Table A.47.2 Duration of Exposure to Cx (Phase 1, OA, RA, Pain)

Table 3.4
Duration of Exposure: All Arthritis Trials[a]

	25 mg	45 mg	50 mg	100 mg	Celecoxib 200 mg QD	200 mg	300 mg	400 mg	Other Cx	Any Dose
OA, RA - CONTROLLED										
1-14 days	14	46	88	230	31	186		59		654
15-42 days	86	107	121	658	208	397		289		1872
43-77 days	0	0	76	564	214	211		52		1141
78-91 days	0	0	388	603	0	1125		240		2354
92-180 days	0	0	17	30	0	282		7		336
181-270 days	0	0	0	0	0	39		0		39
Number Treated	100	153	698	2325	453	2340		615		6376
OA, RA - LONG-TERM OPEN LABEL										
1-14 days			32	1046		866	235	65	5	2315
15-42 days			78	643		661	533	135	8	2129
43-77 days			41	280		382	193	106	1	1013
78-91 days			262	289		320	57	434	1	1363
92-180 days			9	422		857	201	246	2	1737
181-270 days			6	85		593	128	189	2	1003
271-360 days			0	89		314	74	155	0	632
361-450 days			0	36		172	18	46	0	272
451-540 days			0	24		62	11	7	0	104
Number Treated			420	2895		3977	1441	1099	19	9851

Note: All celecoxib regimens are BID unless otherwise specified.
[a] In this table, all patients who received celecoxib in any arthritis trial, controlled or long-term open label, are included. The treatment experience is combined for patients who received celecoxib in a controlled study and continued into the long-term open label study. If the patient started the long term open label study within 14 days after completing the controlled study.
[b] These patients have celecoxib doses of 200 mg AM:300 mg PM, 400 mg AM:300 mg PM, 300 mg AM:200 mg PM, 200 mg AM:200 mg PM 100 mg QD, 100 mg TID, 150 mg QD, or 200 mg QD.
[c] Includes exposure in controlled studies only or exposure in controlled long-term open label studies regardless of the 14 day criteria. Patients are counted once only per treatment group.

Table 3.4
Duration of Exposure: All Arthritis Trials[a]

	25 mg	45 mg	50 mg	100 mg	Celecoxib 200 mg QD	200 mg	300 mg	400 mg	Other Cx	Any Dose
OA, RA - CONTROLLED PLUS LONG-TERM OPEN LABEL[c]										
1-14 days	14	46	88	1361	31	960	235	89	5	2941
15-42 days	86	107	122	1146	208	842	533	284	8	3436
43-77 days	0	0	76	764	214	517	193	124	1	1889
78-91 days	0	0	362	664	0	830	57	199	1	2113
92-180 days	0	0	17	416	0	1074	201	286	2	1996
181-270 days	0	0	0	89	0	430	128	211	1	859
271-360 days	0	0	0	89	0	316	74	156	0	635
361-450 days	0	0	0	36	0	172	18	46	0	272
451-540 days	0	0	0	24	0	62	11	7	0	104
> 540 days	0	0	0	0	0	0	0	0	0	0
Number Treated	100	153	693	4237	453	5208	1441	1371	16	8139

Note: All celecoxib regimens are BID unless otherwise specified.
[a] In this table, all patients who received celecoxib in any arthritis trial, controlled or long-term open label, are included. The treatment experience is combined for patients who received celecoxib in a controlled study and continued into the long term open label study. If the patient started the long-term open label study within 14 days after completing the controlled study.
[b] These patients have celecoxib doses of 200 mg AM:300 mg PM, 400 mg AM:300 mg PM, 300 mg AM:200 mg PM, 200 mg AM:200 mg PM, 100 mg QD, 100 mg TID, 150 mg QD, or 200 mg QD.
[c] Includes exposure in controlled studies only or exposure in controlled/long term open label studies regardless of the 14 day criteria. Patients are counted once only per treatment group.

Table 3.4
Duration of Exposure: Analgesia Trials

	Placebo	25 mg	50 mg	Celecoxib 100 mg	200 mg	400 mg	Active Control
DENTAL PAIN[a]							
1 day	205	50	85	155	156	85	169
2-7 days	0	0	0	0	0	0	0
Number Treated	205	50	85	155	156	85	169
POST-SURGICAL PAIN[b]							
1 day	85			87	83		84
2-7 days	15			30	21		16
Number Treated	100			117	104		100

[a] See Table 3.4 for description of regimens.
[b] See Table 3.5 for description of regimens.

Table A.48 Reasons for Withdrawal (All controlled OA/RA trials)

		Celecoxib					
	Placebo	50 mg BID	100 mg BID	200 mg QD	200 mg BID	400 mg BID	Active Control
No. treated	1864	690	2125	453	2240	615	2768
Completed, %	52.0	59.3	71.6	82.3	72.7	66.7	72.8
Withdrawn, %	48.0	40.7	28.4	17.7	27.3	33.3	27.2
Lost to follow-up	0.9	0.7	0.5	0.7	0.7	0.7	0.7
Entry violation	1.3	0.7	0.7	1.3	0.6	0.5	0.5
Noncompliance	3.1	2.6	2.2	2.4	2.2	2.1	3.0
Treatment failure	36.5	29.1	17.8	9.9	15.5	23.3	12.3
Adverse event	6.1	7.5	7.2	3.3	8.1	6.8	10.7
Adverse event >28 days after last dose	0.0	0.0	0.0	0.0	<0.1	0.0	0.0

Derived from Table 5.8. Data represent percentages of patients unless otherwise specified.

Table A.49 Reasons for Withdrawal (Analgesia trials)

Table 5.10
Reasons for Withdrawal: Analgesia Trials

Number (Percent) of Patients

	Placebo	Celecoxib 25 mg	Celecoxib 50 mg	Celecoxib 100 mg	Celecoxib 200 mg	Celecoxib 400 mg	Active Control
DENTAL PAIN							
TREATED PATIENTS	205	50	85	155	156	85	189
COMPLETED STUDY (a)	18 (8.8)	4 (8.0)	10 (11.8)	47 (30.3)	52 (33.3)	35 (41.2)	60 (31.7)
WITHDRAWN	187 (91.2)	46 (92.0)	75 (88.2)	108 (69.7)	104 (66.7)	50 (58.8)	129 (68.3)
REASON FOR WITHDRAWAL (b)							
LOST TO FOLLOW-UP	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.5)
ADVERSE EVENT	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TREATMENT FAILURE/RESCUE MEDICATION	185 (90.2)	46 (92.0)	74 (87.1)	108 (69.7)	104 (66.7)	49 (57.6)	128 (67.7)
SURGICAL PAIN							
TREATED PATIENTS	100			113	104		106
COMPLETED STUDY	2 (2.0)			2 (1.8)	0 (0.0)		1 (0.9)
WITHDRAWN	98 (98.0)			111 (98.2)	104 (100.0)		105 (99.1)
REASON FOR WITHDRAWAL (b)							
PRE-EXISTING VIOLATION	4 (4.0)			3 (2.7)	2 (1.9)		4 (3.8)
PROTOCOL NON-COMPLIANCE	6 (6.0)			29 (25.7)	19 (18.3)		12 (11.3)
TREATMENT FAILURE	78 (78.0)			76 (67.3)	71 (68.3)		66 (62.3)
ADVERSE EVENT	9 (9.0)			3 (2.7)	12 (11.5)		6 (5.7)

(a) Defined as patients who completed all scheduled assessments.
(b) Mutually exclusive and exhaustive categories

Table A.50 Reasons for Withdrawal: Long-Term Study (024)

Table 5.9
Reasons for Withdrawal: Long-term Open Label Trial

Number (Percent) of Patients

	OA	RA	Combined
TREATED PATIENTS	2556	1945	4499
CONTINUING AS OF 21NOV97	1895 (74.2)	1422 (73.1)	3317 (73.7)
WITHDRAWN	659 (25.8)	523 (26.9)	1182 (26.3)
REASON FOR WITHDRAWAL (a)			
LOST TO FOLLOW-UP	27 (1.1)	19 (1.0)	46 (1.0)
PRE EXISTING VIOLATION	17 (0.7)	6 (0.3)	23 (0.5)
PROTOCOL NON-COMPLIANCE	102 (4.0)	63 (3.2)	165 (3.7)
TREATMENT FAILURE	332 (13.0)	307 (15.8)	639 (14.2)
ADVERSE EVENT	174 (6.8)	122 (6.3)	296 (6.6)
PRE-EXISTING ADVERSE EVENT	6 (0.2)	3 (0.2)	9 (0.2)
ADVERSE EVENT OCCURRED 28 DAYS AFTER LAST DOSE	1 (<0.1)	3 (0.2)	4 (<0.1)

(a) Mutually exclusive and exhaustive categories.

