G. **Compliance:** Compliance was assessed by pill counts at each followup visit (2 Weeks and 6 Weeks). For a patient to be considered evaluable for endoscopy analyses with regard to study drug compliance, the compliance with study medication had to be such that: (a)the patient took at least 70% of the prescribed doses of medication during the 4 week period preceding the Week 6 visit and at least 50% of the prescribed doses during the initial two week period; or if the patient withdrew from the study prior to the Week 6 visit, took at least 70% of the prescribed doses of study medication during the time period prior to withdrawal; and (b)the patient had not missed all study medication on more than 2 consecutive days during the 4-week period preceding the Week 6 visit; or if the patient withdrew from the study prior to the Week 6 visit, had not missed all study medication on more than two consdecutive days during the time period prior to withdrawal.

H. **Monitoring of Adverse Events:** Patients were issued diary cards on which to record occurrence of any symptoms or adverse events, including severity, date started and date stopped. Final laboratory measurements were to be taken no more than 7 days after the final dose of study medication.

I. **Efficacy Parameters:** Primary measures of efficacy for treatment of osteoarthritis were: (1)physician's global assessment of arthritic condition, (2)patient's global assessment of arthritic condition, and (3)osteoarthritis severity index. Values of these measures were to be determined at Week 2 and at Week 6 and compared to baseline values. Secondary measures of arthritis efficacy were: patient assessment of arthritis pain, functional capacity classification, and incidence of patient withdrawal due to lack of osteoarthritis efficacy.

For the assessment of efficacy in preventing gastric and duodenal damage the primary efficacy parameters were to be the gastric and duodenal endoscopic scores. The primary analysis was to consist of chi-square comparison of the outcome (ulcer, no ulcer) over the treatments.

J. **Statistical Methods:** A sample size of 150 patients for each of the Arthrotec arms and for the diclofenac arm of the study was chosen to be sufficient to detect a difference of 14% (18% as compared to 4%) in the ulcer rates of the diclofenac patients as compared to those of the Arthrotec patients at Week 6, assuming two pair-wise comparisons, using alpha=0.025 and power of 0.90, and allowing for a 10% attrition rate for patients in the study.

With regard to efficacy in treatment of osteoarthritis, the sample size was sufficient to detect a difference of greater than 60% in the Physician's Global Assessment improvement rate (assuming an improvement rate of 70% for the diclofenac and Arthrotec groups and 45% for the placebo group) between the Arthrotec groups and the placebo group at Week 6 assuming

three pair-wise comparisons (placebo versus diclofenac, diclofenac versus Arthrotec I, and diclofenac versus Arthrotec II) with a power or 0.90 and alpha = 0.0167 using the arcsin transformation.

For efficacy for treatment of osteoarthritis, the primary efficacy variables (physician's global assessment of arthritic condition, patient's global assessment of arthritic condition, and osteoarthritis severity index) were to be determined at Week 2 and at Week 6 and compared to baseline values. Analyses were to be done by chi-square tests comparing the outcome (improved, worsened, unchanged and unknown) over the four treatments. These analyses were to be done for the intent-to-treat population (all patients randomized) and for the arthritis evaluable cohort. Mean change in the osteoarthritis severity index was to be calculated and changes assessed using Kruskal-Wallis test. Analyses of the secondary arthritis parameters was to be done only for the intent-to-treat population.

The protocol states, "The primary analyses for the assessment of gastric, duodenal and gastroduodenal mucosal damage will consist of chi-square tests comparing the outcome (ulcer, nonulcer) over the treatments," and "The principal pairwise comparisons are between diclofenac 75mg and diclofenac 50mg/misoprostol 200mcg (Arthrotec I) and between diclofenac 75mg and diclofenac 75mg/misoprostol 200mcg (Arthrotec II). An additional pairwise comparison will be done between Arthrotec I and II patients." Thus, for each of the three specified endpoints (gastric ulcer, duodenal ulcer, and "gastroduodenal mucosal damage") there would be 2 comparisons. The Hochberg procedure was to be used to adjust for multiple comparisons.The sponsor does not mention any procedure for dealing with multiple endpoints. Finally, distributions of patients by final endoscopic grade was to be compared among the four treatment groups using the Kruskal-Wallis test. These analyses were to be done for the intent-to-treat population and for the endoscopy evaluable population. Patients missing the Week 6 endoscopy were to be excluded from the pairwise comparisons.

The protocol identified the Endoscopy Evaluable cohort as including patients who:

1. satisfied all inclusion/exclusion criteria, and

2. Took $\geq$70% of the prescribed doses of study medication during the 4-week period preceding the Week 6 visit and $\geq$50% of the presecribed doses during the initial 2-week period; or if the patient withdrew prematurely, took $\geq$70% of the prescribed doses of study medication during the time period priro to withdrawal; and

3. had not missed all study medication on more than 2 consecutive days during the 4-week period preceding the Week 6 visit; or if the patient withdrew prematurely, had not missed all study medication on more

than 2 consecutive days during the time period prior to withdrawal; and

4. underwent the bvaseline endoscopic examination within 7 days prior to the first dose of study medication; and

5. underwent the final endoscopic examination not more tha 2 days after the final dose of study medication; and

6. did not take any of the following medications during the study; NSAIDs (other than aspirin $\leq$325mg daily for non-arthritic reasons); anti-ulcer drugs (other than supplied Amphogel, up to 6 tablets per day); anti-coagulants; or more than 1500mg of calcium carbonate per day; and

7. underwent the specific study visit according to the guidelines described in the protocol: Week 2 Visit = 14 days ($\pm$3 days) and Week 6 = 42 days ($\pm$5 days) from the date of the first dose of study medication.

Laboratory data was to be assessed by comparison of baseline and final values for each patient, by calculating descriptive statistics and by using shift tables.

All statistical tests were to be two-sided and Hochberg's procedure was to be used to adjust for multiple comparisons.

K. **Amendments:** There were two amendments to this study. Amendment 1, dated 3/14/94, changed the diclofenac sodium formulation used from a blue hard gelatin capsule to an enteric-coated formulation and made all test products identical in appearance.

Amendment 2, dated 7/22/94, incorporated a quality-of-life health survey into the study to be completed by the subject at baseline, Week 2 and Week 6 or Final Visits.

L. **Results:**

1. **Enrollment and Baseline Characteristics of Patients:** A total of 452 patients were enrolled in this study. Of these 154 were randomized to diclofenac 75mg, 152 to diclofenac 50mg/misoprostol 200mcg, 175 to diclofenac 75mg/misoprostol 200mcg, and 91 to placebo. Patient enrollment by center is summarized in the following table:

Study 349: Patient Enrollment by Center

Center	Investigator	Placebo	Diclofenac 75mg	Diclofenac 50mg/Misoprostol 200mcg	Diclofenac 75mg/Misoprostol 200mcg
US0001	Aaronson	1	1	1	0
US0002	Halla	2	3	3	3
US0003	Kogut	1	0	1	2
US0004	Lies	1	3	1	1
US0005	Marker	4	5	5	4
US0006	Roth	5	6	6	6
US0007	Sikes	2	4	5	6
US0008	Tindall	3	6	5	5
US0009	Wiesenhutter	3	5	5	6
US0010	Baldassare	0	0	1	1
US0011	Davis	0	1	2	1
US0012	Gaziano	0	1	1	1
US0013	Harris	2	3	2	3
US0014	McAdam	1	2	1	1
US0015	Rosenthal	0	0	2	2
US0016	Shivakumar	2	4	3	5
US0017	Toth	0	3	1	2
US0018	Barish	1	2	2	1
US0019	Ettinger	2	3	4	4
US0020	Fleischman	3	6	4	6
US0021	Pruitt	2	2	3	3
US0022	Unnoppet	1	2	0	1
US0023	Mülligan	0	3	3	2
US0024	Burch	3	4	5	5
US0025	Weaver	4	7	7	7
US0026	McMillen	2	4	5	4
US0027	Brady	2	3	2	3
US0028	Korsten	2	1	2	3
US0029	Brandon	2	3	3	3
US0030	Levy	1	3	3	3
US0031	Markarowski	2	3	3	3
US0032	Liotti	0	1	0	0
US0034	Vakil	0	1	1	1
US0035	D'Hemecourt	2	3	4	6
US0036	Fisher	4	7	6	6
US0037	Cheng	2	4	4	4
US0038	Thompson	4	4	6	5
US0039	Stine	1	2	2	3
US0040	Poirier	5	7	8	8
US0041	Bath	1	3	0	3
US0044	Stanton	4	6	6	7
US0045	Skosky	1	2	2	3
US0046	Dalgin	1	2	1	2
US0047	Spiegel	0	1	1	2
US0048	Jaszewski	0	1	0	2
US0049	Dietz	1	0	1	2
US0050	Zuckerman	2	3	3	3
US0051	Luggen	1	2	3	3
US0052	White	2	4	4	4
US0053	Goldstein	1	1	1	3
US0054	Fogel	2	3	3	2
US0055	Stern	0	1	0	1
US0057	Khan	0	0	1	1
US0058	Zakko	0	0	0	2
US0059	Elbert	3	3	4	5
	Total	91	154	152	175

from sponsor's table, NDA Vol. 1.77, p. 8-13004 through 8-13019

Demographic characteristics of the patients enrolled in this study are summarized in the table below:

Study 349: Demographic and Baseline Characteristics of the Study Population

	Placebo (n=91)	Diclofenac 75mg b.i.d. (n=154)	Diclofenac 50mg/Misoprostol 200mcg t.i.d. (n=152)	Diclofenac 75mg/Misoprostol 200mcg b.i.d. (n=175)
Age (years)				
mean	61.5	62.9	62.3	62.8
median	62	64	63	64
range				
Race (%)				
White/Black/Oriental/Other	87/11/0/2	82/14/0/4	88/9/0/3	86/10/0/4
Gender (%)				
male	32	29	32	33
female	68	71	68	67
Joint Affected (%)				
hip	11	16	22	15
knee	63	65	62	69
both hip and knee	26	19	16	17
Disease Duration (years)				
mean	10.6	11.9	11.9	10.3
median	10	10	10	9
range				
Baseline Endoscopy Findings, gastric/duodenal (%):				
normal (score=0)	70/84	64/88	68/88	69/87
petechiae only (score=1 or 2)	10/5	11/5	12/6	9/6
1-10 erosions (score=3 or 4)	20/11	25/8	20/7	22/7
>10 erosions (score=5 or 6)	0/0	0/0	0/0	0/0
Ulcer (score=7)	0/0	0/0	0/0	0/0
Baseline Osteoarthritis Severity Index:				
mean	13.9	14.2	14.0	14.0
median	14	15	14	14
range				
Baseline Patient Assessment of Arthritis Pain (cm):				
mean	6.4	6.6	6.3	6.6
median	7	7	6	7
range				

from sponsor's tables, NDA Vol. 1.77, pp. 8-13027, 8-13031, and 8-13033

The average age of the study population was about 63 years, most of the patients (about two-thirds) were female, and the knee was the predominant joint assessed in this study. About 80% of patients had a baseline functional status of Class 2 and about 75-80% of patients had a baseline physician's global assessment and patient's global assessment of poor or very poor. The sponsor found no statistically significant differences among the treatment groups in any of the demographic characteristics, in baseline vital signs, in baseline arthritis status, or in baseline endoscopy scores.

2. **Disposition of Patients**: Disposition of the enrolled patients, including whether or not the followup endoscopy was done, is summarized in the table below:

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Study 349: Reasons for Termination of Study Participation

Reason	Number of Patients											
	Placebo			Diclofenac 75mg b.i.d.			Diclofenac 50mg/Misoprostol 200mcg t.i.d.			Diclofenac 75mg/Misoprostol 200mcg b.i.d.		
	Final Endo Done	Final Endo Not Done	Total	Final Endo Done	Final Endo Not Done	Total	Final Endo Done	Final Endo Not Done	Total	Final Endo Done	Final Endo Not Done	Total
Enrolled	80	11	91		15	154		10	152		16	176
Completed	69	1	70		1	126	131	0	131		2	142
Discontinued:												
Lost-to-followup	0	1	1	0	0	0	0	0	0	0	0	0
Protocol Noncompliance	0	0	0	2	1	3	2	1	3	2	2	4
Pre-existing Violation	0	0	0	1	1	2	0	2	2	1	1	2
Treatment Failure	8	6	14	1	2	3	1	1	2	2	2	4
Adverse event	3	3	6	9	11	20	8	6	14	14	9	23

reviewer's original table, based on datasets from sponsor's CANDA submission

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Of the 572 patients treated, a total of 469 (82%) completed the study. Percentages of patients discontinuing prematurely in each treatment group were: placebo group, 23.1%; diclofenac 75mg b.i.d., 18.2%; diclofenac 50mg/misoprostol 200mcg t.i.d., 13.8%; and diclofenac 75mg/misoprostol 200mcg b.i.d., 18.9%. In the placebo group the major reason for failure to complete the study was treatment failure; in all other treatment arms, the major reason for failure to complete the study was adverse events.

