CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-998/S-010

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPTHALMIC DRUG PRODUCTS—HFD-550

sNDA #20,998

Submission date:	
Submission type:	NDA supplement
Received date:	12/19/00
Review date:	
Drug name:	celecoxib
Applicant:	Searle
Pharmacologic category:	analgesic
Proposed indications:	Management of acute pain in adults Treatment of primary dysmenorrhea
Dosage form and route:	oral tablets, 200 mg 200-400 mg/day

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EXECUTIVE SUMMARY

I. Recommendations

The sponsor has demonstrated the efficacy of celecoxib for acute pain. No new risks were identified in this submission. Based on the benefits and risks provided by celecoxib and from a clinical perspective, celecoxib is approvable for the indications of acute pain and dysmenorrhea.

There are no specific phase 4 studies recommended based on this submission.

II. Summary of Clinical Findings

A. Overview of Clinical Program

Celecoxib is an oral non-steroidal anti-inflammatory drug with selective inhibition of cyclooxygenase 2 (Cox-2). This sNDA submission includes 17 trials of which 9 are considered to be pivotal trials. The total number of patients enrolled in the pivotal trials is 1786. The total number of patients exposed to the drug in all reported trials in this sNDA is 3497. The proposed indications for the drug include acute pain and dysmenorrhea.

B. Efficacy

Introduction

In order for a drug to be indicated for the treatment of acute pain, 2 replicated models are needed to demonstrate efficacy. In this submission the sponsor will examine a dental pain model, a post-surgical model, and the model of dysmenorrhea to support the acute pain claim.

Dental pain

Overall, on the basis of onset, magnitude and duration of analgesia, single doses of celecoxib 200 mg or 400 mg exhibited consistent analgesic efficacy versus placebo in the dental (post-oral surgery) pain model. There were 3 pivotal dental pain studies including studies 025, 027, and 070 which examined doses of 100mg, 200 mg, and 400mg (see reviews by M. Averbuch and J. Witter for original submission of this application). These studies demonstrated a significantly greater improvement in pain compared to placebo beginning at 45 minutes to 1 hour post dose and continuing through 7-8 hours post dose for time specific efficacy measures such as pain intensity differences (PID), pain relief (PR), and PRID. Time to rescue medication was significantly longer for celecoxib versus placebo. In study 139, a non-pivotal study for dental pain, time specific pain measures were evaluated out to 24 hours and celecoxib was demonstrated to be significantly better than placebo over this time period. Overall, celecoxib 400mg provided the

shortest onset and longest duration of analgesia to the greatest percentage of patients as well as the greatest magnitude of analgesia, and therefore appeared to be the maximally efficacious dose studied. Doses beyond 400 mg were not evaluated in this submission (although for the treatment of rheumatoid arthritis 400 mg bid was no more efficacious than 200 mg bid; see previous reviews for this indication). It is important to note that the NSAID comparators (ibuprofen 400mg, naproxen sodium 550mg)used in these studies demonstrated a significantly more rapid onset of analgesia and a significantly greater peak response than celecoxib beginning at 30-45 minutes post dose. However, the time to rescue medication was no different.

Dysmenorrhea

Results from the 2 pivotal dysmenorrhea studies 129 and 130, demonstrate that single doses of celecoxib 400 mg were efficacious based on onset, magnitude and duration of analgesia. The clinical primary endpoints included time weighted sum of pain intensity differences through the first 8 hours ($p<.001$) and time weighted sum of pain relief through the first 8 hours ($p<.001$). SPID and TOTPAR are not the Divisions' preferred primary endpoints in acute pain studies. Rather, time to onset of analgesia, time to rescue medication, and time specific measures of efficacy are preferred because they provide a more complete picture of efficacy. In addition, in this case for qd or bid labeling of a drug SPID 8 would not be the most appropriate endpoint.

In these studies measures of pain out to 12 hours were also evaluated and demonstrated a significant difference for celecoxib over placebo. The analgesic efficacy of celecoxib 400 mg was comparable to naproxen sodium 550 mg in magnitude and duration of analgesia in 1 of the 2 studies. In the other study, naproxen was statistically superior to celecoxib.

Post-surgical studies

Results from the post-surgery pain studies (082, 083, 085, 086, 028 considered pivotal by the sponsor; these include orthopedic and general surgery) however, do not support the efficacy of single doses of celecoxib (200 mg was examined) for post-operative pain. Time specific measures of efficacy do not consistently separate from placebo especially at early time points (0-2 hours). Therapies used to treat acute pain preferably should have their onset of action within 1 hour.

Multidose efficacy

The data for the use of celecoxib in multiple doses is somewhat problematic. Studies 129 and 130 for dysmenorrhea were inconclusive due to high patient dropout in the multiple dose period. Some trends suggesting efficacy in the multiple dose period include a numerically superior patient global assessment for celecoxib over placebo as well as a slightly lower pain intensity score before each

dose in study 129. In study 130 patient global evaluation was numerically greater for celecoxib over placebo. Only study 085 (post-surgical) demonstrated significant improvement favoring celecoxib compared to placebo for a number of endpoints including mean maximum pain intensity, and mean patient global assessment among others. Other studies with multiple dose assessment periods did not conclusively demonstrate celecoxib as effective due to the small number of patients requiring remedication on subsequent days, although they provide supportive data. For example, study 074, a study in post-surgical pain, suggested efficacy in the multiple dose period. The mean scores of pain intensity assessments on days 2-4 were statistically significantly favoring celecoxib over placebo. The mean maximum pain intensity scores for celecoxib were significantly different from placebo on days 2-4 (but not day 1). The mean patient Global Evaluation scores for the celecoxib 200 mg BID treatment group were numerically higher than the placebo treatment group on all four study days. For the pairwise comparisons, these differences were statistically significant on study days 2 ($p=0.003$), 3 ($p=0.005$), and 4 ($p=0.009$). In spite of the above, the fact that there is considerable amount of data in regards to the chronic use of celecoxib, albeit in models other than acute pain, provides some reassurance that celecoxib remains efficacious over multiple dose periods, and provides additional information on dose and safety.

One problem area identified by these studies is the high rate of drop out in the short term. The result of this is that it is difficult to assess multidose efficacy. Either new models need to be developed or greater numbers of patients need to recruited so that even with the high dropout rates observed, sufficient numbers of patients will be available after the first 12-24 hours. Subjects available after the single dose period may be re-randomized for the multiple dose period. Alternatively, we can rely of single dose efficacy but this begs the issue of identifying optimal dosing intervals.

In terms of the relationship of efficacy to other drugs available for the same indications, celecoxib was compared to NSAID's including ibuprofen and naproxen sodium, as well as narcotic analgesics including the combination of hydrocodone/acetaminophen. In almost all cases celecoxib was found to be comparable to or less efficacious than these drugs at the endpoints of onset, magnitude of pain relief, and duration. For example, in the dysmenorrhea studies naproxen was statistically superior to celecoxib for measures such as SPID and TOTPAR. The NSAID comparators ibuprofen 400mg and naproxen sodium 550mg used in the post-surgical studies demonstrated a more rapid onset of analgesia and a significantly greater peak response than celecoxib beginning at 30-45 minutes post dose. There are no studies comparing celecoxib to other Cox-2 selective agents. There are no studies to show any unique advantage in terms of efficacy of celecoxib over standards of analgesic care used in the submitted studies as active controls.

The size of treatment effect is difficult to assess from these studies because of the multitude of endpoints and time specific measurements. As an example one can arbitrarily choose to examine SPID (8) and TOTPAR (8) measurements, since these endpoints are consistently utilized in all studies. The scale for pain intensity is 0-3 and for pain relief 0-4. There are 12 measurements in the first 8 hours which provides a maximum score of 36 for SPID and 48 for TOTPAR. If we examine the dysmenorrhea studies, it appears that the treatment effect approximates 50%, that is, scores for celecoxib are 50% better than the scores for the placebo group. Examining SPID(8) and TOTPAR (8), the treatment effect results are even more dramatic in study 139 the post-oral surgery pain model. In study 085 post-orthopedic surgery model, examination of SPID (8) and TOTPAR (8) again shows a 50-100% effect for celecoxib. However, in the dental pain and post-surgical studies the size of treatment effect clearly depends on the endpoints examined, and the specific time points in the trials that are used for analysis.

The sponsor has provided replicated evidence of efficacy in 2 models of acute pain in the single dose period, as well as evidence supportive of efficacy in the multiple dose period. It appears that celecoxib is effective in the treatment of acute pain in terms of onset, duration and magnitude of effect. Celecoxib appears most efficacious for the treatment of acute pain following dental surgery or from dysmenorrhea. Replicated evidence of efficacy was not shown in the 5 pivotal trials for the treatment of acute pain that typically follows major surgery such as a hip or knee replacement. In these cases the clinician may still want to consider the use of a narcotic analgesic to insure the most efficient treatment of pain in the acute post-operative setting.

C. Safety

Celecoxib has been approved for the treatment of the signs and symptoms of osteoarthritis of the hip and knee, and rheumatoid arthritis. Controlled trials in OA in approximately 4200 patients with up to 12 weeks of therapy and in RA in approximately 2100 patients with up to 24 weeks have been performed.

In the present submission pivotal trials in dental pain include 725 patients, trials in post-surgical pain include 818 patients, and trials in dysmenorrhea include 243 females. These are single dose or short term studies not lasting longer than 3-5 days. In the non-pivotal trials a total of 1439 patients are included. No new signals of safety were identified in this submission, in the acute setting at the doses identified.

Serious side effects associated with the use of celecoxib have been identified in the studies involving OA and RA patients including post-marketing reports. These include significant upper GI bleeding, anaphylactoid reactions, rare cases of

severe hepatic reactions including jaundice and fatal fulminant hepatitis, liver necrosis and liver failure, renal decompensation, and asthma.

A new adverse event reported in the dental pain studies and not previously described, is termed alveolar osteitis ("dry socket") (72/633). However the incidence in the celecoixb group was similar to the placebo group. It is likely that this is not related to treatment. There were no additional adverse events reported in the present submission that were not identified in previous studies (for a more complete discussion, please see previous review).

No specific discussion of drug-drug interactions was presented in this submission. However, information is available from the original NDA submission and is presented in the label for celecoxib. Management of these interactions should not pose a significant problem, as these are mostly recognized as potential problems associated with the use of other NSAID's. The present label contains a more complete description of these interactions.

Certainly exposure of individuals in the dysmenorrhea trials even though generally young, is likely to accurately reflect the general population of women that will be exposed to the drug for this indication. Women taking estrogens are at higher risk in terms of thrombotic problems. Additionally, individuals with a hypercoagulable state (such as occurs in the post-operative setting or with systemic lupus erythematosus, for example) may also be at greater risk for thrombotic complications. For the post-surgical studies, individuals with cardiovascular disease, were not specifically excluded from the study (and in fact the study did admit individuals with cardiovascular disease). Therefore, it appears that the study population will, at least to some degree, reflect the general population that will be exposed to the drug. Those individuals involved in the dental pain studies tended to be younger (<30 years of age) and therefore healthier than the older subjects. This may not be entirely representative of the general population undergoing various dental procedures. As such, there may be risks in older populations not seen in these trials. The large CLASS trial provides a robust database for dose, duration, and age although this study was restricted to the OA and RA population and may not represent a population at high risk for thromboembolic events. However, no additive risk for CV thromboembolic events was identified in this trial.

Overall, a wide range of individuals in the general population will likely use this drug for all kinds of acute pain. This includes the elderly who will have more co-morbidities than some of the populations studied in these trials. Nevertheless, celecoxib has already been approved for the signs and symptoms of OA and RA, and individuals with these disorders tend to have more medical problems than the general population. Therefore, based on the overall evaluation it is concluded that the exposure in all trials appears to have addressed potential exposure in the general population.

There are no additional recommended warnings that are not already addressed in the label for celecoxib. These include GI, anaphylactoid reactions, advanced renal disease, and pregnancy. Additional rare adverse events have been identified in post-marketing surveillance and have been added to the revised label for celecoxib.

A number of other drugs are available for the treatment of acute pain including many less selective NSAID's as well as a new Cox-2 inhibitor (rofecoxib), acetaminophen, tramadol (ultram), and various narcotic analgesics. In terms of efficacy, celecoxib does not appear to be more efficacious than other NSAIDs or narcotic analgesics. In terms of safety, celecoxib has potential advantages over NSAIDs and narcotics. For example, narcotics may cause respiratory depression and other opioid effects, which celecoxib does not, and this may prove to be beneficial especially in a postoperative setting. Tramadol may also cause respiratory depression and seizures, and individuals can develop withdrawal symptoms upon abrupt discontinuation. Celecoxib has not been associated with these problems. In terms of GI toxicity celecoxib has not yet been proven to be less toxic to the GI tract than NSAID's as a group. A recent large safety trial (CLASS trial) comparing celecoxib to 2 other NSAID's failed to demonstrate that celecoxib is superior to both comparators combined, in terms of ulcer complications. Acetaminophen may produce hepatic toxicity (although usually not at therapeutic doses), but does not lead to GI ulceration. Celecoxib may also produce liver toxicity. Therefore based on safety, the place for celecoxib in the armamentarium of treatment for acute pain is not yet clearly defined. In general, celecoxib appears to be no more potent (efficacious) nor safer than traditional NSAIDs or narcotics.

