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**PROPRIETARY DRUG NAME<sup>®</sup>/GENERIC DRUG NAME:** Celebrex<sup>®</sup> / Celecoxib

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** See USPI.

**NATIONAL CLINICAL TRIAL NO.:** NCT00290901

**PROTOCOL NO.:** A3191165

**PROTOCOL TITLE:** A six week double-blind, randomized, multicenter comparison study of the analgesic effectiveness of celecoxib 200 mg BID compared to tramadol hydrochloride 50 mg QID in subjects with chronic low back pain

**Study Center(s):** Fifty-six (56) centers in the United States

**Study Initiation and Completion Dates:** 14 March 2006 to 22 February 2007

**Phase of Development:** Phase 3b

**Study Objectives:**

*Primary Objective:* The primary objective of this study was to compare the analgesic effectiveness of celecoxib 200 mg twice daily (BID) and tramadol hydrochloride (HCl) 50 mg 4 times daily (QID) over 6 weeks in subjects with chronic low back pain (CLBP). This was measured by the proportion of subjects who responded successfully to their respective treatments, with ‘successful responders’ defined as subjects who completed 6 weeks of study medication and had a 30% improvement from Baseline to Week 6 on the Numerical Rating Scale-Pain (NRS-Pain).

*Secondary Objectives:* The secondary objectives were (1) to compare the effects of treatment with celecoxib 200 mg BID and tramadol HCl 50 mg QID on improvement in both functionality and quality of life in subjects with CLBP, and (2) to evaluate the tolerability and safety of celecoxib 200 mg BID versus tramadol HCl 50 mg QID in the treatment of subjects with CLBP.

*Exploratory Objective:* The exploratory objective of this study was to examine the correlation between the Low Back Pain Intensity Visual Analog Scale (VAS) score and the NRS-Pain score.

## METHODS

**Study Design:** This was a multicenter, randomized, parallel-group, double-blind, double-dummy active comparator study in subjects with CLBP. A total of 754 eligible subjects were to be enrolled and randomly assigned, in a 1:1 ratio, to treatment with celecoxib 200 mg BID or tramadol HCl 50 mg QID for 6 weeks. The maximum and expected duration of the study for an individual subject, including washout, treatment, and follow-ups, was 8 weeks. There were 5 study visits: Visit 1 – Screening (Day -14 to Day -1); Visit 2 – Baseline (Day 1); Visit 3 – Week 1 ( $\pm 2$  Days); Visit 4 – Week 3 ( $\pm 2$  Days); and Visit 5 – Week 6 ( $\pm 3$  Days)/ Final or Early Termination visit.

Males and females  $\geq 18$  years of age with a diagnosis of CLBP who experienced moderate to severe low back pain at the Baseline Visit, as measured by a score of  $\geq 4$  on the NRS-Pain, and who satisfied all other inclusion and exclusion criteria were eligible to participate in the study. Subjects were assigned at the site, in the order in which they were enrolled into the study, to receive their allocated treatment according to a computer-generated randomization schedule prepared prior to the start of the study.

No rescue medication for CLBP was allowed during the active phase of the study. For non-back pain related medical problems, such as headache requiring analgesics, acetaminophen, up to 1 gram daily, was allowed but was not to be used more than twice in any one week. Subjects who did not complete the study were not replaced.

**Number of Subjects (Planned and Analyzed):** A sample size of 754 subjects (377 evaluable subjects per group) was needed to achieve 80% power to meet the objective of demonstrating non-inferiority. To meet this objective, additional subjects were to be randomized. Thus, a total of 791 randomized subjects (402 celecoxib, 389 tramadol HCl) were treated and analyzed for efficacy and safety.

**Diagnosis and Main Criteria for Inclusion:** Subjects were eligible for the study if they were  $\geq 18$  years old; had CLBP for  $\geq 3$  months requiring regular use of analgesics ( $\geq 4$  days/week) (except for acetaminophen, which could not have been the sole analgesic used); and had moderate to severe low back pain at the Baseline Visit, as measured by a score of  $\geq 4$  on the NRS-Pain, with the primary location of back pain between the 12<sup>th</sup> thoracic vertebra and the gluteal folds with or without radiation into the posterior thigh (classified as Category 1 or 2 according to the classification of the Quebec Task Force on Spinal Disorders).

Subjects were not eligible if they had CLBP that was neurologic in etiology (ie, radiculopathy, neuropathy, myelopathy), with pain extending beyond calf; had back pain attributed to recent major trauma; had surgical intervention for low back pain within 6 months prior to study entry or had multiple spinal surgeries; had any open claim (eg, workman's compensation) or any closed claim related to a back injury within the past 5 years; had taken any NSAID or any analgesic within 72 hours prior to the Baseline visit (subjects taking  $\leq 325$  mg of aspirin for non-analgesic or arthritic reasons, at a stable dose for at least 30 days before the first dose of study medication, were allowed to continue their aspirin regimen for the duration of the study); were taking selective serotonin re-uptake

inhibitors (SSRIs) and/or serotonin non-reuptake inhibitors (SNRIs) or monoamine oxidase inhibitors; had active or suspected esophageal, gastric, pyloric channel, or duodenal ulceration or bleeding within 90 days prior to the first dose of study medication; had a history of gastrointestinal (GI) perforations, obstructions, or bleeding; had a known hypersensitivity to NSAIDs, COX-2 selective inhibitors, or tramadol HCl; had a history of asthma, urticaria, or allergic type reactions after taking aspirin or NSAIDs; had an allergy to sulfonamides; had significant or unstable cardiovascular disease; or were taking or anticipated taking anticoagulants, lithium, muscle relaxants, selective serotonin inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, neuroleptics, carbamazepine, quinidine, or anti-ulcer drugs during the course of the study.

