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: An Open-label Study Evaluating the Safety and Tolerability of Long Term Administration of Hydrocodone/Acetaminophen Extended Release Tablets (Vicodin CR™) in Subjects with Moderate to Severe Chronic Non-malignant Pain

Investigator: Multicenter; Coordinating Investigator was Dave E. Webster, DO

Study Sites: 74 investigative sites in the United States.

Publications: None

Studied Period (Years): First Subject First Visit: 12 Jul 2005 (first subject dosed) Last Subject Last Visit: 12 Dec 2006 (last subject completed dosing)	**Phase of Development:** 3

Objective: The objective of this study was to evaluate the long-term safety and tolerability of Vicodin CR (hydrocodone bitartrate and acetaminophen extended release tablets 15 mg/500 mg) 2 tablets, administered twice daily in subjects with moderate to severe chronic non-malignant pain.

Methodology: Subjects were evaluated for a primary diagnosis of osteoarthritis (OA) of the knee or hip, or mechanical chronic low back pain (CLBP), and were selected for study participation based on inclusion and exclusion criteria. If the subject had multiple conditions (e.g., OA of the knee and hip, or CLBP and OA of the knee), a primary condition (most painful) was to be identified as the condition under evaluation. If the primary condition for entry into the study was OA, the subject was required to identify the most painful joint as the index joint for the study.

Subjects who met the selection criteria entered the Washout Period. During the Washout Period, subjects were to discontinue their current analgesic therapy for OA or CLBP. The length of the analgesic Washout Period was to be at least 5 half-lives of the analgesic used or 2 days, whichever was longer. The maximum length of time allowable between the Screening and Baseline Visits was 21 days. Subjects returned to the study center for the Baseline Visit, and were re-assessed to determine if they continued to meet the eligibility criteria including a score of ≥ 4 on the Subject's Pain Intensity Scale.

Methodology (continued):

At the Baseline Visit, eligible subjects were to begin a 7-day Titration Period. During the Titration Period, subjects began taking 1 tablet Vicodin CR once daily (in the evening) for 3 days, followed by 1 tablet Vicodin CR twice daily (once in the morning, once in the evening) for 4 days. The Titration Period may have been increased for an additional 7 days if the subject, in the opinion of the Investigator, would benefit from an extended Titration Period. During the extended Titration Period, subjects continued to take 1 tablet Vicodin CR twice daily (once in the morning, once in the evening) for 4 days, followed by 1 tablet Vicodin CR in the morning, and 2 tablets Vicodin CR in the evening for 3 days.

At the end of the Titration Period (in most cases this was to be Day 8, or on a case-by-case basis may have been expanded to Day 15), subjects returned to the study center and began the Maintenance Period, during which they took 2 tablets twice daily of Vicodin CR (once in the morning, once in the evening) for 56 weeks. Subjects returned to the study center for scheduled visits during the Maintenance Period. At the end of the Maintenance Period, subjects entered the 1-week study drug Taper Period. During the Taper Period, subjects received 1 tablet Vicodin CR twice daily (once in the morning, once in the evening) for 4 days, followed by 1 tablet once daily (in the evening) for an additional 3 days, after which Vicodin CR was discontinued.

A Follow-up Visit was conducted one week after study drug discontinuation. In addition, the study centers contacted the subject by telephone 30 days after the last dose of study drug administration and questioned subjects 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 (AEs) ongoing since their last contact. All pertinent information was recorded in the subject's source document, including the date and time of the telephone call.

Subjects may have taken acetaminophen as rescue medication during the Washout, Titration, Maintenance, and Taper Periods of the study. Subjects were not to take more than 2000 mg per day. Rescue medication may not have been taken 24 hours prior to scheduled study visits.

Number of Subjects (Planned and Analyzed): Three hundred fifty subjects were planned and 433 subjects were enrolled in the study. All subjects that took at least one dose of study drug (431 subjects) were included in the intent-to-treat (ITT) dataset for safety.

Diagnosis and Main Criteria for Inclusion: Males and females between 21 and 75 years of age, inclusive, who met the American College of Rheumatology Classification criteria for OA of the hip or the knee or had experienced mechanical low back pain, below the 12th thoracic vertebrae for > 3 months and who had taken an analgesic for OA pain or CLBP for the majority of days in the previous 3 months and for at least 4 days/week during 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: 7- to 14-day Titration Period, 56-week Maintenance Period, and 1-week Taper Period

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: None

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Criteria for Evaluation

Efficacy: Efficacy was assessed by determinations of the Pain Intensity Scale (11-point Likert scale), the Brief Pain Inventory (BPI), SF-36v2™ Health Status Survey, the Work Productivity and Activity Impairment Questionnaire, Subject's Global Assessment of Study Drug, and acetaminophen use.

