CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-987

STATISTICAL REVIEW(S)

STATISTICAL REVIEW & EVALUATION

NDA #:	20987
Applicant:	Wyeth Ayerst
Drug Name:	Protonix (Pantoprazole sodium)
Pharmacologic Category of the Drug:	proton pump inhibitor
Indication:	Acute Rx of Erosive Esophagitis associated with GERD
Received Date:	30 June 1998, goal 30 March 1999
Documents Reviewed:	Volumes 1.001-1.338, dated 6mo/30/1998
Project Manager:	Maria Walsh
User Fee Date:	April 30, 1999
Clinical Reviewer:	Hugo Gallo-Torres, M.D., Ph.D.
Primary Reviewer:	Ferrin Harrison, Ph.D.

I. INTRODUCTION

To support their claims of safety and efficacy of the drug in the acute treatment of erosive esophagitis associated with GERD, the sponsor submitted the results of two pivotal studies, 3001-A1-300-US and 3001-A1-301-US, abbreviated 300-US and 301-US in this review.

The design of trial 3001A1-300-US is multicenter, placebo-controlled, and dose response with doses 10, 20, 40mg once daily. The randomization is 1:2:2:2.

The design of trial 3001-A1-301-US is multicenter, doses 20, 40mg once daily versus nizatidine at the approved daily dose for Erosive Esophagitis (EE, 150mg BID.) A reason for using more than one dose of pantoprazole was not found. The randomization is 1:1:1.

There is an integrated summary of safety with acute GERD patients exposed to pantoprazole in controlled clinical trials by Wyeth-Ayerst and Byk Gulden. Totals of 682 patients in these two Wyeth-Ayerst trials, and 2,805 Byk Gulden patients in 12 studies were used in the summary (v1.002), for an overall total of 3,487 patients.

The issues concern the sponsor's claims, in their proposed labeling:

> The recommended adult oral dose is 40 mg given once daily for [redacted] 8 weeks.

[redacted]

This review also gives attention to safety, and to these secondary claims in the proposed labeling:

[redacted]

INDICATIONS AND USAGE
Short-Term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD)

[redacted]

II. COMMON ELEMENTS OF THE DESCRIPTION AND ANALYSES OF TRIALS 3001A1-300-US AND 3001A1-301-US

Both 300-US and 301-US were double blinded. The medication code was given in individual sealed envelopes so the blind could be broken by a local decision, and the sponsor informed.

The inclusion criteria were: patients who were not confined to bed and had endoscopically demonstrated erosive esophagitis, grade 2 or greater on the Hetzel-Dent scale, and at least a single episode, on at least 4 of the previous 7 days, of one of the symptoms typical for reflux esophagitis (i.e., acid regurgitation, daytime heartburn, nighttime heartburn, or dysphagia).

The exclusion criteria are not identical between the two trials, did not include anything surprising to this reviewer, and are omitted for brevity.

Over a third of the patients had Hetzel-Dent EE lesions of grade 3 or 4.

A treatment success for the primary endpoint had the grade of all lesions reduced to 0-1 on the Hetzel-Dent scale. This was assessed by endoscopy at week 0 and week 4, and if unhealed at week 4, there was another endoscopy at week 8. Patients healed at or before the 8th week visit were considered responders (treatment successes); hence the primary analysis is the cumulative analysis at week 8. Originally, the proportions of treatment successes were compared at week 4 and 8 by Fisher's exact test on all sites pooled, and by Cochran-Mantel-Haenszel test stratifying by baseline H. pylori and severity (2 vs. 3-4) of erosive esophagitis, respectively. As requested by this reviewer, the primary endpoint was reanalyzed by a stratified exact odds ratio test. Stratified analyses were conducted by center, baseline H. pylori, baseline severity, age, race and gender. If a patient's endoscopic rating deteriorated by at least two grades during the study, the patient was classified as a nonresponder and withdrawn.

The sponsor's multiple comparisons procedure was to first look for an overall drug versus control result at the 0.05 level. If statistically significant, they could next look at individual drug arms against control. If not significant, the trial would fail to show efficacy. In these two trials (300-US, 301-US) the p-values are easily smaller than 0.05, so other multiple comparison procedures would also yield statistically significant results.

Notation: we will analyze data from the following populations and imputations. The sponsor's ITT is defined as not a true ITT, being limited to patients who took study drug (pantoprazole, nizatidine or placebo). ITT[+] and ITT[-] differ by the imputation, assuming healing if unknown in [+] and generally assuming not healed if unknown in [-]. However, if endoscopic data are available after week 4 but not at week 4, then no imputation (locf or focb) is performed, and the patient is excluded from week 4 analysis. The MITT is limited to having at least one post-baseline endoscopy. The definition of VFE analysis is a kind of compliant or per-protocol patient's analysis, adding at least one endoscopy at week 4 or beyond, 80% compliant (as defined in the protocol), and with no serious protocol violations. Each of these four analyses was defined in either the original protocol or an amendment to the protocol.

ITT[+] (took drug), ITT[-](same), MITT (modified ITT), VFE(valid for efficacy).

ITT[+]: took at least one dose of study drug, assume healed [+] if data missing

ITT[-]: assume not healed [-] if data missing unless missing 4 but week 8 present
MITT: at least one post-baseline endoscopy
VFE: MITT, and at least one endoscopy at week 4 or beyond, 80% compliant, no serious protocol violations

The secondary endpoints were absence of symptoms (nighttime heartburn, daytime heartburn, acid regurgitation, dysphagia) and Gelusil usage (number of tablets.) The four "absence of symptom" endpoints were tested for differences in the same manner as the primary endpoint. Total Gelusil tablet usage was divided by the number of days of participation in the study to obtain an average number of tablets taken per day. Both total tablets and average tablets per day were analyzed by the Kruskal-Wallis test.

In each trial, the ITT analyses at week 8 included patients who were excluded from week 4, for having an endoscopy at week 6 or 8 but not a post-baseline endoscopy before week 4. The sponsor did not wish to assume all healed or unhealed since some patients healed shortly therafter, and some did not heal by the final endoscopy. Consequently, the number of patients increases between week 4 and week 8, from 588 to 603 in 300-US and from 230 to 243 in 301-US.

To address the sensitivity of the analysis to the handling of missing data at 4 weeks, this reviewer conducted a simple ITT[u] (as unfavorable to the sponsor as possible) analysis in each trial. Normally, the statistical reviewer would use one or more reasonable models to examine sensitivity, but the data are so strong in this submission that the most unfavorable model is used for brevity. This four week ITT[u] treats patients with endoscopies at week 6 or 8 but no endoscopy at week 4 as unhealed if on drug, and healed if on control, showing similar rates.

III. DESCRIPTION OF TRIAL 3001A1-300-US (abbreviated 300-US) AND SPONSOR'S ANALYSES AND RESULTS

III.a Description of Trial 3001A1-300-US (300-US)

There were 45 centers with 603 patients, with 4 treatment groups including placebo. The treatment groups and doses were placebo, 10m, 20mg, and 40mg.

