

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20-555/S-003/S-004**

**STATISTICAL REVIEW(S)**

## STATISTICAL REVIEW AND EVALUATION

NDA #: 20-555/S-003

Date: ~~APR 11 1997~~

Drug: Nizatidine (Axid® AR) Tablets

Applicant: Whitehall-Robins Healthcare

Indication: Treatment of Episodic Heartburn

NDA Drug Classification: 1S

Statistical Reviewer: A. J. Sankoh, Ph.D.

Clinical Reviewer: The issues addressed in this review have been discussed with the medical reviewer, Hugo Gallo-Torres, M.D., Ph.D.

Date of Document: December 17, 1996; Date Received by Reviewer: January 28, 1997

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Volumes Reviewed: 1.1, 1.03, 1.17, 1.31-1.44, 1.45-1.55, December 17, 1996

Keywords/Phrases: Episodic heartburn; gender analysis, multiple episodes analysis; treatment-by-center interaction.

### INTRODUCTION

Heartburn, which is the term used to describe a variety of gastrointestinal symptoms treated with over the counter (OTC) medication, is related to the secretion of gastric acid in the parietal cells. Studies have shown that, through reversible binding to the H<sub>2</sub>-receptor sites on gastric parietal cells, nizatidine (a selective H<sub>2</sub>-receptor antagonist) inhibits histamine-mediated gastric acid secretion.

Nizatidine is currently approved as a prescription drug for the treatment of active duodenal ulcer, active benign gastric ulcer, healing and symptomatic relief of erosive esophagitis, and as a non-prescription drug for the prevention of meal-induced heartburn.

This statistical review addresses the efficacy of nizatidine for OTC use in treating/relieving episodic heartburn from two placebo controlled, double-blind, randomized parallel group design pivotal studies (NZ-95-01 and NZ-95-04).



# I. PROTOCOL # NZ-95-01 & NZ-95-04

## 1.1 Study Design

The two studies (# NZ-95-01 and # NZ-95-04) were identically designed as at home, two-phase, placebo controlled, double-blind, multi center, single nizatidine dose, parallel group studies. The objective was to compare the efficacy and tolerability of nizatidine 75 mg capsule (given up to twice daily) versus placebo in the treatment/relief of episodic heartburn.

After initial screening by history (heartburn, medical and gastrointestinal), physical exam, laboratory test and informed consent, patients satisfying the study inclusion criteria entered a one-week single-blind antacid treatment phase, followed by a two-week double-blind placebo/nizatidine treatment phase. The single-blind phase was designed to determine patient's eligibility for continuation into the double-blind phase and to familiarize patients with heartburn assessment methods. Only patients who experienced and treated at least three episodes of heartburn of moderate or greater severity, and had at least 50% of their episodes responding to rescue antacid medication were to continue into the double-blind treatment phase.

During the double-blind phase, patients were allowed to treat (with study medication) up to two episodes of moderate to severe heartburn daily.

Table 1 below summarizes the design and characteristics of the two pivotal studies contained in this review.

Table 1/ Summary of Design Characteristics for Two Pivotal Studies

	Mean Age/Weight	Treatment Duration	Efficacy Evaluation	Sample Size Estimated/Randomized/Analyzed (n)		
NZ-95-01	42 yrs/187 lb	Single-blind phase: 1-wk antacid (up to twice daily); Double-blind phase: 2-wk placebo/Nizatidine 75 mg (1'p to twice daily)	At: 15, 30, 45, 60, 120, 180 Minutes	Estimated DB n: 500; Entered SB: n=757 →	547 Randomized →	ITT Analysis: 537: 83% White (44/56% M/F); from 22 centers
NZ-95-04	44 yrs/187 lbs			Estimated DB n: 500; Entered SB: n=666 →	465 Randomized →	ITT Analysis: 457: 80% White (48/52% M/F); from 24 centers

Data from sponsor's Tables 5, 6, 10 of Volumes 3 (for NZ-95-01) and 17 (for NZ-95-04); DB=double-blind; SB=single-blind; wk=week.

Patients evaluations included episodic heartburn severity assessments at 6 time points (15, 30, 45, 60, 120 and 180 minutes) for three hours after dosing by giving a "YES" or "NO" answer to the question: "Has your heartburn been adequately relieved?". A 4-hour interval from the start of study medication and resolution of one episode was required before a second episode could be treated on any day of the study. At the completion of the 3-hour assessment period, patient also provided a "YES" or "NO" answer to the question: "Was your heartburn completely relieved?"

Patients who experienced insufficient relief during the double-blind treatment phase were permitted to take rescue medication (antacid) after 2 hours of post-dose medication. The time at which antacid was taken and the number of tablets taken were to be recorded in a patient diary for comparison of frequency of rescue antacid use.

### Sample Size Estimation/Randomization

A sample size of 250 patients per treatment group was postulated in order to have at least 80% power for rejecting a two-sided null hypothesis test at a 5% significance level. However, the protocol indicated that enrollment could be stopped if 460 patients completing the double-blind phase were at hand by 08/30/96.

Patients who qualified for the (double-blind) treatment phase were to be randomized within each center in a 1:1 ratio to receive nizatidine 75 mg or placebo. This reviewer did not find problem with the randomization scheme and its implementation.

### Study Objective and Primary Endpoints:

The protocol specified objective of either study was to assess the safety and efficacy of oral nizatidine 75 mg, taken as needed up to twice daily, versus placebo in episodic heartburn relief. Identical efficacy endpoints were identified: one single primary efficacy endpoint, and eight (8) secondary efficacy endpoints in each study. The primary efficacy endpoint is sustained adequate relief score (SARS). This comprised of two components from a patient's efficacy response profile: 1) sustainment of attained adequate relief, and 2) the rapidity with which such relief was attained.

To evaluate this, a categorical score of 0 to 4, based on whether or not a patient achieved sustained adequate relief for each episode and the length of time it took to achieve such relief, was to be recorded in patients' diaries. Attainment of sustained adequate relief of heartburn was assigned a value on this 5-point categorical scale as follows:

Value	Time to Relief/Response Time	Duration of Relief
4:	Within 30 mins/Yes response at 15 or 30 mins	Remaining double-blind 3-Hour Treatment Duration
3:	By 1 hour/ Yes response at 45 or 60 mins	Remaining double-blind 3-Hour Treatment Duration
2:	By 2 hours/ Yes response at 120 mins	Remaining double-blind 3-Hour Treatment Duration
1:	Within 3 hours/ Yes response at 180 mins	No component of sustained relief
0:	No relief Within 3 hours/ antacid usage anytime	No relief

Given the above 5 categories, sustained adequate relief score (SARS) is then calculated as the averaged over the first five (5) episodes per subjects (as in the table below).

### Calculation of Per Patient Averaged Sustained Adequate Relief Score

Patient	Episode #/ Severity Score					Average Score
	#1	2	3	4	5	
x	4	4	4	4	4	20/5 = 4.00
y	2	2	2	2	2	10/5 = 2.00
z	0	0	0	3	0	3/5 = 0.60

The choice of five per patient episodes was based on the suspicion that most patients would experience at least five episodes. The protocol, however, prospectively specified that if fewer than 90% of patients were to experience at least five episodes, the maximum number of episodes for which at least 90% of patients had evaluations would be used in the calculation of the average SARS. The statistical report indicate that four (and not five) episodes were used in this calculation of the average, and thus, in all the analyses included in this sNDA report.

For an episode treated with rescue antacid, a score of zero was to be assigned for all post-antacid usage time points, indicating "no adequate relief".

