Agent: Valdecoxib
Indication: Analgesia, Dysmenorrhea Osteoarthritis, and Rheumatoid Arthritis
Reviewer: Kent Johnson, MD
Date: November 7, 2001
NDA: 21,341

OUTLINE

APPEARS THIS WAY
ON ORIGINAL

EXECUTIVE SUMMARY

1-RECOMMENDATIONS

A. **Approval for the indications of osteoarthritis and rheumatoid arthritis at a dose of 10 mg/day and dysmenorrhea at a dose of 20-mg bid as needed.**

B. **Nonapproval of the acute pain, including opiod-sparing and prevention of operative pain. The only substantial multidose safety database is found in the Coronary Artery Bypass Graft (CABG) Surgery study 035. This study demonstrated an excess of serious adverse events including death in association with the use of paracoxib and valdecoxib 40 mg bid when added to ad lib parenteral narcotic analgesia. The allocation was 2:1 drug versus placebo and the population was highly enriched with patients at high risk for cardiovascular thromboembolic events. Therefore, interpretation of these findings cannot be conclusive at this time. These finding warrants further investigation before valdecoxib can be considered safe and effective for the treatment of pain, particularly multidose therapy in the perioperative setting.**

The dose used in the CABG trial was eightfold higher than the dose proposed for approval for the treatment of osteoarthritis and rheumatoid arthritis and twice the dose proposed for the treatment of dysmenorrhea. In addition the proposed populations is distinctly different than the post-operative setting. The extensive safety database at 10-80mg daily in the arthritis safety database is adequate to support approval of the chronic therapy at 10 mg/day for arthritis and acute dose of 20 mg bid for short term use in dysmenorrhea.

2-SUMMARY OF CLINICAL FINDINGS

a) **Adequate efficacy has been demonstrated in osteoarthritis and rheumatoid arthritis at 10mg/d with no additional efficacy at 20mg/d.**

The safety profile with chronic use in RA and OA is adequate at 10mg/d. At higher total daily doses, the findings of more hypertension and edema are frequently reproduced, and they are formally affirmed in a prospective manner in Trial 47, which directly tested the hypothesis of renal safety at 40 and 80 mg/day. In the analysis of older subpopulations over the age of 65 years edema and hypertension appear to be greater at 20 mg/day compared to 10 mg/ day.

b) **Single-dose analgesia has been demonstrated at 20mg and 40mg in the dental, dysmenorrhea, with supportive data from other surgical models.**

c) **Two studies (024, 037) evaluating prevention or pre-emption of of post-operative pain demonstrated the superiority of valdecoxib 20, 40 and 80 mg over placebo for the endpoints of time to rescue medication as well as proportion of patients taking rescue medication. There was no difference in pain intensity over the first 2 hours in study 024 and 4 hours in study 037. This finding raises conncern over the value of preoperative management of post-operative pain, particularly in regards to the risk versus potential benefit. Data from these two studies should not be considered for labeling until the overall clinical value of such treatment is further defined as well as the safety. Pre-**

operative dosing should be compared to post-operative dosing to adequately characterize the value of pre-operative treatment given the lack of differentiation in pain intensity between valdecoxib and placebo treated subjects.

d) Three studies of opioid sparing were submitted (Trials 35, 51, and 38). While mean opiod dose was lower in subjests treated with valdecoxib 40mg bid in the three studies, results were not replicated for 20-mg bid. Decreases in peak pain intensity were demonstrated in two of the three studies at 40 mg bid. This finding was not replicated for the 20-mg bid dose. Sparing of adverse events was not demonstrated in these studies. In study 035 there was a statistically significant excess of serious adverse events associated with the use of valdecoxib 40-mg bid when added to ad lib narcotic therapy compared with narcotic analgesia alone. The value of "opioid sparing based on numeric differences in total opioid requirement is of unclear and unproven clinical benenfit.

e) No efficacy advantage was demonstrated or suggested for valdecoxib compared to:

i. ibuprofen, naproxen and acetamenophen/oxycodone in anlagesic studies
ii. naproxen, ibuprofen or diclofenac in osteoarthritis studies
iii. naproxen in rheumatoid arthrits studies

3-OVERVIEW OF CLINICAL PROGRAM

ANALGESIA: This NDA consists of a program of analgesia trials to support a claim for acute pain, and a number of trials in osteoarthritis and rheumatoid arthritis to support a claim for chronic use in these conditions. The analgesia program tended to follow drug development programs for acute pain used in the past, relying heavily on single-dose demonstrations of efficacy compared to placebo and active controls, plus PK support demonstrating blood level stability over time and a satisfactory chronic risk/benefit from different indications (osteoarthritis and rheumatoid arthritis) to then *extrapolate* the safety for multiple-dose use in acute pain. The following is the sponsor's request for claims:

> ***An indication for the treatment of acute pain and dysmenorrhea at 40mg/d, with an additional 40mg on day one if needed, and an indication for chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis at a dose of 10mg/day, with the proviso that "some may receive additional benefit at 20mg/day."***

It should be noted that there was the usual interaction with the sponsor regarding the scope and content of their development program. These interactions were more prescriptive in the case of OA and RA, as RA had been recently addressed in a Guidance Document, and the former had been the topic of a number of public meetings during which certain fundamentals such as trial duration, primary endpoints, and statistical methodology, were established. Thus, there was a priori agreement regarding data assessment in OA and RA, but the same cannot be said of analgesia. The agency, in collaboration with outside bodies, has been and remains in the process of formulating current analgesia guidelines, and, in particular, the nature of the evidence base needed to demonstrate efficacy in analgesia. A weakness in the approach used in the past is the extrapolation needed to assert multiple-dose efficacy, rather than having data directly supporting this. In the past, this approach, although not ideal, was deemed acceptable given that agents were drugs which were administered orally and usually showed identical dosing in both the analgesia and arthritis settings. Furthermore, pharmacokinetic paramerters would suggest higher rather than

lower levels on remedication in the acute multi-dose setting. In addition, in many to most acute pain settings, pain intensity typically diminishes rather than increase over time (suggesting that analgesia that is documented to be effective at the time of maximum pain would continue to be adequate as time passed.
An area where extrapolation cannot be made is in the assessment of dosing interval. Single dose efficacy data alone is less robust than comparative multi-dose data in assessing the optimal dosing interval. Although the division is exploring approaches which yields direct multiple-dose evidence and so depends less on extrapolation, the interactions for this NDA preceded this, so in this review the single-dose to multiple-dose extrapolation will be accepted. It is of note that supportive evidence of mulit-dose efficacy was submitted by the sponsor

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The analgesia program consisted of nineteen trials – seven dental, two dysmenorrrhea, and ten in various surgical settings. Only four were designed as multiple-dose trials. The other fifteen all were explicitly designed as single-dose, '

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The dysmenorrhea trials were both 4-part crossover designs. Two surgery trials were designed to test the use of valdecoxib in a pre-emptive manner, given shortly before surgery. All trials were both placebo and active controlled except three which were designed to test a morphine-sparing hypothesis the pre-operative and the two pre-operative dosing studies. The three morphine-sparing trials allowed ad lib morphine use in both arms, so, in effect, they employed a "standard-of-care" as the control arm. The inclusion criteria varied widely across these designs, from patients undergoing the standard third molar extraction in the dental trials, to patients undergoing various modes of anaesthesia delivery (local, regional, spinal, general). This diversity has always been encouraged, as pertinent to any claim is a presumption of generalizability. In this NDA Trial 35 attempted to capture patients with substantial co-morbidity by enrolling patients who had undergone coronary artery bypass graft (CABG) surgery. This was an efficacy as well as a safety trial. The "COX-2 hypothesis" relates to organ specific safety; notably the uppergastrointestinal tract. In discussions with the sponsor the division has emphasized the importance of rigorously testing the overall safety as well as upper gastrointestinal safety of valdecoxib. Given the evolving knowledge of selective COX-2 inhibition, this issue is of growing concern. This trial included a pre-defined basket of serious safety endpoints, called clinically relevant adverse events (CRAEs), which were to be formally adjudicated. In addition study 047 included renal safety endpoints in addition to asymptomatic endoscopically ascertained gastroduodenal ulcers as prespecified endpoints

ARTHRITIS: The arthritis program consisted of early dose-ranging RCTs (Trials 15 and 16), followed by four standard efficacy trials (1 hip OA, 1 knee OA, and 2 RA), one active control, non-inferiority trial in OA (trial 63), and four formal safety trials – Trial 47 (OA/RA), 62 (RA), 48 (OA), and 53 (knee OA), all using a similar endoscopic ulcer primary endpoint, and one (47) also using a renal toxicity composite primary endpoint. These safety trials also collected validated efficacy endpoints, although not encompassing the full primary endpoint spectrum needed for formal efficacy evidence in OA or RA.

4-EFFICACY

ANALGESIA: The analgesia trials were assessed by (1) the improvement in pain over time, (2) the time to the onset of analgesia, and (3) the time to need for re-dosing or rescue medication. All three of these should be substantially inter-correlated, so all were tested at the $p<0.05$ level, and no adjusting for multiplicity was done. However, this threefold endpoint approach was not appropriate for the morphine-sparing trials as they did not collect time to onset of analgesia, nor did they allow rescue medication. In these trials, two measures were used: (1) pain relief, and (2) morphine spared.

By the endpoints noted above, the following number of trials demonstrated efficacy (by either all three endpoints showing statistical significance at a $p<0.05$ or two endpoints, in the case of the morphine-sparing trials): 10mg/d – 4 trials (#5, 14, 35, 24), 20mg/d - 8 trials (#5, 14, 35, 58, 59, 11, 24, 37), 40mg/d – 6 trials (35, 58, 59, 72, 24, 37). So few comparisons to active controls were statistically significantly different, either superior or inferior, that this evidence base is not further considered. Using the criteria of replicated success in two of the three pain models – dental pain, dysmenorrhea, and post-surgical pain, and excluding dosing at 80mg/d or 40mgbid – given evidence to suggest an unacceptable risk-benefit at these levels, the data support clear single-dose efficacy of 20mg, and 40mg. There was no replication of the efficacy of 10 mg based on pain intensity differences.

The clinical relevance of opioid-sparing was not adequately demonstrated. Pre-emptive administration of valdecoxib 20, 40 and 80 mg was associated with longer time to rescue medication compared with placebo in Trials 24 and 37 and number of patients who took rescue medication. Pre-emptive versus post operative dosing efficacy was not tested and peak pain intensity over 2 and 4 hours respectively in the two studies did not differ between placebo and active treatment arms. Therefore the benefit of pre-emptive treatment is not clear, especially in view of the safety concerns in the post-operative setting.

ARTHRITIS: The trials performed for the demonstration of efficacy in RA and OA were conventional and adequate in design. They included three formal efficacy trials in OA (two placebo control trials and one non-inferiority trial using only an active control, and two in RA, both placebo controlled. There were also safety RCTs with safety parameters as primary endpoints that also measured efficacy. These studies employed less standardized athritis efficacy endpoints such as patient and investigator global assessments and time to dropout due to inefficacy.

The analysis of the efficacy results for RA and OA in this NDA were relatively straightforward. Valdecoxib did demonstrate efficacy at the 10mg and 20mg/d dosages in replicated data by usual comparisons with placebo arms, and there were no obvious threats (e.g. a differential dropout pattern) to the validity of these conclusions. Although no formal active control, non-inferiority evidence was pre-specified and pre-agreed upon in this NDA, this NDA, like others in the past, included numerous comparisons with active controls – and these were within the range of what has been seen with prior NDAs. There was no added benefit at 20mg/d, compared to 10mg/d.

5-SAFETY

Note: The review proper contains numerous adverse event tables which are supplied for reference, as the global safety experience of valdecoxib will likely bear critically on approval and labeling. Review comments are made in each section of these databases, but all relevant

safety considerations are captured in the discussions of safety and risk / benefit here in the Executive Summary.

With two notable exceptions – edema and hypertension, valdecoxib was comparable to the standard non-steroidal agents used as active controls in the trials, except for some evidence supporting fewer GI adverse events, and some lessening of opiate side effects (e.g. constipation, dizziness, etc.) in trials with those as active controls. These findings will be reflected in the AE tables in the label. The finding of a greater incidence of edema and hypertension at doses above 20 mg/day, almost uniformly in the databases and clearly when prospectively addressed in formal safety Trials 47 and 62, is of concern, The relationship between these events and the signal of more vascular events at 40mgbid dosing in the predisposed population of Trial 35 (CABG) is unclear. The excess of serious cardiovascular thromboembolic events in the valdecoxib arm of the CABG trial (see analgesic safety table #12) is of note as the entire study population received prophylactic low dose aspirin as part of the standard of care in this setting to minimize just such events. Given the emerging concern over a possible pro-thrombotic action of certain agents in the COX2 class, these data are of concern. These findings were seen at high dose in the peri-operative setting, not in the chronic safety studies of similar high doses.

6. DOSING

Valdecoxib should be limited to 10mg/d in chronic use in OA and RA. At this dose the rates of edema and hypertension appear to be similar to the comparator NSAIDs although formal hypothesis testing was not done in this regard. Edema and hypertension appeared increased at higher doses compared to other NSAIDs.

7. SPECIAL POPULATIONS

Analysis of the pivotal RA and OA trials across age (using 65 and 75 as divisors), gender, and race subpopulations did not show any differences by the primary endpoints used in those trials.

REVIEW PROPER

CLINICAL EXPOSURE

The exposure in patient-years for this NDA and 120-Day Update are shown below.

EXPOSURE – ARTHRITIS TRIALS, PATIENT-YEARS

category	valdecoxib (total daily doses)						naproxen	diclofenac	ibuprofen	placebo
	≤5mg	10mg	20mg	30mg	40mg	80mg				
double-blind	106.5	322.7	396.5		315.5	141.5	291.2	248.3	40	161.1
open		308.1	786.8	0.2	736.0	233.4				
total	106.5	584.1	1135.2	0.2	937.7	308.7				

EXPOSURE – CABG TRIAL (TRIAL 35)

Valdecoxib 40mgbid	7.7 patient-years
Placebo	3.7 patient-years

HUMAN PHARMACOLOGY AND PHARMACOKINETICS – See Platelet function: Relevant PK Studies, under Safety (Clinical), and full Pharmacology and Pharmacokinetics Reviews

CLINICAL STUDIES-EFFICACY

The reader is referred to the statistical reviews as well.

PART I: OSTEOARTHRITIS

DATABASE: The osteoarthritis (OA) database shown in TABLE 1 consists of eight randomized controlled trials (RCT), including two pivotal efficacy studies of three months duration. Although the protocols specified numerous primary and secondary endpoints, none addressed the issue of multiple comparison and alpha-spending for statistical inference. Nonetheless, there is widespread agreement that pain, function, and patient global (PG) should be primary domains in short-term OA trials (i.e. less than one year), and here accepted measures in each of these domains are used as primary efficacy endpoints. The fourth endpoint used is trial withdrawal due to inefficacy. As no trial in this application used rescue medication, adjusting for this covariate dose not arise.

In this NDA the three OA primary endpoints for efficacy were captured as (1) pain by 10cm VAS, (2) function by the full Western Ontario and McMasters University Osteoarthritis (WOMAC) Index, and (3) patient global by 10 cm VAS, although the trials collected further efficacy data. Some trials were designed as safety studies with endoscopic and, in some cases, renal endpoints; the results of these are given in the Safety Section of this review. The control arms used were placebo (plc), naproxen (nap), ibuprofen (ibu), or diclofenac (dicl). Patient entry criteria were OA diagnosis by ACR criteria, plus pain of 4.0cm or more on the 10cm VAS and a patient global of "poor" or "very poor," either de novo or after withdrawal of the patient's prior non-steroidal medication ("flare").

TABLE 1: OA database

Trial	duration, size	arms	primary endpoints
Dose-finding trial			
15 knee OA	6wk, ~80/arm	0.5,1.25,2.5,5,& 10bid,10qd,nap,plc	
Efficacy trials			
49 hip OA	3mo, ~120/arm	5, 10, nap, plc	pain, fctn, PG
53 knee OA	3mo, ~200/arm	5, 10, 20, nap, plc	pain, fctn, PG
48 OA*	3mo, ~200/arm	10,20,ibu,dicl, plc	PG, IG, ineff.
63 knee/hip OA** (ongoing)	6mo, ~260/arm	10, 20, dicl	efficacy, JSN
Safety trials			
48 OA (nos)	3mo, ~200/arm	10,20,ibu,dicl, plc	endoscopic ulcer

47	OA/RA	6mo, ~400/arm	20bid,40bid,nap	renal,endos.ulcer
53	knee OA	3 mos ~200/arm	5, 10, 20, nap, plc	endoscopic ulcer

* Trial 48 – Enrolled patients with the diagnosis of OA, not otherwise specified.

** Trial 63 – Six-month efficacy trial, followed by a six-month open extension to assess joint space narrowing (JSN) at 12 months. (Interim report of 6 month data only)

TRIALS 49 AND 53

PATIENT DISPOSITION: Patients were matched across arms by the usual demographic and clinical criteria (TABLE 2, below). Substantial premature patient withdrawal occurred (25 to 50%) over the three-month trial duration, and most dropouts were due to treatment failure. The dropouts for treatment inefficacy or adverse events are shown below; a small number discontinued for other reasons.

TABLE 2: Trials 49 & 53: Patient Disposition

	Enrolled	Completed	Withdrew	
			Rx. Failure	adverse event
Trial 49				
val 5mg	120	73 (61%)	32 (27%)	10 (8%)
val 10mg	111	65 (59%)	31 (28%)	11 (10%)
naproxen	118	71 (60%)	24 (20%)	15 (13%)
placebo	118	49 (42%)	51 (43%)	7 (6%)
Trial 53				
val 5mg	201	162 (81%)	16 (8%)	12 (6%)
val 10mg	206	150 (73%)	24 (12%)	18 (9%)
val 20mg	202	158 (78%	20 (10%)	11 (5%)
naproxen	205	149 (73%)	13 (6%)	26 (13%)
placebo	205	131 (64%)	42 (20%)	17 (8%)

DROPOUT ANALYSES: TABLES 3 and 4 show comparisons of the status of dropouts versus completers by baseline and end-of-trial means and standard deviations (in parentheses) of various factors. The following parameters are presented: age (yr), percent female, disease duration (yr), pain (0-100 for Trial 49, or 0-68 for Trial 53), patient global (% "poor" for baseline, % "poor" or "very poor" for last visit), and function (0-68 for Trial 53 only). Although some parameters are less sensitive than others at showing differences between dropouts and completers, there was no dropout pattern which might compromise the validity of inferences drawn.

TABLE 3: Trial 49 – Comparison of Baseline / End-of-trial Status: Dropouts vs Completers

arm	placebo		val 5mg/d		val 10mg/d		naproxen	
	d/outs	compl.	d/outs	compl.	d/outs	compl.	d/outs	compl.
BASELINE PARAMETERS								
age	67	58	63	59	66	64	61	66
female	72%	63%	66%	68%	61%	69%	70%	68%
d.dur.	6 (7)	6 (7)	5 (6)	7 (8)	7 (8)	6 (5)	5 (7)	6 (5)
pain	72(15)	67(15)	73(15)	73(15)	78(13)	71(15)	68(16)	70(15)
pt glob	77%	90%	87%	88%	80%	89%	91%	92%

LAST VISIT PARAMETERS								
pain	74(24)	37(27)	71(23)	42(27)	76(25)	30(28)	70(26)	33(28)
pt glob	63%	6%	66%	15%	65%	10%	57%	15%

TABLE 4: Trial 53 – Comparison of Baseline / End-of-trial Status: Dropouts vs Completers

arm	placebo		val 5mg/d		val 10mg/d		val 20mg/d		naproxen	
	d/out	com	d/out	com	d/out	com	d/out	com	d/out	com
BASELINE PARAMETERS										
age	59	61	57	59	61	61	60	60	60	60
sex	58%	68%	56%	65%	70%	63%	70%	66%	64%	62%
d dur	6 (9)	5 (7)	10(11)	6 (9)	8 (9)	5 (7)	6 (8)	7 (8)	5 (10)	7 (8)
pain	11 (3)	11 (4)	11 (3)	11 (3)	11 (3)	11 (3)	12 (3)	11 (3)	11 (3)	11 (3)
fctn	40(11)	39(12)	39(12)	39(11)	40(11)	39(11)	41(11)	38(11)	39(10)	39(11)
glob	4 (.5)	4 (.4)	4 (.5)	4 (.3)	4 (.5)	4 (.4)	4 (.6)	4 (.3)	4 (.4)	4 (.4)
LAST VISIT PARAMETERS										
pain	11 (5)	7 (4)	11 (4)	6 (4)	11 (4)	7 (4)	11(4)	6 (4)	11(4)	6 (4)
fctn	39(14)	25(14)	37(13)	24(12)	35(14)	24(14)	37(14)	23(13)	35(13)	23(14)
glob	4 (1)	2 (1)	4 (1)	2 (1)	3 (1)	2 (1)	4 (1)	2 (1)	3 (1)	2 (1)

RESULTS: The results of primary endpoint analyses and the analysis of withdrawals for inefficacy, plus their respective confidence interval ranges, are shown in TABLE 5.

TABLE 5: Trials 49 & 53: Primary Endpoint Results at 3 Months

	——Baseline / Change from Baseline——			
	Pain	function	Patient global	Inefficacy dropouts
	(0-10 VAS)	(0-68 Likert)	(0-10 VAS)	
1. TRIAL 49				
val 5mg	7.2 / -2.1	54.7 / -12.0* *	4.1 / -1.2 *	32/120 **
val 10mg	7.3 / -2.3 *	52.8 / -14.0 ***	4.1 / -1.3 **	31/111 *
naproxen	6.9 / -2.2	51.8 / -13.8 ***	4.1 / -1.2 *	24/118 ***
placebo	7.1 / -1.5	52.5 / -5.3	4.1 / -0.9	51/118
Trial 53				
val 5mg	7.1 / -3.1	53.0 / -16.8	4.1 / -1.4	12/201 ***
val 10mg	7.2 / -3.0	54.7 / -17.3 *	4.1 / -1.5* *	18/206 *
val 20mg	7.3 / -3.3 *	53.4 / -17.2 *	4.2 / -1.6 **	11/202 **
naproxen	7.2 / -3.2 *	53.7 / -18.0 *	4.1 / -1.4	26/205 ***
placebo	7.1 / -2.6	53.5 / -13.5	4.1 / -1.2	17/205

*, **, *** statistical significance at $p<0.05$, <0.01, and <0.001 levels, respectively, compared to placebo

Note: Comparisons of dropouts by all causes also showed statistical significance for all active arms in Trial 49, and for the valdecoxib 5mg and valdecoxib 20mg arms in Trial 53.

Conclusion:

Trials 49 and 53 are adequate and well controlled studies confirming the efficacy of valdecoxib 10 mg/ day for the treatment of osteoarthritis. Dose ranging study of valdecoxib 20 mg/day in trial 53 did not support added benefit for this dose although a small numeric advantage at withdrawal due to lack of efficacy was seen at the higher dose (8.7% versus 5.4%).

TRIAL 48.

This trial compared valdecoxib 10mg/d, valdecoxib 20mg/d, ibuprofen 800mgTID, and diclofenac 75mgBID over three months, and it used both endoscopic ulcers and four clinical efficacy parameters (patient and investigator globals, and incidence and time to inefficacy withdrawal) as primary endpoints. It was powered by both endoscopic ulcers rates and the two global measures.

TABLE 6: Trial 48: Patient Disposition

	Enrolled	Completed	Withdrew	
			Rx. Failure	Adverse Event
val 10mg	204	150	16	19
val 20mg	219	165	17	20
ibuprofen	207	156	11	27
diclofenac	212	152	12	34
placebo	210	135	45	15

RESULTS:

TABLE 7: Trial 48: Primary Endpoint Results at 3 Months

	Patient global	Inv. global	Withdrawals	
	(0-4 Likert)	(0-4 Likert)	(incidence)	(time to withdrawal)
val 10mg	3.12 / -0.54*	3.01 / -0.60**	16/204***	***
val 20mg	3.07 / -0.59*	3.01 / -0.58*	17/219***	***
ibuprofen	3.16 / -0.63*	3.11 / -0.61*	11/207***	***
diclofenac	2.98 / -0.65***	2.91 / -0.58***	12/212***	***
placebo	3.12 / -0.42	3.01 / -0.36	45/210	

*, **, *** statistical significance at $p<0.05$, <0.01, and <0.001 levels, respectively, compared to placebo

COMPARISONS TO ACTIVE CONTROLS:

Although no study was designed as a non-inferiority trial and none was powered by an equivalence hypothesis, the sponsor nonetheless calculated the so-called Q-statistic, the ratio of the mean change on the test drug to the mean change on the active control, and its 95% confidence interval. Although this method has mathematical properties which make interpretation impossible as the denominator approaches zero, it offers an additional mathematical comparison of two response rates (RR) expressed as a ratio, RR1/RR2, in addition to a difference, R2-R1, and the 95% confidence interval of this quantity has been used in the past to assess NSAID comparability for approval evidence, although not for an

explicit equivalence claim. It was found, from analysis of a number of early NSAID NDAs in OA and RA, that approvability in OA correlated with active control trial demonstrations showing the 95% lower bound of the Q statistic usually 0.6 or more for OA , or 0.7 or more for RA. (A 95% upper bound of the Q of less than one means a statistically significant inferiority has been demonstrated.) It is important to note that this statistical model, with the outcomes as noted, was never proposed as an adequate basis alone for evidence of efficacy of new proposed therapy – randomized evidence from placebo (negative) controlled settings was required. Using this approach one would conclude that all but one of the naproxen comparisons and all of the ibuprofen comparisons were robust, but only two of the four diclofenac comparisons were (see data below).