The objective was to demonstrate a statistically significant ($p \leq .05$) difference in healing rates between the highest dose (40mg) of pantoprazole and placebo. Assuming an estimated healing rate of 70% to 90% for pantoprazole and 20% for placebo, the planned sample size provides greater than 95% power to find a difference between

these two arms. This power and sample size (v1.234) is the result of enhancement to provide patients for a follow-up maintenance study.

III.b Sponsor's Analyses and Results of Trial 3001A1-300-US (300-US)

The actual number of patients enrolled was 603 GERD patients, 82 placebo, 174 at 10mg, 174 at 20mg, and 173 patients at 40mg. The healing rate estimates are in the following **Table A**, showing substantial (over 20%) effects and a sensible dose-response relationship. For brevity, only the ITT[-] and VFE subset analyses are shown in the following table, omitting ITT[+] and MITT since the results of the four analyses are similar.

Table A
Pooled Healing Rates in Study 30001A1-300-US

		Placebo	Pantoprazole 10mg QD	Pantoprazole 20mg QD	Pantoprazole 40mg QD
ITT[-]	4 week	11/81(14%)	72/171(42%)	92/167(55%)	122/169(72%)
ITT[u]	4 week	12/82(15%)	72/174(41%)	92/174(53%)	122/173(71%)
ITT[-]	8 week	27/82(33%)	102/174(59%)	135/174(78%)	152/173(88%)
VFE	4 week	11/77(14%)	72/158(46%)	90/154(58%)	121/161(75%)
VFE	8 week	27/68(40%)	101/153(66%)	132/158(84%)	151/163(93%)

source V1.002 pg. 177, sponsor's Table 5
all four sponsor's analyses had p<.001 for 40mg versus Placebo.

This reviewer's simple ITT[u] analysis yields $p < .0001$ for each comparison of pantoprazole against placebo, using a two-tailed pooled (not stratified by center) Fisher's exact test.

Appendix Table 1 breaks out the healing rates by baseline disease severity, and **Table 3** by baseline helicobacter pylori status. Few patients had baseline helicobacter pylori. Dose-response is unclear for severity 3-4 at 8 weeks. Otherwise the subsets appear consistent with the whole.

Age, gender, height, body mass index, erosive esophagitis severity and H. pylori status are well balanced at baseline. At $0.05 < p < 0.10$, balance is marginal for ethnic origin and weight, per **Appendix Table 19**. As usual in clinical trials, at 12%, there are not enough non-white patients to show that the drug is working for them, but neither does this reviewer see any reason to assume it isn't working. Since $p < .0001$ for each comparison of placebo against 20mg, this reviewer would not suspect that reasonable variations in weight (up to double normal female) would make the 40mg dose

ineffective. Weights in excess of double normal female might be addressed by the biopharm reviewer or attending physician.

Women comprise about 33% of the patients enrolled, so we have confidence in the efficacy for both genders in **Appendix Table 6**. Elderly (age ≥65 years) are about 15% of patients enrolled, so our understanding of efficacy in the elderly is limited, with no patients and no knowledge for juveniles and adolescents, in **Appendix Table 7**.

No single center enrolled more than 28 of the 603 patients, so there could not be a center that drives the result.

Overall, this trial supports efficacy relative to placebo and shows a dose-response for 4 and 8 weeks. Efficacy in the secondary endpoints against placebo is also supported.

III. DESCRIPTION OF TRIAL 3001A1-301-US (abbreviated 301-US) AND SPONSOR'S ANALYSES AND RESULTS

III.a Description of Trial 3001A1-301-US (301-US)

The design is parallel and randomized 1:1:1, with doses 20, 40mg once daily versus nizatidine at the approved daily dose for EE (150mg BID.) The study ran from 12/2mo/1997 to 2/12mo/1997 and the duration of treatment was to be up to 8 weeks.

No Gelusil was to be taken within 1 hour of study drug, nor more than 12 tablets per 24 hour period. Otherwise Gelusil could be taken after any 5 minutes of pain (v1.333 pg. 24).

The sample size of 195 (v1.333 pg. 33) was based on 80% healing at 20mg, 90% healing at 40mg, 35% healing on nizatidine, for deltas of 45% and 55% respectively. They needed 65 patients per group for more than 95% power for these differences, and overpowered to supply patients for a maintenance study, for a total of 244 patients enrolled. They would have 90% power at $\alpha = .05$ and deltas of a 30% difference.

The four subsets (ITT[+], ITT[-], MITT, VFE) are not per protocol but were chosen before breaking the study blind (v1.333 pg. 34). Additional analyses include K-M (Kaplan-Meier) and Wilcoxon for time to absence of symptoms. Gelusil analysis was switched from total tablets to mean tablets per day on trial.

Note: v1.33 pg. 35, the sponsor thinks morning dosing better reduces steady-state

gastric acid inhibition than evening, ref: Mussig S, Witzel L, Luhman R, Schneider A. "Morning and evening administration of pantoprazole. A study to compare the effect on 24-hour intragastric pH". *Eur J Gastroenterol Hepatol.* 9: 1-4, 1997

IIII.b Sponsor's Analyses and Results of Trial 3001A1-301-US (301-US)

The number of patients planned for enrollment was 195; 244 patients were enrolled, and 243 patients took pantoprazole or nizatidine and were analyzed. Taking at least one dose of drug: 80 in 20mg, 81 in 40mg and 82 in nizatidine. 215 completed the study. The rates of Withdrawn/Completers are: 6/74 at 20mg, 9/72 at 40mg, and 13/69 for nizatidine (v 1.333, pg. 36), not significantly different between arms (chi-squared p=.25).

The Primary analysis (healing all lesions to grade 0-1) was Fisher's exact test pooling data from all sites, two sided CMH controlling for baseline severity (2 vs. 3-4), or H. Pylori status, or site. The sponsor gives a definition of the Hetzel-Dent scale on page 22 of V1.333.

The Secondary analysis was by methodologies K-M (Kaplan-Meier) and Wilcoxon: frequency and severity of heartburn by day and night, acid regurgitation, dysphagia on four point scale:
0=no symptoms, 1=mild, 2=moderate interfering with usual activity,
3=disabling interfering with daily routine or sleep.

Diary cards were dispensed to track Gelusil usage. The Kruskal-Wallis test was used to test for Gelusil differences between arms in Gelusil usage.

The sponsor's analysis shows both doses of drug were superior to nizatidine.

Safety assessments were based on reports of adverse events and results of routine physical examinations, electrocardiograms, endoscopy, gastric biopsy, and laboratory determinations. Fasting was required for blood sampling for endoscopy visits. Fisher's exact test was used for safety evaluations of safety variables. No safety issues were noted.

The baseline factors are balanced for age, gender, race, weight, height, body mass index, EE severity and H. pylori status (v 1.333 pp. 38-39), so we have confidence in the stratified analyses in **Appendix Tables 8-9** in this respect. Women are about

30% of the patients enrolled, so we have confidence in the efficacy for women per the stratified analyses in **Appendix Tables 8-9**. Elderly (age ≥65 years) are about 17%, with 11% non-whites, so we don't know much about efficacy in these groups, but per **Appendix Tables 8-9**, there is no reason to assume lack of efficacy.