At the present time there remains an unresolved safety issue, specifically concerning the potential for cardiovascular adverse events, based on the fact that celecoxib and other Cox-2 inhibitors may alter the thromboxane/prostaglandin balance. There are no safety studies at present that have been powered to address this question. The CLASS study, powered to identify GI problems, did not identify any thrombotic or cardiovascular problems. There were no clear signals in the present submission to suggest that this is a problem for celecoxib, although these studies were clearly short term and underpowered to rule out any risk. Even the post-surgical studies, where a hypercoagulable state may exist, did not demonstrate any significant problem.

D. Dosing

For the present submission, the sponsor proposes an initial dose of 400mg followed by 200 mg daily with an additional 200 mg each day as necessary. Celecoxib is approved for use in OA and RA as well as for FAP in doses ranging from 100-200mg twice a day for OA and RA, to 400 mg twice a day for FAP. Studies supporting the dosing schedule requested by the sponsor in this submission include study 070 a dose ranging study that examined 50, 100, 200,

and 400 mg of celecoxib in single doses in a dental pain model, study 139 also in the dental pain model which presents data for efficacy out to 24 hours for the 200 mg dose, and studies 129 and 130 in dysmenorrhea which examined an initial dose of 400 mg followed by 200 mg daily with an additional 200 mg each day as needed. Additional post-surgical studies used 200 mg three times a day as a therapeutic dose. In terms of efficacy, in study 070, celecoxib 400 mg was superior to 50 and 100 mg and in general similar to 200 mg although superior to 200 mg at some efficacy time points. In general celecoxib 400 mg provided the greatest percent of patients with onset of analgesia, the fastest median time to onset of analgesia, the most improved time weighted summed measures of efficacy, and the longest time to rescue medication and lowest percent of patients who took rescue medication. In study 139, superiority over placebo for time specific measures of efficacy was demonstrated even out to 24 hours. A second dose of celecoxib 200 mg allowed an additional 15-24% of patients to complete the first 24 hours of each treatment period. Furthermore, studies 085 and 086 provide data to show that for pain control after the first day, 53% of patients of patients took 2 or less doses of celecoxib to maintain analgesia (for day 2). In terms of dose toxicity relationship, the incidence of individuals with at least one adverse event in the celecoxib 400 mg group was similar to placebo in study 070. Therefore, based on the totality of the data there is a reasonable level of confidence that the dosing regimen chosen by the sponsor for use in acute pain and dysmenorrhea is appropriate. However, celecoxib 400 mg bid was not evaluated nor was 400 mg on day 2 tested. Although celecoxib 400 mg bid was no more efficacious than 200 mg bid for RA, this is a different model and extrapolation to the acute pain setting may not be appropriate.

It may be possible to produce greater efficacy with a dosing regimen consisting of celecoxib 400 mg bid or 400 mg daily with an additional dose of 400 mg as needed. The sponsor has chosen to recommend the lower dose of 200 mg daily which may have somewhat less toxicity, although this is not certain. In the future, it may be of value to study the 400 mg bid dose. Results from the CLASS trial using a dose of 400 mg bid suggest that doses higher than 400 mg daily may be safe when used chronically. An additional unresolved issue concerns the duration of use. The sponsor does not provide a specific guideline for this. In general studies lasted from 3-5 days and this would seem to be an appropriate duration of therapy for the treatment of acute pain. .

E. Special populations

The celecoxib label addresses a number of issues relating to special populations. Safety and effectiveness in pediatric populations has not been assessed.

With respect to age, single doses of celecoxib 200 mg demonstrated consistent analgesic efficacy regardless of age greater or less than 65 in post surgical pain studies (082,083,085,086). There were no patients greater than 65 in the dysmenorrhea and post oral surgery studies. In the proposed revised label for

celecoxib, more than 3300 patients ages 65-74 and about 1300 over 75 took this drug (this includes previous studies as well as the present submission). Although the incidence of adverse events tended to be higher in elderly patients, no substantial differences in safety and effectiveness were observed between these patients and younger subjects.

Single doses of celecoxib 200 mg and 400 mg demonstrated no important differences in analgesic efficacy among patients of different ethnic origins. Although differences were present between the Black and Caucasian/Hispanic groups this may be due to the small number of Blacks in the studies. According to the label a meta-analysis of pharmacokinetic studies suggests a 40% higher AUC of celecoxib in Blacks compared to Caucasians. The clinical significance of this is unknown.

There are no studies in pregnant women. In rabbits administered celecoxib at doses of >150 mg/kg/day an increased incidence of fetal alterations was observed. No studies have been done to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. It is not known if celecoxib is excreted in milk. It is unlikely that the drug will be used to any significant extent in pregnant women.

Clinical trials with celecoxib have shown renal effects similar to other NSAID's. Celecoxib is not recommended for treatment in patients with advanced kidney disease. The label states that when used in patients with moderate hepatic insufficiency the dose should be reduced by approximately 50%. The present studies do not further address these issues.

With respect to gender the pivotal studies involving males and females include the post oral surgery pain (025, 027,070) studies and the postsurgical pain studies (082,083,085,086). In single doses celecoxib at doses of 200 mg or 400 mg showed no significant gender related differences in analgesic efficacy. The studies for dysmenorrhea involved women only. In total 1224 females received celecoxib and 562 males for the proposed indications in the pivotal trials.

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CLINICAL REVIEW

I. Introduction and Background

A. Drug established and proposed

Celecoxib (trade name Celebrex) is a selective inhibitor of cyclooxygenase-2 (Cox-2). The present proposed indications are for the treatment of acute pain and dysmenorrhea. The proposed dose is 400 mg initially followed by 200 mg daily with an additional 200 mg each day as necessary. There is no specified time limit for taking the drug. At present the drug is indicated for adults only.

B. State of Armamentarium

In acutely painful conditions there are a number of alternatives available for treatment. These include the traditional NSAID's such as ibuprofen or naproxen, a new Cox-2 inhibitor rofecoxib (Vioxx), acetaminophen, propoxyphene (Darvon), tramadol (Ultram), and the narcotic analgesics. The selection of drug depends on the clinical situation and the intensity of pain. However, treatment is limited by a number of adverse effects including GI toxicity, respiratory depression etc. New drugs that are more efficacious but with fewer side effects would add to this armamentarium. At present celecoixb does not appear to offer significant advantages in either respect, over traditional treatments, and may be inferior to narcotic analgesics in the treatment of severe acute pain. .

C. Milestones in product development

Celecoxib was approved for the treatment of the signs and symptoms of OA and RA. As part of the original NDA submission the sponsor sought approval for the indication of acute pain. However, the data presented at that time did not support the efficacy in the models tested. Specifically, the sponsor evaluated efficacy in dental pain and orthopedic surgery. Although replicated evidence was provided to demonstrate efficacy in the dental pain model, celecoxib demonstrate efficacy in the post-surgical model. This was based on the finding of inconsistent efficacy in time specific efficacy measures. In addition, celecoxib was less effective than ibuprofen or naproxen in these studies. There were no additional major issues that arose during these trials.

D. Important issues with pharmacologically related agents

Another Cox-2 inhibitor rofecoxib has been approved for the treatment of acute pain, dysmenorrhea, and OA. A recent large study termed VIGOR to evaluate the GI safety of rofecoxib has demonstrated that it is superior to naproxen in terms of a significantly lower incidence of PUB's (perforation, ulceration with pain, and bleeding). However, results from this trial suggest a higher incidence of cardiovascular related problems. The recent large study termed CLASS to

evaluate the GI safety of celecoxib did not demonstrate superiority of celecoxib over the 2 comparators, although there was no cardiovascular signal noted. Additional trials are ongoing.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There are no new issues with regards to the findings from chemistry, animal pharmacology and toxicology, and biopharmaceutics etc. The interested reader is referred to the reviews of the original submission of this NDA in these areas for more details. The reader is also referred to the statistics review included in this sNDA review. A summary of this review is included here:

The sponsor previously submitted an NDA for the acute pain indication, and only the dental pain model succeeded in demonstrating efficacy. In this NDA supplement, the sponsor submitted 6 additional pivotal studies (4 Post-Surgical Pain studies and 2 Primary Dysmenorrhea studies). For each study, the statistical review focused on 5 efficacy variables (PID, PR, PRID, Time to Rescue Medication, Time to Onset of Analgesia), which are considered the most important measurements for the acute pain indication.

Post-Surgical Pain Studies
All 4 studies failed to show significant differences of PID, PR, and PRID between Celecoxib and placebo treatment groups in the first hour after administration. Most of the time specific variable comparisons begin to show significant differences from placebo from 3 hours on. For Time to Rescue Medication, the median times for the Celecoxib treatment group were 3 hour 15 minutes and 3 hour 18 minutes for study 082 and 083, respectively, and longer than 8 hours for both 085, 086. For Time to onset of Analgesia, the median times for the Celecoxib treatment group were between 34 to 46 minutes.

Primary Dysmenorrhea Studies
Study 129 showed significant differences of PID, PR, and PRID between Celecoxib and placebo treatment group from 1.5 hours after administration. Study 130 showed a significant difference from 1.5 hours after taking dose for PID, and from 1 hour for PR, PRID. For Time to Rescue Medication, the median times for the Celecoxib treatment group were over 12 hours for both studies. For Time to onset of Analgesia, the median times for the Celecoxib treatment group were 52 and 53 minutes for study 129 and 130, respectively.

In conclusion, the Post-Surgical Pain Studies failed to demonstrate efficacy for acute pain especially during the first few hours of PID, PR, and PRID. On the other hand, Primary Dysmenorrhea studies demonstrated some evidence of efficacy.

III. Human Pharmacokinetics and Pharmacodynamics

There are no new issues as regards the human pharmacokinetics and pharmacodynamics. The interested reader is referred to the reviews of the original submission of this NDA and to the approved label for more details.

IV. Description of Clinical Data and Sources

A. Overall Data

The source of data is the sponsors clinical trial program.

B. Listings of Clinical Trials

Management of Acute Pain	Study	Short Description
Post-Oral Surgery Pain Studies	005†	Analgesic Efficacy in Postsurgical Dental Pain
	025*†	Dose-Ranging Analgesic Efficacy in Postsurgical Dental Pain
	027*†	Analgesic Efficacy in Postsurgical Dental Pain
	070*†	Dose-Response and Analgesic Efficacy in Postsurgical Dental Pain
	139	Analgesic Efficacy in Postsurgical Dental Pain
Post-Surgical Pain Studies	028*†	Single and Multiple Dose Analgesic Efficacy After Orthopedic Surgery
	029†	Single and Multiple Dose Analgesic Efficacy After General Surgery
	080†	Multiple Dose Analgesic Efficacy After Orthopedic Surgery
	082*	Single Dose Analgesic Efficacy After Orthopedic Surgery
	083*	Single Dose Analgesic Efficacy After General Surgery
	085*	Single and Multiple Dose Analgesic Efficacy After Orthopedic Surgery
	086*	Single and Multiple Dose Analgesic Efficacy After Orthopedic Surgery
	074	Multiple Dose Analgesic Efficacy Post–Hernia Repair Surgery (Europe)
	075	Multiple Dose Analgesic Efficacy Post–Hip Replacement Surgery (Europe)
Primary Dysmenorrhea Pain Studies	129*	Analgesic Efficacy in Primary Dysmenorrhea
	130*	Analgesic Efficacy in Primary Dysmenorrhea
Musculoskeletal Pain Study	078	Analgesic Efficacy in Acute Low Back Pain
Management of Primary Dysmenorrhea	**Study**	**Short Description**
	129*	Analgesic Efficacy in Primary Dysmenorrhea
	130*	Analgesic Efficacy in Primary Dysmenorrhea

*Pivotal efficacy study
†Submitted in the original celecoxib NDA (20-998)

Figure 1: List of clinical trials in this sNDA

Figure 1 (above) lists all the studies included in the present submission. The pivotal studies in support of the indications of acute pain and dysmenorrhea are denoted by an asterisk. Studies addressing the four models of acute pain are listed.

Figure 2 lists in more detail the postsurgical dental pain studies including the location, study design, and doses used. Figure 3 lists the number of patients by study, treatment group, and dose. Figure 4 lists the number of patients by treatment group, the number completing the study and number withdrawn from the study and reason for withdrawal.

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Figure 2: **Postsurgical Dental Pain trials**

Protocol Number Report Number Short Title	Number of Investigators Country Start Date	Study Design	Treatment Regimen(s) Duration of Treatment
P: N49-95-02-005 R: N49-97-16-005 Analgesic Efficacy in Postsurgical Dental Pain	One Investigator U.S.A. 23 August 1995	Single-Center Randomized Single-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group	Celecoxib 100 mg or 400 mg, or Aspirin 650 mg, or Placebo Single dose
P: N49-96-02-025 R: N49-97-16-025 Dose-Ranging Analgesic Efficacy in Postsurgical Dental Pain	One Investigator U.S.A. 9 July 1996	Single-Center Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group	Celecoxib 25 mg, 50 mg, 200 mg, or Ibuprofen 400 mg, or Placebo Single dose
P: N49-96-02-027 R: N49-97-06-027 Analgesic Efficacy in Postsurgical Dental Pain	One Investigator U.S.A. 4 March 1997	Single-Center Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group	Celecoxib 100 mg, 200 mg, or Naproxen sodium 550 mg, or Placebo Single dose
P: N49-97-02-070 R: N49-97-06-070 Dose-Response and Analgesic Efficacy in Postsurgical Dental Pain	One Investigator U.S.A. 17 April 1997	Single-Center Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group	Celecoxib 50 mg, 100 mg, 200 mg, 400 mg, or Naproxen sodium 550 mg, or Placebo Single dose
P: N49-99-02-139 R: N49-00-06-139 Analgesic Efficacy in Postsurgical Dental Pain	One Investigator U.S.A. 11 November 1999	Single-Center Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group	Celecoxib 200 mg capsule or 200 mg oral fine suspension, or Ibuprofen 400 mg, or Placebo Single dose

Information derived from individual clinical study reports.

