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Arthritis Advisory Committee

Food and Drug Administration
Center for Drug Evaluation and Research

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Town Center Hotel
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NDA 20-998, Celebrex™, (celecoxib), Searle

Contents

Agenda and Questions

Volume I

Medical Reviews

Primary Medical Review

Secondary Medical Review

Safety Review

Gastrointestinal Review

Renal Review

Volume II

Statistical Reviews

Osteoarthritis

Rheumatoid Arthritis

Pain

Volume III

Pharmacology Reviews

Biopharmaceutics

Pharmacology/Toxicology

**Celebrex Capsules
(celecoxib)**

NDA 20-998

Medical Officer Review

Submission Date: June 29, 1998
Received Date: June 30, 1998
Review Date: July 8, 1998

Drug Name: Celebrex™

Generic Name: celecoxib

Applicant: G.D. Searle & Co.
4901 Searle Parkway
Skokie, IL 60077

Pharmacologic category: COX-2 inhibitor

Proposed Indication: Management of:

- pain
- rheumatoid arthritis
- osteoarthritis

Dosage forms and route: Oral capsule, 100 and 200 mg

Submission type: Original NDA

Orig NDA # 20-998
HFD-550/Div File
HFD-550/PM/Lutwak
HFD-550/Pharm/Yang
HFD-550/Chem/Bhavnagri
HFD-550/Biopharm/Bashaw
HFD-550/Statistics/Lin
HFD-550/MO/Witter

(James Witter, M.D., Ph.D. Medical Officer)

Celecoxib
NDA # 20-998

Medical Officer Review

Table of Contents

Executive Summary.....5

Background and Overview.....6

Single-Dose (Dental) Analgesia Trials.....

Multiple-Dose Analgesia Trial in Post-Orthopedic Surgery.....

Osteoarthritis Efficacy Trials.....8

Rheumatoid arthritis Efficacy Trials.....24

Celecoxib Integrated Efficacy Review.....

Platelet Safety Review.....

GI Safety Review.....

Renal Safety Review.....

Celecoxib Safety Review.....

Scientific Considerations.....

Overall Conclusions Regarding Celecoxib.....

Labeling Review.....

Appendices.....43

Celecoxib (Cx)
NDA 20-998

Listing of NDA Review Tables

Table 1:	Studies Included in NDA-20-998.....	7
Table 2:	Summary Characteristics of Osteoarthritis Trials.....	8
Table 3:	Number of Patients with OA Studied in All Protocols.....	10
Table 4:	Types/Numbers of Patients in Non-Flare Trials.....	22
Table 5:	Summary Characteristics of Rheumatoid Arthritis Trials.....	24
Table 6:	Number of Patients with RA Studied in All Protocols.....	25
Table 7:	Disposition of Patients in Protocol 024.....	41

Listing of Appendix Tables/Figures:

Table A.1:	Schedule of Observations and Procedures (Protocol 020)
Table A.2:	Baseline demographics (Protocols 020, 021, 054)
Table A.3:	Baseline demographics (Protocols 060, 087)
Table A.4:	WOMAC Index
Table A.5:	Osteoarthritis Severity Index (knee)
Table A.6:	Osteoarthritis Severity Index (hip)
Table A.7:	Physician's Global Assessment (Protocol 054)
Table A.8:	Patient's Global Assessment (Protocol 054)
Table A.9:	Patient's Assessment of Arthritis Pain (Protocol 020)
Table A.10:	Patient's Assessment of Arthritis Pain (Protocol 054)
Table A.11:	WOMAC Pain (Protocol 054)
Table A.12:	WOMAC Pain (Protocol 020)
Table A.13:	WOMAC Stiffness (Protocol 054)
Table A.14:	WOMAC Stiffness (Protocol 020)
Table A.15:	WOMAC Function (Protocol 054)
Table A.16:	WOMAC Function (Protocol 020)
Table A.17:	WOMAC Composite (Protocol 054)
Table A.18:	WOMAC Composite (Protocol 020)
Table A.19:	Withdrawal-Lack of Arthritis Efficacy (Protocols 020, 054)
Table A.20:	Time to Withdrawal-Lack of Arthritis Efficacy (Protocol 054)
Table A.21:	Time to Withdrawal-Lack of Arthritis Efficacy (Protocol 020)
Table A.22.1:	Reasons for Study Termination (Protocols 020, 021, 054)
Table A.22.2:	Reasons for Study Termination (Protocols 060, 087)
Table A.23:	Schedule of Observations and Procedures (Protocol 060)
Table A.24:	Patient's Global Assessment (Protocol 087)

Listing of Appendix Tables/Figures (continued):

Table A.25:	Physician's Global Assessment (Protocol 087)
Table A.26:	Patient's Assessment of Arthritis Pain (Protocol 060)
Table A.27:	Patient's Assessment of Arthritis Pain (Protocol 087)
Table A.28:	WOMAC Pain (Protocol 060)
Table A.29:	WOMAC Pain (Protocol 087)
Table A.30:	Withdrawal-Lack of Arthritis Efficacy (Protocols 060, 087)
Table A.31:	Time to Withdrawal-Lack of Efficacy (Protocols 060, 087)
Table A.32:	Schedule of Observations and Procedures (Protocol 022)
Table A.33:	Baseline demographics (Protocols 022, 023)
Table A.34:	Physician's Global Assessment (Protocol 023)
Table A.35:	Patient's Global Assessment (Protocol 023)
Table A.36:	Number of Tender/Painful Joints (Protocol 022)
Table A.37:	Number of Swollen Joints (Protocol 023)
Table A.38:	ACR-20 Responder Index (Protocol 022-ITT)
Table A.38.3:	ACR-20 Responder Index (Protocol 023-Evaluable)
Table A.39.1:	ACR-50 Responder Index (Protocol 022-ITT)
Table A.39.2:	ACR-50 Responder Index (Protocol 023-ITT)
Table A.40:	Patient's Assessment of Arthritis Pain-VAS (Protocol 023)
Table A.41:	C-Reactive Protein (Protocol 023)
Table A.42:	HAQ Functional Disability Index (Protocol 023)
Table A.43:	Withdrawal-Lack of Arthritis Efficacy (Protocols 022, 023)
Table A.44:	Time to Withdrawal-Lack of Arthritis Efficacy (Protocol 023)
Table A.45:	Summary of Dosage Change-OA/RA (Protocol 024)
Figure A.1:	Patient's Global Assessment-OA/RA (Protocol 024)

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Celecoxib Executive Summary

Significant Issues

- If approved, celecoxib would be the first so-called "COX-2 selective" agent approved in the U.S. In fact, as noted below, it is suggested that celecoxib be called a "specific" COX-2 inhibitor. The biological and clinical implications of this designation are, at present, not fully characterized.
- Although the single-dose, dental pain trials have established that celecoxib is efficacious compared to placebo, the other postsurgical pain trials did not confirm the analgesic properties of the proposed doses.
- Because serum bicarbonates were not measured, the NDA database cannot exclude an adverse effect of celecoxib on acid-base balance.
- Celecoxib is efficacious in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis at the proposed doses.

Highlights

- Endoscopic data with celecoxib have found that it is associated with fewer endoscopically-defined ulcers as compared to duplicate studies with ibuprofen and naproxen. However, celecoxib was associated with fewer ulcers in only one of two such endoscopic studies with diclofenac.
- The overall safety profile of celecoxib suggests at this time that it is generally more comparable to NSAIDs (ibuprofen, diclofenac, naproxen) than to placebo.
- If approved, celecoxib would be the first compound with properties similar to currently understood NSAIDs to successfully employ the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index as well as the American College of Rheumatology (ACR-20) Responder Index for rheumatoid arthritis in a New Drug Application.

BACKGROUND AND OVERVIEW:

Celecoxib (Cx) is the USAN name for 4-[5-(methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide which is a diarylsubstituted pyrazole compound. The trade name for this same compound is *Celebrex* while the code name is *SC-58635*. Cx was originally developed as a "selective" prostaglandin G/H synthase-2 (i.e. *COX-2*) inhibitor. However, during the development of this compound, Cx is now presented as a "specific" COX-2 inhibitor (SCI). According to current thinking, such "SCI inhibitors" at therapeutic doses would inhibit COX-2 and would be maximally effective in treating inflammation and pain, but would not inhibit COX-1 activity involved in normal physiologic function (see below). In fact, many regard this compound as a new class of anti-inflammatory and analgesic agents.

From studies dating back only to the late 1980's and early 1990's, it became clear that there must be another isoform of human cyclooxygenase (COX), the enzyme which catalyzes the rate-limiting step in converting arachidonic acid to prostaglandins (PG), thromboxanes, and leukotrienes. For example, early experiments with endotoxin-treated monocytes showed that the significant increase in PGE₂ was inhibited by dexamethasone, this corticosteroid is not known to alter the transcription of COX-1. Subsequently, the theory has evolved that COX-1 and COX-2 may subserve different roles in the body. Originally, COX-1 was postulated to be a constitutive form of COX involved in "house-keeping" functions, such as maintenance of the gastrointestinal (GI) tract mucosal integrity, normal platelet function, and renal function while COX-2 represented the inducible form of COX involved in inflammation and pain. Similarly, it was postulated early that COX-1 was present in all cells (and, most importantly, in platelets) while COX-2 was only distributed at sites of inflammation, such as arthritic joints; COX-2 was not present in platelets (since they lack the transcriptional machinery necessary to produce this inducible enzyme).

Currently, it is appreciated that the COX story is much more complicated, and potentially much more interesting. For example, it is now accepted that COX-2 can also be constitutively expressed in areas like the kidney and brain whereas previously these areas were felt to be devoid of any significant COX-2. The situation of whether COX-2 is present in the human GI tract has also rapidly evolved in the last few years. Early on, it was felt that COX-2 was not present in the human GI tract but now it is clear that this enzyme is not only present in the lower GI tract, it is a target for prophylactic therapy of colonic cancer. Similarly, COX-2 is now recognized to be increased in the upper GI tract in situations of ulcer healing or infection with *Helicobacter pylori* infection. Conversely, there is an understanding that COX-1 can also be inducible under certain experimental systems and COX-1 may be upregulated in situations when COX-2 is absent or blocked; animals models have been particularly illustrative in this regard. Finally, it is becoming evident that COX-2 may also play important roles in Alzheimer's disease, cardiovascular disease, angiogenesis, along with their already recognized important roles in inflammation, pain and pyrexia.

While on the surface, NDA 20-998 might appear to represent just another drug to review, in reality one could easily argue it represents a test to the various hypotheses of the proposed roles of COX-2 in human health and disease. While reviewing this NDA, the reader is therefore encouraged to constantly question whether we are testing a drug, a theory, or both with this compound? It will be of interest to see where this NDA positions itself in the future in terms of helping to address some of these very important biological and clinical questions.

A total of 51 trials were submitted to support NDA 20-998. As detailed in the Table 1 below, these 51 trials have been divided by the Sponsor into three basic types of studies (Phase 1, Arthritis, Postsurgical analgesia):

Table 1: Studies Included in NDA 20-998

TYPE OF STUDY	NO. OF STUDIES	STUDY NUMBERS
Phase 1		
Single dose	9	001, 006, 009, 018, 019, 037, 044, 084, 088
Multiple dose	11	003, 004, 010, 014, 015, 026, 032, 033, 043, 065, 069
Drug Interaction	7	017, 038, 039, 040, 050, 051, 072
Hepatic Impairment	1	016
Renal Impairment	1	038
Arthritis		
OA		
Pivotal Efficacy	5	020, 021, 054, 060, 087
Supportive	3	042, 013, 047
RA		
Pivotal Efficacy	2	022, 023
Supportive	2	041, 012
OA/RA combined	2	062, 071
Long-term open label	1	024
Postsurgical Analgesia		
Dental pain		
Pivotal Efficacy	3	025, 027, 070
Supportive	1	005
Surgical Pain		
Pivotal Efficacy	1	028
Supportive	2	029, 080
Total	51	

To facilitate review of the clinical aspect of this NDA, several different Divisions within CDER have been engaged. In particular, these consultant reviews have focused on platelet effect and function, along with the effects of Cx on the GI tract and kidneys. This review will attempt to integrate the highlights of these critically important consultant reviews but the interested reader is referred to these original reviews for in-depth details.

Osteoarthritis Efficacy

Ten studies were conducted to establish efficacy in OA. These trials consisted of both placebo-controlled and active-controlled trials with durations from 2 to 12 weeks. Also, a few of the trials (062, 071 and 042) employed "non-flare" designs and different entry criteria, as discussed below. Some basic characteristics of these OA trials are described in Table 2.

Table 2: Summary characteristics of Osteoarthritis trials:

12-Week Pivotal Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-020 R: N49-98-06-020 Celecoxib Comparative Safety and Efficacy vs Naproxen in OA of the Knee	72 Investigators U.S. and Canada 5 Aug 1996	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo
P: N49-98-02-021 R: N49-98-06-021 Celecoxib Comparative Efficacy and UGI Safety vs Naproxen in OA of the Knee	80 Investigators U.S. and Canada 26 Aug 1996	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo
P: N49-96-02-054 R: N49-98-06-054 Celecoxib Comparative Safety and Efficacy vs Naproxen in OA of the Hip	125 Investigators U.S. and Canada 9 Jan 1997	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 50 mg BID, 100 mg BID, or 200 mg BID or Naproxen 500 mg BID or Placebo

6-Week Pivotal Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-060 R: N49-98-06-060 QD vs BID Efficacy in OA of the Knee	51 Investigators United States 29 May 1997	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Celecoxib 200mg QD or Placebo
P: N49-98-02-087 R: N49-98-06-087 QD vs BID Efficacy in OA of the Knee	101 Investigators United States 28 Jan 1998	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Celecoxib 200mg QD or Placebo

Placebo-Controlled Supportive Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-047 R: N49-97-06-047 Dose-ranging Efficacy in OA	26 Investigators United States 9 Jan 1997	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (4 Weeks)	Celecoxib 25 mg BID, 100 mg BID or 400 mg BID or Placebo
P: N49-96-02-013 R: N49-96-16-013 Pilot Efficacy in OA	26 Investigators United States 26 Jan 1996	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (2 Weeks)	Celecoxib 40 mg BID, 100 mg BID or 200 mg BID or Placebo

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Active-Controlled Supportive Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: 149-96-02-042 R: 149-96-06-042 Ex-U.S. OA Trial	129 Investigators 20 countries in Australia, Europe and South Africa 2 Dec 1996	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (6 Weeks)	Celecoxib 100 mg BID or Diclofenac 50 mg BID
P: N49-97-02-062 R: N49-98-06-062 Comparative Incidence of UGI Ulcers: Celecoxib vs Naproxen in Patients with OA and RA	75 Investigators in United States 13 May 1997	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 200 mg BID or Naproxen 500 mg BID
P: N49-97-02-071 R: N49-98-06-071 Comparative Incidence of UGI Ulcers: Celecoxib vs Diclofenac and Ibuprofen in Patients with OA and RA	121 Investigators in United States 21 Jul 1997	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 200mg BID or Diclofenac 75 mg BID or Ibuprofen 800 mg TID

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Reviewer's comment: Since all the placebo-controlled trials employed the same primary endpoints (as noted below), this review will focus primarily on two 12-week protocols (i.e. 020 and 054) to discuss the efficacy and dose-response characteristics of Cx; these trials are considered "pivotal" by the sponsor. In addition, two trials (i.e. 060 and 087) will also be reviewed since these studies explored the question of efficacy with different dosing regimens of Cx (i.e. BID vs. QD). The results of other protocols will be added and/or summarized as appropriate.

Study Characteristics:

As noted in Table 2 above, studies 020 and 054 were double-blind, placebo-controlled, multicenter, parallel group comparisons of Cx versus placebo and naproxen in patients with OA of the knee (020) and hip (054). Protocol 054 was amended on November 4, 1996 (Amendment No. 5), to include only patients with OA of the knee; hip patients were not included in the efficacy analyses. The hip or knee joint studied was designated the "Index Joint".

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Table 3: Number of Patients with OA studied in all protocols (excludes open-label)

Study	Treatment (mg/day)										Total
	Plc	Celecoxib						Naproxen	Diclofenac	Ibuprofen	
		50	80	100	200	400	800	1000	150	2400	
013	71	-	73	-	76	73	-	-	-	-	293
047	101	101	-	-	101	-	99	-	-	-	402
020	203	-	-	203	197	202	-	198	-	-	1003
054	217	-	-	216	207	213	-	207	-	-	1060
021	242	-	-	252	240	233	-	226	-	-	1193
060	231	-	-	-	453	-	-	-	-	-	684
087	243	-	-	-	472	-	-	-	-	-	715
062 ¹	-	-	-	-	-	194 (270)	-	195 (267)	-	-	389 (537)
071 ¹	-	-	-	-	-	272 (366)	-	-	285 (387)	255 (345)	812 (1098)
042	-	-	-	-	346	-	-	-	341	-	687
Total	1308	101	73	671	2092	1187	99	826	626	255	7238

1. Numbers in () = total number of patients with OA studied in these protocols (i.e. remainder had RA)

As can be seen in the table above, between protocols 020 and 054, a total of 2063 patients were enrolled and received at least one dose of study drug as follows:

- placebo 420
- Cx 50 mg BID 419
- Cx 100 mg BID 404
- Cx 200 mg BID 415
- Naproxen 500 mg BID 405

These studies consisted of Arthritis Assessments at pretreatment screening, at Baseline prior to dosing with study drug (i.e. after a flare, see below), and at treatment Week 2, Week 6 and Week 12 following the first dose of study drug (see *Appendix Table A.1* for details of Protocol 020 as an example of the schedule of observations and procedures).

The criteria for demonstrating OA flare depended on whether the patient was currently receiving NSAID/analgesic therapy for his/her OA (Category 1), or was not receiving NSAID/analgesic therapy, and had uncontrolled OA (Category 2). For patients receiving NSAID or analgesic therapy for OA (Category 1), an OA flare was demonstrated if both the Baseline Patient's Global Assessment of Arthritic Condition and the Baseline Physician's Global Assessment of Arthritic Condition were rated as "fair," "poor" or "very poor" and a comparison of the Screening Visit Arthritis Assessments and the Baseline Visit Arthritis Assessments met at least three of the following four criteria:

1. Patient's Assessment of Pain (100 mm VAS) at Baseline of at least 40.
2. An increase of two or more points in the Osteoarthritis Severity Index.
3. An increase of one or more grades in the Patient's Global.
4. An increase of one or more grades in the Physician's Global.

Patients who did not demonstrate an OA flare within 14 days of discontinuing NSAID or analgesic treatment for OA were not eligible for enrollment.

For patients who were not receiving treatment for their OA and whose OA was not controlled (Category 2), an OA flare was demonstrated if they met at least three of the following four criteria during the Baseline Arthritis Assessments:

1. Patient's Assessment of Pain at least 40 mm on VAS;
2. The Osteoarthritis Severity Index was ≥ 7 .
3. The Patient's Global Assessment of Arthritic Condition was "poor" or "very poor".
4. The Physician's Global Assessment of Arthritic Condition was "poor" or "very poor."

Patients satisfying this criteria were assigned a patient number and completed the Baseline Visit. Any patient not satisfying the arthritis flare criteria was not assigned a patient number and was considered a screen failure.

Patients who met the inclusion criteria (see below) were randomly assigned to receive Cx 50 mg BID, Cx 100 mg BID, Cx 200 mg BID, naproxen 500 mg BID, or placebo.

To qualify for inclusion in either trial (020 or 054), candidates must have:

1. Been of legal age of consent or older;
2. For women of childbearing potential, confirmed use of adequate contraception since last menses and confirmed continued use of adequate contraception during the study, were not lactating, and had a negative serum pregnancy test within 14 days prior to the Baseline Arthritis Assessments;
3. Been diagnosed according to the American College of Rheumatology (ACR) criteria as having OA of the knee or hip;
4. Had a Functional Capacity Classification of I-III at the Baseline Visit;
5. Had OA in a flare state at the Baseline Visit; and
6. Provided written informed consent before undergoing any study procedure.

Exclusion criteria included:

1. Any inflammatory arthritis or gout (patients with fibrositis or fibromyalgia were not excluded) or any acute joint trauma at the knee with OA;
2. An anticipated need for any surgical or other invasive procedure (e.g., arthroscopy or lavage) that would have been performed on the knee with OA during the course of the study;
3. Received oral, intramuscular, intra-articular, or soft-tissue injections of corticosteroids within four weeks before the first dose of study medication;

4. Taken any NSAIDs or any analgesic within 48 hours before the Baseline Arthritis Assessments. (Patients taking ≤ 325 mg aspirin per day for non-arthritic reasons, if stable for at least 30 days before the first dose of study medication, were allowed to continue their aspirin regimen for the duration of the study. Patients must have discontinued piroxicam and/or oxaprozin at least four days before the Baseline Arthritis Assessments.);
5. An active malignancy of any type or history of a malignancy. (Patients who had a history of basal cell carcinoma that had been treated were eligible. Patients with a history of other malignancies that had been surgically removed and who had no evidence of recurrence for at least five years before study enrollment were also eligible.);
6. Diagnosed as having or had been treated for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to the first dose of study medication;
7. Active GI disease (e.g., inflammatory bowel disease), a chronic or acute renal or hepatic disorder, or a significant coagulation defect;
8. Abnormal screening laboratory test values > 1.5 x upper limits of normal (ULN) for either aspartate transaminase (AST, SGOT) or alanine transaminase (ALT, SGPT) or any other laboratory abnormalities considered by the Investigator to be clinically significant within 14 days before the Baseline Arthritis Assessments;
9. Known hypersensitivity to COX-2 inhibitors, sulfonamides, or NSAIDs;
10. Received any investigational medication within 30 days before the first dose of study medication or was scheduled to receive an investigational drug, other than study medications described in the protocol, during the course of this study; or
11. Previous admission to this study.

Demographics:

There did not appear to be any remarkable differences in baseline demographics between treatment groups in the 12-week (*Appendix, Table A.2*) or 6-week (*Appendix, Table A.3*) protocols. These patients were mostly elderly, white females with OA involving the knee. However, it is interesting to note (as shown below) that the patients in the knee protocol (020) were generally heavier than those in the hip protocol (054).

Protocol	Weight (kg)	Treatment				
		Placebo	Cx 50 BID	Cx 100 BID	Cx 200 BID	Naproxen 500 BID
020	mean	87.7	88.5	85.8	89.1	90.8
	range	49-176	43-152	50-174	53-186	45-201
054	mean	82.8	83.9	83.1	83.2	83.8
	range	41-154	41-154	44-159	36-145	40-156

Primary/Secondary Endpoints

In the OA studies, the **original** primary endpoints were:

- Patient's Global Assessment of Arthritic Condition
- Patient's Assessment of Arthritis Pain - VAS
- Physician's Global Assessment of Arthritic Condition

The per protocol secondary measures of arthritis efficacy were:

- Functional Capacity Classification
- WOMAC OA Index
- Incidence of Withdrawal Due to Lack of Arthritis Efficacy
- Time to Withdrawal Due to Lack of Arthritis Efficacy
- Osteoarthritis Severity Index (OSI)
- APS Pain Measure
- Patient Assessment of Function
- SF-36 Health Survey.

A modification of the primary and secondary efficacy variables occurred as a result of recommendations from the **Agency**. The principal change was the inclusion of the **WOMAC Index** for osteoarthritis as a primary measure of efficacy. Therefore, the **retrospectively defined primary OA efficacy endpoints included:**

- Patient's Global Assessment of Arthritic Condition
- Patient's Assessment of Arthritis Pain (VAS):
 - "How much pain are you having because of OA in your index hip/knee"
 - 0 mm = no pain, 100 mm = most severe pain
- Physician's Global Assessment of Arthritic Condition
- WOMAC OA Index
 - Composite plus subscores for pain, joint stiffness, and physical function

The **Patient's Global Assessment** is based on the patient's response to the question, "Considering all the ways your arthritis affects you, how are you doing today?" The **Physician's Global Assessment** is based on the patient's disease signs at the time of the visit. The categorical (from grade 1-5, respectively) answers to these questions are:

- | | |
|------------|---|
| •very good | Asymptomatic and no limitation of normal activities |
| •good | Mild symptoms and no limitation of normal activities |
| •fair | Moderate symptoms and limitation of some normal activities |
| •poor | Severe symptoms and inability to carry out most normal activities |
| •very poor | Very severe symptoms with an inability to carry out all normal activities |

The Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index is a tri-dimensional, self-administered questionnaire that probes clinically important, patient-relevant outcomes in patients with OA of the hip and/or knee. The patient responded to 24 component items: 5 regarding pain, 2 regarding stiffness, and 17 regarding physical function (see *Appendix, Table A.4*).

The Osteoarthritis Severity Index (OSI) of the knee (see *Appendix Table A.5*) or hip (see *Appendix Table A.6*) is based on the patient's responses to questions related to pain, walking distance, and activities of daily living. The Osteoarthritis Severity Index is the sum of scores of the eight inquiries and ranges from 0 to 24, with a lower score indicating a better condition.

The physician assessed the **Functional Capacity** of the patient according to Steinbrocker's criteria as noted below (IV patients not enrolled):

Class	Description
I	Complete functional capacity with ability to carry on all usual duties without handicaps
II	Functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints
III	Functional capacity adequate to perform only few or none of the duties of usual occupation or of self care
IV	Largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self care

Quality of Life

Scores of eight domains (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health) for the SF-36 Health Survey were observed at Baseline, Week 2, and Week 12 (or Early Termination).

The APS pain measure consists of five questions:

1. Have you experienced any pain in the past 24 hours? (yes or no)
2. How much pain are you having right now? (0-10)
3. Indicate the worst pain you have had in the past 24 hours. (0-10)
4. Indicate the average level of pain you have had in the past 24 hours. (0-10)
5. Indicate how pain has interfered with you in:
 - General Activity (0-10)
 - Mood (0-10)
 - Walking ability (0-10)
 - Relations with other people (0-10)
 - Sleep (0-10)
 - Normal work, including house work (0-10)
 - Enjoyment of life (0-10)

Patient Populations Analyzed/Statistics:

Intent-to-Treat (ITT) Cohort

The ITT Cohort included all patients who had OA of the index joint (hip/knee), who were randomized to treatment and who had taken at least one dose of study medication. The Last Observation Carried Forward (LOCF) approach was used for either missing data or data that was obtained on days that fell outside the observation window (i.e. > 19 days for Week 2, >49 days for Week 6, and >93 days for Week 12). The LOCF approach was employed in the ITT analyses only.

Evaluable Cohort

The Evaluable Cohort included each patient who satisfied the requirements for the ITT Cohort and met the following criteria:

1. Was diagnosed by the ACR criteria for having OA of the knee/hip;
2. Had a Functional Capacity Classification of I-III at the Baseline Visit;
3. Had OA in a flare state at the Baseline Visit;
4. No inflammatory arthritis, gout or any acute joint trauma at the knee/hip;
5. No corticosteroids within four weeks of the first dose of study medication;
6. Did not take NSAIDs or any analgesic within 48 hours before any study visit;
7. Had baseline arthritis assessments within seven days before the first dose;
8. No surgical or other invasive procedure performed on the knee/hip during the study;
9. Did not take any NSAIDs (other than > 325 mg aspirin/day), oral or injectable corticosteroids, or analgesic (other than acetaminophen \leq 2 g/day for non-arthritic reasons) during the study;
10. Was compliant with study medications as described below:
 - For the Week 2 Visit: took at least 70% of the doses prescribed from Day 1 through the Week 2 Visit; or
 - For the Week 6 Visit: took at least 70% of the doses prescribed from the Week 2 through the Week 6 Visit and took at least 50% of the doses prescribed from Day 1 through the Week 2 Visit; or
 - For the Week 12 Visit: took at least 70% of the doses prescribed from the Week 6 Visit through the Week 12 Visit and at least 50% of the doses prescribed from the Week 2 Visit through the Week 6 Visit and 50% of the doses prescribed from Day 1 through the Week 2 Visit.
11. Underwent the Arthritis Assessments for each visit according to the following schedule:
 - a. 14 ± 5 days after the first dose of study medication for the Week 2 Visit;
 - b. 42 ± 7 days after the first dose of study medication for the Week 6 Visit;
 - c. 84 ± 9 days after the first dose of study medication for the Week 12 Visit; and
 - d. ≤ 2 days after the last dose of study medication for the Final Visit.
12. Had complete primary efficacy data available for each visit under consideration.

Patients who did not have data for all primary efficacy variables at baseline were excluded from all analyses. Evaluability determinations were made prior to unblinding the data and no subsequent revisions were made.