3. Efficacy Analysis: Final endoscopy results are summarized in the table below:

Study 349: Final Endoscopy Results (Intent-to-Treat Population)

	Placebo (n=91)	Diclofenac 75mg b.i.d. (n=154)	Diclofenac 50mg/Misoprostol 200mcg t.i.d. (n=152)	Diclofenac 75mg/Misoprostol 200mcg b.i.d. (n=175)
Number of Patients having final endoscopy (gastric/duodenal*):	80/80	138/138	142/142	159/159
Final Endoscopy Findings, gastric/duodenal* (% of endoscoped):				
normal (score=0)	71/79	43/74	64/84	65/84
petechiae only (score=1 or 2)	8/6	14/8	18/6	15/7
1-10 erosions (score=3 or 4)	17/14	29/12	14/5	16/7
>10 erosions (score=5 or 6)	3/0	3/0	2/1	0/0
Ulcer (score=7)	3/1	11/7	3/6	4/3
Total	100/100	100/100	100/100	100/100

* pyloric channel ulcers are grouped with the duodenal ulcers

reviewer's original table, based on data in sponsor's tables, NDA Vol. 1.77, pp. 8-13038 and 8-13040

At final endoscopy, appearance of the duodenal mucosa in of patients in all treatment groups was normal. (At initial endoscopy , of patients in each group had normal duodenal mucosa). At final endoscopy about 12% of endoscoped diclofenac patients showed duodenal erosions as compared to . of endoscoped diclofenac/misoprostol patients. In all treatment groups the gastric mucosa appeared to be a more frequent site of lesions than the duodenum. At initial endoscopy 64% of diclofenac patients and 70% of placebo patients had normal gastric mucosa. At final endoscopy, only 43% of endoscoped diclofenac patients had a normal gastric mucosa (as compared to 71% of placebo patients). The gastric mucosa was normal in 64% of diclofenac 50mg/misprostol 200mcg patients and in 65% of diclofenac 75mg/misoprostol 200mcg patients, as compared to ititial rates of 68% and 69%, respectively, for these two groups. The percent of diclofenac/misoprostol patients

having gastric erosions was about half that of the diclofenac alone patients (6-7% versus 12%).

The following table summarizes the ulcer occurrence rates for the various treatment groups. In this intent-to-treat analysis patients who have missing data (i.e., who did not have followup endoscopy) are assumed to have no ulcers.

Study 349: Ulcer Rates in the Various Treatment Groups (Intent-to-Treat Analysis)*

	Number of Patients (%)			
	Placebo t.i.d. (n=91)	Diclofenac 75mg b.i.d. (n=154)	Diclofenac 50mg/Misoprostol 200mcg t.i.d. (n=152)	Diclofenac 75mg/Misoprostol 200mcg b.i.d. (n=175)
Gastric Ulcer	2 (2.2%)	15 (9.7%)	4 (2.6%)	7 (4.0%)
Duodenal Ulcer	0 (0%)	7 (4.5%)	8 (5.3%)	1 (0.6%)
Pyloric Channel Ulcer	1 (1.1%)	4 (2.6%)	0 (0%)	3 (1.7%)

* Numbers of patients who did not have followup endoscopy were: 10 placebo, 15 diclofenac, 10 diclofenac 50mg/misoprostol 200mcg, and 14 diclofenac 75mg/misoprostol 200mcg patients.

reviewer's original table, based on information in sponsor's CANDA submission

The following table displays statistical comparisons of ulcer rates among the treatment groups (no adjustments for multiple comparisons) for gastric ulcers, duodenal ulcers and pyloric channel ulcers. The per protocol analysis appropriately specifies that pyloric channel ulcers are to be grouped with the duodenal ulcers.

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Study 349: Comparisons of Ulcer Frequencies Among the Various Treatment Groups (Intent-to-Treat)

Comparison	Numbers of Patients	2-sided p-value*
Gastric Ulcer:		
D75 vs. Placebo	15/154 vs. 2/91	0.035
D50/M200 vs. D75	4/152 vs. 15/154	0.016
D75/M200 vs. D75	7/175 vs. 15/154	0.046
D75/M200 vs. D50/M200	7/175 vs. 4/152	0.553
Duodenal Ulcer + Pyloric Channel Ulcer:		
DU+PU: D75 vs. Placebo	11/154 vs. 1/91	0.035
DU+PU: D50/M200 vs D75	8/152 vs. 11/154	0.637
DU+PU: D75/M200 vs D75	4/175 vs. 11/154	0.060
DU+PU: D75/M200 vs D50/M200	4/175 vs. 8/152	0.238
Duodenal Ulcer:		
DU: D75 vs. Placebo	7/154 vs. 0/91	0.048
DU: D50/M200 vs. D75	8/152 vs. 7/154	0.798
DU: D75/M200 vs. D75	1/175 vs. 7/154	0.028
DU: D75/M200 vs. D50/M200	1/175 vs. 8/152	0.014
Pyloric Channel Ulcer:		
PU: D75 vs. Placebo	4/154 vs. 1/91	0.654
PU: D50/M200 vs. D75	0/152 vs. 4/154	0.123
PU: D75/M200 vs. D75	3/175 vs. 4/154	0.710
PU: D75/M200 vs. D50/M200	3/175 vs. 0/152	0.251

* 2-sided p-value by Fishers Exact test (M. Fan, FDA Biometrics)(no adjustment for multiple comparisons)

D75 = diclofenac 75mg b.i.d.
D50/M200 = diclofenac 50mg/misoprostol 200mcg (Arthrotec I) t.i.d.
D75/M200 = diclofenac 75mg/misoprostol 200mcg (Arthrotec II) b.i.d.

reviewer's original table

Patients treated with diclofenac 75mg showed a higher rate of gastric ulcer and duodenal ulcer than did placebo patients. The diclofenac 50mg/misoprostol 200mcg group and the diclofenac 75mg/misoprostol 200mcg group had significantly fewer patients who developed gastric ulcers as compared to the group of patients treated with diclofenac 75mg alone. For duodenal ulcer, including pyloric channel ulcers, neither diclofenac/misoprostol combination treatment had significantly fewer ulcers than the diclofenac alone group. In the diclofenac alone group 4 of the 11 duodenal ulcers were in the pyloric channel. However, for the diclofenac 75mg/misoprostol 200mcg group, 3 of the 4 duodenal ulcers were in the pyloric channel. The diclofenac 50mg/misoprostol 200mcg group had no pyloric channel ulcers.

The sponsor also performed analysis of ulcer rates for the Endoscopy Evaluable cohort. Results of the sponsor's Endoscopy Evaluable analyses confirmed a statistically significant benefit of diclofenac 50mg/misoprostol 200mcg t.i.d. over diclofenac 75mg b.i.d. alone in preventing gastric ulcers ($p=0.007$). However, gastric ulcer rates in the diclofenac 75mg/misoprostol 200mcg b.i.d. group as compared to the diclofenac 75mg b.i.d. group were not significantly different in the evaluable analysis ($p=0.106$). Again, for duodenal ulcer prevention, there was no difference between the diclofenac alone group and the diclofenac 50mg/misoprostol 200mcg group ($p=0.622$) or the diclofenac 75mg/misoprostol 200mcg group ($p=0.202$). For this analysis 24 (26.4%) placebo patients, 32 (20.8%) diclofenac patients, 23 (15.1%) diclofenac 50mg/misoprostol 200mcg patients, and 41 (23.4%) diclofenac 75mg/misoprostol 200mcg patients were considered non-evaluable. Among these patients the main reasons for endoscopy non-evaluability were either that final endoscopy was not done or that the timing of the final endoscopy was not in the designated range. Fifty-five patients (10 placebo, 14 diclofenac alone, 13 diclofenac 50mg/misoprostol 200mcg, 18 diclofenac 75mg/misoprostol 200mcg patients) had final endoscopy done outside the designated range of 42 ± 7 days. All of these except 2 diclofenac patients, 3 diclofenac 50mg/misoprostol 200mcg patients, and 1 diclofenac 75mg/misoprostol 200mcg patients had final endoscopy done earlier than the designated time. Among patients who underwent final endoscopy earlier than scheduled, duodenal ulcer was found in 4 diclofenac patients, 1 diclofenac 50mg/misoprostol 200mcg patient and 1diclofenac 75mg/misoprostol 200mcg patient. Gastric ulcer was found in 1 diclofenac patient (who also had a duodenal ulcer) who had final endoscopy early and gastric ulcer was found in 1 diclofenac 50mg/misoprostol 200mcg patient who had

follow-up endoscopy late (day 52). All the patients found to have ulcers at at earlier than scheduled final endoscopy were patients who were discontinued from the study prematurely due to adverse events.

A listing of all individual patients who had ulcers diagnosed at final endoscopy is given below:

Study 349: Patients Having Upper Gastrointestinal Ulcers at Final Endoscopy

	Patient Number			
	Placebo (n = 91)	Diclofenac 75mg (n = 154)	Diclofenac 50mg/Misoprostol 200mcg (n = 152)	Diclofenac 75mg/Misoprostol 200mcg (n = 175)
Gastric Ulcers	#187 #514	#22 #48 #733 #311 #177 #179 #282 #763 #769** #360 #401 #450 #532 #598 #797	#18 #21 #112 #673	#100 #289 #323 #354 #356 #526 #674
Pyloric Channel Ulcers	#478	#157[b]* #430[c] #335 #427	none	#63 #927 #642
Duodenal Ulcers	none	#769** #216* #344* #157[b]* #653* #358 #430[c]	#579* #134 #150 #182 #874 #440 #491 #523	#387*

* premature withdrawal [all these were due to adverse event]
* patient had two gastric ulcers and a duodenal ulcer;
[b] patient had a pyloric channel ulcer and a duodenal ulcer;
[c] patient had a pyloric channel ulcer and three duodenal ulcers.

reviewer's original table

These patients were not concentrated in any particular centers.

