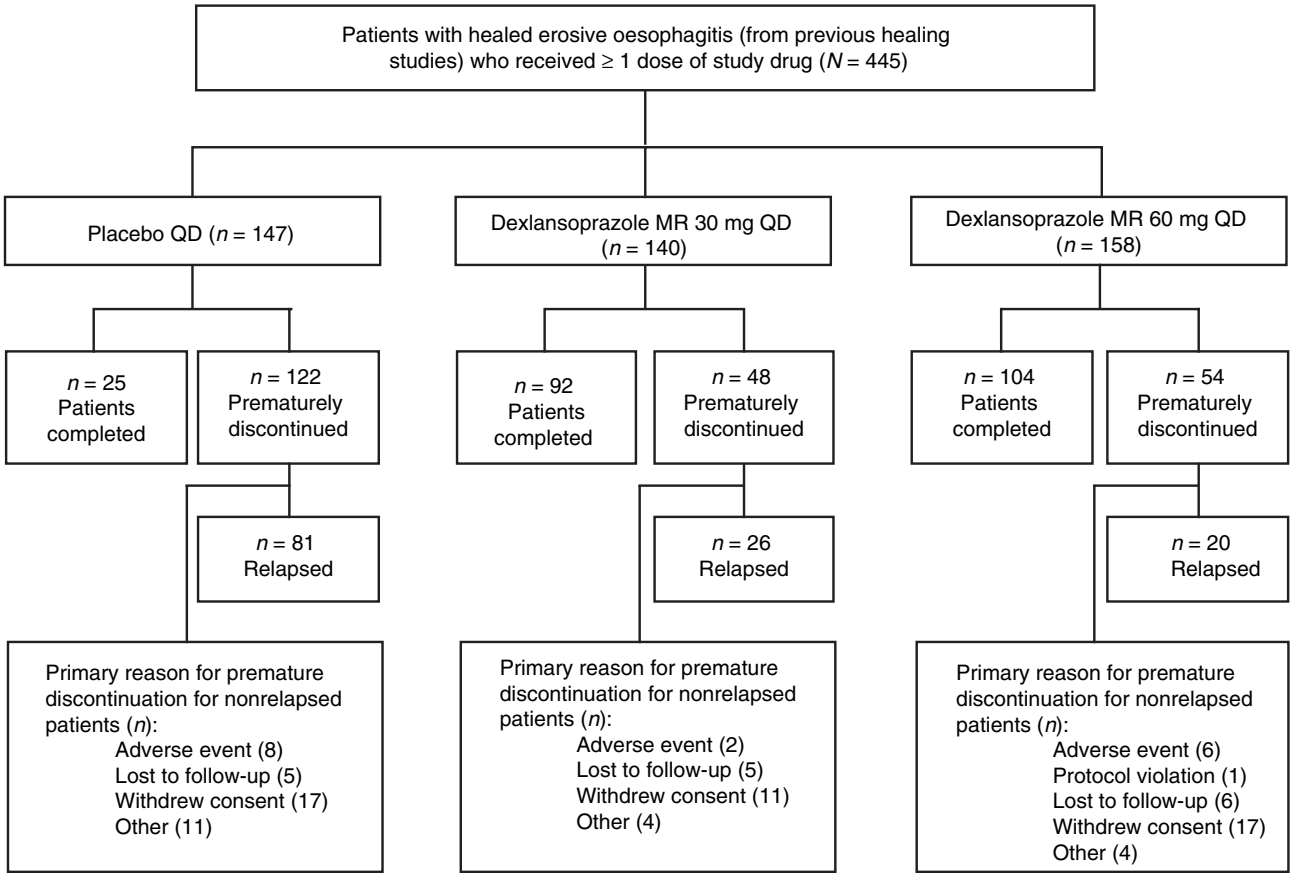

Figure 1. Participant flow diagram. Note: patient status and reasons shown are as per investigators' classification, except for the number relapsed (which includes those with endoscopy showing relapse occurring within 7 days of premature discontinuation). QD = once daily.

were 48–55 percentage points for life-table estimates and 52 percentage points for crude rates. There were no statistically significant differences between the dexlansoprazole MR treatment groups using either method of analysis.

