Observed counts of gastric ulcer by treatment group and observation timepoint are presented in Table 3.3. Endoscopy results for timepoints prior to Week 12 represent results from Early Termination endoscopies. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.4. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing gastric ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 4 (4%) placebo patients, 8 (5%) SC-58635 50 mg BID patients, 7 (5%) SC-58636 100 mg BID patients, 10 (7%) SC-58635 200 mg BID patients and 25 (18%) naproxen 500 mg BID patients. Pairwise comparisons showed the incidence of ulceration in the naproxen group to be significantly greater compared with all other treatment groups ($p \leq 0.004$). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ($p \geq 0.375$) or in the incidence of ulcers among the SC-58635 groups ($p \geq 0.529$). The trend in crude erosion/ulcer rate was similar to that of the crude ulcer rate with the pairwise comparisons showing no statistically significant differences between the placebo and SC-58635 groups ($p \geq 0.459$) or between the SC-58635 dose groups ($p \geq 0.191$) and finding statistically significant differences between the naproxen group and all other treatment groups including placebo ($p<0.001$) (Table 3.4). These results were confirmed by analyses of crude ulcer and erosion/ulcer rates for the Final Visit endoscopy that included all patients who had an endoscopy (i.e., excluding only patients without a follow-up endoscopy). Based on this analysis 5 (2%) placebo patients, 8 (3%) SC-58635 50 mg BID patients, 7 (3%) SC-58635 100 mg BID patients, 10 (5%) SC-58635 200 mg BID patients and 25 (12%) naproxen 500 mg BID patients developed an ulcer. The incidence of ulceration was significantly greater in naproxen 500 mg BID compared with all other treatment ($p<0.005$) and there were no differences between placebo and any SC-58635 groups ($p \geq 0.210$). Further, there was no difference in the incidence of ulceration between any of the SC-58635 groups ($p \geq 0.489$) (Table 3.4).

TABLE 3.3 GASTRIC ENDOSCOPY RESULTS-- N49- 96- 02- 021
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL
ITT - KNEE AND HIP PATIENTS

	PLACEBO		SC-58635 50MG BID		SC-58635 100MG BID		SC-58635 200MG BID		NAPROXEN 500MG BID	
	(N=247)		(N=258)		(N=239)		(N=237)		(N=233)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
WK 2 (2-28)	63	1	30	2	30	1	26	1	19	2
WK 6 (29-76)	37	1	32	3	34	3	41	1	39	5
WK 12 (77-91)	102	2	156	3	148	3	138	8	116	18
>91	10	1	7	0	8	0	6	0	11	0
TOTAL	212	5	225	8	220	7	211	10	185	25

TABLE 3.4 GASTRIC ENDOSCOPY RESULTS (a)- N49- 96- 02- 021 ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE ITT - KNEE AND HIP PATIENTS

	PLACEBO	SC-58635 50MG BID	SC-58635 100MG BID	SC-58635 200MG BID	NAPROXEN 500MG BID	
	(N=247)	(N=258)	(N=239)	(N=237)	(N=233)	OVERALL p-VALUE(d)
WEEK 12						
CRUDE ULCER RATE(a):						
NO ULCER	102(96%)	156(95%)	148(95%)	138(93%)	116(82%)	<0.001
ULCER	4(4%)	8(5%)	7(5%)	10(7%)	25(18%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	141(41/100)	94(32/62)	84(20/64)	89(22/67)	92(34/58)	
CRUDE EROSION/ULCER RATE:						
NO EROSION/ULCER	76(72%)	127(77%)	111(72%)	106(72%)	51(36%)	<0.001
EROSION/ULCER (c)	30(28%)	37(23%)	44(28%)	42(28%)	90(64%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	141(41/100)	94(32/62)	84(20/64)	89(22/67)	92(34/58)	
FINAL						
CRUDE ULCER RATE(b):						
NO ULCER	212(98%)	225(97%)	220(97%)	211(95%)	185(88%)	<0.001
ULCER	5(2%)	8(3%)	7(3%)	10(5%)	25(12%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	30(30/0)	25(25/0)	12(12/0)	16(16/0)	23(23/0)	
CRUDE EROSION/ULCER RATE:						
NO EROSION/ULCER	160(74%)	178(76%)	165(73%)	167(76%)	89(42%)	<0.001
EROSION/ULCER (c)	57(26%)	55(24%)	62(27%)	54(24%)	121(58%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	30(30/0)	25(25/0)	12(12/0)	16(16/0)	23(23/0)	

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. 100MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID
WEEK 12										
ULCER RATE:	0.801	0.375	0.658	0.981	0.593	0.529	<0.001	<0.001	<0.001	0.004
EROSION/ ULCER RATE:	0.756	0.912	0.459	0.191	0.521	0.598	<0.001	<0.001	<0.001	<0.001
FINAL										
ULCER RATE:	0.657	0.210	0.503	0.893	0.509	0.489	<0.001	<0.001	<0.001	0.005
EROSION/ ULCER RATE:	0.573	0.774	0.773	0.336	0.947	0.411	<0.001	<0.001	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the visit window;
Unknown: other cases; Window is (+/-) 7 days of the scheduled time
(b) Based on the final endoscopy result of each patient
(c) Erosion/ Ulcer is defined as an endoscopy score equal to 3,4,5,6,7
(d) Cochran- Mantel- Haenszel test of overall comparison stratified by baseline status (p- value from Row Mean Scores Differ),
'unknown' patients are excluded from the analysis
(e) Cochran- Mantel- Haenszel test of treatment comparison stratified by baseline status (p- value from Row Mean Scores Differ),
'unknown' patients are excluded from the analysis

Observed counts of duodenal ulcer by treatment group and observation timepoint are presented in Table 3.5. Endoscopy results for timepoints prior to Week 12 represent results from Early Termination endoscopies. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.6. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing duodenal ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 3 (2%) SC-58635 200 mg BID patients and 11 (8%) naproxen 500 mg BID patients. No ulcers were reported in patients in the placebo, SC-58635 50 mg BID, and SC-58635 100 mg BID treatment groups. Pairwise comparisons showed the incidence of ulceration in the naproxen group to be significantly greater compared with all other treatment groups ($p \leq 0.012$). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ($p>0.218$) or in the incidence of ulcers among the SC-58635 groups ($p \geq 0.079$). The trend in crude erosion/ulcer rate was similar to that of the crude ulcer rate with the pairwise comparisons showing no statistically significant differences between the placebo and SC-58635 groups ($p \geq 0.487$) or between the SC-58635 dose groups ($p \geq 0.320$) and finding statistically significant differences between the naproxen group and all other treatment groups including

placebo ($p<0.001$) (Table 3.6). These results were confirmed by analyses of crude ulcer and erosion/ulcer rates for the Final Visit endoscopy that included all patients who had an endoscopy (i.e., excluding only patients without a follow-up endoscopy). Based on this analysis 3 (1%) SC-58635 200 mg BID patients and 11 (5%) naproxen 500 mg BID patients developed an ulcer. There were no ulcers in the placebo, or SC-58635 50 mg BID or 100 mg BID groups. The incidence of ulceration was significantly greater in naproxen 500 mg BID compared to all other treatments ($p<0.016$) and there were no differences between placebo and any SC-58635 treatment groups ($p \geq 0.106$). Further, there was no difference in the incidence of ulceration between any of the SC-58635 treatment groups ($p \geq 0.098$) (Table 3.6).

TABLE 3.5 DUODENAL ENDOSCOPY RESULTS -- N49- 96- 02- 021
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL
ITT - KNEE PATIENTS

	PLACEBO		SC-58635 50MG BID		SC-58635 100MG BID		SC-58635 200MG BID		NAPROXEN 500MG BID	
	(N=247)		(N=258)		(N=239)		(N=237)		(N=233)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
WK 2 (2-28)	64	0	32	0	31	0	26	1	20	1
WK 6 (29-76)	38	0	35	0	37	0	41	1	39	5
WK 12 (77-91)	104	0	158	0	151	0	145	1	129	5
>91	11	0	7	0	8	0	6	0	11	0
TOTAL	217	0	232	0	227	0	218	3	199	11

TABLE 3.6 DUODENAL ENDOSCOPY RESULTS (a)- N49- 96- 02- 021
DUODENAL ENDOSCOPY RESULTS (a)
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE
ITT - KNEE PATIENTS

