U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	22,287
Supplement #:	S-021
Drug Name:	Dexilant (dexlansoprazole delayed-release capsules)
Indication(s):	Erosive Esophagitis (healing and maintenance of healed EE and relief of heartburn), and treating heartburn associated with non-erosive gastroesophageal reflux disease (GERD)
Applicant:	Takeda
Dates:	Submission date: September 30, 2015
	Primary review due: June 20, 2016
	PDUFA V: July 30, 2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewers:	Andrejus Parfionovas, Ph.D.
Concurring Reviewers:	Yeh-Fong Chen, Ph.D.
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Keywords: NDA review, pediatric written request, mixed models.

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EXECUTIVE SUMMARY

The sponsor's findings on orally administered dexlansoprazole (Dexilant) delayed-release 60 mg and 30 mg capsules for treating heartburn associated with nonerosive gastroesophageal reflux disease, healing of erosive esophagitis (EE) and maintenance of healed EE and relief of heartburn in adolescent patients were confirmed by the statistical review team. Although data from both efficacy studies supported the use of Dexilant in adolescents, these studies were not statistically powered to detect the effectiveness of Dexilant. Therefore, only descriptive statistics including the observed event rates as well as the corresponding confidence intervals should be described in the product label. Of note, this study was conducted in accordance with the statistical analysis plan prospectively agreed upon by the Agency.

INTRODUCTION

1.1 Overview

This efficacy supplemental (sNDA 22287) was submitted to fulfill the following PREA PMRs:

1788-1: Deferred pediatric study under PREA to evaluate the pharmacokinetics, healing, maintenance of healing, and symptoms of endoscopy proven erosive esophagitis (EE) in patients 12 years to 17 years of age.
1356-5: Deferred pediatric study under PREA for treating heartburn associated with non-erosive GERD in pediatric patient aged 12 years to 17 years.

Dexlansoprazole (Dexilant) is a proton pump inhibitor (PPI) that has been approved in adults for healing of all grades of EE, maintenance of healed EE and relief of heartburn, and treatment of heartburn associated with symptomatic non-erosive GERD.

The studies included in the submission are summarized in Table 1.

Table 1. List of the studies submitted by the sponsor.

Trial	Phase and Design	Type	Treatment arms and sample size	Study Population
T-P107-163	Phase 1, open-label, parallel group, multicenter	PK and Safety	Active drug 30 mg: **18** 60 mg: **18**	Adolescents with symptomatic GERD
TAK-390MR_206	Phase 2, open-label, multicenter	Safety and Effectiveness	Active drug (30 mg): **104**	Adolescents with symptomatic GERD
TAK-390MR_207	Phase 2, **double-blind**, multicenter	Safety and Effectiveness	Active drug: **25** Placebo: **26**	Adolescents with EE and Heartburn

This statistical review mainly focused on the evaluation for Study TAK-390MR_207, because the other two studies in the submission were open-label and not the main study to support Dexilant's efficacy in treating adolescents with EE and heartburn. The brief study description including the sponsor's results for the major efficacy are included in the Appendix B.

The study TAK-390MR_207 protocol was amended twice: Amendment 1 was dated on April 19, 2012, and Amendment 2 was dated on April 25, 2013. The protocol changes, related to the study design, are listed in the Appendix A. The Statistical Analysis Plan (SAP) incorporating the protocol changes was finalized on December 15, 2014.

1.2 Data Sources

The data and program listings submitted by the sponsor are available in the following directory of the CDER' electronic document room (EDR):
\\CDSESUB1\evsprod\NDA022287\0232\m5\datasets\tak-390mr-207

STATISTICAL EVALUATION

1.3 Data and Analysis Quality

The reviewer finds the quality and integrity of the submitted data satisfying and acceptable for the review analysis. The statistical reviewer was able to reproduce the sponsor's primary analysis results from the raw data and trace how the primary endpoint was derived.

1.4 Evaluation of Efficacy for Study TAK-390MR_207

The primary objectives of the study TAK-390MR_207 were to assess:

- Safety and effectiveness of treatment with once daily (QD) oral administration of dexlansoprazole delayed-release (DR) 60 mg capsules for 8 weeks in adolescent subjects with EE.
- Safety and effectiveness of dexlansoprazole DR 30 mg capsules compared to matching placebo for 16 weeks in adolescent subjects for maintenance of healed EE and relief of heartburn.

1.4.1 Study Design and Efficacy Endpoints

This was a phase 2, international (US, Poland, Portugal, and Mexico), multicenter (18 sites), 36 week study in adolescent subjects (aged 12 to 17 years, inclusively) to assess the safety and effectiveness of oral QD administration of:

[1] dexlansoprazole delayed-release 60 mg capsules in subjects with EE, and
[2] dexlansoprazole delayed-release 30 mg capsules or placebo in subjects with healed EE.