Based on baseline assessment of EO before randomization in the EO healing studies, 72% of patients (n = 313) in the ITT population had a LA grade of EO of A or B and 28% (n = 122) had LA grade C or D. In the subgroups analysis of maintenance rates stratified by baseline LA grade of EO, maintenance rates at month 6 by the life-table method were similar (80% and 82% respectively) in the dexlansoprazole MR 30- and 60-mg treatment groups among patients with baseline grade A or B. However, for patients with LA grades C and D at baseline, 63% and 85% had maintained healed EO in the dexlansoprazole MR 30 mg and 60 mg treatment groups respectively (Figure 3). This therapeutic advantage of 22 percentage points for the 60-mg group over the 30-mg group for patients with more severe EO at baseline did not reach statistical significance (P = 0.03936), due to the small number of patients in this analysis. In the placebo group, 30% of patients with baseline LA grade of A or B were maintained at month 6 compared with 15% of patients with baseline grades of C or D. The pattern of findings was similar when analysed by crude rate analysis, with a therapeutic advantage of 16 percentage points for the 60-mg group over the 30-mg group in patients with baseline LA grade C or D oesophagitis (Figure 3).

Maintenance rates also varied according to the dose of PPI received in the preceding healing trials. No patients could be randomized to a higher dose of dexlansoprazole MR than their original healing dose because the lowest dose of dexlansoprazole MR used

Table 1. Demographic characteristics and baseline severity of oesophagitis

Variable	Placebo (n = 147)	Dexlansoprazole MR 30 mg QD (n = 140)	Dexlansoprazole MR 60 mg QD (n = 158)	P-value*
Gender, *n* (%)				
Male	72 (49.0)	69 (49.3)	74 (46.8)	0.897
Female	75 (51.0)	71 (50.7)	84 (53.2)	
Ethnicity, *n* (%)				
Hispanic or Latino	20 (13.6)	21 (15.0)	19 (12.0)	0.754
Non-Hispanic or Latino	127 (86.4)	119 (85.0)	139 (88.0)	
Race, *n* (%)				
American Indian or Alaskan Native	0	0	4 (2.5)	0.116
Asian	3 (2.0)	3 (2.1)	5 (3.2)	
Black	4 (2.7)	6 (4.3)	11 (7.0)	
Native Hawaiian or other Pacific Islander	0	0	1 (0.6)	
White	138 (93.9)	127 (90.7)	135 (85.4)	
Multiracial	1 (0.7)	4 (2.9)	2 (1.3)	
Age, y (mean ± s.d.)	49.5 ± 12.94	47.1 ± 13.15	47.9 ± 11.72	0.274
Weight, kg (mean ± s.d.)	86.2 ± 19.22	89.1 ± 18.96	87.8 ± 20.03	0.460
Height, cm (mean ± s.d.)	169.5 ± 11.00	169.9 ± 9.93	169.4 ± 10.09	0.898
BMI, kg/m^2 (mean ± s.d.)	30.0 ± 6.31	30.9 ± 6.63	30.6 ± 6.79	0.492
Helicobacter pylori–negative, *n* (%)	146 (99.3)	138 (98.6)	155 (98.1)	0.997
EO severity by LA classification at baseline (baseline of the healing study), *n* (%)				
A	51 (34.7)	53 (37.9)	56 (35.4)	0.718
B	57 (38.8)	46 (32.9)	57 (36.1)	
C	34 (23.1)	31 (22.1)	39 (24.7)	
D	5 (3.4)	10 (7.1)	6 (3.8)	
Duration of treatment in the healing study, *n* (%)				
4 week	111 (75.5)	105 (75.0)	119 (75.3)	0.722
8 week	35 (23.8)	35 (25.0)	39 (24.7)	
Previous treatment in the healing study, *n* (%)				
Dexlansoprazole MR 60 mg QD	44 (29.9)	52 (37.1)	49 (31.0)	0.532
Dexlansoprazole MR 90 mg QD	60 (40.8)	45 (32.1)	57 (36.1)	
Lansoprazole 30 mg QD	43 (29.3)	43 (30.7)	52 (32.9)	

BMI, body mass index; EO, erosive oesophagitis; LA, Los Angeles; QD, once daily.
* For gender, ethnicity, race, *Helicobacter pylori* status, LA EE Grade and duration of treatment, P-values are from chi-square tests. For age, weight, height and BMI, the P-values are from one-way ANOVA with treatment as a factor.
No statistically significant difference among treatment groups overall in any of the above variables.