**Study Treatment:** Subjects were randomized in a 1:1 ratio to receive one of two treatments for 6 weeks: celecoxib 200 mg BID or tramadol HCl 50 mg QID.

Study medication was prepared in a double-dummy fashion and administered as double-blind treatment. For each subject, study medication was contained in 2 bottles (Bottle A and Bottle B). All capsules were provided in bottles packed in subject kits. Bottles contained either a 1 week + 2 days, 2 week + 2 days, or 3 weeks + 3 days supply of study drug. Bottle A contained celecoxib 200 mg or placebo capsules in counts of 18, 32 or 48, depending on the respective week of administration. Bottle B contained tramadol HCl 50 mg or placebo capsules in counts of 36, 64, or 96, depending on the respective week of administration. For each subject, a total of 6 labeled bottles were supplied.

Subjects were instructed to take study medication from Bottle A 2 times daily for 6 weeks, and from Bottle B 4 times daily for 6 weeks. Subjects were instructed to start taking study medication immediately upon returning home after the Baseline Visit to ensure that the most complete regimen of study medication was taken on Day 1.

**Efficacy Evaluations:** The primary efficacy evaluation of analgesic effectiveness of study treatment was based on the Numerical Rating Scale (NRS-Pain). NRS-Pain assessments were performed at the Screening, Baseline, Week 1, Week 3, and Week 6 or Final or Early Termination visits. Each subject assessed the severity of his or her low back pain using an NRS-Pain between 0 (No pain) and 10 (Worst possible pain). In order to qualify for the study, a subject had to have a score of  $\geq 4$  on the NRS-Pain at the Baseline Visit.

Secondary evaluations:

*Low Back Pain Intensity Visual Analog Scale (VAS):* Low Back Pain Intensity (VAS) assessments were performed at the Screening, Baseline, Week 1, Week 3, and Week 6 or Final or Early Termination visits. Each subject assessed the severity of his or her low back pain using a 100-mm VAS (0 – 100: ‘no pain’ to ‘worst possible pain’). Based on the question: “During the past day, how much back pain did you have?” the subject was to be

instructed to place a vertical line on the VAS to indicate the magnitude of his or her low back pain.<sup>a</sup>

*Patient's Global Assessment of Disease Activity:* At the Screening, Baseline, and Week 6 or Final or Early Termination visits, each subject rated his or her condition using the Patient's Global Assessment of Disease Activity 5-point scale (1=very good, 2=good, 3=fair, 4=poor, 5=very poor) in response to the question: "Considering all the ways your lower back pain affects you, how are you doing today?"

*Physician's Global Assessment of Disease Activity:* At the Screening, Baseline, and Week 6 or Final or Early Termination visits, the physicians provided an overall evaluation of the subject's low back pain using the Physician's Global Assessment of Disease Activity 5-point scale (1=very good, 2=good, 3=fair, 4=poor, 5=very poor).

*Roland-Morris Disability Questionnaire (RMDQ):* Each subject assessed his/her own disability due to low back pain using the RMDQ worksheet, which consisted of 24 statements of disability, at the Screening, Baseline, Week 1, Week 3, and Week 6 or Final or Early Termination visits.

*Modified Brief Pain Inventory – Short Form (mBPI-sf):* On the mBPI-sf worksheet, each subject rated his/her own pain on a scale from 0 = no pain, to 10 = worst possible pain, and rated the interference of pain on a scale from 0 = does not interfere, to 10 = completely interferes. Each subject completed the mBPI-sf worksheet at Baseline, Week 1, Week 3, and Week 6 or Final or Early Termination visits.

*Medical Outcomes Study (MOS) Sleep Scale:* Each subject completed the MOS Sleep Scale worksheet at the Baseline and Week 6 or Final or Early Termination visits.

*Work Limitations Questionnaire:* The Work Limitations Questionnaire was administered at the Baseline and Week 6 or Final or Early Termination visits.

*Patient's Global Evaluation of Study Medication:* Subjects completed the Patient's Global Evaluation of Study Medication worksheet at the Week 1, Week 3, and Week 6 or Final or Early Termination visits. Subjects were to respond to the question: "In all ways, how would you rate your overall response to the study medication, today?" on a 5-point scale (1=excellent, 4=very good, 3=good, 2=fair, 1=poor).

*Patient Satisfaction Questionnaire:* At the Week 6 or Final or Early Termination Visit, each subject completed the Patient Satisfaction Questionnaire worksheet. Using a 10-point scale (1=very dissatisfied to 10=very satisfied), the subject rated his or her satisfaction with pain relief and with his or her walking and bending ability while using the current back pain therapy.

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<sup>a</sup> On the Case Report Form, subjects were instructed to place a slash '/' across the line in the position that best described their pain during the past day. It should be noted that the Low Back Pain Intensity (VAS) is a validated instrument when the instructions to the subjects are to place a *vertical* line.

**Safety Evaluations:** Safety assessments included monitoring adverse events (AEs), serious adverse events (SAEs), safety laboratory tests, concomitant medications, vital signs, physical examinations, and reasons for discontinuation. AEs, SAEs, concomitant medications, and reasons for discontinuation were monitored throughout the study. Vital signs were measured at each study visit (Screening, Baseline, Week 1, Week 3, and Week 6 or Final or Early Termination). Safety laboratory tests and physical examinations were performed at Screening and at the Week 6 or Final or Early Termination visit.

**Statistical Methods:**

Analysis Populations:

*Intent-to-Treat Population (ITT):* Subjects who were randomized and received at least 1 dose of study medication were included in this population. Subjects were analyzed according to the treatment to which they were randomized (ie, treatment assignment = as randomized).

*Safety Population:* Subjects who were randomized and received at least 1 dose of study medication were included in this population. Subjects were analyzed according to the treatment they received (ie, treatment assignment = as treated).

