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PROPRIETARY DRUG NAME/INN: Bextra

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI

Protocol No.: PROTOCOL A3471018

Protocol Title: Multicenter, Double-Blind, Randomized, Placebo Controlled, Comparison of the Efficacy and Safety of Bextra® (valdecoxib) 10 mg Once Daily and Naproxen 500 mg Twice Daily in Treating the Signs and Symptoms of Rheumatoid Arthritis (RA) in a Severe RA Population

Study Center(s): Sixty-one centers in the United States and Canada

Publications Based on the Study: None

Study Initiation and Completion Dates: 19 February 2003 to 28 January 2005

Phase of Development: Phase 4

Study Objective(s): The primary objective of the study was to compare the efficacy of valdecoxib 10 mg once daily (QD) versus placebo in treating the signs and symptoms of rheumatoid arthritis (RA) in a severe RA population.

The secondary objectives of this study were:

- To assess the safety and tolerability of valdecoxib 10 mg QD and naproxen 500 mg twice daily (BID) in treating the signs and symptoms of RA in a severe RA population
- To assess the efficacy of naproxen 500 mg BID versus placebo in treating the signs and symptoms of RA in a severe RA population and to assess the efficacy of valdecoxib 10 mg QD versus naproxen 500 mg BID in treating the signs and symptoms of RA in a severe RA population

Study Design: This was a multicenter, randomized, double-blind, double-dummy, active comparator and placebo-controlled, parallel-group study. Subjects, meeting inclusion/exclusion criteria, were randomly assigned in a 1:1:1 ratio to receive valdecoxib 10 mg tablets QD, naproxen 500 mg capsules BID, or placebo.

To maintain the blind, subjects were dispensed 2 bottles at each visit, 1 bottle of tablets to take QD and 1 bottle of capsules to take BID.

The treatment duration was 12 weeks. Visits occurred at screening and baseline as well as 1, 6, and 12 weeks after the first dose of study medication. Subjects who discontinued treatment were

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asked to return for an early termination visit. Subjects who did not return for this visit were contacted by the site by phone 2 times and then sent a certified letter asking them to return for the early termination visit and bring the study medication back to the site.

Number of Subjects: Subject disposition is presented in Table S1.

Table S1. Subject Disposition – Randomized Population

Number (%) of Subjects	Valdecoxib 10 mg QD (N=170)	Naproxen 500 mg BID (N=167)	Placebo (N=171)
Treated	170	166	171
Completed*	130 (76.5)	120 (71.9)	90 (52.6)
Discontinued	40 (23.5)	47 (28.1)	81 (47.4)
Insufficient clinical response	24 (14.1)	22 (13.2)	60 (35.1)
Adverse event(s)	9 (5.3)	16 (9.6)	8 (4.7)
Laboratory abnormality(ies)	0 (0.0)	1 (0.6)	0 (0.0)
Subject died	0 (0.0)	0 (0.0)	1 (0.6)
Protocol violation	2 (1.2)	1 (0.6)	3 (1.8)
Lost to follow-up	0 (0.0)	2 (1.2)	0 (0.0)
Subject no longer willing to participate in study	3 (1.8)	5 (3.0)	6 (3.5)
Other	2 (1.2)	0 (0.0)	3 (1.8)
Analyzed for Safety			
Adverse events	170 (100.0)	166 (100.0)	171 (100.0)
Laboratory Data	170 (100.0)	166 (100.0)	170 (99.4)

*p<0.001. From a Cochran-Mantel-Haenszel (CMH) test stratified by center (General Association Statistic).