	PLACEBO	SC-58635 50MG BID	SC-58635 100MG BID	SC-58635 200MG BID	NAPROXEN 500MG BID	OVERALL
	(N=247)	(N=258)	(N=239)	(N=237)	(N=233)	p-VALUE(d)
WEEK 12						
CRUDE ULCER RATE(a):						
NO ULCER	104(100%)	158(100%)	151(100%)	145(98%)	129(92%)	<0.001
ULCER	0(0%)	0(0%)	0(0%)	3(2%)	11(8%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	143(41/102)	100(32/68)	88(20/68)	89(22/67)	93(34/59)	
CRUDE EROSION/ULCER RATE:						
NO EROSION/ULCER	99(95%)	147(93%)	145(96%)	140(95%)	111(79%)	<0.001
EROSION/ULCER (c)	5(5%)	11(7%)	6(4%)	8(5%)	29(21%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	143(41/102)	100(32/68)	88(20/68)	89(22/67)	93(34/59)	
FINAL						
CRUDE ULCER RATE (b):						
NO ULCER	217(100%)	232(100%)	227(100%)	218(99%)	199(95%)	<0.001
ULCER	0(0%)	0(0%)	0(0%)	3(1%)	11(5%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	30(29/1)	26(26/0)	12(12/0)	16(16/0)	23(23/0)	
CRUDE EROSION/ULCER RATE:						
NO EROSION/ULCER	206(95%)	213(92%)	215(95%)	212(96%)	174(83%)	<0.001
EROSION/ULCER (c)	11(5%)	19(8%)	12(5%)	9(4%)	36(17%)	
UNKNOWN(WITHOUT ENDO/WITH ENDO)	30(29/1)	26(26/0)	12(12/0)	16(16/0)	23(23/0)	

p-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. 50MG BID	100MG BID VS. 50MG BID	200MG BID VS. 100MG BID	200MG BID VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS.
WEEK 12										
ULCER RATE:	#	0.218	#	#	0.079	0.142	0.004	<0.001	<0.001	0.012
EROSION/ ULCER RATE:	0.885	0.487	0.629	0.320	0.992	0.533	<0.001	<0.001	<0.001	<0.001
FINAL										
ULCER RATE:	#	0.153	#	#	0.098	0.136	<0.001	<0.001	<0.001	0.016
EROSION/ ULCER RATE:	0.632	0.756	0.106	0.246	0.160	0.599	<0.001	0.002	<0.001	<0.001

(a) No ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the visit window;
Unknown: other cases; Window is (+/-) 7 days of the scheduled time
(b) Based on the final endoscopy result of each patient

(c) Erosion/ Ulcer is defined as an endoscopy score equal to 3,4,5,6,7
(d) Cochran- Mantel- Haenszel test of overall comparison stratified by baseline status (p- value from Row Mean Scores Differ),
'unknown' patients are excluded from the analysis
(e) Cochran- Mantel- Haenszel test of treatment comparison stratified by baseline status (p- value from Row Mean Scores Differ),
'unknown' patients are excluded from the analysis
P- value is not calculable

Reviewer's Comment: In study N49- 96- 02- 021, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group were significantly greater compared with all other treatment groups ($p \leq 0.05$). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ($p>0.05$) or in the incidence of ulcers among the SC-58635 groups ($p \geq 0.05$).

Study N49-98-06-062

Study Design

This was a randomized, double-blind, multicenter, parallel group comparison of the cumulative incidence of gastroduodenal ulcers in OA or RA patients receiving SC-58635 with those receiving naproxen. The study consisted of 12 weeks of treatment with visits occurring at Screening/Baseline, and 4, 8 and 12 weeks after the first dose of study medication. Endoscopies were performed pretreatment and 4, 8, and 12 weeks after the first dose of study medication. Patients who met the inclusion criteria were randomly assigned to receive either SC-58635 200 mg BID or naproxen 500 mg BID for 12 weeks.

STUDY OBJECTIVES

Primary Objective

The primary objective of this study was to compare the cumulative (up to 12 weeks) incidence of gastroduodenal ulcer associated with SC-58635 200 mg BID with that of naproxen 500 mg BID in patients with OA or RA.

UGI ENDOSCOPY AND ARTHRITIS EFFICACY RESULTS

Data Sets Analyzed

All randomized patients who received at least one dose of study medication (n=536) were included in the Endoscopy and Arthritis Efficacy ITT Cohorts.

Counts of gastroduodenal ulcers by treatment group and observation time are presented in Table 3.7. Crude ulcer rates are presented in Table 3.8. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportion of patients developing gastroduodenal ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 18 (9%) SC-58635 200 mg BID patients and 87 (41%) naproxen 500 mg BID patients. These results were confirmed by analysis of Final Visit endoscopies that included all patients who had endoscopy (i.e., excluding only patients without a Week 12 or Early Termination endoscopy). Based on this analysis 20 (8%) SC-58635 200 mg BID patients and 89 (35%) naproxen 500 mg BID patients developed a gastroduodenal ulcer over the course of the study and this difference was statistically significant ($p<0.001$) (Table 3.8).

TABLE 3.7 GASTRODUODENAL ENDOSCOPY RESULTS-- N49- 97- 02- 062 NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

		SC- 58635 200MG BID (N= 269)		NAPROXEN 500MG BID (N= 267)	
STUDY	DAYS	NO ULCER	ULCER	NO ULCER	ULCER
	2-20	12	3	6	3
WEEK 4	(21-35)	242	7	200	44
	36-48	6	0	7	0
WEEK 8	(49-63)	222	5	156	26
	64-76	2	0	1	0
WEEK 12	(77-91)	193	3	127	14
	>91	7	2	3	2

TABLE 3.8 GASTRODUODENAL ENDOSCOPY RESULTS-- N49- 97- 02- 062 ANALYSIS OF CRUDE ULCER RATE-ITT

	SC-58635 200MG BID (N=269)	NAPROXEN 500MG BID (N=267)	p-VALUE(c)
WEEK 0-4			
CRUDE ULCER RATE (a)			<0.001
NO ULCER	242(96%)	200(81%)	
ULCER	10(4%)	47(19%)	
UNKNOWN(WITHOUT & WITH ENDO)	17(5/12)	20(14/6)	
WEEK 0-8			
CRUDE ULCER RATE(a)			<0.001
NO ULCER	222(94%)	156(68%)	
ULCER	15(6%)	73(32%)	
UNKNOWN(WITHOUT & WITH ENDO)	32(3/29)	38(10/28)	
WEEK 0-12			
CRUDE ULCER RATE(a)			<0.001
NO ULCER	193(91%)	127(59%)	
ULCER	18(9%)	87(41%)	
UNKNOWN(WITHOUT & WITH ENDO)	58(3/55)	53(10/43)	
WEEK 0-FINAL(b)			
CRUDE ULCER RATE(a)			<0.001
NO ULCER	246(92%)	168(65%)	
ULCER	20(8%)	89(35%)	
UNKNOWN(WITHOUT & WITH ENDO)	3(3/0)	10(10/0)	

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) Based on the final endoscopy result of each patient.
(c) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. Non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of gastric ulcers by treatment group and observation time are presented in Table 3.9. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.10. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing gastric ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 12 (6%) SC-58635 200 mg BID patients and 74 (37%) naproxen 500 mg BID patients. These results were confirmed by analyses of Final Visit endoscopies that included all patients who had an endoscopy (i.e., excluding only patients without a Week 12 or Early Termination endoscopy). Based on this analysis 13 (5%) SC-58635 200 mg BID patients compared to 76 (30%) naproxen 500 mg BID patients developed an ulcer and this difference was statistically significant ($p<0.001$). The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the difference between the SC-58635 and naproxen groups being statistically significant ($p<0.001$).

TABLE 3.9 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 062
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635 200MG BID (N=269)		NAPROXEN 500MG BID (N=267)	
STUDY DAYS	NOULCER	ULCER	NOULCER	ULCER
2-20	14	1	8	1
WEEK 4 (21-35)	243	6	206	38
36-48	6	0	7	0
WEEK 8 (49-63)	225	2	160	22
64-76	2	0	1	0
WEEK 12 (77-91)	193	3	128	13
>91	8	1	3	2

TABLE 3.10 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 062
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT

	SC-58635 200MG BID (N=269)	NAPROXEN 500MG BID (N=267)	
WEEK 0-12			P-VALUE(d)
CRUDE ULCER RATE (a)			
NO ULCER	193(94%)	128(63%)	<0.001
ULCER	12(6%)	74(37%)	
UNKNOWN (WITHOUT & WITH ENDO)	64(3/61)	65(10/55)	
CRUDE EROSION/ULCER RATE (b)			
NO EROSION/ULCER	162(79%)	65(32%)	<0.001
EROSION/ULCER	43(21%)	137(68%)	
UNKNOWN (WITHOUT & WITH ENDO)	64(3/61)	65(10/55)	
WEEK 0-FINAL (c)			
CRUDE ULCER RATE (a)			
NO ULCER	253(95%)	181(70%)	<0.001
ULCER	13(5%)	76(30%)	
UNKNOWN (WITHOUT & WITH ENDO)	3(3/0)	10(10/0)	
CRUDE EROSION/ULCER RATE (b)			
NO EROSION/ULCER	180(68%)	59(23%)	<0.001
EROSION/ULCER	86(32%)	198(77%)	
UNKNOWN (WITHOUT & WITH ENDO)	3(3/0)	10(10/0)	

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed
within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.
(c) Based on the final endoscopy result of each patient.
(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. Non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of duodenal ulcers by treatment group and observation time are presented in Table 3.11. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.12. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing duodenal ulceration showed a statistically significant treatment difference (p=0.002). Ulcers developed in 8 (4%) SC-58635 200 mg BID patients and 19 (12%) naproxen 500 mg BID patients. These results were confirmed by analyses of Final Visit endoscopies that included all patients who had an endoscopy (i.e., excluding only patients without a Week 12 or Early Termination endoscopy). Based on this analysis, 9 (3%) SC-58635 200 mg BID patients compared to 19 (7%) naproxen 500 mg BID patients developed an ulcer and this difference was statistically significant (p=0.030). The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the difference between the SC-58635 and naproxen groups being statistically significant (p=0.017).

