Table 25

Listing of All Serious Adverse Experiences in Post- Orthopedic Surgery Pain Study

Patient ID	Study Number	Gender	Race	Age	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relation-ship	Action Taken †	Outcome
Assigned Therapy: Placebo/ Placebo											
9220	072002	F	White	71	19	Hemarthrosis	5 days	Moderate	Definitely not	PRx continued	Recovered
9232	072002	F	White	76	16	Pneumonia	8 days	Severe	Definitely not	PRx continued	Recovered
9377	072008	F	White	63	2	Paralytic ileus	3 days	Severe	Definitely not	Discontinued PRx	Recovered
9142	072009	F	White	65	4	Hip disorder	2 days	Severe	Definitely not	Discontinued PRx	Recovered
Assigned Therapy: Rofecoxib 50 mg/ Rofecoxib 25 mg											
9034	072003	F	White	52	17	Coagulation disorder	9 days	Moderate	Definitely not	PRx continued	Recovered
9144	072009	F	White	72	13	Hip disorder	2.33 hours	Severe	Definitely not	PRx continued	Recovered
9329	072009	F	White	67	7	Cellulitis	12 days	Severe	Definitely not	PRx continued	Recovered
Assigned Therapy: Rofecoxib 50 mg/ Rofecoxib 50 mg											
9112	072007	F	Black	64	4	Hematoma	3 days	Severe	Definitely not	PRx continued	Recovered
Assigned Therapy: Naproxen Sodium 550 mg/ Placebo											
9089	072006	F	White	87	7	Femoral fracture	2 days	Severe	Definitely not	PRx continued	Recovered
9089	072006	F	White	87	8	Bacterial sepsis	9 days	Severe	Definitely not	PRx continued	Not recovered ‡
9089	072006	F	White	87	8	Multiple organ failure	9 days	Severe	Definitely not	PRx continued	Not recovered ‡
9089	072006	F	White	87	8	Cardiac arrest	0.08 hours	Severe	Definitely not	PRx continued	Recovered
9089	072006	F	White	87	9	Pulmonary embolism	8 days	Severe	Definitely not	PRx continued	Recovered
9343	072009	F	White	76	42	Pyelonephritis	12 days	Severe	Definitely not	PRx continued	Recovered

† PRx = Prime therapy (study drug).
‡ Patient died of multiple organ failure and bacterial sepsis.

Fatal Serious Clinical Adverse Experiences

One death occurred during the study in the naproxen sodium/placebo group. AN 9089 died of multiple organ failure and bacterial sepsis on Study Day 16 following a femoral fracture on Study Day 7, bacterial sepsis, cardiac arrest, and multiple organ failure starting on Study Day 8, and a pulmonary embolism starting on Study Day 9. The death was not considered to be drug related.

Discontinuations Due to Clinical Adverse Experiences

There were 18 patients (8.3%) who discontinued therapy due to a clinical adverse experience. The percent of patients who discontinued due to a clinical adverse experience was 15.1, 5.4, 7.4, and 5.5% in the placebo/placebo, rofecoxib 50/25-mg, rofecoxib 50/50-mg, and naproxen sodium/placebo groups, respectively.

The percent of patients who discontinued due to drug-related clinical adverse experiences was 3.8, 3.6, 1.9, and 1.8% in the placebo/placebo, rofecoxib 50/25-mg, rofecoxib 50/50-mg, and naproxen sodium/placebo groups, respectively. The incidences of discontinuation due to adverse experiences were not significantly different between treatment groups.

Laboratory Adverse Experiences in the Analgesia Studies

Combined Post-Dental Surgery Pain and Primary Dysmenorrhea Studies

The incidence of adverse experiences was generally similar across all treatment groups. Approximately 2, 0, 1, 1, 0, 3, 1, 2, and 1% of patients in the placebo, ≤12.5-, 25-, 50-, 50/25-, 100-, and ≥200-mg rofecoxib, ibuprofen, and naproxen sodium groups, respectively, reported one or more laboratory adverse experiences. There was no association between treatment with rofecoxib and the incidence of any specific laboratory experiences.