No center enrolled more than 36 of the 244 patients, so the primary results could not be driven by one or two large centers.

Almost all patients received concomitant medication, most of which are hypnotics, sedatives and opioids used during endoscopic procedures.

The healing rates are shown in the following **Table B**, and as against placebo (US-300), the drug is improving over Nizatidine by at least 20 percentage points. For brevity, only two of the sponsor's subset analyses (ITT[-] and VFE) are shown, omitting ITT[+] and MITT, since the four analyses are quite similar.

The simple ITT[u] analysis by this reviewer yields $p \leq .0001$ for each comparison of pantoprazole against nizatidine on a two-tailed pooled (not stratified by center) Fisher's exact test.

Table B
Pooled Healing Rates in Study 3001A1-301-US

		Nizatidine	---- Pantoprazole ----	
		150mg BID	20mg QD	40mg QD
ITT[-]	4 week	16/78(21%)	45/75(60%)	50/77(65%)
ITT[u]	4 week	20/82(24%)	45/80(56%)	50/81(62%)
ITT[-]	8 week	30/82(37%)	59/80(74%)	60/81(74%)
VFE	4 week	16/72(22%)	43/70(61%)	48/75(64%)
VFE	8 week	29/70(41%)	52/72(79%)	58/70(83%)

source V1.002 pg. 178, sponsor's Table 6
all four p<.001 for 40mg pantoprazole versus 150mg BID nizatidine

Appendix Table 2 breaks out the healing rates by baseline disease severity, and **Table 4** by baseline helicobacter pylori status. Few patients had baseline helicobacter pylori, but otherwise the subsets appear consistent with the whole.

For the secondary claims of persistent absence of symptoms relative to nizatidine, **Appendix Tables 10, 12, 14, 16** and **18** provide drug versus placebo concordance with the sponsor's basis, trial 300-US. **Appendix Tables 11, 13, 15, 17** and **18** provide statistically weaker, but direct support for drug versus

nizatidine, trial 301-US. When the p-value drops below 0.05, the sponsor claims a significant change. The sponsor retains that change regardless of the p-value rising above 0.05 at week 8 for acid regurgitation (**Table 18**).

However, if $p < .001$ is required for secondary endpoints, then these claims are not supported. They are supported only at the $p < .05$ level.

V. ADDITIONAL REVIEWER'S COMMENTS

The sponsor's original analysis of the primary endpoint, endoscopically verified ulcer healing, was based on the Cochran-Mantel-Haenszel test, which uses a normal approximation. As requested by this reviewer, the sponsor re-analyzed the data by exact stratified odds ratio test. Since these statistical methodologies answer the same question, one by approximation and one by conditioning on the marginal total, this reviewer is using the exact stratified odds ratio test results, in **Appendix Tables** 5 to 9. These tables contain p-values and odds ratio estimates.

V.a Additional Reviewer's Comments for Submission Preparation

Appendix Tables 5 to 9 were extracted from a little less than a megabyte of MS Word files submitted with the three volumes, after exporting as ASCII text and summarization by a program called "awk". The awk program used is in **Appendix A**, after the **Appendix Tables**. Perhaps it would be useful to the sponsor to develop similar in-house capacity to translate SAS outputs into summary tables. It would also be helpful to this reviewer if the input files were not garbled (missing letters, words and lines haphazardly,) although the enhanced awk program seems adequate to handle the garbling for this submission. Despite areas for improvement, the current level of electronic submission can be reviewed more thoroughly in a limited amount of time (for this experienced reviewer) than paper volumes.

V.b Additional Reviewer's Comments on Trial 30001A1-300-US (300-US)

The study appears well designed, including randomization and more than adequate power to distinguish drug from placebo, and generally to show dose-response. The allocation of patients between centers appears sufficiently dispersed so the study would not be dominated by a few large centers. Due to the high power of the study, small differences between centers may be statistically significant without regulatory implications. However, the high power does not impede an overall result, as shown by

the small overall p-values in analysis stratified by center in **Appendix Tables 5** to **6**.

Appendix Tables 5 to **7** show robustness of the results with respect to stratification by baseline H. pylori, EE severity, site, age, race and gender. The analysis is also robust with respect to the various population analyses (ITT[-], ITT[+], VFE, MITT). The effect size appears to decrease (p-value and sample size increase) between weeks 4 and 8, but retains significance. Each dose of drug appears superior to placebo, but some dose comparisons are weak.

V.c Additional Reviewer's Comments on Trial 30001A1-301-US (301-US)

The study appears well designed, including randomization and generally adequate power to distinguish drug from nizatidine. The allocation of patients between centers appears sufficiently dispersed so the study would not be dominated by a few large centers. No significant treatment by center interaction was found.

Appendix Tables 8 and **9** show the results with respect to stratification by baseline H. pylori, EE severity, site, age, race and gender. The results of this trial differ from 300-US in that dose-response is not shown, so the dose-response (drug 40mg versus 20mg) is segregated into **Table 8**, with the drug versus nizatidine comparisons in **Table 9**. The drug versus nizatidine is robust with respect to the various population analyses (ITT[-], ITT[+], VFE, MITT). The effect size seems to be about the same at 4 and 8 weeks in this less strongly powered study.

VI. REVIEWER'S COMMENTS AND CONCLUSIONS

At a dose of 40mg, the drug appears effective relative to placebo and nizatidine.

According to the results of Appendix Tables 5-7, dose 40mg is superior to 20mg with unadjusted $p < .05$ for all 48 p-values, with some $p > .025$. Trial 301-US has less than half as many patients and fails to show a difference between the 40mg and 20mg doses.

The results for secondary endpoints (day heartburn, night heartburn, regurgitation, and antacid usage on respective days) are at the $p < .05$ level in one trial, 301-US.

The labeling to extend treatment for an additional 8 weeks if healing is not obtained needs to be considered in light of safety concerns, including hypotheses regarding carcinogenesis and hepatotoxicity. The support is pre-clinical for these concerns for this drug, with post marketing support for hepatotoxicity in at least one other proton

pump inhibitor . Such labeling directly encourages doubling the exposure, and may indirectly encourage repetition of therapy or off label use for more than 16 weeks.

OVERALL CONCLUSION

The claims for ulcer healing against placebo and nizatidine appear reasonable, generally at $p < .0001$ for each claim, one trial per claim.

The claims of symptomatic relief in 1-2 days respectively are supported by secondary endpoints comparisons at the $p = .05$ level.

/S/ 5mo/24/1999

Ferrin Harrison, Ph.D.
Mathematical Statistician

This review consists of 11 pages of text, 13 pages of appendix tables, and 2 pages of appendix program.

