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## MEMORANDUM

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**SUBJECT:** Comparative Safety of Celecoxib, Diclofenac and Ibuprofen

### PURPOSE OF CONSULT

The Division of Ophthalmic and Anti-Inflammatory Drug Products (HFD-550) requested a review of the adverse events reported in the Celecoxib Long-Term Arthritis Safety Study (CLASS). Specifically, the Division "would like to request an evaluation of the effect of Celebrex on adverse events and on its effects on the acid-base status, including assessment of changes in serum bicarbonate."

### MATERIALS USED FOR CONSULT

1. NDA 20-998/ S-009 (celecoxib): CLASS Trial database electronic version.
2. NDA 20-998 (celecoxib): my previous consultation for celecoxib, dated 12.10.98.
3. NDA 21-042 (rofecoxib): renal consultation by Juan Carlos Pelayo, M.D., dated 4.30.99.
4. Published materials (see bibliography at end of consultation).
5. Materials submitted by the sponsor at the request of medical reviewers.
6. Draft Primary Medical Review of NDA 20-998/ S-009 by James Witter, M.D., Ph.D.

### 0.0 RÉSUMÉ

The Celecoxib Long-Term Arthritis Safety Study (CLASS) compared the chronic effects of three anti-inflammatory drugs in a population of patients with osteoarthritis and rheumatoid arthritis: celecoxib, diclofenac, and ibuprofen. Patients were followed for clinical events and underwent routine serum chemistries. Low-dose aspirin (ASA) was used by approximately 20% of the study population. Three aspects of the renal and cardiac effects of celecoxib require comment in this consultation, based on the CLASS safety database. The first is the specific issue of the effect of celecoxib on acid-base balance, which derives from an absence of such data in the initial NDA submission. The second issue relates to the renal and cardiac safety of celecoxib when compared with diclofenac and ibuprofen. A final aspect of the CLASS trial to be considered in this consultation is the effect of concomitant use of ASA on the cardiac and renal outcomes.

## 0.0 RÉSUMÉ

### Effect of Celecoxib on Acid-Base Balance

In the original NDA database, the effect of celecoxib on serum bicarbonate ( $\text{HCO}_3^-$ ) was not assessed. There was some evidence of an association between celecoxib use and an increase in serum chloride, which can be interpreted as related to fall in serum  $\text{HCO}_3^-$ . To address this issue, the sponsor measured changes in serum  $\text{HCO}_3^-$  in CLASS and collected adverse events related to changes in systemic acid-base balance. In the analysis (detailed below) between 1 and 2% of the subjects in all three treatment groups had a measured serum  $\text{HCO}_3^- < 20$  meq/dl during the study after starting with a normal baseline  $> 25$  mg/dl. The rate for celecoxib, however, was less than that of the two comparator agents. In addition, there was no increase in reported clinical adverse events related to changes in acid-base balance in the celecoxib group: such adverse events were quite rare in the database for all three drugs. Overall, then, celecoxib, diclofenac and ibuprofen use have been associated with changes in renal acid-base handling, perhaps related to inhibition of COX-1 and COX-2 in the kidney. The CLASS database contains no evidence for an adverse effect of celecoxib on acid-base balance relative to either diclofenac or ibuprofen.

### Comparative Incidence of Renal Adverse Effects for Celecoxib, Diclofenac and Ibuprofen

The rates of reported clinical renal adverse events were low in the database, and there was no consistent clinically-significant adverse effect of celecoxib in the reported parameters of renal safety when compared with either diclofenac or ibuprofen. In particular, the reported rates of uremia, nephrotic syndrome and severe hyperkalemia in CLASS were all less than 1 per 1000 patient-years of exposure for all three drugs. In the CLASS database the renal adverse event profile for celecoxib was not clearly different from that of NSAIDs (as represented by diclofenac and ibuprofen). This includes adverse events reported by investigators (e.g., worsened hypertension or edema, uremia) and those detected through routine laboratory or blood pressure measurements (e.g., increased BUN/Cr or systolic blood pressure).

### Comparative Incidence of Cardiac Adverse Effects for Celecoxib, Diclofenac and Ibuprofen

While there were some differences in the rates of reported clinical cardiac adverse events between the three treatment groups, there was no consistent clinically-significant adverse effect of celecoxib in the reported parameters of cardiac safety when compared with either diclofenac or ibuprofen. Particular concern has been raised regarding a possible pro-thrombotic effect of selective inhibition of COX-2 (for example, by celecoxib). In CLASS, the incidence of adverse events related to cardiac ischemia was higher in the celecoxib group when compared with the two comparators. This difference was most pronounced in the group of patients not taking ASA. However, the differences observed in the rates of adverse events were small and relied on relatively few events. Importantly, the rate for serious adverse events related to cardiac ischemia and for cardiovascular mortality were not increased in the celecoxib group, although the rate of a combined group of adverse events reflecting anginal episodes was highest in the celecoxib group. In the patient population studied in CLASS, these findings exclude a large adverse effect of celecoxib on cardiovascular mortality compared with two non-selective COX inhibitors/ NSAIDs. These findings do not exclude a less significant effect of celecoxib on blood flow leading to less serious clinical outcomes and manifest by differences in the rates for less serious adverse events. In the CLASS database the overall cardiac adverse event profile for celecoxib was not clearly different from that of NSAIDs (as represented by diclofenac and ibuprofen).

### Effect of Aspirin Use on Adverse Events in CLASS

Comparing the effects of the three drugs used in CLASS was complicated by the use of aspirin (ASA) in a sub-group of patients. As the trial randomization was not stratified for ASA use and the amount of ASA used by the patients who took it is not known, comparisons of the ASA- and non-ASA-users have limited power, and can detect only large differences between these two groups. In general, celecoxib, diclofenac and ibuprofen had similar rates of adverse events, regardless of whether the patient also used ASA. Patients who used ASA in all three treatment groups had a higher incidence of worsened hypertension, hyperkalemia and increases in BUN than patients who did not use ASA.

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### 1.0 BACKGROUND AND METHODS

This consultation is focused on the renal and cardiac effects of celecoxib, based on data from a recently completed outcome trial in patients with rheumatoid- and osteo-arthritis: the Celecoxib Long-term Arthritis Safety Study (CLASS). Interest in the effects of celecoxib in on the kidneys and the cardiovascular system comes first from concerns about the comparative safety of selective inhibitors of cyclo-oxygenase type 2 (COX-2) such as celecoxib and rofecoxib, and non-selective COX inhibitors ( e.g., ibuprofen, diclofenac). In addition concerns have been raised about a possible pro-thrombotic effect of the selective COX-2 inhibitors. This is based, in part, on the data in the original NDA databases (see below) and from investigations published since celecoxib's approval (references appear at the end of this review). These investigators have raised a concern about the effect of unopposed inhibition of COX-2 enzyme, leading to decreased production of prostacyclin (a vasodilator), without the combined inhibition of COX-1 (which would prevent platelets from being activated). Two large active-control trials have been performed that are relevant to this issue: CLASS (celecoxib) and VIGOR (rofecoxib). This consultation is restricted to an analysis of CLASS.

#### Cardiac Effects of Celecoxib

In my original consult on celecoxib performed as part of the initial NDA submission, I examined the cardiac laboratory data and adverse events and reached the following conclusions:

"The administration of celecoxib cannot be linked to any rare or unusual cardiac toxicities based on the available data. For some adverse events, including arrhythmias and overall cardiovascular mortality, the data are inadequate to either exclude or confirm an adverse effect of celecoxib.

With regard to cardiovascular adverse events, there is an association between celecoxib administration and worsened hypertension in susceptible individuals. This effect of celecoxib resembles that of other non-steroidal anti-inflammatory drugs (NSAIDs). There was also an association between celecoxib administration and the development of clinically significant edema, again similar to other NSAIDs" (12.10.98).

#### Renal Effects of Celecoxib

In my original consult on celecoxib performed as part of the initial NDA submission, I examined the renal laboratory data and adverse events and reached the following conclusions:

"There was sufficient evidence to conclude that celecoxib has significant renal effects, as reflected in the pattern of lab abnormalities associated with celecoxib administration. This pattern includes a nominally-significant association between celecoxib and an increased incidence of several lab abnormalities: hyperchloremia, hypophosphatemia, and elevated BUN in association with proteinuria. These surrogates for renal toxicity suggest, but do not confirm, a link between celecoxib use and clinically relevant nephrotoxicity. Further, the incidence of the lab abnormalities occurred to a similar extent in both the celecoxib and the active control groups, suggesting that both celecoxib and the other NSAIDs have similar renal effects.

Within the limitations of the database, there is no evidence to suggest that celecoxib has unique renal toxicities not shared with other NSAIDs, or evidence of a renal toxicity caused by other NSAIDs that occurs at a significantly higher incidence rate with celecoxib. In the absence of bicarbonate data, an adverse effect of celecoxib on acid-base balance cannot be excluded, particularly in the context of the observed increase in hyperchloremia. The pattern of adverse events reported in both the controlled and the long-term trials is similar to that expected for NSAIDs.