Diagnosis and Main Criteria for Inclusion: Male and female subjects 18 years or older with a diagnosis of severe RA of at least 6 months in duration. The subject's RA must have been treated with a stable regimen including a non-steroidal anti-inflammatory drug (NSAID) (for at least 4 weeks) as well as at least one of the following with the dosing regimen stable for the indicated time:

- methotrexate (doses up to 25 mg per week) for 30 days
- cyclosporine for at least 12 weeks
- leflunomide (Arava[®]) for at least 12 weeks
- interleukin-1 receptor antagonist anakinra (Kineret[®]) – 12 weeks
- one of the following tumor necrosis factor inhibitors:
 - adalimumab (Humira[®]) minimum of 5 doses on a regular schedule
 - entanercept (Enbrel[®]) for 6 weeks
 - infliximab (Remicade[®]) 3 doses and currently on a stable regimen of infusions not more than every 8 weeks

Subjects diagnosed with any other inflammatory arthritis or having a secondary, non-inflammatory type of arthritis (eg, osteoarthritis (OA) or fibromyalgia) that, in the investigator's opinion, was symptomatic enough to interfere with the evaluation of the effect of valdecoxib on the subject's primary diagnosis of RA were excluded from the study.

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Study Treatment: is presented in Table S2 and the Study Drug Packaging is presented in Table S3.

Table S2. Study Treatment

Study Drug	Dosage Form
Valdecoxib	10 mg/tablet
Valdecoxib	10 mg/tablet
Valdecoxib	10 mg/tablet
Placebo for valdecoxib	0 mg/tablet
Placebo for valdecoxib	0 mg/tablet
Placebo for valdecoxib	0 mg/tablet
Naproxen	500 mg/capsule
Naproxen	500 mg/capsule
Naproxen	500 mg/capsule
Placebo for naproxen	0 mg/capsule
Placebo for naproxen	0 mg/capsule

Table S3. Study Drug – Packaging and Subject Instructions

Treatment Group I – Valdecoxib 10 mg QD	
Bottle A (1 tablet in the morning with breakfast)	Valdecoxib 10 mg tablets
Bottle B (1 capsule in the morning with breakfast, 1 capsule in the evening with food)	Placebo capsule identical to Naproxen 500 mg capsules
Treatment Group II – Naproxen 500 mg BID	
Bottle A (1 tablet in the morning with breakfast)	Placebo tablets to match valdecoxib 10 mg tablets
Bottle B (1 capsule in the morning with breakfast, 1 capsule in the evening with food)	Naproxen 500 mg capsules
Treatment Group III – Placebo	
Bottle A (1 tablet in the morning with breakfast)	Placebo tablets to match valdecoxib 10 mg tablets
Bottle B (1 capsule in the morning with breakfast, 1 capsule in the evening with food)	Placebo capsule identical to Naproxen 500 mg capsules

At the baseline visit and each subsequent visit, the subject was provided with 1 Bottle A and 1 Bottle B and instructions to take 1 tablet from Bottle A (a total of 1 tablet per day) and 1 capsule from Bottle B in the morning with breakfast and 1 capsule from Bottle B in the evening with food (a total of 2 capsules each day).

Evaluations: All baseline assessments were performed prior to discontinuing the current NSAID therapy. At each visit, the Health Assessment Questionnaire was done first.

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Subject Arthritis Assessments:

- Health Assessment Questionnaire (HAQ) Disability Index: The HAQ Disability Index consisted of 20 categorical questions and 23 check box questions. The score for the categorical questions ranged from 0=without any difficulty to 3=unable to do. The score for the check box questions was 0 if the box was not checked, or 2 if the box was checked.
- Patient's Assessment of Arthritis Pain Visual Analog Scale (VAS): Subjects were asked to rate how much pain they were having at the time of the visit because of their arthritis by making a mark along a 100 mm VAS between 0 (no pain) and 100 (most severe pain).
- Patient's Global Assessment of Disease Activity: Subjects answered the following question: "Considering all the ways your arthritis affects you, how are you feeling today?" The subject's response was recorded using a 5-point scale.
- Duration of Morning Stiffness: Morning stiffness was defined by the time elapsed between the time of usual awakening (even if not in the morning) and the time the subject was as limber as he/she will be during a day involving typical activities.