For episodes with missing diary entries before the 3-hour assessment, and no antacid rescue usage entry,

- a) patient's last evaluation (Yes or No) was to be used for all subsequent time points,
- b) if an interim diary time point entry was available, the last entry preceding the missing value was to be used, and
- c) for patients with no 15 minutes entries, a zero point (for no relief) was to be assigned.

### Secondary Endpoints

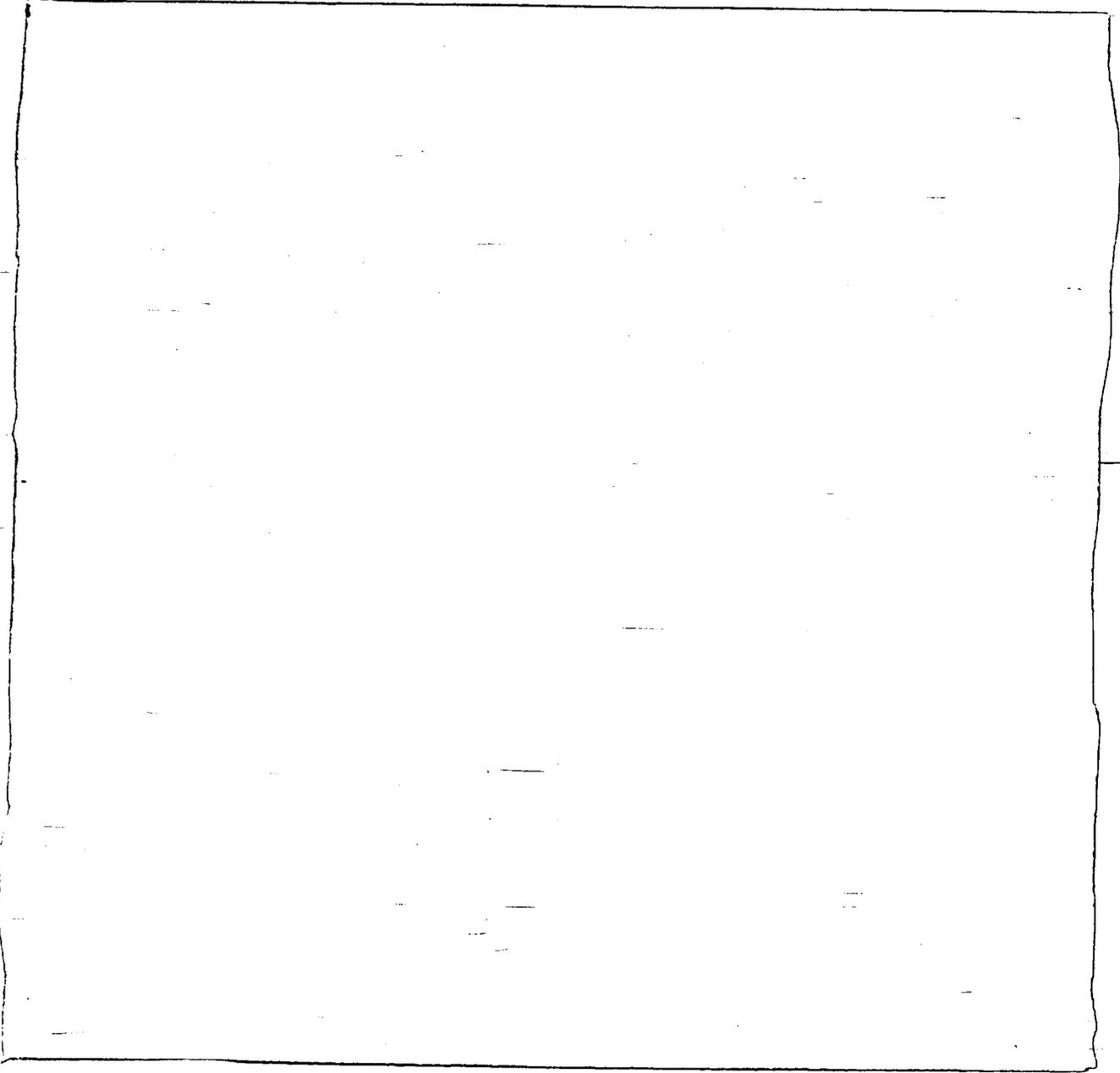
1. Sustained adequate relief score averaged over all episodes within a patient, taking into account the frequency and time at which adequate relief is first attained.
2. Proportion of episodes for which a patient achieves sustained adequate relief regardless of the time attained.
3. Sustained adequate relief score averaged over first k ( $\leq 5$ ) per patient episodes separated by at least twelve (12) hours.
4. Proportion of (first k, all) per patient episodes adequately relieved at each time point separately.
5. Proportion of per patient episodes requiring antacid usage.

6. Proportion of per patient episodes for which complete relief was attained.

7. Sustained adequate relief score for the first episode.

8. Proportion of patients who achieve sustained adequate relief for all of their recorded episodes.

**1.2.0 SPONSOR'S ANALYSIS METHOD**



### 1.2.1 Sponsor's Efficacy Analysis Results

Below is a summary of the sponsor's ITT analysis results for the primary endpoint, SARS.

**Table 3/ Sponsor's ITT Analysis Results**

Endpoint/Treatment		NZ-95-01: Mean Difference = (Niz - Pla)				NZ-95-04: (Mean Difference = (Niz - Pla)			
Efficacy Analysis Results		Plac- ebo Mean	Diff (Niz-Pla)	Trt Eff P-value	Interaction Trt x Site (Trt x Episo)	Plac- ebo Mean	Diff (Niz-Pla)	Trt Eff P-value	Interaction Trt x Site (Trt x Episo)
CMH for SARS	1* 4 Episodes	2.15	.30	.002#	.037	2.11	.28	.016#	.269
	All Episodes	2.13	.33	<.001#	.079	2.11	.24	.028#	.341
GEE for SARS	Linear Model <sup>a</sup>		.34*	<.001	<.001 (.585)		.16*	.190	.045 (.045)
	Logistic Model <sup>b</sup>		.73 (lnOR)	<.001	.016 (.754)		.38	.010	Not Given
	Logistic Model <sup>c</sup>		.73 (lnOR)	<.001	<.001 (.441)		.47	.002	Not Given
	Linear Model <sup>1</sup>		.37	<.001	<.001 (.743)		.32	.029	Not Given
	Linear Model <sup>2</sup>		.34	.004	.030 (.197)		.26	.070	Not Given
Proporti on <sup>3</sup>	Complete Relief	.24	.11	.005	.090	.24	.15	.001	.427
	SAR	.25	.10	.019	.101	.25	.15	.001	.466

\*: Denotes mean difference between nizatidine and placebo adjusted for effects in linear model (treatment, baseline severity of episode, episode number, treatment x episode number, site, treatment x site).

#: 2-sided p-value for treatment effect based on CMH test for row mean score controlling for site.

a: Treatment mean difference based on SARS for all episodes; b: same as 'a' but regardless of time; c: as in 'a' for complete relief at 3 hours.

