



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, Randomized, Multicenter, Double-blind, Study Comparing the Analgesic Efficacy of Extended-release Hydrocodone/Acetaminophen Tablets (Vicodin CR) to Placebo in Subjects With Osteoarthritis		
Coordinating Investigator: Egilius L. H. Spierings, MD		
Study Sites: 102 study centers selected; 83 study centers enrolled subjects in the United States		
Publications: None		
Studied Period (Years): First Subject First Dose: 22 February 2006 Last Subject Last Dose: 21 May 2007	Phase of Development: 3	
Objectives: The primary objective of the study was to compare the analgesic efficacy and safety of Vicodin CR (hydrocodone bitartrate/acetaminophen 15 mg/500 mg extended release tablets) to placebo in subjects with osteoarthritis (OA). 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, randomized, multicenter, double-blind, placebo-controlled study designed to compare the analgesic efficacy and safety of two tablets Vicodin CR administered twice daily compared to placebo in the treatment of moderate to severe pain in subjects with OA. Approximately 800 subjects meeting appropriate criteria for OA of the hip or knee were to be randomized into the study at approximately 100 study centers. Opioid naïve and opioid experienced subjects were eligible for participation. To ensure adequate representation of both these groups, approximately 40% of subjects enrolled in the study were to be opioid experienced, which was defined as those who had taken an opioid (not to include tramadol, butorphanol, buprenorphine, pentazocine or nalbuphine) at least five days weekly for OA pain in the month prior to Screening. At the Screening Visit, subjects were assessed to determine if they met the eligibility criteria for the study, including a diagnosis of OA of the hip or knee as defined by the American College of Rheumatology (ACR) combined clinical and radiological classification criteria. If the subject had more than one joint that met the criteria (i.e., OA of the hip and knee), the subject was required to identify the most painful joint as the index joint for the study. Subjects who identified their knee as the target joint for the study and met the Kellgren and Lawrence classification of OA Grade 1, could have been considered on a case-by-case basis following consultation and approval by the Abbott Medical Monitor provided the subject also met the 1986 ACR Clinical Criteria for Classification of Idiopathic OA of the knee.		



Methodology (continued): Subjects who met the selection criteria at the Screening Visit were eligible to participate in the study. Screening laboratory results as well as radiographic results were reviewed by the study center to confirm selection criteria were met. Radiographs should have been conducted within three years prior to the Screening Visit.

Subjects then entered the Washout Period during which they discontinued their current analgesic therapy for OA pain. The duration of the analgesic Washout Period was to be at least five half-lives of the analgesic used or two days, whichever was longer. Subjects receiving opioid analgesic therapy at study entry should have had their opioid dose slowly tapered to minimize the risk of opioid withdrawal syndrome. The maximum length of time allowable between the Screening and Baseline Visits was 28 days.

Following the Washout Period, subjects returned to the study center for the Baseline Visit, at which time they must have continued to meet all of the selection criteria, including the flare criteria defined below:

- The Subject's Assessment of Arthritis Pain Intensity must have been ≥ 40 mm determined by visual analog scale (VAS), and
- An increase of ≥ 10 mm from the Subject's Assessment of Arthritis Pain Intensity (VAS) obtained at the Screening Visit must have been determined at the Baseline Visit. For those subjects whose screening VAS was ≥ 90 mm, a VAS of at least ≥ 90 mm must have been maintained at Baseline, and
- Subject's Global Assessment of Arthritis Status must have been Fair, Poor, or Very Poor.

Subjects who failed to meet Baseline flare criteria may have repeated the assessments one additional time provided they returned to the study center within 72 hours to complete the assessments.

Eligible subjects were randomized in an equal ratio to receive one of two treatments: two tablets Vicodin CR twice daily or placebo and began a 3-week Titration Period. During the first week of the Titration Period, subjects took one tablet of Vicodin CR or matching placebo once daily (in the evening) for four days followed by one tablet of Vicodin CR or matching placebo twice daily (once in the morning, once in the evening) for 3 days. During the second week of the Titration Period, subjects continued to take one tablet Vicodin CR or matching placebo twice daily (once in the morning, once in the evening) for 7 days. During the third week of the Titration Period, subjects took one tablet Vicodin CR or matching placebo (in the morning) and two tablets Vicodin CR or matching placebo (in the evening) for 7 days.

