2. Study 95-300

Following approval of lansoprazole for short-term healing of active duodenal ulcers (4 weeks) and esophageal erosions (up to 8 weeks), and for indefinite treatment of Zollinger-Ellison syndrome, on 10 May 1995, a protocol was developed in September 1995 for investigation of lansoprazole effects in relief of reflux symptoms in patients with non-erosive GERD (Volume 14, pages 217-257). The rationale was based on the demonstrated effectiveness of lansoprazole 15 and 30 mg/day in enhancing healing rates of erosions, as well as the observed secondary observations of symptom relief. The new study was designed to "look for differences in symptomatic relief of patients with non-erosive GERD given lansoprazole 15 or 30 mg or placebo" (see page 223).

"A Study to Evaluate the Effects of Lansoprazole 15 mg and 30 mg QD versus Placebo on Non-Erosive Gastroesophageal Reflux Disease"

This study was planned to recruit 200 "complete and acceptable" patients at 20 study sites, 80 patients on each lansoprazole arm, and 40 on placebo. The study size was based on results of Study M87-092 in patients with non-erosive GERD, particularly on the mean percentage of days with pain from diary data, assuming the placebo group would show the lansoprazole 15 mg/day group and the lansoprazole 30 mg/day group Using those assumptions and normal approximations, the sponsor estimated that 80 patients per lansoprazole arm and 40 in the placebo arm, would yield more than 90% power to detect differences of between the lansoprazole treatments and placebo, and about 72% power to detect an 11% difference in favor of the lansoprazole 30 mg/day dose, and the two-tailed p=0.05 level.

The primary outcome measure of the study was to be daily patient diary recording of day and night heartburn severity on a scale of 0=none, 1=mild, 2=moderate, and 3=severe. Average daily severity and percentage of days with each symptom over 8 weeks was to be compared by Wilcoxon two-sample testing. The primary analysis was intended for "evaluable" patients who had data "acceptable" for efficacy evaluation, as determined by the project team before unmasking of the randomization assignments to treatment group. Also to be assessed were ITT analyses, and pairwise comparisons of investigator assessments of day and night heartburn as reported to them by the patients at 4 and 8-week visits.

Patient selection was to be based upon screening endoscopy using a modified rating scale* that showed non-erosive, grade 0 or 1 esophagitis (no erosions or ulcerations) and at least moderate GERD symptoms of day or night heartburn on more than half the days during the previous 6 months and at least half the days during the pre-study screening period of up to 10 days. Patients were to be at least 18 years of age, be able to understand and willing to sign informed consent to cooperate with study requirements. Patients were NOT to have Barrett's esophageal changes, current or past stricture requiring dilatation, history of other esophageal disease or esophagogastroduodenal surgical procedures, history of gastrointestinal bleeding, esophageal varices, other major systemic disease, Zollinger-Ellison syndrome, pancreatobiliary disease, malignancies other than basal cell skin

carcinoma, alcohol or drug abuse within a year, need for anticoagulants/digoxin/theophylline, steroids more than 10 mg of prednisone, analgesics beyond doses of up to 325 mg of aspirin within a month, anticholinergics or H2-blocking or prokinetic agents (cisapride, metoclopramide) or proton-pump inhibitors within 12 weeks, receipt of blood products within 12 weeks, abnormal screening laboratory tests (normal ranges at SciCor), nor have child-bearing potential.

*The endoscopic rating scale for esophagitis was changed for that used for M87-092 to a scale developed for TAP Holdings by Drs. Donald Castell, Sidney Cohen, and Malcolm Robinson (see Volume 14, pages 230-1):

Grade	Description
0	Normal- appearing esophageal mucosa by endoscopy
1	Mucosal edema, hyperemia, or friability
2	Erosions of <10% of the area of the distal 5 cm of esophagus
3	Erosions of 10-50% of distal esophagus or ulcer 3-5 mm diameter
4	Erosions of >50% of distal esophagus or ulcer >5 mm diameter

Further, erosions were defined as superficial breaks in the esophageal mucosa less than 3 mm in width, with or without exudate, but not red spots or streaks without mucosal breaks. Red streaks are linear erythematous areas considered hyperemia and indicative of grade 1 esophagitis if nothing worse is apparent. The distal 5 cm of esophagus is that proximal to the gastroesophageal junction, or in Barrett's esophagus proximal to the squamocolumnar junction. Ulcers are discrete lesions with appreciable depth and more than 3 mm in diameter.

The protocol further defines the symptoms that are to be recorded and assessed at biweekly intervals (see pages 231-2, and the Case Report Form (CRF) on pages 277, 282, 286, 291). Heartburn is defined as "a sensation of burning in the esophagus behind the lower part of the sternum." The former term of "upper abdominal burning" that was used in M87-092 is no longer used. Severity of symptoms is again defined, as it was in M87-092, according to a four-point scale:

0	None	No symptom felt or perceived
1	Mild	Symptom does not last long and is easily tolerated
2	Moderate	Symptom causes discomfort and interrupts usual activities
3	Severe	Symptom causes great interference with activities and may be incapacitating

Diaries were to be given to patients for daily recording of the severity of day and of night heartburn, using to 0-3 scale, number of Gelusil tablets taken, the dates, and boxes for each day to indicate if the diary was not completed that day or if the number of Gelusil tablets taken is unknown (see pages 283, 287-8 and 292-3).

Eligible patients were to be randomized to take one capsule of study medication daily each morning of the 8-week study, before breakfast. Study medication will be supplied as opaque gray capsules containing 30, 15, or 0 mg of lansoprazole. Gelusil® tablets (Parke-Davis) containing 0.4 g of the hydroxides of magnesium and aluminum, with acid-neutralizing capacity of 9.7 meq/tablet. After the initial screening visit for explanations, history and physical examination, routine laboratory tests plus serology for Helicobacter pylori antibodies, diary and Gelusil dispensing, patient will return for a baseline visit and endoscopy, updated history, collection of the screening diaries and dispensing the first 4-week diaries and study medication plus more Gelusil, and return for a final visit at 8 weeks for completion of the study. No follow-up endoscopies were to be done as part of the study.

As carried out, Study M95-300 enrolled 214 patients with symptomatic, non-erosive GERD at 18 study sites. Of the 214, 44 were randomized to placebo, 82 to lansoprazole 15, and 88 to lansoprazole 30 mg/day. The investigators for this study included:

Investigator	Patients	Lanso 15	Lanso 30	Placebo
Charles F. Barish, M.D. (8417), Raleigh NC	6M/9F	3M/3F	3M/3F	0M/3F
Donald R. Campbell, M.D. (3508), Kansas City MO	1M/3F	1M/0F	0M/2F	0M/1F
Charles Colip, M.D. (8923), Portland OR	5M/9F	1M/4F	3M/3F	1M/2F
Robert Fisher, M.D. (4444), Philadelphia PA	3M/1F	1M/0F	1M/1F	1M/0F
Christopher Forsmark, M.D. (9999), Gainesville FL	5M/15F	2M/6F	1M/7F	2M/2F
Kevin Geraci, M.D. (5862), Cleveland OH	3M/5F	1M/2F	1M/2F	1M/1F
Basil Hirschowitz, M.D. (4448), Birmingham AL	5M/12F	2M/5F	1M/5F	2M/2F
James V. Jones, M.D. (2940), Ruston LA	7M/8F	4M/2F	3M/3F	0M/3F
David Kogut, M.D. (4257), Statesville NC	7M/7F	2M/4F	4M/2F	1M/1F
Thomas Kovacs, M.D. (4445), Los Angeles CA	10M/4F	3M/2F	4M/2F	3M/0F
Richard Krause, M.D. (9747), Chattanooga TN	9M/10F	3M/4F	4M/4F	2M/2F
David Peura, M.D. (8384), Charlottesville VA	3M/9F	2M/2F	0M/6F	1M/1F
Joel E. Richter, M.D. (4337), Cleveland OH	1M/0F	1M/0F		
Malcolm Robinson, M.D. (3509), Oklahoma City OK	10M/12F	5M/4F	4M/4F	1M/4F
Seymour M. Sabesin, M.D. (3510), Chicago IL	13M/4F	6M/0F	5M/2F	2M/2F
Nayan R. Shah, M.D. (8937), Leonardstown MD	1M/6F	0M/2F	1M/3F	0M/1F
Stephen Sontag, M.D. (3511), Hines IL	7M/0F	3M/0F	2M/0F	2M/0F
Thomas Zarchy, M.D. (11117), Hawthorn CA	2M/2F	0M/2F	2M/0F	
TOTALS	98M/116F	40M/42F	39M/49F	19M/25F

Patient Accounting:

Enrolled, randomized into the study	214	82	88	44
Not eligible to participate*	-3		-2	-1
ITT group for 4-week symptom analyses	211	82	86	43
No diary data completed**	-2	-2		
ITT' group for diary data analyses	209	80	86	43

* Sontag's patient #2181 (52Mc; placebo) and Hirschowitz's patient #2079 (61Fc; lanso 30) had evidence of Barrett's esophageal changes, and Hirschowitz's patient #2136 (45Fb; lanso 30) had grade 2 erosions (see Appendix E.10.B, Part 2, pages 453 and 467, Volume 17). These were considered exclusions and the data collected over 8 weeks were not analyzed for symptom response at the 4-week intervals.
** Colip's patient #2208 (29Fc; lanso 15) and Jones' patient #2046 (20Mc; lanso 15) did not record diary data of day and night heartburn or Gelusil use. They were treated for 38 and 46 days, respectively (see Appendix E.1, pages 004 and 008, Volume 17).