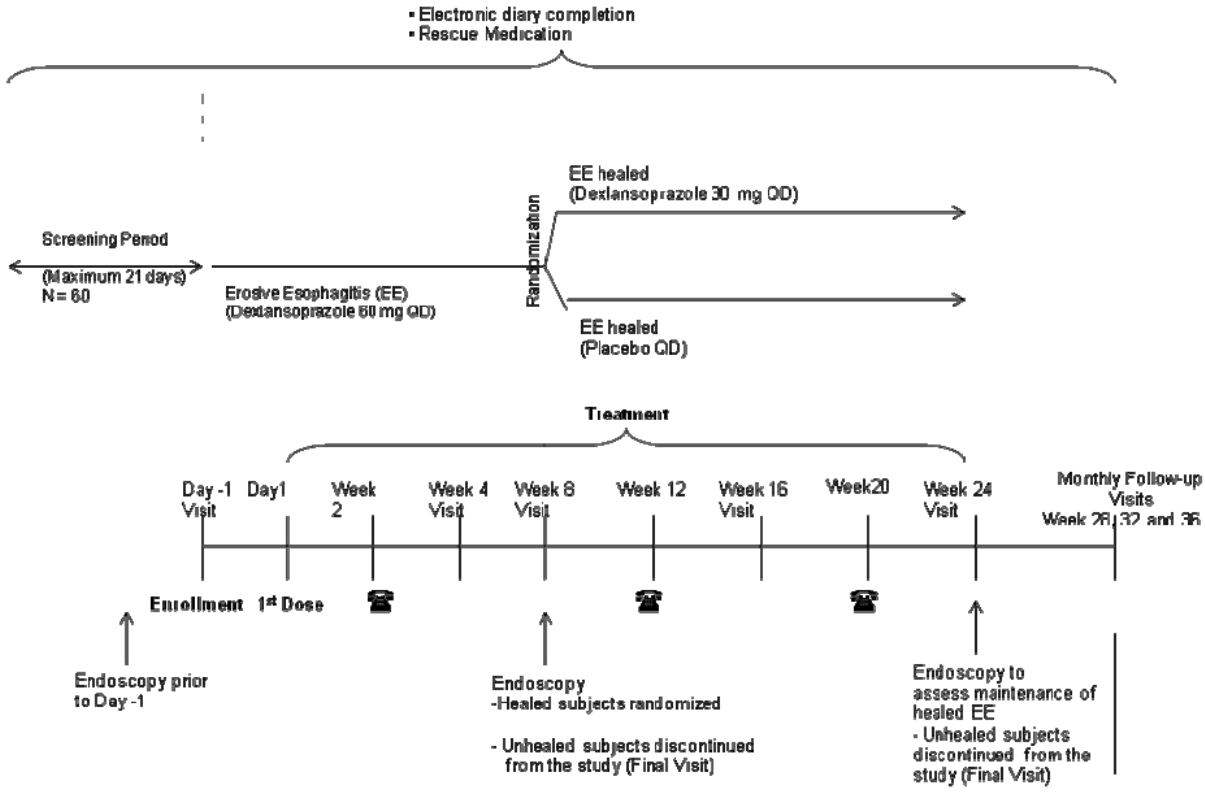
Patients who satisfied the screening evaluation, met all selection criteria, and had endoscopically confirmed EE were enrolled in the Treatment Period. During the first 8 weeks of treatment, all patients received dexlansoprazole 60 mg QD. All patients were contacted by telephone at Week 2, and then returned for clinic visits at Weeks 4 and 8. At the Week 8 Visit, patients underwent endoscopy to assess healing of EE. Patients whose EE had not healed were discontinued from the study.

Patients whose EE was healed at Week 8 were randomized to receive dexlansoprazole 30 mg QD or placebo QD in a 1:1 ratio for an additional 16 weeks to evaluate maintenance of healing.

These subjects were contacted by telephone at Weeks 12 and 20, and returned to the clinic for visits at Weeks 16 and 24.

At the end of the Treatment Period (Week 24), final endoscopies were performed to assess maintenance of healed EE. Patients whose EE had relapsed were discontinued from the study. Patients whose EE remained healed at Week 24 discontinued study drug and entered a Post-Treatment Follow-up Period of up to 3 months after the last dose of study drug. See the schematic study design on Figure 1.

Figure 1. Schematic design on the study TAK-390MR_207.



Source: Sponsor's Figure 9.a of CSR

Efficacy was assessed using endoscopies, eDiary entries, and investigator assessments of GERD.

The efficacy was assessed through the following secondary endpoints[1]:

[1] The crude healing rate of EE at Week 8 (defined as percentage of patients who had healing of EE at Week 8 among subjects who had an endoscopy at Week 8).

[2] The percentage of patients who maintained healing of EE from Week 8 to Week 24 among subjects who had an endoscopy at Week 24.

[3] The percentages of days with neither daytime nor nighttime heartburn over the first 8 weeks of treatment.

[1] Note that the primary endpoint for this study was a safety variable.

