better than diclofenac at week 6 while Arthrotec II was significantly better than placebo at week 12 only. For Patient's Assessment of Arthritis Pain, all three active treatments were significantly better than placebo at week 6 only. For dropouts due to lack of efficacy, all three active treatments were significantly better than placebo (diclofenac 14%, Arthrotec I 15%, Arthrotec II 20.7%, placebo 38.2%). For the Health Assessment Questionnaire, all three active treatments were significantly better than placebo at week 6 and in addition, diclofenac was also significantly better than placebo at week 12. For the Paulus Index, only Arthrotec II was significantly better than placebo at both week 6 and week 12 while diclofenac was significantly better than placebo at week 12. There were no differences among treatments in medical compliance.

Reviewer's Comments

The result of this study is very interesting. The pooled data without regard to center effect seemed to show that all three active treatments were better than placebo, significantly in the ITT population at week 12 but only numerically (non-significant) in the evaluable cohort as defined by the sponsor. In general, the week 2 results (not discussed above since efficacy evaluation on NSAIDs usually put more weights at week 4 and later) were better than those of the weeks 6 and 12. The lack of statistical significant findings in the evaluable cohort points to the weakness of the result of this study.

In general, one would consider an NSAID to be effective if at least 3 of the 4 primary efficacy variables are statistically significantly better than placebo. An NSAID would be considered to be equivalent to an active control if the ratio Q of the mean improvement from baseline between the NSAID and the active control is between 0.8 and 1.2 with its lower 95% confidence limit 0.7 or better. Using this guidance, diclofenac and Arthrotec I have not been shown to be more effective than placebo at week 6 or week 12 while Arthrotec II was more effective than placebo at week 6 (3 of 4 primary efficacy variables better than placebo $p<0.05$ - not shown in this review but in the submission which the sponsor considered them secondary comparisons) but not at week 12 (only 2 of 4 primary efficacy variables with $p<0.05$). For the comparisons between the Arthrotecs and diclofenac, only Arthrotec II met the equivalence criteria at week 12 and may be somewhat better than diclofenac at week 6. Thus, among the three active treatments, Arthrotec II appeared to be the most effective when compared to placebo.

The p-values in Tables 10 and 11 were based on the ANOVA model without the treatment by investigator interaction term. When this interaction term was included, each of the three active treatments became statistically significantly better than placebo

in most primary efficacy variables. However, accompanying these significant main effects, there were also statistically significant treatment by center interactions. Thus, the significant treatment effect becomes difficult to interpret without going into the profiles of the individual centers. Attached in this review are the graphical displays of the profiles of the treatment effects of individual centers extracted from the sponsor's submission. If one pays attention to the comparison between Arthrotec II and placebo (last two columns of the spaghetti plots), one may notice that there were **qualitative treatment by center interactions** in which some centers (4 to 8 out of 20 depending on the efficacy variables and visits) favored placebo over Arthrotec II though the majority of centers favored Arthrotec II over placebo. This indicated that pooling of data among centers may not be appropriate. Another interesting observation is that the treatment effects among the four treatment groups were not too different in most centers except for a few (2 to 4) centers which contributed large differences between placebo and the active treatments. These few centers included the 2 Canadian centers and 2 other U.S. centers. By examining these plots, it can be seen that there was a wide range of placebo responses among centers which may have contributed to the weak results of the study. It is also possible that patients' disease severities were too mild or the dose of the active treatments was too low to separate the active treatments from placebo. The maximum recommended labeling dose for diclofenac is 200 mg per day for RA which is higher than the 150 mg per day in this study.

V. The Non-U.S. RA Studies

There were two non-U.S. RA studies. Both were randomized, double-blind, active controlled, parallel groups, multicenter, 12-week studies comparing Arthrotec I BID-TID with diclofenac 50 mg BID-TID. Protocol IN2-89-02-292 required RA patients of Functional Capacity Classification of I to III whereas Protocol IN2-89-02-289 did not have FCC requirements. The latter protocol included an endoscopy of patients while the former did not. The following is a summary of the results of these studies.

Protocol IN2-89-02-292

This study was conducted between June 1989 and June 1990. Three hundred forty-six (346) randomized patients received at least one dose of study medication (Arthrotec I 177, diclofenac 169). There was a seven-day pretreatment period in which patients were evaluated for eligibility before the 12-week treatment. Patients were randomized and evaluated at baseline after the pretreatment, at weeks 4, 8, and 12, the end of the study period. The regimen of BID or TID was chosen by the

investigator for appropriate control of the patient's arthritis, although changes were allowed during the study. The treatment groups were comparable in demographics and baseline disease severity. The mean age was 56 years and approximately 74% were females. More than 98% of patients were Caucasians. The difference in mean duration of disease between the two groups was significantly different (Arthrotec I 7.8 years, diclofenac 9.3 years). The mean number of Tender/Painful Joints was 18 and the mean number of Swollen Joints was 14. Dropouts were about the same in both treatment groups (21%). Table 12 shows the number of patients by treatment group who dropped out for various reasons.

Table 12. Dropouts By Treatment and Reason

	Lack of Efficacy	Adverse Event	Other	Total
Diclofenac 50 mg n=169	7	28	3	38
Arthrotec I n=177	5	26	5	36
Total n=346	12	54	8	74

Table 13 shows the summary results of the four primary efficacy variables. The definitions of the categories in the Global Assessments are the same as in the U.S. study, i.e., a change of 2 units or more for improved or worsened.

Table 13. Primary Efficacy Variables at Week 4 (ITT population)

Outcome	diclofenac BID-TID N=227	Arthrotec I BID-TID N=228	p & Q* value
Phy.'s Global			
Improved	3%	5%	
Unchanged	94%	92%	
Worsened	2%	1%	
Unknown	1%	2%	p=0.444
Baseline mean	2.55	2.68	Q=1.05 [1.00,1.11]
Least Sq. Mean	2.43	2.53	Q=1.04 [0.98,1.11]
Patient's Global			
Improved	4%	3%	
Unchanged	92%	92%	
Worsened	4%	2%	
Unknown	1%	2%	p=0.781
Baseline mean	2.60	2.68	Q=1.03 [0.98,1.09]
Least Sq. Mean	2.46	2.56	Q=1.04 [0.97,1.12]

Outcome	diclofenac BID-TID N=227	Arthrotec I BID-TID N=228	p & Q* value
Tender/Pain Score			
Improved	14%	13%	
Unchanged	77%	74%	
Worsened	8%	11%	
Unknown	1%	2%	p=0.743
Baseline mean	26.58	26.38	Q=0.99 [0.88,1.12]
Least Sq. Mean	24.11	24.76	Q=1.03 [0.88,1.20]
Swelling Score			
Improved	15%	11%	
Unchanged	72%	73%	
Worsened	12%	13%	
Unknown	1%	2%	p=0.693
Baseline mean	18.01	20.45	Q=1.14 [1.00,1.29]
Least Sq. Mean	15.37	18.64	Q=1.21 [1.05,1.41]

* The Q value is the ratio of the actual mean (baseline) or least squares mean (week 4) between Arthrotec I and diclofenac rather than the least squares mean improvement from baseline. Numbers in brackets are the lower and upper 95% confidence limits of Q. Rationale for using the actual mean rather than improvement from baseline and its interpretation are the same as in the non-U.S. OA studies.

Reviewer's Comments

The comments in the non-U.S. OA studies such as lack of a flare requirement, discretion of the BID and TID assignments, and the problems with the modified Q analysis also apply here. The week 8 and week 12 results were similar to those of week 4 in the percentage of patients with Improved or Worsened categories. However, there was a decreasing trend in the percentage of patients in the Unchanged category and an increasing trend in the percentage of patients in the Unknown category reflecting probably the increase of dropouts over time. The Evaluable Cohort (119 Arthrotec I, 114 diclofenac at week 4) analysis was similar to the ITT analysis. On the surface, the efficacy of Arthrotec I appeared to be similar to diclofenac 50 mg BID/TID in this study. However, this conclusion should be qualified by the undesirable design features similar to the non-U.S. OA studies.

Protocol IN2-89-02-289

This study was conducted between June 1989 and August 1990. Three hundred thirty-nine (339) randomized patients received at

least one dose of study medication (Arthrotec I 164, diclofenac 175). Upper GI endoscopic evaluation was included as a part of the study. The study design was otherwise similar to Protocol IN2-89-02-292. There were only two primary efficacy variables, Physician's and Patient's Global Assessment. The treatment groups were comparable in demographics and baseline disease severity. The mean age was 53 years and approximately 77% were females. Eighty-two percent of patients were Caucasians. The mean duration of disease was 9.2 years. Dropouts were about the same in both treatment groups (20%). Table 14 shows the number of patients by treatment group who dropped out for various reasons.

Table 14. Dropouts By Treatment and Reason

	Lack of Efficacy	Adverse Event	Other	Total
Diclofenac 50 mg n=175	4	15	12	31
Arthrotec I n=164	6	18	8	32
Total n=339	10	33	20	63

Table 15 shows the results of the two primary efficacy variables. The definition of the categories in the Global Assessments is the same as in the previous study.

Table 15. Primary Efficacy Variables at Week 4 (ITT population)

Outcome	diclofenac BID-TID N=175	Arthrotec I BID-TID N=164	p & Q* value
Phy.'s Global			
Improved	7%	4%	
Unchanged	90%	90%	
Worsened	1%	2%	
Unknown	3%	5%	p=0.300
Baseline mean	2.94	2.86	Q=0.97 [0.92,1.03]
Least Sq. Mean	2.64	2.69	Q=1.02 [0.96,1.09]
Patient's Global			
Improved	8%	5%	
Unchanged	87%	89%	
Worsened	2%	1%	
Unknown	3%	5%	p=0.430
Baseline mean	2.98	2.92	Q=0.98 [0.93,1.03]
Least Sq. Mean	2.73	2.73	Q=1.00 [0.94,1.07]

* The Q value is the ratio of the actual mean (baseline) or least squares mean (week 4) between Arthrotec I and diclofenac rather than the least squares mean improvement from baseline. Numbers in brackets are the lower and upper 95% confidence limits of Q. Rationale of using the actual mean rather than improvement from baseline and its interpretation are the same as in the non-U.S. OA studies.

Reviewer's Comments

The comments in the previous study Protocol IN2-89-02-292 also apply here. The results of week 8 and week 12 were similar. The Evaluable Cohort (118 Arthrotec I, 129 diclofenac at week 4) analysis was similar to the ITT analysis. The main objective of this study was to compare the GI endoscopic results between Arthrotec I and diclofenac 50 mg BID-TID. The efficacy comparison was not its main objective as can be seen in its primary efficacy variables which consisted of only global evaluations.

VI. Overall Conclusions

Osteoarthritis

The U.S.-study (Protocol NN2-94-02-349) which employed good design features such as the requirement of flare and a concurrent placebo group clearly demonstrated that Arthrotec I TID and Arthrotec II BID are as effective as diclofenac 75 mg BID in patients with osteoarthritis of the hip and/or knee. All three active treatments are more effective than placebo. The three non-U.S. studies with fewer desirable study design features are supportive to the U.S. study.

Rheumatoid Arthritis

The results of the U.S. study (Protocol NN2-94-02-352) cast doubts that diclofenac 75 mg BID was more effective than placebo in the study population. Thus, the demonstration of equivalence between Arthrotec and diclofenac in this study becomes secondary. It is possible that the disease status of these patients may be too mild which generated a larger placebo response than expected or that diclofenac 150 mg per day may be too low to separate the treatment effect between the active treatments and placebo. The pooling of the data among centers becomes suspect when there were consistent significant qualitative treatment by center interactions in most primary efficacy variables at week 6 and week 12. Only a few centers contributed to the treatment difference between the active treatments and placebo. Another unexplained finding is that Arthrotec II appeared to be more effective than Arthrotec I though both of them have a total

dosage of 150 mg per day of diclofenac.

The non-U.S. studies have many undesirable study features as those of the non-U.S. osteoarthritis studies. They may be used as supportive evidence for the U.S. study. Since the results of the U.S. study are in doubt, the values of the non-U.S. studies become less relevant.