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Figure 3: Number of patients by treatment group in dental pain trials

Study	Number of Patients by Treatment Group										
	Placebo	Celecoxib						Aspirin 650 mg	Ibuprofen 400 mg	Naproxen Sodium 550 mg	Total
		25 mg	50 mg	100 mg	200 mg	400 mg	200 mg[†]				
005	50	-	-	50	-	50	-	50	-	-	200
025	50	50	50	-	50	-	-	-	50	-	250
027	55	-	-	55	56	-	-	-	-	54	220
070	50	-	35	50	50	35	-	-	-	35	255
139	51	-	-	-	49	-	53	-	52	-	205
Total # of Pts.	256	50	85	155	205	85	53	50	102	89	1130

Data derived from individual clinical study reports.
[†]This column refers to the 200 mg oral suspension formulation; all of the other celecoxib doses refer to the capsule formulation.

Figure 4: Number of patients completing and reasons for withdrawal

Study	Number (%) of Patients by Treatment Group						
	Placebo	Celecoxib					Active Comparator
		25 mg	50 mg	100 mg	200 mg	400 mg	200 mg[†]	
005								Aspirin 650 mg
Total Patients	50			50		50		50
Completed	3 (6%)			20 (40%)		22 (44%)		14 (28%)
Withdrawn	47 (94%)	-	-	30 (60%)	-	28 (56%)	-	36 (72%)
Rescue	45 (90%)			30 (60%)		27 (54%)		35 (70%)
Lost to Follow-Up	2 (4%)			-		1 (2%)		1 (2%)
025								Ibuprofen 400 mg
Total Patients	50	50	50		50			50
Completed	4 (8%)	4 (8%)	7 (14%)	-	13 (26%)	-	-	8 (16%)
Withdrawn	46 (92%)	46 (92%)	43 (86%)		37 (74%)			42 (84%)
Rescue	46 (92%)	46 (92%)	43 (86%)		37 (74%)			42 (84%)
027								Naproxen Sodium 550 mg
Total Patients	55			55	56			54
Completed	9 (16%)			17 (31%)	27 (48%)			28 (52%)
Withdrawn	46 (84%)	-	-	38 (69%)	29 (52%)	-	-	26 (48%)[‡]
Rescue	46 (84%)			38 (69%)	29 (52%)			25 (46%)
070								Naproxen Sodium 550 mg
Total Patients	50		35	50	50	35		35
Completed	2 (4%)		3 (9%)	10 (20%)	12 (24%)	13 (37%)		9 (26%)
Withdrawn	48 (96%)	-	32 (91%)	40 (80%)	38 (76%)	22 (63%)	-	26 (74%)
Rescue	48 (96%)		31 (89%)	40 (80%)	38 (76%)	22 (63%)		26 (74%)
Adverse Events	-		1 (3%)	-	-	-		-
139								Ibuprofen 400 mg
Total Patients	51				49		53	52
Completed	6 (12%)				20 (41%)		17 (32%)	8 (15%)
Withdrawn	45 (88%)	-	-	-	29 (59%)	-	36 (68%)	44 (85%)
Rescue	45 (88%)				29 (59%)		36 (68%)	44 (85%)

Data derived from individual clinical study reports.
[†]This column refers to the 200 mg oral suspension formulation; all of the other celecoxib doses refer to the capsule formulation.
[‡]One patient was discharged before the 24-hour assessments.

Withdrawal rates for the placebo group are high, as might be expected. In general with higher doses of celecoxib, a greater percentage of patients completed the study consistent with a dose response.

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Figure 5 lists the dysmenorrhea studies along with the location of the study, design, and dosing schedule. Figure 6 describes the numbers of patients treated and withdrawn.

Figure 5: Dysmenorrhea trials

Protocol Number Report Number Short Title	Number of Investigators Country Start Date	Study Design	Treatment Regimen(s) Duration of Treatment
P: N49-99-02-129 R: N49-00-06-129 Analgesic Efficacy in Primary Dysmenorrhea	One Investigator U.S.A. 13 October 1999	Single-Center Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group Crossover	Day 1/Initial Dose: Celecoxib 400 mg or naproxen sodium 550 mg or placebo. Day 1/Second Dose (if requested): Celecoxib 200 mg (up to a total daily dose of 600 mg) or naproxen sodium 550 mg (up to a total daily dose of 1100 mg on Day 1) or placebo. No less than 12 hours between doses. Days 2 and 3: Celecoxib 200 mg or naproxen sodium 550 mg or placebo up to twice each day, prn. No less than 12 hours between doses. Up to 3 days/3 cycles per patient/crossover to different treatment at subsequent cycles.
P: N49-99-02-130 R: N49-00-06-130 Analgesic Efficacy in Primary Dysmenorrhea	Two Investigators at Two Sites U.S.A. 28 October 1999	Multicenter Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group Crossover	

Information derived from individual clinical study reports.

Figure 6: Numbers of completers and reasons for withdrawal

Study	Number (%) of Patient Observations by Treatment Group		
	Placebo	Celecoxib 400 mg	Naproxen Sodium 550 mg
129			
Total	127	129	126
Completed	68 (54%)	103 (80%)	102 (81%)
Withdrawn	59 (46%)	26 (20%)	24 (19%)
Rescue Medication	58 (46%)	26 (20%)	22 (17%)
Noncompliance	1 (1%)	0 (0%)	2 (2%)
130			
Total	129	124	125
Completed	79 (61%)	94 (76%)	107 (87%)
Withdrawn	50 (39%)	30 (24%)	18 (14%)
Rescue Medication	50 (39%)	30 (24%)	16 (13%)
Lost to Follow-up	--	--	2 (2%)

Data derived from individual clinical study reports.

The numbers of patients completing the study on celecoxib is similar to naproxen and numerically better than placebo.

Figures 7 and 8 list the postsurgical pain studies and treatments.

Figure 7:Postsurgical pain studies including location, design and dosing schedule

Protocol Number Report Number Short Title	Number of Investigators Country Start Date	Study Design	Treatment Regimen(s) Duration of Treatment
P: N49-98-02-085 R: N49-99-06-085 Multiple Dose Analgesic Efficacy After Orthopedic Surgery	12 investigators at 12 sites U.S.A. 29 January 1998	Multicenter Randomized Double-blind Placebo-Controlled Active Comparator-Controlled Single/Multiple Dose Parallel-group	Single Dose Period (through 8 hrs post initial dose): Celecoxib 200 mg, or Hydrocodone 10 mg/acetaminophen 1000 mg, or Placebo Multiple Dose Period: (from 8 hrs post initial dose up to 5 days) Celecoxib 200 mg TID PRN, or Hydrocodone 10 mg/acetaminophen 1000 mg TID PRN
P: N49-98-02-086 R: N49-99-06-086 Multiple Dose Analgesic Efficacy After Orthopedic Surgery	15 investigators at 15 sites U.S.A. 26 January 1998	Multicenter Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Single/Multiple Dose Parallel-Group	Single Dose Period (through 8 hrs post initial dose): Celecoxib 200 mg, or Hydrocodone 10 mg/acetaminophen 1000 mg, or Placebo Multiple Dose Period (from 8 hrs post initial dose up to 5 days) Celecoxib 200 mg TID PRN, or Hydrocodone 10 mg/acetaminophen 1000 mg TID PRN
P: N49-96-02-028 R: N49-98-06-028 Multiple Dose Analgesic Efficacy After Orthopedic Surgery	12 investigators at 12 sites U.S.A. 6 May 1997	Multicenter Randomized Double-Blind Placebo-Controlled Active-Comparator-Controlled Multiple Dose Parallel-Group	Up to 4 daily doses x 5 days: Doses 1 and 2 must be taken ≥ 4 hrs apart; after the 2nd dose, study drug may be taken q 2 hrs PRN. Celecoxib 100 mg or 200 mg: Two consecutive single doses followed by two consecutive single doses of Placebo PRN; or Propoxyphene 100 mg/ Acetaminophen 650 mg QID PRN; or Placebo QID PRN Up to 5 days
P: N49-98-02-082 R: N49-99-06-082 Single Dose Analgesic Efficacy After Orthopedic Surgery	5 investigators at 5 U.S. Sites and 1 Investigator at 1 New Zealand Site 17 February 1998	Multicenter Randomized Double-Blind Placebo-Controlled Active-Comparator-Controlled Single Dose Parallel-Group	Celecoxib 200 mg, or Hydrocodone 10 mg/acetaminophen 1000 mg, or Placebo Single dose
P: N49-98-02-083 R: N49-99-06-083 Single Dose Analgesic Efficacy After General Surgery	7 investigators at 7 U.S. Sites and 1 Investigator at 1 New Zealand Site 20 February 1998	Multicenter Randomized Double-Blind Placebo-Controlled Active-Comparator-Controlled Single Dose Parallel-Group	Celecoxib 200 mg, or Hydrocodone 10mg/acetaminophen 1000 mg or Placebo Single dose
P: N49-96-02-029* R: N49-98-06-029 Multiple Dose Analgesic Efficacy After General Surgery	13 investigators at 13 U.S. Sites and 1 Investigator at 1 New Zealand Site 12 May 1997	Multicenter Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group Multiple Dose	Up to 4 daily doses x 5 days: Doses 1 and 2 must be taken ≥ 4 hrs apart; after the 2nd dose, study drug may be taken q 2 hrs PRN. Celecoxib 100 mg or 200 mg: Two consecutive single doses followed by two consecutive single doses of Placebo PRN; or Propoxyphene 100 mg/ Acetaminophen 650 mg QID PRN; or Placebo QID PRN Up to 5 days
P: N49-97-02-080* R: N49-98-06-080 Multiple Dose Analgesic Efficacy After Orthopedic Surgery	1 investigator at 1 Site U.S.A. 15 December 1997	Single-Center Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group Multiple Dose	Up to 5 days of Celecoxib 200 mg BID, PRN, or Naproxen 500 mg BID PRN, or Placebo BID PRN Up to 5 days

Information derived from individual clinical study reports.
*Data from these studies is not presented in the ISE; refer to section 4.2.1 for an explanation.

Figure 8: Numbers of patients in each postsurgical pain study and the numbers withdrawn.

Study	Number (%) of Patients by Treatment Group				
	Placebo	Celecoxib		Hydrocodone 10 mg/ Acetaminophen 1000 mg	Propoxyphene 100 mg/ Acetaminophen 650 mg
		100 mg	200 mg		
085					
Total Patients	69		67	62	
Completed	27 (39%)		37 (55%)	32 (52%)	
Withdrawn	42 (61%)		30 (45%)	30 (48%)	
Treatment Failure/ Rescue Medication	42 (61%)		29 (43%)	29 (47%)	
Adverse Event	0 (0%)		1 (1%)	1 (2%)	
086					
Total Patients	72		74	74	
Completed	24 (33%)		41 (55%)	33 (45%)	
Withdrawn	48 (67%)		33 (45%)	41 (55%)	
Treatment Failure/ Rescue Medication	48 (67%)		33 (45%)	41 (55%)	
028					
Total Patients	60	68	62		65
Completed	1 (2%)	1 (1%)	0 (0%)		1 (2%)
Withdrawn	59 (98%)	67 (99%)	62 (100%)		64 (98%)
Pre-existing Violation	2 (3%)	3 (4%)	0 (0%)		0 (0%)
Noncompliance	3 (5%)	16 (24%)	10 (16%)		19 (29%)
Treatment Failure/ Rescue Medication	51 (85%)	47 (69%)	43 (69%)		44 (68%)
Adverse Event	3 (5%)	1 (1%)	9 (15%)		1 (2%)
082					
Total Patients	67		70	67	
Completed	8 (12%)		18 (26%)	17 (25%)	
Withdrawn	59 (88%)		52 (74%)	50 (75%)	
Pre-existing Violation	2 (3%)		1 (1%)	1 (1%)	
Noncompliance	0 (0%)		0 (0%)	1 (1%)	
Treatment Failure/ Rescue Medication	56 (84%)		49 (70%)	46 (69%)	
Adverse Event	1 (1%)		2 (3%)	2 (3%)	
029					
Total Patients	40	45	42		40
Completed	1 (3%)	1 (2%)	0 (0%)		0 (0%)
Withdrawn	39 (98%)	44 (98%)	42 (100%)		40 (100%)
Pre-existing Violation	2 (5%)	0 (0%)	2 (5%)		0 (0%)
Noncompliance	5 (13%)	13 (29%)	9 (21%)		13 (33%)
Treatment Failure/ Rescue Medication	27 (68%)	29 (64%)	28 (67%)		22 (55%)
Adverse Event	5 (13%)	2 (4%)	3 (7%)		5 (13%)
083					
Total Patients	67		65	66	
Completed	4 (6%)		16 (25%)	11 (17%)	
Withdrawn	63 (94%)		49 (75%)	55 (83%)	
Noncompliance	1 (1%)		0 (0%)	1 (2%)	
Treatment Failure/ Rescue Medication	61 (91%)		49 (75%)	51 (77%)	
Adverse Event	1 (1%)		0 (0%)	3 (5%)	

Data derived from individual clinical study reports.

