TABLE 10

Study GMR-32022 (3001A1-300-US)

Erosive Esophagitis Healing Rates as a Function of Treatment Group and Length of Treatment

I. ITT [-] POPULATION ANALYSIS

WEEK	PL	PANTO (mg)			Therapeutic Gain (%)/[Statistical Significance = p-value]					
		10	20	40	10 mg vs PL	20 mg vs PL	40 mg vs PL	20 mg vs 10 mg	40 mg vs 10 mg	40 mg vs 20 mg
	[n=81]	[n=171]	[n=167]	[n=169]						
4	11 (13.6%)	72 (42.1%)	92 (55.1%)	122 (72.2%)	28.5% [<0.001]	41.5% [<0.001]	58.6% [<0.001]	13.0% [0.022]	30.1% [<0.001]	17.1% [0.001]
	[n=82]	[n=174]	[n=174]	[n=173]						
8	27 (32.9%)	102 (58.6%)	135 (77.6%)	152 (87.9%)	25.7% [<0.001]	44.7% [<0.001]	55.0% [<0.001]	19.0% [<0.001]	29.3% [<0.001]	10.3% [0.015]

II. ITT [+] POPULATION aNALYSIS

	[n=81]	[n=171]	[n=167]	[n=169]						
4	15 (18.5%)	84 (49.1%)	101 (60.5%)	128 (75.7%)	30.6% [<0.001]	42.0% [<0.001]	57.2% [<0.001]	11/4% [0.038]	26.6% [<0.001]	15.2% [0.003]
	[n=82]	[n=174]	[n=174]	[n=173]						
8	31 (37.8%)	114 (65.5%)	144 (82.8%)	158 (91.3%)	27.7% [<0.001]	45.0% [<0.001]	53.5% [<0.001]	16.3% [<0.001]	25.8% [<0.001]	8.5% [0.024]

Reviewer's Table

ii) Healing rates controlling for baseline severity of EE and H. pylori status

When controlling for baseline severity of EE and separately controlling for baseline *H. pylori* status, the results were similar to those discussed above for the unstratified analyses. All comparisons between each dose of PANTO and PL remained significant at the 0.001 level at Weeks 4 and 8 [in all populations]. Comparisons between PANTO 40 mg and PANTO 10 mg also remained significant at the 0.001 level. The p-values for the comparison of PANTO 20 and 10 mg, and for comparison of PANTO 40 and 20 differed slightly from those obtained in the unstratified analyses. However, the healing rates were still found to be significantly greater for pantoprazole 40 mg than for the 20-mg dose and significantly greater for pantoprazole 20 mg than the 10 mg dose at weeks 4 and 8 [for all populations].

iii) Healing rates in relation to initial severity of EE (Table 11)

As previously noted (Table 8), the proportion of patients who at randomization had EE of grade 3 or more was comparable in the 4 treatment groups (between 34% and 39%). Similarly comparable was the proportion of patients who at randomization had EE of grade 2 (between 62% and 66%). The treatment groups were compared with regards to response within each severity category. As shown in Table 11, in the ITT [-] population analyses, despite the smaller sample sizes in the subgroups, therapeutic gains and statistically significant differences seen for each of the two severity groups were, all in all, similar to those observed in the combined population.

In patients with grade 2 EE at entry after 4 weeks of treatment, each of the dose levels of PANTO (10, 20 and 40 mg) were significantly more effective than PL in the healing of EE lesions. A dose response relationship was seen and the therapeutic gains (over PL) were 33.8%, 47.4% and 62% for the 10, 20 and 40 mg PANTO, respectively. Also, the 20 and the 40 mg of PANTO were superior to the lowest dose (10 mg) with a corresponding therapeutic gain of 13.6% and 28.2%. In addition, the 40 mg PANTO dose was superior to the 20 mg dose with a therapeutic gain of 14.6%.

Similar conclusions can be drawn when considering healing rates at 8 weeks in those patients who had grade 2 EE at randomization. Each of the dose levels of PANTO were significantly more effective than PL in the healing of EE lesions, with therapeutic gains of 23%, 36% and 42% for the 10, 20 and 40 mg PANTO, in a dose-response relationship. The 20 and 40 mg PANTO doses were also superior to the lowest dose (10 mg), with therapeutic gains of 13% and 19%, respectively. However, in this patient population (ITT [-] patients who had grade 2 EE at randomization) the 40 mg dose showed only a 6% therapeutic gain over the 20 mg and this difference was not statistically significant.

TABLE 11

Study GMR-32022 (3001A1-300-US)

Erosive Esophagitis Healing Rates, as a Function of Treatment Group, Length of Treatment and Initial Severity of EE

I. PATIENTS WITH INITIAL SEVERITY OF GRADE 2 EE

WEEK	PL	PANTO (mg)			Therapeutic Gain (%)/[Statistical Significance = p-value]					
		10	20	40	10 mg vs PL	20 mg vs PL	40 mg vs PL	20 mg vs 10 mg	40 mg vs 10 mg	40 mg vs 20 mg
	[n=53]	[n=112]	[n=104]	[n=110]						
4	10 (18.9%)	59 (52.7%)	69 (66.3%)	89 (80.9%)	33.8% [<0.001]	47.4% [<0.001]	**62.0% [<0.001]**	13.6% [0.052]	28.2% [<0.001]	14.6% [0.019]
	[n=54]	[n=114]	[n=108]	[n=113]						
8	25 (46.3%)	79 (69.3%)	89 (82.4%)	100 (88.5%)	23.0% [<0.006]	36.1% [<0.001]	**42.2% [<0.001]**	13.1% [0.028]	19.2% [<0.001]	6.1% [N.S.]

II. PATIENTS WITH INITIAL SEVERITY OF GRADE ≥3 EE

	[n=28]	[n=59]	[n=62]	[n=59]						
4	1 (3.6%)	13 (22.0%)	22 (35.5%)	33 (55.95)	18.4% [0.031]	31.9% [0.001]	**52.3% [<0.001]**	13.5% [N.S.]	33.9% [<0.001]	20.4% [0.029]
	[n=28]	[n=60]	[n=65]	[n=173]						
8	2 (7.1%)	23 (38.3%)	45 (69.2%)	52 (86.7%)	31.2% [<0.002]	62.1% [<0.001]	**79.6% [<0.001]**	30.9% [<0.001]	40.4% [<0.001]	17.5% [0.031]

Reviewer's Table

We now turn our attention to healing rates in those patients with initial severity of grade ≥3 EE. At 4 weeks, all three PANTO treatment groups were significantly more effective than PL in the healing of EE lesions, with dose-related therapeutic gains of 18.4%, 31.9% and 52.3%, respectively. At this time, while the 40 mg PANTO was superior to the 10 mg (therapeutic gain = 34%), the 20 mg dose was not (despite a therapeutic gain of 13.5%). The 40 mg dose was also statistically significantly better than the 20 mg dose (therapeutic gain = 17.5%).

The highest therapeutic gains on this subgroup (EE grade ≥3 at randomization, healing rates at 8 weeks) were seen with the 40 mg PANTO: 80% when compared to PL, 45% when compared to the 10 mg and 18% when compared to the 20 mg dose (lower panel of Table 11). Although the 20 mg dose was also shown to be superior to PL (therapeutic gain of 62%) and to the 10 mg dose (therapeutic gain of 31%), this dose was less effective than the 40 mg dose (therapeutic gain = 18%). Of interest, after 8 weeks of treatment, all therapeutic gains whether comparisons to PL or to the lowest dose of the drug (10 mg) or whether comparison of the 40 vs the 20 mg PANTO, were higher (in the case of the 40 mg considerably higher) among those patients who had EE grade ≥3 at randomization than among those who, at entry, had grade 2 esophagitis (please compare 8 weeks response in upper vs lower panel in Table 11).

iv) Healing rates by investigational site (Table 12)

Listed in the upper panel of Table 12 are the healing rates at 4 and 8 weeks for the 40 mg PANTO dose and PL at the 11 sites that enrolled the majority of patients [see VIII. 10. a) above]. No specific center appears to drive the results. In statistical analyses, the results of which are displayed in the lower panel of Table 12, sites with small patient totals were dropped if there were no patients in one of the Tx groups being compared or all patients in each group had the same response (i.e. all healed or all not healed). In Table 12, the number of sites in which each comparison was based is given in parenthesis (31 to 39 sites, depending upon the comparison). The results were consistent with those based on the pooled analysis that were not stratified by study site.

