



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: Vicodin CR		
Name of Active Ingredient: Hydrocodone/Acetaminophen Extended Release (ABT-712)		
Title of Study: A Randomized, Multicenter, Double-blind Study Comparing the Analgesic Efficacy and Safety of Extended-release Hydrocodone/Acetaminophen (Vicodin CR) to Placebo in Subjects with Acute Pain Following Bunionectomy		
Investigators: Multicenter; Coordinating Investigator was Michael Golf, DPM		
Study Sites: Five investigative sites in the United States		
Publications: None		
Studied Period (Years): First Subject First Visit: 03 Jan 2007 (first subject dosed) Last Subject Last Visit: 12 Apr 2007 (last subject completed dosing)	Phase of Development: 3	
Objectives: <p>The primary objective of this study was to compare the analgesic efficacy and safety of Vicodin CR (hydrocodone and acetaminophen extended-release tablets 15 mg/500 mg) two tablets twice daily (BID) to placebo in the treatment of moderate to severe pain on the day following primary, unilateral, first metatarsal bunionectomy surgery.</p> <p>The secondary objective was to compare the analgesic efficacy and safety of Vicodin CR one tablet BID to placebo in the treatment of moderate to severe pain on the day following primary, unilateral, first metatarsal bunionectomy surgery.</p>		
Methodology: <p>This was a Phase 3, randomized, multicenter, double-blind, placebo-controlled study that consisted of four periods: Screening (not to exceed 21 days from the Screening Visit to the day of surgery), Perioperative (from the beginning of confinement on the day of surgery until the first dose of study drug on the day after surgery), Treatment Period (from the first dose of study drug until 48 hours following the first dose of study drug), and Follow-up (from the completion of the Treatment until the Follow-up Visit seven days [± two days] following the first dose of study drug).</p> <p>After meeting the selection criteria during the Screening Visit, subjects returned to the study center within 21 days for Study Day -1. If subjects continued to meet the selection criteria, pre-operative assessments were collected. The bunionectomy was performed under regional anesthesia using a Mayo block and propofol sedation. Perioperative anesthesia was standardized for all subjects. Upon completion of surgery, designated study personnel ensured continued subject eligibility.</p>		



Methodology (continued):

Postoperative pain in the Perioperative Period was managed via long-acting local analgesia and ketorolac. If further breakthrough pain was experienced by the subject in the Perioperative Period, additional supplemental analgesia may have been provided.

Beginning at approximately four AM on the morning following surgery, randomization and study drug treatment began with the onset of moderate or severe pain intensity per the categorical pain intensity scale and a pain intensity score of ≥ 40 mm on a 100 mm visual analog scale (VAS). Subjects were randomized in an equal ratio to one of three treatment arms: Vicodin CR (one tablet or two tablets), or placebo. Study drug dosing occurred every 12 hours for a total of four doses.

During the Treatment Period, subjects completed multiple assessments of pain intensity and of pain relief. Time to first perceptible pain relief (i.e., onset of pain relief) and time to first meaningful pain relief were determined using the two-stopwatch method. In addition, subjects completed multiple subject global assessments. Subjects may have received rescue/supplemental medications.

If a subject required analgesic rescue medication for breakthrough pain during the Treatment Period, ketorolac 30 mg intravenous or intramuscular was administered every 4-6 hours as needed. Immediately prior to administration of the first dose of analgesic rescue medication, subjects completed a pain intensity assessment. Subjects who required analgesic rescue medication continued to complete all required study procedures. Subjects requiring additional analgesic medication for pain not relieved by study drug or ketorolac were provided with parenteral analgesic medication of short duration which included morphine sulfate and/or oxycodone.

Safety was evaluated throughout the study by physical examinations, vital signs, laboratory tests, electrocardiogram, and monitoring of adverse events (AEs).

Number of Subjects (Planned and Analyzed):

One hundred fifty subjects were planned and 163 subjects were randomized in the study; 53 subjects were randomized to placebo, 54 subjects were randomized to the Vicodin CR 1-tablet treatment group, and 56 subjects were randomized to the Vicodin CR 2-tablet treatment group. All randomized subjects took at least one dose of study drug and were included in the intent-to-treat dataset.

Diagnosis and Main Criteria for Inclusion:

Males and postmenopausal or surgically sterile or practicing one form of birth control females between 18 and 65 years of age, inclusive who were scheduled to undergo primary, unilateral first metatarsal bunionectomy under regional/local anesthesia and sedation, who met the American Society of Anesthesiologists (ASA) criteria for ASA class I (a normal healthy patient) or ASA class II (a patient with mild systemic disease), and who reported pain intensity score of ≥ 40 mm on a 100 mm VAS scale and score of moderate or severe pain on a categorical pain intensity scale on the morning following surgery were eligible to enter the study.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Hydrocodone 15 mg/acetaminophen 500 mg extended release (Vicodin CR) 1-tablet (one active, one placebo) every 12 hours for a total of four doses or 2-tablet (two active) every 12 hours for a total of four doses.