Table A.51 Demographics of All Arthritis Trials

Table 11.1
Demographic Characteristics: North American and International Arthritis Trials

Number (Percent) of Patients

	Placebo	Celecoxib 25-40 mg	Celecoxib 50 mg	Celecoxib 100 mg	Celecoxib 200 mg QD	Celecoxib 200 mg	Celecoxib 400 mg	Active Control
TREATED PATIENTS	1864	253	690	2125	459	2240	615	2766
AGE (YEARS)								
<25	2(0.1)	0(0.0)	3(0.4)	3(0.1)	0(0.0)	9(0.4)	4(0.7)	8(0.3)
25-44	1048(56.4)	251 9.9)	49(6.2)	184(8.7)	39(8.6)	335(15.0)	114(18.5)	349(12.6)
45-64	937(50.3)	125(49.4)	342(49.6)	1064(50.1)	217(47.9)	1164(52.0)	339(55.1)	1635(59.1)
>64	731(39.2)	103(40.7)	302(43.8)	874(41.1)	197(43.5)	732(32.7)	158(25.7)	976(35.3)
MEAN	60.0	60.5	61.7	60.9	62.0	57.9	55.7	58.9
MEDIAN	61.0	62.0	63.0	61.0	63.0	59.0	56.0	59.0
RANGE	18 - 89	28 - 89	21 - 93	22 - 91	29 - 88	20 - 96	21 - 86	19 - 92
ETHNICITY								
ASIAN	4(0.2)	0(0.0)	3(0.4)	9(0.4)	1(0.2)	20(0.9)	5(0.8)	11(0.4)
BLACK	156(8.4)	24(9.5)	81(11.7)	184(8.7)	41(9.1)	201(9.0)	56(9.1)	224(8.1)
CAUCASIAN	1629(87.4)	221(87.4)	591(85.7)	1860(87.5)	391(86.3)	1915(85.5)	509(82.8)	2442(88.3)
HISPANIC	67(3.6)	7(2.8)	13(1.9)	55(2.6)	17(3.8)	91(4.1)	41(6.7)	76(2.8)
OTHER	8(0.4)	1(0.4)	2(0.3)	14(0.7)	3(0.7)	13(0.6)	4(0.7)	13(0.5)
GENDER								
FEMALE	1324(71.0)	176(69.6)	457(66.2)	1496(70.4)	306(67.5)	1597(71.3)	447(72.7)	1908(69.0)
MALE	540(29.0)	77(30.4)	233(33.8)	629(29.6)	147(32.5)	643(28.7)	168(27.3)	860(31.1)
WEIGHT (KG):								
FEMALE								
MEAN	82.1	83.5	84.1	80.4	66.6	77.6	78.7	78.4
MEDIAN	78.3	80.1	80.3	77.0	65.7	73.4	75.4	74.0
RANGE	40.9 - 217.6	47.3 - 175.1	41.4 - 162.7	41.3 - 175.7	49.0 - 159.1	36.3 - 186.3	39.5 - 154.5	39.5 - 201.3
MALE								
MEAN	94.0	95.6	94.9	93.6	77.8	90.6	88.0	91.2
MEDIAN	91.5	93.1	92.5	90.6	63.6	87.1	85.0	87.0
RANGE	56.8 - 175.9	54.9 - 150.9	58.9 - 140.6	51.7 - 177.7	51.3 - 206.8	47.6 - 206.5	51.3 - 144.5	50.7 - 194.1

[illegible] All celecoxib regimens are BID unless otherwise specified. Includes studies 012, 013, 020, 021, 022, 023, 041, 042, 043, 052, 053, 061, 071 and 087.

Table A.52 Adverse events for Cx (100 mg BID, 200 mg BID, 200 mg QD) vs. Placebo and Active Control in North American Arthritis Trials

Adverse Event	Celecoxib*	Placebo	p Value	Celecoxib*	Active Control	p Value
No. treated	3512	1864	-	2890	2098	-
Any event	59.9	54.6	<0.001	63.9	66.7	0.044
Headache	16.8	20.2	0.002	16.0	14.8	-
Dyspepsia	8.4	6.2	0.004	9.9	12.0	0.021
URTI	8.4	6.7	0.029	9.4	9.9	-
Diarrhea	5.4	3.8	0.008	6.2	6.1	-
Nausea	3.6	4.2	-	3.8	5.6	0.002
Abdominal pain	3.5	2.8	-	4.9	8.2	<0.001
Back pain	2.7	3.6	-	3.0	2.0	0.038
Pharyngitis	2.2	1.1	0.003	2.6	1.8	-
Edema peripheral	2.1	1.1	0.007	2.3	2.1	-
Flatulence	2.1	1.0	0.003	2.2	3.7	0.003
Myalgia	1.8	2.1	-	1.7	0.7	<0.001
Constipation	1.8	1.9	-	1.9	4.1	<0.001
Allergy aggravated	1.3	0.8	-	1.4	0.7	0.013
Hypertonia	1.1	0.8	-	1.2	0.2	<0.001
Arthralgia	0.9	1.6	0.021	1.1	1.2	-
Anemia	0.5	0.4	-	0.5	1.6	<0.001
SGPT increased	0.5	0.5	-	0.4	1.0	0.023
Ecchymosis	0.3	0.3	-	0.4	1.0	0.015
Hiatal hernia	<0.1	<0.1	-	0.8	1.4	0.024

Derived from Table 6.3.1. Data are expressed in percentages of patients (except for p values), and include any events with ≥1% incidence in any group and a statistically significant difference ($p \leq 0.05$) between celecoxib and either placebo or active control.
*Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

Table A.53.1 Adverse Events for Cx (400 mg BID) vs. Placebo and Active Control in North American Arthritis Trials

Adverse Event	Celecoxib 400 mg BID	Placebo	p Value	Celecoxib 400 mg BID	Active Control	p Value
No. treated	615	636	-	434	443	-
Any event	60.2	55.3	-	62.0	63.0	-
Headache	14.5	22.0	<0.001	15.2	14.0	-
Dyspepsia	8.1	4.9	0.021	8.8	12.4	-
Diarrhea	6.5	3.5	0.013	6.5	4.1	-
Pruritus	2.9	1.3	0.047	2.5	0.9	-
Vomiting	2.3	0.8	0.037	2.5	1.4	-
Allergy aggravated	1.1	0.2	0.036	1.4	0.5	-
Back pain	0.8	3.6	<0.001	0.9	0.9	-
Constipation	0.8	2.7	0.016	0.7	2.9	0.020
Stomatitis	0.3	0.9	-	0.2	2.5	0.006
Prostatic disorder	0.0	1.2	0.045	0.0	0.8	-

Derived from Table 6.3.2. Data are expressed in percentages of patients (except for p values), and include any events with ≥1% incidence in any group and a statistically significant difference (p≤0.05) between celecoxib and either placebo or active control.

