shown prospectively in a well-controlled study.

The sponsor stated in the NDA supplemental dated December 20, 1995 that results of these four studies (002, 003, 053, and 320) suggest that there may be a dose response characteristic of misoprostol in the prevention of NSAID-induced gastric ulcers. The sponsor then used a logistic regression model to examine the relationship between total daily dose of misoprostol and gastric ulcer incidence for these four studies and concluded that the gastric ulcer rate was related to the total daily dose of misoprostol in these four studies and the observed gastric ulceration rate for the 400 mcg total daily dose from Study 053 is consistent with the rate from the Studies 002/003.

Efficacy data from Study 002 and Study 003 should not be pooled since observed placebo gastric ulcer incidence rates were very different in these two studies (25% for Study 002 and 18% for Study 003).

Furthermore, the sponsor's approach used to show that the efficacy of the two misoprostol regimens for GU prevention are not different is an exploratory analysis in which pooled results (Studies 002 and 003) are used to generate a model from which a dosing regimen is being estimated. This approach could not be substituted for an adequate and well-controlled study.

D. **Overall Summary and Recommendation**

The sponsor's approach, to show that the efficacy of the two misoprostol regimens for GU prevention are not different, is an exploratory analysis. The sponsor pooled results of Studies 002 and 003 to generate a model from which a dosing regimen was estimated. This approach could not be substituted for an adequate and well-controlled study. In this reviewer's assessment the results claimed based on exploratory analysis is hypothesis generating.

The comparison of efficacy of the two misoprostol regimens: 200 mcg BID and 100 mcg QID, for GU prevention should be shown in an adequate and well-controlled study.

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E. Comments to be conveyed to the Sponsor

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

APPEARS THIS WAY
ON ORIGINAL

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

This review consists of 5 pages of text and 1 page of table.

Concur: Dr. Huque /S/ 2/12/97
Dr. Smith /S/ 2/14/97

cc:
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
HFD-720/Chron.
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/02/12/97

APPEARS THIS WAY
ON ORIGINAL

CYTOTEC -002, -003, AND -053

PREDICTED PROBABILITIES AND OBSERVED INCIDENCE OF GASTRIC ULCERS

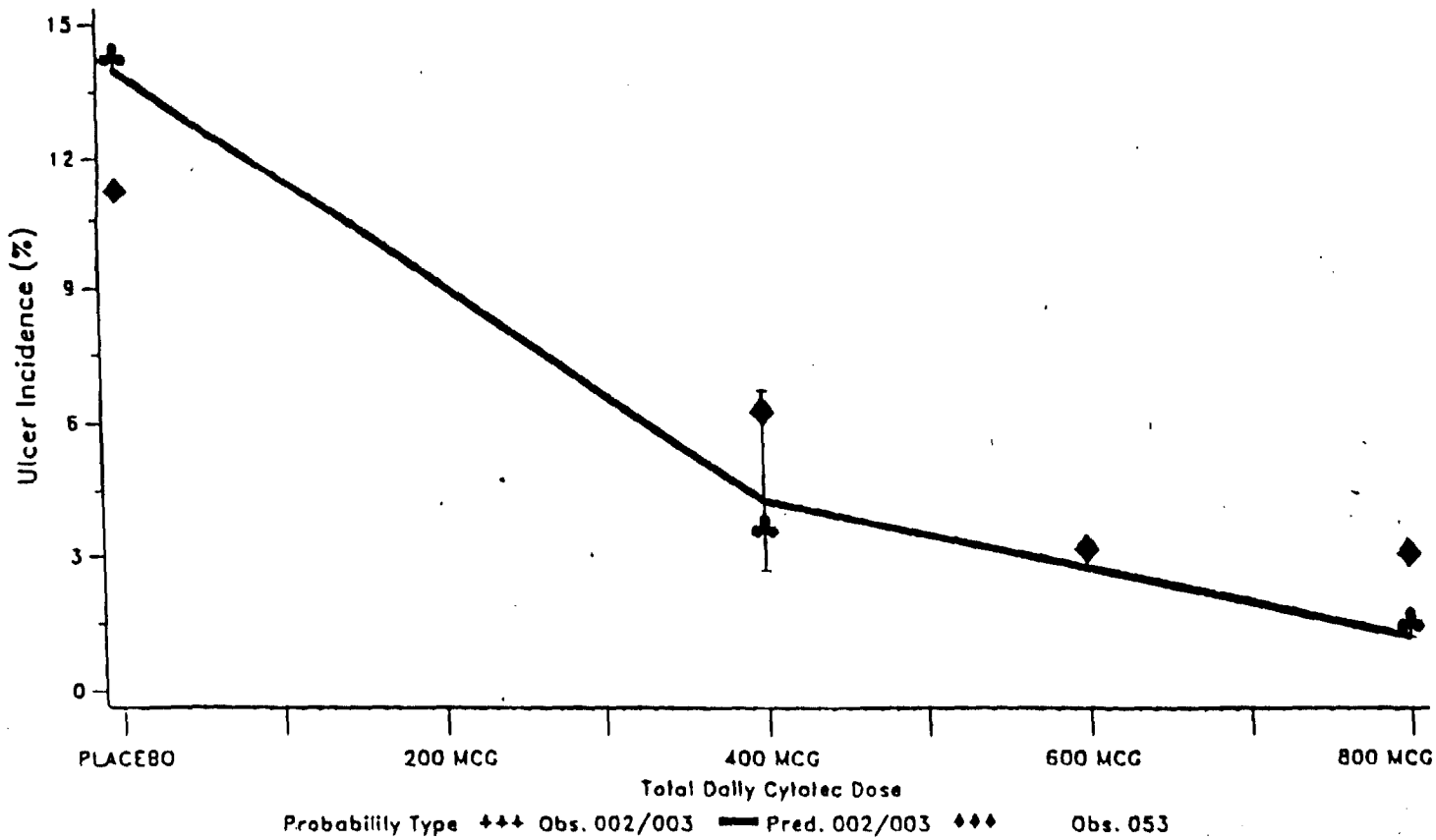

Figure 1
Predicted Probabilities and Observed Incidence of Gastric Ulcers

Strength

Statistical Review and Evaluation
(Amended Review)

DEC - 2 1996

NDA 20-607
Name of Drug : **Arthrotec** (diclofenac sodium/misoprostol)
Applicant : **G. D. Searle & Co.**
Indication : *For the temporary relief of signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankelosing spondilitis*
Dosage : **Arthrotec I (diclofenac 50 mg/misoprostol 200 mg) b.i.d. or t.i.d.**
Arthrotec II (diclofenac 75 mg/misoprostol 200 mg) b.i.d.
Documents Reviewed: Volumes 1.69 and 1.70 dated 12/22/95 of NDA 20-607.
Reviewer : Hoi M. Leung, Ph.D.
Date Completed: 11/27/96

I. Background

The original statistical review (dated 9/23/96) evaluated the efficacy of Arthrotec in the treatment of osteoarthritis and rheumatoid arthritis. There were two single dose post-surgical dental pain studies in this submission. Protocol NN2-90-02-308 compared the coadministration of various doses of misoprostol on the analgesia of diclofenac 50 mg and placebo in patients following dental impaction surgery. Protocol NN2-94-02-351 compared Arthrotec I with diclofenac 50 mg, misoprostol 200 mg and placebo in patients following dental impaction surgery. At the request of HFD-180, these two dental pain studies are evaluated in this review. It should be noted that the sponsor does not intend to make analgesia as an indication in this submission.

Note that the diclofenac component of Arthrotec is diclofenac sodium (Voltaren) which is a delayed release formulation of the immediate release diclofenac potassium (Cataflam). Only Cataflam is indicated for analgesia in U.S.

II. Protocol NN2-90-02-308

Description

This was a single-center, double-blind, placebo-controlled, single dose, parallel group study of orally coadministered doses of misoprostol (50, 100 or 200 mg) on the analgesia of diclofenac 50 mg in patients following dental impaction surgery. To qualify for this study patients must have undergone surgical extraction of an impacted third molar and subsequently experienced moderate to severe pain. There were five treatment groups, namely, the

three doses of misoprostol coadministered with diclofenac 50 mg, diclofenac 50 mg alone and placebo. Pain intensity (both categorical and analog) and pain relief were measured at 30 minutes, 1 hour and hourly up to 8 hours. The primary efficacy measures were pain intensity difference from baseline (PID), pain relief (PR), sum (PRID) of PID and PR. The secondary efficacy variables were percent of patients requiring a rescue medication, time to remedication, percent of patients experiencing at least 50% pain relief and the patient's overall evaluation of the study medication.

Results

A total of 292 patients were randomized to receive study medication. Table 1 below shows the patients' disposition.

Table 1. Patients' Disposition

Treatment Diclo/Miso (mg)/(mg)	Randomized	Completed	Lost to Follow-up	Protocol Violation
50/200	58	54	0	4
50/100	54	49	0	5
50/50	57	47	2	8
50/pbo	61	53	2	6
pbo/pbo	62	54	0	8
Total	292	257	4	31

Of the 257 patients completing the study, 243 of them were classified as evaluable. The two most common reasons for nonevaluability were remedication before two hours and missing more than one evaluation.

Demographics were comparable among treatment groups. The mean age was 23 years. Forty-four percent of the patients were males and 96% of the patients were Caucasian. Surgical trauma rating, maximum degree of impaction and baseline pain severity were also comparable among treatment groups. The average number of molars extracted was 3.5 and the duration of surgery was two and a half hours.

Three contrast statements were used to assess efficacy:

1. Drug Effect - all active medication vs. placebo,

2. Diclofenac Effect - placebo (misoprostol) and diclofenac 50 mg vs. Placebo (misoprostol) and placebo (diclofenac),
3. Misoprostol Effect - all misoprostol and diclofenac 50 mg combinations combined vs. Placebo and diclofenac 50 mg.

The drug effect was statistically significant from 3 through 8 hours for PID and from 2 through 8 hours for PR and PRID for all active medications containing misoprostol. The number of hours with 50% pain relief, time to rescue medication and patient's overall evaluation were also significantly better than placebo for the drug effect contrast. However, Diclofenac alone was not significantly better than placebo in most efficacy variables and most time points. There was generally no significant difference in any efficacy variables between treatments with coadministered diclofenac 50 mg/misoprostol and diclofenac 50 mg alone. Figures 1 and 3 of Protocol NN2-90-02-308 in the appendix show the curves of PID and PR over time for the various treatment groups, respectively. The median time to rescue medication was about 2.5 hours for placebo and diclofenac alone and ranged from 3.0 to 4.4 hours for the other 3 groups.

Nausea and vomiting were the most common adverse events.

Reviewer's Comments

Coadminstration of diclofenac 50 mg with various doses of misoprostol is not the same as fixed dose combination without a head to head comparison. Thus this study does not serve any useful purpose in supporting the fixed dose combination of diclofenac and misoprostol. In addition, the diclofenac sodium is a delayed release formulation which is not suitable for acute pain relief such as dental surgery. Statistical methods used in the analyses such as the non-parametric Kruskal-Wallis test, chi-square test, and log-rank test for time events are appropriate. The results of the study suggest that misoprostol may enhance the analgesic effect of diclofenac alone. However, there was no dose response relationship in misoprostol when it is coadministered with diclofenac. Unfortunately, diclofenac was not shown to be superior to placebo which may cast doubt on the validity of the study. Even though the various doses of misoprostol together with diclofenac 50 mg was superior to placebo, the superiority did not occur until 2 to 3 hours which is considered to be too long for dental pain patients.