Eight (0.60%) of 1338 patients with postrandomization laboratory measurements had one or more laboratory adverse experiences determined by the investigator to be possibly, probably, or definitely drug related. Only 1 patient (0.6%) in the 25-mg rofecoxib group, 1 patient (0.4%) in the 50-mg rofecoxib group, and 1 patient (1.1%) in the 100-mg rofecoxib group had laboratory adverse experiences considered drug related by the investigator (Table 26).

No serious laboratory adverse experiences were reported in this study group. There were no patients in the combined Post-Dental Surgery Pain and Primary Dysmenorrhea Studies who discontinued due to a laboratory adverse experience.

Table 26

Number (%) of Patients With Drug Related †_Laboratory Adverse Experiences by Laboratory Test Category in Combined Post- Dental Surgery Pain and Primary Dysmenorrhea Studies

	Placebo N=446		Rofecoxib ≤ 12.5 mg N=159		Rofecoxib 25 mg N=274		Rofecoxib 50 mg N=291		Rofecoxib 50/25 mg N=179		Rofecoxib 100 mg N=91		Rofecoxib ≥200 mg N=78		Ibuprofen 400 mg N=172		Naproxen 550 mg N=269	
	n	(%)	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)	N	(%)	n	(%)
Patients with one or more adverse experiences	3/ 292	(1.0)	0/ 127	(0.0)	1/ 159	(0.6)	1/ 255	(0.4)	0/ 57	(0.0)	1/ 90	(1.1)	0/ 76	(0.0)	2/ 138	(1.4)	0/ 144	(0.0)
Patients with no adverse experience	289/ 292	(99.0)	127/ 127	(100.0)	158 / 159	(99.4)	254 / 255	(99.6)	57/ 57	(100.0)	89 / 90	(98.9)	76/ 76	(100.0)	136 / 138	(98.6)	144 / 144	(100.0)
Blood Chemistry	3/ 287	(1.0)	0/ 127	(0.0)	1/ 152	(0.7)	0/ 254	(0.0)	0/ 52	(0.0)	1/ 90	(1.1)	0/ 76	(0.0)	1/ 136	(0.7)	0/ 142	(0.0)
Alanine aminotransferase increased	3/ 287	(1.0)	0/ 127	(0.0)	0/ 152	(0.0)	0/ 254	(0.0)	0/ 52	(0.0)	1/ 90	(1.1)	0/ 76	(0.0)	1/ 136	(0.7)	0/ 142	(0.0)
Aspartate aminotransferase increased	1/ 286	(0.3)	0/ 127	(0.0)	0/ 152	(0.0)	0/ 254	(0.0)	0/ 52	(0.0)	1/ 90	(1.1)	0/ 76	(0.0)	1/ 136	(0.7)	0/ 142	(0.0)
Total serum bilirubin increased	0/ 285	(0.0)	0/ 127	(0.0)	1/ 151	(0.7)	0/ 254	(0.0)	0/ 52	(0.0)	0/ 90	(0.0)	0/ 76	(0.0)	0/ 136	(0.0)	0/ 142	(0.0)
Hematology	0/ 286	(0.0)	0/ 127	(0.0)	0/ 152	(0.0)	0/ 253	(0.0)	0/ 56	(0.0)	0/ 90	(0.0)	0/ 76	(0.0)	1/ 138	(0.7)	0/ 141	(0.0)
Platelets decreased	0/ 286	(0.0)	0/ 127	(0.0)	0/ 152	(0.0)	0/ 253	(0.0)	0/ 56	(0.0)	0/ 90	(0.0)	0/ 76	(0.0)	1/ 138	(0.7)	0/ 141	(0.0)
Urinalysis	0/ 285	(0.0)	0/ 127	(0.0)	0/ 156	(0.0)	1/ 253	(0.4)	0/ 53	(0.0)	0/ 90	(0.0)	0/ 76	(0.0)	0/ 138	(0.0)	0/ 143	(0.0)
Glycosuria	0/ 285	(0.0)	0/ 127	(0.0)	0/ 156	(0.0)	1/ 253	(0.4)	0/ 53	(0.0)	0/ 90	(0.0)	0/ 76	(0.0)	0/ 138	(0.0)	0/ 143	(0.0)