Observed Data Cohort

A patient's data at a specific visit were included in this analysis if he or she satisfied the requirements for the ITT Cohort and the corresponding assessment days after the first dose of study medication fell in the following intervals: 14 ± 5 days for Week 2; 42 ± 7 days for Week 6; and 84 ± 9 days for Week 12.

The analyses were performed for Evaluable and Observed Data Cohorts at all scheduled visits and also at the 'Final Visit', which consisted of the last valid observation of the patient.

The Physician's and Patient's Global Assessments were classified based on changes as "improved" (a reduction of at least two grades from Baseline for grades 3-5 or a change in grade from 2 to 1), "no change," or "worsened" (an increase of at least two grades from Baseline for grades 1-3 or a change in grade from 4 to 5) and analyzed by the Cochran-Mantel-Haenszel (CMH) test stratified by center.

Mean change analyses, including the linear trend test for all Cx and placebo groups, and overall and pairwise comparisons for all five treatment groups were performed by using analysis of covariance (ANCOVA) with treatment and center as factors, and the corresponding Baseline score as covariate. Additionally, the Q-Ratio with 95% confidence intervals was calculated by taking the ratio of adjusted mean changes for each Cx treatment groups vs. the naproxen treatment group.

The results of the pairwise comparisons for the Cx 100 mg BID and 200 mg BID treatment groups vs. placebo were interpreted using Hochberg's step-up procedure. P-values of comparisons between Cx 100 mg BID and Cx 200 mg BID vs. placebo for the ITT Cohort were ordered from larger to smaller. The larger p-value was examined first, and, if $p < 0.05$, then it was declared that both doses were significantly different from placebo and no further examination was performed. If the larger p value was > 0.05 , the smaller p-value was checked. If the smaller p-value was ≤ 0.025 , then the corresponding dose was claimed to be significantly different from placebo. For other comparisons, an alpha level of 0.05 was used to summarize the results.

The above categorical and mean change analyses were performed on the ITT Cohort, the Evaluable Cohort and the Observed Data Cohort.

The categorical status of "improved," "no change," or "worsened" for the Global Assessments of Arthritic Condition was also calculated for each patient based on a one-grade change from Baseline. These analyses were performed for the ITT Cohort. In addition, for the ITT Cohort with LOCF approach, differential effects of gender, age and duration of disease were examined by ANCOVA models including factors as follows:

1. Age or gender or duration and center, treatment, and Baseline;
2. Age by gender or age by duration or gender by duration, lower order terms, and center, treatment, and Baseline;
3. Age by treatment, lower order terms, center, and Baseline;
4. Gender by treatment, lower order terms, center, and Baseline; and
5. Duration by treatment, lower order terms, center, and Baseline.

Mean change from Baseline for quality of life data observed at Week 2 and Week 12 or Early Termination was analyzed using ANCOVA with treatment and center as factors and corresponding Baseline score as covariate. This analysis was performed on the ITT Cohort only. For the mean change, a positive value represents an improvement and a negative value represents a worsening.

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Efficacy Results for OA:

Reviewer's comment: The following comments of OA efficacy refer ONLY to the ITT LOCF analysis.

Primary endpoints:

Patient and physician globals in both studies showed that Cx at all doses studied (i.e. 50 mg BID, 100 mg BID, 200 mg BID) was efficacious vs. placebo. For example, the Physician's Global Assessment of Arthritis Pain (see *Appendix Table A.7.1 and A.7.2*) and Patient's Global Assessment of Arthritis Pain (see *Appendix Table A.8.1 and A.8.2*) in protocol 054 shows improvements (categorical and mean analyses) over time in all treatment groups; it should be noted that improvements were based upon a two (2) categorical change in globals (see above). Improvements in the global scores seemed to be maintained during the 12 weeks of this trial. Celecoxib at all doses is better than placebo and comparable to Naproxen but, overall, patients are still symptomatic. With these endpoints, there does not appear to be any additional benefit from the higher doses of Cx. Comparison by Q values also suggests there are no differences between doses of Cx and Naproxen in either the patient or physician global. Results are similar for protocol 020.

Patient's assessment of arthritis pain also demonstrated in both studies that Cx at all doses studied (with the exception of 50 mg BID in protocol 020) was efficacious as compared to placebo. After flare occurred, baseline pain scores appeared comparable (see *Appendix Table/Figure A.9.1-2 and Table/Figure A.10.1-2*) across treatment groups as well as across studies; these pain scores improved ($p < 0.05$, except Cx 50 mg BID in protocol 020) over time with Cx; improvements appeared comparable to those seen with Naproxen. There seemed to be no additional improvement at 12 weeks (in fact, there are some suggestions of waning of response at 12 weeks). Interestingly, comparison by Q values also suggests there are no differences between all doses of Cx and Naproxen. Utilizing these endpoints, there does not appear to be any additional benefit from the higher doses of Cx. Also of note, patients are still apparently symptomatic as judged by the week 12 pain scores.

As noted above, the **WOMAC scores** were added as primary outcomes in the course of the IND development. Both the WOMAC subscales (i.e. pain, stiffness, function) and the WOMAC composite showed Cx at all doses in both trials to be efficacious compared to placebo (see *Appendix A.11-A.18*). Effect sizes were comparable to Naproxen. There were generally consistent differences between the lower (i.e. 50 mg BID) and higher (i.e. 100/200 mg BID) doses of Cx; but not between the higher doses. As noted with the other primary endpoints, patients improved but were still apparently symptomatic.

Secondary endpoints:

In protocols 054 and 020, the **OSI index** correlated well with the results of the primary endpoints at all doses of Cx (data not shown). This index again suggested that there was a dose response between 50 mg BID and the higher doses of Cx but nothing consistently different between the higher doses.

The **SF 36 index** did not generally reveal any significance at the lower dose of Cx used for short periods of time (i.e. 25 and 40 mg BID in studies 047 and 013, respectively), but did show significance for the physical functioning, role physical, bodily pain, vitality, social functioning, and mental health at Cx doses of ≥ 50 mg BID.

Withdrawal due to **lack of arthritis efficacy** (i.e. treatment failure) shows a similar trend in both studies, although the placebo rates differ (see *Appendix A.19*). Higher doses of Cx generally lead to fewer patients withdrawing from the study, this was most evident in protocol 054. Top doses of Cx had similar rates of withdrawal to that of Naproxen.

Time to withdrawal due to lack of arthritis efficacy (see *Appendix A.20-A.21*) showed that all doses of Cx were significantly different than placebo and tended to be similar to Naproxen, especially at the higher doses of Cx; these trends were more obvious in the hip study (054).

As can be seen, the **reasons for study termination** (in all groups) were primarily due to treatment failure in study 020 and 054, as was the case for all the placebo-controlled trials (see *Appendix A.22.1-.2*). There was a decrease in these treatment failure rates, compared to placebo, in the Cx-treated patients which tended to plateau at the higher doses and was similar (sometimes better, sometimes worse) to the rates seen with Naproxen. On the other hand, termination for an adverse event tended to increase with increasing doses of Cx. With one exception (Cx at 100 mg BID, study 020), Cx was comparable to (or better than) Naproxen while tending to be worse than (or comparable to) placebo in terms of adverse event rates. Not unexpectedly, termination due to treatment failure and for adverse events were lower, in these six-week vs. the twelve-week studies.

Other OA Studies

As noted in **Table 3** above, protocol 021 was also a 12 week trial in OA of the knee. The study design, treatments, patient demographics and number of patients treated, as well as primary and secondary endpoints were similar (if not identical) to both protocols 020 and 054. The results of the primary and secondary endpoints show no significant differences from those seen in the other 12 week trials in OA as noted above. The **4-week (047) OA trial** showed Cx 25 mg BID to be ineffective while the 100 mg BID dose of Cx showed significance only for the globals and not the VAS pain scale or WOMAC. However, in this study, a dose of 400 mg BID showed efficacy in all these four primary endpoints.

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Single-dose (QD) vs. multiple-dose (BID) OA trials:

There were two randomized, double-blind, placebo-controlled, parallel group, multicenter six week trials that addressed the issue of alternate dosing schedules for Cx (see **Table 1 and 2** above). Both of these studies (i.e. **protocol 060 and 087**) involved patients with OA of the (“Index joint”) knee that was in “flare” (see definition above for 12 week studies) and they both employed the same doses of Cx, either 200 mg QD (evening, with placebo in the morning) or 100 mg BID (morning and evening). The schedule of observations and procedures in these two trials (for an example in study 060, see *Appendix, Table A.23*) differed primarily in that the SF-36 and samples for PK analysis were not collected in study 087. Inclusion and exclusion criteria for patients to participate in these studies were similar to the 12 week studies discussed above.

Between protocol 060 and 087, a total of 1399 patients were enrolled and received at least one dose of study drug as follows:

•placebo	474 patients
•SC-58635 100 mg BID	472 patients
•SC-58635 200 mg QD	453 patients

Primary measures of arthritis efficacy were Patient’s Global Assessment of Arthritic Condition, Patient’s Assessment of Pain-Visual Analog Scale (VAS), and Physician’s Global Assessment of Arthritic Condition. **Secondary measures of arthritis efficacy** were Functional Capacity Classification, WOMAC Index, Incidence of Withdrawal Due to Lack of Arthritis Efficacy, Time to Withdrawal Due to Lack of Arthritis Efficacy, and Osteoarthritis Severity Index.

The patient **demographics** were comparable to those of the 12 week studies being elderly, white females; there were no obvious imbalances between the treatment groups in these 6 week studies.

Primary endpoints:

Both the **patient and physician’s globals** showed similar trends and effect sizes for patients treated with Cx to those seen at comparable times, and at comparable doses, in the 12 week OA studies (for example in protocol 087, see *Appendix Table A.24.1-.2 and Table A.25.1-.2*); the placebo responses appeared generally more robust in the 6 week studies. Both dosing regimens of Cx were significantly different than placebo while there did not appear to be any difference between the two doses of Cx (either by Q-ratios or p values).

The patient's assessment of arthritis pain also revealed the patients to have been comparable to the patients in the 12-week studies, both in terms of their baseline pain, and their response to treatment (see *Appendix Table A.26 and A.27*). Once again, both dosing regimens of Cx were significantly different than placebo and there did not appear to be any difference between the two doses of Cx.

Secondary endpoints:

The WOMAC index (composite plus subscales) was evaluated in both of these 6-week trials. As can be seen with the WOMAC pain index (*Appendix Table A.28 and Table A.29*), the baseline characteristics of both dosing regimens of Cx appeared similar to that of placebo as well as to the treatment groups in the 12-week studies. Similarly, Cx was significantly different than placebo and did not appear to differ between the two dosing schemes for Cx. Similar results were noted for the WOMAC function, stiffness, and composite scales.

The results of the OSI index were also comparable between these 6-week trials and the 12-week studies. It is not possible to comment on the SF-36 since this was not obtained in protocol 087.

The time to withdrawal due to lack of arthritis efficacy in these 6-week trials was, not unexpectedly, quite different than the results (for all treatment groups) obtained in the 12-week trials in that, overall, not as many patients withdrew in these shorter studies (see *Appendix Table A.30*). However, significantly fewer patients withdrew in the Cx groups compared to placebo and the two dosing schedules of Cx do not appear different in this regard. The results of both the 6-week trials are similar. The time to withdrawal due to lack of arthritis efficacy (see *Appendix Table A.31*) show these same trends.

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Non-Flare vs. Flare Studies:

There were three studies (062, 071, and 042) that allowed patients with OA or RA to enter the trials without the requirement for “flares” as noted in the other OA studies above. One of these trials was conducted outside the U.S. (protocol 042) and will not be discussed here. These studies were intended to evaluate several endpoints as noted in the brief review of study 071 below.

Study 071:

This randomized, double-blind, parallel group, multicenter, 12-week study was designed primarily to compare the cumulative incidence of gastroduodenal ulcers associated with celecoxib 200 mg BID with that of diclofenac 75 mg BID and ibuprofen 800 mg TID in patients with OA or RA. The efficacy and overall safety of celecoxib compared to diclofenac and ibuprofen were also assessed in this trial. Patients were eligible to participate in the study if they had a documented clinical diagnosis of OA or RA (not necessarily in flare) with a Functional Capacity Classification of I-III and required chronic NSAID treatment. At the time of study enrollment, patients underwent an endoscopy to ensure they did not have an esophageal, gastric, pyloric channel, or duodenal ulcer.

The efficacy endpoints for OA in this study were Patient’s Global Assessment of Arthritic Condition and Physician’s Global Assessment of Arthritic Condition. Arthritis Assessments were performed at Baseline and at the Weeks 4, 8, and 12 (or Early Termination) follow-up visits. UGI safety was assessed by serial endoscopy and biopsy and overall safety was assessed by comparison of physical examinations, clinical laboratory tests, and incidence of adverse events between treatment groups.

The table below summarizes the numbers and types of patients studied in protocols 062 and 071.

Table 4: Types/Numbers of Patients Studied in Non-Flare Trials

<i>Study</i>	<i>Diagnosis</i>	<i>Number of Patients Receiving:</i>				<i>Total</i>
		<i>Cx 200 mg BID</i>	<i>Naproxen 500 mg BID</i>	<i>Diclofenac 75 mg BID</i>	<i>Ibuprofen 800 mg BID</i>	
062	OA	194	195	-	-	389
	RA	76	72	-	-	148
071	OA	271	-	285	254	810
	RA	94	-	102	91	287
Total		635	267	387	345	1634

Although patients had OA or RA, it is unclear exactly how this diagnosis was made in these protocols. As indicated by the Inclusion Criteria on the admission CRF, eligibility into these two studies was based upon a clinical diagnosis of OA or RA of at least three months duration. The disease also had to be of sufficient severity to warrant the patient require chronic NSAID therapy. The determination of OA was made by the

investigator; patients with OA of any joint (i.e. ankle, elbow, shoulder, knee, hip) were eligible. Radiologic evidence, other ACR criteria, or other methods of diagnosis were not specifically required by the study protocol.

While it is not possible to draw any accurate comparisons to the placebo-controlled OA and RA (see below) studies, it is of interest that these patients had about a one category difference (at baseline) from the patients studied in the flared OA designs (i.e. baseline of about 2.8 vs. 3.8). Similarly, the treatment responses (or effect size) based upon the patient and physician globals in these patients tended to be about half of those noted in the flared OA studies (i.e. 0.5 vs. 1.0). Also of note, there was a tendency in both trials for more patients to drop from the Cx treatment group vs. the comparator NSAIDs.

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Conclusions from the OA trials:

The following conclusions regarding Cx and treatment of the signs and symptoms of OA are drawn from the information (ITT/LOCF) presented to this point in the randomized clinical trials:

- Cx from 100 mg BID to 200 mg BID is consistently efficacious vs. placebo
- Cx 50 mg BID is not consistently efficacious vs. placebo
- Cx (200 mg BID) is not consistently more efficacious vs. Cx (100 mg BID)
- Cx (100-200 mg BID) has efficacy comparable to Naproxen 500 mg BID
- Cx (100 mg BID) is as efficacious as Cx (200 mg QD)

Rheumatoid Arthritis Efficacy:

Seven studies (see Table 1 above: Studies Included in NDA 20-998), two designated pivotal and five supportive (including the long-term safety study 024), were conducted in patients with RA.

Table 5: Summary Characteristics of Rheumatoid Arthritis Trials:

Placebo- and Active-Controlled Pivotal Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-022 R: N49-98-06-022 Celecoxib Comparative Efficacy and UGI Safety vs Naproxen in RA	81 Investigators U.S. and Canada 6 Sep 1996	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 100 mg BID, 200 mg BID, or 400 mg BID or Naproxen 500 mg BID or Placebo
P: N49-96-02-023 R: N49-98-06-023 Comparative Efficacy and Safety vs Naproxen in RA	77 Investigators U.S. and Canada 7 Aug 1996	Randomized, Double-Blind, Placebo-Controlled, Active Controlled, Multicenter, Parallel (12 Weeks)	Celecoxib 100 mg BID, 200 mg BID, or 400 mg BID or Naproxen 500 mg BID or Placebo

Placebo-Controlled Supportive Study

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-012 R: N49-97-06-012 Pilot Efficacy in RA	29 Investigators United States 1 Feb 1996	Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel (4 Weeks)	Celecoxib 40 mg BID, 200 mg BID or 400 mg BID or Placebo

Active-Controlled Supportive Studies

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: I49-96-02-041 R: I49-98-06-041 Ex-U.S. Efficacy/GI Safety vs Diclofenac in RA	132 Investigators 21 countries in Australia, Europe and South Africa 28 Nov 1996	Randomized, Double-Blind, Active Controlled, Multicenter, Parallel (24 Weeks)	Celecoxib 200 mg BID or Diclofenac SR 75 mg BID
P: N49-97-02-062 R: N49-98-06-062 Comparative Incidence of UGI Ulcers: Celecoxib vs Naproxen in Patients with OA and RA	75 Investigators United States 13 May 1997	Randomized, Double-Blind, Active Control, Multicenter, Parallel (12 Weeks)	Celecoxib 200 mg BID or Naproxen 500 mg BID
P: N49-97-02-071 R: N49-98-06-071 Comparative Incidence of UGI Ulcers: Celecoxib vs Diclofenac and Ibuprofen in Patients with OA and RA	121 Investigators United States 21 Jul 1997	Randomized, Double-Blind, Active Control, Multicenter, Parallel (12 Weeks)	Celecoxib 200mg BID or Diclofenac 75 mg BID or Ibuprofen 800 mg TID

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Uncontrolled Supportive Study

Protocol No. Report No. Short Title	No. of Investigators Country(ies) Start Date	Study Design (Duration of Treatment)	Treatment Regimen(s)
P: N49-96-02-024 R: pending N49-98-08-024 (Interim Data Listings) Long-term Safety in OA and RA	278 Investigators U.S. and Canada 17 Jun 1996	Open Label, Multicenter (1-2 Years)	Celecoxib 200-400mg BID (for RA)

Reviewer's comment: The only protocols of adequate duration and characteristics for review are 022 and 023; this review will focus primarily on the efficacy and dose-response characteristics of Cx from these 12-week trials. Protocols 062 and 071 have been discussed in the OA efficacy section as well as in the GI differentiation section. Similarly, the endoscopic portion of protocol 022 will not be discussed here since this will be covered in detail in the GI differentiation section. The open-label experience, protocol 024, is discussed further on in this review.

Study characteristics:

As noted in Table 5 above, studies 022 and 023 were twelve-week, double-blind, placebo-controlled, multicenter, parallel group comparisons of Cx versus placebo and Naproxen in patients with RA. The table below summarizes the experience with RA in this NDA:

Table 6: Number of Patients with RA studied in all protocols (excludes open-label)

Study	Treatment								Total
	Placebo	Cx (mg, BID)				Naproxen (mg, BID)	Diclofenac (mg, BID)	Ibuprofen (mg, TID)	
		40	100	200	400	500	75	800	
012	85	81	-	82	82	-	-	-	330
022	231	-	240	235	218	225	-	-	1149
023	221	-	228	219	217	218	-	-	1108
041	-	-	-	326	-	329	-	-	655
062 ¹	-	-	-	76 (270)	-	72 (267)	-	-	148 (537)
071 ¹	-	-	-	94 (366)	-	-	102 (387)	91 (346)	287 (1089)
Total	537	81	468	1032	517	844	102	91	3672

1. Numbers in () = total number patients with RA studied in these protocols (i.e. remainder had OA)

As can be seen in the table above, between protocols 022 and 023, a total of 2252 patients with RA were enrolled and received at least one dose of study medication as follows:

These studies (i.e. 022 and 023) were both double-blind, placebo-controlled, multicenter, parallel group comparisons of Cx versus placebo and naproxen in patients with RA. They consisted of 12 weeks of treatment with visits occurring at Pretreatment/Screening, Baseline, and at Weeks 2, 6, and 12 following the first dose of study drug (see *Appendix Table A.32* for details of Protocol 022 as an example of the schedule of observations and procedures). The studies differed primarily in that protocol 022 included an assessment of the UGI safety of Cx with endoscopies performed at Baseline and Week 12 (or Early Termination) with testing done for *Helicobacter pylori* (*H. pylori*) at Baseline and the Week 12 (or Early Termination) Visit. In protocol 023, blood samples were taken (approximately 40 patients/treatment group) at selected sites between day 7 and 28 after the first dose for determination of Cx plasma levels.

Patients with diagnosed **RA in a flare state** were enrolled and randomized to receive Cx 100 mg BID, Cx 200 mg BID, or Cx 400 mg BID, naproxen 500 mg BID, or placebo.

To qualify for study participation, candidates must have:

1. **Been of legal age of consent or older;**
2. **For women of childbearing potential, confirmed use of adequate contraception since last menses and confirmed continued use of adequate contraception during the study, were not lactating, and had a negative serum pregnancy test within 7 days prior to the Baseline Arthritis Assessments**
3. **Been diagnosed as having adult-onset RA of at least three month's duration as defined by the 1987 American College of Rheumatology (ACR) classification criteria**
4. **Had a Functional Capacity Classification of I-III at the Baseline Visit**
5. **Been stable on NSAID therapy and had a Functional Capacity Classification that had not changed for at least one month immediately preceding the NSAID washout period**
6. **Had RA in a flare state within two to seven days after discontinuing NSAID therapy (within four to seven days for patients who received either oxaprozin, piroxicam, or both)**
7. **Provided written informed consent before undergoing any study procedures**

Candidates were not eligible for admission if they met any one of the following:

1. Had been diagnosed with any other inflammatory arthritis
2. Had been diagnosed with a secondary, non-inflammatory type of arthritis (e.g., osteoarthritis or fibromyalgia) that, in the Investigator's opinion, was symptomatic enough to interfere with the evaluation of the effect of Cx on the patient's primary diagnosis of RA
3. Had begun taking any of the following medications or had changed the dosing regimen of any of these medications within 12 weeks before receiving the first dose of study medication:
 - a) Gold salts (including oral gold)
 - b) Sulfasalazine (doses of up to 3 g/day were allowed)
 - c) Azathioprine
 - d) Antimalarials
 - e) Penicillamine;
4. Had begun taking or had changed the dosing regimen of methotrexate within the eight weeks preceding the first dose of study medication. The methotrexate dose was not to exceed 20 mg/week
5. Had begun taking oral corticosteroids or had changed the dose regimen of oral corticosteroids within four weeks before receiving the first dose of study medication (doses of up to 10 mg prednisone or equivalent/day were allowed), or the patient had received intramuscular, intra-articular, or soft-tissue injections of corticosteroids within four weeks before receiving the first dose of study medication
6. Had received any antineoplastic (other than methotrexate \leq 20 mg/week or azathioprine as therapy for RA) during the eight weeks preceding the first dose of study medication
7. Had taken any NSAID (including aspirin) within two days before the Baseline Arthritis Assessments or any analgesic within 24 hours before the Baseline Arthritis Assessments. (Patients taking \leq 325 mg aspirin per day for non-arthritic reasons for at least 30 days before the first dose of study medication were allowed to continue their aspirin regimen for the duration of the study. Patients must have discontinued oxaprozin or piroxicam at least four days before the Baseline Arthritis Assessments.)
8. Had an active malignancy of any type or history of malignancy. (Patients who had a history of basal cell carcinoma that had been treated were eligible. Patients with a history of other malignancies that had been surgically removed and who had no evidence of recurrence for at least five years before study enrollment were also eligible.)
9. Had been diagnosed with or had received treatment for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days before receiving the first dose of study medication
10. Had active GI disease (e.g., inflammatory bowel disease) or has an esophageal, gastric, pyloric channel or duodenal ulcer (an ulcer was defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth) or more than ten erosions in the stomach or more than ten erosions in the duodenum on the Baseline UGI endoscopy
11. Had a history of any gastric or duodenal surgery other than simple oversew;
12. Had chronic/acute renal or hepatic disorder or a significant coagulation defect
13. Had abnormal screening laboratory test values within seven days before the Baseline Arthritis Assessments that were >1.5 x upper limit of normal (ULN)

- for either AST (SGOT) or ALT (SGPT) or any other laboratory abnormality considered by the Investigator to be clinically significant
14. Had a known hypersensitivity to COX-2 inhibitors, sulfonamides, or NSAIDs
 15. Had received any investigational medication within 30 days before the first dose of study medication or was scheduled to receive an investigational drug, other than study medications described in the protocol, during the course of the study
 16. Had previously been admitted to this study.

Reviewer's comment: It should be noted that the exclusion criteria for study 023 (022 included endoscopy) did not include items 10 and 11 noted above.

All study patients had to demonstrate an **arthritis flare** within two to seven days after discontinuing their NSAID or analgesic. Patients receiving oxaprozin or piroxicam must have discontinued these NSAIDs at least four days before the Baseline Arthritis Assessments. An RA flare was demonstrated if the Physician's Global Assessment of Arthritic Condition and the Patient's Global Assessment of Arthritic Condition were "fair," "poor," or "very poor" at the Baseline Visit AND if a comparison of the Screening Arthritis Assessments and the Baseline Arthritis Assessments met criteria 1 and 2 described below **plus** either criterion 3 or 4:

1. **MUST** have had a minimum of six tender joints at Baseline AND an increase of at least two tender or painful joints (or 20% increase in the number of tender/painful joints, whichever was greater) at the Baseline as compared to the Screening Visit
2. **MUST** have had a minimum of three swollen joints at Baseline AND an increase of at least two swollen joints (or 20% increase in the number of swollen joints, whichever was greater) at the Baseline as compared to the Screening Visit
3. A minimum of 45 minutes of morning stiffness at Baseline AND an increase in the duration of morning stiffness of at least 15 minutes as compared to the Screening Visit
4. Patient's Assessment of Pain-Visual Analog Scale measurement of at least 40 mm (on a visual analog scale) at Baseline AND an increase of 10 mm (or 20% increase, whichever was greater) at the Baseline as compared to the Screening Visit

At each follow-up visit, patients were asked the following question: "Since your last visit, have you experienced any symptoms that are not associated with your arthritis?" Any symptom was recorded on the Adverse Signs and Symptoms CRF. Patients who withdrew before the end of the study had all final assessments performed at the time of withdrawal (Early Termination Visit).

Demographics:

There did not appear to be any remarkable differences in baseline characteristics between treatment groups in the 12-week RA trials (see *Appendix Table A.33*). These patients tended to be white females, in their 50's, with a disease duration of approximately 10 years. About 40% of patients used corticosteroids, 65% other disease-modifying anti-rheumatic drugs (DMARDs), and about 50% used methotrexate

(MTX). Approximately 75% of patients in all groups were, therefore, concurrently using corticosteroids or MTX or other DMARDs (data not shown). Patients and their physicians rated the baseline global assessments of arthritis condition as fair. The number of tender and swollen joints were comparable across treatment groups in both studies. Of note, the mean average of the weights of all the patients with RA (i.e. 77-78 kg, data not shown) was substantially different than those patients noted earlier with OA. The demographic characteristics, arthritis history and co-therapy for each individual study were consistent with these pooled results.

Primary/Secondary Endpoints:

The primary measures of arthritis efficacy were:

- **ACR-20 Responder Index;**
- **Patient's Global Assessment of Arthritic Condition;**
- **Number of Tender/Painful Joints;**
- **Number of Swollen Joints;**
- **Physician's Global Assessment of Arthritic Condition.**

ACR-20 responder index:

In order to examine the overall effect of the study drug on the patient's condition, a categorical analysis was performed on all patients who met the ACR-20 criteria as improved compared to Baseline. A patient was classified as "improved" if (compared to baseline) the patient experienced:

- A. $\geq 20\%$ improvement in
 - tender/painful joint count (TJC)
 - swollen joint count (SJC) 20%AND
- B. $\geq 20\%$ improvement in at least three of the following five assessments
 - Physician's Global Assessment of Arthritic Condition
 - Patient's Global Assessment of Arthritic Condition
 - Patient's Assessment of Pain-VAS
 - CRP (as example of acute phase reactant)
 - HAQ Functional Disability Index.