III. Protocol NN2-94-02-351

Description

This was a single-center, double-blind, placebo-controlled,

single dose, parallel group study of orally administered Arthrotec I, diclofenac 50 mg, misoprostol 200 mg or placebo in patients with moderate to severe pain following dental impaction surgery. Except for the treatment groups, the study design features were very similar to the previous study. Measurements of pain intensity and pain relief were made at 30 minutes, 1 hour, 1.5 hours, 2 hours and then hourly for an additional 6 hours.

Results

Two hundred patients were randomized equally into the 4 treatment groups and all patients completed the study. Except for age, demographics were comparable among treatment groups. Placebo patients were slightly older (mean 29 years) compared to the other groups (mean 27 years). Surgical trauma rating, maximum degree of impaction and baseline pain intensity were also comparable among treatment groups. Approximately 75% of the patients had moderate pain at baseline. The mean number of molars extracted was 1.9. The average time of surgery was about 2.5 hours. Arthrotec I was significantly better than diclofenac 50 mg at 1.5, 2, 5 and 7 hours in PID and at hour 2 only for PR. Diclofenac 50 mg was significantly better than placebo in PID and PR beginning 1.0 hour and through the end of the 8 hours of study. There was practically no difference between misoprostol and placebo at any time point in either PID or PR. Figures 1 and 3 of Protocol NN2-94-02-351 in the appendix show the PID and PR curves over time. The other efficacy variables such as proportion of patients experienced at least 50% pain relief, number of patients required rescue medication followed the same pattern as the PID finding. The median time to remedication could not be estimated for Arthrotec I because less than half of the patients needed remedication in that group. The median time to remedication for placebo and misoprostol was about 1.5 hours and that of the diclofenac 50 mg group was 6 hours 18 minutes.

Headache and nausea were the most common adverse events. There were no serious adverse events reported.

Reviewer's Comments

Unlike the previous study, this study shows that both the fixed dose combination Arthrotec I and diclofenac 50 mg were significantly better than placebo and misoprostol 200 mg in all primary efficacy variables beginning at hour 1 and continued through out the end of the 8 hour study. The onset of analgesia was not presented by the sponsor. Using the convention of time to reach a group mean of one unit of PRID, the onset of analgesia

for Arthrotec I was between 30 and 45 minutes and that for diclofenac 50 mg was between 45 minutes and one hour. There was practically no placebo response in this study which is somewhat unusual. The lack of placebo response also magnified the relative analgesic effect of Arthrotec I and diclofenac. Compared to the first study, the baseline pain intensity was milder and the number of molars extracted was also fewer (1.9 vs. 3.5).

The contribution of misoprostol 200 mg in the fixed dose combination in this dental pain study was not clear. In terms of enhancement of analgesia, Arthrotec I was only significantly better than diclofenac in pain relief at hour 2 though it was significantly better than diclofenac at several time points in PID. The benefit of reducing gastrointestinal bleeding from misoprostol was not studied here and it is doubtful whether there will be any difference at all for infrequent use such as dental pain.

IV. Overall Conclusions

Protocol NN2-90-02-308 is irrelevant with respect to the fixed dose combination Arthrotec I since Arthrotec I was not a treatment group in that study. The result of this study shows that coadministration of various doses of misoprostol (50, 100, and 200 mg) with diclofenac 50 mg was superior to placebo in reducing post surgical dental pain beginning 2 to 3 hours but diclofenac 50 mg alone was not significantly different from placebo.

Protocol NN2-94-02-351 which compared Arthrotec I with its two components and placebo shows that both Arthrotec I and diclofenac 50 mg was superior to placebo and misoprostol 200 mg in reducing pain in post dental surgery patients. However, the contribution of misoprostol 200 mg in this combination for such use is not clear whether as an enhancement of analgesia or reduction of gastrointestinal bleeding. Even if such contribution had been demonstrated in this study, a second confirmatory study will be needed for the analgesia indication.

/S/

Hoi M. Leung, Ph.D.
Mathematical Statistician

Concur:

/S/

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

Orig. NDA 20,607

CC:

HFD-550/MO/Neurner
HFD-550/PM/LoBianco
HFD-550/Div. File
HFD-340/Div. Scientific Investigation
HFD-180/MO/Suh
HFD-180/PM/Strongin
HFD-180/Div. File
HFD-725/Stat/Leung
HFD-725/Div. File

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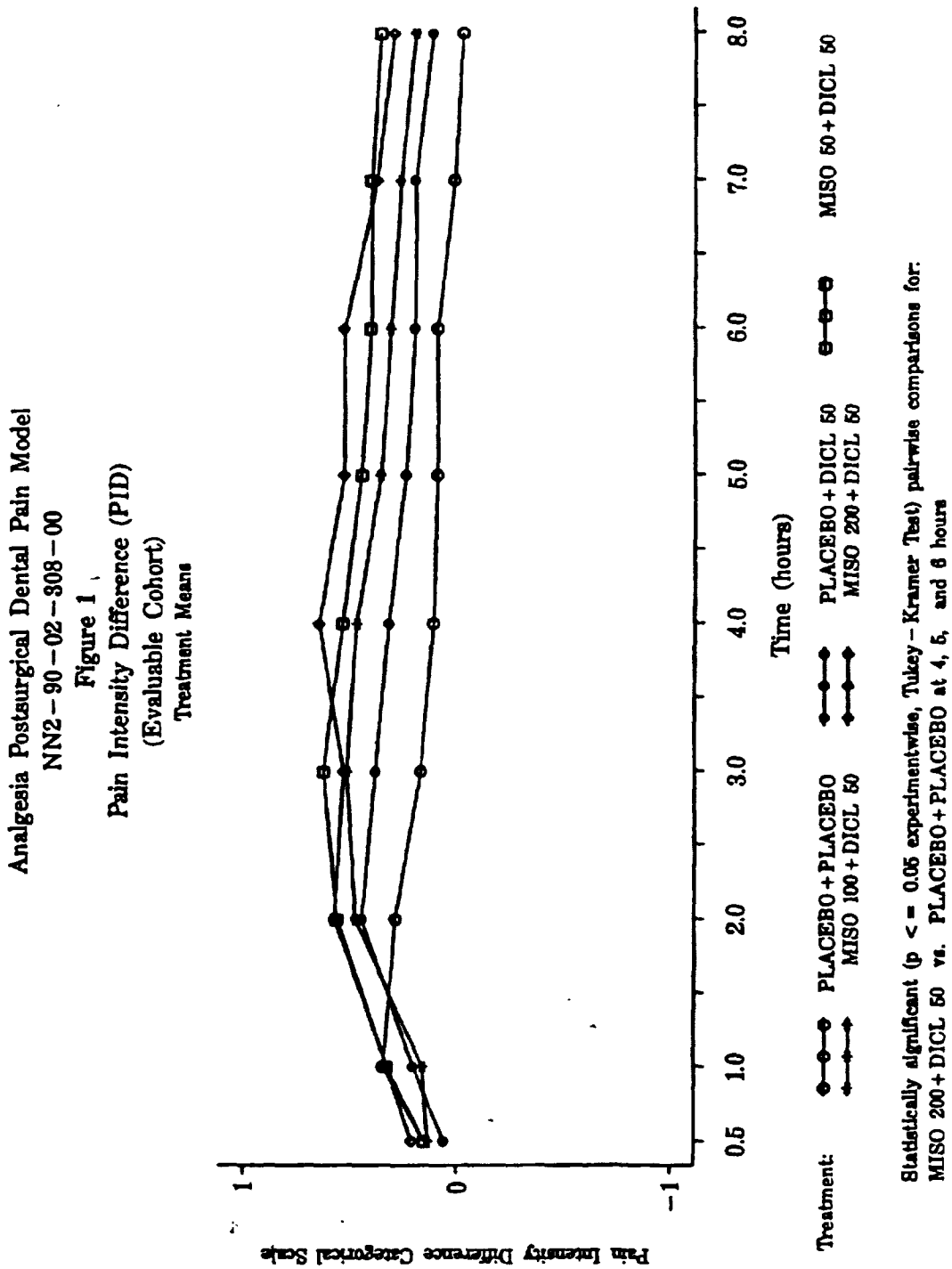
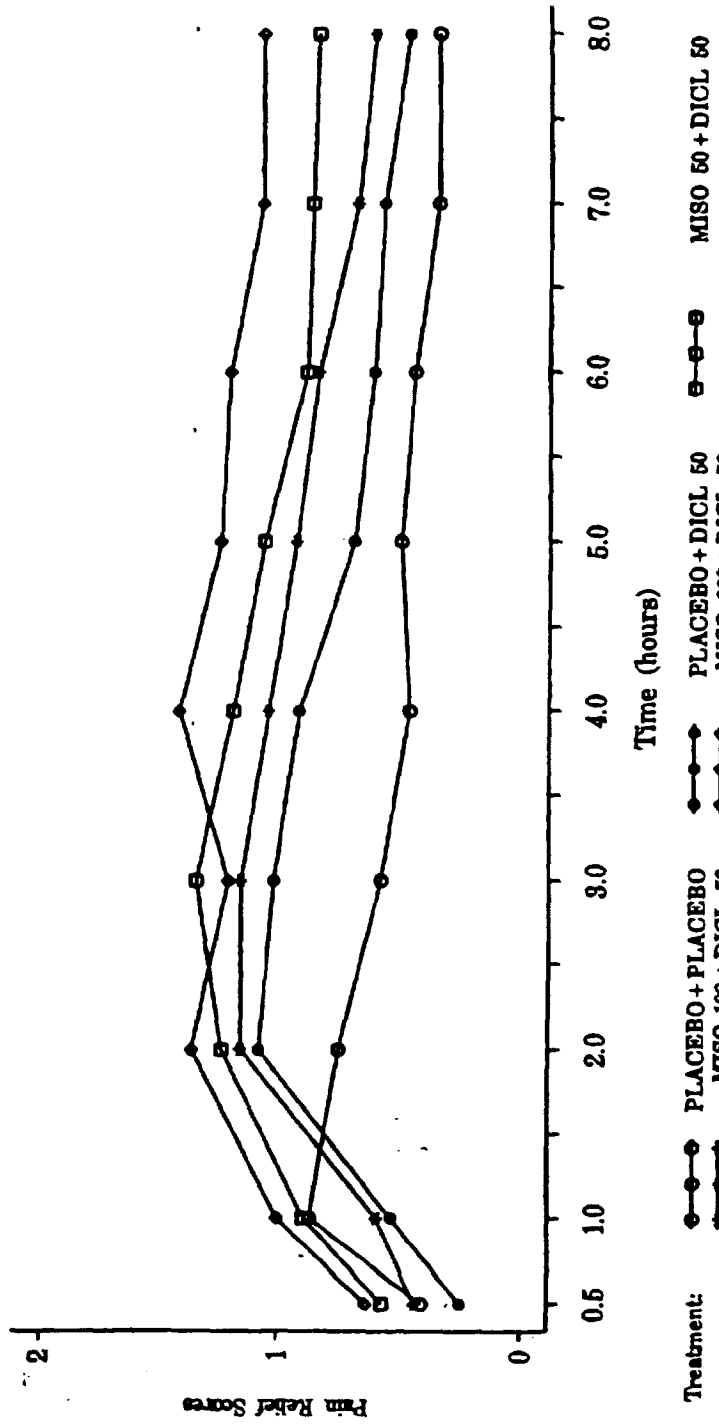

Analgesia Postsurgical Dental Pain Model
NN2-90-02-308-00
Figure 1
Pain Intensity Difference (PID)
(Evaluable Cohort)
Treatment Means
Pain Intensity Difference Categorical Scale
1
0
-1
0.5
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
Time (hours)
Treatment:
PLACEBO + PLACEBO
MISO 100 + DICL 50
PLACEBO + DICL 50
MISO 200 + DICL 50
MISO 50 + DICL 50
Statistically significant (p <= 0.05 experimentwise, Tukey - Kramer Test) pairwise comparisons for:
MISO 200 + DICL 50 vs. PLACEBO + PLACEBO at 4, 5, and 6 hours

Analgesia Postsurgical Dental Pain Model
NN2-90-02-308-00
Figure 3
Pain Relief Scores
(Evaluable Cohort)
Treatment Means



Statistically significant ($p <= 0.05$ experimentwise, Tukey-Kramer Test) pairwise comparisons for:
MISO 200+DICL 50 vs. PLACEBO+PLACEBO at 4, 6, 7 and 8 hours.