## 1.0 BACKGROUND AND METHODS (cont)

### Renal Effects of Celecoxib (cc.it)

While there were no clear cases of celecoxib-induced renal failure requiring dialysis in the controlled database, there were several individuals taking celecoxib who were withdrawn from the long-term open-label trial because of renal adverse events, including acute renal failure (as well as edema and worsening hypertension). It remains to be determined whether severe renal injury will occur following celecoxib at the same rate that is seen with other NSAIDs.

While a through comparison of the renal effects of celecoxib and other NSAIDs has not been performed, the available data suggest that celecoxib resembles other NSAIDs in the majority of the renal effects examined in the NDA. Further, the available data suggest that the renal effects of celecoxib are clearly distinguished from placebo" (12.10.98).

### CLASS

CLASS compared the effects of high doses of celecoxib (400 mg BID) with those of ibuprofen (800 TID) and diclofenac (75 mg BID) in patients with osteoarthritis and rheumatoid. Patients could be treated with aspirin (ASA) if indicated for other medical conditions. Any patient who received ASA during the first 6 months of the study was counted as taking ASA, as opposed to counting only those patients taking ASA on a chronic basis. For details of the trial design the reader is referred to the Medical Review of the trial by James Witter, M.D., Ph.D. The current review will focus on the renal and cardiac safety data, and compare the incidence of laboratory changes and adverse events for celecoxib, ibuprofen and diclofenac.

The data for the cardiac and renal adverse events will be broken into a section on clinical adverse events, detected through spontaneous reporting and a section on changes detected in laboratory measurements, performed routinely throughout the trial period. Given the potential relevant interaction of celecoxib with ASA, special attention will be paid to an analysis based on the concomitant use of ASA.

## 2.0 to 2.2 REVIEW OF CLINICAL DATABASE FROM CLASS

### 2.0 DEMOGRAPHICS AND METHODS

For details regarding the CLASS protocol and methods the reader is referred to the review by James Witter, M.D., Ph.D.

#### 2.0a Extent of Exposure and Demographics

Total exposure to the three treatments in the study is summarized in the table below.

Table 2.0a.1 Exposure to Study Drugs in CLASS<sup>a</sup>.

Treatment Group	Patients Exposed	Patient-Years of Exposure
Celecoxib 400 mg BID	3987	2340
Diclofenac 75 mg BID	1996	1080
Ibuprofen 800 mg TID	1985	1122

a. Data from CLASS electronic submission, NDA 20-998.

This exposure included around a third of the patients in each group who received study drug for  $\leq 3$  months, as well as about half of each patient group who received the study drug for between 9 and 15 months. The study contains around 2300 patients treated with celecoxib, 1100 treated with diclofenac, and 1000 treated with ibuprofen for  $\geq 6$  months.

Table 2.0a.2 Exposure to Study Drugs by Interval<sup>a</sup>.

Interval on Drug	Celecoxib	Diclofenac	Ibuprofen
$\leq 3$ months	1202 (30%)	621 (31%)	715 (36%)
3-6 months	467 (12%)	262 (13%)	246 (12%)
6-9 months	291 (7%)	136 (7%)	130 (7%)
9-12 months	1442 (36%)	913 (46%)	415 (21%)
12-15 months	585 (15%)	64 (3%)	477 (24%)
>15 months	0 (0%)	0 (0%)	2 (<1%)

a. Data from CLASS electronic submission, NDA 20-998 table 10.a.

**2.0b Collection of Adverse Events and Laboratory Measures in the Trial**

**Collection of Clinical Adverse Events**

Clinical adverse events were collected and reported by the investigators to the sponsor throughout the period of the trial. Adverse events were not centrally-adjudicated.

**Collection of Adverse Events Related to Laboratory Measurements**

Labs were to be collected at baseline and again at weeks 4, 13, 26, 39, 52, 65 and week 78 ('Final'). The number of patients with collected lab values varied between visits, as summarized below for selected renal parameters. Urinalyses were not collected routinely during the trial.

**2.0b Collection of Adverse Events and Laboratory Measures in the Trial (cont)**

**Table 2.0b.1 Number of Lab Measurements During CLASS <sup>a</sup>.**

	Celecoxib			Diclofenac			Ibuprofen		
	Total	ASA	No ASA	Total	ASA	No ASA	Total	ASA	No ASA
<b>Week 4</b>									
BUN/ Crt	3676	828	2986	1844	422	1438	1779	385	1423
Potassium	3629	820	2857	1820	418	1418	1757	380	1406
Bicarbonate	3670	827	2891	1838	421	1433	1774	384	1419
<b>Week 26</b>									
BUN/ Crt	2369	528	1889	1159	256	919	1059	236	852
Potassium	2347	523	1872	1149	256	909	1049	233	845
Bicarbonate	2366	527	1887	1153	255	914	1058	236	851
<b>Final</b>									
BUN/ Crt	3692	829	2911	1850	422	1444	1786	386	1429
Potassium	3673	824	2897	1837	420	1433	1770	383	1416
Bicarbonate	3689	829	2908	1845	421	1440	1782	385	1426

a. Data from CLASS electronic submission, tables 2.10.2.1, 2.10.4.1, and T44.1.

**2.1 RENAL AND CARDIAC SAFETY DATA FROM CLASS**

This section will examine four layers of potential adverse effects, beginning with the most serious (Total and Cardiovascular Mortality) and proceeding to Serious Adverse Events (SAEs), Adverse Events (AEs) including laboratory changes and blood pressure measurements, and then to Adverse Events leading to discontinuation.

**2.1a Total Mortality and Cardiovascular Mortality**

In the original NDA too few deaths occurred during the placebo-controlled period of the trials to be interpretable. In the long-term, open-label trial, cardiovascular mortality in deaths per patient-year was examined, arranged by highest dose of celecoxib used. The small numbers of patients obviously make interpretation of such calculated rates difficult, but there is an association between dose of celecoxib and the crude mortality rate due to cardiovascular causes.

**Table 2.1a.1 Cardiovascular Mortality Rates According to Highest Dose of Celecoxib Used, from the Long-term Trial <sup>a</sup>.**

Celecoxib Dose	Number of Deaths	Patient-years of Exposure	Crude Mortality Rate
100 mg	0	519	0%
200 mg	4	1271	0.31%
300 mg	2	340	0.59%
400 mg	3	465	0.64%

a. Data from original NDA Integrated Safety Summary, including Text Tables 65-68 and appendix 4.3.

b. Mortality (for both total and cardiovascular deaths) in deaths/pt-yrs (x100).

In similar fashion, the deaths in CLASS are summarized below, expressed in terms of deaths per person years of exposure to study drug. The majority of the results are based on materials submitted by the sponsor. The reader is referred to the Primary Medical Review by James Witter, M.D., Ph.D. for additional analyses based on individual case report review. Based on relatively few deaths, no excess mortality (total or cardiac) associated with celecoxib use is evident in any analysis.

## 2.1a Total Mortality and Cardiovascular Mortality (cont)

**Table 2.1a.2 Mortality Rates Per Person Years of Exposure From CLASS <sup>a</sup>.**

	Celecoxib N=3987/ 2320 <sup>d</sup>	Diclofenac N=1996/ 1080 <sup>d</sup>	Ibuprofen N=1985/ 1122 <sup>d</sup>
Deaths (All-Cause)	19 (0.8%)	9 (0.8%)	8 (0.7%)
Deaths (All-Cause) on Study Drug <sup>c</sup>	8 (0.3%)	5 (0.5%)	3 (0.3%)
Cardiac Deaths <sup>b</sup>	11 (0.5%)	5 (0.5%)	5 (0.4%)
Cardiac Deaths on Study Drug <sup>c</sup>	5 (0.2%)	4 (0.4%)	3 (0.3%)
Cardiac Deaths on Study Drug <sup>c</sup>	10 (0.4%)	5 (0.5%)	3 (0.3%)

a. Data from electronic data submission, appendix 2.9.1 and pages 2918-3920 of vol. 24.

b. Deaths ascribed to ischemic cardiac causes (excluding 2 cases of CHF).

c. Excludes patients off of study drug for >28 days per the sponsor.

d. Number of patients enrolled/ patient-years of exposure.

e. Excludes patients off of study drug for >28 days per the Primary Medical Reviewer (James Witter, M.D., Ph.D.).

Given the concerns about the potential interaction of celecoxib and ASA (which inhibits COX-1), it is relevant to look at the mortality rates according to the use of ASA. Again, there is no signal for an increased mortality rate in the celecoxib group when compared with the two NSAIDs.