The Patient's and Physician's Global Assessments of Arthritic Condition were made independently. Patient's were asked to answer the question, "Considering all the ways your arthritis affect you, how are you doing today?" Patients rated, and physician's graded, according to the 5-point categorical scale below:

- | | |
|--------------|---|
| 1. Very good | Asymptomatic and no limitation of normal activities |
| 2. Good | Mild symptoms and no limitation of normal activities |
| 3. Fair | Moderate symptoms and limitation of some normal activities |
| 4. Poor | Severe symptoms and inability to carry out most normal activities |
| 5. Very poor | Very severe symptoms that are intolerable; inability to carry out all normal activities |

To determine the Number of Tender/Painful Joints, sixty-eight joints (right and left) were examined for joint tenderness/pain. The joints were as follows:

- Temporomandibular
- Sternoclavicular
- Acromioclavicular
- Shoulder
- Elbow
- Wrist (radiocarpal, carpal, and carpometacarpal considered as one unit)
- Metacarpophalangeals (MCP I, II, III, IV, V)
- Thumb interphalangeal (IP)
- Proximal interphalangeals (PIP II, III, IV, V)
- Distal Interphalangeals (DIP II, III, IV, V)
- Knee
- Hip
- Ankle
- Tarsus (includes subtalar, transverse tarsal, and tarsometatarsal as one unit)
- Metatarsophalangeals (MTP I, II, III, IV, V)
- Great Toe interphalangeal (IP)
- Proximal and distal interphalangeals combined (PIP II, III, IV, V)

In response to pressure or motion, each joint was graded as painful or tender using the scale shown below:

- | | |
|---|---|
| 0 | No response (not tender) |
| 1 | Positive response to questioning (tender) |
| 2 | Spontaneous response elicited (tender and winced) |
| 3 | Withdrawal by patient on examination (tender, winced, and withdrew) |

To determine the **Number of Swollen Joints**, sixty-six joints were also graded for swelling using the same joints as those listed above (for joint pain/tenderness) except that the hip joints were not assessed. The joint swelling scale was graded using the scale below:

- 0 None
- 1 Detectable synovial thickening without loss of bony contours
- 2 Loss of distinctiveness of bony contours
- 3 Bulging synovial proliferation with cystic characteristics

Secondary Measures of Efficacy were:

- **Patient's Assessment of Pain-Visual Analog Scale**
0 mm = no pain, 100 mm = very severe pain
- **Tender/Painful Joints Score**
- **Swollen Joints Score**
- **SF 36 (eight domains, see OA section)**
- **Duration of Morning Stiffness**
average duration for the previous three days
- **HAQ Functional Disability Index (eight areas of daily living, graded on scale from 0 = without any difficulty to 3 = unable to do)**
- **CRP**
- **Incidence of Withdrawal Due to Lack of Arthritis Efficacy**
- **Time to Withdrawal Due to Lack of Arthritis Efficacy**
- **ACR-50 Responder Index**

Patient Populations Analyzed/Statistics:

The ITT Cohort included all patients with RA who were randomized to treatment and who had taken at least one dose of study medication. The Last Observation Carried Forward (LOCF) approach was used for either missing data or data that was obtained on days that fell outside the observation window (i.e. > 19 days for Week 2, > 49 days for Week 6, and > 93 days for Week 12). The LOCF approach was employed in the ITT analyses only.

Evaluable Cohort

A patient was considered evaluable for analysis of arthritis assessments for Week 2, Week 6, Week 12 or Early Termination if, in addition to satisfying the requirements for the ITT Cohort, he or she:

1. Was diagnosed by ACR criteria as having adult onset RA
2. Had a Functional Capacity Classification of I-III at the Baseline Visit

3. Had RA in a flare state at the Baseline Visit
4. Did not have any other inflammatory arthritis or any secondary, noninflammatory-type arthritis that, in the Investigator's opinion, would interfere with the evaluation of Cx
5. Did not receive IM, IA, or soft-tissue injections of corticosteroids or begin or change dose regimen of oral corticosteroids within four weeks before the first dose of study medication
6. Did not begin or change dose regimen of the following within 12 weeks before the first dose of study medication: gold salts, sulfasalazine, azathioprine, antimalarials, or penicillamine;
7. Did not begin or change the dose regimen of methotrexate within eight weeks before the first dose of study drug;
8. Did not take any antineoplastic, other than methotrexate (≤ 20 mg/week) or azathioprine as therapy for RA within eight weeks before the first dose of study medication
9. Did not take any NSAID or analgesic within 24 hours before the Baseline Arthritis Assessments
10. Underwent the Baseline Arthritis Assessments within seven days before the first dose of study drug;
11. Did not take any of the following proscribed medications during the course of the study:
 - any antineoplastic (other than methotrexate ≤ 20 mg/week or azathioprine as treatment for RA)
 - any NSAID (other than aspirin ≤ 325 mg/day)
 - any injectable corticosteroid
 - any analgesic (other than acetaminophen up to 2 g/day for nonarthritic reasons)
12. Did not change dose regimen or initiate treatment with the following during the study: corticosteroids, gold salts, penicillamine, methotrexate, antimalarials, azathioprine, or sulfasalazine;
13. Was compliant with study medication as described below:
 - for the Week 2 Visit, the patient took at least 70% of the doses prescribed from Day 1 through the Week 2 Visit
 - for the Week 6 Visit, the patient took at least 70% of the doses prescribed from the Week 2 Visit through the Week 6 Visit AND at least 50% of the doses prescribed from Day 1 through the Week 2 Visit
 - for the Week 12 Visit, the patient took at least 70% of the doses prescribed from the Week 6 Visit through the Week 12 Visit AND at least 50% of the doses prescribed from the Week 2 Visit through the Week 6 Visit AND at least 50% of the doses prescribed from Day 1 through the Week 2 Visit
14. Underwent the Arthritis Assessments for each visit under consideration according to the following schedule:
 - a. 14 ± 5 days after the first dose of study medication for the Week 2 Visit
 - b. 42 ± 7 days after the first dose of study medication for the Week 6 Visit
 - c. 84 ± 9 days after the first dose of study medication for the Week 12 Visit
 - d. ≤ 2 days after the last dose of study medication for the Final Visit
15. Had complete primary efficacy data available for each visit under consideration.

Evaluability determinations were made prior to unblinding the data and no subsequent revisions were made.

Observed Data Cohort

A patient's data at a specific visit was included in this analyses if he or she satisfied the requirements for the ITT Cohort and the corresponding assessment days after the first dose of study medication fell in the following intervals: 14 days \pm 5 days for Week 2; 42 \pm 7 days for Week 6; and 84 \pm 9 days for Week 12.

Statistical analyses were performed for the Evaluable and Observed Data Cohorts at all scheduled visits and at the Final Visit which consisted of the last valid observation of the patient.

Mean change analyses, including the linear trend test for all Cx and placebo groups and overall and pairwise comparisons for all five treatment groups, were performed on all primary measures of efficacy with the exception of the ACR-20 responder index, using an analysis of covariance (ANCOVA) with treatment and center as factors, and the corresponding Baseline value as a covariate. Additionally, the Q-Ratio with 95% confidence intervals was calculated by taking the ratio of adjusted mean changes for each Cx treatment group versus the naproxen treatment group.

The results of the pairwise comparisons for the Cx 200 mg BID and 400 mg BID treatment groups versus placebo for the ITT Cohort were interpreted using Hochberg's step-up procedure.

For Assessment of Joint Tenderness/Pain and the Assessment of Joint Swelling, a joint was classified as "improved" if a reduction in grade to 0 or a change from 3 to 1 was observed. A joint was classified as "worsened" if an increase in grade from 0, a change in grade from 1 to 3, or a change in grade from 2 to 3 was observed. The median number of "improved" joints was compared between treatment groups using ANCOVA with the Baseline number of joints that had a score greater than zero as the covariate and center and treatment as factors. The number of "worsened" joints was similarly analyzed. In addition, the patient's overall status was considered as "improved" if the difference between the number of improved and the number of worsened joints was greater than or equal to 50% of the number of Baseline joints that had a score greater than zero. A patient was classified as "worsened" if the difference between the number of worsened and the number of improved joints was greater than or equal to 50% of the number of Baseline joints that had a score greater than zero. Patient's overall status was analyzed by the CMH test stratified by center.

For Physician's and Patient's Global Assessments of Arthritic Condition a patient was classified as "improved" if a reduction of at least two grades from Baseline for grades 3 to 5 or a change in grade 2 to 1 was observed. A patient was classified as "worsened" if an increase of at least two grades from Baseline for grades 1 to 3 or a change in grade 4 to 5 was observed. The changes were analyzed by the CMH Test stratified by center. The linear trend test (naproxen group excluded) and pairwise comparisons were performed based on the above CMH tests.

Efficacy Results for RA:

Primary endpoints

Patient and Physician globals

With reference to the ITT analyses, patient and physician globals in both studies (022, 023) showed the baseline characteristics of the patients in all the treatment groups were comparable within, and between trials. Celecoxib, at all doses studied (i.e. 100 mg BID, 200 mg BID, 400 mg BID) was consistently efficacious compared with placebo. Naproxen had the same results with the one exception it did not show significance at week 12 in the categorical analysis of trial 022. For example, the Physician's Global Assessment of Arthritis Condition (see *Appendix Table A.34.1-.2*) and the Patient's Global Assessment of Arthritis Condition (see *Appendix Table A.35.1-.2*) for study 023 (results are similar for 022), shows improvements (categorical and mean change analyses) versus placebo over time in all Cx treatment groups. Although there may be some suggestions of waning over time, improvements in the Cx-treated global scores seemed to be maintained during the 12 weeks of this trial. There does appear to be a difference between 100 mg BID and the higher doses of Cx, but not a consistent dose-response relationship for higher doses of Cx. In certain situations, such as the Physician Globals for protocol 022, higher doses of Cx also appear to be more efficacious than Naproxen; the Q-ratio analysis suggests the same. However, these same trends regarding comparison to Naproxen are not evident in the protocol 023.

With reference to Cx, there were **NO** statistically significant differences compared to placebo (categorical or mean change analyses) at any time point (except the 2 week assessments in both trials and categorical analysis for Cx 200 mg BID in study 022) in either the **evaluable or observed cohorts** in either trial (022, 023) in the Patient or Physician's global assessments (data not shown).

With reference to Naproxen (and considering only protocol 023) and the evaluable or observed cohorts, there were statistically significant differences compared to placebo at all time points (categorical and mean change analysis), with the exception of the Physician global (mean analysis) at week 12 and the Patient Global (categorical) at week 12. In study 022, on the other hand, only the 2 week time points revealed any significant difference compared to placebo for both the physician and patient globals.

Tender/Painful Joint Counts

Considering the ITT analyses, the tender/painful joint counts (TJC) were comparable at baseline (though high, mean of approximately 29 joints) between groups within each study as well as between the two protocols. The placebo response in protocol 022 (see *Appendix, Table A.36.1-.2*) was more robust than that seen in study 023 (data not shown). This may account for the fact that Naproxen did not show significance vs.

placebo at week 12 (mean or categorical) but it did in trial 023. However, all doses of Cx were significantly different (categorical and mean change analyses) than placebo at all times (i.e. weeks 2, 6, 12) in both trials. There were no consistent dose-response trends between the various doses of Cx but the responses appeared durable. Overall, Cx appears comparable to Naproxen; the Q-ratio analysis suggests the same.

With reference to Cx and the **evaluable and observed cohorts** there were **NO** statistically significant differences compared to placebo (categorical or mean change analyses) at any time point (except the 2 week assessments in both trials and a single mean analysis for Cx 100 and 400 mg BID in study 023 at week 6; evaluable and observed, respectively) in either trial (022, 023) (data not shown). Naproxen also showed significance at all two week time points and at 6 weeks (both mean analyses-evaluable and observed).

Swollen Joint Counts

Looking at the ITT analyses, the swollen joint counts (SJC) were comparable at baseline (again high, mean of approximately 21 joints) between groups within each study as well as between the two protocols. Once more, the placebo response was a little more robust for trial 022 (data not shown). Similar to the TJC, Cx was significantly different (categorical or mean change analyses) from placebo at all times points and at all doses in both trials with the notable exception (categorical analysis) of the 100 and 400 mg BID doses in trial 023 (see *Appendix, Table A.37.1-.2*). No obviously consistent dose-response trends were evident between the three doses of Cx, but the responses noted appeared durable throughout the trials. Again, Cx appears comparable to Naproxen; the Q-ratio analysis suggests the same.

With reference to Cx and the **evaluable and observed cohorts**, there were **NO** statistically significant differences (categorical or mean change analyses) compared to placebo at any time point (except for a various doses at the 2 week assessments in both trials) in either trial 022 or 023 (data not shown). The same can be said regarding Naproxen.

ACR-20 and ACR-50 Responder Index

Based on the ACR-20 Responder Index (ITT cohort), there was a statistically significant difference in the percentage of patients classified as responders in all doses of Cx compared to placebo at all time points in both protocols. The one exception to this statement was that significance was not achieved with CX at 100 mg BID in protocol 023 (see *Appendix Table A.38.1-.3*). Once again, there did appear to be a difference in response between 100 mg BID and the higher doses, but not between the higher doses. This distinction between 100 mg BID of Cx and the higher doses is more evident in the ACR-50 (ITT cohort) Responder Index (see *Appendix Table A.39.1-.2*).

However, in the **evaluable cohort** of protocol 023 (see *Appendix Table A.38.3*), only the Naproxen group showed significance in the ACR-20 index; results were the same in the **observed cohort** group of this trial (i.e. only Naproxen showed significance at week 12). On the other hand, there were no significant differences from placebo in the ACR-20 index for any of the treatments (Cx or Naproxen), at any time point, in these other cohorts in protocol 022 (data not shown).

Secondary endpoints

Reviewer's comment: The reader will notice that not all secondary endpoints will be discussed and that some of these endpoints are part of the ACR -20/50 primary endpoints. Only the ITT/LOCF results are noted.

Patient's Assessment of Arthritis Pain (VAS)

The baseline VAS scores were comparable between the groups in both study 023 and 022, as well as between the studies (baseline of approximately 66). In both studies, the analyses of mean changes revealed that there were statistically significant differences from placebo at all doses of Cx and at all time points. The same is true for Naproxen (see *Appendix Table A.40* for example in protocol 023).

C-reactive protein (CRP)

The baseline CRPs showed differences which, in light of the variation in results, is difficult to interpret. There were no statistically significant differences from placebo for any of the doses of Cx at any time point, in either protocol. Naproxen did show significance at only one time point, week 12 in trial 023 (see *Appendix Table A.41*). Of note, as discussed below for protocol 012, Cx also did not seem to effect ESR or Serum Amyloid A levels.

HAQ Functional Disability Index

The baseline HAQ scores were comparable between groups in both studies as well as between the studies (mean around 1.4). There were consistent statistically significant differences for the 200 and 400 mg BID doses of Cx and Naproxen as compared to placebo, but not for Cx at 100 mg BID compared to placebo, in both studies (see *Appendix Table A.42* for example in protocol 023). Q-ratio analysis suggests there is no difference between the higher doses of Cx and Naproxen, but not for Cx at 100 mg BID.

SF 36 Health Survey

Mean change analyses (from baseline to week 12 or early termination) were performed for scores for the eight SF-36 Health Survey domains: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health.

Most domains showed statistically significant improvement compared to placebo in both the Cx and Naproxen doses. The most notable exceptions were the General Health and Role Emotional where protocol 023 did not show any significance for these domains with all doses of Cx whereas the results were exactly opposite in protocol 022 (i.e. all doses of Cx did show significance). In a few other domains in protocol 022, such as the Physical Functioning and Role Physical, there was a separation of the lower dose of Cx (i.e. 100 mg BID) and the higher doses with the latter showing significance (data not shown).

Incidence of Withdrawal Due to Lack of Arthritis Efficacy

The Incidence of Withdrawal Due to Lack of Arthritis Efficacy (treatment failure) for both protocols (see *Appendix Table A.43*) reveals withdrawal of a total of 774 patients (345 and 429 for study 022 and 023, respectively) regardless of treatment. As would be expected if there was a favorable treatment effect over placebo, there were more patients in the placebo groups who withdrew due to lack of arthritis efficacy (51%) compared to any of the Cx treatment groups (27-34%, see pooled results). The differences were in withdrawal rate for all doses of Cx were statistically significant ($p < 0.001$) compared to placebo as noted in both individual trials (data not shown). Although there were more patients in the Cx 100 mg BID group (34%) compared to the Cx 200 mg BID (27%) and 400 mg BID (29%) groups who withdrew due to lack of arthritis efficacy, these differences were not statistically significantly different.

There were also fewer patients in the Naproxen group who withdrew due to lack of arthritis efficacy (30%) than in the placebo group and this difference was again statistically significant ($p < 0.001$). However, there were no significant differences between patients taking any dose of Cx compared to Naproxen as noted in the individual studies.

Time to Withdrawal Due to Lack of Arthritis Efficacy

The results of the analysis of the Time to Withdrawal Due to Lack of Arthritis Efficacy are presented as Kaplan-Meier estimates (see *Appendix Table A.44* for example from study 023). Again, as would be expected if treatment had an effect, in both studies placebo patients tended to withdraw earlier than patients in the Cx treatment groups and this difference in the time to withdrawal was statistically significant ($p < 0.001$); the same can be said for Naproxen. While there was a statistically significant difference

noted in study 023 between Cx 100 mg BID and 400 mg BID, this was not the case in study 022 ($p=0.954$) and so there were no obvious differences between any of the Cx doses in either study. Patients in the Naproxen group also tended to withdraw later than patients in the placebo. Differences between Naproxen and Cx were inconsistent comparing to the lower doses of Cx (i.e. Cx 100 and 200 mg BID) and Naproxen between studies; however, there were consistently no differences seen between Cx 400 mg BID and Naproxen.

Other studies in RA

Of the other studies submitted in support of the indication of RA, only trial 012 will be described briefly here. The other trials are intended primarily to address the GI safety issue (discussed elsewhere in this NDA) and/or have a mixed patient populations with entry criteria unsuited for adequate interpretation.

Study 012

Protocol 012 was a pilot, Phase II, double-blind, placebo-controlled, parallel-group study evaluated the safety and effectiveness of Cx in treating the signs and symptoms in patients with RA in a flare state. Three hundred thirty (330) patients received treatment for four weeks as follows: placebo, 85 patients; Cx 40 mg BID, 81 patients; Cx 200 mg BID, 82 patients; and Cx 400 mg BID, 82 patients. Arthritis assessments and safety evaluations were performed at Baseline and at Weeks 1, 2, and 4.

The measures of arthritis efficacy included: the Patient's and Physician's Global Assessment of Arthritic Condition, Patient Assessment of Arthritis Pain, Number of Tender/Painful Joints, Number of Swollen Joints, Incidence of Withdrawal due to lack of Arthritis Efficacy, Time to Withdrawal, and the ACR 20. With reference to these assessments at week 4 in the ITT population, Cx 40 mg BID was not different than placebo but Cx 200 and 400 mg BID were consistently statistically different than placebo and from Cx 400 mg BID. There were no consistent differences between Cx 200 and 400 mg BID. The ACR 20 response at week 4 was 31%, 51% and 52% for Cx 40, 200, and 400 mg BID, respectively (placebo = 29%). Also of interest, the ESR, CRP and serum amyloid A levels did not seem consistently effected by any of the doses of Cx at any time point.

Conclusions from the RA trials:

The following conclusions regarding Cx and treatment of the signs and symptoms of RA are drawn from the information (ITT/LOCF) presented to this point in the randomized clinical trials:

- Cx from 100 mg BID to 400 mg BID is consistently efficacious vs. placebo
- Cx 200 and 400 mg BID is frequently more efficacious vs. Cx 100 mg BID
- Cx 200 mg BID and 400 mg BID generally have comparable efficacy
- Cx (100 mg-400 mg BID) has efficacy comparable to Naproxen 500 mg BID

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Open-label experience in Osteoarthritis and Rheumatoid Arthritis:

Study N49-96-02-024 is an ongoing, long-term open-label safety study of patients who previously participated in one of following nine phase II or III double-blind controlled studies:

- N49-96-02-012 (RA)
- N49-96-02-013 (OA)
- N49-96-02-020 (OA)
- N49-96-02-021 (OA)
- N49-96-02-022 (RA)
- N49-96-02-023 (RA)
- N49-96-02-054 (OA)
- N49-97-02-062 (OA/RA)
- N49-97-02-071 (OA/RA)

All patients treated in the long-term open label study previously participated in one of nine controlled studies. A 14-day rule was used to determine direct transfer status as follows:

- **If a patient received any celecoxib dose in the controlled study and transferred into the open label study within 14 days, the patient was considered a direct transfer patient and all previous study data were included in the long-term analysis (Day 1 of celecoxib is the first day of the double-blind study);**
- **If a celecoxib patient transferred after 14 days then Day 1 of celecoxib is the first day of the open label study**
- **Patients who received placebo or an active control agent in the double-blind study are evaluated as Day 1 of celecoxib in the open-label study regardless of the gap between studies.**

This multicenter study is/was designed to determine the long-term (up to two years) safety, including an evaluation of the incidence of any clinically significant gastrointestinal events, of Cx administered to patients with osteoarthritis OA or RA. Efficacy assessments (see below) are also being performed. The data cutoff date for the interim data listings included in this NDA is November 21, 1997. The results of the completed trial are pending at this time; it is anticipated to be completed in 12/99.

For two-year patients, visits included the Baseline, at Weeks 2 and 6, and at Months 3, 6, 9, 12, 15, 18, 21, and 24. For patients enrolled for one year, the Month 12 visit is the final study visit. For both two-year and one-year patients, study visits are to include review of any treatment-emergent signs and symptoms experienced since the previous visit. Safety assessments are generally combined for OA and RA.

Measures of arthritis efficacy include:

- Patient's Assessment of Arthritis Pain on the Visual Analog Scale (VAS);
- Patient's Global Assessment of Arthritis;
- Physician's Global Assessment of Arthritis
- Functional Capacity Classification.

These assessments will be performed on all patients at every visit, with the exception of the Patient's Assessment of Arthritis Pain on the Visual Analogue Scale (VAS), with the exception of patients previously enrolled in N49-97-02-062 or N49-97-02-071. Patients will undergo a physical examination at the Baseline visit and every six months thereafter. Clinical laboratory tests will be performed at every study visit. Two-year patients will complete a quality of life assessment (SF-36 Health Survey) at Baseline and every six months thereafter, and a Health Resource Utilization Questionnaire at every visit except Baseline. One-year patients will not complete the SF-36 Health Survey or the Health Resource Utilization Questionnaire at any study visit.

A radiologic examination (i.e., hand and wrist x-rays for patients with RA and either the Index knee or the Index hip for patients with OA) will also be performed at Baseline and the Month 12, or Early Termination, visit for all patients, except those previously enrolled in N49-97-02-062 or N49-97-02-071.

As of the cutoff date, a total of 4499 patients had entered the long-term, open-label safety study. A total of 3256 patients were still active in the study at the cutoff date; the remaining 1243 had prematurely terminated from the study. The longest duration of treatment (patient 0150001) was 522 days.

The table below briefly summarizes the disposition of patients to this point for study 024:

Table 7: Disposition of Patients in Protocol 024

Category	Placebo	Cx (all doses)	NSAIDs	Total
Pts able to enroll	1270	4422	2073	7765
Pts enrolled (%)	860 (68)	2776 (63)	863 (42)	4499 (58)
Pts at 12 months	-	-	-	3256 (72)

Reviewer's comment: There is a discrepancy between the number of patients still active and those that have terminated between this text (i.e. 3256 and 1243, respectively) and tables cited below of 61 patients. In other words, the tables suggest there are 61 patients still receiving Cx that the text states have been terminated from study 024.

In study 024, the doses of Cx allowed have ranged from 100-200 mg BID for OA and 200-400 mg BID for RA. This range was allowed to control symptoms (increased) or for tolerability reasons (reduced). As can be seen (*Appendix, Table A.45*), approximately 70 % of patients with either OA or RA, increased their dose beyond what is felt to be the therapeutic dose during the randomized controlled studies presented in this NDA (i.e. 100 mg BID for OA, 200 mg BID for RA). Of those that did increase their dose, most moved to a dose twice as high (i.e. 200 mg BID for OA, 400 mg BID for RA).

Of the efficacy parameters assessed in protocol 024, the Patient's Global Assessment of Arthritic Condition for OA and RA are presented (see *Appendix, Figure A.1*); results are very similar for the Patient Assessment of Pain (VAS) and the Physician's Global Assessment for both the patients with OA and RA. Regarding figure 7 (OA) and figure 10 (RA) of Appendix figure A.1, it is noted by the sponsor:

"Although approximately 70% of OA patients did escalate the dose, there was no worsening of arthritis status compared to Baseline prior to dose escalation. In addition, following dose escalation, little additional improvement was noted in mean scores compared to patients who took celecoxib 200 mg BID without escalating their dose. This data lends further support to the conclusion that celecoxib 100 mg BID is an efficacious dose and an increase to 200 mg BID does not significantly enhance the efficacy in treating the signs and symptoms of OA."

"Although approximately 75% of RA patients did escalate their dose (to 300 or 400 mg BID), there was no evidence of worsening arthritis status compared to Baseline prior to dose escalation. In addition, following dose escalation, little additional improvement was noted in mean scores compared to patients who took celecoxib 200 mg BID without escalating their dose. This finding lends further support to the conclusion that celecoxib 100 mg BID and 200 mg are efficacious doses and 400 mg BID does not significantly enhance the efficacy in treating the signs and symptoms of RA"

Reviewer's comment: It could just as easily be argued that an escalation of the dose was required to maintain any long-term efficacy of Cx in OA and RA.

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Appendix Tables/Figures

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Table A.1 Schedule of Observations and Procedures (Protocol 020)

	Screening Visit Day -14 to -2	Baseline Visit Day 0	Week 2 Day 14 ±1 day	Week 6 Day 42 ±2 days	Week 12 Day 84 ±2 days	Early Termination
Informed Consent	X					
Medical History	X					
Physical Examination	X				X	X
Clinical Lab Tests (a)	X		X	X(b)	X	X
QOL Assessment (c)		X	X		X	X
OA Assessments	X(d)	X	X	X	X	X
Discontinue NSAID or analgesic (e)	X					
Meet Flare Criteria		X				
Signs and Symptoms		X	X	X	X	X
APS Pain Measure (f)		X				
Patient Assessment of Function (f)		X				
Blood Samples for Plasma PK Levels (g)			X			
Dispense Study Medication		X	X	X		
Return & Count Study Med			X	X	X	X
Dispense Concurrent Medications Diary Card		X	X	X		
Retrieve Concurrent Medications Diary Card			X	X	X	X
<p>a) Clinical laboratory tests included: Hematology (white blood cell [WBC] count with differential, red blood cell [RBC] count, hemoglobin, hematocrit, platelet count [estimate not acceptable], prothrombin time [PT], partial thromboplastin time [PTT]; Biochemistry (sodium, potassium, chloride, calcium, inorganic phosphorus, BUN, creatinine, total protein, albumin, total bilirubin, uric acid, glucose, alkaline phosphatase, AST [SGOT], ALT [SGPT], creatine kinase [CK]); and Urinalysis (pH, specific gravity, WBC, RBC, protein, glucose, ketones, bilirubin). Serum pregnancy test for women of childbearing potential at Screening visit only.</p> <p>b) PT and PTT tests were not performed at the Week 6 Visit.</p> <p>c) SF-36 Health Survey.</p> <p>d) Screening Arthritis Assessment data were collected by Searle but not entered in the database.</p> <p>e) Patients discontinued oxaprozin and/or piroxicam at least four days before the Baseline Arthritis Assessments.</p> <p>f) American Pain Society (APS) Pain Measure and Patient Assessment of Function were completed by the patient during the Baseline Visit and daily for the first seven days of dosing with study medication. Patients enrolled in study prior to 8 August 1996 who already began taking study medication were not required to complete questionnaires.</p> <p>g) Three blood draws were to be taken from 200 patients (approximately 40 per treatment group) at selected sites between Day 7 and 28 after first dose for determination of SC-58635 plasma levels.</p>						

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Table A.2 Baseline demographics (study 020, 021, 054-pooled)

12-Week Pivotal Studies 020, 021, and 054)					
Baseline Characteristic	Placebo (n=664 ^a)	Celecoxib			Naproxen 500 mg BID (n=631)
		50 mg BID (n=671)	100 mg BID (n=644 ^a)	200 mg BID (n=648)	
Baseline Demographic Characteristics					
Age (years)					
Mean (Std. Dev.)	62.3 (10.22)	61.6 (11.09)	61.9 (11.31)	61.9 (11.43)	62.7 (11.09)
Range	30-87	21-93	24-88	25-88	19-89
<65 years - N (%)	361 (54%)	378 (56%)	358 (56%)	353 (54%)	334 (53%)
≥65 years - N (%)	303 (46%)	293 (44%)	286 (44%)	295 (46%)	297 (47%)
Race/Ethnic Origin					
Asian - N (%)	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)
Black - N (%)	59 (9%)	80 (12%)	63 (10%)	71 (11%)	65 (10%)
Caucasian - N (%)	577 (87%)	574 (86%)	569 (88%)	555 (86%)	553 (88%)
Hispanic - N (%)	22 (3%)	13 (2%)	7 (1%)	18 (3%)	11 (2%)
Other - N (%)	4 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)
Gender					
Female - N (%)	466 (70%)	444 (66%)	441 (68%)	451 (70%)	430 (68%)
Male - N (%)	198 (30%)	227 (34%)	203 (32%)	197 (30%)	201 (32%)
Baseline Index Joint and Disease Duration					
Baseline Index Joint					
Knee - N (%)	446 (67%)	455 (68%)	437 (68%)	435 (67%)	424 (67%)
Hip - N (%)	218 (33%)	216 (32%)	207 (32%)	213 (33%)	207 (33%)
Disease Duration - Years					
Mean (Std. Dev.)	9.0 (8.93)	8.4 (8.18)	8.6 (8.00)	8.5 (8.44)	8.8 (8.84)
Range	0.1-52.0	0.1-51.0	0.1-50.0	0.1-51.2	0.1-64.0
<5 years - N (%)	257 (39%)	281 (42%)	255 (40%)	273 (42%)	264 (42%)
≥5 years - N (%)	407 (61%)	390 (58%)	389 (60%)	375 (58%)	367 (58%)

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Table A.3 Baseline demographics (protocol 060, 087-pooled)

Baseline Characteristic	Placebo (n=476)*	Celecoxib	
		100 mg BID (n=474)	200 mg QD (n=454)
Baseline Demographic Characteristics			
Age (years)			
Mean (Std. Dev.)	61.9 (11.49)	62.5 (11.16)	62.0 (11.59)
Range	18-89	27-89	29-88
<65 years - N (%)	260 (55%)	254 (54%)	257 (57%)
≥65 years - N (%)	215 (45%)	220 (46%)	197 (43%)
Race/Ethnic Origin			
Caucasian - N (%)	418 (88%)	408 (86%)	392 (86%)
Black - N (%)	42 (9%)	50 (11%)	41 (9%)
Hispanic - N (%)	7 (1%)	9 (2%)	6 (1%)
Asian - N (%)	1 (<1%)	0 (0%)	1 (<1%)
Other - N (%)	7 (1%)	6 (1%)	14 (3%)
Gender			
Female - N (%)	333 (70%)	321 (68%)	306 (67%)
Male - N (%)	143 (30%)	153 (32%)	148 (33%)
Disease Duration - Years			
Mean (Std. Dev.)	9.1 (8.47)	9.4 (8.79)	9.1 (7.92)
Range	0.1-59.0	0.1-50.0	0.1-60.0
<5 years - N (%)	172 (36%)	158 (33%)	149 (33%)
≥5 years - N (%)	304 (64%)	316 (67%)	305 (67%)

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Table A.4 WOMAC Index

How much pain do you have?