Concur: Dr. Al-Osh /S/ 5/25/99

Dr. Welch /S/ 5/25/99

cc: Archival NDA

HFD-180/ Division Files
HFD-180/ Dr. Talarico
HFD-180/ Dr. Gallo-Torres
HFD-180/ Maria Walsh
HFD-715/ Dr. Nevius
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HFD-715/ Dr. Al-Osh
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Appendix Table 1
Healing Rates by Disease Severity in Trial 30001A1-300-US

4 WEEKS	Grade	Placebo	Pantoprazole 10mg QD	Pantoprazole 20mg QD	Pantoprazole 40mg QD
ITT[-]	2	10/53(19%)	59/112(53%)	69/104(66%)	89/110(81%)
ITT[-]	3-4	1/28(4%)	13/ 59(22%)	13/ 59(22%)	33/ 59(56%)
VFE	2	10/51(20%)	59/102(58%)	68/ 94(72%)	88/102(86%)
VFE	3-4	1/26(4%)	10/ 51(20%)	13/ 56(23%)	33/ 59(56%)

8 WEEKS	Grade	Placebo	Pantoprazole 10mg QD	Pantoprazole 20mg QD	Pantoprazole 40mg QD
ITT[-]	2	25/54(46%)	79/114(69%)	89/108(82%)	100/113(89%)
ITT[-]	3-4	2/28(7%)	25/ 54(46%)	23/ 60(38%)	52/ 60(87%)
VFE	2	25/44(57%)	78/101(77%)	87/ 96(91%)	99/104(95%)
VFE	3-4	2/24(8%)	25/ 44(57%)	23/ 52(44%)	52/ 59(88%)

source V1.002 pg. 180, sponsor's Table 7
see Tables 5-6 for stratified p-values

Appendix Table 2
Healing Rates by Disease Severity in Trial 30001A1-301-US

4 WEEKS	Grade	Nizatidine 150mg BID	Pantoprazole 20mg QD	Pantoprazole 40mg QD
ITT[-]	2	15/56(27%)	36/48(75%)	39/47(83%)
ITT[-]	3-4	1/22(5%)	9/27(33%)	11/30(37%)
VFE	2	15/50(30%)	34/42(81%)	37/45(82%)
VFE	3-4	1/22(5%)	9/28(32%)	11/30(37%)

8 WEEKS	Grade	Nizatidine 150mg BID	Pantoprazole 20mg QD	Pantoprazole 40mg QD
ITT[-]	2	28/57(49%)	44/51(86%)	44/50(88%)
ITT[-]	3-4	2/25(8%)	15/29(52%)	16/31(52%)
VFE	2	27/49(55%)	42/44(96%)	42/43(98%)
VFE	3-4	2/21(10%)	15/28(54%)	16/27(59%)

source V1.002 pg. 181, sponsor's Table 8
see Tables 8-9 for stratified p-values

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Appendix Table 3
Healing Rates by H. pylori status in Trial 30001A1-300-US

4 WEEKS	H. pylori	Placebo	Pantoprazole 10mg QD	Pantoprazole 20mg QD	Pantoprazole 40mg QD
ITT[-]	[+]	2/17(12%)	10/ 31(32%)	20/ 30(67%)	33/ 41(80%)
ITT[-]	[-]	9/64(14%)	62/140(44%)	72/137(53%)	89/128(70%)
VFE	[+]	2/16(13%)	10/ 28(36%)	20/ 28(71%)	32/ 38(84%)
VFE	[-]	9/61(15%)	62/130(48%)	70/126(56%)	89/123(72%)

8 WEEKS	H. pylori	Placebo	Pantoprazole 10mg QD	Pantoprazole 20mg QD	Pantoprazole 40mg QD
ITT[-]	[+]	7/17(41%)	17/ 31(55%)	25/ 31(81%)	38/ 43(88%)
ITT[-]	[-]	20/65(31%)	85/143(59%)	110/143(77%)	114/130(88%)
VFE	[+]	7/16(44%)	17/ 27(63%)	25/ 29(86%)	37/ 39(95%)
VFE	[-]	20/52(39%)	84/126(67%)	107/129(83%)	114/124(92%)

source V1.002 pg. 181, sponsor's Table 10
see Tables 5-6 for stratified p-values

Appendix Table 4
Healing Rates by H. pylori status in Trial 30001A1-301-US

4 WEEKS	H. pylori	Nizatidine 150mg BID	Pantoprazole 20mg QD	Pantoprazole 40mg QD
ITT[-]	[+]	3/13(23%)	9/16(56%)	10/14(71%)
ITT[-]	[-]	13/64(20%)	36/58(62%)	40/63(64%)
VFE	[+]	3/11(27%)	9/15(60%)	10/12(83%)
VFE	[-]	13/60(22%)	34/54(63%)	38/63(60%)

8 WEEKS	H. pylori	Nizatidine 150mg BID	Pantoprazole 20mg QD	Pantoprazole 40mg QD
ITT[-]	[+]	7/14(50%)	14/16(88%)	11/14(79%)
ITT[-]	[-]	23/67(34%)	45/63(71%)	49/67(73%)
VFE	[+]	6/11(55%)	14/15(93%)	11/11(100%)
VFE	[-]	23/59(39%)	43/57(75%)	47/59(80%)

source V1.002 pg. 185, sponsor's Table 11
see Tables 8-9 for stratified p-values

Appendix Table 5
Clinical Trial 300-US Overall Efficacy
Stratification by Baseline H. Pylori, EE Severity, Site, Gender, Age, Race
Pantoprazole 40mg, 20mg, versus Placebo, all QD, all pairings