TABLE 8: Trials 49, 53, and 48: Q-value (95% CI) Comparisons to Active Controls

	comparison	pain	function	pt. global
Trial 49				
	val5mg v nap	0.97(0.67-1.38)	0.65(0.56-1.15)	1.02(0.79-1.30)
	val10mg v nap	1.06(0.75-1.50)	1.04(0.72-1.51)	1.09(0.86-1.40)
Trial 53				
	val5mg v nap	0.98(0.82-1.18)	0.93(0.75-1.15)	0.99(0.85-1.16)
	val10mg v nap	0.96(0.79-1.15)	0.98(0.79-1.21)	1.08(0.93-1.26)
	val20mg v nap	1.03(0.86-1.23)	0.96(0.77-1.19)	1.10(0.95-1.28)
Trial 48		pt. global	inv. global	
	val10mg v ibu	0.98(0.67-1.44)	1.12(0.79-1.60)	
	val20mg v ibu	1.01(0.70-1.49)	1.06(0.75-1.61)	
	val10mg v dicl	0.78(0.55-1.09)	0.93(0.67-1.27)	
	val20mg v dicl	0.80(0.57-1.11)	0.87(0.63-1.20)	

Trial 63: This is an ongoing 6 month trial comparing valdecoxib 10mg/d, valdecoxib 20mg/d, and diclofenac 75mgbid, with a six-month open extension to assess joint space narrowing by x-ray at 12 months. Only the first six month clinical data is available at this time. The protocol notes that the trial, powered at six months, was initially designed as a difference trial with 230 patients per arm adequate (80% power/alpha=0.05) to detect a 15% change in the mean change from baseline of the joint valdecoxib arms compared to the diclofenac control, or, similarly, a 0.22 change in the patient global. The protocol was amended to change from a superiority design to a non-inferiority design (referencing a European regulatory "Points to Consider" on this topic, CPMP, July 27, 2000), wherein the valdecoxib arm would be declared "clinically comparable" if the 95% confidence interval of the difference of it compared to diclofenac was smaller than 15mm (patient pain measure), this figure obtained from a paper by Bellamy (J Rheum 19:451-7, 1992). Powering to this (90% power, experiment-wide alpha of 0.05, and SD=28.4 from Trial 49) also yields about 230 patients per arm.

The trial specified four primary endpoints, the patient pain, global, WOMAC-full, and WOMAC-function. The results below show both the p values and the Q values and its 95% confidence intervals are shown below.

TABLE 9: Trial 63: Patient Disposition

	Enrolled	Completed	Withdrew	
			Rx. Failure	adverse event

val 10mg	259	188	21	19
val 20mg	261	205	22	18
diclofenac	264	187	16	40

TABLE 10: Trial 63: Efficacy Results: P values (1st entry), Q values (95% CI)(2nd entry)

endpoint	val10mg vs diclof	val20mg vs diclof	val10mg vs val20mg
patient pain	0.074, 0.83 (0.67,1.03)	0.169, 0.87 (0.70,1.07)	0.679, 0.96 (0.76,1.20)
patient global	0.051, 0.84 (0.70,1.01)	0.022, 0.82 (0.67,0.98)*	0.728, 1.03 (0.84,1.27)
WOMAC-full	0.006, 0.78 (0.64,0.94)*	0.042, 0.84 (0.69,1.00)	0.481, 0.93 (0.76,1.15)
time-to-rx. failure	0.404	0.472	0.978

* statistically significant, diclofenac superior to valdecoxib

OTHER EFFICACY EVIDENCE

TRIAL 15: This was a six-week dose-response study of valdecoxib at 0.5mgbid to 10mgbid which showed statistically significant improvement in the three primary endpoints at all but the lowest valdecoxib dose.

TRIAL 47: The only other randomized trial in OA with efficacy analyses available was Trial 47, a combined OA/RA trial of renal and GI safety. It employed four pre-defined efficacy endpoints, the patient and investigator global, and the incidence and time-to-dropout for inefficacy. Trial 47 did not use a placebo arm, so no negative control efficacy comparisons could be made, and no statistically significant superiority was show for any pair-wise comparison of active drugs for any of the four endpoints, but this is an insensitive method to detect small differences. As described above, the Q-statistic and its 95% confidence interval offer a method to look in a more discriminating manner for small differences for continuous or interval variables, so this was done for the two global assessments in this trial, showing a Q of 0.73 (0.49-1.02) for the valdecoxib 20mgbid vs naproxen patient global comparison, and a Q of 0.77 (0.54-1.06) for the investigator global. For the valdecoxib 40mgbid vs naproxen comparisons the Q's were 0.77 (0.54-1.06) and 0.86 (0.57-1.09) for the patient and investigator global, respectively.

CONCLUSION

Efficacy is adequately demonstrated in osteoarthritis for valdecoxib at 10mg/d. No additional evidence was demonstrated at higher doses in placebo or active controlled studies.

PART II: RHEUMATOID ARTHRITIS

DATABASE: The rheumatoid arthritis (RA) database consists of five randomized controlled trials -- one early dose-finding study, two pivotal efficacy studies of three month duration, and two safety studies. Patients were enrolled if they fulfilled ACR diagnostic criteria for RA, and displayed an adequate increase in symptoms ("flare") upon discontinuation of the current anti-inflammatory medication.

(Note: The interesting question as to the relation of the degree of flare, and the relation of the baseline, pre-flare state, to that patient's outcome in the trial, is likely not relevant to the internal validity of these trial and was not explored in the NDA.

The RA efficacy studies used a variety of endpoints, including the traditional ACR20 ("success" being defined as at least 20% improvement in number of tender joints and number of swollen joints, plus a 20% improvement in at least three of the remaining five components: patient global, physician global, pain, acute phase reactant, and a functional measure), and the modified Health Assessment Questionnaire (mHAQ). Since the introduction of the ACR20, multiplicity has not been an issue in short-term RA trials, and, as in OA, no rescue medication was used. The main features of the four RCTs are shown in TABLE 9, with control arms being placebo (plc), naproxen (nap), ibuprofen (ibu), or diclofenac (dicl). Two RA safety trials are shown, which are reviewed in the Arthritis Safety Review.

TABLE 9: RA Database

Trial no.	duration, size	arms	primary endpoints
Dose finding trial			
16	6wk, ~80/arm	0.5,1.25,2.5,5,& 10bid,10qd, nap,plc	ACR20
Pivotal efficacy trials			
60	3mo, ~220/arm	10,20,40, nap, plc	ACR20
61	3mo, ~220/arm	10,20,40, nap, plc	ACR20
Safety trials			
47 OA/RA	6mo, ~400/arm	20bid, 40bid, nap	renal,endos.ulcer
62 RA	6mo, ~240/arm	20, 40, diclof	renal,endos.ulcer

RESULTS

TRIALS 60 & 61

PATIENT DISPOSITION: Patients were matched across arms by the usual demographic and clinical criteria (see below, TABLES 11 and 12). As in OA, there was substantial premature patient withdrawal over the three-month trial duration. Inefficacy or adverse event discontinuations are shown in TABLE 10; a few patients dropped out for other reasons.

TABLE 10: Trials 60 & 61 - Patient Disposition

	enrolled	completed	Withdrew	
			Rx Failure	adverse event
Trial 60				
val 10	209	132 (63%)	49 (23%)	11 (5%)
val 20	212	132 (62%)	48 (23%)	12 (6%)
val 40	221	139 (59%)	56 (25%)	19 (9%)
naproxen	226	137 (61%)	57 (25%)	13 (6%)
placebo	222	92 (41%)	102 (46%)	10 (5%)
Trial 61				
val 10	226	137 (61%)	61 (27%)	10 (4%)
val 20	219	137 (63%)	56 (26%)	12 (5%)

val 40	209	137 (66%)	48 (23%)	13 (6%)
naproxen	219	145 (66%)	43 (20%)	21 (10%)
placebo	220	95 (43%)	92 (42%)	9 (4%)

DROPOUT ANALYSES: TABLES 11 and 12 show comparisons of the status of dropouts versus completers by baseline and end-of-trial criteria. The following parameters are presented: age (yr), percent female, disease duration (yr), percent of patients on steroids and methotrexate (mtx), patient global (% "poor" or "very poor"), median tender joint (TJ, 0-68) and swollen joint counts (SJ, 0-66), and mHAQ (0-3). As in osteoarthritis, certain parameters are much more sensitive to change (e.g. the ACR20 success, the mHAQ, and the patient global), but no dropout pattern is discerned which might compromise the validity of inferences drawn.

TABLE 11: Trial 60 – Comparison of Baseline/End-of-trial Status: Dropouts vs Completers

arm	placebo		val 10mg/d		val 20mg/d		val 40mg/d		naproxen	
	d/out	com	d/out	com	d/out	com	d/out	com	d/out	com
BASELINE PARAMETERS										
age	44	57	55	50	56	54	56	56	58	53
sex	73%	76%	66%	74%	80%	79%	79%	82%	77%	77%
d dur	6	8	7	9	7	7	9	8	8	7
ster	33	39	39	38	39	38	39	34	38	33
mtx	60	49	59	50	57	54	53	50	44	52
pain	69	50	70	65	72	57	56	61	65	53
TJ	24	27	30	27	26	27	27	25	23	24
SJ	1	18	18	17	17	17	19	18	16	19
mHAQ	1.38	1.19	1..63	1.38	1.63	1.38	1.50	1.38	1.50	1.13
LAST VISIT PARAMETERS										
pain	52	7	54	11	59	8	53	7	71	11
TJ	22	7	25	5	22	9	22	7	23	6
SJ	15	6	15	7	14	7	16	7	15	6
mHAQ	1.38	0.75	1.03	0.88	1.50	0.80	1.38	0.88	1.03	0.88
ACR20	20%	67%	24%	63%	20%	64%	15%	64%	12%	60%

TABLE 12: Trial 61 – Comparison of Baseline/End-of-trial Status: Dropouts vs Completers

arm	placebo		val 10mg/d		val 20mg/d		val 40mg/d		naproxen	
	d/out	com	d/out	com	d/out	com	d/out	com	d/out	com
BASELINE PARAMETERS										
age	55	58	56	56	56	58	56	53	61	59
sex	73	82	82	83	75	73	68	79	68	79
d dur	8	9	8	10	7	8	8	8	9	8
ster	35	37	35	35	40	37	42	36	34	31
mtx	47	48	38	56	43	49	43	47	44	50
pain	60	48	64	53	57	47	62	53	60	46
TJ	29	26	28	25	26	27	28	26	28	28
SJ	17	17	19	18	17	18	19	17	19	18
mHAQ	1.50	1.38	1.50	1.25	1.63	1.25	1.50	1.38	1.38	1.14
LAST VISIT PARAMETERS										

pain	49	7	44	10	44	7	35	4	60	11
TJ	25	7	20	8	18	8	18	7	22	12
SJ	14	8	14	8	12	8	12	8	14	6
mHAQ	1.38	0.88	1.50	0.75	1.50	0.75	1.25	0.75	1.38	0.75
ACR20	18%	64%	22%	62%	22%	64%	27%	66%	17%	53%

RESULTS:

TABLE 13: Trials 60 & 61: Primary Endpoint Analyses

	3-mo ACR20 Success	Inefficacy Withdrawals
Trial 60		
val 10	103/209 (49%) ***	49/209 (23%)***
val 20	102/212 (48%) ***	48/212 (23%)***
val 40	102/221 (46%) ***	56/221 (35%)***
naproxen	100.225 (44%) **	57/226 (25%)**
placebo	70/222 (30%)	102/222 (46%)
Trial 61		
val 10	103/226 (46%)***	61/226 (27%)***
val 20	103/219 (47%)**	56/212 (26%)***
val 40	104/209 (50%)**	48/209 (23%)***
naproxen	115/219 (53%) ***	43/219 (20%)***
placebo	71/220 (32%)	92/220 (42%)

*, **, *** statistical significance at p<0.05, <0.01, and <0.001 levels, respectively, compared to placebo

Note: Comparison of dropouts from all causes also showed statistical significance for all active treatment arms in both Trials 60 and 61.

For interest, the means and standard deviations of the mHAQ are shown in TABLE 14, and the Q statistic with its 95% confidence interval for active control comparisons of four selected endpoints in TABLE 15. (For a discussion of the Q-statistic, see Comparisons to Active Controls section of Part I: Osteoarthritis, above.) By these data, valdecoxib appears slightly better compared to naproxen in Trial 60 compared to Trial 61, but in neither trial is there much support for a dose-response effect.

TABLE 14: Trials 60 & 61: M-HAQ Results

	Baseline	Change
Trial 60		
val 10	1.3 (0.68)	-0.3 (0.57)***
val 20	1.5 (0.67)	-0.3 (0.51)***
val 40	1.4 (0.69)	-0.3 (0.55)***
naproxen	1.4 (0.69)	-0.3 (0.57)***
placebo	1.4 (0.72)	-0.1 (0.50)

Trial 61		
val 10	1.4 (0.65)	-0.3 (0.52)***
val 20	1.4 (0.68)	-0.3 (0.55)***
val 40	1.3 (0.69)	-0.3 (0.56)***
naproxen	1.4 (0.71)	-0.4 (0.58)***
placebo	1.3 (0.72)	-0.1 (0.49)***

*, **, *** statistical significance at p<0.05, <0.01, and <0.001 levels, respectively, compared to placebo

TABLE 15: Trials 60 & 61 - Q-value (95% CI) Comparisons of Valdecoxib to Naproxen

Trial 60	pt. global	tender joints	swollen joints	mHAQ
val10 v nap	1.02 (0.83-1.15)	0.99 (0.80-1.22)	1.03 (0.83-1.29)	0.97 (0.70-1.32)
val20 v nap	0.91 (0.73-1.13)	0.94 (0.76-1.17)	0.92 (0.75-1.13)	0.84 (0.59-1.17)
val40 v nap	0.94 (0.76-1.16)	1.06 (0.87-1.30)	1.05 (0.87-1.28)	0.89 (0.64-1.23)
Trial 61				
val10 v nap	0.85 (0.65-0.97)	0.84 (0.70-1.01)	0.81 (0.65-0.99)	0.67 (0.47-0.92)
val20 v nap	0.84 (0.68-1.01)	0.82 (0.67-0.99)	0.85 (0.69-1.03)	0.71 (0.51-0.97)
val40 v nap	0.84 (0.68-1.02)	0.97 (0.82-1.16)	0.86 (0.70-1.05)	0.76 (0.55-1.03)

There is no suggestion of added efficacy at 20 mg/day compared to 10mg/day.

OTHER EFFICACY EVIDENCE

TRIAL 16: The dose ranging RA study, Trial 16, failed to demonstrate any statistical separation at 6 weeks for any active treatment arm, including the naproxen control, compared to placebo for the ACR20 endpoint.

TRIAL 47: The only other randomized trial in RA with efficacy analyses available was Trial 47, a combined OA/RA trial of renal/GI safety. It employed four pre-defined efficacy endpoints, the patient and investigator globals, and the incidence and time to dropout for inefficacy. Trial 47 did not use a placebo arm, so no negative control efficacy comparisons could be made, and no statistically significant superiority was show for any pair-wise comparison of active drugs for any of the four endpoints, but this is an insensitive method to detect small differences. As described in the OA Section earlier, the Q-statistic and its 95% confidence interval offer a method to look in a more discriminating manner for small differences for continuous or interval variables, so this was done for the two global assessments in this trial. TABLE 16 displays the Q values for the 614/1218 patient RA subset of this trial, both by all RA patients enrolled with the analysis point being 14 weeks and those enrolled pre-amendment (n=457) using a 26 week point for analysis. (Because of slow enrollment of patients with RA in Trial 47, the protocol was amended to change the RA analysis from week 26 to week 14, allowing enrollment of RA patients for only 14 weeks rather than 26 weeks.)

TABLE 16: Trial 47 Q value comparisons for RA subset

14 wk comparisons		Q (95% CI)

patient global	val20 vs nap	0.89 (0.57-1.34)
	val40 vs nap	0.96 (0.65-1.44)
investigator global	val20 vs nap	0.87 (0.56-1.30)
	val40 vs nap	0.96 (0.64-1.41)
26 wk comparisons		
patient global	val20 vs nap	1.17 (0.68-2.15)
	val40 vs nap	1.00 (0.53-1.86)
investigator global	val20 vs nap	1.30 (0.74-2.51)
	val40 vs nap	0.98 (0.48-1.85)

Conclusions:
There is no suggestion of superiority of valdecoxib compared to naproxen. There is no suggestion of superiority of valdecoxib 40 mg compared to 20mg/day.

TRIAL 62: This six-month efficacy/safety trial had no placebo control, so it only allows comparisons of the valdecoxib 20mg/d and 40mg/d arms with the diclofenac control. The only analyses provided were tests of differences, the results of which are listed below for the ACR20 (by CMH) and for time-to-withdrawal for inefficacy (by log rank).

TABLE 17: TRIAL 62: EFFICACY RESULTS, P VALUES

comparison at 6mo	val20mg vs diclof.	val40mg vs diclof.	val20mg vs val40mg
ACR20	0.843	0.834	0.834
time-to-ineff. w/draw	0.187	0.981	0.405

CONCLUSION

Studies 60 and 61 provide adequate and well controlled evidence of efficacy for valdecoxib 10mg in RA with no evidence of increased efficacy at 20mg or 40mg/d dosing in studies 60, 61, 62 and 47

ANALGESIA EFFICACY

OVERVIEW
The goals of the analgesia program in the valdecoxib NDA were to support labeling claims for the treatment of (1) acute pain, (2) primary dysmenorrhea, and (3) pre-operative administration for the treatment of post-operative pain and 4) opioid sparing. The randomized trial evidence for analgesia in the valdecoxib NDA consisted of seven dental pain trials, two dysmenorrhea trials, two trials in pre/post operative settings using regional anesthesia, and eight trials in various post-operative surgical settings. Five of the latter

3

The other three trials were designed to assess opioid-sparing: Total knee replacement (TKR), total hip replacement (THR), and coronary artery bypass graft (CABG).

rials 52, 38, 51, and 35 (CABG)).

TRIAL DESIGN

The studies and their relevant treatment arms are listed below. Very low (<10mg/d) or very high (>80mg total daily dose) dosing, used only for early dose exploration, is not included. The dental and pre-operative use trials enrolled approximately 50 patients per arm, except for the large CABG trial (Trial 35) which enrolled 311 patients on valdecoxib and 151 on placebo. The dysmenorrhea trials (Trials 65 and 66) were 4-way crossover designs employing 30 patients per trial.

Ibuprofen (ibu) at 400mg or oxycodone/acetaminophen (O/A) at 10mg/1000mg were the most commonly used active controls; rofecoxib (rof), diclofenac (dicl), and naproxen (nap) were also used. Paracoxib, the parenteral prodrug of valdecoxib, was used for initial dosing in Trial 35. Entry criteria differed substantially across trials. Rescue medication was allowed in all except and the three opioid-sparing trials; it consisted of acetaminophen 1000mg in Trials 65 and 66.

TABLE 1: TRIAL DESIGN

Trial Number Arms (sd=single dose)	Valdecoxib Arms (mg qd, unless noted)			Control
DENTAL				
58-sd	20	40		O/A
59-sd	20	40		O/A
64-sd (+optional redose)			40bid	rof
SURGICAL				

52-md (inguinal hernia)

SURGICAL - PRE-OPERATIVE

24-sd (oral surgery)	10	20	40	80	none
37-sd (bunionectomy)	10	20	40	80	none

SURGICAL - OPIOID SPARING*

38-md (TKR)		20bid	40bid
51-md (THR)		20bid	40bid
35-md (CABG)	paracoxib 40 bid IV--> Valde 40bid PO for 14 days		

* note: these 3 trials allowed ad lib use of narcotics, so the hypothesis was "sparing of narcotic use" in a valdecoxib arm versus a placebo arm.

DYSMENORRHEA

65-sd/md	20bid	40bid	nap
66-sd/md	20bid	40bid	nap

VALID ANALYSES

Analgesia trials have traditionally concentrated on single-dose evidence, and this focus impacts trial design, execution, and analysis in a way which renders non-informative most attempts to assess multiple-dosing and dosing regimens.

In this and past NDAs the major mechanism leading to this limitation in meaningful analysis are the high dropout rates in these trials, associated with the models elected and patients enrolled, and the operational conduct itself of trial execution. At the planning stage there is the single-dose focus, with design fundamentals such as the election of primary endpoints and powering being determined by this focus, so it is not unexpected for this limitation to occur. No analytic device can legitimately overcome substantial dropouts, short of the rare circumstance where the results stand up to a worse-case sensitivity analysis, and no imputation technique to date has satisfactorily answered this problem.

In this review this problem cannot be ignored. Trial participation drops precipitously over time due to dropouts. Validity is deemed irretrievably lost in these trials at any point where 50% or more of the patients are missing. Any inference using datasets smaller than this 50% figure is considered to have lost validity. Table 2 below lists the most distal time-point after which dropouts of more than 50% accordingly render analyses pointless. For each arm of each trial three numbers are entered:

1st number = patients initiating trial

2nd number = patients still in trial at the designated primary time-point
3rd number = patients continuing beyond that time-point

No third entry occurs if the second time-point is the end of the trial, as occurred with Trials 38, 51, and 35.

TABLE 2: MAXIMAL TIMEPOINT FOR VALID ANALYSIS (see text for explanation)

Trial	Time	Plc	Val 5	Val 10	Val 20 (or 20bid: #52,65,66, 38,51)	Val 40 (or 40bid: #52,64,80, 65,66,38, 51,35)	Ibu	O/A	Other r=rof. d=diclof. n=nap.
#58	1 hr	52, 52,26			52, 52, 45	50, 50, 45		51, 51, 51	
#59	1 hr	51, 51, 20			49, 49, 43	50, 50, 42		51, 51, 48	
#64	1 hr	41, 41, 18				80, 80,60			82,82,62-r
#24	2hr	57, 54, 16		56, 54, 44	57, 56, 51	57, 53, 48			
#37	4hr	55, 26, 8			56, 43, 30	57, 38, 34			
#65*	12 hr	102, 60, 9			102,69,5&	98, 80,7			98,76,5-n
#66*	12 hr	94, 60, 5			92, 76, 6&	91, 72, 8			93,72,12-n
#38	48hr	70, 34			70, 33 **	69, 37 **			
#51	48hr	71, 61			73, 65**	73, 69			
#35(cabg)	72hr	151, 117				311, 227			

*** Trials #65 and #66 were 4-fold crossover designs of 30 patients per trial**

.. Trials 65, 66, and sed appropriate active control re-dosing (naproxen or diclofenac at 12 hours) and were able to retain adequate patients for analysis at 12 hours.

TABLE 3: PATIENTS ENTERING, REMAINING PATIENTS AT FOUR HOURS

Trial	Plc	Val5	Val10	Val20	Val40	ibu	O/A	rofecoxib
#58	52, 9			45, 35	45, 41		51, 40	
#59	51, 8			49, 37	50, 34		51, 32	
#64*	41, 6				80, 57*			82, 41
#24	57, 10		56, 38	52, 42	57, 47			
#37	55, 8			56, 30	57, 34			

*Trials 64 —— used valdecoxib at 40mgbid

EFFICACY ANALYSIS RESULTS

. The opioid-sparing trials are analyzed only with two measures: SPID and opioid-sparing.

A few trials did not nave these precise endpoints, e.g. Trials 24 and 37, starting in the pre-operative setting, could have no time-zero anchor for the SPID, so here an approximate 1-4hr SPID is used. Also time-to-analgesia was not measured in five trials (Trials 24, 37, 52, 65, 66). t Trials 64 used SPID1
Trials 38 and 51 the SPID48, and Trial 35 the SPID24 and SPID72.

In summary, the efficacy endpoints are as follows:

DENTAL / SURGICAL / DYSMENORRHEA TRIALS
1 - SPID
2 - time-to-analgesia
3 – time-to-rescue-medication use

OPIOID-SPARING TRIALS
1 – SPID
2 – opioid sparing

TABLE 4: EFFICACY COMPARED TO PLACEBO: STATISTICALLY SIGNIFICANT DIFFERENCES ($p<0.05$) OF PRIMARY ENDPOINTS OVER TIME WINDOWS FOR VALID ANALYSIS

SYMBOLS

b	better: statistically, than placebo
s	same: no difference, than placebo
w	worse: statistically, than placebo
n	not measured

ALL TRIALS except opioid sparing

first symbol	summed pain intensity difference
second symbol	time-to-analgesia
third symbol	time-to-rescue-use

OPIOID-SPARING TRIALS

first symbol	peak pain intensity
second symbol	opioid sparing

Trial	Time-window	----Valdecoxib Dose------			
		10mg	20mg	40mg	
DENTAL					
58	0-4 hr	b b b	b b b		
59	0-4 hr	b b b	b b b		
					40bid
64	0-4 hr				b b b
SURGICAL					
52 (ing.h.)					