**Table 2.1a.3 Mortality Rates Per Person Years of Exposure From CLASS Stratified by ASA Use <sup>a</sup>.**

	Celecoxib N=3987/ 2320 <sup>c</sup>	Diclofenac N=1996/ 1080 <sup>c</sup>	Ibuprofen N=1985/ 1122 <sup>c</sup>
Deaths (All-Cause)			
ASA Users	6 (1.2%)	1 (0.4%)	4 (1.6%)
Non-ASA Users	13 (0.7%)	8 (1.0%)	4 (0.5%)
Cardiac Deaths on Study Drug <sup>d</sup>			
ASA Users	2 (0.4%)	0 (0%)	2 (0.8%)
Non-ASA Users	3 (0.2%)	4 (0.5%)	1 (0.1%)
Cardiac Deaths on Study Drug <sup>d</sup>			
ASA Users	5 (1.0%)	0 (0%)	2 (0.8%)
Non-ASA Users	5 (0.3%)	5 (0.6%)	1 (0.1%)

a. Data from electronic data submission, appendix 2.9.1 and pages 2918-3920 of vol. 24 and sponsor submissions to reviewer. Data relates to all reported deaths, irrespective of temporal relationship to last use of drug.

b. Deaths ascribed to ischemic cardiac causes per the sponsor (excluding 2 cases of CHF).

c. Number of patients enrolled/ patient-years of exposure.

d. Excludes patients off of study drug for >28 days per the sponsor.

e. Excludes patients off of study drug for >28 days per the James Witter, M.D., Ph.D.

## 2.1b Serious Renal and Cardiac Adverse Events

The next table summarizes the occurrence of selected serious adverse events (SAEs) relevant to renal and cardiac safety. There were no reported SAEs for acidosis or reduced serum bicarbonate reported. There were also very few reported renal SAEs. Cardiac SAEs were also uncommon, but the rate of reported serious "Combined Atrial SAEs" was higher in the celecoxib group than in the comparator groups. There was a higher rate of Myocardial infarctions (but not Anginal Disorders) in the celecoxib and ibuprofen groups when compared with diclofenac.

**Table 2.1b.1 Renal Serious Adverse Events (SAEs) per 100 Pt-Yrs Reported During CLASS <sup>a</sup>.**

Adverse Event	Celecoxib 400 mg BID n=3987 2320 Pt-Yrs	Diclofenac 75 mg BID N=1996 1080 Pt-Yrs	Ibuprofen 800 mg TID N=1985 1122 Pt-Yrs
Hyper-, Hypo-kalemia <sup>b</sup>	0 (0%)	0 (0%)	0 (0%)
Acidosis <sup>b</sup>	0 (0%)	0 (0%)	0 (0%)
Nephrotic Syndrome <sup>b</sup>	0 (0%)	0 (0%)	0 (0%)
Edema <sup>b</sup>	0 (0%)	0 (0%)	0 (0%)
Uremia	0 (0%)	0 (0%)	1 (<0.1%)
Renal Calculus	4 (0.2%)	0 (0%)	2 (0.2%)

a. Data from electronic data submission, table T43.

b. These SAEs were not reported by investigators.

2.1b Serious Renal and Cardiac Adverse Events (cont)

Table 2.1b.1 Cardiac Serious Adverse Events (SAEs) per 100 Pt-Yrs Reported During CLASS <sup>a</sup>.

Cardiac SAEs	Celecoxib 400 mg BID n=3987 2320 Pt-Yrs	Diclofenac 75 mg BID N=1996 1080 Pt-Yrs	Ibuprofen 800 mg TID N=1985 1122 Pt-Yrs
<b>Atrial Arrhythmias</b>			
Arrhythmia Atrial	2 (<0.1%)	0 (0%)	1 (<0.1%)
Bradycardia	2 (<0.1%)	0 (0%)	0 (0%)
Fibrillation Atrial	9 (0.4%)	2 (0.2%)	3 (0.3%)
Tachycardia Supraventricular	3 (0.1%)	0 (0%)	0 (0%)
<b>Combined Atrial SAEs<sup>b</sup></b>	<b>14 (0.6%)</b>	<b>2 (0.2%)</b>	<b>4 (0.4%)</b>
<b>Angina</b>			
Unstable Angina	8 (0.3%)	4 (0.4%)	0 (0%)
Angina Pectoris	4 (0.2%)	5 (0.5%)	6 (0.5%)
Coronary Artery Disorder	19 (0.8%)	5 (0.5%)	5 (0.4%)
<b>Combined Anginal Disorders<sup>c</sup></b>	<b>30 (1.3%)</b>	<b>14 (1.3%)</b>	<b>10 (0.9%)</b>
<b>Myocardial Infarction</b>	<b>19 (0.8%)</b>	<b>4 (0.4%)</b>	<b>9 (0.8%)</b>
Hypertension Aggravated	2 (<0.1%)	0 (0%)	0 (0%)
<b>Thrombophlebitis Combined<sup>d</sup></b>	<b>8 (0.34%)</b>	<b>6 (0.56%)</b>	<b>1 (0.09%)</b>

a. Data from electronic data submission, table T43 and from sponsor at the request of the reviewer.

b. Sum of atrial arrhythmia, atrial fibrillation, bradycardia and tachycardia.

c. Includes unstable angina, angina pectoris and coronary artery disorder.

d. Includes AEs reported under the following terms: phlebitis, thrombophlebitis, thrombophlebitis arm, thrombophlebitis deep, thrombophlebitis leg, thrombophlebitis leg deep, thrombophlebitis leg superficial.

For the renal SAEs, too few were reported to analyze according to the use of ASA. The table below summarizes the incidence of relevant cardiac SAEs according to the use of ASA.

Table 2.1b.2 Serious Adverse Events (SAEs) per 100 Pt-Yrs Reported During CLASS <sup>a</sup>.

Serious Adverse Event	Celecoxib	Diclofenac	Ibuprofen
<b>ASA Users</b>	<b>N=882 517 Pt-Yrs</b>	<b>N=445 N=239 Pt-Yrs</b>	<b>N=412 249 Pt-Yrs</b>
<b>Atrial Arrhythmias</b>			
Arrhythmia Atrial	2 (0.4%)	0 (0%)	1 (0.4%)
Fibrillation Atrial	4 (0.8%)	1 (0.4%)	3 (1.2%)
Tachycardia Supraventricular	1 (0.2%)	0 (0%)	0 (0%)
<b>Combined Atrial SAEs<sup>b</sup></b>	<b>7 (1.4%)</b>	<b>1 (0.4%)</b>	<b>4 (1.6%)</b>
<b>Angina</b>			
Unstable Angina	6 (1.2%)	4 (1.7%)	0 (0%)
Angina Pectoris	3 (0.6%)	5 (2.1%)	4 (1.6%)
Coronary Artery Disorder	11 (2.1%)	2 (0.8%)	5 (2.0%)
<b>Combined Anginal SAEs<sup>c</sup></b>	<b>20 (3.9%)</b>	<b>11 (4.6%)</b>	<b>9 (3.2%)</b>
<b>Myocardial Infarction</b>	<b>13 (2.5%)</b>	<b>2 (0.8%)</b>	<b>7 (2.8%)</b>
<b>Non-ASA Users</b>	<b>N=3105 1804 Pt-Yrs</b>	<b>N=1551 841 Pt-Yrs</b>	<b>1573 874 Pt-Yrs</b>
<b>Atrial Arrhythmias</b>			
Arrhythmia Atrial	0 (0%)	0 (0%)	0 (0%)
Bradycardia	2 (0.1%)	0 (0%)	0 (0%)
Fibrillation Atrial	5 (0.3%)	1 (0.1%)	0 (0%)
Tachycardia Supraventricular	2 (0.1%)	0 (0%)	0 (0%)
<b>Combined Atrial SAEs<sup>b</sup></b>	<b>6 (0.3%)</b>	<b>1 (0.1%)</b>	<b>0 (0%)</b>
<b>Angina</b>			
Unstable Angina	2 (0.1%)	0 (0%)	0 (0%)
Angina Pectoris	1 (0.1%)	0 (0%)	2 (0.2%)
Coronary Artery Disorder	8 (0.4%)	3 (0.4%)	0 (0%)
<b>Combined Anginal SAEs<sup>c</sup></b>	<b>10 (0.6%)</b>	<b>3 (0.4%)</b>	<b>2 (0.2%)</b>
<b>Myocardial Infarction</b>	<b>6 (0.3%)</b>	<b>2 (0.2%)</b>	<b>2 (0.2%)</b>

a. Data from electronic data submission, Appendix 2.9.4 and 2.9.3.

b. Sum of atrial arrhythmia, atrial fibrillation, bradycardia and tachycardia.

c. Includes unstable angina, angina pectoris and coronary artery disorder.