Figure 1. Pain Intensity Difference (PID) Scores

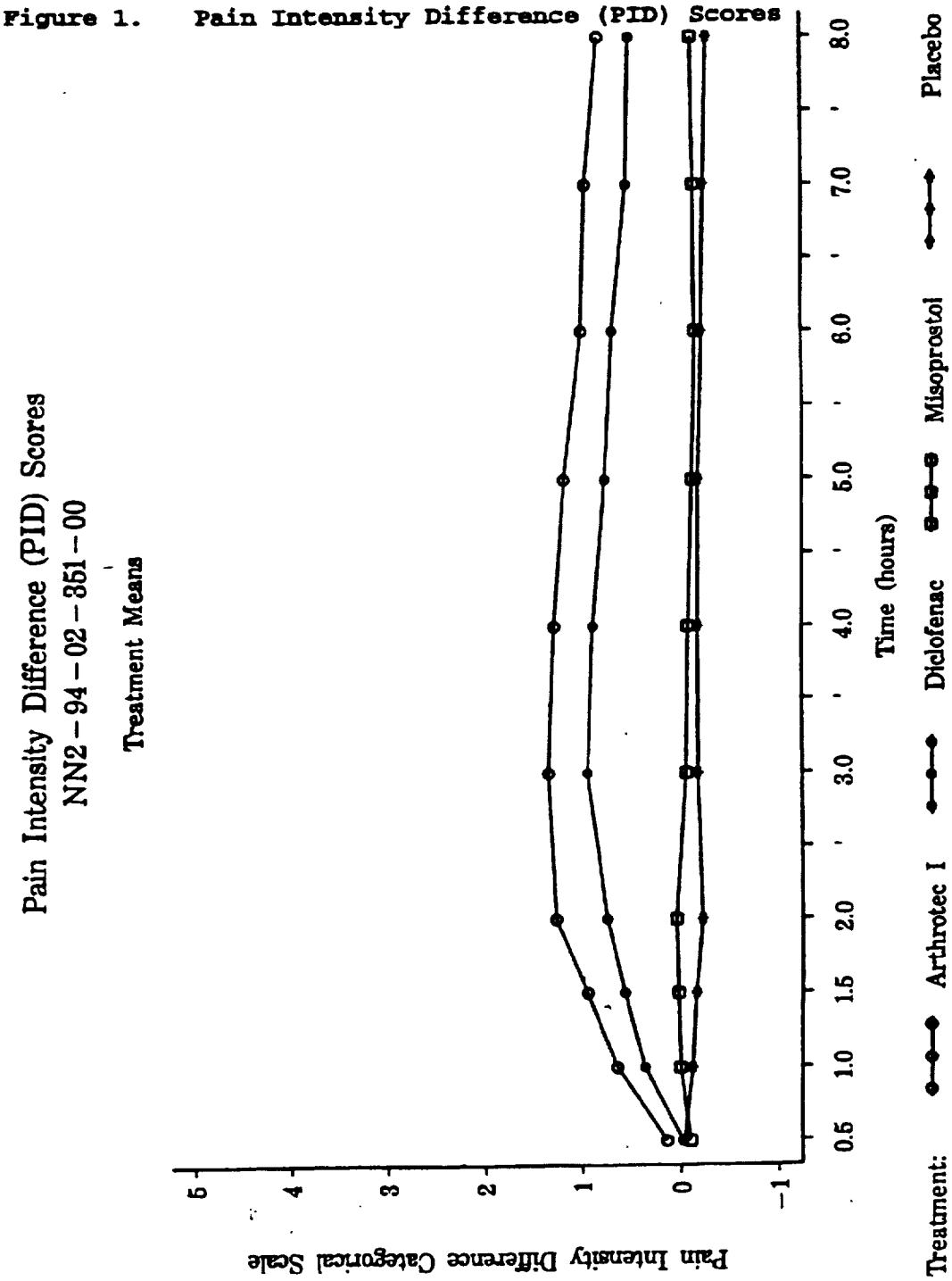
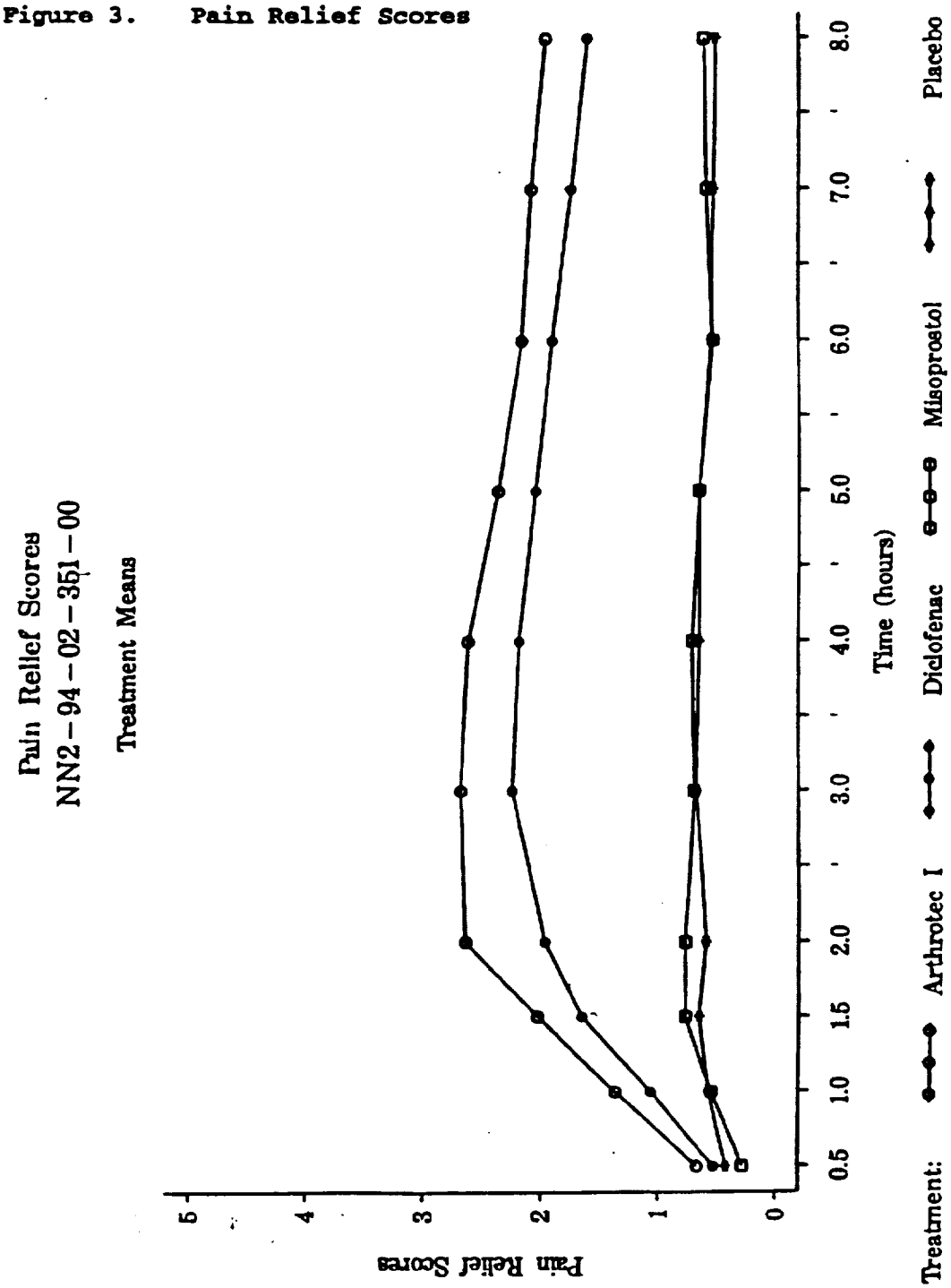


Figure 3. Pain Relief Scores



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HFD-180
EVALUATION AND RESEARCH

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OCT 1 0 1996
NOV - 7 1996

Statistical Review and Evaluation

NDA [illegible]
Name of Drug : **Arthrotec** (diclofenac sodium/misoprostol)
Applicant : **G. D. Searle & Co.**
Indication : *For the temporary relief of signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankelosing spondilitis*
Dosage : **Arthrotec I (diclofenac 50 mg/misoprostol 200 mg) b.i.d. or t.i.d.**
Arthrotec II (diclofenac 75 mg/misoprostol 200 mg) b.i.d.
Documents Reviewed: Volumes 1.1, 1.2, 1.47, 1.71-1.100 dated 12/22/95 of NDA 20-607.
Reviewer : Hoi M. Leung, Ph.D.
Date Completed: 9/23/96

I. Background

Voltaren (diclofenac sodium) is a nonsteroidal anti-inflammatory drug which is indicated for the management of signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA) and ankelosing spondilitis. Cytotec (misoprostol) is indicated for the prevention of NSAID-induced gastric ulcers in patients at high risk of complications from a gastric ulcer. Arthrotec I is a fixed dose combination of diclofenac sodium 50 mg and misoprostol 200 mg and Arthrotec II has a 75 mg diclofenac sodium instead of a 50 mg diclofenac sodium in Arthrotec I. The rationale for the fixed dose combination is for better compliance and convenience for arthritis patients who are at high risk of gastric ulcers. There are four controlled studies in OA and 3 controlled studies in RA. Of these seven controlled studies for OA and RA, one each (placebo and active control) for OA and RA are U.S. study. The others are non-U.S. active controlled studies (without a placebo group). Data for the non-U.S. studies were presented to the FDA in 1993 and was found unacceptable for filing because of the lack of U.S. data, limited dosing options with one fixed combination dosage form (diclofenac 50 mg/ misoprostol 200 mg), lack of a placebo group, and the short duration of treatment. The U.S. studies were conducted later on to address these deficiencies.

This NDA is filed in the Division of Gastrointestinal and Anticoagulation Drug Products, HFD-180. The safety and the claim of fewer GI adverse events than other NSAIDs will be reviewed by HFD-180 and the efficacy review will be conducted by HFD-550. Thus, this statistical review will address the efficacy of Arthrotec only. Discussion will be focused on the two U.S. studies with a summary and comments of the non-U.S. studies. The key issue is whether misoprostol will affect the efficacy of diclofenac in the form of a fixed dose combination.

II. The U.S. OA Study (Protocol NN2-94-02-349)

Study Description

This was a multicenter, double-blind, randomized, parallel groups study with four treatment arms - diclofenac 50 mg/misoprostol 200 mg (Arthrotec I) TID, diclofenac 75 mg/misoprostol 200 mg (Arthrotec II) BID, diclofenac 75 mg BID, and placebo. The patient population consisted of OA patients of the hip and/or knee in a flare state, had a Functional Capacity Classification (FCC) of I to III, and had a documented history of a gastric, pyloric channel, or duodenal ulcer, or more than 10 erosions in the stomach/duodenum endoscopically confirmed. Patients were allowed to take up to six Amphojel tablets per day as needed for relief of GI symptoms during the study. There was a 3 to 14 days of pretreatment period in which patients were screened. During this period it was required that patients demonstrated an OA flare to be eligible for enrollment. The pretreatment period was followed by a six-week treatment period. Patients were evaluated at baseline, week 2 and week 6, the final visit. Medical history, physical examination, endoscopy and laboratory tests were done at baseline and the final visit. Efficacy assessments were done at baseline, week 2 and the final visit which included patients who dropped out of the study prematurely. The primary efficacy variables were Physician's Global Assessment (1 very good -5 very poor), Patient's Global Assessment (1 very good -5 very poor), and the OA Severity Index (0 - 24) which was based on the patient's responses to questions related to OA pain, walking distance, and activities to daily living. Patients were given a diary card at each visit to record information on symptoms and concurrent medications.