Minor adjustments to the dosing regimen (faster or slower dose adjustments) may have been made during the Titration Period, on a case-by-case basis, following consultation and approval by the Abbott Medical Monitor. Faster adjustments for opioid-experienced subjects could have been made during the Titration Period, on a case-by-case basis, following consultation and approval by the Abbott Medical Monitor. If at the end of the 3-week Titration Period, the Investigator did not feel that the subject would be able to tolerate an increase in the dose of Vicodin CR to two tablets twice daily, the subject was discontinued from the study.

At the end of the Titration Period, subjects returned to the study center and began the Maintenance Period, during which they took Vicodin CR two tablets or matching placebo twice daily for 12 weeks.



Methodology (continued): Following completion of the Maintenance Period, subjects were to enter the 1-week study drug Taper Period. During the Taper Period, subjects were to have taken one tablet Vicodin CR or matching placebo twice daily for 4 days, followed by one tablet Vicodin CR or matching placebo once daily (to be taken in the evening) for an additional 3 days, after which study drug was discontinued. At the conclusion of the Taper Period, subjects were to have returned to the study center for Study Visit 12. A Follow-up Visit was to have been conducted 1 week after study drug discontinuation.

Blood samples for drug concentration measurements were drawn at Study Visits 6, 8, and 11.

Subjects were permitted to take acetaminophen as rescue medication during the Washout (but not within 24 hours prior to the Baseline Visit or other scheduled study visits), Titration, Maintenance, and Taper Periods of the study.

Number of Subjects (Planned and Analyzed): Eight hundred (800) subjects were planned, 874 subjects were randomized, and 873 subjects received at least one dose of study drug; 430 subjects received Vicodin CR two tablets and 443 subjects received placebo.

Diagnosis and Main Criteria for Inclusion: Males and females between 21 and 80 years of age, inclusive, who met the American College of Rheumatology (ACR) Classification criteria for OA of the hip or the knee or who met the Kellgren and Lawrence classification of OA Grade 1 and met the ACR Clinical Criteria for Classification of Idiopathic OA of the knee and who had taken therapeutic doses of at least one analgesic for OA pain-for ≥ 4 days/week in the previous three months and for ≥ 5 days/week during each of the previous 4 weeks 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: 17 weeks (3-week Titration Period, 12-week Maintenance Period, 1-week Taper Period and 1-week Follow Up Period)

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

Placebo for hydrocodone and acetaminophen extended release; Lot numbers [REDACTED]

Criteria for evaluation

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Efficacy: The primary efficacy measurement was the percent change from Baseline to the Week 12 evaluation on pain intensity as assessed by the Subject's Assessment of Arthritis Pain Intensity Score (100 mm VAS).

Secondary efficacy variables included: change from Baseline to the Week 12 Maintenance evaluation as assessed by the Subject's Assessment of Arthritis Pain Intensity (VAS); change from Baseline to each scheduled evaluation as assessed by the Subject's Assessment of Arthritis Pain Intensity (VAS); proportion of treatment responders, defined as subjects completing the Maintenance Period and achieving a specified level of improvement (i.e., $\geq 30\%$ or $\geq 50\%$) on the Subject's Assessment of Arthritis Pain Intensity (VAS); cumulative distribution function for percent improvement on the Subject's Assessment of Arthritis Pain Intensity (VAS); Subject's Global Assessment of Study Drug; Subject's and Physician's Global Assessments of Arthritis Status; Western Ontario and McMaster (WOMAC™) Osteoarthritis Index (Normalized WOMAC Score), total score and three subscales; and SF-36v2™ Health Status Survey, including sub-domains, Physical Component Summary (PCS), and



Mental Component Summary (MCS).

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

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

Statistical Methods

Efficacy: The primary efficacy analysis was conducted using the Monte-Carlo exact Kolmogorov-Smirnov test to evaluate the treatment group difference in the distribution of the percent change from Baseline to Week 12 on VAS pain score using the intent-to-treat (ITT) dataset.