## 2.1c Renal and Cardiac Adverse Events

### Clinical Renal Adverse Events

The first table below summarizes the incidence of renal adverse events of interest reported by the investigators. These adverse events were reported in less than 2% of the patients, and occurred more or less equally in the three treatment groups. Related to the question of an effect of celecoxib on acid-base balance, no acidosis or low serum bicarbonate as clinical adverse events were reported. Similarly, in conditions of chronic acidosis, bony demineralization and fractures can occur. In CLASS, the rates of bony fractures were similar in the three treatment groups.

Table 2.1c.1 Renal Adverse Events Reported During Study 35102 (CLASS) <sup>a</sup>.

Adverse Event	Celecoxib 400 mg BID N=3987	Diclofenac 75 mg BID N=1996	Ibuprofen 800 mg TID N=1985
<b>Lab Abnormalities</b>			
BUN increased	45 (1.1%)	34 (1.7%)	18 (0.9%)
Hypokalemia	15 (0.4%)	10 (0.5%)	23 (1.2%)
Hyperkalemia	4 (0.1%)	4 (0.2%)	1 (<0.1%)
Hyponatremia	12 (0.3%)	4 (0.2%)	4 (0.2%)
Hypochloremia	6 (0.2%)	1 (<0.1%)	0 (0%)
Hyperchloremia	1 (<0.1%)	0 (0%)	0 (0%)
Hypophosphatemia	0 (0%)	1 (<0.1%)	2 (0.1%)
Acidosis	0 (0%)	0 (0%)	0 (0%) <sup>b</sup>
Alkalosis	2 (<0.1%)	1 (<0.1%)	2 (0.1%)
Albuminuria	4 (0.1%)	0 (0%)	3 (0.2%)
Hematuria	12 (0.3%)	5 (0.3%)	6 (0.3%)
<b>Clinical Adverse Events</b>			
Pathologic Fracture	5 (0.1%)	1 (<0.1%)	7 (0.4%)
Accidental Fracture	52 (1.3%)	17 (0.9%)	32 (1.6%)
Renal Calculus	21 (0.5%)	3 (0.2%)	6 (0.3%)
Uremia	1 (<0.1%)	0 (0%)	1 (<0.1%)
Renal Failure, Acute	0 (0%)	1 (<0.1%)	0 (0%)

a. Data from electronic submission, NDA 20-998 supplement S-009, Table T41.1.

b. Not reported by investigators for any patient.

**2.1c Reported Renal and Cardiac Adverse Events (cont)**

The next table summarizes selected adverse events according to the use of ASA. The rate of abnormal BUN was higher in all three treatment groups among patients who received ASA in combination with the NSAID/COX-2 Inhibitor. Other adverse events where the reported rate was >0.1% and >2X higher in the celecoxib group are shaded in the table below. Hyperkalemia as an AE was highest in the celecoxib group, regardless of the use of ASA.

**Table 2.1c.2 Selected Renal Adverse Events Reported During CLASS According to ASA Use <sup>a</sup>.**

Adverse Event	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
<b>ASA-Users</b>	<b>N=882</b>	<b>N=445</b>	<b>N=412</b>
<b>Lab Abnormalities</b>			
<b>BUN increased</b>	19 (2.2%)	14 (3.1%)	15 (1.2%)
Hypokalemia	2 (0.2%)	2 (0.4%)	3 (0.7%)
<b>Hyperkalemia</b>	9 (0.3%)	1 (0.2%)	0 (0%)
Hyponatremia	3 (0.3%)	2 (0.4%)	1 (0.2%)
Hypochloremia	0 (0%)	0 (0%)	0 (0%)
Hyperchloremia	0 (0%)	0 (0%)	0 (0%)
Hypophosphatemia	0 (0%)	0 (0%)	1 (0.2%)
Albuminuria	1 (0.1%)	0 (0%)	0 (0%)
Hematuria	4 (0.5%)	2 (0.4%)	2 (0.5%)
<b>Clinical Adverse Events</b>			
Pathologic fracture	0 (0%)	1 (0.2%)	2 (0.5%)
Accidental Fracture	15 (1.7%)	4 (0.9%)	7 (1.7%)
Renal Calculus	3 (0.3%)	0 (0%)	2 (0.5%)
Renal Failure, Acute	0 (0%)	0 (0%)	0 (0%)
Uremia	0 (0%)	0 (0%)	1 (0.2%)
<b>Non-ASA Users</b>	<b>N=3105</b>	<b>N=1551</b>	<b>N=1573</b>
<b>Laboratory Abnormalities</b>			
<b>BUN increased</b>	26 (0.8%)	20 (1.3%)	13 (0.8%)
Hypokalemia	13 (0.4%)	8 (0.5%)	20 (1.3%)
<b>Hyperkalemia</b>	11 (0.4%)	3 (0.2%)	1 (<0.1%)
Hyponatremia	9 (0.3%)	2 (0.1%)	3 (0.2%)
<b>Hypochloremia</b>	6 (0.2%)	1 (<0.1%)	0 (0%)
Hyperchloremia	1 (<0.1%)	0 (0%)	0 (0%)
Hypophosphatemia	1 (<0.1%)	0 (0%)	0 (0%)
Albuminuria	3 (<0.1%)	0 (0%)	0 (0%)
Hematuria	8 (0.3%)	3 (0.2%)	4 (0.3%)
<b>Clinical Adverse Events</b>			
Pathologic fracture	5 (0.2%)	0 (0%)	5 (0.3%)
Accidental Fracture	37 (1.2%)	13 (0.8%)	25 (1.6%)
<b>Renal Calculus</b>	18 (0.6%)	3 (0.2%)	4 (0.3%)
Renal Failure, Acute	2 (<0.1%)	0 (0%)	1 (<0.1%)
Uremia	1 (<0.1%)	0 (0%)	0 (0%)

a. Data from electronic submission, NDA 20-998 supplement S-009, Table T41.2 and T41.3.

### 2.1c Reported Renal and Cardiac Adverse Events (cont)

The next table summarizes the reported rates of cardiac events of interest. None of the adverse events occurred at rates clearly higher in the celecoxib group when compared with the other two active treatments, although the rate of combined "Combined Anginal AEs" was highest in the celecoxib group. Edema was more commonly reported as an AE in the ibuprofen group, while the rates for celecoxib and diclofenac were similar.

**Table 2.1c.3 Cardiac Adverse Events Reported During CLASS<sup>a</sup>**

Adverse Events (AEs)	Celecoxib 400 mg BID n=3987	Diclofenac 75 mg BID n=1996	Ibuprofen 800 mg TID n=1985
<b>Edema</b>			
Edema peripheral	146 (3.7%)	70 (3.5%)	104 (5.2%)
Edema (pooled reporting) <sup>b</sup>	165 (4.1%)	82 (4.1%)	124 (6.2%)
Cardiac Failure	12 (0.3%)	3 (0.2%)	9 (0.5%)
<b>Atrial Arrhythmias</b>			
Arrhythmia Atrial	3 (<0.1%)	0 (0%)	1 (<0.1%)
Bradycardia	3 (<0.1%)	0 (0%)	1 (<0.1%)
Fibrillation Atrial	17 (0.4%)	4 (0.2%)	6 (0.3%)
Tachycardia Supraventricular	3 (<0.1%)	0 (0%)	1 (<0.1%)
<b>Angina</b>			
Unstable Angina	10 (0.3%)	4 (0.2%)	2 (0.1%)
Angina Pectoris	22 (0.6%)	10 (0.5%)	12 (0.6%)
Coronary Artery Disorder	25 (0.6%)	7 (0.4%)	6 (0.3%)
<b>Combined Anginal AEs<sup>c</sup></b>	<b>57 (1.4%)</b>	<b>21 (1.0%)</b>	<b>20 (1.0%)</b>
Myocardial Ischemia	2 (<0.1%)	2 (0.1%)	0 (0%)
Myocardial Infarction	19 (0.5%)	5 (0.3%)	9 (0.5%)
Palpitations	23 (0.6%)	7 (0.4%)	8 (0.4%)
Syncope	14 (0.4%)	11 (0.6%)	7 (0.4%)
<b>Thrombophlebitis</b>			
Thrombophlebitis, Deep	12 (0.3%)	5 (0.3%)	1 (<0.1%)
Thrombophlebitis, Combined <sup>d</sup>	17 (0.43%)	8 (0.40%)	5 (0.25%)
Vasculitis	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)
Hypertension	78 (2.0%)	40 (2.0%)	61 (3.1%)
Hypertension Aggravated	32 (0.8%)	12 (0.6%)	24 (1.2%)

a. Data from electronic submission, NDA 20-998 supplement S-009, Table T41.1.

b. Includes edema, edema generalized, and edema peripheral.

c. Includes unstable angina, angina pectoris and coronary artery disorder.

d. Includes AEs reported under the following terms: phlebitis, thrombophlebitis, thrombophlebitis arm, thrombophlebitis deep, thrombophlebitis leg, thrombophlebitis leg deep, thrombophlebitis leg superficial.

