2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Vicodin CR™	**Volume:**	
Name of Active Ingredient: Hydrocodone bitartrate/ Acetaminophen Extended Release (ABT-712)	**Page:**	
Title of Study: A Phase 3, Open-Label Period Followed by a Randomized, Double-Blind, Placebo-Controlled Study of the Analgesic Efficacy of Extended-Release Hydrocodone/Acetaminophen (Vicodin CR™) Compared to Placebo in Subjects With Chronic Low Back Pain		
Investigator: [redacted] MD redacted information 24Sep2014		
Study Sites: Thirty-one (31) study centers selected; 30 study centers enrolled subjects in the United States.		
Publications: None		
Studied Period (Years): First Subject First Visit: 08 September 2008 Last Subject Last Visit: 03 April 2009		**Phase of Development:** 3b
Objectives: The primary objective of this multicenter Phase 3b study was to compare the analgesic efficacy of 2 tablets of Vicodin CR to placebo when administered twice daily over 4 weeks in subjects with moderate to severe mechanical CLBP. The secondary objective was to assess the effect of Vicodin CR, compared to placebo, on sleep interference by pain. An additional objective of this study was to explore population pharmacokinetics (PK) and the exposure-response relationship of hydrocodone and acetaminophen resulting from administration of Vicodin CR.		
Methodology: This was a Phase 3b, randomized, multicenter, double-blind (DB), placebo-controlled study designed to compare the analgesic efficacy of 2 tablets of Vicodin CR administered twice daily over a 4-week period to placebo in subjects with moderate to severe mechanical CLBP. The study included a Screening Visit, a Washout Period ranging from 2 to 28 days, a 3-week Open-Label (OL) Period, a randomized, 4-week, Double-Blind (DB), placebo-controlled Maintenance Period, a 1-week Taper Period, and a Follow-up Period.		

Methodology (Continued):

Subjects were evaluated for a diagnosis of CLBP and were selected for study participation based on inclusion and exclusion criteria. Subjects who met the selection criteria were to enter the Washout Period, during which they were to discontinue their current analgesic therapy for CLBP. The minimum length of time allowable between the Screening Visit and initiation of the OL Period was 2 days; the maximum length of time was 28 days.

Subjects returned to the study center following the Washout Period and were re-assessed to determine if they met the following OL Baseline Flare Criteria: Subject's Assessment of CLBP Intensity as determined by visual analog scale (VAS) must have been ≥ 40 mm and increased by at least 10 mm as compared to the Screening Visit assessment and the Subject's Global Assessment of CLBP must have been Fair, Poor or Very Poor. For those subjects whose screening VAS was ≥ 85 mm, a VAS of ≥ 85 mm was to be maintained at the OL Baseline Visit.

The first 1 to 2 weeks of the OL Period incorporated a titration phase. During the third week of the OL Period, all subjects received 2 tablets of Vicodin CR twice daily.

Subjects returned to the study center at the end of the 3-week OL Period and were re-assessed to determine eligibility for entering the 4-week DB Maintenance Period of the study. If at the end of the 3-week OL Period, the Investigator did not feel that the subject was able to tolerate dosing with Vicodin CR two tablets twice daily for 4 weeks, the subject was not to be randomized into the DB Maintenance Period and was discontinued from the study.

Subjects who met the randomization criteria were randomly assigned in an equal ratio to receive 1 of 2 treatments for 4 weeks: 2 tablets of Vicodin CR twice daily or matching placebo. Subjects randomized to the placebo group had their OL dose of Vicodin CR tapered (in a blinded manner) over the first week of the DB Maintenance Period to minimize the risk of developing opioid withdrawal syndrome.

Following completion of the DB Maintenance Period, subjects were to have entered the 1-week study drug Taper Period. At the conclusion of the Taper Period, subjects were to return to the study center. A Follow-up Visit was to have been conducted 1 week after study drug discontinuation. In addition, the study centers were to contact the subject by telephone approximately 30 days after the last dose of study drug.

Analgesic rescue medication was permitted only during the Washout Period, the first 10 days of the OL Period, and the Taper Period.

If a subject discontinued from the study prematurely, the subject was to be assessed according to the procedures outlined for premature discontinuation prior to starting the Taper Period.

Number of Subjects (Planned and Analyzed): Three hundred fifty (350) subjects were planned to be enrolled into the OL Period to provide 200 subjects for randomization. Two hundred eighty-five subjects were enrolled in the OL Period and received at least 1 dose of study drug and 222 subjects were randomized and received DB study drug; 109 subjects were assigned to Vicodin CR 2 tablets, and 113 subjects were assigned to placebo.