The sponsor's principal analyses were carried out and reported on an "evaluable" group of 185 patients: 39 on placebo, 69 on lansoprazole 15, and 77 on lansoprazole 30 mg/day treatment. Reasons for excluding the 29 patients from their efficacy analyses were listed as follows in their report (Volume 14, page 053):

number	*reasons for exclusion from efficacy analyses*
22	Violation of admission criteria
9	chronic prestudy use of NSAIDs
5	history of esophageal stricture
2*	evidence of Barrett's esophageal changes*
1*	erosions of esophageal mucosa*
1	previous gastrointestinal surgical procedure
1	less than half of the prestudy heartburn was moderate or severe
1	chronic prestudy use of H2-antagonist
1	no pretreatment period
1	confounding disease
4	No evaluable symptom assessment after start of treatment
3	Less than 14 days of diary data completed during treatment period
3	Chronic use of NSAIDs during treatment period
2**	No diary data recorded**
2	Inability/unwillingness to follow study instructions
2	Took study drug for less than 14 days
1	Less than 14 days of evaluable diary data
29	Total patients "non-evaluable, some for more than one reason"

Patients are identified who were excluded from the sponsor's efficacy analyses in Table 7.1.1, page 98-100, Volume 14, along with the reasons given, and their randomized group assignments are shown in Table 7.1.2 on pages 101-102. Premature exit from the study occurred in 20 patients, 7 from the placebo group of 44 (15.9%), 5 from the lansoprazole 15 mg/day group of 82 (6.1%), and 8 from the lansoprazole 30 mg/day group of 88 (9.1%). Reasons for these early terminations of the study were listed by the sponsor in the report, page 056, Volume 14, and further explained in Table 7.2.4, page 108 of Volume 14. The reasons listed as "other" were in both cases failure of the patients to return for a visit [Sontag's patient #2053 (55Mc; placebo, treated 60 days) and Colip's patient # 2208 (29Fc; lanso 15, treated 38 days)]. "Therapeutic failure" was not further explained or defined in 6 patients on placebo after 14 to 31 days, and 4 on lanso 30 after 27 to 36 days.

Reason for termination of study	placebo	lanso 15	lanso 30
therapeutic failure	6	0	4
adverse event	0	4	4
other	1	1	0
total	7	5	8

The adverse events that caused the 4 patients on lansoprazole 15 mg/day to withdraw prematurely included abdominal pain at 4 days (Robinson's patient #2165; 47Fc), urticaria at 23 days (Kovacs' patient #2269; 28Fc), diarrhea/weakness/bladder retention at 29 days (Sabesin's patient # 2218; 45Mc), and abdominal pain with melena at 46 days (Jones' patient #2046; 20Mc). The other 4 patients on lansoprazole 30 mg/day, the adverse events were pancreatitis at 2 days (Fisher's patient #2119; 43Fb), abdominal pain at 27 days (Jones' patient #2190, 48Fc), amnesia/slurred speech at 50 days (Sabesin's patient #2020; 45Mc), and cardiospasm at 51 days (Jones' patient #2049; 21Fc).

The randomized groups in the "evaluable" subset were similar in all of the demographic characteristics of age, race, gender, height and weight adjusted for gender, smoking, alcohol use, caffeine consumption. However, significantly (p=0.011) more in the placebo group tested positive for Hp serology : 18/39 (48.6%) on placebo, versus 18/69 (26.5%) in those randomized to lansoprazole 15 mg/day and 18/77 (24.3%) in those randomized to lansoprazole 30 mg/day (see Table 7.4.1, pages 109-110, Volume 14). When the 209 patients of the ITT' group were so considered, again the only significant (p=0.031) difference between the randomized groups was that more in the placebo group tested positive by serology for Hp (see page 111).

Efficacy Analyses

Diary Data

The principal efficacy analyses were based on the daily diary recording by patients of their severity of day heartburn and night heartburn, and use of Gelusil tablets. The mean heartburn severity for both 185 evaluable patients and for 209 ITT' patients were calculated, as well as the percentages of days in the first 4 weeks and over the whole 8 weeks of the study. Results for both evaluable and ITT' analyses gave almost identical results, as may be seen from comparing the tabulated calculations reproduced below, and taken from the sponsor's tables 8.1.1. to 8.1.4 on pages 135-142 of Volume 14.

The diary data were to be recorded daily by participating patients, and turned in at visits. Prestudy diary covering up to 21 days, and two diary cards with spaces for up to 35 days, were provided to patients. There were to enter dates, Gelusil tablets taken that day, and the severity code (0=none, 1=mild, 2=moderate, 3=severe) for the day and night heartburn every day. A sample blank diarysheet is reproduced on the following page, to illustrate what data were asked for from the patients.

TAP HOLDINGS INC. FORM 14 Page 19

ABT-006, LANSOPRAZOLE

THERAPY WITH LANSOPRAZOLE FOR NON-EROSIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD)

STUDY NO. M95-300

Patient Number: _____

Patient Initials: _____

4 WEEK 4 DIARY

Date of Visit: _____ (mm/dd/yy)

DIARY SUMMARY
(To include the period from Baseline Day 1 to Week 4. Please include the Study Day 2 date (day following Baseline Day 1 visit) to the Week 4 visit date on this diary summary.)

If patient did not bring diary, instruct patient to return diary at the next visit and complete this form at that time.

DIARY_DETAILS | VISIT = 2

DIARY DAY		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
DATE (mm/dd/yy)																						
CHECK BOX IF NOT COMPLETED	X	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
CHECK BOX IF NO OR UNSURE IF TAKEN UNKNOWN	X	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
NUMBER OF PILLS TAKEN (Enter 0 if none)																						
SEVERITY OF DAY HEARTBURN																						
Check One Box	0 None																					
	1 Mild																					
	2 Moderate																					
	3 Severe																					
SEVERITY OF NIGHT HEARTBURN																						
Check One Box	0 None																					
	1 Mild																					
	2 Moderate																					
	3 Severe																					

WHITE - TAP Original YELLOW - TAP Work Copy PINK - Investigator Copy GOLDENROD - Hardard

Summary of Diary Data, 184 Evaluable Patients, First Four Weeks
mean ± standard deviation

			p-value	
			vs placebo	*vs lanso 15*
Day Heartburn				
average pain severity/day				
placebo	38	1.29 ± 0.57		
lanso 15	69	0.46 ± 0.56	**<0.001**	
lanso 30	77	0.60 ± 0.70	**<0.001**	0.202
mean percent of days with heartburn				
placebo	38	78.4 ± 26.4		
lanso 15	69	30.0 ± 32.7	**<0.001**	
lanso 30	77	36.4 ± 35.5	**<0.001**	0.197
Night Heartburn				
average pain severity/night				
placebo	38	0.96 ± 0.76		
lanso 15	69	0.34 ±0 .54	**<0.001**	
lanso 30	77	0.64 ± 0.75	**<0.001**	**0.009**
mean percent of nights with heartburn				
placebo	38	57.1 ± 37.6		
lanso 15	69	21.7 ± 30.4	**<0.001**	
lanso 30	77	35.9 ± 35.5	<0.001	**0.008**
Gelusil Use				
average number of tablets used/day				
placebo	38	2.76 ± 2.00		
lanso 15	69	0.83 ± 1.26	**<0.001**	
lanso 30	77	1.13 ± 1.57	**<0.001**	0.162
mean percent of days tablets taken				
placebo	38	67.4 ± 32.0		
lanso 15	69	25.2 ± 29.1	**<0.001**	
lanso 30	77	34.4 ± 33.2	**<0.001**	0.098

The above data and calculations were taken from the sponsor's Table 8.1.1, on pages 135-136 of Volume 14. Patients recorded daily in their diaries the severity of day and night heartburn, and Gelusil tablets used, which were surrendered at visits at 4 and 8 weeks on treatment. The severity code used was 0 for none, 1 for mild, 2 for moderate, and 3 for severe heartburn.

Both lansoprazole 15 mg/day and 30 mg/day were very significantly better than placebo in reducing mean heartburn severity over the first 4 weeks of treatment, and lansoprazole 15 mg/day was significantly better than lansoprazole 30 mg/day for treatment of night heartburn. For Gelusil use and day heartburn severity, the lower dose of lansoprazole was somewhat better than the higher dose, but not significantly so.

Summary of Diary Data, 185 Evaluable Patients, Whole Eight Weeks

mean ± standard deviation

			p-value	
Day Heartburn			*vs placebo*	*vs lanso 15*
average pain severity/day				
placebo	39	1.24 ± 0.59		
lanso 15	69	0.39 ± 0.51	**<0.001**	
lanso 30	77	0.54 ± 0.71	**<0.001**	0.387
mean percent of days with heartburn				
placebo	39	76.5 ± 27.3		
lanso 15	69	26.1 ± 29.6	**<0.001**	
lanso 30	77	32.1 ± 35.6	**<0.001**	0.296
Night Heartburn				
average pain severity/night				
placebo	39	0.93 ± 0.76		
lanso 15	69	0.28 ±0 .47	**<0.001**	
lanso 30	77	0.58 ± 0.76	**0.003**	**0.013**
mean percent of nights with heartbum				
placebo	39	55.3 ± 36.9		
lanso 15	69	18.1 ± 26.6	**<0.001**	
lanso 30	77	32.0 ± 35.2	**0.002**	**0.011**
Gelusil Use				
average number of tablets used/day				
placebo	39	2.55 ± 1.94		
lanso 15	69	0.70 ± 1.04	**<0.001**	
lanso 30	77	1.03 ± 1.51	**<0.001**	0.350
mean percent of days tablets taken				
placebo	39	64.2 ± 31.5		
lanso 15	69	22.7 ± 26.3	**<0.001**	
lanso 30	77	30.7 ± 33.1	**<0.001**	0.217

The above data and calculations were taken from the sponsor's Table 8.1.3, on pages 139-140 of Volume 14. Results for the whole period of 8 weeks are almost exactly the same as for the first 4 weeks, and show the marked superiority of both lansoprazole regimens over placebo for reduced the severity and frequency of day and night heartburn, and the significant superiority of the lower dose of lansoprazole for night heartburn amelioration.