[4] The percentage of days with neither daytime nor nighttime heartburn from Weeks 8 to 24 among the subjects who were healed at Week 8.

The analysis datasets were defined as follows:

- For the first 8 weeks of the open-label healing period the efficacy endpoints were summarized using the Full Analysis Set-OL, defined as all subjects who received at least one dose of open-label study drug and had post-baseline data (and baseline data if applicable) for the appropriate efficacy variable.
- For the 16-week double-blind treatment period the efficacy endpoints were summarized using and using the Full Analysis Set-DB, defined as all subjects with healed EE at Week 8 who were randomized and received at least one dose of double-blind study drug and had post-baseline data (and baseline data if applicable) for the appropriate efficacy variable.

1.4.2 Statistical Methodologies to Assess Efficacy Variables

The crude healing rate of EE at Week 8 (open-label period) was summarized descriptively using percent estimate and its 95% exact binomial confidence interval.

The percentage of subjects who maintained healing of EE from Week 8 to Week 24 was compared between treatment groups using Fisher's exact test. The test was not adjusted for covariates. If a subject's final endoscopy was performed prior to the Week 24 Visit and indicated recurrence of EE, the subject was considered to have recurrence of EE at the Week 24 Visit.

The percentages of days with neither daytime, nor nighttime heartburns during the 8 weeks and over Weeks 8 to 24 were summarized descriptively. The percentage was calculated for each subject who had at least 1 daytime or nighttime heartburn record (presence or absence) during the treatment period (first 8 weeks of treatment or over Weeks 8 to 24) by formula:

$$\frac{\textit{\# of heartburn-free days during the treatment period}}{\textit{Total \# of days with day- or night-time heart-burn result marked during the treatment period}} * \textit{100 \%}$$

All entries on a day must have been heartburn-free in order for the day to be counted as a day with neither daytime nor nighttime heartburn.

1.4.3 Patient Disposition, Demographic and Baseline Characteristics

There were 63 subjects enrolled at 18 international sites (see Table 2), but one patient was withdrawn from the trial due to non-compliance. Most of the population was coming from USA (36.5%) and Poland (54.0%). No formal statistical testing for the effect of site was performed by the sponsor.

Table 2. Disposition of the patients' enrollment by country.

Country	Number of sites	Healing phase	Maintenance phase	
		Dexilant 60 mg n (%)	Placebo n (%)	Dexilant 30 mg n (%)
USA	8	23 (36.5)	10 (38.5)	10 (40.0)
Poland	6	34 (54.0)	13 (50.0)	15 (60.0)
Portugal	3	4 (6.3)	3 (11.5)	0 (0.0)
Mexico	1	2 (3.2)	0 (0.0)	0 (0.0)
Totally enrolled	18	63 (100.0)	26 (100.0)	25 (100.0)

Source: Computed by the statistical reviewer, Dr. Andrejus Parfionovas.

The sponsor's summary of patients who discontinued from study early is presented in Table 3.

Table 3.Summary of the patients who discontinued from the study early (computed by the sponsor).

	Open-Label Healing (a)	Double-Blind Maintenance (b)	
Reason for Premature Discontinuation	Dexlansoprazole 60 mg QD N = 62 n (%)	Placebo N = 26	Dexlansoprazole 30 mg QD N = 25
Any reason	4 (6.5)	6 (23.1)	7 (28.0)
Pretreatment event/adverse event	1 (25.0)	0	1 (14.3) (c)
Major protocol deviation	1 (25.0)	0	0
Lost to follow-up	1 (25.0)	0	0
Voluntary withdrawal	1 (25.0)	2 (33.3)	5 (71.4)
Lack of efficacy	0	3 (50.0)	1 (14.3)
Requires treatment with another drug	0	1 (16.7)	0

Source: Clinical Study Report for Study TAK-390MR_207, pg. 5.
(a) Percentage for any reason is based on the total number of enrolled and treated patients in the open-label healing phase. Percentages for individual reasons are based on the total number of patients who prematurely discontinued study drug.
(b) Percentage for any reason is based on the total number of enrolled and treated patients in each treatment group during the double-blind maintenance phase. Percentages for individual reasons are based on the total number of patients in each treatment group who prematurely discontinued study drug.

The demographic and baseline characteristics are summarized in Table 4.

Table 4. Patients' baseline and demographic characteristics.

	Open-Label Period	Double-Blind Period	
Variable	Dexlansoprazole 60 mg QD N = 62	Placebo N = 26	Dexlansoprazole 30 mg QD N = 25
Age (years)			
Mean (SD)	14.8 (1.64)	14.8 (1.75)	14.6 (1.41)
Median	15.0	15.0	15.0
Gender (n, %)			
Male	38 (61.3)	16 (61.5)	14 (56.0)
Female	24 (38.7)	10 (38.5)	11 (44.0)
Race (n, %)			
Black or African American	1 (1.6)	1 (3.8)	0
White	61 (98.4)	25 (96.2)	25 (100.0)
Baseline EE grade (LA classification)			
A	34 (54.8)	16 (61.5)	14 (56.0)
B	26 (41.9)	9 (34.6)	11 (44.0)
C	1 (1.6)	1 (3.8)	0
D	1 (1.6)	0	0

Source: Clinical Study Report for Study TAK-390MR_207, pg. 4.