Physician Arthritis Assessments:

- Assessment of Joint Tenderness/Pain: A physician had to do all joint assessments. A total of 68 joints were assessed, where the possible responses were 0=not tender, 1=tender, 2=tender and winced, and 3=tender, winced, and withdrew. The Tender Joint count was calculated as the total number of joints with a tender/pain joint score >0. Also, the Tender Joint Score was calculated as the sum of the responses received for the 68 joints assessed, where the range of Tender Joint score is from 0 to 204.
- Assessment of Joint Swelling: A total of 66 joints were assessed. These joints were the same as those used to assess tenderness/pain except that right and left hip joints were not included. The possible responses were 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. The Swollen Joint count was calculated as the total number of joints with a swollen joint score >0. Also, the Swollen Joint score was calculated as the sum of the responses received for the 66 joints assessed, where the range of Swollen Joint score is from 0 to 198.
- Physician's Global Assessment of Disease Activity: The investigator assessed how the overall arthritis appeared at the time of the visit.

Other Assessments:

- ACR-N: The smallest degree of improvement from baseline (percentage change from baseline), in the following 3 criteria was calculated: the number of tender joints, the number of swollen joints, and the median of the 5 remaining assessments included in the ACR-20 criteria responder definition.

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- **One-Week Severity of Dyspepsia Assessment (SODA):** The 1-week instrument consists of 3 subscales: Pain scale (Items 1 through 6 indicating satisfaction with pain relief), Non-pain symptoms (Items 7 through 13 indicating satisfaction with non-pain dyspeptic symptoms such as nausea), and Satisfaction (Items 14 through 17 indicating improvement in ability to perform daily activities and overall performance of the drug).
- **SF-36 Acute Health Survey:** The SF-36 Acute Survey includes 36 items covering 8 domains: Physical Functioning; Role-Physical; Bodily Pain; General Health; Vitality; Social Functioning; Role-Emotional; and Mental Health. In turn, the 8 domains combine to form 2 summary scores: Physical Component Summary (PCS - Physical Functioning, Role-Physical, Bodily Pain, General Health) and Mental Component Summary (MCS-Vitality, Social Functioning, Role-Emotional, and Mental Health). This study used the SF-36 Acute Health Survey, with a 1-week recall period.
- **Patient Treatment Satisfaction Scale (PTSS) – Current Pain Medication and Satisfaction With Current Pain Medication:** Includes 6 subscales - General (patient assessment of general health and pain,); Information About Pain and Its Treatment (patient satisfaction with information concerning illness, pain and pain treatment); Medical Care (patient satisfaction with quality of medical care); Current Pain Medication (patient perception of the impact of pain medication on ADLs and QOL); Pain Medication Route of Administration (patient perceptions on the oral, IV or patch routes of administration as applicable); Side Effects of Medication (degree to which patients are bothered by possible side effects of analgesic medications); Satisfaction with Current Pain Medication (patient satisfaction with pain medication efficacy as well as other aspects of the medication and care).

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations:

C-Reactive Protein:

Blood was collected for determination of C-reactive protein. The C-reactive protein was determined by a central laboratory using the turbidometric immunoprecipitation.

Safety Evaluations: Safety assessments included adverse events (AEs), serious adverse events (SAEs), laboratory tests, concomitant medications, vital signs, physical examinations, and reason for discontinuation.

Statistical Methods:

All efficacy analyses were conducted on the Modified Intent-to-Treat (MITT) population, which included all subjects who received at least one dose of study medication and had at least one post-baseline efficacy assessment.

Primary Efficacy Analysis: The primary efficacy variable, the percent of ACR-20 Criteria Responders at Week 12, was analyzed using a Cochran-Mantel-Haenzel (CMH) test, stratified by center. The primary comparison was between valdecoxib 10 mg QD and placebo.

