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 and Safety 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: 63 study centers selected; 62 study centers enrolled subjects in the United States.

Publications: None

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 06 Jun 2006 (first subject dosed)	
Last Subject Last Visit: 30 May 2007 (last subject completed dosing)	

Objectives: The primary objective of this multicenter Phase 3 study was to compare the analgesic efficacy and safety of one or two tablets Vicodin CR (hydrocodone bitartrate 15 mg and acetaminophen 500 mg extended-release tablets) administered twice daily over 12 weeks to placebo in subjects with moderate to severe mechanical chronic low back pain (CLBP).

A secondary objective of this study was to explore population pharmacokinetics (PK) of hydrocodone and acetaminophen resulting from administration of Vicodin CR.

Methodology: This was a Phase 3, multicenter, open-label, followed by randomized, double-blind, placebo-controlled study designed to demonstrate the efficacy and safety of Vicodin CR one or two tablets twice daily, in the treatment of moderate to severe CLBP. The study consisted of 6 periods: a Screening Visit, a 2- to 28-day Washout Period, a 3-week Open-label Period, a randomized, 12-week, Double-blind Maintenance Period, a 1-week Taper Period, and a Follow-up Period.

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 Open-label 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 Open-label 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 Open-label Baseline Visit.

Methodology (continued):

The first 1-2 weeks of the Open-label Period incorporated a titration phase. During the third week of the Open-label Period, all subjects were to receive Vicodin CR two tablets twice daily.

Subjects returned to the study center at the end of the 3-week Open-label Period and were re-assessed to determine eligibility for entering the 12-week Double-blind Maintenance Period of the study. If at the end of the 3-week Open-label Period, the Investigator did not feel that the subject was able to tolerate dosing with Vicodin CR two tablets twice daily for 12 weeks, the subject was not to be randomized into the Double-blind Maintenance Period and was discontinued from the study.

Subjects meeting entry criteria for the Double-blind Maintenance Period were randomly assigned in an equal ratio to receive one of three treatments for 12 weeks: Vicodin CR two tablets twice daily, Vicodin CR one tablet twice daily, or placebo. Subjects randomized to the placebo treatment group had their Open-label dose of Vicodin CR tapered (in a blinded manner) over the first week of the Double-blind Maintenance Period to minimize the risk of developing opioid withdrawal syndrome.

Following completion of the Double-blind 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 study drug discontinuation.

Analgesic rescue medication was permitted during the Washout Period, the first week of the Open-label Period, and the Taper Period.

Number of Subjects (Planned and Analyzed): Seven hundred fifty (750) subjects were planned to be enrolled into the Open-label Period to provide 450 subjects for randomization. Seven hundred seventy subjects were enrolled in the Open-label Period and received at least 1 dose of study drug and 511 subjects were randomized and received double blind study drug; 169 subjects were assigned to Vicodin CR 2 tablet, and 170 subjects were assigned to Vicodin CR 1 tablet, and 172 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 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 Open-Label Period, 12-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 absolute mean pain intensity difference from the Double-blind randomization baseline (immediately prior to entering the Double-blind 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: time to withdrawal due to lack of efficacy during the Double-blind Maintenance Period, pain intensity difference for the Subject's Assessment of CLBP Intensity VAS from Double-blind randomization baseline to each scheduled assessment, Subject's Global Assessment of Study Drug, Subject and Physician's Global Assessment of Back Pain Status, Roland-Morris Disability Questionnaire, and Subject's Assessment of Sleep.

Pharmacokinetic: Values for the pharmacokinetic parameters of hydrocodone and acetaminophen including apparent oral clearance (CL/F) were estimated 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 an analysis of covariance (ANCOVA) with factors for treatment group, study center, and the Double-blind randomization baseline pain intensity score as a covariate. Heterogeneity of treatment effects across study centers was explored. Study centers having less than two subjects per treatment group were combined with other sites for analysis. All statistical tests were two-tailed and considered statistically significant if the p-value was less than or equal to 0.05. The primary comparison was between the Vicodin CR 2 tablet treatment group and the placebo treatment group. If this primary comparison was statistically significant, the comparison between the Vicodin CR 1 tablet group and the placebo group was performed. Additionally, differences between the two Vicodin CR treatment groups were explored. An efficacy evaluable dataset was created excluding efficacy data for subjects who were inadvertently enrolled twice. Treatment group differences in the time to withdrawal due to lack of efficacy, starting from the beginning of the Double-blind Maintenance Period, were analyzed using survival methods.

