



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier: Volume: Page:	(For National Authority Use Only)
Name of Study Drug: ABT-712		
Name of Active Ingredient: Hydrocodone/Acetaminophen		
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-two (32) study centers were initiated in the US, and 31 sites enrolled subjects.		
Publications: None		
Studied Period (Years): First Subject First Visit: 08 September 2008 (First Subject Dosed) Last Subject Last Visit: 17 March 2009 (Last Subject Completed Dosing)	Phase of Development: 3b	
Objectives: <p>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.</p> <p>The secondary objective was to assess the effect of Vicodin CR, compared to placebo, on sleep interference by pain.</p> <p>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.</p>		
Methodology: <p>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, DB, placebo-controlled Maintenance Period, a 1-week Taper Period, and a Follow-up Period.</p> <p>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.</p>		



Methodology (Continued):

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. In addition, subjects had to meet the following randomization criteria: subject provided an affirmative answer to the question "Has this treatment helped your back pain enough so that you would continue to take this medication?" subject assessment of CLBP Intensity (VAS) ≤ 50 mm, subject's assessment of CLBP Intensity (VAS) had decreased by at least 15 mm, compared to the assessment performed 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 believed that the subject was not able to tolerate dosing with Vicodin CR two tablets twice daily for 4 weeks, the subject was not randomized into the DB Maintenance Period and was discontinued from the study.

Subjects meeting the randomization criteria for the DB Maintenance Period were randomly assigned in an equal ratio to receive 1 of 2 treatments for 4 weeks: Vicodin CR two tablets twice daily or placebo. Subjects randomized to the placebo treatment 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 study drug discontinuation.

Analgesic rescue medication was permitted during the Washout Period, the first week of the OL Period, and 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. Three hundred eight (308) subjects were enrolled in the OL Period and received at least 1 dose of study drug and 238 subjects were randomized and received DB study drug; 120 subjects were assigned to Vicodin CR 2 tablet, and 118 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.



<p>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]</p> <p>Duration of Treatment: 3-week OL Period, 4-week DB Maintenance Period, and 1-week Taper Period</p>
<p>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Placebo for hydrocodone and acetaminophen extended release. Lot number: [REDACTED]</p>
<p>Criteria for Evaluation</p> <p>Efficacy: The primary efficacy measurement was the mean pain intensity difference from the DB Baseline (immediately prior to entering the DB Maintenance Period) to each subject's final assessment, using the DB intent to-treat (ITT) dataset. Pain intensity was assessed by the Subject's Assessment of CLBP Intensity score (100 mm VAS).</p> <p>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 Back Pain Status, Subject's Global Assessment of Study Drug, and protocol-allowed rescue medication use.</p> <p>Pharmacokinetic: Plasma concentrations of hydrocodone and acetaminophen were tabulated from blood samples obtained at the DB Baseline visit and at DB Maintenance Weeks 1, 2, 3, and 4.</p> <p>Safety: Safety was evaluated throughout the study by physical examinations, vital signs, laboratory tests, and monitoring of AEs.</p>
<p>Statistical Methods</p> <p>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 <i>P</i> value was less than or equal to 0.05.</p>

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Statistical Methods (Continued):

Efficacy: 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®). 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:

For the primary efficacy variable of change in Subject's Assessment of CLBP intensity by VAS, the mean increase in pain intensity from DB Baseline to final evaluation was statistically significantly smaller for the Vicodin CR treatment group compared to the placebo treatment group. Sensitivity analyses using several different imputation methods yielded similar findings.

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

- 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.
- Mean change in Subject's Assessment of CLBP Intensity (VAS) from DB Baseline to each scheduled evaluation.
- Cumulative distribution functions for percent change and change in pain intensity from OL Baseline to final evaluation in DB Maintenance Period.
- 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:

Blood samples for hydrocodone and acetaminophen assays were collected at DB Baseline and at DB Maintenance Weeks 1, 2, 3, and 4. Plasma concentration values of hydrocodone and acetaminophen were tabulated for each subject and each study visit. The blood samples of the placebo group from Study Visits 6, 7, 8, and 9 were analyzed but were not included in PK analysis. The mean hydrocodone and acetaminophen concentrations values were consistent at each study visit. Before subjects were randomized to the DB Maintenance Period, the mean hydrocodone and acetaminophen concentration values appeared to be similar between the Vicodin CR and placebo treatment groups. The mean plasma concentrations of hydrocodone ranged from 28 to 34 ng/mL for all subjects at DB Baseline and for subjects in the Vicodin CR treatment group at DB Maintenance Weeks 1, 2, 3, and 4. The mean plasma concentrations of acetaminophen ranged from 2520 to 3270 ng/mL for all subjects at DB Baseline and for subjects in the Vicodin CR treatment group at DB Maintenance Weeks 1, 2, 3, and 4.



