# Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial Assessing the Efficacy and Safety of Proton Pump Inhibitor Lansoprazole in Infants with Symptoms of Gastroesophageal Reflux Disease

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**Objective** To assess the efficacy and safety of lansoprazole in treating infants with symptoms attributed to gastroesophageal reflux disease (GERD) that have persisted despite a ≥ 1-week course of nonpharmacologic management.

**Study design** This multicenter, double-blind, parallel-group study randomized infants with persisting symptoms attributed to GERD to treatment with lansoprazole or placebo for 4 weeks. Symptoms were tracked through daily diaries and weekly visits. Efficacy was defined primarily by a ≥ 50% reduction in measures of feeding-related crying and secondarily by changes in other symptoms and global assessments. Safety was assessed based on the occurrence of adverse events (AEs) and clinical/laboratory data.

**Results** Of the 216 infants screened, 162 met the inclusion/exclusion criteria and were randomized. Of those, 44/81 infants (54%) in each group were responders—identical for lansoprazole and placebo. No significant lansoprazole–placebo differences were detected in any secondary measures or analyses of efficacy. During double-blind treatment, 62% of lansoprazole-treated subjects experienced 1 or more treatment-emergent AEs, versus 46% of placebo recipients ($P = .058$). Serious AEs (SAEs), particularly lower respiratory tract infections, occurred in 12 infants, significantly more frequently in the lansoprazole group compared with the placebo group (10 vs 2; $P = .032$).

**Conclusions** This study detected no difference in efficacy between lansoprazole and placebo for symptoms attributed to GERD in infants age 1 to 12 months. SAEs, particularly lower respiratory tract infections, occurred more frequently with lansoprazole than with placebo. *(J Pediatr 2009;154:514-20)*

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Initial diagnosis and treatment of gastroesophageal reflux disease (GERD) often is symptom-based and empiric in adults and children, including infants, a practice generally endorsed by subspecialty guidelines.[1] The power of proton pump inhibitors (PPIs) to suppress gastric acid secretion has led to their widespread use to treat GERD. Despite the absence of a Food and Drug Administration–approved indication for the use of any PPI in children under age 1 year, PPI use in infants is estimated to have increased up to 7-fold between 1999 and 2004.[2] This increased use is based on symptomatic presentation rather than on diagnostic testing, which has been used only in a minority (< 10% in 1 study).[2] Little reliable quality evidence supports this use in infants, however.[3,4] Despite 1997 legislation aimed at increasing robust evidence from clinical trials for pediatric pharmacotherapy,[5] most studies of PPI efficacy and safety in infants published or in progress (clinical trials registration; http://www.clinicaltrials.gov) are not double-blind, randomized, placebo-controlled clinical trials. Of the few that are, several use a withdrawal design that may be inappropriate for evaluating PPIs, which induce acid rebound, and thus dependency, in normal individuals.[6,7]

| | |
|---|---|
| AE | Adverse event |
| GA | Global assessment |
| GERD | Gastroesophageal reflux disease |
| $H_2RA$ | Histamine-2 receptor antagonist |
| I-GERQ | Infant Gastroesophageal Reflux Questionnaire |
| I-GERQ-MH | Infant Gastroesophageal Reflux Questionnaire-Medical History |
| NPM | Nonpharmacologic management |
| PPI | Proton pump inhibitor |
| SAE | Serious adverse event |

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## METHODS

This phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel group study assessed the efficacy and safety of lansoprazole treatment in infants with symptomatic GERD who remained symptomatic with crying, fussing, or irritability (designated "crying" hereinafter) during or within 1 hour after feeding despite at least 1 week of nonpharmacologic management (NPM; conservative therapy, "lifestyle measures"). It comprised 3 periods: pretreatment (1 to 2 weeks before randomization), treatment (maximum 4 weeks of study drug treatment), and posttreatment (Table I; available at www.jpeds.com).

Between June 29, 2006, and May 16, 2007, 16 centers (8 in the United States and 8 in Poland) enrolled infants. A prospective power analysis proposed approximately 160 subjects. Before any study-related activity, informed consent was obtained from parent/guardians of infants age 28 days to < 12 months (for preterm infants, corrected age of 44 weeks but < 12 months) with symptomatic GERD. The study protocol was approved for the US sites by central or local Institutional Review Boards and for the Polish sites by a Central Ethics Committee and the Polish Ministry of Health. (Henceforth the designation "parent" includes nonparent primary caregivers as well.)

### Pretreatment Period: Screening Visit and Nonpharmacologic Management

Infants were further screened through parental completion of the Infant Gastroesophageal Reflux Questionnaire Medical History (I-GERQ-MH) and by 7 to 14 days of NPM before randomization. Previous diagnostic tests used to establish the clinical diagnosis of GERD were documented, but none was required.

**Inclusion/exclusion criteria.** In addition to age, diagnosis, and consent as indicated earlier, inclusion criteria included weight > 2.0 kg and daily diary documented crying during or within 1 hour after ≥ 25% of feeds during the 4 days before randomization despite ≥ 7 days of specified NPM strategies. Exclusion criteria included previous use of a PPI within 30 days or histamine-2 receptor antagonist ($H_2RA$) within 7 days, as well as others; a comprehensive list is given in Appendix 1 (available at www.jpeds.com).