Table A.53.2 Adverse Events: OA vs. RA

	OA				RA			
Adverse Event	Placebo	100 mg BID	200 mg BID	Active Control	Placebo	100 mg BID	200 mg BID	Active Control
No. treated	1329	1311	1208	1388	535	468	706	710
Any event	54.3	59.3	63.8	68.1	55.5	62.6	60.3	63.9
Headache	19.3	17.1	14.1	14.7	22.6	16.7	14.6	15.1
Dyspepsia	6.5	8.2	10.7	12.0	5.6	10.0	8.5	12.1
URTI	6.3	7.2	8.6	9.4	7.7	10.5	9.1	10.8
Diarrhea	3.8	4.8	7.2	7.1	3.7	5.6	5.5	4.2
Abdominal pain	2.8	3.1	6.2	9.1	3.0	4.1	3.4	6.3
Sinusitis	4.1	4.7	5.0	4.3	4.7	5.8	6.2	5.1
Nausea	3.8	3.5	4.0	6.6	5.4	3.8	3.3	3.7
Back pain	3.6	3.0	3.6	2.7	3.6	2.6	1.8	0.8
Injury accidental	2.2	3.5	3.1	3.5	2.4	1.7	2.4	1.7
Edema peripheral	1.3	1.6	3.0	2.4	0.7	1.3	1.8	1.5
Insomnia	2.7	2.6	2.6	2.2	1.3	1.9	2.3	2.5
Flatulence	1.1	1.9	2.3	4.3	0.7	2.8	2.3	2.5
Constipation	1.5	1.9	2.2	4.9	2.8	1.5	1.4	2.4
Pharyngitis	1.1	2.2	2.2	1.9	0.9	2.6	3.0	1.5
Coughing	1.1	1.6	1.6	2.4	1.5	1.9	3.1	1.7
Rash	2.0	2.0	1.5	1.8	2.2	3.0	4.1	1.8

Derived from Tables 7.2 and 8.2. Includes any adverse event with incidence ≥3% in either the celecoxib 100 mg BID or 200 mg BID group or a control group in either OA or RA.

Table A.53.3 Adverse Events with Incidence ≥ 3% in Any Treatment Group: International Arthritis Trials

	6 Week OA (Study 042)		24 Week RA (Study 041)	
Adverse Event	100 mg BID	Active Control	200 mg BID	Active Control
No. treated	346	341	326	329
Any event	43.6	52.8	68.1	72.6
Diarrhea	6.4	7.6	12.0	14.0
Abdominal pain	4.9	6.7	11.0	20.7
Dyspepsia	3.2	6.7	9.8	12.8
Headache	4.3	7.3	9.2	5.8
URTI	2.0	2.3	5.8	9.1
Nausea	3.2	5.0	4.6	8.2
Back pain	1.7	0.3	4.3	2.1
Dizziness	1.7	2.1	3.7	4.0
Edema peripheral	2.0	2.3	3.4	1.5
Fatigue	1.2	0.9	3.4	4.9
Pharyngitis	0.9	0.3	3.4	2.7
Coughing	0.9	0.0	3.1	2.4
Influenza-like symptoms	1.7	1.8	3.1	4.0
Rash	2.3	0.3	2.5	4.0
Pruritus	1.7	2.1	2.1	3.6
Flatulence	1.4	1.5	2.1	4.3
Vomiting	1.2	0.9	1.8	5.2
Anemia	0.0	0.3	1.5	3.0
Stomatitis	0.3	0.6	0.9	3.6

Derived from Table 10.2. All numbers are percentages of patients unless otherwise specified.

Table A.54 Adverse Events Causing Withdrawal; North American Arthritis Trials

Adverse Event	Placebo	Celecoxib 100 mg BID and 200 mg QD/BID	Celecoxib 400 mg BID	Active Control
No. treated	1864	4146	615	2098
Any event	4.4	5.4	6.2	8.3
Dyspepsia	0.6	0.8	0.8	1.6
Rash	0.6	0.8	1.1	0.2
Abdominal pain	0.6	0.7	0.3	2.0
Nausea	0.6	0.5	0.3	0.9
Pruritus	0.2	0.2	0.5	0.0

Derived from Table 6.7. All numbers are percentages of patients unless otherwise specified. Includes any event causing withdrawal for which the Investigator considered the relatedness to study medication uncertain or probable in ≥0.5% of patients in either celecoxib column.

Adverse Event	Celecoxib*	Placebo	p Value	Celecoxib*	Active Control	p Value
No. treated	3512	1864	-	2890	2098	-
Any event	7.3	6.1	-	8.5	9.7	-
Rash	0.9	0.6	-	0.9	0.3	0.004
Abdominal pain	0.7	0.6	-	0.9	2.1	<0.001
Urticaria	0.4	<0.1	0.044	0.4	0.3	-
Pruritus	0.2	0.2	-	0.2	0.0	0.043
Esophageal ulceration	0.0	0.0	-	0.1	0.6	0.003

Derived from Table 6.5.1. Data are expressed in percentages of patients (except for p values), and include any incidences with a statistically significant difference ($p \leq 0.05$) between celecoxib and either placebo or active control.
*Column combines celecoxib 100 mg BID, 200 mg QD, and 200 mg BID.

MEDICAL OFFICER REVIEW
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS HFD-550

NDA#	20-998
NAME:	Celebrex Capsules (Celecoxib)
SPONSOR:	G.D. Searle & Co.
REVIEWER:	Maria Lourdes Villalba, M.D.
DATE REVIEWED:	October 9 – November 30, 1998.
PHARMACOLOGIC CATEGORY:	Cox-2 inhibitor
PROPOSED INDICATIONS:	Management of pain, OA and RA
MATERIALS REVIEWED:	Safety database (initial NDA submission and 120 day safety update)

The initial NDA submission contains safety data from 51 studies, with a total enrollment of 18.439 subjects (13.072 individuals) of whom close to 9400 have received at least one dose of Celecoxib (Cx).

For the purpose of data presentation and analysis, the studies are grouped into the categories shown in Text Table 1 of the ISS (Integrated Summary of Safety): "**Phase I**" (single dose, multiple dose, drug interaction, hepatic impairment, and renal impairment), "**Arthritis**" (subcategorized as OA, RA, combined OA and RA, and long-term open label), and "**Analgesia**" (subcategorized as dental pain and surgical pain). This is a safety review of all Phase I studies and all the arthritis trials.

Text Table 1. Studies in Celecoxib Clinical Program Included in this Summary

Type of Study	No. of Studies	Study Numbers
Phase I		
Single dose	9	001, 006, 009, 018, 019, 037, 044, 084, 088
Multiple dose	11	003, 004, 010, 014, 015, 026, 032, 033, 043, 065, 069
Drug interaction	7	017, 038, 039, 040, 050, 051, 072
Hepatic impairment	1	016
Renal impairment	1	036
Arthritis		
OA		
Pivotal efficacy	5	020, 021, 054, 060, 087
Supportive	3	042, 013, 047
RA		
Pivotal efficacy	2	022, 023
Supportive	2	041, 012
OA/RA combined	2	062, 071
Long-term open label	1	024
Postsurgical analgesia		
Dental pain		
Pivotal efficacy	3	025, 027, 070
Supportive	1	005
Surgical pain		
Pivotal efficacy	1	028
Supportive	2	029, 080
Total	51	

Derived from Tables 1.1 through 1.5.

