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RESEARCH**

*APPLICATION NUMBER:*

**21-341**

**MEDICAL REVIEW**

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

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APPEARS THIS WAY  
ON ORIGINAL

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**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.

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 dysmenorrhea, with supportive data from other

c)

d) Three studies of \_\_\_\_\_ were submitted \_\_\_\_\_.

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

- i. ibuprofen, naproxen \_\_\_\_\_
- ii. naproxen, ibuprofen or diclofenac in osteoarthritis studies
- iii. naproxen in rheumatoid arthritis 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 parameters 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.

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

The dysmenorrhea trials were both 4-part crossover designs. Two trials were designed to test the use of valdecoxib in a manner, given All trials were both placebo and active controlled except three which were designed to test a hypothesis the and the two losing studies. The three 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

This diversity has always been encouraged, as pertinent to any claim is a presumption of generalizability.

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,

the  $p < 0.05$  level, and no adjusting for multiplicity was done.

Using the criteria of replicated success in two of the pain models - dysmenorrhea, and pain, the data support clear single-dose efficacy of

The clinical relevance of was not adequately demonstrated.

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 arthritis 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 oplate 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 \_\_\_\_\_ is unclear. The excess of serious cardiovascular thromboembolic events in the valdecoxib arm of the \_\_\_\_\_ 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 \_\_\_\_\_ 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 - \_\_\_\_\_

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 McMaster 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	Withdrawn	
			Rx. Failure	adverse event
<b>Trial 49</b>				
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%)
<b>Trial 53</b>				
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.
<b>BASELINE PARAMETERS</b>								
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 (3)	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 (0-10 VAS)	function (0-68 Likert)	Patient global (0-10 VAS)	Inefficacy dropouts
<b>1. TRIAL 49</b>				
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
<b>Trial 53</b>				
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)	

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 (1<sup>st</sup> entry), Q values (95% CI)(2<sup>nd</sup> 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 shown 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 for the valdecoxib 20mgbid vs naproxen patient global comparison, and a Q of 0.77 for the investigator global. For the valdecoxib 40mgbid vs naproxen comparisons the Q's were 0.77 and 0.86 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	Withdrawn	
			Rx Failure	adverse event
<b>Trial 60</b>				
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%)
<b>Trial 61</b>				
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
<b>BASELINE PARAMETERS</b>										
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
<b>LAST VISIT PARAMETERS</b>										
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
<b>BASELINE PARAMETERS</b>										
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
<b>LAST VISIT PARAMETERS</b>										

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
<b>Trial 60</b>		
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%)
<b>Trial 61</b>		
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
<b>Trial 60</b>		
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	nt. 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 shown 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) administration for the treatment of and 4, The randomized trial evidence for analgesia in the valdecoxib NDA consisted of trials, two dysmenorrhea trials, two trials in settings using and eight trials in various settings. Five of the latter

[REDACTED]

**TRIAL DESIGN**

[REDACTED]

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.

Entry criteria differed substantially across trials. Rescue medication was allowed in all except [REDACTED] trials; it consisted of [REDACTED]

[REDACTED]

**TABLE 1: TRIAL DESIGN**

[REDACTED]

**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

2<sup>nd</sup> number = patients still in trial at the designated primary time-point  
 3<sup>rd</sup> 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.
-------	------	-----	-------	--------	--	---	-----	-----	--

#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

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

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

**EFFICACY ANALYSIS RESULTS**

... Also time-to-analgesia was not measured in trials (Trials 65, 66).

In summary, the efficacy endpoints are as follows:

\_\_\_\_\_ / DYSMENORRHEA TRIALS

- 1 - SPID
- 2 - time-to-analgesia
- 3 - time-to-rescue-medication use



DYSMENORRHEA  
 65 12 hr  
 66 12 hr

20bid 40bid  
 b n s b n b  
 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			Active Control
		10mg	20mg	40mg	

[Redacted content]

**DYSMENORRHEA**

65 0-12 hr  
66 0-12 hr

s s s s s b nap  
s s b s s b nap

~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~

**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.

~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~

- (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 ~~\_\_\_\_\_~~ examining the shape of the valdecoxib curves may help us estimate dosing intervals. These graphs are supplied below.