**Questionnaires.** *I-GERQ-MH.* This parent-completed questionnaire, adapted from the Infant Gastroesophageal Reflux Questionnaire (I-GERQ)[8] (Appendix 1), identifies symptoms, provocative factors (eg, feeding volume, smoke exposure), and other possible causes for symptoms (eg, allergy). It provides efficient documentation of data at diagnosis.

*I-GERQ-MH Score.* The I-GERQ-MH score (Table II) was computed post hoc to facilitate comparability of the study subjects' overall baseline symptom burden with other infants diagnosed with GERD based on symptomatology. It is adapted from the I-GERQ score (based on 11 items from the I-GERQ), which was previously validated for diagnosing infants with GERD compared with normal infants.[9]

**Nonpharmacologic management.** Parents were required to institute and record in a daily diary (see below) the following NPM strategies[10,11] for 7 to 14 days: (1) reduction of tobacco smoke exposure, (2) 1 or more feeding strategy (frequent burping, frequent small feedings, use of hypoallergenic and thickened formula, or dairy avoidance by breast-feeding mother), and (3) 1 or more positioning strategy (minimizing seated and awake supine positioning, avoiding vigorous handling, particularly postfeeding). Randomization qualification required that NPM failed to reduce meal-related crying to < 25% of all feedings during the final 4 pretreatment period days.

### Treatment Period

Lansoprazole (Takeda Global Research & Development Center, Inc, Deerfield, Illinois), formulated as an investigational suspension of microgranules for weight-based oral dosing, was administered once daily, preceded and followed by a ≥ 30-minute fast, at 0.2 to 0.3 mg/kg/day for infants age ≤ 10 weeks and at 1.0 to 1.5 mg/kg/day for those age >10 weeks.[12,13] Dosing, based on age and weight on day 1 of the double-blind treatment, was unchanged during the treatment. Placebo, formulated identically but without active drug by the same manufacturer, was dosed comparably. Infants were randomized blindly at a drug:placebo ratio of 1:1. (Details on medication dispensing, randomization, blinding, and compliance tracking are given in Appendix 1.) During treatment, NPM judged to be beneficial was continued at the investigator's discretion and documented weekly. Permitted concomitant medications were allowed as needed but were retained at the same dosage if possible, and this was recorded from 7 days before screening through 30 days after the last study drug dose.

After ≥ 1 week of double-blind treatment, infants discontinuing the treatment due to inefficacy (as judged by the site investigator) were eligible for open-label lansoprazole at the investigator's discretion and with parent consent. Dosing was reestablished based on age and weight on day 1 of open-label lansoprazole treatment. Data collection continued for a total of ≤ 4 weeks of treatment; the open-label initial visit also functioned as the double-blind termination visit. Subjects could be discontinued from the study at any time. At premature discontinuation (< 4 weeks of study drug treatment) from either the double-blind or open-label treatment, termination visit procedures were to be performed.

### Post-treatment Period

This period included telephone calls and a safety follow-up visit with global symptom assessment (GA) of symptoms 30 days after the last dose of any study drug (double-blind or open-label). The subjects also completed daily diaries for 7 days before the safety follow-up visit.

### Data Collected

In the daily diaries (Table III), the same parent, if possible, recorded feeding dates/times and symptoms, both

**Table II. Subject characteristics at baseline***

| | Lansoprazole (n = 81) | Placebo (n = 81) | All subjects (n = 162) |
|---|---|---|---|
| Age, weeks† | 16, 4-49 | 18, 4-51 | 16, 4-51 |
| Dosing strata: | | | |
| ≤10 weeks | 38% | 28% | 33% |
| >10 weeks | 62% | 72% | 67% |
| Premature subgroup | n = 20 | n = 24 | n = 44 |
| Gestational age at birth, weeks† | 35, 25-39 | 35, 26-38 | 35, 25-39 |
| Sex, % male | 47% | 53% | 50% |
| Race/ethnicity: | | | |
| Caucasian | 80% | 79% | 80% |
| Non-Caucasian | 20% | 21% | 20% |
| Country: | | | |
| United States | 48% | 36% | 42% |
| Poland | 52% | 64% | 58% |
| Birth weight, kg† | 3.25, 0.5-4.3 | 3.25, 0.9-4.1 | 3.25, 0.5-4.3 |
| Birth length, cm† | 52, 30-57 | 53, 33-60 | 52, 30-60 |
| Baseline weight, kg† | 5.9, 4-9 | 6.2, 4-11 | 6.0, 4-11 |
| Baseline length, cm† | 61, 53-78 | 62, 52-80 | 62, 52-80 |
| Symptoms, % of subjects‡ | | | |
| Crying | 100% | 100% | 100% |
| Regurgitation | 100% | 98% | 99% |
| Stop feeding | 80% | 84% | 82% |
| Refuse feed | 64% | 65% | 65% |
| Arching back | 89% | 89% | 89% |
| Wheezing | 40% | 44% | 42% |
| Coughing | 75% | 72% | 74% |
| Hoarseness | 22% | 31% | 27% |
| Symptoms, mean§ | | | |
| Crying, % of feeds/week | 51% | 52% | 52% |
| Regurgitation, % of feeds/week | 54% | 48% | 51% |
| Stop feeding, % of feeds/week | 21% | 19% | 20% |
| Refuse feed, % of days/week | 40% | 33% | 37% |
| Arching back, % of days/week | 68% | 68% | 68% |
| Wheezing, % of days/week | 21% | 31% | 26% |
| Coughing, % of days/week | 55% | 55% | 55% |
| Hoarseness, % of days/week | 12% | 19% | 15% |
| Provocative factors | | | |
| Smoke exposure: | | | |
| Some | 30% | 23% | 27% |
| None | 70% | 77% | 73% |
| Prestudy anti-acid treatment¶ | 15% | 2% | 9% |
| I-GERQ-MH score†,** | 13 (7-21) | 13 (3-23) | 13 (3-23) |
| I-GERQ-MH score >7** | (78), 96% | (74), 91% | (152), 94% |

There were no significant differences between treatment groups in subject characteristics at baseline.

