2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Item of the Submission:**	**(For National Authority Use Only)**
Name of Study Drug: Vicodin® CR	**Volume:**	
Name of Active Ingredient: Hydrocodone/Acetaminophen Extended Release (ABT-712)	**Page:**	

Title of Study: A Randomized, Multi-Center Double-Blind Study Comparing the Analgesic Efficacy of Extended Release Hydrocodone/Acetaminophen (Vicodin® CR) and Placebo in Subjects with Osteoarthritis

Investigators: Multi-center; Coordinating Investigator was Larry Gilderman, D.O.

Study Sites: 20 investigative sites in the United States.

Publications: None

Studied Period (Years): Initiation Date: 10 August 2004 (first subject dosed) Completion Date: 04 March 2005 (last study procedure)	**Phase of Development:** 2

Objectives:

The primary objective of this study was to compare the safety and analgesic efficacy of Vicodin® controlled-release (CR; hydrocodone bitartrate and acetaminophen extended release tablets 15 mg/500 mg) to placebo, administered twice daily (BID) in subjects with osteoarthritis (OA).

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

Methodology:

This was a Phase 2, randomized, multi-center, double-blind, placebo-controlled study that consisted of 5 periods: Screening/Washout (maximum 21 days), 7-day Titration, 3-week Maintenance, 1-week Study Drug Taper, and Follow-up (Study Day 43 and follow-up phone call 30 days after the last dose of study drug administration). After meeting the selection criteria during the Screening Visit, subjects entered the Washout Period during which they discontinued their current analgesic therapy for OA pain. The length of the Washout Period was at least the length of 5 half-lives of the longest-acting analgesic used. No rescue medication was allowed during the Washout Period. Subjects returned to the study center within 21 days for the Baseline Visit. Subjects who continued to meet the selection criteria as well as Flare Criteria entered the Titration Period. Subjects were randomized in an equal ratio to 1 of 2 treatments: hydrocodone/acetaminophen controlled-release tablets 15 mg/500 mg (hereafter referred to as Vicodin® CR) or placebo. Randomized subjects took 1 tablet of Vicodin® CR or matching placebo BID beginning on the day of the Baseline Visit and continuing for the duration of the 7-day Titration Period.

Methodology (continued):

On Study Day 8, subjects returned to the study center and began the 3-week Maintenance Period, during which they took 2 tablets of Vicodin® CR or matching placebo BID. Subjects returned to the study center for weekly visits scheduled during the Maintenance Period. On Study Day 29, subjects returned to the study center and entered the 1-week Study Drug Taper Period. During this period, subjects took Vicodin® CR 1 tablet or matching placebo BID. Subjects returned to the study center at the end of the Taper Period on Study Day 36, at which time study drug was discontinued.

Drug concentration measurements (pharmacokinetic samples) were drawn on Study Days 15, 22, and 29.

A Follow-up Visit was conducted on Study Day 43. In addition, the sites subsequently contacted the subject by telephone 30 days after the last dose of study drug administration. During this call, subjects were asked questions about their overall health status, including whether or not they had been hospitalized or received emergency treatment, as well as status/resolution of any adverse events ongoing since their last contact with study personnel. All pertinent information was recorded, including the date and time of the telephone call.

During the Titration and Maintenance Periods, subjects completed the following efficacy assessments: the Subject's Assessment of Arthritis Pain Intensity by Visual Analog Scale (VAS), Western Ontario and McMaster (WOMAC) Osteoarthritis Index, Medical Outcomes Study (MOS) Sleep Scale, SF-36v2 Health Status Survey (Acute), and Subject's Global Assessment of Arthritis Status and Subject's Assessment of Study Drug. Additionally, the Investigator completed the Physician's Global Assessment of Arthritis Status.

If a subject required analgesic rescue medication for breakthrough pain during the Titration, Maintenance, or Taper Periods, 500 mg of acetaminophen was administered every 6 hours as needed, not to exceed 2000 mg/day.