A subject was considered an ACR-20 criteria responder if:

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1. The counts for both tender and swollen joints reduced by 20% or more from baseline; and
2. Three out of the following 5 assessments showed a reduction of 20% or more from the baseline assessment:
 - a. Patient's Assessment of Arthritis Pain (VAS);
 - b. Patient's Global Assessment of Disease Activity;
 - c. Physician's Global Assessment of Disease Activity;
 - d. Health Assessment Questionnaire (HAQ) Disability Index; and
 - e. C-Reactive Protein (CRP).

Secondary Efficacy Analyses: Pairwise comparisons between naproxen versus placebo and valdecoxib versus naproxen for the percent of ACR-20 responders at Week 12 was performed using a CMH test, stratified by center.

The overall and pairwise comparisons of the percent of ACR-20 responder at Week 1 and Week 6 were performed using a CMH test, stratified by center.

The overall and pairwise comparisons of mean change from baseline at each visit (Week 1, Week 6, and Week 12) were performed for tender joint count, swollen joint count, patient's assessment of arthritis pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ disability index, CRP, and duration of morning stiffness using analysis of covariance (ANCOVA) with treatment and center as factors, and baseline measurement as a covariate.

Additionally, patient's global assessment of disease activity and physician's global assessment of disease activity was categorized as "improved" (reduction of at least 2 grades from baseline for Grades 3-5 or a change of 1 grade from baseline Grade 2), "unchanged" (neither improved or worsened), or "worsened" (an increase of at least 2 grades from baseline for Grades 1-3 or a change in a grade from 4 to 5). The overall and pairwise comparisons for the above categorical variable (improved, unchanged, worsened) was performed using a CMH test with modified ridit scores, adjusted for the center.

The overall and pairwise comparisons for incidence of withdrawal due to insufficient clinical response were analyzed using a CMH test, adjusted for the center.

The time to withdrawal due to insufficient clinical response was analyzed using survival analysis methods. The median time for each treatment group was estimated using the Kaplan–Meier estimator with Miller's adjustment (Survival Analysis, page 75-75, John Wiley and Sons). Ninety-five percent confidence intervals (CI) on the median time was provided using the method of Simon & Lee (1982). The overall and pairwise comparisons were performed using the Log-rank test, which was used to determine the statistical significance of treatment group differences in the distribution of time to withdrawal due to insufficient clinical response.

The overall and pairwise comparisons were performed for ACR-N and average rescue medication usage per day using analysis of variance (ANOVA) with treatment and center as factors.

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The overall and pairwise comparisons of the mean change from baseline for each domain and each component summary were performed for the SF-36 Acute Health Survey using ANCOVA with treatment and center as factors, and baseline score as a covariate.

Scores of 3 One-Week SODA subscales (Dyspepsia Pain, Non-Pain Symptoms, and Satisfaction with Dyspepsia-Related Health) were calculated. The overall and pairwise comparisons of the mean change from baseline for each One-Week SODA subscale (Dyspepsia Pain, Non-Pain Symptoms, and Satisfaction with Dyspepsia-Related Health) was performed using ANCOVA with treatment and center as factors, and baseline score as a covariate.

Analysis of the PTSS Current Pain Medication and Satisfaction with Current Pain Medication subscales was done on the modified intent-to-treat (MITT) population. The mean scores at Week 1 and Week 6 were analyzed using ANOVA with treatment and center as factors.

Other Planned Analyses: The primary efficacy variable was analyzed for subjects who did not take any rescue medication during the study.

Safety Analyses: Core safety data, including physical examination, vital signs, laboratory measures, and treatment-emergent adverse events (AEs) were analyzed using methods prescribed by Worldwide Safety Standard (WSS) version 3.0.