Characteristics of the patients who had ulcers at the last endoscopy are given in the table below:

Study 349: Patients with Ulcers at Final Endoscopy

Patient #	Investigator	Age (yrs)	Gender (M/F)	Race (W/B/ Other)	Disease Duration (yrs)	Functional Capacity (Inl/fin)	Time in Study (days)	Completion Status	Ulcer Description*
Placebo:									
#187	0016	55	F	W	6.0	II/II	44	completed	three GU (0.6, 0.4 and 0.3 cm diameter)
#478	0038	74	M	W	7.0	II/II	44	completed	PC (0.5cm long)
#514	0040	56	M	W	10.0	II/II	41	completed	GU (0.5cm diameter)
Diclofenac 75mg b.i.d.:									
#22	0002	64	F	W	20.0	II/III	43	completed	GU (0.6cm diameter)
#48	0005	68	F	W	12.0	II/II	42	completed	GU (0.6cm diameter)
#733	0005	77	F	W	5.2	II/II	47	completed	GU (2 cm diameter)
#311	0007	69	F	W	10	II/II	42	completed	GU (0.5cm diameter)
#157	0014	72	F	W	2.0	II/II	32	AE	PC (1.0cm long); DU (0.7cm diameter)
#177	0016	69	F	W	5.5	II/II	42	completed	GU (0.3cm diameter)
#179	0016	62	F	B	14.0	II/II	43	completed	GU (0.5cm diameter)
#216	0019	67	F	W	12.0	I/I	29	AE	DU (0.8cm diameter)
#282	0025	74	F	W	14.0	II/II	41	completed	GU (0.9cm diameter)
#763	0025	78	M	W	24.0	II/II	41	completed	GU (2.5cm diameter)
#769	0025	68	F	W	5.3	II/II	29	AE	two GU (2.1 and 0.5cm diameter); DU (0.5 cm diameter)
#653	0026	70	F	W	30.0	II/II	44	completed	two DU (2.5 and 1.0 cm diameter)
#335	0029	78	M	W	19.0	II/II	42	completed	PC (1.0 cm long)
#344	0030	63	M	W	38.0	II/II	2	AE	DU (0.3cm diameter)
#358	0031	66	M	W	6.0	III/II	38	completed	DU (1.0cm diameter)
#360	0031	67	M	W	10.0	II/II	39	completed	GU (0.5cm diameter)
#401	0035	62	M	B	2.3	II/II	40	completed	GU (0.8cm diameter)
#427	0036	40	F	W	6.0	II/III	43	completed	PC (0.4cm long)
#430	0036	56	M	W	20.0	II/II	40	completed	PC (0.3cm long); three DU (0.4, 0.4, and 0.4 cm diameter)
#450	0037	70	M	W	15.2	II/II	42	completed	GU (0.4cm diameter)
#532	0041	69	F	W	40.0	II/I	43	completed	GU (0.3cm diameter)
#598	0047	80	M	W	10.0	II/II	40	completed	three GU (1.0, 0.4, and 0.3 cm diameter)

#797	0059	76	F	W	10.0	III/II	46	completed	three GU (0.5, 0.4, and 0.4cm diameter)
Diclofenac 50mg/Misoprostol 200mcg t.i.d.:									
#18	0002	77	M	W	30.0	II/II	51	completed	two GU (1cm and 0.5cm diameter)
#21	0002	69	F	W	4.0	II/II	34	completed	three GU (1.0, 0.3, and 0.2 cm diameter)
#112	0010	63	F	W	21.0	II/II	40	completed	GU (2.5cm diameter)
#134	0012	78	F	W	10.0	III/III	43	completed	three DU (0.5, 0.3, and 0.3 cm diameter)
#150	0013	52	M	W	14.0	I/I	47	completed	DU (0.5cm diameter)
#182	0016	62	F	W	10.0	III/III	42	completed	DU (0.4cm long)
#874	0024	59	F	W	1.6	III/II	46	completed	two DU (0.5 and 0.5cm diameter)
#440	0036	43	F	B	8.0	II/I	43	completed	DU (0.5cm diameter)
#491	0039	63	F	W	25.0	II/I	40	completed	DU (0.5cm diameter)
#523	0040	59	M	W	15.0	II/I	41	completed	four DU (0.5, 0.5, and 0.5 cm diameter [3 largest])
#579	0045	83	M	W	10.0	II/II	14	AE	DU (2.0cm diameter)
#673	0053	66	M	B	8.0	II/II	41	completed	GU (0.4cm diameter)
Diclofenac 75mg/Misoprostol 200mcg b.i.d.:									
#100	0009	57	F	W	18.0	II/II	42	completed	GU (0.5cm diameter)
#63	0006	68	F	W	25.0	II/I	42	completed	PC (1.2 cm long)
#927	0016	78	M	W	3.0	II/II	43	completed	PC (0.8cm long)
#289	0026	68	F	W	15.0	II/I	41	completed	GU (1.5cm diameter)
#323	0028	53	M	O	8.0	II/II	42	completed	three GU (0.5, 0.2, and 0.2 cm diameter)
#354	0031	72	M	W	11.0	II/II	43	completed	GU (0.3cm diameter)
#356	0031	70	F	W	5.0	III/II	46	completed	GU (0.3cm diameter)
#387	0034	58	M	W	10.0	II/I	28	AE	DU (0.6cm diameter)
#526	0040	74	F	W	20.0	III/III	41	completed	GU (0.5cm diameter)
#642	0051	58	F	W	10.0	II/I	42	completed	PC (0.9cm long)
#674	0053	41	F	O	3.0	II/II	41	completed	GU (0.6 and 0.3 cm diameter)

* Investigator numbers all are preceded by US; [b]ini = initial, at study entry; fin = final, at final evaluation;
* AE = patient withdrew prematurely due to an adverse event
* DU = duodenal ulcer; GU = gastric ulcer; PC = pyloric channel ulcer; lengths are longest axis of the ulcer

reviewer's original table based on information in sponsor's table, NDA Vol. 1.78, pp. 8-13337 through 8-13368 and Vol. 1.79, pp. 8-13954 through 8-13991 and pp. 8-13992 through 8-14151; Vol. 1.80, pp. 8-14152 through 8-14214

There were no clear unifying factors among the patients who developed ulcers. The age and sex distribution of the patients who developed ulcers did not appear to differ between treatment groups and appeared similar to the age and sex distribution in the overall study population.

Impact of Missing Final Endoscopy - All Discontinued Patients: All patients enrolled did not have followup endoscopy. Because the event rate (ulcer occurrence) in this study is small, I attempted to evaluate the impact of missing endoscopy results on the overall study outcome with regard to ulcer prevention.

Of the 572 patients enrolled and endoscoped at study entry, 522 patients (91%) had followup endoscopy. Of the 50 patients who did not have followup endoscopy, all except 3 were study discontinuations. In the intent-to-treat analyses, the sponsor assumed that none of the discontinued patients missing followup endoscopy had any ulcer. For each treatment group, proportions of discontinued patients having followup endoscopy are summarized in the following table:

Study 349: Endoscopy Rates for Discontinued Patients

	Placebo (n=91)	Diclofenac 75mg (n=154)	Diclofenac 50mg/Misoprostol 200mcg (n=152)	Diclofenac 75mg/Misoprostol 200mcg (n=175)
Number of Discontinued Patients	21	28	21	33
Number of Discontinued Patients Having Followup Endoscopy	11	13	11	19
Percent of Discontinued Patients Having Followup Endoscopy	52%	46%	52%	58%

reviewer's original table

Proportions of discontinued patients endoscoped were similar among the various treatment groups, with the rate for the diclofenac 75mg group being slightly lower than for the misoprostol groups. Therefore, it is not likely that the lack of data from discontinued patients who did not have followup endoscopy significantly influenced the comparative results of the treatments.

Event rates for discontinued patients who underwent followup endoscopy are summarized in the table below:

Study 349: Observed Event Rates for Discontinued Patients Who Underwent Endoscopy

	Placebo	Diclofenac 75mg	Diclofenac 50mg/Misoprostol 200mcg	Diclofenac 75mg/Misoprostol 200mcg
Gastric Ulcer	0/11 (0%)	1/13 (8%)	0	0
Pyloric Channel Ulcer	0	1/13 (8%)	0	0
Duodenal Ulcer	0	5/13 (38%)	1/11 (9%)	1/19 (5%)

reviewer's original table

Impact of Missing Final Endoscopy - Patients Discontinued Due To Adverse Events: All the discontinued patients found to have ulcers at final endoscopy had been discontinued from the study due to adverse events. Endoscopy rates and ulcer occurrence rates for this subpopulation of patients are summarized in the following two tables.

Study 349: Endoscopy Rates for Adverse Event Withdrawals*

	Placebo (n = 91)	Diclofenac 75mg (n = 154)	Diclofenac 50mg/Misoprostol 200mcg (n = 152)	Diclofenac 75mg/Misoprostol 200mcg (n = 175)
Number of AE Withdrawals	6	20	14	23
Number of AE Withdrawals Having Followup Endoscopy	3	9	8	14
Percent of AE Withdrawals Having Followup Endoscopy	50%	45%	57%	61%

* Adverse Event Withdrawals = AE withdrawals = patients withdrawn from the study due to adverse events

reviewer's original table

Final endoscopy rates for patients discontinued due to adverse events were somewhat higher for the diclofenac/misoprostol groups than for the diclofenac 75mg group. Therefore, it is unlikely that failure to obtain followup endoscopy on each adverse event withdrawal influenced the study result in favor of the diclofenac/misoprostol drugs.

Event rates for adverse event withdrawals who underwent followup endoscopy are summarized in the table below:

Study 349: Observed Event Rates for Discontinued Patients Who Underwent Endoscopy

	Placebo	Diclofenac 75mg	Diclofenac 50mg/Misoprostol 200mcg	Diclofenac 75mg/Misoprostol 200mcg
Gastric Ulcer	0/3 (0%)	1/9 (11%)	0	0
Pyloric Channel Ulcer	0	1/9 (11%)	0	0
Duodenal Ulcer	0	5/9 (56%)	1/8 (13%)	1/14 (7%)

reviewer's original table

Additional Analyses: The sponsor also compared the distributions of gastric and duodenal endoscopy scores among the treatment groups at study completion. For gastric endoscopy scores in the intent-to-treat population, the sponsor found highly significant differences in favor of diclofenac/misoprostol for the overall treatment comparison and for diclofenac 75mg as compared to diclofenac 50mg/misoprostol 200mcg and for diclofenac 75mg as compared to diclofenac 75mg/misoprostol 200mcg (p-values, 0.001). However, there was no statistically significant difference between the two diclofenac/misprostol combinations in any comparison for gastric scores. For duodenal lesions, there were no statistically significant differences among treatment groups in either the primary or secondary comparisons. For "patients with any erosion or ulcer" diclofenac 75mg/misoprostol 200mcg tended to have a lower rate than did diclofenac 75mg alone (p-value=0.029); however, this difference was not statistically significant taking into account multiple comparisons.

The sponsor combined the gastric and duodenal endoscopy scores to give a "gastroduodenal score" and performed statistical analysis on the combined scores, demonstrating a benefit of the diclofenac/misoprostol treatments over diclofenac alone in terms of overall endoscopy score distribution, patients with an ulcer, and patients with any erosion or ulcer. However, the benefit reflected in these analyses clearly derives from the gastric endoscopy scores with little contribution of the duodenal endoscopy scores to the result.

Results for the "intent-to-treat" and "endoscopy evaluable" populations for these analyses were similar, except that the result for gastric lesions was somewhat weaker in the endoscopy evaluable

population for the comparison of diclofenac 75mg versus diclofenac 75mg/misoprostol 200mcg. Sponsor's p-values for these comparisons are summarized in the table below:

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Study 349: P-Values for Sponsor's Additional Treatment Comparisons (Intent-to-Treat)

	Overall Treatment Comparison	Primary Pairwise Comparisons		Secondary Pairwise Comparisons
		Diclofenac 75mg BID vs. Diclofenac 50mg/Misoprostol 200mcg TID	Diclofenac 75mg BID vs. Diclofenac 75/Misoprostol 200mcg BID	Diclofenac 50mg/Misoprostol 200mcg TID vs. Diclofenac 75mg/Misoprostol 200mcg BID
Final Gastric Endoscopy Scores:				
Overall Distribution	0.001	0.001	0.001	0.477
Patients with an Ulcer	0.009	0.007	0.034	0.464
Patients with >10 erosions or an ulcer	0.006	0.011	0.004	0.828
Patients with any erosion or ulcer	0.000	0.000	0.000	0.690
Final Duodenal Endoscopy Scores:				
Overall Distribution	0.298	0.154	0.352	0.435
Patients with an Ulcer	0.146	0.756	0.092	0.167
Patients with >10 erosions or an ulcer	0.115	0.950	0.092	0.103
Patients with any erosion or ulcer	0.110	0.071	0.029	0.744
Final Gastroduodenal Endoscopy Scores:				
Overall Distribution	0.002	0.001	0.002	0.266
Patients with an Ulcer	0.005	0.038	0.008	0.617
Patients with >10 erosions or an ulcer	0.005	0.076	0.002	0.187
Patients with any erosion or ulcer	0.000	0.000	0.000	0.649

from sponsor's tables, NDA Vol. 1.77, pp. 8-13036, 8-13038, and 8-13040 through 8-13043

Study 349: P-Values for Sponsor's Additional Treatment Comparisons (Endoscopy Evaluable)

	Overall Treatment Comparison	Primary Pairwise Comparisons		Secondary Pairwise Comparisons
		Diclofenac 75mg BID vs. Diclofenac 50mg/Misoprostol 200mcg TID	Diclofenac 75mg BID vs. Diclofenac 75/Misoprostol 200mcg BID	Diclofenac 50mg/Misoprostol 200mcg TID vs. Diclofenac 75mg/Misoprostol 200mcg BID
Gastric Endoscopy Scores:				
Overall Distribution	0.005	0.002	0.047	0.674
Patients with an Ulcer	0.023	0.007	0.106	0.219
Patients with >10 erosions or an ulcer	0.018	0.006	0.044	0.390
Patients with any erosion or ulcer	0.000	0.000	0.001	0.347
Final Duodenal Endoscopy Scores:				
Overall Distribution	0.480	0.188	0.613	0.211
Patients with an Ulcer	0.260	0.622	0.202	0.079
Patients with >10 erosions or an ulcer	0.154	0.452	0.202	0.046
Patients with any erosion or ulcer	0.293	0.139	0.111	0.919
Final Gastroduodenal Endoscopy Scores:				
Overall Distribution	0.036	0.006	0.082	0.469
Patients with an Ulcer	0.050	0.078	0.037	0.746
Patients with >10 erosions or an ulcer	0.065	0.131	0.023	0.439
Patients with any erosion or ulcer	0.000	0.000	0.002	0.352

from sponsor's tables, NDA Vol. 1.77, pp. 8-13036, 8-13038, and 8-13040 through 8-13043

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The sponsor also examined the results by looking at changes in individual patients' endoscopy scores from baseline (improved, remained same, worsened). Results of between group comparisons for these changes were similar to the results of the between group comparisons of final endoscopy scores.