Statistical Methods

The Chi-square test was used to analyze categorical data and the Kruskal-Wallis nonparametric test was used to analyze continuous data. Two analyses were performed with the data from both Global Assessments; in one (protocol defined), improvement and worsening were defined as a reduction or increase, respectively, of two grades or more; in the other, improvement and worsening were defined as a reduction or increase, respectively, of one grade or more. For missing data, a last observation carried forward method was used. All three primary efficacy variables were performed for both the Intent-to-Treat (ITT) and the Arthritis Evaluable patients. The principal pairwise comparisons were between diclofenac and placebo, diclofenac and Arthrotec I, and diclofenac and Arthrotec II. In addition, the Q-statistic (ratio of the mean improvements from baseline between Arthrotec and diclofenac) and its 95% confidence

interval was also calculated to evaluate the comparability of efficacy between Arthrotec and diclofenac. The planned sample sizes were 150 patients for each of the active treatment groups and 100 patients for the placebo group.

Results

A total of 572 patients was enrolled by 56 investigators. Of these, 154 patients received diclofenac, 152 received Arthrotec I, 175 received Arthrotec II, and 91 received placebo. These patients constituted the ITT population. Patients' demographics were generally comparable among the treatment groups. The mean age was 62 (range 28 -88) and approximately 69% were women. Approximately 86% were Caucasians. Baseline symptoms were generally comparable among treatment groups. Ninety-five percent or more of the patients were rated fair, poor, or very poor in the Physician's and Patient's Global Assessment at baseline.

The dropouts were 18.2% (28/154) for the diclofenac 75 mg BID, 13.8% (21/152) for the Arthrotec I TID, 18.9% (33/175) for the Arthrotec II BID, and 23.1% (21/91) for the placebo group.

The following table is the distribution of dropouts for the four treatments by reason of dropouts.

Table 1. **Reason of Dropout**

	Lack of Efficacy	Adverse Event	Other	Total
Diclofenac 75 mg BID n=154	3	20	5	28
Arthrotec I TID n=152	2	14	5	21
Arthrotec II BID n=175	4	23	6	33
Placebo n=91	14	6	1	21

Most of the dropouts were due to adverse reactions in the active treatment groups and lack of efficacy in the placebo group.

Table 2 is the summary of the three primary efficacy variables at week 6 in the ITT population. The categories of Improved, Unchanged, and Worsened in the two global variables were based on a decrease of 2 units, change of one unit or less, and an increase of 2 units from baseline, respectively. This analysis was stated in the protocol. For the mean change analysis a negative value denotes improvement from the baseline. For the categorical analysis, diclofenac 75 mg BID was significantly better than placebo in Patient's Global Assessment and the OA Severity Index. For the least squares mean change analysis, diclofenac 75 mg BID was significantly better than placebo in all three variables. There were no statistically significant differences between the diclofenac and either of the Arthrotec groups. The Q statistic is the ratio of the least

squares mean change from baseline between Arthrotec and diclofenac and Q_l is its associated 95% lower confidence limit. This statistic is used to evaluate the comparability of a test drug with an active control.

Table 2. Primary Efficacy Variables at Week 6 (ITT population)

Outcome	diclofenac BID N=154	Arthrotec I TID N=152	Arthrotec II BID N=175	Placebo n=91
Phy.'s Global				
Improved	45.4%	46.1%	53.1%	31.9%
Unchanged	53.9%	53.9%	46.3%	68.1%
Worsened	0.6%	0.0%	0.6%	0.0%
Baseline mean	3.86	3.84	3.59	3.85
LSM Change	-1.03	-1.10	-1.16	-0.64
Patient's Global				
Improved	51.3%	45.4%	54.3%	31.9%
Unchanged	48.1%	54.6%	45.7%	64.8%
Worsened	0.6%	0.0%	0.0%	3.3%
Baseline mean	3.99	3.87	3.94	3.84
LSM Change	-1.12	-1.14	-1.23	-0.63
OA Sev. Index				
Baseline mean	14.2	14.0	14.0	13.9
LSM Change	-3.55	-3.18	-3.72	-0.92
Pairwise Comp.	vs. Placebo	vs. Diclofenac	vs. Diclofenac	
Phy.'s Global				
Categorical	p=0.076	p=0.609	p=0.380	
LSM	p=0.002	p=0.508	p=0.198	
Q [Q_l]		1.07 [0.88]	1.13 [0.93]	
Patient's Global				
Categorical	p=0.006	p=0.336	p=0.504	
LSM	p<0.001	p=0.909	p=0.364	
Q [Q_l]		1.01 [0.83]	1.09 [0.90]	
OA Sev. Index				
LSM	p<0.001	p=0.400	p=0.701	
Q [Q_l]		0.90 [0.69]	1.05 [0.82]	

For OA studies with approximately 60 patients per group, the test drug is considered to be comparable to the active control if Q is between 0.8 and 1.2 and the Q_l is greater than 0.6.
The Week 2 results are similar to the Week 6 results. Analysis of secondary efficacy variables such as Patient's Assessment of Arthritis Pain - VAS, incidence of patient withdrawal due to treatment failure, and the Quality of Life (SF-36 Health Surveys

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- only 187 patients with available data) analysis at Week 2 and Week 6 all showed that each of the three active treatment groups was significantly better than placebo and there were no significant differences among the active treatment groups. For the change from baseline of Functional Capacity Classification, there was no overall significant difference among any treatment groups though the active treatment groups were numerically better than placebo. The compliance with study medication was above 90% in all treatment groups.

Reviewer's Comments

The planned sample sizes of this study were 150 patients in each of the active treatment groups and 100 patients in the placebo group. The actual sample sizes in the study were close to the planned sample sizes except for the Arthrotec II groups where 175 patients were enrolled. There was no explanation of the excess enrollments in this group. By examining the data, it seems that there were more Arthrotec II patients who were noncompliant with study medication than other groups.

The dropout rates ranged
in the placebo group. This is considered to be normal for a 6 week study.

The sponsor's primary analysis compared diclofenac with placebo as a validation of the study and compared each of the Arthrotecs to diclofenac for comparability in efficacy. Data were very much consistent that diclofenac was significantly better than placebo in all three primary efficacy variables. A comparison between the Arthrotecs and placebo would have shown that both Arthrotecs were also significantly better than placebo in all three efficacy variables at both Week 2 and Week 6. The OA Severity Index is a basket of OA symptoms that was not routinely used in other OA studies. What we usually see is the severity of pain on motion instead. The pain assessment was used as a secondary efficacy variable in this study.

The Q statistics were between and their 95% lower confidence limits were all above 0.6, meeting the usual standard for demonstrating comparability between a test NSAID and an active control in OA studies. The much larger sample size than the 60 patients per group in this study had the effect of raising the lower limit Q_L. However, judging from the high degree of similarities between the Arthrotecs and diclofenac in all three efficacy variables, it would be hard pressed to conclude that these treatments are not comparable. Thus, this study shows that the efficacy of diclofenac 75 mg BID is similar to Arthrotec I TID and Arthrotec II BID. The more restrictive subset of evaluable patients showed similar findings.

III. The Non-U.S. OA Studies

There were three non-U.S. OA studies. All of them were randomized, double-blind, active controlled, parallel groups, multicenter, 4-week studies comparing Arthrotec I BID-TID with diclofenac and/or other NSAIDs. None of them required a flare of the disease at baseline. Two (Protocols IN2-89-02-296 and IN2-89-02-298) of the three studies had similar protocols which compared Arthrotec I BID-TID with diclofenac 50 mg BID-TID. The third study (IN2-90-02-321) compared Arthrotec I BID with Piroxicam 10 mg BID and Naproxen 375 mg BID. OA patients of hip and/or knee with Functional Capacity Classification of I to III who satisfied a certain entry criteria were eligible. The three primary efficacy variables were the same as those in the U.S. study.

Protocol IN2-89-02-298

This study was conducted between June 1989 and March 1990. Four hundred fifty-five (455) randomized patients received at least one dose of study medication (Arthrotec I 228, diclofenac 227). There was a seven-day pretreatment period in which patients were evaluated for eligibility before the 4-week treatment. Patients were randomized and evaluated at baseline after the pretreatment, at week 2 and week 4, the end of the study period. The regimen of BID or TID was chosen by the investigator for appropriate control of the patient's osteoarthritis, although changes were allowed during the study. The treatment groups were comparable in demographics and baseline disease severity. The mean age was 62 years and approximately 63% were females. More than 97% of patients were Caucasians and the mean duration of disease was 5.8 years. There were more dropouts in the Arthrotec I group (22%) than in the diclofenac group (12%). Table 3 shows the number of patients by treatment group who dropped out for various reasons.

Table 3. Dropouts By Treatment and Reason

	Lack of Efficacy	Adverse Event	Other	Total
Diclofenac 50 mg n=228	2	24	2	28
Arthrotec I n=227	5	38	7	50
Total n=455	7	62	9	78

Table 4 shows the results of the three 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 4. 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	24%	15%	
Unchanged	67%	68%	
Worsened	0%	0%	
Unknown	9%	16%	p=0.015
Baseline mean	3.23	3.19	Q=0.99 [0.96,1.02]
Least Sq. Mean	2.30	2.50	Q=1.09 [1.02,1.16]
Patient's Global			
Improved	22%	23%	
Unchanged	67%	60%	
Worsened	1%	1%	
Unknown	9%	16%	p=0.151
Baseline mean	3.25	3.33	Q=1.03 [0.99,1.07]
Least Sq. Mean	2.42	2.56	Q=1.01 [0.96,1.06]
OA Sev. Index			
Mean Change	-3.39	-2.90	p=0.281
Baseline mean	12.02	11.78	Q=0.98 [0.93,1.03]
Least Sq. Mean	8.71	9.19	Q=1.06 [0.93,1.05]

* 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. Equivalence between the two treatments were defined by the sponsor when 95% confidence intervals are between 0.8 and 1.2. The rationale for using the actual mean score rather than the mean improvement by the sponsor was that the room for improvement would be too small for a stable denominator in Q since there was not a requirement of flare at baseline.

Reviewer's Comments

The study design is not the most desirable in that there was no requirement of flare at baseline and the variable dosing of BID and TID was at the discretion of the investigator. Also, for a short term study, the inclusion of a placebo group would be desirable. The modified Q analysis presents a challenge in the interpretation since there have not been extensive experiences in such analyses when the actual mean value was used instead of the mean improvement. Unlike the mean improvement which has a built-in adjustment for the baseline, the actual mean value does not have this adjustment. This modified analysis was borrowed from

the bioequivalence methodology. Intuitively, the smaller the value of Q and its confidence limits, the better the test drug would be since a small actual mean score represents a better outcome. It can also be seen in this study that the categorical analysis was more sensitive in detecting a difference between the two treatment groups. For example, the Physician's Global Assessments showed that diclofenac was statistically significantly better than Arthrotec I. This significance was maintained even when the category of Unknown was excluded. One may conclude from this study that there was a slight difference in efficacy in favor of diclofenac over Arthrotec I. In addition, there were more dropouts in the Arthrotec I group than in the diclofenac group due to GI adverse events and lack of efficacy.

