ARTHRITIS SAFETY TABLE 16: PATIENT LISTING OF SERIOUS ADVERSE EVENTS OF UNCERTAIN OR PROBABLE RELATION TO STUDY DRUG IN TRIAL 47(6mo) – OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

Study/Patient ID/Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity/ Relationship	DER Number
047/US0129-2724 NAP	65/F	69 77 80 80	79 (O) 79 (O) 80 (O) 80 (O)	Nausea† Vomiting† Gastroenteritis Renal Failure Acute	Mod/Probable Mod/Probable Severe/Probable Severe/Probable Severe/Probable Severe/Uncertain	000509-CL720 000517-CL629
047/US0217-0962 NAP	71/ M	19 19	21 19 (O)	Duodenal Ulcer Hemorrhagic Anemia†	Severe/Probable Severe/Probable	000103-CL895
047/US0228-0752 NAP	51/F	14 18	26 26	Melena† Abdominal Pain†	Severe/Probable Severe/Probable	000907-CL431
047/US0229-0583 V80	65/F	99	233	Hepatitis††	Severe/Probable	000302-CL527
047/US0010-1406 V40	52/ M	173	178	Bradycardia	Severe/Uncertain	000605-CL117
047/US0230-1142 V80	52/F	46	47	GI Hemorrhage†	Severe/Probable	000413-CL960
047/US0287-0368 NAP	77/ M	25	51	Duodenal Ulcer	Severe/Probable	991202-CL934
047/US0202-0301 NAP	67/F	184	ongoing	Bladder carcinoma	Severe/Uncertain	000524-CL032
047/US0304-2585 V80	73/ M	29 29 31	38 38 56	Esophagitis† Anemia† GI Hemorrhage†	Severe/Probable Severe/Uncertain Severe/Probable	000202-CL012
047/US0242-0331 V80	60/F	19	27	Edema peripheral†	Mod/Uncertain	991008-CL780
047/US0221-0650 NAP	41/ M	5 5 5 5 5	6 6 ongoing 6 6	Abdominal pain† Hematemesis† Hemoccult positivity† Nausea† Vomiting†	Severe/Uncertain Mod/Uncertain Mod/Uncertain Severe/Uncertain Severe/Uncertain	991118-CL150
047/US0229-0466 V40	63/F	37	37 (O)	Cerebrovascular disorder†	Severe/Uncertain	991108-CL425
047/US0227-1312 V40	56/F	73	75	Angina pectoris	Severe/Uncertain	000524-CL029
047/US0304-2656 NAP	82/F	14	48	Gastroesophageal Reflux	Mild/Probable	000225-CL384

†Patient prematurely withdrew due to this adverse event. Mod; moderate; NAP, naproxen sodium; V40, valdecoxib 40 mg total daily dose; V80, valdecoxib 80 mg total daily dose; O, ongoing (on date of last dose).

ARTHRITIS SAFETY TABLE 17: PATIENT LISTING: SERIOUS ADVERSE EVENTS IN TRIAL 62(6mo) - RHEUMATOID ARTHRITIS

Patient Number	Serious Adverse Event (Preferred Term)	Treatment	Caused Withdrawal	Relationship to Study Drug
Autonomic Nervous System Disorders				
PL0003-0750	Hypertension	Diclofenac 75 mg BID	Yes	Probable

Patient Number	Serious Adverse Event (Preferred Term)	Treatment	Caused Withdrawal	Relationship to Study Drug
GE0010-0508	Hypertension Aggravated	Diclofenac 75 mg BID	No	None
FR0008-0385	Hypertension Aggravated	Valdecoxib 20 mg QD	Yes	Probable
HU0003-0581	Hypertension Aggravated	Valdecoxib 40 mg QD	No	Uncertain
Body as a Whole				
GE0010-1138	Back Pain	Valdecoxib 20 mg QD	Yes	None
BE0004-0513	Back Pain	Diclofenac 75 mg BID	Yes	None
PL0005-0731	Injury Accidental	Valdecoxib 20 mg QD	No	None
GE0003-0461	Injury Accidental	Diclofenac 75 mg BID	No	None
CO0004-1819	Pain	Diclofenac 75 mg BID	Yes	None
CZ0003-0713	Previously Scheduled Surgery	Diclofenac 75 mg BID	No	None
FI0003-1212	Previously Scheduled Surgery	Diclofenac 75 mg BID	No	None
HU0004-1224	Respite Care	Diclofenac 75 mg BID	No	None
Central and Peripheral Nervous System Disorders				
HU0003-0581	Ataxia	Valdecoxib 40 mg QD	No	Uncertain
HU0003-0581	Dizziness	Valdecoxib 40 mg QD	No	Uncertain
CO0004-1819	Headache	Diclofenac 75 mg BID	Yes	None
HU0003-0581	Headache	Valdecoxib 40 mg QD	No	Uncertain
FR0004-0483	Neuralgia	Valdecoxib 40 mg QD	No	None
SZ0003-1375	Neuralgia	Diclofenac 75 mg BID	Yes	None
Collagen Disorders				
IT0001-0793	Arthritis Rheumatoid Aggravated	Valdecoxib 20 mg QD	No	None
NE0004-1146	Arthritis Rheumatoid Aggravated	Valdecoxib 40 mg QD	Yes	None
NE0004-1154	Arthritis Rheumatoid Aggravated	Valdecoxib 40 mg QD	Yes	None
PL0004-0724	Arthritis Rheumatoid Aggravated	Valdecoxib 40 mg QD	Yes	None
Female Disorders				
HU0004-0595	Breast Neoplasm Malignant Female	Valdecoxib 40 mg QD	Yes	None
UK0001-0050	Breast Neoplasm Malignant Female	Valdecoxib 20 mg QD	No	None
SK0004-0753	Menstrual Disorder	Diclofenac 75 mg BID	No	None
SK0004-0753	Uterine Fibroid	Diclofenac 75 mg BID	No	None
Endocrine Disorders				
DE0003-0362	Hyperparathyroidism	Valdecoxib 20 mg QD	No	None

Patient Number	Serious Adverse Event (Preferred Term)	Treatment	Caused Withdrawal	Relationship to Study Drug
HU0004-1222	Parathyroid Disorder	Valdecoxib 40 mg QD	No	None
Gastrointestinal System Disorders				
IS0001-0556	Abdominal Pain	Valdecoxib 40 mg QD	Yes	Probable
CO0004-1819	Abdominal Pain	Diclofenac 75 mg BID	No	None
DE0002-0889	Abdominal Pain	Diclofenac 75 mg BID	No	None
FR0002-0411	Abdominal Pain	Diclofenac 75 mg BID	No	None
PL0002-0744	Abdominal Pain	Diclofenac 75 mg BID	Yes	Probable
PL0003-0748	Abdominal Pain	Diclofenac 75 mg BID	No	Uncertain
CZ0004-0693	Colitis Ulcerative	Diclofenac 75 mg BID	Yes	None
CO0004-1819	Diarrhea	Diclofenac 75 mg BID	No	None
DE0002-0889	Diarrhea	Diclofenac 75 mg BID	No	None
PL0004-1256	Duodenal Ulcer	Valdecoxib 20 mg QD	Yes	Probable
CZ0004-0693	Duodenal Ulcer	Diclofenac 75 mg BID	Yes	Uncertain
PL0005-0687	Duodenal Ulcer	Diclofenac 75 mg BID	No	Probable
CO0004-1826	Esophagitis	Diclofenac 75 mg BID	Yes	Probable
PL0002-0744	Gastric Ulcer	Diclofenac 75 mg BID	Yes	Probable
PL0005-0686	Gastric Ulcer	Diclofenac 75 mg BID	No	Probable
PL0005-0732	Gastric Ulcer	Diclofenac 75 mg BID	No	Probable
CZ0005-0698	Gastric Ulcer Hemorrhagic	Diclofenac 75 mg BID	No	Probable
FR0008-0386	Gastritis	Valdecoxib 40 mg QD	Yes	Probable
GE0005-0459	Gastritis	Valdecoxib 20 mg QD	Yes	Probable
GE0005-0462	Gastritis	Valdecoxib 20 mg QD	Yes	Probable
HU0008-0594	Gastritis	Valdecoxib 40 mg QD	Yes	Probable
NO0003-1468	Gastritis	Diclofenac 75 mg BID	Yes	Probable
CO0004-1819	Gastroenteritis	Diclofenac 75 mg BID	No	None
CO0003-1836	Gastroenteritis	Diclofenac 75 mg BID	No	None
BE0005-0471	GI Hemorrhage	Valdecoxib 20 mg QD	Yes	Probable
PL0002-0744	GI Hemorrhage	Diclofenac 75 mg BID	Yes	Probable
FI0003-1184	Hematochezia	Diclofenac 75 mg BID	No	Probable

Patient Number	Serious Adverse Event (Preferred Term)	Treatment	Caused Withdrawal	Relationship to Study Drug
FI0003-1184	Hematochezia	Diclofenac 75 mg BID	Yes	Probable
IS0001-0556	Nausea	Valdecoxib 40 mg QD	Yes	Probable
CO0004-1819	Nausea	Diclofenac 75 mg BID	No	None
CO0004-1819	Vomiting	Diclofenac 75 mg BID	No	None
IS0001-0556	Vomiting	Valdecoxib 40 mg QD	Yes	Probable
NO0003-1468	Vomiting	Diclofenac 75 mg BID	Yes	Probable
Heart Rate and Rhythm Disorders				
FR0004-0426	Arrhythmia	Diclofenac 75 mg BID	Yes	Uncertain
CZ0005-0698	Tachycardia Supraventricular	Diclofenac 75 mg BID	No	None
Liver and Biliary System Disorders				
IS0001-0561	Cholecystitis	Valdecoxib 20 mg QD	No	None
IS0001-0561	Cholelithiasis	Valdecoxib 20 mg QD	No	None
CO0004-1819	SGOT Increased	Diclofenac 75 mg BID	No	Uncertain
CO0004-1819	SGPT Increased	Diclofenac 75 mg BID	No	Uncertain
Metabolic and Nutritional Disorders				
AU0003-0324	Dehydration	Valdecoxib 40 mg QD	Yes	Probable
Musculoskeletal System Disorders				
CO0004-1819	Arthrosis	Diclofenac 75 mg BID	Yes	None
SZ0004-1398	Arthrosis	Valdecoxib 20 mg QD	Yes	None
HU0005-0617	Fracture Accidental/ Accident Hospitalization	Valdecoxib 40 mg QD	No	None
HU0005-0617	Fracture Accidental/ Fixation of Clavicle and AC Joint	Valdecoxib 40 mg QD	No	None
PL0005-0731	Fracture Accidental/ Fracture of Right Elbow	Valdecoxib 20 mg QD	No	None
PL0005-0731	Fracture Accidental/ Fracture of Right Radius	Valdecoxib 20 mg QD	No	None
BR0001-1803	Synovitis	Diclofenac 75 mg BID	No	None
Myo-, Endo-, Pericardial and Valve Disorders				
PL0004-1257	Myocardial Infarction	Diclofenac 75 mg BID	Yes	None
NE0004-1147	Myocardial Infarction	Valdecoxib 40 mg QD	No	None
Neoplasm				
IT0001-0793	GI Neoplasm Malignant	Valdecoxib 20 mg QD	No	None
PL0001-0735	Neoplasm	Valdecoxib 40 mg QD	No	None
SA0005-0124	Pulmonary Carcinoma	Valdecoxib 20 mg QD	Yes	None
Platelet, Bleeding, and Clotting Disorders				

Patient Number	Serious Adverse Event (Preferred Term)	Treatment	Caused Withdrawal	Relationship to Study Drug
AU0002-0314	Embolism Pulmonary	Valdecoxib 20 mg QD	No	None
Red Blood Cell Disorders				
AU0002-0314	Pancytopenia	Valdecoxib 20 mg QD	No	None
Resistance Mechanism Disorders				
FI0003-1185	Infection	Valdecoxib 40 mg QD	No	None
PL0005-0727	Infection Bacterial	Valdecoxib 40 mg QD	Yes	None
AU0002-0314	Sepsis	Valdecoxib 20 mg QD	No	None
AU0013-0848	Infection soft tissue	Diclofenac 75 mg BID	No	None
Respiratory System Disorders				
PL0003-0750	Bronchitis	Diclofenac 75 mg BID	No	None
SA0005-0134	Bronchitis	Diclofenac 75 mg BID	No	None
GE0005-0462	Pneumonia	Valdecoxib 20 mg QD	No	None
IS0002-0548	Pneumonia	Valdecoxib 40 mg QD	Yes	None
NZ0006-0335	Pneumonia	Valdecoxib 40 mg QD	No	None
SA0002-0142	Pneumonia	Valdecoxib 40 mg QD	No	None
CO0004-1825	Pneumonia Lobar	Valdecoxib 40 mg QD	No	None
SA0002-0142	Pneumonitis	Valdecoxib 40 mg QD	Yes	None
DE0002-0889	Sinusitis	Diclofenac 75 mg BID	No	Uncertain
AU0003-0324	Upper Respiratory Tract Infection	Valdecoxib 40 mg QD	No	None
Skin and Appendages Disorders				
NO0004-1472	Skin Disorder	Valdecoxib 40 mg QD	No	None
Urinary System Disorders				
PL0001-0737	Hematuria	Valdecoxib 40 mg QD	Yes	None
PL0001-0737	Renal Calculus	Valdecoxib 40 mg QD	Yes	None
AU0002-0314	Renal Failure Acute	Valdecoxib 20 mg QD	No	None
PO0002-0799	Renal Pain	Diclofenac 75 mg BID	No	Uncertain
Vascular (Extracardiac) Disorders				
HU0004-0598	Cerebrovascular disorder	Diclofenac 75 mg BID	No	None
Vision Disorders				
BE0006-0466	Vision Abnormal	Diclofenac 75 mg BID	No	None
White Cell and RES Disorders				
IT0001-0793	Lymphoma-like Disorder	Valdecoxib 20 mg QD	No	None

Derived from Table T33, Appendix 3.4, and Appendix 3.7.2.