The change from Baseline to the Week 12 Maintenance evaluation for the Subject's Assessment of Arthritis Pain Intensity score by VAS using a) Baseline observation carried forward (BOCF), b) worst-observation-carried-forward methodology (WOCF), and (c) mixed imputation BOCF and LOCF (BOCF was used to impute missing data for those subjects who discontinued due to AE, and those subjects who did not have any post-Baseline pain intensity VAS scores, while LOCF was used to impute missing Week 12 Maintenance data for those subjects who discontinued due to all other reasons). For missing data imputation in the ITT dataset was analyzed using analysis of covariance (ANCOVA) with factors for treatment group, study center, prior opioid experience, and the Baseline pain intensity score as a covariate. The Type III sum-of-squares for the least-squares means was used to compute the treatment group contrast. Change from Baseline to the last observation, taken at or before Week 12 visit, on VAS pain intensity score was also analyzed using the ANCOVA model described above. In this analysis, for those subjects who did not have any post Baseline data on VAS pain intensity, their change scores were considered to be zero.

Treatment group differences in the proportion of treatment responders for the change from Baseline to the Week 12 Maintenance 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.

Change and percent change from Baseline to post-Baseline evaluations on VAS pain intensity scores were analyzed using the repeated measures analysis using all observed data.

For the standardized area under the curve (AUC) analysis, missing data were estimated as follows: pain assessment data missing prior to a subject discontinuing from or completing the study were estimated using the average of the two adjacent assessments (i.e., the assessment completed immediately prior to and subsequent to the missing assessment). For the calculation of AUC, zero area under the curve was imputed for all evaluations following study discontinuation. Subjects who did not complete any post-Baseline pain assessments were assigned an AUC value of zero. Additionally, the standardized AUC analysis was performed using a WOCF estimation method. For this analysis, subjects who discontinued the study prior to the end of the Maintenance Period with a final pain intensity score greater than their Baseline score had that Final score carried forward for the planned study duration.

Analyses for the following secondary endpoints were based on a modified ITT data set (ITT_M), in which subjects with no Baseline assessment and/or post Baseline assessment were excluded. The actual scores of the Subject's Global Assessment of Study Drug and the Subject's and Physician's Global Assessments of Arthritis Status at each scheduled evaluation were analyzed using the CMH test for equal row means using study centers and Baseline evaluation score (excluding assessment of study drug) as the stratification factors in separate analyses.

The WOMAC™ total score was normalized to correct for difference in subscale length according to



published scoring guidelines. The SF-36v2™ was scored according to published scoring guidelines. The WOMAC™ Osteoarthritis Index, the SF-36v2™, and the standardized AUC assessments were analyzed using an ANCOVA model with factors for treatment group, study center, prior opioid experience, and the Baseline pain intensity score as covariates.

Pharmacokinetic: Population PK analyses were performed using the actual sampling times relative to dosing. PK 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 patients 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 parameters (pain intensity using VAS) was explored.

Safety: AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®). All treatment-emergent AEs 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 AEs, tabulated by MedDRA preferred term and SOC, was presented. Additionally, the incidence and prevalence of AEs over time was summarized.

For laboratory and vital sign data, mean changes from Baseline to the minimum, maximum, and Final values were analyzed using a one-way ANOVA with treatment as the main effect. Laboratory and vital sign data collected more than 2 days after the last dose of study drug were not included in the change from Baseline analysis.

Laboratory and vital sign results that satisfied the Data Analysis Criteria for Potentially Clinically Significant Laboratory and Vital Sign Findings were identified. Additionally, the number and proportion 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 ECGs, the number and proportion of subjects with shifts from Baseline to the Final evaluation using the following assessment categories: normal, abnormal – not clinically significant, abnormal – clinical significant and missing, were summarized.

Summary/Conclusions

Efficacy Results:

This 17-week study (including a 3-week Titration Period and 12-week Maintenance Period) evaluated the analgesic efficacy of Vicodin CR two tablets twice daily as compared to placebo in the management of subjects with moderate to severe pain due to OA.