Protocol IN2-89-02-296

This study was conducted between June 1989 and June 1990. The study design was similar to Protocol IN2-89-02-298 with an additional feature of endoscopic evaluation at baseline, Week 2, and Week 4. Three hundred sixty-one (361) randomized patients received at least one dose of study medication (Arthrotec I 178, diclofenac 183). The treatment groups were comparable in demographics (except for weight: Arthrotec I 70 kg vs. diclofenac 74 kg, p=.004) and baseline disease severity. The mean age was 60 years and approximately 73% were females. More than 88% of patients were Caucasians and the mean duration of disease was 7.4 years. Table 5 shows the number of patients by treatment group who dropped out for various reasons. There were no dropouts due to lack of efficacy in this study.

Table 5. Dropouts By Treatment and Reason

	Lack of Efficacy	Adverse Event	Other	Total
Diclofenac 50 mg n=183	0	11	8	19
Arthrotec I n=178	0	10	9	19
Total n=361	0	21	17	38

Table 6 shows the results of the three primary efficacy variables.

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Table 6. Primary Efficacy Variables at Week 4 (ITT population)

Outcome	diclofenac BID-TID N=183	Arthrotec I BID-TID N=178	p & Q* value
Phy.'s Global			
Improved	14%	12%	
Unchanged	78%	78%	
Worsened	1%	2%	
Unknown	10%	7%	p=0.681
Baseline mean	3.00	3.00	Q=1.00 [0.96,1.04]
Least Sq. Mean	2.36	2.33	Q=0.99 [0.93,1.05]
Patient's Global			
Improved	18%	21%	
Unchanged	74%	69%	
Worsened	1%	0%	
Unknown	7%	10%	p=0.290
Baseline mean	3.12	3.21	Q=1.03 [0.99,1.07]
Least Sq. Mean	2.40	2.30	Q=0.96 [0.90,1.03]
OA Sev. Index			
Mean Change	-2.99	-2.50	p=0.469
Baseline mean	11.51	11.39	Q=0.99 [0.93,1.05]
Least Sq. Mean	8.85	8.89	Q=1.01 [0.93,1.09]

* 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. Equivalence between the two treatments were defined by the sponsor when 95% confidence intervals are between 0.8 and 1.2. The rationale for using the actual mean score rather than the mean improvement by the sponsor was that the room for improvement would be too small for a stable denominator in Q since there was not a requirement of flare at baseline.

Reviewer's Comments

The comments on study design and the modified Q analysis in Protocol IN2-89-02-298 also apply in this study since their study designs were very similar and the methods of analysis were also identical. The portion of the endoscopy evaluation will be addressed by another statistical reviewer who directly supports HFD-180. The outcomes of this study showed that Arthrotec I BID-TID was comparable to diclofenac 50 mg BID-TID in the three primary efficacy variables.

Protocol IN2-90-02-321

This study was conducted between June 1991 and April 1992. Six hundred forty-three (643) randomized patients received at least one dose of study medication (Arthrotec I BID: 216, Piroxicam 10 mg BID: 217, Naproxen 375 mg BID: 210). There was a seven-day pretreatment period in which patients were evaluated for eligibility before the 4-week treatment. Patients were evaluated at baseline after the pretreatment, at week 2 and week 4, the end of the study period. Endoscopic examinations of the gastric and duodenal mucosa were performed at pretreatment and the end of the study. The treatment groups were comparable in demographics and baseline disease severity. The mean age was 60 years and approximately 76% were females. More than 80% of patients were Caucasians and the mean duration of disease was 7.3 years. Table 7 shows the number of patients by treatment group who dropped out for various reasons.

Table 7. Dropouts By Treatment and Reason

	Lack of Efficacy	Adverse Event	Other	Total
Arthrotec I n=216	0	18	5	23
Piroxicam n=217	0	10	7	17
Naproxen n=210	0	20	5	25
Total n=643	0	48	17	65

Table 8 shows the results of the three primary efficacy variables. The overall p-values for the two global variables are from the chi-square tests among the three treatment groups. There was a statistically significant difference in the OA Severity Index. The significant difference was caused by the difference between Arthrotec I and piroxicam. The Q value is the ratio of the actual mean (baseline) or least squares mean (week 4) between Arthrotec I and piroxicam or Arthrotec I and Naproxen rather than the least squares mean improvement from baseline. Numbers in brackets are the lower and upper 95% confidence limits of Q.

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Table 8. Primary Efficacy Variables at Week 4 (ITT population)

Outcome	Arthrotec I BID N=216	Piroxicam 10mg BID N=217	Naproxen 375mg BID N=210
Phy.'s Global			
Improved	25%	21%	21%
Unchanged	67%	72%	69%
Worsened	0%	0%	0%
Unknown	9%	7%	10%
Overall p=0.706			
Baseline mean	3.42	3.31	3.37
Q [95% CI for Q]		1.03[1.00,1.06]	1.01[0.99,1.04]
Least Sq. Mean	2.42	2.48	2.53
Q [95% CI for Q]		0.98[0.92,1.04]	0.96[0.89,1.02]
Patient's Global			
Improved	36%	31%	28%
Unchanged	55%	62%	62%
Worsened	0%	0%	0%
Unknown	9%	7%	10%
Overall p=0.512			
Baseline mean	3.53	3.44	3.45
Q [95% CI for Q]		1.03[0.99,1.06]	0.98[0.92,1.04]
Least Sq. Mean	2.48	2.57	2.64
Q [95% CI for Q]		0.96[0.90,1.03]	0.94[0.88,1.01]
OA Sev. Index			
Mean Change	-4.27	-3.19	-3.79
Overall p= 0.015			
Baseline mean	12.21	11.35	11.88
Q [95% CI for Q]		1.08[1.02,1.13]	1.03[0.98,1.08]
Least Sq. Mean	8.82	9.05	9.19
Q [95% CI for Q]		0.97[0.89,1.06]	0.96[0.88,1.05]

Reviewer's Comments

The comments on study design and the modified Q analysis in Protocol IN2-89-02-298 also apply in this study since their study designs were very similar except for an additional active control group and the methods of analysis were also similar. The portion of the endoscopy evaluation will be addressed by another statistical reviewer who directly supports HFD-180. The outcomes of this study showed that Arthrotec I BID was comparable to piroxicam 10 mg BID and Naproxen 375 mg BID in the three primary efficacy variables. There appeared to be a slight advantage from Arthrotec I compared to piroxicam 10 mg but the difference was negligible. The analysis of the more restrictive subset of evaluable patients showed similar findings.

IV. The U.S. RA Study (Protocol NN2-94-02-352)

Study Description

This was a multicenter (18 U.S. and 2 Canadian sites), double-blind, randomized, parallel groups study with four treatment arms - Arthrotec I TID, Arthrotec II BID, diclofenac 75 mg BID, and placebo. The patient population consisted of RA patients in a flare state and had a Functional Capacity Classification of I to III. There was a 3 to 14 days of pretreatment period in which patients were screened. During this period it was required that patients demonstrated a RA flare to be eligible for enrollment. The pretreatment period was followed by a 12-week treatment period. Efficacy assessments were made at baseline, week 2, week 6, and week 12, the final visit which included patients who dropped out of the study prematurely. The primary efficacy variables were Physician's Global Assessment (1 very good -5 very poor), Patient's Global Assessment (1 very good -5 very poor), Physician's Assessment of Joint Tenderness/Pain (0 - 3 for each of 68 joints with a total score 0-204) which was based on the patient's responses, and Physician's Assessment of Joint Swelling (0-3 for each of 66 joints with a total of 0-198). Secondary efficacy variables included Functional Capacity Classification, Duration of Morning Stiffness, Patient's Assessment of Arthritis Pain (VAS 0-10 cm), Health Assessment Questionnaire (HAQ), the SF-36 Health Survey, Dropouts due to Lack of Efficacy, and Paulus Index Responder's Analysis. Patients were given a diary card at each visit to record information on symptoms and concurrent medications.

Statistical Methods

The Chi-square test was used to analyze categorical data and the Kruskal-Wallis nonparametric test was used to analyze continuous data for baseline. Two analyses were performed with the data from both Global Assessments; in one (protocol defined), improvement or worsening was defined as a reduction or increase, respectively, of two grades or more; in the other, improvement or worsening was defined as a reduction or increase, respectively, of one grade or more. For missing data, a last observation carried forward method was used. All four primary efficacy variables were performed for both the Intent-to-Treat (ITT) and the Arthritis Evaluable patients. The principal pairwise comparisons were between diclofenac 75 mg BID and placebo, diclofenac 75 mg BID and Arthrotec I TID, and diclofenac 75 mg BID and Arthrotec II BID. The sponsor stated that the categorical data analysis was not powerful or sensitive enough for the patient population's mild disease status and employed the analysis of covariance method in the mean change from baseline. In addition, the Q-statistic (ratio of the mean improvements

between Arthrotec and diclofenac) and its 95% confidence interval was also calculated to evaluate the comparability of efficacy between Arthrotec and diclofenac. The planned sample sizes were 90 patients for each of the active treatment groups and 45 patients for the placebo group.

Results

A total of 380 patients was enrolled by 20 investigators. Of these, 107 patients received diclofenac 75 mg BID, 107 received Arthrotec I TID, 111 received Arthrotec II BID, and 55 received placebo. These patients constituted the ITT population. The evaluable cohort consisted of 284 patients (diclofenac 85/Arthrotec I 77/Arthrotec II 85/placebo 37) at week 2, 224 patients (diclofenac 74/Arthrotec I 58/Arthrotec II 67/placebo 25) at week 6, and 205 patients (diclofenac 65/Arthrotec I 56/Arthrotec II 57/placebo 27) at week 12. Patients' demographics were generally comparable among the treatment groups. The mean age was 56 years (range 28 -81) and 74% were women. Approximately 89% were Caucasians. Baseline symptoms were generally comparable among treatment groups. Ninety percent or more of the patients were rated fair, poor, or very poor in the Physician's and Patient's Global Assessment at baseline. The mean duration of disease was 11.5 years. The mean Tender/Pain score was about 30 and the mean swelling score was about 22. The mean Tender/Pain joint count was about 22 and the mean Swollen joint count was about 15.

Overall, 65.3% of the patients completed the 12-week study. The dropouts were 17.1% (29/107) for the diclofenac 75 mg BID, 37.4% (40/107) for the Arthrotec I TID, 36.0% (40/111) for the Arthrotec II B.I.D., and 41.8% (32/55) for the placebo patients. The following table is the distribution of dropouts for the four treatments by reason of dropouts.

Table 9.

	Reason of Dropout			
	Lack of Efficacy	Adverse Event	Other	Total
Diclofenac 75 mg BID n=107	15	10	4	29
Arthrotec I TID n=107	16	18	6	40
Arthrotec II BID n=111	23	11	6	40
Placebo n=55	21	0	2	23

Tables 10 and 11 are the summary results of the four primary efficacy variables at week 6 and week 12, respectively in the ITT population. The categories of Improved, Unchanged, and Worsened in the two global variables were based on a decrease of 2 units or more, change of one unit or no change, and an increase of 2 units or more from baseline, respectively. This analysis was stated in the protocol. For the mean change, a negative value denotes improvement from the baseline.