ARTHRITIS SAFETY TABLE 18: PATIENT LISTING: SERIOUS ADVERSE EVENTS IN DOUBLE-BLIND PORTION OF TRIAL 63 (6mo) - OSTEOARTHRITIS

Patient Number	Serious Adverse Event (Preferred Term)	32. TREATMENT GROUP	Caused Withdrawal	Relationship to Study Drug
Autonomic Nervous System Disorders				
3162	Encephalopathy Hypertensive	Valdecoxib 10 mg QD	No	None
3224	Vasospasm	Valdecoxib 20 mg QD	No	None
3690	Syncope	Diclofenac 75 mg BID	No	Uncertain
3966	Hypotension Postural	Diclofenac 75 mg BID	No	None
3966	Syncope	Diclofenac 75 mg BID	No	None
4024	Hypertension Aggravated	Valdecoxib 20 mg QD	No	Uncertain
4333	Hypertension	Valdecoxib 20 mg QD	Yes	Uncertain
Body as a Whole—General Disorders				
3009	Sudden Death	Diclofenac 75 mg BID	Yes	None
3182	Treatment Emergent Surgery	Diclofenac 75 mg BID	No	None
3242	Previously Scheduled Surgery	Valdecoxib 10 mg QD	No	None
3242	Previously Scheduled Surgery	Valdecoxib 10 mg QD	No	None
3371	Treatment Emergent Surgery	Valdecoxib 20 mg QD	No	None
3388	Treatment Emergent Surgery	Valdecoxib 10 mg QD	No	None
3437	Treatment Emergent Surgery	Valdecoxib 20 mg QD	No	None
3486	Treatment Emergent Surgery	Valdecoxib 20 mg QD	Yes	None
3520	Chest Pain Non-Cardiac	Valdecoxib 10 mg QD	No	None
3562	Injury-Accidental	Valdecoxib 10 mg QD	No	None
3676	Treatment Emergent Surgery	Diclofenac 75 mg BID	No	None
3685	Treatment Emergent Surgery	Valdecoxib 20 mg QD	No	None
3874	Cyst, NOS	Diclofenac 75 mg BID	No	None
3982	Treatment Emergent Surgery	Valdecoxib 20 mg QD	No	None
4008	Treatment Emergent Surgery	Diclofenac 75 mg BID	No	None
4028	Treatment Emergent Surgery	Valdecoxib 10 mg QD	Yes	None
4058	Injury-Accidental	Valdecoxib 10 mg QD	Yes	None
Cardiovascular Disorders, General				
3268	Cardiac Failure	Diclofenac 75 mg BID	Yes	Uncertain
3544	Unstable Angina	Diclofenac 75 mg BID	No	None
4274	Cardiac Failure	Diclofenac 75 mg BID	Yes	Uncertain
4448	Aneurysm	Valdecoxib 20 mg QD	Yes	None
Central and Peripheral Nervous System Disorders				
3085	Neuralgia	Valdecoxib 10 mg QD	No	None
Endocrine Disorders				
4033	Gynecomastia	Diclofenac 75 mg BID	No	None
Eye Disorders				
3504	Exophthalmos	Diclofenac 75 mg BID	No	None
4275	Hernia Congenital	Valdecoxib 10 mg QD	No	None
Gastrointestinal System Disorders				
3055	Melena	Valdecoxib 20 mg QD	Yes	Probable
3160	Abdominal Pain	Valdecoxib 20 mg QD	No	None
3340	Abdominal Pain	Diclofenac 75 mg BID	Yes	Probable
3370	Gastritis	Valdecoxib 20 mg QD	Yes	Probable
3370	Hematemesis	Valdecoxib 20 mg QD	Yes	Probable
3403	Gastric Ulcer Hemorrhagic	Valdecoxib 20 mg QD	No	Uncertain
3504	Hernia	Diclofenac 75 mg BID	No	None
3674	Duodenal Ulcer	Diclofenac 75 mg BID	No	Probable
3674	Gastric Ulcer	Diclofenac 75 mg BID	No	Probable
3674	Esophagitis	Diclofenac 75 mg BID	No	Probable

3702	Gastric Ulcer	Diclofenac 75 mg BID	Yes	Probable
3718	Diarrhea	Diclofenac 75 mg BID	No	Uncertain
3718	Gastric Ulcer	Diclofenac 75 mg BID	Yes	Probable
3950	Anal Fissure	Valdecoxib 20 mg QD	No	None
4278	Peritonitis	Valdecoxib 10 mg QD	Yes	None
4292	Abdominal Pain	Diclofenac 75 mg BID	No	Probable
4292	Gastric Ulcer	Diclofenac 75 mg BID	Yes	Probable
4296	Gastric Ulcer	Diclofenac 75 mg BID	Yes	Probable
4339	Gastric Ulcer Hemorrhage	Valdecoxib 20 mg QD	Yes	Probable
4346	Diarrhea	Diclofenac 75 mg BID	No	Probable
4346	Diarrhea	Diclofenac 75 mg BID	Yes	Probable
4449	Abdominal Pain	Valdecoxib 10 mg QD	Yes	Probable
4449	Abdominal Pain	Valdecoxib 10 mg QD	Yes	Probable
4449	Gastric Ulcer	Valdecoxib 10 mg QD	Yes	Probable
4456	Gastritis	Diclofenac 75 mg BID	Yes	Probable
4456	Gastritis	Diclofenac 75 mg BID	Yes	Probable
4456	Dyspepsia	Diclofenac 75 mg BID	Yes	Probable
4507	Abdominal Pain	Valdecoxib 20 mg QD	No	None
Heart Rate and Rhythm Disorders				
3707	Bradycardia	Diclofenac 75 mg BID	No	None
3707	Arrhythmia Ventricular	Diclofenac 75 mg BID	No	None
4274	Fibrillation Atrial	Diclofenac 75 mg BID	No	None
Metabolic and Nutritional Disorders				
3164	Diabetes Mellitus	Valdecoxib 20 mg QD	No	None
3690	Hypoglycemia	Diclofenac 75 mg BID	No	None
Musculo Skeletal System Disorders				
3088	Fracture Accidental	Diclofenac 75 mg BID	Yes	None
3475	Arthritis Aggravated	Valdecoxib 10 mg QD	Yes	None
3493	Arthrosis	Diclofenac 75 mg BID	No	None
3518	Fracture Accidental	Valdecoxib 20 mg QD	No	None
3529	Arthritis Aggravated	Valdecoxib 10 mg QD	No	None
3544	Tendon Disorder	Diclofenac 75 mg BID	No	
3557	Fracture Accidental	Diclofenac 75 mg BID	No	None
3946	Arthritis Aggravated	Valdecoxib 10 mg QD	Yes	None
4008	Fracture Accidental	Diclofenac 75 mg BID	No	None
4008	Tendon Disorder	Diclofenac 75 mg BID	No	None
4305	Arthritis	Valdecoxib 10 mg QD	No	None
Myo Endo Pericardial & Valve Disorders				
3158	Myocardial Infarction	Diclofenac 75 mg BID	Yes	None
3377	Myocardial Infarction	Diclofenac 75 mg BID	No	None
3398	Angina Pectoris	Valdecoxib 20 mg QD	Yes	None
4026	Myocardial Infarction	Diclofenac 75 mg BID	Yes	None
4274	Myocardial Infarction	Diclofenac 75 mg BID	No	None
Neoplasm				
3143	Breast Neoplasm Malignant Female	Valdecoxib 20 mg QD	No	None
3310	Neoplasm	Valdecoxib 10 mg QD	No	None
4278	Ovarian Cyst Malignant	Valdecoxib 10 mg QD	Yes	None
4306	Breast Neoplasm Malignant Female	Valdecoxib 10 mg QD	Yes	Uncertain
Psychiatric Disorders				
3966	Depression	Diclofenac 75 mg BID	No	None
Red Blood Cell Disorders				
3707	Anemia	Diclofenac 75 mg BID	No	None
Reproductive Disorders, Female				
3231	Vaginal Hemorrhage	Diclofenac 75 mg BID	No	None
3231	Endometrial Hyperplasia	Diclofenac 75 mg BID	No	None
Reproductive Disorders, Male				
4458	Prostatic Disorder	Valdecoxib 10 mg QD	No	None

Resistance Mechanism Disorders				
3388	Infection	Valdecoxib 10 mg QD	No	None
3442	Infection	Diclofenac 75 mg BID	Yes	None
Respiratory System Disorders				
3370	Pneumonia	Valdecoxib 20 mg QD	No	
3484	Bronchitis	Diclofenac 75 mg BID	No	None
3874	Laryngitis	Diclofenac 75 mg BID	No	None
4076	Dyspnea	Diclofenac 75 mg BID	No	Uncertain
Skin and Appendages Disorders				
3164	Nail Disorder	Valdecoxib 20 mg QD	No	None
3544	Inflammation	Diclofenac 75 mg BID	No	None
Urinary System Disorders				
3208	Urinary Incontinence	Valdecoxib 10 mg QD	No	None
4029	Hematuria	Diclofenac 75 mg BID	No	None
4029	Benign Prostatic Hyperplasia	Diclofenac 75 mg BID	No	None
Vascular Extracardiac Disorders				
3027	Cerebrovascular Disorder	Diclofenac 75 mg BID	Yes	None
3417	Cerebrovascular Disorder	Valdecoxib 20 mg QD	No	None
3417	Hematoma NOS	Valdecoxib 20 mg QD	No	None
3421	Cerebrovascular Disorder	Diclofenac 75 mg BID	No	None
3447	Peripheral Vascular Disease	Valdecoxib 20 mg QD	No	None
3539	Cerebrovascular Disorder	Valdecoxib 20 mg QD	Yes	None
3556	Cerebrovascular Disorder	Valdecoxib 10 mg QD	No	None
3678	Peripheral Ischemia	Valdecoxib 10 mg QD	No	None
4061	Claudication Intermittent	Valdecoxib 10 mg QD	No	None
Vision Disorders				
3495	Cataract	Valdecoxib 20 mg QD	No	None
3495	Lacrimal Duct Obstruction	Valdecoxib 20 mg QD	No	None
3716	Cataract	Valdecoxib 20 mg QD	No	None
3716	Cataract	Valdecoxib 20 mg QD	No	None
3793	Retinal Detachment	Valdecoxib 10 mg QD	No	Uncertain

II. OPEN DATABASE

ARTHRITIS SAFETY TABLE 19: OPEN DATABASE

		Valdecoxib Initial Dosage			
Trial No./Disease	Duration (weeks)	10 mg QD	20 mg QD	40 mg QD	40 mg BID
31-OA	48	X	X		
67-RA	64	X	X	X	
76-OA/RA	52				X

Trial 31 was a one-year study of patients without prior valdecoxib exposure. It began with a 10mg/d dosage, with an option to increasing to 20mg/d for inadequate response. Trials 67 and 76 were open extensions for up to 64 weeks for patients electing to enroll from Trials 60/61 and Trial 47, respectively. For Trial 67 patients were begun on 10mg/d, and for Trial 76, they were continued on the final dose from Trial 47. Trial 31 is complete, whereas a cutoff date of August 15, 2000 was used for the two ongoing trials, 67 and 76. For administrative reasons the open database was divided into an "extended cohort" which captured patients beginning valdecoxib before October 26, 1999, and a long-term open label database, capturing all others.

ARTHRITIS SAFETY TABLE 20: ADVERSE EVENTS (%) WITH INCIDENCE AT LEAST 3%

	Valdecoxib (10-80 mg TDD)	
Adverse Event	Long-Term Open Label Trials	Extended Exposure Cohort
No. treated	2867	157
Any event	73.8	86.0
Autonomic Nervous System Disorders		
Hypertension	3.6	9.6
Hypertension aggravated	2.1	4.5
Body as a Whole – General Disorders		
Allergy aggravated	0.7	3.2
Back pain	2.6	3.2
Edema peripheral	6.0	4.5
Fever	0.8	3.2
Influenza-like symptoms	3.9	6.4
Injury – accidental	7.1	10.8
Central and Peripheral Nervous System Disorders		
Dizziness	3.1	5.1
Headache	8.7	13.4
Gastrointestinal System Disorders		
Abdominal pain	6.3	7.0
Constipation	2.2	4.5
Diarrhea	7.1	9.6
Dyspepsia	7.8	13.4
Flatulence	2.8	5.7
Gastroesophageal reflux	1.7	3.2
Nausea	5.9	12.1
Musculoskeletal System Disorders		
Fracture accidental	1.3	3.2
Myalgia	3.9	4.5
Psychiatric Disorders		
Insomnia	2.2	3.8
Respiratory System Disorders		
Bronchitis	3.2	5.7
Coughing	2.8	7.0
Pharyngitis	2.3	4.5
Rhinitis	2.9	6.4
Sinusitis	6.7	8.9
Upper respiratory tract infection	12.7	18.5
Skin and Appendages Disorders		
Pruritus	1.4	3.2
Rash	3.3	3.2
Urinary System Disorders		
Urinary tract infection	3.1	3.2

The prevalence and incidence rate of adverse events in the long-term open label trials and extended exposure cohort were reviewed (data not shown), including a division into six time periods (1-45, 46-90, 91-180, 181-270, 271-360 days, and greater than 360 days. In general,

the prevalence and incidence rates for the most common adverse events were higher in early time intervals. At the time of the analysis, there were a total patient number in each time interval were 2867, 2580, 2288, 1651, 968, and 99, respectively. No unexpected patterns were observed.