SURGICAL - PRE-OPERATIVE		20mg	40mg	80mg
24	0-4 hr b n b	b n b	b n b	b n b
37	0-4 hr	b n b	b n b	b n b

SURGICAL - OPIOID SPARING		20bid	40bid
38 (TKR)	0-48 hr	b s	b b
51 (THR)	0-48 hr	s b	s b
35 (CABG)	0-72hr		b b

DYSMENORRHEA		20bid	40bid
65	12 hr	b n s	b n b
66	12 hr	b n b	b n b

TABLE 5: EFFICACY COMPARED TO ACTIVE CONTROLS - STATISTICALLY SIGNIFICANT DIFFERENCES ($p<0.05$) OF PRIMARY ENDPOINTS OVER TIME WINDOWS FOR VALID ANALYSIS (Note: No trials were formally powered for equivalence (non-inferiority).

SYMBOLS	
b	better: statistically, than active control
s	same: no difference, than active control
w	worse: statistically, than active control
n	not measured

Trial	Time-window	Valdecoxib Dose 10mg	20mg	40mg	Active Control
DENTAL					
58	0-4 hr		s w w	s s s	O/A
59	0-4		s s s	s s s	
64	0-4 hr			40bid s s b	rof
SURGICAL					
52 (ing.h.)					

DYSMENORRHEA

65	0-12 hr	s s s	s s b	nap
66	0-12 hr	s s b	s s b	nap

SURGICAL TRIALS - PRE-OPERATIVE: Not applicable; no active controls
SURGICAL TRIALS - OPIOID SPARING: Not applicable; no active controls

DURATION OF ACTION OF VALDECOXIB

As noted above there are no adequate multiple-dose data from which to deduce an optimal dosing interval. However, there are indirect ways one might get a sense as to the approximate dosing interval. Several approaches are available using the data presented in the NDA.

(1) A qualitative examination of the full time course curves for patients remaining to the duration of the dental trials (this apporach is heavily influenced by early responses and non-responses such that even placebo does not show a downward slope in pain curves after the initial placebo response).
(2) An examination of the median time-to-rescue or time-to-re-medication.
(3) % of subjects rescuing within 12 or 24 hours
(4) pharmacokinetic data

FULL TRIAL DURATION DATA: The sponsor collected pain-intensity-difference data for the entire trial duration, using LOCF for imputation of trial dropouts. Although comparisons beyond approximately 4 hours are inappropriate because of the short duration-of-action of the active controls, the exceptions being naproxen in Trials 65 and 66 and rofecoxib in Trials 64 and → examining the shape of the valdecoxib curves may help us estimate dosing intervals. These graphs are supplied below.

17

Mean PR Scores (0-24 Hours Postdose), Post-Oral Surgery Analgesia
Study 005

18

APPEARS THIS WAY
ON ORIGINAL

Mean PID (Categorical) Scores (0-24 Hours Postdose), Post-Oral Surgery Analgesia Study 014

19

APPEARS THIS WAY
ON ORIGINAL

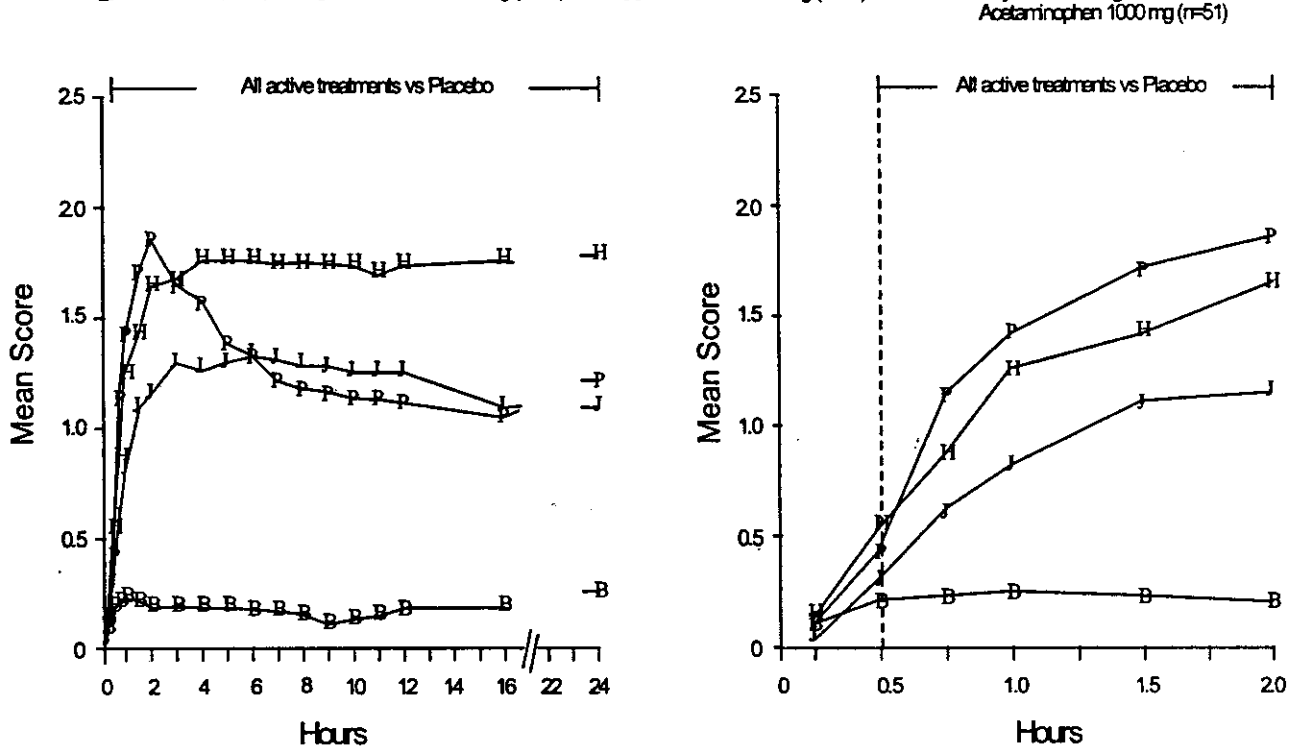
Mean PID (Categorical) Scores (0-24 Hours Postdose), Post-Oral Surgery Analgesia Study 035

20

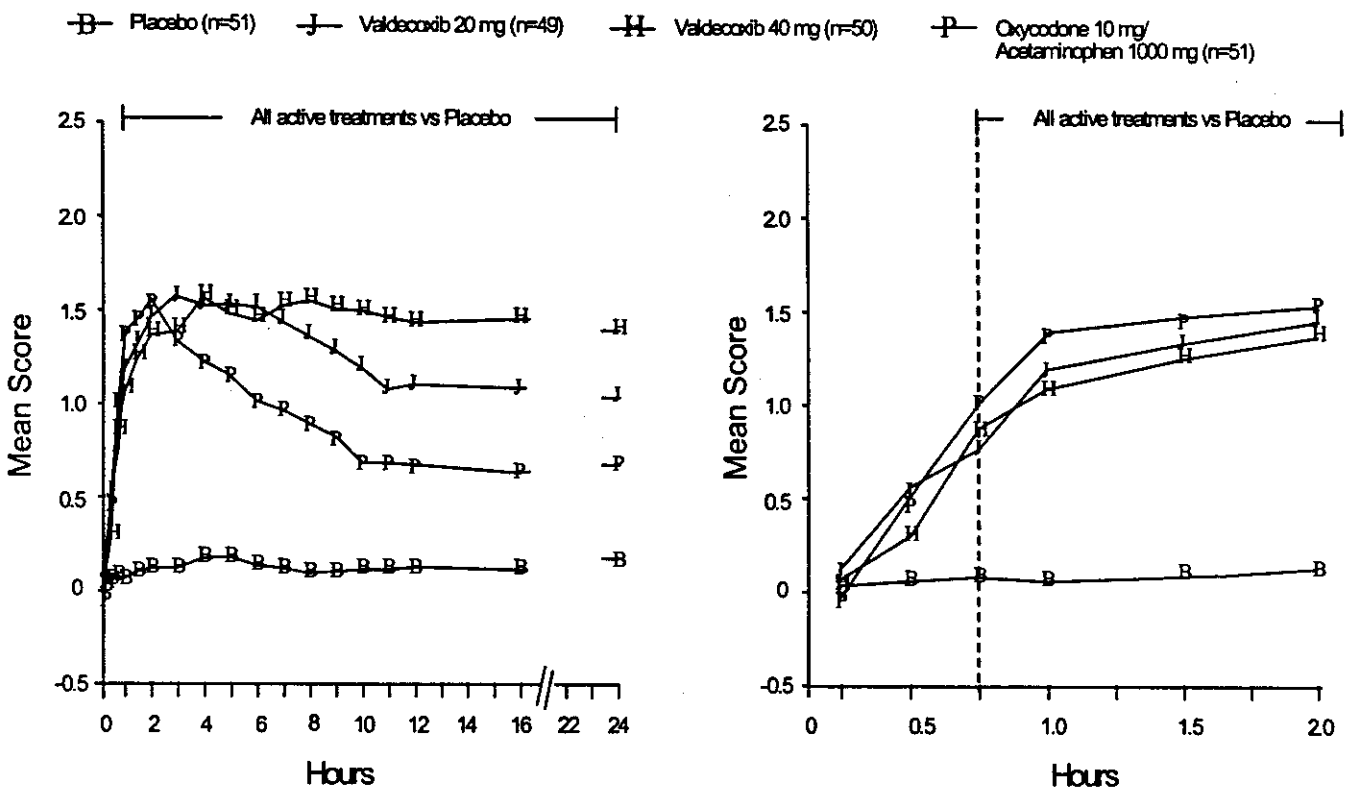
APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Mean PID (Categorical) Scores, Post-Oral Surgery Analgesia Study 058



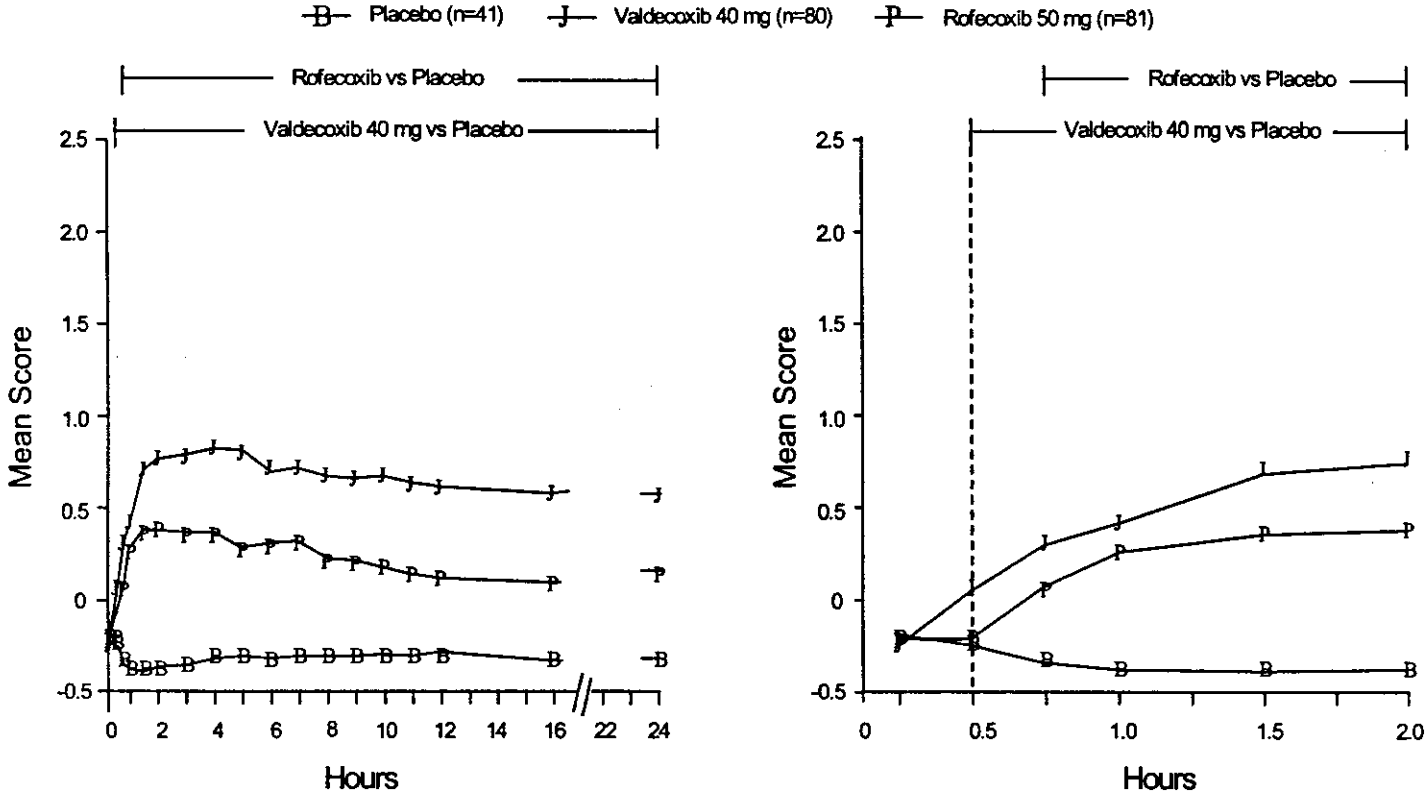
Mean PID (Categorical) Scores, Post Oral-Surgery Analgesia Study 059



APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Mean PID (Categorical) Scores, Post-Oral Surgery Analgesia Study 064



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Mean PID (Categorical) Scores, Post-Oral Surgery Analgesia Study 080

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MEDIAN TIME-TO-RESCUE OR RE-MEDICATION: These data are supplied in Table 6. All comparisons of all treatment arms were significantly different from placebo (by log rank)

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TABLE 6: Time to Rescue Medication, Dental Trials

Study	Median Time to Rescue Medication (hr:min) [1,4]	Proportion of Patients Requiring Rescue Medication [1]
Study 058		
Placebo	**01:05**	**0.85**
Valdecoxib 20 mg	**>24:00**	**0.46**
Valdecoxib 40 mg	**>24:00**	**0.24**
Oxy./acetamino.	**11:17**	**0.55**
Study 059		
Placebo	**01:04**	**0.90**
Valdecoxib 20 mg	**10:53**	**0.57**
Valdecoxib 40 mg	**>24:00**	**0.44**
Oxy./acetamino.	**06:04**	**0.78**
Study 064		
Placebo	**01:18**	**0.93**
Valdecoxib 40 mg	**07:06**	**0.64**
Rofecoxib 50 mg	**03:44**	**0.81**

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Data from the dysmenorrhea studies 065 and 066 is presented below. These results support the efficacy of valdecoxib at 20 and 40 mg as single doses. The median time to rescue and kaplan meier curves for rescue medication use suggest a twice daily dosing regimen as do pharmacokinetic data. The flatness of the pain curves for both placebo and active control groups suggests that these curves would be of minimal value in establishing a dosing interval.
Tables are excerpted from Dr. Lu's statistical review.

Study 065

Table 23. Primary Efficacy Parameters (8 and 12 hours post first dose of study medication)

Parameter	Placebo	Valdecoxib 20 mg	Valdecoxib 40 mg	Naproxen Sodium
Sum of Pain Relief (SPID)				
At 8 hours	7.31 (B)	9.77 (A)	10.87 (A)	10.64 (A)
At 12 hours	11.73 (C)	15.16 (B)	17.39 (A)	16.78 (AB)
Total Pain Relief (TOTPAR)				
At 8 hours	15.05 (B)	18.89 (A)	20.80 (A)	20.55 (A)
At 12 hours	23.78 (B)	29.35 (A)	32.90 (A)	32.29 (A)

a: treatments that have the same letter (A or B) were not significantly different in the distribution of the parameter based on the Fisher's Protected Least Significant Difference (LSD) comparisons

Figure 13. Mean Pain Intensity Difference

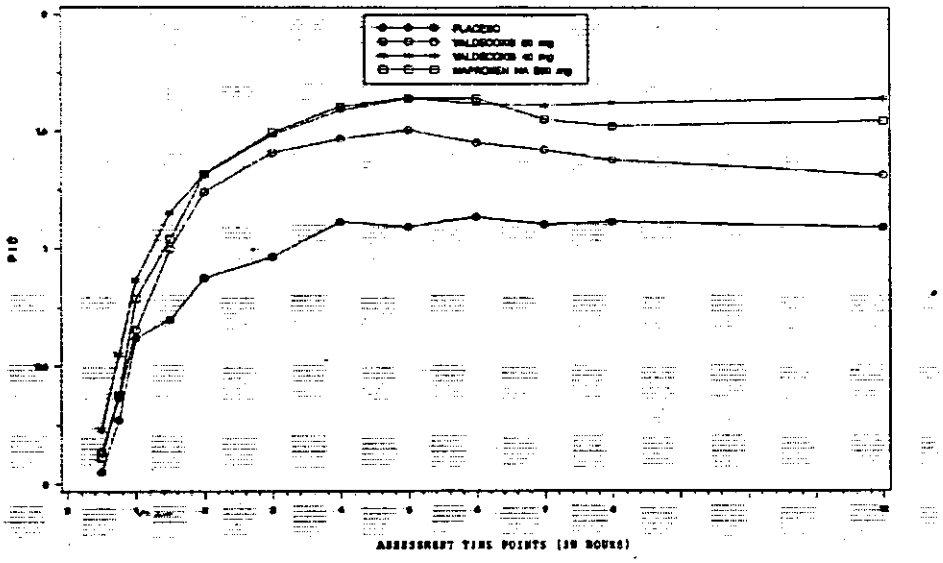
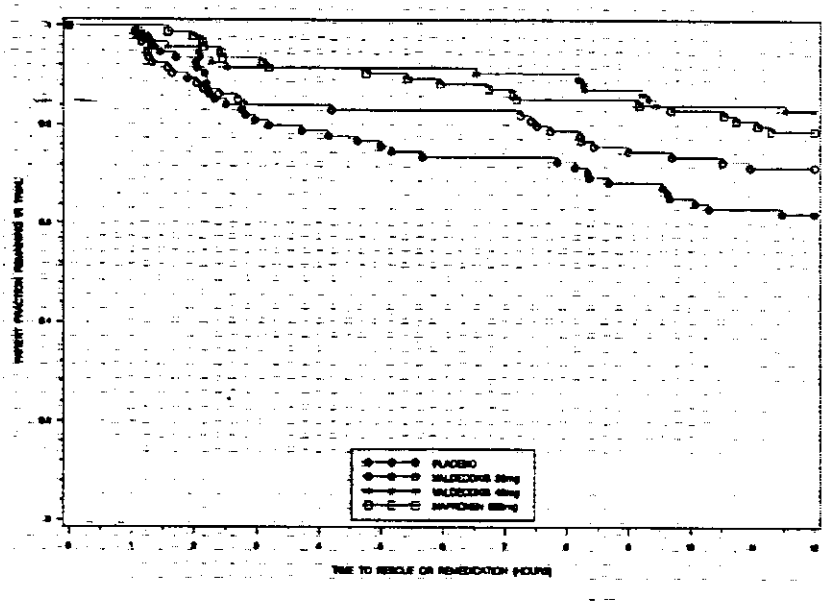


Figure 14. Kaplan-Meier Estimators for Distribution of Time to Rescue Medication or Remedication



Study 066

Table 25. Primary Efficacy Parameters (8 and 12 hours post first dose of study medication)

Parameter	Placebo	Valdecoxib 20 mg	Valdecoxib 40 mg	Naproxen Sodium
Sum of Pain Intensity Difference (SPID)				
At 8 hours	6.41 (B[a])	10.32 (A)	10.36 (A)	10.76 (A)
At 12 hours	10.34 (B)	16.14 (A)	16.45 (A)	16.54 (A)
Total Pain Relief (TOTPAR)				
At 8 hours	14.07 (B)	19.64 (A)	20.94 (A)	20.71 (A)
At 12 hours	21.99 (B)	30.67 (A)	32.94 (A)	31.89 (A)

a: treatments that have the same letter (A or B) were not significantly different in the distribution of the parameter based on the Fisher's Protected Least Significant Difference (LSD) comparisons

Figure 15. Mean Pain Intensity Difference

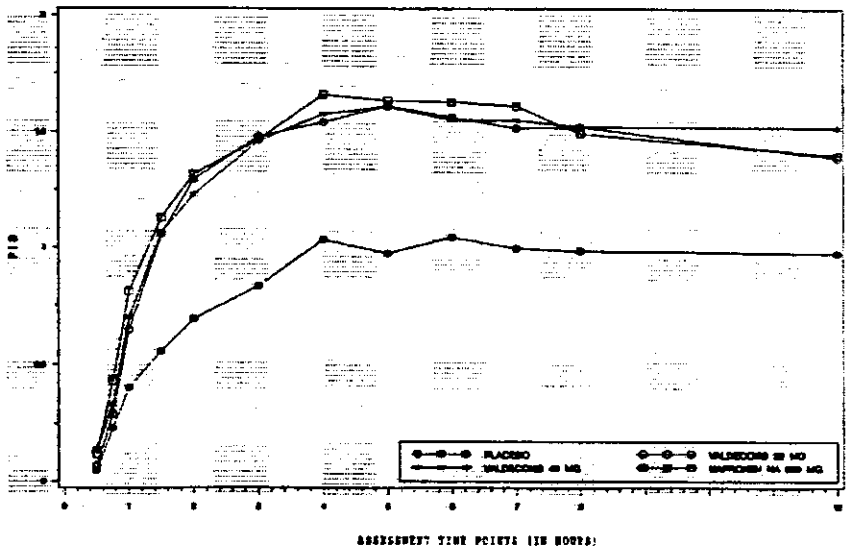
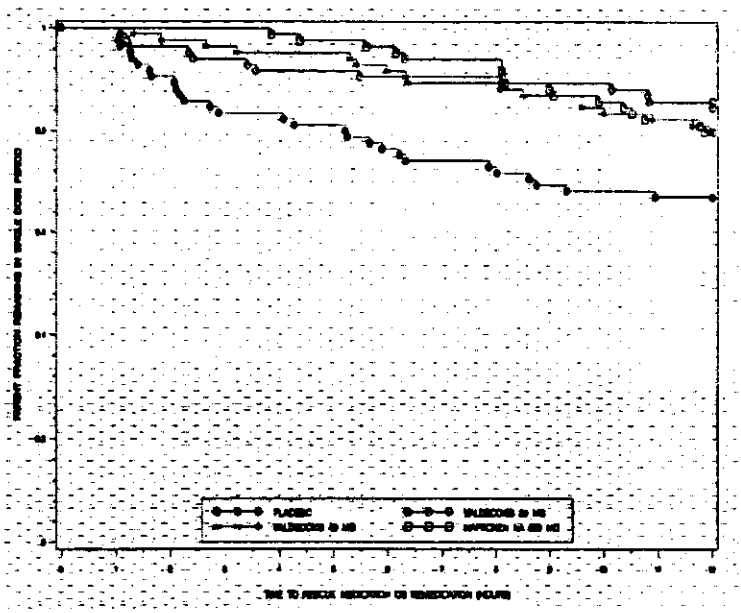


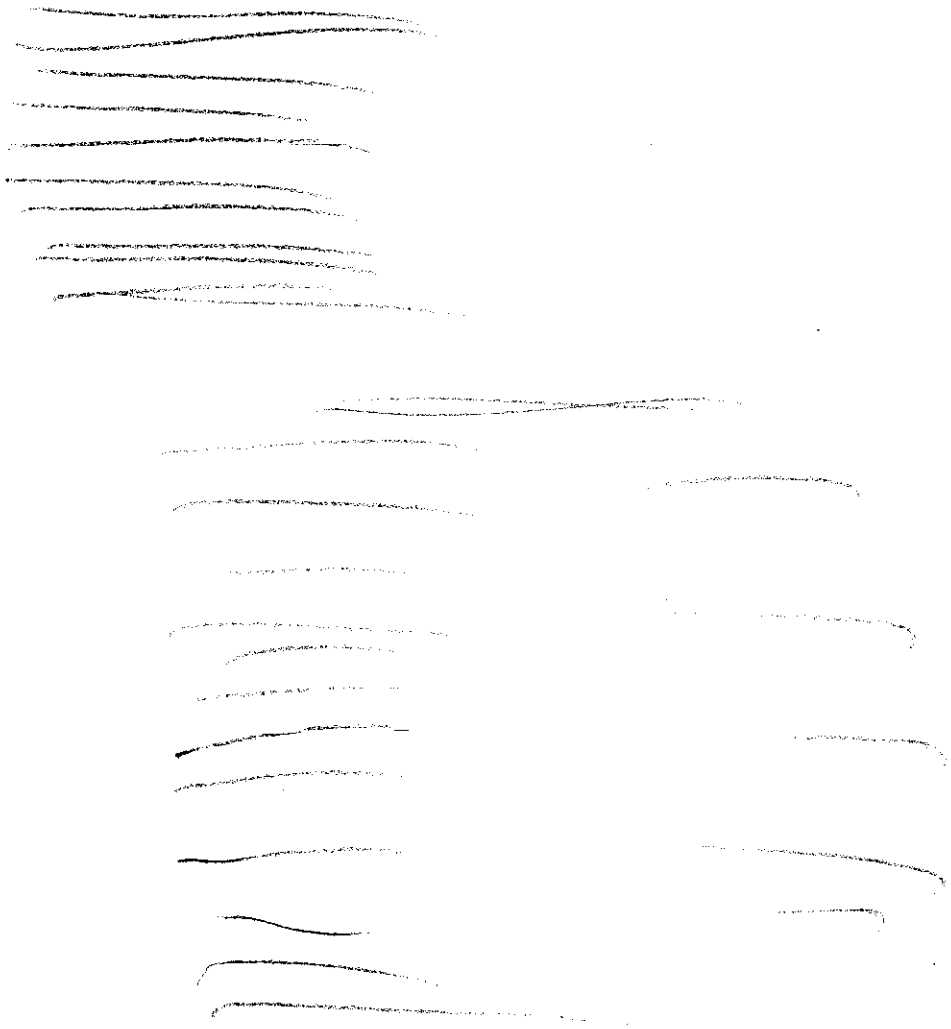
Figure 16. Kaplan-Meier Estimators for Distribution of Time to Rescue Medication or Remedication



Time to onset data is presented in the following tables for the general surgery studies. This is the one parameter where differentiation from placebo was not statistically robust. However, onset within one hour is consistently noted. For further details the reviewer is referred to the statistical review.