TABLE 12
Study GMR-32022 (3001A1-300-US)

EE Healing Rates by Investigational Site

I. Response with PL and 40 mg PANTO at 4 and 8 Weeks in Those 11 Centers that Enrolled >20 Patients Each

Site 300-	Week 4		Week 8	
	PL	PANTO 40 mg	PL	PANTO 40 mg
N5	1/4 (25%)	5/8 (63%)	2/4 (50%)	6/8 (75%)
O8	1/4 (25%)	7/8 (88%)	3/4 (75%)	8/8 (100%)
P0	0/4 (0%)	5/8 (63%)	0/4 (0%)	7/8 (88%)
M4	0/4 (0%)	4/6 (67%)	1/4 (25%)	6/7 (86%)
N7	0/4 (0%)	4/7 (57%)	0/4 (0%)	5/7 (71%)
M8	1/4 (25%)	5/8 (63%)	2/4 (50%)	7/8 (88%)
N8	2/3 (67%)	6/8 (75%)	2/3 (67%)	7/8 (88%)
L5	0/3 (0%)	6/7 (56%)	0/3 (0%)	7/7 (100%)
M1	0/3 (0%)	5/6 (83%)	1/3 (33%)	6/6 (100%)
L2	1/3 (33%)	3/6 (50%)	1/3 (33%)	5/6 (83%)
N2	0/3 (0%)	3/5 (60%)	0/3 (0%)	4/6 (67%)

II. p-values for Pairwise Comparisons (CMH tests) Based on the Number of Specified Sites [in ( )]

Pairwise Comparison	p-Value	(Sites)	p-Value	(Sites)
40 mg vs PL	<0.001	(33)	<0.001	(34)
20 mg vs PL	<0.001	(34)	<0.001	(35)
10 mg vs PL	<0.001	(36)	<0.001	(34)
40 mg vs 10 mg	<0.001	(39)	<0.001	(36)
20 mg vs 10 mg	0.021	(38)	<0.001	(37)
40 mg vs 20- mg	0.001	(35)	0.015	(31)

NOTE: The sponsor's statistical analyses by site also provided a test of the homogeneity of results across study sites. None of these test of homogeneity yielded a test statistic that was significant at the 0.05 level. The only p-value less than 0.10 was seen in the comparison of 10 mg and 20 mg at week 8 (p=0.064). Review of the data showed the healing rate was greater for 20 mg than 10 mg at the majority of sites, but there were nearly as many sites where the response was the same for the two doses or the response was better for 10 mg than for 20 mg.

h) Results of Secondary Efficacy Assessments

Effects on symptoms were investigated by use of daily diary cards. Two types of analyses were performed: relief of any symptom and relief of each symptom (daytime heartburn, nighttime heartburn, regurgitation and dysphagia) separately. The time points at which persistent absence of symptoms[4] was evaluated were Days 1 through 7 and Weeks 2 through 9 (Day 63).

i) Overall absence of GERD symptoms

The sponsor used the life-table approach used to produce survival-type curves for each Tx group representing the time to persistent absence of symptoms. The median time[5] to persistent absence of symptoms was:

Treatment Group	Median Time (days)
PL	65
PANTO 10 mg	54
PANTO 20 mg	49
PANTO 40 mg	28

Statistical comparison of the curves (not shown in this review) showed significant differences between each dose of PANTO and PL indicating persistent absence of symptoms was achieved more quickly with all doses of PANTO than with PL. There were statistically significant differences between the 40-mg dose of PANTO and the 10-mg and 20-mg doses indicating persistent absence of symptoms was attained more quickly with the 40-mg dose. There was no significant difference between the 10-mg and 20-mg doses of PANTO. The life-table approach compared the groups in an overall manner. Persistent absence of symptoms was also analyzed at individual time points over the course of the study.

Summary results are depicted in Table 13 where the sign > signifies that the Tx group being compared was statistically significant different to the group following the > sign. The percentages displayed in this Table represent the proportion of patients with persistent absence of ANY SYMPTOM. All three PANTO doses significantly surpassed PL in attaining persistent absence of symptoms over the course of the trial. Significantly more patients treated with 40 mg of PANTO obtained persistent absence of symptoms than with PL from the second study day through day 63. Greater percentages of patients treated with 20 mg of PANTO than with PL had persistent absence of symptoms from day 5 through day 63. Greater percentages of patients treated with 10 mg of PANTO than with PL had persistent absence of symptoms from study day 6 through day 63.

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[4] Patients were considered as having persistent absence of symptoms on the first day that no symptoms were reported on that day or any subsequent day.

[5] The number of days at which 50% of the patients in the group had obtained a persistent lack of symptoms.

Table 13 shows that the 40-mg dose of PANTO produced persistent absence of symptoms in significantly greater percentages of patients than the 20-mg dose of pantoprazole from the second day through day 49 and in greater percentages of patients than the 10-mg dose from day 1 through day 56. There were no significant differences between the PANTO 10 and 20 mg dose groups in percentages of patients with persistent absence of symptoms at any time.

TABLE 13
Study GMR-32922 (3001A1-300-US)

Cumulative Proportion (%) of Patients[a] With Persistent Absence of Any Symptom

		PANTO (mg)							
Day	PL [n=80]	10 [n=170]		20 [n=170]		40 [n=170]			
1	0	<1%		1%		5%		>10	
2	0	1%		2%		10%	>PL	>10	>20
3	0	4%		4%		11%	>PL	>10	>20
4	0	4%		5%		14%	>PL	>10	>20
5	0	5%		6%	>PL	15%	>PL	>10	>20
6	0	6%	>PL	7%	>PL	15%	>PL	>10	>20
7	0	6%	>PL	8%	>PL	17%	>PL	>10	>20
14	0	10%	>PL	15%	>PL	25%	>PL	>10	>20
21	1%	15%	>PL	20%	>PL	31%	>PL	>10	>20
28	8%	28%	>PL	31%	>PL	49%	>PL	>10	>20
35	10%	34%	>PL	38%	>PL	55%	>PL	>10	>20
42	11%	35%	>PL	40%	>PL	58%	>PL	>10	>20
49	13%	38%	>PL	44%	>PL	59%	>PL	>10	>20
56	18%	49%	>PL	54%	>PL	63%	>PL	>10	
63	23%	55%	>PL	59%	>PL	65%	>PL		

a) Proportion of patients providing symptom data per Tx group
Statistically significant differences between Tx groups are indicated by the sign >.

ii) Absence of daytime heartburn (Table 14)

Each of the three PANTO dose groups had greater percentages of patients with persistent absence than did the PL group when daytime heartburn data were analyzed. The differences were significant for all three doses at all time points except for the comparison between the PANTO 10 mg and PL groups at days 1 and 2. The PANTO 40 mg dose group had significantly greater percentage of patients with persistent absence of daytime heartburn than did the 10 mg dose group at all times. The same was true for the PANTO 20 mg dose group compared with the 10-mg dose group except that at day 21 no significant difference was evident. The 40-mg PANTO dose had greater percentages of patients with persistent absence of daytime heartburn than the pantoprazole 20 mg dose group at 5 of the 15 points of observation (Days 7, 28, 35, 42, and 49).