Strata	Arm	Arm	Week	--- ITT[-] ----	--- ITT[+] ----	--- VFE ----	--- MITT ----
H. Pylori	40mg	Pla	4	p<.0001 OR=16.1	p<.0001 OR=13.4	p<.0001 OR=17.7	p<.0001 OR=17.3
H. Pylori	40mg	Pla	8	p<.0001 OR=14.3	p<.0001 OR=16.7	p<.0001 OR=18.6	p<.0001 OR=18.4
H. Pylori	20mg	Pla	4	p<.0001 OR= 7.9	p<.0001 OR= 6.8	p<.0001 OR= 8.5	p<.0001 OR= 8.5
H. Pylori	20mg	Pla	8	p<.0001 OR= 7.0	p<.0001 OR= 7.9	p<.0001 OR= 7.7	p<.0001 OR= 8.5
Severity	40mg	Pla	4	p<.0001 OR=19.8	p<.0001 OR=17.5	p<.0001 OR=25.8	p<.0001 OR=24.6
Severity	40mg	Pla	8	p<.0001 OR=16.2	p<.0001 OR=21.0	p<.0001 OR=27.9	p<.0001 OR=25.4
Severity	20mg	Pla	4	p<.0001 OR= 9.1	p<.0001 OR= 8.0	p<.0001 OR=11.0	p<.0001 OR=10.5
Severity	20mg	Pla	8	p<.0001 OR= 8.2	p<.0001 OR= 9.8	p<.0001 OR=11.2	p<.0001 OR=11.3
Site	40mg	Pla	4	p<.0001 OR=16.5	p<.0001 OR=13.1	p<.0001 OR=16.3	p<.0001 OR=16.3
Site	40mg	Pla	8	p<.0001 OR=18.3	p<.0001 OR=19.8	p<.0001 OR=22.3	p<.0001 OR=18.8
Site	20mg	Pla	4	p<.0001 OR= 8.5	p<.0001 OR= 6.5	p<.0001 OR= 8.5	p<.0001 OR= 8.6
Site	20mg	Pla	8	p<.0001 OR= 7.3	p<.0001 OR= 8.1	p<.0001 OR= 6.9	p<.0001 OR= 7.8
Gender	40mg	Pla	4	p<.0001 OR=16.0	p<.0001 OR=13.3	p<.0001 OR=17.6	p<.0001 OR=17.2
Gender	40mg	Pla	8	p<.0001 OR=14.4	p<.0001 OR=16.9	p<.0001 OR=18.6	p<.0001 OR=18.6
Gender	20mg	Pla	4	p<.0001 OR= 7.7	p<.0001 OR= 6.7	p<.0001 OR= 8.4	p<.0001 OR= 8.4
Gender	20mg	Pla	8	p<.0001 OR= 6.9	p<.0001 OR= 7.8	p<.0001 OR= 7.6	p<.0001 OR= 8.4
Age	40mg	Pla	4	p<.0001 OR=16.1	p<.0001 OR=13.4	p<.0001 OR=17.8	p<.0001 OR=17.4
Age	40mg	Pla	8	p<.0001 OR=14.3	p<.0001 OR=16.7	p<.0001 OR=18.4	p<.0001 OR=18.4
Age	20mg	Pla	4	p<.0001 OR= 8.2	p<.0001 OR= 7.0	p<.0001 OR= 8.6	p<.0001 OR= 8.6
Age	20mg	Pla	8	p<.0001 OR= 7.1	p<.0001 OR= 7.9	p<.0001 OR= 7.6	p<.0001 OR= 8.4
Race	40mg	Pla	4	p<.0001 OR=15.8	p<.0001 OR=15.1	p<.0001 OR=21.9	p<.0001 OR=19.8
Race	40mg	Pla	8	p<.0001 OR=14.0	p<.0001 OR=17.6	p<.0001 OR=21.6	p<.0001 OR=19.5
Race	20mg	Pla	4	p<.0001 OR= 8.8	p<.0001 OR= 7.6	p<.0001 OR=10.1	p<.0001 OR= 9.6
Race	20mg	Pla	8	p<.0001 OR= 7.3	p<.0001 OR= 8.2	p<.0001 OR= 8.2	p<.0001 OR= 8.8

The OR (Odds Ratio) given is the Conditional Exact Maximum Likelihood Estimate.
Wk is the week, 4 weeks midterm, 8 weeks for full term treatment.
Severity is the baseline severity of EE (Erosive Esophagitis).

Appendix Table 6
Clinical Trial 300-US Overall Efficacy
Stratification by H.Pylori, EE Severity and Site
Pantoprazole 40mg, 20mg, 10mg or Placebo, all QD, all pairings

Strata	Arm	Arm	Week	--- ITT[-] ----	--- ITT[+] ----	--- VFE ----	--- MITT ----
H. Pylori	40mg	20mg	4	p=.0020 OR= 2.1	p=.0047 OR= 2.0	p=.0026 OR= 2.1	p=.0029 OR= 2.1
H. Pylori	40mg	20mg	8	p=.0154 OR= 2.1	p=.0245 OR= 2.2	p=.0154 OR= 2.4	p=.0235 OR= 2.2
H. Pylori	40mg	10mg	4	p<.0001 OR= 3.5	p<.0001 OR= 3.2	p<.0001 OR= 3.6	p<.0001 OR= 3.6
H. Pylori	40mg	10mg	8	p<.0001 OR= 5.1	p<.0001 OR= 5.5	p<.0001 OR= 6.4	p<.0001 OR= 5.9
H. Pylori	20mg	10mg	4	p=.0223 OR= 1.7	p=.0387 OR= 1.6	p=.0243 OR= 1.7	p=.0248 OR= 1.7
H. Pylori	20mg	10mg	8	p=.0002 OR= 2.4	p=.0004 OR= 2.5	p=.0004 OR= 2.6	p=.0002 OR= 2.6
H. Pylori	10mg	Pla	4	p<.0001 OR= 4.6	p<.0001 OR= 4.2	p<.0001 OR= 4.9	p<.0001 OR= 4.9
H. Pylori	10mg	Pla	8	p=.0002 OR= 2.9	p<.0001 OR= 3.1	p=.0004 OR= 2.9	p=.0001 OR= 3.2
Severity	40mg	20mg	4	p=.0014 OR= 2.2	p=.0028 OR= 2.2	p=.0015 OR= 2.3	p=.0016 OR= 2.3
Severity	40mg	20mg	8	p=.0150 OR= 2.1	p=.0231 OR= 2.2	p=.0213 OR= 2.4	p=.0221 OR= 2.3
Severity	40mg	10mg	4	p<.0001 OR= 4.0	p<.0001 OR= 3.8	p<.0001 OR= 4.4	p<.0001 OR= 4.3
Severity	40mg	10mg	8	p<.0001 OR= 5.4	p<.0001 OR= 6.3	p<.0001 OR= 7.5	p<.0001 OR= 6.7
Severity	20mg	10mg	4	p=.0121 OR= 1.8	p=.0203 OR= 1.7	p=.0114 OR= 1.9	p=.0124 OR= 1.8
Severity	20mg	10mg	8	p=.0001 OR= 2.6	p=.0001 OR= 2.9	p=.0001 OR= 3.1	p=.0001 OR= 3.0
Severity	10mg	Pla	4	p<.0001 OR= 5.1	p<.0001 OR= 4.7	p<.0001 OR= 5.8	p<.0001 OR= 5.8
Severity	10mg	Pla	8	p=.0001 OR= 3.3	p<.0001 OR= 3.7	p=.0001 OR= 3.4	p<.0001 OR= 4.0
Site	40mg	20mg	4	p=.0015 OR= 2.2	p=.0035 OR= 2.1	p=.0039 OR= 2.1	p=.0028 OR= 2.2
Site	40mg	20mg	8	p=.0167 OR= 2.0	p=.0264 OR= 2.1	p=.0097 OR= 2.6	p=.0167 OR= 2.3
Site	40mg	10mg	4	p<.0001 OR= 3.8	p<.0001 OR= 3.4	p<.0001 OR= 3.7	p<.0001 OR= 3.9
Site	40mg	10mg	8	p<.0001 OR= 5.4	p<.0001 OR= 5.9	p<.0001 OR= 6.5	p<.0001 OR= 6.1
Site	20mg	10mg	4	p=.0248 OR= 1.7	p=.0560 OR= 1.6	p=.0322 OR= 1.7	p=.0262 OR= 1.7
Site	20mg	10mg	8	p=.0003 OR= 2.3	p=.0005 OR= 2.4	p=.0028 OR= 2.3	p=.0005 OR= 2.5
Site	10mg	Pla	4	p<.0001 OR= 4.2	p<.0001 OR= 4.1	p<.0001 OR= 4.6	p<.0001 OR= 4.4
Site	10mg	Pla	8	p=.0001 OR= 3.0	p<.0001 OR= 3.5	p=.0001 OR= 3.5	p<.0001 OR= 3.4

The OR (Odds Ratio) given is the Conditional Exact Maximum Likelihood Estimate.
Wk is the week, 4 weeks midterm, 8 weeks for full term treatment.