The total number of patients withdrawn from the studies on celecoxib is similar to the number on the narcotic comparator and is either similar to or better than placebo. Most patients withdrawing did so for lack of efficacy.

Figure 9 lists those studies containing multiple dose assessment periods, the location of the studies, design and dosing schedule.

Figure 9: Studies with multiple dose periods (post-surgical)

Protocol Number Report Number Short Title	Number of Investigators/Country/ Start Date	Study Design	Treatment Regimen(s) Duration of Treatment
P: N49-98-02-085 R: N49-99-08-085 Multiple-Dose Analgesic Efficacy After Orthopedic Surgery	12 Investigators at 12 Sites U.S.A. 29 January 1998	Multicenter Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Single/Multiple Dose Parallel-Group	Single Dose Period (through 8 hrs post initial dose): Celecoxib 200 mg, or Hydrocodone 10 mg/acetaminophen 1000 mg, or Placebo Multiple Dose Period: (from 8 hrs post initial dose up to 5 days) Celecoxib 200 mg TID PRN, or Hydrocodone 10 mg/acetaminophen 1000 mg TID PRN
P: N49-98-02-086 R: N49-99-08-086 Multiple-Dose Analgesic Efficacy After Orthopedic Surgery	15 investigators at 15 Sites U.S.A. 26 January 1998	Multicenter Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Single/Multiple Dose Parallel-Group	Single Dose Period (through 8 hrs post initial dose): Celecoxib 200 mg, or Hydrocodone 10 mg/acetaminophen 1000 mg, or Placebo Multiple Dose Period: (from 8 hrs post initial dose up to 5 days) Celecoxib 200 mg TID PRN, or Hydrocodone 10 mg/acetaminophen 1000 mg TID PRN
P: N49-96-02-028 R: N49-98-06-028 Multiple-Dose Analgesic Efficacy After Orthopedic Surgery	12 Investigators at 12 Sites U.S.A. 6 May 1997	Multicenter Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group Multiple Dose	Up to 4 daily doses x 5 days: Doses 1 and 2 must be taken ≥ 4 hrs apart; after the 2nd dose, study drug may be taken q 2 hrs PRN. Celecoxib 100 mg or 200 mg: Two consecutive single doses followed by two consecutive single doses of Placebo PRN; or propoxyphene 100 mg/ acetaminophen 650 mg QID PRN; or Placebo QID PRN Up to 5 days
P: N49-96-02-029 R: N49-98-08-029 Multiple Dose Analgesic Efficacy After General Surgery	13 Investigators at 13 U.S. Sites and 1 Investigator at 1 New Zealand Site 12 May 1997	Multicenter Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group Multiple Dose	Up to 4 daily doses x 5 days: Doses 1 and 2 must be taken ≥ 4 hrs apart; after the 2nd dose, study drug may be taken q 2 hrs PRN. Celecoxib 100 mg or 200 mg: Two consecutive single doses followed by two consecutive single doses of Placebo PRN; or Propoxyphene 100 mg/ Acetaminophen 650 mg QID PRN; or Placebo QID PRN Up to 5 days
P: E49-97-02-074 R: E49-99-06-074 Analgesic Efficacy Post-Hernia Repair Surgery	27 Investigators in 6 Countries (Belgium, Denmark, Netherlands, Spain, Sweden, U.K.) 19 February 1998	Multicenter Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group Multiple Dose	Celecoxib 200 mg BID, or Diclofenac 75 mg SR BID up to 4 days; Tramadol 100 mg QID PRN may be used as rescue up to total daily dose of 400 mg and continue Celecoxib, Diclofenac, or Placebo Up to 4 days
P: E49-97-02-075 R: E49-99-06-075 Analgesic Efficacy Post-Hip Replacement Surgery	29 Investigators in 6 Countries (Belgium, Germany, Netherlands, Spain, Sweden, U.K.) 1 January 1998	Multicenter Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group Multiple Dose	Celecoxib 200 mg BID, or Diclofenac 75 mg SR BID up to 5 days; Tramadol 100 mg QID PRN may be used as rescue up to total daily dose of 400 mg and continue Celecoxib, Diclofenac, or Placebo Up to 5 days
P: N49-97-02-080 R: N49-98-06-080 Multiple-Dose Analgesic Efficacy After Orthopedic Surgery	One Investigator U.S.A. 15 December 1997	Single-Center Randomized Double-Blind Placebo-Controlled Active Comparator-Controlled Parallel-Group Multiple Dose	Up to 5 days of Celecoxib 200 mg BID, PRN, or Naproxen 500 mg BID PRN, or Placebo BID PRN Up to 5 days

Information derived from individual clinical study reports.

Figure 10: Numbers of patients by treatment group and withdrawals for multiple dose studies

Study	Number (%) of Patients by Treatment Group					
	Placebo	Celecoxib		Hydrocodone 10 mg/ Acetaminophen 1000 mg	Propoxyphene 100 mg/ Acetaminophen 650 mg	Diclofenac 75 mg SR BID
		100 mg BID	200 mg BID			
085						
Total Patients			91	85		
Completed			82 (90%)	63 (74%)		
Withdrawn			9 (10%)	22 (26%)		
Treatment Failure	-	-	5 (5%)	18 (21%)	-	-
Noncompliance			0 (0%)	2 (2%)		
Adverse Event			3 (3%)	2 (2%)		
Lost to Follow-Up			1 (1%)	0 (0%)		
086						
Total Patients			94	96		
Completed			75 (80%)	72 (75%)		
Withdrawn			19 (20%)	24 (25%)		
Treatment Failure	-	-	17 (18%)	18 (19%)	-	-
Noncompliance			1 (1%)	1 (1%)		
Adverse Event			1 (1%)	5 (5%)		
028						
Total Patients	60	68	62		65	
Completed	1 (2%)	1 (1%)	0 (0%)		1 (2%)	
Withdrawn	59 (98%)	67 (99%)	62 (100%)		64 (98%)	
Pre-existing Violation	2 (3%)	3 (4%)	0 (0%)	-	0 (0%)	-
Noncompliance	3 (5%)	16 (24%)	10 (16%)		19 (29%)	
Treatment Failure	51 (85%)	47 (69%)	43 (69%)		44 (68%)	
Adverse Event	3 (5%)	1 (1%)	9 (15%)		1 (2%)	
074						
Total Patients	58		112			114
Completed	48 (83%)		105 (94%)			109 (96%)
Withdrawn	10 (17%)		7 (6%)			5 (4%)
Pre-existing Violation	1 (2%)	-	0 (0%)	-	-	0 (0%)
Noncompliance	4 (7%)		4 (4%)			1 (1%)
Treatment Failure	2 (3%)		2 (2%)			1 (1%)
Adverse Event	3 (5%)		1 (1%)			3 (3%)
075						
Total Patients	56		111			116
Completed	47 (84%)		98 (88%)			99 (85%)
Withdrawn	9 (16%)		13 (12%)			17 (15%)
Pre-existing Violation	0 (0%)	-	0 (0%)	-	-	2 (2%)
Noncompliance	4 (7%)		7 (6%)			4 (3%)
Treatment Failure	1 (2%)		0 (0%)			0 (0%)
Adverse Event	4 (7%)		6 (5%)			11 (9%)

Data derived from individual clinical study reports.

Of note, a total of about 300 patients were treated with an initial dose of 400 mg celecoxib in the dysmenorrhea and dental pain studies while none of the patients in the postsurgical pain studies were treated with this as an initial dose. The sponsor is proposing 400 mg as an initial dose for the indications requested. Therefore, initial dose of 400 mg for postsurgical studies would need to be extrapolated from these other studies.

C. Postmarketing Experience

1. Results of post marketing experience include the CLASS trial. This study was performed to examine the incidence of GI events in patients treated with 2-4x the recommended dose of celecoxib for up to one year. Figures are extracted from CLASS review.

Figure 11: Summary of serious adverse events for CLASS study

Adverse Event	Celecoxib (n=3987) 2320.4 pt-yrs	Diclofenac (n=1996) 1080.5 pt-yrs	Ibuprofen (n=1985) 1122.5 pt-yrs
Any serious event	270 (11.6)	111 (10.3)	119 (10.6)
Abdominal pain	6 (0.3)	6 (0.6)	2 (0.2)
Accidental fracture	10 (0.4)	4 (0.4)	9 (0.8)
Accidental injury	3 (0.1)	4 (0.4)	7 (0.6)
Angina pectoris	4 (0.2)	5 (0.5)	6 (0.5)
Atrial fibrillation	9 (0.4)	2 (0.2)	3 (0.3)
Back pain	15 (0.6)	3 (0.3)	9 (0.8)
Cardiac failure	9 (0.4)	2 (0.2)	9 (0.8)
Cellulitis	8 (0.3)	1 (<0.1)	1 (<0.1)
Cerebrovascular disorder	4 (0.2)	6 (0.6)	6 (0.5)
Chest pain	11 (0.5)	5 (0.5)	7 (0.6)
Coronary artery disorder	19 (0.8)	5 (0.5)	5 (0.4)
Deep thrombophlebitis	7 (0.3)	5 (0.5)	1 (<0.1)
GI hemorrhage	7 (0.3)	2 (0.2)	1 (<0.1)
Myocardial infarction	19 (0.8)	4 (0.4)	9 (0.8)
Pneumonia	14 (0.6)	5 (0.5)	5 (0.4)
Syncope	5 (0.2)	4 (0.4)	3 (0.3)
Unstable angina	8 (0.3)	4 (0.4)	0

5 From Table 10.g (p 184); N49-00-06-035-102. Owing primarily to the unequal randomization, results are displayed as normalized for length of exposure, rather than crude incidence rates. Table includes any event experienced by a total of at least 10 patients across the three treatment groups.

Figure 12: Serious adverse events causing withdrawal (CLASS study)

Adverse Event	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Any event (% of patients)	22.4	26.5*	23.0
Abdominal Pain	4.3	6.5*	4.9
Dyspepsia	3.8	4.4	3.9
Rash	2.1	0.7*	1.3*
Nausea	1.7	2.8*	1.8
Diarrhea	1.4	2.7*	0.8*
Flatulence	1.2	1.8	1.4
Gastric ulcer	0.3	0.7	1.0*
SGOT increased	0.1	2.1*	0.1
SGPT increased	0.1	2.3*	0.1
Hepatic function abnormal	<0.1	1.1*	<0.1

1. p<0.05 vs. celecoxib. From Table 10d (p. 180), N49-00-06-035-102.

2. Rare serious adverse events are shown in Figure 13.
For serious renal, cardiovascular, hepatic, and dermatologic adverse events, postmarketing reporting rates were generally less than three per 100,000 patient-years. The incidence of acute renal failure was 3.9 per 100,000 patient-years during postmarketing surveillance.

Figure 13: Rare serious adverse events

Event	Reporting Rate
Cardiovascular	
Vasculitis	8 (0.4)
Liver and biliary	
Hepatitis	9 (0.5)
Jaundice	26 (1.5)
Hepatic failure	8 (0.4)
Hemic and lymphatic	
Agranulocytosis	3 (0.2)
Aplastic anemia	6 (0.3)
Pancytopenia	7 (0.4)
Leukopenia	16 (0.9)
Metabolic	
Hypoglycemia	7 (0.4)
Renal	
Interstitial nephritis	4 (0.2)
Skin	
Erythema multiforme	6 (0.3)
Exfoliative dermatitis	3 (0.2)
Stevens-Johnson syndrome	6 (0.3)
Epidermal necrolysis	2 (0.1)
General	
Anaphylactoid reaction	19 (1.1)
Angioedema	34 (1.9)

All numbers represent number of patients (number per 100,000 patient-years).

This list of adverse events has been added to the proposed revised label.

3. Safety Update Report submitted for this sNDA : There are no newly identified adverse events reported with this supplement compared to the original 120 day safety update. There are 17 new deaths not reported with the original report including 2 patients with "cardiac failure", one with "myocardial infarction," one with "pulmonary embolus", 2 with "pneumonia", one with "sepsis" and one with "bacterial infection".

V. Clinical Review Methods

A. Trials Reviewed:

The sponsor has submitted 17 studies in this sNDA, 9 of which the sponsor has designated as pivotal and 7 of which were reviewed in a previous submission. All of the new trials are reviewed and presented here. The new trial number 139 conducted in a dental pain model of acute pain is reviewed in detail although the sponsor did not consider it a pivotal trial (studies 025, 027, 070, and 005 were

reviewed previously and are not presented here; the previous reviewer determined that these studies supported the indication of acute pain). Studies 129 and 130 are new to this submission, are pivotal and are also reviewed in detail for the indication of dysmenorrhea. Studies 028, 029 are postsurgical studies and were reviewed previously. They were not felt to support the indication of acute pain. The results in the dental pain model along with the results in the dysmenorrhea model were used to support the indication of acute pain.