*No subjects were hospitalized or being tube fed at entry.

†Median, range.

‡From daily diaries prerandomization. Symptom present on at least 1 day.

§From the daily diaries prerandomization. Computed using all subjects (% = 0 for those not reporting symptom).

¶Ranitidine, Mylanta, SMECTA.

**I-GERQ-MH score differed from I-GERQ score in 2 items that, in a small (indeterminate) number of subjects, each could have *decreased* the total score by 1 point, thus increasing specificity/decreasing sensitivity of the cutpoint. For a third item, apnea, the I-GERQ-MH score deleted modifiers, thus possibly *increasing* the I-GERQ-MH score by 6 points in 26 subjects (13 per treatment group). Among these, only 2 (1 per group) would change from GERD to non-GERD (score > 7 to ≤ 7) if those 6 points had been awarded incorrectly. Even if all 26 had not qualified for the 6 points, the median score overall would have decreased by < 1.

feeding-associated (during or ≤ 1 hour after) and not feeding-associated (24-hour recall). Parents and investigators also periodically completed 5-point ("none" to "very severe") GAs of GERD severity scales. Physical examination findings were recorded at each visit.

## Outcome Measures

**Efficacy measures.** Daily diary data for 7 days before randomization served as the baseline for efficacy comparisons. *Primary efficacy variables* were daily diary–documented number and

**Table III. Efficacy**

| | Lansoprazole double-blind (≤4 weeks, n = 81)* | Placebo double-blind (≤4 weeks, n = 81)* | *P* value† | Lansoprazole open-label (1-3 weeks, n = 55)* |
|---|---|---|---|---|
| Primary efficacy: Responder rate, n (%) | 44 (54%) | 44 (54%) | NS | NA |
| Discontinued due to nonefficacy, n (%) | 28 (35%) | 29 (36%) | NS | 0 |
| Individual symptoms‡ | | | | |
| Cry, % of feeds/week (Appendix 2) | −20 | −20 | NS | −19 |
| Regurgitate, % of feeds/week | −14 | −11 | NS | −20 |
| Stop feed soon, % of feeds/week | −7 | −8 | NS | −3 |
| Feed refusal, % of days/week | −14 | −10 | NS | −15 |
| Arching back, % of days/week | −20 | −18 | NS | −33 |
| Coughing, % of days/week | 0 | −9 | NS | −3 |
| Wheezing, % of days/week | −5 | −6 | NS | −12 |
| Hoarseness | 2 | −5 | NS | −9 |
| Global severity assessment§ | | | | |
| Parent: Improved at week 4 | 45 (56%) | 41 (51%) | NS | 44 (80%) |
| Physician: Improved at week 4 | 44 (55%)¶ | 40 (49%) | NS | 47 (85%) |
| Compliance | | | | |
| ≥90% for drug, % of subjects | 93% | 95% | Not tested | 98% |
| ≥90% for daily diary, % of subjects | 96% | 100% | Not tested | 93% |

NS, not significant; NA, not applicable.
*For subjects withdrawn from double-blind treatment before the 4th week, the last week of available data is carried forward to 4th week for the individual symptoms and GAs. The open-label treatment ranged from 1 to 3 weeks, depending on the time of withdrawal from the double-blind treatment; the final week of open-label data is summarized.
†Double-blind treatment comparisons: primary endpoint described in statistical section; Wilcoxon test for changes from baseline in percent of days or feedings with individual symptoms; Fisher exact test for inefficacy discontinuation percent and global assessment percent improved. Compliance was not tested statistically.
‡Mean (ie, averaged across infants) change from pretreatment baseline; intention to treat.
§Improved at least 1 severity level compared with baseline assessment.
¶Data missing from 1 subject: 44/80 (55%).

duration of crying episodes during or ≤ 1 hour after feeding. *Responder status* was determined at week 4 (using final double-blind week for subjects discontinuing early) and was defined as a ≥ 50% reduction from baseline in either percentage of feedings with crying episode(s) or duration (in minutes) of episodes averaged across feedings. *Responder rate* was the percentage of subjects who were responders at week 4. *Secondary efficacy variables* were the frequency of various GERD symptoms quantified in daily diaries, overall GAs by investigators and parents, and the presence of wheezing.

**Safety measures and assessment of adverse events.** Safety was defined and assessed in standard fashion by reported adverse events (AEs), physical examination, and central laboratory data, as detailed in Appendix 1.

### Statistical Methods and Interim Analysis

**Power analysis.** The adaptive design was group sequential (Appendix 1). Prospective sample size determination was based on (1) assumed treatment response by ≥ 50% of the lansoprazole-treated subjects and ≤ 25% of the placebo-treated subjects, (2) an interim analysis, and (3) a 1-sided alpha = .025. A sample size of 160 provided ≥ 80% power to establish the superiority of lansoprazole treatment when the overall study dropout rate was ≤ 20%.