*Evaluable Population:* The Evaluable Population consisted of a subset of the ITT Population and included subjects (1) who were at least 80% compliant with study medication, and (2) who had no major protocol deviations. Major protocol deviation criteria were defined prior to breaking the treatment blind and included (1) NRS-Pain score at baseline <4, and (2) use of one of the following analgesic therapies for >2 days consecutively, or 5 days total throughout the study period:

- Opioids (tramadol, oxycodone, hydrocodone)
- NSAIDs (naproxen, ibuprofen)

Primary analyses for the non-inferiority assessment were performed on the Evaluable Population. Primary endpoint analyses were performed using the ITT Population for sensitivity of the non-inferiority assessment. Second stage testing of superiority was performed on the ITT Population and repeated on the Evaluable Population for sensitivity. All secondary analyses were done on the ITT Population only.

Efficacy Endpoints: The *primary efficacy endpoint* was analgesic effectiveness. Analgesic effectiveness was a composite endpoint of treatment response and tolerability. A subject was considered a treatment responder if the subject was able to achieve a 30% or greater improvement in pain from Baseline to Week 6 as assessed by the NRS-Pain. Tolerability was defined as being able to complete the 6-week study treatment regimen.

The *secondary efficacy endpoints* were:

1. The Numerical Rating Scale (NRS-Pain)
2. Low Back Pain Intensity (VAS)
3. Roland-Morris Disability Questionnaire (RMDQ) total score

4. Modified Brief Pain Inventory Short Form (mBPI-sf) (each pain and interference item score, and pain interference subscale score)
5. Medical Outcomes Study (MOS) Sleep Scale scores
6. Work Limitations Questionnaire scale scores
7. Patient's Global Assessment of Disease Activity
8. Physician's Global Assessment of Disease Activity
9. Patient's Global Evaluation of Study Medication
10. Patient Satisfaction Questionnaire
11. Chronic Low Back Pain Responder Index (derived). A subject was to be considered a responder if all of the following criteria were met:
  - $\geq 30\%$  improvement from Baseline to Final visit in Low Back Pain Intensity (VAS), and
  - $\geq 30\%$  improvement from Baseline to Final visit in the Patient's Global Assessment of Disease Activity, and
  - $< 20\%$  worsening from Baseline to Final visit in functional ability, assessed by the RMDQ.

Primary Efficacy Analysis: For the primary efficacy analysis, a two-stage testing procedure was used. The first step was to examine the non-inferiority of celecoxib 200 mg BID as compared to tramadol HCl 50 mg QID by constructing a 95% confidence interval (CI) for the risk difference between the treatment arms. A lower limit of the 95% CI for the risk difference greater than -10% (from celecoxib – tramadol) would have demonstrated that celecoxib 200 mg BID was not inferior to tramadol HCl 50 mg QID. The risk difference was calculated using a generalized linear model, with treatment and center as factors. For testing of non-inferiority, the primary analysis was performed on the Evaluable Population, and a sensitivity analysis was performed on the ITT Population.

If celecoxib 200 mg BID was found to be non-inferior to tramadol HCl 50 mg QID, then the second step was to test the superiority of celecoxib 200 mg BID over tramadol HCl 50 mg QID using a Cochran-Mantel-Haenszel (CMH) test (general association) test, stratified by center. For this analysis, the Evaluable and ITT Populations were used to test the hypothesis of superiority and were carried out using a two-sided, type I error rate of 0.05.

Secondary Efficacy Analyses: All secondary efficacy analyses were performed on the ITT Population. The changes from baseline for each of the secondary measures listed below were compared between the 2 treatment groups using analysis of covariance (ANCOVA), with treatment and center as factors and baseline value as a covariate. Missing values were imputed by last observation carried forward (LOCF). The 95% CIs around the differences in Least Square Means (LSMs) were provided for these endpoints:

- NRS-Pain
- Low Back Pain Intensity (VAS)
- RMDQ total score
- mBPI-sf (each pain and interference item score, and pain interference subscale score)
- MOS Sleep Scale scores
- Work Limitations Questionnaire scale scores.

In addition to the analyses specified above, for the NRS-Pain, low back pain intensity (VAS), RMDQ total score, and mBPI-sf scores, which were collected at intervals during the study, a

time-weighted average, calculated as area under the curve (AUC) with linear interpolation of missing values, was calculated. Differences between the treatment groups were tested using analysis of variance (ANOVA), with treatment and center as factors, and 95% CIs around the differences were provided.

CMH tests, using row mean scores and adjusting for center, were used to compare the 2 treatments for the following endpoints:

- Patient's and Physician's Global Assessment of Disease Activity
- Patient's Global Evaluation of Study Medication
- Patient Satisfaction Questionnaire.

CMH (general association) tests, stratified by center, were used to compare the 2 treatments for the following endpoints:

- CLBP Responder Index
- MOS Sleep Scale-Optimal.

The incidence of withdrawal due to lack of tolerability was calculated for each treatment group; the CMH (general association) test, adjusting for center, was used.

Exploratory Efficacy Analyses: The correlation between the Low Back Pain Intensity (VAS) score and the NRS-Pain score was explored by generating scatterplots and computing the Pearson correlation coefficients and the concordance correlation coefficients (CCC).

Safety Parameters: AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 10.0. AEs were considered treatment-emergent adverse events (TEAEs) if they occurred within 30 days of the last administration of study medication. All-causality and treatment-related TEAEs were summarized by MedDRA System Organ Class (SOC) and preferred term. Serious adverse event presentations were derived from a separate, centralized, adverse event monitoring database that was continuously updated based on rapidly communicated reports from the investigators to the Sponsor.