Efficacy Results:

Primary Evaluation:

ACR-20 Criteria Responder at Week 12:

The primary efficacy evaluation was the proportion of ACR-20 Criteria Responders at Week 12. The primary comparison between valdecoxib 10 mg QD and placebo showed that approximately 19% more subjects treated with valdecoxib demonstrated improvement in their RA signs and symptoms as measured by ACR-20 criteria and this difference was statistically significant ($p < 0.001$). There was a significant difference ($p < 0.001$) among the 3 treatment groups, as shown in Table S4.

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Table S4. ACR-20 Criteria Responder at Week 12

	Valdecoxib 10 mg QD (N=170)	Naproxen 500 mg BID (N=166)	Placebo (N=169)	p- value^a
Week 12				<0.001
Responder	100 (58.8%)	101 (60.8%)	67 (39.6%)	
Non-Responder	70 (41.2%)	65 (39.2%)	102 (60.4%)	
p-Value for Pairwise Comparisons				
Week 12	Valdecoxib vs Placebo <0.001	Valdecoxib vs Naproxen 0.898	Naproxen vs Placebo <0.001	

a: From Cochran-Mantel-Haenzel (CMH) test stratified by center.

Secondary Evaluations:

The results of the secondary evaluations are presented in Table S5 (LS Mean Change From Baseline). For the pairwise comparisons, significance at the $p \leq 0.05$ level is denoted with an * for valdecoxib vs placebo; † for valdecoxib vs naproxen; and ‡ for naproxen vs placebo.

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Table S5. Secondary Analyses - LS Mean Change (SD) From Baseline

	Valdecoxib 10 mg QD (N=170)	Naproxen 500 mg BID (N=166)	Placebo (N=169)	p-value
Tender Joint Count				
Week 1	-12.6 (0.89)*	-13.4 (0.90) [‡]	-9.4 (0.91)	0.001
Week 6	-13.7 (0.95)*	-15.6 (0.96) [‡]	-10.3 (0.97)	<0.001
Week 12	-14.1 (1.01)*	-16.3 (1.01) [‡]	-10.7 (1.02)	<0.001
Tender Joint Score				
Week 1	-16.4 (1.20) *	-17.8 (1.22) [‡]	-11.2 (1.22)	<0.001
Week 6	-17.5 (1.27) *	-20.1 (1.28) [‡]	-12.5 (1.29)	<0.001
Week 12	-17.8 (1.29) *	-20.6 (1.29) [‡]	-13.0 (1.31)	<0.001
Swollen Joint Count				
Week 1	-8.4 (0.57) *	-7.9 (0.58) [‡]	-6.2 (0.58)	0.008
Week 6	-9.3 (0.62) *	-9.0 (0.62) [‡]	-6.7 (0.62)	0.002
Week 12	-9.7 (0.65) *	-9.6 (0.65) [‡]	-6.8 (0.66)	<0.001
Swollen Joint Score				
Week 1	-9.6 (0.70) *	-9.0 (0.71) [‡]	-6.6 (0.72)	0.003
Week 6	-10.6 (0.78) *	-10.3 (0.78) [‡]	-7.2 (0.79)	0.001
Week 12	-10.7 (0.82) *	-10.9 (0.82) [‡]	-7.2 (0.83)	<0.001
Patient's Assessment of Arthritis Pain (VAS)				
Week 1	-28.1 (1.92) *	-27.5 (1.95) [‡]	-14.3 (1.97)	<0.001
Week 6	-27.6 (2.09) *	-30.2 (2.10) [‡]	-16.0 (2.11)	<0.001
Week 12	-28.5 (2.22) *	-30.8 (2.22) [‡]	-14.9 (2.24)	<0.001
Patient's Global Assessment of Disease Activity				
Week 1	-1.2 (0.07) *	-1.2 (0.07) [‡]	-0.8 (0.07)	<0.001
Week 6	-1.1 (0.08) *	-1.2 (0.08) [‡]	-0.7 (0.08)	<0.001
Week 12	-1.1 (0.08) *	-1.2 (0.08) [‡]	-0.7 (0.08)	<0.001
Physician's Global Assessment of Disease Activity				
Week 1	-1.2 (0.07) * [†]	-1.4 (0.07) [‡]	-0.8 (0.07)	<0.001
Week 6	-1.3 (0.08) *	-1.4 (0.08) [‡]	-0.9 (0.08)	<0.001
Week 12	-1.3 (0.08) *	-1.5 (0.08) [‡]	-0.9 (0.08)	<0.001
Duration of Morning Stiffness				
Week 1	-2.8 (0.48) *	-4.0 (0.49) [‡]	-1.5 (0.49)	<0.001
Week 6	-3.4 (0.49) *	-4.2 (0.49) [‡]	-1.1 (0.49)	<0.001
Week 12	-3.3 (0.50) *	-4.4 (0.50) [‡]	-1.0 (0.51)	<0.001
ACR-20 Criteria Responder at Week 1 and 6				
Week 1				0.004
Responder	90 (52.9%) *	89 (53.6%) [‡]	64 (37.9%)	
Non-Responder	80 (47.1%)	77 (46.4%)	105 (62.1%)	
Week 6				0.004
Responder	97 (57.1%)	107 (64.5%) [‡]	79 (46.7%)	
Non-Responder	73 (42.9%)	59 (35.5%)	90 (53.3%)	
ACR-N				
Week 1	60.2 (2.25) *	59.4 (2.28) [‡]	50.0 (2.30)	<0.001
Week 6	64.5 (2.49) *	66.5 (2.50) [‡]	53.6 (2.50)	<0.001
Week 12	65.1 (2.53) *	68.6 (2.54) [‡]	52.5 (2.55)	<0.001