Table 10. Primary Efficacy Variables at Week 6 (ITT population)

Outcome	diclofenac BID N=107	Arthrotec I TID N=107	Arthrotec II BID N=111	Placebo n=55
Phy.'s Global				
Improved	28.0%	27.1%	28.2%	20.0%
Unchanged	71.0%	72.9%	70.9%	76.4%
Worsened	0.9%	0.0%	0.9%	3.6%
Baseline mean	3.5	3.6	3.4	3.5
LS mean change	-0.92	-0.92	-0.97	-0.66
Patient's Global				
Improved	27.1%	31.8%	30.9%	29.1%
Unchanged	72.0%	67.3%	68.2%	67.3%
Worsened	0.9%	0.9%	0.9%	3.6%
Baseline mean	3.6	3.6	3.6	3.6
LS mean change	-0.79	-0.80	-0.90	-0.63
Tender/Pain				
Baseline mean	28.2	31.5	29.4	29.9
LS mean Change	-10.16	-8.61	-13.34	-4.81
Swelling				
Baseline mean	20.1	23.0	22.6	20.8
LS mean change	-6.48	-5.86	-8.57	-3.53
Pairwise Comp.	vs. Placebo	vs. Diclofenac	vs. Diclofenac	
Phy.'s Global				
Categorical	p=0.286	p=0.594	p=1.000	
LSM	p=0.069	p=0.983	p=0.666	
Q [Q_t]		1.00 [0.77]	1.06 [0.82]	
Patient's Global				
Categorical	p=0.450	p=0.754	p=0.826	
LSM	p=0.486	p=0.930	p=0.397	
Q [Q_t]		1.01 [0.74]	1.14 [0.84]	
Tender/Pain				
LS mean change	p=.062	p=0.511	p=0.174	
Q [Q_t]		0.73 [0.42]	1.32 [0.92]	
Swelling				
LS mean change	p=0.151	p=0.715	p=0.214	
Q [Q_t]		0.77 [0.44]	1.21 [0.81]	

Table 11. Primary Efficacy Variables at Week 12 (ITT population)

Outcome	diclofenac BID N=107	Arthrotec I TID N=107	Arthrotec II BID N=111	Placebo n=55
Phy.'s Global				
Improved	28.0%	25.2%	22.7%	14.5%
Unchanged	70.1%	74.8%	76.4%	81.8%
Worsened	1.9%	0.0%	0.9%	3.6%
Baseline mean	3.5	3.6	3.4	3.5
LS mean change	-0.90	-0.89	-0.81	-0.55
Patient's Global				
Improved	25.2%	28.0%	26.4%	20.0%
Unchanged	72.9%	69.2%	72.7%	76.4%
Worsened	1.9%	2.8%	0.9%	3.6%
Baseline mean	3.6	3.6	3.6	3.6
LS mean change	-0.71	-0.73	-0.75	-0.59
Tender/Pain				
Baseline mean	28.2	31.5	29.4	29.9
LS mean Change	-10.98	-8.82	-12.72	-4.09
Swelling				
Baseline mean	20.1	23.0	22.6	20.8
LS mean change	-6.22	-5.53	-8.03	-3.29
Pairwise Comp.	vs. Placebo	vs. Diclofenac	vs. Diclofenac	
Phy.'s Global				
Categorical	p=0.139	p=0.314	p=0.534	
LSM	p=0.022	p=0.944	p=0.456	
Q [Q_t]		0.99 [0.75]	0.90 [0.66]	
Patient's Global				
Categorical	p=0.624	p=0.793	p=0.823	
LSM	p=0.461	p=0.882	p=0.754	
Q [Q_t]		1.03 [0.71]	1.06 [0.73]	
Tender/Pain				
LS mean change	p=.017	p=0.363	p=0.459	
Q [Q_t]		0.69 [0.40]	1.16 [0.81]	
Swelling				
LS mean change	p=0.165	p=0.692	p=0.294	
Q [Q_t]		0.75 [0.39]	1.17 [0.75]	

For the secondary efficacy variables, there were no significant differences between any pair of treatments at any visit in the Duration of Morning Stiffness and Erythrocyte Sedimentation Rate (ESR). For the Functional Capability Classification (FCC), Arthrotec I was significantly better than placebo at both week 6 and week 12 and was also significantly