† Determined by the investigator to be possibly, probably, or definitely drug related.
‡ This group includes patients from the Primary Dysmenorrhea Studies only (Protocols 055 and 056).
n/ m = Number of patients with laboratory adverse experiences/ number of patients for whom the laboratory test was recorded.
Although a patient may have had two or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

Post-Orthopedic Surgery Pain Study

Of the 218 randomized patients, 208 (95.4%) had at least one laboratory test postrandomization. Laboratory adverse experiences were recorded for 14 (6.4%) of 218 randomized patients. The percent of patients who had one or more laboratory adverse experiences was 11.5, 6.0, 3.8, 5.7% in the placebo/placebo, rofecoxib 50/25-mg, rofecoxib 50/50-mg, and naproxen sodium/placebo groups, respectively. The incidence of adverse experiences was generally similar between all treatment groups.

Two (1.0%) of 208 patients with postrandomization laboratory measurements had one or more laboratory adverse experiences determined by the investigator to be possibly, probably, or definitely drug related—one in the placebo/placebo group and one in the rofecoxib 50/25-mg group.

No serious laboratory adverse experiences were reported in this study group. There were no patients in this study group who discontinued due to a laboratory adverse experience.

Overall Efficacy and Safety of Rofecoxib in Analgesia Trials

The single dose efficacy of 50 mg rofecoxib was apparent on all single-dose end points of analgesic efficacy, including those assessing overall analgesic effect, onset of analgesia, peak analgesic effect, and duration of analgesia in three distinct models of acute pain, post-dental surgery pain, primary dysmenorrhea, and post-orthopedic surgery pain. A fifty milligrams of a single dose of rofecoxib was effective regardless of the patients' age, gender, race, or the severity of baseline pain.

A single dose of fifty milligrams of rofecoxib was generally similar in all measures of analgesic efficacy to 550 mg dose of naproxen sodium (550 mg) in all three analgesia models examined. Fifty milligrams rofecoxib was also generally similar in analgesic efficacy to 400 mg dose of ibuprofen (400 mg) in the post-dental surgery pain model, but 50 mg rofecoxib had a longer duration of action than 400 mg ibuprofen.

The two main concerns regarding this NDA are the analgesic efficacy of rofecoxib during short-term, multiple- dose administration and its maximal effective dose. While the single dose efficacy of rofecoxib is highly consistent in all analgesia studies submitted (9 studies), its short-term, multiple- dose administration efficacy is short of being substantial. In the two pivotal dysmenorrhea studies pain was not measured during the multiple dose administration and the surrogate end points used failed in separating rofecoxib from placebo. In the post orthopedic surgery study rofecoxib separated from placebo during the multiple dose administration in amount of supplemental rescue medication taken and in patient's global assessment but was similar to placebo in pain intensity scores. As for the effective dose of rofecoxib, both the 100 mg and the 200 mg doses were significantly more effective than the 50 mg group in the pivotal dental pain study (071). Only in one other trial the 100 mg dose (but not the 200 mg) was studied and found to be comparable to the 50 mg dose however, this study (027) was a phase II dental pain study that used a different than the proposed to be marketed formulation.

There were no significant rofecoxib treatment related adverse events in the 50-mg treatment groups. However, drug-related adverse experiences do appear to increase with dose escalation beyond the dose of 50 mg, mainly in the "Body as a Whole/Site Unspecified" and in the digestive (mainly nausea) body systems. These single dose and short-term analgesia studies are not expected to be a major source for adverse events incidence. Most safety conclusions should be made on the basis of the longer-term OA studies included in this submission.

Recommendations:

1. This drug is recommended approval for the indication of acute pain and primary dysmenorrhea.
2. The labeling for dosage and administration in regard to dosing schedule for subsequent doses should reflect the available data. (not to exceed 50 mg daily for no longer that 5 days). The 25 mg dose did not separate statistically from placebo and is not rcommanded for multiple dose administration.
3. In light of the greater analgesic effectiveness of the 100 and 200 mg doses that may potentially lead to self overdosing (with no data to support safety of these doses), it is recommended to reflect this hazardous in the labeling for this drug.