Predominant population was of White with only a single Black/African American patient. There were enrolled slightly more male patients (approximately 60%) than females (approximately 40%). The baseline EE grade during the open-label period was mostly grade A and grade B (54.8% and 41.9% respectively). After the randomization the demographic and baseline characteristics appear to be well-balanced between the treatment arms.

1.4.4 Sponsor's Efficacy Results

The sponsor performed the Fisher's exact test for the percentage of patients who maintained healing of EE from Week 8 to Week 24. The other endpoints were summarized descriptively with no formal statistical tests performed.

The sponsor's descriptive summary of results for the crude healing rate of EE at Week 8 (*1st efficacy endpoint*) is presented in Table 5. The sponsor concluded that at the end of 8 weeks of treatment with Dexilant 60 mg QD, the EE was healed in the majority of patients (87.9%).

Table 5. Descriptive summary of the crude healing rate of EE at Week 8.

	Open Label Dexilant 60 mg
Full Analysis Set (Open Label)	n = 62
N at Week 8 (%)	58 (100.0)
Healed	
n (%)	51 (87.9)
(95 % CI)	(76.7, 95.0)
Not healed	
n (%)	7 (12.1)
(95 % CI)	(5.0, 23.3)

Source: Clinical Study Report for Study TAK-390MR_207, Table 15.2.1.1

The sponsor's analysis results for the percent of patients who maintained healing of EE from Week 8 to 24 (*2nd efficacy endpoint*) are presented in Table 6. Note that there were three patients in Dexilant 30 mg group and two patients in Placebo group did not have endoscopy results at Week 24. The sponsor concluded that at the end of the 16-week double-blind maintenance phase, more patients who received Dexilant 30 mg QD maintained healed EE than those who received placebo, however the difference between two groups was not statistically significant.

Table 6. Analysis summary of the percent of patients maintaining EE healing during double-blind period.

	Placebo *(n = 26)*	***Dexilant 30 mg*** *(n = 25)*
Available Endoscopy Results at Week 24	24	22
Maintained healed EE		
n (%)	14 (58.3)	18 (81.8)
(95 % CI)	(36.6, 77.9)	(59.7, 94.8)
Not Maintained healed EE		
n (%)	10 (41.7)	4 (18.2)
(95 % CI)	(22.1, 63.4)	(5.2, 40.3)
Fisher's exact test p-value	0.114	

Source: Clinical Study Report for Study TAK-390MR_207, Table 15.2.1.2

The sponsor's descriptive summary of results for the percentage of days with neither daytime nor nighttime heartburn during the open-label healing phase (*3rd efficacy endpoint*) is presented in Table 7.

Table 7. Percent of days with neither daytime nor nighttime heartburn during open-label period.

Full Analysis Set OL	***Dexilant 60 mg*** *(n = 62)*
Mean (SD)	59.6 (30.46)
Median	65.8
Range (Min–Max)	0—100

Source: Clinical Study Report, Table 15.2.2.1

The sponsor's descriptive summary of results for the percentage of days with neither daytime nor nighttime heartburn during the double-blind maintenance phase (*4th efficacy endpoint*) is presented in Table 8. They concluded that during the double-blind maintenance phase, patients receiving Dexilant 30 mg QD had a greater percentage of days with neither daytime nor nighttime heartburn than patients receiving placebo.

Table 8. Percent of days with neither daytime nor nighttime heartburn during double-blind Period.

Full Analysis Set DB ***Patients with heartburn record present***	***Placebo*** *(n = 26)* *N=26 (100 %)*	***Dexilant 30 mg*** *(n = 25)* *N=24 (100 %)*
Mean (SD)	68.9 (26.04)	76.7 (29.82)
Median	68.1	86.6
Range (Min–Max)	9—100	0—10

Source: Clinical Study Report, Table 15.2.2.2

1.4.5 Reviewer's Results and Conclusions

The statistical reviewer confirmed the sponsor's analysis results for all of the aforementioned four efficacy endpoints. For the first efficacy endpoints, patients were treated for eight weeks and 51 of them had confirmed healed of EE. Those 51 were then randomized to receive either Dexilant 30 mg capsules or placebo, once daily for additional 16 weeks. For the second efficacy endpoint, however, as noted in Section 1.4.4, five patients were excluded from the sponsor's analysis results due to no endoscopy performed at the time of early termination. Although eighty-two percent of patients treated with Dexilant 30 mg capsules remained healed over the four-month treatment period confirmed by endoscopy, the difference between the percentage of responders in the placebo group (i.e., 23.5%) was not statistically significant.