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Hoi M. Leung, Ph.D.
Mathematical Statistician

Concur:

/S/

Ralph Harkins, Ph.D.
Director, Division of Biometrics

Orig. NDA 20,607

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HFD-550/PM/LoBianco
HFD-550/Div. File
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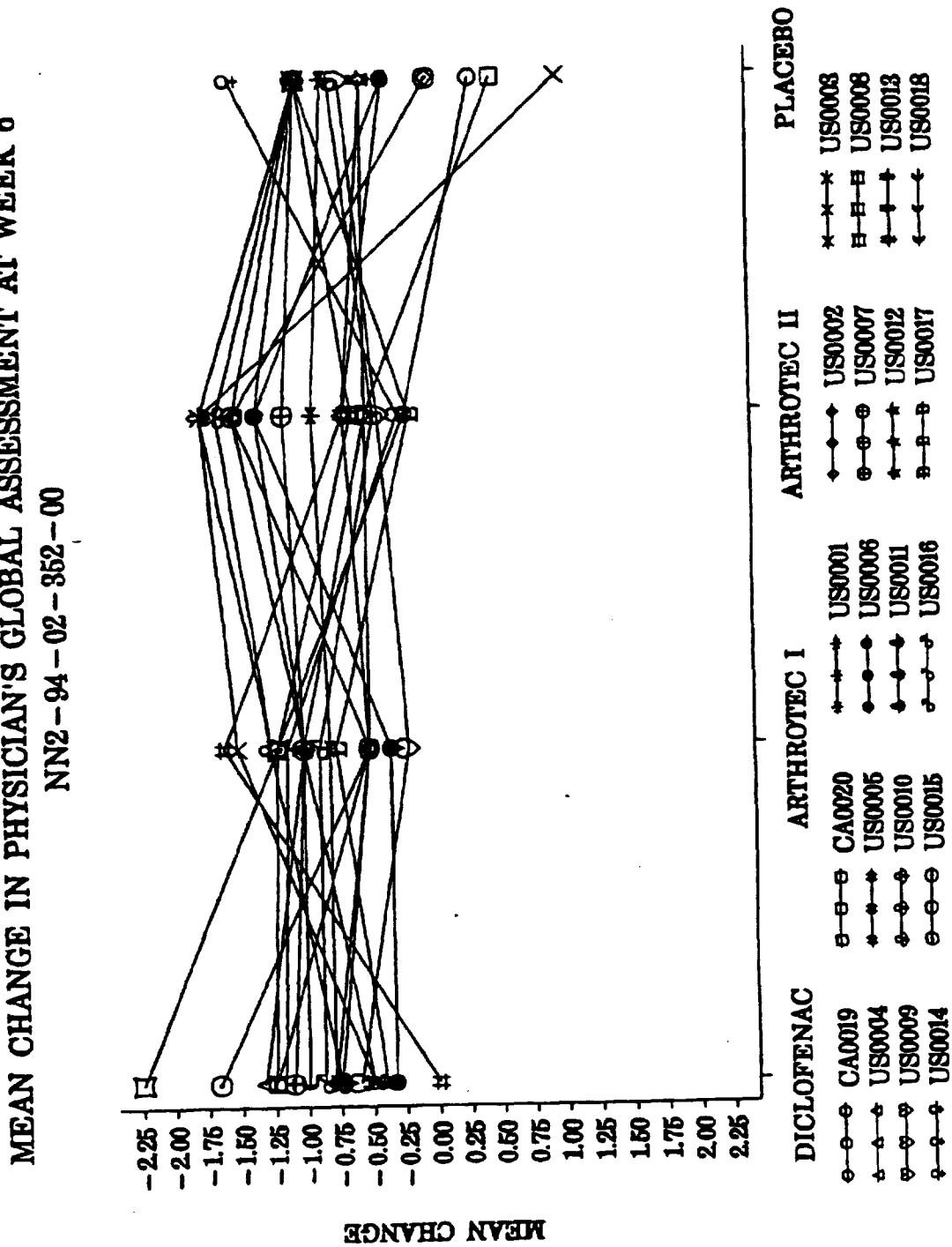
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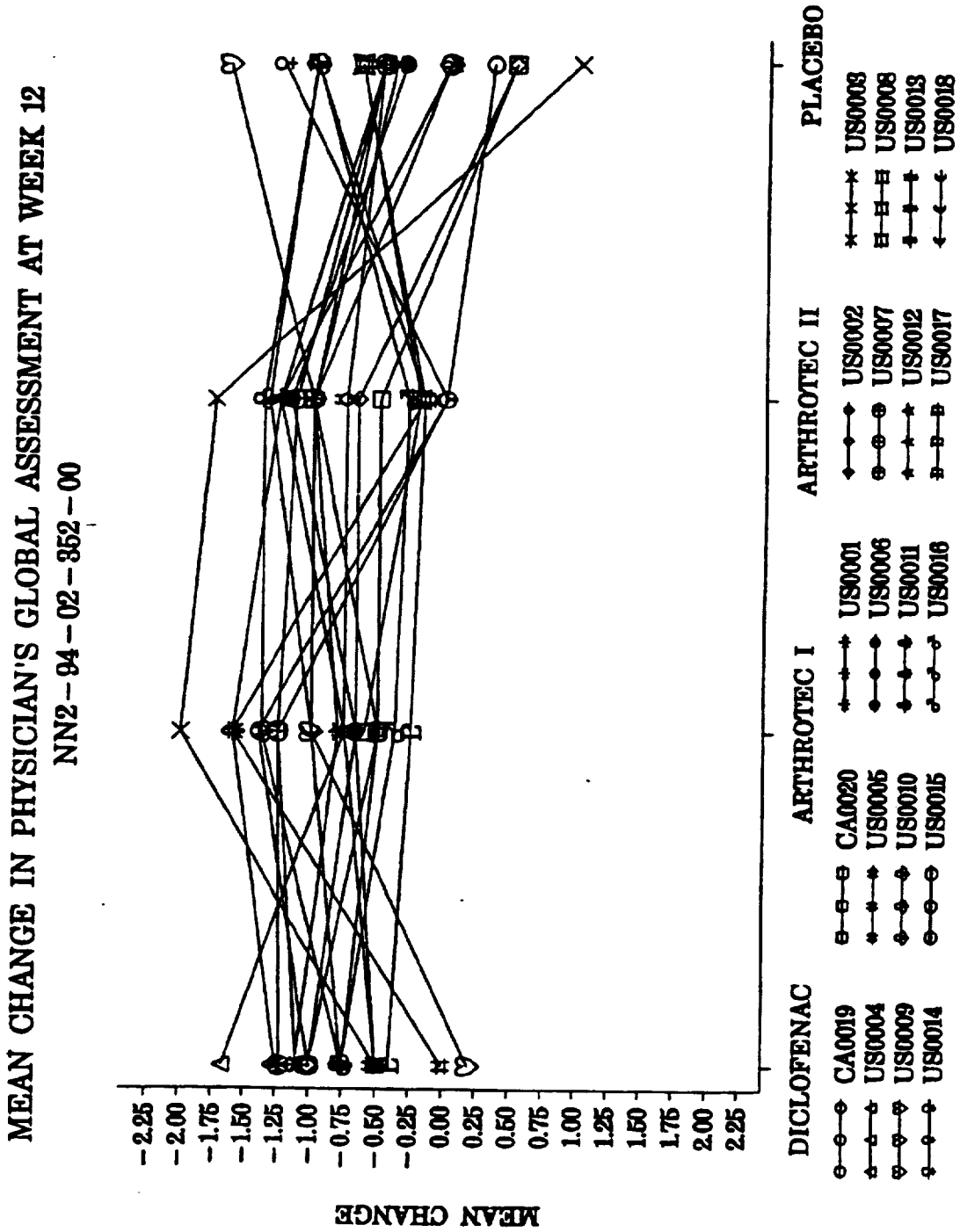
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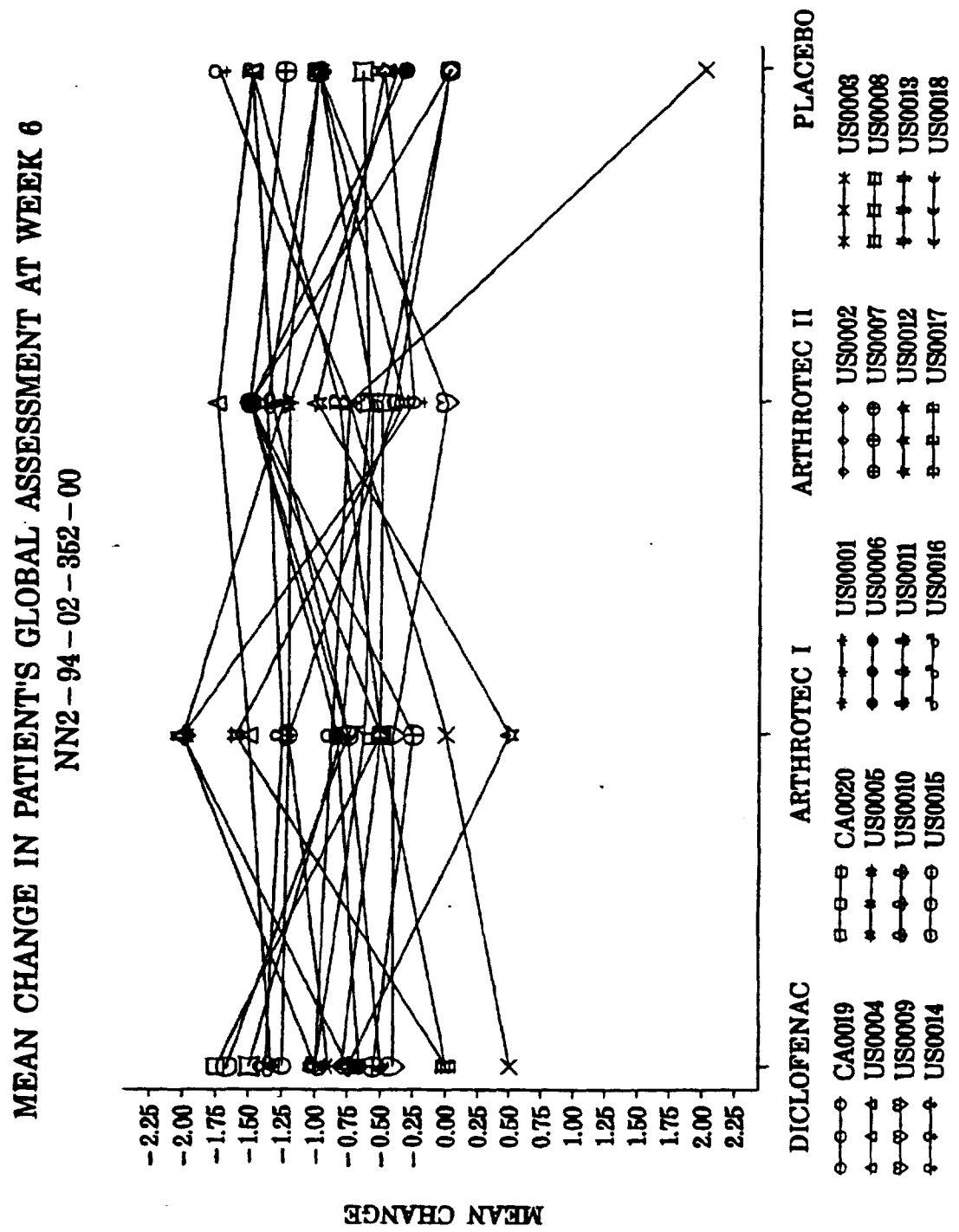