/S/ 4/29/99
M. Averbuch, MD

/S/ 5-19-99

Orig. NDA # 21042
HFD-550/Div File
HFD-550/CSO/Cook
HFD-550/Chem/Ho
HFD-550/Pharm/Wilson
HFD-550/MO/Averbuch/Hyde
HFD-850/Sta/Taneja/Lin

Study Number: 066

Study Dates: 6 October 1997 – 9 February 1998

Title of Study: A Phase III, Randomized, Active-Comparator (ibuprofen) and Placebo-Controlled Trial of the Efficacy of 50 mg of rofecoxib in the Treatment of Postoperative Dental Pain.

Investigator and Location: Steven E. Christensen, D.D.S.

Salt Lake City, UT 84124

Objectives:

The primary objectives of this study were (as defied by the sponsor):

To determine the analgesic effect of a single oral dose of rofecoxib 50 mg compared with that of placebo in the treatment of postoperative dental pain.

The secondary objectives of this study were:

a) To determine the analgesic effect of a single oral dose of rofecoxib 50 mg compared with that of ibuprofen 400-mg in the treatment of postoperative dental pain.
b) To determine the peak, time to onset, and duration of analgesic effects of rofecoxib 50 mg and ibuprofen 400-mg compared with those of placebo in the treatment of postoperative dental pain.
c) To confirm the safety and tolerability of single 50-mg doses of rofecoxib administered to patients with postoperative dental pain.

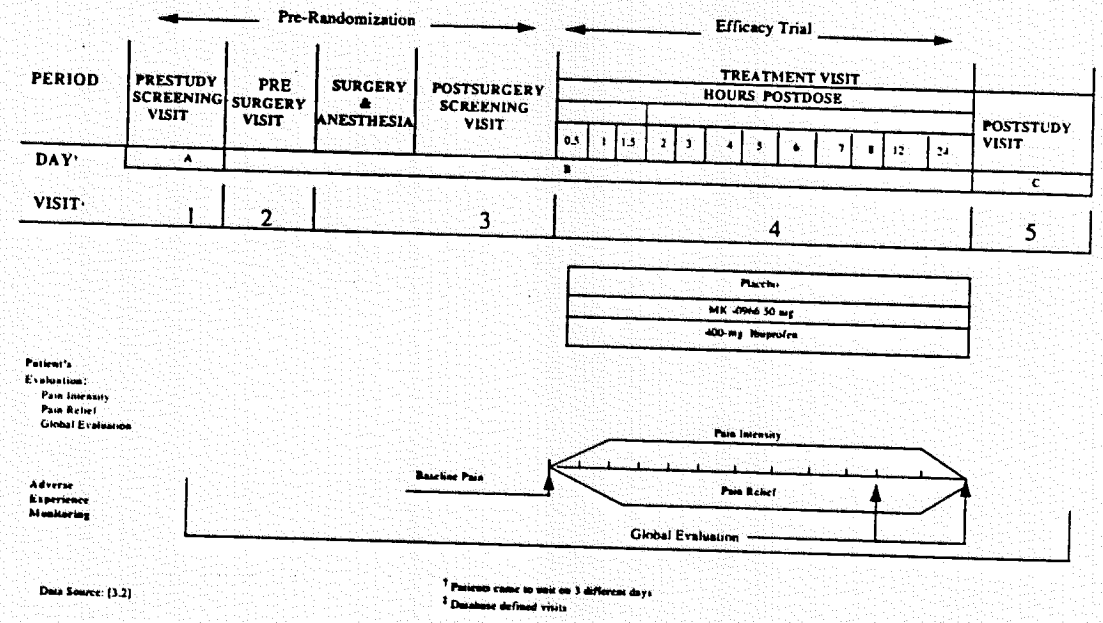
Study Description

This was a single-center, double-blind (with in-house blinding), parallel-group study comparing 50-mg doses of rofecoxib with placebo and 400-mg ibuprofen administered once postoperatively to patients demonstrating moderate to severe dental pain. Patients came in for a total of 5 visits on 3 different days: the Prestudy Study Screening Visit occurred on Day A; the Presurgery Screening Visit, Postsurgery Screening Visit, and Treatment Visit occurred on Day B; and the Poststudy Visit occurred on Day C (Figure 1).