For the protocol-specified primary efficacy analysis, comparing the cumulative distribution of percent change in Subject's Assessment of Arthritis Pain Intensity VAS from Baseline to Week 12 Maintenance (Study Week 15) (using BOCF for missing data imputation), the Vicodin CR treatment group demonstrated marginally statistically significant superiority over the placebo treatment group ($p = 0.055$).

A post-hoc sensitivity analysis for the primary efficacy endpoint was performed (using BOCF for subjects who prematurely discontinued for AEs or who did not have any post-Baseline assessments, and LOCF for subjects who prematurely discontinued for any other reason). This analysis demonstrated



statistically significant superiority of the Vicodin CR treatment group over the placebo treatment group for improvement in pain intensity with a p-value of 0.008.

Results of the secondary efficacy endpoints assessing change in Subject's Assessment of Arthritis Pain Intensity, Subject's and Physician's Global Assessments, WOMAC, and rescue medication use consistently demonstrated greater improvement in the Vicodin CR treatment group as compared to the placebo treatment group, with the vast majority of analyses being statistically significant. The treatment effect of Vicodin CR was seen at the first scheduled assessment (Titration Week 2) and was maintained through 15 weeks of treatment (Week 12 Maintenance). Evidence for the superiority of Vicodin CR to placebo include:

- Mean change in Pain Intensity from Baseline to the Week 12 Maintenance Visit for Vicodin CR as compared to placebo demonstrated the following; using BOCF ($p = 0.126$), WOCF ($p = 0.090$), mixed BOCF and LOCF methodology described above ($p = 0.026$), and LOCF ($p < 0.001$). Note that LOCF in the ITT data set means that the Baseline value is carried forward in subjects who did not have any post-Baseline value.
- Statistically significantly superior mean change in Pain Intensity from Baseline to the Final assessment using BOCF for subjects without post-randomization assessment ($p < 0.001$).
- Statistically significantly superior mean change and percent change in Pain Intensity from Baseline to each scheduled evaluation for Vicodin CR using repeated measures analysis ($p < 0.001$ for all scheduled assessments).
- A statistically significantly greater reduction for Vicodin CR in pain intensity as measured by the standardized AUC score using BOCF (time-interval weighted AUC divided by maximum AUC benefit possible) through the Week 12 Maintenance Visit ($p = 0.006$).
- A higher proportion of subjects in the Vicodin CR treatment group than in the placebo group with:
 - $\geq 30\%$ improvement [42% vs. 39%, $p = 0.348$; 50% vs. 43%, $p = 0.035$; and 66% vs. 50%, $p < 0.001$; using BOCF, mixed BOCF and LOCF, and LOCF, respectively], or
 - $\geq 50\%$ improvement [37% vs. 29%, $p = 0.019$; 41% vs. 32%, $p = 0.003$; and 53% vs. 36%, $p < 0.001$; using BOCF, BOCF and LOCF, and LOCF, respectively].
- Statistically significantly greater benefit for Vicodin CR on Subject's and Physician's Global Assessments of Arthritis Status at Week 12 Maintenance ($p \leq 0.001$).
- Statistically significantly better response for Subject's Global Assessment of Study Drug at Week 12 Maintenance ($p < 0.001$).
- Statistically significantly greater improvement for Vicodin CR at Week 12 Maintenance on WOMAC total score ($p = 0.001$) and all three subscales (Pain, Stiffness, Physical Function [$p = 0.001$ on all measures]).
- Use of acetaminophen for rescue was lower in the Vicodin CR treatment group as compared to the placebo group, with statistically significantly smaller proportions of Vicodin CR treated subjects using acetaminophen, and smaller proportions of days with acetaminophen use, and lower average daily dose of acetaminophen among those using acetaminophen.



With the exception of the evaluation of PCS and bodily pain (statistically significantly improved in the Vicodin CR treatment group), assessment of quality of life using the SF-36v2 Health Status Survey did not demonstrate a statistically significant difference between treatment groups.

Based on these data, it is concluded that in this study, Vicodin CR was efficacious in the management of moderate to severe chronic pain associated with OA.