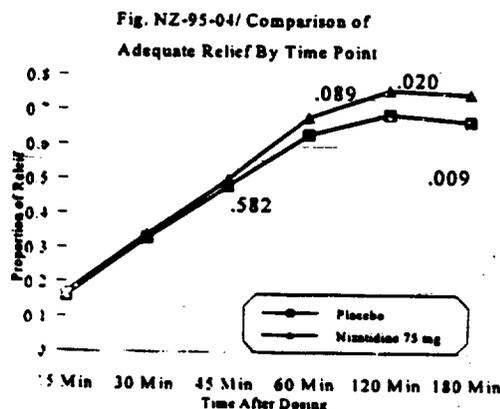
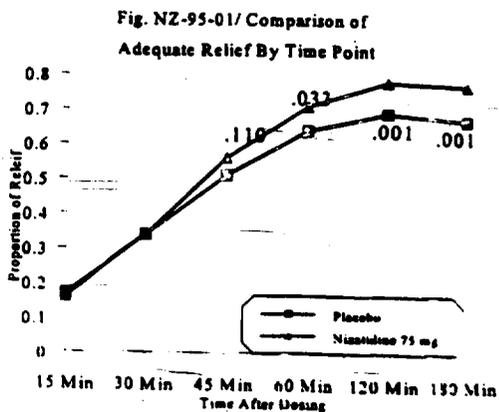
1: Includes episodes of moderate or less baseline severity rating (treatment, episode, and site in model).

2: Includes episodes with moderately severe/severe baseline severity rating (treatment, episode, and site in model).

3: Proportion is based on # of patients reporting relief (for all their episodes) at the 3-hour timepoint (SAR = sustained adequate relief).

Note: Data extracted from Tables B.3, B.4 and B.12(a,b) of volumes 1.3 (for NZ-95-01) and 1.17 (for NZ-95-04).

Figures NZ-95-01 & NZ-95-04, and Tables 4 & 5 below summarize further sponsor's ITT efficacy analysis results by time points for proportion of adequate relief and other endpoints.



**Table 4/ Sponsor's ITT Analysis Results By Time Point**  
(Treatment Mean Difference for Proportion With Adequate Relief for 4 Episodes)

Study #	Minutes After Dosing/ Mean Difference (CMH 2-Sided P-value)					
	15	30	45	60	120	180
NZ-95-01	-.01 (.594)	.02 (.916)	.05 (.110)	.07 (.033)	.09 (<.001)	.10 (<.001)
NZ-95-04	.01 (.514)	.01 (.860)	.02 (.582)	.05 (.089)	.08 (.020)	.08 (.009)

**Table 5/ Sponsor's Other ITT Analysis Results**

Endpoint/Treatment		NZ-95-01: Mean Difference = (Niz - Pla)				NZ-95-04: (Mean Difference = (Niz - Pla)			
Efficacy Analysis Results		Plac Mean	Diff (Niz-Pla)	Trt Eff P-value	Interaction Trt×Site	Plac Mean	Diff (Niz-Pla)	Trt Eff P-value	Interaction Trt×Site
CMH	1 <sup>st</sup> Episode		.40	.003#	.240	2.31	.13	.383#	.103
	1 <sup>st</sup> 4 Episodes**	2.15	.29	.003#	.035		.27	.020#	.504
Proportion of Relief	1 <sup>st</sup> 4 Episodes	.66	.10	<.001	.156	.66	.08	.014	.020
	All Episodes	.66	.10	<.001	.374	.66	.07	.027	.230
proportion	Antacid Usage								
	1 <sup>st</sup> 4 Episodes	.27	-.09	.002	.296	.27	-.06	.022	.459
	All Episodes	.28	-.10	<.001	.700	.27	-.06	.020	.382

\*\* : SARS averaged over first 4 episodes separated by at least 12 hours.

# : 2-sided p-value for treatment effect based on CMH test row mean score controlling for site.

Note: Data extracted from Tables B.5, B.6, B.9 and B.11 of volumes 1.3 (for NZ-95-01) and 1.17 (for NZ-95-04).

**Table 6/ Reviewer's Subgroup ITT Analysis Results**  
(Treatment Mean Difference for Proportion With Complete Relief of all Episodes)

Study #	GENDER		RACE		
	Male	Female	White	Black	Others
NZ-95-01	.10 (.073)	.12 (.050)	.14 (.004)	.02 (.902)	-.17 (.545)
NZ-95-04	.18 (.006)	.11 (.893)	.17 (.003)	Black+Others (.877)	
				.17 (.407)	Black+Others (.778)

For summary of results across centers, see Figures B.1-4 (attached).

### Reviewer's Comments on Sponsor's Analysis Results

#### Study Protocol # NZ-95-01

For study protocol # NZ-95-01, sponsor's efficacy analysis results indicate nizatidine 75 mg is superior to placebo in the relief of episodic heartburn after one hour of dosing. Analyses of the primary efficacy endpoint, sustained adequate relief score (SARS), with respect to the first episode, first 4 episodes, all episodes and first 4 episodes separated by at least 12 hour, by both the Cochran-Mantel-Haenszel (CMH) and the generalized estimating equations (GEE) methods consistently support nizatidine 75 mg superiority over placebo (see Tables 3, 4 and 5 above).

These effectiveness results for the primary efficacy endpoint are also consistently supported by sponsor's secondary efficacy endpoint analysis results such as those for proportion of patients with complete relief of all episodic heartburn, and proportion of episodic heartburns requiring antacid rescue.

Sponsor's analysis results, however, indicate significant treatment-by-site interactions for almost all endpoints analyzed (see attached Figures B.1-B.4, Protocol #NZ-95-01). This reviewer's analysis results (at least for the proportion of patients with adequate relief of all their episodes) are in agreement with the sponsor's treatment-by-site interaction effect findings

It should, however, be noted that no single center or a single group of centers appears to dominate the observed effectiveness results (see attached Figures B.1-B.4, Protocol #NZ-95-01); 15 (71%) of the centers or group of centers in this study showed at least a numerical advantage favoring nizatidine 75 mg.

#### Study Protocol # NZ-95-04

For study protocol # NZ-95-04, sponsor's efficacy analysis results indicate nizatidine 75 mg is superior to placebo in the relief of episodic heartburn. Analysis of the primary efficacy endpoint, sustained adequate relief score (SARS), with respect to the first 4 episodes, all episodes and first 4 episodes separated by at least 12 hour, by both the Cochran-Mantel-Haenszel (CMH) and the generalized estimating equations (GEE) methods consistently support nizatidine 75 mg superiority over placebo (see Tables 3, 4 and 5 above). However, the effectiveness results for this study are not as convincing as those for study protocol #NZ-95-01, even though there is more consistency of results across centers than is observed in study #NZ-95-01. [Also, see attached Figures B.1-B.4, Protocol #NZ-95-04.]

Gender analysis results from the two studies show mixed effectiveness results. For study NZ-95-01, the drug is relatively more effective among females than males (see Table 6 above). This observed gender effectiveness difference in this study may be due to the fact that there were more females than males (302 females vs 235 males, also see Table 1 above). For study #NZ-95-04, however, the drug is dramatically more effective among males than females (see Table 6 above) even though there were more females than males in this study (236 females vs 220, also see Table 1 above). It is, therefore, not clear to this reviewer why the drug appears to have no advantage over placebo among females in this study when it appears to do so in study NZ-95-01, and vice versa.

Race analysis results from both studies are consistent with the observed overall effectiveness results in that the results among whites (at least 80% of patients in both studies) are consistent with the observed overall results. The samples sizes for non-whites are too small to detect and/or confirm any meaningful treatment benefit (see Table 6 above).

Note that sponsor's efficacy analysis results based on the evaluable patient population are consistent with those based on the ITT patient population. These results are therefore not presented in this review. For similar reasons, only selected subgroup analysis results have been examined and presented in this reviewer.

The minimum age requirement for entry into this trial is sixteen years; the pediatric implication of this drug is therefore not clear.

No serious safety issues were reported in this trial.