TABLE 3.11 DUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 062
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635 200MG BID (N=269)		NAPROXEN 500MG BID (N=267)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER
2-20	13	2	6	3
WEEK 4 (21-35)	247	2	234	10
36-48	6	0	7	0
WEEK 8 (49-63)	224	3	177	5
64-76	2	0	2	0
WEEK 12 (77-91)	195	1	140	1
>91	8	1	5	0

TABLE 3.12 DUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 062
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT

	SC-58635 200MG BID (N=269)	NAPROXEN 500MG BID (N=267)	
WEEK 0-12			p-VALUE(d)
CRUDE ULCER RATE (a)			
NO ULCER	195(96%)	139(88%)	0.002
ULCER	8(4%)	19(12%)	
UNKNOWN (WITHOUT & WITH ENDO)	66(3/63)	109(10/99)	
CRUDE EROSION/ULCER RATE (b)			
NO EROSION/ULCER	176(87%)	125(79%)	0.017
EROSION/ULCER	27(13%)	33(21%)	
UNKNOWN (WITHOUT & WITH ENDO)	66(3/63)	109(10/99)	
WEEK 0-FINAL (c)			
CRUDE ULCER RATE (a)			
NO ULCER	257(97%)	238(93%)	0.030
ULCER	9(3%)	19(7%)	
UNKNOWN (WITHOUT & WITH ENDO)	3(3/0)	10(10/0)	
CRUDE EROSION/ULCER RATE (b)			
NO EROSION/ULCER	222(83%)	173(67%)	<0.001
EROSION/ULCER	44(17%)	84(33%)	
UNKNOWN (WITHOUT & WITH ENDO)	3(3/0)	10(10/0)	

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed
within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.
(c) Based on the final endoscopy result of each patient.
(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. Non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Reviewer's Comment: In study N49- 97- 02- 062, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group were significantly greater compared with the SC-58635 group ($p \leq 0.05$).

Study N49- 97- 02- 071

Study Design

This was a randomized, double-blind, multicenter, parallel group comparison of the cumulative incidence of gastroduodenal ulcers in OA or RA patients receiving SC-58635 with those receiving diclofenac or ibuprofen. The study consisted of 12 weeks of treatment with visits occurring at Screening/Baseline, and 4, 8, and 12 weeks after the first dose of study medication. Endoscopies were performed Pretreatment and 4, 8, and 12 weeks after the first dose of study medication. Patients who met the inclusion criteria were

randomly assigned to receive SC-58635 200 mg BID, diclofenac 75 mg BID, or ibuprofen 800 mg TID for 12 weeks.

STUDY OBJECTIVES

Primary Objective

The primary objective of this study was to compare the cumulative (up to 12 weeks) incidence of gastroduodenal ulcers associated with SC-58635 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA.

Counts of patients with gastroduodenal ulcers by treatment group and observation time are presented in Table 3.13. Crude ulcer rates are presented in Table 3.14. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportion of patients developing gastroduodenal ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 25 (9%) SC-58635 200 mg BID patients, 36 (12%) diclofenac 75 mg BID patients, and 78 (28%) ibuprofen 800 mg TID patients. Pairwise comparisons indicated these differences were statistically significant for the SC-58635 200 mg BID group compared to the ibuprofen 800 mg TID group and for the diclofenac group compared to the ibuprofen group ($p<0.001$). These results were confirmed by analysis of Final Visit endoscopies that included all patients who had a posttreatment endoscopy. Based on this analysis, 25 (7%) SC-58635 200 mg BID patients, 36 (10%) diclofenac 75 mg BID patients, and 78 (23%) ibuprofen 800 mg TID patients developed a gastroduodenal ulcer over the course of the study. Pairwise comparisons indicated a statistically significant difference for the SC-58635 treatment group compared to the ibuprofen group and the diclofenac group compared to the ibuprofen group ($p<0.001$) (Table 3.14).

TABLE 3.13 GASTRODUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 071
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635 200MG BID (N=365)		DICLOFENAC 75MG BID (N=387)		IBUPROFEN 800MG TID (N=345)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
2-20	9	0	12	0	8	2
WEEK 4 (21-35)	324	13	332	18	281	40
36-48	14	1	10	1	7	1
WEEK 8 (49-63)	289	6	296	9	226	14
64-76	13	1	10	1	13	1
WEEK 12 (77-91)	269	4	270	7	198	20
>91	6	0	4	0	2	0

TABLE 3.14 GASTRODUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 071 ANALYSIS OF CRUDE ULCER RATE-ITT

	SC-58635 200MG BID (N=365)	DICLOFENAC 75MG BID (N=387)	IBUPROFEN 800MG TID (N=345)	OVERALL p-VALUE(c)	SC-58635 VS DICLOFENAC p-VALUE(c)	SC-58635 VS IBUPROFEN p-VALUE(c)	DICLOFENAC VS IBUPROFEN p-VALUE(c)
WEEK 0-4							
CRUDE ULCER RATE (a)							
NO ULCER	324(96%)	332(95%)	281(87%)	<0.001	0.370	<0.001	<0.001
ULCER	13(4%)	18(5%)	42(13%)				
UNKNOWN(WITHOUT & WITH ENDO)	28(19/9)	37(25/12)	22(15/7)				
WEEK 0-8							
CRUDE ULCER RATE (a)							
NO ULCER	289(94%)	296(91%)	226(80%)	<0.001	0.220	<0.001	<0.001
ULCER	20(6%)	28(9%)	57(20%)				
UNKNOWN(WITHOUT & WITH ENDO)	56(9/47)	63(15/48)	62(12/50)				
WEEK 0-12							
CRUDE ULCER RATE (a)							
NO ULCER	269(91%)	270(88%)	198(72%)	<0.001	0.138	<0.001	<0.001
ULCER	25(9%)	36(12%)	78(28%)				
UNKNOWN(WITHOUT & WITH ENDO)	71(9/62)	81(15/66)	69(11/58)				
WEEK 0-FINAL (b)							
CRUDE ULCER RATE (a)							
NO ULCER	331(93%)	336(90%)	256(77%)	<0.001	0.123	<0.001	<0.001
ULCER	25(7%)	36(10%)	78(23%)				
UNKNOWN(WITHOUT & WITH ENDO)	9(9/0)	15(15/0)	11(11/0)				

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) Based on the final endoscopy result of each patient.
(c) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of patients with gastric ulcers by treatment group and observation time are presented in Table 3.15. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.16. Over the 12 weeks of the study, for patients with known ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week 12 window), the overall comparison of the proportions of patients developing gastric ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 23 (8%) SC-58635 200 mg BID patients, 27 (9%) diclofenac 75 mg BID patients and 60 (23%) ibuprofen 800 mg TID patients and this difference was statistically significant for the SC-58635 group compared to the ibuprofen group and for the diclofenac group compared to the ibuprofen group ($p<0.001$). These results were confirmed by analyses of Final Visit endoscopies that included all patients who had a posttreatment endoscopy. Based on this analysis, 23 (6%) SC-58635 200 mg BID patients compared to 27 (7%) diclofenac 75 mg BID patients and 60 (18%) ibuprofen 800 mg TID patients developed an ulcer and this difference was statistically significant for the SC-58635 group compared to the ibuprofen group as well as the diclofenac group compared to the ibuprofen group ($p<0.001$).

The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the difference between the SC-58635 and ibuprofen group and the difference between the diclofenac and ibuprofen group being statistically significant ($p<0.001$).

