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Office of Translational Sciences
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Statistical Review and Evaluation
Clinical Studies

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 healing of erosive esophagitis
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Biometrics Division: DB3
Statistical Reviewer: Stella Grosser, Ph.D.
Concurring Reviewers: Michael Welch, Ph.D.

Medical Division: Division of Gastroenterological Products
Clinical Team: Tamara Johnson, M.D.
 Ruyi He, M.D., Team Leader
Project Manager: Chantal Phillips

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Table of Contents

1. EXECUTIVE SUMMARY	3
1.1. Conclusions and Recommendations	3
1.2. Brief Overview of Clinical Studies.....	3
1.3. Statistical Issues and Findings	4
2. INTRODUCTION.....	5
2.1. Overview.....	5
2.2. Data Sources	5
3. STATISTICAL EVALUATION.....	5
3.1. Evaluation of Efficacy	5
3.2. Evaluation of Safety.....	15
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS.....	16
4.1. Gender, Race, and Age	16
4.2. Other Special/Subgroup Populations.....	19
5. SUMMARY AND CONCLUSIONS.....	19
5.1. Statistical Issues and Collective Evidence.....	19
5.2. Conclusions and Recommendations	20

1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

Efficacy was demonstrated in these studies for dexlansoprazole at 30, 60 and 90 mg QD in the treatment of symptomatic GERD. The to-be-marketed dose is 30 mg. There was only one study of 30 mg, but the improvement of dex30 relative to placebo is highly statistically significant ($p < 0.0001$) as well as large: subjects in the placebo group had a median of 19% of reported days with neither daytime nor nighttime heartburn, while dex30 had a median of 55%. (b) (4)

1.2. Brief Overview of Clinical Studies

This application seeks approval of dexlansoprazole for healing of EE, maintenance of healed EE, and symptomatic GERD. There were six Phase III studies submitted in support of the efficacy and safety of dexlansoprazole for the proposed indications. Table A1 in the Appendix summarizes these studies. Studies T-EE04-084 and T-EE04-085 were for the healing of EE and studies T-EE04-086 and T-EE05-135 for maintenance of healed EE; these are reviewed by a different statistical reviewer (Dr. Freda Cooner). This review examines studies T-GD04-082 (which includes another protocol T-GD04-083) and T-GD05-137. Both studies were submitted in support of an indication primarily for GERD^{(b) (4)}

Study T-GD04-082 was a randomized, double-blind, multicenter, placebo-controlled, parallel-group, 3-arm study. The objectives of the study were to evaluate efficacy, in relief of daytime and nighttime heartburn over 4 weeks, of dexlansoprazole MR 60 mg QD (dex60) and 90 mg QD (dex90) compared to placebo in subjects with symptomatic, nonerosive GERD; to assess the safety of dex60 and dex90 in subjects with symptomatic, nonerosive GERD; and, secondarily, to assess the efficacy of dex60 and dex90 compared to placebo in relief of nighttime heartburn over 4 weeks as assessed by daily electronic diary.

Subjects with non-erosive GERD took orally 60 mg dexlansoprazole, 90 mg dexlansoprazole or placebo once daily for 4 weeks and returned for study visits after 2 and 4 weeks of treatment.

Nine hundred and eight people were enrolled in the combined study GD04-082 at 157 U.S. sites.

Subjects were 18 years of age or older; identified heartburn as their primary GERD symptom; had history of heartburn episodes for 6 months or longer; experienced

heartburn on at least 4 of the 7 days preceding Day -1; and showed macroscopically normal esophageal mucosa at the screening endoscopy.

The primary efficacy variable was the percentage of days with neither daytime nor nighttime heartburn during treatment as assessed by daily electronic diary.

Study T-GD05-137 was begun (first dose, June 2006) soon after T-GD04-082 finished (last procedure, May 2005). The design was similar to that of T-GD04-082, with the main difference that there were two dexlansoprazole treatment arms dosed at 30 and 60 mg QD instead of 60 and 90 mg QD. Subjects were enrolled and the data was collected under a single protocol.

Nine hundred forty-seven people were enrolled in study GD05-137 at 154 U.S. sites.

1.3. Statistical Issues and Findings

Studies T-GD082 and 083 were combined under Amendment 3 of the protocol, dated March 2006. This date is after the date of the first dose in December 2005 but before the last procedure in May 2006 (and, presumably, the data lock and breaking of the blind). Analyzing the primary endpoint for the studies separately gave results similar to the combined analysis.

A critical issue in the measurement of the primary efficacy outcome is diary compliance. The calculation of the percentage of days with neither daytime nor nighttime heartburn hinges on the total number of days for which either a daytime or nighttime result is marked. There was no imputation of missing data.

Thus, high compliance rates are important.

For study GD04-082 the mean percentages of expected entries that were completed in each treatment group was 88.3%, 87.5%, and 87.6% in the placebo, dexlansoprazole 60 mg, and dexlansoprazole 90 mg treatment groups, respectively. Approximately 70% of the subjects had at least 90% of the entries expected; and 50% of the subjects had at least 96% of the entries expected. These quantities were similar across the treatment groups.