Schedule of Observations and Procedures

Figure 1

Study Schematic



Eligibility:

1) Patient was a male or female and ≥16 years of age. Female patients demonstrated a serum β-HCG consistent with a nongravid state at the prestudy visit and agreed to remain abstinent, use oral contraceptives, or use double-barrier contraception (partner using condom and patient using diaphragm, contraceptive sponge, intrauterine device [IUD], or spermicidal foam/jelly) from the prestudy visit until 24 hours postsurgery. Women who were postmenopausal or status posthysterectomy or tubal ligation were exempt from this requirement.

2) All patients selected had been scheduled to have two or more third molars removed, at least one of which was partially embedded in bone and was a mandibular impaction. Patient may not have had a previous molar extraction within the past 45 days.

3) Patients must have been experiencing moderate to severe pain following the procedure.

4) Patient was willing to avoid excess alcohol or strenuous physical activity (e.g., strenuous or unaccustomed weight lifting, running, bicycling) for the duration of the study and follow-up period.

5) Patient was judged to be in otherwise good health based on medical history, physical examination, and routine laboratory tests.

6) Patient understood the study procedures and agreed to participate in the study by giving written informed consent.

Exclusions:

1) Patient was mentally or legally incapacitated, had significant emotional problems at the time of the study, or had a history of psychiatric disorders.
2) Patients had prior therapy that could interfere with the evaluation of efficacy, safety, or tolerability:

- Any analgesic, aspirin, acetaminophen, or ibuprofen must have been discontinued 24 hours prior to taking study medication. Naproxen (NAPROSYN ™ [Syntex Puerto Rico, Inc., Puerto Rico, U. S. A.]) or naproxen sodium (ANAPROX ™ [Syntex Puerto Rico, Inc., Puerto Rico, U. S. A.], ALEVE ™ [Proctor and Gamble, Ohio, U. S. A.]) must have been discontinued 48 hours prior to taking study medication; NAPRELAN ™ (naproxen sodium, Elan Pharma, Ltd., Thlone, County Westmeath, Ireland) must have been discontinued 72 hours prior to taking study medication.

- Any analgesics or other agents, during the 6 hours preceding surgery, that could have confounded the analgesic responses. Specifically excluded were tricyclic antidepressants, narcotic analgesics, antihistamines, tranquilizers, hypnotics, sedatives, or corticosteroids. Presurgical medications such as nitrous oxide, xylocaine with epinephrine, VALIUM ™ (diazepam, Hoffman- La Roche, Inc., NJ, U. S. A.), VERSED ™ (midazolam hydrochloride, Hoffman- La Roche, Inc., NJ, U. S. A.), BREVITAL ™ (methohexital sodium, Eli Lilly and Company, IN, U. S. A.) atropine, or fentanyl were exempt from this exclusion.

3) Patient had a history of a significant clinical or laboratory adverse event that in the opinion of the investigator contraindicated single- dose therapy with an NSAID such as ibuprofen.

4) Patient had uncontrolled hypertension, uncontrolled diabetes mellitus, renal disease, stroke or neurological disorder, cardiovascular, hepatic or neoplastic disease (patients with adequately treated skin cancer or carcinoma in situ of the cervix may have participated), or a history of any illness that, in the opinion of the investigator, might have confounded the results of the study or posed additional risk to the patient.

5) Patient had any personal or family history of an inherited bleeding disorder.

6) Patient had clinically significant abnormalities of prestudy clinical examination or laboratory safety tests. As a guide, the following values were generally considered clinically significant: Hgb <11 g/ dL, WBC <3500/ cc, platelets <100,000/ cc, AST >1.5 x upper limit of normal (ULN), ALT >1.5 x ULN, bilirubin >1.5 x ULN, alkaline phosphatase >1.5 x ULN, creatinine >2.0 mg/ dL.

