



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, Single-Blind Study Comparing the Analgesic Efficacy and Safety of Extended Release Hydrocodone/Acetaminophen (Vicodin CR™), and Immediate Release Hydrocodone/Acetaminophen (NORCO®) to Placebo in Subjects with Acute Pain Following Bunionectomy		
Investigator: Multicenter; Coordinating Investigator was Michael Golf, DPM		
Study Sites: Three investigative sites in the United States.		
Publications: None		
Studied Period (Years): First Subject Dosed: 07 December 2005 Last Subject Dose: 21 February 2006	Phase of Development: 2	
Objectives: <p>The primary objective of this study was to compare the analgesic efficacy and safety of Vicodin CR (hydrocodone 15 mg/acetaminophen 500 mg extended-release tablets), 2 tablets by mouth, administered as a single dose, to placebo in the treatment of moderate to severe pain on the day following primary, unilateral, first metatarsal bunionectomy surgery.</p> <p>A secondary objective was to compare the analgesic efficacy and safety of NORCO, an immediate-release hydrocodone/acetaminophen combination product (hydrocodone 10 mg/acetaminophen 325 mg), 1 tablet every 4 hours (Q4H) by mouth for 3 doses, to placebo in the treatment of moderate to severe pain on the day following primary, unilateral, first metatarsal bunionectomy surgery.</p> <p>An additional objective was to explore the pharmacokinetic and exposure-response relationship of hydrocodone/acetaminophen in subjects experiencing pain, which will be provided as part of a meta-analysis.</p>		
Methodology: <p>This was a Phase 2, randomized, multicenter, single-blind, placebo-controlled study that consisted of 4 periods: Screening, Perioperative (Day of Surgery), Treatment (Day of Dosing/Post Operation Day 1 [up to 12 hours following the initial dose of study drug]), Follow-up (from the completion of the Treatment Period until the Follow-up Visit 7 days [± 1 day] later).</p>		



Methodology (Continued):

Subjects who met the selection criteria at the Screening Visit were eligible to participate in the study and returned to the study center within 21 days. If subjects continued to meet the selection criteria at this time, pre-operative assessments were performed and confinement at the investigative site began. Bunionectomy was performed utilizing popliteal-sciatic nerve block (PSB) for regional analgesia. Intraoperative management, perioperative care, local and regional anesthetic technique, and sedation practices were standardized for all subjects.

Post-operative pain in the Perioperative Period was managed by the continued use of PSB via continuous infusion of local anesthetic. If additional analgesia was required in the Perioperative Period, subjects could have received oxycodone 5-10 mg oral Q4H-Q6H as needed for pain. No oxycodone was permitted after 0130 (1:30 AM) on the morning following surgery.

At approximately 0200 (2:00 AM) on the morning following surgery, local anesthetic infusion via PSB was discontinued. Starting at 90 minutes, but no more than 8 hours after discontinuation of PSB, subjects indicating a pain intensity level ≥ 40 mm on a 100 mm visual analogue scale (VAS, 100 mm, 0 = no pain and 100 = worst pain imaginable) and a categorical pain score of moderate or severe (4-point scale: none, mild, moderate, severe) were randomized in an equal ratio to 1 of the following 3 treatment arms: Vicodin CR (hydrocodone 15 mg/acetaminophen 500 mg extended-release tablets), NORCO (hydrocodone 10 mg/acetaminophen 325 mg immediate-release tablets), or placebo. Study drug dosing occurred every 4 hours for a total of 3 doses for all subjects, in order to maintain the single-blind methodology.

During the 12-hour Treatment Period, subjects completed multiple assessments of pain intensity and pain relief, and global assessments of study drug. Time to first perceptible pain relief (i.e., onset of pain relief) and time to meaningful pain relief were determined using the 2-stopwatch method.

Subjects could have received analgesic rescue medication during the Treatment Period if needed. Subjects were encouraged to delay the use of any analgesic rescue medication for at least 90 minutes after initial study drug administration.