## RESULTS

**Subject Disposition and Demography:** A total of 1027 subjects were screened. Of the 1027 screened subjects, 796 were randomized to study treatment: 404 to celecoxib 200 mg BID and 392 to tramadol HCl 50 mg QID. Of the 796 randomized subjects, 791 received at least one dose of study treatment: 402 in the celecoxib group and 389 in the tramadol HCl group. A higher percentage of subjects completed study treatment in the celecoxib group (85.6%) than in the tramadol HCl group (69.4%).

In the celecoxib group, 58 (14.4%) subjects discontinued from the study: 22 (5.5%) for reasons related to study medication and 36 (9.0%) for reasons not related to study medication. In the tramadol HCl group, 119 (30.6%) subjects discontinued from the study: 71 (18.3%) for reasons related to study medication and 48 (12.3%) for reasons not related to

study medication. Subject disposition and subjects analyzed are summarized in Table S1, below.

**Table S1. Subject Disposition and Subjects Analyzed**

Number of Subjects	Celecoxib 200 mg BID n (%)	Tramadol HCl 50 mg QID n (%)
<b>Planned</b>	<b>754</b>	
	<b>(377 per group)</b>	
<b>Screened</b>	<b>1027</b>	
<b>Randomized (Assigned to Treatment)</b>	404	392
<b>Treated</b>	<b>402 (100)</b>	<b>389 (100)</b>
Completed	344 (85.6)	270 (69.4)
Discontinued	58 (14.4)	119 (30.6)
Related to study drug	22 (5.5)	71 (18.3)
Adverse event	12 (3.0)	66 (17.0)
Lack of efficacy	10 (2.5)	5 (1.3)
Not related to study drug	36 (9.0)	48 (12.3)
Adverse event	6 (1.5)	6 (1.5)
Subject defaulted	19 (4.7)	19 (4.9)
Other	11 (2.7)	23 (5.9)
<b>Safety Population</b>	402 (100)	389 (100)
<b>ITT Population</b>	402 (100)	389 (100)
<b>Evaluable Population</b>	374 (93.0)	324 (83.3)
<b>All subjects excluded from Evaluable Population</b>	28 (7.0)	65 (16.7)
Reasons for exclusion from Evaluable Population: <sup>b</sup>		
Subject < 80% compliant with study medication	17 (4.2)	50 (12.9)
Subject had major protocol deviation:		
Subject had baseline NRS-Pain score <4	3 (0.7)	0
Subject used concomitant analgesic therapies <sup>a</sup>	8 (2.0)	21 (5.4)
Opioids	2 (0.5)	10 (2.6)
NSAID	7 (1.7)	11 (2.8)

<sup>a</sup> For > 2 days consecutively, or 5 days total throughout the study period.

<sup>b</sup> Subjects may have had more than one reason for exclusion from the Evaluable Population.

Note: Percentages are based on the number of subjects treated.

BID = twice daily; HCl = hydrochloride, ITT = Intent-to-Treat; NRS = numerical rating scale; NSAID = nonsteroidal anti-inflammatory drug; QID = 4 times daily

Demographic and baseline characteristics were generally similar in the 2 treatment groups in both the ITT Population and the Evaluable Population. In the ITT Population, more subjects in each treatment group were female (57.7% celecoxib, 59.1% tramadol HCl). The mean (min – max) age was 49.1 years (18 – 88) in the celecoxib group and 47.9 years (18 – 83) in the tramadol HCl group. The majority of subjects were White (67.4% celecoxib, 60.7% tramadol HCl). The distribution of race among males was similar in the treatment groups. Among females, there was a numerically higher percentage of White subjects in the celecoxib group (65.5%) than in the tramadol HCl group (53.9%), and there was a numerically higher percentage of Black subjects in the tramadol HCl group (25.2%) than in the celecoxib group (19.8%).

**Efficacy Results:**

*Primary Efficacy Results:* In the Evaluable Population, the percentage of successful responders was 66.0% in the celecoxib 200 mg BID group and 56.8% in the tramadol HCl 50 mg QID group. The results of the first step of the two-stage testing procedure for the primary efficacy analysis showed that, in the Evaluable Population, celecoxib 200 mg BID was non-inferior to tramadol HCl 50 mg QID, that is, the lower limit of the 95% CI for the risk difference (95% CI = [0.022, 0.161]) was greater than -10%, the limit defined a priori for concluding non-inferiority. The analysis performed on the ITT Population showed similar results (95% CI = [0.064, 0.196]).

Because celecoxib 200 mg BID was found to be non-inferior to tramadol HCl 50 mg QID, the second step of the two-stage testing procedure for the primary efficacy analysis was performed and demonstrated the superiority of celecoxib 200 mg BID over tramadol HCl 50 mg QID. In the ITT Population, the percentage of successful responders was significantly greater with celecoxib 200 mg BID versus tramadol HCl 50 mg QID (63.2% versus 49.9%, respectively;  $p < 0.001$ ). Similar results were observed in the Evaluable Population (66.0% versus 56.8%, respectively;  $p = 0.013$ ) (Table S2).

**Table S2. Analysis of Effectiveness of Celecoxib Versus Tramadol HCl – Percent of Successful Responders at Week 6/Early Termination**

Analysis Population Responder Index <sup>a</sup> Week 6/ET <sup>b</sup>	Celecoxib 200 mg BID n (%)	Tramadol HCl 50 mg QID n (%)	Risk Difference <sup>c</sup> (95% CI)	p-value <sup>d</sup>
<b>Evaluable Population</b>	(N=374)	(N=324)		
Successful Responder	247 (66.0%)	184 (56.8%)	0.092	0.013
Non-Successful Responder	127 (34.0%)	140 (43.2%)	(0.022, 0.161)	
<b>ITT Population</b>	(N=402)	(N=389)		
Successful Responder	254 (63.2%)	194 (49.9%)	0.130	< 0.001
Non-Successful Responder	148 (36.8%)	195 (50.1%)	(0.064, 0.196)	

<sup>a</sup> Subjects were classified as successful responders if they completed 6 weeks of study medication and had  $\geq 30\%$  improvement from Baseline to Week 6/ET in NRS-Pain.