7) Patient was allergic or intolerant to naproxen sodium, aspirin, ibuprofen, indomethacin, or other NSAIDs or had a history of asthma in association with nasal polyps. Patient was allergic or intolerant to VICODIN ™ (acetaminophen plus hydrocodone bitartrate, Knoll Pharmaceutical Company, NJ, U. S. A.), hydrocodone bitartrate, or acetaminophen.

8) Patient had morbid obesity and demonstrated significant health problems stemming from their obesity.

9) Patients with a recent history (within 5 years) of chronic analgesic or tranquilizer use or dependence.

10) Patient was, at the ti me of the study, a user (including "recreational use") of any illicit drugs or had a history (< 5 years) of drug or alcohol abuse.

11) Patient had donated a unit of blood or plasma or participated in another clinical study within the last 4 weeks.

12) Patient had been in a previous study with rofecoxib.

Treatments Administered (Table 1):

Study Medication	Formulation No.
rofecoxib 50 mg Placebo X ‡	† MR- 3360 MR- 3361
Ibuprofen § 400-mg Placebo Y %	MR- 3557 MR- 3382

† The 50- mg dose consisted of two 25- mg tablets (Phase III, 12.5% formulation).
‡ Placebo X was in the image of the rofecoxib 25- mg tablet.
§ MOTRIN™, McNeil Consumer Products Co., PA, U. S. A.
% Placebo Y was in the image of the ibuprofen 400- mg tablet.

Blinding

Patients received study medication in a single bottle. Each patient received 3 tablets. All bottles were labeled with double-blind, three-part, tear-off labels.
Table 2 shows the bottle contents by treatment.

Table 2
Bottle Contents by Treatment Group

Treatment Group	rofecoxib 25- mg Tablet	Placebo Image of rofecoxib 25- mg Tablet	Ibuprofen 400-mg tablet	Placebo Image of Ibuprofen 400- mg Tablet
Placebo	0	2	0	1
rofecoxib 50 mg	2	0	0	1
Ibuprofen 400 mg	0	2	1	0

Rescue Medication for Dental Pain

During the 24- hour postdose period, a combination analgesic medication consisting of acetaminophen plus hydrocodone bitartrate was administered as "rescue analgesia" (at a dose determined by the investigator) if the patient experienced inadequate pain relief with study medication. Patients were asked to avoid using rescue analgesia during the first 90 minutes postdose to allow the study drug to exhibit an effect. The time the rescue analgesia was used during the 24-hour study was recorded. In the event "rescued" patients continued to experience inadequate pain relief, they received additional doses of acetaminophen plus hydrocodone bitartrate as needed.

Efficacy Assessment:

The patient recorded specific assessments of Pain Relief, Pain Intensity, and Global (overall) Evaluation of the study drug.
Patients were required to fast from all food and drink except water for a minimum of 2 hours prior to obtaining the serum chemistry panel during the pre- and poststudy evaluations and from midnight on the evening prior to surgery. Patients continued to fast, except for beverages, following surgery, and until dosing. Two hours postdose, the patient's diet was advanced as determined by the investigator. The patients remained in the study unit for the ensuing 8 hours and then completed additional assessments as outpatients.

1) Ratings of Pain Intensity and Pain Relief
The following assessments at 0.50, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours postdose:

1. Pain Intensity (none = 0, severe = 3)
2. Pain Relief (none = 0, complete = 4)

2) Time to Confirmed Perceptible Pain Relief (Stopwatch)
Two stopwatches were initiated at the time of dosing. The coordinator instructed the patient to click "off" one stopwatch at the time the patient experienced perceptible pain relief and to click "off" the other stopwatch at the time the patient experienced meaningful pain relief (double-click stopwatch technique). The coordinator recorded the elapsed times on the patient's case report form.

3) Time to Taking Rescue Medication
Patients were instructed to ask the study coordinator for additional medication, as needed, while in the study center. The date and time of this request was recorded by the patient in their diary. If additional medication was taken after the patient left the study center, the date and time of rescue medication was recorded by the patient in their diary.