It was also noted that of the 51 patients in the sponsor's analysis data sets (See Table 6), 13 patients discontinued the study visit prematurely before Week 24 and 5 of these 13 patients were the aforementioned 5 who did not have endoscopy performed. Now that eight of these 13 patients had endoscopy performed and most of them were close to Week 24, this patient population can be named as the completer population.

To assess the impact of the five patients who did not have endoscopy data and considering the intent to treat population, sensitivity analysis by treating the five patients with premature discontinuation as non-responders was conducted by FDA statistical review team. As seen from Table 10, the rates of responders in both treatment groups became smaller than those by the sponsor's completer analysis. In addition, the rate of difference between the Dexilant 30 mg and placebo was 6% smaller than that by the completer analysis (i.e., 24% vs. 18%). Nevertheless, both confidence intervals of the odd ratio contain 1 and they are overlapped with each other.

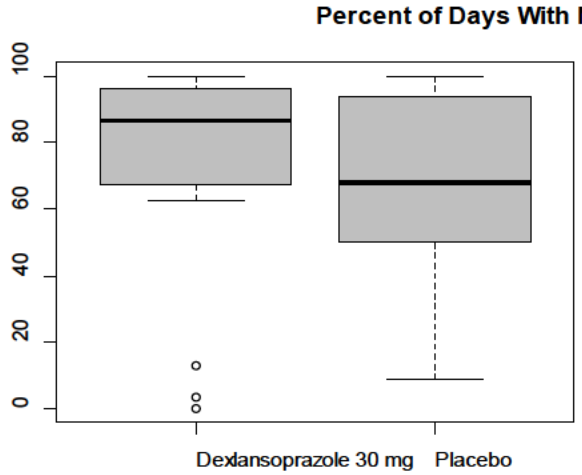
Table 9. Reviewer's analysis of the patients maintained EE healing at the end of DB period.

	Original dataset			***Early dropouts labeled as non-responders***		
	Maintained EE healing at the end of DB period					
	Yes	**No**	**Total**	**Yes**	**No**	**Total**
Dexilant 30 mg	18 (82%)	4 (18%)	22	18 (72%)	7 (28%)	25
Placebo	14 (58%)	10 (42%)	24	14 (54%)	12 (46%)	26
Total	32	14		32	19	51
Responders % difference (Dexilant - Placebo)	24%			18%		
Fisher's exact test **p-value** **odds ratio** **95% CI**	0.1141 3.21 (0.7, 16.7)			0.2492 2.20 (0.6, 8.41)		

Source: computed by the statistical reviewer, Dr. Yeh-Fong Chen.

The statistical reviewer, Dr. Andrejus Parfionovas also explored the difference between the Dexilant and placebo arms in relief of heartburn during the double-blind period and his graph is shown in Figure 2.

Figure 2. Boxplot for the percentage of days with neither daytime nor nighttime heartburns by arms.



Source: computed by the reviewer, Dr. Andrejus Parfionovas.

The boxplots for the two randomized treatment arms visually suggest that patients taking Dexilant 30 mg QD had numerically higher average percentage of days with neither daytime nor nighttime heartburns.

1.5 Evaluation of Safety

The evaluation of safety was not performed and reported here. Please refer to the clinical review for the safety evaluation and report.

FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

1.6 Gender, Age Group, and Geographic Region

This section contains the statistical reviewer's subgroup analysis results for the percent of patients who maintained EE healing during double-blind period for the following subgroups: gender (males, or females), baseline age group (12 to 14 years, or 15 to 17 years), and geographic region (US, or non-US). The race subgroup analysis was not conducted, because only one patient was Black/African American, and the rest were White. The results of the Fisher's exact test are presented in Table 11.

Table 10. Subgroup analyses of the patients maintained EE healing during double-blind period

Subgroup	Dexilant 30 mg n (%)	Placebo n (%)	Fisher's exact test
Males (n=27)	11 (84.6%)	7 (50.0%)	p-value = 0.1032 odds ratio = 5.5000 95% CI: (0.8778. 34.4609)
Females (n=19)	7 (77.8%)	7 (70.00)	p-value = 1.00 odds ratio = 1.5000 95% CI: (0.1886, 11.9271)
12 to 14 years old (n = 20)	9 (100.0%)	7 (63.64%)	p-value = 0.0941 odds ratio = 1.5714 95% CI: (1.0053, 2.4564)
US (n = 18)	7 (77.78)	5 (55.56)	p-value = 0.6199 odds ratio = 2.8000 95% CI: (0.3608, 21.7271)
Non-US (n = 28)	11 (84.62%)	9 (60.00%)	p-value =0.2213 odds ratio = 3.6667 95% CI: (0.5901, 22.7835)

Source: computed by the reviewer Dr. Andrejus Parfionovas

Among all of the subgroups, the difference in the rate of maintenance between Dexilant 30 mg and placebo was largest in the patients from12 to 14 years old. However, due to the small sample size this subgroup, results should be interpreted with caution although Dexilant 30 mg always had higher rates of maintenance. No inconsistency between the subgroup was identified.