<sup>b</sup> Missing values imputed using the method of LOCF at the end of Week 6 or Early Termination.

<sup>c</sup> Risk difference = difference in proportions (celecoxib minus tramadol HCl), adjusted for treatment and center, from a generalized linear model. In first step of two-stage testing procedure, a lower limit of the 95% CI for the risk difference greater than -10% demonstrated celecoxib to be non-inferior to tramadol HCl.

<sup>d</sup> Test of superiority (second step of two-stage testing procedure), based on CMH (general association) test, stratified by center.

Abbreviations: BID = twice daily; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ET = Early Termination; HCl = hydrochloride, ITT = Intent-to-Treat; QID = 4 times daily

*Secondary Evaluations:* All secondary evaluations were analyzed using the ITT Population. Subjects who received celecoxib 200 mg BID had significantly better outcomes related to pain assessments compared with subjects who received tramadol HCl 50 mg QID:

- **NRS-pain:** There was a significantly greater mean decrease (improvement) in NRS-pain scores (using a scale from 0 = no pain, to 10 = worst possible pain) from Baseline to Week 6/Early Termination in the celecoxib group (-3.44) than in the tramadol HCl group

(-3.00) ( $p=0.006$ ); the LS mean treatment difference (celecoxib minus tramadol HCl) in changes in NRS-pain scores to Week 6/Early Termination was -0.47 (95% CI: -0.81, -0.13). Mean changes in NRS-pain scores from Baseline to Week 1 and Week 3 were not significantly different between the 2 treatment groups (mean change to Week 1: -2.41 celecoxib, -2.38 tramadol HCl,  $p=0.736$ ; mean change to Week 3: -3.08 celecoxib, -3.08 tramadol HCl,  $p=0.644$ ). Mean AUC for NRS-pain scores was significantly lower (better) in the celecoxib group (24.4) than in the tramadol HCl group (26.6) ( $p=0.007$ ).

- Low back pain intensity (VAS): There was a significantly greater mean decrease (improvement) in VAS scores (using a 100-mm VAS from 0 = no pain, to 100 = worst possible pain) from Baseline to Week 6/Early Termination in the celecoxib group (-34.58 mm) than in the tramadol HCl group (-30.41 mm) ( $p=0.008$ ); the LS mean treatment difference (celecoxib minus tramadol HCl) in changes in VAS scores to Week 6/Early Termination was -4.70 mm (95% CI: -8.20, -1.21). Mean changes in VAS scores from Baseline to Week 1 and Week 3 were not significantly different between the 2 treatment groups (mean change to Week 1: -23.73 celecoxib, -23.69 tramadol HCl,  $p=0.730$ ; mean change to Week 3: -31.15 celecoxib, -30.39 tramadol HCl,  $p=0.346$ ). Mean AUC for VAS scores was significantly lower (better) in the celecoxib group (231.3) than in the tramadol HCl group (254.4) ( $p=0.004$ ).
- Modified Brief Pain Inventory – Short Form: There were significantly greater mean decreases (improvements) from Baseline to Week 6/Early Termination in mBPI-sf scores (using a scale from 0 = no pain, to 10 = worst possible pain) in the celecoxib group than in the tramadol HCl group for the following assessments: how much pain now (-2.85 versus -2.54, respectively;  $p=0.022$ ), worst pain in past 24 hours (-2.80 versus -2.40, respectively;  $p=0.006$ ), average pain in past 24 hours (-2.64 versus -2.24, respectively;  $p=0.003$ ), pain interference with walking activity (-2.40 versus -1.97, respectively;  $p=0.019$ ), pain interfered with sleep (-2.83 versus -2.21, respectively;  $p=0.001$ ), and pain interfered with normal work (-2.64 versus -2.23, respectively;  $p=0.044$ ). Based on the pain interference subscale (a composite of general activity, mood, walking activity, relation with people, sleep, normal work, and enjoy life scores), there was a significantly greater decrease (improvement) from Baseline to Week 6/Early Termination in the celecoxib group than in the tramadol HCl group (-2.38 versus -2.03, respectively;  $p=0.050$ ). Mean decreases to Week 6/Early Termination in scores for the other pain interference assessments were not significantly different between the 2 treatment groups (general activity: -2.49 celecoxib, -2.17 tramadol HCl,  $p=0.097$ ; mood: -2.12 celecoxib, -1.99 tramadol HCl,  $p=0.647$ ; relations with others: -1.71 celecoxib, -1.48 tramadol HCl,  $p=0.514$ ; enjoyment of life: -2.45 celecoxib, -2.14 tramadol HCl,  $p=0.284$ ). Changes from Baseline to Week 1 and Week 3 were not significantly different between the celecoxib and tramadol HCl groups in any of the mBPI-sf assessments.

Mean AUC for ‘worst pain in past 24 hours’ was significantly smaller (better) in the celecoxib group (29.89) than in the tramadol group (31.96) ( $p=0.014$ ). Mean AUC for ‘average pain in past 24 hours’ was significantly smaller (better) in the celecoxib group (24.95) than in the tramadol HCl group (26.91) ( $p=0.012$ ). Mean AUC for ‘pain interference with sleep’ was significantly smaller (better) in the celecoxib group (20.54)

than in the tramadol HCl group (22.69) ( $p=0.041$ ). Mean AUC for the other mBPI-sf assessments were not significantly different between the 2 treatment groups.

- Patient's Satisfaction Questionnaire (Satisfaction with Pain Relief): At Week 6/Early Termination, the distribution of responses to the 'satisfaction with pain relief' question on the Patient Satisfaction Questionnaire (scored on a scale from 1=very dissatisfied, to 10=very satisfied) was significantly different between the 2 treatment groups ( $p=0.035$ ). A higher percentage of subjects were 'very satisfied' (=10) with pain relief in the celecoxib group (22.3%) than in the tramadol HCl group (19.2%).