### OVERALL CONCLUSIONS

1. The efficacy data in this trial support the effectiveness of nizatidine 75 mg in the treatment/relief of episodic heartburn.

A. J. Sankoh, Ph.D.

/S/

4/7/97

Mathematical Statistician

Concur:

Dr. Huque

/S/

4/7/97

Dr. Smith

/S/

4/8/97

cc:

Archival NDA # 20-555/S-003

HFD - 180

HFD - 180/Dr. Fredd

HFD - 180/Dr. Gallo-Torres

HFD - 180/Mr. Folkendt

HFD - 344/Dr. Lisook

HFD - 720/Dr. Smith

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## STATISTICAL REVIEW AND EVALUATION

NDA #: 20555/SE2 - 004

Drug: Axid 75mg (Nizatidine 75mg)

OCT 28 1997

Drug Classification: S

Indication: Prevention of heartburn, acid indigestion, and sour stomach related to foods and beverages when taken 0 to 60 minutes before eating or drinking.

Sponsor: Whithall Robins Healthcare

Clinical Reviewer: Hugo Gallo-Torres, M.D., Ph.D.

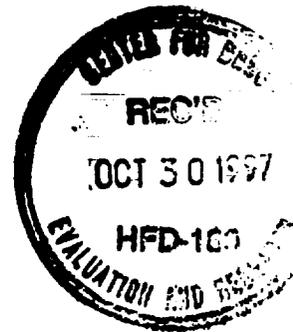
Statistical Reviewer: Mushfiqur Rashid, Ph.D.

Volume Reviewed: Volumes 13-23.

Date Received at CDER: April 9, 1997

45-Day filing Date: May 16, 1997

User Fee Due Date: April 1, 1998



### INTRODUCTION

Heartburn is the most common symptom of gastroesophageal reflux disease. Symptoms are often associated with reflux of acidic gastric contents into the esophagus, producing a burning sensation. Suppression of acid secretion for prevention of heartburn and neutralization of excess acid for treatment of heartburn are the current mainstays of therapy. The most frequent cause of episodic heartburn is food and beverage ingestion, and consumers are reliably able to predict which foods are likely to cause symptoms.

Axid 75mg (Nizatidine 75mg) is currently indicated for nonprescription use for the prevention of meal-related heartburn when taken 30 to 60 minutes before eating or drinking. Note that Nizatidine has been used extensively as prescription doses of 150mg to 300mg per day for the treatment of gastric acid-related disorders such as duodenal ulcers.

This supplemental submission addresses the use of Axid 75mg in the complete prevention of heartburn, acid indigestion, and sour stomach related to foods and beverages when taken 0 to 60 minutes before eating or drinking. The study designs and dose in these trials were identical

to those in the original submission with the exception of time of dosing relative to the start of the test meal and the inclusion of a single 75mg dose of Axid. This submission is designed to support a change to the labeling of the currently marketed product to allow dosing at the time of a meal or up to an hour before eating.

The sponsor has studied the safety and efficacy of the product in complete prevention or reduction in severity of heartburn when administered 0 and 15 minutes prior to consuming food and beverages anticipated provoking heartburn. Two 2-phased (phase III) placebo-controlled multi center studies (NZ-95-02 and NZ-95-03) have been conducted in support of the indication proposed in this supplemental submission.

The first phase is an open (run-in) single-blind qualifying phase where patients who are men or women of at least 16 years of age with at least a three-month history of heartburn responsive to antacids or nonprescription histamine H<sub>2</sub>-receptor antagonists. For the single-blind qualifying meal, subjects received placebo 15 minutes and 0 minutes (immediately) before the meal. After the 0 minute dose, subjects indicated the presence or the absence of heartburn on the 'Heartburn Presence Scale' (HPS) by answering 'Yes' or 'No' to the question "Do you have heartburn - a burning discomfort - at this time."

The procedures and assessments for the double-blind treatment meal were the same as for the single-blind qualifying meal except that subjects were randomized to one of the three groups: placebo at both 15 minutes and immediately before the test meal, Axid 75mg at 15 minutes before and placebo immediately before the test meal, or placebo at 15 minutes before and Axid 75mg immediately before the test meal.

The provocative meals used in these studies was intended to duplicate the meal of chili, nacho cheese tortilla chips, and Coca-Cola. Each subject received the same chilli recipe for both the single blind qualifying and double-blind treatment meals.

The primary efficacy parameter in the two pivotal studies is complete prevention of post-meal heartburn defined as being heartburn free at all post-meal assessment time points.

The secondary efficacy parameters in these trials are as follows:

- 1) the average severity of heartburn across all post-meal assessments within each subject and
- 2) the maximum severity of heartburn across all post-meal assessments within each subject.

## I. STUDY PROTOCOLS NZ-95-02 and NZ-95-03

### 1.1 Study Designs

The purpose in these two protocols was to compare the safety and efficacy of Axid 75mg for the reduction of severity or complete prevention of meal-induced heartburn. This study is described in the protocol as an open label (run-in), inpatient lead-in to a randomly assigned double blind, placebo controlled, parallel-group, outpatient, and multi-center clinical study.

Studies NZ-95-02 and NZ-95-03 were single-dose, multi-center trials with a single blind placebo-qualifying provocative meal (single blind qualifying meal) and a placebo-controlled, randomized, parallel group double-blind treatment provocative meal (double-blind treatment meal) 6 to 10 days later. These studies evaluated the efficacy of Axid 75 mg versus placebo in completely preventing heartburn when taken 15 minutes or immediately before a test meal. Subjects were men and women of 16 years of age or older with at least a 3-month history of heartburn responsive to antacids or nonprescription histamine H<sub>2</sub> receptor antagonists.

For the single blind qualifying meal, subjects received placebo 15 minutes and immediately before the meal. After the 0 minute dose (immediately before eating), subjects indicated the presence or absence of heartburn on the Heartburn Presence Scale (HPS) by answering 'Yes' or 'No' to the question, "Do you have heartburn - a burning discomfort - at this time?"

Subjects also indicated the severity of their heartburn on a 100mm visual analog heartburn severity scale (HSS) with 0mm on the left indicating 'None' and 100mm on the right indicating 'Very Severe' heartburn in their diaries. Subjects then ate a provocative meal consisting of chili, nacho cheese chips, and Coca-Cola.

Subjects recorded in their diaries whether or not they had heartburn on the HPS at 30, 60, 90, 150, and 210 minutes after the start of the test meal. At these same times subjects also indicated the severity of their heartburn on the HSS. Subjects reporting a heartburn severity rating of at least 50mm at least once for any of the post-meal assessments of the single blind qualifying phase were eligible for randomization into the double-blind treatment phase. Subjects were permitted to take rescue antacid after 90 minutes if they needed medication to obtain relief from their heartburn.

The procedures and assessments for the double blind treatment phase were the same as for the single-blind qualifying phase except that subjects were randomized to one of the three treatment groups at both 15 minutes and immediately before the test meal; i.e. Axid 75mg at 15 minutes before and placebo immediately before the test meal, or placebo at 15 minutes before and Axid 75mg immediately before the test meal.

### Sample Size Estimation/Randomization Schemes:

A sample size of approximately 175 subjects per treatment group was planned to achieve 80% (with type 1 error probability of .05) power to detect a significant difference between Axid 75mg administered immediately or 15 minutes prior to a meal. It was assumed that the response rate (completely free of heartburn over the entire 3-hour of post-meal assessment period) was 5% for placebo and 15% for Axid. A 10% improvement over placebo was considered to be a clinical meaningful significance.