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

PAGE 37 → REDACTION 23
PAGE 38 → REDACTION 24



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Conclusion:

The data demonstrate the following:

1. **Dental setting: Single-dose, four-hour efficacy in**
   in trials — 58, and 59 for the 20mg dose, and Trials — 58, and 59 for the 40mg dose.
2. **Post-surgical setting (**
3. **Pre-operative surgical setting: Single-dose, four-hour efficacy in Trials 24 and 37 for**

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20mg and 40mg doses for the primary endpoint of time to rescue. No efficacy was demonstrated related to early post-operative pain intensity differences compared to placebo. No study comparing pre and post-operative dosing for any parameter of efficacy was performed. The clincal relevance of the single primary endpoint in isolation is unclear

4. Opioid-sparing surgical setting: Two-three day efficacy in Trials 38 and 51 at 40mgbid. The clincial relevance of small decreases in mean opioid dose is of unclear clinical significance in view of the safety findings in these studies.

5. Dysmenorrhea setting: Single dose efficacy in Trials 65 and 66 at 20 and 40mgbid dose.

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2. Evidence in use pre-operatively, although successful by the summed pain scores over four hours, shows an absence of superiority to placebo in a simple pain intensity difference at 2 or 4 hours (see Statistical Review). Finally, although there was little previous experience to guide the design and primary endpoint analyses for studies in pre-operative and opioid-sparing settings, the data are not robust enough to draw conclusions regarding the clinical value and relevance of use in such settings.

Based on the safety concerns raised in the CABG study 035, the safe use of valdecoxib in post-operative surgical settings, particularly in patients with underlying cardiovascular disease and at risk of thromboembolic events is not established. These concerns should be addressed in future studies. The safety of valdecoxib at the proposed chronic dose of 10 mg daily is based on extensive experience at 10-80 mg daily in the arthritis population. These data do not suggest safety concerns for use of the chronic dose in the intended population. The reviewer is referred to the safety section of the review.

Future acute pain development programs should directly assess multiple-dose efficacy by the use of designs which directly address multiple dose hypotheses, and inclusion criteria and primary endpoint timing which are aimed at retaining enough patients for interpretable analyses. Rigorous assessment of optimal dosing interval should also be considered.

ANALGESIA APPENDIX TABLE A: PROTOCOL SPECIFIED PRIMARY EFFICACY PARAMETERS

Trial	Powered						Time to:		
		PID	PR	SPID	Totpar	PG	PR	Analg.	RESCUE
58	45minPID	X	X			X	X	X	X
59	45minPID	X	X			X	X	X	X
64	regimen failure	PID1hr, rescue use (%),							

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24*	time rescue								X
37*	time rescue								X
65	spid8, totpar8			8,12hr	8,12hr				
66	spid8, totpar8			8,12hr	8,12hr				
38	MS sparing	MS sparing 0-24 hr for Trials 38 and 51							
51	MS sparing	MS sparing 0-24 and 0-72 hr for Trial 35							
35**									

*Trials 24 and 37 were single-dose, pre-operative studies, with the dose given ~1hr pre-surgery. The time-points are all based on surgical closure as time 0.
**Trial 35 was powered by both a 12mg MS sparing in 0-24hr (ref Pharmacotherapy 10(6 Pt2):127S-131S), 1990), and by an 80% power to detect a 1% incidence "clinically relevant adverse event" in a CABG population" in valdecoxib, estimated to show a 1% occurrence versus placebo, estimated to show a 7% occurrence (ref NEJM 335:1857, 1996)

SAFETY REVIEW

SAFETY STUDIES - TRIALS 47, 62, 48, 53

REPORT ON TRIAL 47

DESIGN: This was a 6 month RCT enrolling 1217 patients with RA or OA into three arms, Valdecoxib 20mgbid, Valdecoxib 40mgbid, and Naproxen 500mgbid, with adjudicated, two primary endpoints: (1) "clinically significant renal events" (defined below) at six months in RA and OA, and (2) endoscopic gastroduodenal ulcers over 14 weeks in RA. (The protocol was amended en route because of slow accrual of RA patients, allowing enrollment for only 14 instead of 26 weeks,

presumably because it was thought this would encourage enrollment. At the same the sample size was increased, reflecting the loss of power by reducing the exposure of part of the RA cohort. Consequently, all OA, and some RA, patients were treated for 6 months.) The initial sample size calculation of 300 patients per arm, predicated on 80% power and 0.05% significance, was to detect (1) a change of 6% in combined valdecoxib arms versus 18% in the naproxen arm for endoscopic ulcers, and (2) a change of 3% of the valdecoxib arms versus 10% in the naproxen arms for a renal event occurring at the 1% incidence level. Usual entry criteria for RA and OA were used, and a baseline endoscopic score (defined below) of 6 or less was required. No arthritis flare was required.

In addition to the two primary safety endpoints – renal and endoscopy (gastroduodenal ulcers) – noted above, there were also four pre-specified efficacy analyses -- patient global, investigator global, and incidence and time-to-withdrawal for inefficacy, and six pre-specified secondary endpoints:

1-Overall safety and tolerability
2-Efficacy by patient and investigator global and by time-to-inefficacy withdrawal
3-Gastric and duodenal ulcers
4-Gastroduodenal, gastric, and duodenal erosions/ulcers
5-Renal function (comparing Valdecoxib 20mgbid and 40mgBID)
6-Gastroduodenal ulcers at 14 weeks for OA and RA

"Clinically significant" renal events were defined as any of the following:

A laboratory criterion (confirmed by repeat observation within 3d):
- 1-creatinine increase over 30% or >1.2mg/dL if baseline <0.9mg/dL
- 2-BUN increase over 200% or >50mg/dL
- 3-total urinary protein/24hr >500 if baseline 0-150, >750 if baseline 151-300, >1000 if baseline 301-500
- 4-K>6mEq/L
- 5-Na<130mEq/L

Or a clinical criterion:
- 1-new or increase in edema
- 2-new or increase in CHF
- 3-increase in BP (>20 systolic, >10 diastolic)
- 4-new or increase in BP rx
- 5-new or increase in diuretic rx

A gastroduodenal ulcer by endoscopy defined as a mucosal break with diameter at least 3mm with unequivocal depth. An ulcer is ranked as 7 in the 0-7 endoscopy score system, with "0" being normal, "1"-"5" being intermediary numbers of erosions, and "6" being more than 25 erosions.

PRIMARY ENDPOINT ANALYSES SPECIFIED IN PROTOCOL

1-Comparison of incidence by Fisher's Exact test
2-Comparison of time to event by log-rank test

Gastroduodenal ulcers by endoscopy at 14 weeks in RA in patients with both a baseline and an exiting endoscopy. Missing data were imputed using intent-to-treat, last-observation-carried-forward.

RESULTS

PATIENT DISPOSITION

A total of 1217 patients were enrolled, 604 with OA and 614 with RA. Due to slow enrollment of RA patients, 157 of these were enrolled for a planned 14 week, rather than a 26 week duration (per Protocol Amendment - June, 2000). The mean age of the patients was 56 years, predominately female (about 70%) and Caucasian (>78%), and the proportion 65 or older was about one-quarter. Mean weight was 82 kg for females, 93 kg for males.

Patients proved to be well matched by multiple baseline variables, including renal and GI parameters, and by presence of CHF, diabetes, hypertension, and peripheral edema. Only three of 1217 had baseline renal insufficiency. There was an imbalance of diuretic use at baseline (val20mg: 9%, val40mg: 14.4%, naproxen 10.4%, p=0.045).

Patient disposition is shown in TABLES 1A, 1B, and 1C. Adverse event withdrawals include those with suspected renal or GI events (subsequently adjudicated by an independent committee to determine if they qualify for being an endpoint).

TABLE 1A: Trial 47 Overall Disposition

	VAL 20mgbid	VAL 40mgbid	NAP 500mgbid
Enrolled	399	403	415
Completed	244	254	253
24 wk completers	207	204	180
14 wk completers	29	35	38
14 wk aSx ulcer*	8	15	35
Withdrawals	155	149	162

*asymptomatic ulcer found at 14wk endoscopic examination

TABLE 1B: Trial 47 Withdrawals

	VAL 20mgbid	VAL 40mgbid	NAP 500mgbid
Total Enrolled	399	403	415
Total Withdrawals	155	149	162
Inefficacy	37	37	38

Adverse event	65	74	76
renal*	6	14	2
GI*	13	19	31
Endoscopy	3	2	10
Other	43	39	33
Noncompliance	45	34	34
Protocol violation	6	1	5
lost to f/u	2	4	9

*withdrawal due to symptoms in the category, then a determination was made as to whether either of the primary endpoints was met

TABLE 1C: Patients with Incomplete Database

Number patients	VAL 20mgbid	VAL 40mgbid	NAP 500mgbid
Enrolled	399	403	415
Missing exiting endoscopy	54	48	51

Review of the patients (data not shown) not completing the trial did not reveal any imbalance across arms of GI or vascular events, or other mal-distributions suggesting a differential dropout pattern which could undermine inferences.

PRIMARY RENAL ENDPOINT

A total of 105 events were adjudicated as renal primary endpoints. These were slightly more prevalent in the RA patients (65 events), compared with OA patients (40 events), but the distribution was otherwise similar. These were distributed as shown in the table below.

TABLE 2A: CLINICALLY SIGNIFICANT RENAL EVENTS

	VAL 20mgbid	VAL 40mgbid	NAP 500mgbid
Enrolled	399	403	415
renal events	34	48*	23*
0-2 wk	19	16	6
3-6 wk	9	14	7
7-10 wk	4	10	9
>10 wk	2	8	1

* $p<0.05$

The pathophysiology of these renal events is shown below.

TABLE 2B: RENAL EVENTS, BY PATHOPHYSIOLOGY

	VAL 20mgbid	VAL 40mgbid	NAP 500mgbid
Renal perfusion/filt.	2	5	2
Tubular dysfctn.	8	10	4
Proteinuria	1	1	1
Edema	6	9	3
Low Na	1	0	0
Worsening BP	24	31*	13*
Worsening CHF	0	1	1
Glom./tub-int. dis.	0	1	2

* $p<0.05$

PRIMARY GI ENDPOINT: ENDOSCOPIC ULCER

PRIMARY ANALYSIS: The analyses were done on the subset of patients with both a baseline and exiting (end-of-study or at premature withdrawal time) endoscopy, which excluded approximately fifty patients per arm or about one-eighth of the total study population (TABLE 1C). Review of these patients (data not shown) did not reveal any pattern suggesting a differential effect which might undermine inferences.

TABLE 3A: Gastroduodenal Endoscopic Ulcers

	VAL 20mgbid	VAL 40mgbid	NAP 500mgbid
crude incidence	15/345 (4%)	27/355 (8%)	66/364 (18%)
OA	6/172	16/175	36/178
RA	9/173	11/180	30/186

Valdecoxib 20mgbid and valdecoxib 40mgbid each statistically differed from naproxen by $p<0.001$.

TABLE 3B: Endoscopic Ulcer by Time of Ascertainment – Week 14 or Withdrawal Time or "For Cause"

Interval	VAL 20mgbid		VAL 40mgbid		NAP 500mgbid	
	no ulcer	ulcer	no ulcer	Ulcer	No ulcer	ulcer
1-19 d	7	0	13	1	10	3
20-49 d	24	3	19	0	24	6
50-77 d	23	2	19	1	15	4
78-105 d	50	7	51	7	54	35
>105 d	226	3	226	8	195	18
Total	330	15	328	27	298	66

Of GI endpoint events (gastroduodenal ulcers) in the valdecoxib 20mg, valdecoxib 40mg, and naproxen arms, 8, 15, and 35 patients, respectively, withdrew before week 14, constituting about one-half of the total ulcers. Although the NDA describes these as asymptomatic from a GI point of view, some would have discontinued for other symptomatology. Review of the reasons for withdrawal (data not shown) did not reveal any differential pattern which might undermine inferences.

RISK FACTOR ANALYSES

Exploratory analyses were done on how suspected risk factors may impact endoscopic outcomes, and whether this occurred differently in valdecoxib compared to naproxen. Factors analyzed are age, history of prior NSAID intolerance, history of prior ulcer, history of prior GI bleed, presence of cardiovascular disease, and presence of current aspirin use. The cardiovascular disease and aspirin use data are subdivided in RA and OA. Two items limit the validity of this exercise: (1) the result of a primary analysis will necessarily bias the result of any analysis of any of its subsets, so the analyses are not independent, and (2) baseline imbalance and small numbers will increase the risk of false conclusions. Therefore, any finding should be considered hypothesis generating.

TABLE 4A: CRUDE INCIDENCE RATES OF ENDOSCOPIC GASTRODUODENAL ULCERS

	Val 20mgbid		Val 40mgbid		Naproxen	
	Number	Percent	Number	Percent	Number	Percent
Overall	15/345	4.5%	27/355	7.6%	66/384	18.1%
Age						
≥ 65	8/99	8.1%	15/107	14%	24/88	27.3%
< 65	7/246	2.8%	12/248	4.8%	42/276	15.2%
Hx NSAID intolerance						
Yes	1/27	3.7%	5/35	14.3%	3/23	13.0%
No	14/318	4.4%	22/320	6.9%	63/341	18.5%
Hx ulcer						
Yes	3/36	8.3%	10/36	27.8%	16/43	37.2%
No	12/309	3.9%	17/319	5.3%	50/321	15.6%
Hx GI bleed						
Yes	1/5	20%	2/6	33.3%	2/7	28.8%
No	14/340	4.1%	25/348	7.2%	64/357	17.9%

TABLE 4B: Endoscopic Ulcers, Crude Incidence Rates

	Cardiovascular Disease?			Aspirin Use?		
	Val20bid	Val40bid	Naproxen	Val20bid	Val40bid	Naproxen
all pts.						
Yes	11/150 7.3%	19/165 11.5%	33/167 19.8%	6/49 12.2%	10/38 26.3%	7/54 13.0%

No	4/195	2.1%	8/190	4.2%	33/197	16.8%	9/296	3.0%	17/317	5.4%	59/310	19.0%
RA												
Yes	6/67	9.0%	6/73	8.2%	13/75	17.3%	2/23	8.7%	3/12	25.0%	4/22	18.2%
No	3/106	2.8%	5/107	4.7%	17/111	15.3%	7/150	4.7%	8/168	4.8%	26/154	15.9%
OA – +												
Yes	5/83	6.0%	13/92	14.1%	20/92	21.7%	1/26	15.4%	7/26	26.9%	3/32	9.4%
No	1/89	1.1%	3/83	3.6%	16/86	18.6%	2/146	1.4%	9/149	6.0%	33/146	22.6%

TABLE 4C shows p values for two questions:

1. Given the drug exposure, does the presence or absence of the risk factor impart a statistically significant difference in endoscopic ulcers, measured with Fisher's Exact?

2. Given the presence of the risk factor, does use of valdecoxib compared to the naproxen control impart a statistically significant difference in endoscopic ulcers, measured by Cochran-Mantel-Haenszel (CMH) test, stratified by factor and controlled by site)? The CMH test assumes that the effect, the relative risk, is the same across strata (eg. younger than 65 versus 65 and older); if it were not there would be a significant interaction between the treatment and the risk factor. There obviously is not data to support the CMH assumption, so I have asked the company to conduct the interaction test (the Bretszel Day Interaction) for this table.

TABLE 4C: P Values - Impact of Selected Risk Factors

	Given the drug, effect of risk factor			Given the risk factor, effect of valdecoxib compared to naproxen	
	Val20mgbid	Val40mgbid	naproxen	Val20 v nap	Val40 v nap
Risk factor					
Age	0.041	0.004	0.016	<0.001	<0.001
Nsaid intol.	1.000	0.167	0.777	<0.001	<0.001
Hx ulcer	0.199	<0.001	0.001	<0.001	<0.001
Hx GI bleed	0.200	0.069	0.415	<0.001	<0.001
CV disease	0.030	0.015	0.496	<0.001	<0.001
ASA use	0.011	<0.001	0.342	<0.001	<0.001

Serious UGI adverse events and withdrawals due to GI adverse events

In this trial there were three serious UGI events associated with bleeding perforation or obstruction on naproxen, compared to two in the valdecoxib 80-mg group and none in the valdecoxib 40-mg group. A list of withdrawals due to adverse events was requested of the sponsor, and submitted on October 2, 2001. It is shown in the Table 4D below.

Table 4D: Withdrawals Due to Adverse Events

	Naproxen (399)	Valde 20 mg bid (n=403)	Valde 40 mg bid (n=415)
HTN	1	2	5
CHF (worsening or new)	-	-	1
MI/DVT/CVA/TIA /PE	-	2	1
Increased bun or creatinine	1	3	3
UGI bleed/anemia	4	3	1

These results suggest that proposed safety benefits must take into account overall safety to be meaningful. This would also apply to a meta-analysis the sponsor has proposed of arthritis and safety studies claiming to show that valdecoxib is associated with fewer clinically relevant UGI ulcers than NSIAD comparators in the database.

Conclusions

1. Valdecoxib both 20 and 40 mg/day was associated with statistically significantly fewer gastroduodenal ulcers than naproxen.
2. There was a dose response trend in ulcer rates between 20 and 40 mg/day valdecoxib.
3. Age over 65, history of peptic ulcer disease, and history of GI bleed all markedly increased the ulcer rate in all treatment groups. The absolute ulcer rates associated with the use of valdecoxib in these high risk populations is similar to the rates seen in the overall population treated with the other NSAIDs.
4. In the valdecoxib groups, concomitant treatment with low dose aspirin was associated with a dose-dependent, four to five-fold increase in ulcer rate in the valdecoxib groups. In the naproxen treated group the ulcer rate associated with concomitant aspirin use trended downward rather than upward. This is a similar trend to that seen between celecoxib and ibuprofen in the CLASS trial comparing complicated ulcer rates – higher event rates with concomitant aspirin use in the celecoxib arm, but a decrease in event rate with concomitant aspirin use in the NSAID comparator group. This again raises the plausibility of an enhanced toxic effect of concomitant nonselective and COX-2 selective inhibition, compared to nonselective *or* selective COX-2 inhibition alone. A recent publication suggested such a phenomenon in an animal model. On the other hand, the valdecoxib Trials 62 and 48 did not show this apparent "protective" effect of diclofenac, and ibuprofen, so these data do not support the hypothesis outlined above and in the reference #1.
5. The significant renal adverse event profile of valdecoxib 40 and 80 mg/day

appears to be inferior to that of naproxen 1 gram/day. The comparative profile of 10-20 mg/day of valdecoxib in studies at these doses did not suggest inferiority to the comparator NSAIDs.

6. A rigorous assessment of the overall comparative safety on valdecoxib versus less selective NSAIDs would require a large clinical outcome study.

1 Wallace, LJ et al. NSAID Induced Gastric damage in rats: Requirement for inhibition of both cyclooxygenase 1 and 2; Gastroenterology 2000; 119:706-714

REPORT ON TRIAL 62

DESIGN: This was a 6 month RCT enrolling 722 patients with RA into three arms, Valdecoxib 20mgbid, Valdecoxib 40mgbid, and Diclofenac 75mgbid. All patients were to be treated for 6 months or to discontinuation. This trial had only an endoscopy at termination, none at baseline. The same scoring system was used for endoscopy as in Trial 47 (above). The primary efficacy endpoints were patient global and the HAQ, both tested by ANOVA with the site and treatment as factors and baseline as a covariate, and the primary safety endpoint was endoscopic gastroduodenal ulcer as in Trial 47, tested by CMH controlling for age, sex, CV disease, ASA use, prior GI intolerance, ulcer or bleed, and H. pylori status. Many secondary endpoints were specified, and an exploratory utility index (EQ-5D Euroquol) was also collected. The trial was powered with three parameters: (1) endoscopic ulcers: 150 patients per arm to detect a 4% valdecoxib rate versus a 15% diclofenac rate, assuming 35% withdrawals without endoscopy, (2) patient global: 230 patients per arm to detect a 7.2 mean change in either valdecoxib arm compared with diclofenac (variability=25), and (3) HAQ: 230 patients per arm to detect a 0.13 change in valdecoxib versus diclofenac (variability = 0.45), all done at an alpha of 0.05 and a beta of 80%, using data from a previous, similarly designed celebrex trial.

RESULTS

PATIENT DISPOSITION

A total of 722 patients were enrolled with RA, 246 to valdecoxib 20mg/d, 237 to valdecoxib 40mg/d, and 239 to diclofenac 75mgbid. Distribution of suspected ulcer risk factors at baseline are shown in Table 1A. Patient disposition is shown in Tables 1B and 1C.

TABLE 1A: Trial 62 – Baseline covariates (%)

	val 20mg/d	val 40mg/d	diclofenac 75mgbid
Hx ulcer	10.6	5.9	5.9

Hx GI bleed	2.4	1.3	1.3
H. pylori positive	38.6	37.1	36.0
Cardiovascular dis	40.2	31.2	41.0
Aspirin use	5.7	5.9	5.4

TABLE 1B: Trial 62 – Overall Patient Disposition

	val 20mg/d	val 40mg/d	diclofenac 75mgbid
Total Enrolled	246	237	239
Total Completed	178 (72%)	179 (24%)	161 (67%)
No exit endoscopy	33	22	31
Total Withdrawals	68 (28%)	58 (24%)	78 (33%)
Inefficacy	23 (9%)	22 (9%)	24 (10%)
Adverse event	24 (10%)	25 (11%)	37 (15%)
Noncompliance	16 (7%)	7 (3%)	10 (4%)
protocol violation	4 (2%)	4 (2%)	7 (3%)
Lost to f/u	1 (<1%)	0 (0%)	0 (0%)

TABLE 1C: Trial 62 – Withdrawals for Adverse Events

Category	VAL 20mg/d	VAL 40mg/d	DICLOF 75mgbid
All AEs	24	22	31
body as a whole	5	1	5
CNS	1	2	3
collagen disorders	0	3	0
female symptoms	0	1	0
GI	11	13	28
CV	3	0	2
metabolic	0	1	1
musc/skeletal	1	0	1
neoplasm	1	0	0
psychiatric	1	0	0
anemia	0	0	1
infection	0	1	0
respiratory	0	2	0
skin	3	0	2
urinary	0	1	0

TABLE 2A: Trial 62 – Endoscopic Ulcers by Time of Ascertainment – Month 6 or Time of Withdrawal

Interval	val 20mg/d		val 40mg/d		diclofenac 75mgbid	
	no ulcer	ulcer	no ulcer	ulcer	no ulcer	ulcer
1-19 d	4	0	5	0	5	2
20-49 d	9	3	11	1	9	5

50-77 d	2	1	10	0	13	2
78-105 d	11	0	9	0	6	2
>105 d	175	8	172	7	141	23
Total	201	12	207	8	174	34

The log rank comparisons for both valdecoxib / diclofenac comparisons showed a p value of <0.001. Analysis of patients missing the final endoscopy (results not shown) did not reveal a differential dropout pattern.

As in Trial 47, exploratory analyses were done on how suspected risk factors may impact endoscopic outcomes, and whether this occurred differently in valdecoxib compared to naproxen. Factors analyzed are age, history of prior NSAID intolerance, history of prior ulcer, history of prior GI bleed, presence of cardiovascular disease, and presence of current aspirin use. Two items limit the validity of this exercise: (1) the result of a primary analysis will necessarily bias the result of any analysis of any of its subsets, so the analyses are not independent, and (2) baseline imbalance and small numbers will increase the risk of false conclusions. Therefore, any inference should be considered hypothesis generating.