ARTHRITIS SAFETY TABLE 21: Adverse Events Causing Withdrawal (%) per 100 Patient-Years with Rate ≥1% by Final Dose: Long-Term Open Label Trials

	Valdecoxib (by Final Dose Prior to Withdrawal)				
Adverse Event	10 mg	20 mg	40 mg	80 mg	Any Dose
No. treated	2044	1820	1268	394	1772
Patient-years	296.6	755.1	418.4	134.0	1606.2
Any event	24.6	14.4	11.7	17.9	15.9
Autonomic Nervous System Disorders					
Hypertension	1.3	0.4	0.0	0.7	0.5
Hypertension aggravated	0.3	0.3	0.0	1.5	0.4
Body as a Whole – General Disorders					
Edema peripheral	2.4	0.9	1.2	1.5	1.3
Fatigue	0.3	0.1	1.2	2.2	0.6
Central and Peripheral Nervous System Disorders					
Dizziness	1.3	0.4	0.5	0.7	0.6
Headache	2.7	0.1	0.5	0.7	0.7
Disorders – Female					
Breast pain female	1.3	0.0	0.0	0.0	0.2
Breast neoplasm malignant female	1.3	0.0	0.0	0.0	0.2
Vaginitis	1.3	0.0	0.0	0.0	0.2
Gastrointestinal System Disorders					
Abdominal fullness	0.7	0.3	0.0	1.5	0.4
Abdominal pain	2.0	1.3	1.2	2.2	1.5
Diarrea	1.0	1.1	0.0	1.5	0.8
Dyspepsia	3.7	0.7	1.0	0.0	1.2
Nausea	1.0	0.4	0.7	1.5	0.7
Skin and Appendages Disorders					
Pruritus	1.3	0.5	0.7	0.0	0.7
Rash	1.7	1.2	0.7	0.0	1.1
Urinary System Disorders					
Creatinine clearance decreased	0.0	0.0	0.0	2.2	0.2

The incidence rates of adverse events causing withdrawal was also analyzed by three 90-day intervals (1-90d, 91-180d, and 181-270d), and most events rates were less than 0.2% in all three intervals. Events with rates higher than 0.2% for these three 90-day intervals were:

ARTHRITIS SAFETY TABLE 22: INCIDENCE RATES BY TIME

Adverse Event	Incidence Rates		
	1-90d	91-180d	181-270d

edema peripheral	**0.4%**	**0.3%**	**0.2%**
headache and diarrhea	**0.3%**	**<0.1%**	**0.1%**
abdominal pain	**0.3%**	**0.3%**	**0.4%**
dyspepsia	**0.5%**	**0.3%**	**0.0%**
rash	**0.5%**	**0.1%**	**0.0%**

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ARTHRITIS SAFETY TABLE 23: SERIOUS ADVERSE EVENTS (NUMBERS)

Adverse Event	Valdecoxib (Final TDD Dose)			
	10 mg	20 mg	40 mg	80 mg
No. treated	2044	1820	1267	394
Event rate per 100 patient-years	10.8	12.4	10.3	7.5
Autonomic Nervous System Disorders				
Overall percentage	0.3	0.7	0.5	0.7
Hypertension aggravated			2/2	
Ileus		3/3		
Body as a Whole –General Disorders				
Overall percentage	2.0	5.0	3.3	0.7
Back pain	2/2	5/5	3/3	
Injury – accidental	1/1	3/4	1/1	
Pain			2/2	
Treatment emergent surgery	¼	27/27	5/6	
Cardiovascular Disorders, General				
Overall percentage	0.0	0.9	0.2	0.7
Cardiac failure		7/7		1/1
Central and Peripheral Nervous System Disorders				
Overall percentage	0.3	0.9	0.2	0.0
Convulsions		2/2		
Disorders, Female				
Overall percentage	0.9	0.4	1.0	0.0
Uterine disorder NOS	1/1	2/2	1/1	
Gastrointestinal System Disorders				
Overall percentage	1.7	2.4	1.0	2.2
Abdominal pain	1/1	2/2		1/1
Gastritis		3/3	1/1	
Intestinal obstruction		2/2		1/1
Heart Rate and Rhythm Disorders				
Overall percentage	0.7	0.8	1.0	0.0
Bradycardia		2/2	1/1	
Fibrillation atrial	1/1	2/2	2/2	
Tachycardia			2/2	
Liver and Biliary System Disorders				
Overall percentage	0.3	0.3	0.7	0.0
Cholelithiasis	1/1		2/2	
Metabolic and Nutritional Disorders				
Overall percentage	0.3	0.4	0.2	0.7
Dehydration		2/2		1/1
Musculoskeletal System Disorders				
Overall percentage	0.3	0.9	0.5	0.0
Tendon disorder		3/3		
Myo, Endo, Pericardial and Valve Disorders				
Overall percentage	1.3	0.8	1.0	0.7
Angina pectoris	1/1	3/4	¾	1/1
Coronary artery disorder	1/1		2/2	

Adverse Event	Valdecoxib (Final TDD Dose)			
	10 mg	20 mg	40 mg	80 mg
Mitral insufficiency			2/2	
Myocardial infarction	1/1	2/2		1/1
Myocardial ischemia	2/2			
Platelet, Bleeding, and Clotting Disorders				
Overall percentage	0.3	0.1	0.5	0.0
Embolism pulmonary	1/1		2/2	
Respiratory System Disorders				
Overall percentage	2.4	0.8	1.4	0.7
Dyspnea			¾	
Pneumonia	2/2	2/2	2/3	1/1
Pulmonary edema		2/2		
Urinary System Disorders				
Overall percentage	0.0	0.7	0.7	0.0
Cystitis		2/2		
Urinary incontinence		2/2	1/1	
Vascular (Extracardiac) Disorders				
Overall percentage	0.7	0.9	1.0	0.0
Cerebrovascular disorder	2/2	4/4	2/2	

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ARTHRITIS SAFETY TABLE 24: PATIENT LISTING OF SERIOUS ADVERSE EVENTS PROBABLY RELATED TO STUDY DRUG

Patient ID/ Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity/ Relationship	DER Number
00070025/V20	71/F	167	169	Bronchospasm	Severe/Uncertain	990820-CL707
00100003/V20	79/F	53	56	Cardiac failure†	Severe/Uncertain	990210-CL662
00120055/V10	69/F	54	56	GI hemorrhage†	Severe/Uncertain	990414-CL859
00140006/V20	57/ M	152 152 152 152	158 168 158 158	Anemia Diverticulosis† Doudenitis GI hemorrhage	Severe/Uncertain Severe/Uncertain Severe/Uncertain Severe/Uncertain	990628-CL798
00160029/V20	55/F	233	236 (O)	Gastric ulcer†	Severe/Probable	991011-CL160
00180038/V20	64/ M	211	233 (O)	Cardiac failure†	Severe/Uncertain	000317-CL536
00180039/V10	68/F	282	285	Emphysema	Severe/Uncertain	000421-CL204
00210024/V20	67/F	48	63	Creatine phosphokinase increased	Moderate/Probable	990413-CL152
00220014/V20	79/ M	137 137	137 (O) 137 (O)	Gastritis† Diverticulitis†	Severe/Uncertain Severe/Uncertain	990623-CL547
1406/V80	52/ M	195 197 173	195 198 178	Syncope† Syncope† Bradycardia	Severe/Uncertain Severe/Uncertain Severe/Uncertain	000620-CL679 000628-CL342 000605-CL117
01200602#/V20	70/F	128	146 (O)	Hepatic function abnormal†	Severe/Uncertain	000330-[illegible]
02670554/V80	77/ M	2	2	Chest pain	Severe/Probable	000609-CL444
0464/V80	58/ M	89	UNK	Gastric ulcer hemorrhagic†	Severe/Probable	000713-CL562
0554/V80	77/ M	2	2	Chest pain	Severe/Probable	000609-CL444
04020700/V40	69/ M	151	(O)	Hypertension aggravated	Severe/Probable	001012-CL313
05050859#/V40	63/ M	187	187 (O)	Embolism pulmonary†	Severe/Uncertain	000531-CL034
05051087/V40	73/F	65 71	83 71 (O)	Gastritis† Duodenal ulcer†	Mod/Uncertain Mod/Uncertain	000627-CL886
05280925/V20	56/ M	18 18	22 22	Angina pectoris Gastritis	Severe/Uncertain Severe/Uncertain	000207-CL259 000207-CL964
05751524/V40	72/F	65	65 (O)	Embolism pulmonary†	Severe/Uncertain	000620-CL656

†Patient prematurely withdrew due to this adverse event. #Patient in extended exposure cohort. Mod, moderate; V10, valdecoxib 10 mg total daily dose; V20, valdecoxib 20 mg total daily dose; V40, valdecoxib 40 mg total daily dose; V80, valdecoxib 80 mg total daily dose; O, ongoing (on date of last dose), UNK, unknown.
*Onset 3 days after final dose.

Six patients experienced serious adverse events that occurred ≥30 days after the last dose of valdecoxib in the long-term open label trials. Of these six patients, one reported a serious adverse event (carcinoma in a valdecoxib 20 mg/d patient) that was considered by the

Investigator to be of uncertain relationship to study drug; the other five were considered by the Investigator to be unrelated to study drug.

ANALGESIA CONTROL DATABASE-COMMENTARY

The following concerns are based on the Analgesic Safety Tables below. In most cases they are repeated in the findings of the arthritis database, and both are discussed in the general discussion in the Executive Summary regarding safety and risk/benefit.

Adverse Events in General: Data from the ——— studies show valdecoxib superior regarding selected narcotic AEs (dizziness, constipation, nausea, vomiting). The ——— show more hypotension, but these data are confounded by presence or absence of pain, and more urinary retention at 80mg/d. Less narcotic AEs (e.g. confusion) again are noted. Dysmenorrhea trials were unrevealing. The ——— trial showed more hypotension (confounded, as above) and more oliguria.

Adverse Events Causing Withdrawal: These data are non-revealing except, again, the increased BUN/creatinine, renal function signal with the ——— trial.

Serious Adverse Events: The ——— study shows numerically more hypotension, MI, renal function abnormality, and CVA, but all involve very small numbers of cases.

ADVERSE EVENTS

ANALGESIA SAFETY TABLE 1: Adverse Events with Incidence ≥3%: ———
(Trials 5, 14, 24, 35, 58, 59, 64, and 80)

		Valdecoxib						
Adverse Event	Pbo	1-10 mg	20 mg	40 mg	80-200 mg	Rof 50 mg	Oxy/APAP	Ibu 400 mg
No. treated	392	458	310	208	318	166	151	151
Any event	52.5	50.4	43.2	41.3	46.2	48.8	70.2	53.0
Central and Peripheral Nervous System Disorders								
Headache	19.9	10.3	11.3	15.4	16.4	12.0	14.6	10.6
Dizziness	6.4	6.8	6.5	4.3	4.4	7.2	35.1	7.3
Gastrointestinal System Disorders								
Alveolar osteitis	10.7	11.8	11.6	10.1	12.9	24.1	13.2	15.2
Nausea	19.6	16.2	9.4	10.1	16.7	16.9	33.1	16.6
Vomiting	9.2	6.8	4.8	4.8	7.2	8.4	22.5	8.6
Skin and Appendages								
Pruritus	1.3	0.7	1.9	1.9	0.6	1.2	1.3	3.3
Psychiatric Disorders								
Somnolence	2.3	2.6	2.6	4.8	2.2	0.0	11.3	2.0

All entries are percentages of patients except No. treated. Pbo, placebo; Rof, rofecoxib; Oxy/APAP, oxycodone 10 mg/acetaminophen 1000 mg; Ibu, ibuprofen.

ANALGESIA SAFETY TABLE 2: Adverse Events with Incidence≥3%· (Trials 10, 11, 32, 33, 37, 52, 72) (Note: Trial 32 was an trial was discontinued secondary to slow enrollment after 23 patients enlisted. It is a part of the safety review, but not of the efficacy review.)

		Valdecoxib					
Adverse Event	Placebo	10 mg	20 mg	40 mg	80 mg	Oxycodone 10 mg/ acetaminophen 1000 mg	NSAIDs
No. treated	378	59	257	330	55	250	203
Any event	51.3	67.8	47.5	47.9	40.0	77.6	55.7
Autonomic Nervous System Disorders							
Hypertension	1.6	0.0	1.2	1.8	0.0	0.8	3.4
Mouth dry	1.6	0.0	0.0	0.6	5.5	1.2	1.0
Body as a Whole – General Disorders							
Abnormal serous wound drainage	0.3	3.4	0.4	0.0	0.0	0.8	0.5
Back pain	0.3	0.0	1.2	0.9	0.0	1.2	3.0
Chest pain non-cardiac	0.0	3.4	0.4	0.6	0.0	0.0	0.5
Fever	5.6	8.5	3.1	3.0	0.0	6.4	9.4
Hot flushes	0.5	1.7	0.0	0.9	0.0	4.0	1.5
Central and Peripheral Nervous System Disorders							
Dizziness	3.4	6.8	2.7	3.9	1.8	10.8	3.9
Headache	5.3	6.8	6.6	5.2	3.6	7.6	4.9
Hypoesthesia	0.0	3.4	0.0	0.0	0.0	0.8	0.0
Gastrointestinal Disorders							
Abdominal pain	4.5	10.2	5.4	2.7	0.0	7.6	6.9
Constipation	4.0	8.5	2.7	5.8	0.0	10.4	4.9
Diarrhea	0.8	3.4	1.2	0.3	0.0	0.4	1.5
Dyspepsia	0.8	5.1	1.6	2.1	1.8	1.6	3.0
Flatulence	4.5	1.7	3.5	4.8	1.8	8.8	6.9
Nausea	21.2	23.7	16.3	15.2	16.4	28.4	19.7
Vomiting	10.1	8.5	8.9	6.1	3.6	16.4	6.4
Heart Rate and Rhythm Disorders							
Bradycardia	0.3	3.4	0.0	0.0	0.0	0.0	0.5
Musculoskeletal System Disorders							
Myalgia	0.5	1.7	0.8	0.3	3.6	0.4	1.0
Psychiatric Disorders							
Insomnia	2.1	3.4	1.9	3.0	0.0	2.8	5.4
Somnolence	2.9	10.2	2.3	3.3	1.8	14.4	7.4
Respiratory System Disorders							
Coughing	0.3	3.4	0.0	0.3	0.0	0.4	2.0
Tachypnea	0.8	6.8	1.9	0.0	0.0	0.4	2.0
Dyspnea	0.5	3.4	0.0	0.3	0.0	0.8	0.5
Skin and Appendages Disorders							
Pruritus	3.4	6.8	2.7	5.5	3.6	8.4	3.0