1.7 Other Special/Subgroup Populations

No other subgroups were analyzed.

SUMMARY AND CONCLUSIONS

1.8 Statistical Issues in Study TAK-390MR_207

The efficacy was assessed as the secondary objective and on the secondary endpoints. No formal sample size calculation was performed for this study. The SAP specified that with a sample size of 60 patients, assuming the incidence rate for an adverse event is 5%, the probability of observing the event in at least one patient during the study is approximately 95%.

The statistical hypotheses were tested using Fisher's exact test with no adjustments for covariates.

The drop-outs and missing data was handled as follows: For overall study drug compliance, any gaps in dosing were ignored when calculating the total, and if the last dose date was missing, then the length of the treatment period was imputed as 70 days for the open-label healing phase and 182 days for the double-blind maintenance phase. The days with missing eDiary results for both daytime and nighttime were excluded from the numerator and denominator. If the last dose date was missing, then the number of days was imputed to 70 days for the open-label healing period and 182 days for the double-blind treatment period. For the PGSQ-A-SF subscale scores (symptom and impact), if more than 50% of the corresponding item scores were missing, then the subscale score was set to missing.

The summary of the patients with protocol deviations is presented in Table 12.

Table 11. Summary of patients with protocol deviations.

	Open-Label Healing	Double-Blind Maintenance	
	Dexlansoprazole 60 mg QD N=62	Placebo N=26	Dexlansoprazole 30 mg QD N=25
At least 1 protocol deviation (a)	27 (43.5)	12 (46.2)	11 (44.0)
Specific protocol deviation category (b)			
Concomitant medication	2 (7.4)	3 (25.0) (c)	3 (27.3)
Entry criteria	8 (29.6)	0	0
Procedure not performed per protocol (primary endpoint and safety related)	19 (70.4)	10 (83.3)	6 (54.5)
Study medication	4 (14.8)	4 (33.3)	3 (27.3)
Withdrawal criteria	0	0	0

Source: Tables 15.1.6.1 and 15.1.6.2.
Note: Subjects may be counted in more than 1 deviation category.
(a) Percentage based on total number of enrolled and treated subjects in each treatment group.
(b) Percentage based on total number of subjects with at least 1 significant deviation.
(c) Includes subjects in both the double-blind maintenance (2 subjects) and follow-up periods (1 subject).

1.9 Collective Evidence

The sponsor's efficacy results of the study TAK-390MR_207 were confirmed by the reviewer to be numerically in a better trend than placebo, but statistically non-significantly different from placebo (Fisher's exact test p-value = 0.1141). The study was not adequately powered, and thus the p-value of the statistical test will not be included in the product labeling.

The statistical reviewer performed the subgroup analysis for gender, age and region in the maintenance phase of the study. In all subgroups, Dexlansoprazole 30 mg QD arm showed a bigger rate of maintenance than placebo. No inconsistency between subgroups was identified.

1.10 Conclusions and Recommendations

Study TAK-390MR_207 was not adequately powered for any formal statistical test, and therefore only descriptive statistics, including the observed event rates and the corresponding confidence intervals, should be included in the product label.

APPENDIX A

The summary of the statistically related amendments to the protocol TAK-390MR_207:

Amendment 1 (April 19, 2012):

- The duodenal biopsies were removed and a serologic test will be used to screen for celiac disease.
- The serum magnesium level required for collection of 24-hour urinary magnesium excretion was corrected to ≤1.1 mEq/L (≤0.55 mmol/L).
- The laboratory tests performed as part of the urinalysis were clarified.
- The electrocardiogram and hepatitis panel were moved from Day -1 Visit to Screening Visit.
- Hepatitis panel was expanded to include hepatitis A and E.
- P450 CYP2C19 genotype testing will not be required when local regulations prohibit it. Storage and use of samples was clarified.

Amendment 2 (April 25, 2013):

- Allowance of the screening endoscopy to have been performed within 1 week prior to signing informed consent and assent has been added.
- A window of 5 days has been added to the Screening Period.
- The number of biopsies required at Screening has been reduced and flexibility for standard of care biopsies has been added.
- Clarification on when screening laboratory evaluations can be performed has been added.
- Helicobacter pylori *(H. pylori)* test procedures have been clarified.
- Exclusion criterion No. 15 has been updated regarding HIV status.
- Exclusion criterion No. 20 regarding alcohol use has been updated to account for regional differences.
- Inclusion criterion #4 and exclusion criterion #9 have been updated to account for allowance of endoscopies done prior to screening and other H. pylori test methods.
- Alternate dosing options have been added.