Of the 452 patients enrolled, 258 patients (57%) were aged 65 years or older. The sponsor compared ulcer rates and endoscopy score distributions among treatment groups for these elderly patients. Generally, results for these comparisons were similar to the results for the overall treatment population for both the intent-to-treat and the endoscopy evaluable populations.

Antiarthritic efficacy: The sponsor's results for the antiarthritic efficacy comparisons are summarized in the following table:

Study 349: Between Group Comparisons of Antiarthritic Efficacy Assessments (Intent-to-Treat Population)

	Primary Pairwise Comparisons			Secondary Pairwise Comparisons		
	Placebo vs. Diclofenac	Diclo50/Miso200 vs. Diclofenac 75mg	Diclo75/miso200 vs. Diclofenac 75mg	Diclo50/Miso200 vs. Placebo	Diclo75/Miso200 vs. Placebo	Diclo50/Miso200 vs. Diclo75/Miso200
Physician's Global:						
Week 2	0.009*	0.599	0.991	0.005*	0.006*	0.621
Week 6	0.076	0.609	0.380	0.029*	0.003*	0.266
Patient's Global:						
Week 2	0.035	0.531	0.469	0.030*	0.002*	0.248
Week 6	0.006*	0.336	0.504	0.013*	0.000*	0.109
Osteoarthritis Severity Index:						
Week 2	0.000*	0.385	0.461	0.000*	0.000*	0.872
Week 6	0.000*	0.518	0.637	0.000*	0.000*	0.256

* statistically significant at the 5% level using Hochberg's step-down procedure.

sponsor's tables, modified, NDA Vol. 1.77, pp. 8-13056, 8-13059, and 8-13061

Both of the Arthrotec treatments were superior to placebo in these comparisons. Diclofenac 75mg b.i.d. alone was superior to placebo in improving the Osteoarthritis Severity at Week 2 and Week 6 but only at Week 2 with regard to the Physician's Global assessment and only at Week 6 with regard to the Patient's Global assessment. For Physician's Global Assessment at Week 6, about 46% of diclofenac patients, 46% of Arthrotec I patients, 53% of Arthrotec II patients, and 32% of placebo patients had improved; only 1 Arthrotec II patient (0.6%) and 1 diclofenac patient (0.6%) had worsening of the Physician's Global over this time. The sponsor found not statistically significant differences between Arthrotec I and Arthrotec II or between either Arthrotec treatment and diclofenac alone in anti-arthritic efficacy

Evaluation of antiarthritic efficacy of Arthrotec is being addressed by FDA Division of Anti-Inflammatory Drug Products.

4. **Safety:** About 87% of patients (74/91 placebo; 135/154 diclofenac 75mg; 130/152 diclofenac 50mg/misoprostol 200mcg; 157/175 diclofenac 75mg/misoprostol 200mcg) in this study experienced adverse events at some time during the study. Adverse event rates ranged from 81% of placebo patients to 90% of diclofenac 75mg/misoprostol 200mcg patients. Events occurring at a frequency of 1% or greater in any of the treatment groups are tabulated in the listing below:

Study 349: Most Frequent Adverse Events

	Percent of Patients Reporting			
	Placebo (n=91)	Diclofenac 75mg (n=154)	Diclofenac50mg/ Misoprostol 200mcg (n=152)	Diclofenac 75mg/ Misoprostol 200mcg (n=175)
Dyspepsia	38.5	44.8	34.2	41.1
Abdominal Pain	16.5	29.2	31.6	29.1
Flatulence	8.8	12.3	20.4	24.0
Diarrhea	9.9	18.2	29.6	21.7
Nausea	7.7	9.7	13.2	14.9
Gastritis	14.3	20.1	10.5	12.0
Headache	20.9	16.2	8.6	10.3
Esophagitis	2.2	3.2	7.9	6.3
Constipation	3.3	9.7	5.3	6.3
Pain	5.5	1.3	2.6	6.3
Duodenitis	8.8	8.4	3.9	5.7
Sinusitis	2.2	1.3	1.3	5.7
Gastric Ulcer	2.2	11.7	2.6	5.1
Arthralgia	6.6	3.9	2.0	3.4
Back Pain	3.3	3.2	1.3	3.4
Dizziness	6.6	5.2	1.3	3.4
Rhinitis	5.5	4.5	7.9	2.9
Vomiting	1.1	6.5	4.6	2.9
Pharyngitis	2.2	0.6	3.3	2.9
Rash	2.2	1.9	2.0	2.3
Gastroesophageal Reflux	2.2	1.9	3.9	1.7
Pruritus	1.1	1.9	2.0	1.7
Dyspnea	2.2	0.6	1.3	1.7
SGOT Increased	0	3.2	0.7	1.7
SGPT Increased	0	3.2	0.7	1.7
Injury-Accidental	2.2	1.3	0.7	1.7
Eructation	0	0.6	0.7	1.7
Myalgia	2.2	0	0.7	1.7
Arthrosis	0	0.6	0	1.7
Duodenal Ulcer	1.1	4.5	5.3	1.1
Migraine	0	0	2.6	1.1
Anxiety	0	1.9	1.3	1.1
Bronchitis	0	1.9	1.3	1.1
Nervousness	3.3	1.9	1.3	1.1
Edema	1.1	1.3	1.3	1.1
Paresthesia	1.1	0.6	1.3	1.1
Edema, Dependent	0	0	1.3	1.1
Mouth Dry	0	0	1.3	1.1
Cramps Legs	1.1	2.6	0.7	1.1
Edema Legs	1.1	1.3	0.7	1.1
Somnolence	2.2	1.3	0.7	1.1
Upper Respiratory Tract Infection	1.1	0.6	0.7	1.1
Hypoesthesia	0	0	0.7	1.1
Fever	0	0	0.7	1.1
Tachycardia	0	1.3	0	1.1
Hypertonia	0	0.6	0	1.1
Asthenia	0	0.6	0	1.1
Bronchospasm	0	0.6	0	1.1
Epistaxis	0	0	0	1.1
Skin Disorder	0	0	0	1.1
Vaginitis*	0	0.9	1.0	0.9
Vaginal Hemorrhage*	0	0	1.0	0.9
Breast Pain, Female*	1.6	0	0	0.9

Study 349: Most Frequent Adverse Events (continued)

	Percent of Patients Reporting			
	Placebo (n=91)	Diclofenac 75mg (n=154)	Diclofenac 50mg/Misoprostol 200mcg (n=152)	Diclofenac 75mg/Misoprostol 200mcg (n=175)
Insomnia	0	1.3	2.0	0.6
Coughing	5.5	2.6	1.3	0.6
Tooth Disorder	2.2	1.3	1.3	0.6
Hypertension	1.1	1.3	1.3	0.6
Pupura	1.1	0.6	1.3	0.6
Esophageal Ulceration	0	1.9	0.7	0.6
Urinary Tract Infection	1.1	0	0.7	0.6
Chest Pain	2.2	4.5	0	0.6
Fatigue	2.2	3.9	0	0.6
Influenza-like Symptoms	0	1.9	0	0.6
Confusion	0	1.3	0	0.6
Heart Disorder	0	1.3	0	0.6
Infection, Viral	1.1	0	0	0.6
Vision Abnormal	0	1.3	0	0.6
Earache	1.1	0	0	0.6
Edema, Generalized	1.1	0	0	0.6
Appetite Increased	0	0	2.0	0
Hot Flushes	0	0	1.3	0
NPN Increased	0	1.9	0.7	0
Rash, Maculo-papular *	1.1	0	0	0
Renal Calculus	1.1	0	0	0
Abscess	1.1	0	0	0
Cholelithiasis	1.1	0	0	0
Syncope	1.1	0	0	0
Moniliasis	1.1	0	0	0
Diplopia	1.1	0	0	0
Furunculosis	1.1	0	0	0
Tongue Edema	1.1	0	0	0

* percentages are specific to females

reviewer's original table, adapted from sponsor's table, NDA Vol. 1.77, pp. 8-13075 through 8-13079

Of the 9 most frequent complaints recorded, 8 were gastrointestinal in nature. Occurrences of these events generally were similar among the treatment groups; however, complaints of flatulence, diarrhea, and nausea appeared more common in the diclofenal/misoprostol groups as compared to the placebo and diclofenac groups.

Overall, 63 patients (about 11% of patients randomized [6.6% of placebo; 13.0% of diclofenac; 9.2% of diclofenac 50mg/misoprostol 200mcg; and 13.1% of diclofenac 75mg/misoprostol 200mcg]) withdrew prematurely from the study because of adverse events. The most frequent adverse event leading to withdrawal was abdominal pain, which led to withdrawal in 31 patients (3 placebo, 12 diclofenac, 5 diclofenac 50mg/misoprostol 200mcg, and 11 diclofenac 50mg/misoprostol 200mcg). Diarrhea, nausea, dyspepsia, flatulence, and vomiting led to withdrawal of an additional 48 patients.

Incidences of withdrawal due to the various events were not significantly different among the treatment groups.

In this study there were only six events judged to be serious. All these occurred in patients in the diclofenac 75mg/misoprostol 200mcg group. Patient #89, a 73 year old white woman, suffered a spontaneous pathological fracture of the tibia on day 18 of treatments and was withdrawn from the study. Patient #567, a 49 year old white man, suffered intestinal obstruction and was withdrawn. Patient #606, a 66 year old black man, experienced moderate epigastric discomfort beginning on day 32 of treatment, nausea and vomiting on day 34 and suffered a myocardial infarction on day 35 of treatment; he was withdrawn from the study.

Of the 2012 adverse events reported in this study, most were judged to be mild or moderate in severity. Severe events were reported in 163 patients (17 placebo patients reported 34 severe events; 45 diclofenac patients reported 97 severe events; 44 diclofenac 50/misoprostol 200mcg patients reported 94 severe events; and 57 diclofenac 75mg/misoprostol 200mcg patients reported 112 severe adverse events).

Study 349: Number of Patients Experiencing Severe Adverse Events

	Severe Adverse Events		Severe Adverse Events Resulting in Study Withdrawal	
	number of patients	number of events	number of patients	number of events
Placebo	17	34	2	3
Diclofenac 75mg b.i.d.	45	97	10	21
Diclofenac 50mg/Misoprostol 200mcg t.i.d.	44	94	11	24
Diclofenac 75mg/Misoprostol 200mcg b.i.d.	57	112	17	30

reviewer's original table, based on infomation in sponsor's CANDA

Five patients were found to have esophageal ulcers at final endoscopy. Three of these patients were on diclofenac (pts #358; #607; #797), one was on diclofenac 50mg/misoprostol 200mcg (pt #596) and one was on diclofenac 75mg/misoprostol 200mcg (pt #167).

There were no deaths in this study.