Packaged lot number: [REDACTED] bulk lot number: [REDACTED] redacted information 29Jul2014

Duration of Treatment:

48 hours; four doses of study drug, each dose administered every 12 hours.



Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Placebo two tablets every 12 hours for a total of four doses

Packaged lot number: [REDACTED]; bulk lot number: [REDACTED]

Criteria for Evaluation redacted information 29Jul2014

Efficacy:

Efficacy was assessed by determinations of pain intensity, pain relief, and subject global assessment of study drug. These assessments included a four-point categorical scale (no pain, mild pain, moderate pain, or severe pain) and 100 mm VAS of pain intensity, a five-point categorical scale of pain relief from Baseline (no relief, a little relief, some relief, a lot of relief, or complete relief), rescue medication use, and a subject global assessment of the study drug for pain (poor, fair, good, very good, excellent). In addition, time to perceptible pain relief and time to first meaningful pain relief were determined via use of a two-stopwatch system.

Pharmacokinetic:

Values for the pharmacokinetic parameters of hydrocodone and acetaminophen, including maximum observed plasma concentration (C_{max}), the minimum observed plasma concentration (C_{min}), time to C_{max} (T_{max}), and the area under the plasma concentration-time curve (AUC) from time 0 to 12 hours (AUC_{12}) were estimated using noncompartmental methods.

Safety:

Adverse events, physical examinations, laboratory data, and vital signs were assessed throughout the study.

Statistical Methods

Efficacy:

The primary efficacy measurement was the time-interval weighted sum of pain intensity difference (SPID) using the VAS scale (100 mm, 0 being "no pain" and 100 being "worst pain imaginable") for the 0 to 12 hour interval following initial study drug administration. The SPID score was a measure of the cumulative pain intensity during treatment, and the area under the pain intensity difference curve was estimated using the linear trapezoidal rule. Treatment group mean differences for the primary efficacy variable were evaluated using an analysis of covariance model with factors for treatment group, Investigator, and the Baseline VAS pain intensity score as a covariate. Heterogeneity of treatment effects across Investigator was explored.

Secondary efficacy variables included the following: time-interval weighted sum of pain relief, SPID using the categorical pain intensity scale, time-interval weighted sum of pain relief and pain intensity difference, perceptible pain relief, meaningful pain relief, rescue/supplemental medication use, pain relief, pain intensity, and subject Global Assessment of Study Drug.

Treatment group differences in pain scores at each scheduled evaluation were analyzed using Fisher's Protected Least Significant Difference (LSD) and analysis of variance (ANOVA) models. Pairwise comparisons of the treatment group means were analyzed using Fisher's LSD, based on an analysis model with factors for treatment group and Baseline pain. The ANOVA analyses were completed using two models. Mean differences in treatment group effects were analyzed using an ANOVA model with factors for treatment group and Baseline pain (no interaction). Treatment-by-Baseline pain intensity interaction was analyzed using an ANOVA model with factors for treatment group, Baseline pain intensity, and the interaction term.



Statistical Methods (continued)

Pharmacokinetic:

Individual hydrocodone and acetaminophen plasma concentrations and pharmacokinetic parameter values were tabulated for each subject and treatment group and summarized with appropriate statistical methods.

Safety:

Treatment-emergent AEs and surgically related events (SRE) were summarized by system organ class and Medical Dictionary for Regulatory Activities (MedDRA®) preferred term. Pairwise comparisons between treatment groups were made using Fisher's exact test for the proportion of subjects reporting a particular AE or SRE. Treatment-emergent AEs were also summarized by severity, relationship to study drug, and prevalence over the dosing intervals.

For laboratory data, mean change from Baseline to the final values was analyzed using a one-way ANOVA with treatment as the main effect. Laboratory results that satisfied the Data Analysis Criteria for Potentially Clinically Significant Laboratory Findings were identified. Additionally, the number and percentage of subjects with shifts from Baseline to the final values using the Data Analysis Criteria for Potentially Clinically Significant Laboratory Findings to define categories (very low, normal, very high, and missing) as well as using normal ranges to define categories (low, normal, high and missing) were summarized.

For vital signs, mean changes from Baseline to the average, minimum, maximum, and final values were analyzed using a one-way ANOVA with treatment as the main effect. Vital sign results satisfying the Criteria for Potentially Clinically Significant Vital Sign Findings were identified.