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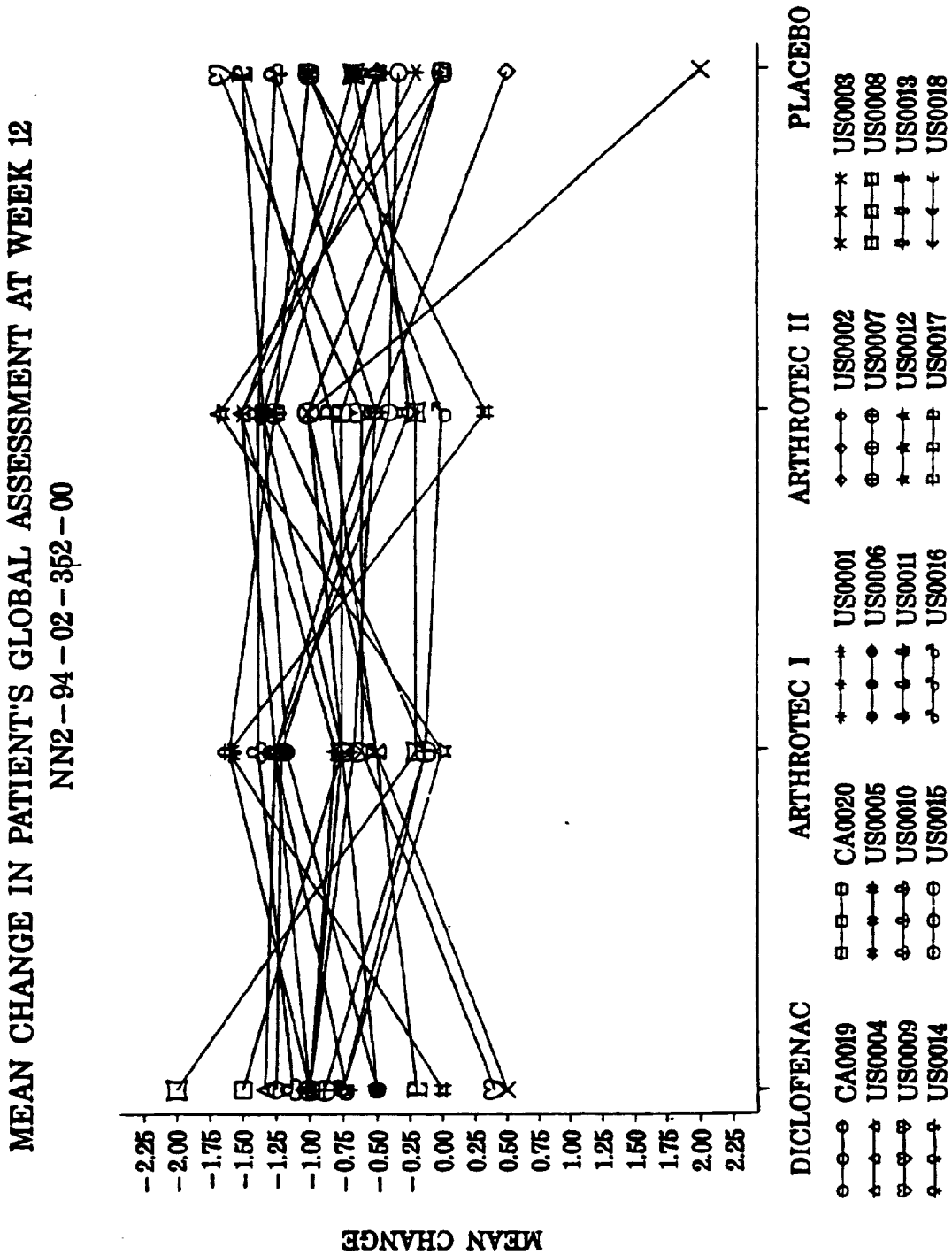
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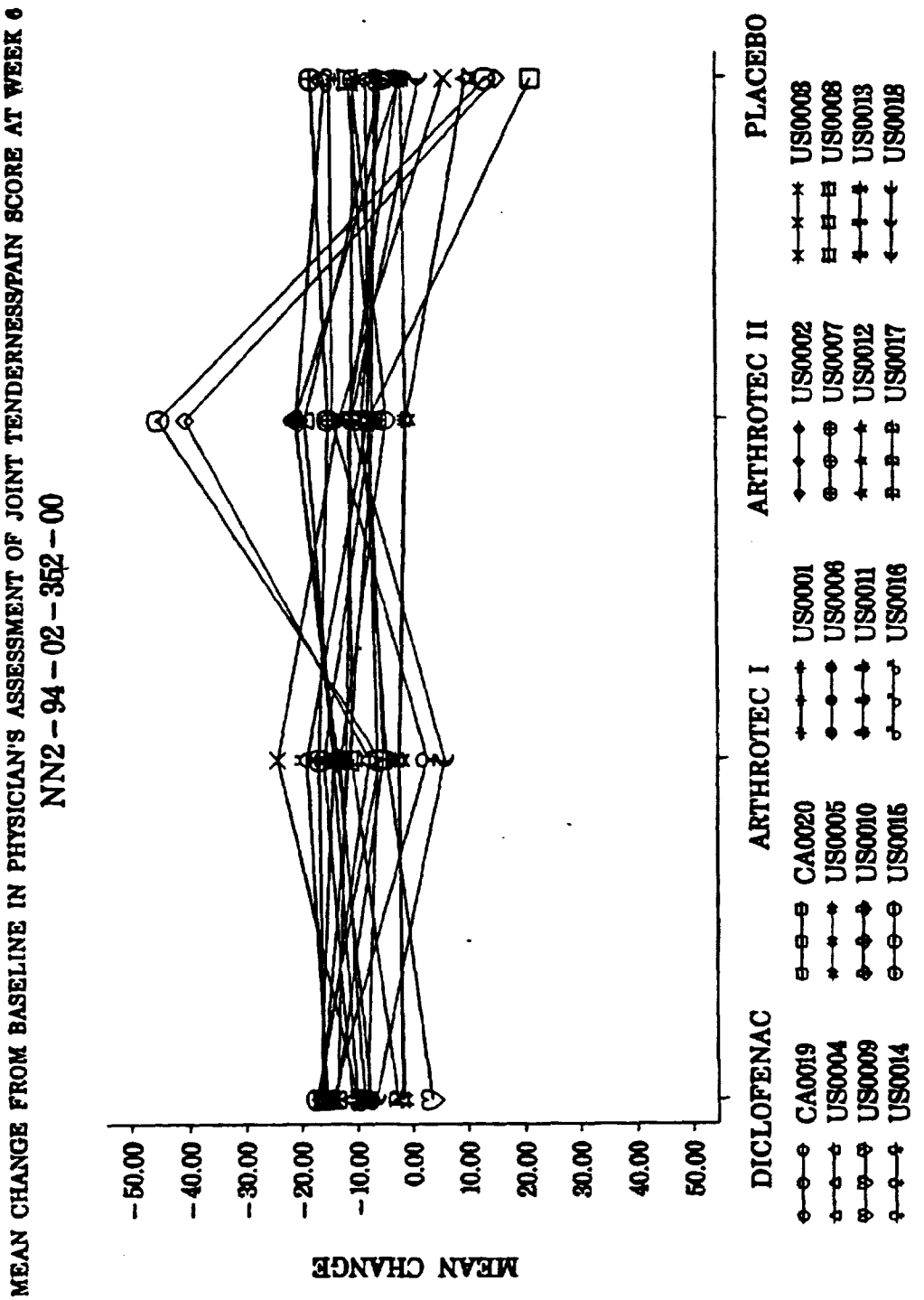
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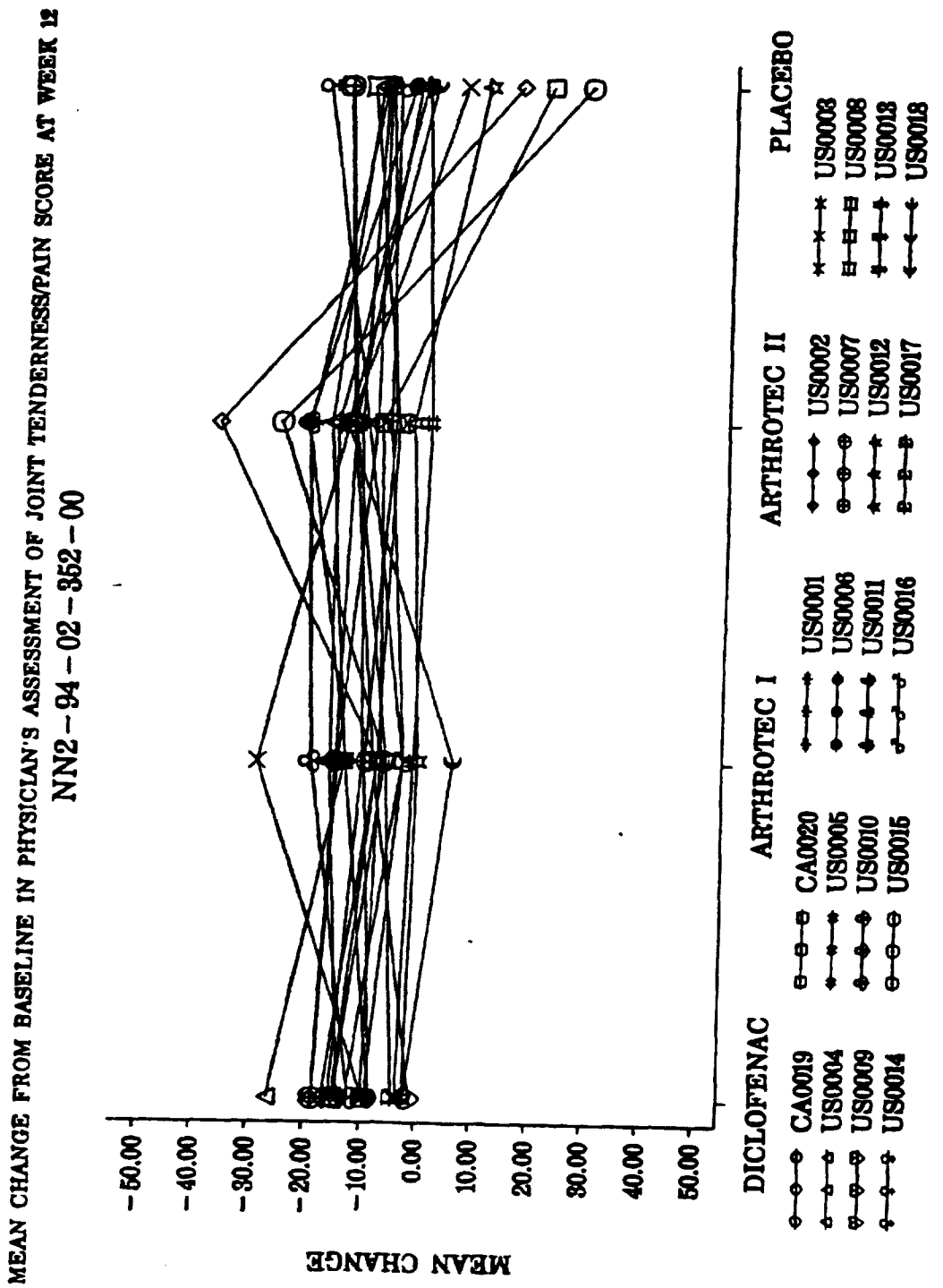
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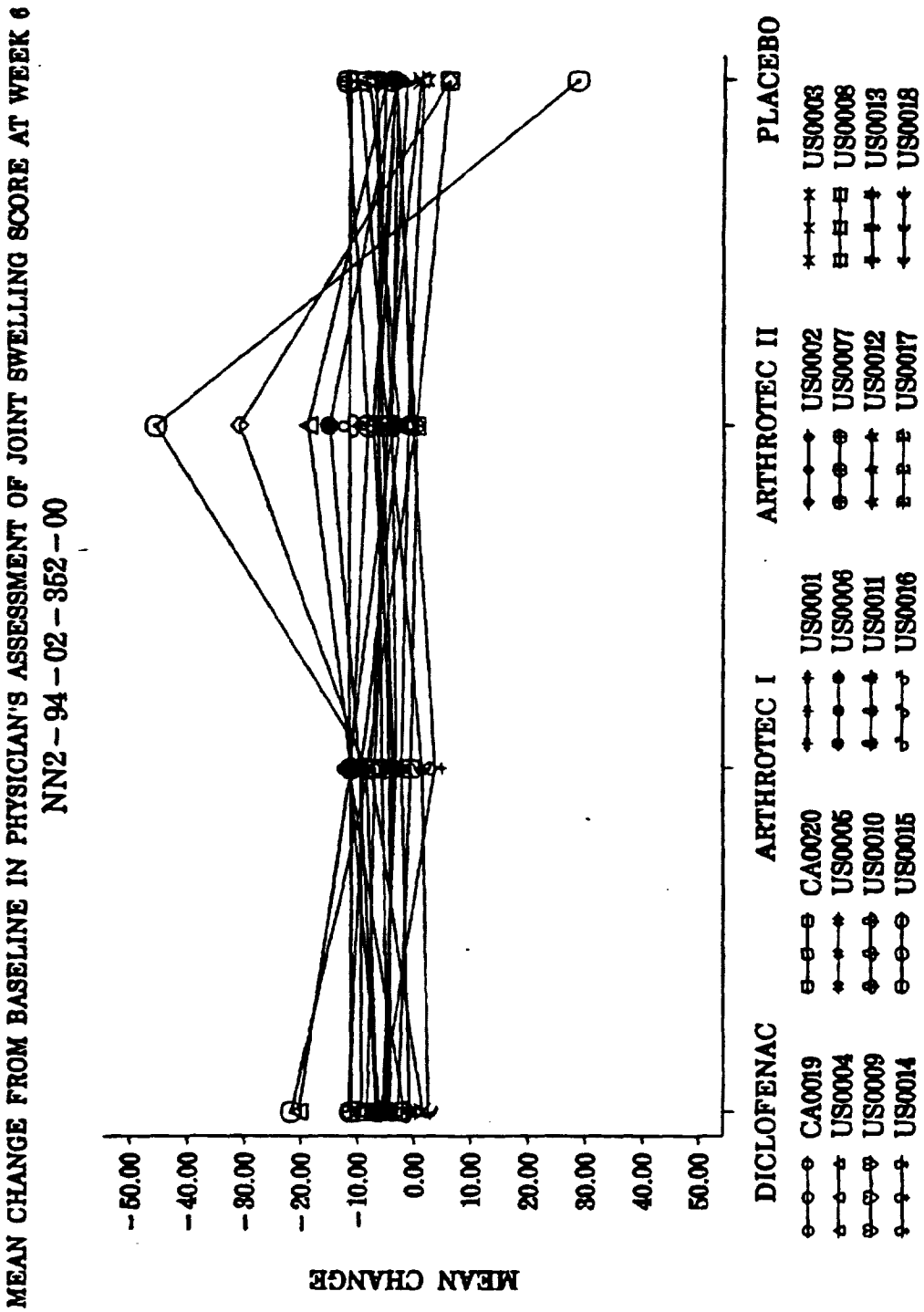
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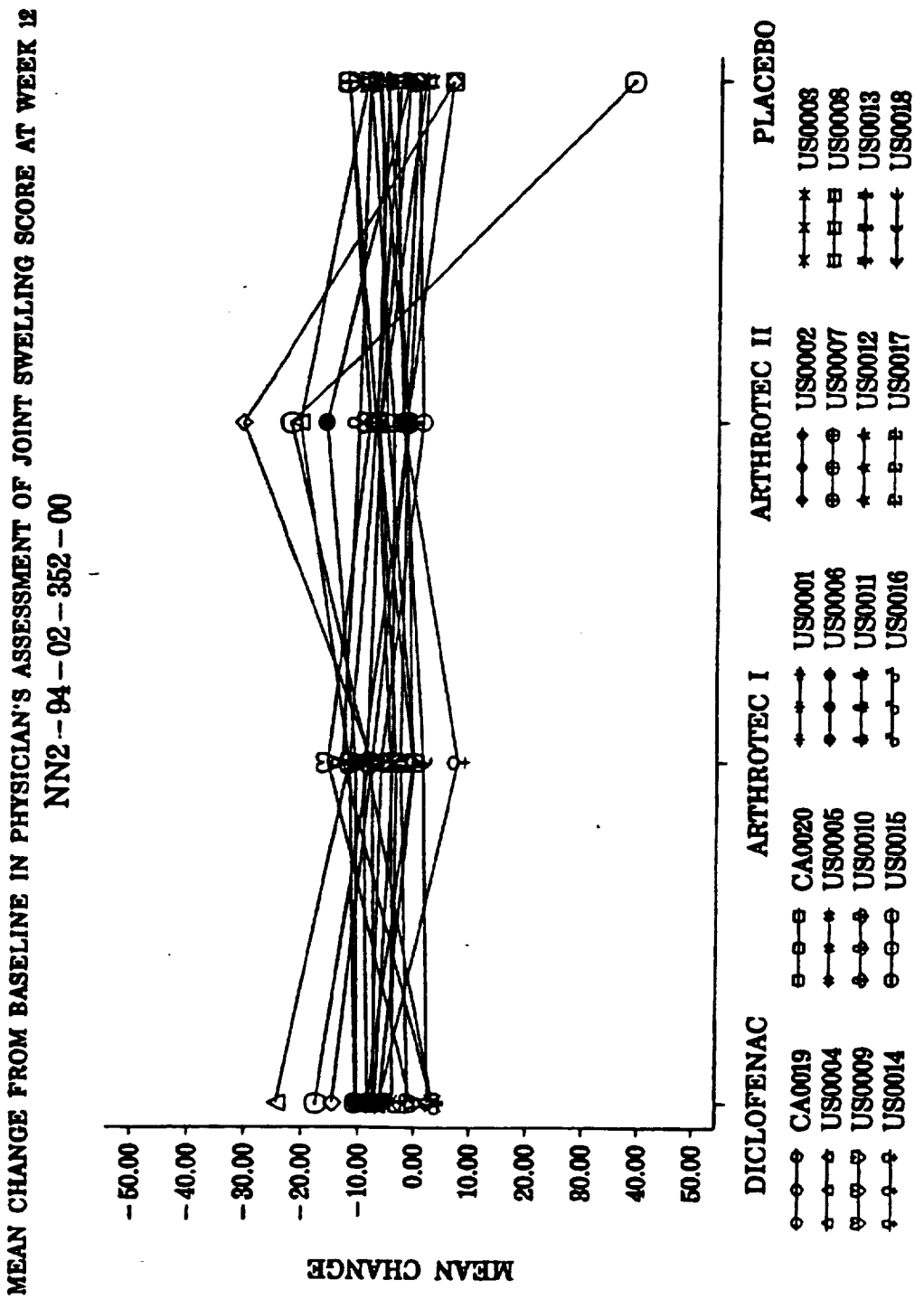
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STATISTICAL REVIEW AND EVALUATION --- NDA

Date:

NDA # 20-607

Applicant: G.D. Searle & Co.