- walking on a flat surface
- going up or down stairs
- at night while in bed
- sitting or lying
- standing upright

Amount of joint stiffness

- How severe is your stiffness after first awakening in the morning?
- How severe is your stiffness after sitting, lying, or resting later in the day?

Ability to move around and to look after yourself - degree of difficulty

- | | |
|------------------------------|------------------------------|
| - descending stairs | - rising from bed |
| - ascending stairs | - taking off socks/stockings |
| - rising from sitting | - lying in bed |
| - standing | - getting in/out of bath |
| - bending to floor | - sitting |
| - walking on flat surface | - getting on/off toilet |
| - getting in/out of car | - heavy domestic duties |
| - going shopping | - light domestic duties |
| - putting on socks/stockings | |

Score: none, mild, moderate, severe, extreme

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Table A.5: Osteoarthritis Severity Index (knee)

Inquiries Related to Pain	Points*
Nocturnal pain	
- none	0
- only on movement or in certain positions	1
- without movement	2
Duration of morning stiffness or pain after getting up	
- none	0
- less than 15 minutes	1
- 15 minutes or more	2
Remaining standing for 30 minutes increases pain	
- no	0
- yes	1
Pain on walking	
- none	0
- only after walking some distance	1
- very early after starting to walk and increasing	2
Pain or discomfort when getting up from the sitting position	
- no	0
- yes	1
Inquiries related to maximum walking distance	
- Unlimited	0
- More than 1 km (0.62 miles), but limited	1
- About 1 km (0.62 miles), about 15 minutes	2
- From 500 to 900 m (547-985 yards, about 8-15 minutes)	3
- From 300 to 500 m (328-547 yards)	4
- From 100 to 300 m (109-328 yards)	5
- Less than 100 m (109 yards)	6
- With one walking stick or crutch	+1
- With two walking sticks or crutches	+2
Inquiries related to activities of daily living*	
- Can you go up a standard flight of stairs?	0 to 2
- Can you go down a standard flight of stairs?	0 to 2
- Can you squat completely?	0 to 2
- Can you walk on uneven ground?	0 to 2

*Point Score: No difficulty = 0; With difficulty = 1; Impossible = 2.

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Table A.6: Osteoarthritis Severity Index (hip)

Inquiries Related to Pain	Points*
Nocturnal pain	
- none	0
- only on movement or in certain positions	1
- without movement	2
Duration of morning stiffness or pain after getting up	
- none	0
- less than 15 minutes	1
- 15 minutes or more	2
Remaining standing for 30 minutes increases pain	
- no	0
- yes	1
Pain on walking	
- none	0
- only after walking some distance	1
- very early after starting to walk and increasing	2
Pain or discomfort when getting up from the sitting position	
- no	0
- yes	1
Inquiries related to maximum walking distance	
- Unlimited	0
- More than 1 km (0.62 miles), but limited	1
- About 1 km (0.62 miles, about 15 minutes)	2
- From 500 to 900 m (547-985 yards, about 8-15 minutes)	3
- From 300 to 500 m (328-547 yards)	4
- From 100 to 300 m (109-328 yards)	5
- Less than 100 m (109 yards)	6
- With one walking stick or crutch	+1
- With two walking sticks or crutches	+2
Inquiries related to activities of daily living*	
- Can you put on socks by bending forward?	0 to 2
- Can you pick up an object from the floor?	0 to 2
- Can you go up a standard flight of stairs?	0 to 2
- Can you get into and out of a car?	0 to 2

*Point Score: No difficulty = 0; With difficulty = 1; Impossible = 2.

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Table A.7.1 Physician's Global Assessment (Protocol 054)

PHYSICIAN'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 1 OF 4: OBSERVED MEANS (d, 10)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58035 50MG BID (N=216)	SC-58035 100MG BID (N=207)	SC-58035 200MG BID (N=213)
BASELINE				
N	217	216	207	213
MEAN	3.8	3.8	3.5	3.5
STD DEV	0.60	0.60	0.56	0.60
WEEK 2				
N	217	216	207	213
MEAN	3.2	2.9	2.7	2.5
STD DEV	0.90	0.83	0.91	0.83
WEEK 4				
N	217	216	207	213
MEAN	3.2	2.8	2.7	2.7
STD DEV	0.91	0.94	0.93	0.94
WEEK 12				
N	217	216	207	213
MEAN	3.2	2.9	2.6	2.6
STD DEV	0.90	0.90	0.95	0.90

(d) This table is based on the last observation carried forward approach.
 (e) Grade ranged from 1 (very good) to 5 (very poor).

PHYSICIAN'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 2 OF 4: CATEGORICAL CHANGE ANALYSIS, NUMBER OF PATIENTS (d, 10)

INTENT-TO-TREAT COHORT (ITT)

	PLACEBO (N=217)	SC-58035 50MG BID (N=216)	SC-58035 100MG BID (N=207)	SC-58035 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	LINZES PHEND p-VALUE (d)
WEEK 2						
IMPROVED (e)	37 (17%)	55 (25%)	40 (19%)	69 (32%)	61 (30%)	<0.001
NO CHANGE (f)	172 (79%)	158 (73%)	145 (70%)	140 (66%)	141 (68%)	
WORSENE (g)	8 (4%)	3 (1%)	2 (1%)	4 (2%)	3 (1%)	
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)	
WEEK 4						
IMPROVED (e)	42 (19%)	58 (27%)	70 (34%)	80 (38%)	61 (30%)	<0.001
NO CHANGE (f)	156 (72%)	144 (67%)	135 (65%)	126 (60%)	139 (67%)	
WORSENE (g)	9 (4%)	4 (2%)	2 (1%)	5 (2%)	5 (2%)	
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)	
WEEK 12						
IMPROVED (e)	39 (18%)	59 (27%)	65 (32%)	62 (30%)	64 (31%)	<0.001
NO CHANGE (f)	169 (78%)	151 (70%)	138 (67%)	145 (68%)	139 (67%)	
WORSENE (g)	9 (4%)	5 (2%)	2 (1%)	5 (2%)	3 (1%)	
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)	

(d) TABLE FOR TREATMENT COMPARISONS (d, 1)

	-----PRIMARY-----				-----SECONDARY-----					
	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG 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 2:	0.001*	<0.001*	0.005	0.346	0.015	0.283	<0.001	0.242	0.020	0.009
WEEK 4:	<0.001*	<0.001*	<0.001	0.510	0.527	0.314	0.003	0.535	0.467	0.193
WEEK 12:	<0.001*	0.009*	0.004	0.217	0.811	0.493	<0.001	0.805	0.421	0.516

(d) This table is based on the last observation carried forward approach.
 (e) Improved is defined as a reduction of at least two grades from baseline for grades 3-5 or a change in grade from 1 to 2.
 (f) No change is defined as an increase of at least two grades from baseline for grades 1-3 or a change in grade from 4 to 5.
 (g) Cochran-Mantel-Haenszel test of linear dose trend stratified by center (Spearman Correlation), Naproxen group was excluded.
 (h) Cochran-Mantel-Haenszel test of treatment comparison stratified by center (Row Mean Scores Differ).
 (*) Statistically significant according to the Hochberg procedure (primary pairwise comparisons only).

Table A.7.2 Physician's Global Assessment-continued (Protocol 054)

INTEND-TO-TREAT GROUP (ITT)							OVERALL p-VALUE(c)	LINEAR TREAT p-VALUE(d)		
PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=209)	SC-58635 150MG BID (N=213)	SC-58635 200MG BID (N=207)	NAPROXEN 500MG BID (N=207)					
WEEK 2							* <0.001	<0.001		
DIFFERED MEAN CHANGE PAIN (AN)	-0.6	-1.9	-1.1	-1.1	-1.1					
SD MEAN CHANGE (AN)	0.94	0.9	0.82	0.93	0.92					
WEEK 6							* <0.001	<0.001		
DIFFERED MEAN CHANGE PAIN (AN)	-1.6	-1.2	-1.2	-1.1	-1.2					
SD MEAN CHANGE (AN)	1.00	1.1	1.01	1.04	0.96					
WEEK 12							* <0.001	<0.001		
DIFFERED MEAN CHANGE PAIN (AN)	-1.6	-1.9	-1.8	-1.1	-1.2					
SD MEAN CHANGE (AN)	0.98	1.04	1.04	1.07	1.05					
95% CI WITH 95% CONFIDENCE INTERVALS (e)										
	50MG BID VS. NAPROXEN		100MG BID VS. NAPROXEN		200MG BID VS. NAPROXEN					
WEEK 2:	-1.88 + 0.71 to -0.97*		-1.28 + 0.85 to -0.44*		-0.81 + 0.84 to -0.02*					
WEEK 6:	-0.99 + 0.82 to -0.17*		-1.00 + 0.85 to -0.19*		-0.65 + 0.59 to -0.06*					
WEEK 12:	-0.91 + 0.76 to -0.09*		-0.97 + 0.81 to -0.16*		-0.80 + 0.73 to -0.07*					
p-VALUES FOR TREATMENT COMPARISONS (f)										
	-----PRIMARY-----			-----SECONDARY-----						
	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 2:	<0.001*	<0.001*	<0.001	0.031	0.054	0.615	<0.001	0.019	0.050	0.671
WEEK 6:	<0.001*	<0.001*	<0.001	0.907	0.490	0.571	<0.001	0.925	0.981	0.555
WEEK 12:	<0.001*	<0.001*	<0.001	0.502	0.899	0.427	<0.001	0.298	0.710	0.245

a. This table is based on the last observation carried forward approach.
 b. Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement.
 c. From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate.
 d. The corresponding ROOT MSE are: 0.796 for week 2, 0.897 for week 6, and 0.916 for week 12.
 e. From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded.
 f. D-RATIO is defined as the ratio of least square mean changes from (a) of SC-58635 group versus Naproxen group.
 (c) From a contrast statement from Analysis of Covariance model in (c).
 * Statistically significant according to the Hochberg procedure (primary pairwise comparisons only).

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Table A.8.1 Patient's global assessment (Protocol 054)

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 1 OF 4: OBSERVED MEANS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)*				
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	216	207	213	207
MEAN	3.8	3.8	3.9	4.0	3.9
STD DEV	0.61	0.64	0.61	0.59	0.64
WEEK 2					
N	217	216	207	213	207
MEAN	3.3	2.9	2.7	2.8	2.7
STD DEV	0.90	0.88	0.85	0.90	0.86
WEEK 6					
N	217	216	207	213	207
MEAN	3.3	2.9	2.8	2.8	2.8
STD DEV	0.97	0.97	0.99	1.00	1.01
WEEK 10					
N	217	216	207	213	207
MEAN	3.4	2.9	2.8	3.0	2.8
STD DEV	0.96	1.01	1.02	1.09	1.06

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 1 (very good) to 5 (very poor)

* By definition, in this and subsequent efficacy tables, the ITT cohort includes only patients who had at least one dose of study medication

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 2 OF 4: CATEGORICAL CHANGE ANALYSIS, NUMBER OF PATIENTS (N) (a)

	INTENT-TO-TREAT COHORT (ITT)					LINEAR TREND p-VALUE (d)
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	
WEEK 2						
IMPROVED (b)	35 (16%)	51 (24%)	67 (32%)	75 (35%)	66 (32%)	<0.001
NO CHANGE	171 (79%)	160 (74%)	137 (66%)	132 (62%)	138 (67%)	
WORSENER (c)	11 (5%)	5 (2%)	3 (1%)	6 (3%)	3 (1%)	
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)	
WEEK 6						
IMPROVED (b)	38 (18%)	67 (31%)	71 (34%)	78 (37%)	63 (30%)	<0.001
NO CHANGE	162 (75%)	143 (66%)	131 (63%)	126 (59%)	139 (67%)	
WORSENER (c)	17 (8%)	6 (3%)	5 (2%)	9 (4%)	5 (2%)	
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)	
WEEK 10						
IMPROVED (b)	36 (17%)	56 (26%)	65 (31%)	61 (29%)	70 (34%)	0.001
NO CHANGE	164 (76%)	153 (71%)	137 (66%)	142 (67%)	131 (63%)	
WORSENER (c)	17 (8%)	7 (3%)	5 (2%)	10 (5%)	6 (3%)	
TOTAL	217 (100%)	216 (100%)	207 (100%)	213 (100%)	207 (100%)	

p-VALUES FOR TREATMENT COMPARISONS (e) :

	PRIMARY				SECONDARY					
	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 2:	<0.001*	<0.001*	0.016	0.044	0.017	0.427	<0.001	0.072	0.954
WEEK 6:	<0.001*	<0.001*	<0.001	0.543	0.423	0.492	<0.001	0.037	0.464	0.246
WEEK 10:	<0.001*	0.007*	0.004	0.250	0.794	0.606	<0.001	0.151	0.677	0.174

(a) This table is based on the last observation carried forward approach

(b) Improved is defined as reduction of at least two grades from baseline for grades 3-5 or a change in grade from 2 to 1

(c) Worsened is defined as an increase of at least two grades from baseline for grades 1-3 or a change in grade from 4 to 5

(d) Cochran-Mantel-Haenszel test of linear dose trend stratified by center (Nonzero Correlation), Naproxen group was excluded

(e) Cochran-Mantel-Haenszel test of treatment comparison stratified by center (Row Mean Scores Differ)

* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.8.2 Patient's global assessment (Protocol 054)

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS PART 3 OF 4: MEAN CHANGE ANALYSIS (a) (b)									
INTENT-TO-TREAT (ITT)									
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	OVERALL P-VALUE (c)	LINEAR SPRINT P-VALUE (d)		
WEEK 2									
OBSERVED MEAN CHANGE	-0.6	-0.9	-1.2	-1.1	-1.2	<0.001	<0.001		
STD DEV	0.94	0.92	0.93	0.96	0.93				
LS MEAN CHANGE (e)	-0.6	-0.9	-1.2	-1.1	-1.2				
WEEK 6									
OBSERVED MEAN CHANGE	-1.5	0.9	-1.1	-1.1	-1.1	<0.001	<0.001		
STD DEV	1.00	1.02	1.05	1.02	0.99				
LS MEAN CHANGE (e)	-0.6	-1.0	-1.1	-1.1	-1.1				
WEEK 12									
OBSERVED MEAN CHANGE	-0.5	-0.8	-1.1	-1.0	-1.1	<0.001	<0.001		
STD DEV	1.06	1.06	1.06	1.07	1.07				
LS MEAN CHANGE (e)	-0.5	-0.9	-1.1	-0.9	-1.1				
Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):									
	50MG BID VS. NAPROXEN		100MG BID VS. NAPROXEN		200MG BID VS. NAPROXEN				
WEEK 2:	0.78 (0.66 to 0.91)		0.97 (0.85 to 1.12)		0.93 (0.80 to 1.07)				
WEEK 6:	0.92 (0.77 to 1.10)		1.01 (0.80 to 1.20)		1.00 (0.84 to 1.17)				
WEEK 12:	0.52 (0.68 to 0.99)		0.95 (0.79 to 1.13)		0.83 (0.68 to 1.00)				
P-VALUES FOR TREATMENT COMPARISONS (f):									
	PRIMARY				SECONDARY				
	100MG BID VS. PLACEBO	100MG BID VS. PLACEBO	50MG BID VS. PLACEBO	100MG BID VS. 50MG BID	200MG BID VS. 50MG BID	200MG BID VS. PLACEBO	NAPROXEN VS. 50MG BID	NAPROXEN VS. 100MG BID	NAPROXEN VS. 100MG BID
WEEK 2:	<0.001*	<0.001*	<0.001	0.004	0.028	0.484	<0.001	0.001	0.712
WEEK 6:	<0.001*	<0.001*	<0.001	0.273	0.375	0.832	<0.001	0.354	0.859
WEEK 12:	<0.001*	<0.001*	<0.001	0.159	0.981	0.146	<0.001	0.036	0.036

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement
 (c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 0.825 for week 2, 0.941 for week 6, and 0.967 for week 12
 (d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
 (e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group
 (f) From a contrast statement from Analysis of Covariance model in (c)
 * Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.9.1 Patient's Assessment of Arthritis Pain (protocol 020)

INTENT-TO-TREAT COHORT (ITT) *					
	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)
BASELINE					
N	201	203	196	201	197
MEAN	69.4	66.9	68.0	68.9	71.4
STD DEV	17.13	18.13	16.17	15.43	14.97
WEEK 2					
N	201	203	196	201	197
MEAN	56.1	49.2	41.9	44.0	42.2
STD DEV	26.24	25.53	25.77	24.96	26.52
WEEK 6					
N	201	203	196	201	197
MEAN	51.1	49.3	41.6	43.8	41.9
STD DEV	29.04	26.83	27.84	27.05	29.07
WEEK 12					
N	201	203	196	201	197
MEAN	52.7	50.9	43.8	45.5	45.8
STD DEV	29.41	28.29	28.05	29.23	29.29

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 0 to 100 (mm) with lower score as better

* By definition, in this and subsequent efficacy tables, the ITT cohort includes only knee patients who had at least one dose of study medication

TABLE 18 PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS) PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)

INTENT-TO-TREAT COHORT (ITT)							
	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)	OVERALL p-VALUE (c)	LINEAR TREND p-VALUE (d)
WEEK 2							
OBSERVED MEAN CHANGE	-13.3	-17.7	-26.1	-24.9	-29.2	<0.001	<0.001
STD DEV	23.28	25.99	26.19	24.81	26.88		
LS MEAN CHANGE (c)	-12.1	-18.4	-26.1	-24.6	-27.3		
WEEK 6							
OBSERVED MEAN CHANGE	-18.3	-17.7	-26.4	-25.1	-29.5	<0.001	<0.001
STD DEV	27.38	29.22	27.76	26.40	30.28		
LS MEAN CHANGE (c)	-16.6	-17.9	-25.9	-24.5	-27.0		
WEEK 12							
OBSERVED MEAN CHANGE	-16.7	-16.0	-24.1	-23.3	-25.6	0.002	<0.001
STD DEV	29.05	29.81	27.31	29.18	29.14		
LS MEAN CHANGE (c)	-15.1	-16.0	-23.1	-22.1	-22.7		
Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):							
	50MG BID VS. NAPROXEN		100MG BID VS. NAPROXEN		200MG BID VS. NAPROXEN		
WEEK 2:	0.67 (0.53 to 0.84)		0.96 (0.80 to 1.15)		0.90 (0.74 to 1.09)		
WEEK 6:	0.66 (0.51 to 0.85)		0.96 (0.78 to 1.18)		0.91 (0.74 to 1.12)		
WEEK 12:	0.70 (0.51 to 0.94)		1.02 (0.80 to 1.30)		0.97 (0.76 to 1.25)		

p-VALUES FOR TREATMENT COMPARISONS (f):

	PRIMARY				SECONDARY					
	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 2:	<0.001*	<0.001*	0.009	0.001	0.010	0.514	<0.001	<0.001	0.643	0.263
WEEK 6:	<0.001*	0.003*	0.628	0.002	0.013	0.579	<0.001	<0.001	0.700	0.346
WEEK 12:	0.003*	0.009*	0.735	0.008	0.023	0.701	0.005	0.014	0.875	0.822

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 0 to 100 (mm) with negative change indicating improvement

(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 23.93 for week 2, 26.22 for week 6, and 27.02 for week 12

(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded

(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group

(f) From a contrast statement from Analysis of Covariance model in (c)

* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table/Figure A.9.2 Patient's Assessment of Arthritis Pain (020)

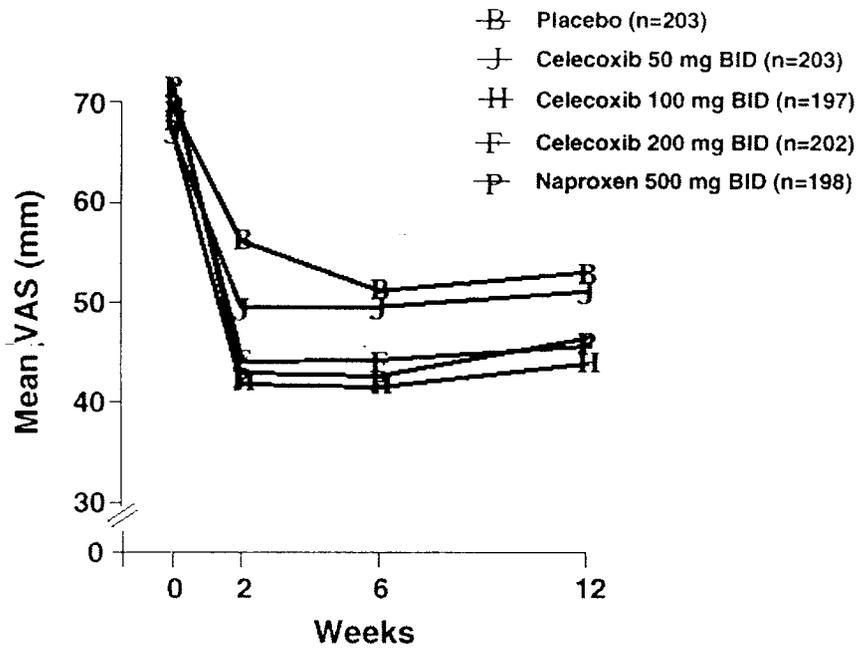


Table A.10.1 Patient's Assessment of Arthritis Pain (protocol 054)

TABLE 18
PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
PART 1 OF 3: OBSERVED MEANS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)				
	PLACEBO (N=217)	SC 58635 50MG BID (N=216)	SC 58635 100MG BID (N=207)	SC 58635 200MG BID (N=213)	DIKLENEN 50MG BID (N=217)
BASELINE					
N	217	216	207	212	217
MEAN	68.2	68.7	67.1	67.8	67.7
STD DEV	14.89	14.92	16.99	15.69	16.4
WEEK 2					
N	217	216	207	213	217
MEAN	57.0	49.4	43.7	44.2	47.1
STD DEV	24.64	25.93	26.09	27.11	26.16
WEEK 6					
N	217	216	207	213	217
MEAN	55.6	47.8	41.0	44.9	47.7
STD DEV	26.11	27.15	27.43	29.65	27.11
WEEK 12					
N	217	216	207	213	217
MEAN	53.4	50.0	44.6	49.0	49.8
STD DEV	25.71	28.09	28.13	28.89	27.11

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 100 (mm) with lower score as better

TABLE 19
PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)					
	PLACEBO (N=217)	SC 58635 50MG BID (N=216)	SC 58635 100MG BID (N=207)	SC 58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)	DIKLENEN 50MG BID (N=217)
WEEK 2						
OBSERVED MEAN CHANGE	11.2	19.3	23.6	23.6	-25.4	-0.001
STD DEV	23.62	24.67	25.46	25.45	24.91	
LS MEAN CHANGE (c)	-11.5	-19.7	-24.4	-24.4	-26.5	
WEEK 6						
OBSERVED MEAN CHANGE	12.6	-20.9	-24.2	-22.8	-23.8	<0.001
STD DEV	25.31	27.04	26.97	28.87	27.68	
LS MEAN CHANGE (c)	-13.2	-21.5	-25.1	-23.9	-24.8	
WEEK 12						
OBSERVED MEAN CHANGE	10.8	18.7	-22.6	18.8	-21.4	<0.001
STD DEV	25.97	28.24	28.25	28.67	28.25	
LS MEAN CHANGE (c)	-11.1	-19.0	-23.3	-19.3	-22.3	
Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):						
	50MG BID VS. NAPROXEN		100MG BID VS. NAPROXEN		200MG BID VS. NAPROXEN	
WEEK 2:	0.74 (0.60 to 0.91)		0.90 (0.76 to 1.10)		0.92 (0.77 to 1.11)	
WEEK 6:	0.87 (0.69 to 1.08)		1.01 (0.82 to 1.24)		0.76 (0.57 to 1.19)	
WEEK 12:	0.75 (0.66 to 1.10)		1.05 (0.83 to 1.32)		0.87 (0.67 to 1.10)	

(c) P-VALUES FOR TREATMENT COMPARISONS (f):

	PRIMARY				SECONDARY					
	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 2:	<0.001*	<0.001*	<0.001	0.039	0.03	0.980	<0.001	0.003	0.250	0.341
WEEK 6:	<0.001*	<0.001*	<0.001	0.145	0.123	0.636	<0.001	0.175	0.509	0.720
WEEK 12:	<0.001*	0.001*	0.002	0.091	0.882	0.123	<0.001	0.109	0.688	0.289

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 100 (mm) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 1.26 for week 2, 25.36 for week 6, and 26.09 for week 12
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group
(f) From a contrast statement from Analysis of Covariance model in (c)
* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table/Figure A.10.2 Patient's Assessment of Arthritis Pain (054)

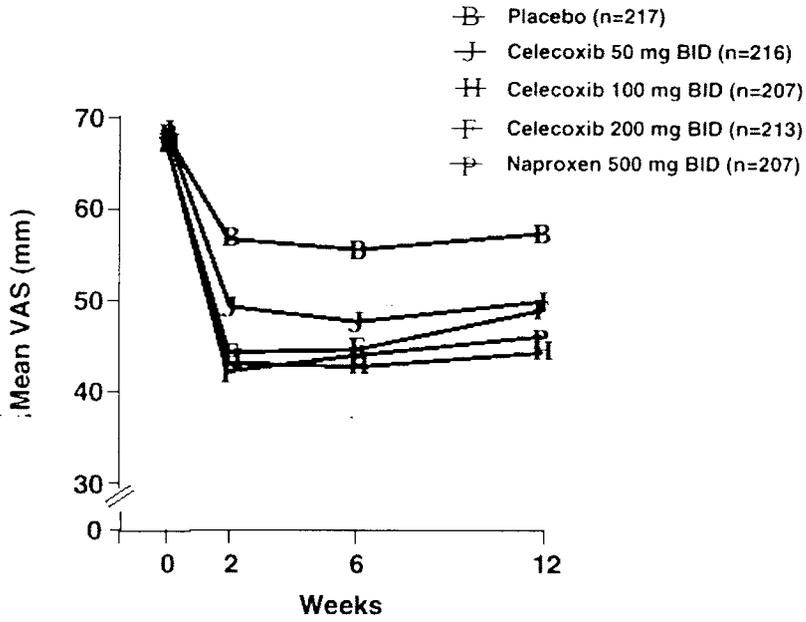


Table A.11 WOMAC pain (protocol 054)