B. Overview of Materials Consulted in Review

The electronically submitted sNDA was used to review the trials. In addition the review of the previous submission of this sNDA was used to assess the efficacy of trials for acute pain.

C. Methods used to Evaluate Data Quality and Integrity

DSI audit was not utilized to assess data integrity for this submission. A DSI audit was performed for the original NDA submission. The present submission consists of multiple studies utilizing multiple investigators. None of the investigators entered an inordinate number of patients that may have biased the data or may have contributed to inappropriate conclusions.

D. Trials were conducted in accordance with accepted ethical standards

E. Evaluation of Financial Disclosure

A certificate of financial interests and arrangements of clinical investigators is provided for all investigators participating in studies 129, 130, and 139. For all other studies no financial disclosure statements are provided because the studies were completed prior to the implementation of 21 CFR part 54.

VI. Integrated Review of Efficacy

A. Conclusions

For the management of acute pain the usual requirement for efficacy is replicated studies in at least 2 models of acute pain. For a single dose of analgesic in the management of acute pain, celecoxib has been shown to be efficacious in 2 models of acute pain including post-surgical dental pain and dysmenorrhea. In the label the statement that [redacted] should be deleted.

B. General Approach to Review of Efficacy

For the post-oral surgery (dental pain) studies, study 139 was reviewed in detail. Studies 025,027, and 070 were reviewed in detail in a previous submission of this sNDA and are summarized in this review. Studies 129 and 130 for dysmenorrhea were reviewed in detail in order to confirm efficacy in a second pain model. Studies 082,083,085,086 were designated as pivotal studies by the sponsor and were reviewed in detail to support efficacy in a third pain model (post-surgery). Studies 074 and 075 were also reviewed to support the efficacy in the post-surgical model. Study 078 was reviewed to support the efficacy in an additional pain model (low back pain). Studies 085, 086, 074, 075 were reviewed to establish efficacy in the multidose period.

C. Detailed Review of Trials by Indication

1. Indication: management of acute pain
    a. trial N49-99-02-139.

Randomized double blind active and placebo controlled single dose comparison of the analgesic activity of celecoxib 200 mg fine suspension, celecoxib 200 mg oral capsule and placebo in a postsurgical dental pain model.

b. objectives/rationale

The primary objective of this study was to compare the analgesic activity of single doses of celecoxib (200 mg) oral fine suspension and celecoxib (200 mg) capsule versus placebo in patients with moderate to severe pain in a post surgical dental pain model. The secondary objectives of the study were 1) to compare the analgesic activity among the suspension or capsule in patients with moderate to severe pain in a postsurgical dental pain model; 2) to compare the analgesic activity of ibuprofen (400 mg) to placebo in patients with moderate to severe pain in the dental pain model; 3) to correlate plasma levels of celecoxib suspension and oral capsule with analgesic activity in patients with moderate to severe pain in a postsurgical dental pain model; and 4) to assess the safety of single doses of celecoxib fine suspension and oral capsule in patients with moderate to severe pain in a postsurgical dental pain model.

The sponsor submitted results of this study to support the efficacy and safety of the capsule form (and not the suspension form which is also used in this trial) of celecoxib for the sNDA. This corresponds to the marketed capsule form used in other trials.

c. design

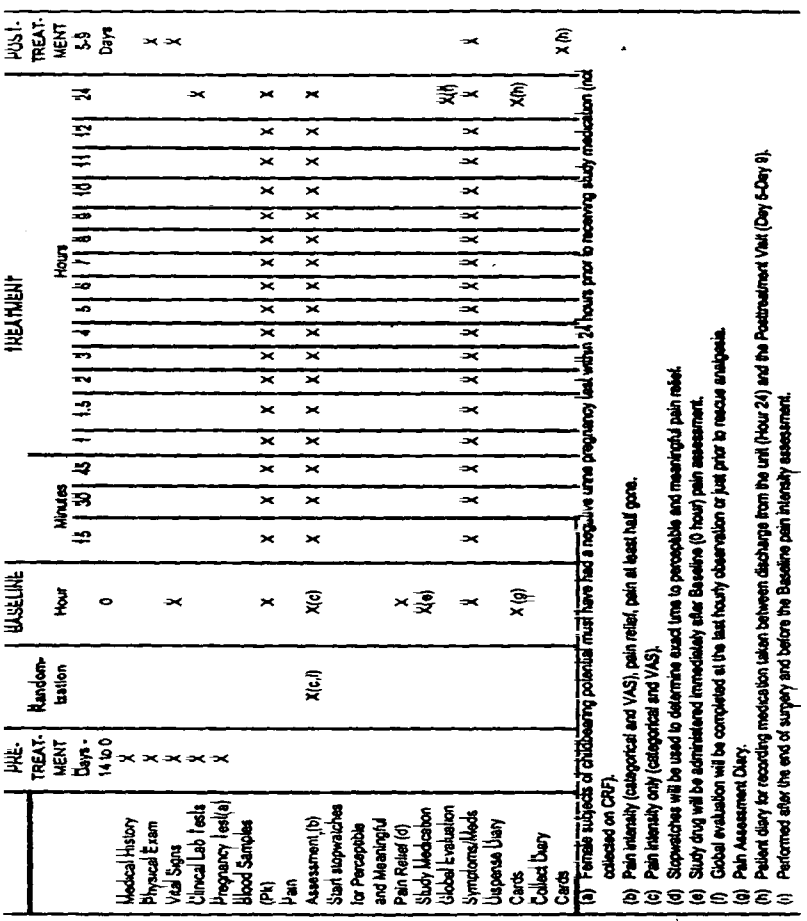
The trial was a double blind triple dummy design.. A group of 205 patients (49 to 53 in each treatment group) requiring extraction of two or more impacted third

molars requiring bone removal, including men and women at least 18 years of age, were randomized to receive a single dose of celecoxib (200 mg) oral fine suspension, celecoxib (200 mg) oral capsule, ibuprofen (400 mg), or placebo. Patients who were experiencing moderate to severe postoperative pain (Categorical) and Pain Intensity (VAS score) > 50 mm within 6 hours following the completion of surgery and met all of the inclusion/exclusion criteria were admitted to the study and were administered their assigned study medication. Times to Perceptible and Meaningful Pain Relief were evaluated using two stopwatches. Pain assessments were collected up to 24 hours after dosing, or until rescue medication was taken. A Patient's Global Evaluation (overall impression) of study medication was recorded at the end of the Treatment period or at the time of rescue. All patients were required to stay in the dental unit up to 24 hours following surgery.

d. protocol

A schedule of observations is shown in Figure 14 (see next page).

Figure 14: Schedule of observations



Inclusion criteria: To have qualified for admission to the study, a candidate must have satisfied the criteria listed below: the patient was 18 years of age or older; if the patient was a female of childbearing potential she was using adequate contraception was not lactating and had a negative urine pregnancy test within 24 hours prior to receiving study medication; the patient was in good health as determined by the investigator o the basis of medical history and physical examination; the patient required surgical extraction of two or more impacted third molar teeth requiring bone removal one of which was mandibular and was experiencing moderate to severe postsurgical dental pain; the patient had a baseline pain intensity of 50 mm on VAS; the patient provided written informed consent.

Exclusion criteria: Candidates were excluded from enrollment in the study if they met any of the criteria listed below: the patient had a history of uncontrolled chronic disease which in the opinion of the investigator would contraindicate study participation; the patient had a history of a gastrointestinal ulcer within the past 6 months or was currently experiencing significant GI complaints as determined by the investigator; the patient had used analgesics or other agents during the 6 hours preceding surgery that could confound the analgesic responses; specifically excluded were tricyclic antidepressants, narcotic analgesic, antihistamines, tranquilizers, hypnotics, sedatives, NSAIDs or corticosteroids; presurgical medications such as xylocaine with epinephrine, Brevital, fentanyl; Demerol and diazepam were exempt for this exclusion although Demerol required 3 hour washout period; the patient had a history of known analgesic or narcotic abuse; the patient was unwilling to abstain form alcohol other than the alcohol used in the preparation of study medication for at least 6 hours prior to the and 24 hours after the dosing with study medication; the patient had received any investigational medication within 30 days prior to the first dose of the study medication or was scheduled to receive an investigation drug other than celecoxib during the course of the study; the patient had a known hypersensitivity to analgesics, NSAIDs, cyclooxygenase inhibitors, lactose or sulfonamides; the patient had any laboratory abnormality which in the opinion of the investigator would contraindicate study participation including AST, ALT, or BUN>1.5x the upper limit of the reference range; the patient had a history or current presence of nasal polyps, bronchospasm, or angioedema induced by NSAIDs; the patient had been previously admitted to the study; the patient was unable to tolerate the equivalent of a glass of beer or wine.

Comment: It is not clear why demerol and diazepam were exempted from exclusion.

2. endpoints

The primary measures of efficacy were: time-specific pain intensity difference (PID-categorical) derived by subtracting the pain intensity scores at the post dose

time points from the baseline score; time-specific pain relief (PR) measured at the post dose time points; time-specific sum of PID on the categorical scale and PR (PRID) at the post dose time points; time to onset of analgesia; and time to rescue medication.

Comment: these are acceptable endpoints and are the ones preferred by the Division

Safety was evaluated based on physical examination, vital signs, laboratory values and adverse events.

3 statistical considerations

All measures of efficacy in this study were derived from patient diaries and represent standard measures employed in studies of analgesic agents. Time specific PID, time specific PRID, and patient's global evaluation were analyzed using a general linear model with treatment as a factor and baseline pain intensity as a covariate. Time specific PR was analyzed using a general linear model with treatment as a factor. Time to onset of analgesia was defined as being equal to time to perceptible pain relief when both perceptible and meaningful pain relief were experienced. Time to perceptible pain relief, time to meaningful pain relief, time to onset of analgesia, time first experienced at least 50% pain relief (starting pain at least half gone) and time to rescue medication were analyzed by survival analysis method. For patients who took rescue medication after 1 hour but prior to 24 hours, missing values after the last recorded value were extrapolated by LOCF and BOCF approaches.

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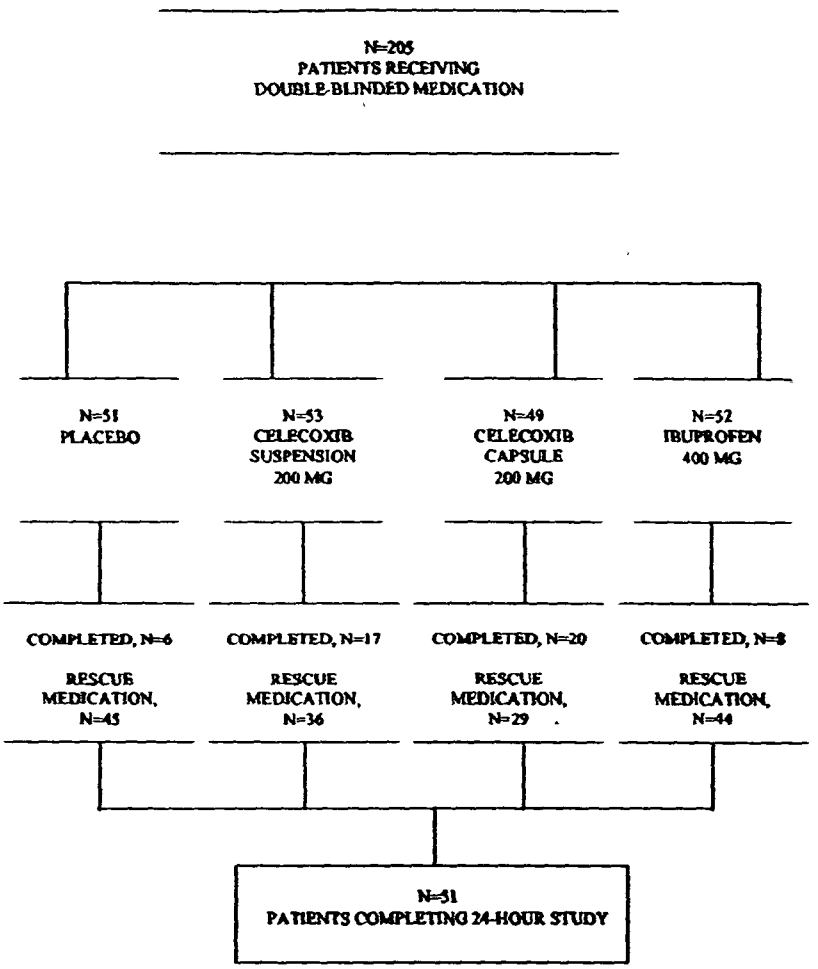
d. Results

Figure 15: Patient disposition



* Note: Data was obtained from Table T2.

Patient disposition and the reasons for termination are provided in Figure 15. Patient demographics and other baseline characteristics did not differ between the groups. Medication compliance was monitored by the site personnel.