Comment: This superiority of lansoprazole 15 mg/day over lansoprazole 30 mg/day for night heartburn treatment, and its at least parity for daytime heartburn, was unexpected by the sponsor. It had been estimated when study size was calculated that lansoprazole 30 mg/day would be better than 15 mg/day, perhaps even significantly so (see protocol Section 9 on Statistical Procedures, pages 242-243, Volume 14).

Figure 8.1.1.a
Mean Severity of Day Heartburn By Study Day
For Evaluable Patients
(3=Severe, 2=Moderate, 1=Mild, 0=None)

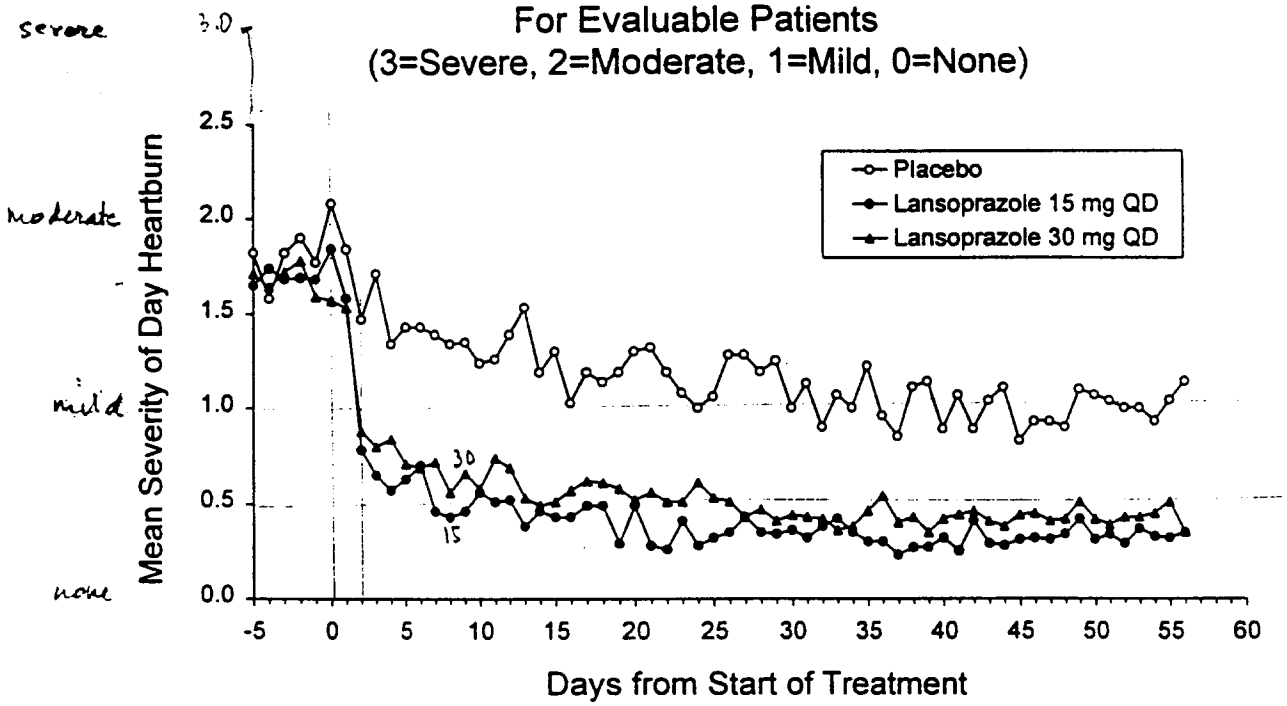
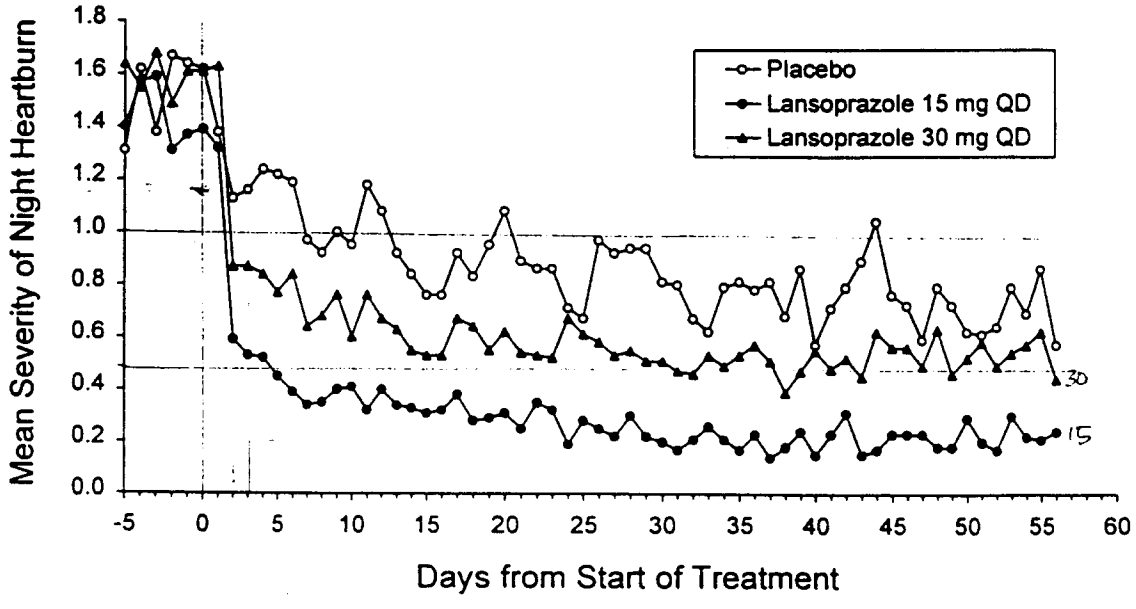


Figure 8.1.1.b
Mean Severity of Night Heartburn By Study Day
For Evaluable Patients
(3=Severe, 2=Moderate, 1=Mild, 0=None)



Summary of Diary Data, 209 ITT' Patients, First Four Weeks
mean ± standard deviation

			p-value	
Day Heartburn				
average pain severity/day			*vs placebo*	*vs lanso 15*
placebo	43	1.28 ± 0.56		
lanso 15	80	0.49 ± 0.57	**<0.001**	
lanso 30	86	0.63 ± 0.70	**<0.001**	0.179
mean percent of days with heartburn				
placebo	43	77.9 ± 25.6		
lanso 15	80	32.7 ± 34.3	**<0.001**	
lanso 30	86	38.4 ± 36.5	**<0.001**	0.193
Night Heartburn				
average pain severity/night				
placebo	43	1.05 ± 0.76		
lanso 15	80	0.38 ±0 .54	**<0.001**	
lanso 30	86	0.65 ± 0.76	**<0.001**	**0.020**
mean percent of nights with heartburn				
placebo	43	60.9 ± 37.1		
lanso 15	80	25.0 ± 32.5	**<0.001**	
lanso 30	86	36.7 ± 36.1	**<0.001**	**0.026**
Gelusil Use				
average number of tablets used/day				
placebo	43	2.63 ± 1.92		
lanso 15	80	0.93 ± 1.33	**<0.001**	
lanso 30	86	1.20 ± 1.62	**<0.001**	0.208
mean percent of days tablets taken				
placebo	43	67.4 ± 30.9		
lanso 15	80	28.3 ± 31.3	**<0.001**	
lanso 30	86	35.7 ± 34.1	**<0.001**	0.135

The above data and calculations were taken from the sponsor's Table 8.1.2, on pages 137-138 of Volume 14.

Comment: The results should be compared to those of the "evaluable" subset of 184 patients above. It is evident that almost exactly the same results are obtained by either analysis, with very minor differences in p-values, and that there was little if anything to be gained from the toil and trouble of selecting out "evaluable" patients for the purpose of optimizing the apparent results.

Summary of Diary Data, 209 ITT' Patients, Whole Eight Weeks
mean ± standard deviation

			p-value	
Day Heartburn				
average pain severity/day			*vs placebo*	*vs lanso 15*
placebo	43	1.23 ± 0.58		
lanso 15	80	0.43 ± 0.53	**<0.001**	
lanso 30	86	0.56 ± 0.71	**<0.001**	0.336
mean percent of days with heartburn				
placebo	43	76.3 ± 27.1		
lanso 15	80	29.0 ± 32.0	**<0.001**	
lanso 30	86	33.9 ± 36.0	**<0.001**	0.281
Night Heartburn				
average pain severity/night				
placebo	43	0.99 ± 0.76		
lanso 15	80	0.32 ±0 .48	**<0.001**	
lanso 30	86	0.59 ± 0.76	**0.003**	**0.027**
mean percent of nights with heartburn				
placebo	43	58.5 ± 37.1		
lanso 15	80	21.5 ± 29.2	**<0.001**	
lanso 30	86	32.6 ± 35.4	**0.002**	**0.027**
Gelusil Use				
average number of tablets used/day				
placebo	43	2.40 ± 1.85		
lanso 15	80	0.81 ± 1.13	**<0.001**	
lanso 30	86	1.09 ± 1.56	**<0.001**	0.395
mean percent of days tablets taken				
placebo	43	63.3 ± 31.8		
lanso 15	80	26.0 ± 29.2	**<0.001**	
lanso 30	86	31.8 ± 33.6	**<0.001**	0.279

The above data and calculations were taken from the sponsor's Table 8.1.4, on pages 141-142 of Volume 14.