Pharmacokinetic Results:

Population PK models for hydrocodone and acetaminophen were developed to describe hydrocodone and acetaminophen plasma concentration-time profiles in subjects with OA. The estimated central value for hydrocodone CL/F was 40.6L/hr, and for hydrocodone V_c/F was 714 L. The estimated central value for acetaminophen CL/F was 33.3 L/hr, and for acetaminophen V_c/F was 245 L. Age, sex, weight, race, body surface area, hepatic laboratory markers, and creatinine clearance were tested as covariates in the pharmacokinetic analysis. Statistically significant effect of creatinine clearance on hydrocodone CL/F and age on acetaminophen CL/F were found during covariate analyses. These covariate 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 two tablets of Vicodin CR dosed every 12 hours in subjects with OA pain. Results of the exposure/response modeling demonstrated that pain intensity using VAS in the Vicodin CR treatment group was statistically significantly lower than the placebo treatment group.

Details of the results of the population PK and exposure/response analyses are presented in a separate PK report.

Safety Results:

This 17-week study evaluated the safety of Vicodin CR two tablets twice daily as compared to placebo in the management of subjects with moderate to severe pain due to OA.

evaluation of treatment-emergent AEs showed that a statistically significantly greater proportion of subjects in the Vicodin CR (86%) treatment group experienced at least one treatment-emergent AE as compared to subjects in the placebo treatment group (66%).

Treatment-emergent AEs occurring in $\geq 5\%$ of subjects in either treatment group included constipation, nausea, headache, somnolence, pruritus, dizziness, vomiting, fatigue, insomnia, diarrhoea, pain in extremity, nasopharyngitis, back pain, upper respiratory tract infection, and arthralgia. The majority of events were possibly or probably related to study drug and mild or moderate in severity.

Among AEs reported by $\geq 5\%$ of subjects in either treatment group, a statistically significantly greater proportion of subjects in the Vicodin CR treatment group reported constipation, nausea, vomiting, dizziness, somnolence, insomnia, and pruritus compared to subjects in the placebo treatment group. Additionally, of those AEs reported by $\geq 5\%$ of subjects in the Vicodin CR treated group and with a prevalence of $\geq 5\%$ in one or more time periods, the incidence of constipation, nausea, headache, somnolence, pruritus, and dizziness, was observed to decrease over time. Furthermore, the prevalence of these AEs declined or remained stable over time.

One subject in the Vicodin CR treatment group died due to acute renal failure 24 days posttreatment. The Investigator considered the event to be severe and not related to study drug. A statistically significantly greater proportion of subjects in the Vicodin CR treatment group, 19 (4%) experienced one or more SAE(s) as compared to subjects in the placebo treatment group, 5 (1%). One subject in the



Vicodin CR treatment group and one subject in the placebo treatment group had a SAE considered to possibly or probably related to study drug.

One hundred (23%) subjects in the Vicodin CR treatment group and 26 (6%) subjects in the placebo treatment group reported treatment-emergent AEs that at least in part led to premature discontinuation from the study. The difference between treatment groups was statistically significant. The most common ($\geq 2\%$ of subjects in either treatment group) treatment-emergent AEs that at least in part led to premature discontinuation from the study were nausea, somnolence, constipation, vomiting, and dizziness. During the Taper Period, seven Vicodin CR subjects and no placebo subjects reported AEs for which the Investigator considered the final diagnosis to be drug withdrawal syndrome.

No cases of hepatic failure or hepatotoxicity were reported in this study. No subject in the Vicodin CR treatment group and two subjects in the placebo treatment group had potentially clinically significant elevations ($\geq 3 \times$ ULN) in AST and/or ALT. While some clinical laboratory assessments, vital signs, and ECG assessments were associated with findings in individual subjects, no remarkable treatment related trends were observed in this generally elderly population with OA.

Conclusions:

In this study, it is concluded that Vicodin CR was efficacious in the management of moderate to severe chronic pain associated with OA. The safety profile of this modified-release combination hydrocodone/acetaminophen treatment was consistent with the known profile of a mu-opioid receptor agonist-containing products.