**Table 1.1 (Reviewer's) / Patient Disposition**

Study #	# of Centers	Design	Oral Dose	Type of Control	Sample Size in DB	# of Patients Per Group in DB
NZ9502	13	DB,PG,R,PC, TP,SD,3-arm	a) Placebo 75mg b) -15 -min Axid 75mg c) 0-min Axid 75mg	placebo	609	Placebo: 204 -15-min Axid: 202 0-min Axid: 203
NZ9503	10	DB, PG, R, PC, TP, SD, 3-arm	a) Placebo 75mg b) -15 -min Axid 75mg c) 0-min Axid 75mg	placebo	555	Placebo: 187 -15-min Axid: 184 0-min Axid: 184

Note:- DB: Double blind; PG: Parallel group; PC: Placebo controlled; TP: Two-phased; PC: Placebo controlled; SD: Single dose; FP: First phase; SP: Second phase; R: Randomized; P: Placebo; T: Treatment; -15 -min: 15 minutes before the provocative meal; 0-min: immediately before the provocative meal.

The protocol indicated that the randomization was performed independently within each center for both the studies. This reviewer did not find any problem with the randomization process.

### Study Objectives and Primary Endpoints:

The primary analysis for establishing efficacy is based on data from the intent-to-treat population (ITT), which consisted of all randomized subjects who took study medication and provided post-meal efficacy data. As mentioned earlier, the efficacy parameters consisted of (1) complete prevention of postmeal heartburn defined as being heartburn free at all post-meal assessment time points, (2) the average severity of heartburn across all post-meal assessments within each subject, and (3) the maximum severity of heartburn across all post-meal assessments within each subject. The primary variable was the percentage of subjects with complete prevention of post-meal heartburn.

## 1.2 Sponsor's Analysis Method and Analysis Plan

### 1.2.1 Data Set Analyzed and Statistical Analysis Plan

The protocols indicated that all treated patients, intent-to-treat (ITT), were to be included in the primary efficacy analysis regardless of compliance. The ITT population was considered to be the primary population for all analyses. The primary efficacy parameter was complete prevention of post-meal heartburn defined as being heartburn free at all post-meal assessment time points.

This reviewer does not disagree with the sponsor's claim that the two treatment groups (randomized as well as evaluable) were comparable (see Table A.1 in the Appendix for some demographic characteristic comparisons) with regard to demographic parameters at baseline.

### 1.2.2 Sponsor's Analysis Results/Reviewer's Analysis and Comments

#### Analysis Based on both Primary and Secondary Endpoints:

In each of the studies, each patient indicated the presence or absence of heartburn on the heartburn presence scale (HPS) by answering 'Yes' or 'No' to the question "Do you have heartburn - a burning discomfort - at this time?"

In Table 1.2 we summarize the results of study NZ-95-02 for both primary and secondary endpoints.

**Table 1.2 (Reviewer's): Primary and Secondary Efficacy Analyses of ITT Population for study NZ-95-02**

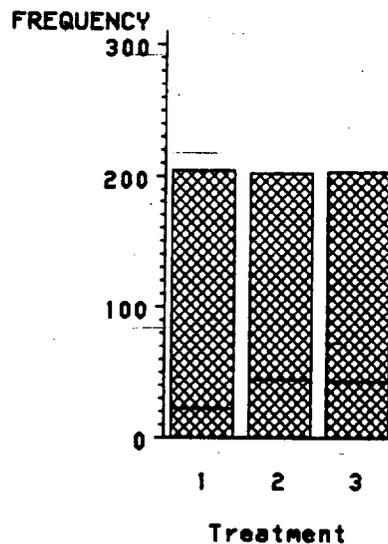
End-Points	Plac (n=204)	-15min Axid (n=202)	plac- (-15min Axid)	p-value	0-min Axid (n=203)	plac- (0min Axid)	p-value
% of subjects without post-meal heartburn	11	22	-11	0.002	22	-11	0.004
Average severity of heartburn (mm)	26	20	6	0.002	19	7	0.001
Maximum severity of heartburn (mm)	44	36	8	0.010	34	10	<0.001

From Table 1, we see that the percentage of subjects without post-meal heartburn was significantly higher in the Axid treated groups (-15min Axid and 0min Axid) than in the placebo group. Also the analyses of secondary efficacy parameters (average severity of heartburn and maximum severity of heartburn) uniformly supported the effectiveness of 0min and -15min Axid 75mg. See also Table A.2 in the appendix for details.

Figure 1 (Reviewer's) gives graphical comparisons of the three treatment groups for the primary endpoint, complete prevention of heartburn.

## Study NZ-95-02

Figure 1: Heartburn Absence vs Presence  
Treatment: 1=Placebo 2=-15min Axid 3=0min Axid  
Lower Rectangle: Heartburn Absence  
Upper Rectangle: Heartburn Presence



We summarize the results of study NZ-95-03 in Table 1.3.

**Table 1.3 (Reviewer's) : Primary and Secondary Efficacy Analyses of ITT Population at in study NZ-95-03**

End-points	plac (n=187)	-15min Axid (n=184)	place- (-15min Axid)	p-value	Omin Axid (n=184)	place- Omin Axid	p-value
% of subjects without post-meal heartburn	14	19	-5	0.166	27	-13	.001
Average severity of heartburn (mm)	24	19	5	0.006	19	5	.003
Maximum severity of heartburn (mm)	42	33	9	0.004	32	10	.001

In study NZ-95-03, the percentage of subjects without post-meal heartburn was significantly higher in the Axid treatment group Omin Axid 75mg than in the placebo group. Although there was no significant difference between the Axid treatment group -15min Axid 75mg and placebo with respect to percentage of subjects without postmeal heartburn, there is a numerical trend favoring the treated group over the placebo group. If one were to remove center 0309 from the analysis, the data would show a significant difference (p-value .012) favoring -15min Axid over placebo. From the results summarized in figures 2 and 3, one can visualize the impact of center 0309.

**STUDY NZ-95-03**

Heartburn Absence (HB) Vs Heartburn Presence (Lower Rectangle: HB Absence; Upper Rectangle: HB Presence). Treatment: 1=Placebo 2=-15min Axid 3=Omin Axid Axid

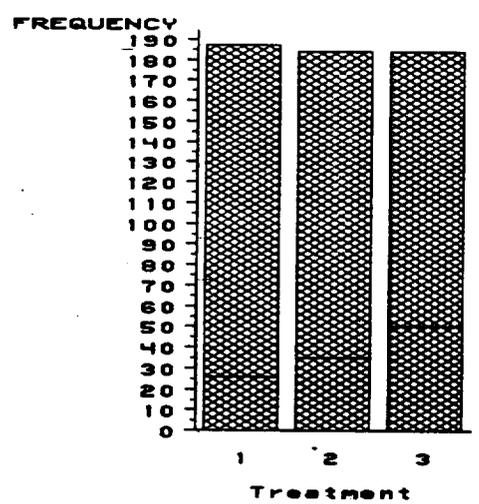


Figure 2 (Reviewer's): All Centers

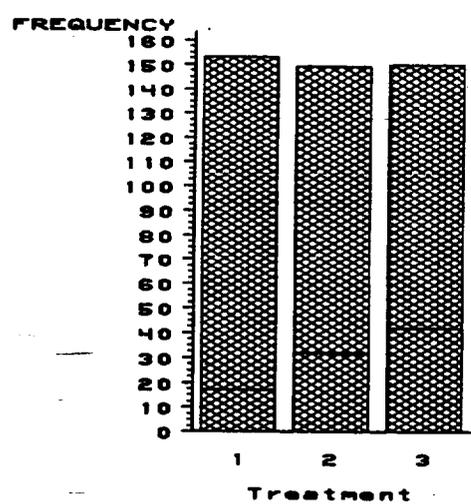


Figure 3: (Reviewer's): All Centers Except 0309

Also analyses of secondary efficacy parameters (average severity of heartburn and maximum severity of heartburn) uniformly supported the effectiveness of Omin Acid 75mg and -15min. Acid 75mg. See Table A.2 in the appendix for details.