Treatment group mean differences in the change from Double-blind baseline (immediately prior to entering the Double-blind Maintenance Period) to each subject's worst observation as well as to each scheduled assessment during the Double-blind Maintenance Period, were analyzed for the Subject's Assessment of CLBP Intensity VAS. For the Roland-Morris Disability Questionnaire, treatment group mean difference in the percent change from Double-blind randomization baseline to final evaluation during the Double-blind Maintenance Period was analyzed.

The mean differences in the change from Double-blind baseline for the Subject's Assessment of CLBP Intensity VAS, the Roland-Morris Disability Questionnaire, and the Subject's Assessment of Sleep were analyzed using ANCOVA utilizing the same analysis model used for the primary efficacy variable. Additionally, change from Double-blind baseline to each evaluation for the Subject's Assessment of CLBP was analyzed using the repeated measures analysis. The actual scores for the Subject's Global Assessment of Study Drug, the Subject's Global Assessment of Back Pain Status, and the Physician's Global Assessments of Back Pain Status at each scheduled evaluation following randomization were analyzed using the CMH test for equal row means, first with study centers and then with Double-blind baseline evaluation score as separate stratification factors.

Statistical Methods (continued)

Treatment group differences in the cumulative distribution function for change from Double-blind randomization baseline to final assessment using the Subject's Assessment of CLBP Intensity VAS were assessed using the Monte-Carlo exact Kolmogorov-Smirnov test.

Pharmacokinetic: Population pharmacokinetic analyses were performed using the actual sampling times relative to dosing. Pharmacokinetic models were built using a non-linear mixed-effect modeling approach with the NONMEM software. The structure of the starting PK model was based on the PK analysis of data from previous studies in pain subjects and healthy subjects. Apparent oral clearance (CL/F) of hydrocodone and acetaminophen were the PK parameters of major interest in the NONMEM analyses. The relationship between hydrocodone and acetaminophen exposure and efficacy parameter (pain intensity using VAS) was explored.

Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®). 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 double-blind period, treatment group differences were evaluated using Fisher's exact test for the proportion of subjects reporting a particular AE. A summary of the severity and relationship to study drug of all treatment-emergent AEs, tabulated by MedDRA preferred term and SOC, was presented for each treatment group. Additionally, the incidence and prevalence of AEs over time were summarized. Subjects reporting more than one AE for a given MedDRA preferred term were counted only once for that term using the most severe incident in each study period. Subjects reporting more than one type of event within a SOC were counted only once for that SOC. Laboratory data were analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses were the mean changes from open-label 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 open-label 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 Open-label Period, mean changes from open-label baseline to final values were summarized. For the Double-blind Maintenance Period, mean changes from open-label 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: For the primary efficacy variable of change in Subject's Assessment of CLBP intensity VAS score, the mean increase in pain intensity from DB Baseline to Final evaluation was statistically significantly lower for the Vicodin CR 2 tablet and Vicodin CR 1 tablet treatment groups as compared to the placebo treatment group (p-value <0.001 and 0.002, respectively). Analyses using several different imputation methods yielded similar findings and the same conclusions.

The superiority of treatment with Vicodin CR 2 tablet and 1 tablet compared to treatment with placebo was consistent across multiple secondary efficacy endpoints including the following measures:

- Cumulative distribution of percent change and change in pain intensity from OL Baseline to Final evaluation in DB Maintenance Period.
- Time to premature discontinuation due to lack of efficacy in the DB Maintenance Period.

- Mean change in Subject's Assessment of CLBP Intensity (VAS) from DB Baseline to each scheduled evaluation using LOCF and repeated measures.
- Subject's Global Assessment of Back Pain status at DB Maintenance Week 12 using LOCF.
- Physician's Global Assessment of Back Pain status at DB Maintenance Week 12 using LOCF
- Subject's Global Assessment of Study Drug at DB Maintenance Week 12 using LOCF.
- Mean percent change in Roland-Morris disability score from DB Baseline to final evaluation.
- Mean change in Subject's Assessment of Sleep (interference) from DB Baseline to DB Maintenance Week 12 using LOCF.

For the vast majority of endpoints, the Vicodin CR 2 tablet treatment group demonstrated a numerical advantage as compared to the Vicodin CR 1 tablet treatment group, with statistical superiority for a few analyses.