For GD05-137, diary compliance was similar in the placebo (mean percentage of expected entries completed = 86.3%), dex30 QD (83.6%), and dex60 (84.7%) treatment groups. Around 63% of the subjects had at least 90% of the entries expected; and 50% of the subjects had at least 95 % of the entries expected. These quantities were similar across the treatment groups.

These rates seem to be acceptably high in both studies. Furthermore, because the number of missing subjects was small, results from sensitivity analyses differed little from the results of the primary analysis.

2. INTRODUCTION

2.1. Overview

Dexlansoprazole is an enantiomer of lansoprazole, a proton-pump inhibitor (PPI) currently approved for a variety of indications, including healing of erosive esophagitis (EE), maintenance of healed EE, and symptomatic GERD. This application seeks approval of dexlansoprazole for healing of EE, maintenance of healed EE, and symptomatic GERD.

There were six Phase III studies submitted in support of the efficacy and safety of dexlansoprazole for the proposed indications. Table A1 in the Appendix summarizes these studies. Studies T-EE04-084 and T-EE04-085 were for the healing of EE and studies T-EE04-086 and T-EE05-135 for maintenance of healed EE; these are reviewed separately. This review examines studies T-GD04-082 (which includes another protocol T-GD04-083) and T-GD05-137. Both studies were submitted in support of an indication primarily for GERD (b) (4)

2.2. Data Sources

Datasets and study reports are in eCTD format in the EDR under \\Cdsesub1\evsprod\NDA022287\0000

3. STATISTICAL EVALUATION

3.1. Evaluation of Efficacy

Study T-GD04-082

Studies T-GD04-082 and T-GD04-083 were identical protocols carried out at the same time. Amendment 3 to each of these protocols specified that the data obtained from both protocols would be combined and analyzed together. Because the two protocols were modified to create a single study, the overall significance level was reduced from 0.05 (as stated in the original protocols) to 0.0025 in the combined analysis to establish the efficacy of dexlansoprazole MR. The analyses are submitted in the T-GD04-082 clinical study report and no separate analyses of the original protocols were performed (Statistical Analysis Plan, Section 9.7.1.1, p. 60-61). In this review the two protocols are referred to as a single study T-GD04-082.

Study Design:

Study T-GD04-082 was a randomized, double-blind, multicenter, placebo-controlled, parallel-group, 3-arm study. The objectives of the study were to evaluate efficacy, in

relief of daytime and nighttime heartburn over 4 weeks, of dexlansoprazole MR 60 mg QD (dex60) and 90 mg QD (dex90) compared to placebo in subjects with symptomatic, nonerosive GERD; to assess the safety of dex60 and dex90 in subjects with symptomatic, nonerosive GERD; and, secondarily, to assess the efficacy of dex60 and dex90 compared to placebo in relief of nighttime heartburn over 4 weeks as assessed by daily electronic diary.

Subjects with non-erosive GERD took orally 60 mg dexlansoprazole, 90 mg dexlansoprazole or placebo once daily for 4 weeks and returned for study visits after 2 and 4 weeks of treatment.

The study was carried out at 157 sites, all in the U.S.

Subjects were 18 years of age or older; identified heartburn as their primary GERD symptom; had history of heartburn episodes for 6 months or longer; experienced heartburn on at least 4 of the 7 days preceding Day -1; and showed macroscopically normal esophageal mucosa at the screening endoscopy.

Sample Size Calculations

A total of 900 subjects were planned to be enrolled into Studies T-GD04-082 and T-GD04-083 to ensure 720 subjects with symptomatic non-erosive GERD would complete the study (assuming a 20% dropout rate). The sample size of 240 subjects per treatment group would provide at least 95% power at the 0.00125 level of significance to detect a mean difference of 30% between a TAK-390MR dose (60%) and placebo (30%) in the mean percentage of days with neither daytime nor nighttime heartburn during treatment. The test of this primary efficacy variable uses Hochberg's method at the 0.0025 significance level; however, 0.00125 was used in the power calculation to ensure power even if only 1 of the doses is effective. The placebo rate was estimated from prior lansoprazole studies. The common standard deviation was assumed to be 35%.

Efficacy

The primary efficacy variable was the percentage of days with neither daytime nor nighttime heartburn during treatment as assessed by daily electronic diary. The percentage of days with neither daytime nor nighttime heartburn was calculated for each subject who had at least 1 daytime or nighttime heartburn result (yes or no) during treatment by calculating the days that were heartburn-free out of the total number of days for which either a daytime or nighttime result is marked. Thus, days missing diary results for both daytime and nighttime were excluded from the numerator and denominator.

The secondary efficacy variable was the percentage of days without nighttime heartburn as assessed, similarly to the primary efficacy variable, by daily electronic diary.

Analyses for the primary and secondary efficacy variables were conducted on separate efficacy populations, which included all randomized subjects who received at least one

dose of study drug and completed the appropriate diary entry on at least one day during treatment. Subjects with confirmed Barrett's esophagus and/or definite dysplastic changes were excluded from the efficacy analyses.

The percentage of days with neither daytime nor nighttime heartburn during treatment and the percentage of days without nighttime heartburn during treatment were summarized by treatment group.