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

Number of Subjects (Planned and Analyzed): Ninety subjects were planned and 91 subjects were randomized in the study; 31 subjects were randomized to placebo, 31 subjects were randomized to NORCO, and 29 subjects were randomized to Vicodin CR. All randomized subjects who received a dose of study drug were included in the intent-to-treat datasets.

Three subjects (Subjects [REDACTED]) were incorrectly dosed (instead of receiving active Vicodin CR and NORCO placebo for dose 1 and NORCO placebo for doses 2 and 3, these subjects received active Vicodin CR for doses 2 and 3) and excluded from the Efficacy Evaluable dataset (considered the primary dataset for all efficacy analyses) and pharmacokinetic analyses.

In addition, the following subjects were also excluded from the pharmacokinetic analyses:

- Subject [REDACTED], in the Vicodin CR treatment group, who had blood samples collected only up to 0.75 hour postdose
- Subjects [REDACTED] who received LORTAB® around 6, 10, and 4 hours postdose, respectively
- Subjects randomized to the placebo treatment group



Diagnosis and Main Criteria for Inclusion:

Males and females between 18 and 65 years of age, inclusive, who were scheduled to undergo primary, unilateral, first metatarsal bunionectomy surgery under regional anesthesia (Mayo block) and propofol 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), who reported moderate or severe pain per a categorical pain intensity scale between 90 minutes and 8 hours after discontinuation of PSB, and who were willing to remain at the study center for approximately 48 hours were eligible for the study.

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

Hydrocodone 15 mg/acetaminophen 500 mg extended release (Vicodin CR) 2 tablets as a single dose.
Lot number: [REDACTED]

Duration of Treatment: 3 doses over 12 hours, with each dose administered every 4 hours.

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

Hydrocodone 10 mg/acetaminophen 325 mg immediate release (NORCO) 1 tablet Q4H for 3 doses.

Lot number: [REDACTED]

Placebo for hydrocodone 15 mg/acetaminophen 500 mg extended release (Vicodin CR).

Lot number: [REDACTED]

Placebo for hydrocodone 10 mg/acetaminophen 325 mg immediate release (NORCO).

Lot number: [REDACTED] redacted information 29Jul2014

Criteria for Evaluation

Efficacy:

Efficacy was assessed by determinations of pain intensity, pain relief, and subject global evaluation. These assessments included a 4-point categorical scale (no pain, mild pain, moderate pain, or severe pain) and 100 mm VAS of pain intensity, a 5-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 evaluation of the study drug for pain (poor, fair, good, very good, excellent). In addition, time to perceptible pain relief and time to meaningful pain relief were determined via use of 2 stopwatches.

Pharmacokinetic:

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

Safety:

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



Statistical Methods

For all efficacy and safety endpoints, the primary comparisons were between the Vicodin CR treatment group and the placebo treatment group. Additionally, the NORCO treatment group and the placebo treatment group were compared. In addition to the planned treatment comparisons, the Vicodin CR and NORCO treatment groups were also compared.

Efficacy:

For all efficacy analyses, except rescue medication use, data obtained after a subject received rescue medication was completely excluded from analyses.

The primary efficacy endpoint was the time interval weighted sum of pain intensity difference (SPID) using the 100 mm VAS for the 0 to 12 hours following initial study drug administration. Treatment group mean differences for the primary efficacy endpoint were evaluated using analysis of variance (ANOVA) with factors for treatment group and study center.

Secondary efficacy analyses include the following: SPID (categorical and VAS) for each scheduled evaluation, time interval weighted sum of pain relief (TOTPAR) for each scheduled evaluation, time interval weighted sum of pain relief and pain intensity difference (SPRID) scores for each scheduled evaluation, time to perceptible pain relief and time to meaningful pain relief, time to first analgesic rescue medication, Subject global evaluation, and pain relief (PR), pain intensity (PI), and pain intensity difference (PID) at each scheduled evaluation.

The TOTPAR, SPID, and SPRID were calculated through the first 12 hours following initial study drug dosing. The time interval weighted pain scores were analyzed using ANOVA, utilizing the same analysis model used for the primary efficacy variable. The time to subject's first perceptible and meaningful pain relief, and time to analgesic rescue medication were analyzed using Log rank statistics from nonparametric survival models. Wald statistics from Cox proportional hazards models (with Kaplan-Meier estimates of median time to event) were used to compare the placebo treatment group to each of the other 2 treatment groups (i.e., Vicodin CR and NORCO).