Results for the whole period of 8 weeks are again almost exactly the same as for the first 4 weeks, and show the marked superiority of both lansoprazole regimens over placebo for reduced the severity and frequency of day and night heartburn, and the significant superiority of the lower dose of lansoprazole for night heartburn amelioration. Night heartburn severity is consistently less than day heartburn, in all of the analyses, evaluable or ITT, four either 4 or 8 weeks.

Comment: The diary pages (see blank CRF, pages 266-307, Volume 14) have spaces for patients to enter

for each study day, the date (month/day), the number of Gelusil tablets taken, and the severity, on a scale of 0 to 3, of the say heartburn and night heartburn. Blocks are also provided to check if the diary was not completed that date and if the number of Gelusil tablets taken was not known. Diary sheets were provided for up to 21 pre-study days (page 283), to be distributed at the screening visit and collected on the day of visit 1 when the randomized treatment was to be started. Diary sheets for up to 35 days (see pages 287-8 and 292-3) were distributed for recording those data during the first and second 4 weeks of the study.

Summaries of the diary counts of Gelusil tablets used and heartburn severity over the pre-study period and the two 28-day periods of the study are shown in Appendix E.8, for each patient. Not provided in the submission are listings of the data for the three variables for each day for each patient. Analyses of the data from the diary sheets were used to generate the analyses displayed in Tables 8.1.1 to 8.1.4 of the report (pages 135-142, Volume 14, and shown in the text of the report in Tables 8.1.a and 8.1.b, and to generate the graphic displays 8.1.1.a and 8.1.1.b on report pages 066-067. The results of these calculations are also shown in this review, above.

When study size was calculated (see protocol Section 9 on Statistical Procedures, pages 242-243, Volume 14, it was projected that lansoprazole 30 mg/day would be better (reduce the expected percentage of days with pain from 55% on placebo to 22%) than 15 mg/day (to 33%). This did not happen.

Perhaps the most compelling presentation of data in all of the sponsor's submission is the graphic display in Figures 8.1.1.a and 8.1.1.b on pages 066 and 067 of Volume 14 that reports on the new study M95-300. One does not need statistical analysis to see at a glance that lansoprazole is far better than placebo in reducing the mean severity of daytime and nighttime heartburn in the subset of evaluable patients. It is also evident that the lower dose of lansoprazole 15 mg/day is actually more effective in preventing heartburn at night that wakes and disturbs the patients' sleep.

The data from which the graphs were developed, day-by-day changes in heartburn symptoms, as so powerfully shown in the graphs, appear in the submission in Volume 50. Summary data from the diary cards are listed in Appendix E.8, meaning 28-day average daily counts of Gelusil tablets taken and day or night heartburn experienced.. It is suggested that the sponsor consider preparing for the labeling similar graphs or tables showing results at Days 1,2, 3, 5, 7, 14, 28 and 56 for day and night heartburn. Even more convincing might be a display of the data showing the differences (reductions) in heartburn severity day-by-day, rather than mean values for the whole groups.

The highly significant reductions in day and night heartburn severity are major clinical benefits, and to a great extent overcome the weakness of having only one valid, prospective clinical trial in support of the requested supplemental indication. The two other studies submitted were really only hypothesis-generating exercises, where suggestions that lansoprazole could be shown to reduce symptoms of GERD were developed by retrospective subset analyses on patients who did not happen to have esophageal mucosal erosions at the time of their prestudy endoscopy, but who were allowed to remain in the studies anyway, and some symptom data were gathered. Gelusil tablet consumption is a confirming "mirror image" of the heartburn reduction findings.

The principal finding of the M95-300 study is that the proper dose of lansoprazole for symptomatic treatment of non-erosive GERD should be 15 mg/day rather than the 30 mg/day shown to be more effective in healing erosive esophagitis and approved for that indication in 1995. This was not the expected result, as indicated by the statistical assumptions made for the M95-300 study size. It was stated in the protocol that the estimates that 80 patients in each lansoprazole dose-group and 40 in the placebo arm should be sufficient to demonstrate with more than 90% power the superiority of lansoprazole over placebo for reducing the number of days with daytime ***abdominal pain****. It was projected that the percentage of days with pain would be in the placebo-treated group, and in patients treated with lansoprazole 15 mg/day, in those treated with lansoprazole 30 mg/day. It was further estimated that the study of that size, 80 patients in each of the lansoprazole arms, might have approximately 72% power to detect the 11% difference showing the superiority of the higher lansoprazole dosing regimen. The results of M95-300 do not support those assumptions. The assumptions were based on the retrospective analyses of M87-092, a study designed to show the healing power of lansoprazole for patients with erosive esophagitis.*

Depending on which set of data are considered, the findings of M95-300 were that patients on placebo had day heartburn after treatment for 4 or 8 weeks about 77% of the days (expected 55%). However, patients treated with lansoprazole 15 mg/day had daytime heartburn on only about 29% of the days (expected 33%), while patients treated with lansoprazole 30 mg/day had about 35% of the days with day heartburn (expected 22%). Thus, the lansoprazole 30 mg/day for some reason was not as effective as the lower dose, in this study of patients with frequent and moderately severe heartburn but no erosive esophagitis. The greater-than-expected persistence of days with heartburn in the placebo-treated group, even higher than the entry criteria that required all candidates for the study to have at least 50% of the days or nights with heartburn, simply made the difference between placebo and lansoprazole effects more striking and much more significant statistically. The actual number of days of daytime heartburn for the lansoprazole 15 mg/day regimen was fairly close (29%) to that estimated from M87-092 data for day abdominal pain (33%).

The definitions of symptoms in M87-092 were not precise, and fewer of the patients in the subset of 106 with no erosions, and the focus was on abdominal pain rather than heartburn. The protocols and even the CRFs do not precisely define these symptoms, nor are the exact definitions of "day" and "night" provided. It would be reassuring if all of the patients were recording in diaries based on the same understanding of pain or heartburn occurring in the daytime or nighttime.

Investigators' Assessments of Responses

Another way of looking at relief from the symptoms of daytime and nighttime heartburn was done by analyzing the investigators' scoring of the retrospective reports for the past period prepared by patients at the immediate pre-study visit and the visits after 4 and 8 weeks of treatment. At each visit, patients were asked to score their symptoms for the past period, the pre-study period of 7-10 days, the first 4 weeks of study treatment, and the second 4 weeks of treatment. The blank sheets to be filled out by the patients are in the CRF (pages 277,282, 286, 291) and reproduced below:

TAP HOLDINGS INC.

FORM 9 Page 18

ABT-006, LANSOPRAZOLE

THERAPY WITH LANSOPRAZOLE FOR NON-EROSIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD)
STUDY NO. M95-300

Patient Number: _____

Patient Initials: _____

WEEK 4

SYMPTOM ASSESSMENT

Date of Visit: _____

INSTRUCTIONS: Record symptoms which occurred over the past 2 weeks.

Check box if none. ☐ 0

VISIT = 2 SIGNS_SYMP

SYMPTOM	SEVERITY* (Check one box below.)							
	0	None	1	Mild	2	Moderate	3	Severe
Day Abdominal Pain								
Night Abdominal Pain								
Day Heartburn								
Night Heartburn								
Painful Swallowing								
Dysphagia								
Belching								
Regurgitation (Gastroesophageal)								
Fullness/Bloating/Early Satiety								
Abdominal Distension								
Anorexia								
Nausea								
Vomiting								
Flatulence/Abdominal Rumbling								
Diarrhea								
Constipation								
Hematemesis								
Melena								
Patient's Overall Symptoms								

*SEVERITY

Mild = Symptom does not last long and is easily tolerated

Moderate = Symptom causes discomfort and interrupts usual activities.

Severe = Symptom causes great interference with usual activities and may be incapacitating.

WHITE - TAP Original YELLOW - TAP Work Copy PINK - Investigator Copy GOLDENROD - Hardcard

It is of some interest to ask which of the symptoms that were inquired about were most prevalent and most severe in the sample of patients selected for study M95-300. Data are available that show that all of them had reported day heartburn, not surprising since it was the requirement for participation. Appendix D.3.2 provides numbers of patients who had various symptoms, as listed on the Symptom Assessment sheets, at baseline for 211 of the patients in the ITT group, and even the three patients excluded because they had Barrett's esophageal changes or erosion at endoscopy have listing of their symptoms in Appendix E.9.A in Volume 17, pages 393 and 418. In order of frequency:

	symptom	*severe*	*moderate*	*mild*	*none*	***present***	*total*
DHB	*day heartburn*	*37*	*153*	*24*	*0*	*214*	*214*
NHB	*night heartburn*	*67*	*106*	*27*	*14*	*200*	*214*
BEL	*belching*	*27*	*73*	*75*	*39*	*175*	*214*
FLA	*flatulence/abdominal rumbling*	*36*	*70*	*68*	*40*	*174*	*214*
REG	*gastroesophageal regurgitation*	*34*	*85*	*49*	*46*	*168*	*214*
FUL	*fullness/bloating/early satiety*	*30*	*69*	*54*	*61*	*153*	*214*
ABD	*abdominal distension*	*15*	*67*	*43*	*89*	*125*	*214*
DAP	*day abdominal pain*	*18*	*57*	*50*	*89*	*125*	*214*
NAP	*night abdominal pain*	*15*	*45*	*36*	*118*	*96*	*214*
NAU	*nausea*	*9*	*20*	*58*	*127*	*87*	*214*
DYS	*dysphagia*	*4*	*18*	*41*	*151*	*63*	*214*
DIA	*diarrhea*	*3*	*25*	*34*	*152*	*62*	*214*
CON	*constipation*	*1*	*21*	*36*	*156*	*58*	*214*
PFS	*painful swallowing*	*3*	*12*	*19*	*180*	*34*	*214*
ANX	*anorexia*	*1*	*10*	*21*	*182*	*32*	*214*
VOM	*vomiting*	*4*	*4*	*13*	*193*	*21*	*214*
MEL	*melena*	*1*	*0*	*6*	*207*	*7*	*214*
HEM	*hematemesis*	*0*	*0*	*1*	*213*	*1*	*214*
OSS	*overall symptoms*	*22*	*165*	*26*	*0*	*213*	*213*

Comment: One patient, Geraci # 2193, failed to check the space for OSS in the baseline sheet. Not all of these symptoms are characteristic of GERD, but overlap into other clinical syndromes such as irritable bowel syndrome, "dyspepsia," peptic ulcer, gastrointestinal bleeding, ordinary constipation, etc. Among patients selected for heartburn symptoms associated with GERD, this distribution of symptom frequency and severity is notable. In Study M87-092, in which patients were selected for esophageal erosive disease rather than primarily for symptoms, abdominal pain seemed to impress the investigators and sponsors more.