For the clinical laboratory parameters there were only two statistically

significant shifts from normal to outside normal range values during the study: in the diclofenac, diclofenac 50mg/misoprostol 200mcg, and diclofenac 50mg/misoprostol 200mcg groups there was a shift from normal to high values for ALT (SGPT)($p<0.004$), and in the diclofenac alone group there was a statistically significant shift in serum creatinine from normal to high values ($p=0.008$). With regard to mean changes during the study, hematocrit decreased in all treatment groups except placebo. Small changes in the means were seen for WBC, serum creatinine, AST and ALT in some treatment groups. However, these changes were small and not clinically meaningful. These statistically significant changes are summarized in the following table:

Study 349: Statistically Significant ($p<0.05$) changes in Laboratory Measurements (final-Baseline) within Treatment Groups

	Normal Range	Mean Change* (mean baseline value-mean final value)			
		Placebo	Diclofenac75mg b.i.d	diclofenac 50mg/misoprostol 200mcg t.i.d.	diclofenac 75mg/misoprostol 200mcg b.i.d.
Alkaline phosphatase (U/L)	M&F, age M&F, age≥59	—	—	—	3.110
Hematocrit (%/100)		—	-0.011	-0.011	-0.006
White blood cell count (10*9/L)		—	-0.267	-0.243	—
Creatinine (mcmol/L)		-2.736	—	—	—
AST (SGOT) (U/L)	M, F	—	3.878	3.196	—
ALT (SGPT) (U/L)	M,<69: M,≥69: F,<69: F≥69:	—	7.838	7.318	—

* Negative values indicate decreases from baseline.

sponsor's table, modified, NDA Vol. 1.77, p. 8-13089 and Vol. 1.81, pp. 8-14843 through 8-14882

Two (1.3%) diclofenac alone patients, 2 (1.3%) diclofenac 50mg/misoprostol 200mcg patients, and 3 (1.7%) diclofenac 50mg/misoprostol 200mcg patients had AST or ALT values 3-times the upper limit of normal. In the patients on diclofenac 50mg/misoprostol 200mcg and one of the patients on diclofenac alone, values normalized over 2-6 weeks after study completion. Follow-up values were not available for the 2 patients on Diclofenac 50mg/misoprostol 200mcg and for one of the diclofenac alone

patients. Some information about these patients is summarized in the following table:

Study 349: Patients Having Liver Enzymes Elevated above 3-Times Normal Upper Limit

Pt #	Treatment	Age	Sex	Initial-Final Values	Other Info
US0005-729	Diclofenac	67	F	AST: ALT Bili:	No symptoms.
US0048-607	Diclofenac	70	M	AST ALT:	No symptoms. No concurrent meds.
US0024-275	Diclofenac 50mg/Misoprostol 200mcg	71	F	AST: ALT alk phos:	No symptoms.
US0028-320	Diclofenac 50mg/Misoprostol 200mcg	55	M	AST ALT	No symptoms. hx: asymptomatic carrier of hepatitis B; also on ciprofloxacin
US0040-508	Diclofenac 75mg/Misoprostol 200mcg	72	M	AST ALT:	No symptoms. (event coded as hepatitis)
US0040-510	Diclofenac 75mg/Misoprostol 200mcg	60	F	AST ALT	No related symptoms.
US0049-620	Diclofenac 75mg/Misoprostol 200mcg	68	F	AST ALT bili alk phos	Hx hepatitis, 1966. Several episodes of abdominal pain during study

reviewer's original table, based on inforamtion in NDA Vol. 1.77, pp. 8-13090 through 8-13093 and sponsor's CANDA

This incidence of elevated liver enzymes is in keeping with the adverse hepatic reactions described in the labeling for diclofenac. Misoprostol in this study did not appear to contribute an additional risk.

M. **Reviewer's Comments:** In this study, patients treated with diclofenac 50mg/misoprostol 200mcg t.i.d. showed lower rates of gastric ulcer than did those treated with Diclofenac 75mg b.i.d. alone (2.6% vs. 9.7%; p=0.016). Also, the diclofenac 75mg/misoprostol 200mcg b.i.d. group appeared to show a lower gastric ulcer rate than did the diclofenac alone group (4.0% vs. 9.7%; p=0.035); however, this difference was not statistically significant when multiple comparisons (diclofenac 50mg/misoprostol 200mcg vs. diclofenac 75mg, diclofenac 75mg/misoprostol 200mcg vs. diclofenac 75mg, and diclofenac 75mg/misoprostol 200mcg vs. diclofenac 50mg/misoprostol 200mcg) are taken into account. There was no statistically significant difference between diclofenac 75mg/misoprostol 200 mcg b.i.d. and

diclofenac 50mg/misoprostol 200mcg t.i.d. in gastric ulcer rates.

For prevention of duodenal ulcer neither of the two diclofenac/misoprostol combinations was demonstrated to be effective in this study, though there was a trend in favor of diclofenac 75mg/misoprostol 200mcg b.i.d. being effective in this regard (p=0.060). Duodenal ulcer (including pyloric channel) rates in the three groups were: diclofenac 75mg b.i.d. alone, 7.1%; diclofenac 50mg/misoprostol 200mcg t.i.d., 5.3%; and diclofenac 75mg/misoprostol 200mcg b.i.d., 2.3%).

The safety profile for the diclofenac/misoprostol combinations as compared to placebo in this study showed a higher incidence of gastrointestinal-type complaints such as abdominal pain, diarrhea, and flatulence. However, rate of abdominal pain with the diclofenac/misoprostol combinations was comparable to that with misoprostol alone; the rates of diarrhea and flatulence were greater and the rate of gastritis lower with the diclofenac/misoprostol combination as compared to with diclofenac alone.

Rates of withdrawal due to adverse events were comparable among the groups receiving diclofenac (diclofenac alone, 13.0%; diclofenac 50mg/misoprostol 200mcg t..i.d., 9.2%; diclofenac 75mg/misoprostol 200mcg b.i.d., 13.1%). The adverse event withdrawal rate for placebo patients was 6.6%.

In conclusion, this study strongly supports efficacy of diclofenac 50mg/misoprotol 200mcg t.i.d. in preventing gastric ulcer in these osteoarthritis patients. Also, it suggests efficacy of diclofenac 75mg/misoprostol 200mcg b.i.d. in preventing gastric ulcers. No clear dose response relationship was seen for gastric ulcer prevention the misoprostol component of the combination in this study. This study does not provide substantial support for diclofenac/misoprostol combination in the prevention of duodenal ulcers.

II. **Protocol: IN2-89-02-296:** A Comparison of the Efficacy and Upper Gastrointestinal Safety of a Fixed Combination of Misoprostol/Diclofenac Versus Diclofenac Alone in Treating the Signs and Symptoms of Osteoarthritis (NDA Vol. 1.73, p. 8-11319 through 1.74, p. 8-12044)

A. **Investigators:** This study was carried out from June 23, 1989 to June 5, 1990 at 32 sites in 11 countries. [Note: Fifty-two investigators in 12 countries were recruited, but some did not enroll any patients]. Principal investigators who enrolled patients are listed below:

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from sponsor's table, NDA Vol. 1.73, pp. 8-11529 through 8-11537

B. **Objectives:** The objectives of this study were: (1)to compare the upper gastrointestinal mucosal damage associated with diclofenac 50mg/misoprostol 200mcg combination tablet as compared to diclofenac 50mg alone; and (2)to compare the efficacy of these two drugs in treating the signs and symptoms of osteoarthritis.

C. **Design:** This was a multicenter, multinational, randomized, parallel group study of diclofenac 50mg/misoprostol 200mcg combination versus diclofenac 50mg alone when taken b.i.d. or t.i.d. for 4 weeks. The dosage regimen (b.i.d. or t.i.d.) was decided by the investigator, based on the patient's arthritic condition. The regimen (b.i.d. or t.i.d.) could be changed during the study. There was no placebo group.

D. **Subjects:** These were to be 400 patients (200 patients per treatment group) of the legal age of consent having osteoarthritis of the hip and/or knee of at least 3 months duration, a Functional Capacity Classification of I-III, and requiring continuous NSAID therapy for the duration of the study. Criteria for

diagnosis of osteoarthritis and scales for Functional Capacity Classification, were the same as for Study 349 (described under I.D. and I.F. above). There was no requirement for a prior history of gastrointestinal ulcer or erosive disease and the patients' osteoarthritis was not required to be in a 'flare' state. Exclusion criteria were essentially the same as for Study 349, with the following additional exclusions: history of substance abuse; use of antaineoplastics, gold salts, penicillamine, antimalarials or colchicine withiin 30 days of study. Use of all antiulcer drugs (including antacids) is excluded during the study. Also, the sponsor stipulated that patients having any rheumatic disease, psoriasis, acute joint trauma at the site of osteoarthritis, any musculoskeletal disorder of the lumbosacral area, syphilitic neurotpathy, ochronosis, or metabolic bone disease are excluded from participation.

E. **Study Drugs:** Patients were randomized to either diclofenac 50mg or diclofenac 50mg/misoprostol 200mcg combination. Treatment assignment was randomized using a computer generated randomization scheme. Study drugs were:

- Diclofenac 50mg/misoprostol 200mg tablets - These were plain white tablets having an organic-based enteric coating. [The formulation the sponsor intends to market is an aqueous-based enteric coated tablet].

- Diclofenac 50mg tablets - These consisted of identical plain white tablets having placebo in a fixed combination with 50mg diclofenac sodium.

Each patient received two bottles each containing 60 tablets of study medication. One bottle was given at study admission and the second bottle was given at the 2-week visit.

F. **Study Plan:** Within 7 days prior to beginning study medication patients were to have physical examination, medical history taken, clinical laboratory testing, arthritis assessment and endoscopic examination.

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.

Arthritis assessment consisted of: (a) the Physician's Assessment of Arthritic Condintion (which included Osteoarthritis Severity Index, Articular Index of Joint Tenderness [grading of pain on motion or tenderness in 48 joints], and Physician's Global Assessment of Arthritic Condition); and (b) the Patient's Assessment of Arthritic Condition (which included Patient's Assessment of Joint Pain and Patient's Global Assessment of Arthritic Condition).

Qualified patients were randomized to diclofenac 50mg/misoprostol 200mcg or diclofenac 50mg. The dosing regimen for each patient was set individually by the investigator as b.i.d. or t.i.d. based upon the patient's arthritic condition. Patients on a b.i.d. regimen were to take the study medication with breakfast and with the evening meal. Patients on a t.i.d. regimen were to take the study medication with breakfast, lunch and the evening meal.

The sponsor's schedule for study events is shown below:

Study 296: Schedule of Observations and Procedures

	Pretreatment Period	Day 0	Treatment Period*	
	Week 0		Week 2	Week 4 (or Final Visit)
Medical History	X			
Physical Examination	X			X
Concurrent Medication	X		X	X
Symptoms	X		X	X
Clinical laboratory tests	X			X
Arthritis assessment	X		X	X
Endoscopic examination	X			X
Study medication dispensing		X	X	

* Week 2 visit is 14 $\pm$ 2 days; Week 4 visit is 28$\pm$2 days

sponsor's table, NDA Vol. 1.73, p. 8-11431

G. **Compliance:** Compliance was assessed by pill counts at followup visits.

H. **Monitioring of Adverse Events:** Adverse events were to be recorded and asssessed as to severity, seriousness, outcome and any intervention. Physical examination and clinical laboratory tests were to be repeated at study completion.

I. **Efficacy Parameters:** The principal measures for evaluating mucosal damage were the gastric and duodenal endoscopic scores in each patient prior to and after study.

For antiarthritic efficacy the principal measures for efficacy were: (1) osteoarthritis severity index, (2) physician's global assessment of arthritic condition, and (3) patient's global assessment of arthritic condition.

J. **Statistical Methods:** Assuming an ulcer rate of 15% in the diclofenac group, the sponsor estimated that the sample size of 200 patients per treatment arm would be adequate to discriminate an ulcer rate of 5% in the combination product group with a power of 0.9. For arthritis symptoms, the sponsor estimated the sample size would be adequate to detect a significant treatment difference if the combination produce is less than 80% as effective as diclofenac alone with a power of 0.9. (All tests 2-sided).

K. **Amendments:** There was one amendment to this protocol dated 1/8/90. This amendment incorporated changes requested by the Australian Department of Health that patients with moderate to severe heart failure of significant coagulation defect be excluded froom study participation and that patients on continuous NSAIDs (including aspirin) be excluded and specifying that, in addition to already prohibited medications, patients not use lithium, digoxin, or cyclosporin while on study.