Name of Drug: Arthrotec (Diclofenac sodium/misoprostol) 50 mg/200 mcg / 75 mg/200 mcg Tablets

Indication: Treatment of the sign and symptoms of osteoarthritis and rheumatoid arthritis

Documents Reviewed: Vol. 1.1, 1.2, 1.130-1.176, 1.353 dated December 26, 1995

Medical Reviewer: This review has been discussed with the medical officer, Kathy Robie-Suh, M.D., Ph.D. (HFD-180)

A. **Background**

Arthrotec tablets are a fixed combination of either 50 mg diclofenac sodium/200 mcg misoprostol (Arthrotec 50) or 75 mg diclofenac sodium/200 mcg misoprostol (Arthrotec 75).

In the current NDA, the sponsor seeks approval of Arthrotec for acute and chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at risk of developing NSAID-induced gastroduodenal ulcers.

In support of this claim, the sponsor had submitted seven pivotal studies. Three pivotal RA and four pivotal OA trials were performed.

Indication	Pivotal Trial	Arthrotec 50	Arthrotec 75	Endoscopies Performed
RA	NN2-94-02-352	X	X	
	IN2-89-02-289	X		X
	IN2-89-02-292	X		
OA	NN2-94-02-349	X	X	X
	IN2-89-02-296	X		X
	IN2-89-02-298	X		
	IN2-90-02-321	X		X

Three pivotal studies (one placebo-controlled and two active-controlled) were conducted to evaluate the efficacy of Arthrotec in RA. Study NN2-94-02-352 was placebo-controlled study conducted in the U.S. and Canada, and Studies IN2-89-02-292 and IN2-89-02-289 were active-controlled, multinational clinical trials.

Four pivotal studies (one placebo-controlled and three active-controlled) were conducted to evaluate the efficacy of Arthrotec in OA. Study NN2-94-02-349 was placebo-controlled study conducted in the U.S., and Studies IN2-89-02-298, IN2-89-02-296 and IN2-90-02-321 were active-controlled, multinational clinical trials.

Four endoscopy studies (one RA and three OA) have been conducted with the Arthrotec fixed combination product. In three studies (RA Study IN2-89-02-289 and OA Studies IN2-89-02-296, and NN2-94-02-349) of these studies, the efficacy was compared with that of diclofenac, and in one (OA Study IN2-90-02-321) with that of piroxicam and naproxen.

All four studies excluded patients with active significant UGI mucosal damage (defined as the presence of more than 10 erosions in the stomach; more than 10 erosions in the duodenum; or an ulcer in the esophagus, stomach, pyloric channel or duodenum) on pre-treatment endoscopy.

Additionally, OA Study NN2-94-02-349 enrolled only patients with prior documented history of NSAID-induced GI injury (i.e., erosions or ulcers).

Each patient underwent a post-treatment endoscopy, conducted after four weeks in OA Studies IN2-89-02-296 and IN2-90-02-321, after six weeks in OA Study NN2-94-02-349 and after 12 weeks in RA Study IN2-89-02-289.

In RA Study IN2-89-02-289 and OA Study IN2-89-02-296, dose regimens were assigned by the investigator for controlling the patient's arthritis and could be adjusted during the study. In OA Study NN2-94-02-349, the dose regimen was determined by the randomization schedule, not the investigator.

Endoscopies included examination of the esophageal, gastric, pyloric channel and duodenal mucosa. The number of petechiae, erosions and ulcers, and the size and location of each ulcer were

recorded. An erosion was defined as a lesion producing a definite break in the mucosa but without depth, and an ulcer was defined as any break in the mucosa with unequivocal depth (RA Study IN2-89-02-289 and OA Study IN2-89-02-296) and a break ≥3 mm with unequivocal depth (OA Study NN2-94-02-349).

Endoscopic observations were converted to scores using an eight-point scale (0=no normal mucosa; 7=any ulcer). This mucosal scoring scale is a modification of a five-point scale developed by Lanza.

Mucosal Scoring Scale

Score	Observation
0	No visible lesions (I.e., normal mucosa)
1	1-10 petechiae
2	>10 petechiae
3	1-5 erosions
4	6-10 erosions
5	11-25 erosions
6	>25 erosions
7	Ulcer of any size

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Separate scores were assigned to the gastric mucosa and the duodenal mucosa. Any finding in the pyloric channel was included in the duodenal score. In addition, each patient was assigned an overall gastroduodenal score, which was the higher of the gastric and the duodenal scores.

The principal analyses of mucosal damage consisted of treatment group comparisons of final endoscopic scores and changes in the endoscopic scores.

The overall distribution of final endoscopic scores was analyzed using Chi-square tests. Separate treatment comparisons were performed for gastroduodenal scores, gastric scores, and duodenal scores.

Treatment group comparisons of the proportions of patients with and without the following outcomes were performed using Chi-square tests:

1. Presence of ulceration (i.e., a final score of 7),

2. Presence of more than 10 erosive lesions or ulceration (i.e., a final score 5 or more), and

3. Presence of any erosive lesions or ulceration (i.e., a final score of 3 or more).

Note: the outcome of "presence of any erosive lesions or ulceration (score 3 or more)" was specified only in the protocols for study 349. Furthermore, this outcome might not be appropriate since only patients with the baseline endoscopic score of 4 or less were included in the study and the endpoint of the score of 3 or more in final endoscopy included patients who were improved from endoscopic score 4 to 3 from the baseline. This outcome does not measure the UGI mucosal damage correctly based on the changes in the endoscopic score. This outcome might not be clinically meaningful.

The outcome of "presence of more than 10 lesions or ulceration (score of 5 or more)" was specified in the protocols for all studies except study 349. In measuring any deterioration of mucosal status, the outcome of presence or absence of ulceration and presence or absence of mucosal damage of grade 5 or greater seems appropriate.

After consulting with Medical Officer, Dr. Robie-Suh, it was determined that the outcome of presence of ulceration (score of 7) would be considered as primary endpoint. The outcome of presence of more than 10 lesions or ulceration (score of 5 or more) would be considered as secondary endpoint.

These two outcomes would be focused in this review.

Separate Chi-square tests were performed for each of the outcomes for gastroduodenal, gastric, and duodenal scores.

All of these analyses were performed for both the Intent-to-Treat cohort and the Endoscopy Evaluable Cohort of patients:

Intent-to-Treat Cohort --- A patient was included in the Intent-to-Treat Cohort if he/she was randomized and had received at least one dose of study medication.

Endoscopy Evaluable Cohort --- A patient was considered evaluable for endoscopy if, in addition to satisfying the requirements for the Intent-to-Treat Cohort, he/she satisfied some requirements. For example for 4-week study, she/he:

1. has pretreatment gastric and duodenal endoscopy scores of 4 or less (i.e., damage less severe than 11 erosions);

2. had not taken any of the prohibited medications during the trial or during the 30 days preceding the trial:

3. had not taken antiulcer therapy or therapeutic doses of NSAIDS during the trial;

4. overall, took at least 70% of the prescribed doses of the study medication;

5. had not missed all study medication on more than two consecutive days during the two-week treatment period prior to the final endoscopy;

6. had the prestudy endoscopy within 7 days prior to starting study medication;

7. underwent the final endoscopy at 28 ± 7 days from date of first dose of study medication; and

8. had complete endoscopy data available.

This reviewer will address the efficacy and safety of Arthrotec regarding gastroduodenal damage in these four studies.

B. **RA Study IN2-89-02-289**

This study has been reviewed extensively by medical reviewer (See Medical Officer's Review by Dr. Robie-Suh dated . This reviewer will review this study statistically briefly.

1. Description of Study

This was a randomized, double-blind, parallel group, multicenter (44 centers) study comparing Arthrotec (a fixed combination of diclofenac/misoprostol) with diclofenac/placebo. The one of the objectives of this study was to compare the upper gastrointestinal mucosal damage associated with Arthrotec (diclofenac 50 mg/misoprostol 200 mcg fixed combination) with that associated with diclofenac 50 mg alone.

Patients were randomized to Arthrotec 50 or diclofenac 50 mg/placebo; however, the assignment to BID or TID regimen was left to the investigator's discretion depending on the patient's symptoms. Also, patients were allowed to move from the BID regimen to the TID regimen and vice versa during the study.

Each patient underwent a post-treatment endoscopy, conducted after 12 weeks in this study.

The primary analysis for the assessment of mucosal damage would consist of log-linear analysis, with investigator, treatment, regimen, and outcome (presence or absence of ulceration) and their interactions as factors. This analysis would be repeated with the outcome defined as presence or absence of mucosal damage of grade 5 or greater as defined in the eight-point grading system. In addition, the distributions of patients by final endoscopic grade would be compared for the two treatments by means of a Kruskal-Wallis test.

The sample size of 200 patients per treatment group was chosen. Assuming that approximately 15% of the group treated with diclofenac alone would develop ulcers during the study, the sample size is sufficient to detect a treatment difference (using two-sided statistical tests of significance at the 5% level), if Arthrotec failure rate is 5% or less, with a power of at least 0.9.

2. Sponsor's Analysis

A total of 345 patients were enrolled in this study. Six of these patients were randomized, but were withdrawn from the study before taking any study medication. These six patients were, therefore, eliminated from all analyses.

Of the 339 patients who took at least one dose of study medication, 164 received Arthrotec 50 and 175 received diclofenac 50 mg/placebo.

The numbers of patients assigned to receive study medication twice or three times daily were similar in both treatment groups. Eighty-one of the patients (81, 49%) in the arthrotec group were assigned to a BID regimen, compared with 75 patients (43%) in the diclofenac/placebo group.

Of the 339 patients in the Intent-to-Treat Cohort, 276 completed the study (132, Arthrotec 50; 144 diclofenac 50 mg/placebo). A total of 33 patients withdrew due to adverse events (18, Arthrotec 50; 15 diclofenac 50 mg/placebo).

One hundred and sixty-five patients (165; 80, Arthrotec 50; 85 diclofenac 50 mg/placebo) were judged to be evaluable for endoscopic assessments.

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at the baseline is given in Table 1.

As seen from Table 1, there were no statistically significant differences among the treatment groups with respect to age, gender, race, disease duration, and baseline gastric and duodenal endoscopy score.

Comparisons of baseline assessments of arthritis status showed no significant treatment group differences in the physician's and patient's global assessment, and functional capacity.

2.2 **Sponsor's Analysis of Endoscopy Data**

For evaluation of prevention of gastrointestinal lesions, only patients having both pretreatment and follow-up (final) endoscopy were considered in the sponsor's Intent-to-Treat cohort. It included 292 patients with endoscopy data, 139 of whom received Arthrotec 50 BID or TID and 153 of whom received diclofenac 50 mg/placebo BID or TID. Thirteen percent (13%) of the diclofenac 50 mg/placebo patient and 17% of the Arthrotec patients did not have the final endoscopy done.

The results of the final gastric endoscopy scores and final duodenal endoscopy scores for all patients who underwent final endoscopy are given below.

Final Gastric and Duodenal Endoscopy Scores --- Study 289 (Intent-to-Treat Cohort)

Score	Number of Patients (%)			
	Final Gastric Endoscopy Scores		Final Duodenal Endoscopy Scores	
	Arthrotec 50 (N=137)	Diclofenac 50 mg/Placebo (N=153)	Arthrotec 50 (N=137)	Diclofenac 50 mg/Placebo (N=153)
0	106 (77%)	101 (66%)	128 (94%)	130 (86%)
1	9 (6%)	13 (8%)	4 (3%)	2 (1%)
2	3 (2%)	3 (2%)	0 (0%)	0 (0%)
3	10 (7%)	24 (16%)	2 (1%)	5 (3%)
4	1 (1%)	5 (3%)	1 (1%)	2 (1%)
5	3 (2%)	1 (1%)	0 (0%)	1 (1%)
6	1 (1%)	0 (0%)	0 (0%)	0 (0%)
7	4 (3%)	6 (4%)	2 (1%)	12 (8%)

Tables 16 and 17 on pages 39 and 41 in IN2-90-06-289.