Analyses presented by the sponsor in this study considered the investigators' opinions of heartburn symptoms, as shown in Tables 8.2.1 to 8.2.4, pages 143-150, Volume 14, for evaluable and ITT groups after 4 and 8 weeks of treatment compared to prestudy severity. Examples of these analyses are reproduced below for 211 patients of the ITT group, for 4 and 8 weeks of treatment:

CHANGES IN HEARTBURN SEVERITY AT 4 WEEKS, ITT PATIENTS (211)

Day Heartburn

at baseline			at week 4 visit: none (0)	mild (1)	moderate (2)	severe (3)	row mean
mild	24	placebo					0.50
		lanso 15					0.86
		lanso 30					0.63
moderate	151	placebo					1.50
		lanso 15					0.67
		lanso 30					0.86
severe	36	placebo					2.11
		lanso 15					1.00
		lanso 30					1.54

Cochran-Mantel-Haenszel Q:	placebo vs lansoprazole 15, =	21.30	**$p < 0.001$**
	placebo vs lansoprazole 30, =	12.72	**$p < 0.001$**
	lanso 15 vs lanso 30, =	2.06	$p = 0.151$

Night Heartburn

at baseline			at week 4 visit: none (0)	mild (1)	moderate (2)	severe (3)	row mean
none	14	placebo					0.50
		lanso 15					0.00
		lanso 30					1.00
mild	26	placebo					1.00
		lanso 15					0.56
		lanso 30					0.23
moderate	104	placebo					1.50
		lanso 15					0.54
		lanso 30					0.89
severe	67	placebo					2.29
		lanso 15					0.77
		lanso 30					1.57

Cochran-Mantel-Haenszel Q:	placebo vs lansoprazole 15, =	27.73	**$p < 0.001$**
	placebo vs lansoprazole 30, =	8.09	**$p < 0.001$**
	lanso 15 vs lanso 30, =	9.50	**$p = 0.002$**

Comment: Note that again both doses of lansoprazole are significantly better than placebo, for both day and night heartburn, and the lower lansoprazole dose is significantly superior at night.

CHANGES IN HEARTBURN SEVERITY AT 8 WEEKS, ITT PATIENTS (211)

Day Heartburn

at baseline			at week 8 visit: none (0)	mild (1)	moderate (2)	severe (3)	row mean
mild	24	placebo					1.50
		lanso 15					0.43
		lanso 30					0.50
moderate	151	placebo					1.47
		lanso 15					0.63
		lanso 30					0.69
severe	36	placebo					1.89
		lanso 15					1.43
		lanso 30					1.69

Cochran-Mantel-Haenszel Q:	placebo vs lansoprazole 15, =	22.69	**p < 0.001**
	placebo vs lansoprazole 30, =	16.92	**p < 0.001**
	lanso 15 vs lanso 30, =	0.56	p = 0.454

Night Heartburn

at baseline			at week 8 visit: none (0)	mild (1)	moderate (2)	severe (3)	row mean
none	14	placebo					0.00
		lanso 15					0.25
		lanso 30					1.00
mild	26	placebo					1.00
		lanso 15					1.00
		lanso 30					0.15
moderate	104	placebo					1.25
		lanso 15					0.49
		lanso 30					0.78
severe	67	placebo					2.29
		lanso 15					0.73
		lanso 30					1.56

Cochran-Mantel-Haenszel Q:	placebo vs lansoprazole 15, =	18.80	**p < 0.001**
	placebo vs lansoprazole 30, =	4.59	**p = 0.032**
	lanso 15 vs lanso 30, =	7.09	**p = 0.008**

Comment: At 8 weeks again both doses of lansoprazole are significantly better than placebo, for both day and night heartburn, and the lower lansoprazole dose is significantly superior at night.

in Appendix D.3.1 With respect to **other** symptoms of GERD, similar analyses of symptom sheets at 8 weeks are tabulated in Appendix D.3.1, pages 156-172 of Volume 14 for 'evaluable" patients who had the symptom at baseline, and in Appendix D.3.2, pages 173-189 of Volume 14 for ITT patients. The latter set is summarized below:

Significant Reduction of Other GERD Symptoms, ITT Patients

		at baseline					**after 8 weeks**	
	symptom	*severe*	*moderate*	*mild*	*none*	*total*	L15	L30
BEL	*belching*	*26*	*72*	*74*	*39*	*211*	**0.040**	0.095
FLA	*flatulence/abdominal rumbling*	*36*	*69*	*67*	*39*	*211*	N.S.	N.S.
REG	*gastroesophageal regurgitation*	*34*	*84*	*51*	*42*	*211*	**0.002**	**0.009**
FUL	*fullness/bloating/early satiety*	*30*	*69*	*53*	*59*	*211*	N.S.	N.S.
ABD	*abdominal distension*	*15*	*67*	*42*	*87*	*211*	N.S.	N.S.
DAP	*day abdominal pain*	*18*	*56*	*50*	*87*	*211*	N.S.	N.S.
NAP	*night abdominal pain*	*15*	*45*	*36*	*115*	*211*	**0.014**	N.S.
NAU	*nausea*	*9*	*20*	*58*	*124*	*211*	N.S.	N.S.
DYS	*dysphagia*	*4*	*17*	*41*	*149*	*211*	N.S.	N.S.
DIA	*diarrhea*	*3*	*25*	*33*	*150*	*211*	N.S.	N.S.
CON	*constipation*	*1*	*21*	*36*	*153*	*211*	**0.050**	N.S.
PFS	*painful swallowing*	*3*	*12*	*19*	*177*	*211*	N.S.	N.S.
ANX	*anorexia*	*1*	*10*	*21*	*179*	*211*	N.S.	N.S.
VOM	*vomiting*	*4*	*4*	*13*	*190*	*211*	N.S.	N.S.
MEL	*melena*	*1*	*0*	*6*	*204*	*211*	N.S.	N.S.
HEM	*hematemesis*	*0*	*0*	*1*	*210*	*211*	N.S.	N.S.
DHB	*day heartburn*	*36*	*152*	*23*	*0*	*211*	**<0.001**	**<0.001**
NHB	*night heartburn*	*67*	*104*	*26*	*14*	*211*	**<0.001**	**0.032**
OSS	*overall symptoms*	*22*	*162*	*26*	*0*	*210*	**0.002**	0.098

Comment: Certain other symptoms were significantly reduced by lansoprazole treatment, compared to placebo, as retrospectively assessed by patients using the periodic symptom sheet and evaluated by the investigator. These findings are in addition to the highly significant reduction in day heartburn, by the same approach. Data for 4-week analyses of other symptoms were not provided by the sponsor.

By this approach, again, the lansoprazole dose of 15 mg/day is apparently significantly better than the higher dose for symptoms of belching and night abdominal pain, as well as for night heartburn and the overall assessment of symptoms by the patients. Both doses are superior to placebo for reduction of symptoms of day heartburn and regurgitation

Safety Results

This relatively small study adds little to the vast amount of information on the short-term safety of lansoprazole at these already approved doses and in literally millions of patient-years of clinical experience.

The premature terminations have been mentioned above, and narrative summaries on these patients have been presented by the sponsor (pages 075-078, Volume 14). Of these the pancreatitis in Fisher's patient #2119 occurred in a 43-year-old black woman with a history of alcohol abuse and previous pancreatitis attacks who had abdominal pain for two weeks before the study, which she had not revealed to the investigator when she was enrolled in this study. The two patients of Dr. Sabesin who left the study early included: 1) #2218, a 45-year-old man with mild diarrhea, urinary hesitancy and fatigue, coded in COSTART as urinary retention, which implied an overstatement of his problem; and 2) #2020, a 45-year-old white man with a history of seizures, hypoglycemia, depression, chronic fatigue syndrome, and elevated liver enzymes. He quit the study because of loss of short-term memory, hesitant thought and speech, symptoms that he had reported previously after taking antacids and H2-blocking agents.

There were no deaths of patients participating in this study, but three patients were hospitalized for problems that did not appear to be caused by study medications, and two of them were on placebo. The other, Jones' patient #2049, a 21-year-old white woman with a history of migraine headaches, depression, irritable bowel syndrome, endometriosis, and bronchitis developed right upper quadrant pain after 51 days on lansoprazole 30 mg/day. The hospital workup was essentially negative, and she was diagnosed as having esophageal spasm (cardiospasm) which resolved after treatment with ranitidine, cisapride, and more lansoprazole.

The incidence of minor symptoms was generally no greater in the lansoprazole-treated patients than in those on placebo, except for the now-familiar increased incidence of diarrhea, abdominal discomfort/pain, and headache. In this particular set of patients pharyngitis and sinusitis occurred also more frequently in the lansoprazole-treated patients than in the placebo group, but the numbers were small and no clinically important consequences ensued.