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN HIP OA
N49-96-02-054

TABLE 21.1
WOMAC PAIN
PART 1 OF 2: OBSERVED MEANS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)				
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	216	207	213	207
MEAN	10.6	10.5	10.6	10.8	10.5
STD DEV	3.24	3.43	3.33	2.95	3.04
WEEK 2					
N	217	216	207	211	207
MEAN	10.0	8.8	8.1	8.5	9.4
STD DEV	3.66	3.85	3.62	3.57	3.74
WEEK 12					
N	217	216	207	213	207
MEAN	9.7	9.0	8.5	8.5	8.0
STD DEV	3.98	3.99	4.22	4.20	3.94

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with lower score as better

	INTENT-TO-TREAT COHORT (ITT)					OVERALL p-VALUE (c)	LINEAR TRENDS p-VALUE (d)
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)		
WEEK 2							
OBSERVED MEAN CHANGE	-0.6	-1.7	-2.5	-2.5	-2.7	<0.001	<0.001
STD DEV	3.09	3.30	3.26	3.27	3.20		
LS MEAN CHANGE (e)	-0.7	-1.8	-2.6	-2.5	-2.9		
WEEK 12							
OBSERVED MEAN CHANGE	0.9	-1.5	-2.1	-2.4	-2.5	<0.001	<0.001
STD DEV	3.66	3.41	3.56	3.31	3.61		
LS MEAN CHANGE (e)	-1.0	-1.7	-2.0	-2.4	-2.7		

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 2:	<0.001	<0.001	<0.001	0.004	0.009	0.804	<0.001	<0.001	0.394	0.271
WEEK 12:	<0.001	<0.001	0.034	0.093	0.708	0.607	<0.001	0.002	0.179	0.407

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

Table A.12 WOMAC pain (protocol 020)

TABLE 21.1
WOMAC PAIN
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT TO TREAT COHORT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)
BASELINE					
N	201	197	196	201	198
MEAN	10.7	10.7	10.5	10.7	11.0
STD DEV	3.41	3.18	3.36	3.36	2.97
WEEK 2					
N	201	197	196	201	198
MEAN	10.0	8.7	7.6	7.9	8.2
STD DEV	3.89	3.77	3.78	3.85	4.00
WEEK 12					
N	201	197	196	201	198
MEAN	9.4	8.6	7.4	7.9	8.4
STD DEV	4.40	4.09	4.17	4.19	4.25

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 20 with lower score as better

INTENT TO TREAT COHORT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)	OVERALL P-VALUE (c)	LINEAR TREND P-VALUE (d)			
WEEK 2										
OBSERVED MEAN CHANGE	-0.8	-2.0	-2.9	-2.8	-2.8	<0.001	<0.001			
STD DEV	2.98	3.18	3.29	3.58	3.95					
LS MEAN CHANGE (e)	-0.7	-2.0	-3.0	-2.8	-2.7					
WEEK 12										
OBSERVED MEAN CHANGE	-1.4	-2.1	-3.1	-2.8	-2.6	<0.001	<0.001			
STD DEV	3.84	3.59	3.66	3.84	3.91					
LS MEAN CHANGE (e)	-1.2	-2.0	-3.1	-2.7	-2.4					
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 2:	<0.001	<0.001	<0.001	0.901	0.310	0.520	<0.001	0.024	0.340	0.751
WEEK 12:	<0.001	<0.001	0.326	0.302	0.049	0.259	0.001	0.310	0.028	0.339

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 20 with negative change indicating improvement
 (c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
 (d) From a contrast statement from Analysis of Covariance model in (c). Naproxen group was excluded
 (e) From a contrast statement from Analysis of Covariance model in (c)

Table A.13 WOMAC stiffness (protocol 054)

TABLE 21.2
WOMAC JOINT STIFFNESS
PART 1 OF 2: OBSERVED MEANS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)				
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	216	207	211	205
MEAN	4.6	4.7	4.6	4.7	4.6
STD DEV	1.42	1.48	1.58	1.48	1.60
WEEK 2					
N	217	216	207	212	207
MEAN	4.4	4.0	3.7	3.7	3.6
STD DEV	1.49	1.59	1.60	1.62	1.62
WEEK 12					
N	217	216	207	213	207
MEAN	4.3	3.9	3.7	3.7	3.6
STD DEV	1.58	1.61	1.77	1.68	1.68

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 8 with lower score as better

	INTENT-TO-TREAT COHORT (ITT)					OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)		
WEEK 2							
OBSERVED MEAN CHANGE	-0.3	-0.8	-1.0	-1.0	-1.0	<0.001	<0.001
STD DEV	1.37	1.45	1.59	1.56	1.54		
LS MEAN CHANGE (e)	-0.3	-0.8	-1.0	-1.0	-1.1		
WEEK 12							
OBSERVED MEAN CHANGE	-0.3	-0.8	-0.9	-1.0	-1.0	<0.001	<0.001
STD DEV	1.61	1.50	1.67	1.75	1.56		
LS MEAN CHANGE (e)	-0.4	-0.8	-1.0	-1.0	-1.1		

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 2:	<0.001	<0.001	<0.001	0.044	0.031	0.695	<0.001	0.007	0.498	0.564
WEEK 12:	<0.001	<0.001	0.004	0.148	0.132	0.959	<0.001	0.017	0.354	0.379

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 8 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c). Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

Table A.14 WOMAC stiffness (protocol 020)

TABLE 21.2
WOMAC JOINT STIFFNESS
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)
BASELINE					
N	202	197	196	201	196
MEAN	4.9	4.8	4.7	4.9	5.0
STD DEV	1.35	1.31	1.47	1.50	1.40
WEEK 2					
N	202	197	196	201	196
MEAN	4.5	4.4	4.5	4.6	4.7
STD DEV	1.59	1.64	1.65	1.62	1.69
WEEK 12					
N	202	197	196	201	196
MEAN	4.4	4.4	4.5	4.7	4.9
STD DEV	1.72	1.73	1.71	1.69	1.71

a) This table is based on the last observation carried forward approach
b) Scale ranged from 0 to 8 with lower score as better

INTENT-TO-TREAT COHORT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)	OVERALL p-VALUE (c)	LINEAR TREND p-VALUE (d)
WEEK 2							
OBSERVED MEAN CHANGE	-0.4	-0.9	-1.2	-1.3	-1.3	<0.001	<0.001
STD DEV	1.33	1.49	1.58	1.66	1.83		
LS MEAN CHANGE (e)	-0.3	-0.9	-1.2	-1.2	-1.1		
WEEK 12							
OBSERVED MEAN CHANGE	-0.6	-0.9	-1.2	-1.2	-1.0	<0.001	<0.001
STD DEV	1.61	1.63	1.57	1.71	1.90		
LS MEAN CHANGE (e)	-0.5	-0.9	-1.2	-1.1	-1.1		

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 500MG VS. PLACEBO	NAPROXEN 500MG VS. 50MG BID	NAPROXEN 500MG VS. 100MG BID	NAPROXEN 500MG VS. 200MG BID
WEEK 2:	<0.001	<0.001	<0.001	0.019	0.027	0.694	<0.001	0.091	0.510	0.613
WEEK 12:	<0.001	<0.001	0.013	0.004	0.149	0.447	<0.001	0.154	0.446	0.995

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 8 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

Table A.15 WOMAC function (protocol 054)

TABLE 11.3
WOMAC PHYSICAL FUNCTIONING
PART 1 OF 2: OBSERVED MEANS (BY CO)

	INTENT-TO-TREAT COHORT (ITT)				
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=215)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	215	207	211	207
MEAN	35.5	34.1	34.9	35.4	34.7
STD DEV	11.30	12.29	12.14	11.13	12.01
WEEK 7					
N	217	215	207	212	207
MEAN	33.3	29.2	27.2	27.6	26.5
STD DEV	12.60	12.73	12.32	12.71	12.43
WEEK 12					
N	217	215	207	213	207
MEAN	32.5	29.3	25.2	28.2	26.8
STD DEV	12.99	13.64	14.75	13.79	13.20

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 68 with lower score as better

	INTENT-TO-TREAT COHORT (ITT)					OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=215)	NAPROXEN 500MG BID (N=207)		
WEEK 7							
OBSERVED MEAN CHANGE	0.2	-4.9	-7.7	-7.9	8.2	<0.001	<0.001
STD DEV	9.28	12.36	10.11	10.72	9.96		
LS MEAN CHANGE (e)	-5.3	-5.4	-8.1	-8.1	-8.2		
WEEK 12							
OBSERVED MEAN CHANGE	-3.0	-4.8	-6.7	-7.3	-7.9	<0.001	<0.001
STD DEV	10.94	10.91	11.17	12.58	11.34		
LS MEAN CHANGE (e)	-3.2	-5.5	-7.0	-7.5	-8.4		

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 7:	<0.001	<0.001	<0.001	0.005	0.004	0.945	<0.001	<0.001	0.470	0.511
WEEK 12:	<0.001	<0.001	0.023	0.142	0.047	0.609	<0.001	0.004	0.160	0.369

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 68 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

Table A.16 WOMAC function (protocol 020)

INTENT-TO-TREAT COHORT (ITT) - KNEE PATIENTS ONLY					
	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)
BASELINE					
N	184	174	176	181	180
MEAN	36.0	36.2	35.4	35.3	36.6
STD DEV	10.83	10.76	11.77	12.29	10.58
WEEK 8					
N	184	174	176	181	180
MEAN	33.0	29.3	26.2	26.9	28.1
STD DEV	12.52	13.06	12.88	12.94	13.23
WEEK 12					
N	184	174	176	181	180
MEAN	31.7	29.4	26.1	27.4	28.5
STD DEV	13.94	14.09	14.38	14.20	14.90

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 68 with lower score as better

**TABLE 21.3
 WOMAC PHYSICAL FUNCTIONING
 PART 2 OF 2: MEAN CHANGE ANALYSIS (a) (b)**

INTENT-TO-TREAT COHORT (ITT) - KNEE PATIENTS ONLY							
	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 8							
OBSERVED MEAN CHANGE	-2.9	-6.9	-9.1	-8.4	-8.5	<0.001	<0.001
STD DEV	9.32	9.85	11.19	11.39	12.53		
LS MEAN CHANGE (e)	-2.6	-6.8	-9.3	-8.5	-8.3		
WEEK 12							
OBSERVED MEAN CHANGE	-4.3	-6.8	-9.2	-7.9	-8.1	<0.001	<0.001
STD DEV	11.21	11.61	12.26	12.62	13.23		
LS MEAN CHANGE (e)	-3.9	-6.8	9.5	-8.1	-7.8		

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 8:	<0.001	<0.001	<0.001	0.021	0.113	0.460	<0.001	0.257	0.233	0.647
WEEK 12:	<0.001	<0.001	0.018	0.033	0.301	0.255	0.001	0.438	0.170	0.794

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 68 with negative change indicating improvement
 (c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
 (d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
 (e) From a contrast statement from Analysis of Covariance model in (c)

Table A.17 WOMAC composite (protocol 054)

TABLE 21.4
WOMAC COMPOSITE SCORE
PART 1 OF 2: OBSERVED MEANS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)				
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)
BASELINE					
N	217	214	207	211	205
MEAN	50.7	49.3	50.2	50.9	49.8
STD DEV	14.98	16.07	16.06	14.33	16.68
WEEK 2					
N	217	216	207	210	207
MEAN	47.7	42.0	39.0	39.6	37.4
STD DEV	10.45	17.40	17.60	17.09	16.98
WEEK 12					
N	217	215	207	213	207
MEAN	46.5	42.2	40.4	40.3	38.4
STD DEV	17.68	18.66	19.99	18.92	17.97

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 96 with lower score as better

WOMAC COMPOSITE SCORE
PART 2 OF 2: MEAN CHANGE ANALYSIS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)					OVERALL p-VALUE (c)	LINEAR TREND p-VALUE (d)
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)		
WEEK 2							
OBSERVED MEAN CHANGE	-3.1	-7.3	-11.2	-11.4	-12.0	<0.001	<0.001
STD DEV	12.59	13.97	13.91	14.22	13.74		
LS MEAN CHANGE (e)	-3.4	-8.0	-11.7	-11.7	-12.7		
WEEK 12							
OBSERVED MEAN CHANGE	-4.0	-7.2	-9.7	-10.6	-11.5	<0.001	<0.001
STD DEV	18.07	14.73	15.28	16.83	19.43		
LS MEAN CHANGE (e)	-4.6	-8.0	-10.3	-11.0	-12.4		

p-VALUES FOR TREATMENT COMPARISONS (a):

	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 2:	<0.001	<0.001	<0.001	0.093	0.003	0.985	<0.001	<0.001	0.395	0.492
WEEK 12:	<0.001	<0.001	0.014	0.117	0.038	0.613	<0.001	0.002	0.138	0.425

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 96 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) From a contrast statement from Analysis of Covariance model in (c)

Table A.18 WOMAC composite (protocol 020)

TABLE 21.4
WOMAC COMPOSITE SCORE
PART 1 OF 2: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	50-58635 50MG BID (N=203)	50-58635 100MG BID (N=197)	50-58635 200MG BID (N=201)	NAPROXEN 500MG BID (N=196)
BASELINE					
N	182	174	175	181	177
MEAN	51.6	51.8	50.5	51.0	50.9
STD DEV	14.80	14.29	15.67	16.36	15.97
WEEK 1					
N	182	174	175	181	177
MEAN	47.5	42.1	37.4	38.5	40.8
STD DEV	17.34	17.69	17.46	17.69	18.50
WEEK 12					
N	182	174	175	181	177
MEAN	45.5	42.3	37.2	39.0	41.0
STD DEV	19.32	19.25	19.46	19.31	20.69

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 96 with lower score as better

TABLE 21.4
WOMAC COMPOSITE SCORE
PART 2 OF 2: MEAN CHANGE ANALYSIS (a) (b)

INTENT-TO-TREAT COHORT (ITT) - KNEE PATIENTS ONLY

	PLACEBO (N=203)	50-58635 50MG BID (N=203)	50-58635 100MG BID (N=197)	50-58635 200MG BID (N=201)	NAPROXEN 500MG BID (N=198)	OVERALL P-VALUE (c)	LINEAR TEND P-VALUE (d)
WEEK 1							
OBSERVED MEAN CHANGE	-4.1	-9.7	-13.1	-12.5	-12.7	<0.001	<0.001
STD DEV	12.95	13.82	14.91	15.76	17.19		
LS MEAN CHANGE (e)	-3.6	-9.7	-13.4	-12.5	-11.9		
WEEK 12							
OBSERVED MEAN CHANGE	-6.1	-9.5	-13.3	-12.0	-11.9	<0.001	<0.001
STD DEV	15.58	15.76	16.40	17.45	18.19		
LS MEAN CHANGE (e)	-5.6	-9.6	-13.6	-12.1	-11.3		

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 1:	<0.001	<0.001	<0.001	0.012	0.051	0.549	<0.001	0.137	0.296	0.650
WEEK 12:	<0.001	<0.001	0.016	0.019	0.146	0.354	<0.001	0.325	0.173	0.655

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 96 with negative change indicating improvement
 (c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
 (d) From a contrast statement from Analysis of Covariance model in (c). Naproxen group was excluded
 (e) From a contrast statement from Analysis of Covariance model in (c)

Table A.19 Withdrawal due to lack of Arthritis Efficacy (020, 054)

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN OA
N49-96-02-020

TABLE 22
INCIDENCE OF WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)										
	PLACEBO (N=203)	SC-58635 50MG BID (N=203)	SC-58635 100MG BID (N=197)	SC-58635 200MG BID (N=202)	NAPROXEN 500MG BID (N=198)					
NUMBER WITHDRAWN DUE TO LACK OF ARTHRITIS EFFICACY	79 (39%)	61 (30%)	40 (20%)	49 (24%)	52 (26%)					
p-VALUES FOR OVERALL COMPARISONS (a):	<0.001									
p-VALUE FOR LINEAR TREND TEST (b):	<0.001									
p-VALUES FOR TREATMENT COMPARISONS (c):										
	50MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG 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
	0.076	<0.001	0.002	0.029	0.219	0.400	0.008	0.438	0.190	0.647

(a) Fisher's Exact test for all five treatment groups

(b) Cochran-Mantel-Haenszel test of linear dose trend (Nonzero Correlation), Naproxen group was excluded

(c) Pairwise Fisher's Exact test

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN HIP OA
N49-96-02-054

TABLE 22
INCIDENCE OF WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)										
	PLACEBO (N=217)	SC-58635 50MG BID (N=216)	SC-58635 100MG BID (N=207)	SC-58635 200MG BID (N=213)	NAPROXEN 500MG BID (N=207)					
NUMBER WITHDRAWN DUE TO LACK OF ARTHRITIS EFFICACY	112 (52%)	76 (35%)	61 (29%)	55 (26%)	51 (25%)					
p-VALUES FOR OVERALL COMPARISONS (a):	<0.001									
p-VALUE FOR LINEAR TREND TEST (b):	<0.001									
p-VALUES FOR TREATMENT COMPARISONS (c):										
	50MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG 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
	<0.001	<0.001	<0.001	0.224	0.037	0.445	<0.001	0.000	0.319	0.523

(a) Fisher's Exact test for all five treatment groups

(b) Cochran-Mantel-Haenszel test of linear dose trend (Nonzero Correlation), Naproxen group was excluded

(c) Pairwise Fisher's Exact test

Table A.20 Time to Withdrawal-Lack of Arthritis Efficacy (054)

TABLE 23
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 1 OF 2: KAPLAN-MEIER ESTIMATES OF PROPORTION OF PATIENTS
WHO DID NOT WITHDRAW DUE TO LACK OF ARTHRITIS EFFICACY
INTENT-TO-TREAT COHORT (ITT)

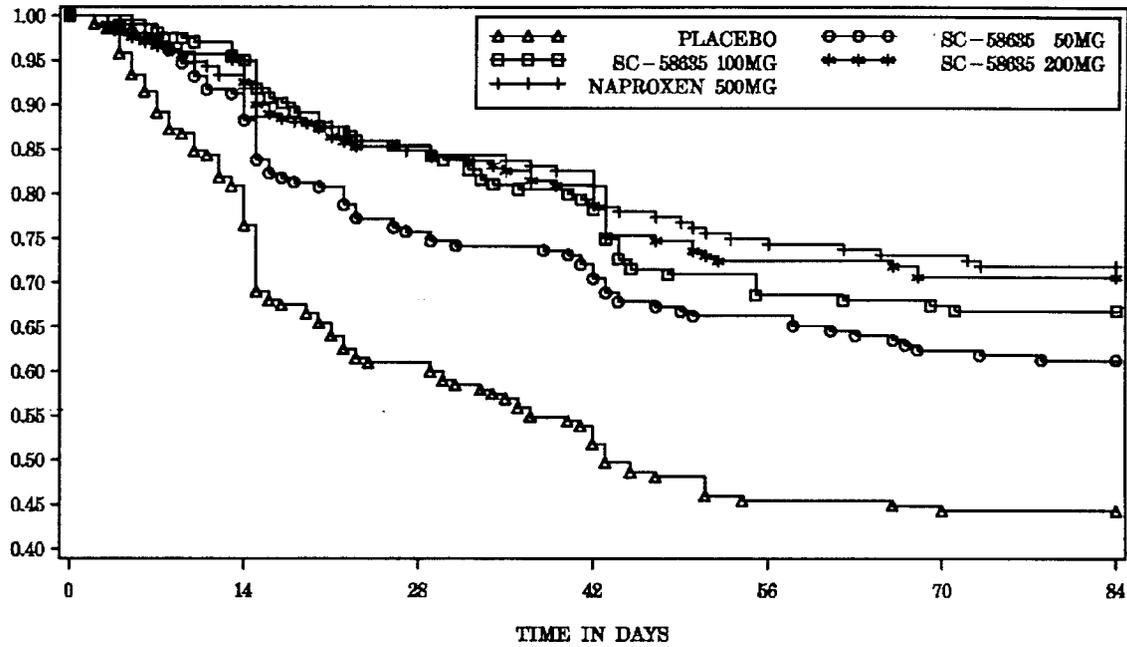


TABLE 23
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 2 OF 2: LOG-RANK TESTS FOR TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
INTENT-TO-TREAT COHORT (ITT)

p-VALUE FOR OVERALL COMPARISONS (a): <0.001

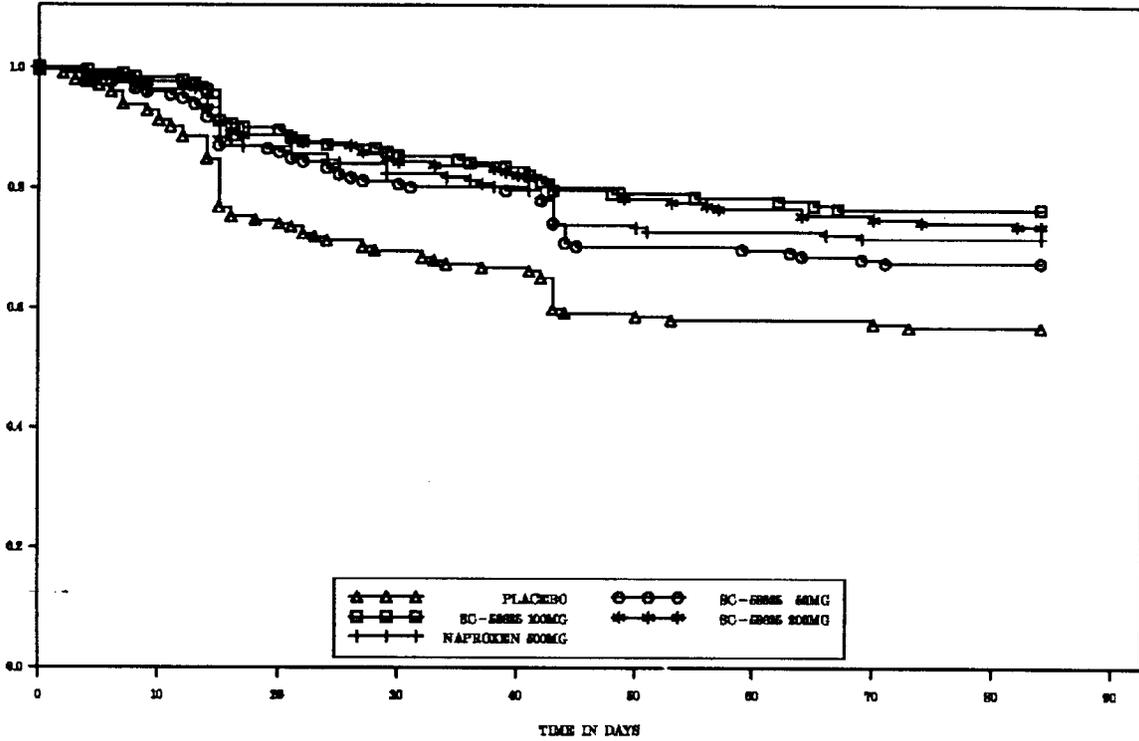
p-VALUES FOR TREATMENT COMPARISONS (b):

50MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG 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
<0.001	<0.001	<0.001	0.159	0.046	0.544	<0.001	0.024	0.369	0.772

(a) From log-rank test for all five treatment groups
 (b) From pairwise log-rank test

Table A.21 Time to Withdrawal-Lack of Arthritis Efficacy (020)

TABLE 22
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 1 OF 2: KAPLAN-MEIER ESTIMATES OF PROPORTION OF PATIENTS WHO DID NOT WITHDRAW DUE TO LACK OF ARTHRITIS EFFICACY
INTENT-TO-TREAT COHORT (ITT)



SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN OA
M49-96-02-020

TABLE 23
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 2 OF 2: LOG-RANK TESTS FOR TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)

p-VALUE FOR OVERALL COMPARISONS (a): <0.001

p-VALUES FOR TREATMENT COMPARISONS (b):

50MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG 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
0.017	<0.001	<0.001	0.065	0.142	0.648	0.002	0.420	0.295	0.530

(a) From log-rank test for all five treatment groups

(b) From pairwise log-rank test

Table A.22.1 Reasons for Study Termination (020, 021, 054)

Study	Number of Osteoarthritis Patients by Treatment Group				
	Placebo	Celecoxib			Naproxen
		50 mg BID	100 mg BID	200 mg BID	500 mg BID
Study 020^a	(n=204 ^b)	(n=203)	(n=197)	(n=202)	(n=198)
Total Completed	91 (45%)	118 (58%)	116 (59%)	129 (64%)	116 (59%)
Total Withdrawn	113^b (55%)	85 (42%)	81 (41%)	73 (36%)	82 (41%)
Lost to Follow-up	3 (1%)	1 (<1%)	3 (2%)	1 (<1%)	3 (2%)
Pre-Existing Violation	3 (1%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Protocol Non-Compliance	12 (6%)	4 (2%)	7 (4%)	2 (<1%)	8 (4%)
Treatment Failure	79 (39%)	61 (30%)	40 (20%)	49 (24%)	52 (26%)
Adverse Event	16 (8%)	18 (9%)	31 (16%)	21 (10%)	18 (9%)
Study 021^a	(n=242)	(n=252)	(n=240 ^b)	(n=233)	(n=226)
Total Completed	119 (49%)	168 (67%)	165 (69%)	154 (66%)	147 (65%)
Total Withdrawn	123 (51%)	84 (33%)	75^b (31%)	79 (34%)	79 (35%)
Lost to Follow-up	5 (2%)	1 (<1%)	0 (0%)	2 (<1%)	1 (<1%)
Pre-Existing Violation	2 (<1%)	3 (1%)	1 (<1%)	1 (<1%)	0 (0%)
Protocol Non-Compliance	13 (5%)	8 (3%)	7 (3%)	4 (2%)	8 (4%)
Treatment Failure	89 (37%)	56 (22%)	51 (21%)	49 (21%)	40 (18%)
Adverse Event	14 (6%)	16 (6%)	16 (7%)	23 (10%)	30 (13%)
Study 054	(n=218 ^b)	(n=216)	(n=207)	(n=213)	(n=207)
Total Completed	79 (36%)	111 (51%)	111 (54%)	119 (56%)	118 (57%)
Total Withdrawn	139^b (64%)	105 (49%)	96 (46%)	94 (44%)	89 (43%)
Lost to Follow-up	2 (<1%)	4 (2%)	0 (0%)	2 (<1%)	1 (<1%)
Pre-Existing Violation	3 (1%)	2 (<1%)	0 (0%)	3 (1%)	1 (<1%)
Protocol Non-Compliance	5 (2%)	6 (3%)	8 (4%)	9 (4%)	7 (3%)
Treatment Failure	112 (52%)	76 (35%)	61 (29%)	55 (26%)	51 (25%)
Adverse Event	16 (7%)	17 (8%)	27 (13%)	25 (12%)	29 (14%)
Pooled 12-Week Pivotal Studies	(n=664 ^b)	(n=671)	(n=644 ^b)	(n=648)	(n=631)
Total Completed	289 (44%)	397 (59%)	392 (61%)	402 (62%)	381 (60%)
Total Withdrawn	375^b (56%)	274 (41%)	252^b (39%)	246 (38%)	250 (40%)
Lost to Follow-up	10 (2%)	6 (2%)	3 (<1%)	5 (<1%)	5 (<1%)
Pre-Existing Violation	8 (1%)	6 (2%)	1 (<1%)	4 (<1%)	2 (<1%)
Protocol Non-Compliance	30 (4%)	18 (6%)	22 (3%)	15 (2%)	23 (4%)
Treatment Failure	284 (42%)	193 (29%)	152 (24%)	153 (24%)	143 (23%)
Adverse Event	46 (7%)	51 (8%)	74 (11%)	69 (11%)	77 (12%)

Derived from Individual Study Reports

a) Includes only patients with OA of the knee.

b) Total number of patients includes three patients (one in the placebo group [Study 020], one in the placebo group [Study 054], and one in the celecoxib 100 mg BID group [Study 021]), who were randomized into a study but did not receive study medication and are not included in the ITT Cohort.