TABLE 14
Study GMR-32022 (3001A1-300-US)

Cumulative Proportion (%) of Patients With Persistent Absence of Daytime Heartburn

		PANTO (mg)									
	PL	10		20			40				
Day	[n=80]	[n=170]		[n=170]			[n=170]				
1	0	4%		12%	>PL	>10	15%	>PL	>10		
2	0	5%		15%	>PL	>10	23%	>PL	>10		
3	0	9%	>PL	18%	>PL	>10	26%	>PL	>10		
4	0	9%	>PL	20%	>PL	>10	29%	>PL	>10		
5	0	11%	>PL	22%	>PL	>10	29%	>PL	>10		
6	0	11%	>PL	22%	>PL	>10	32%	>PL	>10		
7	0	13%	>PL	24%	>PL	>10	35%	>PL	>10	>20	
14	0	22%	>PL	34%	>PL	>10	42%	>PL	>10		
21	6	33%	>PL	42%	>PL		48%	>PL	>10		
28	9	42%	>PL	56%	>PL	>10	68%	>PL	>10	>20	
35	11	49%	>PL	61%	>PL	>10	72%	>PL	>10	>20	
42	14	50%	>PL	61%	>PL	>10	74%	>PL	>10	>20	
49	19	54%	>PL	66%	>PL	>10	76%	>PL	>10	>20	
56	29	64%	>PL	76%	>PL	>10	79%	>PL	>10		
63	36	68%	>PL	80%	>PL	>10	83%	>PL	>10		

iii) Absence of nighttime heartburn (Table 15)

Persistent absence of nighttime heartburn was significantly greater at most time points with all three doses of PANTO than with PL. Significantly greater percentages of patients treated with 10 mg of PANTO than with PL experienced persistent absence of

symptoms starting at the second day and lasting from that time to the end of the trial. Both the 20 and 40 mg PANTO groups had significantly greater percentages of patients with persistent absence than the PL group at **all observation times**. The 40 mg pantoprazole group had significantly greater percentages of patients with persistent absence than the 20-mg group in an inconsistent fashion: at Tx days 1, 3, 4, and 7, and every 7 days thereafter through day 49. There was no difference between the groups in persistent absence at days 2, 5, 6, 56 or 63. Significant differences in the percentage of patients with persistent absence were found from day 1 through day 56 between the 40 mg and 10 mg groups.

TABLE 15
Study GMR-32022 (3001A1-300-US)

Cumulative Proportion (%) of Patients With Persistent Absence of Nighttime Heartburn

		PANTO (mg)								
Day	PL [n=80]	10 [n=170]		20 [n=170]			40 [n=170]			
1	3%	9%		13%	>PL		22%	>PL	>10	>20
2	4%	12%	>PL	18%	>PL		28%	>PL	>10	
3	4%	13%	>PL	21%	>PL		32%	>PL	>10	>20
4	4%	15%	>PL	23%	>PL		34%	>PL	>10	>20
5	4%	16%	>PL	26%	>PL	>10	35%	>PL	>10	
6	4%	17%	>PL	26%	>PL	>10	36%	>PL	>10	
7	4%	18%	>PL	27%	>PL	>10	38%	>PL	>10	>20
14	5%	24%	>PL	34%	>PL		48%	>PL	>10	>20
21	10%	31%	>PL	42%	>PL	>10	56%	>PL	>10	>20
28	23%	43%	>PL	54%	>PL		68%	>PL	>10	>20
35	26%	50%	>PL	62%	>PL	>10	73%	>PL	>10	>20
42	31%	54%	>PL	64%	>PL		75%	>PL	>10	>20
49	39%	59%	>PL	68%	>PL		78%	>PL	>10	>20
56	56%	70%	>PL	76%	>PL		82%	>PL	>10	
63	63%	76%	>PL	80%	>PL		84%	>PL		

iv) Absence of Regurgitation (Table 16)

Overall comparisons between all four Tx groups showed differences at days 1 through 29 but these results are probably driven by the effect of the PANTO 40 mg dose. This dose group had significantly greater percentages of patients with persistent absence of regurgitation than did the PL group at all times through day 49. The 20 mg pantoprazole group had significantly greater percentages with persistent absence of regurgitation than the PL group on Day 1, and then from Day 6 through Day 29. The PANTO 10 mg group had significantly greater percentages with persistent absence of regurgitation than did the

PL group only from Day 21 through Day 49. The 40-mg dose was significantly more effective than the 20-mg dose only from Day 1 through Day 5 and the 10-mg dose only from Day 1 through Day 7. There were no significant differences in proportions of patients with persistent absence of regurgitation at any time between the 10 and 20 mg PANTO dose groups.

TABLE 16
Study GMR-32022 (3001A1-300-US)

Cumulative Proportion (%) of Patients with Persistent Absence of Regurgitation

		PANTO (mg)							
Day	PL [n=80]	10 [n=170]		20 [n=170]		40 [n=170]			
1	10%	17%		22%	>PL	33%	>PL	>10	>20
2	15%	19%		24%		36%	>PL	>10	>20
3	16%	21%		27%		38%	>PL	>10	>20
4	18%	25%		28%		39%	>PL	>10	>20
5	18%	28%		28%		40%	>PL	>10	>20
6	18%	28%		31%	>PL	40%	>PL	>10	
7	19%	29%		31%	>PL	40%	>PL	>10	
14	25%	38%		39%	>PL	48%	>PL		
21	30%	45%	>PL	50%	>PL	55%	>PL		
28	39%	59%	>PL	58%	>PL	68%	>PL		
35	44%	66%	>PL	68%	>PL	75%	>PL		
42	48%	69%	>PL	71%	>PL	77%	>PL		
49	56%	74%	>PL	75%	>PL	78%	>PL		
56	69%	80%		78%		82%			
63	74%	82%		81%		84%			

v) Absence of dysphagia (Table 17)

Dysphagia was reported less frequently than the other individual symptoms. At Day 1, ca. half of the patients in each Tx group had achieved a condition of persistent absence of dysphagia which suggests that many patients were not experiencing dysphagia at the start of therapy. The proportion of patients with persistent absence of dysphagia gradually increased during the course of the study and was approximately 90% for all treatment groups at day 63. The only significant difference among all four groups was found at Day 35 when dysphagia was absent in a larger percentage of patients treated with 40 mg of PANTO than PL patients, a finding likely occurring by chance and without clinical importance.

TABLE 17
Study GMR-32022 (3001A1-300-US)

Cumulative Proportion (%) of Patients With Persistent Absence of Dysphagia

Day	PL [n=80]	PANTO (mg) 10 [n=170]	20 [n=170]	40 [n=170]	
1	55%	51%	47%	55%	
2	58%	56%	51%	59%	
3	60%	59%	54%	60%	
4	60%	60%	57%	62%	
5	60%	61%	58%	64%	
6	60%	62%	59%	66%	
7	60%	62%	60%	66%	
14	64%	68%	65%	75%	
21	66%	72%	69%	79%	
28	70%	76%	78%	84%	
35	74%	80%	81%	88%	>PL
42	76%	84%	84%	89%	
49	80%	88%	86%	89%	
56	86%	91%	88%	90%	
63	90%	92%	89%	91%	

vi) Antacid use (Table 18)

Whether the results were expressed as total tablet usage over the course of the trial or the average number of tablets per day, each of the three doses of PANTO were significantly different from PL: the patients treated with PANTO used less Gelusil than the PL patients (Table 9.4.3A). The PANTO 40 mg group used less Gelusil than the PANTO 10 mg and 20 mg groups and differences between the 40-mg dose and the two lower doses were statistically significant. There was no statistically significant difference between the 10-mg and 20-mg doses of PANTO.

TABLE 18
Study GMR-32022 (3001A1-300-US)

Medium Gelusil Tablet Usage

Tx Group	n	Total Tablets Median (25P-75P)[a]	Tablets per Day Median (25P-75P)
PL	78	126.5 (46.0 – 232.0)	2.30 (1.15 – 4.91)
PANTO 20 mg	171	41.0 (14.0 – 112.0)	0.93 (0.31 – 2.89)
PANTO 20 mg	167	32.0 (10.0 – 85.0)	0.88 (0.27 – 2.45)
PANTO 40 mg	168	15.0 (4.0 – 46.5)	0.47 (0.12 – 1.56)

a) 25th through 75th percentiles

i) Results of Safety Evaluations

i) Extent of exposure (Table 19)

Depicted in this Table is the cumulative duration of exposure of [redacted] in study –300 US. For any PANTO dose, the starting number of patients (521 = 100%) was the same during the first week but starts to decrease steady from the second week onwards, with a very marked decrease after Week 4 (second endoscopy which may have shown healing of EE and a reason to W/D patient from the trial) so that, by Week 8 there remained only 178 patients (34%).

