CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020607

STATISTICAL REVIEW(S)

18 years or older satisfying the ARA criteria (for RA) or ACR criteria (for OA), and a functional capacity classification of I-III and requiring NSAID therapy would be qualified. Patients excluded were those with known or suspected active peptic ulceration or gastrointestinal bleeding and other conditions which might preclude the use of an NSAID. The primary efficacy variables were Physician's and Patient's Global Assessments (5-point scale, very good to very poor). The secondary efficacy variables were Duration of Morning Stiffness, Assessment of Night Pain (4-point scale) for both RA and OA patients (baseline, weeks 4, 8, and 12) and Health Assessment questionnaires (HAQ) (RA only) or Osteoarthritis Severity Index (OA only) at baseline and end of study.

Statistical Methods

Protocol Method of Analysis

The protocol identifies two patient populations, the Intent-to-Treat (ITT) which includes all patients who had taken any study medication and the Protocol Evaluable Patients which is a subset of the ITT population by excluding those who violated any significant inclusion or exclusion criteria. All assessments of arthritic condition, except duration of morning stiffness, will generate ordered categorical data which will be analyzed by logistic regression. The model for the analysis will, if necessary, include other factors correlated with outcome, such as age, sex, site, country, duration of treatment, tablet consumption and concomitant medication. If the variable duration of morning stiffness is approximately normally distributed, it will be analyzed by analysis of variance; otherwise, it too will be reduced to an ordered categorical response.

Sponsor's Deviation in Method of Analysis

All randomized patients were included in the ITT analysis without excluding those who took no medication or who were found to be ineligible after admission, since there were only three such patients in each of these two categories.

Last observation carried forward (LOCF) was used in the ITT analysis instead of the protocol method of assigning the worst score because some patients deteriorated by only one grade and withdrew.

Because there was some imbalance in the arthritis assessments of patients between the two treatment groups at baseline, particularly among RA patients, analyses of global assessments and night pain were based on changes from baseline

rather than absolute score at each follow-up visit. Morning stiffness data were also reduced to categorical data and analyzed by logistic regression. Demographic variables, duration of treatment, tablet consumption and concomitant medication were included as potential covariates in the logistic regression analyses.

Results of the Study

Fifty-one (51) investigators in 10 countries participated in this study. Only 10 investigators enrolled 10 or more patients. A total of 253 patients was randomized to Arthrotec 75 and 261 patients to diclofenac 75 mg SR. The disposition of the patients is shown in the table below by RA and OA.

Reasons for Dropouts by RA and OA

	Arthrotec 75	Diclofenac 75 mg SR	Overall
RA patients			
Completed	102 (69.9%)	105 (67.7%)	207 (68.8%)
Lost to follow-up	1 (0.7%)	0 (0)	1 (0.3%)
Dropouts	43 (29.5%)	50 (32.3%)	93 (30.9%)
Protocol violation	7 (4.8%)	7 (4.5%)	14 (4.7%)
Treatment failure	5 (3.4%)	7 (4.5%)	12 (4.0%)
Adverse events	31 (21.2%)	36 (23.2%)	67 (22.3%)
Total	146 (100.0%)	155 (100.0%)	301 (100.0%)
OA patients			
Completed	75 (70.1%)	79 (74.5%)	154 (72.3%)
Lost to follow-up	1 (0.9%)	4 (3.8%)	5 (2.3%)
Dropouts	31 (29.0%)	23 (21.7%)	54 (25.4%)
Protocol violation	6 (5.6%)	4 (3.8%)	10 (4.7%)
Treatment failure	3 (2.8%)	0 (0)	3 (1.4%)
Adverse events	22 (20.6%)	19 (17.9)	41 (19.2%)
Total	107 (100.0%)	106 (100.0%)	213 (100.0%)

The demographics were well balanced between treatments. The mean age was 59 years and slightly over two-thirds (Overall 68.7%; RA 65.8% vs. OA 72.8%) of the patients were females. Fifty-nine percent (59%) of the patients had RA and 42% had OA. Three patients had both RA and OA and were considered as RA patients for the purpose of the analysis. The mean duration of disease was 9.2 years for Arthrotec patients and 7.9 years for diclofenac patients. The average number of joints affected was 11 in both treatments.

RA Patients

The baseline global assessments were imbalanced with a greater percentage of patients with a ***Very Good*** assessment in the diclofenac 75 mg SR group than in the Arthrotec group. The other efficacy variables were generally comparable between the treatment groups.

	p-val	Arthrotec 75		Diclofenac 75 mg SR	
Physician's Global		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			5 (3.4)		3 (1.9)
Very Good		1 (0.7)	17 (11.6)	11 (7.1)	13 (8.4)
Good		47 (32.2)	55 (37.7)	47 (30.3)	64 (41.3)
Fair	.139	74 (50.7)	48 (32.9)	76 (49.0)	56 (36.1)
Poor		21 (14.4)	20 (13.7)	20 (12.9)	17 (11.0)
Very Poor		3 (2.1)	1 (0.7)	1 (0.6)	2 (1.3)
All		146 (100.0)	146 (100.0)	155 (100.0)	155 (100.0)
Patient's Global		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			4 (2.7)		3 (1.9)
Very Good		4 (2.7)	12 (8.2)	10 (6.5)	14 (9.0)
Good		37 (25.3)	50 (34.2)	42 (27.1)	65 (41.9)
Fair	.986	74 (50.7)	48 (32.9)	74 (47.7)	43 (27.7)
Poor		25 (17.1)	25 (17.1)	25 (16.1)	26 (16.8)
Very Poor		6 (4.1)	7 (4.8)	4 (2.6)	4 (2.6)
All		146 (100.0)	146 (100.0)	155 (100.0)	155 (100.0)
Night Pain		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			4 (2.7)		4 (2.6)
Not Bothered		40 (27.4)	54 (37.0)	51 (32.9)	72 (46.5)
Bothered a Little	.286	58 (39.7)	43 (29.5)	47 (30.3)	45 (29.0)
Bothered a Lot		42 (28.8)	40 (27.4)	54 (34.8)	26 (16.8)
Bothered Terribly		6 (4.1)	5 (3.4)	3 (1.9)	8 (5.2)
All		146 (100.0)	146 (100.0)	155 (100.0)	155 (100.0)
Morning Stiffness (min)		N mean (SE)		N mean (SE)	
Baseline	NA	145 88.3 (7.04)		154 78.2 (6.52)	
Final		142 69.9 (6.00)		150 63.2 (7.21)	
Health Assess. Qustionnaire		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown		1 (0.7)	8 (5.5)	2 (1.3)	13 (8.4)
0 - 10		48 (32.9)	56 (38.4)	54 (34.8)	69 (44.5)
11 - 20		43 (29.5)	35 (24.0)	56 (36.1)	34 (21.9)
21 - 30	.790	28 (19.2)	21 (14.4)	27 (17.4)	24 (15.5)
31 - 40		22 (15.1)	23 (15.8)	13 (8.4)	13 (8.4)
41 - 50		4 (2.7)	3 (2.1)	3 (1.9)	2 (1.3)
Total		146 (100.0)	146 (100.0)	155 (100.0)	155 (100.0)

OA Patients

Baseline of the various efficacy variables was generally balanced between the two treatments with a slightly poorer rating in the Arthrotec group than in the diclofenac group.