P-values for Treatment Comparisons (Intent-to-Treat Cohort)

Treatment Comparison	Final Gastric Endoscopy Scores	Final Duodenal Endoscopy Scores
With an ulcer[a]	0.641	0.011
With more 10 erosions or an ulcer[b]	0.627	0.007

P-value was obtained by Chi-square test.
[a] Compare patients with scores of 0-6 vs. those with scores of 7.
[b] Compare patients with scores of 0-4 vs. those with scores of 5-7.
Tables 16 and 17 on pages 39 and 41 in IN2-90-06-289.

Statistically significantly fewer endoscoped Arthrotec 50 patients had duodenal ulcers (endoscopy score=7) as compared to diclofenac 50 mg/placebo patients (p=0.011); for gastric ulcers the between group difference was not statistically significant (p=0.641).

The treatment comparison of the number of patients with a score of 5 or more failed to show any significant treatment difference in the gastric region.

The findings in the Endoscopy Evaluable cohort were similar to those described above.

The five adverse events of highest incidence in the Arthrotec 50 group were: abdominal pain, diarrhea, dyspepsia, nausea and flatulence. However, the incidence of abdominal pain was higher in the diclofenac/placebo group. The incidences of the others were greater in the Arthrotec group than in the diclofenac/placebo group.

3. Reviewer's Evaluation

3.1 Review's Comments on Study Design

The study protocol did not specifically state that patient's regimen could be changed back and forth between the BID and TID; however, examination of the data from the study showed that in fact this was allowed as seen below.

Dosing	Arthrotec 50 (N=164)	Diclofenac 50 mg/placebo (N=175)
*BID -	39	34
*TID -	19	19
BID-BID-BID	42	41
TID-TID-TID	64	81

*dosage regimen switched

Thirty-nine arthrotec patients (39, 24%) and 34 diclofenac/placebo patients (19%) had dosage regimen changed from BID to TID during the course of study. Nineteen patients from each treatment group had dosage regimen changed from TID to BID.

The investigator assigned the dosage regimen, either BID or TID, to control the patient's arthritis. So, patients were not assigned randomly the dosage regimen, either BID or TID.

The impact of dose changes during the study on results was not clear and needs to be investigated by the sponsor.

3.2 **Impact of Missing Final Endoscopy of Incidence of Duodenal Ulcer --- Patients Discontinued Due to Adverse Event**

It should be noted that only 15% (3/20) of Arthrotec 50 adverse event withdrawals had both pretreatment and final endoscopies as compared to 43% (7/16) of diclofenac 50 mg/placebo adverse event withdrawals.

Of the 16 diclofenac 50 mg/placebo patients discontinued prematurely due to adverse events, 7 had final endoscopy done and duodenal ulcers were found in 3 of these an event rate of 3/7 (43%); of the 20 Arthrotec patients discontinued prematurely due to adverse events, 3 had final endoscopy done and no duodenal ulcers were found. (No gastric ulcers were found in any of the adverse event withdrawals in either treatment group).

As requested by the medical officer, this reviewer performed a reanalysis of duodenal ulcer occurrence using the worse case scenario where all "unknown" (i.e., missing final endoscopy) adverse event withdrawals are assumed to have duodenal ulcer rate the same as the rate seen in the placebo patients who were endoscoped (43%). The results were documented in Medical Officer's Review dated March 14, 1996 and were given in Table 2.

As seen from Table 2, based on this analysis, it appears that the statistically significant difference in duodenal ulcer rates could be due to disparity between treatment groups in the proportion of adverse event withdrawals who were endoscoped.

C. **OA Study IN2-89-02-296**

1. **Description of Study**

This is a multinational (11 countries with 32 investigators), double-blind, randomized, parallel-group study of four weeks duration. This study compared the efficacy and upper GI safety of a fixed combination tablet of diclofenac 50 mg and misoprostol 200 mcg (Arthrotec 50) with that of a fixed combination tablet of diclofenac 50 mg and placebo.

The design of study was similar to that of study 289.

Patients must have been diagnosed as having had osteoarthritis of the hip and/or knee for at least three-months, with a functional capacity classification of I-III.

Each patient underwent a post-treatment endoscopy, conducted after 4 weeks in this study.

2. **Sponsor's Analysis**

A total of 362 patients were enrolled in this study. One of these patients was randomized, but was withdrawn from the study before having taken any study medication. This patient was, therefore, eliminated from all analyses.

Of the 361 patients who took at least one dose of study medication, 178 received Arthrotec 50 and 183 received diclofenac 50 mg/placebo, BID or TID.

The numbers of patients assigned to receive study medication twice or three times daily were similar in both treatment groups. One hundred and twenty-nine of the patients (129, 72%) in the arthrotec group were assigned to a BID regimen, compared with 130 patients (71%) in the diclofenac/placebo group.

Of the 361 patients, 323 completed the study (159, Arthrotec 50; 164, diclofenac 50 mg/placebo).

Two hundred and forty-seven patients (247, 121, Arthrotec 50; 126, diclofenac 50 mg/placebo) were judged to be evaluable for endoscopic assessments.

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at the baseline is given in Table 3.

As seen from Table 3, there were no statistically significant differences among the treatment groups with respect to age, gender, race, disease duration, and baseline gastric and duodenal endoscopy score

However, there was a statistically significant difference between the two groups in terms of weight (p=0.004), though this was not considered to be medically meaningful. The mean weight of the Arthrotec 50 group was 70.4 kg, while that of the diclofenac 50 mg/placebo was 73.8 kg.

Comparisons of baseline assessments of arthritis status showed no significant treatment group differences in the physician's and patient's global assessment, and functional capacity.

2.2 Sponsor's Analysis of Endoscopy Data

For evaluation of prevention of gastrointestinal lesions, only patients having both pretreatment and follow-up (final) endoscopy were considered in the sponsor's Intent-to-Treat cohort. It included 329 patients with endoscopy data, of whom 162 received Arthrotec 50 BID or TID and 167 received diclofenac 50 mg/placebo BID or TID. Thirty-two (32) patients, 16 per treatment group, had no follow-up endoscopy data.

The results of the final gastric endoscopy scores and final duodenal endoscopy scores for all patients who underwent final endoscopy are given below.

Final Gastric and Duodenal Endoscopy Scores --- Study 296 (Intent-to-Treat Cohort)

Score	Number of Patients (%)			
	Final Gastric Endoscopy Scores		Final Duodenal Endoscopy Scores	
	Arthrotec 50 (N=162)	Diclofenac 50 mg/Placebo (N=167)	Arthrotec 50 (N=161)	Diclofenac 50 mg/Placebo (N=167)
0	117 (72%)	102 (61%)	146 (91%)	141 (84%)
1	21 (13%)	22 (13%)	8 (5%)	15 (9%)
2	2 (1%)	1 (1%)	0 (0%)	0 (0%)
3	16 (10%)	32 (19%)	5 (3%)	8 (5%)
4	3 (2%)	5 (3%)	2 (1%)	0 (0%)
5	1 (1%)	2 (1%)	0 (0%)	0 (0%)
6	2 (1%)	0 (0%)	0 (0%)	0 (0%)
7	0 (0%)	3 (2%)	0 (0%)	3 (2%)

Tables 19 and 20 on pages 41 and 43 in IN2-90-06-296.

P-values for Treatment Comparisons --- Study 296 (Intent-to-Treat Cohort)

Treatment Comparison	Final Gastric Endoscopy Scores	Final Duodenal Endoscopy Scores
With an ulcer[a]	0.087	0.088
With more 10 erosions or an ulcer[b]	0.501	0.088

P-value was obtained by Chi-square test.
[a] Compare patients with scores of 0-6 vs. those with scores of 7.
[b] Compare patients with scores of 0-4 vs. those with scores of 5-7.
Tables 19 and 20 on pages 41 and 43 in IN2-90-06-296.

Three patients in the diclofenac 50 mg/placebo group developed gastric ulcers during the four-week study period, compared with no patients in the Arthrotec 50 group. This difference, however, did not reach statistical significance.

The treatment comparison of the number of patients with a score 5 or more failed to show any significant treatment difference.

No significant treatment difference in the overall distribution of final duodenal endoscopy scores was seen.

Duodenal ulcers were found in three patients in the diclofenac 50mg/placebo group but were not observed in any patients in the Arthrotec 50 group. This difference was not statistically significant.

Four percent (4%) of the Arthrotec 50 patients had duodenal erosion or ulcers present (i.e., a score of 3 or more), compared with 7% of the diclofenac 50mg/placebo patients. However, neither this treatment difference nor the comparison of patients with a score of 5 or more was statistically significant.

The findings in endoscopy evaluable cohort of patients were similar to those described above.

The five adverse events of highest incidence in the Arthrotec 50 group were: abdominal pain, diarrhea, dyspepsia, nausea and flatulence. The incidences of all of these GI complaints were

greater in the Arthrotec 50 group than in the diclofenac 50 mg/placebo group.

3. Reviewer's Evaluation

3.1 Review's Comments on Study Design

The study protocol did not specifically state that patient's regimen could be changed back and forth between the BID and TID; however, examination of the data from the study showed that in fact this was allowed as seen below.

Dosing	Arthrotec 50 (N=178)	Diclofenac 50 mg/placebo (N=183)
BID -	4	7
TID -	4	0
BID - BID	107	108
TID - TID	41	52
BID - TID	18	15
TID - BID	4	1

APPEARS THIS WAY ON ORIGINAL

Eighteen arthrotec patients (18, 10%) and 15 diclofenac/placebo patients (8%) had dosage regimen changed from BID to TID. Only a few patients (4 arthrotec and 1 diclofenac/placebo) had dosage regimen changed from TID to BID.

The investigator assigned the dosage regimen, either BID or TID, to control the patient's arthritis. So, patients were not assigned randomly the dosage regimen, either BID or TID.

The impact of dose changes during the study on results was not clear and needs to be investigated by the sponsor.

3.2 Reviewer's Comments on Sponsor's Results on Primary Endpoint

The Chi-square test used by the sponsor may not be valid for some

of treatment comparisons (e.g., over distribution and with an ulcer) because some of the cells have expected counts less than 5. The resulting p-value would be deflated. For example, if the more appropriate method (e.g., the Fisher exact test) was used. The p-value for treatment comparison of gastric ulcer incidences would be 0.248 instead of 0.087 from the Chi-square test. So, the sponsor's results could be misleading.

D. **OA Study NN2-94-02-349**

1. **Description of Study**

This is a multicenter (55 investigators), double-blind, placebo-controlled, randomized, parallel-group study of six weeks duration.

This study compared the incidences of gastric ulcers associated with the use diclofenac and Arthrotec 50 and Arthrotec 75 in OA patients.

Patients would be randomly assigned to receive either diclofenac 75 mg BID, Arthrotec 50 TID, Arthrotec 75 BID or placebo.

The design of study was similar to that of study 296.

The patient must demonstrate an OA flare and have a prior documented history of a gastric, pyloric channel or duodenal ulcer, or greater than ten erosions in the stomach or greater than ten erosions in the duodenum to be eligible for enrollment. However, the patient must not have an esophageal, gastric, pyloric channel or duodenal ulcer or more than ten erosions in the stomach or duodenum.

The dose regimen was determined by the randomization schedule, not by the investigator.

Each patient underwent a post-treatment endoscopy, conducted after 6 weeks in this study.

An erosion was defined the same as in RA study 289, but an ulcer was defined as any break in the mucosa with a break ≥3 mm with unequivocal depth.

The primary analyses for the assessment of gastric, duodenal and gastroduodenal mucosal damage consisted of chi-square tests comparing the outcome (ulcer, no ulcer) over the treatments. These analyses would be repeated with the outcome defined as presence or absence of mucosal damage of grade 3 or greater.

The principal pairwise comparisons were between diclofenac and Arthrotec 50 and between diclofenac and Arthrotec 75. An additional pairwise comparison would be done between Arthrotec 50 and 75 patients.

A sample size of 112 patients per treatment group is required to detect a difference between a physician's global assessment improvement rate of 70% in diclofenac, Arthrotec 50 and 75 groups and a 45% improvement rate in the placebo group with a power of 0.90 and, alpha=0.0167 (to accommodate 3 pairwise comparisons: placebo versus diclofenac, diclofenac versus Arthrotec 50, and diclofenac versus Arthrotec 75, with an experiment wise rate of 0.05), using the Cassagrande and Pike procedure which assume equal sample size in each treatment. This sample size was subsequently adjusted to take into consideration the sample size requirement for the comparison of the expected ulcer rates.

Based on previous studies it is assumed that 18% of diclofenac and 4% of Arthrotec 50 or 75 treated patient will show endoscopically confirmed gastric ulcers after six weeks of treatment. Calculations using the Cassagrande and Pike method show that a sample size of 136 patients per treatment group is required to detect this difference assuming two pairwise comparisons (diclofenac versus Arthrotec 50 and diclofenac versus Arthrotec 75), using alpha=0.025 and power=0.90

Hochberg's step-down procedure will be used for planned pairwise comparisons.

2. **Sponsor's Analysis**

Five hundred seventy-two (572) patients were randomized to receive either Arthrotec 50 TID (152 patients), Arthrotec 75 BID (175 patients), diclofenac 75 mg BID (154 patients) or placebo (91 patients).

Of the 572 patients in the Intent-to-Treat Cohort, 469 completed

the study (126 diclofenac 75 mg BID, 131 Arthrotec 50 TID, 142 Arthrotec 75 BID, and 70 placebo).