Diagnosis and Main Criteria for Inclusion: Males and females between ages 21 and 75, inclusive, who had a diagnosis of CLBP below the 12th thoracic vertebrae and above the crease of the buttocks for at least 6 months duration and who had taken therapeutic doses of at least 1 analgesic for CLBP for 4 days/week in the previous 3 months and 5 days/week during each of the previous 4 weeks prior to screening were eligible for the study.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Hydrocodone and acetaminophen extended-release tablets 15 mg/500 mg (Vicodin CR) administered orally. Lot numbers: [redacted]

Duration of Treatment: 3-week OL Period, 4-week Maintenance Period, and 1-week Taper Period.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Placebo for hydrocodone and acetaminophen extended-release. Lot numbers: [redacted]

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Criteria for Evaluation

Efficacy: The primary efficacy measurement was the mean pain intensity difference from the DB randomization baseline (immediately prior to entering the DB Maintenance Period) to each subject's final assessment as assessed by the Subject's Assessment of CLBP Intensity VAS (100 mm).

Secondary efficacy assessments included the following: Chronic Pain Sleep Inventory, Subject's Assessment of Sleep Interference by Pain, pain intensity difference for the Subject's Assessment of CLBP Intensity VAS from DB randomization baseline (immediately prior to entering the DB Maintenance Period) to each scheduled assessment and final assessment, time to withdrawal due to lack of efficacy during the DB Maintenance Period, Subject's Global Assessment of Study Drug, Subject's Global Assessment of Back Pain Status, and protocol-allowed rescue medication use.

Pharmacokinetic: Values for the pharmacokinetic parameters of hydrocodone and acetaminophen including apparent oral clearance (CL/F) were tabulated using population pharmacokinetic modeling procedures.

Safety: Safety was evaluated throughout the study by physical examinations, vital signs, laboratory tests, and monitoring of AEs.

Statistical Methods

Efficacy: Treatment group mean differences for the primary efficacy variable were evaluated using ANCOVA with factors for treatment group, study center, and the DB Baseline pain intensity score as a covariate. All statistical tests were two-tailed and considered statistically significant if the *P* value was less than or equal to 0.05.

The mean differences in the change from DB Baseline for the Subject's Assessment of Sleep Interference by Pain, Chronic Pain Sleep Inventory, and pain intensity difference for the Subject's Assessment of CLBP Intensity VAS, were analyzed using ANCOVA utilizing the same analysis model used for the primary efficacy variable. Treatment group differences in the time to premature discontinuation due to lack of efficacy, starting from the beginning of the DB Maintenance Period, were analyzed by log-rank statistics from nonparametric survival models. Additionally pain intensity difference for the Subject's Assessment of CLBP Intensity VAS was analyzed using the repeated measures analysis and ANCOVA using LOCF methodology. Treatment group differences in the cumulative distribution function for change and percent change from OL Baseline, as well as change from DB Baseline (immediately prior to entering the DB Maintenance Period) to final assessment using the Subject's Assessment of CLBP Intensity VAS, were assessed using the Monte-Carlo exact Kolmogorov-Smirnov test. The actual scores for the Subject's Global Assessment of Study Drug and the Subject's Global Assessment of Back Pain Status at each scheduled evaluation following randomization were analyzed using the CMH test for equal row means scores with study centers and DB Baseline evaluation score as stratification factors in separate analyses. Protocol-allowed rescue medication (acetaminophen) used during the OL Period for CLBP pain, as well as acetaminophen used for any reason, were summarized separately by weekly intervals (e.g., Study Days 1 to 7, 8 to 14).

Pharmacokinetic: Individual hydrocodone and acetaminophen plasma concentrations and PK parameter values for DB Baseline and DB Weeks 1, 2, 3, and 4 were tabulated and summarized with appropriate statistical methods.

Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 11.1. Treatment-emergent AEs (i.e., those which began or worsened in severity after initiation of study drug in each period) were tabulated by system organ class (SOC) and MedDRA preferred term for each treatment group. For the DB period, treatment group differences were evaluated using Fisher's exact test for the proportion of subjects reporting a particular AE.

Laboratory data were analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses were the mean changes from OL Baseline to the final values for each laboratory variable. Laboratory data values were categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Additionally, the number and proportion of subjects with shifts from OL 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) were summarized.

For vital signs, during the OL Period, mean changes from OL Baseline to final values were summarized. For the DB Maintenance Period, mean changes from OL Baseline to the minimum, maximum, and final values were analyzed using a 1-way ANOVA with treatment as the main effect.

Summary/Conclusions

Efficacy Results: The primary efficacy endpoint was change in Pain Intensity VAS from DB Baseline to the final evaluation of the DB Maintenance Period. At DB final evaluation, the mean increase in pain intensity from DB Baseline was statistically significantly lower for the Vicodin CR treatment group compared to the placebo treatment group. This finding supports the conclusion that there is a difference between Vicodin CR treatment and placebo in change in Pain Intensity VAS. Analyses using several different imputation methods yielded supportive findings. The superiority of treatment with Vicodin CR compared to placebo also was consistent across multiple secondary endpoints:

- Chronic Pain Sleep Inventory: mean change from DB Baseline to each scheduled assessment and to the final evaluation.
- Subject's Assessment of Sleep Interference by Pain: mean change from DB Baseline to each scheduled assessment and to the final evaluation.
- Time to premature discontinuation due to lack of efficacy in the DB Maintenance Period.
- Pain intensity change for the Subject's Assessment of CLBP Intensity VAS from DB Baseline to each scheduled assessment following randomization.
- Cumulative distribution function for change and percent change from OL Baseline as well as change from DB Baseline to final evaluation on the Subject's Assessment of CLBP Intensity VAS.
- Subject's Global Assessment of Back Pain status at each scheduled assessment.
- Subject's Global Assessment of Study Drug at each scheduled assessment.