Net Benefit

On balance the clinical benefits of very striking reduction in symptoms of heartburn, especially at night, in patients who had histories of moderate and severe symptoms that interfered substantially with their normal activities and sleep, far outweighed any risks. The doses of lansoprazole used in this study, 15 and 30 mg daily for 8 weeks, are approved for several indications and for up to a year for maintenance of healing of duodenal ulcer and erosive esophagitis. The findings of this study, M95-300, further suggest that the lower dose of lansoprazole 15 mg is fully effective and that there is no justification for using the higher dose in the great majority of patients. No subgroup of GERD patients was identified in this study who might need the higher dose of lansoprazole for clinical relief of heartburn symptoms.

E. Other Supportive Clinical Trials

3. Study D75p501

This study was carried out in the U. K. from August 1988 to March 1990, by five investigators who enrolled 229 patients with endoscopically confirmed reflux esophagitis. Patients were randomized to receive lansoprazole 30 mg or lansoprazole 60 mg daily or ranitidine 150 mg twice daily for 4 to 8 weeks. The primary aim of the study was to show superiority of lansoprazole over ranitidine in healing the erosive lesions of the esophagus.

The report of the study, except for Attachment I, was submitted previously in support of NDA 20-406 on 12 November 1993, Volume 2.217. It is resubmitted in this application, in Volumes 19-22.

As carried out, the study called for initial endoscopy to classify patients as to the severity of their mucosal lesion by endoscopic inspection, using a modified Savary-Miller scale that defined the grade of the mucosal lesions as:

Grade 0	Normal
Grade 1	Erythema/edema and friability, with contact bleeding
Grade 2	Isolated erosions
Grade 3	Confluent ulceration
Grade 4	Stricture formation

Patients with strictures or normal mucosa were excluded from the study, and those with Grades 2-4 grading were stratified before randomization in blocks of three patients into:

Stratum A = Grade 1 esophagitis
Stratum B = Grades 2 or 3 esophagitis

After establishment of baseline eligibility, stratification, and randomization, patients were treated for 4 weeks (±3 days) and then re-endoscoped. If healed (to Grade 0) AND symptoms were relieved, then treatment was stopped and the patient was observed on no therapy for another 4 weeks. If not healed or still symptomatic, another 28 ± 3 days of blinded treatment was continued and a final endoscopy was done. If healed and asymptomatic, followup was continued for 4 weeks, but if either unhealed or symptomatic the patients were discontinued from study and referred for alternative treatment, but also followed for another 4 weeks.

Symptoms evaluated were heartburn, regurgitation, and dysphagia, graded by the physician for **heartburn** as 0 = no episode within past week, 1 = 1 to 3 episodes in past week, 2 = 4 to 6 episodes within past week, and 3 = 7 or more episodes in past week. A separate assessment was also made of whether the heartburn was sufficiently severe as to interfere with normal activities. For **dysphagia**, the scale used was 0 = none, 1 = occasionally with solids only, 2 = consistently with solids and occasionally with liquids, and 3 = consistently with both solids and liquids. Regurgitation was scored as 0 = none, 1 = occasionally (once daily), 2 = regularly with straining or position

change, and 3 = regularly and interferes significantly with normal activities (e.g., nocturnal coughing and choking). Patients were also asked to make an overall assessment of response.

The primary outcome was comparison of the proportion of patients healed on the three regimens. It had been assumed that 50% of patients in the ranitidine control arm would be healed, and that 70% would be healed in at least one of the lansoprazole groups, so it was calculated that 70 patients in each treatment arm would provide a power of 80% to detect a significant ($\alpha = 0.05$, two-tailed) difference.

As performed, 229 patients were enrolled, 77 to ranitidine 150 mg b.i.d., 77 to lansoprazole 30 mg daily, and 75 to lansoprazole 60 mg daily. Of these, 57 were Stratum A and 172 Stratum B:

	total	lanso 30	lanso 60	ranitidine
Stratum A (Grade 1)	57	19	20	18
Stratum B (Grades 2 and 3)	172	58	55	59

Investigators included:

K. Bardhan, Rotherham	A	8	2	4	2
	B	82	28	26	28
C. Hawkey, Nottingham	A	9	3	3	3
	B	33	11	11	11
R. Long, Nottingham	A	33	11	11	11
	B	45	15	15	15
A. Morgan, Keighley	A	0			
	B	1			1
K. Wormsley, Dundee	A	7	3	2	2
	B	11	4	3	4

Of the 229 enrolled, 9 were considered ineligible for various reasons, including:

significant underlying disease	1			1
prior surgical procedure	2		1	
concomitant illness/disease	2		1	1
pre-study medication	4	2	1	1
age violation	1	1		
all reasons for ineligibility	9	3	3	3

	total	lanso 30	lanso 60	ranitidine

Of the 229, 23 patients withdrew from the study or were discontinued for the following reasons:

adverse event	8	1	2	5
protocol violation	12	2	7	3
patient request	2			2
other reason	1			1
all reasons for withdrawal	23	3	9	11

The adverse event causing early withdrawal in patients on lansoprazole 30 mg/day was nausea with dizziness and headache in Long's patient #131. The events in the two patients on lansoprazole 60 mg/day were: 1) syncope in Long's patient #130, and 2) constipation and abdominal pain in Bardhan's patient #212. Patients on ranitidine withdrew because of deafness (Long #132), nausea (Long #185), salivation and abdominal pain (Long #390), gastrointestinal bleeding (Bardhan #264), loose stools and fatigue (Bardhan #278). Two patients requested to leave the study because of continued symptoms while on ranitidine, Bardhan's patient #232 and Hawkey's patient #121.

Protocol violations were mostly missed appointments, except for two patients on ranitidine diagnosed after entry as having colon cancer and one lansoprazole 60 mg/day who took cimetidine during the study. The "other" reason was a missed endoscopy appointment at week 8.

Healing Efficacy

Results of repeat endoscopic evaluations at week 4 and week showed the following results:

	lanso 30	lanso 60	ranitidine
At week 4			
healed, to normal Grade 0 mucosa	63/75	49/68	29/74
(% healed)	(84.0)	(72.1)	(39.2)
95% confidence interval, in %	73 to 91	59 to 82	28 to 51
At week 8			
healed, to normal Grade 0 mucosa	70/76	59/65	37/70
(% healed)	(92.1)	(90.8)	(52.9)
95% confidence interval, in %	82 to 97	80 to 96	40 to 55

The two lansoprazole regimens were significantly superior ($p<0.001$) to ranitidine in healing of esophagitis (all three grades 1, 2, 3) at both 4 and 8 weeks, but not significantly different from each other ($p=0.684$) at week 4 or at week 8 ($p=0.777$).

Further analyses or "per protocol" subgroups, and making adjustments for missed endoscopies rather than assuming failure if no data were available, reached the same conclusions.
Comment: The dose of ranitidine used for comparison in this study was not the approved dose for

*healing erosive esophagitis, which is 150 mg **four** times daily. The dose of 150 mg twice daily is approved in the United States for treatment of GERD. The results of this U.K. study in concluding superiority of lansoprazole over ranitidine are therefore questionable. However, it was demonstrated that lansoprazole 30 mg/day is an adequate dose for healing esophagitis, and nothing is gained by using 60 mg/day.*

Symptom Relief

In the whole study of patients with grades 1, 2, and 3 esophagitis, **heartburn frequency** was "somewhat" improved, significantly ($p<0.001$)more for both lansoprazole groups than for ranitidine at week 4, but no difference between the two lansoprazole doses ($p=0.335$). By week 8, ranitidine had caught up a little, but lansoprazole was still significantly better than ranitidine, lansoprazole 30 mg/day ($p=0.033$) and lansoprazole 60 mg/day ($p=0.013$), and no difference between the lansoprazole doses ($p=0.981$).

For the **severity of regurgitation** symptoms, there was no significant difference between the treatment groups at either week 4 or week 8, although all three regimens produced "some" improvement compared to baseline.

Severity of dysphagia similarly showed no significant difference between the treatment groups at either week 4 or week 8, although all three treatment groups showed "some" improvement compared to baseline.

Patients recorded in their diaries the severity of their symptoms of day and night pain, and analyses of the results showed no significant differences between treatment regimens in the reduction of day pain, but **night pain** was reduced significantly more by lansoprazole 30 mg/day ($p=0.038$) and lansoprazole 60 mg/day ($p=0.026$) than by ranitidine, but there was no significant difference ($p=0.908$) between the two lansoprazole doses.

Use of antacid tablets was significantly more reduced by lansoprazole 30 mg/day ($p=0.008$) and lansoprazole 60 mg/day ($p=0.001$) than by ranitidine, but again no difference between the lansoprazole regimens ($p=0.241$).