Dose and duration of exposure to Cx: Single dose studies were performed with doses ranging from 5mg p.o. to 1200 mg p.o. The highest doses used for multiple dose pharmacologic studies were up to 600 mg twice a day for 8 days. Chronic dosing in arthritis patients ranged from 100 mg BID to 400 mg bid for 24 months (2 ex-US combined OA/RA trials).

Adverse experiences were monitored during study visits and by diary cards reviewed at each study visit. Adverse events included signs or symptoms, clinically significant laboratory abnormalities, or any abnormality detected during physical examination. All data on each adverse event were recorded onto a case report form along with the Investigator's opinion of intensity: mild, moderate and severe; seriousness (FDA definition) and relationship to study drug (none, uncertain, probable). Relationship to study drug was also evaluated Terms used by the investigators to describe each adverse event were translated into the World Health Organization Adverse Reaction (WHOa.r.t.) terminology. In the arthritis studies, symptoms of arthritis of the type under study in a given trial were generally not considered as adverse events, except if they met the criteria for a serious event. Similarly, in the surgical analgesia studies, pain arising from the surgical procedure was

not considered to be an adverse event. In the studies in which routine UGI endoscopies were performed, only symptomatic patients were considered to have had an adverse event, but all of the data related to the ulcer were included in the analyses of endoscopy findings.

Phase I trials

Single dose studies:

Nine single dose studies involved a total of 312 healthy subjects (248 men, 64 women), ages 18 to 55, who received single oral doses of Cx of 5, 25, 50, 100, 200, 300, 400, 600, 800, 900 or 1200 mg. All studies were randomized. Seven studies were open label crossover studies, comparing different Cx doses or different Cx formulations; studies 001 and 009 were double-blind, placebo controlled; study 009 included ibuprofen as an active comparator. There were very few adverse events; there were no serious adverse events; two events causing withdrawal (mild toothache and appendictis following a single dose of Cx 200 mg, in study 084) were not considered to be related to study medication.

Two subjects in the 900 mg group (study 001), experienced elevation of liver enzymes. Laboratory values returned within the normal range within three to eight days of dosing for both of these subjects; additionally, laboratory values following re-challenge of the 900 mg dose in one of the subjects were all within the normal ranges.

Multiple-Dose studies

Phase I Multiple Dose studies included a total of eleven studies. All studies were randomized; seven were DB, three open label and one single blind; seven studies were placebo-controlled and five were active comparator-controlled. In addition to clinical evaluation, laboratory and adverse events monitoring, Study 014 included endoscopic examinations. Most adverse events were mild or moderate in severity. There were no serious adverse events during these trials.

There were only four withdrawals due to adverse events. Two subjects (one in the Cx 40 mg and one in the Cx 200 mg), were withdrawn from study 003 due to abnormal labs (increased creatine kinase and increased SGOT, respectively). A young placebo subject with prepatellar bursitis was withdrew from study 015, ("Comparison of the SC-58635 PK profile in Elderly and Young subjects"). One patient with headaches withdrew from the ibuprofen arm in study 065.

Drug interaction studies - There were seven pharmacokinetic interaction studies: 017 (with MTX in women with RA); 038 (with lithium carbonate in healthy adults); 039 (with glyburide in subjects with Type II Diabetes Mellitus), 040 (with warfarin), 050

(with diphenylhydantoin in healthy subjects), 051 (with tolbutamide in healthy subjects), 072 (with fluconazole and ketoconazole in healthy subjects).

[Reviewer's comment: there were no formal interaction studies with ASPIRIN].

Two subjects in study 050 and five subjects in study 072 (3 in the fluconazole group and two in the ketoconazole group) had clinically relevant changes in hematocrit levels (≥ 5%) at post-treatment. These changes were attributed to study-related phlebotomy.

Most adverse events were mild or moderate in severity. There was only one serious adverse event and it was not related to study drug (appendicitis in study 071). One subject withdrew from study 038 because of a urinary tract infection that required medication not permitted in the study. One placebo subject withdrew from the study 039 due to hypoglycemia. There were no deaths.

Clinical and laboratory data in patients with very high concentration of Celecoxib. The FDA PK team was concerned about possible adverse events among 6 patients who presented particularly high plasma Cx concentrations. Our review revealed no outstanding adverse events (Table 2), except for one patient with decreased hematocrit from 49 % at entry to 44 % at 2 weeks (unlikely to be due to a single dose of Cx). However safety laboratory studies were obtained after 48 hours and some transient effect could have been missed. Lab measurements were done at

baseline, day 2, 4, 6, 8, 10, 12 and 14 post dose (study 015)
baseline, day 4 and day 8 post dose (065)
baseline and 3 weeks post dose (072)
baseline, 2, 6 and 12 weeks post dose (020)

Table 2. Clinical manifestations and laboratory in patients with high Cx plasma concentration.

Patient/ trial	Gender/ race/age	Celecoxib dose (mg)	Signs/ Symptoms	Hematology	Electrolytes	LFT's
221/015	73 C F	200 BID	Urticaria (d2) Diarrhea (d4) Sinusitis (d6)	Mild eosinophilia 10 % (n=0–3%) (d4)	↑ K: 5.1 (n=3.8-5.1) (d2 and d6)	Minimal ↑Alk phos :124 (n=23 – 120) (d6 and d10)
222/015	68 C F	200 BID	Intermittent dizziness	Mild eosinophilia 7% (d6)		
012/065	33 C M	600 BID		Minimal↑PT: 13.3(d4) and ↓ lymphocyte: 19% (n= 24%)		
031/072	33 C M	200 SD	Eye pain, peri orbital discomfort			
827/020	68 B F	100 BID				
461/020	80 B F	200 BID		↓ HTC: from 49% at baseline to 44% at 2 w and 40% at 6 w		

Hepatic Impairment. Study 016 was an open label, randomized, single and multiple dose PK evaluation study of Celecoxib in subjects with and without hepatic impairment in 12 mildly hepatically impaired subjects; 11 moderately hepatically impaired; and 25 normal subjects. Subjects were given one Cx 100 mg capsule on day 1 and 8, and one 100 mg capsule BID on days 4 to7. Most adverse events were mild and with the exception of two cases of diarrhea and one case of dyspepsia, were determined to be unrelated to the study drug. There were no withdrawals and no deaths. No significant laboratory changes were detected.

Renal Impairment. Study 036 was a randomized, DB, PC and AC, parallel study of 75 subjects (36 men, 39 women) ages 39 to 81, with stable chronic renal insufficiency, who received **SC 200 mg BID,** naproxen 500 mg BID for **seven days,** or placebo on days 1 to 6 and a single morning dose on day 7. There were no serious adverse events and no deaths. Two withdrawals in the placebo group (one headache, one confusion) were not considered to be related to study drug.

[**Reviewer's comment:** In summary, from the phase I studies, Celecoxib appears to have an acceptable safety profile at the doses explored . Most adverse events were mild or moderate, there were a few withdrawals and serious adverse events, most of them probably unrelated to the drug, and there were no deaths. Two patients presented reversible elevation of LFT's after a single dose of Cx, 900 mg.

Six patients who showed very high Cx plasma concentrations, had not particularly concerning clinical or laboratory adverse event.

Regarding the 7 patients who showed clinically significant drop in hematocrit in study 050 and 072, it is not completely clear to me whether it was just due to repeated flebotomy or if there is another explanation. In this study fluconazole and ketoconazole significantly affected Cx metabolism.

In study 016, 23 patients with hepatic impairment received Cx 100 mg BID for 4 days (only 4 days). Hepatic impairment resulted in an increased mean trough concentration with greater hepatic impairment associated with increased mean trough plasma concentrations. Celecoxib was well tolerated without significant changes in LFT's. Does it mean that patients will similarly tolerate 200 mg BID for longer periods? Does this justify the "no need for dose adjustment" in patients with mild to moderate hepatic impairment? Since no patients with severe hepatic impairment were studied, Celecoxib should probably not be used in this population.