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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 meler 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

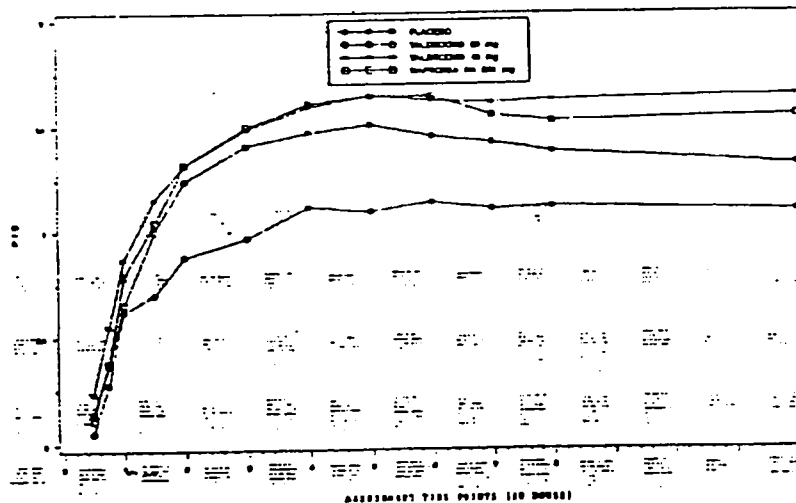
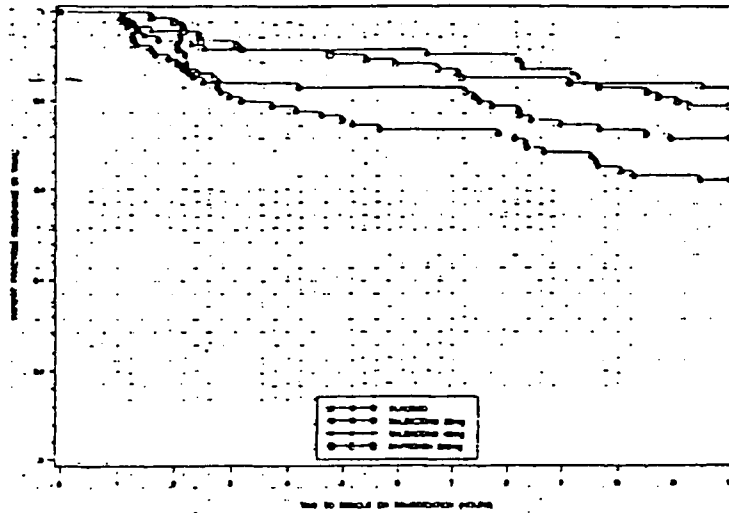


Figure 14. Kaplan-Meier Estimators for Distribution of Time to Rescue Medication or Remediation



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 <sup>a</sup> )	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