Safety: Safety was assessed by AE monitoring and assessments of laboratory and vital sign evaluations.

Statistical Methods

No statistical tests were performed in this single-arm, open-label study.

Efficacy: Item numbers 3-6, 8, and 9 of the BPI were summarized individually for each scheduled assessment. Additionally, the Pain Intensity Scale, SF-36v2™ Health Status Survey, the Work Productivity and Activity Impairment Questionnaire, and the Subject's Global Assessment of Study Drug were summarized individually for each scheduled assessment.

The SF-36v2™ Health Status Survey and the Work Productivity and Activity Impairment Questionnaire were each scored according to published scoring guidelines.

Safety: Treatment-emergent AEs were tabulated by Medical Dictionary for Regulatory Activities (MedDRA®) system organ class (SOC) and preferred term. Additional summaries for treatment-emergent AEs with onset prior to the end of the Maintenance Period, as well as treatment-emergent AEs with onset after the end of the Maintenance Period were tabulated separately by 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 average, minimum, maximum, and final values were summarized for each 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. In addition, laboratory and vital sign results that satisfied the Data Analysis Criteria for Potentially Clinically Significant Laboratory/Vital Sign Findings were identified. The number and percentage 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 the normal ranges to define categories (low, normal, high, and missing), were summarized.

Summary/Conclusions

Efficacy Results: A mean reduction (improvement) in Subject's Assessment of Pain Intensity (11 point Likert scale) was observed by the first evaluation at Week 4 of the Maintenance Period and maintained over the duration of the study through Week 56. Results of the BPI demonstrated improvements in pain intensity, pain relief and pain interference assessments beginning with the first evaluation at Week 4. These improvements were maintained through Week 56. Improvements (reductions) from Baseline in the percent of work impairment while working due to health, percent overall work impairment due to health, and percent activity impairment due to health were observed at each scheduled evaluation, and were maintained through Week 56. No appreciable difference in the percent of work time missed due to health was observed. Improvements from Baseline in the 8 sub-domains of the SF-36v2 Health Status Survey, the PCS, and the MCS were observed at each scheduled evaluation and were maintained through Week 56.

Summary/Conclusions (continued)

Efficacy Results (continued): The proportion of subjects assessing study drug as very good or excellent increased from Week 4 (57%) to Week 40 (74%) and was maintained out to Week 56 (74%).

Acetaminophen use for rescue or any reason (including rescue) was greatest during the first 30 days and tended to decrease or generally remain stable throughout the duration of the trial.

Safety Results:

The majority of subjects (86%) reported at least 1 treatment-emergent AE. The most frequently reported treatment-emergent AEs were constipation, nausea, headache, somnolence, pruritus, nasopharyngitis, upper respiratory tract infection, dizziness, vomiting, diarrhea, insomnia, fatigue, back pain, anxiety, depression, and influenza.

A total of 61% of subjects reported at least one possibly or probably treatment-related AE.

Sixteen percent of subjects reported at least one severe AE. Nausea was the only severe AE that was reported in ≥ 2% of subjects.

The incidence of constipation, nausea, headache, somnolence, pruritus, dizziness and vomiting was highest in the first 30 days of study drug administration and decreased substantially thereafter, remaining low for the duration of the study.

Whereas the prevalence of constipation decreased slightly but remained fairly stable over time, the prevalence of nausea, headache, somnolence, pruritus, dizziness and vomiting decreased after the first 30 days and then remained low over time.

One subject died due to cardiac arrest (event was considered not related by the investigator) 41 days posttreatment.

Twenty-five (6%) subjects experienced 1 or more serious AE, none of which were considered by the Investigator to be possibly or probably related to study drug.

The most common reason for study discontinuation was due to AEs; 124 (29%) subjects prematurely discontinued from study drug at least in part due to 1 or more treatment-emergent AE(s). The most frequently reported AEs (≥ 2%) leading to discontinuation were nausea, somnolence, constipation, dizziness, vomiting, headache, and fatigue.

There were no reports of hepatotoxicity. In one subject ([redacted]) with elevations of AST and ALT that were 12.2 X ULN and 7.6 X ULN, respectively the elevations resolved within two days. The elevations were considered to be secondary to cholecystitis, in a subject with a complicated clinical course requiring surgery. redacted information 29Jul2014

Six (1%) of subjects had a final diagnosis of drug withdrawal syndrome as per the investigator.

Overall, Vicodin CR two tablets twice daily did not demonstrate clinically meaningful changes in laboratory parameters or vital sign results.

Conclusions: Based on these data, it is concluded that in this study, Vicodin CR was efficacious in the management of chronic non-malignant pain over a duration of 56 weeks. The safety profile of Vicodin CR in this study was consistent with that of a *mu*-opioid receptor agonist containing agent.