### 2.1c Reported Renal and Cardiac Adverse Events (cont)

The next table summarizes selected cardiac adverse events according to the use of ASA. As expected, the patients taking ASA had a higher incidence of cardiac ischemic events in all three groups (they could be receiving ASA following a cardiac event like an MI). The combined rate of anginal disorders was numerically higher in the celecoxib treatment group for both ASA-using and non-ASA-using patients, compared with diclofenac and ibuprofen. In the patients not receiving ASA, the rate of Myocardial Infarction was also highest in the celecoxib group (0.2%) compared with the other two drugs (0.1%). Patients taking celecoxib but not ASA also had a greater than 2X greater incidence of atrial fibrillation than patients taking the comparator drugs. Of interest, patients who took ASA did not have an increased rate of hypertension or edema reported.

Table 2.1c.4 Selected Cardiac Adverse Events Reported During CLASS According to ASA Use <sup>a</sup>.

Adverse Events (AEs)	Celecoxib	Diclofenac	Ibuprofen
<b>ASA-Users</b>	<b>N=882</b>	<b>N=445</b>	<b>N=412</b>
<b>Edema</b>			
Edema peripheral	35 (4.0%)	17 (3.8%)	23 (5.6%)
Edema (pooled reporting) <sup>b</sup>	38 (4.3%)	20 (4.5%)	28 (6.8%)
<b>Atrial Arrhythmias</b>			
Arrhythmia Atrial	3 (0.3%)	0 (0%)	1 (0.2%)
Fibrillation Atrial	8 (0.9%)	2 (0.4%)	4 (1.0%)
Tachycardia Supraventricular	1 (0.1%)	0 (0%)	0 (0%)
<b>Angina</b>			
Unstable Angina	8 (0.9%)	4 (0.9%)	1 (0.2%)
Angina Pectoris	13 (1.5%)	8 (1.8%)	6 (1.5%)
Coronary Artery Disorder	15 (1.7%)	3 (0.7%)	5 (1.2%)
Combined Anginal AEs <sup>c</sup>	36 (4.1%)	15 (3.4%)	12 (2.9%)
Myocardial Ischemia	1 (0.1%)	2 (0.4%)	0 (0%)
Myocardial Infarction	13 (1.5%)	3 (0.7%)	7 (1.7%)
Hypertension	24 (2.7%)	14 (3.1%)	19 (4.6%)
Hypertension Aggravated	12 (1.4%)	2 (0.4%)	7 (1.7%)
<b>Thrombophlebitis</b>			
Thrombophlebitis, Deep	3 (0.2%)	2 (0.4%)	1 (0.2%)
Thrombophlebitis, Combined <sup>d</sup>	3 (0.2%)	3 (0.4%)	1 (0.2%)
Vasculitis	1 (0.1%)	0 (0%)	0 (0%)
<b>Non-ASA Users</b>	<b>N=3105</b>	<b>N=1551</b>	<b>N=1573</b>
Edema peripheral	111 (3.6%)	53 (3.4%)	81 (5.1%)
Edema (pooled reporting) <sup>b</sup>	127 (4.1%)	61 (3.9%)	96 (6.1%)
<b>Atrial Arrhythmias</b>			
Arrhythmia Atrial	0 (0%)	0 (0%)	0 (0%)
Bradycardia	3 (<0.1%)	0 (0%)	1 (<0.2%)
Fibrillation Atrial	9 (0.3%)	2 (0.1%)	2 (0.1%)
Tachycardia Supraventricular	2 (<0.1%)	0 (0%)	1 (0.1%)
<b>Angina</b>			
Unstable Angina	2 (<0.1%)	0 (0%)	1 (<0.1%)
Angina Pectoris	9 (0.3%)	2 (0.1%)	6 (0.4%)
Coronary Artery Disorder	10 (0.3%)	4 (0.3%)	1 (<0.1%)
Combined Anginal Disorders <sup>c</sup>	21 (0.7%)	6 (0.4%)	8 (0.5%)
Myocardial Ischemia	1 (<0.1%)	0 (0%)	0 (0%)
Myocardial Infarction	6 (0.2%)	2 (0.1%)	2 (0.1%)
Hypertension	54 (1.7%)	26 (1.7%)	42 (2.7%)
Hypertension Aggravated	20 (0.6%)	10 (0.6%)	17 (1.1%)
<b>Thrombophlebitis</b>			
Thrombophlebitis, Deep	9 (0.3%)	3 (0.2%)	0 (0%)
Thrombophlebitis, Combined <sup>d</sup>	14 (0.45%)	5 (0.3%)	4 (0.25%)
Vasculitis	1 (<0.1%)	0 (0%)	1 (<0.1%)

a. Data from electronic submission, NDA 20-998 supplement S-009, Table T41.1.

b. Includes edema, edema generalized, and edema peripheral.

c. Includes unstable angina, angina pectoris and coronary artery disorder.

d. Includes AEs reported under the following terms: phlebitis, thrombophlebitis, thrombophlebitis arm, thrombophlebitis deep, thrombophlebitis leg, thrombophlebitis leg deep, thrombophlebitis leg superficial.

### 2.1d Cardiac and Renal Adverse Events Causing Discontinuation

Selected renal and cardiac adverse events leading to discontinuation are summarized below. Discontinuations for these events were rare and occurred equally in the three treatment groups. Of note, discontinuations for thrombotic cardiac events were not significantly different in the three groups.

Table 2.1d.1 Renal and Cardiac Adverse Events Leading to Discontinuation During CLASS <sup>a</sup>.

Adverse Event	Celecoxib 400 mg BID n=3987	Diclofenac 75 mg BID n=1996	Ibuprofen 800 mg TID n=1985
<b>Renal</b>			
Hypertension	10 (0.3%)	3 (0.2%)	5 (0.3%)
Edema, peripheral	21 (0.5%)	6 (0.3%)	15 (0.8%)
BUN Increased	13 (0.3%)	10 (0.5%)	3 (0.2%)
Uremia	1 (<0.1%)	0 (0%)	0 (0%)
Acute Renal Failure	0 (0%)	1 (<0.1%)	0 (0%)
<b>Cardiac</b>			
Cardiac failure	4 (0.1%)	1 (<0.1%)	5 (0.3%)
Myocardial Infarction	9 (0.2%)	2 (0.1%)	7 (0.4%)
Cardiac Arrest	1 (<0.1%)	4 (0.2%)	1 (<0.1%)
Combined Anginal Disorders <sup>b</sup>	12 (0.3%)	5 (0.3%)	5 (0.3%)
Combined Thrombophlebitis <sup>c</sup>	6 (0.2%)	3 (0.2%)	2 (0.1%)

a. Data from electronic submission, NDA 20-998 supplement S-009, Table T42.1.

b. Includes unstable angina, angina pectoris and coronary artery disorder.

c. Includes AEs reported under the following terms: phlebitis, thrombophlebitis, thrombophlebitis arm, thrombophlebitis deep, thrombophlebitis leg, thrombophlebitis leg deep, thrombophlebitis leg superficial.

There were no reported withdrawals for acidosis or reduced serum bicarbonate.

### 2.1e Changes in Laboratory Parameters and Special Measurements

The sponsor routinely collected laboratory and blood pressure data during the trial, as summarized in section 2.0b above. The first section below relates to the changes in laboratory measures during the trial. These changes can be analyzed in several different ways, falling into two general groups: analysis of mean changes and analysis of extreme individual changes. The first part will be concerned with the mean changes.

#### Mean Changes from Baseline

##### 1. Changes in blood Urea Nitrogen (BUN) and Serum Creatinine (SCr)

No clinically relevant differences between the three treatment groups were seen at any time point for the changes in mean BUN or SCr. The reported differences, some of which achieved nominal statistical significance, were quite small and not clinically-relevant. For example, at 26 weeks the increase in mean SCr was 2.1 for celecoxib and 4.2 U/L ( $p < 0.001$  per sponsor). This difference or 2.1 U/L is the same as a difference of 0.02 mg/dl (see Table 44.1 in electronic submission for details).

This conclusion was not altered when the populations that took ASA or not were examined separately (data not shown).

##### 2. Changes in potassium, phosphate, bicarbonate, chloride

Similar to the changes observed for BUN and Cr, while there were numerical differences that achieved nominal statistical significance, none of them were of clinical significance (see table T44.1 for details).

This conclusion was not altered when the populations that took ASA or not were examined separately.