For outcomes related to functioning, there were numerically greater changes for celecoxib 200 mg BID versus tramadol HCl 50 mg QID, but there were no significant differences between the 2 treatment groups:

- Roland-Morris Disability Questionnaire: Based on the subjects' assessments of their own disability due to low back pain, the mean decrease (improvement) in RMDQ total score from Baseline to Week 6/Early Termination was numerically greater in the celecoxib group (-4.45) than in the tramadol HCl group (-3.86); however, the difference between the 2 treatment groups was not statistically significant ( $p=0.180$ ). Mean changes from Baseline to Week 1 and Week 3 were not significantly different between the 2 treatment groups (mean change to Week 1: -2.95 celecoxib, -2.76 tramadol HCl,  $p=0.639$ ; mean change to Week 3: -3.80 celecoxib, -3.71 tramadol HCl,  $p=0.965$ ). Mean AUC for the RMDQ total scores was not statistically significantly different between the 2 treatment groups (mean AUC: 46.4 celecoxib, 47.4 tramadol HCl;  $p=0.605$ ).
- Medical Outcomes Sleep Scale: For all of the MOS Sleep Scale total scores, there were numerically greater changes (improvements) from Baseline to Week 6/Early Termination in the celecoxib group versus the tramadol HCl group; however, none of the mean changes from Baseline to Week 6/Early Termination was statistically significantly different between the 2 treatment groups. Mean changes from Baseline to Week 6/Early Termination for each of the sleep scales, where negative change indicates improvement for all scales below except 'quantity of sleep' and 'sleep adequacy,' were:
  - *Sleep disturbance (scale, 0-100)*: -16.47 celecoxib, -15.36 tramadol HCl ( $p=0.465$ ).
  - *Snoring (scale, 0-100)*: -6.40 celecoxib, -4.52 tramadol HCl ( $p=0.258$ ).
  - *Awaken shortness of breath or headache (scale, 0-100)*: -7.34 celecoxib, -6.58 tramadol HCl ( $p=0.624$ ).
  - *Quantity of sleep (scale, 0-24 hours)*: 0.47 celecoxib, 0.39 tramadol HCl ( $p=0.311$ ).
  - *Sleep adequacy (scale, 0-100)*: 9.47 celecoxib, 7.74 tramadol HCl ( $p=0.317$ ).
  - *Somnolence (scale, 0-100)*: -9.13 celecoxib, -7.96 tramadol HCl ( $p=0.374$ ).
  - *Sleep problem index I (scale, 0-100)*: -11.19 celecoxib, -10.11 tramadol HCl ( $p=0.333$ ).
  - *Sleep problem index II (scale, 0-100)*: -12.77 celecoxib, -11.31 tramadol HCl ( $p=0.193$ ).

For the MOS Sleep Optimal Scale, changes from Baseline to Week 6/Early Termination were significantly different between the 2 treatment groups ( $p=0.041$ ); a higher percentage of celecoxib-treated subjects had an improvement from baseline compared with tramadol-treated subjects (21.9% versus 17.5%, respectively).

- **Work Limitations Questionnaire:** For all of the Work Limitations scale scores, there were numerically greater decreases (improvements) from Baseline to Week 6/Early Termination in the celecoxib group versus the tramadol HCl group; however, none of the changes from Baseline to Week 6/Early Termination was significantly different between the 2 treatment groups. Mean changes from Baseline to Week 6/Early Termination for each of the scale scores (based on a scale, 0=limited none of the time, to 100=limited all of the time), where negative change indicates improvement, were:
  - *Time scale:* -12.97 celecoxib, -11.82 tramadol HCl (p=0.551).
  - *Physical scale:* -13.99 celecoxib, -13.25 tramadol HCl (p=0.718).
  - *Output scale:* -11.86 celecoxib, -11.07 tramadol HCl (p=0.686).
  - *Mental-interpersonal scale:* -8.70 celecoxib, -8.49 tramadol HCl (p=0.906).
  - *WLQ index score:* -3.41 celecoxib, -3.20 tramadol HCl (p=0.642).
- **Patient's Satisfaction Questionnaire (Satisfaction with Walking/Bending Ability):** At Week 6/Early Termination, a higher percentage of subjects were 'very satisfied' (=10) with walking/bending ability in the celecoxib group (17.7%) than in the tramadol HCl group (15.3%). However, the overall distribution of responses to the 'satisfaction with walking/bending ability' question (scored on a scale from 1=very dissatisfied, to 10=very satisfied) was not significantly different between the 2 treatment groups (p=0.106).

Overall impressions of health, measured by the Patient's and Physician's Global Assessments of Disease Activity, did not show significant differences between the 2 treatment groups:

- For the Patient's Global Assessment of Disease Activity, subjects used a 5-point scale (1 = very good, 2 = good, 3 = fair, 4 = poor, 5 = very poor) in response to the question: "Considering all the ways your lower back pain affects you, how are you doing today?" There were no significant differences between the 2 groups in the distribution of responses at Week 6/Early Termination (p=0.250) or in changes from Baseline to Week 6/Early Termination (p=0.257). The majority of subjects experienced 'no change' in disease activity at Week 6/Early Termination (72.0% celecoxib, 74.7% tramadol HCl).
- For the Physician's Global Assessment of Disease Activity, the physician provided an overall evaluation of the subject's low back pain using the same 5-point scale as for the Patient's Global Assessment. There were no significant differences between the 2 groups in the distribution of the Physician's Global Assessment at Week 6/Early Termination (p=0.187) or in changes from Baseline to Week 6/Early Termination (p=0.845). The majority of subjects experienced 'no change' in disease activity at Week 6/Early Termination (74.0% celecoxib, 74.8% tramadol HCl).