The actual scores of the subject global assessment were analyzed at each scheduled evaluation using CMH methodology for equal row means with study centers as the stratification factor.

Absolute PR, PI, PID, and PRID (PR+PID) were analyzed using Fisher's Protected Least Significant Difference (LSD) and ANOVA models. The ANOVA analyses were completed using 3 different models. Two models included a test for treatment effects using a model with factors for treatment group and baseline categorical pain (no interaction) as well as a model with factors for treatment group and investigator (no interaction). A third model included a test for the treatment-by-baseline pain intensity interaction using a model with factors for treatment group, baseline categorical pain intensity, and the interaction.

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:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®). All treatment-emergent adverse events (i.e., those which began or worsened in severity after initiation of study drug), as well as adverse events that began in the interval between the end of surgery and time of initial study drug dosing, and adverse events that began after the first dose of rescue medication, were tabulated by system organ class (SOC) and MedDRA preferred term. A summary of the severity and relationship to study drug of all treatment-emergent adverse events, tabulated by MedDRA preferred term and SOC, was presented. Surgically Related Events (SREs) were coded using MedDRA and tabulated by MedDRA preferred term.

For laboratory data, mean change from baseline to final values were 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, both the Vicodin CR and NORCO treatment groups demonstrated statistically significantly higher (better) mean 0-12 hour time-interval weighted SPID VAS scores as compared to placebo ($p < 0.001$ and $p = 0.003$, respectively).

The vast majority of the secondary efficacy endpoints evaluating time to onset, magnitude and duration of effect, proportion of treatment responders, proportion of subjects using rescue medication and time to rescue, and Subject's Global Assessment of Study Drug demonstrated the superiority of Vicodin CR and NORCO compared to placebo.

Both Vicodin CR and NORCO demonstrated statistically significant superior results compared to placebo for the secondary time-interval weighted pain assessments of TOTPAR 0 – 12 hours ($p = 0.001$ and $p = 0.002$, respectively), categorical SPID 0 – 12 hours ($p < 0.001$ and $p = 0.017$, respectively), and SPRID 0 - 12 hours ($p < 0.001$ and $p = 0.003$, respectively).

The analysis of mean pain assessments for the 12 hours following the initial dose of study drug (PID, PR, PRID, and PI scores) demonstrated that Vicodin CR and NORCO treatment groups were generally statistically significantly better than placebo starting at the 1- to 1.5-hour time points and continuing over the majority of time points through 12 hours.

Median time to perceptible and meaningful PR was shorter in the Vicodin CR and NORCO treatment groups compared to the placebo treatment group. However, this study was not powered to make statistical comparisons for this endpoint.

The proportions of subjects showing $\geq 50\%$ reduction in VAS PI score were statistically significantly greater in each of the Vicodin CR (62%) and NORCO (52%) treatment groups compared to the placebo treatment group (23%; $p = 0.004$ and $p = 0.016$, respectively).



The proportion of subjects requiring rescue medication was statistically significantly lower for the Vicodin CR and NORCO treatment groups, compared to the placebo treatment group (46%, 61%, and 90%, respectively; $p < 0.001$ and $p = 0.016$, respectively). Also, the time to the first rescue medication use within 12 hours of initial dose was statistically significantly longer for the Vicodin CR treatment group ($p = 0.001$) and the NORCO treatment group ($p = 0.030$) as compared to the placebo treatment group.

The distribution of responses to the Subject's Global Assessment of Study Drug was statistically significantly better in the Vicodin CR and NORCO treatment group as compared to placebo for the vast majority of time points ($p \leq 0.006$ and $p \leq 0.012$, respectively).

Overall, the two active treatment groups demonstrated similar efficacy profiles as compared to placebo, as might be expected for treatments that deliver similar total doses of active ingredients (hydrocodone and acetaminophen) over 12 hours. To statistically evaluate this observed similarity in efficacy, post-hoc analyses were performed comparing the Vicodin CR and NORCO treatment groups for all efficacy endpoints.