TABLE 3.15 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 071
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635 200MG BID (N=365)		DICLOFENAC 75MG BID (N=387)		IBUPROFEN 800MG TID (N=345)	
STUDY DAYS	NO ULCER	ULCER	NO ULCER	ULCER	NO ULCER	ULCER
2-20	9	0	12	0	8	2
WEEK 4 (21-35)	325	12	336	14	294	27
36-48	14	1	10	1	7	1
WEEK 8 (49-63)	290	5	299	7	230	10
64-76	13	1	10	1	13	1
WEEK 12 (77-91)	270	4	274	4	199	19
>91	6	0	4	0	2	0

TABLE 3.16 GASTRIC ENDOSCOPY RESULTS- N49- 97- 02- 071
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT

	SC-58635 200MG BID (N=365)	DICLOFENAC 75MG BID (N=387)	IBUPROFEN 800MG TID (N=345)	OVERALL p-VALUE(d)	SC-58635 VS DICLOFENAC p-VALUE(d)	SC-58635 VS IBUPROFEN p-VALUE(d)	DICLOFENAC VS IBUPROFEN p-VALUE(d)
WEEK 0-12							
CRUDE ULCER RATE(a)							
NO ULCER	270(92%)	274(91%)	199(77%)	<0.001	0.515	<0.001	<0.001
ULCER	23(8%)	27(9%)	60(23%)				
UNKNOWN(WITHOUT & WITH ENDO)	72(9/63)	86(15/71)	86(11/75)				
CRUDE EROSION/ULCER RATE(b)				<0.001	0.224	<0.001	<0.001
NO EROSION/ULCER	226(77%)	223(74%)	117(45%)				
EROSION/ULCER	67(23%)	78(26%)	142(55%)				
UNKNOWN(WITHOUT & WITH ENDO)	72(9/63)	86(15/71)	86(11/75)				
WEEK 0-FINAL (c)							
CRUDE ULCER RATE							
NO ULCER	333(94%)	345(93%)	274(82%)	<0.001	0.534	<0.001	<0.001
ULCER	23(6%)	27(7%)	60(18%)				
UNKNOWN(WITHOUT & WITH ENDO)	9(9/0)	15(15/0)	11(11/0)				
CRUDE EROSION/ULCER RATE							
NO EROSION/ULCER	221(62%)	228(61%)	105(31%)	<0.001	0.426	<0.001	<0.001
EROSION/ULCER	135(38%)	144(39%)	229(69%)				
UNKNOWN(WITHOUT & WITH ENDO)	9(9/0)	15(15/0)	11(11/0)				

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed
within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.
(c) Based on the final endoscopy result of each patient for crude ulcer rate and based on the highest score for each patient during treatment for crude erosion/ ulcer rate.
(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Counts of patients with duodenal ulcers by treatment group and observation time are presented in Table 3.17. Crude ulcer rates and crude erosion/ulcer rates are presented in Table 3.18. Over the 12 weeks of the study, for patients with know ulcer outcome (i.e., an ulcer prior to Week 12 or a scheduled endoscopy within the Week12 window), the overall comparison of the proportions of patients developing duodenal ulceration showed a statistically significant treatment difference ($p<0.001$). Ulcers developed in 3 (1%) SC-58635 200 mg BID patients, 14 (5%) diclofenac 75 mg BID patients, and 22 (9%) ibuprofen 800 mg TID patients and these differences were statistically significant for the SC-58635 group compared to the ibuprofen group ($p<0.001$), and for the SC-58635 group compared to the diclofenac group ($p=0.007$). These results were confirmed by analyses of Final Visit endoscopies that included all patients who had a posttreatment endoscopy. Based on this analysis 3 (<1%) SC-58635 200 mg BID patients compared to 14

(4%) diclofenac 75 mg BID patients and 22 (7%) ibuprofen 800 mg TID patients developed an ulcer and these differences were statistically significant for the SC-58635 group compared to the ibuprofen group ($p<0.001$) and for the SC-58635 group compared to the diclofenac group ($p=0.008$).

The results of the analyses of cumulative crude erosion/ulcer rate from 0-Week 12 was similar to that of the cumulative crude ulcer rate with the differences between the SC-58635 and ibuprofen groups and the SC-58635 and diclofenac groups and the diclofenac and ibuprofen groups being statistically significant at 0-Week 12 ($p\leq 0.015$).

TABLE 3.17 DUODENAL ENDOSCOPY RESULTS- N49- 97- 02- 071
NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL-ITT

	SC-58635 200MGBID (N=365)		DICLOFENAC 75MGBID (N=387)		IBUPROFEN 800MGTID (N=345)	
STUDYDAYS	NOULCER	ULCER	NOULCER	ULCER	NOULCER	ULCER
2-20	9	0	12	0	10	0
WEEK4 (21-35)	336	1	342	8	305	16
36-48	15	0	11	0	8	0
WEEK8 (49-63)	294	1	303	2	236	4
64-76	14	0	11	0	14	0
WEEK12 (77-91)	272	1	273	4	216	2
>91	6	0	4	0	2	0

TABLE 3.18 DUODENAL ENDOSCCPY RESULTS- N49- 97- 02- 071
ANALYSIS OF CRUDE ULCER RATE AND EROSION/ ULCER RATE-ITT

	SC-58635 200MG BID (N=365)	DICLOFENAC 75MG BID (N=387)	IBUPROFEN 800MG TID (N=345)	OVERALL p-VALUE (d)	SC-58635 VS DICLOFENAC p-VALUE (d)	SC-58635 VS IBUPROFEN p-VALUE (d)	DICLOFENAC VS IBUPROFEN p-VALUE (d)
WEEK 0-12							
CRUDE ULCER RATE (a)							
NO ULCER	272 (99%)	273 (95%)	216 (91%)	<0.001	0.007	<0.001	0.055
ULCER	3 (1%)	14 (5%)	22 (9%)				
UNKNOWN (WITHOUT & WITH ENDO)	90 (9/81)	100 (15/85)	107 (11/96)				
CRUDE EROSION/ULCER RATE (b)							
NOEROSION/ULCER	258 (94%)	252 (88%)	191 (80%)	<0.001	0.003	<0.001	0.015
EROSION/ULCER	17 (6%)	35 (12%)	47 (20%)				
UNKNOWN (WITHOUT & WITH ENDO)	90 (9/81)	100 (15/85)	107 (11/96)				
WEEK 0-PINAL (c)							
CRUDE ULCER RATE							
NO ULCER	353 (99%)	358 (96%)	312 (93%)	<0.001	0.008	<0.001	0.093
ULCER	3 (<1%)	14 (4%)	22 (7%)				
UNKNOWN (WITHOUT & WITH ENDO)	9 (9/0)	15 (15/0)	11 (11/0)				
CRUDE EROSION/ULCE RRATE							
NO EROSION/ULCER	314 (88%)	307 (83%)	248 (74%)	<0.001	0.006	<0.001	0.008
EROSION/ULCER	42 (12%)	65 (17%)	86 (26%)				
UNKNOWN (WITHOUT & WITH ENDO)	9 (9/0)	15 (15/0)	11 (11/0)				

(a) No Ulcer: endoscopy performed within the visit window without ulcer; Ulcer: ulcer detected prior to or within the window; Unknown: other cases; Window is (+/- 7 days) of the scheduled time.
(b) No Erosion/ Ulcer: endoscopy performed within the visit window with a status between 0 and 2; Erosion/ Ulcer: endoscopy performed
within the visit window with a status between 3 and 7 or an ulcer defined prior to the visit window; Unknown: other cases.
(c) Based on the final endoscopy result of each patient for crude ulcer rate and based on the highest score for each patient during treatment for crude erosion/ ulcer rate.
(d) Cochran- Mantel- Haenszel test of treatment comparison for known ulcer vs. non- ulcer stratified by baseline score (p- value from Row Mean Scores Differ).

Reviewer's Comment: In study N49- 97- 02- 071, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group to be significantly greater compared with the SC-58635 group and the diclofenac group ($p \leq 0.05$). There was no difference in the incidence of gastroduodenal and gastric ulcers

in the SC-58635 group and the diclofenac group ($p>0.05$). The incidence of duodenal ulcers in the diclofenac group was significantly greater compared with the SC-58635 group ($p \leq 0.05$).

There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ($p>0.05$) or in the incidence of ulcers among the SC-58635 groups ($p \geq 0.05$).

4. Integrated safety:

12 week studies

The 12-week studies and the 6-week studies were pooled separately for the safety analysis. The results are listed in Tables 4.1-4.8. The frequencies of reported adverse events are listed by body system and treatment groups. Individual adverse events within a certain body system are listed (in italic) if the p-value for the differences among treatment groups were ≤ 0.05 and the percentage for at least one of the treatment groups exceeds 1%. The p-values were from the Mantel-Haenszel chi-square test. Since the Mantel-Haenszel chi-square test is only asymptotically reliable, and the frequencies of reported adverse events are usually low, caution should be exercised while interpreting these p-values.