For the Patient's Global Evaluation of Study Medication, subjects were asked: "In all ways, how would you rate your overall response to study medication, today?" At Week 6/Early Termination, there was a significant difference in the distribution of responses between the 2 treatment groups (p<0.001). At Week 6/Early Termination, higher percentages of subjects reported 'excellent,' 'very good,' and 'good' in the celecoxib group than in the tramadol HCl group (excellent: 21.8% versus 19.7%; very good: 33.1% versus 24.7%; good: 25.9% versus

22.2%, respectively). At Week 1 and Week 3, responses were not significantly different between the 2 treatment groups (Week 1,  $p=0.880$ ; Week 3,  $p=0.361$ ).

Based on the CLBP responder index, which is a composite measure of 3 items in the outcome domains of pain ( $\geq 30\%$  improvement in low back pain intensity [VAS]), functioning ( $< 20\%$  worsening in RMDQ), and overall impression of health ( $\geq 30\%$  improvement in Patient's Global Assessment of Disease Activity), a significantly higher percentage of subjects responded to treatment in the celecoxib group (50.7%) than in the tramadol HCl group (43.7%) ( $p=0.043$ ).

A significantly higher percentage of subjects in the tramadol HCl group (13.4%) withdrew due to lack of tolerability than in the celecoxib group (1.2%) ( $p<0.0001$ ). The most common reasons for permanent withdrawal due to lack of tolerability were: in the tramadol HCl group, nausea (37/389; 9.5%) and dizziness (27/389; 6.9%), and in the celecoxib group, dyspepsia (2/402; 0.5%) and somnolence (2/402; 0.5%).

Within both treatment groups, VAS scores and NRS-Pain scores were highly correlated at Week 1, Week 3, and Week 6/Early Termination (Pearson correlation coefficient: range, 0.90 to 0.94; Lin's CCC, range, 0.89 to 0.93). No statistical testing of correlation was performed.

**Safety Results:** The percentage of subjects who reported at least 1 TEAE was smaller in the celecoxib group than in the tramadol HCl group (all-causality: 47.5% versus 59.1%, respectively; treatment related: 31.1% versus 45.8%, respectively). The number of subjects with SAEs in both treatment groups was small (2 [0.5%] subjects, celecoxib; 5 [1.3%] subjects, tramadol HCl). None of the SAEs was considered by the investigator to be related to study medication.

The percentage of subjects with TEAEs leading to permanent discontinuation was smaller in the celecoxib group than the tramadol HCl group (all-causality: 5.0% celecoxib, 18.3% tramadol HCl; treatment related: 3.5% celecoxib, 16.7% tramadol HCl). An overview of TEAEs is summarized in Table S3, below.

**Table S3. Overview of Treatment-Emergent Adverse Events – Safety Population**

	All Causality		Treatment Related	
	Celecoxib 200 mg BID (N=402)	Tramadol HCl 50 mg QID (N=389)	Celecoxib 200 mg BID (N=402)	Tramadol HCl 50 mg QID (N=389)
<b>Number of TEAEs</b>	470	730	256	545
<b>Subjects (n [%]) with:</b>				
≥ 1 TEAE	191 (47.5%)	230 (59.1%)	125 (31.1%)	178 (45.8%)
SAEs	2 (0.5%)	5 (1.3%)	0	0
Severe TEAEs	10 (2.5%)	30 (7.7%)	5 (1.2%)	23 (5.9%)
TEAE leading to permanent discontinuation	20 (5.0%)	71 (18.3%)	14 (3.5%)	65 (16.7%)
TEAE leading to dose reduction or temporary discontinuation	20 (5.0%)	29 (7.5%)	11 (2.7%)	17 (4.4%)

Abbreviations: BID = twice daily; HCl = hydrochloride, QID = 4 times daily; SAE = serious adverse event;  
 TEAE = treatment-emergent adverse event  
 Includes data up to 30 days after last dose of study drug.  
 SAEs: according to the investigator's assessment

All-causality TEAEs in the System Organ Class *gastrointestinal disorders* occurred more frequently in the tramadol HCl group than in the celecoxib group (36.0% versus 23.4%, respectively).

A higher percentages of subjects in the tramadol HCl group than in the celecoxib group reported treatment-related TEAEs of nausea (19.5% tramadol HCl, 4.2% celecoxib), headache (9.5% tramadol HCl, 7.2% celecoxib), dizziness (14.1% tramadol HCl, 4.0% celecoxib), somnolence (9.5% tramadol HCl, 3.0% celecoxib), vomiting (8.7% tramadol HCl, 0% celecoxib), constipation (6.9% tramadol HCl, 2.0% celecoxib), and pruritis (5.1% tramadol HCl, 1.2% celecoxib).

The most frequently reported (>5% of subjects in either treatment group) all-causality and treatment-related TEAEs are summarized in Table S4, below.

**Table S4. Incidence of All-Causality and Treatment-Related TEAEs in > 5% of Subjects in Either Treatment Group – Safety Population**

MedDRA Preferred Term	All-Causality TEAEs		Treatment-Related TEAEs	
	Celecoxib 200 mg BID (N=402) n (%)	Tramadol HCl 50 mg QID (N=389) n (%)	Celecoxib 200 mg BID (N=402) n (%)	Tramadol HCl 50 mg QID (N=389) N (%)
Nausea	28 (7.0%)	88 (22.6%)	17 (4.2%)	76 (19.5%)
Headache	49 (12.2%)	61 (15.7%)	29 (7.2%)	37 (9.5%)
Dizziness	23 (5.7%)	61 (15.7%)	16 (4.0%)	55 (14.1%)
Somnolence	15 (3.7%)	39 (10.0%)	12 (3.0%)	37 (9.5%)
Vomiting	8 (2.0%)	37 (9.5%)	0	34 (8.7%)
Constipation	9 (2.2%)	33 (8.5%)	8 (2.0%)	27 (6.9%)
Pruritus	7 (1.7%)	26 (6.7%)	5 (1.2%)	20 (5.1%)
Diarrhea	22 (5.5%)	14 (3.6%)	15 (3.7%)	12 (3.1%)
Fatigue	14 (3.5%)	21 (5.4%)	11 (2.7%)	19 (4.9%)