4) Patient's Global Evaluation
At 8 and 24 hours postdose, or at the time the patient took rescue medication, the patient answered the following question in the diary:
"How would you rate the study medication you received for pain?"
"POOR," "FAIR," "GOOD," "VERY GOOD," or "EXCELLENT."

Statistical Analysis

All randomized patients were included in the intent-to-treat approach to the efficacy analysis. There was no protocol violator in this study and there was only 1 patient who requested rescue medication prior to 90 minutes. Thus, the per-protocol analysis was considered not necessary.

A listing of statistical analyses performed on efficacy (primary and other end points) and safety end points is in Table 3.

Table 3

Listing of End Points and Their Statistical Analyses

End Point	Statistical Analysis
Efficacy	
Overall Analgesic Effect	
TOPAR8 (primary), SPID8, Patient's Global Evaluation at 8 and at 24 hours	Analysis of variance (ANOVA) model †, plot of LSMean with 84% CI, plot and summary table of percent of patients in each category of the Global Evaluation score by treatment group at 8 and at 24 hours postdose
Onset of Analgesic Effect	
Time to Confirmed Perceptible Pain Relief (Stopwatch Time to Perceptible Pain Relief, confirmed by the second stopwatch), Time to PID ≥1	Cox proportional hazards regression model †, non- parametric log-rank test, Kaplan- Meier estimates of 25, 50, and 75th percentiles and 95% CI for the 50th percentile, plot of cumulative proportion of patients with meaningful Pain Relief or PID ≥1 over time (1-Kaplan-Meier estimates of survival function), bar chart of incidence rates; logistic regression† on the proportions of patients who experienced onset of analgesia
Peak Analgesic Effect	
Peak Pain Relief and Peak PID	ANOVA, plot of LSMean with 84% CI †
Duration of Analgesic Effect	
Time to Rescue Medication Use	Cox proportional hazards regression model *, non- parametric † log-rank test, Kaplan- Meier estimates of 25, 50, and 75th percentiles and 95% CI for the median, plot of cumulative proportion of patients taking rescue medication over time (1-Kaplan- Meier estimates of survival function), bar chart of incidence rates
Percent of Patients Who Took Rescue Medication	Logistic regression model †, bar chart of proportion of patients taking rescue medication for each treatment
Pain Relief, PID, PRID at 12 and 24 hours	ANOVA †, plot of LSMean with 84% CI
Pain Assessment at Each Time Point	
Pain Relief, PID, PRID, APAR, APID	ANOVA †, plot of mean with 84% confidence interval over time
TOPAR, SPID	ANOVA †, plot of mean with 84% confidence interval over time

Table 3 (Cont.)

Listing of End Points and Their Statistical Analyses

Safety	
Vital Signs and Laboratory Safety Parameters	
Percent of patients with pre-defined changes in vital signs and laboratory parameters	Fisher's exact test
Observed or log (observed value) for some laboratory parameters	Summary statistics, plot of observed mean and mean change from baseline with 84% confidence limits over time
End Point	Statistical Analysis
Adverse Experience Counts	
Number (%) of patients with adverse experiences (including by category)	Fisher's exact test
† Model included treatment and baseline Pain Intensity as factors. The treatment-by-baseline Pain Intensity was tested and removed from the model, if it was found not significant at the 5% level.	

RESULTS:

Disposition of Patients

One hundred and fifty one (151) patients were enrolled in this study and were randomized to receive one of three treatments: 50 patients received rofecoxib 50mg, 51 patients received ibuprofen 400 mg, and 50 patients received placebo.
Baseline demographic characteristics are presented in table 4.
The treatment groups were comparable for age, race and gender. For all patients, the age range was 15 to 26 years. Across treatment groups, 50% of the patients were male and 93% were white.