in the healing studies was 60 mg, which is the highest dose used in this maintenance study. However, 51 patients previously treated with lansoprazole 30 mg were randomized to dexlansoprazole MR 60 mg in the maintenance study. Maintenance rates in these patients were 76.1% by life table analysis at month 6. By life table analysis, more than 85% of patients healed with dexlansoprazole MR 90 mg maintained their healing in both the dexlansoprazole MR 30-mg and 60-mg groups after 6 months of maintenance treatment in this trial. Similarly, patients healed with dexlansoprazole MR 90 mg in the preceding trials showed high 6-month maintenance rates of >70% by the crude rate analysis for both dexlansoprazole MR 30-mg and 60-mg doses. These high maintenance rates were not achieved by patients healed with dexlansoprazole MR 60 mg or lansoprazole 30 mg in the preceding EO healing trials.

Among patients who experienced a recurrence of EO, the median time to recurrence was significantly longer for the dexlansoprazole MR 30-mg and 60-mg groups (42 and 61 days, P = 0.00087 and P = 0.0015

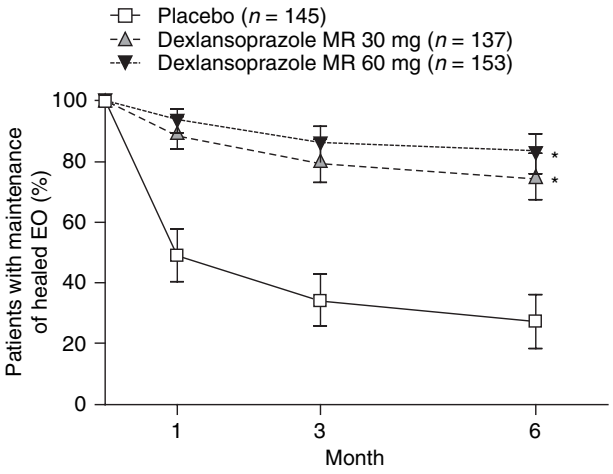

Figure 2. Cumulative life-table rates of maintenance of healed EE, intent-to-treat patients. *$P < 0.0025$ vs. placebo (Hochberg's procedure, log rank test).

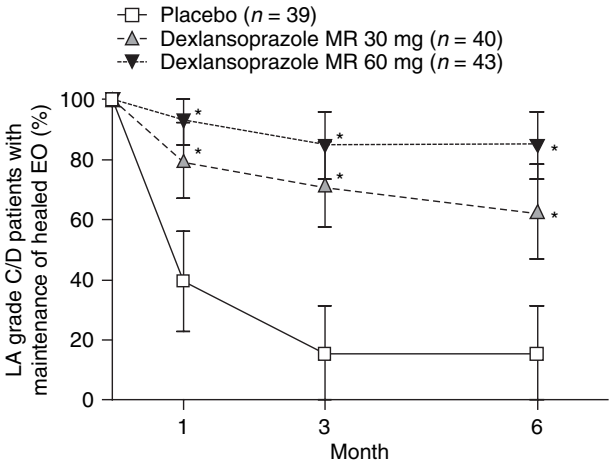

Figure 3. Cumulative life-table rates of maintenance of healed EE, intent-to-treat patients with baseline Los Angeles classification C or D. *$P < 0.0025$ vs. placebo (Hochberg's procedure; log rank test).

respectively; Wilcoxon rank sum test) compared with the placebo group (30 days).

Symptom control

The percentage of 24-h heartburn-free days based on daily diary was significantly greater in each of the dexlansoprazole MR treatment groups than in the placebo group ($P < 0.0025$; Hochberg's procedure). The percentage of nights without heartburn was also significantly greater in both dexlansoprazole MR treatment groups than in the placebo group ($P < 0.0025$; Hochberg's procedure) (Figure 4).

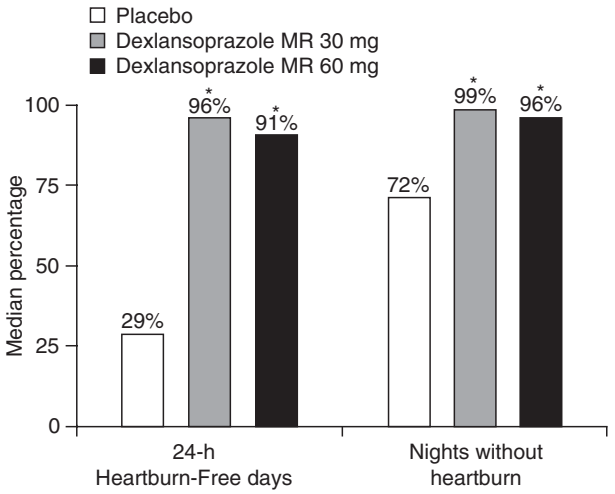

Figure 4. Median percentage of 24-h heartburn-free days and median percentage of nights without heartburn during treatment. *$P < 0.0025$ vs. placebo (Hochberg's procedure; Wilcoxon rank sum tests).