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ANALGESIA SAFETY TABLE 3: Adverse Events with Incidence≥3%
(Trials 38 and 51)

		Valdecoxib Total Daily Dose		P-value	
Adverse Event	Placebo	40 mg	80 mg	40 mg vs Placebo	80 mg vs Placebo
No. treated	141	143	142		
Any event	78.0	72.0	74.6	-	-
Autonomic Nervous System Disorders					
Hypotension	5.7	4.9	6.3	-	-
Body as a Whole – General Disorders					
Back pain	0.0	3.5	1.4		
Fever	29.1	7.7	3.5	<0.001	<0.001
Central and Peripheral Nervous System Disorders					
Headache	4.3	3.5	4.9	-	-
Dizziness	7.8	9.1	5.6	-	-
Gastrointestinal System Disorders					
Constipation	6.4	7.0	7.0	-	-
Nausea	36.9	37.8	47.2	-	-
Vomiting	20.6	28.0	19.7	-	-
Psychiatric Disorders					
Anorexia	1.4	3.5	0.7	-	-
Confusion	5.0	2.8	0.7	-	0.036
Insomnia	2.1	3.5	0.7	-	-
Somnolence	5.0	1.4	1.4	-	-
Red Blood Cell Disorders					
Anemia	5.0	6.3	7.7	-	-
Skin and Appendages Disorders					
Pruritus	5.0	11.2	9.9	-	-
Urinary System Disorders					
Oliguria	2.1	2.8	3.5	-	-
Urinary retention	1.4	3.5	6.3	-	-

All entries are percentages of patients except No. treated and p-values.

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ANALGESIA SAFETY TABLE 4: Adverse Events with Incidence≥3%: Primary Dysmenorrhea (Trials 65 and 66)

	Crossover Study Treatment Period			
		Valdecoxib		
Adverse Event	Placebo	20 mg BID PRN	40 mg BID PRN	Naproxen sodium 550 mg BID PRN
No. treated	196	194	189	191
Any event	21.4	18.6	21.2	14.1
Headache	15.3	10.8	7.9	7.3
Nausea	1.5	2.1	3.2	1.6

Derived from Table T14.2. Includes Studies 065 and 066. All entries are percentages of patients except No. treated.

ANALGESIA SAFETY TABLE 5: Adverse Events with at least 10% incidence or difference of p<0.05: g

Adverse Event	Placebo	Parecoxib Sodium/ Valdecoxib 40 mg q12h	P-value
No. treated	151	311	
ANY EVENT	89.4	89.1	-
Autonomic Nervous System Disorders			
Hypotension	6.0	12.5	0.034
Body as a Whole – General Disorders			
Edema peripheral	13.9	16.4	
Fatigue	20.5	18.3	
Fever	21.2	4.2	<0.001
Central and Peripheral Nervous System Disorders			
Dizziness	17.9	11.9	-
Gastrointestinal System Disorders			
Constipation	37.1	37.3	-
Nausea	38.4	44.0	-
Vomiting	11.3	13.8	-
Heart Rate and Rhythm Disorders			
Fibrillation atrial	19.9	15.8	
Tachycardia	14.6	7.1	0.017
Tachycardia supraventricular	0.0	3.2	0.035
Psychiatric Disorders			
Insomnia	15.2	19.0	-
Somnolence	12.6	11.6	-
Respiratory System Disorders			
Abnormal breath sounds	13.9	14.1	
Bronchospasm	6.6	1.9	0.014
Pleural effusion	17.2	7.4	0.002
Urinary System Disorders			
Oliguria	9.9	14.5	-

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ANALGESIA SAFETY TABLE 6: Analysis of Adverse Events with difference of P<0.05: (Trials 35, 58, 59, 5, 14, 35)

Adverse Event	Valdecoxib 20-40 mg	Oxycodone 10 mg/ acetaminophen 1000 mg	P-value	Valdecoxib 20-40 mg	Ibuprofen 400 mg	P-value
No. treated	303	151	-	203	151	-
Any event	39.6	70.2	<0.001	40.9	53.0	0.031
Dizziness	5.6	35.1	<0.001	4.9	7.3	-
Nausea	8.9	33.1	<0.001	12.3	16.6	-
Vomiting	5.0	22.5	<0.001	5.9	8.6	-
Somnolence	3.0	11.3	<0.001	2.0	2.0	-

Data are expressed in percentages of patients (except for p-values and No. treated), and include any events with a statistically significant difference ($p \leq 0.05$) between valdecoxib and the comparator.

ANALGESIA SAFETY TABLE 7: Adverse Events with a Difference of p<0.05: Pooled Valdecoxib (20-40 mg) vs Active Comparators: Trials 10, 11, 32, 33, 52, and 72)

Adverse Event	Valdecoxib 20-40 mg	Oxycodone 10 mg/ acetaminophen 1000 mg	P-value	Valdecoxib 20-40 mg	NSAIDs	P-value
No. treated	337	250	-	408	203	-
Any event	58.5	77.6	<0.001	50.7	55.7	-
Body as a Whole – General Disorders						
Edema peripheral	0.3	0.8	-	0.2	2.0	0.044
Fever	4.7	6.4	-	3.9	9.4	0.009
Hot flushes	0.6	4.0	0.006	0.5	1.5	-
Central and Peripheral Nervous System Disorders						
Dizziness	4.7	10.8	0.006	2.5	3.9	
Hypertonia	0.3	2.0	-	0.0	2.0	0.012
Gastrointestinal System Disorders						
Constipation	5.6	10.4	0.041	6.4	4.9	-
Nausea	17.5	28.4	0.002	14.2	19.7	-
Vomiting	8.3	16.4	0.004	7.6	6.4	-
Psychiatric Disorders						
Somnolence	3.3	14.4	<0.001	2.0	7.4	0.002
Respiratory System Disorders						
Coughing	0.3	0.4	-	0.2	2.0	0.044

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ADVERSE EVENTS CAUSING WITHDRAWAL

ANALGESIA SAFETY TABLE 7: Adverse Events Causing Withdrawal with Incidence ≥1% (Trials 10, 11, 32, 33, 37, 52, and 72)

		Valdecoxib					
Adverse Event	Placebo	10 mg	20 mg	40 mg	80 mg	Oxycodone 10 mg/ acetaminophen 1000 mg	NSAIDs
No. treated	378	59	257	330	55	250	203
Any event	3.2	6.8	5.1	2.4	0.0	8.8	5.9
Body as a Whole – General Disorders							
Chest pain non-cardiac	0.0	1.7	0.0	0.0	0.0	0.0	0.0
Fever	0.5	0.0	0.0	0.0	0.0	0.0	1.0
Central and Peripheral Nervous System Disorders							
Headache	1.3	1.7	1.2	0.3	0.0	1.2	1.0
Gastrointestinal System Disorders							
Abdominal pain	0.3	1.7	1.2	0.0	0.0	0.0	0.0
Nausea	0.5	0.0	0.0	0.3	0.0	0.4	1.0
Vomiting	0.8	1.7	2.3	0.9	0.0	3.6	1.0
Psychiatric Disorders							
Insomnia	0.0	0.0	0.0	0.0	0.0	0.0	1.0
Skin and Appendages Disorders							
Pruritus	0.0	0.0	0.0	0.0	0.0	1.2	0.0

All entries are percentages of patients except No. treated.

ANALGESIA SAFETY TABLE 8: Adverse Events Causing Withdrawal with Incidence ≥1%: (Trials 38 and 51)

		Valdecoxib Total Daily Dose		P-value	
Adverse Event	Placebo	40 mg	80 mg	40 mg vs Placebo	80 mg vs Placebo
No. treated	141	143	142	-	-
Any event	6.4	4.9	0.7	-	0.010
Nausea	0.7	1.4	0.0	-	-
Vomiting	1.4	0.7	0.0	-	-

All entries are percentages of patients except No. treated and p-values.

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ANALGESIA SAFETY TABLE 9: Adverse Events Causing Withdrawal with Incidence ≥1%:

Adverse Event	Placebo	Parecoxib Sodium / Valdecoxib 40 mg q12h
No. Treated	151	311
ANY EVENT	13.2	16.7
Autonomic Nervous System Disorders		
Hypotension	0.0	1.0
Central and Peripheral Nervous System Disorders		
Dizziness	1.3	0.6
Gastrointestinal System Disorders		
Nausea	2.0	2.6
Vomiting	2.0	1.6
Metabolic and Nutritional Disorders		
BUN increased	0.0	1.0
Creatinine increased	1.3	1.9
Myo-, Eno-, Pericardial and Valve Disorders		
Pericarditis	0.0	1.3
Respiratory System Disorders		
Pneumonia	1.3	0.0
Urinary System Disorders		
Renal function abnormal	0.7	1.3
Vascular (Extracardiac) Disorders		
Cerebrovascular disorder	0.7	1.0

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SERIOUS ADVERSE EVENTS

ANALGESIA SAFETY TABLE 10: Serious Adverse Events: ——— (Trials 10, 11, 32, 33, 37, 52, and 72)

		Valdecoxib TDD					
Adverse Event	Placebo	10 mg	20 mg	40 mg	80 mg	Oxycodone 10 mg/ acetaminophen 1000 mg	NSAIDs
No. treated	378	59	257	330	55	250	203
Overall percentage of any event	2.6	3.4	1.2	1.8	0.0	3.6	4.4
Any event	10/11	2/2	3/5	6/7	0	9/11	9/12
Ileus	2/2			1/1		2/2	
Infection	1/1		1/1			2/2	1/1
Hematoma NOS	1/1					2/2	
Treatment-emergent surgery						1/1	2/2

Entries represent patients with a serious adverse event / number of episodes unless otherwise indicated. Episodes can represent multiple serious adverse events or multiple occurrences of the same serious adverse event. Only non-zero values are shown except for percentages.

Serious Adverse Events: ——— trials: In the ——— trials (38 and 51), no one serious adverse event was reported by more than one patient – for patient listing, see below.

Serious Adverse Events: Primary dysmenorrhea (trials 65 and 66): One patient treated with naproxen sodium 550 mg experienced a serious adverse event of appendicitis which was considered by the Investigator to be unrelated to study drug. No other serious adverse events were reported in the primary dysmenorrhea trials.

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ANALGESIA SAFETY TABLE 11: Serious Adverse Events with Uncertain / Probable Relation to Study Medication (during or within 30 days post-treatment): Patient Listing

Study/Patient ID/Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity/ Relationship	DER Number
010/NZ0001-0096 Oxy/APAP	71/F	11	15	Thrombophlebitis	Severe/Uncertain	000208-CL457
010/NZ0001-0099 Ibuprofen 400 mg	51/F	24	29	Thrombophlebitis	Severe/Uncertain	000208-CL453
010/NZ0001-0279 Ibuprofen 400 mg	72/ M	1	5	Postoperative tissue swelling	Mod/Uncertain	990720-CL980
011/US0002-0105 Oxy/APAP	42/F	2	9	Ileus	Severe/Uncertain	991102-CL030
011/US0002-1010 Oxy/APAP	46/F	2	4	Ileus†	Severe/Uncertain	000119-CL708
011/US0002-1012 PBO	63/F	2	8	Ileus	Mod/Uncertain	000328-CL063
011/US0004-0184 Ibuprofen 400 mg	76/F	2 4	5 (O)	Cardiac failure Thrombophlebitis deep	Severe/Uncertain Severe /Uncertain	991207-CL131
038/US0004-0060 PBO	78/ M	9	10	Confusion	Mild/Uncertain	000616-CL925
038/US0004-0068 V40	59/F	2 2 2 2	4 2 2 4	Acidosis (metabolic)† Acidosis (respiratory)† Dyspnea† Renal Failure Acute†	Severe/Probable Severe/Uncertain Severe/Uncertain Severe/Probable	000908-CL943
038/US0007-0155 V40	75/F	2	5	GI hemorrhage	Mild/Uncertain	000522-CL609
051/FI0001-0330 PBO	59/F	7 7	17 17	Intestinal perforation Peritonitis	Severe/Uncertain Severe/Uncertain	000518-CL899
052/SP0004-0221 PBO	45/ M	1	2	Vomiting	Mod/Probable	000419-CL364

†Patient prematurely withdrew due to this adverse event. Mod; moderate;
Oxy/APAP, oxycodone 10 mg/acetaminophen 1000 mg; PBO, placebo; V40, valdecoxib 40 mg total daily dose.
(O) ongoing (on date of last dose).