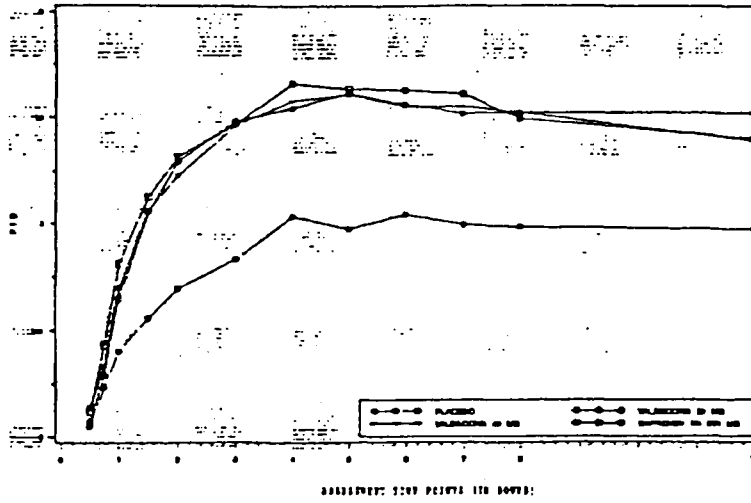
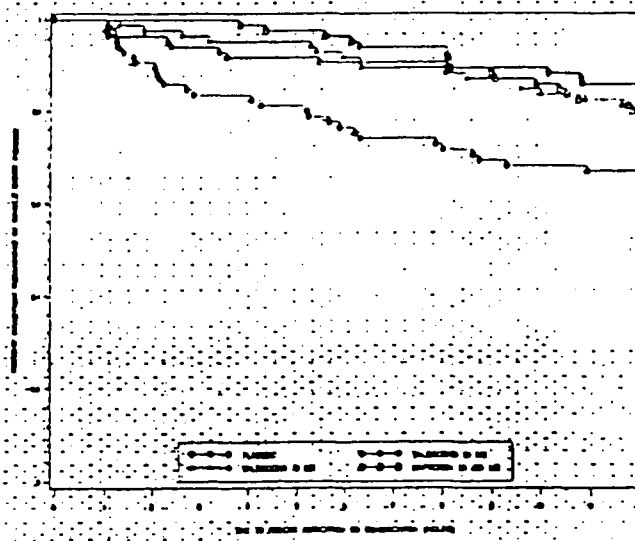


Figure 16. Kaplan-Meier Estimators for Distribution of Time to Rescue Medication or Remedication



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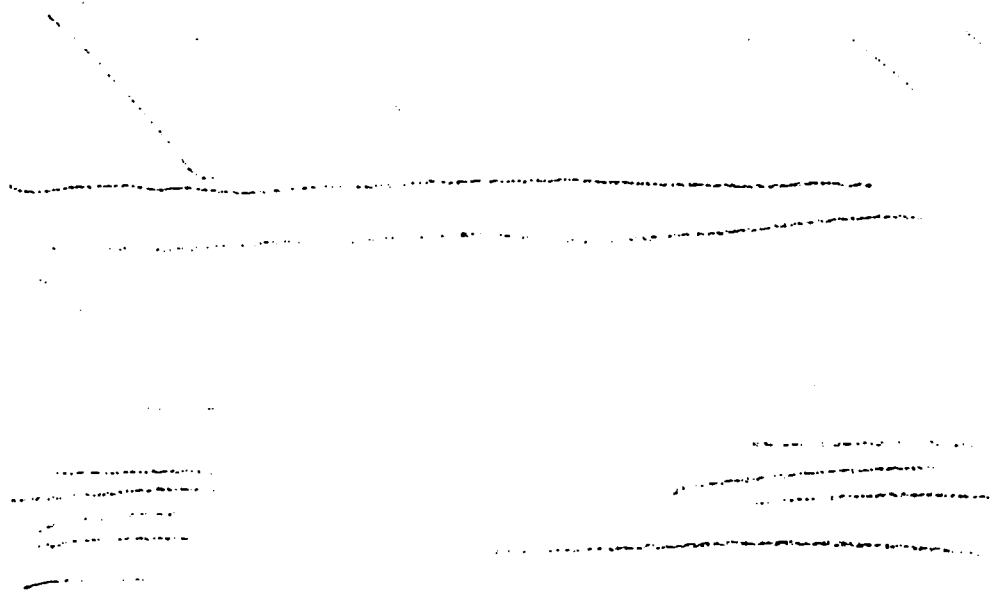
**Conclusion:**

The data demonstrate the following:

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



**ANALGESIA APPENDIX TABLE A: PROTOCOL SPECIFIED PRIMARY EFFICACY PARAMETERS**

Trial	Powered	Time to:							
		PID	PR	SPID	Totpar	PG	PR	Analg.	RESCUE

65	spid8, totpar8			8,12hr	8,12hr				
66	spid8, totpar8			8,12br	8,12hr				

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**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 time 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

Gastrointestinal 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 Bretz Day Interaction) for this table.