Based on daily diary data, the mean severity of 24-h and nighttime heartburn during the entire treatment period was statistically significantly lower in the dexlansoprazole MR treatment groups compared with placebo. There were no statistically significant differences between the dexlansoprazole MR treatment groups.

According to data reported in the daily diaries, patients in both dexlansoprazole MR treatment groups had a significantly greater percentage of days without use of rescue medication during treatment compared with patients in the placebo group (medians of 98%, 96%, and 44% respectively for dexlansoprazole MR 30 mg, dexlansoprazole MR 60 mg and placebo).

Results of the GERD symptoms investigator assessment indicated that heartburn, acid regurgitation, dysphagia, belching and epigastric pain were significantly less severe at month 1 and at the final visit for both dexlansoprazole MR treatment groups compared with placebo ($P < 0.0025$) except for dysphagia in the dexlansoprazole MR 60-mg group at the final visit. For reasons of the high placebo dropout rate after month 1, there were too few patients in the placebo group at months 3 and 6 for the statistical analysis to be meaningful. At the final visit, investigators assessed that 67% and 63% of patients receiving dexlansoprazole MR 30 and 60 mg respectively had no heartburn compared with 17% of patients who received placebo.

Patient-reported outcome results from the PAGI-QOL questionnaire showed that patients treated with dexlansoprazole MR 30 mg and 60 mg experienced significant improvement in the diet and food habits subscale from Day-1 to the final visit vs. placebo-treated patients. For the PAGI-SYM, the dexlansoprazole MR 30-mg and 60-mg groups showed significant improvement on the heartburn/regurgitation subscale and total PAGI-SYM scores compared with the placebo group. There were no statistically significant differences between the active treatment groups. For both sets of questionnaire results, mean scores for the placebo group deteriorated, while the dexlansoprazole MR groups maintained the mean scores observed at Day-1.

Safety

Of the 445 patients, 29%, 47% and 53% respectively experienced at least 1 treatment-emergent AE on placebo, dexlansoprazole MR 30 mg and dexlansoprazole MR 60 mg. Of the AEs experienced by ≥5% in any treatment group, only upper respiratory tract infections (URTI), diarrhoea and joint-related signs and symptoms were reported significantly more frequently in a dexlansoprazole MR treatment group compared with placebo.

Most patients randomized to placebo relapsed and discontinued the study within the first month of treatment. Thus, treatment-emergent AEs per 100 PM of exposure were calculated and are given in Table 2.

Table 2. Treatment-emergent adverse events occurring in ≥1 patient per 100 patient-months (PM) of exposure

	Treatment group: *n* (# with events per 100 PM of exposure)			
		Dexlansoprazole MR		
MedDRA high-level term, preferred term	Placebo (*n* = 147) (Avg PM = 1.9)	30 mg (*n* = 140) (Avg PM = 4.6)	60 mg (*n* = 158) (Avg PM = 4.6)	Total (*n* = 298) (Avg PM = 4.6)
Total patients with ≥1 adverse event§	43 (15.2)	66 (10.4)*	83 (11.5)	149 (11.0)
Gastritis (excl. infective)	7 (2.5)	2 (0.3)†	8 (1.1)	10 (0.7)
Gastritis				
Upper respiratory tract infections	1 (0.4)	14 (2.2)*	17 (2.4)*	31 (2.3)
Acute sinusitis, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection				
Dyspeptic signs and symptoms	6 (2.1)	3 (0.5)*	4 (0.6)*	7 (0.5)
Dyspepsia, epigastric discomfort, eructation				
Gastrointestinal and abdominal pains (excl. oral and throat)	5 (1.8)	3 (0.5)	5 (0.7)	8 (0.6)
Abdominal pain, abdominal pain, upper, abdominal pain lower, abdominal tenderness				
Oesophageal ulcers and perforation	4 (1.4)	0†	0†	0
Erosive oesophagitis				
Diarrhoea (excl. infective)	1 (0.4)	5 (0.8)	8 (1.1)	13 (1.0)
Diarrhoea				
Musculoskeletal and connective tissue signs and symptoms	2 (0.7)	3 (0.5)	8 (1.1)	11 (0.8)
Back pain, musculoskeletal chest pain, musculoskeletal pain, neck pain, pain in extremity				
Joint related signs and symptoms	1 (0.4)	7 (1.1)‡	0‡	7 (0.5)
Arthralgia, joint swelling				