Table 4

Baseline Patient Characteristics by Treatment Group

	Placebo (N= 50)		rofecoxib 50 mg (N= 50)		Ibuprofen 400 mg (N= 51)		Total (N= 151)	
	n	(%)	N	(%)	n	(%)	n	(%)
Gender								
Female	22	(44.0)	27	(54.0)	27	(52.9)	76	(50.3)
Male	28	(56.0)	23	(46.0)	24	(47.1)	75	(49.7)
Race								
Asian	1	(2.0)	1	(2.0)	2	(3.9)	4	(2.6)
Black	1	(2.0)	0	(0.0)	0	(0.0)	1	(0.7)
European	0	(0.0)	1	(2.0)	0	(0.0)	1	(0.7)
Hispanic- American	1	(2.0)	1	(2.0)	1	(2.0)	3	(2.0)
Polynesian	1	(2.0)	0	(0.0)	0	(0.0)	1	(0.7)
White	46	(92.0)	47	(94.0)	48	(94.1)	141	(93.4)
Age								
≤ 20	45	(90.0)	47	(94.0)	50	(98.0)	142	(94.0)
21 to 30	5	(10.0)	3	(6.0)	1	(2.0)	9	(6.0)
Mean		17.9		17.6		17.3		17.6
SD		2.40		1.94		1.70		2.03
Median		17.0		17.0		17.0		17.0
Range		15 to 26		15 to 25		15 to 22		15 to 26

Summary of Dental Surgery

The degree of impaction, number of molars extracted and baseline pain intensity were comparable across all treatment groups (table 5).

Table 5

Additional Patient Characteristics by Treatment Group

	Placebo (N= 50)	rofecoxib 50 mg (N= 50)	Ibuprofen 400 mg (N= 51)	Total (N= 151)
Baseline Pain Intensity: n (%) Patients				
Moderate	46 (92.00)	46 (92.00)	45 (88.24)	137 (90.73)
Severe	4 (8.00)	4 (8.00)	6 (11.76)	14 (9.27)
Duration of Surgery (Minutes)				
Mean	21.91	22.70	24.74	23.14
SD	8.420	7.827	8.313	8.223
Median	20.00	20.00	20.00	20.00
Range	5 to 47	10 to 45	13 to 60	5 to 60
Number of Teeth Removed				
Mean	3.72	3.86	3.82	3.80
SD	0.64	0.45	0.77	0.63
Median	4.00	4.00	4.00	4.00
Range	2 to 4	2 to 4	2 to 6	2 to 6
Impaction Score (1 to 5 Scale)				
Mean	4.58	4.66	4.73	4.66
SD	0.68	0.57	0.45	0.57
Median	5.00	5.00	5.00	5.00
Range	2.5 to 5	2 to 5	3 to 5	2 to 5

Accounting for Patients in the Analysis

All of the 151 patients who entered the study completed as specified in the protocol. All patients who took study medication recorded a baseline pain intensity score of moderate or severe and recorded at least one pain evaluation postdose. Therefore, all patients were included in the efficacy analysis of rofecoxib (Table 6). There were 92, 54, and 82.4% of the patients in the placebo, 50-mg rofecoxib, and 400-mg ibuprofen groups, respectively, who used rescue medication 1.5 to 24 hours postdose. There was 1 patient (AN 7092 in the rofecoxib group) who took rescue medication during the protocol predetermined minimum time (90 minutes), which was required for the test medication to have onset of efficacy. No patient was excluded due to a protocol violation. Therefore, the per-protocol analysis was not performed. All 151 randomized patients were included in the safety analysis.

Table 6
Accounting for Patients in the Statistical Analysis

Study Status	Placebo n (%)	rofecoxib 50 mg n (%)	Ibuprofen 400 mg n (%)	Total
ENTERED:	50 (100%)	50 (100%)	51 (100%)	151
Included in the "Intent- to-Treat" analysis	50 (100%)	50 (100%)	51 (100%)	151
Did not take rescue medication 1.5 to 24 hours postdose	4 (8.0%)	22 (44.0%)	9 (17.6%)	35
Took rescue medication after 90 minutes	46 (92.0%)	27 (54.0%)	42 (82.4%)	115
Took rescue medication prior to 90 minutes	0	1 (2.0%)	0	1
Other protocol violator	0	0	0	0