**Statistical methods.** All statistical analyses were conducted at the Statistics Department of Takeda Global Research & Development Center, Inc. All randomized infants administered 1 or more dose(s) of study drug were included in the intention-to-treat data set for efficacy and safety analyses.

In the primary efficacy analysis, the difference between treatment groups in responder rate was tested by comparing the standardized binomial test statistic of the difference (standardized *z*-score) with the predetermined final analysis decision boundary to establish the superiority of lansoprazole (1-sided test; $\alpha = 0.025$). All other tests were 2-sided ($\alpha = 0.05$). The details of the secondary endpoint analytical methods are given in Appendix 1.

For the safety analysis, comparisons between treatment groups were made using the Fisher exact test for percentages of subjects with treatment-emergent AEs, laboratory and vital sign values outside prespecified limits, and shifts in laboratory values from baseline relative to normal reference ranges, and analysis of variance for mean changes from baseline in laboratory, vital sign, and growth values.

## RESULTS

### Subjects

Baseline characteristics and subject accounting of the 162 randomized subjects included in the intention-to-treat analysis are presented in Table II and the Figure (available at www.jpeds.com), respectively.

**Table IV. Adverse events**

| | Lansoprazole double-blind (n = 81) | Placebo double-blind (n = 81) | *P* value* | Lansoprazole open-label (n = 55) |
|---|---|---|---|---|
| Cumulative treatment exposure, subject-weeks | 257 | 245 | — | 144 |
| AE collection weeks, median, range† | 8.3, 1-9 | 8.3, 1-9 | NS | 7.3, 5-8 |
| AEs‡ | 50 (62%) | 37 (46%) | NS | 34 (62%) |
| Upper respiratory infections | 18 (22%) | 17 (21%) | NS | 11 (20%) |
| Constipation, GERD | 9 (11%): 5,4§ | 3 (4%): 2,1§ | NS | 3 (5%): 2,1 |
| Dermatitis, eczema | 8 (10%) | 6 (7%) | NS | 8 (15%) |
| Ear infections | 8 (10%) | 5 (6%) | NS | 6 (11%) |
| Fever | 8 (10%) | 2 (2%) | NS | 7 (13%) |
| Lower respiratory tract infection | 6 (7%) | 2 (2%) | NS | 1 (2%) |
| Respiratory tract congestion | 0 | 0 | NS | 3 (5%) |
| Rhinorrhea | 6 (7%) | 4 (5%) | NS | 4 (7%) |
| Candidiasis | 5 (6%) | 3 (4%) | NS | 3 (5%) |
| Diarrhea (excluding infective) | 4 (5%) | 5 (6%) | NS | 4 (7%) |
| Vomiting | 4 (5%) | 1 (1%) | NS | 2 (4%) |
| Alkaline phosphatase increase | 2 (2%) | 5 (6%) | NS | 0 |
| Viral infection | 2 (2%) | 5 (6%) | NS | 6 (11%) |
| SAEs¶ | 10 (12%) | 2 (2%) | .032 | 2 (4%) |
| Lower respiratory tract infection | 4 (5%) | 1 (1%) | NS | 0 |
| Diarrhea | 2 (2%) | 0 | NS | 0 |
| Ileus | 1 (1%) | 0 | NS | 0 |
| Dehydration | 1 (1%) | 0 | NS | 0 |
| Ear infection (otitis media) | 0 | 1 (1%) | NS | 1 (2%) |
| Upper respiratory infection | 1 (1%) | 0 | NS | 0 |
| Epididymal infection | 1 (1%) | 0 | NS | 0 |
| Arachnoid cyst | 1 (1%) | 0 | NS | 0 |
| Cellulitis | 1 (1%) | 0 | NS | 0 |
| Febrile convulsion | 0 | 0 | NS | 1 (2%) |
| *Klebsiella* infection | 0 | 0 | NS | 1 (2%) |

NS, not significant.

*Double-blind treatment comparisons: Fisher exact test for AE percentage; Wilcoxon test for weeks of AE collection.

†For the double-blind period, "collection weeks" includes 30 days posttreatment for those subjects who did not enter open-label treatment. For open-label period, this includes 30 days posttreatment for all subjects who entered open-label treatment.

‡Overall number (percentage) of subjects with 1 or more treatment-emergent AE(s). Subsequent indented rows: AEs reported by ≥ 5% of subjects during either double-blind or open-label treatment, number (%).

§The last 2 numbers are numbers for subjects with constipation and (worsened) GERD tabulated separately.

¶Overall number (percentage) of subjects with 1 or more treatment-emergent SAE(s). Subsequent indented rows: SAEs reported by any subjects. Subjects with SAEs involving more than 1 category are listed in each category, so the sum from categories may exceed the total number of subjects with SAEs.

## Efficacy

The interim analysis of the primary endpoint (Appendix 1) indicated that enrollment should continue to completion. Lansoprazole and placebo produced identical responder numbers (54%) (Table III). The secondary sensitivity analyses and subgroup analyses also demonstrated similar efficacy for lansoprazole and placebo. Responder rates were greater in the 131 subjects who continued NPM into the double-blind period (63%) compared with the 31 subjects not continuing NPM (19%), but NPM continuation did not affect the responder rate difference between the 2 treatment groups. The treatment groups did not differ significantly in terms of any secondary efficacy measure.