REANALYSES OF THE SUBSET OF 57 PATIENTS WITH NON-EROSIVE ESOPHAGITIS

Most pertinent to this submission for use of lansoprazole in treatment of GERD symptoms in non-erosive esophagitis were 57 patients of the 229 studied in D75p501 who had only grade 1 esophagitis at entry. The material submitted for this application was based on a re-analysis of the 57 patients who had been found to have non-erosive esophagitis. The analysis was done under contract to the sponsor submitting this application, and summarized in Volume 20, pages 001-224 of this submission as Attachment I. The Attachment consists of data listings and statistical analyses prepared

Study D75p501 non-erosive subset:		total	lanso 30	lanso 60	ranitidine
Stratum A (Grade 1)		57	19	20	18
Investigators:					
K. Bardhan, Rotherham	A	8	2	4	2
C. Hawkey, Nottingham	A	9	3	3	3
R. Long, Nottingham	A	33	11	11	11
K. Wormsley, Dundee	A	7	3	2	2

The listings provided in Attachment I simply delete the patients of Study D75p501 who had grade 2 or 3 esophagitis. When the remaining patients who had only grade 1 (no erosions) esophagitis are considered, it is evident that the numbers for each investigator for each of the three treatment regimens are quite small. Since healing was not an issue, only the secondary issues of symptom relief are pertinent in the reanalyses of the subset. Results of the analyses are brief, and are summarized on just two pages of the eport, pages 003-005 of Volume 20. Comparison by χ^2 test of the three treatment groups (2 df) for each symptom showed:

Table 1: SYMPTOMS (PHYSICIAN)

	χ^2 statistic	df	p-value
Week 4			
heartburn	**9.21**	2	**0.01**
regurgitation	0.45	2	0.80
dysphagia	1.15	2	0.56
Week 8			
heartburn	**7.67**	2	**0.02**
regurgitation	0.47	2	0.79
dysphagia	3.44	2	0.18

Only heartburn was significantly different in this analysis of the treatments. There was no significant difference between the lansoprazole regimens, but lansoprazole 30 mg daily was significantly superior to ranitidine 150 mg twice daily in relieving heartburn. After 8 weeks, lansoprazole 60 mg daily also became significantly better than ranitidine. Pairwise comparisons between treatments for symptoms showing significant differences (heartburn), using the Wilcoxon test for p-values, showed:

Week 4	
lanso 30 vs ran 150	**p=0.003**
lanso 60 vs ran 150	p=0.150
lanso 30 vs lanso 60	p=0.090
Week 8	
lanso 30 vs ran 150	**p=0.025**
lanso 60 vs ran 150	**p=0.025**
lanso 30 vs lanso 60	p=0.999

Data from the patients' diary cards on which they had recorded day pain and night pain severity, and use of antacid tablets, showed no overall differences between the three treatment groups by use of χ^2 analysis and use of the Kruskal-Wallis test for the p-values:

Table 2: SYMPTOMS (DIARY CARD)

	χ^2 statistic	df	p-value
day pain	0.19	2	0.91
night pain	0.84	2	0.66

Table 3: ANTACID USAGE

antacid use	0.11	2	0.9

When incidence of adverse events was considered, again there were no significant differences among the three treatment groups, by similar calculations:

Table 4: ADVERSE EVENTS

diarrhea	3.39	2	0.18
gastrointestinal symptoms	0.94	2	0.63
overall symptoms	1.05	2	0.59

There was a slight increase in diarrhea in the lansoprazole-treated patients (3/20 in the lansoprazole 60 mg/day group, compared to none in the lansoprazole 30 mg/day group, and 1/18 in the placebo group. The difference was not significant.

Laboratory test differences from means at baseline to 4 or 8-week means showed no significant treatment group differences at week 4. At week 8, significant treatment group differences were noted only for blood hemoglobin and hematocrit, but not for red cell count, white cell count, platelets, or serum concentrations of enzyme activities, electrolytes, or chemical measurements:

TABLE 5: LABORATORY TESTS

test	Week 4		Week 8	
	F-statistic	p-value	F-statistic	p-value
hematocrit	1.31	0.28	**6.13**	**0.008**
hemoglobin	0.68	0.51	**3.88**	**0.038**
erythrocytes	0.54	0.59	3.08	0.07
leukocytes	0.00	0.99	0.79	0.47
platelets	1.32	0.28	1.11	0.35
sodium	0.36	0.70	0.82	0.45
potassium	0.36	0.70	2.91	0.07
chloride	0.75	0.48	0.23	0.80
calcium	0.62	0.54	0.30	0.74
phosphorus	2.47	0.10	1.21	0.32
urea nitrogen	0.38	0.69	0.65	0.53
creatinine	0.87	0.42	0.94	0.40
protein	2.33	0.11	2.06	0.15
albumin	1.59	0.22	1.27	0.30
bilirubin	2.05	0.14	2.16	0.14
aspartate aminotransferase	0.55	0.58	0.46	0.63
alanine aminotransferase	1.51	0.23	0.51	0.61
alkaline phosphatase	2.63	0.08	2.75	0.08
γ-glutamyltransferase	1.49	0.24	0.07	0.94

Comment: The statistically significant change in average hematocrit and hemoglobin at week 8 but not at week 4 in this subset analysis was not noted or discussed by the sponsor. Tables for the changes were provided by in the statistical re-analysis, Attachment I, Volume 20, pages 210 and 211. Shown there is a drop in mean hemoglobin for the lansoprazole 60 group from 14.2 at baseline to 13.7 at week 8 (page 211), and a drop from "0.5 to 0.4" in hematocrit (page 210). Such a change could be produced by even one patient with gastrointestinal bleeding in such a small sub-group, but no patient was so identified by the sponsor nor the change explained.

The sponsor does not provide any overall explanation or interpretation of the results of the statistical reanalysis of the subset of 57 patients from Study D75p501 who did not have erosions, beyond the p-values listed above. The conclusion of the report on the full study reiterated in Volume 19 simply states that lansoprazole 30 mg is a recommended dose for healing erosive esophagitis.

F. Other Studies and Information

No other clinical data was submitted in support of this application for use of lansoprazole in the treatment of symptoms of non-erosive GERD.

G. Integrated Summary of Effectiveness Data

The sponsor provides in Volume 24 of this submission a recapitulation of the results of the two older studies M87-092 (U.S.) and D75p501 (U.K.) and the recent study M95-300 U.S.). It is argued (see page 009 of Volume 24) that both studies done in the United States were double-blind, randomized, and placebo-controlled, and were conducted with strict adherence to IND regulations and Good Clinical Practice. It is further argued that these constitute two adequate and well controlled trials in support of the application.

Study D75p501, carried out in the U.K., is proposed as supportive because some source documents were not available for review by the sponsor, although it was randomized and double-blind, but controlled by ranitidine 150 mg twice daily rather than by placebo.

Comment: This reviewer disagrees with the sponsor in this proposal. Results of both M87-092 and D75p501 were submitted previously in support of NDA 20-406 in November 1993, and were used as grounds for approval of lansoprazole for healing and symptom relief of all grades of erosive esophagitis, at a dose of 30 mg daily for up to 8 weeks (short-term). Both studies included some patients who did not have esophageal erosions at baseline, but only mucosal friability with contact-induced bleeding or edema/hyperemia; many of them had GERD-associated symptoms, however.

The reanalyses submitted with this application deal with 106 of the 292 patients in M87-092 and 57 of the 229 patients in D75p501 who had non-erosive esophagitis. The studies were not originally designed to assess symptom relief but were focussed on healing erosions or ulcerations in the more severe grades of reflux esophagitis. These retrospective analyses simply reconsider those studies and search for clinical symptoms that were shown to improve significantly more on treatment with lansoprazole than on either placebo or ranitidine 150 mg twice daily. That search for statistically significant symptomatic improvement generated very useful hypotheses, namely a focus on relief of day and night heartburn, for further testing in the new study M95-300. Although the results of that new study are very persuasive, it represent just one study that is acceptable as principal support for this requested application. The results of both of the retrospective analyses are noted with interest and considered as supportive.

Although Volume 24 goes on to repeat and re-summarize the results of the above studies, there is no need to repeat that discussion here. Of much greater concern are the arguments made by the sponsor about the proper dose and regimen in Section 8.6.3, page 011, Volume 24 of this submission, that provides somewhat more rationale than the very brief statement in Volume 1, page 270 of this submission, Section 2.7.5.

Sponsor's Dosing Recommendation for Treatment of Non-erosive GERD Symptoms

In the very short Section 2.7.5 of Volume 1, the sponsor cites the two controlled trial M87-092 and M95-300 as support for use of lansoprazole as well tolerated and efficacious for relief of symptoms of non-erosive GERD. Once daily dosing is stated to be convenient for patients and to increase their compliance with the regimen. It is simply stated that "we recommend short-term treatment (four to eight weeks) with lansoprazole 30 mg QD for symptomatic relief in patients with gastroesophageal reflux disease."

In returning to this issue in somewhat more expanded argument, the sponsor states in Section 8.6.3 in Volume 24, page 011, that lansoprazole should be taken before meals, based on data elsewhere submitted indicating better bioavailability and inhibition of gastric acid secretion. Further, it is stated that once-daily dosing is effective. Pharmacokinetic and pharmacodynamic data summarized and submitted elsewhere are cited to establish that lansoprazole, over an oral dosing range from 7.5 to 30 mg, shows increasing inhibition of gastric acid secretion, but above 30 mg little or no increase in normal subjects. Oral doses from are cited to show linear dose proportionality, But because of considerably lower gastric acid suppression by 7.5 mg, the doses evaluated clinically have ranged from The section concludes with a statement that no dosing adjustment is needed for elderly patients, nor for patients with impaired hepatic function or renal insufficiency, but "in these populations, doses above 30 mg are not indicated unless there is a compelling clinical condition that warrants additional gastric acid suppression."

It is further stated, in Section 8.6.4.3 (page 040-1, Volume 24) that "in all three controlled clinical trials which enrolled patients with non-erosive GERD, lansoprazole 30 mg daily consistently provided superior symptom relief as compared to either placebo or ranitidine." It is stated that in Study M95-300, "lansoprazole 15 mg daily provided better relief of night heartburn than lansoprazole 30 mg daily." However, it is also stated that in Study M87-092, lansoprazole 30 and 60 mg daily were superior to placebo in relieving day and night abdominal pain and decreasing Gelusil use during the first 4 weeks and over the whole 8 weeks of the treatment period. In that study, lansoprazole was not significantly different from placebo in reducing the percentage of days and night patients had abdominal pain during the first 4 weeks and over the 8 weeks of the study.