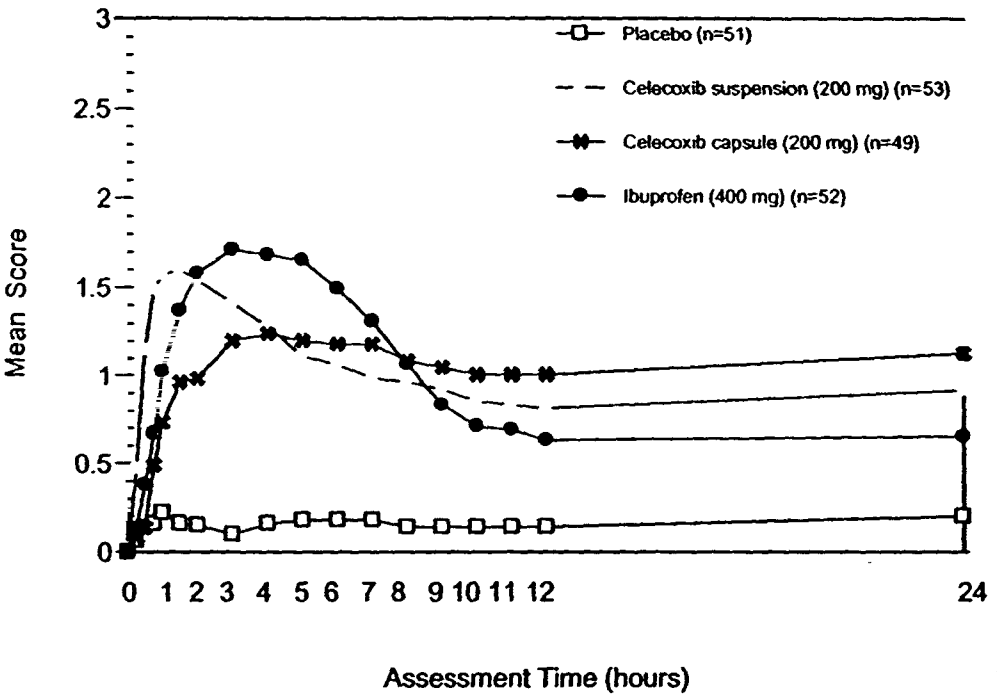
Of note, only 51 patients out of a starting group of 205 completed the 24 hour study. Most patients required rescue medication and were withdrawn from the study. However, greater numbers of patients in the celecoxib group completed the study compared to placebo or ibuprofen.

efficacy endpoint outcomes

Analysis of primary efficacy measures:

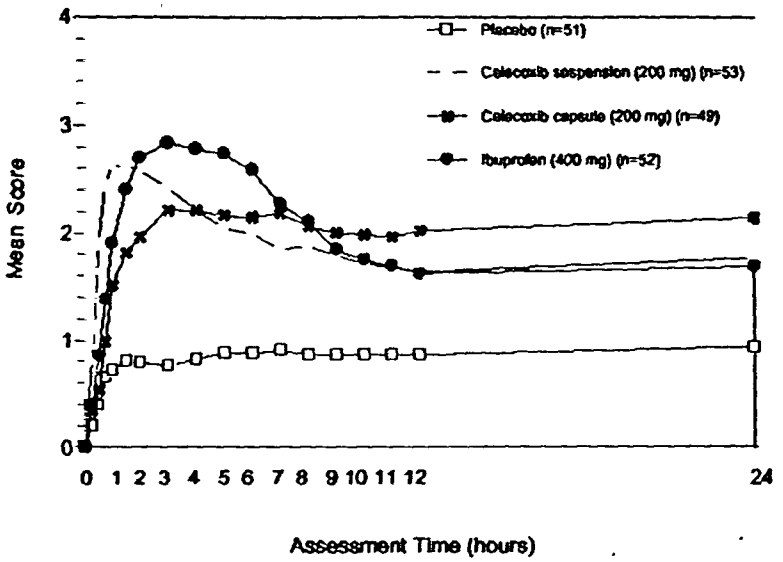
Mean PID scores (categorical-LOCF) are shown in Figure 16. Results obtained from this approach show that celecoxib capsule was statistically significantly superior to placebo at each time point starting at .75 hours. Ibuprofen separated from celecoxib and placebo by .5 hours. By .75 hours celecoxib showed no difference from ibuprofen. Differences from placebo for both persisted through 24 hours, although after 9 hours celecoxib was numerically superior to ibuprofen.

Figure 16: Mean PID scores



The mean PR (LOCF) scores are shown in the next figure (17). Results from the LOCF approach again show that celecoxib capsule was statistically significantly superior to placebo at each assessment through 24 hours starting at 1 hour. However, ibuprofen was significantly superior to placebo starting at .5

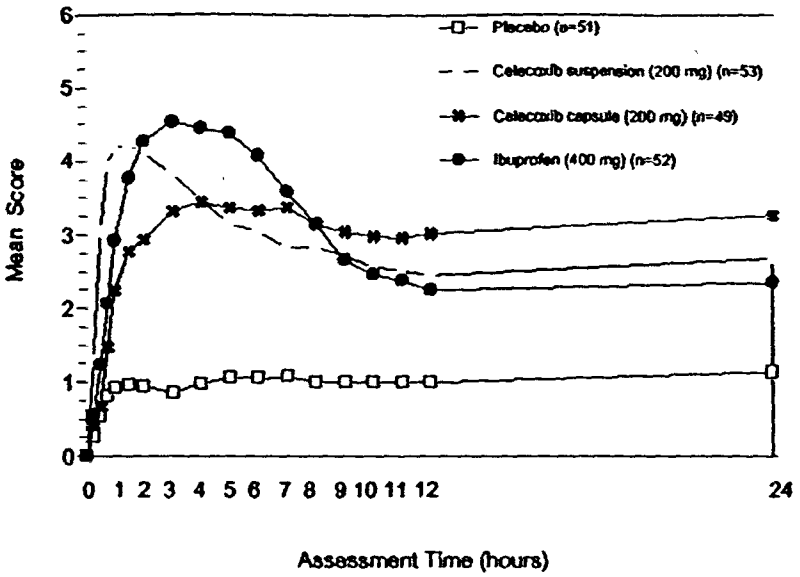
Figure 17: Mean PR scores



hours. Again, both remained significantly superior to placebo out to 24 hours.

The mean PRID for each treatment are presented in figure 18. Results obtained from the LOCF approach demonstrate that celecoxib capsule was statistically significantly superior to placebo at each assessment starting at .75 hours. However, ibuprofen was significantly superior to celecoxib and placebo starting at .5 hours but statistically no different from celecoxib by .75 hours. Both remained superior to placebo out to 24 hours.

Figure 18: Mean PRID scores



The time to onset of analgesia is shown in Figure 19. All active treatment groups showed statistically significant differences from the placebo group, and ibuprofen was superior to celecoxib capsule.

Figure 19: Time to onset of Analgesia

Treatment Group	Patients Who Experienced Analgesia N (%)	Median Time to Onset of Analgesia (hr:min)[†]
Placebo (N = 51)	10 (20%)	> 24:00 [C]
Celecoxib suspension, 200 mg (N = 53)	43 (81%)	00:19 [A]
Celecoxib capsule, 200 mg (N = 49)	31 (63%)	00:40 [B]
Ibuprofen, 400 mg (N = 52)	43 (83%)	00:28 [A]

Source: Table T11

[†] Kaplan-Meier estimate
[‡] Log-rank test applied as in Fisher's protected LSD. Treatments with the same letter (A, B, or C) are not statistically significantly different from one another.

Figure 20: Time to rescue medication

Treatment Group	Patients Who Required Rescue Medication N (%)	Median Time to Rescue Medication (hr:min)[1][2]
Placebo (N = 51)	45 (88%)	01:26 [B]
Celecoxib suspension, 200 mg (N = 53)	36 (68%)	07:06 [A]
Celecoxib capsule, 200 mg (N = 49)	29 (59%)	09:02 [A]
Ibuprofen, 400 mg (N = 52)	44 (85%)	08:08 [A]

Source: Table T12

[1] Kaplan-Meier estimate
[2] Log-rank test applied as in Fisher's protected LSD. Treatments with the same letter (A or B) are not statistically significantly different from one another.

The time to rescue medication is shown in Figure 20. All active treatment groups showed statistically significant differences from the placebo group. There were no statistically significant differences between the active treatment groups.

Analysis of secondary efficacy measures:

For the following endpoints, all active treatment groups showed statistically significant differences from placebo that favored the treatment groups (using LOCF) including: time to perceptible relief, time to meaningful pain relief, time first experienced at least 50% pain relief, pain intensity difference (PID-VAS), peak pain intensity difference and peak pain relief (PPID and PPR), patient's global evaluation, sum of pain intensity difference (SPID-categorical), sum of pain intensity difference (SPID-VAS), sum of pain relief (TOTPAR), sum of PRID scores (SPRID), and percent of patients experiencing at least 50% pain relief.

e. reviewers comments/conclusions of study results

On the basis of study 139, and in conjunction with the previous studies of celecoxib in the dental pain model (see previous reviews for details of additional studies), a single dose of celecoxib capsule (200 mg) appears to be an efficacious analgesic for patients with moderate to severe postsurgical dental pain.

A review of studies 025 (25, 50, 200 mg single dose), 027 (100, 200 mg single dose), 070 (50, 100, 200, 400 mg single dose), 005 (100, 400 mg single dose) demonstrated that celecoxib showed significantly greater improvement in pain compared to placebo for measures such as PR, PRID, PID starting at 45 minutes to 1 hour post dose and continuing through 7-8 hours post dose. In general, a positive dose response was present and the celecoxib dose of 400 mg exhibited a numerically greater and longer analgesic efficacy than celecoxib 50 mg, 100 mg, and 200 mg doses and placebo. However, ibuprofen 400 mg and naproxen sodium 550 mg showed consistent significant superiority in all pain measurements over celecoxib starting at .75 hours for ibuprofen and .5 hours for naproxen in study 027. Additionally time to rescue was significantly longer for celecoxib compared to placebo and best at the 400 mg dose. Celecoxib 200 or 400 mg showed a significantly shorter time to perceptible pain relief compared to placebo. For further detail of these studies the reader is referred to the review of the original NDA by Drs. Averbuch and Witter.

The results of the present study 139 compare favorably with these results. Specifically, at the chosen 200 mg single dose, celecoxib showed significantly greater improvement in pain compared to placebo starting at .75-1 hour post dose for the time specific efficacy measures. In addition the time to onset of analgesia as well as the time to rescue medication was significantly different from placebo. The present study met all the primary endpoints. **Furthermore, these studies demonstrated that celecoxib was superior to placebo even out to 24 hours, supporting the dosing regimen of daily treatment.**

Therefore, single doses of celecoxib 200 mg or 400 mg, appear to provide consistent efficacy over placebo in this model of pain, although at the earliest time points ibuprofen and naproxen appear to be superior to celecoxib. The 400 mg dose demonstrated somewhat greater efficacy than the 200 mg dose. The dosing interval of 24 hours is supported by the time specific efficacy curves. The median time to rescue of 9 hours in those that needed rescue, supports the sponsors' labeling that an additional dose may be taken if necessary.

2 Indication -Treatment of dysmenorrhea

a. Trial 3N-49-99-02-129

This is a randomized double blind active and placebo controlled trial using a crossover design to assess the analgesic activity of celecoxib in the treatment of patients with primary dysmenorrhea, a second model of acute pain.

b. Objectives and rationale

The primary objective of this study was to compare the analgesic efficacy of celecoxib versus placebo in the treatment of patients with moderate to severe menstrual cramping pain associated with primary dysmenorrhea. The time to

onset was also assessed. The secondary objectives were to compare the analgesic efficacy of naproxen sodium to placebo and to evaluate the safety of celecoxib.

c. Design

The trial was a double blind three way crossover design to include celecoxib, naproxen sodium, and placebo. Each patient was randomized to one of 6 treatment sequences in a complete and balanced block design, and potentially received each drug during one of 3 menstrual cycles (see Figure 21). Duration

Figure 21: Crossover block design

Period	Treatment Sequence					
	S1	S2	S3	S4	S5	S6
P1	Celecoxib	Placebo	Naproxen Na	Celecoxib	Placebo	Naproxen Na
P2	Naproxen Na	Celecoxib	Placebo	Placebo	Naproxen Na	Celecoxib
P3	Placebo	Naproxen Na	Celecoxib	Naproxen Na	Celecoxib	Placebo

Source: Protocol

of each treatment was up to three days. Initial treatment for each cycle consisted of one dose of the active study medication with placebo for the other 2 treatments, or placebo for both active treatments.

Figure 22: Protocol and evaluations

	Pretreatment		Each Treatment Period						End of Study (f)
			Single Dose Day 1		Multiple Dose			Monthly Follow-up (e)	
	Screening	Baseline	0 hour	(a)	End of 12 hours	Day 2	Day 3		
Informed Consent	X								
Inclusion/ Exclusion	X								
Medical History	X								
Physical Exam	X								X
Vital Signs	X	X							X
Clinical Lab	X								X
Pregnancy Test (b)	X	X	X					X	X
Drug Dispensed		X						X	
Drug Taken			X		PRN	PRN	PRN		
Pain Assessments (c)			X	X		X	X		
Global Evaluation (d)					X	X	X		
Drug Accountability								X	X
Concomitant Meds Review		X	X	X	X	X	X	X	X
Diary Cards		X	X	X	X	X	X	X	X
Adverse Events (g)		X	X	X	X	X	X	X	X

Source: Protocol

(a) 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hours after dosing

(b) If the patient did not take study medication for a cycle, she was required to have an additional urine pregnancy test at least 2 weeks prior to the anticipated dosing date in the next menstrual cycle.