Table A.22.2 Reasons for Study Termination (060, 087)

Study	Number of Osteoarthritis Patients by Treatment Group		
	Placebo	Celecoxib	
		100 mg BID	200 mg QD
Study 060	(n=232)	(n=231)	(n=223)
Total Completed	146 (63%)	194 (84%)	182 (82%)
Total Withdrawn	86 (37%)	37 (16%)	41 (18%)
Lost to Follow-up	2 (<1%)	4 (2%)	2 (<1%)
Pre-Existing Violation	2 (<1%)	2 (<1%)	2 (<1%)
Protocol Non-Compliance	6 (3%)	2 (<1%)	7 (3%)
Treatment Failure	56 (24%)	18 (8%)	21 (9%)
Adverse Event	20 (9%)	11 (5%)	9 (4%)
Study 087	(n=244)	(n=243)	(n=231)
Total Completed	164 (67%)	194 (80%)	191 (83%)
Total Withdrawn	80 (33%)	49 (20%)	40 (17%)
Lost to Follow-up	1 (<1%)	0 (0%)	1 (<1%)
Pre-Existing Violation	4 (2%)	6 (2%)	4 (2%)
Protocol Non-Compliance	8 (3%)	7 (3%)	5 (2%)
Treatment Failure	55 (23%)	27 (11%)	24 (10%)
Adverse Event	12 (5%)	9 (4%)	6 (3%)
Pooled 6-Week Pivotal Studies	(n=476)	(n=474)	(n=454)
Total Completed	310 (65%)	388 (82%)	373 (82%)
Total Withdrawn	166 (35%)	86 (18%)	81 (18%)
Lost to Follow-up	3 (1%)	4 (1%)	3 (1%)
Pre-Existing Violation	6 (1%)	8 (2%)	6 (1%)
Protocol Non-Compliance	14 (3%)	9 (2%)	12 (3%)
Treatment Failure	111 (23%)	45 (9%)	45 (10%)
Adverse Event	32 (7%)	20 (4%)	15 (3%)

Derived from Individual Study Reports

Table A.23 Schedule of Observations and Procedures (Protocol 060)

	Pretreatment Period		Treatment Period		
	Screening Visit (-14 to -2 days)	Baseline Visit (Day 0)	Week 2 (Day 14) (±2 days)	Week 6 (Day 42) (±4 days)	Early Termination
Informed Consent	x				
Medical History	x				
Physical Exam	x			x	x
Clinical Lab Tests ^a	x		x	x	x
SF-36 Health Survey		x		x	x
OA Assessments ^b	x ^c	x	x	x	x
Discontinued NSAID or Analgesic ^d	x				
Meet Flare Criteria		x			
Signs & Symptoms		x	x	x	x
Dispense Study Med		x	x		
Return & Count Study Med			x	x	x
Dispense Con Med Diary Card		x	x		
Retrieve Con Med Diary Card			x	x	x
Blood Sample For PK ^e			x	x	

(a) Clinical laboratory tests included: **Hematology** (white blood cell [WBC] count, hemoglobin, hematocrit, platelet count [estimate not acceptable]) and **Biochemistry** (BUN, creatinine, total bilirubin, alkaline phosphatase, AST [SGOT], ALT [SGPT], creatine kinase [CK]). **Urinalysis** (pH, specific gravity, WBC, red blood cell [RBC], protein, glucose, ketones, bilirubin) at Screening Visit only. Serum pregnancy test for women of childbearing potential at Screening Visit only.

(b) Patient's Global Assessment of Arthritic Condition, Patient's Assessment of Pain - Visual Analog Scale (VAS), Physician's Global Assessment of Arthritic Condition, Functional Capacity Classification, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Osteoarthritis Severity Index.

(c) Screening arthritis assessment data was not collected by Searte. Patient's Assessment of Pain (VAS) and WOMAC were not performed at the Screening Visit.

(d) Patient discontinued NSAID or analgesic use within 48 hours or at least five half-lives before the Baseline Arthritis Assessments, whichever was greater.

(e) Blood samples were collected at selected investigational sites only.

Table A.24.1 Patient's global assessment (protocol 087)

SC-58635 QD VS BID EFFICACY IN KNEE OA
N49 98 02 087

TABLE 11
PATIENT'S GLOBAL ASSESSMENT OF OSTEOARTHRITIS
PART 1 OF 4: OBSERVED MEANS (a) (b)

	INTENT TO TREAT SUBSET (ITT) *		
	PLACEBO (N 243)	SC-58635 100MG BID (N 241)	SC-58635 200MG QD (N 231)
BASELINE			
N	243	241	231
MEAN	3.9	3.9	3.8
STD DEV	0.60	0.58	0.60
WEEK 2			
N	243	241	231
MEAN	3.0	2.7	2.7
STD DEV	0.90	0.91	0.85
WEEK 4			
N	243	241	231
MEAN	3.0	2.8	2.6
STD DEV	1.02	0.99	0.95

(a) This table is based on the last observation carried forward approach.

(b) Scale ranged from 1 (very good) to 5 (very poor).

* By definition, in this and subsequent efficacy tables, the ITT subset includes only patients who had at least one dose of study medication.

	PLACEBO	SC-58635 100MG BID	SC-58635 200MG QD	P VALUE (c)
	(N 243)	(N 241)	(N 231)	
WEEK 2				0.001
IMPROVED (d)	56 (23%)	90 (37%)	71 (31%)	
NO CHANGE	176 (73%)	157 (65%)	160 (69%)	
WORSENEDE (e)	11 (5%)	5 (2%)	0 (0%)	
TOTAL	243 (100%)	241 (100%)	231 (100%)	
WEEK 4				0.004
IMPROVED (d)	60 (25%)	90 (37%)	67 (29%)	
NO CHANGE	163 (67%)	143 (59%)	143 (62%)	
WORSENEDE (e)	19 (8%)	6 (2%)	1 (0.4%)	
TOTAL	243 (100%)	241 (100%)	231 (100%)	
P VALUES FOR TREATMENT COMPARISONS (d) :				
	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID	
WEEK 2:	<0.001	0.009	0.107	
WEEK 4:	0.020	0.001	0.478	

(a) This table is based on the last observation carried forward approach.

(b) Improved is defined as reduction of at least two grades from Baseline for grades 3-5 or a change in grade from 2 to 1.

(c) Worstened is defined as an increase of at least two grades from Baseline for grades 1-2 or a change in grade from 4 to 5.

(d) Cochran-Mantel-Haenszel test stratified by Center (Row Mean Scores Differ).

Table A.24.2 Patient's Global Assessment (Protocol 087)

SC-58635 QD VS BID EFFICACY IN KNEE OA
N49 98-02 087

TABLE 15
PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 3 OF 4: MEAN CHANGE ANALYSIS (A) (B)

INTENT TO TREAT CONCEPT (ITT)				
	PLACERO (N 243)	SC-58635 100MG BID (N-241)	SC-58635 200MG QD (N 241)	P-VALUE (A)
WEEK 2				
ADJUSTED MEAN CHANGE	0.6	-1.2	1.1	<0.001
STD DEV	0.99	0.99	0.94	
LC MEAN CHANGE (C)	-0.8	-1.1	-1.1	
WEEK 6				
ADJUSTED MEAN CHANGE	-0.8	-1.1	-1.3	<0.001
STD DEV	1.10	1.06	1.05	
LC MEAN CHANGE (C)	0.8	-1.1	1.2	
C RATIO WITH 95% CONFIDENCE INTERVALS (D): 200MG QD VS. 100MG BID				
WEEK 2:		1.00 (0.95 to 1.05)		
WEEK 6:		1.13 (0.96 to 1.33)		
P-VALUES FOR TREATMENT COMPARISONS (A):				
	100MG BID VS. PLACERO	200MG QD VS. PLACERO	200MG QD VS. 100MG BID	
WEEK 2:	<0.001	<0.001	0.963	
WEEK 6:	0.008	<0.001	0.176	

(A) This table is based on the last observation carried forward approach.
 (B) The 5 anchors from 1 (very good) to 5 (very poor) with negative change indicating improvement
 are fit in Analysis of Covariance model with treatment and center as factors and baseline value as covariate.
 (C) The corresponding LC95% CIs are 0.847 for week 2, and 0.971 for week 6
 (D) (C) RATIO is defined as the ratio of least square mean changes from (C), of SC-58635 200MG QD versus SC-58635 100MG BID
 (E) From a contrast statement from Analysis of Covariance model in (B)

Table A.25.1 Physician's Global Assessment (protocol 087)

SC-58635 QD VS BID EFFICACY IN KNEE OA
N09 99 02 087

TABLE 17
PHYSICIAN'S GLOBAL ASSESSMENT OF ANTHROPIC
PART 1 OF 4: OBSERVED MEANS (a) (b)

INTENT TO TREAT COHORT (1177)

	PLACEBO (N 243)	SC-58635 100MG BID (N 241)	SC-58635 200MG QD (N 231)
BASELINE			
N	243	240	231
MEAN	3.8	3.8	3.7
STD DEV	0.57	0.51	0.56
WEEK 2			
N	241	241	231
MEAN	3.0	2.6	2.7
STD DEV	0.63	0.84	0.72
WEEK 6			
N	243	241	231
MEAN	3.0	2.7	2.6
STD DEV	0.94	0.91	0.89

(a) This table is based on the last observation carried forward approach.
 (b) Scale ranged from 1 (very good) to 5 (very poor)

	PLACEBO (N 243)	SC-58635 100MG BID (N 241)	SC-58635 200MG QD (N 231)	P VALUE (a)
WEEK 2				
IMPROVED (b)	47 (19%)	93 (39%)	48 (21%)	0.004
NO CHANGE	166 (77%)	144 (60%)	164 (71%)	
WORSENE (c)	5 (2%)	3 (1%)	11 (5%)	
TOTAL	243 (100%)	240 (100%)	231 (100%)	
WEEK 6				
IMPROVED (b)	59 (24%)	64 (27%)	80 (35%)	0.012
NO CHANGE	172 (71%)	151 (63%)	151 (65%)	
WORSENE (c)	12 (5%)	5 (2%)	0 (0%)	
TOTAL	243 (100%)	240 (100%)	231 (100%)	
P VALUES FOR TREATMENT COMPARISONS (d) :				
	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID	
WEEK 2:	<0.001	0.008	0.032	
WEEK 6:	0.022	0.004	0.813	

(a) This table is based on the last observation carried forward approach.
 (b) Improved is defined as reduction of at least two grades from Baseline for grades 3-5 or a change in grade from 2 to 1.
 (c) Worsened is defined as an increase of at least two grades from Baseline for grades 1-3 or a change in grade from 4 to 5.
 (d) Cochran-Mantel-Haenszel test stratified by center (ROW Mean Scores Differ)

Table A.25.2 Physician's Global Assessment (protocol 087)

SC-58645 QD VS BID EFFICACY IN ENDE SA
N99 98 02 181

TABLE 17
PHYSICIAN'S GLOBAL ASSESSMENT OF ENTKRITIL
(PART 3 OF 4: MEAN CHANGE ANALYSIS (a) (b))

INTENT TO TREAT COMBET (c)(1)

	PLACEBO (N 243)	SC-58645 100MG BID (N 211)	SC-58645 200MG QD (N 231)	P-VALUE (d)
WEEK 2				
OBSERVED MEAN CHANGE	0.8	1.0	1.1	<0.001
STD DEV	0.97	0.87	0.84	
95% MEAN CHANGE (e)	-0.7	1.1	1.1	
WEEK 6				
OBSERVED MEAN CHANGE	-1.8	-1.1	-1.2	<0.001
STD DEV	1.01	0.96	1.01	
95% MEAN CHANGE (e)	0.8	1.0	1.2	

D-RATIO WITH 95% CONFIDENCE INTERVALS (d): 200MG QD VS. 100MG BID

WEEK 2:	0.96 ± 0.84 to 1.10
WEEK 6:	1.03 ± 0.97 to 1.32

P-VALUES FOR TREATMENT COMPARISONS (e):

	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID
WEEK 2:	<0.001	<0.001	0.557
WEEK 6:	0.001	<0.001	0.105

(a) This table is based on the last observation carried forward approach.
 (b) Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement.
 (c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate.
 The corresponding ROOT MSE are: 0.786 for week 2, and 0.890 for week 6.
 (d) D-RATIO is defined as the ratio of least square mean changes from (a), of SC-58645 200MG QD versus SC-58645 100MG BID.
 (e) From a contrast statement from Analysis of Covariance model in (c).

Table A.26 Patient's Assessment of Arthritis Pain (protocol 060)

INTENT-TO-TREAT COHORT (ITT)			
	PLACEBO (N=231)	SC-58635 100MG BID (N=231)	SC-58635 200MG QD (N=222)
BASELINE			
N	231	231	222
MEAN	68.1	67.8	68.0
STD DEV	15.16	16.52	16.74
WEEK 2			
N	231	231	222
MEAN	55.5	42.7	42.0
STD DEV	24.65	24.59	23.75
WEEK 6			
N	231	231	222
MEAN	54.0	40.3	41.0
STD DEV	26.00	28.01	26.29

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 100 (mm) with lower score as better

SC-58635 QD VS BID EFFICACY IN KNEE OA
 M49-96-02-060

TABLE 17
 PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
 PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)

INTENT-TO-TREAT COHORT (ITT)				
	PLACEBO (N=231)	SC-58635 100MG BID (N=231)	SC-58635 200MG QD (N=222)	D-VALUE(c)
WEEK 2				
OBSERVED MEAN CHANGE	-12.6	-25.1	-25.9	<0.001
STD DEV	24.55	25.18	25.05	
LS MEAN CHANGE (c)	-12.9	-25.5	-26.1	
WEEK 6				
OBSERVED MEAN CHANGE	-14.1	-27.5	-26.9	<0.001
STD DEV	25.88	27.78	28.41	
LS MEAN CHANGE (c)	-14.8	-28.5	-27.7	
Q-RATIO WITH 95% CONFIDENCE INTERVALS (d): 200MG QD VS. 100MG BID				
WEEK 2:	1.02 (0.85 to 1.23)			
WEEK 6:	0.97 (0.81 to 1.17)			
D-VALUES FOR TREATMENT COMPARISONS (e):				
	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID	
WEEK 2:	<0.001	<0.001	0.780	
WEEK 6:	<0.001	<0.001	0.747	

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 100 (mm) with negative change indicating improvement
 (c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 23.37 for week 2, and 25.69 for week 6
 (d) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 200MG QD versus SC-58635 100MG BID
 (e) From a contrast statement from Analysis of Covariance model in (c)

Table A.27 Patient's Assessment of Arthritis Pain (protocol 087)

	INTENT TO TREAT COHORT (ITT)		
	PLACEBO (N 243)	SC-58835 100MG BID (N 241)	SC-58835 200MG QD (N 231)
BASELINE			
N	243	241	231
MEAN	66.2	67.6	65.2
STD DEV	16.81	16.47	16.48
WEEK 2			
N	243	241	231
MEAN	54.1	49.5	44.4
STD DEV	25.33	24.15	24.39
WEEK 6			
N	243	241	231
MEAN	42.3	45.6	42.8
STD DEV	22.89	22.61	24.39

(a) This table is based on the last observation carried forward approach.
 (b) Scale ranged from 0 to 100 (mm) with lower score as better.

**SC-58835 QD VS BID EFFICACY IN KNEE OA
 N40 98 02 067**

**TABLE 16
 PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
 PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)**

	INTENT TO TREAT COHORT (ITT)			P-VALUE (c)
	PLACEBO (N 243)	SC-58835 100MG BID (N 241)	SC-58835 200MG QD (N 231)	
WEEK 2				<0.001
OBSERVED MEAN CHANGE	14.1	24.1	29.8	
STD DEV	24.75	20.35	24.44	
LS MEAN CHANGE (d)	-12.4	-22.5	-21.1	
WEEK 6				0.002
OBSERVED MEAN CHANGE	-15.6	-22.0	-22.5	
STD DEV	27.37	28.92	28.74	
LS MEAN CHANGE (d)	15.0	-21.2	23.9	
D-RATIO WITH 95% CONFIDENCE INTERVALS (d): 200MG QD VS. 100MG BID				
WEEK 2:	0.94 (0.76 to 1.15)			
WEEK 6:	1.11 (0.88 to 1.40)			
P-VALUES FOR TREATMENT COMPARISONS (e):				
	100MG BID VS. PLACEBO	200MG QD VS. PLACEBO	200MG QD VS. 100MG BID	
WEEK 2:	<0.001	<0.001	0.520	
WEEK 6:	0.011	<0.001	0.344	

(a) This table is based on the last observation carried forward approach.
 (b) Scale ranged from 0 to 100 (mm) with negative change indicating improvement.
 (c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate.
 The corresponding FOST HST area is 23.42 for week 2, and 16.46 for week 6.
 (d) D-RATIO is defined as the ratio of least square mean changes from (d), of SC-58835 200MG QD versus SC-58835 100MG BID.
 (e) From a contrast statement from Analysis of Covariance model in (c).

Table A.28 WOMAC pain (protocol 060)

SC 58615 QIP 15 BID EFFICACY IN KNEE OA
N24-9c-02-040

TABLE 10.1
WOMAC PAIN
PART 1 OF 2: OBSERVED MEANS (a) (1)

	INTEND-TO-TREAT GROUPS (ITT)		
	PLACEBO (N=731)	SC-58615 100MG BID (N=731)	SC-58615 200MG QD (N=722)
BASELINE			
N	231	230	220
MEAN	10.3	10.3	10.2
STD DEV	3.45	3.49	3.62
WEEK 6			
N	231	230	220
MEAN	8.9	7.3	7.5
STD DEV	4.00	3.99	4.19

(a) This table is based on the last observation carried forward approach.
(b) Scale ranged from 0 to 30 with lower score as better.

	DIFFERENTIAL TREAT COMPARISONS (ITT)			P-VALUE (b)
	PLACEBO (N=731)	SC-58615 100MG BID (N=731)	SC-58615 200MG QD (N=722)	
WEEK 6				<0.001
OBSERVED MEAN CHANGE	-1.4	-3.0	-2.7	
STD DEV	3.52	3.52	3.94	
95% MEAN CHANGE (c)	1.5	3.1	2.9	
P-VALUE FOR TREATMENT COMPARISONS (d)				
WEEK 6:				
100MG BID VS. PLACEBO		<0.001		
200MG QD VS. PLACEBO		<0.001		
200MG QD VS. 100MG BID			0.473	

(a) This table is based on the last observation carried forward approach.
(b) Scale ranged from 0 to 30 with negative change indicating improvement.
(c) 95% Confidence Interval for Mean Change with treatment and center as factors and Baseline Value as covariate.
(d) From a contrast statement from Analysis of Covariance model in (c).

Table A.29 WOMAC pain (protocol 087)

SC-58635 QD VS BID EFFICACY IN KNEE OA
N49 98 02 087

TABLE 19.1
WOMAC PAIN
PART 1 OF 2: OBSERVED MEANS (a) (b)

	INTENT TO TREAT COHORT (ITT)		
	PLACEBO (N 243)	SC-58635 100MG BID (N 241)	SC-58635 200MG QD (N 251)
BASELINE			
N	239	239	226
MEAN	10.5	10.1	10.1
STD DEV	3.33	3.43	3.52
WEEK 6			
N	243	243	231
MEAN	8.7	7.4	7.1
STD DEV	4.11	4.47	4.08

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with lower score as better

	INTENT TO TREAT COHORT (ITT)			P VALUE (c)
	PLACEBO (N 243)	SC-58635 100MG BID (N 241)	SC-58635 200MG QD (N 251)	
WEEK 6				
Observed Mean Change	1.8	2.6	3.0	<0.001
STD DEV	4.07	4.32	4.57	
LS MEAN CHANGE (d)	-1.6	-2.6	-3.0	
P-VALUES FOR TREATMENT COMPARISONS (d):				
	100MG BID VS PLACEBO	200MG QD VS PLACEBO	200MG QD VS 100MG BID	
WEEK 6:	0.009	<0.001	0.276	

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 0 to 20 with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate
(d) From a contrast statement from Analysis of Covariance model in (c)

Table A.30 Withdrawal due to lack of Arthritis Efficacy (060, 087)

SC-58635 QD VS BID EFFICACY IN KNEE OA
N49-96-02-060

TABLE 21
INCIDENCE OF WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)			
	PLACEBO (N=231)	SC-58635 100MG BID (N=231)	SC-58635 200MG QD (N=222)
NUMBER WITHDRAWN DUE TO LACK OF ARTHRITIS EFFICACY	56 (24%)	18 (8%)	21 (9%)
p-VALUES FOR OVERALL COMPARISONS (a): <0.001			
p-VALUES FOR TREATMENT COMPARISONS (b):			
	100MG BID VS. PLACEBO ----- <0.001	200MG QD VS. PLACEBO ----- <0.001	200MG QD VS. 100MG BID ----- 0.616

(a) Fisher's Exact test
(b) Pairwise Fisher's Exact test

SC-58635 QD VS BID EFFICACY IN KNEE OA
N49-98-02-087

TABLE 20
INCIDENCE OF WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)			
	PLACEBO (N=243)	SC-58635 100MG BID (N=241)	SC-58635 200MG QD (N=231)
NUMBER WITHDRAWN DUE TO LACK OF ARTHRITIS EFFICACY	55 (23%)	27 (11%)	24 (10%)
p-VALUES FOR OVERALL COMPARISONS (a): <0.001			
p-VALUES FOR TREATMENT COMPARISONS (b):			
	100MG BID VS. PLACEBO ----- <0.001	200MG QD VS. PLACEBO ----- <0.001	200MG QD VS. 100MG BID ----- 0.282

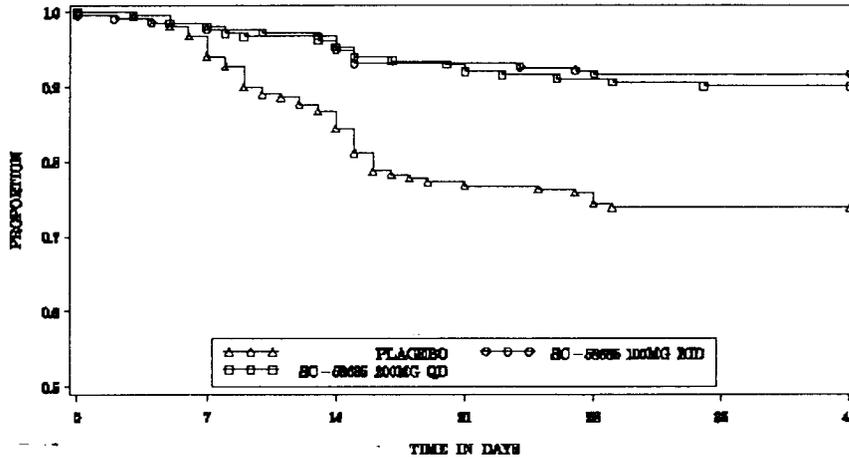
(a) Fisher's Exact test
(b) Pairwise Fisher's Exact test

Table A.31 Time to Withdrawal-Lack of Arthritis Efficacy (060, 087)

SC-58635 QD VS BID EFFICACY IN KNEE OA
N49-98-02-086

TABLE 22
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 1 OF 2: KAPLAN-MEIER ESTIMATES OF PROPORTION OF PATIENTS
WHO DID NOT WITHDRAW DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)



SC-58635 QD VS BID EFFICACY IN KNEE OA
N49-98-02-087

TABLE 21
TIME TO WITHDRAWAL DUE TO LACK OF ARTHRITIS EFFICACY
PART 1 OF 2: KAPLAN-MEIER ESTIMATES OF PROPORTION OF PATIENTS
WHO DID NOT WITHDRAW DUE TO LACK OF ARTHRITIS EFFICACY

INTENT-TO-TREAT COHORT (ITT)

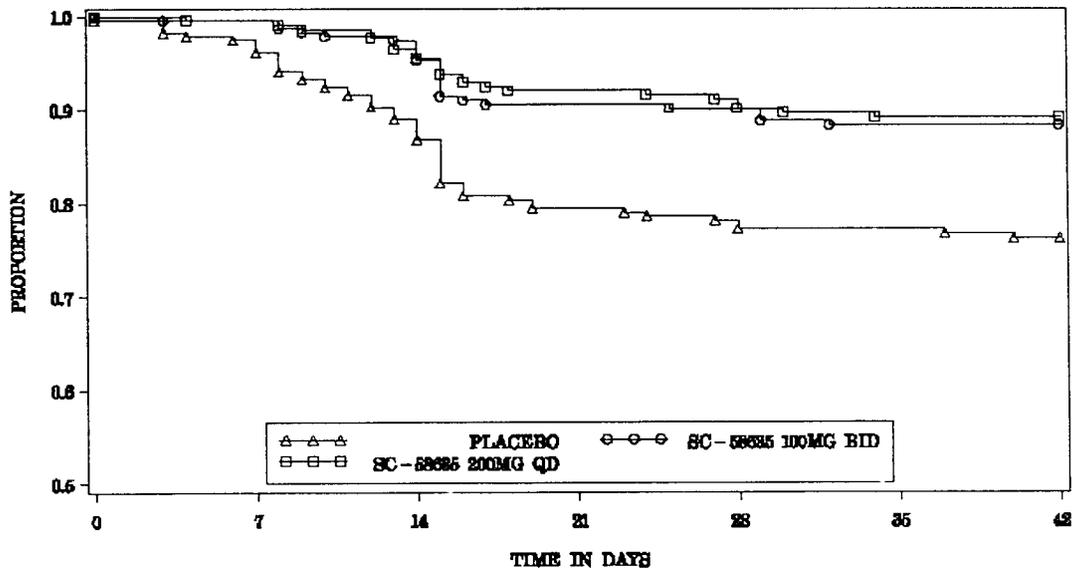


Table A.32 Schedule of Observations and Procedures (protocol 022)

	Screening Visit -7 to -2 day	Baseline Visit (Day 0)	Week 2 (Day 14) (-1 day)	Week 6 (Day 42) (-3 days)	Week 12 (Day 84) (-5 days)	Early Termination
Informed Consent	X					
Medical History	X					
Physical Examination	X				X	X
Clinical laboratory tests (a)	X		X	X (b)	X	X
Discontinue NSAID (c)	X					
Meet Flare Criteria		X				
C-Reactive Protein		X	X	X	X	X
Rheumatoid Factor	X					
SF-36 Health Survey		X			X	X
Health Assessment Questionnaire (HAQ)		X	X	X	X	X
RA Assessments	X (d)	X	X	X	X	X
UGI Endoscopy	X (e)				X	X
Signs and Symptoms		X	X	X	X	X
Dispense Study Medication		X	X	X		
Return and Count Study Medication			X	X	X	X
Dispense Concurrent Meds Diary Card		X	X	X		
Collect Concurrent Meds Diary Card			X	X	X	X
<p>(a) Clinical laboratory tests included Hematology (white blood cell [WBC] count with differential, red blood cell [RBC] count, hemoglobin, hematocrit, platelet count [estimate not acceptable], prothrombin time [PT], and partial thromboplastin time [PTT]); Biochemistry (sodium, potassium, chloride, calcium, inorganic phosphorus, blood urea nitrogen [BUN], creatinine, total protein, albumin, total bilirubin, uric acid, glucose, alkaline phosphatase, AST [SGOT], ALT [SGPT], creatine kinase [CK]); and Urinalysis (pH, specific gravity, WBC, RBC, protein, glucose, ketones, bilirubin). FlexSure® (Baseline) and CLOtest at Final Visit for <i>H. pylori</i>. Serum pregnancy test was performed within seven days before Baseline Arthritis Assessments for women of childbearing potential.</p> <p>(b) PT and PTT were not performed at the Week 6 Visit.</p> <p>(c) Patients discontinued oxaprozin and/or piroxicam at least four days before the Baseline Arthritic Assessments.</p> <p>(d) Screening arthritis assessment data were collected by Searle but not entered into the database.</p> <p>(e) Pretreatment (Baseline) endoscopy must have been performed within seven days before the first dose of study medication.</p>						

Table A.33 Baseline demographics (study 022, 023-pooled)

Text Table 44. Pooled Baseline Demographic Characteristics and Disease Status for RA Patients By Treatment Group (All Randomized Patients: Pooled Pivotal Studies 022 and 023)