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ANALGESIA SAFETY TABLE 12: Summary of Serious Adverse Events:

Adverse Event	Placebo	Parecoxib sodium/ Valdecoxib 40 mg q12h
No. treated	151	311
Overall percentage of any event	9.9	19.0
Any event	15/28	59/118
Autonomic Nervous System Disorders		
Overall percentage	0.0	1.3
Hypotension		2/2
Body as a Whole – General Disorders		
Overall percentage	0.0	6.4
Chest pain non-cardiac		2/2
Deep sternal wound infection		2/2
Sternal serous wound drainage ABN		2/2
Sternal wound dehiscence		3/3
Sternal wound infection		5/5
Superficial sternal wound infection		2/2
Wound infection – non-sternal		2/2
Cardiovascular Disorders, General		
Overall percentage	1.3	1.3
Cardiac failure	2/2	3/3
Gastrointestinal System Disorders		
Overall percentage	0.0	2.9
Duodenal ulcer perforated		2/2
GI hemorrhage		3/3
Vomiting		2/2
Heart Rate and Rhythm Disorders		
Overall percentage	2.6	1.3
Arrhythmia atrial	2/2	1/1
Fibrillation atrial	1/1	2/2
Metabolic and Nutritional Disorders		
Overall percentage	0.0	1.3
Creatinine increase		3/3
Musculoskeletal System Disorders		
Overall percentage	0.7	0.6
Sternal instability	1/1	2/2
Myo, Endo, Pericardial, and Valve Disorders		
Overall percentage	1.3	2.6
Myocardial infarction	1/1	5/5
Platelet, Bleeding, and Clotting Disorders		
Overall percentage	0.7	0.6
Embolism pulmonary		2/2
Red Blood Cell Disorders		
Overall percentage	0.0	0.6
Postoperative anemia		2/3
Resistance Mechanism Disorders		
Overall percentage	0.0	1.6
Infection bacterial		2/2
Sepsis		2/2
No. treated	151	311

Entries represent patients with a serious adverse event / number of episodes unless otherwise indicated. Episodes can represent multiple serious adverse events or multiple occurrences of the same serious adverse event. Only non-zero values are shown except for percentages.

Respiratory System Disorders		
Overall percentage	4.0	4.8
Hypoxia		2/2
Pleural effusion	1/1	7/7

Pneumonia	3/3	4/4
Urinary System Disorders		
Overall percentage Renal function abnormal	0.7	1.6 3/3
Vascular (Extracardiac) Disorders		
Overall percentage Cerebrovascular disorder Thrombophlebitis deep	0.7 1/2	3.9 9/10 3/3

Entries represent patients with a serious adverse event / number of episodes unless otherwise indicated. Episodes can represent multiple serious adverse events or multiple occurrences of the same serious adverse event. Only non-zero values are shown except for percentages.

ANALGESIA SAFETY TABLE 13: Serious Adverse Events Probably Related to Study Medication (during or within 30 days post-treatment) Ongoing Trials

Study/Patient ID/Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity/ Relationship	DER Number
062/CZ0004-0693	67/F	41	40 (O)	Duodenal ulcer	Mild/Uncertain	None
062/FI0003-1184	71/F	25 36	32 41	Hematochezia† Hematochezia	Mod/Probable Mod/Probable	None
062/FR0008-0385	73/ M	15	16	Hypertension†	Severe/Probable	000502-CL363
062/IS0001-0556	52/F	18 18	21 21	Nausea† Vomiting†	Severe/Probable Severe/Probable	000810-CL608
062/UK0006-0088	56/ M	2	6	Dyspepsia†	Mod/Uncertain	000705-CL764

†Patient prematurely withdrew due to this adverse event. (O), ongoing (on date of last dose); Mod; moderate.

IV. VITAL SIGNS

ARTHRITIS SAFETY VITAL SIGN TABLE 1: BLOOD PRESSURE

Trials 15, 16, 48, 49, 53, 60, 61	Val10-20/d	NSAIDs	placebo
N	2147	1233	1045
Change in SBP	0.2***	-0.3***	-1.8
Change in DBP	-0.2***	-0.5***	-1.4

Trials 60, 61 (all RA patients)	Val40/d	naproxen	placebo
N	413	421	412
Change in SBP	0.5***#	-1.1	-2.4
Change in DBP	0.0**#	-0.8	-1.2

Trial 47	Val20bid	Val40bid	naproxen
N	387	394	404
Change in SBP	-0.2	-0.7##	-1.4
Change in DBP	-0.6	0.1	-0.8

Trial 62	Val20/d	Val40/d	diclofenac
N	228	228	212

Change in SBP	**-0.6**	**1.1**	**0.0**
Change in DBP	**-1.1**	**1.1#**	**-0.7**
Trial 63	**Val10/d**	**Val20/d**	**diclofenac**

, **, **	**statistically significant at the p<0.05, <0.01, and 0.001 levels compared with placebo**
#, ##, ###	**statistically significant at the p<0.05, <0.01, and 0.001 levels compared with active comparator**

Comment: The interpretation BP data from all short-term analgesia trials is confounded by the effect of continued pain in some patients which will tend to increase BP, and the effect of [illegible] (as in Trials 35, 38 and 51) which will tend to lower BP, so analysis here is unlikely to be valid. Furthermore, all trials allowed instituting or changing BP regimens during the trial, which if not adjusted for will mitigate finding any differences across arms. Accordingly, analyses of BP changes in all the arthritis trials by the following subgroups were requested:

1. Patients on no BP or diuretic at outset and remained so throughout the trial.
2. Patients on BP/diuretic at outset with no change during the trial.
3. Patients newly started BP/diuretic or with change in regime during the trial.

The table shows a number of circumstances where the mean BP comparisons between arms reach statistical significance

All arthritis trial: Number of patients in three subgroups, according to BP regimens

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trial	no rx outset, during	stable rx	increase regimen
15	all val = 282 *d	all val = 179	all val = 11
	plc = 52 *d	plc = 25	plc = 2
	nsaid = 41	nsaid = 24	nsaid = 3
16	all val = 321	all val = 151	all val = 6
	plc = 61	plc = 23	plc = 0
	nsaid = 54	nsaid = 27	nsaid = 2
47	val 20mg = 260 *s	val 20mg = 92 *s	val 20mg = 38
	val 40mg = 247	val 40mg = 103	val 40mg = 45
	nap = 275 *s	nap = 101 *s	nap = 29
48	all val = 256	all val = 118	all val = 11
	plc = 120	plc = 58	plc = 3
	nsaid = 221	nsaid = 142	nsaid = 8
49	all val = 138 *s	all val = 70	all val = 5
	plc = 75	plc = 26	plc = 3
	nsaid = 68 *s	nsaid = 32	nsaid = 3
53	all val = 341	all val = 203 *d	all val = 20
	plc = 115	plc = 62 *d	plc = 8
	nsaid = 113	nsaid = 66	nsaid = 8
60	all val = 401 *s	all val = 181 *d	all val = 15
	plc = 138 *s	plc = 63 *d	plc = 3
	nsaid = 144	nsaid = 65	nsaid = 7
61	all val = 430 *s,d	all val = 171	all val = 19
	plc = 143 *s,d	plc = 63	plc = 2
	nsaid = 152	nsaid = 49	nsaid = 4
62	val 20mg = 167	val 20mg = 54	val 20mg = 7
	val 40mg = 181 *d	val 40mg = 34	val 40mg = 13
	dicl = 158 *d	dicl = 39	nap = 5
63 (wk 26)	val 20mg = 123	val 20mg = 82	val 20mg = 25
	val 40mg = 128	val 40mg = 78	val 40mg = 29
	dicl = 125	dicl = 69	dicl = 35

***s and *d: statistically significant less change in systolic or diastolic BP in the control, compared to the valdecoxib arm. Formal P value tests were not done on the number of patients in the "increase regimen" group and denominators are often not balanced at baseline.**

ARTHRITIS SAFETY VITAL SIGN TABLE 2: WEIGHT

Trials 15,16,48,49,53,60,61	Val10-20/d	NSAIDs	placebo
Change in weight – female	0.35	0.42	-0.04
Change in weight – male	0.41	0.55	-0.36
Trials 60, 61 (all RA patients)	Val40/d	naproxen	placebo
Change in weight - female	0.26	0.32	-0.34
Change in weight – male	0.22	0.96	-0.77
Trial 47	Val20bid	Val40bid	naproxen
Change in weight – all patients	0.53	0.54	0.60
Trial 62	Val20/d	Val40/d	diclofenac
Change in weight – all patients	0.31	0.43	0.37

All comparisons of valdecoxib or NSAID were statistically significant compared with placebo; none of the between drug comparisons were significant.

Comment: A similar phenomena could be occurring with these data if there were patients who have been having their diuretics changed amidst the trial.

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V. LABORATORY DATA

Methodology: Mid-Range and Extreme Value Limits for Evaluation of Clinical Laboratory Tests

ARTHRITIS SAFETY LABORATORY TABLE 1: NORMAL VALUES

Laboratory Test	Lower Extreme	Lower Mid-Range Limit	Higher Mid-Range Limit	Higher Extreme
		Hematology		
White blood cells (WBC)	2.0×10^9/L	4.0×10^9/L	12.0×10^9/L	20.0×10^9/L
Neutrophils	0.50×10^9/L	1.00×10^9/L	11.00×10^9/L	20.00×10^9/L
Lymphocyte count	0.50×10^9/L	1.00×10^9/L	6.00×10^9/L	20.00×10^9/L
Eosinophil count	N/A	0.00×10^9/L	0.70×10^9/L	0.99×10^9/L
Red blood cells (RBC)	3.0×10^{12}/L	4.0×10^{12}/L	6.3×10^{12}/L	7.5×10^{12}/L
Hemoglobin	6.0 g/dL or >3.0 g/dL decrease	10.0 g/dL	16.0 g/dL	18.0 g/dL
Hematocrit	0.25 or >0.10 decrease	0.30	0.50	0.60
Platelet count	25×10^9/L	100×10^9/L	450×10^9/L	600×10^9/L
		Coagulation		
Partial thromboplastin time (PTT)	N/A	N/A	40.0 sec	59.0 sec
Prothrombin time (PT)	N/A	N/A	18.0 sec	36.0 sec
		Clinical chemistry		
Bilirubin (total)	N/A	N/A	26 µmol/L	35 µmol/L
AST (SGOT)	N/A	N/A	75 U/L	200 U/L
ALT (SGPT)	N/A	N/A	75 U/L	200 U/L
Alkaline phosphatase	N/A	N/A	200 U/L	500 U/L
Gamma-glutamyl transpeptidase	N/A	N/A	75 U/L	200 U/L
Lactate dehydrogenase	N/A	N/A	N/A	350 U/L
Creatinine	N/A	N/A	177 µmol/L	265 µmol/L
BUN	N/A	N/A	9.3 mmol/L	14.3 mmol/L
Glucose	2.2 mmol/L	2.8 mmol/L	8.9 mmol/L	19.4 mmol/L
Uric acid	119 µmol/L	149 µmol/L	476 µmol/L	714 µmol/L
Creatine phosphokinase (CPK)	N/A	N/A	180 U/L	300 U/L
Sodium	120 mmol/L	135 mmol/L	145 mmol/L	160 mmol/L
Potassium	2.0 mmol/L	3.5 mmol/L	5.0 mmol/L	6.0 mmol/L
Chloride	75 mmol/L	90 mmol/L	110 mmol/L	130 mmol/L
Calcium	>15% below Baseline, or <1.70 mmol/L	2.0 mmol/L	2.74 mmol/L	3.74 mmol/L
Inorganic phosphorus	0.32 mmol/L	0.97 mmol/L	1.61 mmol/L	2.42 mmol/L
Bicarbonate	15 mmol/L	20 mmol/L	30 mmol/L	35 mmol/L
Cholesterol (total)	N/A	3.1 mmol/L	6.5 mmol/L	7.8 mmol/L
Triglycerides	N/A	0.1 mmol/L	2.8 mmol/L	5.7 mmol/L
Total protein	30 g/L	55 g/L	85 g/L	100 g/L
Albumin	20 g/L	30 g/L	60 g/L	75 g/L
Laboratory Test	Lower Extreme	Lower Mid-Range Limit	Higher Mid-Range Limit	Higher Extreme

Urinalysis				
Protein	N/A	N/A	Trace	1+ (300 mg/24h)
Blood	N/A	N/A	Trace	1+
Glucose	N/A	N/A	Trace	1+ (1 g/24h)
pH	N/A	4.0	8.0	8.5
Specific gravity	N/A	1.003	1.030	1.040
RBC	N/A	0/hpf	5/hpf	10/hpf
WBC	N/A	0/hpf	10/hpf	20/hpf
Ketones	N/A	N/A	Trace	1+
Urine bilirubin	N/A	N/A	Trace	1+

Methodology: Selected laboratory variables are summarized with FDA recommended contingency tables. Pairs of variables are cross-tabulated according to criteria calculated from on-treatment values as noted in the table below.