TABLE 4A: CRUDE INCIDENCE RATES OF ENDOSCOPIC ULCERS

	Val 20mgbid		Val 40mgbid		Diclofenac 75 mg bid	
	Number	Percent	Number	Percent	Number	Percent
Overall	12/213	5.6%	8/215	3.7%	34/208	16.3%
Age						
≥ 65	6/58	10.3%	2/42	4.8%	11/56	19.6%
< 65	6/155	3.9%	6/173	3.5%	23/152	15.1%
Hx NSAID intolerance						
Yes	3/25	12%	1/23	4.3%	4/19	21.1%
No	9/188	4.8%	7/192	3.6%	30/189	15.9%
Hx ulcer						
Yes	2/25	8%	1/12	8.3%	3/10	30%
No	10/188	5.3%	7/203	3.4%	31/198	15.7%
Hx GI bleed						
Yes	1/6	16.7%	0/3	0%	3/3	100%
No	11/207	5.3%	8/212	3.8%	31/205	15.1%
CV disease						
Yes	8/84	9.5%	3/68	4.4%	16/84	19.0%
No	4/129	3.1%	5/147	3.4%	18/124	14.5%
Aspirin use						
Yes	0/11	0%	3/9	33.3%	4/10	40.0%
No	12/202	5.9%	5/206	2.4%	30/198	15.2%

TABLE 4B shows p values for two questions:

1. Given the drug exposure, does the presence or absence of the risk factor impart a statistically significant difference in endoscopic ulcers (measured with Fisher's Exact)?

2. Given the presence of the risk factor, does use of valdecoxib compared to the diclofenac control impart a statistically significant difference in endoscopic ulcers (measured by Cochran-Mantel-Haenszel test, stratified by factor and controlled by site)?

TABLE 4B: P Values - Impact of Selected Risk Factors

	Given the drug, effect of risk factor			Given the risk factor, effect of valdecoxib compared to diclofenac	
	Val20mgbid	Val40mgbid	Diclofenac	Val20 v Diclofenac	Val40 v Diclofenac
Risk factor					
Age	0.092	0.656	0.526	<0.001	<0.001
Nsaid intol.	0.154	0.602	0.523	<0.001	<0.001
Hx ulcer	0.637	0.373	0.212	<0.001	<0.001
Hx GI bleed	0.297	1.000	0.004	<0.001	<0.001
CV disease	0.067	0.710	0.446	<0.001	<0.001
ASA use	1.000	0.003	0.061	<0.001	<0.001

Conclusions:

1. **In Trial 62, valdecoxib 20 mg bid and 40mg bid were both associated with statistically significantly fewer endoscopic gastroduodenal ulcers than diclofenac 75 mg bid. No dose response relationship was evident between the two valdecoxib groups.**
2. **The risk of gastroduodenal ulcers was increased in the high risk groups as displayed in tables 4A and 4B. There was no paradoxical decrease in ulcer rate in the diclofenac group as was seen in the naproxen group in study 47.**

REPORT ON TRIAL 48

DESIGN: This was a 3 month RCT comparing valdecoxib 10mg/d, valdecoxib 20mg/d, ibuprofen 800mgTID, diclofenac 75mgBID, and placebo. Patients were required to have the diagnosis of OA but this was not further specified, and they required the absence of ulcers by endoscopy at baseline. The primary endpoint was gastroduodenal ulcers by endoscopy at end of trial (3 months) or sooner if withdrawn, compared using the Cochran-Mantel-Haenszel test controlling for site,

with the primary comparisons being the summed valdecoxib arms compared with ibuprofen, and the summed valdecoxib arms compared with diclofenac. Four efficacy endpoints were also prespecified – patient global, physician global, and incidence and time to withdrawal for treatment failure, and these efficacy results are described in the Arthritis Efficacy Review.

TABLE 1A: Trial 48 – Patient Disposition

arm	val 10mg/d	val 20mg/d	ibuprofen	diclofenac	placebo
randomized	204	219	207	212	210
completed	150	165	156	152	135
no final endos.	15	21	23	25	32
withdrawn	54	54	51	60	75
inefficacy	16	17	11	12	45
adverse event	19	20	27	34	15
noncompl.	16	9	10	9	7

TABLE 2A: Trial 48 – Endoscopic Ulcers, Crude Incidence Rates

	val 10mg/d	val 20mg/d	ibuprofen	diclofenac	placebo
Number (%)	7/189 (3.7%)	7/198 (3.5%)	25/184 (13.5%)	25/187 (13.4%)	8/178 (4.5%)

All comparisons of valdecoxib arms with control arms (ibuprofen and diclofenac) are statistically significant at the <0.001 level.

TABLE 2B: Trial 48 - Endoscopic Ulcers (numbers of patients) by Time of Ascertainment: Week 13 or Time of Withdrawal

days	val 10mg/d		val 20mg/d		ibuprofen		diclofenac		placebo	
ulcer?	no	yes	no	yes	no	yes	no	yes	no	yes
1-19 d	7	1	9	0	8	0	10	0	13	1
20-49d	19	1	15	3	12	2	13	4	26	1
50-93d	151	5	163	4	134	23	138	21	127	6
>93	5	0	4	0	5	0	1	0	4	0
total	182	7	191	7	159	25	162	25	170	8

Patients without final endoscopy did not show by analysis (not shown) any differential pattern which might undermine inference.

TABLE 3A: Trial 48: Crude Incidence Rates of Endoscopic Ulcers by Risk Factor

	val 10mg/d		val 20mg/d		ibuprofen		diclofenac		placebo	
	no.	%	no.	%	no.	%	no.	%	no.	%
overall	7/182	4%	7/191	4%	25/159	16%	25/162	15%	8/205	4%
age										
≤65	1/130	1%	4/128	3%	9/110	8%	11/106	10%	4/108	4%
>65	6/59	10%	3/70	4%	16/74	22%	14/81	17%	4/70	6%

ns int?										
yes	0/14	0%	1/14	7%	3/15	20%	1/15	7%	1/12	8%
no	7/175	4%	6/184	3%	22/169	13%	24/172	14%	7/166	4%
hxulcer										
yes	1/23	4%	3/28	11%	3/24	13%	4/31	13%	1/20	5%
no	6/166	4%	4/170	2%	22/160	14%	21/156	14%	7/158	4%
hx bleed										
yes	0/2	0%	1/3	33%	0/4	0%	2/5	40%	0/3	0%
no	7/187	4%	6/195	3%	25/180	14%	23/182	13%	8/175	5%
CV dis										
yes	4/86	5%	3/96	3%	19/105	18%	13/97	13%	5/80	6%
no	3/103	3%	4/102	4%	6/79	8%	12/90	13%	3/98	3%
ASA?										
yes	3/18	17%	2/29	7%	10/31	32%	10/34	29%	0/28	0%
no	4/171	2%	5/169	3%	15/153	10%	15/153	10%	8/150	5%

Conclusions:

1. **In Trial 48, valdecoxib 10 mg/day and 20mg/day were both associated with statistically significantly fewer endoscopic gastroduodenal ulcers than ibuprofen 800 mg tid or diclofenac 75 mg bid. No dose response relationship was evident between the two valdecoxib groups.**
2. **Generally, the risk of gastroduodenal ulcers was increased in the high risk groups as displayed in table 3A . There was no paradoxical decrease in ulcer rate in either the ibuprofen or diclofenac group as was seen in the naproxen group in Trial 47.**

REPORT ON TRIAL 53

DESIGN: This is both a safety and efficacy trial enrolling patients with knee OA to five arms: valdecoxib 5mg/d, 10mg/d, and 20mg/d, naproxen 500mgBID, and placebo. The efficacy results were reported in the Arthritis Efficacy Review. The safety component consisted of a baseline endoscopy, by which the absence of ulcers needed for entry was documented, and a three month (or withdrawal point) endoscopy, with the primary safety endpoint being new gastroduodenal ulcers so detected. The primary analyses were prespecified as pair-wise comparisons of the valdecoxib arms to the naproxen arm.

TABLE 1: Trial 53 – Patient Disposition

arm	val 5mg/d	val 10mg/d	val 20mg/d	naproxen	placebo

randomized	201	206	202	205	205
completed	162	150	158	149	131
no endoscopy	13	32	17	22	27
withdrawn	39	56	44	56	74
inefficacy –	16	20	24	13	42
adverse event	12	18	11	26	17
noncompl.	6	9	8	12	9

TABLE 2A: Trial 53: RESULTS: CRUDE INCIDENCE OF ENDOSCOPIC ULCER RATES

	val 5mg/d	val 10mg/d	val 20mg/d	naproxen	placebo
Number (%)	6/188 (3.2%)	5/174 (2.9%)	10/185 (5.4%)	18/183 (9.9%)	8/178 (4.5%)

P value comparisons for the valdecoxib 5mg, 10mg, and 20mg compared with naproxen were 0.015, 0.008, and 0.329, respectively.

TABLE 2B: Trial 53 – Endoscopic Ulcers (numbers of patients) by Time of Ascertainment: Week 13 or Time of Withdrawal

days	val 5mg/d		val 10mg/d		val 20mg/d		naproxen		placebo	
ulcer?	no	yes	no	yes	no	yes	no	yes	no	yes
1-19 d	7	1	8	1	5	0	7	2	15	2
20-49d	11	1	10	0	18	0	16	3	19	3
50-93d	161	4	149	3	148	10	139	13	133	3
>93	3	0	2	1	4	0	3	0	3	0
total	182	6	169	5	175	10	165	18	170	8

Note: Analysis (not shown) of patients without final endoscopy did not show a differential loss pattern which might undermine inference.

TABLE 3A: Trial 53: Crude Incidence Rates of Endoscopic Ulcers by Risk Factor

	val 5mg/d		val 10mg/d		val 20mg/d		naproxen		placebo	
	no.	%	no.	%	no.	%	no.	%	no.	%
overall	6/188	3%	5/175	3%	10/185	5%	18/183	10%	8/178	4%
age										
≤65	6/126	5%	4/110	4%	8/116	7%	9/121	7%	4/111	4%
>65	0/62	0%	1/64	2%	2/69	3%	9/62	15%	4/67	6%
ns int?										
yes	1/13	8%	0/14	0%	0/15	0%	2/14	14%	0/8	0%
no	5/175	3%	5/160	3%	10/170	6%	16/169	10%	8/170	5%
hxulcer										
yes	3/21	14%	1/22	5%	2/26	8%	5/29	17%	1/19	5%

no	3/167	2%	4/152	3%	8/159	5%	13/154	8%	7/159	4%
hx bleed										
yes	0/0	0%	0/2	0%	0/2	0%	0/3	0%	1/2	50%
no	6/188	3%	5/172	3%	10/183	6%	18/180	10%	7/176	4%
CV dis										
yes	4/100	4%	2/93	2%	6/102	6%	12/103	12%	4/94	4%
no	2/88	2%	3/81	4%	4/83	5%	6/80	8%	4/82	5%
ASA?										
yes	0/28	0%	3/22	14%	0/27	0%	2/25	8%	3/30	10%
no	6/160	4%	2/152	1%	10/158	6%	16/158	10%	5/148	3%

Given the small numbers in almost all cases, it is hard to argue that this subgroup analysis tends to support or detract from the signal seen in the risk factor analysis of the other GI safety Trials (47, 48 and 62).

Conclusions:

1. **In study 053, valdecoxib 5 mg/day and 10 mg/day were associated with statistically significantly fewer endoscopic gastroduodenal ulcers compared to naproxen 500 mg bid. A dose response relationship was suggested between the valdecoxib 10 mg/day and valdecoxib 20 mg/day.**
2. **No difference was demonstrated in gastroduodenal ulcer rates between valdecoxib 20 mg daily and naproxen 500 mg bid. The final ulcer rate in this study for naproxen is lower than previous studies. The statistically significantly lower ulcer rates compared to naproxen seen at two to four times higher doses of valdecoxib in Trial 47 is of note.**

REPORT ON TRIAL 35

This analgesia study comparing paracoxib/valdecoxib and placebo in patients undergoing CABG surgery was designed to test opioid-sparing, as reported in the Analgesia Efficacy section of this review. This trial was also specifically designed to test a safety hypothesis, using a pre-defined basket of safety endpoints, called "clinically relevant adverse events" (CRAEs), which included many serious vascular endpoints. The trial was powered using both a morphine sparing and a CRAE event rate calculation. In the trial analysis, there were 80 such events (25.7%) in the 311 paracoxib/valdecoxib patients, compared with 23 (15.2%) in the 151 placebo patients (p=0.012, by Fisher's Exact). The patient numbers for the particular events are shown in Table 1 below.

Note: The reader is also referred to an in depth analysis of this important trial in the Paracoxib Medical Review by James Witter M.D. PhD. It is attached *in toto* in the appendix.

Table 1: Clinically Relevant Adverse Events (CRAEs): Prespecified Endpoint

event	placebo	para/valdecoxib

deaths	**0**	**4**
myocardial infarction	**1**	**1**
cerebrovascular accident	**1**	**9**
deep venous thrombosis	**0**	**3**
pulmonary embolism	**0**	**2**
congestive heart failure	**1**	**4**
renal dysfunction / failure	**7**	**29**
infection	**11**	**29**
pulmonary complication	**4**	**19**
pericarditis	**1**	**4**
GI event	**0**	**4**
major non-GI bleed	**2**	**0**

Discussion: These data, along with the other analyses in Dr. Witter's review (appendix) are manifestations of an increase in vascular events rates, which coupled with the signals seen elsewhere in this database (for example, Trial 47 and the adverse event tables shown later in this review) all contributes to the concern that there may be a component of increased thrombogenicity associated with this agent.

PLATELET FUNCTION: RELEVANT PK STUDIES

In view of incomplete understanding of the balance of pro- and anti-thrombogenic factors in the presence of COX2 inhibition, relevant PK studies were reviewed (see Integrated Summary of Safety, pp 305-323/6718, and individual study reports). The full Pharmacology Review can be consulted for greater detail.

A total of five randomized, blinded studies listed below were done on normal volunteers to investigate various aspects of platelet function in the presence of valdecoxib and certain non-steroidal controls (diclofenac, naproxen, and ibuprofen).

	age	valdecoxib arms	controls
Trial 21	**18-55**	**10mgbid, 25mgbid**	**naproxen, diclofenac**
Trial 23	**65-95**	**10mgbid**	**ibuprofen**
Trial 42	**65-95**	**40mgbid**	**ibuprofen**
Trial 43	**18-55**	**40mgbid**	**naproxen, diclofenac**
Trial 93-031	**18-55**	**paracoxib 40mgbid IV**	**placebo, aspirin**

The first four trials used identical seven-day designs, measuring bleeding time, platelet aggregation in response to arachidonate, serum thromboxane B_2 (a stable metabolite of thromboxane A_2), and urinary 11-dehydrothromboxane B_2 (a thromboxane B_2 metabolite excreted in the urine). The fifth (Trial 93-031) was a three day exposure to IV paracoxib or placebo, followed by administration of 325mg aspirin on day four, with bleeding time, platelet activation by arachidonate, collagen, and ADP, and serum thromboxane B_2 measured.

COX1 is described as mediating the formation of thromboxane A_2 from arachidonic acid in the membrane of activated platelets. Bleeding time is a clinical measure of effect of the final common pathway of the complicated process of platelet activation and aggregation. The measurement of bleeding time is known to be highly variable (although why this is the case is not well understood) and this has lead to the measurement of more stable by-products

(such as serum thromboxane B_2 and its urinary metabolite) in the process trying to understand the physiology. Therefore, there is no basis for the use of bleeding time as a surrogate, and any claim that platelet alteration by a drug translates into a clinical benefit will need substantiation with an outcome trial.

In what follows, the results for bleeding time first, and platelet aggregation studies second, are presented. Results of the serum and urinary metabolite studies are presented in the Pharmacology Review.

Results:

Trials 21, 23, 42, 43: INCREASE IN BLEEDING TIME (SECONDS) AT 4 HOURS

	first day							last day						
trial	plc	v10	v25	v40	dicl	nap	ibu	plc	v10	v25	v40	dicl	nap	ibu
21	-26	22	7		-12	14		-4	22	44		5	43	
23	6	17					79	20	5					86
42	12			0			106	37			9			72
43	57			69	92	156		39			35	85	115	

Trials 21, 23, 42, 43: CHANGE FROM BASELINE (PERCENT) IN PLATELET AGGREGATION IN RESPONSE TO ARACHIDONATE AT 4 HOURS

	first day							last day						
trial	plc	v10	v25	v40	dicl	nap	ibu	plc	v10	v25	v40	dicl	nap	ibu
21	0	-1	2		-36	-83		-5	0	3		-23	-81	
23	2	0					-56	2	2					-38
42	-9			-10			-48	0			0			-50
43	1			-4	-55	-83		0			3	40	80	

Trial 93-031: INCREASE IN BLEEDING TIME (SECONDS) AFTER ASPIRIN (325 mg) GIVEN ON DAY 4 (all entries given as mean, median)

placebo (9 patients)		paracoxib (10 patients)	
pre-aspirin	155, 157	pre-aspirin	165, 146
4 hr post	254, 213	4 hr post	172, 173
8 hr post	256, 240	8 hr post	210, 186
22 hr post	252, 210	22 hr post	208, 185

CHANGE FROM BASELINE (PERCENT) IN PLATELET AGGRE-GATION IN RESPONSE TO ARACHIDONATE, COLLAGEN, AND ADP AT 4 HOURS

	placebo (9 patients)	paracoxib (10 patients)
arachidonate	-97%	-98%
collagen	-94%	-86%
ADP	-20%	+2%

Discussion:

The study design used was intended to demonstrate lack of prolongation of bleeding time the results suggest a blunting of aspirin effects on bleeding time. As this would

have major clinical implications if it were confirmed, it will need to be highlighted in the label at this point, and further work is clearly going to be necessary.

DEATHS

A total of 22 deaths have been reported in the NDA and the 120-Day Update. Fifteen occurred during a blinded trial, five in open extensions, and two in an ongoing trial (Trial 40) which remains blinded.

29

study	DB/Open	age/sex	rx	duration	cause	post ?
16	DB	72/M	val 10mg	1d	ASCVD	yes
16	DB	78/F	val 5mg	11d	suspect cardiac arrest	no
16	DB	79/F	val 10mg	45d	trauma	?
48	DB	77/F	ibu	57d	complication-AVR	no
53	DB	77/M	val 5mg	11d	vent. fibrillation	no
53	DB	87/M	nap	69d	MVA	no
35	DB	58/M	para/val	2d	duodenal ulcer	yes
35	DB	69/F	para/val	10d	probable MI	yes
35	DB	67/M	para/val	7d	sepsis, wound infection, pneumonia	yes
35	DB	62/M	para/val	4d	massive hem. CVA	no
62	DB	79/F	val 20mg	15d	pulm. embolist	yes
62	DB	74/M	val 20mg	20d	GI bleed	yes
62	DB	64/F	val 20mg	98d	lymphoma, sepsis	no
62	DB	72/M	val 20mg	76d	metastatic lung CA	no
63	DB	74/F	dicl	135d	MI	no
67	open	78/F	val 40mg	145d	CABG, pulm. infarct/hemorrhage	yes
67	open	67/M	val 40mg	81d	"abdominal mass"	no
67	open	45/M	val 40mg	305d	bilat. pulm. emboli	yes
67	open	72/F	val 40mg	317d	pulm. fibrosis	no
67	open	60/M	val 40mg	297d	unknown	no
40	DB	71/M	(blinded)	38d	met. adenoCA	?
40	DB	50/F	(blinded)	6d	met. breast CA	?

Deaths

The total double-blind exposure for all doses of valdecoxib is 1283 patient-years (107, 323,397,316, 142 patient-years for 1-5mg, 10mg, 20mg, 40mg, and 80mg valdecoxib total daily dose, respectively) , compared to 291 patient-years for naproxen, 248 patient-years for diclofenac, 40 patient-years for ibuprofen, and 161 patient-years for placebo. Thus, the crude death rate in the unblinded controlled studies for valdecoxib is 0.9% (12/1283) compared to 0.52% (3/579) in comparator NSAIDs (p=NS, by Fisher's Exact). Given the 2:1 (parecoxib/valdecoxib: placebo) randomization in the CABG trial the 4 deaths in that study may bias the rates. This study was in an enriched population for serious cardiovascular

adverse events and used a dose not proposed for chronic use. The rates excluding this trial are 0.6% for valdecoxib compared to 0.5% for the NSAID comparators.
The rate of cardiovascular thromboembolic deaths (including arrhythmia, MI and PVD) in the controlled database was 0.5% (6/1283) for valdecoxib and 0.3% (2/579) for the NSAID groups combined. Excluding the CABG study the rates for such events was 0.3% (4/1283) for valdecoxib and 0.3% for NSAID comparators. The number of events was small and there was no pattern seen based on dose or duration of therapy. Excluding the CABG trial there was no clear signal for differences in event rates between valdecoxib and comparator NSAIDs. A large outcome study employing chronic dose therapy would be needed to address this issue further. Such as study would include overall safety including cardiovascular, renal and GI endpoints as well as overall deaths and serious adverse events.

II. ADVERSE EVENTS

There are adverse event signals for the following items, as evidenced by the arthritis safety tables noted:

40mg valdecoxib worse than placebo

1-Hypertension
Tables 3B, 4, and 9. Trial 47 shows that at 80mg per day this AE approaches 10%. See also Vital Sign section of the Safety Review
2-Edema
Tables 3B, 3C, and 9. Also weight data from Vital Sign
3-Dizziness
Table 3B
4-Abdominal Pain
Table 3B
5-Increased BUN/Cr
Table 4

10-20mg valdecoxib worse than placebo

1-Edema
Table 9 (RA), and weight data
2-Vomiting
Table 8 (RA)

40mg valdecoxib worse than comparator NSAID

1-Hypertension
Trial 47 review (part of renal endpoint)
Table 5 (Trial 62-RA)
See also section on Vital Signs, and multiple BP analyses there
Trial 63 – SBP/DBP worse in val20/d c/w diclof
2-Edema
Trial 47 review (part of renal endpoint)
3-Pruritis

Table 4 (Trial 47)
4-Increased Cr / renal, generally
Table 4 (Trial 47); specific endpoints of Trial 47

No signal for overall safety inferiority was seen for 10-20mg valdecoxib compared to NSAID comparators.

Requested Cardiovascular Safety Analysis in High Risk Patients

Concerns have been raised regarding COX-2 selective agents and cardiovascular safety following outcome study (VIGOR) of one such agent. Based on these concerns a subanalysis of cardiovascular events in high risk patients was requested by the reviewer. The following tables do not suggest a higher risk of cardiovascular events in an enriched population of "high risk" or "at risk" patients for valdecoxib compared to the NSAID comparators. The small number of patients exposed precludes robust comparisons.

HIGH RISK PATIENTS*: Rates of Serious Thromboembolic Cardiovascular Adverse Events**

Adverse Event	Placebo	Valdecoxib (10 mg)	Valdecoxib (20 mg)	Valdecoxib (40 mg)	Valdecoxib (80 mg)	NSAIDs
n	106	174	144	93	42	248
Exposure (patient yrs.)	12.5	49.4	46.8	22.7	11.5	71.3
Events	2	3	1	1	1	6
Incidence (%)	1.9	1.7	0.7	1.1	2.4	2.4
Events/100 pt yr	16.0	6.1	2.0	4.4	8.7	8.4

* Patients with history of angina, CAD, MI, and CVA in studies 015, 016, 047, 048, 049, 053, 060, 061, 062, 063.

** FDA defined, including MI, myocardial ischemia, unstable angina, cardiac arrest, sudden cardiac death, CVA/TIA, PE, venous thrombosis, embolism, peripheral gangrene, and peripheral ischemia.