#### Analysis Based on the Primary Endpoint at Each Time point:

In the following table (Table ) we summarize the difference of the percentages of subjects without heartburn for each time point for both studies NZ-95-02 and NZ-95-03.

**Table 1.4/ Sponsor's ITT Analysis By Individual Time Point  
Difference in Proportions of Subjects With Heartburn Presence (extracted from sponsor's  
Table B.6, page 76, volume 13 and Table B.6, page 85, volume 18)**

<u>Minutes After Dosing/Proportion Difference - placebo-acid(two-sided p-value)</u>						
Study # /Comparisons	0	30	60	90	150	210
<b><u>NZ-95-02</u></b>						
Pl. VS. Omin Acid	.02(.200)	.08(.114)	.09(.045)	.09(.038)	.17(.000)	.16(.001)
Pl. VS. -15min Acid	0(.999)	.03(.517)	.12(.015)	.12(.011)	.14(.001)	.13(.007)
<b><u>NZ-95-03</u></b>						
Pl. VS. Omin Acid	-.01(.317)	.02(.752)	.09(.063)	.18(.006)	.20(.000)	.20(.000)
Pl. VS. -15min Acid	-.01 (.324)	.00(.857)	.06(.248)	.10(.034)	.16(.001)	.14(.003)

In study NZ-95-02 there are significant differences in the proportions of subjects with heartburn presence between placebo and the treated groups (Omin Acid 75mg and -15min Acid 75mg) after one hour of taking the provocative meal. However, in study NZ-95-03 there are significant differences in the proportion of subjects with heartburn presence between placebo group and the treated groups (Omin Acid 75mg and -15min Acid 75mg) after 90 minutes of taking the provocative meal. Thus, indicating significant treatment benefit was realized 30 minutes earlier in study NZ-95-02 than in study NZ-95-03.

### Analysis Based on the Primary Endpoint by Investigators:

In the following table (Table 1.5) we summarize the differences in the percentages of subjects without heartburn for study NZ-95-02 by investigators.

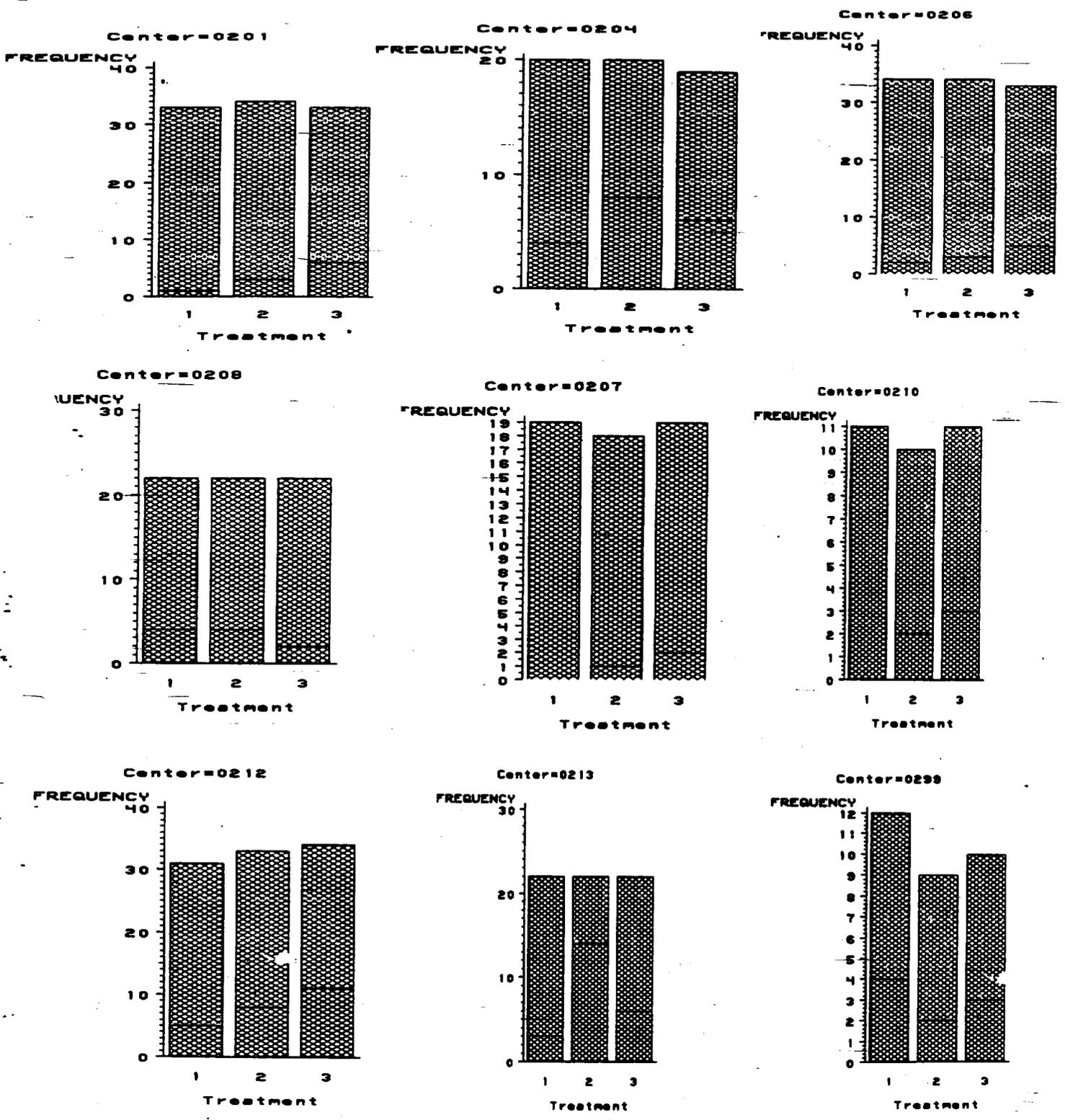
**Table 1.5 (Reviewer's)/ Percentage of Subjects Without Post-Meal Heartburn Among ITT Population in Study NZ-95-02 by Investigators**

Center	Placebo		Omin Axid		Omin Axid - Placebo			-15min Axid		-15min Axid Placebo		
	n	%	n	%	diff. (%)	p-value	App. 95% CI	n	%	diff.(%)	p-value	App. 95% CI
0201	33	3	33	18	15	.047	(.5, 29.8)	34	9	6	.321	(-5.6, 17.1)
0204	20	20	19	32	12	.414	(-16.4, 39.6)	20	40	20.0	.173	(-8.4, 48.4)
0206	34	6	33	15	9	.218	(-5.5, 24.1)	34	9	3	.645	(-9.6, 15.5)
0207	19	0	19	11	11	.152	(-3.7, 24.7)	18	6	6	.304	(-5.3, 16.4)
0208	22	18	22	9	-9	.385	(-29.7, 11.5)	22	18	0	1.0	(-23.3, 23.3)
0210	11	0	11	27	27	.069	(-.3, 54.9)	10	20	20	.128	(-6.1, 46.1)
0212	31	16	34	32	16	.132	(-4.5, 36.9)	33	24	8	.424	(-11.7, 28.0)
0213	22	14	22	27	14	.268	(-10.4, 37.7)	22	64	50	.001	(24.7, 75.3)
0299	12	33	10	30	-3	.870	(-44.2, 37.6)	9	22	-11	.586	(-51.2, 29.0)
Total	204	11	203	22	11	.004	(3.4, 17.5)	202	22	11.	.002	(4.3, 17.9)

Note: diff: the difference between the two treatments; p-value has been computed using the combined treatment groups (Mantel -Haenzel standard error of the difference); Approximate confidence intervals are based on within group standard errors.