Appendix Table 7
Clinical Trial 300-US Overall Efficacy
Stratification by Gender, Age and Race
Pantoprazole 40mg, 20mg, 10mg or Placebo, all pairings

Strata	Arm	Arm	Week	--- ITT[-] ----	--- ITT[+] ----	--- VFE ----	--- MITT ----
Gender	40mg	20mg	4	p=.0015 OR= 2.1	p=.0033 OR= 2.0	p=.0018 OR= 2.1	p=.0020 OR= 2.1
Gender	40mg	20mg	8	p=.0155 OR= 2.1	p=.0246 OR= 2.2	p=.0152 OR= 2.5	p=.0164 OR= 2.2
Gender	40mg	10mg	4	p<.0001 OR= 3.6	p<.0001 OR= 3.3	p<.0001 OR= 3.7	p<.0001 OR= 3.7
Gender	40mg	10mg	8	p<.0001 OR= 5.4	p<.0001 OR= 6.0	p<.0001 OR= 7.0	p<.0001 OR= 6.4
Gender	20mg	10mg	4	p=.0162 OR= 1.7	p=.0360 OR= 1.6	p=.0222 OR= 1.7	p=.0175 OR= 1.7
Gender	20mg	10mg	8	p=.0001 OR= 2.5	p=.0002 OR= 2.6	p=.0003 OR= 2.7	p=.0001 OR= 2.7
Gender	10mg	Pla	4	p<.0001 OR= 4.7	p<.0001 OR= 4.3	p<.0001 OR= 5.2	p<.0001 OR= 5.1
Gender	10mg	Pla	8	p=.0001 OR= 2.9	p<.0001 OR= 3.2	p=.0003 OR= 3.1	p<.0001 OR= 3.3
Age	40mg	20mg	4	p=.0021 OR= 2.0	p=.0047 OR= 2.0	p=.0026 OR= 2.1	p=.0029 OR= 2.1
Age	40mg	20mg	8	p=.0217 OR= 2.0	p=.0251 OR= 2.1	p=.0157 OR= 2.4	p=.0237 OR= 2.2
Age	40mg	10mg	4	p<.0001 OR= 3.6	p<.0001 OR= 3.2	p<.0001 OR= 3.6	p<.0001 OR= 3.6
Age	40mg	10mg	8	p<.0001 OR= 5.1	p<.0001 OR= 5.5	p<.0001 OR= 6.4	p<.0001 OR= 5.9
Age	20mg	10mg	4	p=.0116 OR= 1.8	p=.0211 OR= 1.7	p=.0167 OR= 1.7	p=.0173 OR= 1.8
Age	20mg	10mg	8	p=.0001 OR= 2.5	p=.0002 OR= 2.6	p=.0004 OR= 2.7	p=.0001 OR= 2.7
Age	10mg	Pla	4	p<.0001 OR= 4.6	p<.0001 OR= 4.2	p<.0001 OR= 4.9	p<.0001 OR= 4.9
Age	10mg	Pla	8	p=.0002 OR= 2.9	p<.0001 OR= 3.1	p=.0004 OR= 2.9	p=.0001 OR= 3.2
Race	40mg	20mg	4	p=.0021 OR= 2.1	p=.0045 OR= 2.0	p=.0023 OR= 2.2	p=.0020 OR= 2.1
Race	40mg	20mg	8	p=.0219 OR= 2.0	p=.0361 OR= 2.0	p=.0232 OR= 2.3	p=.0343 OR= 2.1
Race	40mg	10mg	4	p<.0001 OR= 3.6	p<.0001 OR= 3.1	p<.0001 OR= 3.5	p<.0001 OR= 3.5
Race	40mg	10mg	8	p<.0001 OR= 5.3	p<.0001 OR= 5.5	p<.0001 OR= 6.6	p<.0001 OR= 5.9
Race	20mg	10mg	4	p=.0158 OR= 1.7	p=.0283 OR= 1.6	p=.0225 OR= 1.7	p=.0177 OR= 1.7
Race	20mg	10mg	8	p=.0001 OR= 2.6	p=.0001 OR= 2.7	p=.0002 OR= 2.8	p=.0001 OR= 2.9
Race	10mg	Pla	4	p<.0001 OR= 4.6	p<.0001 OR= 4.2	p<.0001 OR= 5.0	p<.0001 OR= 4.9
Race	10mg	Pla	8	p=.0002 OR= 2.9	p=.0001 OR= 3.2	p=.0003 OR= 3.1	p=.0001 OR= 3.3

The OR (Odds Ratio) given is the Conditional Exact Maximum Likelihood Estimate.
Wk is the week, 4 weeks midterm, 8 weeks for full term treatment.

Appendix Table 8
Clinical Trial 301-US Overall Efficacy
Pantoprazole 40mg versus 20mg, both QD
Stratification by Site, Baseline HP or Severity, and Age, Race and Gender

Strata	Arm	Arm	Week	--- ITT[-] ---	--- ITT[+] ---	--- VFE ---	--- MITT ---
H. Pylori	40mg	20mg	4	p=.6180 OR=1.2	p=.8631 OR=1.1	p=.8629 OR=1.1	p=.8595 OR=1.1
H. Pylori	40mg	20mg	8	p=1 OR=1.0	p=.6965 OR=0.8	p=.5196 OR=1.4	p=.8431 OR=0.9
Severity	40mg	20mg	4	p=.4580 OR=1.4	p=.6935 OR=1.2	p=.8457 OR=1.2	p=.5533 OR=1.3
Severity	40mg	20mg	8	p=1 OR=1.1	p=.8321 OR=0.9	p=.6253 OR=1.4	p=1 OR=0.9
Site	40mg	20mg	4	p=.6096 OR=1.2	p=.8627 OR=1.1	p=.7265 OR=1.2	p=.7234 OR=1.2
Site	40mg	20mg	8	p=1 OR=1.0	p=.8473 OR=0.9	p=.5189 OR=1.4	p=1 OR=0.9
Gender	40mg	20mg	4	p=.6117 OR=1.2	p=.8602 OR=1.1	p=.8629 OR=1.1	p=.8582 OR=1.1
Gender	40mg	20mg	8	p=1 OR=1.0	p=.8469 OR=0.9	p=.6714 OR=1.2	p=.8461 OR=0.9
Age	40mg	20mg	4	p=.6165 OR=1.2	p=.8629 OR=1.1	p=.8639 OR=1.1	p=.8601 OR=1.1
Age	40mg	20mg	8	p=1 OR=1.0	p=.8473 OR=0.9	p=.6719 OR=1.2	p=.8466 OR=0.9
Race	40mg	20mg	4	p=.6084 OR=1.2	p=.8609 OR=1.1	p=.8608 OR=1.1	p=.7216 OR=1.2
Race	40mg	20mg	8	p=1 OR=1.0	p=.8471 OR=0.9	p=.6673 OR=1.3	p=.8474 OR=0.9

The OR (Odds Ratio) given is the Conditional Exact Maximum Likelihood Estimate.
Wk is the week, 4 weeks midterm, 8 weeks for full term treatment.