TABLE 19
Study GMR-32022 (3001A1-300-US)

Cumulative[a] Duration of Exposure to Pantoprazole

Tx Group/Dose	Cumulative Duration of Exposure (Weeks)									
	≥1 day	≥ 1	≥ 2	≥3	≥4	≥5	≥6	≥7	≥8	≥9
Any PANTO	521 (100)[b]	521 (100)	518 (99)	498 (96)	482 (93)	222 (43)	194 (37)	188 (36)	178 (34)	61 (12)
PANTO 10 mg	174 (100)	174 (100)	172 (99)	164 (94)	158 (91)	94 (54)	85 (49)	84 (48)	77 (44)	25 (14)
PANTO 20 mg	174 (100)	174 (100)	173 (99)	166 (95)	158 (91)	75 (43)	68 (39)	65 (37)	64 (37)	23 (13)
PANTO 40 mg	173 (100)	173 (100)	173 (100)	168 (97)	166 (96)	53 (31)	41 (24)	39 (23)	37 (21)	13 (8)
PL	82 (100)[c]	82 (100)	81 (99)	78 (95)	77 (94)	66 (80)	64 (78)	60 (73)	58 (71)	18 (12)

This Table corresponds to sponsor's Table 10.1A., with minor modifications.
a) Cumulative exposure is the number of patients who took the drug for at least the time interval defined.
b) Number in parenthesis is percentage of patients exposed to pantoprazole.
c) Number in parenthesis is percentage of patients treated with placebo.

ii) Deaths/other serious and potentially serious AEs

- Pt. 300P2-0002 was an 80-y old F with a Hx of arteriosclerotic heart disease and diabetes. She received PANTO 10 mg, had finished the acute study [redacted] and completed her second visit

- 6 days before she had a cardiac arrest and died after a brief hospitalization due to MI. The death was considered unrelated to test medication.

- 31 patients were identified as having serious events during the trial, with the following distribution:

	PL	5 (6.1%)
PANTO	10 mg	12 (6.9%)
	20 mg	7 (4.0%)
	40 mg	7 (4.0%)

These 31 SAEs were listed in sponsor's Table 10.3.1.2.A., without causal relationship of the event.

- 17 had events that were determined by the investigator to be unrelated to test med.

- 14 were coded as possibly related; 4 of these were experienced by patients on PL; the other 10 showed no pattern in AE experiences.

iii) AEs leading to discontinuation

In their Table 10.3.1.3A the sponsor tabulated these data by treatment group and body system of AEs that were cited as being the cause for premature withdrawal from the trial. There were no trends or statistically significant differences among or between Tx groups.

iv) Adverse events

- 2 or more AEs were reported by the following proportion of patients in the 4 arms of the trial. Also listed is the proportion of patients for which the drug relationship was not specified or that the investigator considered possibly, probably or definitely drug related.

			Drug Relationship Not Specified
	PL	48 (59%)	16 (20%)
PANTO	10 mg	108 (62%)	40 (23%)
	20 mg	101 (58%)	37 (21%)
	40 mg	90 (52%)	31 (18%)

- Overall, Treatment-Emergent Adverse Events (TEAE) were distributed as follows:

	PL	43 (52%)
	10 mg	99 (57%)
	20 mg	94 (54%)
	40 mg	83 (48%)

- The most common TEAE[6] are listed in Table 20, grouped by body system. There was no statistically significant difference in the incidence of TEAE among the 3 PANTO dose groups. As seen in this Table, headache was the most common TEAE (by %) for all Tx groups; it is also noted that diarrhea was reported with the same frequency (8%) as headache in only the 10-mg PANTO Tx group. Patients in the PL group reported rates of headache and diarrhea that were similar to those in the PANTO Tx groups.

TABLE 20
Study GMR-32022 (3001A1-300-US)

Commonly Reported (≥3%) TEAE: Number (%) of Patients

Body System Adverse Event	PL [n=82]	PANTO (mg) 10 [n=174]	20 [n=174]	40 [n=173]	p-Value[a]
Any AE (1 or More)	43 (52)	99 (57)	94 (54)	83 (48)	N.S.
Body As a Whole	21 (26)	45 (26)	45 (26)	34 (20)	N.S.
Abdominal Pain	5 (6)	11 (6)	5 (3)	7 (4)	N.S.
Asthenia	0	3 (2)	7 (4)	1 (<1)	N.S.
Headache	**10 (12)**	**14 (8)**	**21 (12)**	**12 (7)**	N.S.
Digestive System	18 (22)	48 (28)	39 (22)	33 (19)	N.S.
Diarrhea	**4 (5)**	**14 (8)**	**8 (5)**	**11 (6)**	N.S.
Eructation	1 (1)	6 (3)	5 (3)	2 (1)	N.S.
Flatulence	2 (2)	5 (3)	4 (2)	7 (4)	N.S.
Nausea	7 (9)	8 (5)	7 (-4)	9 (5)	N.S.
Vomiting	2 (2)	5 (3)	8 (5)	6 (3)	N.S.
Respiratory System	8 (10)	21 (12)	13 (7)	17 (10)	N.S.
Pharyngitis	5 (6)	12 (7)	7 (4)	7 (4)	N.S.

This Table corresponds to sponsor's Table 10.2.2.1A., with major modifications.
a) Fisher's Exact Test

v) Changes in laboratory parameters

- The numbers of treated patients with potentially clinically important test results were summarized in sponsor's Table 10.4.1.1A. The data were grouped by laboratory assessment and patient identification number. These data revealed no clinically important differences between study groups.

- In general, the changes in laboratory parameters reflected sporadic or transient increases or decreases that returned to baseline values during the course of therapy.

- Nonetheless, 2 patients had increases in transaminase values of clinical importance (see Table 21) and one of these was withdrawn from the trial. However, it is worth mentioning that sporadic elevation in transaminases, without concomitant increases

[6] Reported by at least 3% of patients in any group.

in bilirubin or other enzymes, have been reported with other PPIs (i.e. omeprazole) and also with H_2-receptor antagonists (i.e. cimetidine, ranitidine, nizatidine).

TABLE 21
Study GMR 32022 (3001A1-300-US)

Patients With Clinically Important Elevations in Serum Transaminases

Treatment Patient Number	Age (y)	Sex	Days of Therapy	Lab Test Value	Comments
PANTO 10 mg 300K6-0007[a]	49	F	7	198 U/L (SGOT); 160 U/L (SGPT)	Patient had elevated liver enzymes present at pre-study visit a protocol violation, SGOT and SGPT values were >5 times the ULNR of 34 U/L at the start of the trial. SGOT and SGPT values remained high during the study.
PANTO 40 mg 300O9-0008	40	M	31	132 U/L (SGOT); 227 U/L (SGPT)	Increased SGOT and SGPT values were reported >3x the UL (34 U/L) at both pre-study and week 4 of therapy. Patient was able to complete the trial.

This Table corresponds to sponsor's Table 10.4.1.2.1.1A and 1B., with minor modifications.
a) Patient's primary reason for D/C was protocol violation (elevated SGOT and SGPT at baseline), on therapy clinically important test results were considered a secondary reason for D/C

vi) Changes in vital signs and routine P.E.

There were no clinically important or statistically significant changes in vital sign or P.E. measurements in these study groups.

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vii) Changes in serum gastrin levels

There seemed to be a correlation between serum gastrin levels and *H. pylori* status. Baseline serum gastrin levels were similar across Tx groups for both positive and negative *H. pylori* at baseline and treated with 40 mg of PANTO. Patients negative for *H. pylori* at baseline had lower serum gastrin levels in all Tx groups compared to those patients positive for *H. pylori* at baseline. Serum gastrin levels reflected a dose response effect regardless of *H. pylori* status at baseline, but was most apparent in patients positive for *H. pylori*. Not unexpectedly, the 40 mg PANTO group had **significantly greater** serum gastrin values than the 10 mg or 20 mg group at 4 or 8 weeks. Both the 40 mg and 20 mg groups had significantly greater values than the placebo group. A listing of patients with serum gastrin levels greater than 150 pg/ml was provided in sponsor's Supportive Table 17. Below is a comparison of the median serum gastrin levels as a function of time and *H. pylori* status in the 4 Tx groups.