Pharmacokinetic Results: Population PK models for hydrocodone and acetaminophen were developed to describe hydrocodone and acetaminophen plasma concentration-time profiles in subjects with CLBP. The estimated central value for hydrocodone CL/F was 50.3 L/h and for hydrocodone V_c/F was 277 L. The estimated central value for acetaminophen CL/F was 32.4 L/hr and for acetaminophen V_c/F was 151 L. Age, sex, weight, race, body surface area, hepatic laboratory markers and calculated creatinine clearance were tested as covariates in the pharmacokinetic analysis. Statistically significant effect of age on hydrocodone CL/F and body surface area on acetaminophen CL/F were found during covariate analyses. These covariates effects were not considered to be clinically significant and no covariate-dependent dose adjustment is necessary.

A linear exposure/response model optimally characterized the relationship between the clinical response (pain intensity using VAS) and the combined hydrocodone and acetaminophen concentrations (exposure) for one and two tablet(s) of Vicodin CR dosed every 12 hours in subjects with CLBP. Results of the exposure-response modeling demonstrated that Vicodin CR was effective in the management of CLBP.

Safety Results: Of the 770 subjects who received at least one dose of study drug during the OL Period, 506 (66%) subjects experienced at least one treatment-emergent AE. Treatment-emergent AEs occurring in ≥ 5% of subjects during the OL Period included dizziness, headache, somnolence, constipation, nausea, vomiting, pruritus, and fatigue.

One non-randomized subject died due to cardiac arrest on Day 24 (4 days post-treatment) in the OL Period. The Investigator considered the event to be severe and probably not related to study drug. No other SAEs were reported during the OL Period. One hundred twenty-four (16%) subjects reported treatment-emergent AEs that at least in part led to premature discontinuation from the OL Period of the study.

The proportion of subjects who experienced at least one treatment-emergent AE with onset after the start of the DB Maintenance Period was similar in the Vicodin CR 2 tablet, Vicodin CR 1 tablet, and placebo treatment groups (53%, 44%, and 46%, respectively).

Treatment-emergent AEs with onset after the start of the DB Maintenance Period occurring in ≥ 5% of subjects in any treatment group included headache, constipation, diarrhoea, and nausea. Nausea and constipation were experienced by a statistically significantly greater proportion of subjects in the Vicodin CR 2 tablet treatment groups as compared to the placebo treatment group. Somnolence was experienced by a statistically significantly greater proportion of subjects in the Vicodin CR 1 tablet

treatment group as compared to the placebo treatment group and pain was experienced by a statistically significantly greater proportion of subjects in the Vicodin CR 1 tablet treatment group as compared to the Vicodin CR 2 tablet and placebo treatment groups.

Nine subjects (two in each of the Vicodin CR treatment groups and five in the placebo treatment group) reported SAEs during the DB Maintenance Period. Twenty-eight subjects reported treatment-emergent AEs with onset after the start of the DB Maintenance Period that at least in part led to premature discontinuation from the DB Maintenance Period of the study, 11 (7%) in the Vicodin CR 2 tablet treatment group, 11 (6%) subjects in the Vicodin CR 1 tablet treatment group, and six (3%) subjects in the placebo treatment group.

Three Vicodin CR 2 tablet subjects and no Vicodin CR 1 tablet or placebo subjects reported AEs for which the Investigator considered the final diagnosis to be drug withdrawal syndrome.

No events of hepatic failure or hepatic impairment were observed. Two subjects met the toxicity based stopping criteria for AST and ALT (≥ 5 x ULN) and resulted in premature discontinuation from the study. One of the subject's [redacted] AST and ALT values were improving while on study drug. The other subject [redacted] who discontinued study drug treatment after 37 days, had a prolonged course of AST and ALT elevations that persisted for approximately 6 months after study drug discontinuation. The greatest elevation in AST and ALT occurred 2 months after the last dose of study drug. The AST and ALT elevations eventually resolved, and total bilirubin was normal throughout. Although relationship to study drug cannot be fully excluded, the prolonged course of AST and ALT elevation after discontinuation of treatment is not consistent with acetaminophen induced hepatotoxicity. The subject had no associated clinical sequelae. Other clinical laboratory and vital sign assessments were generally unremarkable across all treatment groups.

Conclusions: In this study, it is concluded that Vicodin CR one and two tablets twice daily were effective in a dose-dependent manner for the management of CLBP. 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 containing product.

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