## Safety

Treatment-emergent AEs occurred in 62% of the lansoprazole-treated subjects and in 46% of the placebo-treated subjects during the double-blind treatment ($P = .058$) (Table IV). Events judged to be treatment-related did not differ between the 2 groups (15% for lansoprazole vs 16% for placebo). Of the 55 subjects who entered open-label treatment, 62% experienced AEs. Most of the AEs were mild or moderate.

Treatment-emergent serious AEs (SAEs) during double-blind treatment were significantly more frequent in the lansoprazole group compared with the placebo group (10 vs 2; $P = .032$); 2 additional subjects experienced SAEs during open-label lansoprazole treatment. Lower respiratory tract

and lung infections, the most frequent SAEs in the double-blind treatment, occurred in 5% of the lansoprazole group and 1% of the placebo group (not significant). No SAE was identified as being treatment-related. All infants with SAEs were hospitalized. No deaths occurred.

In 5 infants (1 double-blind lansoprazole, 3 double-blind placebo, 1 open-label lansoprazole), the alkaline phosphatase level was $\geq 2$ times the upper limit of normal (prespecified) but normalized during follow-up; 4 of these events were considered AEs. There were no other clinically meaningful laboratory findings in either individual values or treatment comparisons for any analyses. No significant differences between treatment groups in terms of vital signs, growth, and physical examination findings were identified.

## DISCUSSION

This placebo-controlled, double-blind study assessed PPI efficacy in infants with symptoms attributed to GERD. The findings are important in the determination of appropriate management strategies for such patients. Strengths of this study include the design, the large number of subjects (for an infant study), and the predetermined power analysis, although the assumption of actual versus anticipated placebo response (54% vs $\leq$ 25%) was not borne out.

Possible limitations of the study include those related to subject selection. First, crying is nonspecific for GERD.[1] Second, the prerandomization acid-suppressive treatment in 9% of the subjects (15% of those randomized to double-blind lansoprazole) may have selected nonresponders. Third, the post hoc baseline I-GERQ-MH scores suggest possible inclusion of 10 with physiological reflux (ie, score $<$ 7), although they do indicate the general diagnostic severity of the symptoms.[9] Finally, the limited comprehensiveness of the screening NPM (compared with that reported previously[10,11,14]) may not have completely excluded infants with either physiological reflux (although it did exclude 12% [22/184] of infants otherwise available for randomization) or milk or soy allergy (although extensively hydrolyzed formula was used for 69% of infants who received any formula, and maternal dairy avoidance was used for 86% of breast-fed infants). Limitations could also include aspects of treatment: (1) dose (although pharmacokinetic and pharmacodynamic studies support the doses used[12,13,15]), (2) duration (although 4 weeks of PPI treatment produces a symptomatic response in controlled trials in older children and adults with nonerosive GERD[16,17]), or (3) appropriate target (acid/nonacid; see below). Allowing entry to open-label treatment after only 1 week of double-blind treatment (17 subjects) also may have decreased the double-blind response rate. Finally, the outcome variables might be suboptimal; crying is nonspecific for pain due to esophageal luminal acid exposure,[1] and the diaries and GAs were not prevalidated.

Published double-blind, randomized, placebo-controlled trials of PPI efficacy for infants with GERD symptoms are few, small (10 to 50 patients), and of brief duration (1 to 2 weeks of PPI).[18-20] Nonetheless, all have demonstrated—as our study did—that the PPI and placebo produced similar improvement in crying, despite the significantly greater reduction of esophageal acid exposure with the PPI. The sample size and treatment duration of the present study were considerably greater than those in any previous infant double-blind, randomized, placebo-controlled PPI trial. Another unique strength was its screening NPM and prerandomization documentation of symptom burden by a prevalidated instrument.

These studies' vigorous placebo responses may reflect the natural history of symptoms[21] and/or the cumulative efficacy of NPM.[10,11,14] Expectation bias also may have contributed to our study's 80% to 85% global response ("improvement") rates after open-label lansoprazole treatment, compared with 55% to 56% after double-blind lansoprazole treatment. Awareness of the possibility of not receiving active drug may produce lower responses during double-blind treatment.

Most symptoms attributed to infant GERD likely are unaccompanied by esophageal erosions, and, like nonerosive reflux disease in adults, may be less responsive to PPI therapy. In adults and older children, this diminished PPI responsiveness may reflect inclusion of functional symptoms and nonacid reflux, along with symptoms due to "pre-erosive" acid damage.[17,23] In infants with reflux, nonacid reflux could produce symptoms from "volume reflux," as explored by multichannel intraluminal impedance; crying is temporally associated equally with acid and nonacid reflux.[24] Infants' verbal limitations also limit specificity of pain description, so meal-associated crying could be due to gastric distension as well as heartburn.[25] Thus, another explanation for the study's findings could be that the subjects may not have had GERD, but rather had physiological regurgitation accompanied by crying from other causes. Such symptoms usually resolve during infancy, because of interventions, passage of time, and/or additional parental support;[14,21] however, studies of similar infants documenting a close temporal relationship between reflux episodes and crying support a possible causal relationship.[24,26]

Should these infants, with symptoms attributed to GERD but unresponsive to powerful acid suppression by PPIs, be considered to have infant "nonerosive reflux disease" (reflux *disease,* despite the absence of erosions or responsiveness to PPI, because histological abnormalities, when present, tend to persist[21])? Or should they be considered to have gastroesophageal reflux (and not *disease* at all, despite the appearance of considerable associated or coincident discomfort, because these symptoms generally resolve during infancy[14,21])? This is somewhat a matter of semantics, subject to debate. Nonetheless, our findings substantially clarify the appropriate management of these infants.