## 2.1c Changes in Laboratory Parameters and Special Measurements (cont)

### Extreme Changes from Baseline

The table below summarizes the incidence of extreme laboratory values at any time during the course of the study after the baseline values for the three study groups. These analyses are derived from patients with a normal lab values at baseline. While there are differences between the study groups for individual measurements, overall the lab extremes occurred at more or less similar rates in the three treatments groups. Examples of this variability include:

1. Increases in serum K<sup>+</sup> occurred more frequently in patients taking celecoxib. This finding reinforces the observed increased rate of clinical adverse events associated with celecoxib use (see table 2.1.c.1 above).
2. Decreased serum HCO<sub>3</sub> occurred more frequently in patients taking ibuprofen.
3. Increased serum creatinine (to ≥1.5 mg/dl) occurred more frequently in both ibuprofen and diclofenac, when compared with celecoxib. Additional analyses related to changes in serum creatinine appear below.

Table 2.1e.1 Extreme Laboratory Values from Entire Study Period in CLASS<sup>a</sup>

Lab Test	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
<b>BUN (mmol/l)</b>			
>7.1 <sup>d</sup>	1281/3141 (40.8%)	549/1552 (35.4%)*	513/1539 (33.3%)
>14.3 <sup>d</sup>	31/3692 (0.8%)	20/1849 (1.1%)	16/1786 (0.9%)
<b>Creatinine (mmol/l)</b>			
>133 <sup>c</sup>	47/2684 (1.1%)	37/1848 (2.0%)*	30/1786 (1.7%)*
>265.2 <sup>c</sup>	1/3692 (<0.1%)	0/1850 (0%)	0/1786 (0%)
<b>Potassium (meq/l)</b>			
<3.5	89/3670 (2.4%)	46/1836 (2.5%)	116/1766 (6.6%)*
<3.0	7/3673 (0.2%)	7/1837 (0.4%)	11/1770 (0.6%)*
>5.0	406/3657 (11.1%)	182/1825 (10.0%)*	119/1758 (6.8%)*
>6.0	11/3673 (0.3%)	3/1837 (0.2%)*	0/1770 (0%)*
<b>Chloride (mmol/l)</b>			
<75	0/3690 (0%)	0/1847 (0%)	0/1786 (0%)
<90	7/3690 (0.2%)	1/1847 (<0.1%)	4/1786 (0.2%)
>110	86/3690 (2.3%)	28/1847 (1.5%)*	51/1785 (2.9%)
>120	0/3690 (0%)	0/1847 (0%)	0/1786 (0%)
<b>Bicarbonate (mmol/l)</b>			
<20	44/3687 (1.2%)	22/1844 (1.2%)	34/1782 (1.9%)*
<15	1/3689 (<0.1%)	2/1844 (0.1%)	0/1782 (0%)
>35	13/3689 (0.4%)	7/1844 (0.4%)	1/1782 (0.2%)
<b>Phosphate (mmol/l)</b>			
<0.32	0/3676 (0%)	0/1841 (0%)	0/1771 (0%)
<0.64	19/3676 (0.5%)	16/1841 (0.9%)	15/1771 (0.8%)
<0.96	791/3572 (22.1%)	471/1775 (26.5%)*	399/1705 (23.3%)
>2.10	0/3676 (0%)	1/1841 (<0.1%)	1/1771 (<0.1%)
>2.42	0/3676 (0%)	0/1841 (0%)	1/1771 (<0.1%)

a. Data from electronic submission table T45.1 and at request of reviewer.

b. \* values differ from celecoxib at p<0.05 per sponsor.

c. Corresponds to a serum creatinine of 1.5 and 3.0 mg/dl respectively.

d. Corresponds to a BUN of 20 and 40 mg/dl respectively.

These analyses were done according to the use of ASA and, for the most part, mirror the combined analysis. Of interest, the incidence of hyperkalemia (>5.0 meq/dl) and the incidence of elevated BUN (>20 and >40 mg/dl) were higher in all three groups when concomitant ASA was used. Hypokalemia was more common in the group who did not receive ASA.

2.1c Changes in Laboratory Parameters and Special Measurements (cont)

Table 2.1e.2 Extreme Laboratory Values from Entire CLASS Study Period By ASA Use <sup>a</sup>.

Lab Test	Celecoxib 400 mg BID		Diclofenac 75 mg BID		Ibuprofen 800 mg TID	
	ASA	NoASA	ASA	NoASA	ASA	NoASA
<b>BUN (mmol/l)</b>						
>7.1 <sup>d</sup>	280658 (4.6%)	10012483 (40.3%)	117322 (36.3%)	4321230 (35.1%) <sup>a,b</sup>	115312 (36.9%)	3981227 (32.4%) <sup>a</sup>
>14.3 <sup>d</sup>	12829 (1.4%)	02863 (0%)	9421 (2.1%)	01428 (0%)	5386 (1.3%)	01400 (0%)
<b>Creatinine (mmol/l)</b>						
>133 <sup>c</sup>	9826 (1.1%)	322858 (1.1%)	14421 (3.3%) <sup>a</sup>	231427 (1.6%)	10386 (2.6%)	201400 (1.4%)
>265.2 <sup>c</sup>	1829 (0.1%)	02864 (0%)	0422 (0%)	01428 (0%)	0386 (0%)	01400 (0%)
<b>Potassium (meq/l)</b>						
<3.5	10824 (12%)	792846 (2.8%)	9419 (2.2%)	371417 (2.9%)	20383 (5.2%) <sup>a</sup>	961383 (6.9%) <sup>a</sup>
<3.0	0824 (0%)	72849 (0.2%)	1420 (0.2%)	61417 (0.4%)	3383 (0.8%)	81387 (0.6%)
>5.0	95820 (11.6%)	3112837 (11.0%)	56416 (13.5%)	1261409 (8.9%) <sup>a</sup>	40383 (10.4%)	791375 (5.7%) <sup>a</sup>
>6.0	0824 (0%)	112849 (0.4%)	1420 (0.2%)	21417 (0.1%)	0383 (0%)	01387 (0%)
<b>Chloride (mmol/l)</b>						
<75	0829 (0%)	02861 (0%)	0422 (0%)	01425 (0%)	0386 (0%)	01400 (0%)
<90	0829 (0%)	72861 (0.2%)	0422 (0%)	11425 (<0.1%)	1386 (0.3%)	31400 (0.3%)
>110	25829 (3.0%)	612361 (2.1%)	6422 (1.4%)	221425 (1.5%)	14385 (3.6%)	371400 (2.6%)
>120	0829 (0%)	02861 (0%)	0422 (0%)	01425 (0%)	0386 (0%)	01400 (0%)
<b>Bicarbonate (mmol/l)</b>						
<20	8829 (1.0%)	362858 (1.3%)	4421 (1.0%)	181423 (1.3%)	10385 (2.6%) <sup>a</sup>	241397 (1.7%)
<15	0829 (0%)	12860 (<0.1%)	1421 (0.2%)	11423 (<0.1%)	0385 (0%)	01397 (0%)
>35	5829 (0.6%)	82860 (0.3%)	1421 (0.2%)	61423 (0.4%)	0385 (0%)	31397 (0.2%)
<b>Phosphate (mmol/l)</b>						
<0.32	0824 (0%)	02852 (0%)	0421 (0%)	01420 (0%)	0383 (0%)	01388 (0%)
<0.64	3824 (0.4%)	162852 (0.6%)	4421 (1.0%)	121420 (0.8%)	2383 (0.5%)	131388 (0.9%)
<0.96	171796 (21.5%)	6202776 (22.3%)	102407 (25.1%)	3691368 (27.0%) <sup>a</sup>	80367 (21.8%)	3191342 (23.8%)
>2.10	0824 (0%)	02852 (0%)	0421 (0%)	11420 (<0.1%)	0383 (0%)	11388 (<0.1%)
>2.42	0824 (0%)	02852 (0%)	0421 (0%)	01420 (0%)	0383 (0%)	11388 (<0.1%)

- a. Data from electronic submission appendix 2.11.2.1 and 2.11.2.2 and at request of reviewer. Shown are maximum values from any time during trial relative to baseline.
- b. \* values differ from celecoxib at p<0.05 per sponsor.
- c. Corresponds to a serum creatinine of 1.5 and 3.0 mg/dl respectively.
- d. Corresponds to a BUN of 20 and 40 mg/dl respectively.

Because of the important interaction between changes in BUN and serum creatinine (SCr) the incidence of the development of combined abnormalities of these two lab measurements in patients with normal BUN and creatinine at baseline was examined (shown below). In this analysis, celecoxib use was not associated with an increased rate of renal injury.

Table 2.1e.3 Incidence of Combined Abnormalities in BUN and SCr in CLASS <sup>a,b</sup>.

Parameter	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
BUN ≥14.3 mmol/l and SCr ≥159 mmol/l <sup>c</sup>	4 (0.1%)	1 (<0.1%)	5 (0.3%)
BUN >7.1 and SCr >133 mmol/l <sup>d</sup>	150/3702 (1.4%)	43/1852 (2.3%)	32/1807 (1.8%) <sup>a</sup>

- a. Data from electronic datasets table T48 and at request of reviewer from sponsor. Patients with normal renal function at baseline.
- b. SCr = serum creatinine.
- c. Corresponds to a BUN/Cr of 40/3.0 mg/dl.
- d. Corresponds to a BUN/Cr of 20/1.5 mg/dl.