In study 036, 40 patients with stable chronic renal insufficiency tolerated Cx 200 mg BID for 7 days. Again, this is a short period. Can we extrapolate that patients with more severe renal impairment will tolerate this dose for longer periods? Celecoxib should be used with caution in patients with renal insufficiency].

Arthritis trials – O.A, R.A and combined trials.

Osteoarthritis trials (eight trials: 020, 021, 054, 013, 042, 047, 060, 087)

Two to six-week OA studies.

There were five randomized, double blind, multi-center, parallel studies, that compared different doses of Celecoxib (ranging from 25 mg BID to 400 mg BID for 4 weeks and 200 QD for 6 weeks) to placebo, in patients with OA of the knee in a flare state (013, 047, 060, 087), or to an active comparator (diclofenac 50 mg BID) in patients with OA of the hip or knee of more than 6 months (study 042) (Table 3: randomization; Table 4: serious adverse events and events requiring withdrawal). 2787 patients were randomized. 2778 patients actually received at least one dose of study drug.

Table 3. Randomization in two to six-week OA studies

Treatment	Study 013 (2 weeks)	Study 042 (6 weeks)	Study 047 (4 weeks)	Study 060 (6 weeks)	Study 087 (6 weeks)
Placebo	71		101	232	244
Cx 25 or 40 mg bid	73		101		
Cx 100 mg bid or 200 mg q.d.	76	347	101	454	474
Cx 200 mg bid	76				
Cx 400 mg bid			99		
Diclofen 50 mg bid		341			
total	293	688	402	686	718

Table 4. Two to six week OA trials. Adverse events requiring withdrawal and serious adverse events, (013 (2w), 047(4w), 042, 060, 087(6w)). S = Serious event. N = thought to be not related to study drug by Searle Medical Monitor.

Total number of patients	Placebo N= 648	SC 25 or 40 mg BID N=174	SC 100 mg BID or 200 QD N=1452	SC 200 mg BID N=76	SC 400 mg BID N=99	Diclofenac 50 mg BID N=341
Dyspepsia	1		2		1	1
Diarrhea	2		3		1	5
Abdominal Pain	6	1	5			7
Nausea/vomiting	4		9			2
Esophagitis/gastritis						1
G.I. bleeding		1 N S (rec)				
Abdominal fullnes, nausea			1			
Palpitations						
CHF			2 (one arr S N,)	1 (arr) SN		
Chest pain, CAD	1 (MI) S N	1 N,	1 S N 1 S, 1 S N. DEATH			
Headache	1		1 N			1
Dizziness	2		3 N.			
Hyperesthesia, numbness, tingling	1		2 N			
Anxiety/irritabilit	1		1			
Insomnia			1			
Rash/urticaria/ allergic reaction	4 (one S)	1	11	1	2	1
Skin lesion			1			
Pruritus	1			1	2	
Back pain			2 N			
Arthralgia/myalgia	1 1 N				1	
Peripheral pain	1 N	1 N	2 N.			1 N
Accidental injury	2 N,		1 N S			1
Malignancy	2 S N,					
Hematuria						1 N
Fatigue	1					1
Dyspnea			1 N			
Respiratory inf: URI, bronchitis pneumonia,	1 N		2 N			1
Broncospasm		1	1 S			
Phlebitis						1 N
Weight gain			1			
Alopecia			1 N			
Hemol uremic S.					1 S N	
Edema	1 (face)		2			1
Renal insuff	1 N					
Septic arthritis			1 S N			
Herpes Zoster			1 S N			
Stomatitis			1 N			
Dry mouth	1 N					
Tox due to Non study drug	1 S					
Hyperglycemia			1 S			
Elevated CPK	2 N		1 N			
Elevated SGOT/SGPT						3
Decreased WBC						1
Hyperkalemia					1	
Anemia			1			

Serious events with no withdrawal:

Trial 013: none
Trial 042: Diclofenac: 1 angina N, 1 scheduled TKR N
Trial 047: Placebo 1 Lung Ca N,
Celecoxib 25 bid – 1 rectal hemorrhage N,
Cx 100 bid – 1 chest pain and bronchospasm N
Trial 060: Placebo Urinary incontinence N
Cx 100 bid – 1 CHF N, 1 CVA N
Trial 087: Cx 200 QD – 1 basal cell Ca, N.

12 week OA trials

Included three double-blind, placebo-controlled and active-controlled, multicenter (U.S. and Canada), parallel studies with a total of 3369 patients, ages 19 to 93, with OA of the knee or hip in a flare state, randomized to receive SC-58635 50 mg capsules BID, 100 mg BID or 200 mg BID; Naproxen 500 mg BID; or placebo, for 12 weeks. Table 5 shows patient randomization. Table 6 shows adverse events requiring withdrawal and serious adverse events. There was only one serious event considered to be related to the study drug (patient in study 054 with abdominal pain and possible ileus). There were no deaths.

Table 5. Randomization in 12-week OA studies:

	Study 020	Study 021	Study 054	Total
Placebo (n)	220	247	218	685
Celecoxib 50 bid	218	258	216	692
Celecoxib 100 bid	217	240	207	664
Celecoxib 200 bid	222	237	213	672
Naproxen	216	233	207	656

Table 6. Adverse events requiring withdrawal, study 020, 021, 054 .
S = Serious event. N = thought to be not related to study drug by Searle Medical Monitor.

Total number of patients	Placebo N=685	SC 50 mg BID N=692	SC 100 mg BID N=664	SC 200 mg BID N=672	Naproxen 500 mg BID N=656
Dyspepsia	6	6	10	9	16
Diarrhea	2	5	4	3	3
Abdominal Pain	2	8	5 (+ one pt with abd abcess, N)	9	18
Nausea/vomiting	6	3	4	2	8
Obstruction	1 (intest gangrena) SN	1 small bowel S N	1 small bowel S N		
Upper G.I. bleeding	1		-1 (gastric ulcer)		5 (one S)
Abdominal fullnes, flatulence			1	1	2
Pancreatitis			1 S N		
Stomatitis		0136 N			
Rectal burning			1		
Palpitations/arrhyt	1 A.fib N,	2 (one SVT SN)	2		1
CAD	1		1 S N	3 S N	1 S N
CHF				1 S N	
HTN/aggr HTN			1	4 (one S, two N)	
Headache	2	3	3 (2 N)	1	1
Dizziness	1	1	3	2	1
Tinnitus			1	2 N	
Depression/ somnolence			2 N	1	2
Anxiety/irritability/ insomnia		1	3	2	
Abnormal gait				1 N	
Hypersthesia/numb			1		
CVA	1	1 N	2 N	1 (w/ HTN)	
Rash/urticaria/allergic reaction	1	9	7 (one had swollen lips)	14	8
Pruritus	1		2	1	
Bronchospasm	1	1 N			
Skin lesion			0284 N dermatitis)		
Herpes Zoster			0857 N		
Arthralgia/myalgia	2	1	2 N	1 N	
Back pain	4	1	3 N	2 N	1
Peripheral pain			1 N	1 N	
Accidental injury	2	1 N	2 S N		3 N
Miscellaneous rheum. complaints	1	1 SN	2 N (one gout attack)	1	
Malignancy	2	1 S N	3 S N	1 S N	2 S N
Fatigue/dyspnea	2		1	2 N	
Pulm embolism				1 S N	2 S N
URI/Bronchitis/ pneumonia	1 N	1 N		2 N (one S pneumonia)	
Edema	1		2 N (one face ede)		
Flebitis		1 N			
Miscell.		1 goiter N		1 temp arteritis	1 fibroids, 1 ecchym. 1 hyperglyc
Elevated CPK			1 N		
Elev. Creatinine		1- proteinuria and per. ed		1	
↑ SGOT/SGPT	1		1		
Anemia		1	1 + proteinuria and thrombocytemia		3
Leukopenia	1 N				

Rheumatoid Arthritis Trials (022, 023, 041, 012).