Comparisons between the treatment groups were made using Wilcoxon rank-sum tests. The overall 0.0025 level of significance for the multiple comparisons of each dexlansoprazole MR dose to placebo was controlled using Hochberg's method. Comparisons between doses of dexlansoprazole were exploratory.

Results

Demographics

No statistically significant differences were observed among treatment groups for any baseline demographic characteristics. Overall, the majority of subjects were female (71%), White (81%), not Hispanic or Latino (80%), ≥ 45 years of age (60%), and had a BMI < 30.0 kg/m² (59%). 13% of the subjects were Black and 11% were ≥ 65 years of age. No statistically significant differences were observed among treatment groups for any baseline demographic characteristics. Demographic characteristics of subjects in the population analyzed for efficacy were similar to those in the all-subjects population.

Patient Disposition

Nine hundred and eight people were enrolled in the combined study GD04-082 and included in the safety population; 894 constitute the primary efficacy population, which the sponsor refers to as the ITT population for heartburn and I call the modified ITT (mITT) population. This group excluded 6 subjects with confirmed Barrett's esophagus; the remaining 8 excluded lacked any diary entry for heartburn. There were 292, 312 and 304 subjects taking placebo, dex60 and dex90, respectively, in the safety population; 2, 6, and 6 of these were not included in the efficacy analysis for heartburn. Approximately 8% of the patients discontinued prematurely; the numbers and reasons were similar across the treatment groups.

Efficacy Results

Efficacy results are shown in Tables 1 and 2. There was a statistically significant difference in favor of dexlansoprazole between placebo and each dose of dexlansoprazole for both the primary and secondary endpoints. Subjects in the placebo group had a median of (b) (4) of reported days with neither daytime nor nighttime heartburn, while (b) (4) of reported days free (Table 1). The effect of dexlansoprazole was apparent by day 3 and evident through the end of the study (Figure 1). Subjects in the placebo group had a median of (b) (4) of reported days without

nighttime heartburn, while dex60 had a median of (b) (4) and dex90 had (b) (4) of reported days free (Table 2).

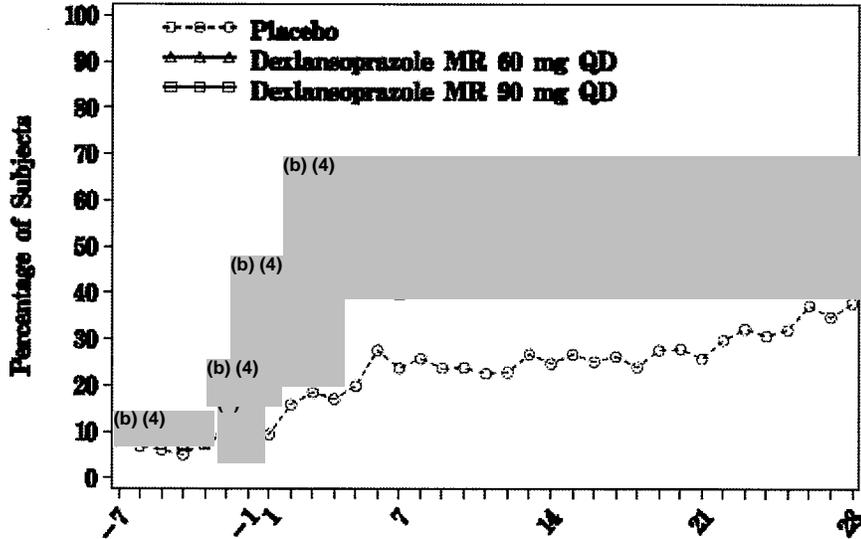
Table 1. Percentage of Days with Neither Daytime nor Nighttime Heartburn during Treatment: mITT Subjects

Measurement	Placebo (N=290)	Dexlansoprazole MR	
		60 mg QD (N=306)	90 mg QD (N=298)
Percentage of Days With Neither Daytime nor Nighttime Heartburn			(b) (4)
Median	17.0		
Mean (SD)	24.9 (25.7)		
p-value Dexlansoprazole MR vs. Placebo			

Note: p-values are based on pairwise comparisons using the Wilcoxon rank-sum test.
 † Statistically significant difference versus placebo when using Hochberg’s method of multiple comparisons to maintain a significance level of 0.0025.

Source: CSR, Table 11.4.1.1.1.a

Figure 1. Percentage of Subjects with Neither Daytime nor Nighttime Heartburn by Day: mITT Subjects



(Source: CSR Figure 11.4.1.1.1.a.)

Table 2. Percentage of Days without Nighttime Heartburn during Treatment: mITT Subjects

Measurement	Placebo (N=290)	Dexlansoprazole MR	
		60 mg QD (N=306)	90 mg QD (N=298)
Percentage of Days Without Nighttime Heartburn		(b) (4)	
Median	51.0		
Mean (SD)	49.6 (34.1)		
p-value Dexlansoprazole MR vs. Placebo			

Note: p-values are based on pairwise comparisons using the Wilcoxon rank-sum test.

† Statistically significant difference versus placebo when using Hochberg's method of multiple comparisons to maintain a significance level of 0.0025.