Study GMR-32022 (3001A1-300-US)

Median Serum Gastrin Levels (pg/ml)

Tx Group	H. pylori Status [+]			H. pylori Status [-]		
	Median [n] Basekube	Median [n] 4-week	Median [n] 8-week	Median [n] Baseline	Median [n] 4-week	Median [n] 8-week
PL	54 [17]	51 [12]	52 [13]	47 [63]	46 [40]	45.5 [42]
PANTO 10 mg	56 [30]	59 [19]	64.5 [16]	48.5 [140]	53 [94]	52 [61]
PANTO 20 mg	54 [30]	86.5 [24]	75 [7]	45.5 [138]	52 [100]	52.5 [54]
PANTO 40 mg	61.5 [42]	126.5 [30]	284 [5]	49 [126]	66 [93]	64.5 [30]

viii) EKG changes

- 43 patients were identified as having potentially clinically important changes in EKG results (see distribution below). The medical monitor concluded that none of these patients had EKG changes of clinical importance.

Overall interpretation

	No. (%) of Pts. with EKG Changes of Potential Clinical Importance
PL	9 (10.9%)
PANTO 10 mg	11 (6.3%)
20 mg	13 (7.4%)
40 mg	10 (5.7%)

a) Pt. 3005-0002 was noted to have premature ventricular contractions (PVC) on the EKG at the 8 week visit. No PVC were found either on the original baseline evaluation or on subsequent EKGs. An extensive cardiac work-up was done including a stress test without positive findings. The investigator determined that this patient's EKG coincidentally captured PVCs that were not of clinical significance. No other EKG findings were of clinical importance.

ix) Gastric inflammation changes

The sponsor summarized this information in their Tables 10.6.2A and 10.6.2B. Changes in inflammation were stratified by *H. pylori* status and biopsy zone (midbody, prepyloric). Higher inflammation scores were observed in patients positive for *H. pylori* regardless of Tx group. The majority of patients with an overall increase in inflammation scores of two or more were positive for *H. pylori* and occurred within the midbody zone. The majority of patients with an overall decrease in inflammation scores of two or more were also *H. pylori* positive but occurred within the prepyloric zones. For the PANTO Tx groups, the majority of inflammation changes that were increases occurred within the midbody zone. Decreases in inflammation scores for the PANTO 20 mg and 40 mg

groups occurred primarily within the prepyloric zone; inflammation changes generally increased within this zone for the 10 mg group. An approximately equal number of changes in inflammation scores in either direction were seen in the prepyloric zone for the PL group.

11. Sponsor's Conclusions

"The results of this study indicate that pantoprazole in doses of 10, 20 or 40 mg was significantly more effective than placebo in healing lesions and treating secondary symptoms associated with erosive esophagitis. Differences from placebo in healing were seen by 4 weeks and differences in the persistent absence of symptoms were seen in the first week. The 40-mg dose of pantoprazole provided the greatest healing rates at 4 and 8 weeks and was more effective than the 10-mg and 20-mg doses in the healing of the severe grade 3 or 4 EE lesions. All treatments were well tolerated. No clinically significant drug-related differences between the treatments were seen in the safety analysis."

12. Reviewer's Additional Comments

Clinical trial under Protocol –300-US is one of two critical multicenter studies submitted by the sponsor of this NDA in support of the approval of pantoprazole for the "short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease (GERD)". This U.S. trial consisted of four parallel arms: three fixed doses of PANTO (10, 20 or 40 mg once-a-day) and placebo, an adequate negative control. The primary hypothesis was that 4 to 8 weeks of PANTO 40 or 20 mg per day will be more effective than placebo in the healing of erosive esophagitis and in the rapid relief of associated daytime and nighttime heartburn. Although a well-designed protocol was used, it is not a good idea to withdraw from the trial patients whose esophagitis have healed at week 4 because in many instances, the esophageal lesions may recur (and this could have been seen by week 8 endoscopy), even when the active treatment is continued.

The trial was apparently well-executed. Adherence to the inclusion-exclusion criteria precluded randomization of patients with diseases, conditions or concomitant treatments that may confound the results. The randomization process accomplished four well-balanced groups with respect to the pre-stipulated number of patients per arm, demographics, severity (Hetzel-Dent scale) of reflux esophagitis, *Helicobacter Pylori* status (80% of the enrolled patients were *H. pylori* negative) and the most commonly used concomitant medications. Analyses of results included evaluations in ITT, MITT and VFE population. Of these three, the reviewer's comments emphasize results of analyses in the ITT [-] population because this was the most conservative statistical approach: patients who had missing endoscopic data were expressed as patients not being healed. [However, results of analyses in the ITT [+], MITT and VFE populations allowed the same conclusions on efficacy as those arrived at using the ITT [-] population.] Not unexpectedly, a larger proportion of placebo-treated patients did not complete the trial primarily because of lack of therapeutic response (sometimes identified by the investigator as an adverse event). Although the sponsor's relative day ranges for

endoscopy were wider than desirable, the reviewer does not believe that narrower time intervals for endoscopy would have a significant impact on results.

Examining results of the ITT [-] population, in study –300-US, unequivocal response, as judged by hard endoscopic criteria, was already shown after 4 weeks of treatment: the healing rates in the PANTO groups (42.1 to 42.2%) were all significantly higher than the placebo group (a low 13.6%). A dose-response relationship was seen, with therapeutic gains [over placebo] of 28.5%, 41.5% and 58.6%, respectively, for the 10, 20 and 40 mg PANTO, all highly statistically significant ($p<0.001$). In addition, both the 20 and 40 mg of PANTO were superior to the lower PANTO dose (10 mg), with therapeutic gains of 13% ($p=0.022$) and 30.1% ($p<0.001$), respectively. Furthermore, the sponsor's proposed dose of PANTO (40 mg QD) was significantly more effective than 20 mg QD (therapeutic gain = 17.1%, $p=0.001$). These responses at 4 weeks did not significantly increase by an additional 4 weeks of treatment. At this time of comparison (healing rates at 8 weeks) the therapeutic gains for comparisons of —— doses vs placebo, the 20 and 40 mg vs the 10 mg dose and the 40 vs 20 mg PANTO were similar to those therapeutic gains shown at 4 weeks; again, all of these comparisons yielded highly statistically significant differences (p-value <0.001 for all comparisons except 40 vs 20 mg for which the p-value was 0.015). These results after 4 and 8 weeks of treatment in the ITT [-] population were confirmed in results of analyses in the ITT [+] population. In the main, analyses in the MITT and those in the VFE populations confirmed those in the ITT analysis.

The results of erosive esophagitis healing rates by initial severity of the esophageal lesions were predictable. The placebo response in patients whose initial esophagitis was grade 2 (mild) was higher (19% at 4 weeks, 46% at 8 weeks) than those patients whose initial esophagitis was grade ≥3 (moderate to severe) (4% at 4 weeks; 7% at 8 weeks). Another way of expressing this concept is saying that more severe lesions are more difficult and take longer to heal. In comparison to placebo, the same dose of PANTO (whether 10, 20 or 40 mg QD) heals grade 2 esophageal lesions faster and more effectively than grade ≥3 lesions. For instance, with 40 mg QD, in patients whose esophagitis was grade 2 at baseline, the therapeutic gain of 62% at 4 weeks decreased to 42% at 8 weeks; conversely, in those whose esophagitis at baseline was grade ≥3, the therapeutic gain (over placebo) was 52% at 4 weeks and this increased considerably to 80% by 8 weeks. Since there were not too many patients with grade 4 (severe) esophagitis included in the ≥3 pooled category, the reviewer concludes that PANTO 40 mg **provided the greatest healing rates for both mild and moderate esophagitis.** Experience with esophagitis of the severe type is too limited and no firm conclusions can be drawn at this time.

With respect to EE symptoms, the four groups were comparable at baseline. The PANTO 40 mg dose was significantly more efficacious – beginning in the first week of therapy – than placebo in the persistent absence of any symptom, daytime heartburn, nighttime heartburn and regurgitation associated with erosive esophagitis. The other two doses of PANTO (10 and 20 mg) showed inconsistent results on symptoms. Although all three PANTO groups used significantly fewer Gelusil tablets than those in the placebo

group, this antacid usage was significantly less in the 40 mg group than the two lower doses of PANTO.