Table 4.1 lists the frequencies of all reported adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: Gastro-intestinal system, skin and appendages. Within "body as a whole", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): Dema Peripheral, allergic reaction, and chest pain. Within "General and peripheral nervous system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): headache. Within "Gastro-intestinal system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): Abdominal pain, constipation, dyspepsia, flatulence, vomiting. Within "Musculo-skeletol system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): arthralgia. Within "skin and appendages", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): rash. Within "urinary system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): micturition frequency.

Table 4.1 Number of Subjects Reporting All-Causalities Adverse Events (12 week studies)

	Placebo	50mg BID	100mg BID	200mg BID	Naproxan	
Body System	N=685	N=692	N=664	N=672	N=656	
	N(%)	N(%)	N(%)	N(%)	N(%)	P-Value*
APPLICATION SITE DISORDERS	5 (0.7)	5 (0.7)	12(1.8)	6(0.9)	2(0.3)	0.576
AUTONOMIC NERVOUS SYSTEM DISORDERS	11(1.6)	5(0.7)	13(2.0)	19(2.8)	14(2.1)	0.052
BODY AS A WHOLE-GENERAL DISORDERS	109(15.9)	106(15.3)	115(17.3)	120(17.9)	105(16.0)	0.536
DEMA PERIPHERAL	8(1.2)	14(2.0)	12(1.8)	25(3.7)	15(2.3)	0.026
ALLERGIC REACTION	0(0.0)	0(0.0)	3(0.5)	7(1.0)	1(0.2)	0.048
CHEST PAIN	3(0.4)	2(0.3)	4(0.6)	6(0.9)	9(1.4)	0.016
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	163(23.8)	148(21.4)	160(24.1)	150(22.3)	121(18.4)	0.057
HEADACHE	140(20.4)	115(16.6)	129(19.4)	110(16.4)	90(13.7)	0.003
ENDOCRINEDISORDERS	1(0.1)	0(0.0)	2(0.3)	0(0.0)	4(0.6)	0.099
GASTRO-INTESTINAL SYSTEM DISORDERS	158(23.1)	161(23.3)	171(25.8)	183(27.2)	222(33.8)	<.001
ABDOMINAL PAIN	21(3.1)	28(4.0)	29(4.4)	34(5.1)	37(5.6)	0.014
CONSTIPATION	11(1.6)	10(1.4)	14(2.1)	17(2.5)	35(5.3)	<.001
DYSPEPSIA	53(7.7)	55(7.9)	54(8.1)	69(10.3)	79(12.0)	0.002
FLATULENCE	8(1.2)	16(2.3)	11(1.7)	10(1.5)	24(3.7)	0.018
VOMITING	3(0.4)	6(0.9)	9(1.4)	10(1.5)	9(1.4)	0.049
HEARING AND VESTIBULAR DISORDERS	5(0.7)	6(0.9)	6(0.9)	5(0.7)	2(0.3)	0.350
HEARTRATE AND RHYTHM DISORDERS	4(0.6)	5(0.7)	3(0.5)	6(0.9)	6(0.9)	0.421
LIVER AND BILIARY SYSTEM DISORDERS	6(0.9)	5(0.7)	5(0.8)	5(0.7)	7(1.1)	0.722
METABOLIC AND NUTRITIONAL DISORDERS	14(2.0)	30(4.3)	26(3.9)	37(5.5)	23(3.5)	0.076
MUSCULO-SKELETAL SYSTEM DISORDERS	38(5.5)	31(4.5)	33(5.0)	34(5.1)	20(3.0)	0.088
ARTHRALGIA	15(2.2)	12(1.7)	7(1.1)	6(0.9)	7(1.1)	0.030
MYO ENDO PERICARDIAL & VALVE DISORDERS	5(0.7)	1(0.1)	5(0.8)	7(1.0)	2(0.3)	0.941
NEOPLASM	3(0.4)	3(0.4)	5(0.8)	2(0.3)	2(0.3)	0.627
PLATELET, BLEEDING & CLOTTING DISORDERS	8(1.2)	7(1.0)	8(1.2)	6(0.9)	12(1.8)	0.377
PSYCHIATRICDISORDERS	43(6.3)	35(5.1)	42(6.3)	41(6.1)	38(5.8)	0.975
RED BLOOD CELL DISORDERS	1(0.1)	3(0.4)	3(0.5)	4(0.6)	4(0.6)	0.178
REPRODUCTIVE DISORDERS, FEMALE	5(0.7)	8(1.2)	8(1.2)	5(0.7)	9(1.4)	0.485
REPRODUCTIVE DISORDERS, MALE	2(0.3)	1(0.1)	1(0.2)	2(0.3)	0(0.0)	0.408
RESISTANCE MECHANISM DISORDERS	9(1.3)	18(2.6)	19(2.9)	15(2.2)	14(2.1)	0.470
RESPIRATORY SYSTEM DISORDERS	120(17.5)	136(19.7)	145(21.8)	137(20.4)	133(20.3)	0.194
SKIN AND APPENDAGES DISORDERS	49(7.2)	46(6.6)	31(4.7)	35(5.2)	33(5.0)	0.044
RASH	21(3.1)	15(2.2)	13(2.0)	8(1.2)	10(1.5)	0.017
SPECIAL SENSES OTHER, DISORDERS	0(0.0)	2(0.3)	2(0.3)	1(0.1)	0(0.0)	0.779
URINARY SYSTEM DISORDERS	19(2.8)	20(2.9)	26(3.9)	24(3.6)	20(3.0)	0.557
MICTURITION FREQUENCY	0(0.0)	3(0.4)	7(1.1)	5(0.7)	5(0.8)	0.048
VASCULAR (EXTRACARDIAC) DISORDERS	3(0.4)	3(0.4)	6(0.9)	3(0.4)	3(0.5)	0.944
VISIONDISORDERS	9(1.3)	13(1.9)	11(1.7)	8(1.2)	9(1.4)	0.698
WHITECELLANDRESDISORDERS	5(0.7)	2(0.3)	2(0.3)	0(0.0)	3(0.5)	0.242

*p values were from the Mantel-Haenszel chi-square test

Table 4.2 lists the frequencies of all reported treatment related (relationship with treatment coded as "uncertain" or "probable" by the investigators) adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: Autonomic nervous system, Gastro-intestinal system. Within "central and peripheral nervous system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): cramped legs. Within "Gastro-intestinal system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): Abdominal pain, constipation, dyspepsia, flatulence, nausea, vomiting. Within "respiratory system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): coughing. Within "skin and appendages", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): rash.

Table 4.2 Number of Subjects Reporting Treatment-Related Adverse Events (12 week studies)