ARTHRITIS SAFETY LABORATORY TABLE 2: CONTINGENCY TABLE

Table Type	Variable 1 and Criteria	Variable 2 and Criteria
3 by 3	Hematocrit largest decrease <5%, 5-9.9%, ≥10%	Hemoglobin largest decrease <1g/dL, 1-2g/dL, >2g/dL
2 by 2	Maximum BUN <14.3 mmol/L, ≥ 14.3 mmol/L	Maximum creatinine <159 µmol/L, ≥159 µmol/L
2 by 3	Maximum total bilirubin <1.8 x ULN, ≥1.8 x ULN	Maximum alkaline phosphatase <1.2 x ULN, 1.2-3 x ULN, ≥3 x ULN
3 by 3	Maximum SGPT (ALT) <1.2 x ULN, 1.2-3x ULN, ≥3 x ULN	Maximum SGOT (AST) <1.2 x ULN, 1.2-3 x ULN, ≥ 3 x ULN

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ARTHRITIS SAFETY LABORATORY TABLE 3: Analysis of Mean Changes in Laboratory Values from Baseline to Final Visit between Valdecoxib and NSAIDs: Trials 15, 16, 48, 49, 53, 60, 61

	Mean Change from Baseline			Mean Change from Baseline		
Laboratory Test	Placebo	Valdecoxib 10-20 mg TDD	NSAIDs	Placebo	Valdecoxib 40 mg TDD	NSAIDs
Hemoglobin (g/dL)	-0.01	-0.13*#	-0.27	-0.01	-0.27*	-0.21
Hematocrit	-0.002	-0.005*#	-0.011	0.000	-0.007*	-0.005
RBC ($x10^{12}$/L)	0.02	-0.02*#	-0.08	0.01	-0.07*	-0.07
Platelet count ($x10^9$/L)	3.0	-6.3*#	1.3	0.1	-13.7*#	-5.0
PT (sec)	0.03	-0.09#	-0.02	0.13	-0.16*	-0.10
APTT (sec)	-0.05	-0.06#	-0.38	0.13	0.25	-0.25
Lymphocyte count ($x10^9$/L)	0.009	-0.046*	-0.026	-0.017	-0.048	-0.054
Eosinophil count ($x10^9$/L)	-0.003	0.004*#	0.034	-0.010	0.006*#	0.028
Basophil count ($x10^9$/L)	-0.001	-0.002#	0.000	-0.001	0.002	0.001
Total bilirubin (µmol/L)	-0.1	-0.1#	-0.4	-0.2	-0.7*	-0.8
Alkaline phosphatase (U/L)	1.1	-0.2*#	-1.4	1.9	1.6#	-0.8
AST (SGOT) (U/L)	-0.3	-0.1#	0.6	0.0	0.6	-0.4
ALT (SGPT) (U/L)	0.2	-0.2#	1.9	0.0	-0.5	-1.4
LDH (U/L)	-3.7	1.9*	4.8	-1.4	5.1*	6.1
Creatine kinase (U/L)	-2.9	1.4#	11.9	2.5	30.4*	13.4
Creatinine (µmol/L)	0.0	-0.6	0.2	0.0	1.2#	-0.8
BUN (mmol/L)	-0.23	0.42*#	0.63	-0.15	0.89*	0.86
Potassium (mmol/L)	-0.04	0.02*	0.02	-0.03	0.09*	0.07
Chloride (mmol/L)	0.4	0.6*#	0.9	0.4	1.3*	1.3
Bicarbonate (mmol/L)	-0.2	0.0#	-0.4	-0.3	-0.5	-0.5
Uric acid (µmol/L)	3.3	1.2#	-4.3	0.2	9.4*#	-7.1
Glucose (mmol/L)	0.21	0.08	0.05	0.10	-0.13*	-0.07
Total protein (g/L)	-0.4	-0.9*#	-1.4	-0.4	-1.0#	-1.8
Albumin (g/L)	-0.7	-0.6#	-0.1	-0.5	-0.4#	0.3
Calcium (mmol/L)	-0.005	-0.009#	-0.020	-0.014	-0.020	-0.021
Inorganic phosphorous (mmol/L)	-0.017	-0.002#	-0.050	-0.028	0.002#	-0.038
Urine specific gravity	0.0004	0.0005#	0.0012	0.0008	0.0006#	0.0016

Derived from Tables T24.1.1 and T24.1.2. Includes Studies 015, 016, 048, 049, 053, 060, and 061 (Studies 060 and 061 only for valdecoxib 40 mg TDD comparisons). Entries are mean changes from Baseline to final visit, and include all changes that were statistically significantly different ($p \leq 0.05$) between valdecoxib and placebo or NSAIDs.

*Statistically significantly different from placebo treatment group ($p \leq 0.05$).

#Statistically significantly different from NSAID treatment group ($p \leq 0.05$).

ARTHRITIS SAFETY LABORATORY TABLE 4: Analysis of Mean Changes in Laboratory Values from Baseline to Final Visit between Valdecoxib and NSAID: Trial 47

	Mean Change from Baseline		
Laboratory Test	Valdecoxib 40 mg TDD	Valdecoxib 80 mg TDD	NSAID
Hemoglobin (g/dL)	**-0.14**	**-0.25#**	**-0.07**
Hematocrit	**-0.006**	**-0.008#**	**-0.002**
RBC ($x10^{12}$/L)	**-0.07**	**-0.09#**	**-0.03**
PT (sec)	**-0.19**	**-0.25#**	**0.02**
Lymphocyte count ($x10^9$/L)	**-0.067#**	**-0.046#**	**0.005**
Eosinophil count ($x10^9$/L)	**-0.004#**	**0.032**	**0.027**
Creatine kinase (U/L)	**-4.0#**	**0.6#**	**16.8**
BUN (mmol/L)	**0.90**	**1.06#**	**0.70**
Potassium (mmol/L)	**0.03#**	**0.08#**	**0.00**
Uric acid (µmol/L)	**7.3**	**14.7#**	**1.9**
Albumin (g/L)	**-0.3#**	**-0.6#**	**0.3**
Inorganic phosphorus (mmol/L)	**0.025#**	**0.016#**	**-0.015**
Urine specific gravity	**0.0001#**	**-0.0001**	**0.0013**

Entries are mean changes from Baseline to final visit, and include all changes that were statistically significantly different ($p \leq 0.05$) between valdecoxib 20 mg BID and NSAIDs or between valdecoxib 40 mg BID and NSAIDs.

#Statistically significantly different from NSAID treatment group ($p \leq 0.05$).

ARTHRITIS SAFETY LABORATORY 5: Extreme Laboratory Values with Incidence of ≥1% in Any Treatment Group at the Final Visit: Trials 15, 16, 48, 49, 53, 60, 61

Lab Test and Extreme Criterion	Placebo	Valdecoxib TDD				NSAIDs
		1-5 mg	10 mg	20 mg	40 mg	
Creatine kinase > 300 U/L						
Final	**7/1080 (0.6)**	**18/783 (2.3)**	**14/1240 (1.1)**	**9/966 (0.9)**	**7/422 (1.7)**	**35/1289 (2.7)**
Urine RBC > 10/hpf						
Final	**29/911 (3.2)**	**10/321 (3.1)**	**26/941 (2.8)**	**27/816 (3.3)**	**11/416 (2.6)**	**42/1131 (3.7)**
Urine WBC > 20/hpf						
Final	**27/923 (2.9)**	**19/349 (5.4)**	**20/942 (2.1)**	**27/822 (3.3)**	**11/420 (2.6)**	**39/1133 (3.4)**
Urine protein above +						
Final	**6/1072 (0.6)**	**4/772 (0.5)**	**6/1234 (0.5)**	**5/964 (0.5)**	**8/422 (1.9)**	**9/1279 (0.7)**
Urine glucose above +						
Final	**9/1075 (0.8)**	**8/771 (1.0)**	**8/1232 (0.6)**	**8/967 (0.8)**	**9/421 (2.1)**	**11/1279 (0.9)**

Expressed as number of patients with extreme value/number of patients tested (%). Patients were not counted if they also had an extreme value at Baseline.

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ARTHRITIS SAFETY LABORATORY TABLE 6: Extreme Laboratory Values with Incidence ≥1% in Any Treatment Group at the Final Visit: Trial 47

Lab Test and Extreme Criterion	Valdecoxib		NSAID
	40 mg TDD	80 mg TDD	
Creatine kinase > 300 U/L			
Final	**6/388 (1.5)**	**8/392 (2.0)**	**13/398 (3.3)**
Urine glucose above +			
Final	**4/383 (1.0)**	**3/389 (0.8)**	**5/398 (1.3)**
Urine RBC > 10/hpf			
Final	**14/383 (3.7)**	**16/390 (4.1)**	**15/400 (3.8)**
Urine WBC > 20/hpf			
Final	**15/382 (3.9)**	**16/391 (4.1)**	**14/399 (3.5)**

Expressed as number of patients with extreme value/number of patients tested (%). Patients were not counted if they also had an extreme value at Baseline.

-ARTHRITIS SAFETY LABORATORY TABLE 7: Selected Laboratory Shift Results from Baseline to Final Visit: Trials 15, 16, 48, 49, 53, 60, 61

Laboratory Test at Final Visit	Placebo	Valdecoxib 10-20 mg TDD	NSAIDs
Hemoglobin			
Extreme low	**none**	**3/2118 from normal**	**4/1298 from normal**
Low	**1/1090 from normal**	**11/2118 from normal**	**5/1298 from normal**
Hematocrit			
Extreme low	**1/1087 from normal**	**1/2187 from normal** **1/18 from high** **1/6 from low**	**2/1298 from normal**
Low	**None**	**4/2187 from normal**	**2/1298 from normal**
RBC			
Extreme low	**None**	**none**	**1/1215 from normal**
Low	**29/1001 from normal**	**91/2060 from normal**	**98/1215 from normal**
WBC			
Extreme low	**None**	**none**	**none**
Low	**18/1026 from normal**	**23/2069 from normal**	**14/1221 from normal**
Platelet count			
Low	**none**	**3/2154 from normal**	**1/1261 from normal**
High	**9/1061 from normal**	**18/2154 from normal**	**11/1261 from normal**
Extreme high	**none**	**3/49 from high**	**1/1261 from normal** **3/23 from high**
Eosinophil count			
High	**3/1087 from normal**	**8/2209 from normal**	**9/1296 from normal**
Extreme high	**1/1 from high**	**1/2209 from normal**	**4/1296 from normal** **2/2 from high**
PT			
High	**none**	**none**	**none**
Extreme high	**1/1065 from high**	**none**	**1/1281 from high**
APTT			
High	**9/1052 from normal**	**26/2122 from normal**	**9/1259 from normal**
Extreme high	**1/1052 from normal**	**2/2122 from normal**	**2/1259 from normal**
Creatinine			
High	**1/1093 from normal**	**none**	**1/1301 from normal**
Extreme high	**1/1093 from normal**	**none**	**none**
BUN			
High	**11/1062 from normal**	**54/2156 from normal**	**45/1265 from normal**
Extreme high	**1/30 from high**	**4/2156 from normal** **4/67 from high**	**4/33 from high**
Uric acid			
High	**16/877 from normal**	**34/1661 from normal**	**18/1086 from normal**
Extreme high	**1/1877**	**none**	**none**
Total protein			
Extreme low	**none**	**none**	**none**
Low	**none**	**3/2205 from normal**	**none**
Albumin			
Extreme low	**none**	**none**	**none**
Low	**3/1089 from normal**	**11/2217 from normal**	**7/1290 from normal**

Laboratory Test at Final Visit	Placebo	Valdecoxib 10-20 mg TDD	NSAIDs
Sodium			
Extreme low	none	none	none
Low	11/1048 from normal	35/2129 from normal	18/1257 from normal
Potassium			
High	21/1042 from normal	63/2087 from normal	44/1226 from normal
Extreme high	1/1042 from normal 1/34 from high	2/2087 from normal 1/91 from high	1/1226 from normal none
Laboratory Test at Final Visit	Placebo	Valdecoxib 10-20 mg TDD	NSAIDs
Urine protein			
High	16/1035 from normal	26/2124 from normal	30/1236 from normal
Extreme high	5/1035 from normal 1/23 from high	10/2124 from normal 1/45 from high	7/1236 from normal 2/30 from high
Urine RBC			
High	14/849 from normal	29/1643 from normal	23/1068 from normal
Extreme high	27/849 from normal 2/25 from high	45/1643 from normal 8/57 from high	38/1068 from normal 4/28 from high
Creatine kinase			
High	41/992 from normal	64/2022 from normal	59/1166 from normal
Extreme high	3/995 from normal 4/68 from high	11/2022 from normal 12/151 from high	14/1166 from normal 21/103 from high
Glucose			
Low	none	none	none
High	29/1040 from normal	51/2118 from normal	31/1239 from normal
Extreme high	3/48 from high	5/97 from high	none
SGOT			
High	1/1089 from normal	5/2225 from normal	8/1301 from normal
Extreme High	1/1089 from normal	none	none
SGPT			
High	7/1091 from normal	8/2229 from normal	13/1296 from normal
Extreme High	none	1/2222 from normal 1/6 from high	5/1288 from normal

Normal indicates a wider range than standard normal ranges; see Table 4.a for ranges.

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ANALGESIA SAFETY LABORATORY TABLE 1: Mean Changes with a difference of $p<0.05$ in Laboratory Values - Baseline to Final Visit: Valdecoxib 20-40mg/d versus Placebo: (Trials 5, 14, 24, 35, 58, 59, 64, and 80)

	Mean Change from Baseline	
Laboratory Test	Placebo	Valdecoxib 20-40 mg
Hemoglobin (g/dL)	-0.07	-0.26
RBC ($x10^{12}$/L)	-0.02	-0.09
Platelet count ($x10^{9}$/L)	-4.4	-10.5
PT (sec)	0.21	0.08
PTT (sec)	-1.16	0.17
WBC ($x10^{9}$/L)	1.03	0.73
Lymphocyte count ($x10^{9}$/L)	-0.232	-0.308
Monocyte count ($x10^{9}$/L)	0.109	0.062
Creatinine (µmol/L)	-1.4	-3.5
BUN (mmol/L)	-1.34	-0.95
Chloride (mmol/L)	-0.8	0.3
Total protein (g/L)	-1.2	-2.9
Albumin (g/L)	-1.3	-2.6
Calcium (mmol/L)	-0.013	-0.047
Inorganic phosphorous (mmol/L)	-0.063	-0.110
Urine specific gravity	-0.0042	-0.0029
Urine pH	0.20	0.32

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ANALGESIA SAFETY LABORATORY TABLE 2: Mean Changes in Laboratory Values with a difference of p<0.05 of Valdecoxib 20-40mgd versus placebo or active control – Baseline to final visit: ——— Trials

	Mean Change from Baseline			Mean Change from Baseline		
Laboratory Test	Placebo	Valdecoxib 20-40 mg	Oxy/APAP	Placebo	Valdecoxib 20-40 mg	Ibuprofen 400 mg
Hemoglobin (g/dL)	0.07	-0.26*#	-0.08	-0.36	-0.56*	-0.48
Hematocrit	0.010	0.00*	0.003	-0.010	-0.011	-0.017
RBC ($x10^{12}$/L)	0.03#	-0.08*#	-0.03	-0.12	-0.19*	-0.18
Platelet count ($x10^9$/L)	-5.0	-9.8*	-8.2	-5.8	-13.7*	-10.2
PT (sec)	0.14	-0.01*#	0.15	0.31#	0.08*	0.17
APTT (sec)	0.07	-0.53*	-0.05	-0.09	-0.37	-0.37
WBC ($x10^9$/L)	1.12	0.76*	0.98	1.08	0.90	1.15
Lymphocyte count ($x10^9$/L)	-0.203	-0.282*	-0.244	-0.177#	-0.352*	-0.270
Monocyte count ($x10^9$/L)	0.115	0.072*	0.099	0.125	0.083*	0.088
Eosinophil count ($x10^9$/L)	-0.027	0.000*	-0.019	-0.032	-0.011	-0.016
Basophil count ($x10^9$/L)	0.003#	-0.004*	-0.005	-0.001	-0.004	0.001
Creatinine (µmol/L)	-0.4	-3.1*#	0.2	-2.0	-2.6	-2.0
BUN (mmol/L)	-1.29	-0.86*#	-1.29	-1.42	-0.96*#	-1.11
Sodium (mmol/L)	-0.2	0.4*	0.3	-0.1	0.0	-0.2
Chloride (mmol/L)	-0.8	0.6*#	-0.5	-0.8	0.1	-0.4
Glucose (mmol/L)	0.35	0.28	0.26	0.30#	0.21#	0.74
Total protein (g/L)	-1.2	-3.2*#	-1.9	-1.7#	-3.6*#	-2.7
Albumin (g/L)	-1.4	-2.8*#	-1.9	-1.4#	-2.9*	-2.5
Calcium (mmol/L)	-0.020	-0.055*#	-0.030	-0.028#	-0.064*	-0.050
Inorganic phosphorous (mmol/L)	-0.045	-0.108*	-0.097	-0.040	-0.079	-0.065
Urine specific gravity	-0.0042	-0.0021*	-0.0028	-0.0047	-0.0048	-0.0057

Trials 35, 58, and 59 for comparison versus oxycodone 10 mg/acetaminophen 1000 mg and 5, 14, and 35 for comparison versus ibuprofen 400 mg. *Statistically significantly different from placebo treatment group (p≤0.05). #Statistically significantly different from active comparator (oxycodone 10 mg/acetaminophen 1000 mg or ibuprofen 400 mg) treatment group (p≤0.05).