Source: CSR, Table 11.4.1.2.a

Study T-GD05-137

Study T-GD05-137 was begun (first dose, June 2006) soon after T-GD04-082 finished (last procedure, May 2005). The design was similar to that of T-GD04-082, with the main difference that there were two dexlansoprazole treatment arms dosed at 30 and 60 mg QD instead of 60 and 90 mg QD. Subjects were enrolled and the data was collected under a single protocol.

Study Design

Study T-GD05-137 was a randomized, double-blind, multicenter, placebo-controlled, parallel-group, 3-arm study. The objectives of the study were to evaluate the efficacy, in relief of daytime and nighttime heartburn over 4 weeks, of dexlansoprazole MR 30 mg QD (dex30) and 60 mg QD (dex60) compared to placebo in subjects with symptomatic, nonerosive GERD; to assess the safety of dex30 and dex60 in subjects with symptomatic, nonerosive GERD; and, secondarily, to assess the efficacy of dexlansoprazole MR (30 mg QD and 60 mg QD) compared to placebo in relief of nighttime heartburn over 4 weeks as assessed by daily electronic diary

Subjects with non-erosive GERD took orally 30 mg dexlansoprazole, 60 mg dexlansoprazole or placebo once daily for 4 weeks and returned for study visits after 2 and 4 weeks of treatment.

The study was carried out at 154 sites in the U.S.

Subjects were 18 years of age or older; identified heartburn as their primary GERD symptom; had history of heartburn episodes for 6 months or longer; experienced

heartburn on at least 4 of the 7 days preceding Day -1; and showed macroscopically normal esophageal mucosa at the screening endoscopy.

Sample Size Calculations

Nine hundred subjects were planned to be enrolled in studies T-GD05-137 to ensure 720 subjects with symptomatic non-erosive GERD would complete the study (assuming a 20% dropout rate). The sample size of 240 subjects per treatment group was planned to provide at least 95% power at the 0.00125 level of significance to detect a mean difference of 30% between a TAK-390MR dose (60%) and placebo (30%) in the mean percentage of days with neither daytime nor nighttime heartburn during treatment. The test of this primary efficacy variable uses Hochberg's method at the 0.0025 significance level; however 0.00125 was used in the power calculation to ensure power even if only 1 of the doses is effective. The placebo rate was estimated from prior lansoprazole studies. The common standard deviation was assumed to be 35%.

Efficacy

The primary efficacy variable was the percentage of days with neither daytime nor nighttime heartburn during treatment as assessed by daily electronic diary. The percentage of days with neither daytime nor nighttime heartburn was calculated for each subject who had at least 1 daytime or nighttime heartburn result (yes or no) during treatment by calculating the days that were heartburn-free out of the total number of days for which either a daytime or nighttime result is marked. Thus, days missing diary results for both daytime and nighttime were excluded from the numerator and denominator.

The secondary efficacy variable was the percentage of days without nighttime heartburn as assessed by daily electronic diary.

Analyses for the primary and secondary efficacy variables were conducted on separate efficacy populations, which included all randomized subjects who received at least one dose of study drug and completed the appropriate diary entry on at least one day during treatment. Subjects with confirmed Barrett's esophagus and/or definite dysplastic changes were excluded from the efficacy analyses.

The percentage of days with neither daytime nor nighttime heartburn during treatment and the percentage of days without nighttime heartburn during treatment were summarized by treatment group.

Comparisons between the treatment groups were made using Wilcoxon rank-sum tests. The overall 0.0025 level of significance for the multiple comparisons of each dexlansoprazole MR dose to placebo was controlled using Hochberg's method. Comparisons between doses of dexlansoprazole were exploratory.

Results

Demographics

No statistically significant differences were observed among treatment groups for any baseline demographic characteristics. Overall, the majority of subjects were female (71%), White (82%), not Hispanic or Latino (81%), ≥ 45 years of age (58%), and had a BMI < 30.0 kg/m² (61%). 14% of the subjects were Black and 12% were ≥ 65 years of age. No statistically significant differences were observed among treatment groups for any baseline demographic characteristics. Demographic characteristics of subjects in the population analyzed for efficacy were similar to those in the all-subjects population.

Patient Disposition

Nine hundred forty-seven people were enrolled in study GD05-137 and included in the safety population, while 929 constitute the primary efficacy population, which the sponsor refers to as the ITT population for heartburn and I call the mITT population. This group excluded 6 subjects with confirmed Barrett's esophagus (3 in dex 60 and 3 in placebo); the remaining 12 excluded lacked any diary entry for heartburn. There were 317, 315 and 315 subjects taking placebo, dex30 and dex60, respectively, in the safety population; 7, 3, and 8 of these were not included in the efficacy analysis for heartburn. Approximately 8% of the patients discontinued prematurely; the numbers and reasons were similar across the treatment groups.