Appendix Table 9
Clinical Trial 301-US Overall Efficacy
Pantoprazole 40mg or 20mg QD versus nizatidine 150mg BID
Stratification by Site, Baseline HP or Severity, and Age, Race and Gender

Strata	Arm	Arm	Week	--- ITT[-] ----	--- ITT[+] ---	--- VFE ----	--- MITT ----
H. Pylori	40mg	150mg	4	p<.0001 OR= 6.9	p<.0001 OR=4.9	p<.0001 OR= 6.1	p<.0001 OR= 6.8
H. Pylori	40mg	150mg	8	p<.0001 OR= 4.8	p=.0001 OR=4.0	p<.0001 OR= 7.0	p<.0001 OR= 4.9
H. Pylori	20mg	150mg	4	p<.0001 OR= 5.8	p<.0001 OR=4.5	p<.0001 OR= 5.5	p<.0001 OR= 6.1
H. Pylori	20mg	150mg	8	p<.0001 OR= 5.0	p<.0001 OR=4.8	p<.0001 OR= 5.2	p<.0001 OR= 5.6
Severity	40mg	150mg	4	p<.0001 OR=12.7	p<.0001 OR=7.6	p<.0001 OR=10.7	p<.0001 OR=14.1
Severity	40mg	150mg	8	p<.0001 OR= 8.5	p<.0001 OR=6.4	p<.0001 OR=20.1	p<.0001 OR= 9.8
Severity	20mg	150mg	4	p<.0001 OR= 8.3	p<.0001 OR=6.2	p<.0001 OR= 9.7	p<.0001 OR=10.2
Severity	20mg	150mg	8	p<.0001 OR= 7.6	p<.0001 OR=7.5	p<.0001 OR=13.6	p<.0001 OR=11.8
Site	40mg	150mg	4	p<.0001 OR= 7.7	p<.0001 OR=4.9	p<.0001 OR= 8.0	p<.0001 OR= 8.2
Site	40mg	150mg	8	p<.0001 OR= 5.7	p<.0001 OR=4.4	p<.0001 OR= 8.7	p<.0001 OR= 6.0
Site	20mg	150mg	4	p<.0001 OR= 7.7	p<.0001 OR=5.1	p<.0001 OR= 7.1	p<.0001 OR= 7.5
Site	20mg	150mg	8	p<.0001 OR= 5.4	p<.0001 OR=5.0	p<.0001 OR= 5.8	p<.0001 OR= 6.0
Gender	40mg	150mg	4	p<.0001 OR=10.4	p<.0001 OR=6.6	p<.0001 OR= 7.5	p<.0001 OR= 9.7
Gender	40mg	150mg	8	p<.0001 OR= 5.3	p<.0001 OR=4.4	p<.0001 OR= 7.2	p<.0001 OR= 5.1
Gender	20mg	150mg	4	p<.0001 OR= 6.0	p<.0001 OR=5.0	p<.0001 OR= 6.3	p<.0001 OR= 6.7
Gender	20mg	150mg	8	p<.0001 OR= 5.0	p<.0001 OR=5.1	p<.0001 OR= 5.9	p<.0001 OR= 5.9
Age	40mg	150mg	4	p<.0001 OR= 7.1	p<.0001 OR=5.1	p<.0001 OR= 6.1	p<.0001 OR= 7.0
Age	40mg	150mg	8	p<.0001 OR= 4.8	p<.0001 OR=4.0	p<.0001 OR= 6.6	p<.0001 OR= 4.8
Age	20mg	150mg	4	p<.0001 OR= 5.7	p<.0001 OR=4.4	p<.0001 OR= 5.6	p<.0001 OR= 6.1
Age	20mg	150mg	8	p<.0001 OR= 4.8	p<.0001 OR=4.6	p<.0001 OR= 5.4	p<.0001 OR= 5.4
Race	40mg	150mg	4	p<.0001 OR= 7.0	p<.0001 OR=4.8	p<.0001 OR= 6.0	p<.0001 OR= 7.0
Race	40mg	150mg	8	p<.0001 OR= 4.8	p=.0001 OR=3.9	p<.0001 OR= 6.5	p<.0001 OR= 4.7
Race	20mg	150mg	4	p<.0001 OR= 6.3	p<.0001 OR=4.5	p<.0001 OR= 5.8	p<.0001 OR= 6.6
Race	20mg	150mg	8	p<.0001 OR= 4.9	p<.0001 OR=4.4	p<.0001 OR= 5.1	p<.0001 OR= 5.3

The OR (Odds Ratio) given is the Conditional Exact Maximum Likelihood Estimate.
Wk is the week, 4 weeks midterm, 8 weeks for full term treatment.

Appendix Table 10
Cumulative Persistent Absence of Symptoms in Trial 30001A1-300-US

Day	Placebo	Pantoprazole 10mg QD	Pantoprazole 20mg QD	Pantoprazole 40mg QD	40mg vs. Placebo
1	0/80(0%)	1/170(0%)	2/170(1%)	9/170(5%)	p=.0612
2	0/80(0%)	2/170(1%)	4/170(2%)	17/170(10%)	p=.0019
7	0/80(0%)	11/170(6%)	14/170(8%)	29/170(17%)	p<.0001
14	0/80(0%)	17/170(10%)	26/170(15%)	42/170(25%)	p<.0001
28	6/80(8%)	47/170(28%)	53/170(31%)	84/170(49%)	p<.0001
56	14/80(18%)	84/170(49%)	91/170(54%)	107/170(63%)	p<.0001

sources V1.002 pg. 188, sponsor's Table 14
and reviewer's calculations for 2-tailed Fisher's exact test

Appendix Table 11
Cumulative Persistent Absence of Symptoms in Trial 30001A1-301-US

Day	Nizatidine 150mg BID	Pantoprazole 20mg QD	Pantoprazole 40mg QD	40mg vs. Nizatidine
1	0/80(0%)	6/78(8%)	4/79(5%)	p=.0586
2	0/80(0%)	7/78(9%)	5/79(6%)	p=.0284
7	1/80(1%)	12/78(15%)	9/79(11%)	p=.0092
14	3/80(4%)	18/78(23%)	17/79(22%)	p=.0007
28	10/80(13%)	38/78(49%)	33/79(42%)	p<.0001
56	23/80(29%)	51/78(65%)	48/79(61%)	p=.0001

sources V1.002 pg. 189, sponsor's Table 15
and reviewer's calculations for 2-tailed Fisher's exact test

Appendix Table 12
Cumulative Persistent Absence of Nighttime Heartburn
Clinical Trial 30001A1-300-US