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

APPEARS THIS WAY
ON ORIGINAL

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HFD-550/MO/Neurner
HFD-550/PM/LoBianco
HFD-550/Div. File
HFD-340/Div. Scientific Investigation
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HFD-180/PM/Strongin
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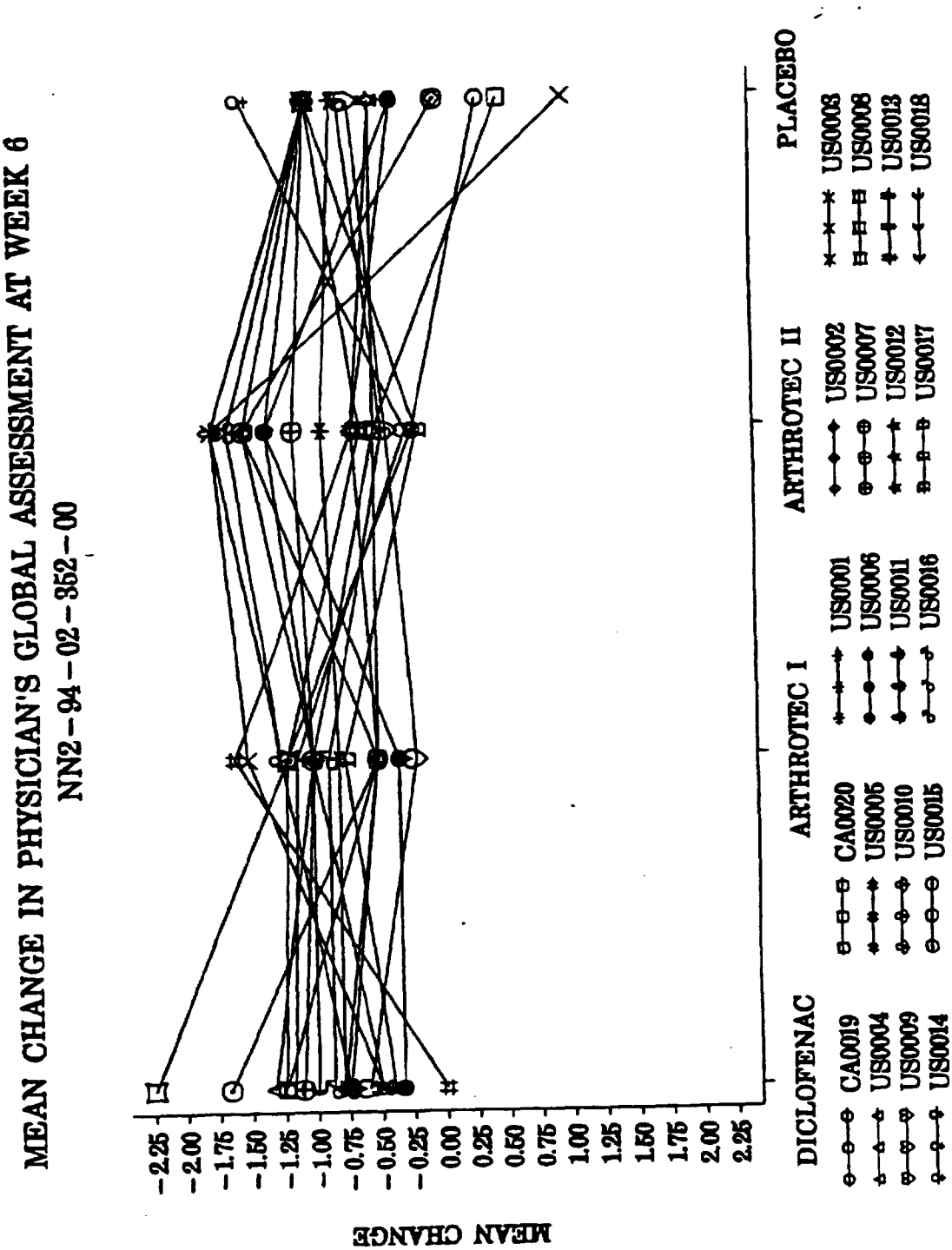
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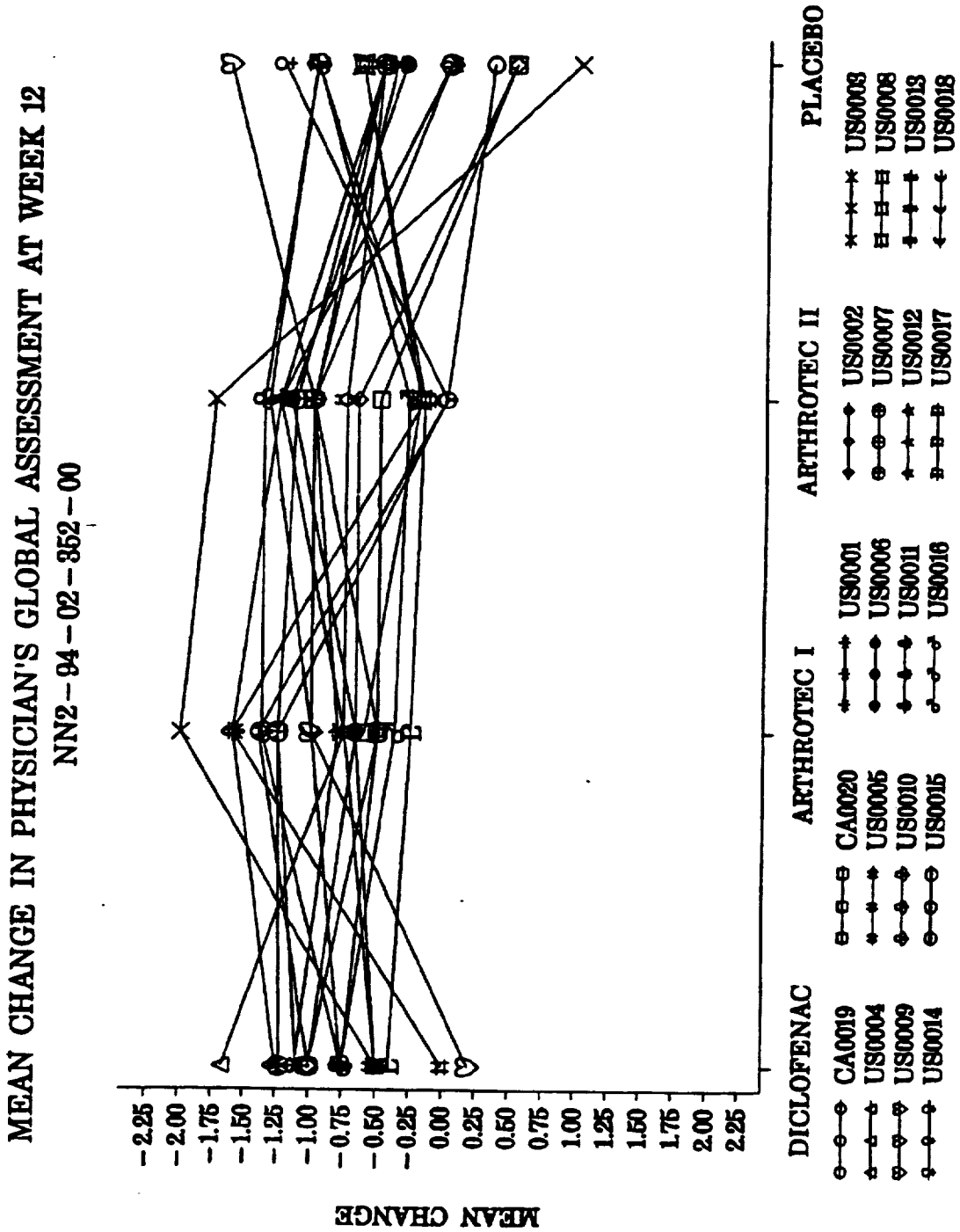
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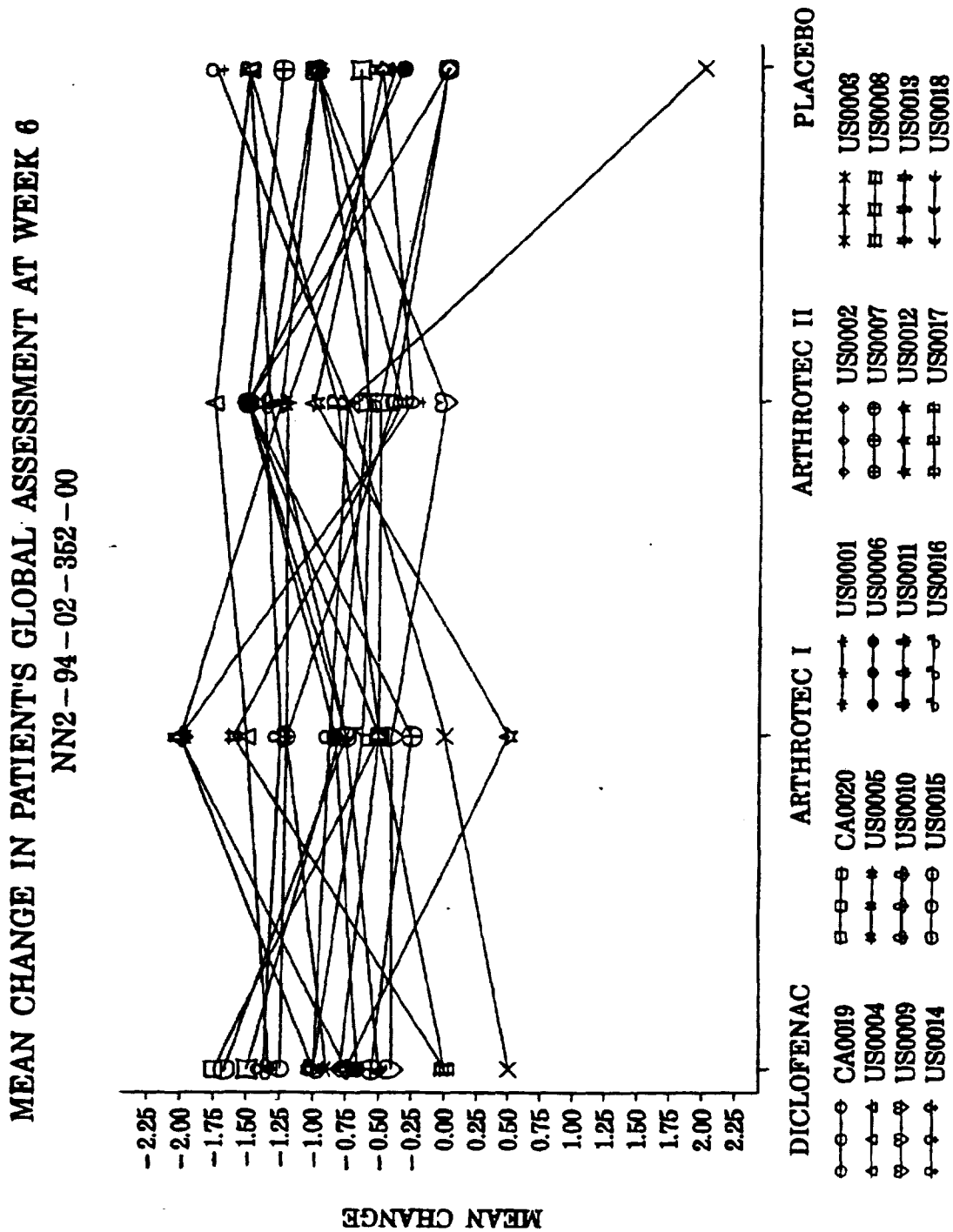
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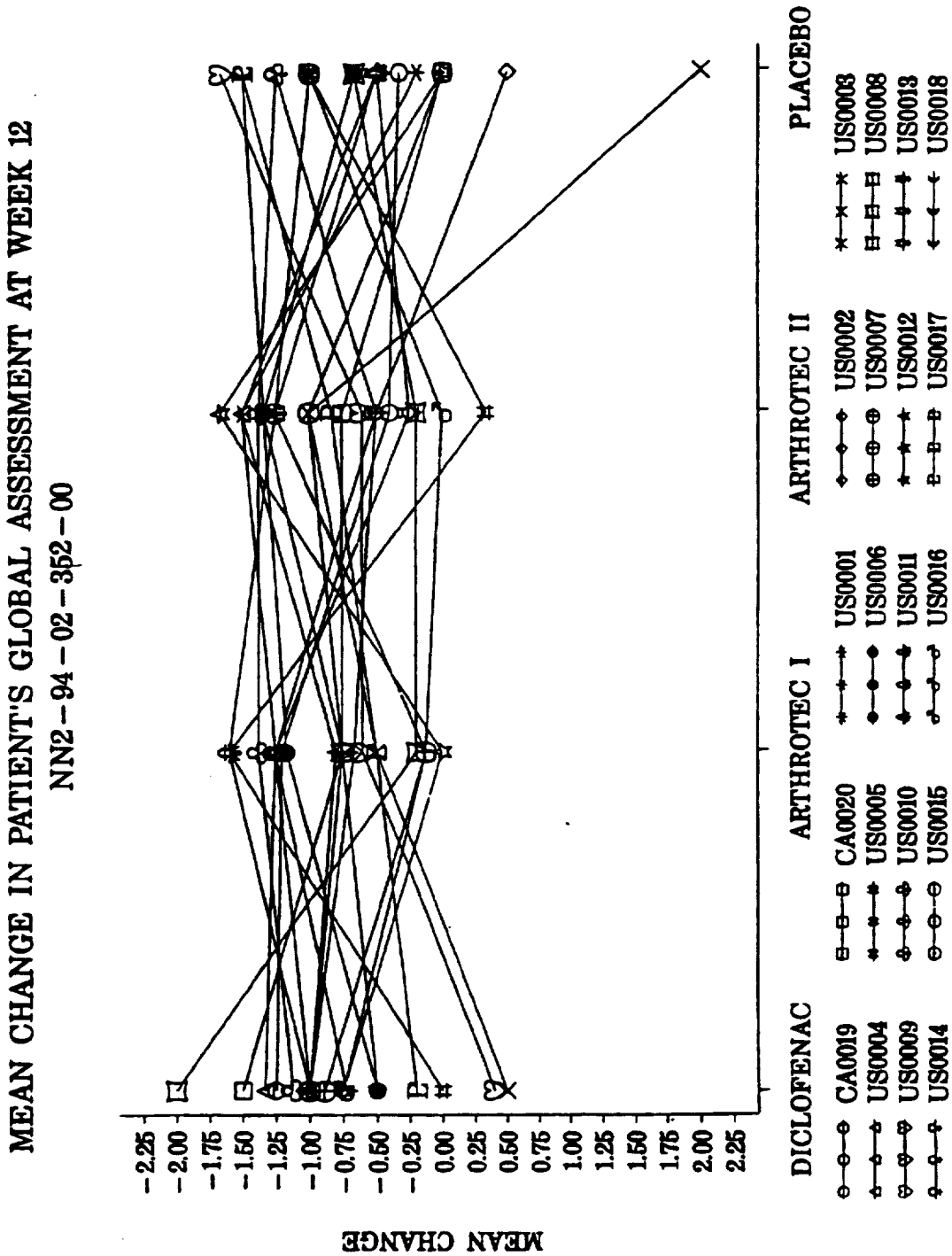
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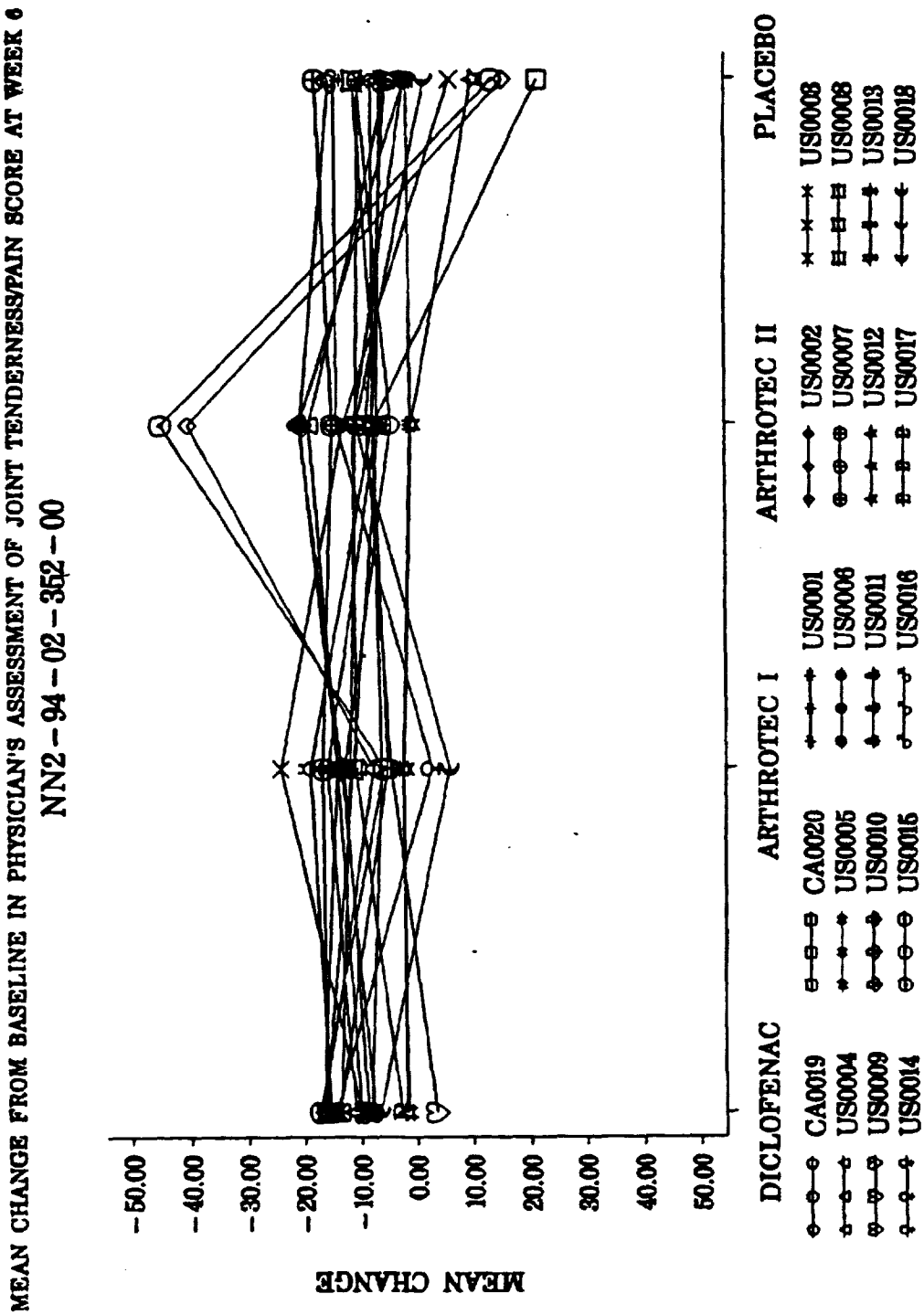
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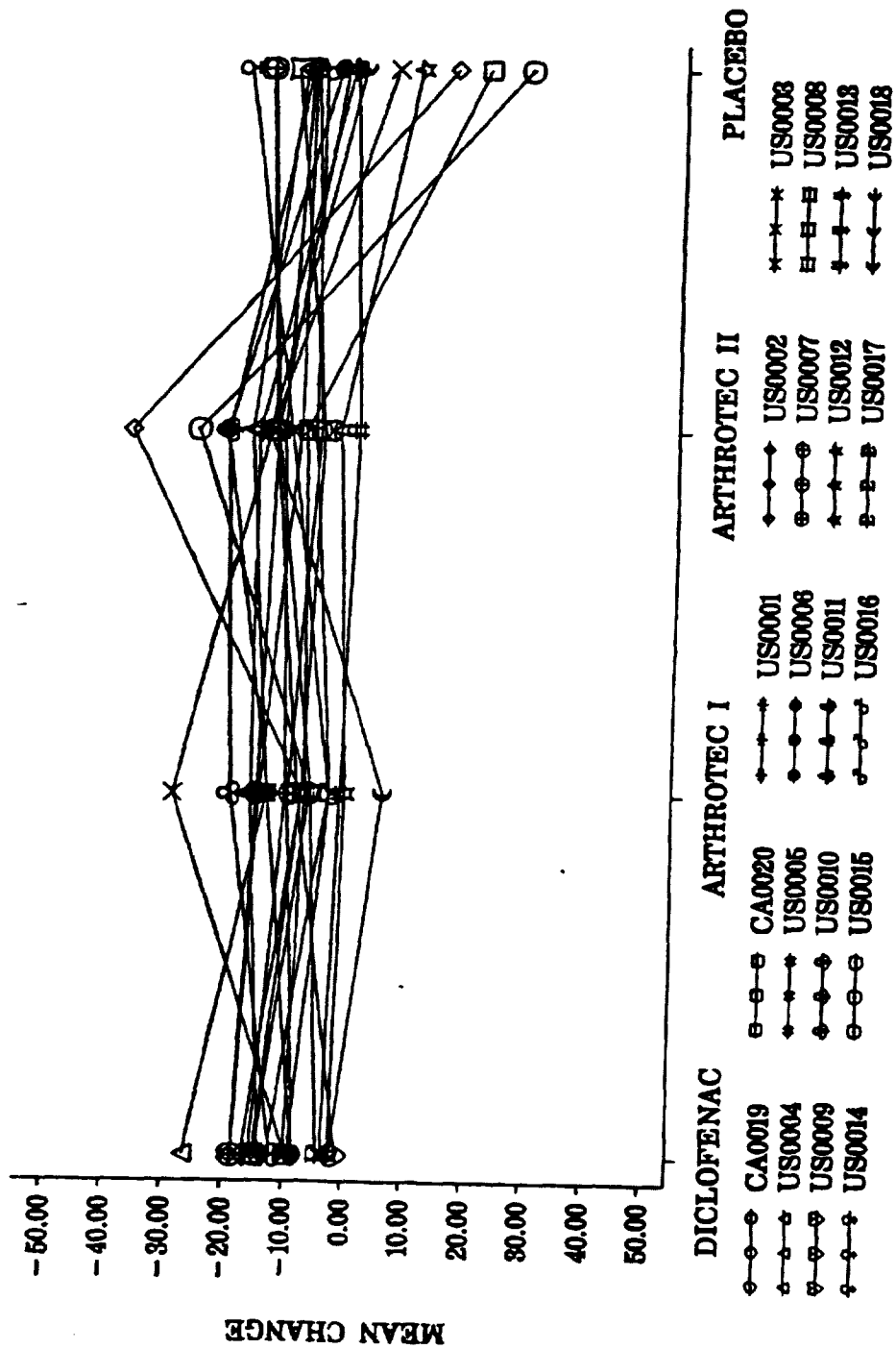
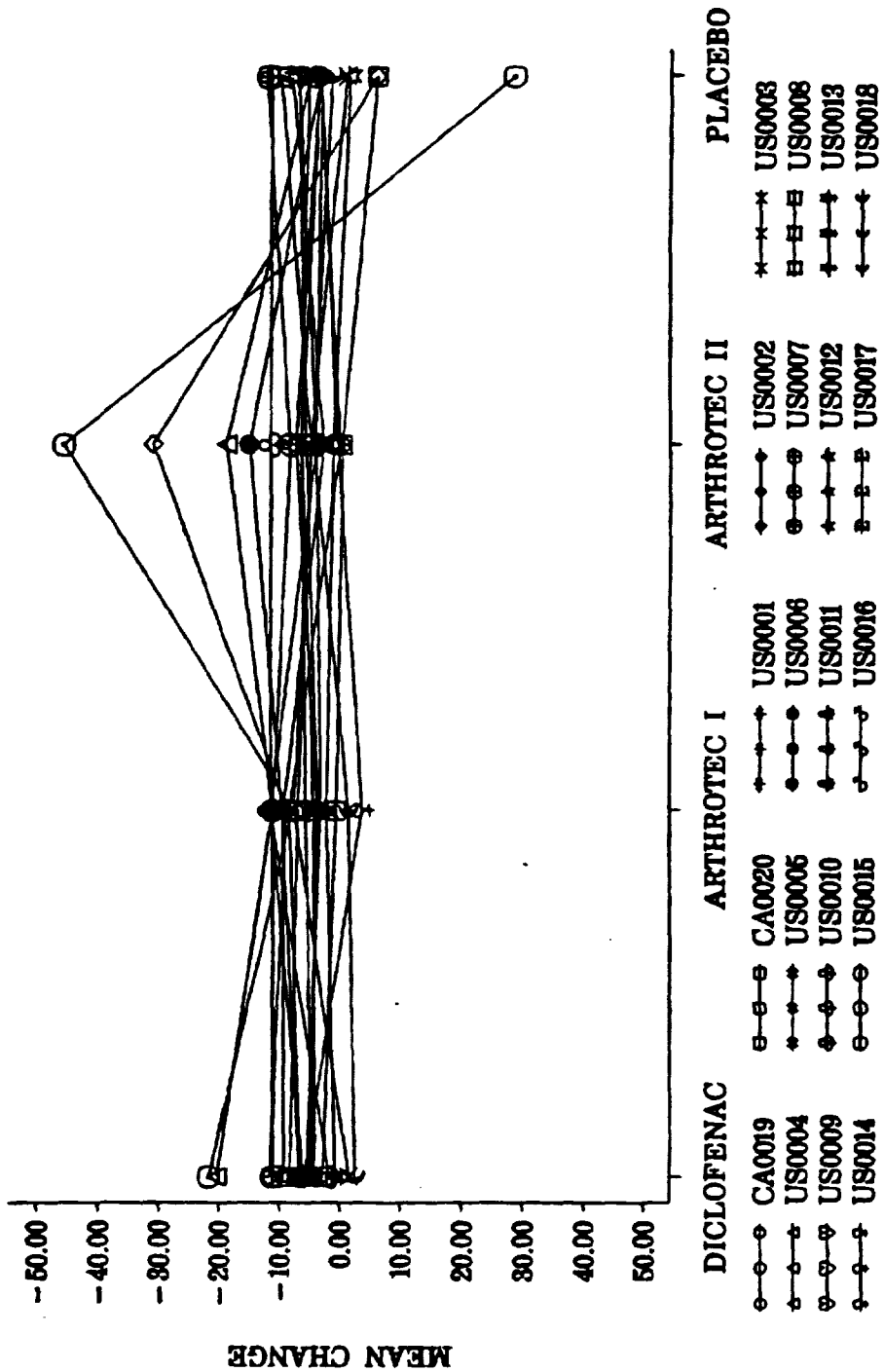
MEAN CHANGE FROM BASELINE IN PHYSICIAN'S ASSESSMENT OF JOINT TENDERNESS/PAIN SCORE AT WEEK 12