ANALGESIA SAFETY LABORATORY TABLE 3: Mean Changes with a Difference of p<0.05 of valdecoxib 20-40mg/d vs placebo or active control: Laboratory Values - Baseline to Final Visit: ——— Trials

	Mean Change from Baseline			Mean Change from Baseline		
Laboratory Test	Placebo	Valdecoxib 20-40 mg	Oxy/ APAP	Placebo	Valdecoxib 20-40 mg	NSAIDs
Hemoglobin (g/dL)	-0.03	-0.14	-0.03	-0.10	-0.31*	-0.18
Hematocrit	0.000	-0.004	-0.001	-0.002	-0.010*	-0.006
RBC ($x10^{12}$/L)	-0.03	-0.05	-0.02	-0.04	-0.11*	-0.07
Platelet count ($x10^9$/L)	0.3	0.5	5.8	1.0	-3.1#	3.3
PT (sec)	-0.14	-0.27#	-0.04	-0.13	-0.23	-0.18
WBC count ($x10^9$/L)	0.36	-0.84*#	0.03	0.47	-0.50*	-0.22*

Neutrophil count ($x10^9$/L)	0.355	-0.875*#	-0.105*	0.502	-0.478*	-0.236*
Monocyte count ($x10^9$/L)	0.044	-0.032*#	0.020	0.001	-0.029	-0.030
Eosinophil count ($x10^9$/L)	0.031	0.060*	0.046	0.032	0.043	0.035
Total bilirubin (µmol/L)	0.1	-0.8*	-0.9*	0.2	-0.4	-0.6*
AST (SGOT) (U/L)	1.3	0.6#	2.2*	0.4	-0.4	-1.7
ALT (SGPT) (U/L)	0.5	-0.1#	1.4*	-0.2	-0.8*	-1.2
BUN (mmol/L)	-0.28	0.25*#	-0.20	-0.28	0.13*	-0.06*
Sodium (mmol/L)	0.0	1.0*#	0.3	0.1	0.9*	0.8
Potassium (mmol/L)	-0.16	-0.11*	-0.14	-0.14	-0.12	-0.05*
Chloride (mmol/L)	-0.8	0.4*#	-0.5	-0.6	0.7*#	0.4*
Total protein (g/L)	1.5	1.9	2.2*	0.8	0.2#	1.0
Albumin (g/L)	-0.1	-0.1	0.0	-0.4	-0.9#	-0.4
Inorganic phosphorus (mmol/L)	-0.058	-0.024	-0.009*	-0.066	-0.036*	-0.051

Trials 10, 11, 32, 33, and 72 for comparison of valdecoxib versus oxycodone 10 mg/acetaminophen 1000 mg and Studies 10, 11, 32, 33, and 52 for comparison of valdecoxib versus NSAIDs.
*Statistically significantly different from placebo treatment group ($p \leq 0.05$).
#Statistically significantly different from active comparator (oxycodone 10 mg/acetaminophen 1000 mg or NSAIDs) treatment group ($p \leq 0.05$).

(Comparison of valdecoxib 20-40 mg versus placebo with all (Trials 10, 11, 32, 33, 37, 52, and 72), showed similar results.)

ANALGESIA DAFETY LABORATORY TABLE 4: Mean Changes with a difference to $p<0.05$ in Laboratory Values Valdecoxib 40mg/d and 80mg/d and Placebo – Baseline to final visit: Trials 38 and 51)

	Mean Change from Baseline		
Laboratory Test	Placebo	Valdecoxib 40 mg TDD	Valdecoxib 80 mg TDD
Hemoglobin (g/dL)	-2.01	-2.14	-2.15*
Hematocrit	-0.061	-0.060	-0.064*
WBC count ($x10^9$/L)	3.09	1.03*	1.01*
Neutrophil count ($x10^9$/L)	3.278	1.354*	1.386*
Lymphocyte count ($x10^9$/L)	-0.414	-0.544*	-0.559*
Monocyte count ($x10^9$/L)	0.207	0.114*	0.084*
Eosinophil count ($x10^9$/L)	-0.025	0.091*	0.080*
Total bilirubin (µmol/L)	4.0	1.0*	1.8*
Creatinine (µmol/L)	-6.5	-4.6	-1.0*
Sodium (mmol/L)	-4.8	-1.8*	-1.4*
Potassium (mmol/L)	-0.31	-0.18*	-0.16*
Chloride (mmol/L)	-4.2	-0.5*	0.0*
Glucose (mmol/L)	1.80	1.51	0.87*
Total protein (g/L)	-8.8	-10.7*	-9.7*
Albumin (g/L)	-7.3	-8.3*	-7.7*
Inorganic phosphorus (mmol/L)	-0.394	-0.351	-0.308*

*Statistically significantly different from placebo, $p \leq 0.05$.

(Primary Dysmenorrhea Trials- Mean changes in laboratory values were not calculated due to the crossover nature of the study design.)

ANALGESIA SAFETY LABORATORY TABLE 5: Mean Changes in Laboratory Values from Screening to the End
Placebo· Other timepoints for analysis could be period presented here.

	Mean Change from Screening		
Laboratory Test	Placebo	Parecoxib sodium/ Valdecoxib 40 mg q12h	p-value
Hemoglobin (g/dL)	-2.43	-2.85	<0.001
Hematocrit	-0.058	-0.074	<0.001
Platelet count ($x10^9$/L)	280.1	235.3	0.003
AST (SGOT) (U/L)	-2.3	-4.2	0.018
Creatinine (µmol/L)	5.5	13.1	0.035
BUN (µmol/L)	0.67	1.85	0.001
Sodium (mmol/L)	-1.1	-0.3	0.028
Potassium (mmol/L)	0.37	0.53	0.009
Chloride (mmol/L)	-1.9	0.0	<0.001
Bicarbonate (mmol/L)	0.6	-0.2	0.026
Total protein (g/L)	0.6	-1.2	<0.001
Calcium (mmol/L)	0.041	0.011	0.016

Entries are mean changes from Baseline to final visit, and include all changes that were statistically significantly different ($p \leq 0.05$) between parecoxib/valdecoxib 40 mg q12h and placebo.

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ANALGESIA SAFETY LABORATORY TABLE 6: Extreme Laboratory Values with Incidence ≥1%: Trials

Lab Test and Extreme Criterion	Placebo	Valdecoxib (Total Daily Dose)				Oxy/APAP	NSAID
		1-10 mg	20 mg	40 mg	80-200 mg		
Uric acid <119 µmol/L							
Final	1/103 (1.0)	0/0	1/101 (1.0)	1/100 (1.0)	0/0	2/101 (2.0)	0/0
Calcium <1.70mmol or >15% decrease from Baseline							
Final	0/311	0/456	0/310	1/208 (0.5)	0/158	0/150	2/150 (1.3)
Total bilirubin >35 µmol/L							
Final	0/311	5/454 (1.1)	1/309 (0.3)	0/208	0/158	0/150	2/150 (1.3)
Creatine kinase >300 U/L							
Final	6/310 (1.9)	5/454 (1.1)	1/309 (0.3)	3/207 (1.4)	1/158 (0.6)	1/150 (0.7)	2/150 (1.3)
Urine RBC above 10/hpf							
Final	6/160 (3.8)	0/55	3/158 (1.9)	2/156 (1.3)	3/57 (5.3)	3/101 (3.0)	0/0
Urine WBC above 20/hpf							
Final	1/159 (0.6)	0/55	2/157 (1.3)	1/157 (0.6)	0/57	1/101 (1.0)	0/0
Urine blood above +							
Final	5/148 (3.4)	17/398 (4.3)	5/150 (3.3)	2/50 (4.0)	3/101 (3.0)	4/49 (8.2)	12/147 (8.2)

Trials 5, 14, 24, 35, 58, and 59. No clinical laboratory determinations were done in Studies 064 and 080. oxy/APAP, oxycodone 10 mg/acetaminophen 1000 mg; NSAID, ibuprofen 400 mg Expressed as number of patients with extreme value/number of patients tested (%).

No statistically significant differences were observed between valdecoxib 20-40 mg and placebo or any active comparator.

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ANALGESIA SAFETY LABORATORY TABLE 7: Extreme Laboratory Values with Incidence ≥1% at Final Visit: ← Trials

Lab Test and Extreme Criterion	Placebo	Valdecoxib				Active Comparator	
		10 mg	20 mg	40 mg	80 mg	Oxy/APAP	NSAIDs
Hematocrit <0.25 or >0.10 decrease from Baseline							
Final	2/285 (0.7)	2/52 (3.8)	2/203 (1.0)	2/271 (0.7)	0/52 (0.0)	2/209 (1.0)	2/162 (1.2)
RBC <3.0x10^{12}/L							
Final	3/306 (1.0)	2/52 (3.8)	1/220 (0.5)	4/298 (1.3)	0/54 (0.0)	2/219 (0.9)	3/181 (1.7)
Calcium <1.70 mmol/L or 15% decrease from Baseline							
Final	2/317 (0.6)	0/55 (0.0)	0/241 (0.0)	1/313 (0.3)	0/54 (0.0)	0/236 (0.0)	2/190 (1.1)
Total bilirubin >35 μmol/L							
Final	1/314 (0.3)	1/53 (1.9)	0/236 (0.0)	1/314 (0.3)	0/54 (0.0)	0/230 (0.0)	0/185 (0.0)
Creatine kinase > 300 U/L							
Final	31/276 (11.2)	3/37 (8.1)	20/205 (9.8)	29/274 (10.6)	8/52 (15.4)	26/193 (13.5)	6/156 (3.8)
Urine protein above +							
Final	1/303 (0.3)	2/52 (3.8)	2/225 (0.9)	3/295 (1.0)	0/53 (0.0)	1/220 (0.5)	1/173 (0.6)
Urine glucose above +							
Final	1/303 (0.3)	0/53 (0.0)	1/226 (0.4)	3/292 (1.0)	0/53 (0.0)	2/220 (0.9)	2/174 (1.1)
Urine ketones +							
Final	5/301 (1.7)	0/47 (0.0)	6/222 (2.7)	8/294 (2.7)	1/53 (1.9)	6/218 (2.8)	4/166 (2.4)
Urine RBC > 10/hpf							
Final	18/280 (6.4)	7/47 (14.9)	12/215 (5.6)	26/279 (9.3)	3/53 (5.7)	19/194 (9.8)	9/153 (5.9)
Urine WBC > 20/hpf							
Final	8/301 (2.6)	1/52 (1.9)	8/226 (3.5)	11/294 (3.7)	2/53 (3.8)	4/220 (1.8)	5/174 (2.9)

Trials 10, 11, 32, 33, 37, 52, and 72. Expressed as number of patients with extreme value/number of patients tested (%). Patients were not counted if they also had an extreme value at Baseline. Oxy/APAP, oxycodone 10 mg/acetaminophen 1000 mg.