Efficacy Results

Efficacy results are shown in Tables 3 and 4. There was a statistically significant difference in favor of dexlansoprazole between placebo and each dose of dexlansoprazole for both the primary and secondary endpoints. Subjects in the placebo group had a median of 19% of reported days with neither daytime nor nighttime heartburn, while dex30 had a median of 55% and dex60 had — of reported days free (Table 1). The effect of dexlansoprazole was immediate and sustained (Figure 2). Subjects in the placebo group had a median of 52% of reported days without nighttime heartburn, while dex30 had a median of 81% and dex60 had — of reported days free (Table 2).

b(4)

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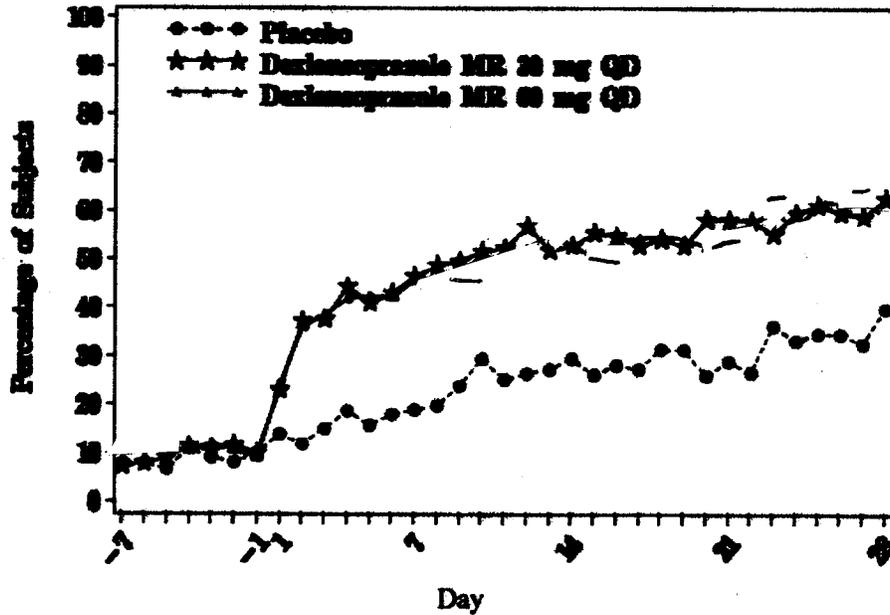
Table 3: Percentage of Days with Neither Daytime nor Nighttime Heartburn during Treatment: mITT Subjects

Measurement	Placebo (N=310)	Dexlansoprazole MR	
		30 mg QD (N=312)	60 mg QD (N=307)
Percentage of Days With Neither Daytime nor Nighttime Heartburn			
Median	18.5	54.9	
Mean (SD)	25.0 (25.6)	50.3 (33.9)	
p-value Dexlansoprazole MR vs. Placebo		<0.00001†	

Note: p-values are based on pairwise comparisons using the Wilcoxon rank-sum test.
 † Statistically significant difference versus placebo when using Hochberg's method of multiple comparisons to maintain a significance level of 0.0025.

Source: CSR, Table 11.4.1.1.1.a

Figure 2: Percentage of Subjects with Neither Daytime nor Nighttime Heartburn by Day: mITT Subjects



(Source: CSR Figure 11.4.1.1.1.a.)

Table 4: Percentage of Days without Nighttime Heartburn during Treatment: mITT Subjects

Measurement	Placebo (N=308)	Dexlansoprazole MR	
		30 mg QD (N=311)	60 mg QD (N=307)
Percentage of Days Without Nighttime Heartburn			
Median	51.7	80.8	(b) (4)
Mean (SD)	47.1 (32.6)	67.6 (34.1)	
p-value Dexlansoprazole MR vs. Placebo		<0.00001†	
p-value Dexlansoprazole MR 30 mg vs. 60 mg			

Note: p-values are based on pairwise comparisons using the Wilcoxon rank-sum test.
† Statistically significant difference versus placebo when using Hochberg's method of multiple comparisons to maintain a significance level of 0.0025.
Source: CSR, Table 11.4.1.2.a

Reviewer's comments

Combined vs. Separate Protocols

Studies T-GD082 and 083 were combined under Amendment 3 of the protocol, dated March 2006. This date is after the date of the first dose in December 2005 but before the last procedure in May 2006 (and, presumably, the data lock and breaking of the blind). I confirmed that analyzing the primary endpoint the studies separately gave results similar to the combined analysis (Tables 5a and 5b). Inference is based on the Wilcoxon rank-sum test.

Table 5a: Percentage of Days with Neither Daytime nor Nighttime Heartburn during Treatment: mITT Subjects, Study T-GD082

Measurement	Placebo (N=131)	Dexlansoprazole MR	
		60 mg QD (N=140)	90 mg QD (N=139)
Percentage of Days With Neither Daytime nor Nighttime Heartburn			
Median	17.9		(b) (4)
Mean (SD)	25.7 (26.1)		
p-value Dexlansoprazole MR vs. Placebo			

Table 5b: Percentage of Days with Neither Daytime nor Nighttime Heartburn during Treatment: mITT Subjects, Study T-GD083

Measurement	Placebo (N=157)	Dexlansoprazole MR	
		60 mg QD (N=166)	90 mg QD (N=157)
Percentage of Days With Neither Daytime nor Nighttime Heartburn		(b) (4)	
Median	16.1		
Mean (SD)	24.3 (25.4)		
p-value Dexlansoprazole MR vs. Placebo			

Diary Compliance, Missing Data and Sensitivity Analyses.