* $P < 0.05$ vs. placebo, Conditional Exact test.
† $P < 0.01$ vs. placebo, Conditional Exact test.
‡ $P < 0.01$ difference between dexlansoprazole MR treatment groups, Conditional Exact test.
§ Patients with ≥1 adverse events within a level of the MedDRA term are counted only once in that level.

URTI was the only AE that occurred at a significantly higher rate on dexlansoprazole MR than placebo. Most URTI events were mild-to-moderate in severity. The AEs of gastritis (as defined by symptoms), dyspeptic signs and symptoms and EO were reported at a higher rate in the placebo group than in at least one of the dexlansoprazole MR treatment groups. There was no dose response observed in the rates of these AEs between the dexlansoprazole MR treatment groups. Nine patients experienced ≥1 serious AE during the study; none was determined to be related to study drug. No patients died during the course of the study.

The statistically significant differences in changes from baseline in percentage of patients with shifts outside the normal range or potentially clinically important laboratory values for either dexlansoprazole MR treatment group compared with placebo were small and not considered to be clinically significant.

Increases in serum gastrin for the dexlansoprazole MR treatment groups were within ranges expected with PPI treatment, given that all patients received active treatment for 4 to 8 weeks in the previous EO healing trials;[22, 23] median increases from baseline to month 6 were 63 pg/mL and 88 pg/mL for the dexlansoprazole MR 30 mg and 60 mg doses respectively. Median gastrin levels for patients on placebo returned to baseline within 1 month of discontinuation of PPI treatment received in the healing trials. There were no other clinically meaningful differences in vital signs, physical examinations or clinical laboratory results among treatment groups. There were no biopsy findings of intestinal metaplasia with dysplasia, neuroendocrine cell proliferation or adenocarcinoma at the final visit.

DISCUSSION

GERD is the most common gastrointestinal disorder diagnosis in the United States accounting for 5.5 million office visits per year.[24] As Americans continue to live longer and incur more risk factors, such as obesity, the incidence and severity of GERD will probably increase. Increasing age has been found to be associated with a higher prevalence of severe EO.[25] Obesity has been associated with more frequent GERD symptoms, an increased prevalence of EO, and increased severity of GERD symptoms.[25–27] GERD also has a major impact on patients' QOL, similar in magnitude to diabetes and hypertension.[28, 29] As EO is a chronic, relapsing disease, there is a need for effective long-term maintenance therapy in most patients.

In investigative trials for PPIs, patients entering maintenance of EO healing trials typically are first healed and the efficacy of a subsequent maintenance therapy is then assessed. In this study, we assessed dexlansoprazole MR, a novel dual delayed-release formulation of a PPI, as maintenance therapy for patients with healed EO. Four hundred forty five patients healed by dexlansoprazole MR 60 mg or 90 mg or lansoprazole 30 mg in the previous 2 EO healing studies were enrolled into this maintenance study.

Dexlansoprazole MR 30 mg and 60 mg administered QD were highly effective and significantly superior to placebo for maintenance of healed EO and relief of heartburn over 6 months. The therapeutic gain in maintenance rates for dexlansoprazole MR vs. placebo was similar by life-table estimates (48–55 percentage points) and crude rate analysis (52 percentage points) in this trial. Crude rates are a more conservative measure of efficacy because patients who prematurely discontinue with their last endoscopy showing no recurrence are considered to have recurred. The life table estimates in this trial are likely to be more reflective of true maintenance rates because patients who prematurely discontinue are censored according to the day of their last endoscopy. Therefore, maintenance rates of 75% for dexlansoprazole MR 30 mg and 83% for dexlansoprazole MR 60 mg may be seen in clinical practice.

The high relapse rate observed in the placebo-treated patients by month 1 in this trial using life table estimates (~51%) demonstrates the natural time course of relapse in EO patients who discontinue PPI therapy. The relapse rate at month 6 among placebo recipients (73%) is consistent with that seen within 12 months in patients who discontinued therapy in other PPI maintenance studies.[4–7] These observations affirm the importance of continuing effective maintenance therapy.