L. **Results:**

1. **Enrollment and Baseline Characteristics of Patients**: A total of 361 patients were randomized and took study medication. (One patient was randomized but was withdrawn prior to taking any study medication). The enrollment of patients by center is shown in the table below:

Study 296: Enrollment of Patients by Center

Investigator No.	Investigator	Diclofenac 50mg/Placebo BID-TID	Diclofenac 50mg/Misoprostol 200mcg BID-TID	Total
XI3043	Ahmad	3	3	6
XI1922	Appelboom	2	1	3
XI1371	Arvanitakis	1	1	2
XI2025	Bolten	3	3	6
XI2883	Bombardier	0	1	1
XI2768	Bouchez	3	4	7
XI3220	Chapman	2	1	3
XI1254	Cohen	2	3	5
XI2018	De Buisseret	1	1	2
XI2721	Docquier	1	0	1
XI2949	Gartner	1	2	3
XI2725	Hemmer	2	2	4
XI3049	Hercules	6	4	10
XI3048	Hernandez	9	11	20
XI3046	Karras	5	6	11
XI2953	Kirchhoff	6	2	8
XI3102	Maleitzke	6	6	12
XI2783	Mello Gomes	30	30	60
XI3064	Mills	3	6	9
XI2885	Nagant de Deuxchaisnes	1	0	1
XI3127	Newman	54	53	107
XI3119	Pattin	2	1	3
XI2887	Pena	6	4	10
XI2028	Raeman	1	2	3
XI2956	Rassi	12	12	24
XI2888	Saenz	9	8	17
XI2814	Schreiber	2	2	4
XI3116	Sebert	1	0	1
XI2940	Stasse	3	3	6
XI2823	Tremblay	2	2	4
XI2775	Verdickt	4	3	7
XI1470	Yeomans	0	1	1
	Total	183	178	361

sponsor's table modified, NDA Vol. 1.73, p. 8-11359

Although 32 centers enrolled patients in this study, 46% of patients came from 2 centers (Newman and Mello Gomes).

Study 296: Demographic and Baseline Characteristics of the Study Population

	Diclofenac 50mg/Placebo b.i.d.-t.i.d. (n=183)	Diclofenac 50mg/ Misoprostol 200mcg b.i.d.-t.i.d. (n=178)
Age (years)		
mean	61.3	59.2
median	60.0	58.0
range		
Race (%)		
White/Black/Oriental/Other	87/3/1/9	89/3/0/8
Gender (%)		
male	30	24
female	70	76
Disease Duration (% of patients)%:		
0-0.9 year	6	4
1-4.9 years	37	38
5- 9.9 years	23	29
10-14.9 years	20	17
≥15 years	15	12
Baseline Endoscopy Findings, gastric/duodenal (%):		
normal (score = 0)	67/84	68/87
petechiae only (score = 1 or 2)	14/8	10/7
1-10 erosions (score = 3 or 4)	18/8	20/4
>10 erosions (score = 5 or 6)	0/0	0/0
Ulcer (score = 7)	0/0	1/1
Unknown	1/1	1/1
Baseline Osteoarthritis Severity Index:		
mean	11.20	11.15
Initial Dosing Regimen:		
b.i.d.	132 (72.1%)	129 (72.5%)
t.i.d.	51 (27.9%)	49 (27.5%)
Dosing Regimen Changed During Study (number of patients)	18	22

* There was 1 patient with a score of 5.

from sponsor's tables, NDA Vol. 1.73, pp. 8-11365, 8-11368 through 8-11369, 8-11371, 8-11539 through 8-11552

The treatment groups were well-matched for demographic features. The average age of patients was about 60 years. About three-fourths of patients were females. Most patients had had osteoarthritis for 1-

10 years and baseline endoscopy findings in most patients were normal. The sponsor did find a statistically significant difference between groups in weight on study admission. Mean weight of the diclofenac/placebo patients was 73.8kg and of the diclofenac/misoprostol patients was 70.4kg ($p=0.004$). This difference is not likely to be clinically meaningful. About 3/4 of the patients in both treatment groups were assigned to a b.i.d. regimen on study admission.

Baseline gastric endoscopy scores were not available for 2 diclofenac patients and 2 diclofenac/misoprostol patients. And baseline duodenal endoscopy scores were not available for 2 diclofenac patients and 1 diclofenac/misoprostol patient.

Most patients in both treatment groups were assigned to a b.i.d. regimen at the beginning of the treatment and remained on that regimen throughout the study. However, 18 (9.8%) of diclofenac/placebo patients had the regimen changed during the study (17 patients were changed from b.i.d. to t.i.d. and 1 patient was changed from t.i.d. to b.i.d.). Similarly, for diclofenac/misoprostol patients, 22 (12.4%) of the patients had the regimen changed (18 from b.i.d. to t.i.d. and 4 from t.i.d. to b.i.d.). Compliance rates did not differ significantly between the treatment groups.

2. Disposition of Patients: Of the 361 patients enrolled 323 patients (164 diclofenac/placebo and 159 diclofenac/misoprostol) completed the study. Reasons for premature discontinuation of the 38 patients who failed to complete are summarized in the table below:

Study 296: Reasons for Termination of Study Participation

Reason	Number of Patients					
	Diclofenac 50mg/Placebo b.i.d.-t.i.d.			Diclofenac 50mg/Misoprostol 200mcg b.i.d.-t.i.d.		
	Final Endo Done	Final Endo Not Done	Total	Final Endo Done	Final Endo Not Done	Total
Enrolled	167	16	183	162	16	178
Completed	164	0	164	159	0	159
Discontinued:						
Lost-to-followup	0	5[a]	5	0	6[b]	6
Protocol Noncompliance	0	3	3	0	3	3
Pre-existing Violation	0	0	0	0	0	0
Treatment Failure	0	0	0	0	0	0
Adverse event	3[c]	8	11	3	7	10

[a] Two of these patients had neither initial nor final endoscopy; [b] One of these patients had neither initial nor final endoscopy; [c] One patient had a gastric ulcer on final endocscopy

reviewer's original table, based on datasets from sponsor's CANDA submission and NDA Vol. 1.73, pp. 8-12295 through 8-12319

Thirty-eight patients withdrew prior to study completion; 21 of these

withdrew because of adverse events. Adverse events leading to withdrawal included abdominal pain in 2 diclofenac/placebo patients and 6 diclofenac/misoprostol patients, diarrhea in 1 diclofenac/placebo patient and 3 diclofenac/misoprostol patients, dyspepsia in 1 diclofenac/placebo patient and 1 diclofenac/misoprostol patient and nausea in 1 diclofenac/placebo patient and 1 diclofenac/misoprostol patient. Other events leading to withdrawal of only one patient were chest pain, constipation, dizziness and abnormal thinking, hemorrhagic gastric ulcer, flu symptoms, and eructation in the diclofenac/placebo group and anxiety, rash, face edema, and malaise in the diclofenac/misoprostol group.

One patient in the diclofenac/misoprostol group (#XI2949-0238), a 71 year old white woman, was found to to have gastric cancer. She was classified as withdrawn due to a protocol violation. Also, two patients who had ulcers at initial endoscopy (patient #XI3046-6909, who had 3 gastric ulcers and 1 duodenal ulcer and patient #XI3127-593, who had a duodenal ulcer at initial endoscopy) were nevertheless entered into the study; both were randomized to diclofenac/misoprostol and both patients completed the study and no ulcers were seen on final endoscopy.

3. **Efficacy Analysis**: Final endoscopy results are summarized in the table below:

Study 296: Final Gastric and Duodenal Endoscopy Results

	Diclofenac 50mg/Placebo b.i.d.-t.i.d. (n = 183)	Diclofenac 50 ~~75mg~~/Misoprostol 200mcg b.i.d.-t.i.d. (n = 178)
Number of Patients having final endoscopy (gastric/duodenal*):	167/167	162/161
Final Endoscopy Findings, gastric/duodenal* (% of endoscoped):		
normal (score = 0)	61/84	72/91
petechiae only (score = 1 or 2)	14/9	14/5
1-10 erosions (score = 3 or 4)	22/5	12/4
>10 erosions (score = 5 or 6)	1/0	2/0
Ulcer (score = 7)	2/2	0/0
Total	100/100	100/100

* pyloric channel ulcers are grouped with the duodenal ulcers

reviewer's original table, based on data in sponsor's tables, NDA Vol. 1.73, pp. 8-11374 and 8-11376

Appearance of the duodenal mucosa was normal in about of endoscoped patients in both treatment groups was normal. The gastric mucosa appeared normal in of patients. The overall distribution of gastric endoscopy scores or of duodenal endoscopy scores did not differ significantly between treatment groups (p-values = 0.086 and 0.099, respectively).

The following table summarizes the ulcer occurrence rates for the various treatment groups. In this intent-to-treat analysis patients who have missing data (i.e., who did not have followup endoscopy) are assumed to have no ulcers.

Study 296: Ulcer Rates in the Various Treatment Groups (Intent-to-Treat Analysis)

	Number of Patients (%)	
	Diclofenac 50mg/Placebo b.i.d.-t.i.d. (n = 183)	Diclofenac 50mg/Misoprostol 200mcg b.i.d.-t.i.d. (n = 178)
Gastric Ulcer	3 (2%)	0 (0%)
Duodenal Ulcer	3 (2%)	0 (0%)
Pyloric Channel Ulcer	0 (0%)	0 (0%)
Unknown	16 (8.7%)	16 (9.0%)

reviewer's original table, based on information in sponsor's CANDA submission and NDA Vol. 1.75 pp. 8-12320 through 8-12376

By the sponsor's analysis, the difference in ulcer frequencies between the two treatment groups was not statistically significant for either gastric ulcer (p = 0.087) or duodenal ulcer (p = 0.088). The impact of the missing endoscopy results on the outcome was not assessed.

4. **Safety**: In this study, 56.3% of diclofenac/placebo patients and 67.4% of diclofenac/misoprostol patients reported adverse events. The most frequent adverse events in this study are shown in the table below:

Study 296: Most Frequent Adverse Events

Event	Number of Patients (%)	
	Diclofenac 50mg/Placebo b.i.d.-t.i.d.	Diclofenac 50mg/Misoprostol 200mcg b.i.d.-t.i.d.
Abdominal pain	34 (18.6%)	57 (32.0%)
Diarrhea	22 (12.0%)	32 (18.0%)
Nausea	2 (1.1%)	19 (10.7%)
Dyspepsia	8 (4.4%)	16 (9.0%)
Flatulence	6 (3.3%)	16 (9.0%)
Gastritis	32 (17.5%)	13 (7.3%)
Headache	20 (10.9%)	12 (6.7%)

From sponsor's table, NDA Vol. 1.73, p. 8-11397 and 8-11398

There were no deaths during this study; however, one patient, a 69 year old woman randomized to diclofenac/placebo was admitted to hospital with dizziness and a hemoglobin of 5.9g/dl but no other complaints 14 days after starting study medication. Endoscopy revealed several gastric ulcers with evidence of recent bleeding. The patient was discontinued from the study, received blood transfusion and subsequently was treated with misoprostol. It is not clear whether the study blind was broken for this patient during this episode. Eleven diclofenac/placebo patients and 10 diclofenac/misoprostol patients were discontinued from this study due to adverse events (mainly abdominal pain, diarrhea, dyspepsia, nausea).

One patient #XI2949-238, a 71 year old woman randomized to diclofenac/misoprostol, was discontinued from the study after 15 days of treatment because of gastric carcinoma diagnosed from the pretreatment biopsy. Only a gastric erosion was noted on initial endoscopy. The sponsor classified this patient as withdrawn due to protocol violation.

Also, three female patients all on diclofenac/misoprostol experienced episodes of vaginal bleeding judged to be related to the study medication.

With regard to laboratory values, there was a slight decrease in hemoglobin and a slight increase in SGOT and SGPT in both treatment groups over the course of the study. There was also a slight decrease in hematocrit, platelet count and a slight increase in alkaline phosphatase in the diclofenac/misoprostol group and a slight decrease in WBC and serum creatinine in the diclofenac/placebo group. There were no statistically significant differences in numbers of patients having shifts in any laboratory values from normal range to increased or decreased values. These differences were not considered clinically

meaningful.

M. **Reviewer's Comments:** In this study, the gastric ulcer and duodenal ulcer rates in osteoarthritis patients treated with diclofenac 50mg/misoprostol 200mcg b.i.d.-t.i.d. were not demonstrated to be different from those rates in patients treated with diclofenac 50mg b.i.d.-t.i.d. alone. The fact that dosing regimen (b.i.d. or t.i.d.) was not randomized compromises the interpretation of the efficacy results. This study does not provide support for efficacy of diclofenac/misoprostol fixed combination for prevention of NSAID-induced gastric ulcers or duodenal ulcers.