Safety was evaluated throughout the study by physical examinations, vital signs, laboratory tests (including pregnancy tests for all female subjects), and monitoring of adverse events.

Number of Subjects (Planned and Analyzed):

One hundred twenty (120) subjects were planned and 121 subjects were enrolled; 62 subjects were assigned to placebo and 59 subjects each were assigned to Vicodin® CR. One hundred twenty (120) subjects (62 placebo, 58 Vicodin® CR) received at least 1 dose of study drug and were included in the intent-to-treat dataset. Forty-seven (47) subjects (20 placebo, 27 Vicodin® CR) prematurely discontinued study drug.

Diagnosis and Main Criteria for Inclusion:

Males and females between 21 and 75 years of age, inclusive, who were judged to be in generally good health at screening based upon the results of a medical history, physical examination, laboratory profile, and 12-lead electrocardiogram (ECG), who met the American College of Rheumatology (ACR) Classification criteria for OA of the hip or the ACR Classification criteria for OA of the knee, and who had taken an analgesic for arthritis pain for the majority of days in the previous 3 months and for ≥ 4 days per week during the previous 4 weeks were eligible for the study.

At baseline, subjects must have continued to meet selection criteria as well as the following Flare Criteria: Subject's Assessment of Arthritis Pain Intensity by VAS of ≥ 40 mm; a ≥ 10-mm increase from the Screening Visit in the Subject's Assessment of Arthritis Pain Intensity by VAS; and a Subject's Global Assessment of Arthritis Status of fair, poor, or very poor.

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 05-126-4P and 07-142-4P

Duration of Treatment: 1 week titration (1 tablet BID), 3 weeks maintenance (2 tablets BID), and 1 week taper (1 tablet BID).

Reference Therapy, Dose and Mode of Administration, Lot Number:

Placebo administered orally, Lot number 07-136-4P

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was the pain intensity difference from baseline to each subject's final evaluation as assessed by the Subject's Assessment of Arthritis Pain Intensity by VAS.

Secondary efficacy endpoints included WOMAC Osteoarthritis Index (Likert version), total score and 3 subscales (Pain, Stiffness, Physical Function); MOS Sleep Scale, including 7 subscales and 2 overall indexes; pain intensity difference as assessed by the Subject's Assessment of Arthritis Pain Intensity by VAS (at each scheduled assessment other than final); Subject's Global Assessment of Study Drug; Subject's and Physician's Global Assessments of Arthritis Status; time-interval weighted measure of pain intensity difference from baseline (area under the curve [AUC]) divided by the maximum benefit possible for an individual subject; treatment responders, defined as subjects achieving a specified level of improvement from baseline to each scheduled assessment on the Subject's Assessment of Arthritis Pain Intensity by VAS; and SF-36 Health Status Survey (Acute), including sub-domains, physical component summary, and mental component summary.

Pharmacokinetic:

Pharmacokinetic parameters of hydrocodone, hydromorphone, and acetaminophen that were assessed included apparent oral clearance (CL/F). Additional parameters may have been calculated if useful in the interpretation of the data.

Safety:

Safety was assessed by physical examinations, vital signs, laboratory tests (including pregnancy tests for all female subjects), and monitoring of adverse events.

Statistical Methods:

For all efficacy endpoints, decisions regarding the efficacy of Vicodin® CR were made on the basis of 1-sided tests at alpha=0.10 for superiority *vs.* placebo. All safety tests were 2-sided. Efficacy analyses were performed using an intent-to-treat dataset that included all randomized subjects who received at least 1 dose of study drug.

Efficacy:

Treatment group mean differences for the primary efficacy variable were evaluated using analysis of variance (ANOVA) with factors for treatment group, study center, and treatment group by study center interaction.

The principal AUC analysis of the pain intensity difference was the time-interval weighted area under the curve divided by the maximum AUC benefit possible for an individual subject (approximate observed baseline score multiplied by planned study duration, where study duration included the 1-week titration and 3-week maintenance) for the Subject's Assessment of Arthritis Pain Intensity score by VAS. The area under the pain intensity curve was estimated using the linear trapezoidal rule. The pain intensity AUC was a measure of cumulative pain intensity differences from baseline for the Titration and Maintenance Periods.