APPENDIX B Brief Description of Study TAK-390MR_206 for Efficacy Evaluation

(Directly Extracted from Sponsor's Clinical Study Report)

Title: A Phase 2 Open-Label, Multicenter, 4-Week Study to Assess the Safety and Effectiveness of Daily Oral Administration of Dexlansoprazole Delayed-Release Capsules for Relief of Heartburn, in Adolescent Subjects Aged 12 to 17 Years With Symptomatic Non-Erosive Gastroesophageal Reflux Disease

Study Objective

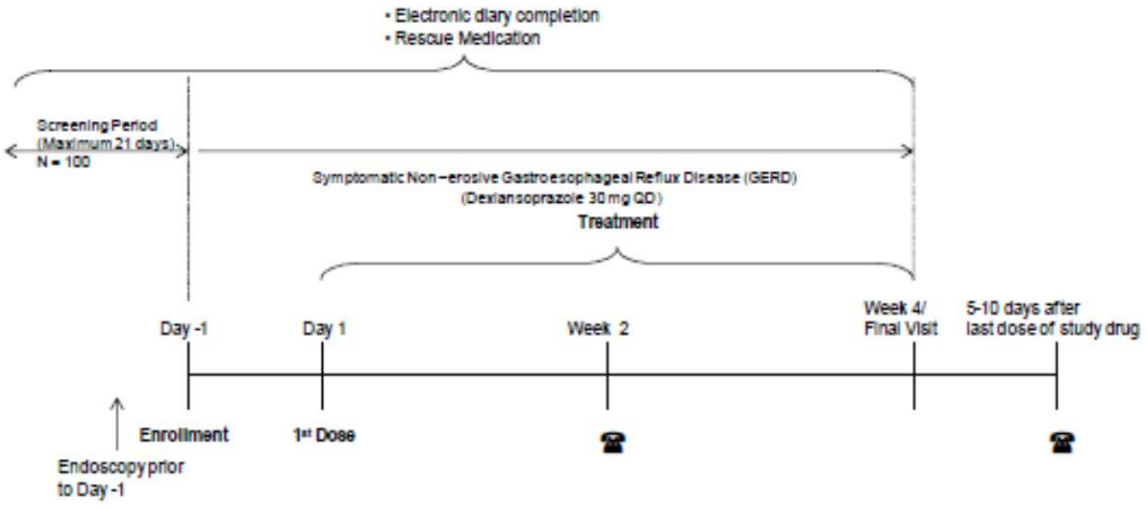
To assess the safety and effectiveness of treatment with once daily (QD) oral administration of dexlansoprazole delayed-release capsules (30 mg) in adolescent subjects aged 12 to 17 years with symptomatic non-erosive GERD.

Study Design

This was a phase 2, open-label, multicenter, 4-week study to evaluate the safety and effectiveness of once-daily oral administration of dexlansoprazole delayed-release 30 mg capsules in adolescent subjects with symptomatic non-erosive GERD.

The study was to enroll approximately 100 adolescent subjects (male or female), aged 12 to 17 years (inclusive) at approximately 71 sites in North America, Latin America, and Europe. The study consisted of 2 periods (Screening and Treatment). The Screening Period lasted 21 (+ 5) days. The minimum number of days for the Screening Period was the time it took for the subject to have symptoms on 3 of any 7 days, the endoscopy performed, and the Day -1 Visit completed. The Treatment Period lasted 4 weeks for all subjects. A schematic of the study design is shown in the following Figure 3.

Figure 3. Schematic of Study Design for Study TAK_390MR_206



Source: Sponsor's Figure 9.2 of CSR

The sponsor emphasized the following:

The design and sample size proposed in this study were appropriate for the evaluation of the safety and effectiveness of PPI treatment in adolescents with symptomatic non-erosive GERD when treated for 4 weeks. The results of a PK study in adolescents (Study T-P107-163) indicated that the PK profile of dexlansoprazole 30 mg and 60 mg in adolescents was similar to that previous reported for healthy adults. Therefore, for this study in adolescents, dexlansoprazole 30 mg was selected for subjects with symptomatic non-erosive GERD as in the adult population.

The inclusion/exclusion criteria proposed for this study were appropriate to select a study population of male and female subjects, aged 12 to 17 years of age, with symptomatic non-erosive GERD. To participate in this study, subjects had a medical history of GERD symptoms for at least 3 months prior to Screening, as assessed by the investigator. In addition, subjects documented heartburn symptoms in an eDiary during the Screening Period, and were only eligible to participate in the study if they documented the presence of heartburn for 3 of any 7 days; this criteria is consistent with the Montreal Definition and Classification of GERD for adults. Once the diary qualification criteria were met, screening endoscopies were performed, and only subjects with non-erosive endoscopic findings were enrolled into the study.