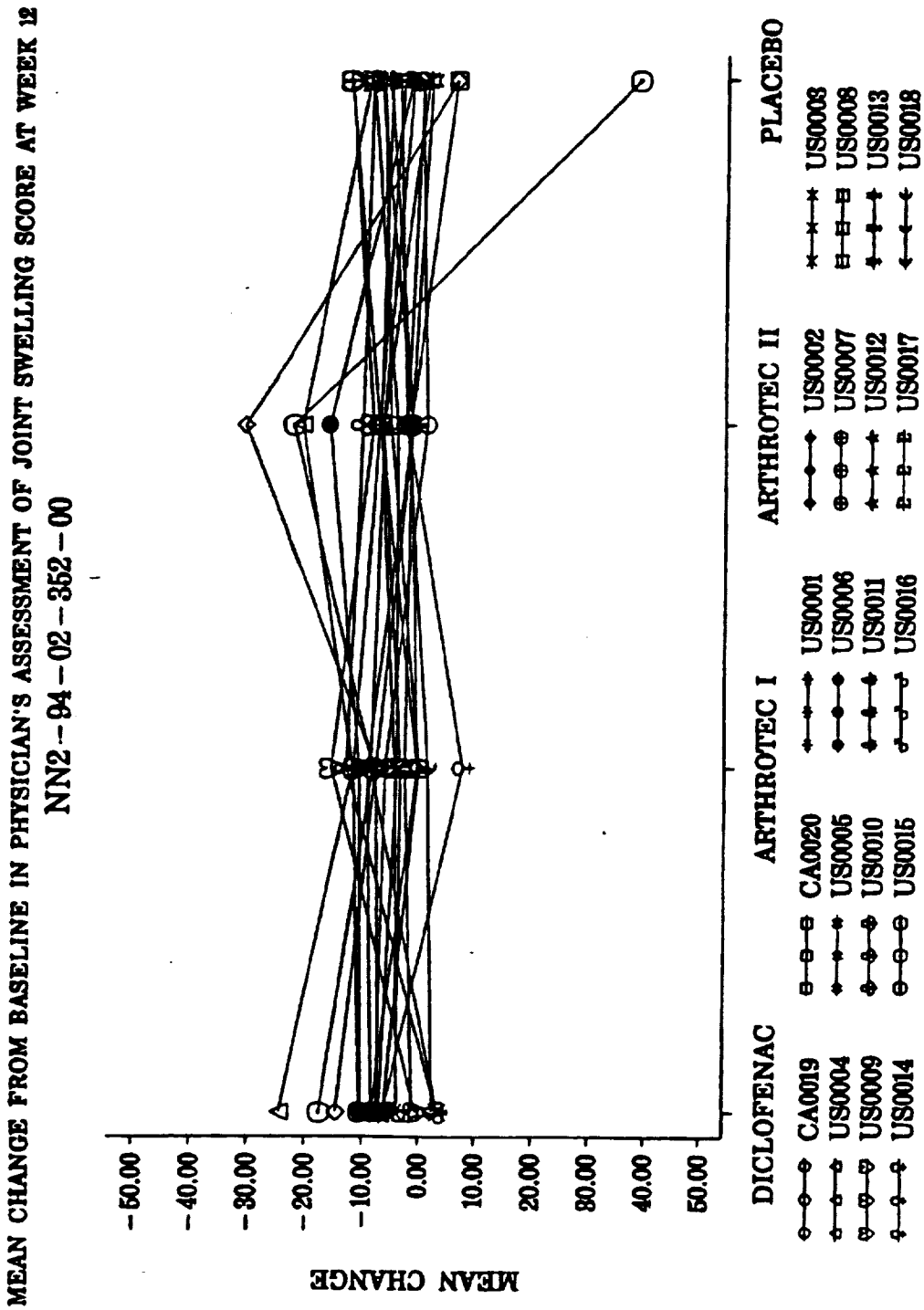
NN2-94-02-352-00



MEAN CHANGE FROM BASELINE IN PHYSICIAN'S ASSESSMENT OF JOINT SWELLING SCORE AT WEEK 6

NN2-94-02-352-00

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STATISTICAL REVIEW AND EVALUATION --- NDA

CENTER FOR DRUG EVALUATION AND RESEARCH
SEP 11 1996
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SEP 23 1996
HFD-180

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

APPEARS THIS WAY ON ORIGINAL

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.