The safety of the diclofenac/misoprostol combination was comparable to that in other trials. The types and frequency of adverse events were in keeping with the labeling of misoprostol and diclofenac. Generally both treatments were well-tolerated in this study.

III. **Protocol: IN2-90-02-321:** A Comparative Efficacy and Upper Gastrointestinal Safety Study of a Fixed Combination of Diclofenac 50mg/Misoprostol 200mcg Versus Piroxicam 10mg or Naproxen 375mg BID in Treating the Signs and Symptoms of Osteoarthritis (NDA Vol. 1.75, p. 8-12045 through 1.76, p. 8-12961)

A. **Investigators:** This study was carried out from June 14, 1991 to April 10, 1992 at 51 sites in 13 countries.

B. **Objectives:** The objectives of this study were: (1) To compare endoscopically the upper gastrointestinal mucosal damage associated with a fixed combination of diclofenac/misoprostol with that associated with piroxicam or naproxen; (2) To compare the antiarthritic efficacy of a diclofenac/misoprostol fixed combination versus piroxicam or naproxen in treating the signs and symptoms of osteoarthritis as determined by global assessments of arthritic condition, arthritis pain assessments, and assessments of functional capacity. Safety of naproxen, prioxicam, and diclofenac/misoprostol combination also were to be assessed.

C. **Design:** This was a multinational, randomized, double-blind, placebo-control, parallel group comparison of 3 antiarthritic treatments (piroxicam 10mg b.i.d., naproxen 375mg b.i.d. and diclofenac 50mg/misoprostol 200mcg b.i.d.) given for 4 weeks.

D. **Subjects:** These were to be 600 males or females (200 patients per treatment group) of the legal age of consent having osteoarthritis of the hip and/or knee of at least 3 months duration, a Functional Capacity Classification of I-III, and Physician and Patient Global Assessment of Arthritic Condition classifications of "fair", "poor" or "very poor" and requiring continuous NSAID therapy for the duration of the study. Criteria for diagnosis of

osteoarthritis, scales for Functional Capacity Classification, and scales for Physician and Patient Global Assessment of Arthritic Condition were the same as for Study 349 (described under **I.D.** and **I.F.** above). Patients must have been experiencing joint pain at time of study entry.

There was no requirement for a prior history of gastrointestinal ulcer or erosive disease.

Exclusion criteria were essentially the same as for Study 349, with the following additional exclusions: history of substance abuse; use of antineoplastics, gold salts, penicillamine, antimalarials or colchicine withiin 30 days of study. Patients were not to have used NSAIDs within 10 days or any analgesic (other than acetaminophen) within 2 days of initial arthritis assessments.

E. **Study Drugs:** Patients were randomized to receive placebo b.i.d., diclofenac 50mg/misoprostol 200mcg combination b.i.d., prioxicam 10mg b.i.d., or naproxen 375mg b.i.d. Because naproxen was given as a capsule and diclofenac/misoprostol as a tablet, a double-dummy technique was used to preserve the blinding. Each patient received 1 capsule and 1 tablet two times each day.

Study drugs used in this trial were:

- diclofenac/misoprostol tablets
  diclofenac sodium 50mg and misoprostol 200mcg,
- placebo tablets -
- piroxicam
- naproxen -
- placebo capsules

F. **Study Plan:** Patients each had a complete medical history (including arthritis history) taken and physical examination, assessment of functional capacity and endoscopy done, within 7 days prior to administration of the first dose of study medication.

Physician's Assessments of Arthritic Condition (Osteoarthritis Severity Index and Physician's Global Assessment of Arthritic Condition and Functional Capacity Classification) were done essentially as in Study 349. For the Patient's Assessment of Arthritic Condition, Patient's Global Assessment of

Arthritic Condition was done as in Study 349 but for Patient's Assessment of Joint Pain, a categorical scale (1 = no joint pain; 2 = pain following rest, or morning stiffness; 3 = pain following exercise; 4 = pain during non-weight bearing movement; 5 = pain at rest, during the night, or continuous pain) was used rather than the visual analogue scale used in Study 349.

Patients were to have endoscopy within 7 days prior to first dose of study medication. In this study the definition for an erosion was the same as in Study 349 (i.e., any break in the mucosa without depth), but the definition for ulcer was slightly different. In Study 321, an ulcer was defined as "any lesion with unequivocal depth" while in Study 349 ulcer was defined as "any break in the mucosa at least 3 mm in diameter with unequivocal depth".

Clinical laboratory studies were the same as for Study 349 except that urine pregnancy test was acceptable in this study to rule out pregnancy.

Treatment with study drug was for 4 weeks. Patients were to visit clinic for followup at 2 weeks [14 (±2) days] and at Week 4 [28 (±2) days] from the first day of study medication. The schedule of study procedures is shown below:

Study 321: Schedule of Observations and Procedures

	Pretreatment Period	Day 0	Treatment Period	
	Screening (Days -7 - 0)		Week 2 (+2 days)	Week 4 (+2 days)
Medical History	X			
Physical Examination	X			X
Concurrent Medication	X		X	X
Adverse Signs and Symptoms	X		X	X
Clinical Laboratory Tests	X			X
Arthritis Assessment	X		X	X
Endoscopic Examination	X			X
Study Medication Dispensing		X	X	

sponsor's table, modified, NDA Vol. 1.75, p. 8-12160

Use of medications other than study drug was to be recorded on the patient case report forms. Use of the following medications during the study was specifically excluded: antineoplastics, corticosteroids (including intra-articular injections), gold salts, penicillamine, antimalarials, colchicine, lithium, cyclosporin, digoxin, antiulcer drugs (including antacid), NSAIDs (including aspirin) and analgesics (other than acetaminophen).

Patients were to record concurrent medications and adverse events on diary cards which were to be reviewed with the investigator at each study visit.

Unlike Study 349, no provision was made for patients to have access to antacid for relief of gastrointestinal pain during the study.

G. **Compliance:** Compliance was to be assessed by pill counts at each clinic visit. With regard to study medication compliance, a patient was to be considered evaluable if overall at least 70% of the prescribed doses were taken and if patient had not missed all study medication on more than 2 consecutive days during the 2-week treatment period prior to the final endoscopy.

H. **Monitoring of Adverse Events:** Patients were to record adverse events on diary cards and were to be reviewed with the investigator. Events were to be graded for severity, seriousness and outcome.

I. **Efficacy Parameters:** The primary efficacy criterion for assessment of mucosal damage was to be gastric and duodenal endoscopic score at Week 4 as compared to at baseline. Pyloric channel ulcers were to be counted with duodenal ulcers.

For assessing efficacy for treatment of osteoarthritis, the primary parameters were Osteoarthritis Severity Index, Physician's Global Assessment of Arthritic Condition, and Patient's Global Assessment of Arthritic Condition.

Primary analyses were to be done for the intent-to-treat population (all patients treated) for the Week 4 outcome.

J. **Statistical Methods:** Sample size of 200 patients per treatment group was chosen to be sufficient to detect a difference of 20% with 90% power in patients worsening on treatment between diclofenac/misoprostol and the other treatments assuming that 80% of the piroxicam and naproxen patients did not worsen during treatment. Also, assuming that 15% of patients on piroxicam or naproxen developed ulcers during study, the sample size was estimated to be sufficient to detect a between group treatment difference with 90% power if the diclofenac/misoprostol ulcer rate was 3.8% or less.

The principal efficacy analyses were to compare efficacy parameters at beginning of study to those at study completion. For assessment of mucosal damage comparisons were to be made using log-linear analysis with investigator, treatment and outcome (presence or absence of ulcer) as factors. The analysis was to be repeated using mucosal grade of 5 or above versus mucosal grade of less than 5 as outcome measure.

For determination of efficacy in treatment of osteoarthritis, primary analyses were to consist of log-lionear analyses with investigator, treatment, and outcome as

factors for the osteoarthritis severity index, physician's global assessment, and patient's global assessment using the Week 4 outcomes. Also, changes from baseline to Week 2 would be determined. Changes in the Osteoarthritis Severity Index from baseline to Week 2, Week 4, and final visit were to be compared for the three treatments using Kruskal-Wallis test. Secondary measures of efficacy (i.e. Functional Capacity Classification and Patient's Assessment of Joint Pain were to be assessed using non-parametric methods.

Clinical laboratory tests were to be reviewed and tabulated and abnormal values identified. Adverse events were to be tabulated.

All statistical tests were to be done at the 5% level of significance (two-tailed). No mention was made of adjustment for multiple comparisons.

K. **Amendments:** The protocol was amended twice. Amendment I (3/8/91) applied to the Australian centers only and provided that patients having malignancy of any type or moderate to severe cardiac failure were to be excluded from study participation. Amendment 2 (5/6/91) stipulated that patients who had taken any NSAIDs (including aspirin) within 10 days, or any analgesic [other than acetaminophen (paracetamol) within 2 days, prior to the initial arthritis assessments. Both amendments were made prior to enrollment of any patients.

L. **Results:**

1. Enrollment and Baseline Characteristics of Patients: A total of 644 patients were enrolled in this study. One patient was withdrawn prematurely from the study due to pneumonia and the patient's records were stolen. The enrollment of patients by center is summarized in the following table:

Study 321: Patient Enrollment by Center

Center	Investigator	Diclofenac/Misoprostol	Piroxicam	Naproxen	Total
AU0066	Zilko	1	0	0	1
AU0067	Smallwood	1	2	2	5
AU0068	Yeomans	1	1	0	2
BE0012	Francx	1	1	0	2
BE0013	Verdickt	3	4	3	10
BE0016	Janssens	1	2	0	3
BE0017	Bouchez	1	0	1	2
BR0020	Chahade	8	8	8	24
BR0021	Cossermelli	8	8	8	24
BR0022	Lederman	8	8	8	24
CA0032	Mathieu	3	3	3	9
CA0033	Ahmad	1	2	2	5
CA0034	Arneja	1	1	2	4
CA0036	Dunne	2	2	3	7
CA0037	Ganguli	1	2	2	5
CA0038	Larkai	2	0	1	3
CA0040	Morelli	0	1	0	1
FR0058	Lecureuil	1	2	0	3
FR0060	Tauveron	0	0	1	1
FR0061	Neveur	1	0	0	1
FR0062	Glowinski	0	0	1	1
FR0063	Brousson	0	1	0	1
GE0026	Bolten	2	1	2	5
GE0027	Rassi	6	6	6	18
GE0028	Zeeh	6	6	6	18
GE0029	Gromnica-Ihle	1	0	0	1
GE0044	Storck	3	3	2	8
GE0045	Maleitzke	3	2	3	8
ME0023	Marban-Arcos	20	20	20	60
NE0019	Bruyn	6	6	4	16
PO0030	Porto	10	10	10	30
PO0031	Melo Gomes	20	20	20	60
PO0046	Ribeiro da Silva	9	10	10	29
SW0050	Lindeberg	1	0	1	2
SW0051	Nerman	1	0	0	1
SW0052	Norlin	1	0	0	1
UK0065	MCKenna	3	3	2	8
US0001	Appelrouth	5	5	5	15
US0002	Baetti	0	2	1	3
US0003	Cheatum	0	1	0	1
US0004	Ettlinger	7	7	6	20
US0005	Karr	2	3	2	7
US0006	Makarowski	3	4	4	11
US0007	Mcadam	3	4	3	10
US0008	Roth	16	17	16	49
US0009	Tindall	4	3	4	11
US0010	Toth	7	7	7	21
US0011	Zelman	4	2	3	9
US0047	Halla	2	2	2	6
VZ0024	Hernandez	16	15	16	47
VZ0025	Herrera	10	10	10	30
Total		216	217	210	643

sponsor's table, NDA Vol. 1.75, pp. 8-12083 through 8-12084

Demographic features of the randomized patients are summarized in the following table:

Study 321: Demographic and Baseline Characteristics of the Study Population

	Diclofenac 50mg/ Misoprostol 200mcg b.i.d. (n=216)	Piroxicam 10mg b.i.d. (n=217)	Naproxen 375mg b.i.d. (n=210)
Age (years)			
mean	60.7	58.7	59.5
median	61.5	59.0	61.0
range			
Race (%)			
White/Black/Oriental/Other	82/8/0/10	79/10/1/10	80/10/0/10
Gender (%)			
male	24	25	23
female	76	75	77
Disease Duration (% of patients)%:			
0-0.9 year	6	8	4
1-4.9 years	33	43	38
5- 9.9 years	32	20	28
10-14.9 years	18	15	14
≥15 years	11	14	15
Baseline Endoscopy Findings, gastric/duodenal (%):			
normal (score = 0)	67/94	65/88	70/93
petechiae only (score = 1 or 2)	7/2	8/4	6/3
1-10 erosions (score = 3 or 4)	26/4	27/9	23/4
>10 erosions (score = 5 or 6)	0/0	0/0	0*/0
Ulcer (score = 7)	0/0	0/0	0/0
Baseline Osteoarthritis Severity Index:			
mean	11.93	11.0	11.51

* There was 1 patient with a score of 5.

from sponsor's tables, NDA Vol. 1.75, pp. 8-12091, 8-12093, and 8-12094

The treatment groups were well-matched for demographic and baseline features. The average age of patients was about 60 years. About three-fourths of patients were females. Most patients had had osteoarthritis for and baseline endoscopy findings in most were normal.