### 2.1c Changes in Laboratory Parameters and Special Measurements (cont)

These same data, grouped according to ASA use, appear below. For mild increases in BUN and SCr, the rate were lowest in the celecoxib group overall, regardless of the use of ASA.

**Table 2.1c.4 Incidence of Combined Abnormalities in BUN and SCr in CLASS Grouped by ASA Use <sup>a, b</sup>**

Parameter	Celecoxib 400 mg BID		Diclofenac 75 mg BID		Ibuprofen 800 mg TID	
	ASA	No ASA	ASA	No ASA	ASA	No ASA
BUN ≥14.3 mmol/l and SCr ≥159 mmol/l <sup>c</sup>	5/834 (0.6%)	9/2868 (0.3%)	1/423 (0.2%)	5/1429 (0.4%)	3/390 (0.8%)	4/1417 (0.3%)
BUN > 7.1 and SCr > 133 mmol/l <sup>d</sup>	12/834 (1.4%)	38/2868 (1.3%)	17/423 (4.0%)	26/1429 (1.8%)	11/390 (2.8%)	21/1417 (1.5%)

a. Data at request of reviewer from sponsor. Based on patients with normal renal function at baseline.

b. SCr – serum creatinine.

c. Corresponds to a BUN/Cr of 40/3.0 mg/dl.

d. Corresponds to a BUN/Cr of 20/1.5 mg/dl.

### 2.1f Changes in Blood Pressure

In the original NDA submission database, celecoxib use was associated with increased hypertension when compared with placebo (as commonly seen for NSAIDs). The sponsor analyzed the changes in blood pressure (BP) recorded for those subjects in CLASS with both baseline and at least one follow-up BP reading. The changes in the mean BP for the three treatment groups hovered around 0 for the trial and were of little clinical significance. The incidence of abnormal elevations in BP is summarized below. No clinically-significant differences between the treatment groups were apparent. Similar findings were seen when the patients were grouped according to ASA use (not shown).

**Table 2.1f.1 Incidence of BP Elevations During CLASS <sup>a</sup>.**

Parameter	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID
Sitting Systolic BP ≥15% Increase over baseline at final visit			
All Patients	315/2925 (10.8%)	163/1434 (11.4%)	173/1387 (12.5%)
ASA Users	87/653 (12.6%)	38/327 (11.6%)	39/287 (13.6%)
Non-ASA Users	233/2272 (10.3%)	125/1107 (11.3%)	134/1100 (12.2%)
Sitting Diastolic BP ≥15% Increase over baseline at final visit			
All Patients	298/2925 (10.2%)	146/1434 (10.2%)	134/1387 (9.7%)
ASA Users	70/63 (10.7%)	33/327 (10.1%)	30/287 (10.5%)
Non-ASA Users	228/2272 (10.0%)	113/1107 (10.2%)	104/1100 (9.5%)

a. Data from electronic submission Table T54 and from sponsor at reviewer's request.

### 3.0 SUMMARY

The Celecoxib Long-Term Arthritis Safety Study (CLASS) compared the effects of three anti-inflammatory drugs in a population of patients with osteoarthritis: celecoxib, diclofenac, and ibuprofen. The majority of patients did not receive aspirin (ASA), although around 20% of the patients received ASA and were available for separate analysis. The aspects of the safety database from CLASS to be commented on in this consultation are focused on the comparative renal and cardiac effects of celecoxib, diclofenac and ibuprofen.

#### 3.1 Comparative Effects of Celecoxib, Diclofenac and Ibuprofen on Acid-Base Balance

In the original celecoxib NDA database, serum bicarbonate ( $\text{HCO}_3^-$ ) levels were not measured. In the NDA there was an association between celecoxib use and an increase in serum chloride, which can be interpreted as related to fall in serum  $\text{HCO}_3^-$ . To address if celecoxib affected acid-base balance, the sponsor measured changes in serum  $\text{HCO}_3^-$  in CLASS and collected adverse events related to changes in systemic acid-base balance. The data above support the following conclusions:

1) Between 1 and 2% of the subjects in all three treatment groups had a measured  $\text{HCO}_3^- < 20$  meq/dl during the study after starting with a normal baseline  $> 25$  mg/dl. The rate for celecoxib, however, was the same as for diclofenac and less than celecoxib (Table 2.1e.1).

2) There was no increase in reported clinical adverse events related to changes in acid-base balance in the celecoxib group: such adverse events were quite rare in the database for all three drugs (Tables 2.1b.1 and 2.1c.1).

3) Finally, bony fractures, as a marker for chronic metabolic acidosis, occurred at equal rates in the three treatment groups (Tables 2.1c.1 and 2.1c.2).

#### Conclusion Regarding Acid-Base Balance

Overall, then, celecoxib, diclofenac and ibuprofen use are uncommonly associated with changes in acid-base balance. Such effects may be mediated by the inhibition of COX-1 and COX-2 known to be expressed in the kidney. In CLASS celecoxib, diclofenac and ibuprofen had similar overall effects on acid-base balance.

#### 3.2 Comparative Incidence of Renal Adverse Effects for Celecoxib, Diclofenac and Ibuprofen

The use of NSAIDs has been associated with several severe forms of renal injury including Nephrotic Syndrome and acute renal failure leading to uremia. In addition, NSAID use has been associated with asymptomatic increases in serum creatinine and BUN (see references at end of consult for details). There is uncertainty about the exact incidence of these changes following long-term NSAID use, with estimates ranging from 1:100 to  $< 1:1000$ . Less severe renal injury was assessed in two ways in CLASS: clinical events reported as adverse events and changes in serum markers of renal injury (BUN/ creatinine) from routine blood draws performed during the trial. The data from CLASS support the following conclusions regarding the occurrence of renal adverse events in the population studied:

#### Renal Serious Adverse Events

1) The rate of severe renal injury during therapy with celecoxib, diclofenac or ibuprofen was very low, with no reported cases of Nephrotic Syndrome or life-threatening hyperkalemia, and one case of uremia (table 2.1b.1).

#### Renal Adverse Events

2) Less severe clinical renal adverse events were reported in a small percentage of the population (table 2.1c.1).

3) Hyperkalemia was more commonly reported as an adverse event in the patients receiving celecoxib, while hypokalemia was more commonly reported in the patients receiving NSAIDs (table 2.1c.1).

4) BUN increase was more commonly reported as an adverse event in the diclofenac group (table 2.1c.1).

5) Edema as an adverse event was reported in 3-5 % of the population, and was reported with equal frequency in the celecoxib and ibuprofen treatment groups (3-4%). A higher incidence of edema was reported in the ibuprofen group (5-6%) (table 2.1c.3).

### 3.2 Comparative Incidence of Renal Adverse Effects for Celecoxib, Diclofenac and Ibuprofen (cont)

#### Renal Adverse Events (cont)

6) Hypertension as an adverse event was reported less in the celecoxib group (2.7%) than in the diclofenac (3.1%) or ibuprofen (4.6%) groups (table 2.1c.4). Changes in Blood Pressure (BP) were analyzed for those subjects with more than one reading during the trial (section 2.1f). The incidence of significant increases in systolic or diastolic BP above baseline were relatively common (10-15%), but occurred equally in all three treatment groups (table 2.1f.1).

7) As urinalyses were not routinely collected no conclusions can be reached about the comparative effects of the three drugs on urinary protein. Hematuria was reported uncommonly in all three treatment groups (table 2.1c.1).

#### Laboratory Adverse Events

8) Small changes in mean chemistries were reported that are of little clinical significance (section 2.1e).

9) Large individual changes from baseline were uncommon in all three treatment groups, making it difficult to attribute observed differences to individual drug effects (table 2.1c.1).

10) Increases in serum potassium to  $>5.0$  and  $>6.0$  meq/l occurred more frequently in patients receiving celecoxib than for either diclofenac or ibuprofen. The difference between the rate of  $K^+ >5.0$  for celecoxib (11.1%) and ibuprofen (6.8%) achieved nominal statistical significance (table 2.1e.1).

11) Increases in BUN to  $>20$  mg/dl were more common in the celecoxib group (40.8%) than in the diclofenac (35.4%) or ibuprofen (33.3%) groups. However, the rate of increased serum creatinine to  $>1.5$  mg/dl was higher in the diclofenac group (2.0%) when compared with celecoxib (1.1%). The latter difference achieved nominal statistical significance.

12) The incidence of combined abnormalities in BUN and creatinine was also analyzed. The rates for these combined endpoints, starting from a normal baseline, were lowest in the celecoxib group, regardless of the concomitant use of ASA (tables 2.1e.3 and 2.1e.4). For example, the percentage of patients with a BUN  $>20$  mg/dl and creatinine  $>1.5$  mg/dl was lowest in the celecoxib group (1.4%) when compared with ibuprofen (1.8%) or diclofenac (2.3%).