Baseline Characteristic	Number of Patients by Treatment Group				
	Placebo (n=452)	Celecoxib			Naproxen 500 mg BID (n=443)
		100 mg BID (n=468)	200 mg BID (n=454 ^a)	400 mg BID (n=435 ^a)	
Age (years)					
Mean (Std. Dev.)	54.2 (12.42)	55.1 (11.99)	54.0 (12.09)	54.0 (12.10)	55.9 (12.09)
Range	23-84	22-85	20-90	21-85	21-82
<65 years - N (%)	350 (77%)	364 (78%)	351 (77%)	344 (79%)	321 (72%)
≥65 years - N (%)	102 (23%)	104 (22%)	103 (23%)	91 (21%)	122 (28%)
Race/Ethnic Origin					
Asian - N (%)	1 (<1%)	4 (<1%)	6 (1%)	4 (<1%)	1 (<1%)
Black - N (%)	36 (8%)	42 (9%)	35 (8%)	35 (8%)	34 (8%)
Caucasian - N (%)	391 (87%)	394 (84%)	380 (84%)	364 (84%)	377 (85%)
Hispanic - N (%)	23 (5%)	25 (5%)	32 (7%)	28 (6%)	28 (6%)
Other - N (%)	1 (<1%)	3 (<1%)	1 (<1%)	4 (<1%)	3 (<1%)
Gender					
Female - N (%)	336 (74%)	346 (74%)	328 (72%)	314 (72%)	313 (71%)
Male - N (%)	116 (26%)	122 (26%)	126 (28%)	121 (28%)	130 (29%)
Disease Duration - Years					
Mean (Std. Dev.)	10.3 (±9.91)	10.7 (±9.01)	10.4 (±9.32)	10.3 (±8.77)	11.0 (±9.80)
Range	0.3-60.0	0.3-53.0	0.3-53.0	0.3-58.0	0.3-55.0
<5 years - N (%)	159 (35%)	135 (29%)	166 (37%)	150 (34%)	143 (32%)
≥5 years - N (%)	293 (65%)	333 (71%)	288 (63%)	285 (66%)	300 (68%)
Corticosteroid Use					
Yes - N (%)	175 (39%)	209 (45%)	172 (38%)	154 (35%)	167 (38%)
No - N (%)	277 (61%)	259 (55%)	282 (62%)	281 (65%)	276 (62%)
Methotrexate Use					
Yes - N (%)	192 (42%)	221 (47%)	205 (45%)	202 (46%)	200 (45%)
No - N (%)	260 (58%)	247 (53%)	249 (55%)	233 (54%)	243 (55%)
Other DMARD Use					
Yes - N (%)	148 (33%)	153 (33%)	139 (31%)	132 (30%)	149 (34%)
No - N (%)	304 (67%)	315 (67%)	315 (69%)	303 (70%)	294 (66%)

Pooled Pivotal Studies 022 and 023)

Baseline Measure	Number of Patients by Treatment Group				
	Placebo (n=452)	Celecoxib			Naproxen 500 mg BID (n=443)
		100 mg BID (n=468)	200 mg BID (n=454 ^a)	400 mg BID (n=435 ^a)	
Patient's Global Assessment of Arthritic Condition - N (%)					
Very Good	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Good	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fair	169 (37%)	181 (39%)	184 (41%)	175 (40%)	189 (43%)
Poor	227 (50%)	230 (49%)	212 (47%)	204 (47%)	209 (47%)
Very Poor	56 (12%)	57 (12%)	58 (13%)	56 (13%)	45 (10%)
Number of Tender/Painful Joints					
Mean (Std. Dev.)	28.7 (14.55)	28.2 (14.40)	29.6 (14.99)	28.8 (14.36)	28.2 (14.01)
Range	5-66	6-68	3-68	6-68	6-67
Number of Swollen Joints					
Mean (Std. Dev.)	20.9 (11.83)	20.5 (11.68)	21.7 (12.29)	20.7 (11.80)	20.6 (12.11)
Range	3-61	3-62	2-64	0-62	3-62
Physician's Global Assessment of Arthritic Condition - N (%)					
Very Good	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Good	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Fair	199 (44%)	207 (44%)	183 (40%)	182 (42%)	191 (43%)
Poor	220 (49%)	218 (47%)	227 (50%)	216 (50%)	219 (50%)
Very Poor	33 (7%)	42 (9%)	44 (10%)	37 (9%)	32 (7%)

Table A.34.1 Physician's Global Assessment (Protocol 023)

TABLE 20
PHYSICIAN'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 1 OF 4: OBSERVED MEANS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)				
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)
BASELINE					
N	221	228	218	217	218
MEAN	3.6	3.7	3.7	3.7	3.7
STD DEV	0.61	0.65	0.64	0.62	0.63
WEEK 2					
N	221	228	218	217	218
MEAN	3.3	2.9	2.7	2.8	2.7
STD DEV	0.90	0.86	0.84	0.80	0.82
WEEK 6					
N	221	228	218	217	218
MEAN	3.2	2.9	2.8	2.8	2.7
STD DEV	1.01	0.93	0.95	0.91	0.87
WEEK 12					
N	221	228	218	217	218
MEAN	3.3	3.0	2.9	2.8	2.8
STD DEV	1.00	0.95	0.93	0.92	0.92

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 1 (very good) to 5 (very poor)

* By definition, in this and subsequent efficacy tables, the ITT cohort includes only patients who had at least one dose of study medication

PHYSICIAN'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 2 OF 4: CATEGORICAL CHANGE ANALYSIS, NUMBER OF PATIENTS (%) (a)

	INTENT-TO-TREAT COHORT (ITT)					LINEAR TREND D-VALUE (d)
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)	
WEEK 2						
IMPROVED (b)	22 (10%)	44 (19%)	60 (28%)	46 (21%)	55 (25%)	<0.001
NO CHANGE	187 (85%)	179 (79%)	151 (69%)	171 (79%)	161 (74%)	
WORSENER (c)	12 (5%)	5 (2%)	7 (3%)	0 (0%)	2 (<1%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	
WEEK 6						
IMPROVED (b)	30 (14%)	42 (18%)	54 (25%)	39 (18%)	52 (24%)	0.009
NO CHANGE	177 (80%)	178 (78%)	158 (72%)	177 (82%)	164 (75%)	
WORSENER (c)	14 (6%)	8 (4%)	6 (3%)	1 (<1%)	2 (<1%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	
WEEK 12						
IMPROVED (b)	27 (12%)	42 (18%)	48 (22%)	44 (20%)	55 (25%)	0.001
NO CHANGE	178 (81%)	179 (79%)	164 (75%)	171 (79%)	160 (73%)	
WORSENER (c)	16 (7%)	7 (3%)	6 (3%)	2 (<1%)	3 (1%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	

D-VALUES FOR TREATMENT COMPARISONS (e) :

	PRIMARY		SECONDARY							
	200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
WEEK 2:	<0.001*	<0.001*	<0.001	0.120	0.423	0.204	<0.001	0.097	0.931	0.273
WEEK 6:	0.001*	0.016*	0.035	0.115	0.753	0.181	<0.001	0.109	0.885	0.156
WEEK 12:	0.003*	0.001*	0.004	0.410	0.681	0.820	<0.001	0.096	0.285	0.229

(a) This table is based on the last observation carried forward approach

(b) Improved is defined as reduction of at least two grades from baseline for grades 3-5 or a change in grade from 2 to 1

(c) Worsened is defined as an increase of at least two grades from baseline for grades 1-3 or a change in grade from 4 to 5

(d) Cochran-Mantel-Haenszel test of linear dose trend stratified by center (Nonzero Correlation), Naproxen group was excluded

(e) Cochran-Mantel-Haenszel test of treatment comparison stratified by center (Row Mean Scores Differ)

* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.34.2 Physician's Global Assessment-continued (Protocol 023)

PHYSICIAN'S GLOBAL ASSESSMENT OF ARTERITIS PART 3 OF 4: MEAN CHANGE ANALYSIS (a) (b) INTENT-TO-TREAT COHORT (ITT)										
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)	OVERALL p-VALUE (c)	LINEAR TREND p-VALUE (d)			
WEEK 2										
OBSERVED MEAN CHANGE	-0.4	-0.8	-1.0	-0.9	-1.0	<0.001	<0.001			
STD DEV	0.88	0.92	0.93	0.87	0.90					
LS MEAN CHANGE (c)	-0.3	-0.8	-1.0	-0.9	-1.0					
WEEK 6										
OBSERVED MEAN CHANGE	-0.4	-0.7	-0.9	-0.9	-1.0	<0.001	<0.001			
STD DEV	0.96	0.96	1.03	0.89	0.95					
LS MEAN CHANGE (c)	-0.4	-0.7	-0.8	-0.8	-0.9					
WEEK 12										
OBSERVED MEAN CHANGE	-0.3	-0.7	-0.8	-0.8	-0.9	<0.001	<0.001			
STD DEV	0.94	0.97	1.02	0.92	0.98					
LS MEAN CHANGE (c)	-0.3	-0.6	-0.8	-0.8	-0.9					
Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):										
	100MG BID VS. NAPROXEN			200MG BID VS. NAPROXEN		400MG BID VS. NAPROXEN				
WEEK 2:	0.78 (0.65 to 0.93)			0.98 (0.83 to 1.15)		0.89 (0.75 to 1.05)				
WEEK 6:	0.75 (0.60 to 0.92)			0.89 (0.73 to 1.08)		0.88 (0.73 to 1.07)				
WEEK 12:	0.73 (0.58 to 0.92)			0.88 (0.71 to 1.08)		0.91 (0.73 to 1.12)				
p-VALUES FOR TREATMENT COMPARISONS (f):										
	-----PRIMARY-----			-----SECONDARY-----						
	200MG BID VS.	400MG BID VS.	100MG BID VS.	200MG BID VS.	400MG BID VS.	400MG BID VS.	NAPROXEN VS.	NAPROXEN VS.	NAPROXEN VS.	NAPROXEN VS.
	PLACEBO	PLACEBO	PLACEBO	100MG BID	100MG BID	200MG BID	PLACEBO	100MG BID	200MG BID	400MG BID
WEEK 2:	<0.001*	<0.001*	<0.001	0.009	0.154	0.244	<0.001	0.004	0.790	0.153
WEEK 6:	<0.001*	<0.001*	<0.001	0.113	0.121	0.972	<0.001	0.004	0.205	0.193
WEEK 12:	<0.001*	<0.001*	<0.001	0.135	0.070	0.750	<0.001	0.005	0.199	0.334

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 0.787 for week 2, 0.868 for week 6, 0.883 for week 12
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group
(f) From a contrast statement from Analysis of Covariance model in (c)
* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.35.1 Patient's Global Assessment (Protocol 023)

TABLE 17
PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 1 OF 4: OBSERVED MEANS (a) (b)

INTENT-TO-TREAT COHORT (ITT)					
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)
BASELINE					
N	221	228	218	217	218
MEAN	3.7	3.7	3.7	3.7	3.7
STD DEV	0.68	0.67	0.66	0.64	0.63
WEEK 2					
N	221	228	218	217	218
MEAN	3.4	2.9	2.7	2.7	2.7
STD DEV	0.96	0.90	0.88	0.82	0.83
WEEK 6					
N	221	228	218	217	218
MEAN	3.4	3.0	2.8	2.9	2.8
STD DEV	1.04	0.96	1.00	0.96	0.94
WEEK 12					
N	221	228	218	217	218
MEAN	3.4	3.1	2.9	3.0	2.8
STD DEV	1.05	0.98	0.98	0.92	0.94

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 1 (very good) to 5 (very poor)

* By definition, in this and subsequent efficacy tables, the ITT cohort includes only patients who had at least one dose of study medication

PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS
PART 2 OF 4: CATEGORICAL CHANGE ANALYSIS, NUMBER OF PATIENTS (%) (a)

INTENT-TO-TREAT COHORT (ITT)						
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)	LINEAR TREND p-VALUE (d)
WEEK 2						
IMPROVED (b)	24 (11%)	49 (21%)	54 (25%)	61 (28%)	61 (28%)	<0.001
NO CHANGE	183 (83%)	174 (76%)	158 (72%)	152 (70%)	154 (71%)	
WORSENEED (c)	14 (6%)	5 (2%)	6 (3%)	4 (2%)	3 (1%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	
WEEK 6						
IMPROVED (b)	27 (12%)	44 (19%)	54 (25%)	45 (21%)	53 (24%)	0.001
NO CHANGE	176 (80%)	177 (78%)	156 (72%)	168 (77%)	160 (73%)	
WORSENEED (c)	18 (8%)	7 (3%)	8 (4%)	4 (2%)	5 (2%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	
WEEK 12						
IMPROVED (b)	29 (13%)	40 (18%)	50 (23%)	41 (19%)	57 (26%)	0.007
NO CHANGE	171 (77%)	180 (79%)	160 (73%)	169 (78%)	157 (72%)	
WORSENEED (c)	21 (10%)	8 (4%)	8 (4%)	7 (3%)	4 (2%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	

p-VALUES FOR TREATMENT COMPARISONS (e) :

	PRIMARY				SECONDARY					
	200MG BID vs. PLACEBO	400MG BID vs. PLACEBO	100MG BID vs. PLACEBO	200MG BID vs. 100MG BID	400MG BID vs. 100MG BID	400MG BID vs. 200MG BID	NAPROXEN vs. PLACEBO	NAPROXEN vs. 100MG BID	NAPROXEN vs. 200MG BID	NAPROXEN vs. 400MG BID
WEEK 2:	<0.001*	<0.001*	<0.001	0.688	0.171	0.335	<0.001	0.099	0.352	0.959
WEEK 6:	0.001*	0.001*	0.004	0.374	0.742	0.618	<0.001	0.217	0.828	0.371
WEEK 12:	0.002*	0.007*	0.016	0.294	0.813	0.411	<0.001	0.026	0.302	0.083

(a) This table is based on the last observation carried forward approach

(b) Improved is defined as reduction of at least two grades from baseline for grades 3-5 or a change in grade from 2 to 1

(c) Worsened is defined as an increase of at least two grades from baseline for grades 1-3 or a change in grade from 4 to 5

(d) Cochran-Mantel-Haenszel test of linear dose trend stratified by center (Nonzero Correlation), Naproxen group was excluded

(e) Cochran-Mantel-Haenszel test of treatment comparison stratified by center (Row Mean Scores Differ)

* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.35.2 Patient's Global Assessment-continued (Protocol 023)

TABLE 17 PATIENT'S GLOBAL ASSESSMENT OF ARTHRITIS PART 3 OF 4: MEAN CHANGE ANALYSIS (a) (b) INTENT-TO-TREAT COHORT (ITT)										
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)	OVERALL p-VALUE (c)	LINEAR TREND p-VALUE (d)			
WEEK 2										
OBSERVED MEAN CHANGE	-0.4	-0.8	-1.0	-1.0	-1.0	<0.001	<0.001			
STD DEV	0.93	0.99	0.90	0.90	0.91					
LS MEAN CHANGE (c)	-0.3	-0.6	-1.0	-1.0	-1.0					
WEEK 6										
OBSERVED MEAN CHANGE	-0.4	-0.7	-0.8	-0.8	-0.9	<0.001	<0.001			
STD DEV	0.96	0.99	1.04	0.95	0.99					
LS MEAN CHANGE (c)	-0.3	-0.7	-0.8	-0.8	-0.9					
WEEK 12										
OBSERVED MEAN CHANGE	-0.3	-0.6	-0.8	-0.7	-0.9	<0.001	<0.001			
STD DEV	0.97	0.97	1.01	0.96	1.00					
LS MEAN CHANGE (c)	-0.3	-0.6	-0.8	-0.7	-0.9					
Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):										
	100MG BID VS. NAPROXEN			200MG BID VS. NAPROXEN		400MG BID VS. NAPROXEN				
WEEK 2:	0.78 (0.64 to 0.93)			0.95 (0.81 to 1.12)		0.94 (0.80 to 1.11)				
WEEK 6:	0.75 (0.59 to 0.94)			0.92 (0.74 to 1.13)		0.88 (0.70 to 1.08)				
WEEK 12:	0.66 (0.50 to 0.86)			0.89 (0.71 to 1.12)		0.82 (0.65 to 1.04)				
p-VALUES FOR TREATMENT COMPARISONS (f):										
	-----PRIMARY-----				-----SECONDARY-----					
	200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
WEEK 2:	<0.001*	<0.001*	<0.001	0.024	0.032	0.913	<0.001	0.004	0.548	0.478
WEEK 6:	<0.001*	<0.001*	<0.001	0.081	0.197	0.656	<0.001	0.010	0.405	0.201
WEEK 12:	<0.001*	<0.001*	0.001	0.024	0.122	0.479	<0.001	<0.001	0.304	0.083

(a) This table is based on the last observation carried forward approach
(b) Scale ranged from 1 (very good) to 5 (very poor) with negative change indicating improvement
(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate.
the corresponding ROOT MSE are: 0.826 for week 2, 0.914 for week 6, 0.909 for week 12
(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group
(f) From a contrast statement from Analysis of Covariance model in (c)
* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.36.1 Number of Tender/Painful Joints (Protocol 022)

N43 96 02 (12)

**TABLE 20
NUMBER OF TENDER/PAINFUL JOINTS
PART 1 OF 5: OBSERVED MEANS (a) (b)**

	INTENT TO TREAT GROUP (ITT)				
	PLACEBO (N 231)	SC-58635 100MG BID (N 240)	SC-58635 100MG BID (N 235)	SC-58635 400MG BID (N 217)	NAPROXEN 500MG BID (N 225)
BASELINE					
N	231	240	235	217	225
MEAN	25.7	29.6	31.0	26.2	29.3
STD DEV	14.84	14.94	15.24	14.81	14.27
WEEK 2					
N	231	240	235	217	225
MEAN	21.8	18.5	18.8	16.9	18.0
STD DEV	15.43	15.19	15.77	14.38	15.20
WEEK 6					
N	231	240	235	217	225
MEAN	20.8	18.4	18.7	16.5	18.2
STD DEV	15.85	14.39	15.71	14.59	15.15
WEEK 12					
N	231	240	235	217	225
MEAN	21.1	17.9	18.4	16.5	18.8
STD DEV	15.27	14.24	16.24	14.96	16.06

(a) This table is based on the last observation carried forward approach
(b) Data ranged from 0 to 66 with lower score as better

**NUMBER OF TENDER/PAINFUL JOINTS
PART 2 OF 5: PATIENTS' OVERALL STATUS IN CHANGE FROM BASELINE, NUMBER OF PATIENTS (a) (b)**

	INTENT TO TREAT GROUP (ITT)					TRENDS p VALUE (a)
	PLACEBO (N 231)	SC-58635 100MG BID (N 240)	SC-58635 100MG BID (N 235)	SC-58635 400MG BID (N 217)	NAPROXEN 500MG BID (N 225)	
WEEK 2						0.001
IMPROVED (b)	72 (31%)	104 (43%)	112 (48%)	103 (47%)	105 (47%)	
NO CHANGE	148 (64%)	129 (54%)	116 (49%)	108 (49%)	112 (50%)	
WORSENE (c)	11 (5%)	9 (4%)	9 (4%)	6 (3%)	6 (3%)	
TOTAL	231 (100%)	240 (100%)	235 (100%)	217 (100%)	225 (100%)	
WEEK 6						0.004
IMPROVED (b)	89 (39%)	116 (49%)	108 (46%)	109 (50%)	108 (48%)	
NO CHANGE	126 (55%)	107 (45%)	122 (52%)	104 (48%)	105 (47%)	
WORSENE (c)	16 (7%)	15 (6%)	5 (2%)	4 (2%)	12 (5%)	
TOTAL	231 (100%)	240 (100%)	235 (100%)	217 (100%)	225 (100%)	
WEEK 12						0.014
IMPROVED (b)	88 (38%)	127 (53%)	115 (49%)	104 (48%)	98 (44%)	
NO CHANGE	126 (55%)	96 (40%)	112 (48%)	105 (48%)	112 (50%)	
WORSENE (c)	17 (7%)	17 (7%)	8 (3%)	8 (4%)	15 (7%)	
TOTAL	231 (100%)	240 (100%)	235 (100%)	217 (100%)	225 (100%)	

(a) p VALUE FOR TREATMENT COMPARISONS (a)

	PRIMARY				SECONDARY			
	210MG BID VS PLACEBO	400MG BID VS PLACEBO	100MG BID VS PLACEBO	100MG BID VS 100MG BID	400MG BID VS 500MG BID	NAPROXEN VS 500MG BID	NAPROXEN VS 500MG BID	NAPROXEN VS 500MG BID
WEEK 2	0.001*	0.001*	0.002	0.314	0.277	0.940	0.971	0.549
WEEK 6	0.001*	0.001*	0.007	0.854	0.439	0.416	0.831	0.788
WEEK 12	0.001*	0.001*	0.002	0.781	0.791	0.754	0.225	0.091

(a) This table is based on the last observation carried forward approach
(b) Improved is defined as number of improved joints minus number of worsened joints is larger than or equal to 50% of the number of joints with baseline score > 0
(c) Worsened is defined as number of worsened joints minus number of improved joints is larger than or equal to 50% of the number of joints with baseline score > 0
(d) Cochran-Mantel-Haenszel test of linear dose trend stratified by center (Nonsignificant Correlation). Naproxen group was excluded
(e) Cochran-Mantel-Haenszel test of treatment comparison stratified by center (How Mean Scores Differ)
(f) Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.36.2 Number of Tender/Painful Joints-(Protocol 022)

PART 3 OF 5: MEAN CHANGE ANALYSIS (a) (b)									
INTENT-TO-TREAT COHORT (ITT)									
	PLACEBO (N=217)	SC-56635 100MG BID (N=249)	SC-56635 200MG BID (N=235)	SC-56635 400MG BID (N=217)	NAPROXEN 400MG BID (N=225)	OVERALL P-VALUE (c)	LINEAR TRENDS P-VALUE (d)		
WEEK 2									
UNADJUSTED MEAN CHANGE	-0.6	-11.9	-12.2	-11.3	-10.2	<0.001	<0.001		
STD DEV	11.51	11.36	12.77	11.66	11.67				
LS MEAN CHANGE (e)	-0.5	-11.7	-12.0	-11.0	-10.0				
WEEK 6									
UNADJUSTED MEAN CHANGE	-1.0	-11.1	-11.3	-11.7	-10.1	0.014	<0.001		
STD DEV	14.25	14.16	17.05	13.57	13.51				
LS MEAN CHANGE (e)	-0.9	-11.0	-11.0	-11.5	-10.0				
WEEK 12									
UNADJUSTED MEAN CHANGE	-0.6	-11.6	-12.4	-11.7	-9.1	<0.001	<0.001		
STD DEV	14.07	14.14	13.99	13.59	13.16				
LS MEAN CHANGE (e)	-0.5	-11.5	-12.3	-11.4	-10.1				
C-RATIO WITH 95% CONFIDENCE INTERVALS (e):									
	100MG BID VS. NAPROXEN		200MG BID VS. NAPROXEN		400MG BID VS. NAPROXEN				
WEEK 2:	1.05 (0.67 to 1.27)		1.11 (0.92 to 1.34)		1.11 (0.92 to 1.34)				
WEEK 6:	1.07 (0.67 to 1.33)		1.14 (0.92 to 1.40)		1.16 (0.94 to 1.42)				
WEEK 12:	1.19 (0.96 to 1.49)		1.22 (0.96 to 1.52)		1.23 (0.99 to 1.54)				
P-VALUES FOR TREATMENT COMPARISONS (f):									
	PRIMARY			SECONDARY					
	100MG BID VS. PLACEBO	400MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 400MG BID
WEEK 2:	<0.001*	<0.001*	<0.001	0.511	0.535	0.982	0.001	0.607	0.247
WEEK 6:	0.001*	<0.001*	0.005	0.001	0.450	0.604	0.045	0.403	0.232
WEEK 12:	<0.001*	<0.001*	0.001	0.010	0.735	0.916	0.103	0.104	0.055

(a) This table is based on the last observation carried forward approach
 (b) Scale ranged from 0 to 48 with negative change indicating improvement
 (c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 11.005 for week 2, 12.177 for week 6, 12.585 for week 12
 (d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded
 (e) C-RATIO is defined as the ratio of least square mean changes from (e), of SC-56635 group versus Naproxen group
 (f) From a contrast statement from Analysis of Covariance model in (c)
 * Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.37.1 Number of Swollen Joints (Protocol 023)

TABLE 19
NUMBER OF SWOLLEN JOINTS
PART 1 OF 5: OBSERVED MEANS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)				
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)
BASELINE					
N	221	228	218	217	218
MEAN	19.7	20.0	21.2	20.5	20.6
STD DEV	11.95	11.77	11.69	10.93	12.00
WEEK 2					
N	221	228	218	217	218
MEAN	16.0	13.7	13.6	13.7	13.4
STD DEV	12.73	10.78	11.10	9.18	10.22
WEEK 6					
N	221	228	218	217	218
MEAN	15.8	13.8	14.2	13.5	13.6
STD DEV	13.43	10.87	12.21	9.59	11.32
WEEK 12					
N	221	228	218	217	218
MEAN	16.0	13.9	14.4	13.6	13.9
STD DEV	13.39	10.81	12.26	9.47	11.76

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 0 to 66 with lower score as better

* By definition, in this and subsequent efficacy tables, the ITT cohort includes only patients who had at least one dose of study medication

NUMBER OF SWOLLEN JOINTS
PART 2 OF 5: PATIENT'S OVERALL STATUS IN CHANGE FROM BASELINE, NUMBER OF PATIENTS (%) (a)

	INTENT-TO-TREAT COHORT (ITT)					LINEAR TREND p-VALUE (d)
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)	
WEEK 2						
IMPROVED (b)	66 (30%)	72 (32%)	89 (41%)	68 (31%)	86 (39%)	0.191
NO CHANGE	136 (62%)	147 (64%)	120 (55%)	142 (65%)	127 (58%)	
WORSENEED (c)	19 (9%)	9 (4%)	9 (4%)	7 (3%)	5 (2%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	
WEEK 6						
IMPROVED (b)	81 (37%)	76 (33%)	90 (41%)	76 (35%)	93 (43%)	0.324
NO CHANGE	117 (53%)	144 (63%)	121 (56%)	132 (61%)	117 (54%)	
WORSENEED (c)	23 (10%)	8 (4%)	7 (3%)	9 (4%)	8 (4%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	
WEEK 12						
IMPROVED (b)	67 (30%)	73 (32%)	90 (41%)	74 (34%)	92 (42%)	0.069
NO CHANGE	133 (60%)	145 (64%)	119 (55%)	134 (62%)	113 (52%)	
WORSENEED (c)	21 (10%)	10 (4%)	9 (4%)	9 (4%)	13 (6%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	

p-VALUES FOR TREATMENT COMPARISONS (e) :

	PRIMARY				SECONDARY					
	200MG BID VS.	400MG BID VS.	100MG BID VS.	200MG BID VS.	400MG BID VS.	400MG BID VS.	NAPROXEN VS.	NAPROXEN VS.	NAPROXEN VS.	NAPROXEN VS.
	PLACEBO	PLACEBO	PLACEBO	100MG BID	100MG BID	200MG BID	PLACEBO	100MG BID	200MG BID	400MG BID
WEEK 2:	0.003*	0.468	0.385	0.054	0.879	0.022	0.010	0.095	0.764	0.065
WEEK 6:	0.033	0.896	0.931	0.033	0.653	0.101	0.051	0.047	0.902	0.081
WEEK 12:	0.002*	0.269	0.524	0.024	0.701	0.083	0.007	0.074	0.669	0.148

(a) This table is based on the last observation carried forward approach

(b) Improved is defined as number of improved joints minus number of worsened joints is larger than or equal to 50% of the number of joints with baseline score > 0

(c) Worsened is defined as number of worsened joints minus number of improved joints is larger than or equal to 50% of the number of joints with baseline score > 0

(d) Cochran-Mantel-Haenszel test of linear dose trend stratified by center (Nonzero Correlation), Naproxen group was excluded

(e) Cochran-Mantel-Haenszel test of treatment comparison stratified by center (Row Mean Scores Differ)

* Statistically significant according to the Hochberg procedure (primary pairwise comparisons only)

Table A.37.2 Number of Swollen Joints (Protocol 023)