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at the baseline is given in Table 4.

As seen from Table 4, the treatment groups were comparable in terms of age, race, gender, height, weight, affected joint, disease duration, baseline gastric and duodenal endoscopy scores, physician's or patient's global assessments, baseline OA severity index, and functional capacity classification.

2.2 **Sponsor's Analysis of Endoscopy Data**

Five hundred nineteen (519) patients (138 diclofenac 75 mg BID, 142 Arthrotec 50 TID, 159 Arthrotec 75 BID, and 80 placebo) underwent a final endoscopy and are included in the Intent-to-Treat cohort endoscopy analyses.

Four hundred fifty-two (452) patients (122 diclofenac 75 mg BID, 129 Arthrotec 50 TID, 134 Arthrotec 75 BID, and 67 placebo) were evaluable for endoscopic analyses.

The distribution of final gastric endoscopy scores in the four treatment groups is given below.

2.2.1 **Final Gastric Endoscopy Scores**

Final Gastric Endoscopy Scores --- Study 349
(Intent-to-Treat Cohort)

Number of Patients (%)

Score	Diclofenac 75 mg BID (N=138)	Arthrotec 50 TID (N=142)	Arthrotec 75 BID (N=159)	Placebo (N=80)
0	60 (43%)	91 (64%)	103 (65%)	57 (71%)
1	12 (9%)	18 (13%)	15 (9%)	4 (5%)
2	7 (5%)	7 (5%)	9 (6%)	2 (3%)
3	32 (23%)	18 (13%)	22 (14%)	10 (13%)
4	8 (6%)	1 (1%)	3 (2%)	3 (4%)
5	4 (3%)	3 (2%)	0 (0%)	2 (3%)
6	0 (0%)	0 (0%)	0 (0%)	0 (0%)
7	15 (11%)	4 (3%)	7 (4%)	2 (3%)

Table 17 on page 74 in IN2-95-06-349

P-values for Treatment Comparisons --- Study 349
(Intent-to-Treat Cohort)

Treatment Comparison	Diclofenac 75 mg BID vs. Arthrotec 50 TID	Diclofenac 75 mg BID vs. Arthrotec 75 BID	Arthrotec 50 TID vs. Arthrotec 75 BID
With an ulcer[a]	0.007*	0.034	0.464
With more 10 erosions or an ulcer[b]	0.011*	0.004*	0.828

P-value was obtained by Chi-square test.
[a] Compare patients with scores of 0-6 vs. those with scores of 7.
[b] Compare patients with scores of 0-4 vs. those with scores of 5-7.
* Statistically significant at the 5% level for primary pairwise comparison using Hochberg's step-down procedure.

Pairwise treatment comparisons revealed statistically significant differences in gastric ulcer incidence when diclofenac 75 mg BID was compared with Arthrotec 50 TID..

2.2.2 **Final Duodenal Endoscopy Scores**

The distribution of final duodenal endoscopy scores in the four treatment groups is given below.

Final Duodenal Endoscopy Scores --- Study 349
(Intent-to-Treat Cohort)

Number of Patients (%)

Score	Diclofenac 75 mg BID (N=138)	Arthrotec 50 TID (N=142)	Arthrotec 75 BID (N=159)	Placebo (N=80)
0	102 (74%)	119 (84%)	133 (84%)	63 (79%)
1	9 (7%)	8 (6%)	9 (6%)	4 (5%)
2	2 (1%)	0 (0%)	2 (1%)	1 (1%)
3	15 (11%)	5 (4%)	10 (6%)	11 (14%)
4	1 (1%)	1 (1%)	1 (1%)	0 (0%)
5	0 (0%)	1 (1%)	0 (0%)	0 (0%)
6	0 (0%)	0 (0%)	0 (0%)	0 (0%)
7	9 (7%)	8 (6%)	4 (3%)	1 (1%)

Table 18 on page 76 in IN2-95-06-349

P-values for Treatment Comparisons --- Study 349
(Intent-to-Treat Cohort)

Treatment Comparison	Diclofenac 75 mg BID vs. Arthrotec 50 TID	Diclofenac 75 mg BID vs. Arthrotec 75 BID	Arthrotec 50 TID vs. Arthrotec 75 BID
With an ulcer[a]	0.756	0.092	0.167
With more 10 erosions or an ulcer[b]	0.950	0.092	0.103

P-value was obtained by Chi-square test.
[a] Compare patients with scores of 0-6 vs. those with scores of 7.
[b] Compare patients with scores of 0-4 vs. those with scores of 5-7.
* Statistically significant at the 5% level for primary pairwise comparison using Hochberg's step-down procedure.

Pairwise treatment comparisons demonstrated no statistically significant differences in the incidence of duodenal ulcers between the diclofenac 75 mg BID group and the Arthrotec 50 TID

or Arthrotec 75 BID groups.

No statistically significant differences were found between Arthrotec 50 TID and Arthrotec 75 BID in any of the endoscopic analyses.

Analyses of results of the Endoscopy Evaluable cohort showed differences similar to those described above.

The five events of highest incidence in the Arthrotec 50 TID and Arthrotec 75 BID groups were dyspepsia, abdominal pain, diarrhea, and nausea.

Sixty-three (63) patients withdrew from study due to adverse events: 20 diclofenac 75 mg BID patients (13%), 104 Arthrotec 50 TID patients (9%), 23 Arthrotec 75 BID patients (13%), and six placebo patients (7%).

3. **Reviewer's Evaluation**

This study was well-controlled and conducted. The dose regimen was determined by the randomization schedule, not by the investigator.

Pairwise treatment comparisons demonstrated no statistically significant differences in incidence of gastric ulcers between the Arthrotec 75 BID group and diclofenac 75 mg BID group ($p=0.034$) after adjusting for multiple comparisons by the Hochberg's procedure. However, the proportions of patients with 11 or more gastric erosions or ulcer (score of 5 or more) were significantly lower in the Arthrotec 75 BID than in the diclofenac 75 mg BID group ($p=0.004$).

So, study 349 provides some evidence of the efficacy of the Arthrotec 75 BID against diclofenac 75 mg BID for prevention of developing NSAID-induced gastric ulcer.

E. **IN2-90-02-321**

1. **Description of Study**

The study was a multicenter (71 investigators), double-blind, randomized, active-controlled, parallel-group trial.

The primary objective of this study was to compare the gastroduodenal damage associated with the use of Arthrotec 50 with that associated with piroxicam 10 mg BID or naproxen 375 mg BID when administered to patients with osteoarthritis for four weeks.

The design of this study was similar to that of Study 296. But dose regimen was fixed and would be not changed by the investigator.

Patients must have been diagnosed as having had osteoarthritis of the hip and/or knee for at least three-months, with a functional capacity classification of I-III.

Each patient underwent a post-treatment endoscopy, conducted after 4 weeks in this study.

The primary analysis for the assessment of mucosal damage would consist of log-linear analysis, with investigator, treatment and outcome (presence or absence of ulceration) and their interactions as factors, to test for statistically significant treatment interactions. The analysis would be repeated with the outcome defined as presence or absence of mucosal damage of grade 5 or greater. In addition, the distribution of patients by final endoscopic grade would be compared for the three treatment groups using the Kruskal-Wallis test.

The sample size of 200 patients per treatment group (600 patients in all) was chosen on the basis of clinical judgement. Assuming that approximately 15% of either the piroxicam or naproxen treated groups develop ulcers during the study, the sample size would be sufficient to detect a treatment difference, with a power of at least 0.9 (using two-sided tests of significance at the 5% level), if Arthrotec ulcer incidence rate was 3.8% or less. This ulcer incidence permitted three pairwise treatment comparisons at the combined 5% significance level using the Bonferroni approach.

2. **Sponsor's Analysis**

Six hundred and forty-four (644) patients were randomly assigned to receive either Arthrotec 50 BID (216 patients), piroxicam 10 mg BID (218 patients), or naproxen 375 mg BID (210 patients).

Data on one piroxicam patient was lost and remains unavailable for efficacy analysis.

Of the 643 patients in the Intent-to-Treat cohort, 578 completed the study (193, Arthrotec; 200, piroxicam; 185, naproxen). A total of 65 patients withdrew before completion (23, Arthrotec; 17, piroxicam; 25, naproxen). A total of 48 patients withdrew from study due to adverse events (18, Arthrotec; 10, piroxicam; 20, naproxen).

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at the baseline is given in Table 5.

As seen from Table 5, the treatment groups were comparable in terms of height, weight, baseline gastric and duodenal endoscopy scores, baseline assessments of osteoarthritis status (Physician's and Patient's Global Assessment, Functional Capacity, and Patient's Assessment of Joint Pain).

A statistically significant treatment group difference was noted in the baseline Osteoarthritis Severity Index ($p=0.024$). The mean Osteoarthritis Severity Index for patients randomized to Arthrotec was 11.93. The mean index was 11.00 for the piroxicam group and 11.51 for the naproxen group. This difference was not considered medically meaningful.

Baseline endoscopy scores of the gastric mucosa showed a significantly different distribution between U.S. and ex-U.S. patients, with a higher percentage of U.S. patients having a normal gastric mucosa (83%) at the baseline compared to ex-U.S. patients (62%).

2.2 **Sponsor's Analysis of Endoscopy Data**

Forty-one (41) patients (16, Arthrotec; 13, piroxicam; 12, naproxen) did not have a final endoscopy performed. These patients were not included in the Intent-to-Treat cohort analysis.

Four hundred and seventy-nine (479) patients (158, Arthrotec; 164, piroxicam; 157, naproxen) were judged to be evaluable for

endoscopic assessments.

Chi-square tests were used to compare final gastroduodenal, gastric and duodenal endoscopy scores and changes from pre- to posttreatment endoscopy scores.

2.2.1 **Final Gastric Endoscopy Scores**

The distribution of final gastric endoscopy scores in the three treatment groups is given below.

Final Gastric Endoscopy Scores --- Study 321
(Intent-to-Treat Cohort)

Number of Patients (%)

Score	Arthrotec 50 BID (N=200)	Piroxicam 10 mg BID (N=204)	Naproxen 375 mg BID (N=198)
0	156 (78%)	112 (55%)	73 (37%)
1	14 (7%)	13 (6%)	17 (9%)
2	4 (2%)	4 (2%)	4 (2%)
3	19 (10%)	48 (24%)	56 (28%)
4	4 (2%)	10 (5%)	17 (9%)
5	0 (0%)	3 (1%)	15 (8%)
6	0 (0%)	0 (0%)	1 (1%)
7	3 (2%)	14 (7%)	15 (8%)

Table 17 on page 50 in IN2-92-06-321

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P-values for Treatment Comparisons --- Study 321
(Intent-to-Treat Cohort)

Treatment Comparison	Arthrotec 50 BID vs. Piroxicam 10 mg BID	Arthrotec 50 BID vs. Naproxen 375 mg BID	Piroxicam 10 mg BID vs. Naproxen 375 mg BID
With an ulcer[a]	0.007*	0.004*	0.782
With more 10 erosions or an ulcer[b]	0.002*	0.000*	0.024

P-value was obtained by Chi-square test.
[a] Compare patients with scores of 0-6 vs. those with scores of 7.
[b] Compare patients with scores of 0-4 vs. those with scores of 5-7.
* Statistically significant at the 1.7% level (pairwise comparisons)

Fourteen (14) patients (7%) in the piroxicam group and 15 patients (8%) in the naproxen group developed gastric ulcers during the four-week study period, compared with three patients (2%) in the Arthrotec group. Pairwise comparisons between the three treatment groups demonstrated statistically significant differences between Arthrotec and piroxicam, Arthrotec and naproxen, but not between piroxicam and naproxen.

Seventeen (17) patients (8%) in the piroxicam group and 31 patients (16%) in the naproxen group showed clinically significant gastric lesions including ulcers (i.e., a score of 5 or more) compared with three patients (2%) in the Arthrotec group. Pairwise treatment comparisons of these gastric lesions reached statistical significance in favor of Arthrotec versus piroxicam and naproxen.

2.2.2 **Final Duodenal Endoscopy Scores**

The distribution of final duodenal endoscopy scores in the three treatment groups is given below.

Final Duodenal Endoscopy Scores --- Study 321
(Intent-to-Treat Cohort)

Number of Patients (%)

Score	Arthrotec 50 BID (N=200)	Piroxicam 10 mg BID (N=204)	Naproxen 375 mg BID (N=198)
0	181 (91%)	173 (85%)	159 (80%)
1	6 (3%)	3 (1%)	7 (4%)
2	1 (1%)	0 (0%)	0 (0%)
3	8 (4%)	14 (7%)	20 (10%)
4	4 (2%)	3 (1%)	6 (3%)
5	0 (0%)	1 (1%)	3 (2%)
6	0 (0%)	0 (0%)	0 (0%)
7	0 (0%)	10 (5%)	3 (2%)

Table 18 on page 52 in IN2-92-06-321

P-values for Treatment Comparisons --- Study 321
(Intent-to-Treat Cohort)

Treatment Comparison	Arthrotec 50 BID vs. Piroxicam 10 mg BID	Arthrotec 50 BID vs. Naproxen 375 mg BID	Piroxicam 10 mg BID vs. Naproxen 375 mg BID
With an ulcer[a]	0.002*	0.081	0.055
With more 10 erosions or an ulcer[b]	0.001*	0.013*	0.239

Table 18 on page 52 in IN2-92-06-321
P-value was obtained by Chi-square test.
[a] Compare patients with scores of 0-6 vs. those with scores of 7.
[b] Compare patients with scores of 0-4 vs. those with scores of 5-7.
* Statistically significant at the 1.7% level (pairwise comparisons).