Important caveats are that our findings results do not apply to infants with erosive disease or GERD-promoting disorders, or to children over age 1 year. The acid suppression demon-

strated by PPIs in infants[12,13,18-20] should be as efficacious for erosive disease in infants as in older children.[22,27,28] GERD-promoting disorders, such as repaired esophageal atresia, chronic neuromuscular disease, chronic respiratory disease, large hiatal hernias, and obesity, are more likely to induce erosive disease that benefits from PPI treatment.[27-30]

The difference in SAEs (particularly lower respiratory infections) between the lansoprazole-treated and placebo-treated groups possibly can be attributed to unmeasured confounding factors. However, the prospective placebo-controlled design provides authority, and the recent identification of similar concerns in other publications[31,32] mandates further attention. If our subjects replicate the general population of infants treated for GERD symptoms with PPIs (as we intended), then it is reasonable to extrapolate these findings to the general use of PPIs in this group until demonstrated otherwise. Our data underscore the importance of avoiding drugs without demonstrated efficacy.

In summary, this study found no difference in efficacy between lansoprazole and placebo in treating infants with symptomatic GERD. SAEs, particularly lower respiratory tract infections, occurred more frequently with double-blind lansoprazole than with placebo.

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## APPENDIX 1: METHODS, DETAILS

### Exclusion Criteria

Exclusion criteria included (1) several categories of unstable clinically significant disease, laboratory results, or surgery; (2) coexisting esophageal disease or upper gastrointestinal congenital anomaly; (3) participation in other drug research; (4) previous use of a PPI within 30 days or a $H_2RA$ within 7 days; (5) discontinuation of previous $H_2RA$ for study eligibility; (6) allergy to any component or excipient of any PPI; (7) requirement for continuous tube feedings; (8) history of acute life-threatening events attributed to GERD; (9) unstable doses or levels of various medications; and (10) anticipated noncompliance.

### I-GERQ Instruments

The Infant Gastroesophageal Reflux Questionnaire (I-GERQ) was developed by Susan Orenstein, MD (© 1992, 2002, University of Pittsburgh). Further information and licensing is available from the author at sro.pitt.edu@verizon.net.

The I-GERQ Score (© University of Pittsburgh) is based on 11 items from the I-GERQ. It was previously validated for diagnosing infants with GERD using the gold standard of abnormal esophageal biopsy and/or abnormal esophageal pH probe study compared with normal infants. Further information and licensing is available from the author at sro.pitt.edu@verizon.net.

### Treatment Period

**Treatments.** At each visit, medication was dispensed in kits of single-use bottles of drug to be reconstituted, using water from multiple-use water bottles, to a concentration of 1.0 or 2.0 mg/mL, within 45 minutes before administration. All dispensed kits, containing used and unused bottles, were to be returned to evaluate compliance.

### Randomization

Eligible infants were randomized (1:1 ratio) to lansoprazole or placebo. Double-blind treatment assignments were made through a central Web-based system according to a schedule that was computer-generated by Takeda Global Research & Development Center, Inc and concealed to study personnel.

### Blinding

Appearance, reconstitution, and administration of lansoprazole and placebo were identical. All study drug kit labels contained an emergency use–only blind-breaking panel; the central randomization site also could enable emergency blind-breaking.

### Compliance

Compliance was assessed at study visits based on the number of returned kits, daily diaries, and parental interview.

### Safety Measures and Assessment of AEs

Investigators assessed AEs conventionally, as serious or not; as severe, moderate, or mild in severity; and as to relationship to study drug: definite, possible, or unrelated (another etiology was highly likely). An SAE was predefined as any event resulting in any of the following outcomes: death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, persistent disability/incapacity, or a congenital anomaly/birth defect. An important medical event that was not life-threatening or did not require hospitalization could have been considered serious if, based on appropriate medical judgment, it jeopardized the subject or required medical or surgical intervention to prevent one of the foregoing outcomes.

Treatment-emergent AEs encompassed all AEs with onset or worsening on or after day 1 of drug exposure up to 30 days after last dose; treatment-related AEs were treatment-emergent AEs considered by site investigators to have a definite or possible relationship to the study drug. Treatment-emergent AEs were collected and categorized (using Medical Dictionary for Regulatory Activities coding) throughout the study. Changes from baseline in laboratory data and vital signs were evaluated, and values outside predefined limits were identified.

Other safety variables included changes in weekly vital signs and growth parameters (weight and length).

### Statistical Methods

Secondary sensitivity analyses of the primary endpoint used the Fisher exact test to compare responder rates between the 2 treatment groups under different analysis conditions: (1) classifying subjects discontinuing double-blind treatment early as "nonresponders" regardless of whether final available diary data met the "responder" threshold (1-sided Fisher exact test); (2) deriving baseline values over a shorter period (4 days vs. 7 days; 1-sided Fisher exact test), which ensured that baseline values were derived using diary entries made after at least 3 full days of pretreatment NPM; or (3) adjusting for duration of pretreatment NPM (7 to 10 days vs 11 to 14 days; Cochran-Mantel-Haenszel test).