	Placebo	50mg BID	100mg BID	200mg BID	Naproxan	
Body System	N=685	N=692	N=664	N=672	N=656	
	N(%)	N(%)	N(%)	N(%)	N(%)	P-Value*
APPLICATION SITE DISORDERS	0(0.0)	2(0.3)	4(0.6)	3(0.4)	1(0.2)	0.469
AUTONOMIC NERVOUS SYSTEM DISORDERS	5(0.7)	3(0.4)	7(1.1)	12(1.8)	10(1.5)	0.020
BODY AS A WHOLE-GENERAL DISORDERS	35(5.1)	52(7.5)	56(8.4)	59(8.8)	45(6.9)	0.126
CARDIOVASCULAR DISORDERS, GENERAL	1(0.1)	0(0.0)	0(0.0)	1(0.1)	1(0.2)	0.661
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	93(13.6)	75(10.8)	99(14.9)	85(12.6)	68(10.4)	0.264
CRAMPS LEGS	1(0.1)	2(0.3)	1(0.2)	7(1.0)	6(0.9)	0.008
ENDOCRINE DISORDERS	0(0.0)	0(0.0)	1(0.2)	0(0.0)	1(0.2)	0.306
GASTRO-INTESTINAL SYSTEM DISORDERS	109(15.9)	121(17.5)	135(20.3)	144(21.4)	171(26.1)	<.001
ABDOMINAL PAIN	16(2.3)	24(3.5)	26(3.9)	28(4.2)	33(5.0)	0.009
CONSTIPATION	8(1.2)	7(1.0)	10(1.5)	10(1.5)	24(3.7)	0.001
DYSPEPSIA	41(6.0)	44(6.4)	44(6.6)	54(8.0)	65(9.9)	0.003
FLATULENCE	7(1.0)	14(2.0)	10(1.5)	9(1.3)	20(3.0)	0.039
NAUSEA	21(3.1)	19(2.7)	20(3.0)	26(3.9)	31(4.7)	0.048
VOMITING	1(0.1)	4(0.6)	7(1.1)	9(1.3)	6(0.9)	0.033
HEARING AND VESTIBULAR DISORDERS	3(0.4)	3(0.4)	4(0.6)	3(0.4)	2(0.3)	0.762
HEARTRATE AND RHYTHM DISORDERS	1(0.1)	3(0.4)	2(0.3)	6(0.9)	5(0.8)	0.050
LIVER AND BILIARY SYSTEM DISORDERS	5(0.7)	5(0.7)	4(0.6)	5(0.7)	5(0.8)	0.936
METABOLIC AND NUTRITIONAL DISORDERS	12(1.8)	18(2.6)	16(2.4)	27(4.0)	15(2.3)	0.193
MUSCULO-SKELETAL SYSTEM DISORDERS	15(2.2)	12(1.7)	16(2.4)	14(2.1)	6(0.9)	0.191
MYO ENDO PERICARDIAL & VALVE DISORDERS	3(0.4)	1(0.1)	3(0.5)	3(0.4)	1(0.2)	0.709
NEOPLASM	3(0.4)	2(0.3)	1(0.2)	1(0.1)	0(0.0)	0.067
PLATELET, BLEEDING & CLOTTING DISORDERS	6(0.9)	4(0.6)	5(0.8)	4(0.6)	7(1.1)	0.717
PSYCHIATRIC DISORDERS	27(3.9)	23(3.3)	31(4.7)	29(4.3)	24(3.7)	0.847
RED BLOOD CELL DISORDERS	1(0.1)	2(0.3)	2(0.3)	3(0.4)	4(0.6)	0.136
REPRODUCTIVE DISORDERS, FEMALE	3(0.4)	3(0.4)	6(0.9)	4(0.6)	3(0.5)	0.815
REPRODUCTIVE DISORDERS, MALE	0(0.0)	1(0.1)	0(0.0)	1(0.1)	0(0.0)	0.982
RESISTANCE MECHANISM DISORDERS	4(0.6)	8(1.2)	4(0.6)	5(0.7)	7(1.1)	0.624
RESPIRATORY SYSTEM DISORDERS	29(4.2)	41(5.9)	43(6.5)	43(6.4)	29(4.4)	0.737
COUGHING	1(0.1)	4(0.6)	3(0.5)	3(0.4)	8(1.2)	0.029
SKIN AND APPENDAGES DISORDERS	35(5.1)	32(4.6)	20(3.0)	27(4.0)	23(3.5)	0.111
RASH	17(2.5)	12(1.7)	9(1.4)	8(1.2)	7(1.1)	0.026
SPECIAL SENSES OTHER, DISORDERS	0(0.0)	2(0.3)	2(0.3)	0(0.0)	0(0.0)	0.500
URINARY SYSTEM DISORDERS	10(1.5)	8(1.2)	15(2.3)	10(1.5)	8(1.2)	0.935
VASCULAR (EXTRACARDIAC) DISORDERS	1(0.1)	1(0.1)	2(0.3)	1(0.1)	2(0.3)	0.563
VISION DISORDERS	4(0.6)	9(1.3)	7(1.1)	4(0.6)	4(0.6)	0.559
WHITE CELL AND RES DISORDERS	3(0.4)	0(0.0)	2(0.3)	0(0.0)	1(0.2)	0.264

* p values were from the Mantel-Haenszel chi-square test

Table 4.3 lists the frequencies of all reported severe adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: platelet, bleeding and clotting system, reproductive system (female). Within "Gastro-intestinal system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): dyspepsia.

Table 4.3 Number of Subjects Reporting All-Causalities Severe Adverse Events (12 week studies)

	Placebo	50mgBID	100mgBID	200mgBID	Naproxan	
Body System	N=685	N=692	N=664	N=672	N=656	
	N(%)	N(%)	N(%)	N(%)	N(%)	P-Value*
APPLICATIONSITEDISORDERS	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.487
AUTONOMIC NERVOUS SYSTEM DISORDERS	0(0.0)	0(0.0)	0(0.0)	2(0.3)	1(0.2)	0.095
BODY AS A WHOLE-GENERAL DISORDERS	8(1.2)	10(1.4)	9(1.4)	16(2.4)	5(0.8)	0.909
CARDIOVASCULAR DISORDERS, GENERAL	1(0.1)	1(0.1)	0(0.0)	1(0.1)	1(0.2)	0.974
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	17(2.5)	17(2.5)	16(2.4)	14(2.1)	15(2.3)	0.677
GASTRO-INTESTINAL SYSTEM DISORDERS	16(2.3)	15(2.2)	16(2.4)	12(1.8)	23(3.5)	0.308
DYSPEPSIA	1(0.1)	5(0.7)	4(0.6)	5(0.7)	8(1.2)	0.031
HEART RATE AND RHYTHM DISORDERS	1(0.1)	1(0.1)	1(0.2)	0(0.0)	1(0.2)	0.748
LIVER AND BILIARY SYSTEM DISORDERS	2(0.3)	0(0.0)	1(0.2)	0(0.0)	2(0.3)	0.971
METABOLIC AND NUTRITIONAL DISORDERS	0(0.0)	1(0.1)	1(0.2)	0(0.0)	0(0.0)	0.633
MUSCULO-SKELETAL SYSTEM DISORDERS	6(0.9)	4(0.6)	3(0.5)	7(1.0)	1(0.2)	0.313
MYO ENDO PERICARDIAL& VALVE DISORDERS	3(0.4)	0(0.0)	0(0.0)	4(0.6)	0(0.0)	0.621
NEOPLASM	1(0.1)	1(0.1)	1(0.2)	0(0.0)	2(0.3)	0.724
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	0(0.0)	0(0.0)	1(0.1)	3(0.5)	0.012
PSYCHIATRIC DISORDERS	3(0.4)	1(0.1)	3(0.5)	1(0.1)	1(0.2)	0.370
REPRODUCTIVE DISORDERS, FEMALE	0(0.0)	0(0.0)	1(0.2)	0(0.0)	3(0.5)	0.031
RESISTANCE MECHANISM DISORDERS	2(0.3)	0(0.0)	2(0.3)	1(0.1)	1(0.2)	0.803
RESPIRATORY SYSTEM DISORDERS	6(0.9)	7(1.0)	2(0.3)	5(0.7)	5(0.8)	0.627
SKIN AND APPENDAGES DISORDERS	3(0.4)	5(0.7)	3(0.5)	1(0.1)	2(0.3)	0.282
URINARY SYSTEM DISORDERS	0(0.0)	1(0.1)	2(0.3)	0(0.0)	0(0.0)	0.704
VASCULAR (EXTRACARDIAC) DISORDERS	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0.160
VISION DISORDERS	0(0.0)	0(0.0)	2(0.3)	0(0.0)	0(0.0)	0.982
WHITE CELL AND RES DISORDERS	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.487

*p values were from the Mantel-Haenszel chi-square test

Table 4.4 lists the frequencies of all reported treatment related (relationship with treatment coded as "uncertain" or "probable" by the investigators) severe adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: platelet, bleeding and clotting system.

Table 4.4 Number of Subjects Reporting Treatment-Related severe Adverse Events (12 week studies)

	Placebo	50mgBID	100mgBID	200mgBID	Naproxan	
Body System	N=685	N=692	N=664	N=672	N=656	
	N(%)	N(%)	N(%)	N(%)	N(%)	P-Value*
AUTONOMIC NERVOUSSYSTEMDISORDERS	0(0.0)	0(0.0)	0(0.0)	2(0.3)	1(0.2)	0.095
BODY AS A WHOLE-GENERAL DISORDERS	2(0.3)	5(0.7)	3(0.5)	7(1.0)	0(0.0)	0.782
CARDIOVASCULAR DISORDERS, GENERAL	1(0.1)	0(0.0)	0(0.0)	0(0.0)	1(0.2)	0.982
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	8(1.2)	7(1.0)	10(1.5)	5(0.7)	6(0.9)	0.540
GASTRO-INTESTINAL SYSTEM DISORDERS	7(1.0)	13(1.9)	13(2.0)	8(1.2)	18(2.7)	0.088
METABOLIC AND NUTRITIONAL DISORDERS	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.487
MUSCULO-SKELETAL SYSTEM DISORDERS	4(0.6)	1(0.1)	1(0.2)	3(0.4)	0(0.0)	0.171
MYO ENDO PERICARDIAL & VALVE DISORDERS	1(0.1)	0(0.0)	0(0.0)	1(0.1)	0(0.0)	0.632
NEOPLASM	1(0.1)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.138
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.3)	0.042
PSYCHIATRIC DISORDERS	2(0.3)	0(0.0)	1(0.2)	0(0.0)	1(0.2)	0.500
REPRODUCTIVE DISORDERS, FEMALE	0(0.0)	0(0.0)	1(0.2)	0(0.0)	1(0.2)	0.306
RESISTANCE MECHANISM DISORDERS	1(0.1)	0(0.0)	1(0.2)	1(0.1)	1(0.2)	0.699
RESPIRATORY SYSTEM DISORDERS	2(0.3)	1(0.1)	0(0.0)	1(0.1)	1(0.2)	0.549
SKIN AND APPENDAGES DISORDERS	2(0.3)	5(0.7)	2(0.3)	1(0.1)	2(0.3)	0.446
URINARY SYSTEM DISORDERS	0(0.0)	0(0.0)	1(0.2)	0(0.0)	0(0.0)	0.987
VASCULAR (EXTRACARDIAC) DISORDERS	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0.160