In study –300-US, results of safety evaluations demonstrated that doses of 10, 20 or 40 mg of PANTO, given once-a-day, were generally safe and well-tolerated. One death occurred in a 10 mg PANTO group patient that had a medical history of heart disease. The patient had completed the acute phase of the trial and continued into the maintenance phase. The cause of death was cardiac arrest, the event was considered unrelated to treatment with PANTO. There were no differences between the PANTO groups and placebo in the incidence of serious adverse events or discontinuantions because of adverse events. Most AEs were minor and resolved with discontinuation of treatment. The side effect profile of PANTO appears to be as that of other PPIs: the most frequent adverse event for all treatment groups was headache. The rate of occurrence of treatment-emergent adverse events was similar among all treatment groups. Other than the expected significant increases in serum gastrin (because PANTO is a PPI and all PPIs induce hypergastrinemia), there were no clinically significant changes observed in laboratory screens.

IX. STUDY GMR-32023 (3001A1-301-US)

"Comparison of the Clinical Efficacy and Safety of Pantoprazole 20 mg or 40 mg Once Daily and Nizatidine 150 mg Twice Daily in Patients With Symptomatic Erosive Esophagitis"

Date of Report: 20 May 1998

1. Hypothesis:

Four to eight weeks of PANTO 40 mg once daily will be more effective than the approved dose of NIZ (150 mg b.i.d.) in the healing of EE and in the rapid relief of associated daytime and nighttime heartburn.

Study Dates 12 February 1997 (Date of First Enrollment) to 02 December 1997 (Date of Last Completion)

2. Objective:

The aim of this study was to evaluate the safety and efficacy of pantoprazole 20 mg or 40 mg taken once daily in the morning compared with that of nizatidine 150 mg taken twice daily in patients with reflux symptoms and endoscopically proven erosive esophagitis at grade 2 or greater according to the Hetzel-Dent Scale.

[NOTE: Only some aspects of the study protocol will be highlighted in this review because the design and execution and most aspects of this trial were as described in detail above for study GMR-32022 (3001A1-300-US).]

3. Study Population

This was adequate for this type of study. The inclusion criteria and reasons for exclusion of patients from the trial were the same as in study –300-US (Table 4). In the main, the study population consisted of patients with symptomatic, endoscopically-proven erosive esophagitis.

4. Overall Study Design and Schedule of Evaluations

From the review of the evidence, this was a multicenter, randomized, double-blind, 3-arm, parallel trial that investigated the efficacy of ——— (20 or 40 mg once-a-day) in comparison to a NIZ control (150 mg b.i.d.) in patients with symptomatic EE. The allocation of Tx was 1:1:1 with respect to the number of patients that received test medication (NIZ or PANTO). It was expected to enroll 195 at ca. 20 investigative centers; 150 patients were expected to complete the trial (50 patients per arm). Instead, 244 patients were enrolled and 243 took test medication (one patient was dispensed test medication but never took any doses). Of the 243 patients that were analyzed, 215 completed the trial. The two doses of PANTO were chosen to examine dose-related differences in healing rates. The NIZ control group is appropriate because this drug is approved for this indication and is being used at the recommended dose and regimen. The NIZ group provides a good control for the conduct and methodology of the trial and a standard against which to compare the safety and efficacy of ———

The study was executed in a fashion similar to that for study –300-US. The checklist for clinical and laboratory measurements detailed in Table 5 was the same and, as in that trial, there were 5 visits (at Weeks 0, 2, 4, 6 and 8) and 3 endoscopies: at initial visit (study Week 0), visit 2 (study Week 4) and visit 4 (study Week 8). Final efficacy and safety determinations were to be made for all patients with endoscopic evidence of healing to grade 1 or less at study Week 4 or 8 or on the last day the patient took a full dose of test medication.

5. Clinical Supplies/Randomization/Selection of Timing of Dose for Each Patient/Blinding

- The source for PANTO and its PL was Byk Gulden, from Germany while NIZ and its PL (HGC #0) was provided by Wyeth-Ayerst, Montreal, Canada. The dosage strengths and formulation and batch numbers of test medications were as follows:

Study GMR-32023 (3001A1-301-US)

TEST MEDICATION BATCH NUMBERS

Test Medication	Strength (units)	Formulation No.	Batch No.	Source
Pantoprazole 20 mg	20 mg tablets	0930664C	296060	Byk Gulden Germany
Pantoprazole 40 mg	40 mg tablets	0930665C	296440	Byk Gulden Germany
Placebo for pantoprazole	Yellow film-coated tablet	0930666C	296540	Byk Gulden Germany
Nizatidine 150 mg	150 mg capsule	0930612D	9620560	Wyeth-Ayerst Montreal, Canada
Placebo HCG #0	Opaque grey capsule	093020D	9620052	Wyeth-Ayerst Montreal, Canada

A computerized randomization schedule was provided by the Biostatistics Section of W-AR. A program based on the SAS® PLAN procedure was used to generate the randomization table. The study was designed so that an equal number of patients would be assigned to each Tx group. Block randomization was done and each study site was provided with a block (or blocks) of random numbers. Each block consisted of six numbers, two for each Tx group. This was to ensure that after every sixth patient randomized at a site, the desired balance of two patients in each Tx group would be achieved. At each site, randomization numbers were to be assigned consecutively in ascending numerical order at the time the patient was given his or her first package of test medication. Sponsor's Appendix A provided a listing by patient of their patient number, their randomization number, the Tx group to which they were assigned, and the date on which test medication was dispensed. If the randomization process was carried out as planned, then as the randomization numbers increase, the date of study drug dispensation should increase chronologically. A review of the listing showed this was true in all but a few instances. With the exception of two patients, all patients took the study medication to which they were randomized.

Pt. 30197-0007, who was randomly assigned to the NIZ group correctly took NIZ for the first two weeks of the study. At the week 2 visit, however, the patient was mistakenly given a package of PANTO 20 mg tablets which he took during his remaining two weeks in the study. Pt.301A7-0005 was randomly assigned to the PANTO 40 mg group but she was hospitalized for acute respiratory distress prior to taking any test medication.

Adequate procedures were used to institute and preserve the blinding of the trial: a double-dummy technique. The test medication(s) at matching PL(s) were of identical appearance. The patients enrolled in the trial were randomly assigned to receive one of the following treatments.

1) One pantoprazole 20-mg enteric-coated tablet, taken once daily in the morning
One nizatidine placebo capsule, taken in the morning and in the evening.

2) One pantoprazole 40-mg enteric-coated tablet, taken once daily in the morning.
One nizatidine placebo capsule taken in the morning and in the evening.

3) One pantoprazole placebo tablet, taken once daily in the morning. One nizatidine 150 mg capsule, taken later in the morning and in the evening.

Patients received Gelusil antacid tablets to be taken as needed for symptomatic relief after 5 or more min. of retrosternal pain, acid regurgitation, or dysphagia, but not within 1 h before or after taking test medication. No more than 12 tablets were to be taken in a 24-h period.

PANTO, NIZ, and their matching PLs were packaged and coded by Wyeth-Ayerst Laboratories and were supplied to the investigator as identical-appearing blister packs. At the beginning of the trial and at each follow-up visit, each patient received one box of 100 Gelusil antacid tablets and three blister pack cards of test medication. One blister pack card contained a 17-day supply of either yellow oval PANTO tablets (20 mg or 40 mg) or an identical-appearing PL; and two blister pack cards contained a 17-day supply of double-encapsulated NIZ capsules (150 mg) or an identical-appearing PL. Preprinted labels on the packets of investigational drug[7] and box of Gelusil antacid tablets contained the study number and randomization number.

6. Prior and Concomitant Therapy; Compliance

These were assessed as in study –300-US: the same type of medications were permitted or proscribed during the trial. Percent compliance was calculated from the number of tablets provided and the number returned; antacid usage was accounted for in the same manner. Pts. were considered compliant if they had taken at least 80% of the test medication over the full course of the trial.