Safety Results:

Of the 308 subjects who received at least 1 dose of study drug during the OL Period, 202 subjects (66%) experienced at least one treatment-emergent AE. Treatment-emergent AEs occurring in $\geq 5\%$ of subjects in either randomization status group during the OL Period were constipation, nausea, somnolence, headache, dizziness, vomiting, pruritus, fatigue, and abdominal pain upper. The majority of subjects had AEs considered by the Investigator to be either mild or moderate in severity and probably related to study drug.

No deaths occurred in the study.

One nonrandomized subject experienced an SAE (PT: diverticular perforation) during the OL Period. The subject was hospitalized and discontinued from the study. The Investigator considered the event to be severe and probably not related to study drug. No other SAEs were reported during the OL Period. Thirty-six subjects (12%) experienced one or more treatment-emergent AEs that at least in part led to premature discontinuation during the OL Period. Additionally, 4 other subjects had AEs with onset in the OL period that later led to discontinuation in the DB period.

Similar percentages of subjects in the placebo and Vicodin CR groups experienced at least one treatment-emergent AE with onset after the start of the DB Maintenance Period: 36% in the placebo group and 42% in the Vicodin CR group.

Treatment-emergent AEs with onset after the start of the DB Maintenance Period occurring in $\geq 2\%$ of subjects in any treatment group were nausea, headache, constipation, nasopharyngitis, diarrhea, urinary tract infection, upper respiratory tract infection, vomiting, blood triglycerides increased, anxiety, cough, oropharyngeal pain, arthralgia, neck pain, and sinus headache. Of the subjects who had AEs with onset after the start of the DB Maintenance Period, the majority of subjects in each treatment group had AEs considered by the Investigator to be either mild or moderate in severity and not related or probably not related to study drug. No statistically significant differences between treatment groups were observed for any individual AE. However, a statistically significant difference between the groups was observed in proportion of subjects with infections and infestations AEs: 10 subjects (9%) in the placebo group had infections and infestations AEs compared to 22 subjects (18%) in the Vicodin CR group.

Two subjects in the placebo group experienced treatment-emergent SAEs during the DB Maintenance Period; no subjects in the Vicodin CR group experienced treatment-emergent SAEs. Three subjects reported treatment-emergent AEs with onset after the start of the DB Maintenance Period that at least in part led to premature discontinuation of study drug during the DB Maintenance Period (1 subject in the placebo group and 2 subjects in the Vicodin CR group).

One subject experienced an AE included in the SMQ of drug abuse, dependence, and withdrawal following the OL Period; the subject was not randomized to DB treatment. An additional subject (placebo treatment group) experienced an AE included in the SMQ of drug abuse, dependence, and withdrawal following the end of the OL Period and during the first week of the DB Maintenance Period (placebo taper).



Safety Results (Continued):

Two subjects had elevated liver function tests that met potentially clinically significant criteria of greater than 3× ULN. Both were asymptomatic. One nonrandomized subject [REDACTED] with a normal baseline ALT had an ALT value of 169 U/L on Day 22. The value on Day 29 (7 days post-treatment) was 77 U/L and the subject was discontinued from study drug. Two subjects in had elevated liver function tests during the DB Maintenance Period. One subject [REDACTED] in the Vicodin CR group with an elevated AST level at baseline, had post-Baseline AST values > 3× ULN on Day 36, and post treatment days 1 and 9, that decreased to 57 U/L on post-treatment Day 35. This subject's alkaline phosphatase levels were also elevated throughout the study and on post-treatment Day 35. redacted information 24Sep2014

Conclusions:

In this study, it is concluded that 2 tablets Vicodin CR twice daily was efficacious 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/acetaminophen-containing product.