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

Risk factor	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
Age	0.041	0.004	0.016	<0.001	<0.001
Nsaid intoler.	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
M/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 NSAID 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 Euroqol) 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

Risk factor	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
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	
	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%
hx ulcer										
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	5/174	10/185	18/183	8/178
(%)	(3.2%)	(2.9%)	(5.4%)	(9.9%)	(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	
	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%
hsulcer										
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.

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 \_\_\_\_\_ and a CRAE event rate calculation. In the trial analysis, there were 80 such events (25.7%) in the 311 \_\_\_\_\_ /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 \_\_\_\_\_

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

event	placebo	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 \_\_\_\_\_ 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

The first four trials used identical seven-day designs, measuring bleeding time, platelet aggregation in response to arachidonate, serum thromboxane B<sub>2</sub> (a stable metabolite of thromboxane A<sub>2</sub>), and urinary 11-dehydrothromboxane B<sub>2</sub> (a thromboxane B<sub>2</sub> metabolite excreted in the urine). The fifth

COX1 is described as mediating the formation of thromboxane A<sub>2</sub> 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<sub>2</sub> 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**

trial	first day							last day						
	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**

trial	first day							last day						
	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	

**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.

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. embolism	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 ——— 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 this 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 this 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 a 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 pL 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-OA	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
<b>Body as a Whole</b>						
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
<b>Central and Peripheral Nervous System Disorders</b>						
Headache	7.5	7.1	5.2	8.1	7.4	5.2
<b>Gastrointestinal System Disorders</b>						
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
<b>Respiratory System Disorders</b>						
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
<b>Body as a Whole</b>					
Edema peripheral	2.4	0.7	2.2	<0.001	-
<b>Gastrointestinal System Disorders</b>					
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	-
<b>Autonomic Nervous System Disorders</b>					
Hypertension	2.8	0.5	1.6	0.006	-
<b>Body as a Whole</b>					
Edema peripheral	2.3	0.5	0.9	0.020	-
<b>Central and Peripheral Nervous System Disorders</b>					
Dizziness	2.3	0.5	2.9	0.020	-
<b>Gastrointestinal System Disorders</b>					
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	-

APPEARS THIS WAY  
ON ORIGINAL

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
<b>Body as a Whole</b>					
Edema peripheral	2.6	1.0	2.9	0.022	-
Pain	0.4	1.5	0.6	0.023	-
<b>Central and Peripheral Nervous System Disorder</b>					
Headache	5.6	8.3	4.5	0.034	-
<b>Gastrointestinal System Disorders</b>					
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
<b>Liver and Biliary System Disorders</b>					
SGPT increased	0.3	0.5	1.6	-	0.001
SGOT increased	0.3	0.5	1.5	-	0.003

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

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 n	Valdecoxib 20mgBID vs Naproxen	Valdecoxib 40mg BID vs Naproxen
No. treated	399	403	415	-	-
Any event	83.7	84.6	85.8	-	-
<b>Autonomic Nervous System Disorders</b>					
Hypertension	5.5	9.2	4.6	-	0.012
<b>Body as a Whole - General Disorders</b>					
Chest pain non-cardiac	0.3	1.5	1.9	0.038	-
Edema	4.5	7.2	4.3	-	-
peripheral					
Influenza-like symptoms	5.0	6.2	6.0	-	-
Injury accidental	5.3	5.5	4.1	-	-
<b>Central and Peripheral Nervous System Disorders</b>					
Dizziness	3.8	2.2	3.1	-	-
Headache	13.5	12.9	15.9	-	-
<b>Gastrointestinal System Disorders</b>					
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	-	-
<b>Metabolic and Nutritional Disorders</b>					
Creatinine increase	1.8	2.0	1.2	0.035	0.019
Weight increase	3.0	2.7	2.9	-	-
<b>Musculoskeletal System Disorders</b>					
Myalgia	5.0	3.7	4.6	-	-
<b>Psychiatric Disorders</b>					
Insomnia	2.5	3.7	2.7	-	-
<b>Red Blood Cell Disorders</b>					
Anemia	3.8	4.0	3.1	-	-
<b>Respiratory System Disorders</b>					
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	-	-
<b>Skin and Appendages Disorders</b>					
Pruritus	2.0	2.5	0.2	0.019	0.005
Rash	3.5	3.5	2.7	-	-
<b>Urinary System Disorders</b>					
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)
<b>3. AUTONOMIC NERVOUS SYSTEM DISORDER</b>			
Hypertension	4 (1.6)	9 (3.8)	3 (1.3)
<b>4. BODY AS A WHOLE</b>			
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)
<b>Central and Peripheral Nervous System Disorders</b>			
Dizziness	5 (2.0)	7 (3.0)	9 (3.8)
Headache	22 (8.9)	15 (6.3)	19 (8.0)
<b>5. GASTRO-INTESTINAL SYSTEM DISORDERS</b>			
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)
Dyspepsia	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)
<b>31. RESPIRATORY SYSTEM DISORDERS</b>			
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