The WOMAC normalized total score was normalized to correct for difference in subscale length (Normalized WOMAC Score) according to published scoring guidelines. The MOS Sleep Scale and SF-36 were each scored according to published scoring guidelines.

The WOMAC Osteoarthritis Index, the MOS Sleep Scale, and SF-36 and the pain intensity AUC assessments were analyzed using ANOVA utilizing the same analysis model used for the primary efficacy variable.

The actual scores of the Subject's Global Assessment of Study Drug and the Subject's and Physician's Global Assessments of Arthritis Status were analyzed at each scheduled evaluation using the Cochran-Mantel-Haenszel (CMH) test for equal row means with study centers as the stratification factor.

Treatment group differences in the proportion of treatment responders for the change from baseline to each evaluation using the Subject's Assessment of Arthritis Pain Intensity score (VAS) were assessed by a CMH test for equal row means with study center as the stratification factor. Treatment responders for each scheduled assessment during the Maintenance Period were defined as subjects who completed that assessment and achieved a specified level of improvement (each level was summarized separately; $\geq 30\%$, $\geq 40\%$, or $\geq 50\%$ improvement) for the change from baseline using the pain intensity score.

Treatment comparisons were made between the treatment groups for the proportion of subjects taking rescue acetaminophen using Fisher's exact test. Additionally, treatment group comparisons were made for the proportion of subjects taking > 2000 mg of acetaminophen on a single day and the proportion of subjects taking acetaminophen for more than 3 days per week.

Pharmacokinetic:

Individual hydrocodone, hydromorphone, and acetaminophen plasma concentrations on Study Days 15, 22, and 29 were tabulated and summarized with appropriate statistical methods. Pharmacokinetic analyses will be presented in a separate report.

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. The structure of the starting PK model was based on the PK analysis of data from previous studies in pain patients and healthy subjects. Apparent oral clearance of hydrocodone, hydromorphone, and acetaminophen were the PK parameters of major interest in the NONMEM analyses. If the data permitted reliable estimation of other PK parameters, the absorption rate constant and volume of distribution were also to be estimated. If an absorption rate constant could not have been estimated, then a fixed value based on previous experience in adults was used.

The relationship between plasma concentrations and efficacy parameters was explored.

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 randomized study drug) were tabulated by system organ class and MedDRA preferred term for each treatment group. Treatment group differences were evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. A summary of the severity and relationship to study drug of all treatment-emergent adverse events, tabulated by MedDRA preferred term and system organ class, was presented for each treatment group. Subjects reporting more than 1 adverse event for a given MedDRA preferred term were counted only once for that term using the most severe incident. Subjects reporting more than 1 type of event within a system organ class were counted only once for that system organ class. Analyses by subgroup were performed as appropriate.

For vital signs, mean changes from baseline to the average, minimum, maximum, and final values were analyzed using a 1-way ANOVA with treatment as the main effect. Vital sign results that satisfied the Abbott-specified potentially clinically significant vital sign criteria were identified.

Laboratory data were analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses were the mean change from 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. Low or high laboratory values were flagged in the data listings. Laboratory results that satisfied the Abbott-specified potentially clinically significant laboratory criteria were identified. Additionally, the number and percentage of subjects with shifts from baseline to the final values using the potentially clinically significant laboratory criteria to define categories (very low, normal, very high, and missing) were summarized.

Concurrent medication use was summarized by treatment group.

Summary/Conclusions:

Efficacy Results:

The primary efficacy measure in this study, mean change from baseline to the Final Visit in the Subject's Assessment of Arthritis Pain Intensity by VAS, demonstrated that Vicodin® CR was statistically significantly superior to placebo in decreasing pain intensity in subjects with OA (mean changes of 38.5 and 26.7, respectively; $p \leq 0.10$). A secondary efficacy measure, change from baseline to each visit as assessed by the Subject's Assessment of Arthritis Pain Intensity by VAS, also demonstrated statistically significantly superior results for Vicodin® CR compared to placebo.