	p-val	Arthrotec 75		Diclofenac 75 mg SR	
Physician's Global		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			5 (4.7)		6 (5.7)
Very Good		4 (3.7)	13 (12.1)	2 (1.9)	14 (13.2)
Good		33 (30.8)	43 (40.2)	29 (27.4)	44 (41.5)
Fair	.537	54 (50.5)	32 (29.9)	59 (55.5)	28 (26.4)
Poor		15 (14.0)	13 (12.1)	16 (15.1)	14 (13.2)
Very Poor		1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
All		107 (100.0)	107 (100.0)	106 (100.0)	106 (100.0)
Patient's Global		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			5 (4.7)		6 (5.7)
Very Good		5 (4.7)	15 (14.0)	3 (2.8)	17 (16.0)
Good		29 (27.1)	36 (33.6)	29 (27.4)	33 (31.1)
Fair		49 (45.8)	33 (30.8)	47 (44.3)	33 (31.1)
Poor	.690	20 (18.7)	16 (15.0)	25 (23.6)	13 (12.3)
Very Poor		4 (3.7)	2 (1.9)	2 (1.9)	4 (3.8)
All		107 (100.0)	107 (100.0)	106 (100.0)	106 (100.0)
Night Pain		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			6 (5.6)		6 (5.7)
Not Bothered		24 (22.4)	40 (37.4)	19 (17.9)	43 (40.6)
Bothered a Little		43 (40.2)	36 (33.6)	44 (41.5)	39 (36.8)
Bothered a Lot	.233	30 (28.0)	22 (20.6)	32 (30.2)	13 (12.3)
Bothered Terribly		10 (9.3)	3 (2.8)	11 (10.4)	5 (4.7)
All		107 (100.0)	107 (100.0)	106 (100.0)	106 (100.0)
Morning Stiffness (min)		N mean (SE)		N mean (SE)	
Baseline		107 30.5 (4.41)		104 38.2 (5.73)	
Final	NA	101 24.3 (4.22)		98 26.4 (5.40)	
OA Sev. Index		number (%)		number (%)	
		Baseline	Final	Baseline	Final
Unknown			9 (8.4)	2 (1.9)	9 (8.5)
0 - 5		7 (6.5)	18 (16.8)	5 (4.7)	16 (15.1)
6 - 10		32 (29.9)	35 (32.7)	24 (22.6)	34 (32.1)
11 - 15		56 (52.3)	33 (30.8)	63 (59.4)	40 (37.7)
16 - 20	.187	11 (10.3)	11 (10.3)	12 (11.3)	7 (6.6)
> 20		1 (0.9)	1 (0.9)		
Total		107 (100.0)	107 (100.0)	106 (100.0)	106 (100.0)

The tables above are the summary statistics of the efficacy variables at baseline and the final visit. The p-values are the differences between the two treatment groups using the change from baseline method which categorizes patients into several categories - Improved by at least 2 grades, Improved by 1 grade, No change, Worsened by 1 grade, and Worsened by at least 2 grades. The p-value for Morning Stiffness was not provided by the sponsor except that it was stated that there was no statistically significant difference. Note that the p-values were derived from logistic regression analyses with a number of covariates but the details of the models and output of the analyses were not provided.

III. Reviewer's Comment

This was the first study to compare Arthrotec with the diclofenac slow release formulation in OA and RA patients. Previous studies all compared Arthrotec with the enteric coated diclofenac sodium. There are several design flaws that make the study results difficult to interpret though on surface, the efficacy of Arthrotec 75 and diclofenac 75 mg SR looked alike in the study population. The following is a list of deficiencies in its study design.

1. There was no placebo controlled group in the study. This raises the question of internal validity of the study especially in view of the results from a previous U.S. RA study (NN2-94-02-352: see statistical review dated 9/24/96) in which Arthrotec could not be distinguished from placebo in many study centers.

2. The set of efficacy variables used was different from what we used to see, especially in RA studies. Of the four primary efficacy variables that FDA used in evaluating RA efficacy, only the two global measurements (Physician's and Patient's) were employed in this study. The two objective measurements, number of painful joints and number of swollen joints were not measured. Instead, the night pain, morning stiffness, and the Health Assessments Questionnaire (HAQ) were used. We have no experience in these other 3 variables regarding their sensitivity in efficacy measurement. It is less a problem in the OA subpopulation. The three primary efficacy variables that FDA used in the OA evaluation are the Physician's Global Assessment, Patient's Global Assessment, and a variable that measures pain. In this study, besides the two global assessments, there was the OA severity index which served as a pain measurement.

3. The study was not a truly double-blind study. The Arthrotec 75 and diclofenac 75 mg SR tablets are different in appearance. The blinding was achieved by packaging all tablets in identical

foil strips. Thus, when a patient opened a package, the identity of the drug would be disclosed to the patient.

4. The study design did not include a flare at baseline. Patients had already been maintained a stable disease condition when they entered into the study. Thus, there was very little difference in each of the efficacy measures between baseline and the end of the study. It is not known what proportion of patients would need treatment during the 12-week study period and what proportion of patients would have spontaneous remission. Because of the *no flare* design, the Q-analysis was not done and could not have been meaningfully interpreted anyway. The Q-statistic is the ratio of the mean improvement from baseline between the test drug and the active control. The lower bound of the 95% confidence interval of Q is used to decide whether the test drug is at least as good as the control. If the mean improvement of either the test or the control drug is not significantly different from zero as in the present situation, the 95% confidence interval of Q would fail to exist. The sponsor had tried to circumvent this situation in previous non-U.S. studies with the *no flare* design by using the mean score at a final visit instead of the mean improvement score in the Q-analysis (see previous statistical review dated 9/23/96). However, as pointed out by this reviewer, we have no experience in evaluating this alternative approach.

5. One of the protocol amendments allowed patients to use concomitant analgesics. Other than the statement by the sponsor that concomitant medications would be used as a covariate in the logistic regression analysis, no details are provided as to the impact of the concomitant analgesics. The use of concomitant analgesics usually blurs the difference between treatment groups.

IV. Conclusions

This non-U.S. study of mixed OA and RA patients compared Arthrotec 75 bid to diclofenac 75 mg SR bid. The deficiencies of the design include the lack of placebo control, the method of blinding (patients were not blinded), the lack of objective measures (number of painful joints and number of swollen joints) in RA efficacy assessments, the lack of the flare condition at baseline and the absence in the evaluation of the impacts of concomitant analgesics. These undesirable features of the study design do not provide convincing statistical evidence that the two drugs are comparable in efficacy.

APPEARS THIS WAY
ON ORIGINAL

/S/

Hoi M. Leung, Ph.D.
Mathematical Statistician

Concur:

/S/

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

Archive: NDA 20-607

cc:
IND
HFD-550/MO/Witter
HFD-550/PM/LoBianco
HFD-550/Act.Dir./Chambers
HFD-550/Div. File
HFD-340/Div. Sci. Inv.
HFD-180/MO/Suh
HFD-180/PM/Strongin
HFD-180/Div. File
HFD-180/Div.Dir./Fredd
HFD-725/Stat/Leung
HFD-725/Div. File

APPEARS THIS WAY
ON ORIGINAL

STATISTICAL REVIEW AND EVALUATION --- NDA

Date: FEB 18 1997

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 sign and symptoms of osteoarthritis and rheumatoid arthritis

Documents Reviewed: NDA Supplemental Vol. 1-4 (Study 013) Dated December 17, 1996

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

Key Words: Ulceration, Intent-to-Treat, ulcer size

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 in December 26, 1995. These studies had been reviewed and documented in Statistical Review and Evaluation --- NDA dated September 11, 1996.

Among seven pivotal studies, it was found that the six-week, placebo-controlled OA study (protocol 349), which enrolled only patients with a history of UGI ulcer or erosive disease, provided support of the efficacy of the Arthrotec 50 TID over diclofenac 75 mg BID and also provided some evidence of efficacy of the Arthrotec 75 BID over diclofenac 75 mg BID for prevention of

developing NSAID-induced gastric ulcer for OA patients.

However, for prevention of developing NSAID-induced duodenal ulcer for OA patients, study 349 failed to support the efficacy of either the Arthrotec 50 TID or the Arthrotec 75 BID over diclofenac 75 mg BID.

There is a need of another study which replicates the results of study 349 regarding gastric lesion incidence.

The sponsor has submitted the report for Arthrotec study 013 to provide this replication.

This reviewer will address the efficacy and safety of Arthrotec regarding gastroduodenal damage in this review.

B. **Study I88-94-02-013**

1. **Description of Study**

This was a randomized, double-blind, parallel group, multicenter (51 investigators) study comparing Arthrotec 75 and diclofenac 75 mg slow release (SR), administered twice daily for 12 weeks in the treatment of patients with rheumatoid arthritis or osteoarthritis.