- No statistically significant treatment differences were observed between the two active groups in the analysis of 0-12 hour time-interval weighted pain assessments following the initial dose of study drug.
- Vicodin CR demonstrated statistically significant superior scores at the 5-hour time point for PID VAS and PRID, at the 4- to 6-hour time points for PI VAS, and at the 4- to 7-hour time points for PID categorical and PI categorical as compared to the NORCO treatment group.
- The NORCO treatment group was not statistically significantly superior to the Vicodin CR treatment group at any time point.

Pharmacokinetic Results:

Mean \pm standard deviation (SD) pharmacokinetic parameters of hydrocodone after administration of Vicodin CR and NORCO are listed in the following table.

		Mean \pm SD Pharmacokinetic Parameters of Hydrocodone			
		Subject Groups			
Pharmacokinetic Parameters (units)		2 Tablets Vicodin CR, Single Dose (N = 25)	1 Tablet NORCO, Q4H \times 3 Doses (N = 13)	1 Tablet NORCO, Q4H \times 1 Dose (N = 13)	1 Tablet NORCO, Q4H \times 2 Doses (N = 2 ^a)
T _{max}	(h)	5.43 \pm 3.72	8.62 \pm 2.53	2.50 \pm 1.48	0.88
C _{max}	(ng/mL)	25.4 \pm 6.44	33.0 \pm 10.2	18.6 \pm 4.38	27.5
AUC ₀₋₁₂	(ng•h/mL)	199 \pm 58.7	222 \pm 59.2	88.4 \pm 17.5 ^b	162

a. Standard deviation was not calculated.

b. N = 12



Mean ± SD pharmacokinetic parameters of acetaminophen after administration of Vicodin CR and NORCO are listed in the following table.

Pharmacokinetic Parameters (units)		Mean ± SD Pharmacokinetic Parameters of Acetaminophen			
		Subject Groups			
		2 Tablets Vicodin CR, Single Dose (N = 25)	1 Tablet NORCO, Q4H × 3 Doses (N = 13)	1 Tablet NORCO, Q4H × 1 Dose (N = 13)	1 Tablet NORCO, Q4H × 2 Doses (N = 2 ^a)
T _{max}	(h)	3.32 ± 2.24	6.23 ± 3.76	1.97 ± 0.86	0.63
C _{max}	(µg/mL)	4.14 ± 1.12	5.72 ± 2.44	3.33 ± 1.46	7.57
AUC ₀₋₁₂	(µg•h/mL)	26.3 ± 6.99	32.7 ± 9.37	11.1 ± 2.11 ^b	31.0

a. Standard deviation was not calculated.

b. N = 12

Compared to NORCO-treated group, the mean C_{max} value for both hydrocodone and acetaminophen in Vicodin CR-treated group were slightly higher than that in subjects receiving only 1 dose of NORCO, but slightly lower than that in subjects receiving 3 consecutive doses of NORCO. The mean AUC₀₋₁₂ value for hydrocodone and acetaminophen in Vicodin CR was similar to NORCO Q4H (3 doses) group.

Mean C_{max} and AUC₀₋₁₂ values for hydrocodone and acetaminophen in both Vicodin CR and NORCO Q4H (3 doses) groups were consistent with values from previous Phase 1 and Phase 2 studies.

Safety Results:

Similar proportions of subjects in the Vicodin CR (62%), NORCO (58%), and placebo (61%) treatment groups experienced at least one AE. Treatment-emergent AEs occurring in ≥ 5% of subjects in any treatment group included nausea, vomiting, headache, dizziness, somnolence, fatigue, hypotension, and abdominal pain upper. Nausea was experienced by a statistically significantly greater proportion of subjects in the NORCO treatment group compared to subjects in the placebo treatment group.

No subject experienced a SAE and no subject prematurely discontinued study drug due to an AE.

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

Conclusions:

This study demonstrated the similar analgesic efficacy and safety of Vicodin CR and NORCO as compared to placebo in the treatment of moderate to severe pain in subjects with post unilateral bunionectomy surgery.