Obesity is an important concern in the US and higher BMI has been associated with symptoms of GERD.[26, 27] Interestingly, the mean BMI of patients across treatment groups in this study was >30 kg/m^2 and was consistent. Patients' BMI did not influence maintenance of healing rates in this study. The role of weight reduction has not been well studied in obese GERD patients and there are no definitive data available to suggest modifying treatment in this subgroup.[30, 31]

There was no statistically significant difference in the maintenance rates seen with dexlansoprazole MR

30 mg and 60 mg in the current trial. However, the 60-mg dose may provide additional clinical benefit over the 30-mg dose in patients with moderate-to-severe EO. More patients with LA grades C and D EO maintained healing with the 60-mg dose than with the 30-mg dose (22% using the life-table analysis and 16% difference via crude rate analysis). However, these differences were not statistically significant. Further studies with dexlansoprazole MR would be required to determine how it compares with existing agents for maintenance of healed EO.

The clinical benefit in maintenance rates observed with the higher dose in this study is consistent with data published in the 2004 Cochrane review of maintenance therapy for EO; this reported an overall relapse rate of 29.1% in those taking reduced doses of PPIs for 24–52 weeks compared with 17.5% in patients continued on a standard healing dose.[9] This is likely to be of particular importance for those with more severe EO, who may be at a greater risk for developing complications.[7, 9]

In the current study, dexlansoprazole MR 30 mg and 60 mg were also highly effective in maintaining patient-reported relief of daytime and nighttime heartburn over 6 months. Most patients remained nearly symptom-free during treatment, with median percentages of 24-h heartburn-free days of 96% and 91% for dexlansoprazole MR 30-mg and 60-mg treatment groups respectively compared with 29% for placebo. These findings are noteworthy given that relief of heartburn for 24 h was a more difficult endpoint to achieve than relief of daytime or nighttime heartburn alone. Additional clinical endpoints, including mean severity of heartburn, percentage of days without using rescue medication and severity of GERD symptoms as assessed by the investigator, confirmed the superior efficacy for dexlansoprazole MR 30 mg and 60 mg over placebo. The percentage of days without rescue medication use for both dexlansoprazole MR treatment groups paralleled the percentage of days without heartburn. Results from the PAGI-QOL and PAGI-SYM questionnaires were also consistent with the efficacy results. Decreases in symptom severity translated into significant improvement in the QOL scores for the diet and food habits subscale of both dexlansoprazole MR treatment groups compared with placebo. The improvement in this QOL subscale is a relevant finding and may reflect fewer restrictions on diet and food habits for patients taking dexlansoprazole MR.

Dexlansoprazole MR 30 mg and 60 mg were well tolerated. Patient months of exposure were used to normalize the data because the average exposure in the dexlansoprazole MR groups was 2.4 times higher than in the placebo group. When data were analysed per 100 PM of exposure, the placebo group had an overall rate of AEs similar to the dexlansoprazole MR treatment groups. There was a higher rate of URTI per 100 PM of exposure reported in the dexlansoprazole MR treatment groups compared with the placebo group in this trial. However, none of these URTIs involved any lower respiratory tract infections, i.e., pneumonia. The rate of lower respiratory tract infections in all phase 3 trials with dexlansoprazole MR was low (≤1.1%) and comparable across all dose groups (placebo; dexlansoprazole MR 30, 60, and 90 mg).[32] In the current trial, diarrhoea was reported more frequently in the dexlansoprazole MR treatment groups compared with placebo; however, differences between groups were not statistically significant. These findings are similar to those seen in earlier trials with lansoprazole.[22] There were no unexpected findings in laboratory values, mean serum gastrin levels or in gastric biopsies.

In conclusion, dexlansoprazole MR 30 mg and 60 mg administered QD were highly effective and superior to placebo in maintaining healed EO at 6 months and in controlling heartburn according to all assessments. Most patients receiving dexlansoprazole MR were heartburn-free for over 90% of treatment days. Dexlansoprazole MR 60 mg provided additional clinical benefit over dexlansoprazole MR 30 mg in maintaining healed EO among patients with more severe baseline grades of EO. Dexlansoprazole MR 30 mg and 60 mg administered for 6 months were well tolerated by patients with healed EO.

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Lois Larsen, PhD, was an employee of TAP Pharmaceutical Products Inc. at the time of the study conduct and analysis.

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