Numerous secondary endpoints were analyzed, including changes in the WOMAC, the Subject's Global Assessment of Study Drug, the Subject and Physician's Global Assessment of Arthritis Status, a responder analysis for percent improvement from baseline, the SF-36v2, the MOS Sleep Scale, and use of rescue medication.

Analysis of the WOMAC normalized total index and the 3 subscales, from baseline to scheduled study visit timepoints, revealed minimal mean differences between the Vicodin® CR and placebo treatment groups.

Efficacy Results (Continued):

Statistically significantly superior results over placebo were observed for the Subject's Global Assessment of Study Drug at almost all scheduled study visit timepoints. For the Subject's Global Assessment of Arthritis Status, although not statistically significant, superior results were seen in the Vicodin® CR treatment group compared to the placebo treatment group at all timepoints. Additionally, statistically significant treatment group differences were observed for the Physician's Global Assessment of Arthritis Status at the Day 8, Day 15, Day 22, and Day 29 Visits, with better responses in the Vicodin® CR treatment group compared to the placebo treatment group.

Greater proportions of subjects in the Vicodin® CR treatment group compared to the placebo group were treatment responders, with treatment response defined as ≥ 30%, ≥ 40%, or ≥ 50% improvement for the change from baseline to each evaluation using the Subject's Assessment of Arthritis Pain Intensity by VAS; statistically significant treatment differences for the proportions of subjects showing ≥ 50% improvement were observed at the Day 15, Day 22, and Day 29 Visits.

Analysis of the MOS Sleep Scale change from baseline to final study visit revealed minimal mean differences between the Vicodin® CR and placebo treatment groups. In general, results favored Vicodin® CR over placebo, however the differences between treatment groups were generally not statistically significant.

The proportion of subjects using rescue medication was statistically significantly lower in the Vicodin® CR treatment group than in the placebo treatment group at Day 8 (7% *vs.* 27%), Day 15 (5% *vs.* 18%), and at any time from Day 1 to end of treatment (16% *vs.* 44%).

Safety Results:

A statistically significantly greater proportion of the subjects in the Vicodin® CR treatment group (69%) experienced at least 1 treatment-emergent adverse event compared to subjects in the placebo treatment group (45%). Nausea, somnolence, pruritus, and lethargy were experienced by statistically significantly greater proportions of subjects in the Vicodin® CR treatment group compared to subjects in the placebo treatment group.

One death was reported in the study: a [redacted] woman in the Vicodin® CR treatment group died on Study Day 10. The death certificate indicated the cause of death to be "undetermined natural causes." The Investigator considered the event to be possibly related to study drug, with acute cardiopulmonary disease as an alternative etiology. No other deaths or serious adverse events were reported during the study. redacted information 29Jul2014

Eighteen (31%) subjects in the Vicodin® CR treatment group and 6 (10%) subjects in the placebo treatment group prematurely discontinued from study drug due to a primary reason of adverse event. One additional placebo subject prematurely discontinued from study drug at least in part due to adverse events. Most of the adverse events leading to discontinuation were considered by the Investigator to be possibly or probably related to study drug.

Clinical laboratory and vital signs assessments were unremarkable for both treatment groups.

Conclusions:

Vicodin® CR was statistically significantly superior to placebo in the primary efficacy measure, the mean change from baseline to Final Visit in the Subject's Assessment of Arthritis Pain Intensity by VAS. Results for the majority of the secondary efficacy endpoints generally suggested an improved response in the Vicodin® CR treatment group over the placebo treatment group, although the differences between groups was not always statistically significant. The adverse event profile of Vicodin® CR is consistent with that of a *mu*-opioid containing analgesic. One death was reported in the Vicodin® CR treatment group, with the cause of death recorded as "undetermined natural causes."