AT RISK PATIENTS*: Rates of Serious Thromboembolic Cardiovascular Adverse Events**

Adverse Event	Placebo	Valdecoxib (10 mg)	Valdecoxib (20 mg)	Valdecoxib (40 mg)	Valdecoxib (80 mg)	NSAIDs
n	503	665	773	646	258	1144
Exposure (patient yr.)	72.7	197.8	261.9	186.7	93.2	356.5
Events	0	1	4	3	1	7
Incidence (%)	0.0	0.2	0.5	0.5	0.4	0.6
Events/100 pt. yr	0.0	0.5	1.5	1.6	1.1	2.0

* Patients with a history of hypertension, hyperlipidemia, or smoking (but not angina, CAD, MI, or CVA) in same studies as in above table

* same as above table

ARTHRITIS SAFETY TABLE 1: CONTROLLED DATABASE

Trial No./Disease	Duration (weeks)	Placebo	0.5-5 mg	10 mg QD	10mg BID	20 mg QD	40 mg QD	40 mg BID	NSAIDs
5-OA	6	X	X	X	X				X
16-RA	6	X	X	X	X				X
48-OA	12	X		X		X			X
49-OA	12	X	X	X					X
53-OA	12	X	X	X		X			X
60-RA	12	X		X		X	X		X
61-RA	12	X		X		X	X		X
47-RA/OA	26						X*	X	X
62-RA	26					X	X		X
63-0A	26			X		X			X

*dosed as 20bid

ADVERSE EVENTS IN THE CONTROLLED DATABASE – ARTHRITIS SAFETY TABLES 2-6

ARTHRITIS SAFETY TABLE 2: EVENTS (%) WITH AN INCIDENCE AT LEAST 3% IN TRIALS 15/16 (6wk) and 48/49/53/60/61 (3mo)

Dose (mg/day)	Placebo	1-5 mg	10 mg	20 mg	40 mg	NSAIDs
No. treated	1142	818	1284	1012	430	1347
Any event	49.7	52.9	54.6	57.1	58.1	62.7
Body as a Whole						
Edema peripheral	0.7	0.7	1.9	3.0	2.3	2.2
Injury accidental	2.5	2.2	3.1	3.0	3.0	3.0
Central and Peripheral Nervous System Disorders						
Headache	7.5	7.1	5.2	8.1	7.4	5.2
Gastrointestinal System Disorders						
Abdominal fullness	1.7	1.2	1.9	2.2	3.3	2.7
Abdominal pain	5.7	5.4	6.2	6.6	9.1	10.1
Constipation	1.6	1.5	1.3	1.7	2.1	5.1
Diarrhea	4.1	4.2	5.4	5.5	6.0	6.2
Dyspepsia	5.8	7.2	7.7	7.4	8.4	12.0
Flatulence	3.5	2.4	3.0	4.1	4.0	5.3
Nausea	5.9	5.9	6.9	6.2	7.4	7.9
Respiratory System Disorders						
Rhinitis	1.3	0.5	0.7	0.6	3.0	1.5
Sinusitis	2.5	2.4	3.1	2.0	2.8	2.8
Upper resp tract infection	6.1	5.0	5.9	5.7	5.6	5.8

ARTHRITIS SAFETY TABLE 3A: EVENTS (%) WITH AN INCIDENCE AT LEAST 1% AND P<0.05 IN TRIALS 15/16 (6wk) and 48/49/53 (3mo)

	Valdecoxib 10-20mg/d combined	Placebo	NSAIDs	Valdecoxib vs Placebo	Valdecoxib vs NSAIDs
No. treated	2296	1142	1347	-	-
Any event	55.7	49.7	62.7	0.001	<0.001
Body as a Whole					
Edema peripheral	2.4	0.7	2.2	<0.001	-
Gastrointestinal System Disorders					
Abdominal pain	6.4	5.7	10.1	-	<0.001
Constipation	1.5	1.6	5.1	-	<0.001
Dyspepsia	7.6	5.8	12.0	-	<0.001
Flatulence	3.4	3.5	5.3	-	0.009
Gastritis	0.7	0.7	1.6	-	0.027
Stomatitis	0.7	0.2	1.0	0.047	-
Vomiting	1.1	1.7	2.4	-	0.006

ARTHRITIS SAFETY TABLE 3B: EVENTS (%) WITH AN INCIDENCE AT LEAST 1% AND P<0.05 IN TRIALS 60/61 (3mo) - RA only

Adverse Event	Valdecoxib 40 mg/d	Placebo	Naproxen	Valdecoxib vs Placebo	Valdecoxib vs Naproxen
No. treated	430	442	444	-	-
Any event	58.1	45.5	61.7	<0.001	-
Autonomic Nervous System Disorders					
Hypertension	2.8	0.5	1.6	0.006	-
Body as a Whole					
Edema peripheral	2.3	0.5	0.9	0.020	-
Central and Peripheral Nervous System Disorders					
Dizziness	2.3	0.5	2.9	0.020	-
Gastrointestinal System Disorders					
Abdominal pain	9.1	5.0	9.0	0.023	-
Constipation	2.1	2.3	4.7	-	0.040
Stomatitis	1.9	0.0	1.1	0.003	-

ARTHRITIS SAFETY TABLE 3C: EVENTS (%) WITH INCIDENCE AT LEAST 1% AND P<0.05 IN OSTEOARTHRITIS IN TRIALS 15(6wk) and 48/49/53 (3mo)

Dose (mg/d)	Valdecoxib 10-20mg/d, combined	Placebo	NSAIDs	Valdecoxib vs Placebo	Valdecoxib vs NSAIDs
No. treated	1182	613	816	-	-
Any event	57.1	53.7	64.7	0.176	<0.001
Body as a Whole					
Edema peripheral	2.6	1.0	2.9	0.022	-
Pain	0.4	1.5	0.6	0.023	-
Central and Peripheral Nervous System Disorder					
Headache	5.6	8.3	4.5	0.034	-
Gastrointestinal System Disorders					
Abdominal pain	7.2	6.7	11.3	-	0.002
Constipation	1.7	1.3	5.5	-	<0.001
Dyspepsia	8.9	7.0	12.9	-	0.005
Liver and Biliary System Disorders					
SGPT increased	0.3	0.5	1.6	-	0.001
SGOT increased	0.3	0.5	1.5	-	0.003

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ARTHRITIS SAFETY TABLE 4: EVENTS (%) WITH AN INCIDENCE AT LEAST 3%OR P<0.05 IN TRIAL 47 (6mo) -OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

Adverse Event	Valdecoxib 20 mg BID	Valdecoxib 40 mg BID	naproxen	Valdecoxib 20mgBID vs Naproxen	Valdecoxib 40mg BID vs Naproxen
No. treated	399	403	415	-	-
Any event	83.7	84.6	85.8	-	-
Autonomic Nervous System Disorders					
Hypertension	5.5	9.2	4.6	-	0.012
Body as a Whole – General Disorders					
Chest pain non-cardiac	0.3	1.5	1.9	0.038	-
Edema peripheral	4.5	7.2	4.3	-	-
Influenza-like symptoms	5.0	6.2	6.0	-	-
Injury accidental	5.3	5.5	4.1	-	-
Central and Peripheral Nervous System Disorders					
Dizziness	3.8	2.2	3.1	-	-
Headache	13.5	12.9	15.9	-	-
Gastrointestinal System Disorders					
Abdominal pain	7.5	9.9	15.9	<0.001	0.012
Constipation	4.5	4.5	9.2	0.012	0.008
Diarrhea	7.0	10.7	6.5	-	0.034
Duodenal ulcer	1.0	0.2	1.9	-	0.038
Dyspepsia	17.8	13.9	19.5	-	0.039
Flatulence	4.0	3.7	4.6	-	-
Gastric ulcer	0.5	1.7	2.4	0.038	-
Gastritis	1.3	1.5	4.6	0.006	0.013
Gastroesophageal reflux	4.0	1.7	2.7	-	-
Nausea	7.5	6.5	9.6	-	-
Stomatitis	2.3	3.7	1.0	-	0.010
Tooth disorder	2.0	2.7	4.1	-	-
Vomiting	3.5	3.0	3.9	-	-
Metabolic and Nutritional Disorders					
Creatinine increase	1.8	2.0	1.2	0.035	0.019
Weight increase	3.0	2.7	2.9	-	-
Musculoskeletal System Disorders					
Myalgia	5.0	3.7	4.6	-	-
Psychiatric Disorders					
Insomnia	2.5	3.7	2.7	-	-
Red Blood Cell Disorders					
Anemia	3.8	4.0	3.1	-	-
Respiratory System Disorders					
Bronchitis	3.3	4.5	3.1	-	-

Adverse Event	Valdecoxib 20 mg BID	Valdecoxib 40 mg BID	naproxen	Valdecoxib 20mgBID vs Naproxen	Valdecoxib 40mg BID vs Naproxen
Coughing	4.5	7.7	5.5	-	-
Pharyngitis	4.8	5.2	3.4	-	-
Rhinitis	5.5	4.2	3.1	-	-
Sinusitis	10.3	8.2	6.0	0.029	-
Upper resp tract infection	16.8	19.8	16.1	-	-
Adverse Event	**Valdecoxib 20mgbid**	**Valdecoxib 40mgbid**	**Naproxen**	**Valdecoxib 20mgbid vs Naproxen**	**Valdecoxib 40mgbid mg vs Naproxen**
No. treated	399	403	415	-	-
Any event	83.7	84.6	85.8	-	-
Skin and Appendages Disorders					
Pruritus	2.0	2.5	0.2	0.019	0.005
Rash	3.5	3.5	2.7	-	-
Urinary System Disorders					
Albuminuria	2.8	3.5	3.4	-	-
Creatinine clearance decreased	1.8	3.0	2.7	-	-
Urinary tract infection	3.8	3.2	3.9	-	-

ARTHRITIS SAFETY TABLE 5: EVENTS (%) WITH AN INCIDENCE AT LEAST 3% OR P<0.05 IN TRIAL 62 (6mo) - RHEUMATOID ARTHRITIS

	Valdecoxib		Diclofenac
	20 mg QD N = 246	40 mg QD N = 237	75 mg BID N = 237
2. ANY EVENT	164 (66.7)	154 (65.0)	172 (72.6)
3. AUTONOMIC NERVOUS SYSTEM DISORDER			
Hypertension	4 (1.6)	9 (3.8)	3 (1.3)
4. BODY AS A WHOLE			
Back Pain	11 (4.5)	8 (3.4)	4 (1.7)
Edema Peripheral	7 (2.8)	5 (2.1)	7 (3.0)
Injury-Accidental	8 (3.3)	4 (1.7)	8 (3.4)
Central and Peripheral Nervous System Disorders			
Dizziness	5 (2.0)	7 (3.0)	9 (3.8)
Headache	22 (8.9)	15 (6.3)	19 (8.0)
5. GASTRO-INTESTINAL SYSTEM DISORDERS			
Abdominal Fullness	2 (0.8)	1 (0.4)	7 (3.0)
Abdominal Pain	23 (9.3)	26 (11.0)	36 (15.2)
Constipation	1 (0.4)*	3 (1.3)	7 (3.0)
Diarrhea	14 (5.7)	24 (10.1)	19 (8.0)
Dyspepsia	33 (13.4)	35 (14.8)	43 (18.1)
Esophagitis	8 (3.3)	0 (0.0)*	6 (2.5)
Gastric Ulcer	3 (1.2)*	4 (1.7)*	16 (6.8)
Gastritis	9 (3.7)	11 (4.6)	14 (5.9)
Gastroesophageal Reflux	6 (2.4)*	2 (0.8)	0 (0.0)

Nausea	19 (7.7)	17 (7.2)	23 (9.7)
6. VOMITING	7. 9 (3.7)	8. 7 (3.0)	8 (3.4)
9. LIVER AND BILIARY SYSTEM DISORDERS			
10. SGOT INCREASED	11. 0 (0.0)*	12. 1 (0.4)*	9 (3.8)
13. SGPT INCREASED	14. 0 (0.0)*	15. 2 (0.8)*	11 (4.6)
16. PSYCHIATRIC DISORDERS			
17. INSOMNIA	18. 9 (3.7)	19. 6 (2.5)	5 (2.1)
20. RED BLOOD CELL DISORDERS			
21. ANEMIA	22. 5 (2.0)	23. 5 (2.1)	7 (3.0)
24. RESPIRATORY SYSTEM DISORDERS			
Bronchitis	6 (2.4)	3 (1.3)	10 (4.2)
Upper Resp. Tract Inf.	10 (4.1)	15 (6.3)	12 (5.1)
* p-value is ≤ 0.05 versus diclofenac			

ARTHRITIS SAFETY TABLE 6: EVENTS (%) WITH AN INCIDENCE AT LEAST 3% OR P<0.05 IN DOUBLE-BLIND PORTION OF TRIAL 63 (6mo) -OSTEOARTHRITIS

	Valdecoxib		Diclofenac
	10 mg QD N = 259	20 mg QD N = 261	75 mg BID N = 262
25. ANY EVENT	168 (64.9)	173 (66.3)	190 (72.5)
26. AUTONOMIC NERVOUS SYSTEM DISORDER			
Hypertension	8 (3.1)	12 (4.6)	13 (5.0)
Hypertension Aggravated	3 (1.2)*	8 (3.1)	11 (4.2)
27. BODY AS A WHOLE			
Back Pain	10 (3.9)	14 (5.4)	13 (5.0)
Edema Peripheral	12 (4.6)	9 (3.4)	14 (5.3)
Influenza-Like Symptoms	8 (3.1)	13 (5.0)	13 (5.0)
Injury-Accidental	14 (5.4)	15 (5.7)	13 (5.0)
Peripheral Pain	4 (1.5)	2 (0.8)	8 (3.1)
Central and Peripheral Nervous System Disorders			
Dizziness	14 (5.4)	12 (4.6)	14 (5.3)
Headache	11 (4.2)	25 (9.6)	17 (6.5)
28. GASTRO-INTESTINAL SYSTEM DISORDERS			
Abdominal Pain	19 (7.3)*	26 (10.0)*	50 (19.1)
Constipation	2 (0.8)*	6 (2.3)	11 (4.2)
Diarrhea	11 (4.2)*	19 (7.3)	23 (8.8)
Dypepsia	13 (5.0)*	20 (7.7)	29 (11.1)
Gastric Ulcer	2 (0.8)	1 (0.4)*	8 (3.1)
Gastritis	1 (0.4)*	7 (2.7)	9 (3.4)
Nausea	12 (4.6)	15 (5.7)	22 (8.4)
29. METABOLIC AND NUTRITIONAL DISORDERS			
Creatine Phosphokinase Increased	8 (3.1)	5 (1.9)	10 (3.8)
30. MUSCULO-SKELETAL SYSTEM DISORDERS			
Fracture Accidental	0 (0.0)*	2 (0.8)	7 (2.7)

Myalgia	**6 (2.3)**	**8 (3.1)**	**13 (5.0)**
31. RESPIRATORY SYSTEM DISORDERS			
Bronchitis	**6 (2.3)**	**8 (3.1)**	**8 (3.1)**
Coughing	**5 (1.9)**	**9 (3.4)**	**9 (3.4)**
Pharyngitis	**5 (1.9)**	**3 (1.1)**	**8 (3.1)**
Upper Resp. Tract Inf.	**26 (10.0)**	**21 (8.0)**	**22 (8.4)**
*** p-value is ≤ 0.05 versus diclofenac**			

EVENTS CAUSING WITHDRAWAL IN THE CONTROLLED DATABASE – ARTHRITIS SAFETY TABLES 7-12

ARTHRITIS TABLE 7 A: EVENTS (%) CAUSING WITHDRAWAL WITH AN INCIDENCE AT LEAST 1% IN TRIALS 15/16 (6wk) and 48/49/53/60/61(3mo)

Dose (mg/d)	Placebo	1-5 mg	10 mg	20 mg	40 mg	NSAIDs
No. treated	1142	818	1284	1012	430	1347
Any event	6.0	7.2	7.2	6.0	7.4	11.0
Abdominal pain	1.4	1.1	1.6	1.4	1.6	3.0
Diarrea	0.4	0.2	0.8	0.2	0.7	1.0
Dyspepsia	1.0	1.3	1.2	0.5	1.4	2.0
Nausea	0.9	0.5	0.9	0.7	0.9	1.4

ARTHRITIS SAFETY TABLE 7B: VALDECOXIB 10MG/D AND 20MG/D COMBINED

Adverse Event	Valdecoxib 10-20 mg/d combined	Placebo	NSAIDs	Valdecoxib vs Placebo	Valdecoxib vs NSAIDs
No. treated	2296	1142	1347	-	-
Any event	6.7	6.0	11.0	-	<0.001
Abdominal pain	1.5	1.4	3.0	-	0.004
Dyspepsia	0.9	1.0	2.0	-	0.007

ARTHRITIS TABLE 8: EVENTS (%) CAUSING WITHDRAWAL (%) WITH AN INCIDENCE AT LEAST 1% IN OSTEOARTHRITIS IN TRIALS 15(6wk) and 48/49/53(3mo)

Adverse Event	Placebo	1-5 mg	10 mg	20 mg	NSAIDs
No. treated	613	562	683	499	816
Any event	7.5	7.3	9.1	6.4	13.6
Abdominal pain	1.5	0.7	2.0	1.6	3.8
Diarrea	0.5	0.4	1.0	0.2	1.6
Dyspepsia	1.1	1.6	2.0	0.2	2.5
Nausea	1.0	0.7	1.2	0.6	1.2

ARTHRITIS SAFETY TABLE 9: EVENTS (%) CAUSING WITHDRAWAL WITH AN INCIDENCE AT LEAST 1% AND P<0.05 IN RHEUMATOID ARTHRITIS IN TRIALS 16(6wk) and 60/61(3mo) – RA only

Dose (mg/d)	Valdecoxib 10-20mg/d, combined	Placebo	Naproxen	Valdecoxib vs Placebo	Valdecoxib vs Naproxen
No. treated	1114	529	531	-	-
Any event	54.2	45.2	59.7	<0.001	0.038
Body as a Whole – General Disorders					
Edema peripheral	2.2	0.4	1.1	0.005	0.171
Fatigue	0.7	1.7	1.9	-	0.042
Halitosis	0.3	0.2	1.3	-	0.016
Gastrointestinal System Disorders					
Abdominal pain	5.5	4.5	8.3	-	0.031
Constipation	1.3	1.9	4.5	-	<0.001
Dyspepsia	6.2	4.3	10.5	-	0.003
Gastroenteritis	1.2	0.2	1.3	0.046	-
Vomiting	1.0	2.3	2.4	0.045	0.027
Respiratory System Disorders					
Rhinitis	0.6	1.1	2.3	-	0.006

Dose (mg/d)	Placebo	1-5 mg	10 mg	20 mg	40 mg	NSAIDs
No. treated	529	256	601	513	430	531
Any event	4.3	7.0	5.2	5.7	7.4	7.0
Abdominal pain	1.3	2.0	1.2	1.2	1.6	1.7
Dyspepsia	0.8	0.8	0.3	0.8	1.4	1.3
Nausea	0.8	0.0	0.7	0.8	0.9	1.7

ARTHRITIS SAFETY TABLE 11: EVENTS (%) CAUSING WITHDRAWAL WITH AN INCIDENCE OF AT LEAST 1% OR P ≤0.05 IN TRIAL 47 (6mo) - RHEUMATOID ARTHRITIS

Adverse Event	Valdecoxib 20mgbid	Valdecoxib 40mgbid	NSAID	Valdecoxib 20mgbid vs Naproxen	Valdecoxib 40mgbid vs Naproxen
No. treated	399	403	415	-	-
Any event	16.3	18.1	17.6	-	-
Autonomic System Disorders					
Hypertension	0.5	1.7	0.2	-	0.036
Body as a Whole – General Disorders					
Edema peripheral	0.5	1.7	0.2	-	0.036
Gastrointestinal System Disorders					
Abdominal pain	1.5	2.7	3.4	-	-
Duodenal ulcer	1.0	0.2	1.2	-	-
Dyspepsia	2.3	2.2	3.4	-	-
Esophageal ulceration	1.0	0.0	0.5	-	-
Gastric ulcer	0.3	1.5	1.7	-	-
Gastritis	0.3	0.0	2.2	0.021	0.004
Nausea	1.3	0.5	1.9	-	0.108
Vomiting	0.5	0.2	1.2	-	-
Skin and Appendages Disorders					
Rash	0.0	1.0	0.7	-	-

ARTHRITIS SAFETY TABLE 11: EVENTS (%) CAUSING WITHDRAWAL WITH AN INCIDENCE OF AT LEAST 1% OR P ≤0.05 IN TRIAL 62(6mo) - RHEUMATOID ARTHRITIS

Event	Valdecoxib 20 mg QD	Valdecoxib 40 mg QD	Diclofenac 75 mg SR BID
Any event	24 (9.8%)	25 (10.5%)	36 (15.2%)
Collagen Disorders			
Arthritis Rheumatoid Aggravated	0 (0.0)	3 (1.3)	0 (0.0)
GI System Disorders			
Abdominal Pain	1 (0.4)*	3 (1.3)	10 (4.2)
Diarrhea	1 (0.4)	0 (0.0)	4 (1.7)
Dyspepsia	4 (1.6)	5 (2.1)	7 (3.0)
Gastric Ulcer	0 (0.0)	1 (0.4)	4 (1.7)
Gastritis	2 (0.8)	3 (1.3)	4 (1.7)
Nausea	2 (0.8)	4 (1.7)	6 (2.5)
Vomiting	2 (0.8)	4 (1.7)	6 (2.5)

Derived from Table T32. All values are number (%) of patients.
*Statistically significantly different from diclofenac at p<0.05.

ARTHRITIS SAFETY TABLE 12: EVENTS (%) CAUSING WITHDRAWAL WITH AN INCIDENCE OF AT LEAST 1% OR P ≤0.05 IN TRIAL 63(6mo) - OSTEOARTHRITIS

	Valdecoxib		Diclofenac
	10 mg QD	20 mg QD	75 mg BID

	N = 259	N = 261	N = 262
Any Event	23 (8.9)	30 (11.5)	49 (18.7)
Gastro-intestinal System Disorders			
Abdominal Pain	5 (1.9)*	4 (1.5)*	18 (6.9)
Diarrhea	0 (0.0)	0 (0.0)	5 (1.9)
Dyspepsia	0 (0.0)	1 (0.4)	3 (1.1)
Gastritis	0 (0.0)	3 (1.1)	4 (1.5)
Gastric Ulcer	2 (0.8)	1 (0.4)	7 (2.7)
Nausea	1 (0.4)	2 (0.8)	4 (1.5)
Vomiting	2 (0.8)	0 (0.0)	3 (1.1)
* p-value ≤ 0.05 versus diclofenac			

SERIOUS EVENTS IN THE CONTROLLED DATABASE – ARTHRITIS SAFETY TABLES 13-18

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ARTHRITIS SAFETY TABLE 13: SERIOUS ADVERSE EVENTS (NUMBERS) IN TRIALS 15/16(6wk) and 48/49/53/60/61(3mo)

Dose (mg/d)	Placebo	1-5 mg	10 mg	20 mg	40 mg	NSAIDs
No. treated	1142	818	1284	1012	430	1347
Overall percentage of any event	2.4	1.7	1.6	1.6	1.6	2.1
Any event	27/38	14/17	20/35	16/24	7/12	28/44
Autonomic Nervous System Disorders						
Overall percentage	0.0	0.0	0.0	1.0	0.5	0.0
Hypertension aggravated					2/2	
Body as a Whole – General Disorders						
Overall percentage	0.5	0.5	0.5	<0.1	0.5	0.2
Back pain	2/2		1/1			1/1
Injury – accidental			2/4			1/1
Treatment-emergent surgery	1/1		2/2			
Disorders, Female						
Overall percentage	0.3	0.2		0.3		0.1
Breast neoplasm malignant female	1/1			2/2		
Gastrointestinal System Disorders						
Overall percentage	0.4	0.1	0.2	<0.1	0.2	0.5
Abdominal pain	1/1		1/1			2/2
Diverticulitis	2/2					1/1
Gastric ulcer						2/2
Gastritis	1/1					2/2
Musculoskeletal System Disorders						
Overall percentage	0.0	0.2	<0.1	<0.1	0.0	0.0
Fracture accidental		2/2	1/1			
Myo, Endo, Pericardial and Valve Disorders						
Overall percentage	0.2	0.4	0.2	0.3	0.2	0.6
Angina pectoris	1/1					2/2
Coronary artery disorder	2/2		1/1	1/1		5/5
Myocardial infarction	1/1	3/3	3/3	1/1	1/1	2/2
Respiratory System Disorders						
Overall percentage	0.5	0.2	0.5	0.3	0.0	<0.1
Pneumonia	2/2		4/4			
Vascular (Extracardiac) Disorders						
Overall percentage	<0.1	0.0	0.0	<0.1	0.5	<0.1
Cerebrovascular disorder	1/1			1/1	2/2	2/2

For specific adverse events, values represent number of patients with a serious adverse event / number of episodes. Episodes can represent multiple, different serious adverse event or multiple occurrences of the same serious adverse event. Only non-zero values are shown except for percentages.