*p≤0.05 for valdecoxib vs placebo; [†] p≤0.05 for valdecoxib vs naproxen; [‡] p≤0.05 for naproxen vs placebo.

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One-Week Severity of Dyspepsia Assessment (SODA):

There was no significant difference in the LS mean change from baseline ($p \leq 0.05$) among the 3 treatment groups for any of the 3 measures – Dyspepsia Pain, Non-Pain Symptoms or Satisfaction With Dyspepsia-Related Health. There was a significant difference for the adjusted pairwise comparison of valdecoxib vs naproxen at Week 12 for Dyspepsia Pain (-1.90 and 0.20, respectively, $p=0.031$) and for valdecoxib vs placebo at Week 12 for Non-Pain Symptoms (0.50 and -0.33, respectively, $p=0.022$).

SF-36 Acute Health Survey:

There was a significant difference in the LS mean change from baseline ($p \leq 0.05$) among the 3 treatment groups at Weeks 1, 6, and 12 for Physical Functioning, Role-Physical, Bodily Pain, Social Functioning, Physical Component, and Mental Component.

There were significant differences for the pairwise treatment comparisons for valdecoxib vs placebo for all of the measures at all timepoints except for General Health, Weeks 6 and 12; Vitality, Week 6; Role – Physical, Week 6; and Mental Health, Weeks 1, 6, and 12. Naproxen vs placebo was significantly different ($p < 0.05$) for all of the measures at all timepoints except General Health, Weeks 6 and 12; and Role Emotional, Weeks 1 and 12. There were no significant differences between valdecoxib vs naproxen except for Mental Health at Weeks 1 and 12.

Health Assessment Questionnaire (HAQ) Disability Index:

There was a significant difference ($p < 0.001$) among the 3 treatment groups at Weeks 1, 6, and 12. For the pairwise comparisons, there was a significant difference between valdecoxib vs placebo at $p < 0.001$ for Weeks 1 and 6 and $p=0.002$ for Week 12. Naproxen vs placebo was significantly different at $p < 0.001$ for all weeks.