Pharmacokinetic Results: The mean hydrocodone and acetaminophen concentration values were consistent at each study visit. Due to the time variation in collecting each sample, there is a large variability in the hydrocodone and acetaminophen concentrations at each study visit. Before subjects were randomized to the DB Period, the mean hydrocodone and acetaminophen concentration values appeared to be similar between the Vicodin CR and placebo treatment groups.

Due to significant changes in the developmental strategy of Vicodin CR, the protocol-planned population pharmacokinetic analyses as well as the exposure-response analyses were not conducted for this study.

Safety Results: Of the 285 subjects who received at least 1 dose of study drug during the OL Period, 166 subjects (58%) experienced at least 1 treatment-emergent AE. Treatment-emergent AEs with onset after the start of the OL Period occurring in ≥ 5% of all subjects enrolled included constipation, nausea, somnolence, pruritus, vomiting, headache, and dizziness. The majority of subjects had AEs considered by the Investigator to be either mild or moderate in severity and possibly or probably related to study drug.

One nonrandomized subject experienced an SAE (PT: renal failure acute) during the OL Period. The subject was discontinued from the study. After discontinuation of study drug and discontinuation of Keflex, the subject recovered. The Investigator considered the event to be severe and probably related to study drug. No other SAEs were reported during the OL Period. Twenty-nine subjects (10%) reported treatment-emergent AEs during the OL Period that led to premature discontinuation from the OL Period of the study.

In the OL period, two subjects met the criteria for PCS values of liver enzymes post-treatment or PCS values that worsened post treatment. Subject [redacted], randomized to placebo, had an ALT value at the end of the OL period greater than 3 × ULN. Subsequently, following randomization to placebo, this subject's ALT values became normal. These findings were not reported as an AE. One other subject ([redacted]) had an ALT value that met stopping criteria (≥ 5 × ULN) at OL Baseline but was entered into the OL period. The subject was discontinued on Study Day 5, and was reported as having an AE of hepatic enzymes increased starting on Study Day 1. The values decreased in subsequent lab reports. Both subjects were asymptomatic.

During the OL Period, 8 other subjects were reported to have AEs beginning on Study Day 1 related to laboratory abnormalities in OL Baseline reports. These AEs are included in the AE tables and did not significantly change the incidence of AEs overall.

Of the subjects who received at least 1 dose of study drug during the DB Maintenance Period, 51% in the Vicodin CR group and 37% in the placebo group experienced at least 1 treatment-emergent AE with onset after the start of the DB Maintenance Period. Treatment-emergent AEs with onset after the start of the DB Maintenance Period occurring in ≥ 2% of subjects in either treatment group were nausea, headache, vomiting, pain, pyrexia, back pain, constipation, diarrhea, nasopharyngitis, somnolence, arthralgia, contusion, chills, fatigue, upper respiratory tract infection, urinary tract infection, cough, influenza, and oropharyngeal pain. A statistically significant difference between the groups was observed in the proportion of subjects with AEs of nausea: 4 subjects (4%) in the placebo group had AEs of nausea compared with 17 subjects (16%) in the Vicodin CR group. Of the subjects who had AEs with onset after the start of the DB Maintenance Period, the majority of subjects in the Vicodin CR and placebo treatment groups had AEs considered by the Investigator to be either mild or moderate in severity and not related or probably not related to study drug. Three subjects each in the placebo group and the Vicodin CR group reported treatment-emergent AEs leading to premature discontinuation.

One subject in the Vicodin CR group experienced an SAE during the DB Maintenance Period. Subject [redacted], who had an SAE of intestinal obstruction, was eventually determined to have had previously undiagnosed intestinal narrowing. Since the Vicodin CR OROS tablet is nondeformable and does not appreciably change in shape in the gastrointestinal tract, Vicodin CR OROS should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic; for example, esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum).

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Safety Results (Continued): The changes in vital signs are consistent with known effects of opioids on these parameters. Other clinical laboratory and vital sign assessments were generally unremarkable across all treatment groups. No deaths occurred in this study.
Conclusions: In this study, it is concluded that Vicodin CR 2 tablets twice daily was efficacious for the management of CLBP. Vicodin CR OROS should not be administered to patients with preexisting severe gastrointestinal narrowing, as these subjects may be at increased risk of obstruction (SAE - Subject [redacted]). Other than noted, the safety profile of this modified-release combination hydrocodone/acetaminophen product in this study was consistent with the known profile of a *mu*-opioid receptor agonist/acetaminophen-containing product.

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