ARTHRITIS SAFETY TABLE 14: PATIENT LISTING OF SERIOUS ADVERSE EVENTS OF UNCERTAIN OR PROBABLE RELATION TO STUDY DRUG IN TRIALS 15/16(6wk) and 48/49/53/60/61(3mo)

Study/Patient ID/Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity/ Relationship	DER Number
015/US0032-0450/ PBO	54/ M	30	33	Abdominal pain	Mod/Uncertain	971222-CL326
015/US0033-0462/ NAP	62/ M	10 10	10 (O) 10 (O)	Gastric Ulcer† Gastritis†	Severe/Probable Severe/Probable	971212-CL430
048/US0038-0231/ DIC	59/F	47	50	Pancreatitis	Severe/Uncertain	990715-CL929
048/US0046-1154/ DIC	71/F	23 25	25 28	Abdominal pain† Gastritis	Severe/Uncertain Mild/Uncertain	991102-CL242 000218-CL193
048/US0051-1118/ DIC	62/F	70 70	73 73	Diarrhea† Hematochezia†	Severe/Probable Severe/Probable	991215-CL470
048/US0078-1059/ DIC	53/F	85	85 (O)	Hepatic function abnormal	Mild/Probable	991112-CL774
048/US0085-1205/ DIC	68/ M	32 32	56 56	Coronary artery disorder Myocardial ischemia	Severe/Uncertain Severe/Uncertain	000104-CL310
048/US0086-0720/ V10	73/F	52	52 (O)	Anemia	Mild/Uncertain	991026-CL71
049/US0010-0173/ V10	78/F	68	74	Nausea	Mod/Uncertain	990820-CL716
049/US0108-0427/ NAP	50/F	37 40	39 40 (O)	Chest pain non-cardiac Abdominal pain†	Mod/Probable Mod/Probable	990817-CL537
053/CA0016-0884/V20	63/ M	78	78	Dyspnea	severe/Probable	991123-CL234
053/US0114-1173/ V20	61/F	30 33 33	33 (O) 33 (O) 33 (O)	Chest pain non-cardiac Palpitation† Myalgia	Severe/Uncertain Severe/Uncertain Mod/Uncertain	000211-CL770
060/US0120-1511/ V20	73/F	9 9 9	15 15 15	Ileus† Nausea† Vomiting†	Severe/Uncertain Severe/Uncertain Severe/Uncertain	000210-CL621
060/US0436-1358/ V40	57/ M	69	69	Myocardial infarction	Severe/Uncertain	000424-CL329
061/US0115-1454/ NAP	52/ M	53 53	55 55	Gastric Ulcer GI Hemorrhage†	Severe/Probable Severe/Probable	000419-CL479
061/050115-1455/ V40	62/F	46 49	46 49 (O)	GI Hemorrhage† Anemia†	Severe/Probable Severe/Probable	000502-CL414
061/US0534-1094/ PBO	77/F	22	25	Chest pain	Severe/Uncertain	000310-CL633

†Patient prematurely withdrew due to this adverse event. Mod; moderate; PBO, placebo; NAP, naproxen sodium; DIC, diclofenac; V10, valdecoxib 10 mg total daily dose; V20, valdecoxib 20 mg total daily dose; V40, valdecoxib 40 mg total daily dose; O, ongoing (on date of last dose).

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ARTHRITIS SAFETY TABLE 15: SERIOUS ADVERSE EVENTS (NUMBERS) IN TRIAL 47 (6mo) – OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

Dose (mg/d)	Valde. 20mgbid	Valde.40mgbid	Naproxen
No. treated	399	403	415
Overall percentage of any event	3.5	5.2	6.2
Any event	14/16	21/30	26/44
Application Site Disorders			
Overall percentage	0.2	0.0	0.5
Cellulitis			2/2
Body as a Whole – General Disorders			
Overall percentage	1.0	1.0	1.7
Treatment emergent surgery	¾	1/1	4/4
Cardiovascular Disorders, General			
Overall percentage	0.2	0.5	0.0
Cardiac failure		2/2	
Gastrointestinal System Disorders			
Overall percentage	0.0	1.0	1.9
Abdominal pain			2/2
GI hemorrhage		2/2	1/1
Nausea			3/3
Vomiting			3/3
Liver and Biliary System Disorders			
Overall percentage	0.0	0.7	0.2
Cholecystitis		2/2	1/1
Red Blood Cell Disorders			
Overall percentage	0.0	0.2	0.5
Anemia		1/1	2/2
Respiratory System Disorders			
Overall percentage	0.5	0.7	1.0
Dyspnea			2/2
Pneumonia	1/1	3/3	1/1

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	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
Fetal Disorders				
3504	Exophthalmos	Diclofenac 75 mg BID	No	None
4275	Hernia Congenital	Valdecoxib 10 mg QD	No	None
Gastro-intestinal 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-CL304
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 dental pain studies show valdecoxib superior regarding selected narcotic AEs (dizziness, constipation, nausea, vomiting). The surgical trials 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 CABG 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 CABG trial.

Serious Adverse Events: The CABG 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%: Oral Surgery (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%: General Surgery (Trials 10, 11, 32, 33, 37, 52, 72) (Note: Trial 32 was an trial in patients S/P THR which 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

ANALGESIA SAFETY TABLE 3: Adverse Events with Incidence≥3%: Opioid-Sparing (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: Opioid Sparing (Trial 35 -CABG)

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: Oral Surgery (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≤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: General Surgery (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

ADVERSE EVENTS CAUSING WITHDRAWAL

ANALGESIA SAFETY TABLE 7: Adverse Events Causing Withdrawal with Incidence ≥1%: General Surgery (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%: Opioid-Sparing Surgery (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.

ANALGESIA SAFETY TABLE 9: Adverse Events Causing Withdrawal with Incidence ≥1%: Opioid Sparing (Trial 35 -CABG)

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: General Surgery (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: Opioid-sparing trials: In the opioid-sparing 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.

ANALGESIA SAFETY TABLE 11: Serious Adverse Events with Uncertain / Probable Relation to Study Medication (during or within 30 days post-treatment): General Surgery and Opioid-Sparing 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).

ANALGESIA SAFETY TABLE 12: Summary of Serious Adverse Events: Opioid-Sparing (Trial 35-CABG)

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 rescue with opiates (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

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 x 10^9/L	4.0 x 10^9/L	12.0 x 10^9/L	20.0 x 10^9/L
Neutrophils	0.50 x 10^9/L	1.00 x 10^9/L	11.00 x 10^9/L	20.00 x 10^9/L
Lymphocyte count	0.50 x 10^9/L	1.00 x 10^9/L	6.00 x 10^9/L	20.00 x 10^9/L
Eosinophil count	N/A	0.00 x 10^9/L	0.70 x 10^9/L	0.99 x 10^9/L
Red blood cells (RBC)	3.0 x 10^{12}/L	4.0 x 10^{12}/L	6.3 x 10^{12}/L	7.5 x 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 x 10^9/L	100 x 10^9/L	450 x 10^9/L	600 x 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≤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≤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.

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 40 mg TDD	Valdecoxib 80 mg TDD	NSAID
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**	**2/2087 from normal**	**1/1226 from normal**
	1/34 from high	**1/91 from high**	**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**	**10/2124 from normal**	**7/1236 from normal**
	1/23 from high	**1/45 from high**	**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**	**45/1643 from normal**	**38/1068 from normal**
	2/25 from high	**8/57 from high**	**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**	**11/2022 from normal**	**14/1166 from normal**
	4/68 from high	**12/151 from high**	**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**	**5/1288 from normal**
		1/6 from high	

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

ANALGESIA

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: Oral Surgery (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

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: Oral Surgery 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: General Surgery 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≤0.05).
#Statistically significantly different from active comparator (oxycodone 10 mg/acetaminophen 1000 mg or NSAIDs) treatment group (p≤0.05).

(Comparison of valdecoxib 20-40 mg versus placebo with all general surgery (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: Opioid-Sparing (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≤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 of the PO Period between Parecoxib Sodium/ Valdecoxib and Placebo: Opioid-sparing (Trial 35 – CABG). Other timepoints for analysis could be post-surgery, end of Day 1, end of IV period, or end of hospitalization, in addition to the end of PO 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%: Oral Surgery 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: General Surgery 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: Opioid-Sparing Surgery (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%: Opioid-Sparing (Trial 35 – CABG)

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.

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.

ANALGSIA SAFETY LABORAATORY TABLE 11: Selected Laboratory Shift Results from Baseline to Final Visit: Oral Surgery 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.

ANANLGESIA SAFETY LABORATORY TABLE 12: Selected Laboratory Shift Results from Baseline to Final Visit: General Surgery 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: General Surgery 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.

Opioid-sparing Trials: The shifts observed for valdecoxib 40 mg/d, valdecoxib 80 mg/d, and placebo in the opioid-sparing surgery trials were similar to the comparison of valdecoxib 20-40 mg versus placebo in the general surgery trials 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 CABG surgery trial 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.

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.

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.

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≤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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Appendix 1

Excerpt from Medical Officer's Review of NDA [redacted]

Study 035-Coronary Artery Bypass Graft (CABG):

Reviewer's comment: Owing to the unique role that the CABG trial has in this NDA, this trial will be reviewed separately.

Study 035 was designed to evaluate the general safety and analgesic efficacy of parecoxib and valdecoxib in patients who had undergone a first-time, isolated, coronary artery bypass graft (CABG) via median sternotomy. Patients (N=462) were randomized to receive placebo (N=151) or active (N=311) treatment, which consisted of IV or IM parecoxib 40 mg every 12 hours for at least 72 hours, followed by oral valdecoxib 40 mg every 12 hours, for a minimum total of 14 days. Both placebo and active treatment groups received standard of care medication in addition to study medication, with supplementary pain medication (morphine during the IV phase and codeine 30 mg/acetaminophen 300 mg [Tylenol #3 ®] or, at ex-US sites, codeine 30 mg/paracetamol 500 mg [Tylox ®, Gelonida ®]) available throughout the trial. Per the study protocol, all patients were required to be taking low dose aspirin (<325 mg daily) during the study. Over 90% of the patients were in compliance with this requirement.

Patients who participated in the CABG study were as follows for the placebo and the parecoxib/valdecoxib treatment groups, respectively:

- angina, 92.7 and 90.7%
- hypertension, 77.5 and 71.4%
- congestive heart failure, 3.9 and 4.5%
- atherosclerotic cardiovascular disease, 83.4 and 85.5%
- cerebrovascular disease (transient ischemic attacks and cerebrovascular accidents), 4.6 and 5.8%
- diabetes mellitus, 19.9 and 22.8%
- hyperlipidemia, 62.9 to 64.6%

Reviewer's comment: The treatment groups appear to be balanced with regards to these risk factors and co-morbid conditions.

Evaluation of safety was the primary objective of this study. Due to the complexity of post-operative medical-surgical care and the potential for the occurrence of a

large number events which are routine post-CABG surgical occurrences, a 5-member independent committee was established to review the adverse data on a selected number of "Clinically Relevant" adverse events (CRAEs). CRAE members did not participate as investigators in this trial. A "Parecoxib 035 -CABG study algorithm" was be used as a guide in forwarding case materials to the CRO safety specialist. These CRAEs were defined as follows:

- **Death**
  - **All cause death following randomization within 30 days of last dose of study drug**
- **Cardiovascular Events**
  - **myocardial infarction. New onset (post-randomization) myocardial infarction diagnosed by finding at least two of the following four criteria:**
    - **Prolonged (>20 min) typical chest pain not relieved by rest and/or nitrates**
    - **Enzyme level elevation, either by:**
      CK-MB >5% of total CPK
      CK greater than 2x normal
      LDH subtype 1>LDH subtype 2
      troponin >0.2 micrograms/ml
    - **New wall motion abnormalities**
    - **Serial ECG (at least two) showing changes from baseline or serially in ST-T**
      and/or Q waves that are 0.03 seconds in width and/or > or + one third of the
      total QRS complex in two or more contiguous leads
- **severe myocardial ischemia**
  - **an acute event characterized by the onset of ischemic ECG changes in an**
    ECG done for a specific clinical event, which resolve over time without reaching the
    above definitions of myocardial infarction
- **cerebrovascular accident (CVA, TIA, or hemorrhage)**
  - **a new onset central neurologic event of either focal or global nature, with unequivocal**
    physical or cognitive findings, which may be accompanied by a confirmatory diagnostic test (angiography, MRI, brain scan).
- **peripheral arterial occlusion**
  - **a new clinical event characterized by clearly reduced pulses or with evidence of regional ischemia, accompanied by a confirmatory arterial vascular study (invasive or non-invasive). In the absence of a positive diagnostic test, the suspicion must be sufficiently compelling to require specific medical treatment (aggressive anti-coagulation) or surgical intervention.**

- **deep vein thrombosis**
    - **a syndrome consisting of increased unilateral or bilateral leg swelling, warmth and edema, with confirmatory documentation based on a positive diagnostic test (venous ultrasonography, angiography, magnetic resonance imaging, radionucleotide scan or impedance plethysmography). In the absence of a positive diagnostic test, the suspicion must be sufficiently compelling to require full dose anti-coagulation.**
- **pulmonary embolism**
    - **an event consisting of chest pain or dyspnea and/or hypoxemia with confirmatory angiography or ventilation-perfusion scanning (high probability V/Q scan or moderate probability V/Q scan with compelling clinical picture).**
- **Pericarditis**
    - **a clinical event consisting of an evolving, non-ischemic pattern of PR, ST segment and T-wave changes without evolution of a new Q waves, without accompanying significant myocardial enzyme elevation. Clinical symptoms consisting of chest pain, a rub, or fever may or may not be present. Imaging studies, if performed, show no evidence of new wall motion abnormalities, myocardial ischemia or infarction. Therapeutic intervention (e.g., NSAIDs or steroids), in the absence or additional information, does not establish the diagnosis.**
- Congestive Heart Failure (new onset or exacerbation)
    - **due to the complexity of identifying the precise etiology of new onset or exacerbation of congestive heart failure in a clinical trial setting wherein study volunteers are receiving parenteral fluid administration during the time of study drug use, the adjudication of this adverse event occurrence was divided into two time frameworks: a) During the post-operative phase of parenteral fluid administration and for 96 hours following discontinuation of parenteral fluid administration; b) commencing at a point 96 hours following discontinuation of parenteral fluid administration and through to the end of study. This "time framework" division of the study was intended to provide an opportunity to assess the occurrence of primary cardio-pulmonary destabilization as a cause of heart failure versus a study drug effect upon the kidney producing salt and water retention with subsequent congestive heart failure. The diagnosis of new onset or worsening of congestive heart failure was made by standard clinical assessment of relevant medical history, physical,**

radiological examination and hemodynamic monitoring, together with blood chemical evaluation and confirmation of myocardial function impairment by one or more standard cardiac imaging techniques (such as echocardiography).

- Renal Failure/Dysfunction
  - **Reduced Renal Perfusion/Filtration**
    - **in the absence of acute hypovolemia due to a nonrenal cause, other causes of reduced**

renal perfusion, obstructive uropathy, or other documented alternative cause of intrinsic renal disease, the presence of any one of the following would be defined as reduced renal perfusion/filtration event:

- **An increase of serum creatinine >30% if baseline creatinine >0.9 mg/dL (or >1.2 mg/dL if baseline creatinine <0.9 mg/dL) and verified by a second determination**
- **BUN > 200% from baseline or, with a baseline value in the upper limit of normal an absolute value >50 mg/dL and verified by a second determination**
- **An absolute serum creatinine >1.7 mg/dL and BUN >45 mg/dL verified by second determination**
- **Acute renal failure of recent onset as shown by hospital evaluation**

- **Systemic fluid, electrolyte, and metabolic abnormalities**
  - **In the absence of other obvious causes, the presence of the following would be defined as a fluid, electrolyte and metabolic abnormality:**
    - **Serum potassium >6.0 mEq/L (verified)**
    - **Serum sodium <130 mEq/L (verified)**
    - **Serum bicarbonate <20 mEq/L and chloride >110 mEq/L and other evidence of tubular dysfunction (elevated urinary amino acid excretion or elevated urinary beta-microglobulin excretion or inappropriately high urine pH or abnormal serum potassium)**
    - **New onset, sustained urinary dipstick proteinuria (3+ or greater magnitude (verified by a second determination)**
    - **New onset or worsening of edema of distal extremities or generalized edema as evidenced by either of the following:**
    - **weight gain of >2 kg and an increase in 1+ on a semi-quantitative clinical assessment of edema (1+ to 4+ scale) verified by a second determination**
    - **any report of edema with evidence of a clinical consequence (an increase of systolic blood pressure > 20 mg Hg or an increase of diastolic blood pressure > 10 mg Hg on tow consecutive daily determinations or two-consecutive visits; initiation or increase in daily dose of diuretic or**

antihypertensive drugs to treat edema; discontinuation of study drug to treat the edema.

- **Interference with blood pressure regulation**
  - **In the absence of alternative medicinal, volumetric on other clinical interventions or evidence of medical noncompliance, dietary indiscretion with respect to salt intake, superimposed alternative cause for secondary hypertension, or a concurrent condition necessitating use or change in diuretics/antihypertensives, the presence of any one of the following would be defined as a renal event of the NSAID-induced interference with blood pressure regulation type:**
    - **An increase of systolic blood pressure ≥ 20 mm Hg and ≥ 140 mm Hg or an increase of diastolic blood pressure ≥10 mm Hg and ≥ 90 mm Hg on two consecutive daily determinations**
    - **Any increase in systolic or diastolic blood pressure accompanied by the initiation of antihypertensive medication**
    - **Any increase in systolic or diastolic blood pressure accompanied by the escalation of antihypertensive drug therapy (e.g., increase in dose, addition of a new agent, substitution of a more potent agent)**
- **Glomerular or Tubulo-interstitial Disease**
  - **A condition which resolves all or in part upon discontinuation of drug and which occurs in the absence of other causes of glomerular or tubulo-interstitial disease is defined as a glomerular or tubulo-interstitial renal event by the presence of the following:**
    - **Proteinuria >3+ or greater verified by a second determination**
    - **Active urinary sediment (hematuria, excess tubular epithelial cells, or pyuria)**
    - **Histopathologic or imaging evidence of glomerular or tubulointerstitial disease**
    - **Evidence of renal dysfunction as manifested by one of the following:**
      - **An increase of serum creatinine >30% if baseline creatinine > 0.9 mg/dL (or ≥ 1.2 mg/dL if baseline creatinine ≤ 0.9 mg/dL) and verified by a second determination**
      - **An increase of BUN >200% from baseline or, with the baseline value in the upper limit of normal, an absolute value =50 mg/dL and verified by a second determination**

- **A serum creatinine ≥ 1.7 mg/dL and BUN ≥ 45 mg/dL verified by second determination.**

- Gastrointestinal Event (bleeding, perforation or obstruction) consisting of the following nine categories:
  - **UGI Bleeding (one of seven traditional clinical presentations):**
    - **Hematemesis with a gastric or duodenal ulcer or large erosion proven by endoscopy or a UGI barium x-ray**
    - **A gastric or duodenal ulcer or large erosion proven by endoscopy with evidence of active bleeding or stigmata of a hemorrhage (visible vessel or attached clot to base of an ulcer)**
    - **Melena with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium x-ray**
    - **Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium x-ray and with bleeding as evidenced by a fall in hematocrit of > 5% or a reduction of hemoglobin of ≥ 1.5 g/dL from baseline**
    - **Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium x-ray and with bleeding as evidenced by orthostasis (changes to postural vital signs; increase in pulse rate of >20 beats/min and/or a decrease in systolic blood pressure of >20 mm Hg and/or diastolic blood pressure of >10 mm Hg)**
    - **Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium x-ray and with bleeding as evidenced by a need for blood transfusion of two or more units**
    - **Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or UGI barium x-ray and with bleeding as evidenced by blood in the stomach as determined by endoscopy or nasogastric aspiration. A separate analysis assigning suspected UGI bleeding events to one of the following alternate categories will also be done:**
    - **Hematemesis with a gastric or duodenal ulcer or large erosion proven by endoscopy or a UGI barium x-ray, and**
      - **a drop in hemoglobin >2 g/dL with adequate hydration or if urgent transfusion required, final hemoglobin (approximately 12-24 hours after the last urgent transfusion) < pre-bleed hemoglobin (within assay variability) or**
      - **hypotension (defined as less than 90/60) or orthostatic hypotension**
    - **A gastric or duodenal ulcer or large erosion proven by endoscopy with evidence of active bleeding or stigmata of recent hemorrhage (visible vessel or attached clot to base of an ulcer) and**
      - **a drop in hemoglobin >2 g/dL with adequate hydration or if urgent transfusion required, final hemoglobin (approximately**

12-24 hours after the last urgent transfusion) < pre-bleed hemoglobin (within assay variability) or

- **hypotension (defined as less than 90/60) or orthostatic hypotension**

- **Melena with a gastric or duodenal ulcer or large erosion proven by endoscopy or a UGI barium x-ray; and**
  - **a drop in hemoglobin >2 g/dL with adequate hydration or if urgent transfusion required, final hemoglobin (approximately 12-24 hours after the last urgent transfusion) < pre-bleed hemoglobin (within assay variability); or**
  - **hypotension (defined as less than 90/60) or orthostatic hypotension**
- **Hemoccult positive stools with a gastric or duodenal ulcer or large erosion proven by endoscopy or a UGI barium x-ray, and**
- **hypotension (defined as less than 90/60) or orthostatic hypotension**

- **UGI Perforation**
  - **An opening in the wall of the stomach or duodenum requiring surgery, or laparoscopic repair but only if the evidence is unequivocal (free air, peritoneal irritation signs, etc.)**
- **Gastric Outlet Obstruction**
  - **Opinion of clinician with endoscopic or UGI barium x-ray documentation. Endoscopic evidence would include tight edematous pylorus with an ulcer in the pyloric channel, inability to pass the endoscope tip into the duodenal bulb or descending duodenum, or retained fluid/food in the stomach. UGI barium x-ray evidence of obstruction would include; (1) a dilated stomach, (2) a slowly emptying stomach in a patient with clinical evidence of outlet obstruction and in some instances with an ulcer seen in the channel or duodenal bulb or (3) severe narrowing and edema obstructing the outlet of the stomach. Ulcers documented by endoscopy or UGI barium x-ray and with no evidence of GI bleeding will be summarized separately as will other symptomatic GI complaints.**

- Major non-GI bleed (requiring transfusion)
  - **New onset post-randomization bleeding due to a non-GI source (single or multi-site) accompanied by either transfusion of 2 or more units of PRBCs, or a Hgb drop of 3 gm/dL or greater, (or 9 hematocrit points) which is unrelated to the sequelae of hemodilution.**
- Infection (requiring institution of antibiotics)
  - **A documented or suspected infectious process (based on a documented constellation of signs and symptoms, with suspected source), requiring new antibiotic or antiviral therapy or a change in pre-existing antibiotic regimen.**
- Pulmonary complications (non-infectious)

- **atelectasis or decline in respiratory function, requiring intervention consisting of non-routine post-operative respiratory care (e.g., bronchoscopy, reintubation, or non intubation ventilatory modalities)**
- **development of new, persistent (beyond 72 hours) non-LLL, symptomatic non-infectious infiltrates**
- **pleural effusion requiring drainage or which compromise pulmonary function as manifested by dyspnea or other discrete symptoms of respiratory compromise or which requires anti-inflammatory therapy**
- **ARDs or other forms non-cardiac pulmonary edema**
- **pneumothorax or persistent air leak**

The "Events Committee" reviewed all AEs (blinded to treatment assignment) submitted by investigators which potentially meet any of the above categories. The committee verified that the AE meet pre-defined definitions, and made a judgment whether the event was "probably, possibly or remotely related" or "not related" to study drug treatment and the date of onset of the event.

Reviewer's comment: As noted above, a 4-member (external) Gastrointestinal Events Committee (GEC) and Renal Events Committee (REC) were also established for this study. Of note, no events in the valdecoxib "long-term" safety study (91-048) were adjudicated by the GEC to be clinically significant.

Table 66 summarizes the duration of exposure to either parecoxib or valdecoxib in study 035. As noted earlier, patients were given parecoxib for the first 3 days after surgery (IV dosing period) and they were then switched to oral valdecoxib. Also noted earlier, most of the patients in this trial were male (85%), Caucasian (93%) with an approximate mean age of 60 years.

Table 66: Duration of Exposure: CABG Surgery Trial (035)[1]

Days	Placebo (%)	Parecoxib/Valdecoxib 40 mg Q12H (%)
1-4	22 (15)	40 (13)
5-7	6 (4)	15 (5)
>7	123 (81)	256 (82)
Total	151	311

1 From Table T.3.3, N93-00-07-816.

Incidences of Clinically Relevant Adverse Events (CRAEs)

Table 67 **summarizes the clinically relevant adverse events as defined and adjudicated by the events committee discussed above.**

During the entire study period, 25.7% of parecoxib/valdecoxib patients and 15.2% of placebo patients had a CRAE; this difference was statistically significant. All events listed, with the exception of myocardial infarctions and major non-GI bleeds, were numerically more frequent for parecoxib/valdecoxib during the entire study period.

Table 67: Incidence of Clinically Relevant Adverse Events (CRAEs)- Study 035[1,2]

Event	PLACEBO (N=151)	Parecoxib/Valdecoxib 40 mg (N=311)
	Entire Study	Entire Study
Any Event (%)	23 (15.2)	80 (25.7)*
Death	0.0	4 (1.3)
Myocardial infarction	1 (0.7)	1 (0.3)
Cerebrovascular accident	1 (0.7)	9 (2.9)
Deep vein thrombosis	0.0	3 (1.0)
Pulmonary embolism	0.0	2 (0.6)
Congestive heart disease	1 (0.7)	4 (1.3)
Pericarditis	1 (0.7)	4 (1.3)
Renal failure/dysfunction	7 (4.6)	29 (9.3)
GI event	0.0	4 (1.3)
Major non-GI bleed	2 (1.3)	0.0
Infection	11 (7.3)	29 (9.3)
Pulmonary complication	4 (2.6)	19 (6.1)

1 Derived from Table 9g and Table T5.7.1, N93-00-07-816. Numbers in () are percentages.
2 * p-value by Fischer's exact test = 0.012. There were no other statistically significant results noted by the sponsor.