Subgroup evaluations of the primary endpoint retrospectively conducted on the data included the effects of (1) age strata (1 to 3, 4 to 6, and 9 to 12 months), (2) country (US/Poland sites), (3) age-based dosing strata (0.2 to 0.3 and 1.0 to 1.5 mg/kg/dose), and (4) continuing/not continuing NPM into double-blind treatment.

Secondary efficacy analyses compared the effects of lansoprazole and placebo on individual symptoms (change from baseline in percent of days or feedings with symptom, Wilcoxon test), GAs and airway complications (percent of subjects with shifts from baseline in severity rating, Fisher exact test), and growth (changes from baseline, 1-way analysis of variance with treatment as the factor). Subset analyses for some symptoms (eg, including or not including subjects without the symptom at baseline) also used the Wilcoxon test.

For those subjects who entered open-label treatment, descriptive symptom summaries (change from pretreatment baseline at each open-label week in percent of feedings or days with diary-collected symptoms and shifts from baseline in the GA severity ratings) were tabulated using all subjects. No comparisons of open-label results were made based on previous double-blind treatment assignment.

### Interim Analysis and Further Information Regarding Statistical Design and Powering

The adaptive group sequential design included a single interim analysis on the primary efficacy endpoint when the first 80 subjects (50% of planned enrollment) had completed the study. The objective of that analysis was to determine whether to stop the study prematurely due to either efficacy or futility of the study drug. There was to be no adjustment to sample size or study protocol based on results of the interim analysis. The null hypothesis for the study was that lansoprazole is either less efficacious than or as efficacious as placebo. The alternative hypothesis was that lansoprazole is more efficacious than placebo. The test statistic used at both the interim and the final analysis was the standardized binomial test statistic of the difference between treatment groups in the proportion of subjects classified as responders to treatment (standardized $z$-score). The group sequential design ensured that for the primary efficacy variable, the significance for the study was maintained overall at a $P$ value of .025 (1-sided test).

The interim analysis was performed by an independent statistician. The interim $z$-score (known only to that statistician and the department head until study completion) was compared to the predetermined lower (stop for futility if $\leq$ 1.0089) and upper (stop for efficacy if $\geq$ 2.6623) interim decision boundaries; the study was to continue to the originally determined recruitment number if the $z$-score was between the 2 boundaries. The decision to stop or continue was the only information communicated to study personnel. During the final analysis, superiority of lansoprazole pediatric suspension was to be claimed if the final analysis $z$-score was $\geq$ 1.8825.

The interim and final boundaries were calculated using the methods proposed by Pampollona and Tsiatis[1] and by Kittelson and Emerson[2] with assumed treatment response by $\geq$ 50% of lansoprazole and $\leq$ 25% of placebo subjects. This calculation assumed a 1-sided test ($\alpha$ = 0.025) test using O'Brien-Fleming methodology[3] in support of the alternative hypothesis (efficacy) and Pocock methodology[4] in support of the null hypothesis (futility).

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**Appendix 2. Efficacy: Details of Crying Parameters**

| Crying parameters | Lansoprazole double-blind (≤4 weeks, n = 81) | Placebo double-blind (≤4 weeks, n = 81) | *P* value (Wilcoxon rank-sum test) | Lansoprazole open-label (1-3 weeks, n = 55) |
|---|---|---|---|---|
| Percentage of feeds, mean (SD) | | | | |
| Baseline* | 51.0 (20.39) | 52.4 (20.46) | | 49.1 (20.73) |
| Final† | 31.0 (25.41) | 32.4 (28.13) | | 30.5 (28.76) |
| Change‡ | −19.9 (23.10) | −19.9 (23.83) | .794 | −18.6 (23.60) |
| Minutes postfeed, mean (SD)§ | | | | |
| Baseline* | 7.9 (6.05) | 9.0 (7.25) | | 8.9 (7.99) |
| Final† | 4.3 (5.52) | 4.9 (6.20) | | 3.7 (4.97) |
| Change‡ | −3.6 (5.40) | −4.1 (6.63) | .830 | −5.2 (7.45) |
| Minutes/day, mean (SD)¶ | | | | |
| Baseline* | 47.0 (37.30) | 55.4 (46.11) | | 54.0 (48.07) |
| Final† | 22.1 (29.96) | 27.6 (36.57) | | 20.4 (27.83) |
| Change‡ | −25.0 (31.86) | −27.8 (41.41) | .963 | −33.6 (46.95) |

SD, standard deviation.

*Calculated using the 7-day interval before the first dose.

†Calculated using the final 7-day interval. Double-blind, week 4 or last available week carried forward (LOCF); open-label, week 3 or LOCF.

‡Change from baseline value; calculated before rounding.

§Duration of crying during or within 1 hour after feeding. For feedings with no crying, 0 minutes was assigned. Each subject's minutes postfeed was averaged across all feedings in the interval.

¶Total duration of crying per day. For feedings with no crying, 0 minutes was assigned. Each subject's minutes/day was cumulated across all feeds and averaged across all days in the interval.