Patient Treatment Satisfaction Subscale (PTSS):

There was a significant difference among the 3 treatment groups for both Weeks 1 and 12 for the Current Pain Medication (< 0.001) and the Satisfaction With Current Pain Medication ($p < 0.001$) subscales. For the pairwise comparisons, there was a significant difference between valdecoxib vs placebo for the Current Pain Medication measure at Week 1 ($p < 0.001$) and Week 12 ($p=0.014$) and for the Satisfaction With Current Pain Medication at Week 1 ($p < 0.001$) and Week 12 ($p=0.019$). There was a significant difference between naproxen vs placebo for both Weeks 1 and 12 for both measures ($p < 0.001$).

Incidence of Withdrawal due to Insufficient Clinical Response:

There was a significant difference among the 3 treatment groups ($p < 0.001$) as well as for the pairwise comparisons of valdecoxib vs placebo and naproxen vs placebo ($p < 0.001$).

Average Rescue Medication Usage Per Day:

The proportion of subjects who used rescue medication was 35.3%, 33.1%, and 42.0% in the valdecoxib, naproxen, and placebo groups, respectively ($p=0.172$). The LS Mean (SE) for the average rescue medication usage per day in milligrams for the valdecoxib, naproxen, and

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placebo groups was 485.9(86.18), 218.4(88.50), and 534.7(79.12), respectively. This difference was significant among the 3 treatment groups (p=0.012).

For the pairwise comparisons, there was no significant difference between valdecoxib vs placebo (p=0.658), while there was a significant difference between naproxen vs placebo (p=0.005) and valdecoxib vs naproxen (p=0.021).

Pharmacokinetic, Pharmacodynamic, and/or Other Results:

C-Reactive Protein:

There was no significant difference among the 3 treatment groups and no significant difference was seen for any of the pairwise comparisons.

Safety Results: Table S6 below presents information on treatment-emergent AEs. The number of AEs was similar between the treatment groups, however, twice as many subjects in the naproxen group compared with the valdecoxib or placebo groups had to discontinue from the study due to an AE (9.6%, 4.7%, and 4.7%, respectively).

Table S6. Treatment-Emergent Adverse Events – Safety Population

n (%)	Valdecoxib 10 mg QD (N=170)		Naproxen 500 mg BID (N=166)		Placebo (N=170)	
	All Causality	Treatment-Related	All Causality	Treatment-Related	All Causality	Treatment-Related
Number of AEs	193	55	181	47	176	50
Subjects with AEs	92 (54.1)	42 (24.7)	92 (55.4)	34 (20.5)	90 (52.9)	36 (21.2)
Subjects with SAEs	1 (0.6)	1 (0.6)	2 (1.2)	0 (0.0)	4 (2.4)	0 (0.0)
Subjects with severe AEs	8 (4.7)	3 (1.8)	7 (4.2)	1 (0.6)	13 (7.6)	2 (1.2)
Subjects discontinued due to AEs*	8 (4.7)	7 (4.1)	16 (9.6)	7 (4.2)	8 (4.7)	4 (2.4)
Subjects with dose reduced or temporary discontinuation due to AE	9 (5.3)	5 (2.9)	7 (4.2)	0 (0.0)	6 (3.5)	2 (1.2)

Includes data up to 7 days after last dose of study drug.

Except for the Number of Adverse Events, subjects are counted only once per treatment in each row.

* Includes subjects who discontinued who had received at least one dose of study medication.

Adverse events by body system reported in ≥5% of subjects are presented in Table S7 below. Gastrointestinal (GI) system disorders were the most commonly reported AEs (by body system) reported in 24.1%, 25.9%, and 19.4% of subjects in the valdecoxib, naproxen, and placebo groups, respectively. Most of the GI events were considered to be treatment-related.