The safety and efficacy measurements and the clinical and routine laboratory procedures used in this study are standard and generally accepted. The endpoints regarding heartburn symptoms are similar to those used in the adult studies with dexlansoprazole. The heartburn assessment in the subject's eDiary and the GERD Symptoms Investigator Assessment used to assess the subject's GERD symptoms are similar to those used in previous lansoprazole studies in pediatrics and dexlansoprazole studies in adults. The heartburn eDiary previously used in dexlansoprazole adult studies for the assessment of heartburn was modified and adapted for use in the 12- to 17-year old pediatric population. All modifications to the eDiary underwent cognitive debriefing to ensure the diary was appropriate for use in the 12- to 17-year-old pediatric GERD population.

Major Efficacy Endpoint and Analysis

Efficacy was assessed using eDiaries, investigator assessments of GERD, and subject-reported PGSQ-A-SF assessments. The percentage of days with neither daytime nor nighttime heartburn over the 4 weeks of treatment was assessed by eDiary.

The percentage of days with neither daytime nor nighttime heartburn over the 4 weeks of treatment was summarized descriptively; this was determined for each subject who had at least 1 daytime or nighttime heartburn result (presence or absence of heartburn) during the 4 weeks of treatment (up to last dosing day or Day 35, whichever was first), calculated as follows:

$$\text{\% of days with neither daytime nor nighttime heartburn} = \frac{\text{(\# of heartburn-free days* during Treatment Period)}}{\text{(total \# of days with daytime or nighttime heartburn result marked during Treatment Period)}} \times 100\%$$

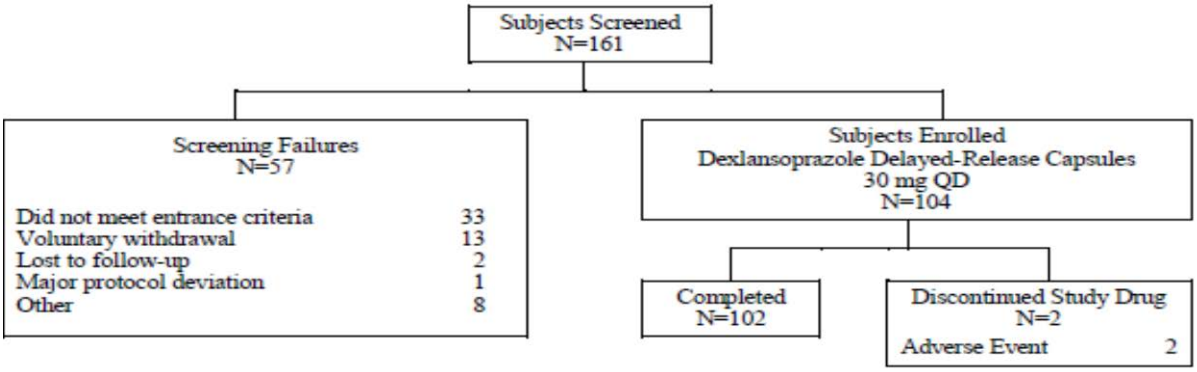
* All entries on a day must have been heartburn-free in order for the day to be counted as a day with neither daytime nor nighttime heartburn.

The days with missing eDiary results for both daytime and nighttime were excluded from the numerator and denominator. If a subject prematurely terminated, the Treatment Period was defined as from first dose date to last dose date + 1 day. If the last dose date was missing, then 35 days was imputed as the length of the treatment period.

Disposition of Patients and Efficacy Results

A total of 104 subjects were enrolled into the study and 102 subjects completed treatment. Two subjects (7036-004 and -008) discontinued due to adverse events. Subject 7036-004, a 16-yearold female subject, withdrew due to moderate GERD on Day 15, and Subject 7036-008, a 17-year-old male subject, withdrew due to moderate dizziness on Day 10. The following Figure 4 shows the detailed disposition of patients.

Figure 4 Disposition of Patients for Study TAK_390MR_206



The following Table 15 displays the sponsor's analysis results for the main efficacy endpoint. That is, percentage of days with neither daytime nor night-time heartburn over the 4 weeks of treatment as well as the percentage of days without night-time or without day-time heartburn during treatment separately.

Table 12 Sponsor's Efficacy Results for the Main Efficacy Endpoint for Study TAK-390MR_206

Main Efficacy Endpoint and its Component during Treatment	**Number of subjects (%)** TAK-390MR 30 mg (N=104)
Percent of Days With Neither Daytime nor Night-time Heartburn	
Mean (SD)	47.1 (32.18)
Median (Minimum, Maximum)	47.3 (0, 100)
Percent of Days Without Night-time Heartburn	
Mean (SD)	69.1 (30.66)
Median (Minimum, Maximum)	80.5 (0, 100)
Percent of Days Without Daytime Heartburn	
Mean (SD)	55.2 (32.23)
Median (Minimum, Maximum)	59.3 (0, 100)

Source: Sponsor's Table 15.2.1 of CSR

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/s/

ANDREJUS PARFIONOVAS
06/24/2016

YEH FONG CHEN
06/24/2016
Due to conflict interest, Dr. Andrejus Parfionovas recused himself from reviewing this NDA submission on 6/7/2016. This review was completed by Dr. Yeh-Fong Chen.