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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
<b>Body as a Whole - General Disorders</b>					
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
<b>Gastrointestinal System Disorders</b>					
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
<b>Respiratory System Disorders</b>					
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

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ARTHRITIS SAFETY TABLE 11: EVENTS (%) CAUSING WITHDRAWAL WITH AN INCIDENCE OF AT LEAST 1% OR  $P \leq 0.05$  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  $P \leq 0.05$  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
<b>Autonomic Nervous System Disorders</b>						
Overall percentage	0.0	0.0	0.0	1.0	0.5	0.0
Hypertension aggravated					2/2	
<b>Body as a Whole - General Disorders</b>						
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			
<b>Disorders, Female</b>						
Overall percentage	0.3	0.2		0.3		0.1
Breast neoplasm malignant female	1/1			2/2		
<b>Gastrointestinal System Disorders</b>						
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
<b>Musculoskeletal System Disorders</b>						
Overall percentage	0.0	0.2	<0.1	<0.1	0.0	0.0
Fracture accidental		2/2	1/1			
<b>Myo, Endo, Pericardial and Valve Disorders</b>						
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
<b>Respiratory System Disorders</b>						
Overall percentage	0.5	0.2	0.5	0.3	0.0	<0.1
Pneumonia	2/2		4/4			
<b>Vascular (Extracardiac) Disorders</b>						
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/US0037-0450/ PBO	54/ M	30	33	Abdominal pain	Mod/Uncertain	971222-CL326
015/US0033-0462/ NAP	62/ M	10	10 (O) 10 (O)	Gastric Ulcer <sup>1</sup> Gastritis <sup>1</sup>	Severe/Probable Severe/Probable	971212-CL430
048/US0038-0231/ DIC	59/F	47	50	Pancreatitis	Severe/Uncertain	990715-CL919
048/US0046-1154/ DIC	71/F	23 25	25 28	Abdominal pain <sup>1</sup> Gastritis	Severe/Uncertain Mild/Uncertain	991102-CL242 000218-CL193
048/US0051-1118/ DIC	62/F	70 70	73 73	Diarrhea <sup>1</sup> Hematochezia <sup>1</sup>	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 <sup>1</sup>	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 <sup>1</sup> Myalgia	Severe/Uncertain Severe/Uncertain Mod/Uncertain	000211-CL770
060/US0120-1511/ V20	73/F	9 9 9	15 15 15	Dizziness <sup>1</sup> Nausea <sup>1</sup> Vomiting <sup>1</sup>	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 <sup>1</sup>	Severe/Probable Severe/Probable	000419-CL479
061/050115-1455/ V40	62/F	46 49	46 49 (O)	GI Hemorrhage <sup>1</sup> Anemia <sup>1</sup>	Severe/Probable Severe/Probable	000502-CL414
067/US0534-1094/ PBO	77/F	22	25	Chest pain	Severe/Uncertain	000510-CL633

<sup>1</sup> 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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