		Pantoprazole			
Day	Placebo	10mg QD	20mg QD	40mg QD	40mg vs. Placebo
1	2/80(3%)	16/170(9%)	22/170(13%)	38/170(22%)	p<.0001
2	3/80(4%)	31/170(12%)	31/170(18%)	47/170(28%)	p<.0001
7	3/80(4%)	46/170(18%)	46/170(27%)	64/170(38%)	p<.0001
14	4/80(5%)	57/170(24%)	57/170(34%)	82/170(48%)	p<.0001
28	18/80(23%)	92/170(43%)	92/170(54%)	115/170(68%)	p<.0001
56	45/80(56%)	129/170(70%)	129/170(76%)	139/170(82%)	p<.0001

source V1.002 pg. 190, sponsor's Table 16
and reviewer's calculations for 2-tailed Fisher's exact test

Appendix Table 13
Cumulative Persistent Absence of Nighttime Heartburn
Clinical Trial 30001A1-301-US

	Nizatidine	Pantoprazole		40mg vs.
Day	150mg BID	20mg QD	40mg QD	Nizatidine
1	6/80(8%)	18/78(23%)	16/79(20%)	p=.0226
2	7/80(9%)	21/78(27%)	17/79(22%)	p=.0280
7	10/80(13%)	27/78(35%)	25/79(32%)	p=.0041
14	12/80(15%)	35/78(45%)	34/79(43%)	p=.0001
28	26/80(33%)	49/78(63%)	49/79(62%)	p=.0002
56	48/80(60%)	64/78(82%)	62/79(78%)	p=.0159

sources V1.002 pg. 190, sponsor's Table 17
and reviewer's calculations for 2-tailed Fisher's exact test

Appendix Table 14
Cumulative Persistent Absence of Daytime Heartburn
Clinical Trial 30001A1-300-US

		Pantoprazole			
Day	Placebo	10mg QD	20mg QD	40mg QD	40mg vs. Placebo
1	0/80(0%)	7/170(4%)	20/170(12%)	26/170(15%)	p<.0001
2	0/80(0%)	9/170(5%)	26/170(15%)	39/170(23%)	p<.0001
7	0/80(0%)	22/170(13%)	41/170(24%)	59/170(35%)	p<.0001
14	0/80(0%)	37/170(22%)	57/170(34%)	71/170(42%)	p<.0001
28	7/80(9%)	72/170(42%)	95/170(56%)	115/170(68%)	p<.0001
56	23/80(29%)	109/170(64%)	129/170(76%)	134/170(79%)	p<.0001

source V1.002 pg. 192, sponsor's Table 18
and reviewer's calculations for 2-tailed Fisher's exact test

Appendix Table 15
Cumulative Persistent Absence of Daytime Heartburn
Clinical Trial 30001A1-301-US

	Nizatidine	Pantoprazole		40mg vs.
Day	150mg BID	20mg QD	40mg QD	Nizatidine
1	6/80(8%)	12/78(15%)	12/79(15%)	p=.1411
2	6/80(8%)	17/78(22%)	17/79(22%)	p=.0163
7	6/80(8%)	23/78(29%)	19/79(24%)	p=.0046
14	7/80(9%)	27/78(35%)	27/79(34%)	p=.0001
28	17/80(21%)	48/78(62%)	44/79(56%)	p<.0001
56	37/80(46%)	61/78(78%)	55/79(70%)	p=.0038

sources V1.002 pg. 192, sponsor's Table 19
and reviewer's calculations for 2-tailed Fisher's exact test

Appendix Table 16
Cumulative Persistent Absence of Acid Regurgitation
Clinical Trial 30001A1-300-US

		Pantoprazole			
Day	Placebo	10mg QD	20mg QD	40mg QD	40mg vs. Placebo
1	8/80(10%)	29/170(17%)	37/170(22%)	56/170(33%)	p=.0001
2	12/80(15%)	32/170(19%)	41/170(24%)	61/170(36%)	p=.0006
7	15/80(19%)	49/170(29%)	53/170(31%)	68/170(40%)	p=.0009
14	20/80(25%)	64/170(38%)	67/170(39%)	81/170(48%)	p=.0009
28	31/80(39%)	100/170(59%)	99/170(58%)	116/170(68%)	p<.0001
56	55/80(69%)	136/170(80%)	132/170(78%)	140/170(82%)	p=.0214

source V1.002 pg. 193, sponsor's Table 20
and reviewer's calculations for 2-tailed Fisher's exact test

Appendix Table 17
Cumulative Persistent Absence of Acid Regurgitation
Clinical Trial 30001A1-301-US

	Nizatidine	Pantoprazole		40mg vs.
Day	150mg BID	20mg QD	40mg QD	Nizatidine
1	10/80(13%)	25/78(32%)	26/79(33%)	p=.0024
2	12/80(15%)	29/78(37%)	27/79(34%)	p=.0058
7	12/80(15%)	34/78(44%)	35/79(44%)	p=.0001
14	17/80(21%)	40/78(51%)	41/79(52%)	p=.0001
28	28/80(35%)	54/78(69%)	53/79(67%)	p=.0001
56	57/80(71%)	63/78(81%)	66/79(84%)	p=.0675

sources V1.002 pg. 193, sponsor's Table 21
and reviewer's calculations for 2-tailed Fisher's exact test

Appendix Table 18
Median Gelusil Tablet Usage

Trial	Treatment Group	n	Total Tablets Median(25%- 75%)	Tablets per Day Median(25%-75%)
300US	Placebo	78	126.5(46.0-232.0)	2.30(1.15-4.91)
	Pantoprazole 10mg QD	171	41.0(14.0-112.0)	0.93(0.31-2.89)
	Pantoprazole 20mg QD	167	32.0(10.0- 85.0)	0.88(0.27-2.45)
	Pantoprazole 40mg QD	168	15.0(4.0- 46.5)	0.47(0.12-1.56)
301US	Nizatidine 150mg BID	80	67.5(24.0-142.5)	1.61(0.07-1.88)
	Pantoprazole 20mg QD	79	21.0(3.0- 65.0)	0.47(0.14-1.44)
	Pantoprazole 40mg QD	78	18.5(5.0- 61.0)	0.58(0.42-3.02)

sources V1.002 pg. 204, sponsor's Tables 26-27

2-tailed p-values based on 2-sample Wilcoxon Rank-Sum, normal approximation with continuity correction 0.5

		total	daymean
300US	Pantoprazole 40mg vs. 20mg	p=.1063	p=.0038
	Pantoprazole 20mg vs. 10mg	p=.0004	p=.1535
	Pantoprazole 10mg vs. Pla	p=.0001	p=.0001
	Pantoprazole 40mg vs. Pla	p=.0001	p=.0001

		total	daymean
301US	Pantoprazole 40mg vs. 20mg	p=.8202	p=.6117
	Pantoprazole 20mg vs. Niza	p=.0001	p=.0001
	Pantoprazole 40mg vs. Niza	p=.0001	p=.0001

300US p-values from ERS V1.338 pp. 283, 286, 285, 288, 293, 290, 292, 295

301US p-values from ERS V1.342 pp. 353, 354, 355, 357, 358, 359