2. **Disposition of Patients**: Of the 643 patients enrolled, 65 patients (23 diclofenac/misoprostol, 17 piroxicam, and 25 naproxen) were withdrawn from the study prior to completion. Reasons for premature withdrawal are summarized below:

Study 321: Reasons for Termination of Study Participation

Reason	Number of Patients								
	Diclofenac 50mg/Misoprostol 200mcg b.i.d.			Piroxicam 10 mg b.i.d.			Naproxen 375mg b.i.d.		
	Final Endo Done	Final Endo Not Done	Total	Final Endo Done	Final Endo Not Done	Total	Final Endo Done	Final Endo Not Done	Total
Enrolled	200	16	216	204	13	217	198	12	216
Completed	193	0	193	200	0	200	185	0	185
Discontinued:									
Lost-to-followup	0	0	0	0	4	4	0	1	1
Protocol Noncompliance	0	5	5	0	3	3	0	4	4
Pre-existing Violation	0	0	0	0	0	0	0	0	0
Treatment Failure	0	0	0	0	0	0	0	0	0
Adverse event	7	11	18	4*	6	10	13	7	20

* One piroxicam patient had a gastric ulcer at study withdrawal (treatment day 17)

reviewer's original table, based on datasets froms sponsor's CANDA submission and NDA Vol. 1.75, pp. 8-12295 through 8-12319

Sixty-five patients withdrew priror to study completion; forty-eight of these patients withdrew because of adverse events. For patients who withdrew prematurely the mean time on study medication was 13.7 days for the diclofenac/misoprostol group (median, 10 days; range for the piroxicam group the mean was 8.8 days (median, 7 range); for the naproxen group the mean was 12.9 days (median, 9 days; range

One piroxicam patient (#919) who withdrew prematurely because of an adverse event had a gastric ulcer on at study withdrawal (treatment day 17). No other patients who withdrew prematurely and had final endoscopy were found to have ulcers.

3. **Efficacy Analysis**: Final endoscopy results are summarized in the table below:

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Study 321: Final Gastric and Duodenal Endoscopy Results

	Diclofenac 75mg/Misoprostol 200mcg b.i.d. (n=216)	Piroxicam 10mg b.i.d. (n=217)	Naproxen (n=210)
Number of Patients having final endoscopy (gastric/duodenal*):	200/200	204/204	198/198
Final Endoscopy Findings, gastric/duodenal* (% of endoscoped):			
normal (score=0)	78/91	55/85	37/80
petechiae only (score=1 or 2)	9/4	8/1	11/4
1-10 erosions (score=3 or 4)	12/6	29/8	37/13
>10 erosions (score=5 or 6)	0/0	1/0	9/2
Ulcer (score=7)	2/0	7/5	1/0
Total	100/100	100/100	100/100

* pyloric channel ulcers are grouped with the duodenal ulcers

reviewer's original table, based on data in sponsor's tables, NDA Vol. 1.75, pp. 8-12099 and 8-12101

Appearance of the duodenal mucosa in of endoscoped patients in all treatment groups was normal. Duodenal erosions were seen in 6% of diclofenac/misoprostol patients and in 8% of piroxicam patients but in 15% of naproxen patients. However, duodenal ulcers were seen only in piroxicam patients. About 6.4% of patients did not undergo final endoscopy.

Gastric lesions were more common than duodenal lesions in all treatment groups. Thirty-seven percent of endoscoped naproxen patients and 55% of endoscoped piroxicam patients had normal gastric mucosa as compared to 78% of diclofenac/misoprostol patients.

The following table summarizes the ulcer occurrence rates for the various treatment groups. In this intent-to-treat analysis patients who have missing data (i.e., who did not have followup endoscopy) are assumed to have no ulcers.

Study 321: Ulcer Rates in the Various Treatment Groups (Intent-to-Treat Analysis)

	Number of Patients (%)		
	Diclofenac 50mg/Misoprostol 200mcg b.i.d. (n=216)	Piroxicam 10mg b.i.d. (n=217)	Naproxen 375mg b.i.d. (n=210)
Gastric Ulcer	3 (1.4%)	12(5.5%)	15 (7.1%)
Duodenal Ulcer	0 (0%)	8 (3.7%)	2 (1.0%)
Pyloric Channel Ulcer	0 (0%)	2 (0.9%)	1 (0.5%)

reviewer's original table, based on information in sponsor's CANDA submission and NDA Vol. 1.75 pp. 8-12320 through 8-12376

Significantly fewer diclofenac/misoprostol patients had duodenal (including pyloric channel) ulcers as compared to piroxicam patients ($p=0.002$) and as compared to naproxen patients ($p=0.001$). The proportions of patients with gastric ulcers also was significantly less for the diclofenac/misoprostol group as compared to the piroxicam group ($p=0.007$) and the naproxen group ($p=0.004$).

4. **Safety:** Sixty-eight percent of patients (60.2% of diclofenac/misoprostol, 69.6% of piroxicam, and 74.8% of naproxen) reported adverse events during this study. Adverse events occurring at a frequency of 2% or greater in the diclofenac/misoprostol group are listed in the table below:

Study 321: Most Frequent Adverse Events in Diclofenac/Misoprostol Patients

	Diclofenac 50mg/Misoprosotol 200mcg b.i.d.(n=216)	Piroxicam 10mg b.i.d. (n=217)	Naproxen 375mg b.i.d. (n=210)
Abdominal pain	20.8%	15.7%	17.6%
Diarrhea	18.1%	5.5%	4.8%
Headache	10.2%	8.8%	5.2%
Dyspepsia	8.3%	11.5%	9.5%
Nausea	8.3%	5.1%	8.6%
Flatulence	7.4%	3.7%	6.7%
Gastritis	5.1%	21.7%	37.6%
Dizziness	4.2%	2.3%	0.5%
Duodenitis	4.2%	8.3%	14.3%
Eructation	2.8%	0.9%	1.4%

from sponsor's table, NDA Vol. 1.75, p. 8-12121 through 8-12123

In addition to these events, patients on naproxen also had a frequent

complaint of constipation (7.6% of patients).

In this study, 8.3% of diclofenac/misoprosotol patients, 4.6% of piroxicam patients, and 9.3% of naproxen patients withdrew prematurely due to adverse events. No patients died during this study.

With regard to clinical laboratory measurements, all treatment groups experienced a slight decrease in hemoglobin and hematocrit during the study. The piroxicam group had a slight decrease in platelet count and the naproxen group had a slight decrease in SGOT. The diclofenac/misoprostol group had a slight increase in SGPT and the naproxen group had a slight decrease in SGPT. These differences were not clinically meaningful. There was a significant difference between treatment groups in numbers of patients having shifts in SGPT values between high, normal, and low ranges, with numbers of diclofenac/misoprostol patients having elevated SGPT values increasing during the study while numbers of patients with elevated SGPT values decreased in the piroxicam and naproxen groups during the study.

M. **Reviewer's Comments:** In this study diclofenac 50mg/misoprostol 200mcg combination b.i.d. was superior to both piroxicam 10mg b.i.d. and naproxen 375mg b.i.d. in preventing gastric ulcers and duodenal ulcers in patients treated for 4 weeks. It is not clear whether either the piroxicam or naproxen formulations used in this study are bioequivalent to marketed formulations of these products, so the adequacy of this study as a comparative study of the efficacy of the diclofenac/misoprostol combination as compared to marketed naproxen and piroxicam products cannot be fully assessed.

The three treatments were generally well-tolerated during this 4-week study. More diclofenac/misoprostol patients experienced diarrhea as compared to the piroxicam and naproxen patients and SGPT tended to be higher in diclofenac/misoprostol treated patients. The adverse event profile of the diclofenac/misoprostol combination drug in this study was similar to that of approved misoprostol and diclofenac.

As far as approval of the diclofenac/misoprostol combination as an effective medication for preventing gastrointestinal damage while effectively treating signs and symptoms of osteoarthritis is concerned, this study is of limited usefulness, since there is no diclofenac alone treatment arm for comparison.

IV. **Protocol: IN2-89-02-289**: A Comparison of the Efficacy and Upper Gastrointestinal Safety of a Fixed Combination of Misoprostol/Diclofenac Versus Diclofenac Alone in Treating the Signs and Symptoms of Rheumatoid Arthritis (NDA Vol. 1.85, p. 8-16405 through 1.86, p. 8-17260)

Study 289, was evaluated in my review
Briefly, in this study 342 patients were randomized to diclofenac 50mg/placebo b.i.d. or t.i.d. or to diclofenac 50mg/misoprostol 200mcg b.i.d. or t.i.d. for 4 weeks. The dosing regimen (b.i.d. or t.i.d.) was not randomly assigned but was selected by the investigator for each patient. Endoscopy was done prior to randomization and at 4 weeks and endoscopic findings were scored. At study completion, 292 (85%) of the 342 patients randomized underwent endoscopy. The proportion of endoscoped patients in the diclofenac/misoprostol group having duodenal (including pyloric channel) ulcers was significantly less than in the diclofenac/placebo group (1% vs. 8%; p-value = 0.008); for gastric ulcer there was no statistically significant difference (3% of diclofenac/misoprostol patients, 4% of diclofenac/placebo patients; p = 0.571).

Though there appeared to be a benefit in prevention of duodenal ulcers, there was an imbalance between the two treatment groups in the endoscopy rates and endoscopy results for patients withdrawn prematurely due to adverse events that may have affected the result. Of 16 diclofenac /placebo patients withdrawn 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%); no gastric ulcers were found. Of 20 diclofenac/misoprostol patients withdrawn prematurely due to adverse events, only 3 had final endoscopy done and no ulcers were found. A sensitivity analysis revealed that the imbalance in endoscopy rates for the adverse event withdrawals in this study could have biased the restults in favor of the diclofenac.misoprostol combination. Also, because treatment regimen (b.i.d. or t.i.d.) was not randomized but was left to the discretion of the investigator for each patient, there was no standardized daily dose for either of the treatment groups. Because of these problems, this study was judged not to provide strong support for the efficacy of the diclofenac 50mg/misoprostol 200mcg combination product in preventing duodenal or gastric ulcer.

With regard to safety, the overall adverse event profile of diclofenac/misoprostol in this study was consistent with that in the approved labeling for Cytotec (misoprostol). Gastrointestinal-type complaints (e.g., abdominal pain, diarrhea, dyspepsia, nausea) predominated in both treatment groups. Numerically more diclofenac/misoprostol patients than diclofenac/placebo patients discontinued the study because of adverse events. Thus, in this study misoprostol did not appear to enhance the overall

tolerability of the arthritis treatment. There were two deaths, one diclofenac/misoprostol patients died due to myocardial infarction and one diclofenac/placebo patient died of metastatic breast cancer.

V. **Protocol: EB2-87-02-269:** Protocol to Identify and to Treat Clinically Significant Upper GI Lesions Induced by NSAIDs and Subsequently to Evaluate, in a Double-Blind, Placebo Controlled, Parallel Group Study, the Effect of Misoprostol, When Coadministered with Diclofenac Two or Three Times Daily, in Preventing Gastroduodenal Lesions in Patients with Rheumatoid or Osteoarthritis (NDA Vol. 1.101, p. 8-24148 through 1.103, p. 8-25588)

Dates for the beginning and end of this study are not given.

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