Randomization was stratified for rheumatoid arthritis (RA) and osteoarthritis (OA) patients to ensure equivalent numbers of patients with RA in each treatment group and equivalent numbers of patients with OA in each treatment group.

Separate randomizations were used for patients with RA or OA and patients were randomized in blocks of six for each center.

The primary objective of the study was to compare the antiarthritic efficacy and the gastroduodenal mucosal damage associated with Arthrotec 75 BID and diclofenac 75 mg SR BID in patients with either rheumatoid arthritis or osteoarthritis.

This was one of the first major endoscopic studies in which endoscopic examination had been employed solely at the end of the study, thereby mimicking clinical practice in that a proportion of the patients enrolled would almost certainly have had pre-

existing ulceration and were not excluded from the study.

A single endoscopic examination of mucosa of stomach and duodenum was performed at final follow-up. Numbers of petechiae, erosions, ulcers and presence of intramucosal or intraluminal blood was recorded.

An erosion was defined as a lesion producing a definite break in the mucosa but without depth. An ulcer was defined as any lesion with unequivocal depth, regardless of size.

The primary response variable was the proportion of patients with a gastroduodenal ulcer, and the significance of treatment differences were assessed by Fisher's exact test. In addition, gastric and duodenal ulceration rates were assessed separately and tested in the same way.

Erosive lesions in the stomach and duodenum were assigned the following scores:

Erosive lesions	0	none
	1	1-3 erosions
	2	4-10 erosions
	3	>10 erosions
	4	ulcer

If patients failed to undergo endoscopy at their final visit, they were excluded from analyses of endoscopically determined results. However, if they cited a serious gastrointestinal event (perforation, ulceration or bleeding) as a reason for withdrawal, they were assigned the worst possible outcome for that response and included in the analyses.

Power calculations were carried out for two primary response variables - the gastroduodenal ulceration rate and the Global Assessment of Arthritic Condition. This study required two hundred patients per treatment group with a known endoscopic outcome. That sample size provided 80% power to detect the expected treatment difference (4% ulceration Arthrotec; 11% diclofenac) with one-sided tests carried out at the 5% level of significance.

This was on the basis that a previous study had shown an

Statistical Review and Evaluation
(Amended Review #2)

NDA 20-607 (Related:IND 32,708)
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 mcg) b.i.d. or t.i.d.**
Arthrotec II (diclofenac 75 mg/misoprostol 200 mcg) b.i.d.
Documents Reviewed: Volumes 1-4 dated 12/17/96 of NDA 20-607.
Reviewer : Hoi M. Leung, Ph.D.
Previous Statistical Reviews Dated: 9/23/96 and .11/27/96
Date Completed: 3/10/97

MAR 10 1997

I. Background

This latest submission is a study report to which the sponsor wants to cross-reference to NDA 20-607. The study protocol is identified as I88-94-02-013. This was a multicenter, multinational, randomized, double blind, parallel group comparison of Arthrotec 75 (diclofenac sodium 75 mg and misoprostol 200 mcg) and diclofenac 75 mg slow release, administered twice daily in patients with rheumatoid arthritis or osteoarthritis. The duration of the treatment period was 12 weeks. This was the first study which compared Arthrotec with the slow release formulation of diclofenac. Previous studies of Arthrotec compared with the enteric coated formulation of diclofenac. This review will only address the efficacy portion of the study. The statistical aspects of the ulcer incidences and other adverse events of this study will be addressed by the reviewing statistician who directly supports HFD-180.

II. Study Description (Protocol I88-94-02-013)

The primary objective of the study was to compare the anti-arthritic efficacy and the upper gastrointestinal safety (as assessed by endoscopy) of Arthrotec 75 BID and diclofenac 75 mg SR BID in the treatment of patients with rheumatoid arthritis (RA) or osteoarthritis (OA). The secondary objectives were to compare the tolerability of the two treatments for various adverse events. Endoscopy was only performed at the end of the study but not before.

Randomization was stratified by type of arthritis (RA or OA) and by center with a block size of six. Blinding was achieved by foil/foil packing of the study drug supplies and return of unused medication to a third party for tablet-return counts. Patients

ulceration rate of approximately 11% on diclofenac and 4% on diclofenac/misoprostol (Arthrotec). It was assumed that Arthrotec 75 mg would not cause more ulcers than diclofenac 75 mg SR, and that one-sided significance testing would therefore be appropriate.

To attain the required number of 200 patients per treatment group with known endoscopic outcomes it was assumed, based on experience of earlier studies, that there was a 20% drop-out rate. Consequently, it was projected to enroll 500 patients.

The design of this study using a sample size 200 per treatment group provided 80% power to detect a difference between 50% on one treatment and 35.8% (or 64.2%) on the other for Physician's or Patient's Global Assessments, using two-sided tests carried out at the 5% level of significance.

2. **Sponsor's Analysis**

A total of 514 patients were enrolled into study, which was conducted by 51 European investigators. Two hundred fifty-three (253) were randomized to received Arthrotec 75 and 261 to receive diclofenac 75 mg SR.

The proportion of withdrawals were very similar in the two treatment groups, 29% (74) on Arthrotec 75 and 28% (73) on diclofenac 75 mg SR.

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 between the treatment groups with respect to age, gender, and type of arthritis and disease duration.

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

There was slightly greater proportion of patients on Arthrotec 75 with a history of prior gastroduodenal ulceration or upper

gastrointestinal hemorrhage (14.3 vs 10.3 on diclofenac 75 mg SR). In addition, there was a greater percentage of patients particularly with RA, with a global assessment of arthritic condition designated as 'very good' on admission in the diclofenac 75 mg SR group (for physicians' global assessment, 7.1% for diclofenac 75 mg SR vs 0.7% for Arthrotec 75).

For the patients who did not undergo endoscopy, the time spent on study medication was the same in both treatment groups and there was no evidence to suggest that there was any selection bias between groups.

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

There were 210 patients on Arthrotec 75 and 216 on diclofenac 75 mg SR who underwent the an endoscopic evaluation at final follow-up.

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

Protocol I88-94-02-013
Number of Patients with Erosive Lesion at Final Endoscopy

	Number of Patients (%)			
	Final Gastric Endoscopy		Final Duodenal Endoscopy	
	Arthrotec 75 7444 (N=210)	Diclofenac 75 mg SR (N=216)	Arthrotec 75 (N=209)	Diclofenac 75 mg SR (N=215)
None	177 (84%)	124 (57%)	193 (92%)	181 (84%)
1-3 Erosion	15 (7%)	31 (14%)	9 (4%)	9 (4%)
4-10 Erosion	5 (2%)	14 (7%)	3 (1%)	6 (3%)
>10 Erosion	2 (1%)	15 (7%)	0 (0%)	5 (2%)
Ulcer	11 (5%)	32 (15%)	4 (2%)	14 (7%)

Copied from Table 15, I88-96-06-013, page 52.

P-values for Treatment Comparison --- Protocol I88-94-02-013

Treatment Comparison	Final Gastric Endoscopy	Final Duodenal Endoscopy
With an ulcer	0.001	0.028

Fisher's exact test

Ulcers were defined as all lesions with unequivocal depth on the basis that even small lesions could be of full thickness leading to bleeds and/or perforation.

With regard to erosive damage, gastroduodenal ulceration, the primary endpoint, occurred in 6.7 % of the Arthrotec 75 group compared with 19.4% on diclofenac 75 mg SR (p=0.001). The differences in ulceration rate for the stomach and the duodenum separately were also statistically significant (see table above).

However, many previous studies have taken a cut-off of ≥5mm as the criterion for ulceration. Results of gastric ulceration and duodenal ulceration when ulcers were defined as ≥5mm are given below.