Summary/Conclusions

Efficacy Results:

For the protocol-specified primary endpoint, each of the Vicodin CR treatment groups demonstrated statistically significantly higher mean 0-12 hour time interval weighted SPID VAS scores as compared to the placebo treatment group.

The secondary time-interval weighted pain assessments of SPID categorical, time-interval weighted sum of pain relief score (TOTPAR), and sum of the pain relief and pain intensity difference (SPRID) scores over the 12 hours following initial dose of study drug also demonstrated statistically significantly better pain control for each of the Vicodin CR treatment groups as compared to the placebo treatment group for each of the time intervals assessed.

The analysis of mean pain assessments for the 12 hours following the initial dose of study drug (pain intensity difference, pain relief [PR], pain relief + pain intensity difference, and pain intensity scores) demonstrated that each of the Vicodin CR treatment groups were generally statistically significantly better than the placebo treatment group starting at the 0.75 - to 1.0-hour time points and continuing over the majority of time points through 12 hours.



Summary/Conclusions

Efficacy Results (continued):

Median time to onset of perceptible pain relief was 29 minutes in the placebo group, 28 minutes in the Vicodin CR 1-tablet treatment group, and 24 minutes in the Vicodin CR 2-tablet treatment group. Statistically significantly greater proportions of subjects in each of the Vicodin CR treatment groups experienced perceptible (Vicodin CR 2-tablet only), meaningful, and confirmed perceptible pain relief compared to the placebo treatment group. Additionally, the proportions of subjects showing $\geq 30\%$, $\geq 50\%$, or $\geq 70\%$ reduction in pain intensity, as assessed by VAS scores for 0-12 hours following the initial dose of study drug, were statistically significantly greater in each of the Vicodin CR treatment groups than in the placebo treatment group. The proportions of subjects using any rescue medication within 12 hours of the initial dose of study drug were statistically significantly lower in the Vicodin CR 1-tablet and Vicodin CR 2-tablet treatment groups (72% and 48%, respectively) compared to the placebo group (91%).

While each dose of Vicodin CR was superior to placebo, the Vicodin CR 2-tablet treatment group was consistently superior to the Vicodin CR 1-tablet treatment group, with statistically significant differences observed in all efficacy variables at most scheduled evaluations, consistent with a dose response.

Pharmacokinetic Results:

The pharmacokinetics of hydrocodone and acetaminophen, following administration of Vicodin CR every twelve hours, were dose-proportional between the 1-tablet and 2-tablet groups. Systemic exposures (C_{max} and AUC_{12}) of hydrocodone and acetaminophen were consistent with exposures observed in previous Phase 1 and Phase 2 studies.

Safety Results:

Statistically significantly greater proportions of the subjects in the Vicodin CR 1-tablet (80%) and Vicodin CR 2-tablet (96%) treatment groups experienced at least one treatment-emergent AE compared to subjects in the placebo treatment group (58%). Additionally, the difference between the Vicodin CR 2-tablet and placebo treatment groups in the incidence of treatment-emergent AEs was statistically significant.

Treatment-emergent AEs occurring in $\geq 10\%$ of subjects in any treatment group included nausea, vomiting, somnolence, headache, dizziness, and pruritus. Dizziness, nausea, and pruritus were each experienced by a statistically significantly greater proportion of subjects in each of the Vicodin CR treatment groups compared to placebo subjects. Nausea and vomiting were each experienced by a statistically significantly greater proportion of subjects in the Vicodin CR 2-tablet treatment group compared to the Vicodin CR 1-tablet treatment group. The incidences of somnolence and vomiting were statistically significantly higher in the Vicodin CR 2-tablet treatment group as compared to the placebo treatment group.

No subject died during the course of the study. One subject in the Vicodin CR 1-tablet group experienced an SAE of deep vein thrombosis that was considered to be severe and probably not related to study drug. One subject in the Vicodin CR 2-tablet group experienced an SAE of pulmonary embolism that was considered to be severe and not related to study drug.

Four (7%) subjects in the Vicodin CR 2-tablet treatment group prematurely discontinued from study drug due to AEs. Each of the subjects prematurely discontinued study drug due to AEs that were considered by the Investigator to be probably related to study drug.

The clinical laboratory and vital sign assessments were generally unremarkable for all treatment groups.



Conclusions:

This study demonstrates the analgesic efficacy of Vicodin CR as compared to placebo in the management of moderate to severe pain in subjects with post unilateral bunionectomy surgery. The safety profile of Vicodin CR demonstrates an AE profile consistent with a *mu*-opioid-receptor-agonist containing agent.

The pharmacokinetics of hydrocodone and acetaminophen, following administration of Vicodin CR every twelve hours, were dose-proportional between the 1-tablet and 2-tablet treatment groups.