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Table S7. Treatment-Emergent Adverse Events by Body System Reported by ≥5% of Subjects – Safety Population

n (%)	Valdecoxib 10 mg QD (N=170)	Naproxen 500 mg BID (N=166)	Placebo (N=170)
All Causalities			
Body as a Whole – General Disorders	21 (12.4)	25 (15.1)	14 (8.2)
Central and Peripheral Nervous System Disorders	26 (15.3)	23 (13.9)	26 (15.3)
Gastrointestinal System Disorders	41 (24.1)	43 (25.9)	33 (19.4)
Respiratory System Disorders	22 (12.9)	26 (15.7)	22 (12.9)
Skin and Appendages Disorders	10 (5.9)	3 (1.8)	7 (4.1)
Treatment-Related			
Gastrointestinal System Disorders	30 (17.6)	24 (14.5)	22 (12.9)

An AE (at body system level), which occurs more than once in the same subject is only counted once in the row; however, if a given subject had AEs in 2 or more body systems, that subject contributes once for each different body system.

Most AEs were mild or moderate in severity. Dyspepsia was the most commonly reported treatment-related AE (8.8%, 6.0%, and 2.4% in the valdecoxib, naproxen, and placebo group, respectively). Other commonly reported treatment-related AEs were headache in 2.4%, 3.0%, and 4.1% and abdominal pain in 2.9%, 2.4%, and 3.5% of the subjects in the valdecoxib, naproxen, and placebo groups, respectively.

The most commonly reported non-treatment-related AEs in the valdecoxib, naproxen, and placebo groups included: headache in 12.4%, 10.8%, and 11.8%, respectively; dyspepsia 10.0%, 8.4%, and 2.9%, respectively; and upper respiratory tract infection in 4.7%, 6.6%, and 8.2%, respectively.

There were 170, 163, and 166 subjects evaluated for laboratory abnormalities in the valdecoxib, naproxen, and placebo groups, respectively. Of those subjects with normal screening values, 33.5%, 35.0%, and 30.7% subjects in the valdecoxib, naproxen, and placebo groups, respectively, had a laboratory abnormality at the end of treatment.

A total of 7 treatment-emergent serious adverse events (SAEs) were reported in this study – 1 in the valdecoxib group, 2 in the naproxen group, and 4 in the placebo group.

The SAE in the valdecoxib group was ‘arthritis rheumatoid aggravated’ reported in a 57-year-old female subject. This SAE was considered to be related to study treatment.

The SAEs in the naproxen group were ‘pneumonia’ reported in a 71-year-old male, with an unknown causality and ‘cerebrovascular disorder’ and ‘myocardial infarction’ reported in a 67-year-old female. These events were considered to be related to the subject’s history of high cholesterol and hypertension.

CLINICAL STUDY SYNOPSIS

The SAEs in the placebo group included a ‘myocardial infarction’ reported in a 69-year-old male, which was considered to be due to organic heart disease; impotence’ due to Peyronie’s disease and ‘micturition disorder’ due to a penile prosthesis placement reported in a 65-year-old male; ‘fracture accidental’ reported in a 74-year-old female due to a fall; and ‘cellulitis’ reported in a 75-year-old female due to another illness.

There was one death in this study. Subject 10191018, a 69-year-old male who was randomized to the placebo group, experienced a myocardial infarction on Day 8 of study treatment.

Conclusion(s):

- Valdecoxib 10 mg QD was superior to placebo in treating signs and symptoms of severe RA for 12 weeks
- A total of 58.8% of subjects in the valdecoxib group compared with 39.6% of subjects in the placebo group were ACR-20 responders at Week 12. This result was significantly different ($p < 0.001$)
- The number of ACR-20 responders was also significantly different between naproxen (60.8%) and placebo, but not between valdecoxib and naproxen ($p = 0.898$)
- The majority of secondary assessments showed that both valdecoxib and naproxen were efficacious for treatment of severe RA signs and symptoms relative to placebo, and valdecoxib was similar to naproxen

Valdecoxib 10 mg QD administered for 12 weeks to subjects with severe RA was safe and well-tolerated.

Based on a report dated: 13 December 2005