The RA trials were multicenter, randomized, double blind, parallel studies involving a total of 3237 patients (863 men, 2374 women), ages 20 to 90, (2828 Caucasian, 208 Black, 161 Hispanic, 19 Asian , 21 other) with RA in a flare state (012, 022 and 023) or with stable RA (041), who received Celecoxib ranging from 40 mg BID for four weeks up to 400 mg BID for 12 weeks and 200 mg BID for 24 weeks (Table 7: randomization, Table 8: Adverse events requiring withdrawal and serious AE).

Table 7. Randomization in RA trials

Treatment	Study 012 (4 weeks)	Study 022 and 023* (12 weeks)	Study 041** (24 weeks)
Placebo	85	452	
Cx 40 mg bid	81		
Cx 100 mg bid		468	
Cx 200 mg bid	82	454	326
Cx 400 mg bid	82	434	
Naprox 500 mg bid		443	
Diclofenac SR 75 mg bid			329
total	330	2251	655

*Studies 022 and 023 had similar design. Study 022 specifically evaluated UGI safety and involved patients with no significant lesions on endoscopy. ** Study 041 was an ex-US study (Australia, Europe, South Africa, New Zealand and Israel) evaluate that also particularly evaluated GI safety.

Table 8. RA trials. Adverse events requiring withdrawal and serious adverse events, (012 (4 w), 022, 023 (12 w), 41(24 w)) S = Serious event N = found to be not related to study drug by Searle Med Monitor

Total number of patients	Placebo N=537	40 mg BID N=81	SC 100 mg BID N=468	SC 200 mg BID N=862	SC 400 mg BID N=951	Naproxen 500 BID N= 443 , or Diclofenac 75 mg BID (*D*) N=329
Dyspepsia	2	1	3	5	5	6 (one S)+ *8 D*
Diarrhea	1		1	6	2	*5 + 5 D*
Abdominal Pain	2		4	10	1	*7 + 27 D*
Nausea/vomiting	1			5	1	*1 + 3 D*
Esophagitis/gastritis				1		
S.Bowel obstruct						*1 D* N
G.I. bleeding/ ulcer				1		*6 D (one S)*
Abdominal fullnes, flatulence					1	*2 D*
Palpitations				1 N	2	
CHF				1 N		
Chest pain, CAD	1 SN, 1(MI),SN		2 S (one MI, N)	1 S N		1 N
Headache	3			2	1	*1 D*
Dizziness				1+ headac & face edema	1	*2 + 2 D*
Tinnitus	1		1 (+ otitis med & periorb edema)		2	1
Hyperesthesia, numbness, tingling				1 N		
Depress/somnolence	1			1,		1 + *1 D* S
Anxiety/irritabilit			1			*1 D*
CVA				1 SN		1 SN
Rash/urticaria/allergic reaction	6 + 1 (+ face edema & broncosp)		4	16 (one w/ periorb edema, one w/ face edema, one w/ angioedema)	12 (one w/ swollen face and laringeal edema. one w/ face edema, one w/ sob, two w/ numbness & paresthesias, one w/ rigors & chills, one w/ anaphylactoid react N),	3 + *1 D*
Pruritus			3			
Bronchospasm	1					
Skin disorder				2 skin ulceration N, 1 fingertip excoriations N,	1 skin ulcer (diabetic ulcer), 1 vasculitic lesions both hands 1 contact dermatitis	
Accidental injury					1 SN	
Malignancy			1 SN	2 S N (one DEATH)	1 SN	
Fatigue/dyspnea			1	3		
Pulm embolism						*1 D* SN
Resp inf: URI, bronchitis, pneu.	1			3 N		
Phlebitis						*2 D* N
Edema	face 1			1 Face & mouth	1 periph	1
Leg cramps			1	1		
Kidney stone	1 SN					
Stomatitis				1		
Miscell.					1 epistaxis	*1 D* S N (r-v fistula)

↑BUN/creatinine				0519/41		2 D
↑ SGOT/SGPT			0288/22	0915/23		
Hipokalemia			0663/23			
Anemia				0785/22 N (+ thrombocytemia		1 D S

Serious Adverse Events without withdrawal:

Trial 012: none

Trial 023:
1 Myocardial Infarction , SC 200 bid (N)
1 Basal skin cell ca. Naproxen
1 Accidental injury, diabetic, gangrenous toe (SC 200 bid) (N)
1 colon CA in SC 100 bid
1 Cholecystitis on placebo

Additional adverse event of note in trial 023: # 0895 (neuropathy, syncope (N), fungal infection ringworm)

Trial 022:
Placebo1 chest pain , 2 skin malignancy N
Naproxen 500 mg bid: 1 facial cellulitis , aggravated RA 1 patient
Celecoxib: 1upper resp. infection. N. SC 100 bid,
1 pneumonia N SC 200 bid, 1 bronchitis N SC 200 bid
1 angina pectoris – SC 400 bid,
1 aggravated HTN (N) SC 400 bid

Trial 041:
Diclofenac 75 mg bid: 1 back pain, 1 lymphangitis, 1 gastroenteritis,1 CTS release, 1 amputation of little toe,
1 cellulitis. 1 pyometra,
Celecoxib 200mg bid: 1 Septic arthritis (post op) "shoulder sepsis" S N,1 Myocardial Infarction. S N,
1 depression S N, 1 dyspnea, 2 pneumonia S N, 3 accidental injury S N.
1 anemia + pleural effusion

COMBINED OA AND RA.

There were two 12 weeks, ex-US trials involving a total of 1695 patients with OA and RA of the knee and hip. Table 9 shows patient randomization. Table 10 shows adverse events requiring withdrawal and serious adverse events.

Treatment	Study 062 (patients)	Study 071
Celecoxib 200 mg BID	299	366
Naproxen 500 mg BID	297	
Diclofenac SR 75 BID		387
Ibuprofen 800 mg TID		346

Table 9. Combined OA, RA trials. Adverse events requiring withdrawal and serious adverse events (062 and 071 (12 weeks, ex US)) S = Serious event. N = thought to be not related to study drug by Searle Medical Monitor.

Total number of patients		Cx 200 mg BID N = 636	Ibuprofen 800 mg TID N = 346	Diclofenac 75 mg BID N = 387	Naproxen 500 bid N = 267
Dyspepsia		2	3	11	2
Diarrhea		1		4	
Abdominal Pain		3	7	8 (one N)	6
Nausea/vomiting		4	5	2	2
Constipation				1	
Esophagitis/gastritis/ gerd		2		2	3
S.Bowel obstruct					1 S
G.I. bleeding/ gastric ,duodenal, esoph ulceration		2 S (one intestinal perforation N),	7	7 (two N)	5
Abdominal fullnes, flatulence			1	1	
Palpitations		1/71		1	1S (arr), 1 S N
CHF		1/71			
Chest pain, CAD		3/62 S N	1/71 MI S N	1/62 S N	1 MI, S N
Syncope/ sudden death		1/71	1/71 sudden DEATH, S N		
Hypertension		1 S		1 N, 1 DEATH , S N	1 N
Hypotension			1		
Dizziness			3/71		1
Tinnitus/deafness		1			
Hyperesthesia, numbness, tingling				2 (one N)	
Depression/somnolence			1/71	1	
Abnormal gait/ dystonia		1			
CVA					1 DEATH (brain stem infarct) S N
Rash/urticaria/allergic reaction Skin disorder		2 (one N)	2/71	2 (one anaph shock) 1 soft tissue inf. N	3
Arthralgia/myalgia/ worsening arthritis					1
Accidental injury		2		1 S N	
Malignancy		1 S N,		1 S N	
Dyspnea		1	1	1 COPD exac S N	1 N
Resp inf.: URI, bronchitis, pneum.		2 (one otitis media + deafness) N		1 S N	
Cough			1		
Pleural eff					1 S N
Edema			Face 1/71	Face 2/71	Face 1/62.
Miscell		1 S N (kidney stone)		1 Breast enlargement	
Urinary infection		1 N			1 S N
↑BUN/creatinine			1		1
Abnormal liver, ↑SGOT/SGPT		1			3
Anemia			3		1