Protocol I88-94-02-013
Gastric Ulceration Rate When Ulcers were defined as ≥5mm

Treatment	Rate	vs Diclofénac 75 mg SR p-value
Arthrotec 75	9/210 (4%)	0.003
Diclofenac 75 mg SR	26/216 (12%)	

Fisher's exact test

Protocol I88-94-02-013
Duodenal Ulceration Rate When Ulcers were defined as ≥5mm

Treatment	Rate	vs Diclofenac 75 mg SR p-value
Arthrotec 75	3/209 (1%)	0.031
Diclofenac 75 mg SR	11/215 (5%)	

Fisher's exact test

As seen from the table above, when ulcers were defined as ≥5mm, the differences in ulceration rate for the stomach and the

duodenum separately were also statistically significant.

The main drug-related adverse events were GI in nature. Withdrawals rates for abdominal pain and diarrhea were lower on Arthrotec 75 than diclofenac 75 mg SR. Withdrawals for nausea, vomiting, dyspepsia and flatulence were higher on Arthrotec 75 than diclofenac 75 mg SR.

3. **Reviewer's Evaluation**

3.1 **Reviewer's Comments on Study Design**

The design of this study was different from that of study 349. In study 349, 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.

In this study, endoscopic examination had been employed solely at the end of the study, thereby mimicking clinical practice in that a proportion of the patients enrolled would almost certainly have had pre-existing ulceration and were not excluded from the study.

3.2 **Reviewer's Comments on Randomization**

The sponsor did not submit the predetermined randomization sequence code and actual treatment assignment. Randomization could not be evaluated. But as seen from the sponsor's listing of enrollment by investigator and treatment, patients were well allocated between treatment groups with maximum difference of two patients.

3.3 **Lack of Baseline Endoscopic Evaluation**

Due to lack of baseline endoscopic evaluation, it was unknown whether there was statistically significant differences among the treatment groups with respect to baseline gastric and duodenal endoscopy score.

Sponsor's efficacy analysis was based on the assumption that two treatment groups were comparable with respect to gastric and duodenal endoscopy score at baseline. But, this assumption might not be true and could not be verified. This might cast doubt about the results of efficacy analysis. The results could be biased in favor of the Arthrotec due to baseline imbalance.

However, for prevention of developing NSAID-induced gastric ulcer, in view of small p-value (p=0.001), the baseline imbalance in gastric endoscopy score if existed might have negligible effect on the efficacy results in terms of significance.

3.4 Reviewer's Comments on Primary Endpoint

In this study, the primary endpoint measured the ulceration rate instead of ulcer incidence rate. The primary endpoint measured in this study was different from that in study 349.

The sponsor's analysis was not an Intent-to-Treat analysis but an evaluable analysis. It did not include all randomized patients but included 210 patients in the Arthrotec 75 group and 216 in the diclofenac 75 mg SR group who underwent the an endoscopic evaluation at final follow-up.

The results of the final gastric endoscopy scores and final duodenal endoscopy scores for an Intent-to-Treat analysis are given below.

Protocol I88-94-02-013
Number of Patients with Erosive Lesion at Final Endoscopy
Intent-to-Treated Analysis

	Number of Patients (%)			
	Final Gastric Endoscopy		Final Duodenal Endoscopy	
	Arthrotec 75 (N=253)	Diclofenac 75 mg SR (N=261)	Arthrotec 75 (N=252)	Diclofenac 75 mg SR (N=261)

Unknown	43 (17%)	45 (17%)	44 (17%)	46 (19%)
None	177 (70%)	124 (48%)	192 (76%)	181 (69%)
1-3 Erosion	15 (6%)	31 (12%)	9 (4%)	9 (3%)
4-10 Erosion	5 (2%)	14 (5%)	3 (1%)	6 (2%)
>10 Erosion	2 (1%)	15 (6%)	0 (0%)	5 (2%)
Ulcer	11 (4%)	32 (12%)	4 (2%)	14 (5%)

Copied from Table 15, I88-96-06-013, page 52.

P-values for Treatment Comparison --- Protocol I88-94-02-013

Treatment Comparison	Final Gastric Endoscopy	Final Duodenal Endoscopy
With an ulcer	0.001	0.028

Fisher's exact test

As seen from the table above, the findings in the Intent-to-Treat analysis were similar to those given by the sponsor in terms of significance.

The results of Intent-to-Treat analyses of gastric ulcer and duodenal ulcer when ulcers were defined as ≥5mm are given below.

Protocol I88-94-02-013
Gastric Ulceration Rate When Ulcers were defined as ≥5mm
Intent-to-Treat Analysis

Treatment	Rate	vs Diclofenac 75 mg SR p-value
Arthrotec 75	9/253 (4%)	0.005
Diclofenac 75 mg SR	26/261 (10%)	

Fisher's exact test

Protocol I88-94-02-013
Duodenal Ulceration Rate When Ulcers were defined as ≥5mm
Intent-to-Treat Analysis

Treatment	Rate	vs Diclofenac 75 mg SR p-value
Arthrotec 75	3/253 (1%)	0.054
Diclofenac 75 mg SR	11/261 (4%)	

Fisher's exact test

As seen from the table above, when ulcers were defined as ≥5mm, the findings in the Intent-to-Treat analysis were similar to those given by the sponsor in terms of significance for gastric ulcer. For duodenal ulcer, contrary to sponsor's finding, the results of ITT analysis revealed that Arthrotec 75 BID was statistically marginally significantly different from diclofenac 75 mg SR BID (p=0.054).

3.5 Gastric Ulceration and Duodenal Ulceration Rates by Patient

This reviewer performed an analysis of ulceration rate for gastric ulcer and duodenal ulcer for OA patients and RA patients. The results are given below.

Protocol I88-94-02-013
Number of Patients with Gastric Ulcer by Patient
Intent-to-Treat Analysis

Patient	Arthrotec 75 BID	Diclofenac 75 mg SR BID	Between Treatment p-value[1]	CMH p-value[2]
Osteoarthritis	2/107 (1.9%)	15/106 (14.2%)	<0.001	<0.001
Rheumatoid arthritis	9/146 (6.2%)	17/155 (11.0%)	0.153	

[1]Fisher's Exact test
[2]Cochran-Mantel-Haenszel statistics controlling for strata

Protocol I88-94-02-013
Number of Patients with Duodenal Ulcer by Patient
Intent-to-Treat Analysis

Patient	Arthrotec 75 BID	Diclofenac 75 mg SR BID	Between Treatment p-value[1]	CMH p-value[2]
Osteoarthritis	1/107 (0.9%)	8/106 (7.5%)	0.019	0.019
Rheumatoid arthritis	3/146 (2.1%)	6/155 (3.9%)	0.503	

[1]Fisher's Exact test
[2]Cochran-Mantel-Haenszel statistics controlling for strata

As seen from the tables above, for OA patients, the Arthrotec 75 BID was statistically significantly different from diclofenac 75 mg SR BID for both gastric ulcer and duodenal ulcer. But, for RA patients, there was no treatment difference for both gastric

ulcer and duodenal ulcer; treatment differences were small.

3.6 **Sensitivity Analysis on Duodenal Ulcer**

For prevention developing NSAID-induced of duodenal ulcer, this reviewer did the following sensitivity analysis to find out how many alternations in ulceration status would change the 2-sided p-value from the observed p-value to greater than 0.05, keeping sample sizes fixed. The results for study 013 are given in Table 2.

(1) In case 1, the Arthrotec 75 ulceration rate was varied, keeping the diclofenac 75 mg SR ulceration rate fixed at 5.4%.

(2) In case 2, the diclofenac 75 mg SR ulceration rate was varied, keeping the Arthrotec 75 ulceration rate fixed at 1.6%.

(3) In case 3, both Arthrotec 75 and Diclofenac 75 mg SR ulceration rates were varied.

Case 1 results indicates that a change of 0.4% from the observed Arthrotec rate of 1.6%, changes the 2-sided p-value (by Fisher's Exact test) from (greater 5%). This difference of 0.4% is numerically equivalent to 1 ulcerated Arthrotec patient in the numerator of the ulceration rate when given that the sizes of the Arthrotec and diclofenac 75 mg SR are 253 and 261, respectively, and the diclofenac ulceration rate is 5.4%.