*p values were from the Mantel-Haenszel chi-square test

Reviewer's comments :

In the three 12-week studies, the frequencies of reported adverse events by body system in the treatment groups were statistically significantly different (Table 4.1) in the Gastro-intestinal system ($p<0.001$, with naproxan group having the highest frequency), skin and appendages. ($p=0.044$, the placebo group had the highest frequency) and the respiratory system ($p=0.024$, the two SC-58635 groups had the highest frequency). The frequencies of the following reported adverse events (by individual events) in the treatment groups were statistically significantly different (Table 4.1): Dema Peripheral ($p=0.026$, SC-58635 200 mg bid group had the highest frequency), allergic reaction ($p=0.048$, SC-58635 200 mg BID group had the highest frequency), and chest pain ($p=0.016$, the naproxan group had the highest frequency), headache ($p=0.003$, placebo group had the highest frequency), Abdominal pain ($p=0.014$, the SC-58635 200 mg BID group and the naproxan group had the highest frequencies), constipation ($p<0.001$, the naproxan group had the highest frequency), dyspepsia ($p=0.002$ the SC-58635 200 mg BID group and the naproxan group had the highest frequencies), flatulence ($p=0.018$, the naproxan group had the highest frequency), vomiting ($p=0.049$, the SC-58635 100 and 200 mg BID groups and the naproxan group had higher frequencies), arthralgia ($p=0.030$, the placebo group had highest frequency), rash ($p=0.017$, the placebo group had the highest frequency), micturition frequency($p=0.048$, the placebo group had lowest frequency).

The frequencies of reported treatment-related adverse events by body system in the treatment groups were statistically significant (Table 4.2) in the autonomic nervous system ($p=0.020$, with the SC-58635 200 mg BID group and the naproxan group having the highest frequencies), the Gastro-intestinal system ($p<0.001$, with naproxan group having the highest frequency), heart and rhythm system ($p=0.05$, with the SC-58635 200 mg BID group and the naproxan group having the highest frequencies). The frequencies of the following reported adverse events (by individual events) in the treatment groups were statistically significant (Table 4.2): Leg cramps ($p=0.008$, the SC-58635 200 mg BID group and the naproxan group had the highest frequencies), abdominal pain ($p=0.009$, the SC-58635 200 mg BID group and the naproxan group had the highest frequencies), constipation ($p=0.001$, the naproxan group had the highest frequency), dyspepsia ($p=0.003$, the SC-58635 200 mg BID group and the naproxan group had the highest frequencies), flatulence ($p=0.039$, the naproxan group had the highest frequency), nausea ($p=0.048$, the naproxan group had the highest frequency), vomiting ($p=0.033$, the SC-58635 100 and 200 mg BID groups and the naproxan group had higher frequencies), coughing ($p=0.029$, the naproxan group had highest frequency), rash ($p=0.026$, the placebo group had the highest frequency).

The frequencies of reported severe adverse events by body system in the treatment groups were statistically significantly different (Table 4.3) in the platelet, bleeding and clotting system ($p=0.020$, the SC-58635 200 mg BID group and the naproxan group had higher frequencies), female reproductive system ($p=0.031$, the naproxan group had the highest frequency). The frequencies of the following reported adverse events (by individual events) in the treatment groups were statistically significantly different (Table 4.3): dyspepsia ($p=0.031$, the naproxan group had the highest frequency).

The frequencies of reported severe treatment-related adverse events by body system in the treatment groups were statistically significant (Table 4.4) in the platelet, bleeding and clotting system ($p=0.042$, the naproxan group being the only group with this event).

6 week studies:

Table 4.5 lists the frequencies of all reported adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: Musculo-skeletol system, respiratory system.

Table 4.5 Number of Subjects Reporting All-Causalities Adverse Events (6 week studies)

Body System	Placebo	100mg BID	200mg QD	
	N=476	N=474	N=454	
	N (%)	N (%)	N (%)	P-Value*
APPLICATION SITE DISORDERS	0(0.0)	3(0.6)	1(0.2)	0.513
AUTONOMIC NERVOUS SYSTEM DISORDERS	7(1.5)	8(1.7)	8(1.8)	0.725
BODY AS A WHOLE-GENERAL DISORDERS	60(12.6)	61(12.9)	48(10.6)	0.346
CARDIOVASCULAR DISORDERS, GENERAL	0(0.0)	2(0.4)	0(0.0)	0.998
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	103(21.6)	88(18.6)	96(21.1)	0.839
ENDOCRINE DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
GASTRO-INTESTINAL SYSTEM DISORDERS	66(13.9)	89(18.8)	71(15.6)	0.446
HEARING AND VESTIBULAR DISORDERS	4(0.8)	5(1.1)	3(0.7)	0.772
HEART RATE AND RHYTHM DISORDERS	1(0.2)	2(0.4)	1(0.2)	0.969
LIVER AND BILIARY SYSTEM DISORDERS	0(0.0)	3(0.6)	0(0.0)	0.998
METABOLIC AND NUTRITIONAL DISORDERS	8(1.7)	7(1.5)	9(2.0)	0.728
MUSCULO-SKELETAL SYSTEM DISORDERS	23(4.8)	15(3.2)	11(2.4)	0.045
MYO ENDO PERICARDIAL & VALVE DISORDERS	1(0.2)	0(0.0)	1(0.2)	0.978
NEOPLASM	1(0.2)	1(0.2)	0(0.0)	0.388
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	2(0.4)	1(0.2)	0.457
PSYCHIATRIC DISORDERS	20(4.2)	16(3.4)	14(3.1)	0.356
RED BLOOD CELL DISORDERS	0(0.0)	1(0.2)	2(0.4)	0.146
REPRODUCTIVE DISORDERS, FEMALE	4(0.8)	2(0.4)	6(1.3)	0.436
REPRODUCTIVE DISORDERS, MALE	1(0.2)	0(0.0)	1(0.2)	0.978
RESISTANCE MECHANISM DISORDERS	5(1.1)	10(2.1)	6(1.3)	0.720
RESPIRATORY SYSTEM DISORDERS	39(8.2)	55(11.6)	58(12.8)	0.024
SKIN AND APPENDAGES DISORDERS	26(5.5)	17(3.6)	15(3.3)	0.096
SPECIAL SENSES OTHER, DISORDERS	0(0.0)	0(0.0)	2(0.4)	0.077
URINARY SYSTEM DISORDERS	9(1.9)	6(1.3)	4(0.9)	0.182
VASCULAR (EXTRACARDIAC) DISORDERS	0(0.0)	2(0.4)	1(0.2)	0.457
VISION DISORDERS	6(1.3)	4(0.8)	8(1.8)	0.506
WHITE CELL AND RES DISORDERS	1(0.2)	0(0.0)	1(0.2)	0.978

*p values were from the Mantel-Haenszel chi-square test

Table 4.6 lists the frequencies of all reported treatment related (relationship with treatment coded as "uncertain" or "probable" by the investigators) adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: Musculo-skeletol system.