A critical issue in the measurement of the primary efficacy outcome is diary compliance. The calculation of the percentage of days with neither daytime nor nighttime heartburn hinges on the total number of days for which either a daytime or nighttime result is marked. Days missing diary results for both daytime and nighttime were excluded from the numerator and denominator. Patients with no diary recordings were excluded completely from the ITT analysis. There was no imputation of missing data, and the only sensitivity analyses conducted by the sponsor looked at relative completers (subjects with at least 7, 14, or 21 days of electronic diary data during treatment).

Thus, high compliance rates are important.

For study GD04-082 the mean percentages of expected entries that were completed in each treatment group was 88.3%, 87.5%, and 87.6% in the placebo, dex 60, and dex90 treatment groups, respectively. Approximately 70% of the subjects had at least 90% of the entries expected; and 50% of the subjects had at least 96% of the entries expected. These quantities were similar across the treatment groups.

For GD05-137, diary compliance was similar in the placebo (mean percentage of expected entries completed = 86.3%), dex30 QD (83.6%), and dex60 (84.7%) treatment groups. Around 63% of the subjects had at least 90% of the entries expected; and 50% of the subjects had at least 95 % of the entries expected. These quantities were similar across the treatment groups.

These rates seem to be acceptably high in both studies.

In addition to verifying the applicant’s efficacy analyses, I conducted a worst case sensitivity analysis. I imputed the highest percentage observed in any dexlansoprazole-treated subject (100%) to the missing placebo-treated subjects; and, conversely, the lowest percentage observed in the placebo group (0%) to the missing dexlansoprazole

subjects. Because the number of missing subjects was small, there was little effect upon the means (Tables 6a, 6b).

Table 6a Worst-Case Analysis Percentage of Days with Neither Daytime nor Nighttime Heartburn during Treatment: All Randomized Subjects, Study T-GD04-082

Measurement	Placebo (N=292)	Dexlansoprazole MR	
		60 mg QD (N=312)	90 mg QD (N=304)
Percentage of Days With Neither Daytime nor Nighttime Heartburn – Mean	25.5	(b) (4)	

Table 6b Worst-Case Analysis Percentage of Days with Neither Daytime nor Nighttime Heartburn during Treatment: All Randomized Subjects, Study T-GD05-137

Measurement	Placebo (N=317)	Dexlansoprazole MR	
		30 mg QD (N=315)	60 mg QD (N=315)
Percentage of Days With Neither Daytime nor Nighttime Heartburn – Mean	26.7	49.8	(b) (4)

3.2. Evaluation of Safety

An increased rate of adverse events, particularly cardiovascular (CV) and injury-related events, was observed in the dexlansoprazole treated patients. The safety assessment by Dr. Tamara Johnson of the Division of Gastroenterological Products (DGP) reviews six well-controlled Phase 3 studies (two per proposed indication) and one Phase 3 open-label long-term study. This analysis included re-adjudication of possible CV events and calculation of incidence rates by Dr. Johnson. For more details, see the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1. Gender, Race, and Age

Subgroup analyses for the primary efficacy variable are shown below in Tables 7a (Study T-GD04- 082) and 7b (Study T-GD0-137)

Gender For the primary efficacy variable, there was very little difference in the response to dexlansoprazole between men and women.

Age In study 082, there was very little difference in the response to dexlansoprazole by age. Study 137 showed high percentages for the ≥ 65 group relative to the younger subjects; this was seen in an elevated response in the placebo group as well as the two dexlansoprazole groups.

Race Generally, whites relative to blacks showed an elevated response in the placebo group as well as the two dexlansoprazole groups. (“other” has too few to draw meaningful conclusions) The one exception to this was the blacks in study 082, in the dex60 treatment group.

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Table 7a. Subgroup analyses, Study T-GD04- 082 (source: CSR, Table 14.2.4)

Subgroup	Placebo (N=290)			TAK-390MR 60 mg QD (N=306)			TAK-390MR 90 mg QD (N=298)					
	n	Mean	SD	Median	n	Mean	SD	Median	n	Mean	SD	Median
Percentage of Days With Neither Daytime nor Nighttime Headburn												
Age (Years)												
<45	106	26.2	29.1	15.7								
45-65	145	23.7	23.6	17.4								
≥65	39	26.4	26.6	19.5								
Gender												
Male	76	24.9	25.2	19.2								
Female	214	25.0	25.9	15.4								
Race												
White	239	24.5	24.8	17.6								
Black	34	25.7	29.8	13.9								
Other	19	29.5	32.0	15.8								

(b) (4)

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Table 7 b. Subgroup analyses, primary efficacy variable, Study T-GD05-137 (Source: CSR, Table 14.2.4)

Subgroup	Placebo (N=310)			TAK-390MR 30 mg QD (N=312)			TAK-390MR 60 mg QD (N=307)			
	n	Mean	SD	n	Mean	SD	n	Mean	SD	Median
Percentage of Days with Neither Daytime nor Nighttime Heartburn										
Age (Years)										
<45	126	25.3	24.8	129	47.8	33.0	54.5			
45-<65	146	22.2	25.0	148	51.0	34.6	53.5			
>=65	38	35.3	28.4	35	57.0	34.1	64.3			
Gender										
Male	80	21.7	26.1	84	49.6	36.3	55.4			
Female	230	26.2	25.3	228	50.6	33.1	54.8			
Race										
White	249	25.5	25.4	265	52.5	33.1	57.7			
Black	44	24.5	26.5	37	41.6	36.6	40.0			
Other	15	15.8	24.7	8	26.7	35.8	13.6			

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(b) (4)

4.2. Other Special/Subgroup Populations

No other subgroups were identified.