Case 2 results indicates that a change of 0.8% from the observed Diclofenac rate of 5.4%, changes the 2-sided p-value (by Fisher's Exact test) from (greater 5%). This difference of 0.8% is numerically equivalent to 2 ulcerated diclofenac patients in the numerator of the ulceration rate when given that the sizes of the Arthrotec and diclofenac 75 mg SR are 253 and 261, respectively, and the Arthrotec ulceration rate is 1.6%.

Case 1 and 2 results also indicate that alternations in the ulceration status of 1 patient in the Arthrotec group or 2 patients in the diclofenac group (i.e. from non-ulcerated to

ulcerated in the Arthrotec group or from ulcerated to non-ulcerated in the diclofenac group) could change the observed 2-sided p-value 0.028 to greater than 0.05.

Case 3 results indicate that a change in the status of just a change of 1 Arthrotec patient from non-ulcerated to ulcerated, when there was a change of 1 diclofenac patient from ulcerated to non-ulcerated would cause a shift in the 2-sided p-value from 0.028 to a p-value of greater than 0.05.

C. **Overall Summary and Recommendation**

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

Study 013 provide some evidence of the efficacy of the Arthrotec 75 BID against diclofenac 75 mg BID for prevention of developing NSAID-induced gastric ulcer for OA patients.

However, due to lack of baseline endoscopic evaluation and different study design from Study 349, the results of this study could only be considered as supporting evidence and but could not be considered as a replication of those shown in Study 349.

2. **Prevention of Developing NSAID-induced Duodenal Ulcer**

From the reviewer's sensitivity analysis of prevention of developing NSAID-induced duodenal ulcer, it was found that a change in the ulceration status of just 1 Arthrotec patient from non-ulcerated to ulcerated, when there was no change or a change of 1 diclofenac patients from ulcerated to non-ulcerated would cause a shift in the 2-sided p-value from 0.028 to a p-value of greater than 0.05.

The results of this study were on borderline and not robust as seen in reviewer's sensitivity analysis. Hence, the study 013 failed to providing supporting evidence of the efficacy of the Arthrotec 75 BID against diclofenac 75 mg SR BID for prevention of developing NSAID-induced duodenal ulcer.

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

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

/S/

Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 13 pages of text and 2 pages of tables.

Concur: Dr. Huque /S/ 2/12/97
Dr. Smith 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/02/06/97

Table 1 Comparability of Treatment Groups at Baseline --- Protocol 013

Intent-to-Treat Population

Variable	Level	Arthrotec 75 mg BID (n=253)	Diclofenac 75 mg SR BID (n=261)	between treatment p-value
Sex	Male	79 (31%)	82 (31%)	0.963
	Female	174 (69%)	179 (69%)	
Age (mean)		59.2	59.5	
Height (cm) (mean)				
Weight (kg) (mean)				
History of Gastroduodenal or Upper GI Haemorrhage	Gastric ulcer	22 (9%)	16 (6%)	0.266
	Duodenal ulcer	7 (3%)	6 (2%)	0.736
	Upper GI Haemorrhage	7 (3%)	5 (2%)	0.523
History of Arthritic	Osteoarthritis	107 (42%)	106 (41%)	0.699
	Rheumatoid Arthritis	146 (58%)	155 (59%)	
Duration of Disease (yrs)		9.2	7.9	
Physician's Global Assessment	Very Good	5 (2%)	13 (5%)	0.238
	Good	80 (32%)	76 (29%)	
	Fair	128 (51%)	135 (52%)	
	Poor	36 (14%)	36 (14%)	
	Very Poor	4 (2%)	1 (1%)	
Patient's Global Assessment	Very Good	9 (4%)	13 (5%)	0.724
	Good	66 (26%)	71 (27%)	
	Fair	123 (49%)	121 (46%)	
	Poor	45 (18%)	50 (19%)	
	Very Poor	10 (4%)	6 (2%)	

P-values for other variables were obtained by this reviewer using Pearson's Chi-square test.

Table 2 Sensitivity Analysis for Duodenal Ulcer for Study 013

Case 1: Diclofenac ulceration rate fixed at the observed rate of 5.4%
(14 patients ulcerated over the total 261 patients).

Number of Arthrotec Patients: 253
Number of Diclofenac Patients: 261

Number Ulcerated in th Numerator of the Ulceration Rates		Ulceration Rate			Fisher's Exact test 2-tailed
Arthrotec	Diclofenac	Arthrotec	Diclofenac	Difference	p-value
4	14	1.6%	5.4%	-3.8%	0.028
5	14	2.0%	5.4%	-3.4%	0.059

Observed number of patients ulcerated for this trial.
Observed ulceration rates for this trial.

Case 2: Arthrotec ulceration rate fixed at the observed rate of 1.6%
(4 patients ulcerated over the total 253 patients).

Number of Arthrotec Patients: 253
Number of Diclofenac Patients: 261

Number Ulcerated in th Numerator of the Ulceration Rates		Ulceration Rate			Fisher's Exact test 2-tailed
Arthrotec	Diclofenac	Arthrotec	Diclofenac	Difference	p-value
4	14	1.6%	5.4%	-3.8%	0.028
4	13	1.6%	5.0%	-3.4%	0.046
4	12	1.6%	4.6%	-3.0%	0.073

Observed number of patients ulcerated for this trial.
Observed ulceration rates for this trial.

Case 3: Arthrotec ulceration rate varied; Diclofenac ulceration rate varied.

Number of Arthrotec Patients: 253
Number of Diclofenac Patients: 261

Number Ulcerated in th Numerator of the Ulceration Rates		Ulceration Rate			Fisher's Exact test 2-tailed
Arthrotec	Diclofenac	Arthrotec	Diclofenac	Difference	p-value
4	14	1.6%	5.4%	-3.8%	0.028
4	13	1.6%	5.0%	-3.4%	0.046
4	12	1.6%	4.6%	-3.0%	0.073
5	14	2.0%	5.4%	-3.4%	0.059
5	13	2.0%	5.0%	-3.0%	0.091

Observed number of patients ulcerated for this trial.
Observed ulceration rates for this trial.

MEMORANDUM OF STATISTICAL CONSULTATION -- NDA

Date: FEB 18 1997

NDA #: 20-607

Application: G.D. Searle & Co.

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

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

Documents Reviewed: General Correspondence Dated December 23, 1996
NDA Suppl. Vol. 1-2 Dated December 20, 1995

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

Key Words: Test of equivalence, pooling studies

Per Dr. Kathy Robie-Suh request, this reviewer has reviewed the sponsor's correspondence regarding comparing efficacy of misoprostol 100 mcg QID versus misoprostol 200 mcg BID.

A. Background

The sponsor was asked to provide information to determine whether changes in the misoprostol daily dose interval (e.g. BID versus QID) for the same total daily dose affects the efficacy and safety of that component of Arthrotec. The sponsor has provided response in the correspondence.

B. Sponsor's Analysis

The efficacy of misoprostol 100 mcg QID has not been compared directly with those of misoprostol 200 mcg BID. However, each dosing regimen has been evaluated in separate studies.

Misoprostol 100 mcg QID was evaluated in Studies U81-86-02-002 and U81-86-02-003 (002/003). Both studies had identical designs and included patients with osteoarthritis treated with NSAIDs who

continued these medications for the duration of the trials. A total of 421 patients were enrolled in the two studies combined, 143 were randomized to misoprostol 100 mcg QID, 140 to misoprostol 200 mcg QID and 138 to placebo. Patients underwent upper gastrointestinal (UGI) endoscopies at baseline and weeks 4, 8, and 12.

Misoprostol 200 mcg BID was evaluated in two studies of 12 weeks duration, Study S81-89-02-053 (053) and Study NN2-94-02-352 (352). Study 352 did not include UGI endoscopies. Study 053 included 1,618 patients with various underlying arthritides, receiving a variety of NSAIDs, who were randomized to misoprostol or placebo for 12 weeks. A total of 462 patients were randomized to misoprostol 200 mcg BID, 474 to 200 mcg TID, 228 to 200 mcg QID, and 454 to placebo. Patients underwent UGI endoscopies at baseline, weeks 4, 8, and 12.

The incidences of gastric ulcers (GU) in the misoprostol 100 mcg QID and misoprostol 200 mcg BID groups are given below.