Table 4.6 Number of Subjects Reporting Treatment-Related Adverse Events (6 week studies)

Body System	Placebo	100mg BID	200mg QD	
	N=476	N=474	N=454	
	N (%)	N (%)	N (%)	P-Value*
APPLICATION SITE DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
AUTONOMIC NERVOUS SYSTEM DISORDERS	5(1.1)	3(0.6)	5(1.1)	0.944
BODY AS A WHOLE-GENERAL DISORDERS	15(3.2)	16(3.4)	10(2.2)	0.396
CARDIOVASCULAR DISORDERS, GENERAL	0(0.0)	1(0.2)	0(0.0)	0.999
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	37(7.8)	32(6.8)	40(8.8)	0.564
GASTRO-INTESTINAL SYSTEM DISORDERS	46(9.7)	56(11.8)	47(10.4)	0.723
HEARING AND VESTIBULAR DISORDERS	1(0.2)	1(0.2)	2(0.4)	0.513
HEART RATE AND RHYTHM DISORDERS	1(0.2)	2(0.4)	1(0.2)	0.969
LIVER AND BILIARY SYSTEM DISORDERS	0(0.0)	3(0.6)	0(0.0)	0.998
METABOLIC AND NUTRITIONAL DISORDERS	5(1.1)	5(1.1)	7(1.5)	0.497
MUSCULO-SKELETAL SYSTEM DISORDERS	6(1.3)	4(0.8)	0(0.0)	0.020
MYO ENDO PERICARDIAL & VALVE DISORDERS	0(0.0)	0(0.0)	1(0.2)	0.212
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
PSYCHIATRIC DISORDERS	10(2.1)	7(1.5)	7(1.5)	0.507
RED BLOOD CELL DISORDERS	0(0.0)	0(0.0)	2(0.4)	0.077
REPRODUCTIVE DISORDERS, MALE	0(0.0)	0(0.0)	1(0.2)	0.212
RESISTANCE MECHANISM DISORDERS	0(0.0)	1(0.2)	1(0.2)	0.370
RESPIRATORY SYSTEM DISORDERS	4(0.8)	7(1.5)	7(1.5)	0.339
SKIN AND APPENDAGES DISORDERS	18(3.8)	6(1.3)	10(2.2)	0.111
SPECIAL SENSES OTHER, DISORDERS	0(0.0)	0(0.0)	2(0.4)	0.077
URINARY SYSTEM DISORDERS	2(0.4)	1(0.2)	0(0.0)	0.158
VASCULAR (EXTRACARDIAC) DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
VISION DISORDERS	4(0.8)	0(0.0)	5(1.1)	0.639

*p values were from the Mantel-Haenszel chi-square test

Table 4.7 lists the frequencies of all reported severe adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were not statistically significantly different (p> 0.05 by the Mantel-Haenszel chi-square test) in all the body systems.

Table 4.7 Number of Subjects Reporting All-Causalities Severe Adverse Events (6 week studies)

Body System	Placebo	100mg BID	200mg QD	
	N=476	N=474	N=454	
	N (%)	N (%)	N (%)	P-Value*
AUTONOMIC NERVOUS SYSTEM DISORDERS	2(0.4)	0(0.0)	0(0.0)	0.084
BODY AS A WHOLE-GENERAL DISORDERS	9(1.9)	3(0.6)	5(1.1)	0.263
CARDIOVASCULAR DISORDERS, GENERAL	0(0.0)	1(0.2)	0(0.0)	0.999
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	5(1.1)	8(1.7)	8(1.8)	0.369
GASTRO-INTESTINAL SYSTEM DISORDERS	7(1.5)	9(1.9)	5(1.1)	0.652
METABOLIC AND NUTRITIONAL DISORDERS	2(0.4)	0(0.0)	0(0.0)	0.084
MUSCULO-SKELETAL SYSTEM DISORDERS	3(0.6)	1(0.2)	0(0.0)	0.067
MYO ENDO PERICARDIAL & VALVE DISORDERS	1(0.2)	0(0.0)	1(0.2)	0.978
NEOPLASM	1(0.2)	0(0.0)	0(0.0)	0.221
PSYCHIATRIC DISORDERS	1(0.2)	1(0.2)	0(0.0)	0.388
REPRODUCTIVE DISORDERS, FEMALE	0(0.0)	0(0.0)	2(0.4)	0.077
RESISTANCE MECHANISM DISORDERS	0(0.0)	3(0.6)	0(0.0)	0.998
RESPIRATORY SYSTEM DISORDERS	0(0.0)	2(0.4)	1(0.2)	0.457
SKIN AND APPENDAGES DISORDERS	5(1.1)	1(0.2)	1(0.2)	0.070
URINARY SYSTEM DISORDERS	1(0.2)	0(0.0)	0(0.0)	0.221

*p values were from the Mantel-Haenszel chi-square test

Table 4.8 lists the frequencies of all reported treatment related (relationship with treatment coded as "uncertain" or "probable" by the investigators) severe adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were not statistically significantly different (p> 0.05 by the Mantel-Haenszel chi-square test) in all the body systems.

Table 4.8 Number of Subjects Reporting Treatment-Related severe Adverse Events (6 week studies)

Body System	Placebo N=476	100mg BID N=474	200mg QD N=454	
	N (%)	N (%)	N (%)	P-Value*
AUTONOMIC NERVOUS SYSTEM DISORDERS	2(0.4)	0(0.0)	0(0.0)	0.084
BODY AS A WHOLE-GENERAL DISORDERS	3(0.6)	1(0.2)	0(0.0)	0.067
CARDIOVASCULAR DISORDERS, GENERAL	0(0.0)	1(0.2)	0(0.0)	0.999
CENTRAL ANDPERIPHERAL NERVOUS SYSTEM DISORDERS	4(0.8)	3(0.6)	3(0.7)	0.742
GASTRO-INTESTINAL SYSTEM DISORDERS	6(1.3)	5(1.1)	2(0.4)	0.194
METABOLIC AND NUTRITIONAL DISORDERS	1(0.2)	0(0.0)	0(0.0)	0.221
MUSCULO-SKELETAL SYSTEM DISORDERS	1(0.2)	0(0.0)	0(0.0)	0.221
MYO ENDO PERICARDIAL & VALVE DISORDERS	0(0.0)	0(0.0)	1(0.2)	0.212
PSYCHIATRIC DISORDERS	1(0.2)	0(0.0)	0(0.0)	0.221
RESPIRATORY SYSTEM DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
SKIN AND APPENDAGES DISORDERS	3(0.6)	0(0.0)	1(0.2)	0.233

*p values were from the Mantel-Haenszel chi-square test

Reviewer's comments : In the two 6-week studies, the frequencies of reported adverse events by body system in the treatment groups were statistically significant (Table 4.5) in the musculo-skeletal system (p=0.045, Placebo group had the highest frequency) and the respiratory system (p=0.024, the two SC-58635 groups had higher frequencies). The frequencies of reported treatment related adverse events by body system in the treatment groups were statistically significant (Table 4.6) in the musculo-skeletal system (p=0.020, Placebo group had the highest frequency). The frequencies of all other reported adverse events, reported treatment-related adverse events, reported severe adverse events, reported treatment-related severe adverse events for the treatment groups were not statistically significant.

Reviewer's Summary and Conclusion (which may be conveyed to the sponsor):

Efficacy Results:

In Studies N49-96-02-020, N49-96-02-021and N49-98-06-054, the SC-58635 100 mg BID, and SC-58635 200 mg BID groups were demonstrated to be statistically superior to the placebo group in the treatment of OA of the knee for signs and symptoms, in terms of the primary efficacy variables. There were no statistically significant differences between the SC-58635 100 mg BID, SC-58635 200 mg BID groups, and the naproxan 500mg BID group. These results were supported by the analyses of the secondary and the supportive variables.

In Studies N49-98-06-060 and N49-98-02-087, the SC-58635 100 mg BID, and SC-58635 200 mg QD groups were demonstrated to be statistically superior to the placebo group in the treatment of OA of the knee, in terms of the primary efficacy variables. There were no statistically significant differences between the SC-58635 100 mg BID, and SC-58635 200 mg QD groups in these variables. These results were supported by the analyses of the secondary and the supportive variables.

Gastro-intestinal results:

In study N49- 96- 02- 021, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen 500mg BID group was significantly greater compared with all other treatment groups ($p \leq 0.05$). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ($p > 0.05$) or in the incidence of ulcers among the SC-58635 groups ($p \geq 0.05$).

In study N49- 97- 02- 062, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen 500mg BID group was significantly greater compared with the SC-58635 200mg BID group ($p \leq 0.05$).

In study N49- 97- 02- 071, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the Ibuprofen 800mg TID group was significantly greater when compared to the SC-58635 200mg BID group and the diclofenac 75mg BID group ($p \leq 0.05$). There was no difference in the incidence of gastroduodenal and gastric ulcers in the SC-58635 group and the diclofenac group ($p > 0.05$). The incidence of duodenal ulcers in the diclofenac group was significantly greater compared with the SC-58635 group ($p \leq 0.05$).

Conclusion:

The sponsor demonstrated that the SC-58635 100mg BID, 200 bid, 200mg QD groups were statistically superior to the placebo group in the treatment of the signs and the symptoms of OA of the knee, or the hip. The SC-58635 groups had lower incidence of ulceration (gastroduodenal, gastric, duodenal) than the naproxan 500mg BID group. In general, the frequency of reported adverse events for the SC-58635 groups were lower than the naproxan 500mg BID group.

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