5. SUMMARY AND CONCLUSIONS

5.1. Statistical Issues and Collective Evidence

Combined vs. Separate Protocols

Studies T-GD082 and 083 were combined under Amendment 3 of the protocol, dated March 2006. This date is after the date of the first dose in December 2005 but before the last procedure in May 2006 (and, presumably, the data lock and breaking of the blind). I confirmed that analyzing the primary endpoint for the studies separately gave results similar to the combined analysis (Tables 5a and 5b)

Diary Compliance, Missing Data and Sensitivity Analyses

A critical issue in the measurement of the primary efficacy outcome is diary compliance. The calculation of the percentage of days with neither daytime nor nighttime heartburn hinges on the total number of days for which either a daytime or nighttime result is marked. Days missing diary results for both daytime and nighttime were excluded from the numerator and denominator. Patients with no diary recordings were excluded completely from the ITT analysis. There was no imputation of missing data, and the only sensitivity analyses conducted by the sponsor looked at relative completers (subjects with at least 7, 14, or 21 days of electronic diary data during treatment).

Thus, high compliance rates are important.

For study GD04-082 the mean percentages of expected entries that were completed in each treatment group was 88.3%, 87.5%, and 87.6% in the placebo, dex 60, and dex90 treatment groups, respectively. Approximately 70% of the subjects had at least 90% of the entries expected; and 50% of the subjects had at least 96% of the entries expected. These quantities were similar across the treatment groups.

For GD05-137, diary compliance was similar in the placebo (mean percentage of expected entries completed = 86.3%), dex30 QD (83.6%), and dex60 (84.7%) treatment groups. Around 63% of the subjects had at least 90% of the entries expected; and 50% of the subjects had at least 95 % of the entries expected. These quantities were similar across the treatment groups.

These rates seem to be acceptably high in both studies.

In addition to verifying the applicant's efficacy analyses, I conducted a worst case sensitivity analysis. I imputed the highest percentage observed in any dexlansoprazole-treated subject (100%) to the missing placebo-treated subjects; and, conversely, the lowest percentage observed in the placebo group (0%) to the missing dexlansoprazole subjects. Because the number of missing subjects was small, there was little effect upon the means (Tables 6a, 6b).

5.2. Conclusions and Recommendations

Efficacy was demonstrated in these studies for dexlansoprazole at 30, 60 and 90 mg QD in the treatment of symptomatic GERD. The to-be-marketed dose is 30 mg. There was only one study of 30 mg, but the improvement of dex30 relative to placebo is highly statistically significant ($p < 0.0001$) as well as large: subjects in the placebo group had a median of 19% of reported days with neither daytime nor nighttime heartburn, while dex30 had a median of 55%. (b) (4)

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Appendix

The tables below, taken from the sponsor's Table 2.7.6.a in the "Synopsis of Individual Studies" summarizes these studies.

Notes:

- Studies T-EE04-086 and T-EE04-087 are identical protocols and the data obtained from both protocols will be combined and analyzed as 1 clinical study. Since the 2 protocols are being modified to a single robust study, the overall significance level will be reduced from 0.05 to 0.0025 to establish the efficacy of TAK-390MR. A single analysis will be undertaken under the T-EE04-086 protocol and no separate analyses of the original 2 protocols will be performed (SAP, Section 3.1.1, p. 12/75).
- Studies T-GD04-082 and T-GD04-083 were identical protocols and, as mentioned in Amendment 3 to each of these protocols, the data obtained from both protocols were combined and analyzed together. Because the 2 protocols were modified to create a single robust study, the overall significance level was reduced from 0.05 (as was stated in the original protocols) to 0.0025 in the combined analysis to establish the efficacy of dexlansoprazole MR. The analyses are submitted in the T-GD04-082 clinical study report and no separate analyses of the original protocols were performed (SAP, Section 9.7.1.1, p. 60-61).