Duodenal ulcers were observed in 10 patients (5%) in the piroxicam group and three patients (2%) in the naproxen group but were not observed in any patients in the Arthrotec group. Pairwise comparisons between the three treatment groups demonstrated statistically significant differences only between Arthrotec and piroxicam. Comparisons between Arthrotec and naproxen failed to reach statistical significance.

Eleven (11) patients (5%) in the piroxicam group and six (3%) in the naproxen group had clinically significant duodenal lesions including ulcer (i.e., a score of 5 or more), while no patients receiving Arthrotec experienced such damage. Pairwise comparisons between the three treatment groups demonstrated statistically significant differences between Arthrotec and piroxicam, Arthrotec and naproxen, but not between piroxicam and naproxen.

3. **Reviewer's Evaluation**

The diclofenac 50 mg BID was not included in this study. The superiority of Arthrotec 50 BID over either piroxicam 10 mg BID or naproxen 375 mg BID does not imply the superiority of Arthrotec 50 BID over diclofenac 50 mg BID.

F. **Overall Summary and Recommendation**

1. **Prevention of Developing NSAID-induced Gastric Ulcer**

Arthrotec 50 BID-TID (protocols 296 and 289)

In an OA study (protocol 296), after four weeks of treatment with Arthrotec 50 BID-TID or diclofenac 50 mg BID-TID, no significant differences were observed between treatment groups in terms of the number of patients with gastric ulcer.

In the second, a RA study (protocol 289), after 12 weeks of treatment with the same dosing regimens, no significant differences were observed between treatment groups in terms of the number of patients with gastric ulcer.

Both studies 296 and 289 failed to provide support of the efficacy of Arthrotec 50 BID-TID for prevention of developing NSAID-induced gastric ulcers. The p-value for the primary efficacy endpoint according to the sponsor's analysis was 0.641 for study 289 and 0.087 for study 296.

Arthrotec 50 BID (protocol 321)

In the four-week, active-controlled OA trial (protocol 321) comparing Arthrotec 50 BID with piroxicam 10 mg BID and naproxen 375 mg BID, pairwise treatment comparisons of gastric ulcers reached statistically significance in favor of Arthrotec 50 BID

versus piroxicam 10 mg BID and naproxen 375 mg BID.

Study 321 provides support of the efficacy of the Arthrotec 50 BID against piroxicam 10 mg BID and naproxen 375 BID for prevention of developing NSAID-induced gastric ulcers. However, superiority of Arthrotec 50 BID to diclofenac 50 mg BID has not been demonstrated in this trial.

Arthrotec 50 TID (protocol 349)

In the six-week, placebo-controlled OA study (protocol 349), which enrolled only patients with a history of UGI ulcer or erosive disease, the proportions of patients with gastric ulcers were significantly lower in the Arthrotec 50 TID than in the diclofenac 75 mg BID.

Study 349 provides support of the efficacy of the Arthrotec 50 TID against diclofenac 75 mg BID for prevention of developing NSAID-induced gastric ulcer.

Arthrotec 75 BID (protocol 349)

In the six-week, placebo-controlled OA study (protocol 349), which enrolled only patients with a history of UGI ulcer or erosive disease, pairwise treatment comparisons demonstrated no statistically significant differences in incidence of gastric ulcers between the Arthrotec 75 BID and diclofenac 75 mg BID group after adjusting for multiple comparisons by the Hochberg's procedure.

However, the proportions of patients with 11 or more gastric erosions or ulcer (score of 5 or more) were significantly lower in the Arthrotec 75 BID than in the diclofenac 75 mg BID group.

Study 349 provides some evidence of the efficacy of the Arthrotec 75 BID against diclofenac 75 mg BID for prevention of developing NSAID-induced gastric ulcer.

2. Prevention of Developing NSAID-induced Duodenal Ulcer

Arthrotec 50 BID-TID (protocols 296 and 289)

In an OA study (protocol 296), after four weeks of treatment with

Arthrotec 50 BID-TID or diclofenac 50 mg BID-TID, no significant differences were observed between treatment groups in terms of the number of patients with ulcer for duodenal ulcers.

In the second, a RA study (protocol 289), after 12 weeks of treatment with the same dosing regimens, it was observed that statistically significantly fewer endoscoped Arthrotec 50 patients had duodenal ulcer (score=7) as compared to diclofenac 50 mg/placebo. However, this significant result was doubtful due to the fact of a large discrepancy between treatment groups in the proportion of adverse event withdrawals having final endoscopy (56% of diclofenac/placebo; 15% of Arthrotec). This might compromise the statistical analysis of the between treatment group difference in duodenal ulcer rate.

Study 296 failed to provide support of the efficacy of Arthrotec 50 BID-TID. Study 289 provides some support of the efficacy of Arthrotec 50 BID-TID against diclofenac 50 mg BID-TID in terms of prevention of developing NASID-induced duodenal ulcer. However, the results are not replicated in study 296. The superiority might be due to the discrepancy between treatment groups in the proportion of adverse event withdrawals having final endoscopy.

Arthrotec 50 BID (protocol 321)

In the four-week, active-controlled OA trial (protocol 321) comparing Arthrotec 50 BID with piroxicam 10 mg BID and naproxen 375 mg BID, pairwise treatment comparisons of duodenal ulcers demonstrated statistically significant difference only between Arthrotec 50 BID and piroxicam 10 mg BID. Comparisons between Arthrotec 50 BID and naproxen 375 mg BID failed to reach statistical significance.

Study 321 provides support of the efficacy of the Arthrotec 50 BID against piroxicam 10 mg BID for prevention of developing NSAID-induced duodenal ulcers. However, superiority of Arthrotec 50 BID to diclofenac 50 mg BID has not been demonstrated in this trial.

Arthrotec 50 TID (protocol 349)

In the six-week, placebo-controlled OA study (protocol 349), which enrolled only patients with a history of UGI ulcer or

erosive disease, pairwise treatment comparisons demonstrated no statistically significant differences in incidence of duodenal ulcers between the Arthrotec 50 TID and diclofenac 75 mg BID group.

Study 349 failed to support of the efficacy of the Arthrotec 50 TID against diclofenac 75 mg BID for prevention of developing NSAID-induced duodenal ulcer.

Arthrotec 75 BID (protocol 349)

In the six-week, placebo-controlled OA study (protocol 349), which enrolled only patients with a history of UGI ulcer or erosive disease, pairwise treatment comparisons demonstrated no statistically significant differences in incidence of duodenal ulcers between the Arthrotec 75 BID and diclofenac 75 mg BID group.

Study 349 failed to support of the efficacy of the Arthrotec 75 BID against diclofenac 75 mg BID for prevention of developing NSAID-induced duodenal ulcer.

G. **Comments to be conveyed to the Sponsor**

The contents of Section F may be conveyed to the sponsor.

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/S/
Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 29 pages of text and 5 pages of tables.

concur: Dr. Huque /S/ 9/9/96
Dr. Smith

cc: /S/ 9/11/96
Archival NDA 20-607
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Robie-Suh
HFD-180/Mr. Strongin
HFD-344/Dr. Lisook
HFD-720

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HFD-720/Chron.
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/09/09/96

Table 1 Comparability of Treatment Groups --- Protocol 289

Intent-to-Treat Population

Variable	Level	Diclofenac/ Misoprostol 50 mg/200 mcg BID-TID (n=164)	Diclofenac/ Placebo 50 mg/0 mcg BID-TID (n=175)	between treatment p-value
Sex	Male	41 (25%)	38 (22%)	0.475
	Female	123 (75%)	137 (78%)	
Age (mean)		53.2	53.4	0.843
Height (cm) (mean)		162.6	162.5	0.608
Weight (kg) (mean)		66.2	65.2	0.568
Race	Caucasian	130 (79%)	148 (85%)	0.132
	Black	10 (6%)	3 (2%)	
	Oriental	1 (1%)	0 (0%)	
	Other	23 (14%)	24 (14%)	
Disease Duration	<0.5 (years)	3 (2%)	4 (2%)	0.285
	0.5 - 0.9	5 (3%)	6 (3%)	
	1.0 - 4.9	40 (24%)	52 (30%)	
	5.0 - 9.9	45 (27%)	48 (27%)	
	10.0 - 14.9	45 (27%)	34 (19%)	
	> 15.0	26 (16%)	31 (18%)	
Endoscopy Scores Gastric	0	107 (65%)	112 (64%)	0.463
	1	10 (6%)	16 (9%)	
	2	3 (2%)	2 (1%)	
	3	29 (18%)	36 (21%)	
	4	15 (9%)	9 (5%)	
	5	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	
	unknown	0 (0%)	0 (0%)	
Endoscopy Scores Duodenal	0	150 (91%)	149 (85%)	0.347
	1	2 (1%)	5 (3%)	
	2	0 (0%)	1 (1%)	
	3	9 (5%)	17 (10%)	
	4	3 (2%)	2 (1%)	
	5	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	
	unknown	0 (0%)	1 (1%)	
Physician's global assessment	Very good	5 (3%)	3 (2%)	0.802
	Good	55 (34%)	51 (29%)	
	Fair	70 (43%)	83 (47%)	
	Poor	32 (20%)	36 (21%)	
	Very Poor	2 (1%)	2 (1%)	
Patient's global assessment	Very good	5 (3%)	3 (2%)	0.678
	Good	48 (29%)	52 (30%)	
	Fair	75 (46%)	77 (44%)	
	Poor	32 (20%)	34 (19%)	
	Very Poor	4 (2%)	9 (5%)	
Functional Capacity	I	18 (11%)	17 (10%)	0.752
	II	110 (67%)	123 (70%)	
	III	34 (21%)	31 (18%)	
	IV	2 (1%)	4 (2%)	

Compiled from Tables 10-13, pages 31-35, IN2-90-06-289.
P-values for age, height, weight, and disease duration were obtained usisng Mann-Whitney nonparametric test.
P-values for other variables were obtained using Pearson's chi-square test.

Table 3 Comparability of Treatment Groups --- Protocol 296

Variable	Level	Intent-to-Treat Population: Diclofenac/ Misoprostol 50 mg/200 mcg BID-TID (n=178)	Intent-to-Treat Population: Diclofenac/ Placebo 50 mg/0 mcg BID-TID (n=183)	between treatment p-value
Sex	Male	43 (24%)	54 (30%)	0.252
	Female	135 (76%)	129 (70%)	
Age (mean)		59.2	61.3	0.110
Height (cm) (mean)		160.5	161.7	0.342
Weight (kg) (mean)		70.4	73.8	0.004
Race	Caucasian	158 (89%)	160 (87%)	0.785
	Black	5 (3%)	5 (3%)	
	Oriental	0 (0%)	1 (1%)	
	Other	15 (8%)	17 (9%)	
Disease Duration	<0.5 (years)	0 (0%)	4 (2%)	0.514
	0.5 - 0.9	7 (4%)	7 (4%)	
	1.0 - 4.9	68 (38%)	67 (37%)	
	5.0 - 9.9	51 (29%)	42 (23%)	
	10.0 - 14.9	30 (17%)	36 (20%)	
	> 15.0	22 (12%)	27 (15%)	
Endoscopy Scores Gastric	0	121 (68%)	123 (67%)	0.600
	1	18 (10%)	22 (12%)	
	2	0 (0%)	3 (2%)	
	3	25 (14%)	24 (13%)	
	4	11 (6%)	9 (5%)	
	5	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	
	7	1 (1%)	0 (0%)	
	unknown	2 (1%)	2 (1%)	
Endoscopy Scores Duodenal	0	155 (87%)	153 (84%)	0.375
	1	12 (7%)	14 (8%)	
	2	0 (0%)	0 (0%)	
	3	6 (3%)	13 (7%)	
	4	2 (1%)	1 (1%)	
	5	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	
	7	2 (1%)	0 (0%)	
	unknown	1 (1%)	2 (1%)	
Physician's global assessment	Very good	2 (1%)	1 (1%)	0.981
	Good	36 (20%)	39 (21%)	
	Fair	103 (58%)	105 (57%)	
	Poor	36 (20%)	37 (20%)	
	Very Poor	1 (1%)	1 (1%)	
Patient's global assessment	Very good	2 (1%)	4 (2%)	0.802
	Good	27 (15%)	33 (18%)	
	Fair	94 (53%)	97 (53%)	
	Poor	49 (28%)	43 (23%)	
	Very Poor	6 (3%)	6 (3%)	
Functional Capacity	I	22 (12%)	17 (9%)	0.583
	II	128 (72%)	133 (73%)	
	III	28 (16%)	33 (18%)	
	IV	0 (0%)	0 (0%)	
OA severity index (mean)		11.15	11.20	0.783

Compiled from Tables 13-16, pages 32-37, IN2-90-06-296.
P-values for age, height, weight, disease duration, and osteoarthritis severity index were obtained using Mann-Whitney nonparametric test.
P-values for other variables were obtained using Pearson's chi-square test.