Abbreviations: BID = twice daily; HCl = hydrochloride, MedDRA = Medical Dictionary for Regulatory Activities; QID = 4 times daily; TEAE = treatment-emergent adverse event

The most frequently reported (>2% of subjects in either treatment group) all-causality TEAEs leading to discontinuation of study medication are summarized in Table S5. No more than 2 celecoxib-treated subjects were discontinued for any one particular TEAE among all TEAEs reported.

**Table S5. Incidence of All-Causality TEAEs Leading to Discontinuation of Study Medication (> 2% of Subjects in Either Treatment Group) – Safety Population**

MedDRA Preferred Term	Celecoxib 200 mg BID (N=402) n (%)	Tramadol HCl 50 mg QID (N=389) n (%)
Nausea	1 (0.2%)	37 (9.5%)
Dizziness	1 (0.2%)	27 (6.9%)
Vomiting	0	15 (3.9%)
Headache	1 (0.2%)	13 (3.3%)
Fatigue	2 (0.5%)	8 (2.1%)

Abbreviations: BID = twice daily; HCl = hydrochloride, MedDRA = Medical Dictionary for Regulatory Activities; QID = 4 times daily; TEAE = treatment-emergent adverse event

The percentage of subjects with TEAEs leading to dose reduction or temporary discontinuation of study medication was smaller in the celecoxib group than the tramadol HCl group (all-causality TEAEs: 5.0% celecoxib, 7.5% tramadol HCl; treatment-related TEAEs: 2.7% celecoxib, 4.4% tramadol HCl). The most frequently reported (>2% of subjects in either treatment group) all-causality TEAEs resulting in temporary discontinuation or dose reduction of study medication were vomiting (0.5% celecoxib, 2.6% tramadol HCl), nausea (1.0% celecoxib, 2.1% tramadol HCl), and dizziness (0.2% celecoxib, 2.1% tramadol HCl). The total number of all-causality TEAEs leading to dose reduction or temporary discontinuation was greater in the tramadol HCl group (74 total

events [30 mild, 35 moderate, 9 severe]) than in the celecoxib group (37 total events [24 mild, 10 moderate, 3 severe]).

There were no deaths reported in this study. Six (6) subjects (1 celecoxib, 5 tramadol HCl) reported a total of 11 SAEs in this study; none of the SAEs was considered by the investigator to be related to study medication. Two (2) subjects were permanently discontinued due to SAEs (1 celecoxib-treated subject due to schizophrenia with suicidal ideation, and 1 tramadol-treated subject due to bronchitis). All SAEs are listed by subject in Table S6, below.

**Table S6. Serious Adverse Events by Treatment Group**

Sex/race/ age (years)	MedDRA Preferred Term	SAE Study Start/Stop Day	Severity/ Outcome	Action Taken/ Causality
<b>Celecoxib 200 mg BID</b>				
F/Black/61	Schizophrenia <sup>a</sup> Suicidal ideation <sup>a</sup>	19/22	Moderate/Recovered	Permanently discontinued/Not related
<b>Tramadol HCl 50 mg QID</b>				
M/White/69	Coronary artery stenosis Carotid artery stenosis Aneurysm Unstable angina	42/unknown	Unknown/Recovered	None (Post-therapy: treatment period completed)/Not related
F/other/49	Road traffic accident Multiple fractures	25/38	Moderate/Recovered	None/Not related
F/White/64	Dyspnea	22/unknown	Unknown/Recovered	None/Not related
F/Black/67	Bronchitis	2/19	Moderated/Recovered with sequelae	Permanently discontinued/Not related
M/White/63	Chest pain	54/58	Severe/Recovered	None (Post-therapy: treatment period completed)/Not related

<sup>a</sup> One SAE was reported (investigator term = schizophrenia w/suicidal ideations); this event was split into 2 MedDRA terms in the adverse event monitoring database.

Note: Serious adverse event data are derived from a separate, centralized, adverse event monitoring database that was continuously updated based on rapidly communicated reports from the investigators to the sponsor. Abbreviations: BID = twice daily; F = female; HCl = hydrochloride, M = male; MedDRA = Medical Dictionary for Regulatory Activities; QID = 4 times daily; SAE = serious adverse event

No subjects were permanently discontinued from study treatment due to abnormal laboratory test results. There were no notable laboratory or vital signs abnormalities in this study.

**CONCLUSIONS:** In this 6-week study, celecoxib 200 mg BID was significantly more effective than tramadol hydrochloride 50 mg QID in the treatment of pain associated with moderate to severe chronic low back pain, measured by the proportion of subjects who responded successfully to their respective treatments, with ‘successful responders’ defined as subjects who completed 6 weeks of study medication and had a 30% improvement from Baseline to Week 6 on the Numerical Rating Scale-Pain (NRS-Pain). Outcomes related to functioning showed numerical improvements in both groups but few reached statistical significance. The CLBP responder index (pain, function, and patient’s global assessment) demonstrated that a significantly higher percentage of subjects responded to treatment in the

celecoxib group than in the tramadol HCl group. Since there was a differential dropout rate between treatments, it is unclear how this bias may have influenced the outcomes results.

Celecoxib 200 mg BID was better tolerated than tramadol HCl 50 mg QID, with fewer subjects experiencing adverse events overall and fewer subjects discontinuing treatment due to adverse events.