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type Number of Subjects (M/F)	Study and Control Drugs, Dose, Route and Regimen	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and Safety	T-GD04-082	To assess the efficacy in relief of daytime and nighttime heartburn over 4 weeks as assessed by daily electronic diary of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to placebo in subjects with symptomatic, nonerosive GERD; to assess the safety of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to placebo in subjects with symptomatic, nonerosive GERD. The secondary objective was to assess the efficacy of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to placebo in relief of nighttime heartburn over 4 weeks as assessed by daily electronic diary	Randomized, double-blind, multicenter, placebo-controlled, parallel-group, 3-arm Placebo (265/643)	60 mg oral dexlansoprazole MR QD or 90 mg oral dexlansoprazole MR QD or oral placebo QD	Subjects with Symptomatic Nonerosive GERD	4 weeks

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type Number of Subjects (M/F)	Study and Control Drugs, Dose, Route and Regimen	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and Safety	T-GD05-137	To assess the efficacy in relief of daytime and nighttime heartburn over 4 weeks as assessed by daily electronic diary of dexlansoprazole MR (30 mg QD and 60 mg QD) compared to placebo in subjects with symptomatic, nonerosive GERD; to assess the safety of dexlansoprazole MR (30 mg QD and 60 mg QD) compared to placebo in subjects with symptomatic, nonerosive GERD. The secondary objective was to assess the efficacy of dexlansoprazole MR (30 mg QD and 60 mg QD) compared to placebo in relief of nighttime heartburn over 4 weeks as assessed by daily electronic diary	Randomized, double-blind, multicenter, placebo controlled, parallel-group, 3-arm Placebo (274/673)	30 mg oral dexlansoprazole MR QD or 60 mg oral dexlansoprazole MR QD or oral placebo QD	Subjects with Symptomatic Nonerosive GERD	4 weeks

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type Number of Subjects (M/F)	Study and Control Drugs, Dose, Route and Regimen	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and Safety	T-EE04-084	To assess the efficacy and safety in healing EE over 8 weeks of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to lansoprazole delayed-release capsules (30 mg QD) in subjects with endoscopically proven EE; the secondary objectives were to assess the efficacy of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to lansoprazole delayed-release capsule (30 mg QD) in healing EE over 4 weeks in subjects with endoscopically proven EE and in healing EE over 8 weeks in subjects with endoscopically proven moderate or severe EE	double-blind, active-controlled Active 1111/927	60 mg oral dexlansoprazole MR QD or 90 mg oral dexlansoprazole MR QD or 30 mg oral lansoprazole delayed release QD	Subjects with EE	4 or 8 week

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type Number of Subjects (M/F)	Study and Control Drugs, Dose, Route and Regimen	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and Safety	T-EE04-085	To assess the efficacy and safety in healing EE over 8 weeks of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to lansoprazole delayed-release capsules (30 mg QD) in healing EE over 8 weeks in subjects with endoscopically proven EE; the secondary objectives were to assess the efficacy of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to lansoprazole delayed-release capsules (30 mg QD) in healing EE over 4 weeks in subjects with endoscopically proven EE and in healing EE over 8 weeks in subjects with endoscopically proven moderate or severe EE	Randomized, double-blind, active-controlled Active 1091/963	60 mg oral dexlansoprazole MR QD or 90 mg oral dexlansoprazole MR QD or 30 mg oral lansoprazole delayed release QD	Subjects with EE	4 or 8 week

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type Number of Subjects (M/F)	Study and Control Drugs, Dose, Route and Regimen	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy and Safety	T-EE04-086	To assess the efficacy in maintenance of healed EE and safety of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to placebo in subjects with healed EE; the secondary objectives were to assess the efficacy of dexlansoprazole MR (60 mg QD and 90 mg QD) compared to placebo in relief of daytime and nighttime heartburn over 6 months through the collection of daily diaries in subjects with healed EE	Randomized, double-blind, placebo- controlled Placebo 235/216	60 mg oral dexlansoprazole MR QD or 90 mg oral dexlansoprazole MR QD or oral placebo QD	Subjects with Healed EE	6 Months

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Type of Study	Study Identifier	Objective(s) of the Study	Study Design Control Type Number of Subjects (M/F)	Study and Control Drugs, Dose, Route and Regimen	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
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/s/

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12/16/2008 03:48:57 PM
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Mike Welch
1/6/2009 01:58:08 PM
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Concur with review.

NDA Number: 22-287

Applicant: TAP Pharmaceuticals

Stamp Date: Dec. 31 2007

Drug Name: Dexlansoprazole NDA/BLA Type: NDA

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			

Background

Dexlansoprazole is an enantiomer of lansoprazole, a proton-pump inhibitor currently approved for a variety of indications, including healing of erosive esophagitis (EE), maintenance of healed EE, and symptomatic GERD. This application seeks approval of dexlansoprazole for healing of EE, maintenance of healed EE, and symptomatic GERD.

Datasets and study reports are in eCTD format in the EDR under
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Overview of studies

There were six “efficacy and safety” Phase III studies submitted in support of the proposed indications. The tables below, taken from the sponsor’s Table 2.7.6.a in the “Synopsis of Individual Studies” summarizes these studies.

Notes:

- Studies T-EE04-086 and T-EE04-087 are identical protocols and the data obtained from both protocols will be combined and analyzed as 1 clinical study. Since the 2 protocols are being modified to a single robust study, the overall significance level will be reduced from 0.05 to 0.0025 to establish the efficacy of TAK-390MR. A single analysis will be undertaken under the T-EE04-086 protocol and no separate analyses of the original 2 protocols will be performed (SAP, Section 3.1.1, p. 12/75).
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