Serious AE without withdrawal:

Trial 062:
Naproxen: 2 dyspnea, 1 SVT, 1 intestinal obstruction
Celecoxib 200 bid: 1 psychotic episode N, 1 aggravated hypertensionN, 1 pleural effusion N

Trial 071
Ibuprofen 800 mg TID: 1 pyelonephritis, 1 emergent surgery
Diclofenac 75 mg BID: 1 Angina pectoris, 1 COPD exacerbation, 1 atrial flutter, 1 scheduled surgery
Celecoxib 200 mg bid: 1 urinary infection N, 1 basal cell ca N, 1 depression aggravated, 1 scheduled surgery, 1 emergent surgery.

Deaths among patients enrolled in controlled arthritis trials:

There were eight deaths during the controlled trials or within 28 days after end of treatment (four on Celecoxib and four receiving other NSAIDS). Five deaths were due to cardiovascular causes, two of them in patients receiving Celecoxib and three in patients receiving an active comparator.

Laboratory changes

There were no clinically meaningful or concerning changes in hematologic laboratory parameters (hemoglobin, hematocrit, WBC, platelet count, PT, PTT), chemistry values (BR, ALK phosp, AST, ALT, BUN, creatinine, glucose, protein, electrolytes, calcium) or urinalysis. There was a higher number of patients who developed 1 + glucosuria compared to placebo ($P<0.05$) in 12 week studies, but this finding was not accompanied by a parallel increase in mean glucose values.

Data analysis of adverse events during controlled arthritis trials

After an initial safety review of all the controlled arthritis trials, statistical comparison of the number of selected serious adverse events and adverse events causing withdrawal for Celecoxib (50 to 400 mg BID doses), placebo and active comparators, was requested to Searle on 10/28/98 and provided to FDA on 11/2/98.

All OA, RA and combined OA/RA trials were divided in two groups:
a) < 12 weeks duration (012, 013, 042, 047, 060, 087)
b) ≥ 12 weeks duration (020, 021, 022, 023, 041, 054, 062, 071)

Selected AE to be analyzed:

I - Gastrointestinal
- a) Hard GI endpoints (perforation, obstruction, UGI bleeding)
- b) Dyspepsia
- c) Abdominal pain
- d) Nausea

II - Cardiovascular: a) Palpitations, arrhythmia
b) Congestive heart failure
c) Angina/ coronary artery disease/ cardiac chest pain
d) Hypertension/ aggravated hypertension

III – Skin a) rash, urticaria, allergic skin reaction, dermatitis
b) skin ulceration/skin lesion (exclude skin malignancies)

IV – Allergic reaction (excluding skin rash)/ anaphylactoid reaction/ anaphylactic shock, bronchospasm/ asthma/ angioedema

V – Infections a) respiratory (otitis, rhinitis, pharyngitis, upper respiratory, sinusitis, bronchitis, pneumonia)
b) urinary (cystitis, bladder, kidney, pyelonephritis)
c) sepsis
d) septic arthritis, joint infection
e) skin infection, herpes zoster

Summary of the analysis performed by Searle, based on Searle's database (my numbers may look different because some patients withdrew with more than one event and I chose only one, may be different from the one chosen by Searle):

Gastrointestinal adverse events:

Among <12 week trials:
There was one serious GI event in a patient receiving Celecoxib 100 mg BID. Neither the placebo nor the active comparator groups had serious GI adverse events. The incidence of dyspepsia, nausea and abdominal pain severe enough to require withdrawal was neither different to placebo nor to the active comparators.

Among ≥ 12 week trials.
For major GI events (Perforation, Ulcers and Upper GI Bleeding) serious and causing withdrawal, there was a statistically significant difference in favor of Celecoxib when compared to active comparators (1 vs. 9 cases, $p< 0.001$). (Although Dr. Goldkind has questioned 2 of the 9 cases among the active comparator group). Dyspepsia and abdominal pain requiring withdrawal were significantly higher among active comparators than among Celecoxib and placebo patients.

> **[Reviewer's comment:** Regarding the incidence of major GI complications, Celecoxib a the doses proposed (100 and 200 mg BID) seems to have a safety profile superior to other NSAIDS (0.2 % per patient-year compared to 1.3 % per patient-year among NSAIDS). There was not statistically significant difference in the number of important UGI events among patients receiving Celecoxib compared to placebo, but that

does not mean that they are equivalent. There was a small number of total events; in order to show equivalence to placebo, much larger trials would be needed.

Of note, there was no significant number of patients withdrawn due to elevated liver function test. However, it may be appropriate to look at LFT's in a subset of patients withdrawn due to other GI adverse events, for instance, abdominal pain and nausea]

Cardiovascular events:
Among the ≥ 12 week trials there were 16 CAD related events among patients on Celecoxib (0.4%), 5 among active controls (0.2%) and 6 among placebo (0.5 %). The differences were not statistically significant. The incidence of arrhythmia was < 0.1 % for all groups.

<12 week trials, the incidence of CAD related events and for arrhythmia was 0.1 % or less for all groups.

Skin ulceration– In the November 2 Searle's database analysis there was only one case of skin ulcer in a placebo <12 w patient. Among the skin lesions causing withdrawal there was 1 in Cx 200mg bid in the ≥ 12 w trials (one case of a patient with a diabetic ulcer and gangrenous toe).

[**Reviewer's comment**: In view of the skin lesions seen in dogs during preclinical toxicity studies, case reports of all new skin ulcers that appeared during Celecoxib controlled and uncontrolled trials were reviewed. There were 14 new ulcers, nine of them in patients taking Celecoxib, most of them in the lower extremities, in patients with a previous history of diabetes mellitus, CAD, HTN or peripheral edema. Most of the patients were taking prednisone and/or MTX. Most ulcerations were considered to be not related to study medication. Among patients taking Celecoxib, there was one patient with a nasal ulceration and stomatitis (There was actually another patient with a nasal ulceration in the same trial, but he had an upper respiratory infection and flu symptoms). One patient with skin vasculitis of the hands, was withdrawn and considered by the Investigator to be of UNCERTAIN relationship to study drug. One patient had periungueal excoriations (conceivably also due to vasculitis); the patient was withdrawn from the study and the adverse event was considered to be of PROBABLE relationship to the study drug. Of note, there were no new ulcers in the placebo group. In summary, there are several factors that may be involved in the development of skin ulcers: peripheral vascular disease, ischemia, venous insufficiency; infection; drug induced vasculitis. The incidence of new skin ulcerations with Celecoxib was no higher than with active comparators].

Allergy - There was a high incidence of different kinds of skin rash. Skin rash was a

frequent cause of withdrawal across all Celecoxib doses. These rashes were most likely allergic and should alert us to the possibility of more severe allergic reactions.