Comment: These arguments do not make a case for choosing a daily dose of lansoprazole 30 mg over lansoprazole 15 mg for this indication, relief of heartburn and other symptoms in patients with non-erosive esophagitis. Study D75p501 was useless for this distinction, since no 15 mg dose of lansoprazole was studied; it will be ignored for this argument. Study M87-092 was a retrospective exercise in apparent data dredging and search for p-values less than 0.05 among a great many symptomatic variables, including 19 symptoms, day vs night, 4 weeks vs 8 weeks. In that study abdominal pain was not well defined, nor were the exact periods of time that constituted "day" vs "night" for patients to record. Although lansoprazole 15 mg daily did not reach statistically significant differences in relieving night abdominal pain, it showed a strong trend toward superiority over placebo and was significantly superior for relieving day time pain than placebo. It does not appear to have been taken into consideration that the patients with non-erosive esophagitis in the

subset of that study had more severe pain symptoms at baseline than patients in the two other groups, but merely compared mean values for groups. If **improvement** in symptoms for each patient is considered, lansoprazole 15 mg/day clearly was at least as good as and apparently slightly better than either higher dose, 30 or 60 mg/day, of lansoprazole (see graph on page 19). Nevertheless, Study M87-092 was not designed to assess symptoms primarily, the number of patients in each group of the subset reanalyzed was small, and the retrospective analyses are suspect. Further, the analysis used, comparing mean values, is less pertinent clinically than considering what proportions of patients on each regimen achieve a unequivocal clinical benefit such as two grades of reduction of pain, from severe to mild or none, and from moderate to none.

Most compelling, and the primary basis for concluding that this application is approvable for a dose of lansoprazole 15 mg daily, are the results of the new study, M95-300. Although it is just one study, and not overly large, it is extremely persuasive that a real clinical benefit is obtained from treating patients suffering from frequent and moderate-to severe heartburn associated with non-erosive GERD, using a dose of lansoprazole 15 mg once daily in the morning before breakfast. The data shown in the sponsor's Figures 8.1.1.a and 8.1.1.b demonstrate that the relief is prompt and sustained, that there is no superiority of a 30 mg daily dose, and that for relief of night heartburn the 15 mg daily dose is significantly better. That this result did not agree with theory based on previous pharmacokinetic or pharmacodynamic considerations, or was not what was expected when Study M95-300 was designed, do not detract from the conclusion that the recommended dose should be 15 mg of lansoprazole daily before breakfast for up to 8 weeks for relief of heartburn and other symptom associated with non-erosive GERD.

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H. Integrated Summary of Safety Information

These studies involved only 377 patients (106 in M87-092, 57 in D75p501, and 214 in M95-300), so that new issues with regard to safety would not have been expected, in view of the enormous amount of clinical experience that has been gained over many years in probably millions of patients exposed to lansoprazole dose of 15 or 30 mg/day, some at 60 mg/day or more, for many weeks up to a year or more. Of the 377 patients reported as participating in these two sub-studies and one full study, 288 received lansoprazole, 71 placebo, and 18 ranitidine:

Study	total	placebo	lanso 15	lanso 30	lanso 60	ranitidine
M87-092	106	27	23	24	32	
D75p501	57			19	20	18
M95-300	214	44	82	88		
combined	377	71	105	131	52	18

Adverse events did occur, but there was no pattern of newly emerging events that suggested important differences between the treatment groups other than perhaps diarrhea and abdominal discomfort/pain, especially in the lansoprazole 60 mg/day group.

There were no deaths among any of the participating patients. Some serious events occurred, including hospitalizations, but none of them appeared to have been caused by lansoprazole. A total of 13 lansoprazole-treated patients were terminated prematurely from one or another of the three studies, according to the sponsor's summary report (Volume 25, pages 018-020). Three of the patients had events that the investigator believed were explained by other causes than lansoprazole (pancreatitis, cardiospasm, alcoholism), five had mildly-to-moderately severe gastrointestinal reactions including diarrhea, abdominal discomfort/pain, and the others had non-gastrointestinal events of similar severity.

There were no laboratory changes, electrocardiographic changes, vital sign changes in these studies that were noteworthy, as reported by the sponsor in the overview sections 8.7.3.3 and 8.7.3.4 on page 021, and there were no patients who needed dose adjustment of digoxin or theophylline regimens that they were taking.

In summary, the sponsor concluded in Section 8.7.10, page 076 of Volume 25 that no clinically significant differences were noted in the incidences of adverse events between groups of patients randomized to lansoprazole treatment at doses of 15, 30, or 60 mg/day for up to 8 weeks, compared to incidences in comparator groups randomized to placebo or ranitidine. They concluded that lansoprazole was well tolerated in these short-term studies of patients with non-erosive GERD.

Comment: Review of the three clinical studies does not reveal any notable cases of problems that would cause the reviewer to take exception to the sponsor's findings, summary, and conclusions. As stated, a great deal has been learned about the safety of lansoprazole in the many previous studies submitted for close review and approval, comprising thousands of patients, and from reported experiences post-marketing in millions of patients.

I. Drug Abuse and Overdosage Information

No cases of overdose or drug abuse were encountered in these studies. In humans, doses of up to 180 mg/day for more than 3 years have been well tolerated in patients who may need such doses, such as those with Zollinger-Ellison syndrome. Rats and mice have been given oral doses of up to 5000 mg/kg, or about 250 times the human dose, with no deaths of the animals noted, only changes in color of the urine.

However, lansoprazole is extensively bound to protein in the plasma, and is not readily dialyzable; no specific antidote is known, so treatment in event of overdose can only be supportive and symptomatic.

J. Integrated Summary of Benefits and Risks of the Drug

The sponsor's section on net benefit (Section 8.9.1, pages 004-014, Volume 26) reviews the three studies again, and concludes that lansoprazole was shown to be effective in relieving symptoms associated with GERD, with few associated risks. The once-daily dosing is believed to increase patients compliance with prescribed regimens, and the program of lansoprazole treatment with 15 or 30 mg daily for up to 8 weeks appears beneficial with little toxicity.

Comment: The reviewer concurs that lansoprazole, especially in a dose of 15 mg daily for up to 8 weeks has very little risk in the vast majority of patients, and for those with distressing or sometimes severely interfering or disabling symptoms of GERD-associated heartburn and other symptoms the benefit far exceed the risk.

III. *Comments and Discussion*

Many comments have been made along the way in reviewing the sponsor's studies one-by-one, and the reader is directed to those comments. In summary, the data very strongly suggest that the proper dose of lansoprazole to be recommended is 15 mg daily for up to 8 weeks for treatment of heartburn and other GERD-associated symptoms in patients with non-erosive esophagitis. There is no convincing data to bolster the sponsor's claim that the dose should be 30 mg daily. On the contrary, 30 mg daily actually appears to be significantly less effective for relieving nighttime heartburn, although this is shown by only one study, M95-300.

However, the data obtained from the retrospective re-analyses of M87-092 and D75p501 subsets of patients with non erosions were very suggestive of probable clinical benefit from lansoprazole treatment with 15, 30 or 60 mg/day, better than placebo or better even than the currently approved dose of ranitidine 150 mg twice daily for treatment of GERD symptoms. The information learned from the retrospective analyses was very valuable, but did not establish the optimum dose. When used to design the new study, M95-300, however, it produced compelling results demonstrating the clinical value of lansoprazole 15 mg daily for this indication. The results are strong enough, in this reviewer's opinion, that the one "pivotal" trial suffices to support a recommendation for approval of lansoprazole for treatment of heartburn and other symptoms of GERD in patients with non-erosive esophagitis. They do not support the sponsor's request for approval of a 30 mg daily dose.

We have concern about long-term use of lansoprazole, as for other proton-pump inhibiting agents, in patients with chronic Hp infection of their gastric mucosa, Serologic testing in M95-300 showed that about 32% of patients had antibodies to Hp in the ITT (209 patients) group, somewhat more in the 43 randomized to placebo (19, or 46.3%) than in those randomized to lansoprazole 15 mg/day (23/80, 29.1%) or to lansoprazole 30 mg/day (22/86, 26.5%). The clinical significance of this was not discussed by the sponsor, although the day and night heartburn results were controlled for Hp status (see Appendices D.2.3.1 to D.2.4.2, pages 012-019, Volume 16).

IV. Regulatory Recommendations

It is recommended that lansoprazole 15 mg once daily before breakfast for up to 8 weeks be approvable for treatment of patients with heartburn and other symptoms associated with non-erosive GERD. The sponsor's request for a daily dose of 30 mg is considered not approvable.

The data from Study M95-300 are the principal support for this recommendation of approval, and it is suggested that the sponsor prepare either a graph or table, preferably of the ITT group, in which the responses are displayed for each treatment group, lansoprazole 15 mg/day, lansoprazole 30 mg/day, and placebo. it is further suggested that data for both day heartburn and night heartburn responses be shown, for either mean severity scores or for changes from baseline.

It is suggested that the sponsor should consider issues of how patients, who fail to respond to this regimen, or who have recurrence of symptoms after responding to and completing the regimen, should be managed. Specifically, the sponsor is asked to consider in such cases if recommendations should be made to patients and physicians to undertake more extensive investigation of the problem by endoscopy or other methods.

The potential long-term consequences of possibly repeated 8-week periods of treatment of this chronic clinical problems, which may accumulate to months and years if labeling instructions are not followed exactly, are also of concern, and should be addressed by the sponsor in response to the recommendation and these suggestions.

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John R. Senior, M.D., Medical Officer — 19 Dec '97 (date)
Division of Gastrointestinal and Coagulation Drug Products

cc:
NDA 20-406/SE1-016
HFD-180
HFD-180/LTalarico
HFD-180/JSenior
HFD-181/MWalsh
HFD-720/FHarrison
f/t 12/19/97 jgw
MED/N/20406712.0JS

/S/ 12-19-97

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V. References

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