7. Evaluation Criteria

These were the same as described in detail for study –300-US.

a) Efficacy

- The primary endpoint for demonstrating efficacy was the resolution of all macroscopic esophageal lesions or ulceration to grade 1 or 0 by the Hetzel-Dent

[7] At the time that the medication was dispensed to the patient, the patient's initials and number, date, and directions for taking the medications were indicated on the label. The medication code for each patient was provided in individual sealed envelopes that were code labeled according to the randomization schedule. In the event of an emergency, the individual patient's envelope could be opened to identify the medication being taken. All envelopes and unused medication were to be returned to W-AR at the end of the trial.

scale, as confirmed by endoscopy. This procedure was to be performed at baseline, at Week 4 (visit 2) and, if necessary, at Week 8 (visit 4).

- The secondary endpoint for demonstrating efficacy was the absence of typical symptoms of reflux esophagitis (daytime and nighttime HB symptoms, regurgitation and dysphagia). In addition, Gelusil use was recorded to determine if the use of antacid tablets differed among the Tx groups.

b) Safety

As in study –300-US, safety assessments were based on reports of AEs, results of routine P.E., EKGs, endoscopy, gastric Bx, and laboratory determinations.

8. Data Quality Assurance

The procedures instituted to ensure that the data collected were accurate, consistent, complete and reliable were all adequate. The database was properly verified through a series of steps and at the end, was of high quality.

9. Statistical Methodology

a) Determination of Sample Size

As mentioned above, the primary objective of this study was to demonstrate a significant ($p \leq 0.05$) difference in healing rates between PANTO and NIZ. Pre-study estimates of the healing rates were 80% for PANTO 20 mg, 90% for PANTO 40 mg and 35% for NIZ. The estimated healing rate with NIZ (35%) is reasonable based on previous data with this drug (see Table 1). The estimated therapeutic gains (over NIZ) were 45% for PANTO 20 mg and 55% for PANTO 40 mg. The sponsor notes that sample size calculations based on rates of 35% and 80% show that, even if conservative assumptions are made about the alpha level for statistical significance, 35 patients per group would be sufficient for 90% power to show a difference between **at least one dose of PANTO** and NIZ. In choosing the final sample size, the need to have patients available for enrollment into a subsequent maintenance study was also taken into consideration. The sample was increased to 65 per group for this reason. This sample size provides only 26% power to detect a difference between the two doses of PANTO at the 0.05 level if the rates are 80% and 90% as hypothesized. In order to have power in the 80 to 90% range with 65 patients per group, the difference in rates would have to be approximately 25% (e.g., 60% versus 85%).

b) Details of Statistical and Analytical Procedures

In an approach similar to that used in study –300-US, there were changes in the statistical analyses originally planned in the protocol. Reproduced below is the sponsor's section on statistical methodology including the changes in planned analyses.

Analyses were performed on three patient populations consisting of intent-to-treat (ITT) patients (divided into 2 subgroups, positive [+][8] and negative [-], modified intent-to-treat patients (MITT) and evaluable or valid-for-efficacy (VFE) patients.

The primary efficacy endpoint variable was the endoscopic resolution of all macroscopic esophageal erosion or ulceration to grade 1 or 0 according to the Hetzel-Dent scale. Endoscopy assessments were to be made at baseline (week 0), visit 2 (week 4), and visit 4 (week 8). The proportions of responders in each of the three Tx groups were compared at the week 4 and 8 endpoints by using Fisher's exact probability test; data from all sites were pooled. The secondary efficacy endpoint was the absence of typical reflux symptoms of daytime heartburn, nighttime heartburn, regurgitation, and dysphagia. The secondary efficacy endpoint of symptom absence was tested for proportional differences in the same manner as the primary efficacy endpoint variable. The total Gelusil tablet usage was divided by the number of days on study to obtain an average number of tablets taken per day. Both total tablets and average tablets per day were analyzed using the Kruskal-Wallis test.

Two additional analyses of healing rates were performed. Healing rates were compared in two subgroup analyses, defined by the severity of erosive esophagitis at baseline and separately by the results of tests for *Helicobacter pylori* (positive or negative) at baseline. For comparisons that used severity at baseline, patients were divided into subgroups according to their Hetzel-Dent score (score of 2 versus score of 3 or 4). Cochran-Mantel-Haenszel analyses were performed, controlling for either baseline severity or *H. pylori* status. Additionally, Fisher's exact test was used for comparisons between treatments within each severity and *H. pylori* subgroup. Comparisons of the incidence of individual adverse events across treatment groups were made by using Fisher's exact probability test.

10. Results

a) Disposition of Patients/Number of Patients by Site

- The disposition of the 244 patients that were **randomized** into the trial can be summarized as follows:

	Study Arm	Disposition		Total
		Withdrawn	Completed	
Total Enrolled [n=244]	NIZ 150 mg b.i.d.	13	69	82
	PANTO 20 mg	6	74	80
	PANTO 40 mg	9	72	82[a]
		28	**215**	**244**

a) Includes Pt. 301A7-0005 who was randomly assigned to the PANTO 40 mg group but took no test med. The Pt. was described in a narrative in sponsor's supportive Table 11.

Definitions of Study Populations Analyzed for Efficacy:
ITT = Received at least one dose of test med. [Also included in the safety analysis.]
MITT = Received at least one dose of test med. + had at least one post-baseline endoscopic assessment.
VFE = All patients from the MITT population who were 80% compliant, had at least one endoscopy at week 4 or beyond, and had no serious protocol violations.

[8] The definitions were the same as per study -300-US. ITT [+] patients were identified as any patients who took test medication, including those who did not complete the study according to the protocol. Any missing healing data for those patients who only had baseline data was expressed as the *patient healed*. ITT [-] patients who had only baseline data were identified similarly to the ITT [+] patients except their missing healing data was expressed as *patient not healed*. MITT patients were defined as those who had at least one postbaseline endoscopic evaluation. Evaluable patients included all patients who satisfied the MITT patients were defined as those who had at least one postbaseline endoscopic evaluation. Evaluable patients included all patients who satisfied the MITT definition and had at least one endoscopy at week 4 or

- Test medication was shipped to the 26 sites listed in Table 22. Four of these sites [Cooper (30184), Miner (301B2), Safdi (301A9) and Smith (30193)] did not enroll any patients. The 22 remaining sites randomized a total of 244 patients.

  - The following 11 centers enrolled 10 or more patients each.

Site	Total n
Kovacs (30199)	36
Winston (30196)	30
Berry (30181)	19
Giannella (30185)	16
Avner (30180)	13
Hee (30187)	13
Riff (301A8)	12
Wilcox (30195)	12
Meier (301A0)	11
Campbell (30183)	10
Gitlin (30186)	10

  - 11 remaining centers enrolled between 3 and 9 patients each.

TABLE 22
GMR-32023 (3001A1-301-US)

Number of Patients Randomized by Investigator

Investigator Name (Number)	NIZ (mg BID)	PANTO (mg QD)		Total
	150	20	40	
Avner (30180)	4	5	4	13
Berry (30181)	6	6	7	19
Blitstein (30182)	1	1	1	3
Campbell (30183)	3	3	4	10
Cooper (30184)	0	0	0	0
DeVault (30197)	2	1	3	6
Giannella (30185)	5	6	5	16
Gitlin (30186)	4	3	3	10
Hee (30187)	4	5	4	13
Johnson (30191)	2	1	2	5
Kornfield (30189)	2	0	1	3
Kovacs (30199)	12	12	12	36
Meier (301A0)	3	4	4	11
Miner (301B2)	0	0	0	0
Movva (301B0)	3	2	2	7
Orchard (30190)	2	3	3	8
Person (301B1)	1	1	1	3
Pruitt (301A7)	3	2	2	7
Riff (301A8)	4	4	4	12
Rodgers (30192)	2	0	0	2
Safdi (301A9)	0	0	0	0
Smith (30193)	0	0	0	0
Snape (30194)	3	3	2	8
Weisman (30179)	2	4	3	9
Wilcox (30195)	4	4	4	12
Winston (30196)	10	10	10	30
TOTAL n	**82**	**80**	**81**	**243[a]**

a) Pt. 301A7-0005 is not included among these 243 because this pt. did not take any test med. after randomization.

b) Reasons for Withdrawal (Table 23)

- 215 patients completed the trial. As shown in this Table, failure to return was the common primary reason for discontinuation. There were numerical but not statistically significant differences among the Tx groups in the proportion of patients who withdrew from the trial.