Incidence of NSAID-Induced Gastric Ulcers

	Study 002/003		Study 053	
	Misoprostol 100 mcg QID (N=193)	Placebo (N=196)	Misoprostol 200 mcg BID (N=462)	Placebo (N=454)
GU Incidence	7 (3.6%)	28 (14.3%)	29 (6.3%)	51 (11.2%)
P-value	<0.05		<0.001	

Copied from page 10 of Response to FDA letter of 22 November 1996.

Both regimens were associated with significantly lower incidences of GU compared to placebo. In a logistic regression dose response analysis, submitted to FDA an addendum to misoprostol NDA, S-019 on December 20, 1995, the incidence of GU for the 200 mcg BID regimen fell within the 95% confidence interval of that for 100 mcg QID (Figure 1). Therefore, (according to the sponsor) the efficacy of the two misoprostol regimens for GU prevention are not different.

C. **Reviewer's Comments and Evaluation**

Studies 002 and 003 were pivotal studies submitted in the original NDA submission and compared efficacy of misoprostol 200 mcg QID and 100 mcg QID versus placebo in preventing NSAID-induced gastrointestinal damage. Both misoprostol QID doses were shown to be effective in preventing NSAID-induced gastric ulcers in Study 002, but in Study 003 only misoprostol 200 mcg QID was shown to be effective (see below).

Incidence of Gastric Ulcers

Study	Regimen	Rate
002	Miso 200 mcg QID	1/76 (1.4%)*
	Miso 100 mcg QID	5/77 (6.5%)*
	Placebo	19/76 (25%)
003	Miso 200 mcg QID	2/65 (3.1%)*
	Miso 100 mcg QID	5/66 (7.6%)
	Placebo	11/62 (17.7%)

*Statistically significantly better than placebo at the 5% level.
Compiled from Table 5, page 4 from Study Report 002 and 003, respectively.

In this correspondence the sponsor presents combined results of these two studies and indicates that in the pooled results misoprostol 100 mcg QID is effective in preventing NSAID-induced gastric ulcers.

It is unclear to this reviewer why the number of patients and incidence of gastric ulcers in the combined results presented in the sponsor's correspondence and report (N81-95-07-825) are different from those obtained from the individual study reports for Study 002 and Study 003. The incidence rate of gastric ulcers was much lower than those from the individual study (3.6% versus 6.5% and 7.6%, respectively for Studies 002 and 003). The sponsor's combined results are biased in favor of misoprostol 100 mcg QID.

The sponsor's approach to show that the efficacy of the two misoprostol regimens for GU prevention are not different is

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.

E. Comments to be conveyed to the Sponsor

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

/S/

APPEARS THIS WAY
ON ORIGINAL

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
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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