(c) Pain intensity (categorical), pain relief, time to onset of perceptible pain relief and meaningful pain relief. On Days 2 and 3, pain intensity was assessed prior to dosing and prior to rescue medication, and maximum pain intensity was assessed at bedtime.

(d) Or prior to rescue medication.

(e) Within 1 week after end of the menstrual cycle.

(f) Within 1 week after end of the third menstrual cycle in which patient was treated.

(g) Recorded in patient diary when occurred

d. Protocol

1 population

Women of age 18-44 with a history of primary dysmenorrhea with moderate to severe menstrual cramping pain requiring analgesic medication for at least four of the previous six menstrual cycles were enrolled. Each patient was randomized to

one of six treatment groups such that each patient received one of the three treatment regimens during each of three menstrual cycles:

1)Celecoxib 400 mg initial dose , day one followed by celecoxib 200 mg every 12 hours prn up to a total daily dose of 400 mg on days 2 and 3.
2) Naproxen sodium 550 mg initial dose, day 1 followed by a single dose of naproxen 550 mg every 12 hours prn up to a total daily dose of 1100 mg on days 2 and 3.
3) Placebo to match celecoxib and naproxen capsules.

Treatment began with the onset of moderate to severe menstrual cramping pain after the start of menses in each of three menstrual cycles. During the single dose assessment period, pain assessments were made at the designated time points up to 12 hours after first dose. During the multiple dose assessment period patients completed pain assessments before additional doses. The protocol and evaluations are shown in Figure 22.

Patients who were enrolled in this study had to satisfy the following criteria:
1. The patient was female, between the ages of 18 and 44 years old, with a regular menstrual cycle (28 ±7 days).
2. The patient had a history of primary dysmenorrhea with moderate to severe menstrual cramping pain requiring analgesic medication for at least four of six previous menstrual cycles prior to enrollment.
3. The patient was in satisfactory health (with the exception of the condition being studied) as determined by the Investigator on the basis of medical history and physical examination.
4. The patient had a complete physical exam (including pelvic and normal pap smear) performed by an Investigator/Sub-Investigator associated with this study. The patient did not have to undergo a pap smear at screening if she had a normal pap smear performed within six months prior to the screening visit and the results were normal.
5. The patient or patient's partner was using an adequate method(s) of contraception (see exclusion criteria #5).
6. The patient was not lactating or breast feeding, and had a negative urine pregnancy test at screening and at Baseline.
7. The patient agreed to take the first dose of study medication when the menstrual cramping pain associated with primary dysmenorrhea was moderate to severe and menses had begun.
8. The patient provided written informed consent prior to admission to this study and was willing and able to comply with study restrictions and requirements.
9. The patient had access to a telephone or pager in order to communicate with the clinical site.
10. The patient had onset of primary dysmenorrhea within 5 years of menarche.

A patient was excluded from this study if she met any one of the criteria listed below:

1. Chronic use of analgesics or non-steroidal anti-inflammatory medications (NSAIDs), tranquilizers, muscle relaxants, tricyclic antidepressants, and neuroleptics (patients had to abstain from such drugs within twelve hours prior to taking study medication through the end of study participation).
2. The patient had used naproxen, Vioxx, or any long acting NSAID (e.g., piroxicam and oxaprozin) within five days of taking study medication.
3. In the opinion of the Investigator (based upon physical examination and/or previous diagnostic evaluations and/or abnormal pap smear) the patient had secondary dysmenorrhea and/or evidence of disease or abnormality of the reproductive organs.
4. The patient was pregnant or breast-feeding.
5. The patient was using an intrauterine device, had received an injection of Depo-Provera®, Lupron Depot, or other GnRH analogues, a Norplant ® implant, or had taken oral contraceptives within six months prior to study entry. Patients who had been on a stable oral contraceptive dose but who continued to have moderate to severe menstrual cramping pain associated with primary dysmenorrhea for the six months prior to study entry were allowed to enroll in the study.
6. The patient had any cognitive impairment that would, in the Investigator's opinion, preclude study participation or compliance with protocol mandated procedures.
7. The patient had dysphagia, difficulty swallowing capsules and tablets, or was unable to tolerate oral medication.
8. The patient had been diagnosed as having or had treatment initiated for esophageal, gastric, pyloric channel, or duodenal ulceration within the 30 days prior to receiving the first dose of study medication.
9. The patient had a history of uncontrolled chronic disease, which, in the opinion of the Investigator, would have contraindicated study participation or confounded interpretation of results.
10. The patient at the time of enrollment was or had been treated (i.e., surgery, chemotherapy, radiation therapy, etc.) and/or had been in remission for any cancer other than basal cell carcinoma for less than two years prior to screening.
11. The patient had any laboratory abnormality at screening, which, in the opinion of the Investigator, would have contraindicated study participation, including AST, ALT, BUN, or creatinine =1.5 times the upper limit of the reference range.
12. The patient had lactose intolerance which required significant dietary modification or treatment with enzyme supplementation.
13. The patient had a history of hypersensitivity to any NSAID, cyclooxygenase inhibitor, sulfonamides, opiates or any analgesic which had a cross sensitivity to the medications used in this study.
14. The patient had a history of known alcohol, analgesic, or other substance abuse
(including sedatives and hypnotics) within the two years prior to screening.
15. The patient at the time of enrollment was receiving agents that could have confounded assessment of analgesic activity. Such medications included tricyclic anti-depressants and neuroleptics.

16. The patient was unwilling to abstain from the routine use of NSAIDs and analgesics during this study.
17. The patient had received any investigational medication within the 30 days prior
to the first dose of study medication or was scheduled to receive any investigational drug other than celecoxib during the course of this study.
18. The patient was unwilling to abstain from alcohol six hours prior to the first dose of study medication through the three days of pain assessments in each cycle.
19. The patient had been previously admitted to this study.
20. The patient had a history of vomiting during the first two days of menstrual flow.

2 Endpoints

The primary measures of efficacy were: summed pain intensity differences through 8 hours (SPID8), total pain relief through 8 hours (TOTPAR8). The secondary measures of efficacy for the single dose assessment period included (but were not limited to): time to onset of analgesia; time to rescue medication; time to perceptible pain relief; time to meaningful pain relief. For the multiple dose assessment period: daily maximum pain intensity; number of patients who dropped out due to treatment failure/rescue medication; patient global evaluation; pain intensity before each dose for that day.

Comment: The Division does not recommend TOTPAR and SPID as primary endpoints because they do not provide a complete picture of the characteristics of an acute analgesic (see below).

Safety was evaluated based on physical exam, vital signs, laboratory values and adverse events.

3 Statistical considerations

Patients in the six treatment sequences were compared using analysis of variance with treatment sequence as a factor with respect to the following baseline variables: age, height, weight, temperature, pulse, respiration rate, systolic blood pressure, diastolic blood pressure, age at onset of primary dysmenorrhea, and number of days pain experienced in a cycle. Treatment sequences were compared with respect to race/ethnic origin using Fisher's Exact test. Treatments with respect to baseline pain intensity were compared using Cochran-Mantel-Haenszel test stratified by treatment sequence.

SPID, TOTPAR, SPRID, etc were analyzed by ANOVA with fixed effect for treatment, period, sequence and random effect for patient.

For the time to onset of analgesia, time to rescue medication, time to perceptible pain relief, time to meaningful pain relief, and the median time to the event for each treatment period was calculated using Kaplan-Meier estimator with Miller's adjustment. Treatment periods were compared by Cox regression stratified by patient.

Safety analyses were performed. The incidence of adverse events causing withdrawal and serious adverse events were tabulated. The incidence of adverse events by treatment period within body system and incidence of adverse events causing withdrawal were summarized.

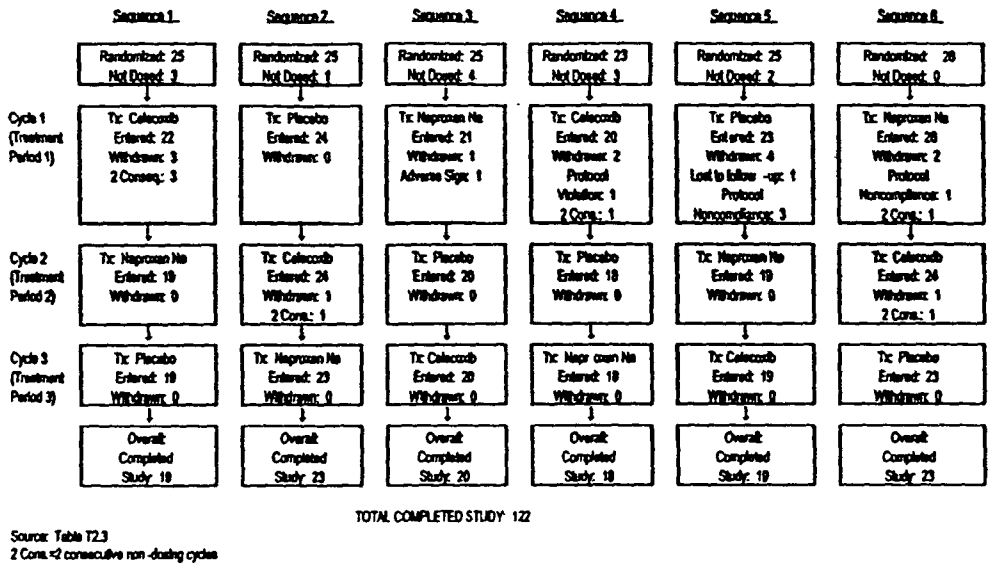
d. Results
1 Patient disposition

Figure 23 presents the disposition of patients by treatment sequence and cycle. Figure 24 presents the disposition of patients by treatment sequence and study medication. There were 87 protocol deviations/violations due to "post cycle" 1,2 ,3 visit out of window and 8 deviations/violations due to dose not taken according to protocol.

The study cohort consisted of 122 patients who took study medication in all three treatment periods (149 patients were originally randomized). Six patients withdrew consent, 3 patients moved or were lost to follow up, 3 patients started other medications (including Neurontin, Aleve, OCP), one had a sulfa allergy, one had elevated AST/ALT, one had an adverse sign (not enumerated), and the remainder had more than 2 consecutive cycles without pain. There were no differences across treatment sequences for symptoms associated with dysmenorrhea. Baseline characteristics for the randomized patients did not demonstrate any significant differences between the groups except for the mean weight (p=.0347).

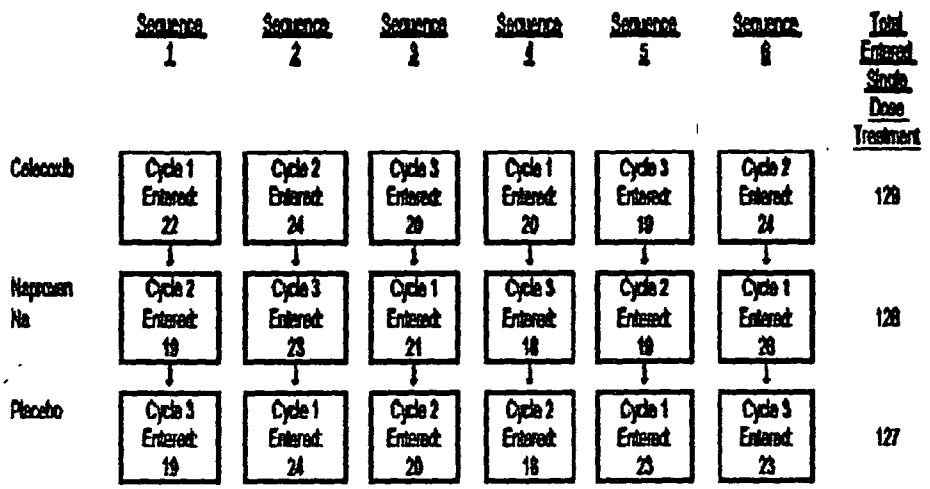
Comment: The number of patient withdrawals was unlikely to contribute significantly to the outcome of this study.

Figure 23: Disposition of patients by treatment sequence and cycle



Source: Table T2.3
2 Cons.=2 consecutive non-dosing cycles

Figure 24: Disposition of patients by treatment sequence and study medication



Source: Table 2.3

Treatment compliance was monitored by counting the number of capsules at each follow-up visit.

2 Efficacy endpoints outcomes

Analysis of primary endpoints:

Results of SPID (8) based on LOCF are shown in Figure 25. The mean SPID (8) in the celecoxib treatment period was significantly greater than in the placebo treatment period (scoring on scale of 0-3 with a range of –8 to 24). The mean score in the naproxen group was significantly greater that the mean of the celecoxib treatment group.

Figure 25: SPID 8 results

Treatment	Mean
Naproxen Na 550 mg (N=122)	11.48 (A)
Celecoxib 400 mg (N=122)	10.06 (B)
Placebo (N=122)	5.96 (C)

Source: Table T7.1
(a) From ANOVA with fixed effects for baseline PI, treatment, period, sequence and random effect for patient. Treatments with the same letter are not significantly different from each other.

Analysis of TOTPAR(8) based on LOCF approach is presented in Figure 26. The mean TOTPAR score for the celecoxib treament period was significantly greater than the mean for the placebo treatment period (scoring on a scale of 0-4 with a range of 0-32). There was no significant difference between the TOTPAR scores for the naproxen and celecoxib treatment periods.