One statistically significant difference was observed in the above table -- a statistically significantly higher proportion of the valdecoxib 20-40 mg group had extremely high creatine kinase (9.8%, 30/306) compared to the NSAID group (3.8%, 6/156) at the final visit. (check w/ sponsor – numbers don't match********)

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ANALGESIA SAFETY LABORATORY TABLE 8: Extreme Laboratory Values with Incidence ≥1% in Any Treatment Group at the Final Visit: (Trials 38 and 51)

Lab Test and Extreme Criterion	Placebo	Valdecoxib (Total Daily Dose) 40 mg	80 mg
Hemoglobin <6.0 g/dL or >3.0 g/dL decrease from Baseline			
Final	24/125 (19.2)	39/131 (29.8)	34/130 (26.2)
Hematocrit <0.25 or >0.10 decrease from Baseline			
Final	16/119 (13.4)	20/120 (16.7)	32/123 (26.0)
RBC >3.0 x 10^{12}/L			
Final	17/125 (13.6)	15/131 (11.5)	26/128 (20.3)
PT ratio <0.50			
Final	0/46	1/47 (2.1)	1/46 (2.2)
Lymphocyte count <0.50 x 10^{9}/L			
Final	2/123 (1.6)	3/129 (2.3)	0/128
Calcium <1.70 mmol/L or 15% decrease from Baseline			
Final	22/128 (17.2)	25/137 (18.2)	23/136 (16.9)
Total bilirubin >35 µmol/L			
Final	1/128 (0.8)	2/136 (1.5)	1/136 (0.7)
Creatine kinase >300 U/L			
Final	27/125 (21.6)	30/132 (22.7)	39/133 (29.3)
Urine protein above +			
Final	6/108 (5.6)	0/112	1/116 (0.9)
Urine glucose above +			
Final	3/108 (2.8)	2/112 (1.8)	4/116 (3.4)
Urine ketones above +			
Final	2/107 (1.9)	1/112 (0.9)	2/116 (1.7)
Urine RBC > 10/hpf			
Final	23/106 (21.7)	16/109 (14.7)	19/113 (16.8)
Urine WBC > 20/hpf			
Final	4/106 (3.8)	7/111 (6.3)	6/116 (5.2)

Expressed as number of patients with extreme value/number of patients tested (%). Patients were not counted if they also had an extreme value at Baseline.

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A statistically significant difference in the proportion of patients with extreme laboratory values was observed between the valdecoxib 80 mg TDD and placebo treatment groups for hematocrit. The proportions of patients with extreme laboratory values were higher in the valdecoxib 80 mg/d treatment group. A statistically significant differences in the proportion of patients with extreme laboratory values was observed between the valdecoxib 40 mg/d and placebo treatment groups for urine protein, with a higher proportion of patients with extreme urine protein reported in the placebo treatment group.

ANALGESIA SAFETY LABORATORY TABLE 9: Extreme Laboratory Values with Incidence ≥1%:

Lab Test and Extreme Criterion	Placebo	Parecoxib Sodium/Valdecoxib 40 mg q 12h
Hemoglobin <6.0 g/dL or >3.0 g/dL decrease from post-surgery Baseline		
Final	4/138 (2.9)	4/283 (1.4)
Hematocrit <0.25 or >0.10 decrease from post-surgery Baseline		
Final	5/129 (3.9)	6/272 (2.2)
Platelet count >600 x 10^9/L		
Final	15/130(11.5)	27/264 (10.2)
Lymphocyte count <0.50 x 10^9/L		
Final	0/136	3/283 (1.1)
WBC >20.0 x 10^9/L		
Final	1/138 (0.7)	3/283 (1.1)
Eosinophil count >0.99 x 10^9/L		
Final	3/136 (2.2)	1/283 (0.4)
Creatine kinase >300 U/L		
Final	2/128 (1.6)	9/261 (3.4)
BUN >14.3 mmol/L		
Final	5/145 (3.4)	15/298 (5.0)
Potassium >6.0 mmol/L		
Final	0/143	3/285 (1.1)
Urine specific gravity >1.040		
Final	1/138 (0.7)	3/284 (1.1)
Urine protein above +		
Final	6/138 (4.3)	5/285 (1.8)
Urine glucose above +		
Final	3/138 (2.2)	1/283 (0.4)
Urine blood above +		
Final	9/137 (6.6)	15/285 (5.3)

Expressed as number of patients with extreme value/number of patients tested (%). Patients were not counted if they also had an extreme value at Baseline.

No statistically significant differences in the proportion of patients with extreme laboratory values were observed between the parecoxib/valdecoxib 40 mg q 12h and placebo treatment groups for any laboratory value.

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ANALGESIA SAFETY LABORATORY TABLE 10: Extreme Laboratory Values with Incidence ≥1%: Primary Dysmenorrhea Trials

Lab Test and Extreme Criterion	Placebo	Valdecoxib		Naproxen sodium 550 mg BID PRN
		20 mg BID PRN	40 mg BID PRN	
Calcium <1.70 mmol/L or >15% decrease from Baseline				
Final	0/32	0/37	0/38	1/37 (2.7)
Creatine kinase >300 U/L				
Final	0/32	2/37 (5.4)	0/38	0/37
Urine specific gravity > 1.040				
Final	1/32 (3.1)	0/38	0/39	0/38
Urine ketones above +				
Final	1/32 (3.1)	1/38 (2.6)	0/38	0/37
Urine RBC > 10/hpf				
Final	1/32 (3.1)	3/38 (7.9)	1/39 (2.6)	1/38 (2.6)
Urine WBC > 20/hpf				
Final	0/32	2/38 (5.3)	0/39	2/38 (5.3)

Trials 65 and 66. Expressed as number of patients with extreme value/number of patients tested (%). Patients were not counted if they also had an extreme value at Baseline.

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ANALGSIA SAFETY LABORAATORY TABLE 11: Selected Laboratory Shift Results from Baseline to Final Visit: [illegible] Trials

Laboratory Test at Final Visit	Placebo	Valdecoxib 20-40 mg
RBC		
Extreme low	none	none
Low	10/306 from normal	16/506 from normal
APTT		
High	3/251 from normal	none
Extreme high	none	none
Sodium		
Extreme low	none	none
Low	4/301 from normal	6/511 from normal
Potassium		
High	6/301 from normal	11/497 from normal
Extreme high	none	none
Urine protein		
High	none	4/513 from normal
Extreme high	none	none
Urine RBC		
High	7/152 from normal	3/299 from normal
Extreme high	6/152 from normal	5/299 from normal
Creatine kinase		
High	5/273 from normal	12/454 from normal
Extreme high	3/273 from normal	2/454 from normal
	3/31 from high	2/53 from high
Glucose		
Extreme low	none	none
Low	none	none
High	3/311 from normal	3/518 from normal
Extreme high	none	none
SGOT		
High	none	none
Extreme High	none	none
SGPT		
High	none	1/518 from normal
Extreme High	none	none

Trials 5, 14, 24, 35, 58, and 59. Only selected laboratory values with shifts in more than two patients are included. Normal indicates a wider range than standard normal ranges; see Table 4.a for ranges. No clinical laboratory determinations were done in Studies 064 and 080.

The shifts observed for the comparisons of valdecoxib 20-40 mg TDD with hydrocodone 10 mg/acetaminophen 1000 mg and ibuprofen 400 mg were similar to those observed for valdecoxib 20-40 mg TDD versus placebo.

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ANANLGESIA SAFETY LABORATORY TABLE 12: Selected Laboratory Shift Results from Baseline to Final Visit: ——— Trials

Laboratory Test at Final Visit	Placebo	Valdecoxib 20-40 mg
Hemoglobin		
Extreme low	2/282 from normal	1/457 from normal
Low	7/282 from normal	17/457 from normal
Hematocrit		
Extreme low	1/265from normal 1/17 from low	1/445 from normal 3/22 from low
Low	5/266 from normal	21/445 from normal
RBC		
Extreme low	3/67 from low	5/133 from low
Low	29/237 from normal	49/385 from normal
WBC		
Extreme low	None	none
Low	1/269 from normal	3/476 from normal
Platelet count		
Low	None	1/516 from normal
High	None	none
Extreme high	None	none
Eosinophil count		
High	1/309 from normal	none
Extreme high	None	1/519 from normal
PT		
High	None	none
Extreme high	None	none
APTT		
High	3/299 from normal	7/508 from normal
Extreme high	none	none
Creatinine		
High	None	none
Extreme high	1/317 from normal	1/555 from normal
BUN		
High	none	none
Extreme high	None	none
Total protein		
Extreme low	None	none
Low	5/281 from normal	15/481 from normal
Albumin		
Extreme low	None	none
Low	9/265 from normal	25/467 from normal
Sodium		
Extreme low	None	none
Low	14/287 from normal	16/510 from normal
Potassium		
High	1/275 from normal	6/501 from normal
Extreme high	None	1/13 from high
Urine protein		
High	7/285 from normal	15/487 from normal
Extreme high	1/285 from normal none	4/487 from normal 1/24 from high
Urine RBC		
High	9/245 from normal	15/407 from normal
Extreme high	14/245 from normal 4/9 from high	33/407 from normal 5/26 from high

Selected Laboratory Shift Results from Baseline to Final Visit: [illegible] Trials (continued)

Laboratory Test at Final Visit	Placebo	Valdecoxib 20-40 mg
Creatine kinase		
High	39/216 from normal	74/369 from normal
Extreme high	19/216 from normal 12/53 from high	25/369 from normal 24/97 from high
Glucose		
Extreme low	None	1/513 from normal
Low	1/302 from normal	3/513 from normal
High	8/302 from normal	13/513 from normal
Extreme high	1/10 from high	1/513 from normal
SGOT		
High	2/315 from normal	3/548 from normal
Extreme High	none	none
SGPT		
High	1/311 from normal	2/547 from normal
Extreme High	none	none

Trials 10, 11, 32, 33, 37, 52, and 72. Normal indicates a wider range than standard normal ranges; see Table 4.a for ranges.

[illegible] Trials: The shifts observed for valdecoxib 40 mg/d, valdecoxib 80 mg/d, and placebo in the [illegible] rials were similar to the comparison of valdecoxib 20-40 mg versus placebo in the [illegible] rials with some exceptions. A higher percentage of patients in all treatment groups with normal values at Baseline had shifts to low or extreme low values for hemoglobin, hematocrit, RBC, total protein, albumin, sodium, and potassium, and a higher percentage of patients in all treatment groups had shifts to high or extremely high creatine kinase values.

The laboratory shifts observed in the [illegible] rial are generally consistent with the analyses of extreme laboratory values (Appendix 5.7). Few patients shifted to extreme values, and the results were similar in the placebo and parecoxib sodium/valdecoxib treatment groups.

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VI. ANALYSIS BY AGE AND GENDER

RISK FACTOR TABLE 1: AGE - Risk Differences Compared by Age Groups in Controlled Arthritis Trials: Valdecoxib (10-20 mg/d) vs. Placebo

	<65 Years			≥65 Years		
	Valdecoxib 10-20mg/d, combined	Placebo	RD	Valdecoxib 10-20mg/d, combined	Placebo	RD
No. treated	1565	743	-	731	399	-
Influenza-like symptoms	2.3	2.3	0.0	0.5	2.0	-1.5
Bronchitis	0.6	1.7	-1.1	1.2	0.3	1.0

Trials 015, 016, 048, 049, 053, 060, and 061. Entries are % of patients except where otherwise noted. Table includes all events for which the difference between risk differences was statistically significant at $p \leq 0.05$, and for which at least 20 events (10 events in each stratum) occurred overall.

RISK FACTOR TABLE 1B: AGE - Risk Differences Compared by Age Groups in Controlled Arthritis Trials: Valdecoxib (10-20mg/d) vs. NSAIDs

	<65 Years			≥65 Years		
	Valdecoxib 10-20mg/d, combined	NSAIDs	RD	Valdecoxib 10-20mg/d, combined	NSAIDs	RD
No. treated	1565	888	-	731	459	-
Mouth dry	1.2	0.7	0.5	1.0	2.2	-1.2
Headache	6.9	6.8	0.1	5.6	2.2	3.4
Constipation	1.8	4.7	-2.9	0.8	5.9	-5.1

Trials 015, 016, 048, 049, 053, 060, and 061. Entries are % of patients except where otherwise noted. Table includes all events for which the difference between risk differences was statistically significant at $p \leq 0.05$, and for which at least 20 events (10 events in each stratum) occurred overall.

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RISK FACTOR TABLE 1C: AGE - Risk Differences Compared by Age Groups in Controlled Arthritis Trials: Valdecoxib (10-20 mg/d) vs. NSAIDs

	<75 Years			≥75 Years		
	Valdecoxib 10-20mg/d, combined	NSAIDs	RD	Valdecoxib 10-20mg/d, combined	NSAIDs	RD
No. treated	2108	1218	-	188	129	-
Nausea	7.0	7.9	-0.9	2.1	8.5	-6.4
Upper respiratory tract infection	5.9	6.3	-0.4	5.3	0.8	4.5

Trials 015, 016, 048, 049, 053, 060, and 061. Entries are % of patients except where otherwise noted. Table includes all events for which the difference between risk differences was statistically significant at $p \leq 0.05$, and for which at least 20 events (10 events in each stratum) occurred overall.

RISK FACTOR TABLE 2: GENDER - Risk Differences Compared by Gender in Controlled Arthritis Trials: Valdecoxib 10-20 mg/d, combined vs. Placebo

	Males			Females		
	Valdecoxib 10-20mg/d, combined	Placebo	RD	Valdecoxib 10-20mg/d, combined	Placebo	RD
No. treated	638	347	-	1658	795	-
Upper respiratory tract infection	3.9	6.9	-3.0	6.6	5.8	0.8

Trials 015, 016, 048, 049, 053, 060, and 061. Entries are % of patients except where otherwise noted. Table includes all events for which the difference between risk differences was statistically significant at $p \leq 0.05$, and for which at least 20 events (10 events in each stratum) occurred overall.

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RISK FACTOR TABLE 2B: GENDER - Risk Differences Compared by Gender in Controlled Arthritis Trials: Valdecoxib 10-20mg/d vs. NSAIDs

	Males			Females		
	Valdecoxib 10-20mg/d, combined	NSAIDs	RD	Valdecoxib 10-20mg/d, combined	NSAIDs	RD
No. treated	638	387	-	1658	960	-
Influenza-like symptoms	0.8	2.3	-1.5	2.1	1.9	0.2
Hyperglycemia	1.3	0.5	0.7	0.4	1.0	-0.6
Blurred vision	0.5	1.8	-1.3	0.5	0.2	0.3

Trials 015, 016, 048, 049, 053, 060, and 061. Entries are % of patients except where otherwise noted. Table includes all events for which the difference between risk differences was statistically significant at $p \leq 0.05$, and for which at least 20 events (10 events in each stratum) occurred overall.

120 day safety update:

The 120 day safety update was reviewed and revealed no differences in adverse event than those reflected in the original NDA.

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