From the above table it can be seen that there is a consistent advantage trend of favoring Axid 75mg taken either 15 minutes before a meal or immediately before a meal relative to placebo for all centers except centers 0299 (both treatments) and 0208 (Omin Axid 75mg). In figures 4-12 we display heartburn absence versus heartburn presence for each center. Note that, there is no significant treatment by site interaction effect as evidenced by the test of homogeneity p-value (=0.383).

**Figure 4-12 (Reviewer's): Heartburn Presence Vs Heartburn Absence by Center**  
Treatment: 1=Placebo 2=-15min Axid 3=0min Axid  
Lower Rectangle: Heartburn Absence Upper Rectangle: Heartburn Presence



In the following table (Table 1.6) we summarize the differences of the percentages of subjects without heartburn for study NZ-95-03 by investigators.

**Table 1.6 (Reviewer's)/ Percentage of Subjects Without Post-Meal Heartburn Among ITT Population in Study NZ-95-03 by Investigators.**

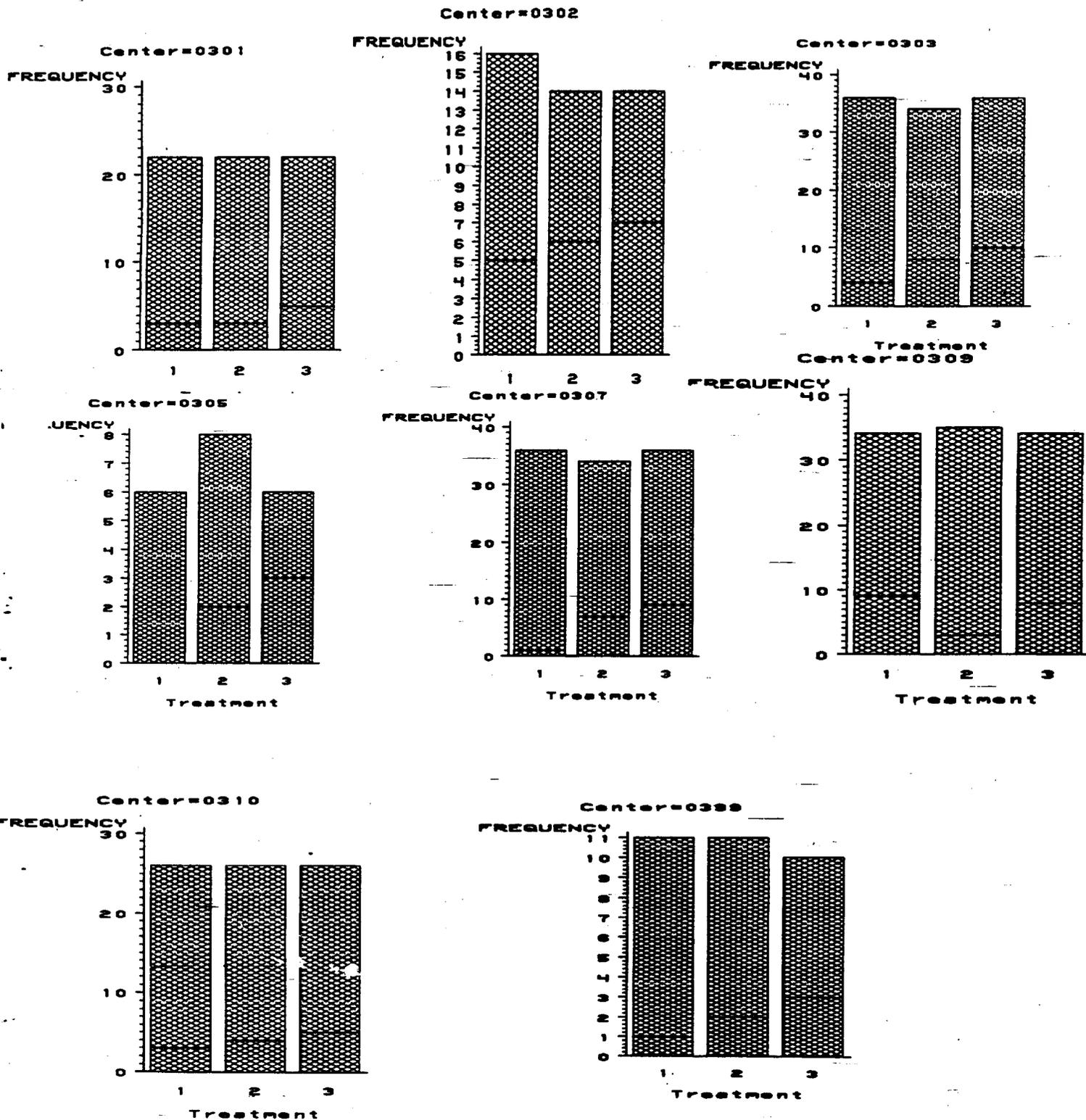
Center	Placebo		0min Axid		0min Axid - Placebo			-15min Axid		(-15min Axid) - Placebo		
	n	%	n	%	d (%)	p-value	App. 95% CI	n	%	d	p-value	App. 95% CI
0301	22	14	22	23	9	.440	(-14.1, 32.3)	22	14	0.0	1.0	(-20.8, 20.8)
0302	16	31	14	50	19	.304	(-17.2, 54.7)	14	43	12	.518	(-24.1, 47.3)
0303	36	11	36	28	17	.076	(-1.5, 34.8)	34	24	12	.171	(-5.4, 30.2)
0305	6	0	6	50	50	.056	(6.2, 93.8)	8	25	25	.202	(-7.1, 57.1)
0307	36	3	36	25	22	.007	(6.9, 37.6)	34	21	18	.020	(3.0, 32.6)
0309	34	26	34	24	-3	.781	(-23.8, 17.9)	35	9	-18	.052	(-35.7, -1)
0310	26	12	26	19	8	.446	(-12.2, 27.6)	26	15	4	.687	(-15.0, 22.7)
0399	11	9	10	30	21	.234	(-13.9, 55.7)	11	18	9	.544	(-20.7, 38.99)
Total	187	14	184	27	13	.001	(5.4, 21.6)	184	19	5	.166	(-2.2, 12.8)

Note: d: the difference between the two treatments; p-value has been computed using the combined treatment groups (Mantel - Haenzel standard error of the difference); Approximate confidence intervals are based on within group standard errors.

The results reported in the above table show a consistent numerical advantage favoring Axid 75mg taken either 15 minutes before a meal or immediately before a meal relative to placebo for all centers except center 0309. Note that overall there is no significant differences (p-value .166) between placebo and -15min Axid 75mg. Furthermore there is no significant treatment by center interaction effect of at the .05 level as evidenced by the test of homogeneity p-value (=0.110) for the all center-pooled results. There is, however, a numerical trend favoring placebo over the treatments (0min and -15min, p-value .781) and a statistically significant difference (p-value .052) for placebo versus -15min treatment comparisons for center 0309.