Reviewer's comment: Of a total of 13 myocardial infarctions (Figure 8b, I93-00-06-035), 11 events (2-placebo, 9-parecoxib/valdecoxib) were sent to the Events committee for adjudication. Only 2 events (patient 1128-placebo; patient 0130-parecoxib/valdecoxib) were adjudicated as meeting the predefined criteria for a CRAE as noted in the table above. Of the nine remaining events (1-placebo, 8-parecoxib/valdecoxib) all were felt to either have occurred prior to drug or did not meet the criteria. One event that was felt not to meet criteria in the

parecoxib/valdecoxib group was a death (patient 1136, see appendix of this review for summary).

Risk Factors for Clinically Relevant Adverse Events

A number of risk factors including age (with 65 and 70 years as cut points), gender, BMI, baseline serum creatinine or creatinine clearance, diabetes, CHF, CVD, hypertension, smoking status, time to extubation, use or time on heart pump, pre-operative NSAIDs, pre-operative or concurrent aspirin/salicylate or their interactions were evaluated (data not shown, Table T5.7.3; N93-00-07-816). Comparisons within group and subgroups was by Fisher's exact test, while interactions were compared by Breslow-Day testing were stratified by risk factor.

Within the parecoxib/valdecoxib treatment group, patients with body mass index (BMI)
≥30 kg/m^2 (p=0.014) or with a positive history of cerebrovascular disease **(p=0.008) were more likely to have a CRAE than patients without a previous cerebrovascular disease or with BMI <30 kg/m^2. Among placebo patients, those who were** current smokers **were significantly more likely to have a CRAE (p=0.011) than were other patients in the placebo group.**

When the incidence of CRAEs was analyzed for the interaction of risk factor and treatment group, history of cerebrovascular disease (p=0.038) and being a current smoker (p=0.007) were identified. History of cardiovascular disease was associated with a higher incidence of CRAEs than was a negative history of cardiovascular disease (52 v. 24%, respectively) for parecoxib/valdecoxib, while the reverse was noted for placebo (0 v. 16%, respectively). Current smokers had a higher incidence of CRAEs than did other patients in the placebo group, while current smokers had a slightly lower incidence of CRAEs than did other patients in the parecoxib/valdecoxib group.

A stepwise logistic regression analysis of potential risk factors revealed within the parecoxib/valdecoxib group, age ≥65 years (OR: 2.14; CI: 1.11, 4.08), BMI ≥ 30 (OR: 1.85; CI: 1.07, 3.21), and prior CVD (OR: 2.95; CI: 1.16, 7.58) were predictive variables associated with risks for CRAE. However, the analysis also suggested that age ≥ 70 years was protective (OR: 0.55; CI: 0.22, 1.33). That patients between 65 and 69 years of age are at greater risk of a CRAE, but patients at least 70 years of age are at a reduced risk, suggests some instability of the model.

Other variables associated with an increased risk for CRAEs noted when the analysis involved all patients included history of diabetes, preoperative aspirin therapy and baseline creatinine ≥106 umol/L **(OR: 6.54; CI: 2.03 - 21.11).**

Comparative studies for CABG:

In an attempt to put the results of study 035 into context with respect to current standards of care and outcome, comparative outcome data from two other studies of CABG surgery patients were included in the NDA.

The first of these two studies, EPI 2, is a prospective, international, multicenter, observational study of patients undergoing CABG and/or valve surgery with or without concurrent cardiac or non-cardiac procedures. The study is being conducted by the Ischemia Research and Education Foundation, in conjunction with the Multicenter Study of Perioperative Ischemia, which is a consortium of approximately 300 investigators and 160 academic centers that, since November 1996, have enrolled more than 5,000 patients at 69 centers. The present database was locked at the end of June 2000. This study includes consenting adult patients (between 18 and 75 years, inclusive) undergoing an isolated, primary CABG via median sternotomy with a NYHA Class I - III classification or had a cardiac ejection fraction of at least 35%, and who had preoperative aspirin treatment **(325 mg/day) maintained throughout the study.**

The second source of comparative data is the Society for Thoracic Surgery (STS) database, compiled and maintained by the Society for Thoracic Surgery. Previous published results from this database included patients undergoing a primary, isolated CABG procedure between 1990 and 1994, followed by standard care postoperatively. STS data used for comparison in the present report included results through 1997.

A comparison of the incidences of CRAEs among the three databases is shown in Table 68. **Since both the EPI 2 and STS databases ended adverse event collection at the time of hospital discharge, the data from study 035 includes only events occurring before hospital discharge. Also, the column of EPI 2 data labeled "Matched Patients" contains only patients who would have satisfied the inclusion/exclusion criteria for Study 035 and were treated at sites included in Study 035. Recognizing the limitations of comparisons between trials, the EPI 2 and STS databases help to add perspective to the data obtained in trial 035.**

Table 68: Comparative Outcome Data from Two Observational Databases[1]

Adverse Events to Hospital Discharge	Study 035		EPI 2		STS
	Placebo N = 151 n (%)	Parecoxib/ Valdecoxib N = 311 n (%)	Patients Matched to 035 Sites & Entry Criteria N = 547 N (%)**	All Patients N = 3449 n (%)**	All Patients N = 161,018 n (%)
Death	0 (0)	3 (1.0)	3 (0.6)	103 (3.0)	2972 (1.7)‡
MI	0 (0)	1 (0.3)	9 (1.7)	146 (4.2)	1771 (1.1)
CVA accident (+TIA)	1 (0.7)	8 (2.6)	18 (3.2)	245 (7.1)	3703 (2.3)
Deep vein thrombosis	0 (0)	3 (1.0)	0 (0)	4 (0.1)	—
Pulmonary embolism	0 (0)	1 (0.3)	—	—	524 (0.3)

Infection	**9 (6.0)**	**13 (4.2)**	**81 (15.0)**	**586 (17.0)**	**—**
Surgical wound infection* **	**3 (2.0)**	**7 (2.2)**	**15 (3)**	**140 (4)**	**4214 (2.6)**
Renal dysfunction†	**6 (4.0)**	**27 (8.7)**	**100 (41)**	**1009 (50)**	**—**
Major renal CRAE††	**3 (2.0)**	**8 (2.6)**	**4 (0.7)**	**97 (2.8)**	**5063 (3.1)**
GI event†††	**0 (0)**	**3 (1.0)**	**4 (0.7)**	**50 (1.5)**	**3939 (2.5)**

1 **** Percentages calculated based on number of patients with available data for a given event. *** Surgical wound infection is a subset of all reported infections. ‡ N = 174,806 for death rate in STS. † Includes both renal failure and renal dysfunction in the 035 database. †† Serum creatinine > 2.0 mg/dL and increase of > 0.7 mg/dL from Baseline. ††† Includes bleeds, perforations, and obstructions for study 035, and bleeds for EPI 2 database.**

Adverse Events-Study 035:

Selected adverse events occurring in study 035 are presented in Table 69. **The overall incidence of adverse events (over 80%) in each treatment group, likely reflects the population studied and the surgical procedure and post-operative course.**

For example, some of the most common adverse events were constipation, nausea and vomiting. The lack of any difference in the placebo versus the "add-on" group of parecoxib/ valdecoxib to this "standard of care", suggests that any opioid-sparing effects of these agents is not apparent at a clinical level **i.e. less of the events commonly ascribed to opioids. The results with somnolence, pruritis and respiratory depression would tend to support this lack of an obvious beneficial clinical effect on sparing opioid-related events.**

Among other commonly reported gastrointestinal adverse events **(ulceration, hemorrhage, hemoccult positivity SGOT/SGPT increases), the trends suggest more of these events in the parecoxib/valdecoxib group as compared to the placebo group. Of note, post-operative anemia was more common in the parecoxib/valdecoxib group as compared to placebo.**

The cardiovascular and renal events **noted tend to have somewhat mixed results. While there were significantly lower incidences of tachycardia, there were significantly more episodes of supraventricular tachycardia and hypotension in the parecoxib/valdecoxib group; however, this hypotension did not seem to reflected in episodes of syncope, dizziness or vertigo. On the other hand, events such as hypertension, myocardial infarction, cerebrovascular disorder, hypokalemia, BUN increases, oliguria, and acute renal failure were generally numerically higher in the parecoxib/valdecoxib group.**

Pulmonary events **such as pleural effusion, bronchospasm, pneumonia, and upper respiratory tract infections were significantly less frequent in the parecoxib/valdecoxib group compared to the placebo group; the latter effects did not seem to persist until the end of the study. Episodes of pulmonary embolism or atelectasis did not differ between the treatment groups. Although there were**

significantly fewer events listed as fever, this did not seem to translate into higher infection rates (data not shown).

Most adverse events were mild or moderate in severity (Appendices 4.7.1-4.8.2, N93-00-07-816, data not shown).

During the entire study period, 20.3% (63/311) and 17.2% (26/151) of patients who received parecoxib/valdecoxib and placebo, respectively, experienced a severe adverse event.

Table 69: Incidence of Selected Adverse Events- Study 035[1,2]

Event	PLACEBO (N=151)		Parecoxib/Valdecoxib 40 mg (N=311)	
		Entire Study		Entire Study
Any Event (%)		135 (89.4)		277 (89.1)
Gastrointestinal				
Duodenal ulcer (perforated)		0		2 (0.6)
Gastric Ulcer		0		1 (0.3)
GI hemorrhage		0		3 (1.0)
Hematemesis		1 (0.7)		4 (1.3)
Hemoccult positivity		0		2 (0.6)
SGOT increased		3 (2.0)		11 (3.5)
SGPT increased		4 (2.6)		12 (3.9)
Constipation		56 (37.1)		116 (37.3)
Nausea		58 (38.4)		137 (44.0)
Vomiting		17 (11.3)		43 (13.8)
Dyspepsia		6 (4.0)		19 (6.1)
Abdominal Pain		5 (3.3)		12 (3.9)
Cardiovascular/Renal				
Hypertension-aggravated		2 (1.3)		7 (2.3)
Hypotension		9 (6.0)		39 (12.5)*
Syncope		1 (0.7)		5 (1.6)
Dizziness		27 (17.9)		37 (11.9)
Vertigo		0		1 (0.3)
Edema				
Generalized		7 (4.6)		9 (2.9)
Peripheral		21 (13.9)		51 (16.4)
Tachycardia		22 (14.6)		22 (7.1)*
Supraventricular		0		10 (3.2)*
tachycardia		30 (19.9)		49 (15.8)
Atrial fibrillation		6 (4.0)		22 (7.1)
Hypokalemia		1 (0.7)		10 (3.2)
BUN increased		3 (2.0)		2 (0.6)
Angina Pectoris		1 (0.7)		6 (1.9)

Myocardial Infarction	[	15 (9.9)	[	45 (14.5)
Oliguria		0		2 (0.6)
Acute renal failure		2 (1.3)		9 (2.9)
Abnormal Renal Function		1 (0.7)		8 (2.6)
Cerebrovascular Disorder		1 (0.7)		0
Peripheral Ischemia		0		2 (0.6)
Thrombophlebitis, deep		1 (0.7)		7 (2.3)
Pericarditis		1 (0.7)		4 (1.3)
Hematoma		1 (0.7)		0
Vasculitis	]		]	
Pulmonary/Post-operative				
Fever	[	32 (21.3)	[	13 (4.2)*
Pulmonary Embolism		0		2 (0.6)
Atelectasis		14 (9.3)		16 (5.1)
Bronchospasm		10 (6.6)		6 (1.9)*
Pleural Effusion		26 (17.2)		23 (7.4)*
Pneumonia		4 (2.6)		4 (1.3)
Respiratory Depression		2 (1.3)		6 (1.9)
URTI		5 (3.3)		3 (1.0)
Post-op incisional pain		7 (4.6)		6 (1.9)
Thrombocytopenia		0		5 (1/6)
Post-op anemia		8 (5.3)		28 (9.0)
Somnolence		19 (12.6)		36 (11.6)
Headache		2 (1.3)		8 (2.6)
Confusion	]	10 (6.6)	]	16 (5.1)
Skin				
Rash	[ ]	4 (2.6)	[ ]	2 (0.6)
Pruritis		4 (2.6)		6 (1.9)

1 Derived and revised from Table T5.3.1, N93-00-07-816.
2 * indicates statistically significantly different at $p < 0.05$.

Incidence of Adverse Events Causing Withdrawal

The incidences of adverse events causing withdrawal are shown in Table 70. During the entire study period, 13.2% of patients in the placebo group and 16.7% of patients in the parecoxib/valdecoxib group withdrew from the study due to an adverse event.

. Statistical comparisons did not reveal any significant differences in the overall or individual event rates between treatment groups.

Table 70: Incidence of Adverse Events Causing Withdrawal ≥ 1%- Study 035[1,2]

Event	PLACEBO (N=151)		Parecoxib/Valdecoxib 40 mg (N=311)	
		Entire Study		Entire Study
Any Event (%)		20 (13.2)		52 (16.7)
Gastrointestinal				
Nausea	[ ]	2.0	[ ]	2.6
Vomiting		2.0		1.6
Cardiovascular/Renal				

Hypotension	[	0	[	1.0
Cerebrovascular Disorder		0.7		1.0
Dizziness		1.3		0.6
BUN increased		0		1.0
Creatinine increased		1.3		1.9
Pericarditis		0		1.3
Renal function abnormal		0.7		1.3
Pulmonary/Post-operative				
Pneumonia		1.3		0

1 Derived and revised from Table T5.4, N93-00-07-816. Data are expressed as percentage of total.

2 There were no P-values (by Fisher's exact test) ≤ 0.05 for any differences between the treatment groups.

Demographic Subgroup Analyses of Adverse Events

Interaction p-values were considered valid whenever at least 20 events were reported provided these events gave at least 10 events within each stratum. Subgroup analyses of adverse events were carried out for patients stratified by age **(both <65 vs. =65 years and <75 vs. =75 years), gender, race and weight.** Race **(Table T5.6.4, N93-00-07-816) and age (<75 vs. =75 years; Table T5.6.2, N93-00-07-816) identified such small numbers of black patients (6) and patients =75 (11) that useful analyses could not be made for these groups. Analysis of adverse events (data not shown, Table T5.6.3, N93-00-07-816)** by gender or weight **(Table T5.6.5, N93-00-07-816) noted a greater incidence of fever in female patients treated with parecoxib/valdecoxib but a higher incidence of fever was greater for placebo-treated male patients. However, the relatively small number of female patients with events (5) makes these comparisons of limited use. Analysis of adverse events by weight (≤70 kg vs. >70 kg) noted differences in the incidence of vomiting and confusion.**

Analysis of adverse events (data not shown, Table T5.6.1, N93-00-07-816) by patients <65 years **(209 and 94 patients for parecoxib/valdecoxib and placebo, respectively)** versus **≥65 (102 and 57 patients for parecoxib/valdecoxib and placebo, respectively) in trial 035 noted a significant interaction (p=0.032, Breslow-Day testing stratified by age) for anemia. The incidence of** postoperative anemia was higher for patients **<65** years **(20 events, 9.6%) than ≥65 years (8 events, 7.8%)** receiving parecoxib/valdecoxib. **Among patients receiving placebo, the incidence of postoperative anemia was lower for patients <65 years (2 events, 2.1%) compared to patients ≥65 years (6 events, 10.5%). Other comparisons by age yielded small numbers of events rending any clinical comparison of limited use.**

[redacted]

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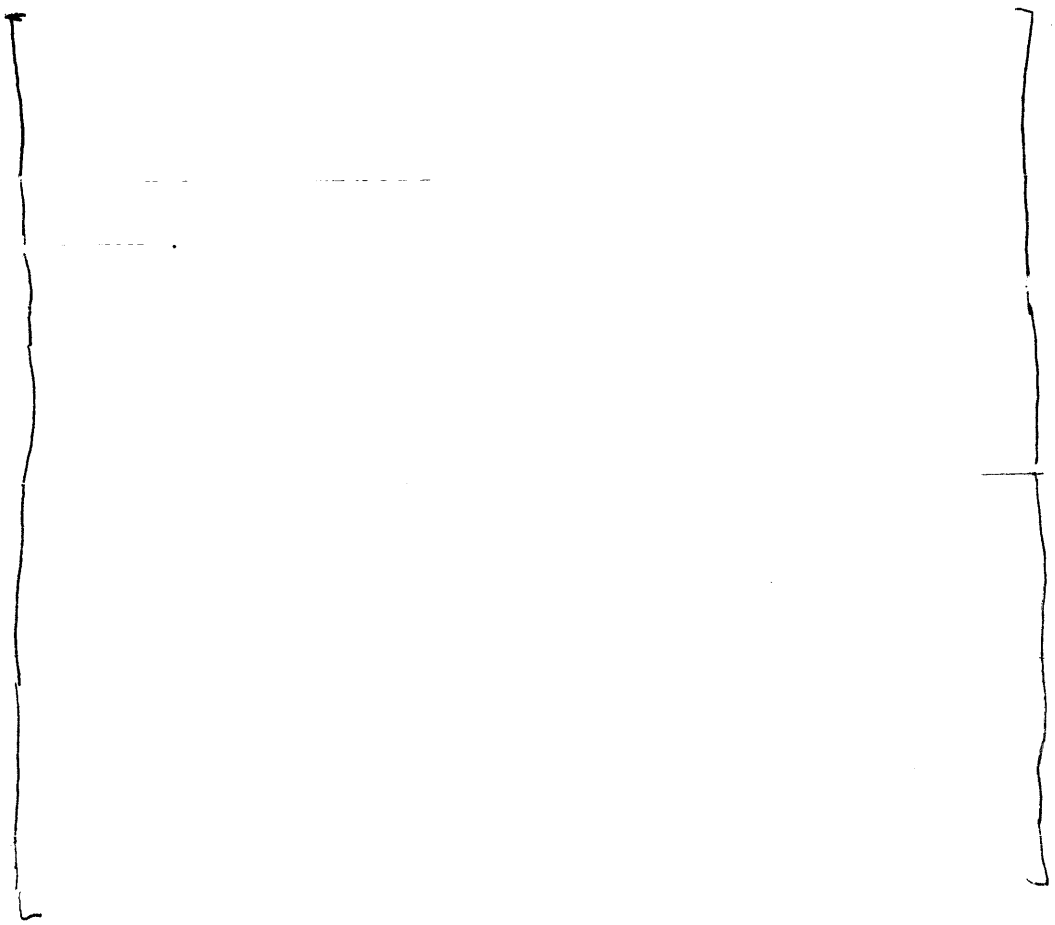

Serious Adverse Events

Serious adverse events that occurred in two or more patients in either treatment group during the [redacted] and the entire study are summarized in Table 72. **A total of 146 serious adverse events were reported in 74 patients (118 events in 59 patients and 28 events in 15 patients who received parecoxib/valdecoxib or placebo, respectively). These serious events represent 19.0% and 9.9% (entire study) or [redacted] of patients receiving parecoxib/valdecoxib and placebo, respectively. With the lone exceptions of [redacted] and atrial arrhythmia (entire study), there were as many, but usually more, events in the parecoxib/valdecoxib as compared to the placebo-treated group.**

This trend towards more serious adverse events in the parecoxib/valdecoxib group includes gastrointestinal events, thromboembolic and other cardiovascular events, renal events, and infectious episodes.

Table 72: Incidence of Serious Adverse Events- Study 035[1]

Event	PLACEBO (N=151)		Parecoxib/Valdecoxib 40 mg (N=311)	
	[redacted]	Entire Study	[redacted]	Entire Study
Total number of patients (%)	[redacted]	15 (9.9%)	[redacted]	59 (19.0)
Total number of events	[redacted]	28	[redacted]	118
Gastrointestinal				
Duodenal ulcer (perforated)	[redacted]	0	[redacted]	2
GI hemorrhage		0		3
Vomiting		0		2
Cardiovascular/Renal				
Cerebrovascular disorder	[redacted]	1	[redacted]	9
Thrombophlebitis		0		3
Hypotension		0		2
Chest pain (non cardiac)		0		2
Cardiac failure		2		3
Atrial arrhythmia		2		1
Atrial fibrillation		1		2
Creatinine increase		0		3
Myocardial infarction		1		5
Renal function abnormal		0		3
Pulmonary/Post-operative				
Sternal (deep) wound infection	[redacted]	0	[redacted]	2
Sternal wound infection		0		7
Infection (non sternal)		0		2
Sternal wound drainage		0		2
Sternal wound dehiscence		0		3
Sternal instability		1		2
Bacterial infection		0		2
Sepsis		0		2
Post-op anemia		0		2
Hypoxia		0		2
Pleural effusion		1		7
Pneumonia		3		4

1 Derived and revised from Table T5.5, N93-00-07-816. Data are expressed as number of patients. Only those groups with ≥ 2 patients in any treatment group are included.

Deaths

Four deaths occurred among patients receiving the parecoxib/valdecoxib treatment regimen; there were no deaths among the placebo group. Narratives of these deaths can be found in the appendix of this review. A 58-year-old male patient (035-CA0203-0145), [redacted], died on Day 15 (counting first dose day as Day 1) from a duodenal ulcer. A 69-year-old female patient (035-GE0402-1136), [redacted] and thirteen doses of

valdecoxib, expired on Day 19 due to a probable myocardial infarction. A 67-year-old male patient (035-UK0303-0938), [redacted] and six doses of oral valdecoxib, died on Day 12 from septicemia, sternal wound infection, and bronchopneumonia. A 62-year-old male (035-US0127-0231), [redacted] expired on Day 6 from massive left cerebellar infarct with brainstem compression (listed as "impression") and herniation.

Summary of Safety Results for Analgesia Study, CABG Surgery Model

- **Most patients (>80%) in either treatment group were exposed for > 7 days.**
- **The overall incidence of adverse events (over 80%) in each treatment group, likely reflects the population studied and the surgical procedure and post-operative course.** [redacted]
- [redacted]
- **During the entire study period, 20.3% (63/311) and 17.2% (26/151) of patients who received parecoxib/valdecoxib and placebo, respectively, experienced a severe adverse event.**
- [redacted]
- **During the entire study period, 25.7% of parecoxib/valdecoxib patients and 15.2% of placebo patients had a clinically relevant adverse event; this difference was statistically significant. All events, with the exception of myocardial infarctions and major non-GI bleeds, were also numerically more frequent for parecoxib/valdecoxib during the entire study period.**
- **Differential risk factors for developing clinically relevant adverse events in the parecoxib/valdecoxib group included prior history of cerebrovascular disease and body mass index of ≥ 30 kg/m^2 and history of cardiovascular disease while current cigarette smoking was a risk factor for placebo patients. For both groups, by logistic regression analysis, history of diabetes, preoperative aspirin therapy and baseline creatinine >106 umol/L also increased risk: the latter was the most predictive risk factor for developing an event.**
- **Although the adverse event rates in study 035 were within the expected background rates noted in other CABG trials, high-risk patients, such as those identified above may have a higher risk of adverse events with parecoxib/valdecoxib.**
- **Trends with commonly reported gastrointestinal adverse events (ulceration, hemorrhage, hemoccult positivity SGOT/SGPT increases, post-op anemia)**

suggest more of these events in the parecoxib/valdecoxib group as compared to the placebo group.

- The cardiovascular and renal events noted tend to have somewhat mixed results. While there were significantly lower incidences of tachycardia, there were statistically significantly more episodes of supraventricular tachycardia and hypotension in the parecoxib/valdecoxib group; however, this hypotension did not seem to reflected in episodes of syncope, dizziness or vertigo. On the other hand, events such as hypertension, myocardial infarction, cerebrovascular disorder, hypokalemia, BUN increases, oliguria, and acute renal failure were generally numerically higher in the parecoxib/valdecoxib group.
- Pulmonary events such as pleural effusion, bronchospasm, pneumonia, and upper respiratory tract infections were significantly less frequent in the parecoxib/valdecoxib group compared to the placebo group; the latter effects did not seem to persist until the end of the study.
- During the entire study period, 13.2% of patients in the placebo group and 16.7% of patients in the parecoxib/valdecoxib group withdrew from the study due to an adverse event.

- [redacted]
- [redacted]

- Serious adverse events occurred in 19.0% and 9.9% (entire study) or [redacted] of patients receiving parecoxib/valdecoxib and placebo, respectively. With the lone exceptions of [redacted] and atrial arrhythmia (entire study), there were as many, but usually more, events in the parecoxib/valdecoxib as compared to the placebo-treated group. This trend towards more serious adverse events in the parecoxib/valdecoxib group includes gastrointestinal events, thromboembolic and other cardiovascular events, renal events, and infectious episodes.
- Four deaths occurred among patients receiving the parecoxib/valdecoxib treatment regimen; there were no deaths among the placebo group. Causes of death included duodenal ulcer, probable myocardial infarction, septicemia, and cerebellar infarct with brainstem compression and herniation.
- Any opioid-sparing effects by the addition of parecoxib/valdecoxib is not apparent by comparing the pattern of adverse events (i.e. constipation, nausea, vomiting, somnolence, pruritis, respiratory depression) to the standard of care/placebo group. Events commonly ascribed to opioids tended to be more, not less, common in the parecoxib/valdecoxib group.