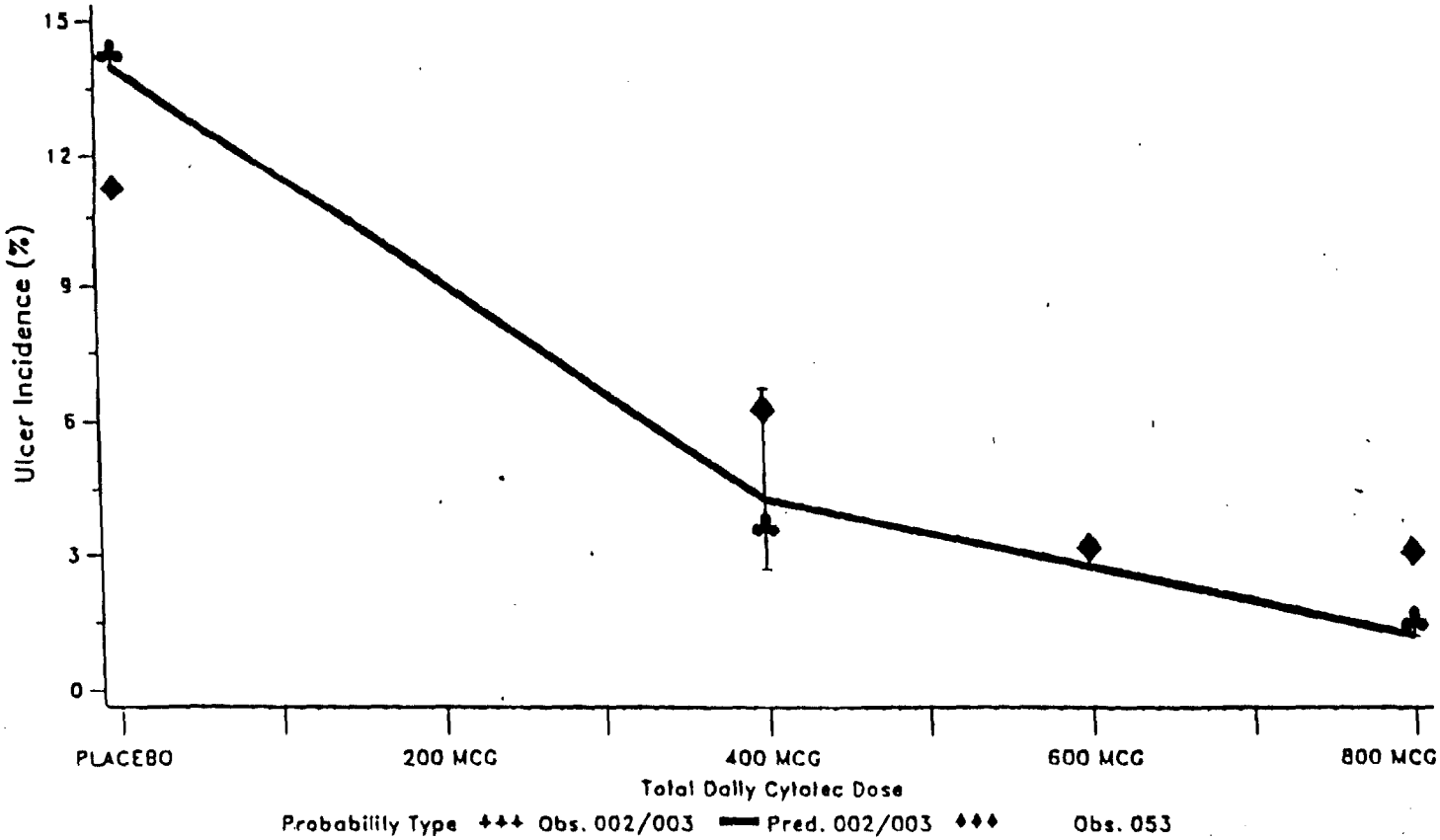

Figure 1
Predicted Probabilities and Observed Incidence of Gastric Ulcers

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
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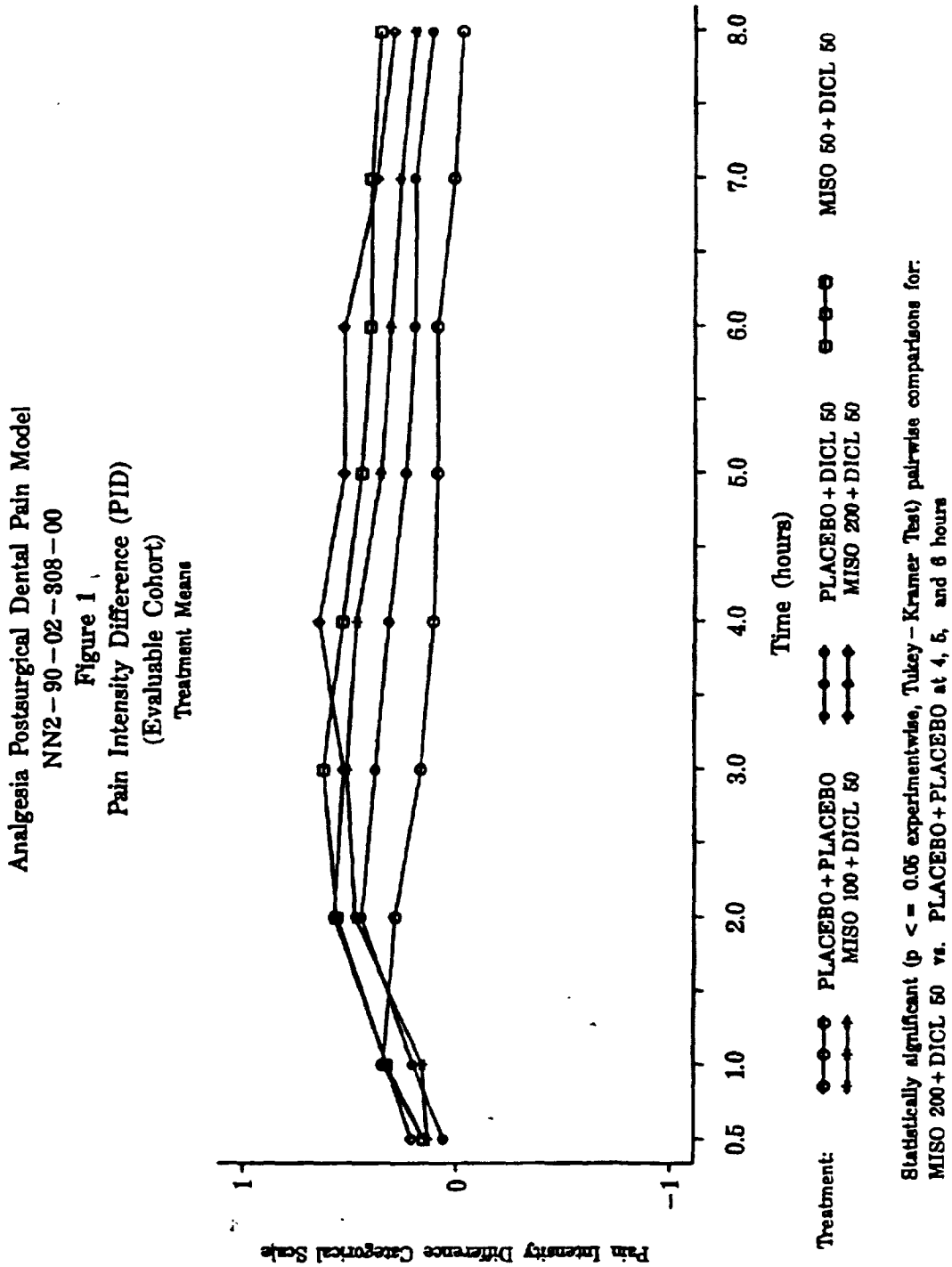

Analgesia Postsurgical Dental Pain Model
NN2-90-02-308-00
Figure 1
Pain Intensity Difference (PID)
(Evaluable Cohort)
Treatment Means
Pain Intensity Difference Categorical Scale
1
0
-1
0.5
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
Time (hours)
Treatment:
PLACEBO+PLACEBO
MISO 100+DICL 50
PLACEBO+DICL 50
MISO 200+DICL 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, 6, and 8 hours

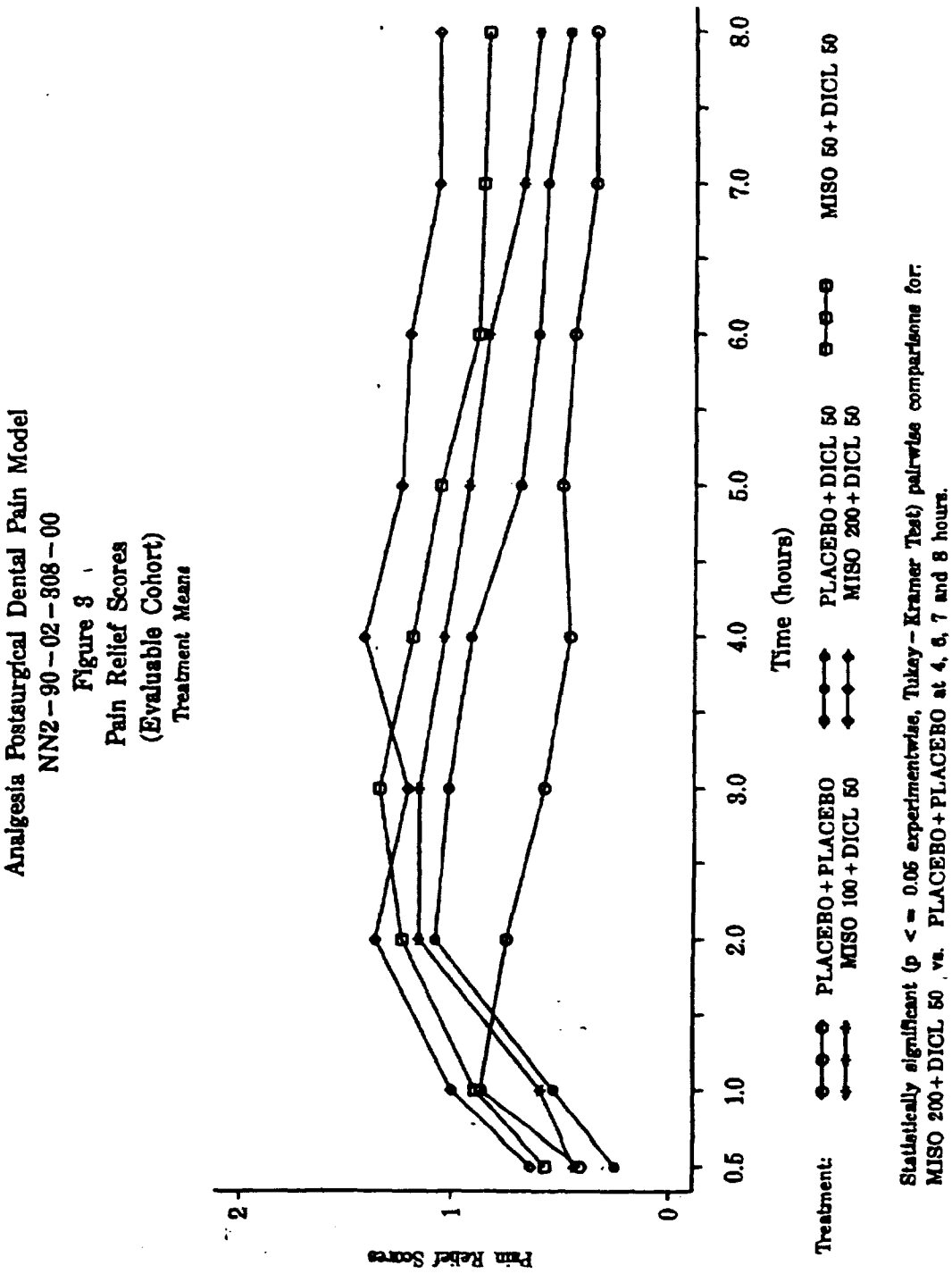

Analgesia Postsurgical Dental Pain Model
NN2-90-02-808-00
Figure 3
Pain Relief Scores
(Evaluable Cohort)
Treatment Means
Pain Relief Scores
0
1
2
0.5
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
Time (hours)
Treatment:
PLACEBO+PLACEBO
MISO 100+DICL 50
PLACEBO+DICL 50
MISO 200+DICL 50
MISO 50+DICL 50
Statistically significant (p <= 0.05 experimentwise, Tukey-Kramer Test) pairwise comparisons for:
MISO 200+DICL 50 vs. PLACEBO+PLACEBO at 4, 6, 7 and 8 hours.