In figures 12-19, we compare heartburn absence versus presence for study NZ-95-03 by center.

**Figure 12-19(Reviewer's): Heartburn Presence Vs Heartburn absence by Center**  
**Treatment: 1=Placebo 2=-15min Axid 3=0min Axid**  
**Lower Rectangle: Heartburn Absence Upper Rectangle: Heartburn Presence**



Note that upon exclusion of center 0309 from the analysis data, the statistical findings in favor of -15min Axid approaches significance (p-value .012), thus indicating the impact of center 0309 on the overall result.

### 1.3 Other Subsets Analysis and Reviewer's Comments

In the following we consider subsets analysis for both studies.

**Table 1.7/ (Reviewer's) Postmeal Heartburn Presence (%) by Gender**

Study and Sub-group	Heartburn Presence/ Sample Size(%)			Placebo - Omin Axid		Placebo - (-15min) Axid	
	Placebo	Omin Axid	-15min Axid	% Difference	p-value	% Difference	p-value
<b>NZ-95-02</b>							
Sex							
Male	86/97 (89)	56/78(72)	72/87(83)	17	.005	6	.251
Female	94/107 (88)	103/125 (82)	85/115(74)	6	.248	14	.009
<b>NZ-95-03</b>							
Sex							
Male	59/66 (89)	62/88 (70)	64/81(79)	19	.007	10	.081
Female	102/ 121(84)	72/96 (75)	85 /103 (83)	9	.080	1	.899

Gender analyses from the study NZ-95-02 show mixed effectiveness results. For placebo versus Omin Axid 75mg comparisons, the result for males are consistent with the overall effectiveness findings while that for females is not although there are more females than males. The opposite is observed for placebo versus -15min Axid mg comparisons. For study NZ-95-03, similar trends are observed regarding Omin Axid 75mg. For placebo versus -15mg Axid 75mg comparisons, there are indications of positive trends for Axid in both gender groups.

#### **1.4 Sponsor's Safety Event Summary Results and Reviewer's Comments:**

The safety population used in these studies consisted of all patients who were dispensed study drug and were dispensed a meal at the qualifying run-in visit (Visit 2).

Data across all studies revealed that Axid 75mg was very well tolerated. During the treatment phase of the studies, 4.1% patients in the Omin Axid 75mg, 2.3% patients in the -15min 75mg, and 2.8% patients in the placebo group experienced at least one adverse event. Eleven placebo subjects reported at least one adverse experiences versus nine subjects in the -15min group, and sixteen in the Omin group.

The incidence of adverse experiences between studies was similar for Axid 75 treated groups and the placebo treatment group. There was no significant difference between any Axid 75 groups and placebo within any body system or individual adverse experience. Most of the adverse experience were rated mild or moderate. Severe adverse experiences were reported by 2 placebo-treated subjects (both headache), 1 subject in the -15min Axid 75 treatment group (dyspepsia) and four subjects in the Omin Axid 75 treatment group (headache, dyspepsia, nausea).

## **II INTEGRATED SUMMARY:**

### **2.1 Integrated Efficacy Summary/Reviewer's Summary and Comments**

Two placebo-controlled studies (NZ-95-02 and NZ-95-03) conducted in the United States (US) provide the primary data in support of the efficacy of Axid 75mg (when taken 15 minutes or immediately before a provocative meal) completely preventing heartburn.

Analysis of the primary efficacy parameter, complete prevention of meal induced heartburn, revealed a significantly lower value in the Axid 75mg groups than in the placebo group at the treatment visit when the two studies NZ-95-02 and NZ-95-03 are combined and the drug is taken immediately or 15 minutes prior to a provocative meal. However, study NZ-95-03 did not convincingly support (p-value .166) the efficacy of Axid 75mg with respect to complete prevention when taken fifteen minutes before a provocative meal.

In the following table we present gender analyses for the combined studies. Gender analysis summarized below show that both treatments Omin and -15min Axid 75 are effective in complete prevention of heartburn within sex.

Table 1.8/ (Reviewer's) Postmeal Heartburn Presence (%) by Gender for Pooled Data

Sub-group	Sample Size(%)			Placebo - 0min Axid		Placebo - (-15min) Axid	
	Placebo	0min Axid	-15min Axid	% Difference	p-value (exact, two-tailed)	% Difference	p-value (exact, two-tailed)
Sex							
Male	163 (89)	166 (71)	168 (81)	18	< .001	8	.047
Female..	228 (86)	221 (79)	218 (78)	7	.062	8	.035

### III OVERALL REVIEWER'S COMMENTS/CONCLUSIONS:

#### Conclusions:

1. In this reviewer's assessments, the efficacy data in studies NZ-95-02 and NZ-95-03 indicate that Axid 75mg is significantly effective in the complete prevention of heartburn symptoms in patients 16 years or older when administered immediately (0-min) prior to consuming food and beverages anticipated to provoke heartburn. Regarding Axid 75mg taken 15 minutes before a meal provoking heartburn, the effectiveness results favoring Axid 75 mg are not as convincing as those in favor of Axid-75 mg taken immediately before the provoking meal. In this reviewer's assessments, however, there is enough evidence to conclude that the -15min Axid 75mg treatment group is also effective in this trial.

In addition, both studies showed that Axid 75mg significantly reduced both the average and the maximum heartburn severity when taken immediately or 15 minutes prior to a provocative meal.

2. In this reviewer's assessments, the safety data in studies NZ-95-02 and NZ-95-03 indicate that Axid 75mg is well tolerated.

3. Because the minimum age requirement for the three studies is at least sixteen years, it is not known what implications this trial will have for patients who are less than sixteen years old.

/S/

16/27/97

Mushfiqur Rashid, Ph. D.  
Mathematical Statistician

## Appendix -

**Table A.1/ Summary of Demographic and Background Characteristics (extracted from sponsor's Table 2, page 10, volume 13)**

Study	ITT Population	Age range (mean)	Gender % M/F	Race % C/B/A/H/O
NZ-95-02	Total: 609	16-74 (39)	43/57	65/22/1/12/1
	Placebo: 204	16-69 (39)	47/53	63/22/1/13/2
	-15min Axid 75mg: 202	17-72 (40)	43/57	65/22/1/12/1
	Omin Axid 75mg: 203	16-74 (38)	38/62	66/21/1/10/2
NZ-95-03	Total: 555	16-74 (37)	42/58	74/14/1/11/0
	Placebo: 187	16-69 (37)	35/65	72/15/2/11/1
	-15min Axid 75mg: 184	17-72 (38)	44/56	74/14/2/10/1
	Omin Axid 75mg: 184	16-74 (35)	48/52	75.5/12/.5/12/0

Note: C/B/A/H/O=Caucasian/ Black/Asian/Hispanic/ Others

**Table A.2/ Percentage of Subjects With Reduction of Heartburn Severity During Double-Blind Treatment Meal (extracted from sponsor's Table 4, page 12, volume 13)**

Study	Placebo	-15min Axid 75mg	p-value	Omin Axid 75mg	p-value
NZ-95-02	(n=204)	(n=202)		(n=203)	
% of subjects with average severity less than or equal to 25mm	55	67	0.010	68	0.008
% of subjects with maximum severity less than or equal to 25mm	30	43	0.006	46	0.001
NZ-95-03	(n=187)	(n=184)		(n=184)	
% of subjects with average severity less than or equal to 25mm	56	69	0.009	67	0.027
% of subjects with maximum severity less than or equal 25mm	33	46	0.009	49	0.001