TABLE 23
Study GMR-32023 (3001A1-301-US)

Number and Proportion (%) of Patients Who Withdrew by Primary Reason

Primary Reason	NIZ 150 mg BID [n=82]	PANTO (mg QD) 20 [n=80]	PANTO (mg QD) 40 [n=82]	p-Value[a]
Any	13 (15.9)	6 (7.5)	9 (11.1)	N.S.
AE[b]	1 (1.2)	0	1 (1.2)	N.S.
Other nonmedical event	0	1 (1.3)	1 (1.2)	N.S.
Protocol violation	2 (2.4)	0	3 (3.7)	N.S.
Failed to return	4 (4.9)	2 (2.5)	3 (3.7)	N.S.
Patient request	3 (3.7)	1 (1.3)	1 (1.2)	N.S.
Unsatisfactory response – efficacy	3[b] (3.7)	2 (2.5)	0	N.S.

This Table corresponds to sponsor's Table 8.1.3A, with major modifications.

a) Pearson's Chi-square test
b) Patient 30187-0005 was withdrawn from the trial because of an AE (increased heartburn); however, the investigator listed unsatisfactory response as the primary reason for withdrawal.

c) Protocol Deviations

This information was presented in sponsor's supportive Table 2 and is summarized below.

- 5 patients had protocol violations that resulted in their premature withdrawal from the study.
  - Pts. 30191-0006, 30195-0021 and 30195-0006 were noncompliant with test medication or study visits.
  - Pt. 30196-0017 had Barrett's esophagitis.
  - Pt. 30197-0007[9] was randomly assigned to the NIZ group but actually received NIZ 150 mg for 2 weeks and PANTO 20 mg for 2 weeks.

[9] This patient completed 4 weeks in the study and was analyzed in the NIZ group. At baseline he was negative for *H. pylori* and his esophageal erosion/ulceration was graded as mild. He was healed at 4 weeks, and the hearling carried forward to 8 weeks. Although he was listed with the patients who D C. Patient 30197-0007 completed 4 weeks on the trial and was healed, thereby fulfilling the criteria for study completion. This patient was erroneously included in the valid-for-efficacy analysis. The conclusions of the VFE analysis are the same whether or not this patient is included.

d) Data Showing Comparability of Treatment Groups at Baseline

1) Demographic and Disease Baseline Characteristics (Table 24)

At baseline, the three treatment groups were similar (to each other) for age, gender, ethnic origin, weight, height, body mass, grade of EE severity [64% of the patients had mild (grade 2) esophagitis, 27% had moderate (grade 3) esophagitis and only 8% had severe (grade 4) esophagitis, *H. pylori* status [83% were H.P. [-] and 17% were H.P. [+] and concomitant medications [98% of the pts. received concomitant meds.].

TABLE 24
Study GMR-32023 (3001A1-301-US)

Data Showing Comparability of Treatment Groups at Baseline:
Pre-Treatment and Concomitant Medications

Characteristic		NIZ (mg QD) 150 [n=82]	PANTO (mg QD) 20 [n=80]	PANTO (mg QD) 40 [n=81]	Total [n=243]	p-Value
I. DEMOGRAPHICS						
Age (y)	Mean	48.9	47.4	49.0	48.4±13.5[a]	N.S.[e]
Age group	18-64	84.1	83.8%	80.2%	201 (82.7%)	
	≥65	15.9	16.3%	19.8%	42 (17.3%)	N.S.[f]
Gender (%)	F	32.9	28.8	29.6	74 (30.5%)	
	M	67.1	71.3	70.4	169 (69.5%)	N.S.[f]
Ethnic Origin (%)	Black	3.7%	7.5%	6.2%	14 (5.8%)	
	Hispanic	3.7%	7.5%	4.9%	13 (5.3%)	
	White	92.7%	85.0%	88.9%	216 (88.9%)	N.S.[f]
Weight (Kg)	Mean	86.1	86.5	86.5	86.3±17.5[b]	N.S.[e]
Height (cm)	Mean	[n=81] 172.0	[n=79] 173.3	173.9	[n=241] 173.1±9.7[c]	N.S.[e]
Body Mass Index [Kg/(cm**0.01)²]	Mean	[n=81] 29.2±4.4	[n=79] 28.8±5.8	28.6±6.2	[n=241] 28.9±5.5[d]	N.S.[e]
II. REFLUX ESOPHAGITIS SEVERITY						
Grade (Hetzel-Dent Scale)	2	69.5%	63.8%	61.7%	158 (65.0%)	
	3	22.0%	28.8%	27.2%	63 (25.9%)	
	4	8.5%	7.5%	11.1%	22 (9.1%)	N.S.[f]
III. H. PYLORI STATUS						
Baseline (*H. pylori* status)	Negative	[n=81] 67 (82.7%)	[n=79] 63 (79.7%)	67 (82.7%)	[n=241] 197 (81.7%)	
	Positive	14 (17.3%)	16 (20.3%)	14 (17.3%)	44 (18.3%)	N.S.[g]
IV. COMMON CONCOMITANT MEDICATIONS (≥20%)						
Any non-study medication		97.5%	98.7%	98.7%	239 (98.3%)	N.S.
Hypnotics and sedatives[a]		73.1%	65.0%	71.6%	170 (69.9%)	N.S.
Opiods[b]		68.2%	56.2%	62.9%	152 (62.5%)	N.S.
Other analgesics and antipyretics		39.0%	33.7%	41.9%	93 (38.2%)	N.S.
Antihemorrhoidals for topical use		20.7%	23.7%	28.3%	59 (24.2%)	N.S.
Antipruritics, incl antihistamines, anesthetics, etc.		17.0%	21.2%	20.9%	48 (19.7%)	N.S.

This Table is a composite of sponsor's Table 8.2.A and 8.3.A. with substantial modifications.
a, b, c and d) ±S.D.
e) Based on one-way ANOVA
f) Based on Fisher's exact test
g) Fisher's exact test

2) Number of Patients in the Three Population Analyses

The number of patients comprising each of the three populations analyzed (ITT, MITT and VFE) for primary efficacy parameters and those analyzed for secondary assessment of efficacy is given in Table 25.

The aim of the study was to randomize 195 with a 1:1:1 ratio of enrollment at cs. 20 investigative centers; 150 of these were expected to be completed.

Instead, the number of patients randomized into the trial (243) exceeded the original goal of the study by 48 patients.

As shown in Table 25, 16 patients included in the ITT analysis were excluded from the MITT; 6 patients from the MITT population group were excluded from the VFE analyses.

TABLE 25
Study GMR-32023 (3001A1-301-US)

Number of Patients Analyzed for Efficacy

Population Subset	NIZ (mg BID)	PANTO (mg QD)		Total
	150	20	40	
I. ANALYSES OF PRIMARY EFFICACY ASSESSMENT				
Intent-to-treat analysis	82	80	81	243
Modified intent-to-treat analysis	74	75	78	227
Valid for efficacy analysis	72	73	76	221[a]
II. PATIENTS ANALYSES FOR SECONDARY ASSESSMENTS				
Any EE symptom	80	78	79	237
Gelusil tablet usage	80	79	78	237

This Table is a composite of sponsor's Tables 9.1A and 9.1B, with major modifications.

a) The distribution of the 22 patients that were excluded from the VFE analysis was:

NIZ	PANTO (mg)	
	20	40
10	7	5

There were no statistically significant differences among the Tx groups in the proportion of patients excluded from VFE analysis [p=0.410].

e) Endoscopy Relative Ranges

For analyses purposes, the endoscopy data were grouped into the same time intervals specified for study –300-US.

It is worth reiterating that every patient who received test medication was included in the ITT population. If there was no post-baseline endoscopy for a given patient, both weeks 4 and 8 were assigned values. They were assigned a value of healed for the ITT [–] analysis and a value of not-healed for the ITT [-] analysis. For those patients who did have post-baseline data, the following rules were applied: if the patient had weeks 4 and 8 data, the data was left "as-is". If the patient's last endoscopy was at week 2, that