Table 2 Reanalysis of Duodenal Ulcer Occurrence with Arthrotec 50 as Compared to Diclofenac 50 mg/Placebo --- Study 289

Analysis	Diclofenac/Placebo (n = 175)	Diclofenac/Misoprostol (n = 164)	P-Value[b]
Equal probability imputation using LOCF[c] for all patients except for "unknown"[a] adverse event withdrawals for whom the placebo incidence rate of 43% for "unknown" adverse event withdrawals for both misoprostol and placebo	16/175[d]	9/164	0.218
Equal probability imputation excluding "unknown" except for "unknown" adverse event withdrawals for whom the placebo incidence rate of 43% for "unknown" adverse event withdrawals for both misoprostol and placebo	16/162	9/156	0.213
Equal probability imputation using placebo incidence rate (8%) for both "unknown" misoprostol and "unknown" placebo patients who were not adverse event withdrawals and the placebo incidence rate of 43% for "unknown" adverse event withdrawals for both misoprostol and placebo.	17/175	10/164	0.235
Equal probability imputation using misoprostol incidence rate (1%) for both "unknown" misoprostol and "unknown" placebo patients who were not adverse event withdrawals and the placebo incidence rate of 43% for "unknown" adverse event withdrawals for both misoprostol and placebo.	16/175	9/164	0.218
Equal probability imputation using misoprostol incidence rate (1%) for "unknown" placebo patients who were not adverse event withdrawals and placebo incidence rate (8%) for "unknown" misoprostol patients who were not adverse event withdrawals and the placebo incidence rate of 43% for "unknown" adverse event withdrawals for both misoprostol and placebo.	16/175	10/164	0.315

[a] "unknown" refers to missing (not done) final endoscopy
[b] p-value = 2-sided p-value determined by Fisher's exact test (M. Fan, FDA Biometrics)
[c] LOCF = last observation carried forward
[d] pyloric channel ulcers (2 diclofenac/placebo and 1 diclofenac/misoprostol) are counted with the duodenal ulcers.

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Table 4 Comparability of Treatment Groups --- Protocol 3

Intent-to-Treat Population

Variable	Level	Diclofenac 75 mg BID (n=154)	Arthrotec 50 mg TID (n=152)	Arthrotec 50 mg BID (n=175)	Placebo (n=91)	between treatment p-value
Sex	Male	44 (29%)	49 (32%)	58 (33%)	29 (32%)	0.831
	Female	110 (71%)	103 (69%)	117 (67%)	62 (68%)	
Age (mean)		62.9	62.3	62.8	61.5	0.505
Height (cm) (mean)		167.5	167.0	166.8	167.5	0.868
Weight (kg) (mean)		88.9	87.4	84.7	89.1	0.276
Race	Caucasian	127 (92%)	134 (89%)	151 (86%)	79 (87%)	0.814
	Black	21 (14%)	14 (9%)	17 (10%)	10 (11%)	
	Oriental	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	Other	6 (4%)	4 (3%)	7 (4%)	2 (2%)	
Disease Duration (yrs) (mean)		11.9	11.9	10.3	10.6	0.389
Endoscopy Scores Gastric	0	98 (64%)	103 (68%)	120 (69%)	64 (70%)	0.938
	1	11 (7%)	11 (7%)	13 (7%)	6 (7%)	
	2	6 (4%)	7 (5%)	4 (2%)	3 (3%)	
	3	33 (21%)	23 (15%)	33 (19%)	16 (18%)	
	4	6 (4%)	8 (15%)	5 (3%)	2 (2%)	
	5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Endoscopy Scores Duodenal	0	135 (88%)	134 (88%)	153 (87%)	76 (84%)	0.625
	1	6 (4%)	7 (5%)	7 (4%)	3 (3%)	
	2	1 (1%)	1 (1%)	3 (2%)	2 (2%)	
	3	12 (8%)	9 (6%)	9 (5%)	10 (11%)	
	4	0 (0%)	1 (1%)	3 (2%)	0 (0%)	
	5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Physician's global assessment	Very good	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.092
	Good	3 (2%)	2 (1%)	8 (5%)	1 (1%)	
	Fair	30 (19%)	26 (17%)	36 (21%)	14 (15%)	
	Poor	107 (69%)	119 (78%)	120 (69%)	74 (81%)	
	Very Poor	14 (9%)	5 (3%)	11 (6%)	2 (2%)	
Patient's global assessment	Very good	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.093
	Good	4 (3%)	3 (2%)	6 (3%)	1 (1%)	
	Fair	26 (17%)	30 (20%)	24 (14%)	22 (24%)	
	Poor	92 (60%)	103 (68%)	123 (70%)	59 (65%)	
	Very Poor	32 (21%)	16 (11%)	22 (13%)	9 (10%)	
Functional Capacity	I	6 (4%)	4 (3%)	11 (6%)	4 (4%)	0.449
	II	124 (81%)	126 (83%)	145 (83%)	70 (77%)	
	III	24 (16%)	22 (14%)	19 (11%)	17 (19%)	
	IV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
OA severity index (mean)		14.2	14.0	14.0	13.9	0.898

Compiled from Tables 11-15, pages 63-69, IN2-95-06-349.
P-values for age, height, weight, disease duration, and osteoarthritis severity index were obtained using Kruskal-Wallis nonparametric test.
P-values for other variables were obtained using Pearson's chi-square test.

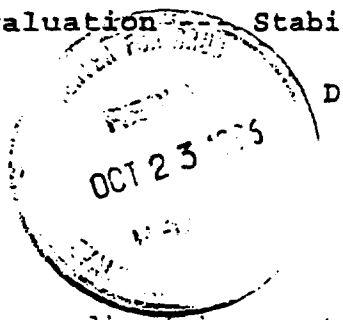
Table 5 Comparability of Treatment Groups --- Protocol 321

Intent-to-Treat Population

Variable	Level	Diclofenac/ Misoprostol 50 mg/200 mcg BID (n=216)	Piroxicam 10 mg BID (n=217)	Naproxen 375 mg BID (n=210)	between treatment p-value
Sex	Male	52 (24%)	55 (25%)	48 (23%)	0.835
	Female	164 (76%)	162 (75%)	162 (77%)	
Age (mean)		60.7	58.7	59.5	0.117
Height (cm) (mean)		161.4	161.8	162.6	0.898
Weight (kg) (mean)		77.5	76.3	77.2	0.294
Race	Caucasian	177 (82%)	172 (79%)	169 (80%)	0.982
	Black	17 (8%)	21 (10%)	20 (10%)	
	Oriental	1 (0%)	2 (1%)	1 (0%)	
	Other	21 (10%)	22 (10%)	20 (10%)	
Disease Duration (years)	<0.5	4 (2%)	6 (3%)	1 (0%)	0.395
	0.5 - 0.9	9 (4%)	10 (5%)	9 (4$)	
	1.0 - 4.9	72 (33%)	94 (43%)	79 (38%)	
	5.0 - 9.9	69 (32%)	44 (20%)	59 (28%)	
	10.0 - 14.9	39 (18%)	33 (15%)	30 (14%)	
	>15.0	23 (11%)	30 (14%)	32 (15%)	
Endoscopy Scores Gastric	0	145 (67%)	141 (65%)	146 (70%)	0.847
	1	12 (6%)	16 (7%)	11 (5%)	
	2	3 (1%)	2 (1%)	3 (1%)	
	3	31 (14%)	34 (16%)	23 (11%)	
	4	25 (12%)	24 (11%)	26 (12%)	
	5	0 (0%)	0 (0%)	1 (0%)	
	6	0 (0%)	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	0 (0%)	
	unknown	0 (0%)	0 (0%)	0 (0%)	
Endoscopy Scores Duodenal	0	202 (94%)	191 (88%)	195 (93%)	0.318
	1	4 (2%)	8 (4%)	6 (3%)	
	2	0 (0%)	0 (0%)	0 (0%)	
	3	5 (2%)	12 (6%)	4 (2%)	
	4	5 (2%)	6 (3%)	5 (2%)	
	5	0 (0%)	0 (0%)	0 (0%)	
	6	0 (0%)	0 (0%)	0 (0%)	
	7	0 (0%)	0 (0%)	0 (0%)	
	unknown	0 (0%)	0 (0%)	0 (0%)	
Physician's global assessment	Very good	0 (0%)	1 (0%)	0 (0%)	0.284
	Good	3 (1%)	4 (2%)	2 (1%)	
	Fair	126 (58%)	148 (68%)	135 (65%)	
	Poor	75 (35%)	50 (23%)	58 (28%)	
	Very Poor	12 (6%)	14 (7%)	14 (7%)	
Patient's global assessment	Very good	0 (0%)	1 (0%)	0 (0%)	0.377
	Good	3 (1%)	3 (1%)	2 (1%)	
	Fair	107 (50%)	129 (59%)	122 (58%)	
	Poor	85 (39%)	62 (29%)	66 (32%)	
	Very Poor	21 (10%)	22 (10%)	19 (9%)	
Functional Capacity	I	18 (8%)	35 (16%)	21 (10%)	0.059
	II	165 (76%)	160 (74%)	164 (78%)	
	III	33 (15%)	22 (10%)	24 (11%)	
	IV	0 (0%)	0 (0%)	0 (0%)	
OA severity index (mean)		11.93	11.00	11.51	0.024

Compiled from Tables 12-15, pages 42-45, IN2-92-06-321.
P-values for age, height, weight, disease duration, and osteoarthritis severity index were obtained using Kruskal-Wallis nonparametric test.
P-values for other variables were obtained using Pearson's chi-square test.

Statistical Review and Evaluation -- Stability



Date: OCT 21 1996

NDA #: 20-607

Applicant: G. D. Searle & Company

Name of Drug: Arthrotec (diclofenac sodium/misoprostol) Tablets

Documents Reviewed: Original Amendment Dated February 23, 1996
Amendment Dated March 8, 1996

A. Background

In this NDA submission, the sponsor has submitted 12 months stability data for Arthrotec and has requested a 36 month expiration dating period for this drug product. Dr. George Chen, reviewing chemist in HFD-180, has requested a statistical review and evaluation of the sponsor's stability data analyses.

The sponsor performed the analysis of 25 °C assay and degradation product data from the primary stability studies for diclofenac sodium/misoprostol drug product. Included for stability analysis are bottles and paper/foil/foil/paper strips for two different strength tablets: 50 mg diclofenac sodium/200 mcg misoprostol (50/200) and 75 mg diclofenac sodium/200 mcg misoprostol (75/200).

This review will only address on potency data in the 25°C storage.

B. Sponsor's Results

All lots have been on stability for 52 weeks except for lots 480110, 480100, and 480090 which have been on stability for 104 weeks.

Values for assay and for the degradation products are reported as percent of label claim. All values for the degradation products reported at their limit of quantitation of <0.5% were set to 0.25% for calculations.

The sponsor used the FDA SAS DRUG Formulation Stability Program

(3/09/92) to generate the results of the estimated dating period in months for all the lots in the various package types.

The program performs the expiration dating period estimation based on linear regression analysis. For each package type, each set of three lots was submitted into the program to initially test for equalities of intercepts and/or slopes.

Based on a full-vs-reduced model approach, pooling of intercepts and/or slopes was performed where appropriate. For each fit, the standard errors of the mean predicted values were used to generate a one-sided 95% lower confidence bound for assay and a one-sided 95% upper confidence bound for degradation products. For both diclofenac sodium and misoprostol assay, the lower specification limits of 90% was used to estimate expiry. For SC-29636, SC-32759 and SC-33188, the respective upper specification limits of 3.5%, 2.0% and 0.7% were used to estimate expiry.

The resulting estimated dating periods in months for all the lots in the various package types are summarized in Table 1.

C. Reviewer's Results

This reviewer ran the Division's routine stability program and had verified the sponsor's estimated dating periods for all the lots in three package types for 50/200 and 75/200 strength for diclofenac sodium, misoprostol, and SC-29636.

With respect to all five quantities:

Diclofenac Sodium	90%-110%
Misoprostol	90%-110%
SC-29636	≥3.5%
SC-32759	≥2.0%
SC-33188	≥0.7%

expiration dating periods for all the lots in the various package types are:

Strength	Lot No.	Est. Expiration Dating Period (Months)
50/200	653310	48
	653320	48
	664680	35
	653310	29
	653320	37
	664680	34
	480110	13
	480100	16
	480090	43
	653310	48
	653320	48
	664680	48
75/200	651060	48
	651050	48
	661070	47
	651060	48
	651050	48
	661070	48
	651060	37
	651050	48
	651070	48

D. **Summary and Conclusion**

Overall, an expiration dating period of 37 months seems justifiable for batches for all package types for 75/200 strength.

For 50/200 strength, shorter expiration dating periods of 29 and 13 months appear reasonable for 100-cc bottle and paper/foil/foil/paper strip, respectively.

/S/
Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 4 pages of text and 1 page of table.

concur: Dr. Huque /S/ 10/16/96
Dr. Smith /S/ 10/18/96

cc:
Archival NDA 20-607
HFD-180
HFD-180/Dr. Chen
HFD-180/Dr. Gibbs
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/10/11/96

TABLE 1

STATISTICAL ANALYSIS OF 25 °C PRIMARY STABILITY DATA

STRENGTH[1]	STABILITY NUMBER	LOT NUMBER	ESTIMATED DATING PERIOD IN MONTHS				
			DICLOFENAC SODIUM	MISOPROSTOL	SC-29636[2]	SC-32739[2]	SC-33188[2]
50/200	8754	653310	48	48	48	48	48
	8755	653320	48	48	48	48	48
	8763	664680	48	48	35	48	48
	8752	653310	48	29	48	48	48
	8753	653320	48	37	48	48	48
	8762	664680	48	34	48	48	48
	8676	480110	84	13	84	84	84
	8677	480100	84	16	84	84	84
	8678	480090	79	43	84	84	84
75/200	8756	653310	48	48	48	48	48
	8757	653320	48	48	48	48	48
	8764	664680	48	48	48	48	48
	8745	651060	48	48	48	48	48
	8746	651050	48	48	48	48	48
	8747	651070	48	47	48	48	48
	8742	651060	48	48	48	48	48
	8743	651050	48	48	48	48	48
	8744	651070	48	48	48	48	48
	8748	651060	48	48	37	48	48
	8749	651050	48	48	48	48	48
	8750	651070	48	48	48	48	48

1 mg diclofenac sodium/mg misoprostol
2 Values reported as <0.5 set to 0.25 for calculations