NUMBER OF SWOLLEN JOINTS							
PART 3 OF 5: MEAN CHANGE ANALYSIS (a) (b)							
INTENT-TO-TREAT COHORT (ITT)							
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)	OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
WEEK 2							
OBSERVED MEAN CHANGE	-3.8	-6.3	-7.6	-6.8	-7.2	<0.001	<0.001
STD DEV	9.23	8.32	9.57	8.18	9.08		
LS MEAN CHANGE (c)	-3.9	-6.3	-7.1	-6.6	-6.8		
WEEK 6							
OBSERVED MEAN CHANGE	-3.9	-6.2	-7.0	-6.9	-7.0	0.003	0.001
STD DEV	10.01	9.46	9.42	8.98	8.99		
LS MEAN CHANGE (c)	-3.8	-5.9	-6.2	-6.4	-6.4		
WEEK 12							
OBSERVED MEAN CHANGE	-3.7	-6.0	-6.8	-6.9	-6.6	0.006	0.002
STD DEV	10.40	9.61	9.70	9.67	10.05		
LS MEAN CHANGE (c)	-3.7	-5.9	-6.0	-6.4	-6.1		
Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):							
	100MG BID VS. NAPROXEN		200MG BID VS. NAPROXEN		400MG BID VS. NAPROXEN		
WEEK 2:	0.92 (0.74 to 1.15)		1.04 (0.85 to 1.29)		0.96 (0.77 to 1.20)		
WEEK 6:	0.93 (0.71 to 1.20)		0.97 (0.75 to 1.25)		1.00 (0.77 to 1.29)		
WEEK 12:	0.97 (0.73 to 1.28)		0.99 (0.75 to 1.31)		1.04 (0.79 to 1.37)		

p-VALUES FOR TREATMENT COMPARISONS (f):

	-----PRIMARY-----				-----SECONDARY-----					
	200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	400MG BID VS. NAPROXEN PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
	PLACEBO	PLACEBO	PLACEBO	100MG BID	100MG BID	200MG BID	PLACEBO	100MG BID	200MG BID	400MG BID
WEEK 2:	<0.001*	<0.001*	<0.001	0.244	0.698	0.443	<0.001	0.453	0.681	0.721
WEEK 6:	0.002*	0.001*	0.006	0.725	0.563	0.822	<0.001	0.546	0.803	0.981
WEEK 12:	0.004*	0.001*	0.006	0.866	0.582	0.706	0.003	0.818	0.952	0.751

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 0 to 66 with negative change indicating improvement

(c) From Analysis of Covariance model with treatment and center as factors and Baseline value as covariate, the corresponding ROOT MSE are: 7.375 for week 2, 8.151 for week 6, 8.456 for week 12

(d) From a contrast statement from Analysis of Covariance model in (c), Naproxen group was excluded

(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group

(f) From a contrast statement from Analysis of Covariance model in (c)

* Statistically significant according to the Hochberg procedure(primary pairwise comparisons only)

Table A.38.1 ACR-20 Responder Index (Protocol 023-ITT)

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN RA
N49-96-02-023

TABLE 16
CATEGORIAL STATUS BASED ON THE ACR RESPONDERS INDEX (20%) (a)
NUMBER OF PATIENTS (%)

	INTENT-TO-TREAT COHORT (ITT)					LINEAR TREND P-VALUE (c)
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)	
WEEK2						
IMPROVED (b)	55 (25%)	95 (42%)	101 (46%)	93 (43%)	97 (44%)	<0.001
NOT IMPROVED	166 (75%)	133 (58%)	117 (54%)	124 (57%)	121 (56%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	
WEEK6						
IMPROVED (b)	60 (27%)	87 (38%)	89 (41%)	94 (43%)	101 (46%)	<0.001
NOT IMPROVED	161 (73%)	141 (62%)	129 (59%)	123 (57%)	117 (54%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	
WEEK12						
IMPROVED (b)	50 (23%)	68 (30%)	86 (39%)	79 (36%)	91 (42%)	<0.001
NOT IMPROVED	171 (77%)	160 (70%)	132 (61%)	138 (64%)	127 (58%)	
TOTAL	221(100%)	228(100%)	218(100%)	217(100%)	218(100%)	

P-VALUE FOR TREATMENT COMPARISONS (d):

	PRIMARY				SECONDARY						
	200MG BID 400MG BID		100MG BID 200MG BID		400MG BID 400MG BID		NAPROXEN 500MG BID		NAPROXEN 200MG BID		NAPROXEN 400MG BID
	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.	VS.	
	PLACEBO	PLACEBO	PLACEBO	100MG BID	100MG BID	200MG BID	PLACEBO	100MG BID	200MG BID	400MG BID	400MG BID
WEEK2 :	<0.001*	<0.001*	<0.001	0.261	0.835	0.348	<0.001	0.537	0.698	0.507	0.507
WEEK6 :	0.002*	<0.001*	0.015	0.507	0.299	0.661	<0.001	0.096	0.294	0.507	0.507
WEEK12 :	<0.001*	0.002*	0.060	0.038	0.198	0.432	<0.001	0.011	0.595	0.242	0.242

Notes: The ITT cohort includes only patients who had at least one dose of study medication

(a) This table is based on the last observation carried forward approach

(b) Improved: At least 20% improvement from baseline in the number of tender/painful joints and in the number of swollen joints as well as at least 20% improvement from baseline in at least three of the following assessments:

1) Physician's Global 2) Patient's Global 3) Patient's Assessment of Pain 4) C-Reactive Protein 5) RAQ Functional Disability Index

(c) Cochran-Mantel-Haenszel test of linear dose trend stratified by center, p-value for Nonzero Correlation, naproxen was excluded

(d) Cochran-Mantel-Haenszel test of treatment comparison stratified by center, p-value for Row Mean Scores Differ

* Statistically significant according to the Hochberg procedure(primary pairwise comparisons only)

Table A.38.2 ACR-20 Responder Index (Protocol 022, ITT)

SC-59615 COMPARATIVE EFFICACY AND UOI SAFETY VS NAPROXEN IN RA
N49 96-02 022

TABLE 18
CATEGORICAL STATUS BASED ON THE ACR RESPONDER INDEX (20%) (a)
NUMBER OF PATIENTS (N)

	PLACEBO (N 111)	INTENT TO TREAT GROUP (ITT)				NAPROXEN 500MG BID (N 125)	TOTAL (N 1000)
		SC-59615 100MG BID (N 141)	SC-59615 200MG BID (N 215)	SC-59615 400MG BID (N 173)	NAPROXEN 500MG BID (N 125)		
WEEK 2							
IMPROVED (b)	71 (63%)	97 (69%)	115 (53%)	89 (51%)	120 (96%)	681 (68%)	0.001
NOT IMPROVED	40 (36%)	44 (31%)	100 (46%)	84 (48%)	53 (42%)	319 (32%)	
TOTAL	111 (100%)	141 (100%)	215 (100%)	173 (100%)	173 (100%)	1000 (100%)	
WEEK 12							
IMPROVED (b)	84 (76%)	93 (66%)	114 (53%)	87 (50%)	120 (96%)	604 (60%)	0.001
NOT IMPROVED	27 (24%)	48 (34%)	101 (47%)	86 (49%)	53 (42%)	396 (39%)	
TOTAL	111 (100%)	141 (100%)	215 (100%)	173 (100%)	173 (100%)	1000 (100%)	
WEEK 24							
IMPROVED (b)	65 (58%)	95 (67%)	103 (48%)	84 (48%)	111 (90%)	559 (56%)	0.005
NOT IMPROVED	46 (42%)	46 (33%)	112 (52%)	89 (51%)	64 (52%)	441 (44%)	
TOTAL	111 (100%)	141 (100%)	215 (100%)	173 (100%)	173 (100%)	1000 (100%)	

P-VALUE FOR TREATMENT COMPARISONS (b):

	PRIMARY				SECONDARY					
	200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 200MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 100MG BID
WEEK 2	<0.001*	<0.001*	<0.001	0.340	0.486	0.140	<0.001	0.048	0.028	0.561
WEEK 12	<0.001*	0.015*	0.008	0.035	0.691	0.047	0.038	0.017	0.021	0.878
WEEK 24	<0.001*	0.010*	0.005	0.073	0.956	0.320	0.049	0.445	0.077	0.762

(a) This table is based on the last observation carried forward approach.
 (b) Improved: At least 20% improvement from baseline in the number of tender/painful joints and in the number of swollen joints as well as at least 20% improvement from baseline in at least three of the following assessments:
 1) Physician's Global 2) Patient's Global 3) Patient's Assessment of Pain 4) C-Reactive Protein 5) RAQ Functional Disability Index
 (c) Cochran-Mantel-Haenszel test of linear dose trend stratified by center, p-value for Nonzero Correlation; naproxen was excluded
 (d) Cochran-Mantel-Haenszel test of treatment comparison stratified by center, p-value for Row Mean Scores Differ
 * Statistically significant according to the Dunnett procedure (primary pairwise comparisons only)

Table A.38.3 ACR-20 Responder Index (Protocol 023-Evaluable)

CLINICAL COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN RA
N39-04-02-023

APPENDIX 12.1.1
CATEGORICAL STATUS BASED ON THE ACR RESPONDER INDEX (20%)
(NUMBER OF PATIENTS (%))

	TREATMENT GROUPS						P-VALUE (2)
	PLACEBO (N 220)*	ESICARICIN 100MG BID (N 220)*	ESICARICIN 200MG BID (N 219)*	ESICARICIN 400MG BID (N 217)*	NAPROXEN 500MG BID (N 216)*	LINEAR TREND P-VALUE (3)	
WEEK 4							0.113
IMPROVED (4)	81 (37%)	87 (40%)	92 (42%)	82 (38%)	82 (38%)		
NOT IMPROVED	139 (63%)	133 (60%)	127 (58%)	135 (62%)	134 (62%)		
WEEK 8							0.083
IMPROVED (4)	89 (41%)	91 (41%)	88 (40%)	96 (44%)	91 (42%)		
NOT IMPROVED	131 (59%)	129 (59%)	131 (60%)	121 (56%)	125 (58%)		
WEEK 12							0.021
IMPROVED (4)	104 (47%)	101 (46%)	104 (47%)	95 (44%)	91 (42%)		
NOT IMPROVED	116 (53%)	119 (54%)	115 (53%)	122 (56%)	125 (58%)		
FINAL							0.011
IMPROVED (4)	108 (49%)	107 (48%)	104 (47%)	97 (45%)	91 (42%)		
NOT IMPROVED	112 (51%)	113 (52%)	115 (53%)	120 (55%)	125 (58%)		

FOOTNOTES FOR TREATMENT COMPARISON (1-3)

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	ESICARICIN 100MG BID VS. ESICARICIN 200MG BID	ESICARICIN 200MG BID VS. ESICARICIN 400MG BID	ESICARICIN 400MG BID VS. NAPROXEN 500MG BID	NAPROXEN 500MG BID VS. PLACEBO	NAPROXEN 500MG BID VS. 200MG BID	NAPROXEN 500MG BID VS. 100MG BID
WEEK 4 :	0.018	0.021	0.018	0.769	0.850	0.908	0.001	0.138	0.154
WEEK 8 :	0.611	0.549	0.173	0.910	0.134	0.155	0.048	0.090	0.010
WEEK 12 :	0.442	0.133	0.239	0.033	0.069	0.525	0.009	0.014	0.064
FINAL :	0.105	0.037	0.010	0.136	0.045	0.643	0.004	0.037	0.083

(4) Improved: At least 20% improvement from baseline in the number of tender/painful joints and in the number of swollen joints as well as at least 20% improvement from baseline in at least three of the following assessments: 1) Physician's Global; 2) Patient's Global; 3) Patient's Assessment of Pain; 4) C-Reactive Protein; 5) HAQ Functional Disability Index.

(1) Cochran-Mantel-Haenszel test of linear dose trend stratified by center, p-value for Nonzero Correlation, naproxen was excluded.

(2) Cochran-Mantel-Haenszel test of treatment comparison stratified by center, p-value for Row Mean Scores Differ.

* All randomized patients.

Table A.39.1 ACR-50 Responder Index (Protocol 022-ITT)

022-ITT COMPARATIVE EFFICACY AND DD1 SAFETY VS NAPROXEN IN FA
(N= 96 (2: 022)

TABLE 31
CATEGORICAL STATUS BASED ON THE ACR RESPONDER INDEX (50%) (a)
NUMBER OF PATIENTS (N)

	INTENT-TO-TREAT COHORT (ITT)					LITHEAR TREND P VALUE (b)
	200MG BID (N=211)	400MG BID (N=240)	800MG BID (N=235)	1600MG BID (N=217)	NAPROXEN 500MG BID (N=225)	
ACR50						
IMPROVED (c)	111 (53%)	111 (46%)	139 (59%)	141 (65%)	129 (57%)	<0.001
NOT IMPROVED	100 (47%)	129 (54%)	96 (41%)	76 (35%)	96 (43%)	
TOTAL	211(100%)	240(100%)	235(100%)	217(100%)	225(100%)	
ACR50						
IMPROVED (c)	147 (70%)	129 (54%)	140 (60%)	136 (63%)	129 (57%)	<0.001
NOT IMPROVED	64 (30%)	111 (46%)	95 (40%)	81 (37%)	96 (43%)	
TOTAL	211(100%)	240(100%)	235(100%)	217(100%)	225(100%)	
ACR50						
IMPROVED (c)	137 (65%)	129 (54%)	141 (60%)	131 (60%)	129 (57%)	<0.001
NOT IMPROVED	74 (35%)	111 (46%)	94 (40%)	86 (40%)	96 (43%)	
TOTAL	211(100%)	240(100%)	235(100%)	217(100%)	225(100%)	

(a) VALUE FOR TREATMENT COMPARISON (b)

	200MG BID	400MG BID	1000MG BID	1600MG BID	800MG BID	1600MG BID	NAPROXEN	NAPROXEN	NAPROXEN	NAPROXEN
	VS PLACEBO	VS PLACEBO	VS PLACEBO	VS 1000MG BID	VS 1600MG BID	VS 1600MG BID	VS PLACEBO	VS 1000MG BID	VS 1600MG BID	VS 1600MG BID
ACR50	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
DD1	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
DD1	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001

(a) Values are based on the last observation carried forward approach.

(b) Values are based on the last observation carried forward approach.

(c) Values are based on the last observation carried forward approach.

(d) Values are based on the last observation carried forward approach.

(e) Values are based on the last observation carried forward approach.

Table A.39.2 ACR-50 Responder Index (Protocol 023-ITT)

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN RA
N49 96 02 023

TABLE 13
CATEGORICAL STATUS BASED ON THE ACR RESPONDER INDEX (ITT) (a)
NUMBER OF PATIENTS (b)

	INTENT TO TREAT (ITT) (c)					LINEAR TREND P-VALUE (d)
	PLACEBO (n = 111)	SC-58635 100MG BID (n = 118)	SC-58635 200MG BID (n = 118)	SC-58635 400MG BID (n = 121)	NAPROXEN 500MG BID (n = 119)	
WEEK 0						
IMPROVED (a)	124 (11%)	141 (12%)	171 (15%)	211 (18%)	191 (16%)	0.002
NOT IMPROVED	204 (19%)	221 (19%)	182 (16%)	140 (12%)	160 (13%)	
TOTAL	211(100%)	228(100%)	219(100%)	210(100%)	217(100%)	
WEEK 8						
IMPROVED (a)	151 (14%)	221 (19%)	251 (18%)	251 (12%)	321 (15%)	<0.001
NOT IMPROVED	206 (19%)	236 (20%)	183 (8%)	192 (9%)	180 (8%)	
TOTAL	211(100%)	228(100%)	218(100%)	210(100%)	216(100%)	
WEEK 12						
IMPROVED (a)	131 (6%)	231 (10%)	381 (17%)	271 (13%)	391 (18%)	0.002
NOT IMPROVED	206 (9%)	236 (10%)	180 (8%)	190 (9%)	179 (8%)	
TOTAL	211(100%)	228(100%)	218(100%)	210(100%)	216(100%)	

P-VALUE FOR TREATMENT COMPARISONS (d):

	100MG BID VS. PLACEBO	400MG BID VS. PLACEBO	100MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
WEEK 0	<0.001	0.010	0.019	0.115	0.790	0.142	<0.001	0.075	0.420	0.129
WEEK 8	0.001	0.044	0.745	0.047	0.583	0.147	0.006	0.111	0.330	0.180
WEEK 12	<0.001	0.017	0.061	0.030	0.519	0.111	<0.001	0.024	0.110	0.110

Note: The ITT cohort includes only patients who had at least one dose of study medication.

(a) This table is based on the last observation carried forward approach.

(b) Improved: At least 20% improvement from baseline in the number of tender/painful joints and in the number of swollen joints as well as at least 50% improvement from baseline in at least three of the following assessments:

(1) Physician's Global; (2) Patient's Global; (3) Patient's Assessment of Pain; (4) Short-form Health Survey Physical Functioning Score.

(c) Cochran-Mantel-Haenszel test of linear dose trend stratified by center; p-value for Nonzero Correlation; naproxen was excluded in Cochran-Mantel-Haenszel test of treatment comparisons stratified by center; p-value for Row Mean Scores Differ.

Table A.40 Patient's Assessment of Arthritis Pain-VAS (Protocol 023)

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN RA
N49-96-02-023

TABLE 21
PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
PART 1 OF 3: OBSERVED MEANS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)				
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)
BASELINE					
N	220	228	218	216	218
MEAN	68.1	66.1	67.9	67.8	66.8
STD DEV	19.57	20.13	19.90	19.70	18.48
WEEK 2					
N	220	228	218	217	218
MEAN	58.7	45.8	41.4	42.2	40.6
STD DEV	27.15	26.25	25.10	24.62	24.36
WEEK 6					
N	221	228	218	217	218
MEAN	60.5	47.8	46.5	45.6	43.7
STD DEV	27.86	27.74	28.38	26.39	25.77
WEEK 12					
N	221	228	218	217	218
MEAN	62.0	51.0	47.0	48.7	44.6
STD DEV	27.88	28.41	29.03	26.48	27.43

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 0 to 100 mm with lower score as better

* By definition, in this and subsequent efficacy tables, the ITT cohort includes only patients who had at least one dose of study medication

PATIENT'S ASSESSMENT OF ARTHRITIS PAIN (VAS)
PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)					OVERALL p-VALUE (c)	LINEAR TREND p-VALUE (d)
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)		
WEEK 2							
OBSERVED MEAN CHANGE	-9.4	-20.3	-26.5	-25.6	-26.2	<0.001	<0.001
STD DEV	25.81	24.27	24.12	23.61	25.02		
LS MEAN CHANGE (e)	-8.8	-20.7	-26.8	-25.1	-26.1		
WEEK 6							
OBSERVED MEAN CHANGE	-7.4	-18.3	-21.4	-22.2	-23.1	<0.001	<0.001
STD DEV	25.59	25.94	28.80	27.60	26.35		
LS MEAN CHANGE (e)	-6.1	-18.3	-20.4	-21.1	-22.5		
WEEK 12							
OBSERVED MEAN CHANGE	-6.1	-15.1	-20.9	-19.0	-22.1	<0.001	<0.001
STD DEV	25.07	26.83	29.12	27.10	27.77		
LS MEAN CHANGE (e)	-5.5	-15.5	-20.4	-18.5	-22.0		
Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):							
	100MG BID VS. NAPROXEN		200MG BID VS. NAPROXEN		400MG BID VS. NAPROXEN		
WEEK 2:	0.79 (0.65 to 0.96)		1.00 (0.84 to 1.18)		0.96 (0.80 to 1.14)		
WEEK 6:	0.81 (0.63 to 1.03)		0.90 (0.72 to 1.14)		0.94 (0.75 to 1.17)		
WEEK 12:	0.71 (0.53 to 0.92)		0.93 (0.73 to 1.18)		0.84 (0.65 to 1.07)		

p-VALUES FOR TREATMENT COMPARISONS (f):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
WEEK 2:	<0.001	<0.001	<0.001	0.014	0.046	0.655	<0.001	0.012	0.962	0.620
WEEK 6:	<0.001	<0.001	<0.001	0.380	0.233	0.753	<0.001	0.073	0.364	0.555
WEEK 12:	<0.001	<0.001	<0.001	0.042	0.226	0.418	<0.001	0.007	0.519	0.146

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 0 to 100 (mm) with negative change indicating improvement

(c) From Analysis of Covariance model with treatment and center as factors and baseline value as covariate, the corresponding ROOT MSE are: 22.76 for week 2, 24.84 for week 6, and 25.35 for week 12

(d) From a contrast statement from analysis of Covariance model in (c), Naproxen group was excluded

(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group

(f) From a contrast statement from Analysis of Covariance model in (c)

Table A.41 C-Reactive Protein (Protocol 023)

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN RA
N49-96-02-023

TABLE 26.1
C-REACTIVE PROTEIN
PART 1 OF 2: OBSERVED MEANS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)				
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)
BASELINE					
N	215	222	214	210	210
MEAN	15572.1	16464.0	17887.9	15590.5	15481.0
STD DEV	15608.32	19890.11	20419.69	15790.92	18677.37
WEEK 2					
N	220	228	218	216	217
MEAN	15154.5	16592.1	17367.0	16935.2	14023.0
STD DEV	16015.79	20979.44	20191.55	17566.50	14229.42
WEEK 6					
N	221	228	218	217	218
MEAN	16470.6	17693.0	17243.1	18838.7	14504.6
STD DEV	18308.60	22025.47	19269.39	20799.01	15386.34
WEEK 12					
N	221	228	218	217	218
MEAN	18040.7	16877.2	16825.7	17963.1	13756.9
STD DEV	27587.43	20610.35	18969.70	19711.54	13783.06

(a) This table is based on the last observation carried forward approach

(b) Unit of measurement : ug/L

* By definition, in this and subsequent efficacy tables, the ITT cohort includes only patients who had at least one dose of study medication

C-REACTIVE PROTEIN
PART 2 OF 2: MEAN CHANGE ANALYSIS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)					OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)		
WEEK 2							
OBSERVED MEAN CHANGE	-325.6	333.3	-359.8	1409.5	-1352.4	0.168	0.159
STD DEV	12853.82	11978.74	15069.37	12330.92	12025.87		
LS MEAN CHANGE (c)	-300.7	703.6	374.8	1535.4	-1247.1		
WEEK 6							
OBSERVED MEAN CHANGE	1004.7	1369.4	-542.1	1347.6	-823.8	0.016	0.172
STD DEV	15781.95	13404.89	12134.44	15726.68	13705.46		
LS MEAN CHANGE (c)	1420.0	2106.5	395.5	3871.3	-340.8		
WEEK 12							
OBSERVED MEAN CHANGE	2604.7	536.0	-967.3	2595.2	-1600.0	0.040	0.912
STD DEV	26246.44	14431.49	14446.40	16625.43	12311.82		
LS MEAN CHANGE (c)	2778.4	1236.1	37.6	2990.0	-1269.8		
Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):							
	100MG BID VS. NAPROXEN		200MG BID VS. NAPROXEN		400MG BID VS. NAPROXEN		
WEEK 2:	-0.56 (NON-ESTIMABLE)		-0.30 (NON-ESTIMABLE)		-1.23 (NON-ESTIMABLE)		
WEEK 6:	-6.18 (NON-ESTIMABLE)		-1.16 (NON-ESTIMABLE)		-11.4 (NON-ESTIMABLE)		
WEEK 12:	-0.97 (NON-ESTIMABLE)		-0.03 (NON-ESTIMABLE)		-2.35 (NON-ESTIMABLE)		

p-VALUES FOR TREATMENT COMPARISONS (f):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	100MG BID VS. 100MG BID	200MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
WEEK 2:	0.383	0.561	0.115	0.775	0.472	0.320	0.417	0.091	0.164	0.018
WEEK 6:	0.595	0.432	0.061	0.186	0.175	0.008	0.179	0.060	0.574	0.001
WEEK 12:	0.333	0.088	0.896	0.452	0.273	0.068	0.012	0.117	0.418	0.009

(a) This table is based on the last observation carried forward approach

(b) Unit of measurement : ug/L with negative change indicating improvement

(c) From Analysis of Covariance model with treatment and center as factors and baseline value as covariate, the corresponding ROOT MSE are: 11963 for week 2, 13440 for week 6, and 16562 for week 12

(d) From a contrast statement from analysis of Covariance model in (c), Naproxen group was excluded

(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group

(f) From a contrast statement from Analysis of Covariance model in (c)

Table A.42 HAQ Functional Disability Index (Protocol 023)

SC-58635 COMPARATIVE EFFICACY AND SAFETY VS NAPROXEN IN RA
N49-96-02-023

TABLE 25
HAQ FUNCTIONAL DISABILITY INDEX
PART 1 OF 3: OBSERVED MEANS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)				
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)
BASELINE					
N	219	226	217	216	218
MEAN	1.4	1.4	1.3	1.3	1.4
STD DEV	0.68	0.70	0.67	0.63	0.68
WEEK 2					
N	221	228	218	217	218
MEAN	1.3	1.1	1.0	1.0	1.1
STD DEV	0.67	0.69	0.68	0.64	0.67
WEEK 6					
N	221	228	218	217	218
MEAN	1.3	1.2	1.1	1.0	1.1
STD DEV	0.72	0.71	0.72	0.66	0.69
WEEK 12					
N	221	228	218	217	218
MEAN	1.3	1.3	1.1	1.1	1.1
STD DEV	0.73	0.70	0.73	0.67	0.68

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 0 to 3 with lower score as less disability

* By definition, in this and subsequent efficacy tables, the ITT cohort includes only patients who had at least one dose of study medication

HAQ FUNCTIONAL DISABILITY INDEX
PART 2 OF 3: MEAN CHANGE ANALYSIS (a) (b)

	INTENT-TO-TREAT COHORT (ITT)					OVERALL p-VALUE(c)	LINEAR TREND p-VALUE(d)
	PLACEBO (N=221)	SC-58635 100MG BID (N=228)	SC-58635 200MG BID (N=218)	SC-58635 400MG BID (N=217)	NAPROXEN 500MG BID (N=218)		
WEEK 2							
OBSERVED MEAN CHANGE	-0.1	-0.2	-0.3	-0.3	-0.3	<0.001	<0.001
STD DEV	0.44	0.42	0.45	0.47	0.47		
LS MEAN CHANGE (c)	-0.1	-0.2	-0.3	-0.3	-0.3		
WEEK 6							
OBSERVED MEAN CHANGE	-0.1	-0.2	-0.3	-0.3	-0.3	<0.001	<0.001
STD DEV	0.49	0.43	0.51	0.52	0.48		
LS MEAN CHANGE (c)	-0.1	-0.2	-0.3	-0.3	-0.3		
WEEK 12							
OBSERVED MEAN CHANGE	-0.1	-0.1	-0.2	-0.2	-0.3	<0.001	<0.001
STD DEV	0.49	0.44	0.51	0.53	0.48		
LS MEAN CHANGE (c)	-0.1	-0.1	-0.2	-0.2	-0.3		
Q-RATIO WITH 95% CONFIDENCE INTERVALS (e):							
	100MG BID VS. NAPROXEN		200MG BID VS. NAPROXEN		400MG BID VS. NAPROXEN		
WEEK 2:	0.83 (0.59 to 1.15)		1.08 (0.82 to 1.45)		1.05 (0.79 to 1.42)		
WEEK 6:	0.69 (0.43 to 1.04)		1.07 (0.76 to 1.51)		0.99 (0.69 to 1.41)		
WEEK 12:	0.56 (0.30 to 0.90)		0.94 (0.64 to 1.38)		0.98 (0.67 to 1.43)		

p-VALUES FOR TREATMENT COMPARISONS (f):

	100MG BID VS. PLACEBO	200MG BID VS. PLACEBO	400MG BID VS. PLACEBO	200MG BID VS. 100MG BID	400MG BID VS. 100MG BID	400MG BID VS. 200MG BID	NAPROXEN VS. PLACEBO	NAPROXEN VS. 100MG BID	NAPROXEN VS. 200MG BID	NAPROXEN VS. 400MG BID
WEEK 2:	<0.001	<0.001	<0.001	0.080	0.124	0.837	<0.001	0.244	0.560	0.707
WEEK 6:	0.006	<0.001	<0.001	0.025	0.074	0.658	<0.001	0.065	0.698	0.956
WEEK 12:	0.103	<0.001	<0.001	0.031	0.017	0.813	<0.001	0.012	0.738	0.923

(a) This table is based on the last observation carried forward approach

(b) Scale ranged from 0 to 3 with negative change indicating improvement

(c) From Analysis of Covariance model with treatment and center as factors and baseline value as covariate, the corresponding ROOT MSE are: 0.424 for week 2, 0.458 for week 6, and 0.462 for week 12

(d) From a contrast statement from analysis of Covariance model in (c), Naproxen group was excluded

(e) Q-RATIO is defined as the ratio of least square mean changes from (c), of SC-58635 group versus Naproxen group

(f) From a contrast statement from Analysis of Covariance model in (c)