**Table 1. Study Flow Chart**

| | Pretreatment period | | Double-blind treatment period/open-label treatment | | | | | Posttreatment period | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Procedure | Screening visit | Day-7 to -14 : NPM* | Dosing day 1: (randomization) | Week 1: Visit | Week 2: Visit† | Week 3: Visit† | Week 4: Termination visit‡ | Week 5: Phone call† | Week 6: Phone call† | Week 7: Phone call† | Week 8: Safety follow-up visit† | Any time: Unscheduled visit§ |
| Study visit number | 1 | | 2 | 3 | 4 | 5 | 6 | | | | 7 | |
| Informed consent¶ | X‖ | | | | | | | | | | | |
| IWES contact | X | | X | X | X | X | X | | | | X | |
| Medical history¶ | X** | | | | | | | | | | | |
| I-GERQ-MH¶ | X | | | | | | | | | | | |
| Complete physical exam | X | | | | | | X | | | | X | X |
| Brief physical exam | | | X | X | X | X | | | | | | |
| Vital signs, height/weight | X | | X | X | X | X | X | | | | X | X |
| Clinical laboratory tests | X†† | | | | | | X | | | | X‡‡ | X |
| Concomitant medications | X | | X | X | X | X | X | X | X | X | X | X |
| NPM | | X | X§§ | X§§ | X§§ | X§§ | X§§ | | | | | |
| Study drug dispensed | | | X¶¶ | X¶¶*** | X¶¶*** | X¶¶*** | | | | | | |
| Compliance review | | | | X | X | X | X | | | | | |
| Daily diary¶ | | X | X | X | X | X | X | | | X | X††† | |
| Physician and parent GA of GERD severity¶ | | | X | X | X | X | X | | | | X††† | |
| Parent GA of change in GERD symptoms¶ | | | | | | | X‡‡‡ | | | | X†††,§§§ | |
| Treatment-emergent (on or after day 1) AEs recorded | | | | X | X | X | X | X | X | X | X | X |

IWES, interactive Web-based enrollment system.
*Pretreatment period consisted of 7 to 14 days of NPM.
†Visit/telephone call windows: ± 2 days of the scheduled visit/telephone call, relative to dosing day 1 of the double-blind treatment period.
‡Before beginning the open-label treatment, subjects underwent the double-blind termination visit procedures.
§At unscheduled visits, additional procedures were performed when judged medically necessary by the investigator.
¶Language: For Polish sites, all documents provided to parents were translated by a company providing certified translators, reviewed by Dr. Furmaga-Jablonska for medical accuracy, and approved by the Central Ethics Committee and Ministry of Health.
‖Written informed consent was obtained before screening visit procedures and again before the start of any open-label treatment.
**Included recording any previous diagnostic tests used to establish the GERD diagnosis (suspected, symptomatic, or endoscopic).
††Screening clinical laboratory analysis was to be completed within 14 days before dosing day 1 of the double-blind treatment period.
‡‡At the week 4 or termination visit, laboratory values investigator-assessed as abnormal were to be repeated.
§§NPM continued through the double-blind and open-label treatment periods, unless the investigator determined that these strategies were of no benefit.
¶¶Dose calculation based on age and body weight on dosing day 1 of the double-blind treatment, and to be unchanged during the double-blind treatment.
***Dose calculation based on age and body weight on day 1 of the open-label treatment, and to be unchanged during the open-label treatment.
†††Only subjects who completed 4 weeks of treatment with study drug.
‡‡‡Parent-rated global change in GERD symptoms at the week 4 termination visit compared with dosing day 1 of the double-blind treatment.
§§§Parent-rated global change in GERD symptoms compared with the week 4 termination visit.

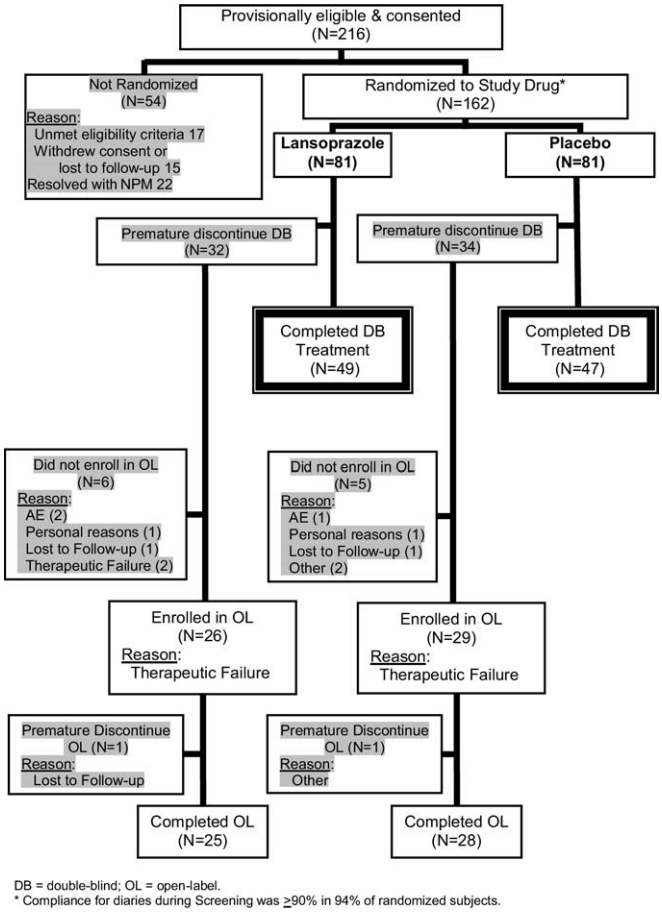


**Figure.** Subject accounting. Shown is the flow of subjects through the study. Compliance for diary completion during screening was ≥ 90% in 94% of randomized subjects. N, number of subjects; DB, double-blind treatment; OL, open-label treatment.