Figure 26: TOTPAR results

Treatment	Mean
Naproxen Na 550 mg (N=122)	20.59 (A)
Celecoxib 400 mg (N=122)	18.28 (A)
Placebo (N=122)	12.82 (B)

Source: Table T8.1
(a) From ANOVA with fixed effects for baseline PI, treatment, period, sequence and random effect for patient. Treatments with the same letter are not significantly different from each other.

Of note, the scores for efficacy endpoints for the naproxen treated groups were always significantly greater than placebo.

Analysis of secondary endpoints:

The differences between the celecoxib treatment period and placebo and between naproxen and placebo for the time to onset of analgesia were significantly different (52 minutes for celecoxib, 45 minutes for naproxen, 65 minutes for placebo), although probably of little clinical relevance, at least for celecoxib (see Figure 27).

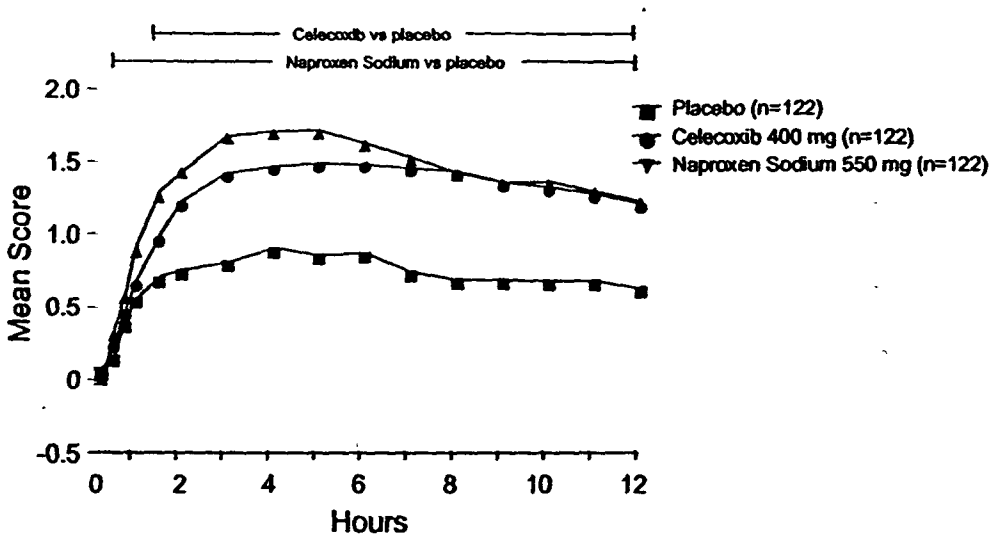
Figure 27: Time to onset of analgesia

Treatment	Patients Who Experienced Analgesia		Median Time	
	N	%	HH:MM	(A, B)
Naproxen Sodium 550 mg (N=122)	105	86%	00:45	(A)
Celecoxib 400 mg (N=122)	93	76%	00:52	(A)
Placebo (N=122)	72	59%	01:05	(B)

Source: Table T13
(a) Kaplan-Meier estimate
(b) COX regression stratified by patient applied as in Fishers protected LSD. Treatments with the same letter are not significantly different from each other.

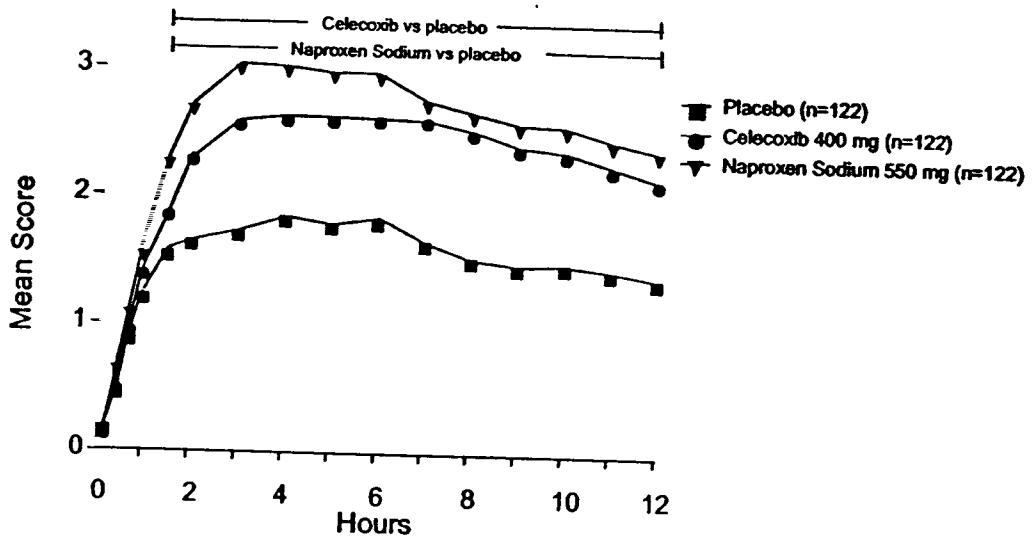
The mean PID (Figure 28) score during celecoxib treatment was significantly different from the mean score during the placebo treatment period at 1.5 through 12 hours. The mean score during the naproxen treatment period was significantly different from the mean score during the placebo treatment period starting at 0.75 hour through 12 hours.

Figure 28: Mean PID scores



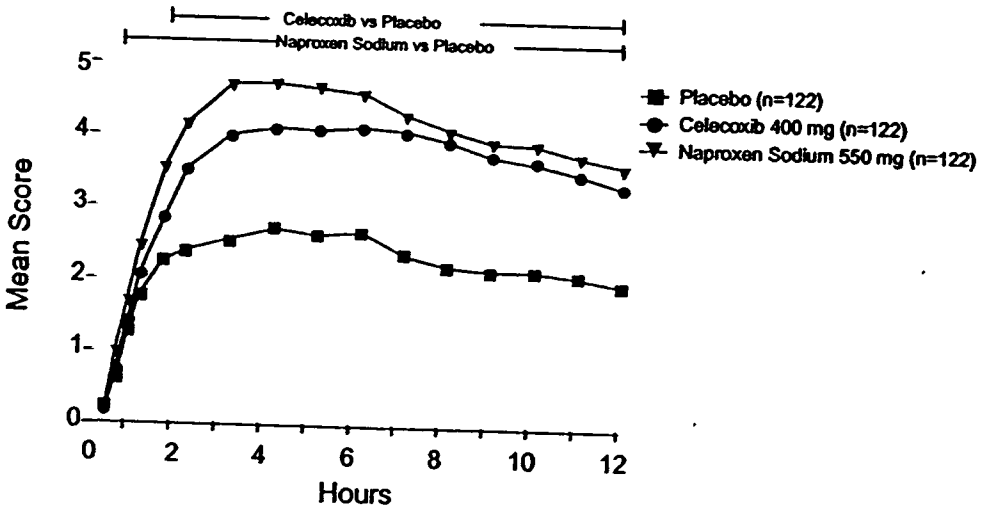
The mean PR score (Figure 29) in the celecoxib treatment period was significantly different from the effect of placebo at 1.5 hours through 12 hours. The mean PR score for the naproxen sodium treatment period was significantly different from the mean score during the placebo treatment period starting at 1.5 hours through 12 hours.

Figure 29: Mean PR scores



The mean PRID (Figure 30) score in the celecoxib treatment period was significantly different from the mean score during the placebo treatment period starting at 1.5 hours, and remained significant through 12 hours.

Figure 30: Mean PRID scores



In addition, the following endpoints were significantly different between celecoxib and placebo in favor of the active treatment celecoxib: time to rescue medication (see Figure 31);

Figure 31: Time to rescue medication

Treatment	Patients Who Took Rescue Medication		Median Time	
	N	%	HH:MM	(A, B)
Naproxen Sodium 550 mg (N=122)	24	20%	>12:00	(A)
Celecoxib 400 mg (N=122)	25	20%	>12.00	(A)
Placebo (N=122)	57	47%	>12.00	(B)

Source. Table T14
(a) Kaplan-Meier estimate
(b) COX regression stratified by patient applied as in Fishers protected LSD. Treatments with the same letter are not significantly different from each other.

mean PPID (peak pain intensity difference) (1.81 for celecoxib versus 1.37 for placebo versus 2.00 for naproxen); SPID (12) (15.43 for celecoxib versus 8.75 for placebo versus 16.94 for naproxen); mean PPR (3.04 for celecoxib versus 2.58 for placeob versus 3.44 for naproxen); mean TOTPAR (12) (27.82 for celecoxib versus 18.89 for placebo versus 30.85 for naproxen); SPRID (8) and SPRID (12); patients global evaluation.

However, the time to onset of perceptible pain relief was not significantly different between the celecoxib, naproxen and placebo groups. The time to onset of meaningful pain relief was not significantly different between the celecoxib and placebo groups, but was different between the naproxen and placebo groups.

Fifty percent of patients in the celecoxib and the naproxen sodium treatment periods compared to 35% of patients during the placebo treatment period required only one dose of study medication in the first 24 hours of the treatment period. A second dose of study medication was sufficient to allow another 24%, 27% and 12% of patients in the celecoxib, naproxen sodium and placebo treatment periods, respectively, to complete the first 24 hours of each treatment period.

The number of patients remedicating on days 2 and 3 declined rapidly and therefore the results of the efficacy measures during the multi-dose assessment period were inconclusive. After the first day of dosing in each period, the majority of patients did not require additional study medication.

Re-analysis of efficacy data

Due to the fact that this study appeared to be overpowered in the sense that each treatment group had approximately 120 subjects (for pain studies the Analgesic Guidance recommends to include no more than 50-60 subjects per arm to provide statistically as well as clinically meaningful data), and that the population analyzed by the sponsor did not include 27 patients who were part of the original randomization), the Agency requested that the sponsor perform several additional analyses as described.

A. Analysis using the modified ITT population (to include those patients who took study medication) for cycle 1 only, to include all primary and secondary endpoints. The purpose of this analysis was to restrict the number of patients to approximately 40 since this data included only cycle 1 and there was no pooling of subjects due to crossover.

B. Modified ITT population (to include those patients who took study medication who completed any cycle for all cycles combined using the cross over design.*
(The purpose of this analysis was to re-analyze the data as the sponsor did originally but with the modified population).

*The analyses in 2 should include data for SPID8, 12; TOTPAR8, 12; time to rescue medication; and data at 12 hours for PID, PR, PRID (12 hour data should be for those individuals not requiring rescue medication at 12 hours; analyses for maximum pain intensity in Day 2 assessed at bedtime). Include pairwise p values for all analyses described above as well as the pairwise p-values for the original analyses for the endpoints above.

The following methods of imputation was used:
1. If only one observation (one cycle) is available: for each individual patient impute this to other cycles.
2. If data is available from 2 cycles: for each individual patient if placebo is missing, impute results from celecoxib for the placebo; if celecoxib is missing impute data from placebo; if naproxen is missing, then impute data from placebo.

For (A): SPID8, 12 and TOTPAR8, and 12 all remain significantly different from placebo (Figure 32).

Figure 32: Re-analysis of SPID and TOTPAR

Treatment	SPID8*	SPID12	TOTPAR8	TOTPAR12
Naproxen	11.2 (6.27) A	15.47 (9.99) A	20.36 (9.23) A	29.27 (14.58) A
Celecoxib	11.42 (5.95) A	16.69 (9.49) A	20.87 (9.11) A	30.80 (14.11) A
Placebo	6.74 (7.23) B	10.08 (10.99) B	13.95 (10.92) B	20.95 (17.48) B
Rx p value	<.001	.003	.001	.006

*Mean (STD)

Pairwise comparisons with placebo reveal that celecoxib and naproxen are both significantly different. Additional analyses for SPRID8 and 12 are also significantly different from placebo. For PID, PR, and PRID celecoxib separates from placebo starting at 1.5 hours (similar to naproxen) and is no longer different from placebo at hour 10. The median time to onset of analgesia is significantly shorter than placebo (32 vs 52 minutes). Time to rescue is significantly shorter for celecoxib.

Further analyses using the conservative imputation method (B) described above provide results consistent with the sponsors' original analyses.

e. Reviewers comments and conclusions

On the basis of study 129 celecoxib appears to be an efficacious analgesic for patients with moderate to severe pain associated with dysmenorrhea. All primary endpoints were significantly in favor of celecoxib over placebo. The sponsor did not identify the more commonly accepted endpoints for acute analgesia trials as primary endpoints (eg PID, PR, PRID, time to rescue, time to analgesia) but rather secondary endpoints. Nevertheless, these endpoints were supportive of the efficacy of celecoxib. However, time to onset of perceptible and meaningful pain relief was not significantly better for celecoxib. Importantly, a re-analysis requested by the Division using 2 different approaches supports the efficacy of celecoxib. For a more complete discussion see additional comments after study 130 below.

3. Indication -Treatment of dysmenorrhea

a. Trial N49-00-06-130

A multicenter randomized double blind active and placebo controlled crossover multiple dose assessment of the analgesic activity of celecoxib in the treatment of patients with primary dysmenorrhea.

b. Objectives/rationale

The primary objective of the study was to compare the analgesic efficacy of celecoxib versus placebo in the treatment of patients with moderate to severe menstrual cramping pain associated with primary dysmenorrhea. The time to onset was also assessed. The secondary objectives of the study were to compare the analgesic efficacy of naproxen to placebo and to evaluate the safety of celecoxib.

c. Design