#### Effect of ASA Use on Renal Adverse Events

Given that use of ASA in this population would indicate a higher level of pre-existing cardiovascular disease, interpretation of adverse events according to the use of ASA is difficult. The following differences were seen in the CLASS database analysis according to the use of ASA:

13) Increases in BUN were reported more commonly (approximately 3X more common) in the group treated with ASA and any one of the three NSAIDs (table 2.1c.2).

14) Too few severe clinical renal events (renal failure, uremia, nephrotic syndrome) occurred for analysis. Hypertension was more commonly reported as an adverse event in patients taking ASA (table 2.1c.4).

15) For adverse events related to laboratory measurements, decreases in serum phosphate and increases in serum potassium, BUN or creatinine were more commonly seen in patients who took ASA along with one of the three NSAIDs (table 2.1e.2). In particular, the increased incidence of serum  $K^+ >5.0$  and BUN  $>20$  mg/dl in patients taking ASA achieved nominal statistical significance.

16) For adverse events related to laboratory measurements, decreases in serum potassium occurred more commonly in patients not taking ASA (table 2.1e.2).

17) The incidence of combined abnormalities in BUN and creatinine was analyzed. The rates for these combined endpoints were lowest in the celecoxib group, regardless of the concomitant use of ASA (tables 2.1e.3 and 2.1e.4).

### 3.2 Comparative Incidence of Renal Adverse Effects for Celecoxib, Diclofenac and Ibuprofen (cont)

#### Conclusion Regarding Renal Effects of Celecoxib, Diclofenac and Ibuprofen

Serious renal adverse event linked to the three NSAIDs used in the study were rare (occurring at less than 1:1000 patient-years of exposure). For the less severe renal adverse effects, no clear differences were seen between celecoxib and the two NSAIDs, although there were differences between celecoxib and one of the NSAIDs for some adverse events. In particular, worsened hypertension and worsened edema were not clearly less frequent with celecoxib when compared with both diclofenac and ibuprofen. There was a tendency for more hyperkalemia in patients treated with celecoxib compared with both NSAIDs, but this effect occurred in a small fraction of the patients and was not associated with an increased rate of severe hyperkalemia. Additionally, worsened hypertension appeared to be more common in patients who took ASA. There was also a trend towards fewer combined increases in serum creatinine and BUN in the celecoxib group, but the clinical significance of this difference is not clear. In the CLASS study, the pattern of renal adverse events for celecoxib was not distinguished from that of NSAIDs (as typified by diclofenac and ibuprofen).

### 3.3 Comparative Incidence of Cardiac Adverse Effects for Celecoxib, Diclofenac and Ibuprofen

NSAIDs have been reported to have a variety of cardiovascular effects, including worsening hypertension and edema (see above). Recently, particular concern has been raised regarding a possible pro-thrombotic effect of selective inhibition of COX-2 (for example, by celecoxib). The data from the CLASS trial support the following conclusions about the cardiac effects of celecoxib, diclofenac and ibuprofen:

#### Cardiac Serious Adverse Events and Mortality

1) While the long-term data from the original celecoxib NDA suggested a dose-dependent effect on cardiac mortality (table 2.1a.1), the rates for total and cardiovascular mortality were similar in the CLASS trial celecoxib, diclofenac and ibuprofen (table 2.1a.2). This conclusion was not altered when the patients were divided according to their use of ASA (table 2.1a.3).

2) Reported serious adverse events (SAEs) were infrequent to rare in the CLASS trial (table 2.1b.1). The rate of "Combined Anginal AEs", was higher in the celecoxib group when compared with diclofenac or ibuprofen. This pattern was independent of the concomitant use of ASA (table 2.1b.2). For myocardial infarctions, there were 32 events reported as SAEs in the trial population as a whole, and the rates were 0.8%, 0.4% and 0.8% for celecoxib, diclofenac and ibuprofen respectively.

3) Reported SAEs for "Combined Atrial Arrhythmias" were infrequent, but occurred most frequently in the celecoxib group (0.6%) than in the diclofenac (0.2%) or ibuprofen (0.4%) groups (table 2.1b.1). For patients not taking ASA, incidence for these same groups was 1.7%, 0.1% and 0% respectively (table 2.1b.2).

#### Cardiac Adverse Events

4) Ischemic cardiac events were reported in <1% of the population of CLASS. For the "Combined Anginal AEs" the rate for the celecoxib group (1.4%) was higher than the diclofenac or ibuprofen groups (1.0%). Myocardial infarctions were reported as adverse events in 33 patients in total (out of 7968 patients enrolled): 19 (0.5%) with celecoxib, 5 (0.3%) with diclofenac, and 9 (0.5%) with ibuprofen (table 2.1c.3).

5) Atrial arrhythmias reported as AEs occurred more frequently in the celecoxib group than in either of the comparator drug groups (table 2.1c.3).

6) Heart failure reported as AEs occurred at similar rates in the three treatment groups (0.2 to 0.5%) (table 2.1c.3).

#### Effect of ASA Use on Cardiac Adverse Events

7) When the cardiac deaths were divided according to the use of ASA, the mortality rates for celecoxib, diclofenac and ibuprofen were similar, although each category had few events (table 2.1a.3). For example, among the 13 deaths in patients not taking ASA, the mortality rates for celecoxib, diclofenac and ibuprofen were 0.3%, 0.6%, and 0.2% respectively.

8) For serious adverse events (SAEs), the rate of ischemic cardiac events was highest in the celecoxib group for the "Combined Anginal SAEs," "Combined Atrial SAEs" and "Myocardial Infarctions" (table 2.1b.2).

### 3.3 Comparative Incidence of Cardiac Adverse Effects for Celecoxib, Diclofenac and Ibuprofen

#### Conclusion Regarding Cardiac Effects of Celecoxib, Diclofenac and Ibuprofen

The CLASS trial data do not support a large adverse effect of celecoxib on cardiovascular mortality or on serious adverse events related to thrombosis relative to either diclofenac or ibuprofen. The data do not exclude a less apparent pro-thrombotic effect of celecoxib, such as might be reflected in the relative rates of cardiac adverse events related to ischemia.

The observed differences in the rates of atrial arrhythmias are derived from small numbers of patients and lack supportive evidence from other sources ( e.g., animal models, post-marketing data) and their clinical relevance cannot be determined.

In the CLASS trial, the cardiac adverse event profile for celecoxib was not clearly different from that of NSAIDs (as represented by diclofenac and ibuprofen).

### 4.0 CONCLUSIONS/ RECOMMENDATIONS

The CLASS trial exposed subjects with osteoarthritis and rheumatoid arthritis to one of the three study drugs for varying periods of time, including approximately 2300 patients treated with celecoxib, 1100 patients treated with diclofenac and 1000 patients treated with ibuprofen for  $\geq 6$  months. Two issues are relevant to this consult: the effect of celecoxib on acid-base balance and the relative rates of renal and cardiac adverse events see in the CLASS trial. The data analyzed above support the following conclusions related to these three issues:

1. The CLASS database contains no evidence for an adverse effect of celecoxib on acid-base balance relative to either diclofenac or ibuprofen.

2. The CLASS database does not support a large adverse effect of celecoxib on cardiovascular mortality or on serious adverse events related to thrombosis relative to either diclofenac or ibuprofen. The data do not exclude a less apparent pro-thrombotic effect of celecoxib, reflected in the relative rates of cardiac adverse events related to ischemia. Detecting such an effect would require a much larger database than CLASS.

3. In the CLASS database the cardiac and renal adverse event profiles for celecoxib were not clearly different from that of NSAIDs (as represented by diclofenac and ibuprofen). This includes adverse events reported by investigators ( e.g., worsened hypertension or edema, uremia) and those detected through routine laboratory or blood pressure measurements ( e.g., increased BUN/ Cr<sub>t</sub> or systolic blood pressure).

4. The data suggesting an increased rate of supraventricular arrhythmias in patients taking celecoxib compared to diclofenac and ibuprofen are provocative but require additional investigation.

5. Hyperkalemia, however measured, was consistently more frequent in patients taking celecoxib than for diclofenac or ibuprofen, but these differences were small and not reflected in an increase in serious adverse events related to hyperkalemia.

6. A lack of information about specific use of ASA in CLASS limits the interpretation of analyses done with and without ASA use. No clear clinical effect of concomitant use of ASA with celecoxib, diclofenac or ibuprofen was identified, although worsened hypertension was more somewhat more common when ASA was used by patients taking any of the three drugs.

7. Additional analyses are needed to address the generalizability of the results from CLASS and other large clinical trials using NSAIDs to the use of NSAIDs in the general population.

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