[**Reviewer's comment:** The pathophysiologic mechanism responsible for NSAID-induced allergy is not known. It is thought to depend on inhibition of cycloxigenase (COX 1, 2 or both?) coupled with upregulation of 5-lipoxigenase dependent pathways.

Two cases of bronchospasm were seen among placebo. No major allergic reactions were seen in the active comparator group. However there were cases of angioedema, laryngeal edema, bronchospasm, and anaphylactoid reaction (1 each) among Celecoxib patients. These trials were not powered to detect infrequent adverse events.

These trials excluded patients with known allergy to NSAID and sulfa drugs and were not powered to detect infrequent adverse events. We agree with the sponsor that Celecoxib should be used with caution in people with known allergy to other NSAIDs and AVOIDED in patients with allergy to sulfa drugs].

Incidence of serious infections – Although there was a high incidence of upper respiratory infections, bronchitis and even pneumonia among patients in these trials, there were not statistically significant differences in the number of serious events or infections requiring withdrawal among patients receiving Cx compared to placebo and active comparators.

Renal – Regarding renal adverse events and laboratory, Celecoxib has a safety profile comparable to a mild NSAID. The incidence of peripheral edema among patients in Celecoxib 200 mg QD, 200 mg BID and 400 mg BID was 2.9 %, 2.6 % and 2.4 % respectively, compared to 1.1 % in placebo patients and 2.1 % among thee active comparators. The significance of the mild increase in chloride among Celecoxib patients, particularly without bicarbonate data is difficult to interpret. The three special renal studies were underpowered to detect infrequent serious adverse events (even active comparators appeared to be benign to the kidney and no cases of papillary necrosis or nephrotic syndrome were detected among any group). One case of hemolytic uremic syndrome was seen in one patient taking Celecoxib.

The incidence of glucosuria (1 + = 1 g/24 hours) among patients enrolled in 12 week North American arthritis trials was 2.4 % for Celecoxib (100 and 200 mg BID) compared to 1.6 % for placebo patients and 1.3 % for patients taking Naproxen (Table 81, page 141 Celebrex A.C. Briefing document). However, the baseline mean glucose did not change significantly (increased by 0.239 mmol/L).

Long term open label study (024 in OA and RA)

This is a long term safety study of patients who previously participated in one of nine phase II or III double blind studies, who were enrolled in this study to complete two years of treatment (doses range from 100 to 400 mg BID). At the time of the cutoff date (11/21/97) 4499 patients had entered the study (2361 from direct roll-over and 2138 from indirect roll-over). 3256 patients were still active and 1234 had prematurely terminated from the study. No one had completed the study.

The incidence of most common adverse events, adverse events requiring withdrawal and serious adverse events, was similar to the one seen in the controlled arthritis trials. There seem to be an apparent higher incidence of cardiovascular disease but the difference is corrected when adjusted for duration of patient exposure.

DEATHS-
There were a total ten deaths during the long term open label trial up to the cutoff date of the ISS; none of them was attributed to study medication:

One subarachnoid hemorrhage, day 15 on Cx 200 mg BID (confirmed at autopsy)
One adenocarcinoma, day 110 on Cx 400 mg BID
One "natural causes" day 12 on Cx 400 mg BID (after aproxx. 150 days on lower doses)
One CHF and respiratory failure , day 228 on Cx 200 BID
One COPD, day 193 on Cx 300 mg BID
One probably massive coronary ischemia, day 131 on Cx 200 BID
One ischemic heart disease, day 147 on Cx 200 mg BID (confirmed at autopsy)
Three acute myocardial infarction (two patients on Cx 400 mg BID, day 210 and day 334; one patient on Cx 300 mg BID for 6 days).

The high number of CV events probably reflects the high prevalence of CV disease among the adult and elderly population studied in these trials. However it is difficult to draw definitive conclusions without an adequate control population.

120 day Safety Update

The 120 day Safety Update contains information from 2 Phase I studies (007 and 079 = 144 patients on Celecoxib), the long term open label arthritis trial (024 = 5155 patients) and 4 surgical pain studies (082, 083, 085 and 086 = 330 patients). This update also contains information for serious adverse events and deaths among a Ex-US long term safety study (058), ongoing analgesia studies (074, 075 and 078), protocols under other IND's - Alzheimer's disease (2 studies) and Cancer chemoprevention (2 studies) – as well as two Japanese trials.

Phase I trials.

Study 007 was a DB, r, PC single dose study to evaluate the antipyretic effect of 25, 100 200 and 400 mg of Celecoxib in endotoxin-induced fever in healthy male subjects. The most common AE overall were rigors and headache, which seem to be expected in a study of endotoxin-induced fever.

Study 079 is a DB, R, P and naproxen controlled study to evaluate the safety and effects on platelet and renal function of high doses of Celecoxib (800 and 1200 mg BID in healthy subjects. There were no novel adverse events.

There were no serious AE and no deaths.

Long term open label study

No novel adverse events were seen in this trial, compared with the controlled trials. Similar to the ISS, the most common adverse events were upper respiratory tract infection, headache, dyspepsia, sinusitis and accidental injury. The overall incidence of adverse events are higher in the long term open label study than in the North American controlled trials, reflecting the longer duration of exposure.

The most common AE causing withdrawal were rash, GI symptoms (dyspepsia, abdominal pain, diarrhea, gastric ulcer) headache, dizziness, myocardial infarction, pruritus, anemia, and malignancy. None of the serious adverse events were considered to be related to study drug.

Sixteen myocardial infarctions occurred in the long term open label trial since the database cutoff for the ISS. All had one or several predisposing factors. The rate of serious MI was 0.012 per patient-year in the long term open label study, 0.017 per patient- year, in the controlled trials among patients on Cx (all doses) and 0.033 per patient-year among placebo.

No particularly concerning or unexpected serious adverse events were reported.

Clinically significant upper GI events in the long term open label study:

The rate of clinically significant UGI events in the long term open label study was 0.18 % per patient-year (compatible with the rate of 0.2% per patient-year observed in the controlled arthritis trials). Between November 22, 1997 (cut off date for the ISS) and July 24, 1998 (cut off date for the 120 day safety update), there have been two new clinically significant UGI events. One patient was an 85 y. o. male with RA and a history of gastric ulcer, who developed a gastric lesion with evidence of active bleeding requiring two units of packed red blood cells while on Cx 200 mg BID (day 434). The other patient was a 47 y. o. woman with RA and history of gastroduodenal ulcers who developed hematemesis with documented gastric and esophageal ulcers, while on Cx 400

mg BID (day 67 at that dose, but she has been on 100, 200 and 300 mg BID for the previous 3 months).

Surgical pain studies

Two were single-dose trials in patients after orthopedic surgery or general surgery. Two were multiple dose trials in patients after orthopedic surgery. Most common adverse events in the single dose studies with incidence >3 % were nausea, vomiting, headache somnolence and dizziness. Most common adverse events in multiple dose studies with incidence of >3 % were similar to single dose studies, with the addition of pruritus and increased sweating.

AE causing withdrawal: thirteen patients withdrew from the single dose studies; five withdrew from multiple dose studies. There were no novel adverse events.

DEATHS

The 120 day safety update reports a total of nine deaths. Six of them occurred in the open label long term study and three occurred in two ongoing blinded trials. None of the deaths were considered to be related to study medication.

In summary: The information contained in the 120 day safety update is concordant with previous data submitted in this NDA. Celecoxib, at the dose of 100 and 200 mg BID, seems to have an acceptable safety profile.

Villalba

Maria Lourdes Villalba, MD
M.O., DAAODP

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John Hyde, MD, PhD
Acting Deputy Director, DAAODP

HDF 550 Div file
HDF 550/MO/JHyde
HDF 550/MO/MLVillalba
HDF 550/MO/JWitter