Figure 1. Pain Intensity Difference (PID) Scores

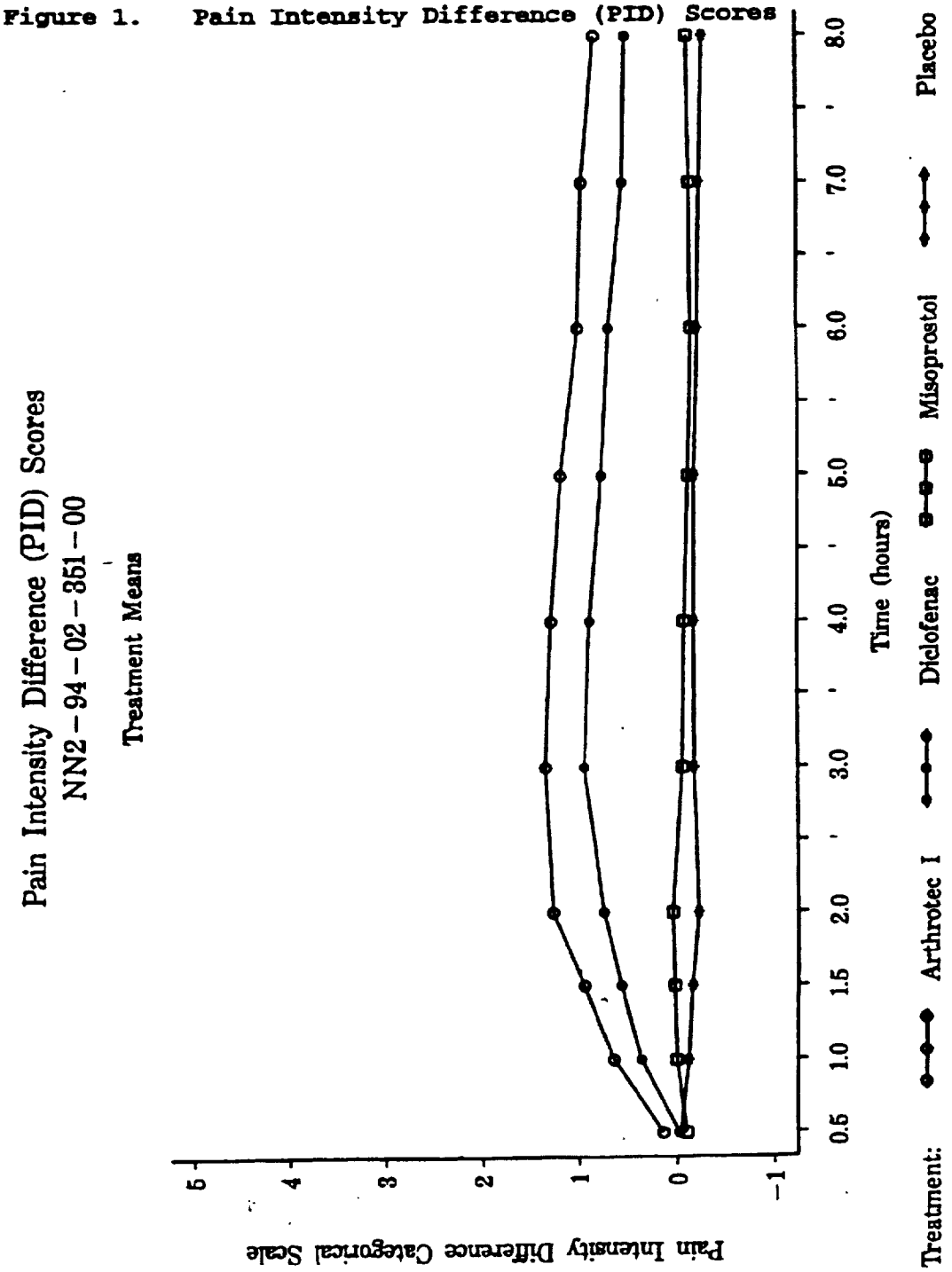
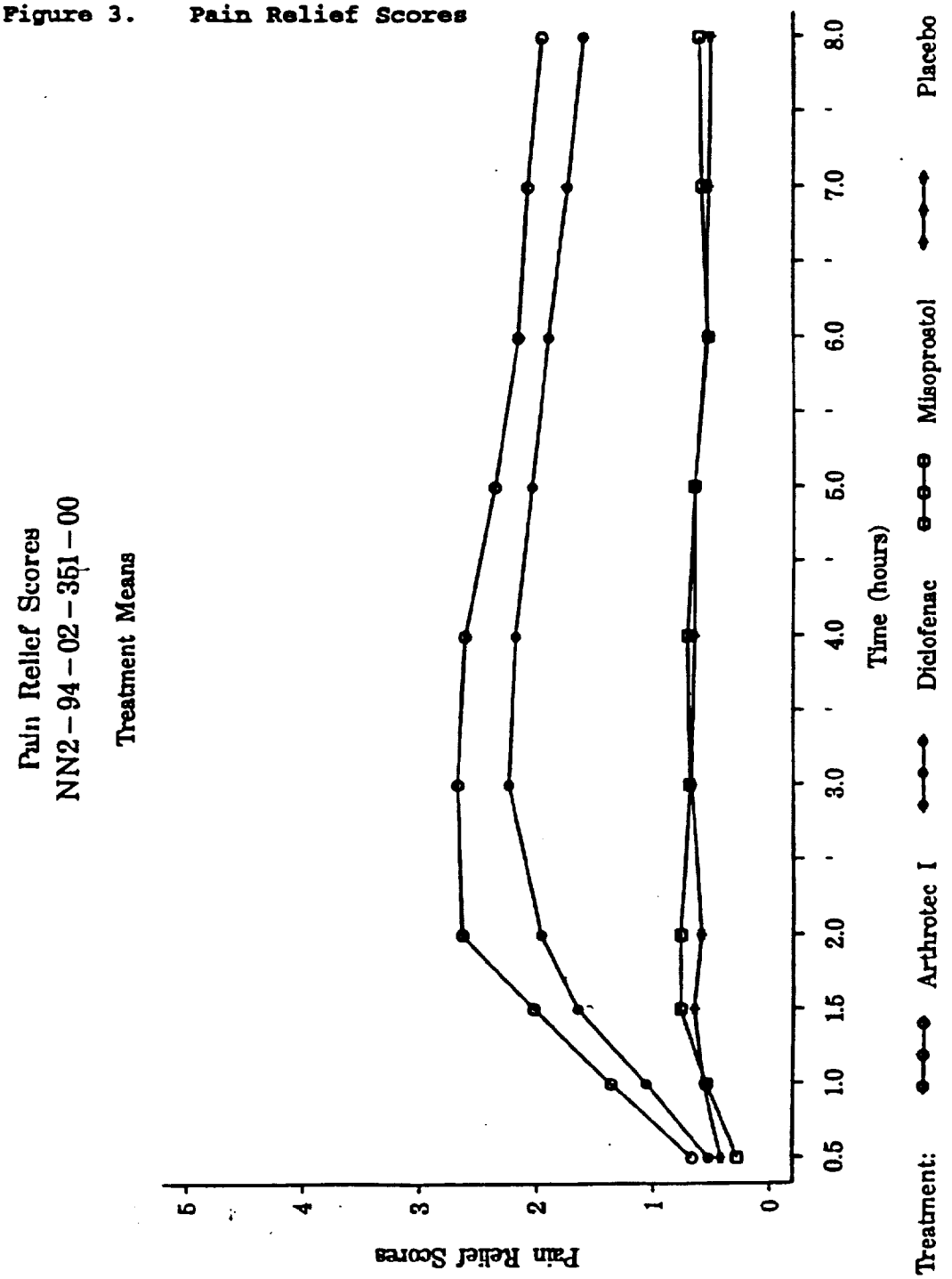


Figure 3. Pain Relief Scores



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Statistical Review and Evaluation

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 1.1, 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

- 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_1. 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.

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.

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_1]		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_1]		1.01 [0.74]	1.14 [0.84]	
Tender/Pain				
LS mean change	p=.062	p=0.511	p=0.174	
Q [Q_1]		0.73 [0.42]	1.32 [0.92]	
Swelling				
LS mean change	p=0.151	p=0.715	p=0.214	
Q [Q_1]		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_1]		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_1]		1.03 [0.71]	1.06 [0.73]	
Tender/Pain				
LS mean change	p=.017	p=0.363	p=0.459	
Q [Q_1]		0.69 [0.40]	1.16 [0.81]	
Swelling				
LS mean change	p=0.165	p=0.692	p=0.294	
Q [Q_1]		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