2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-712 Hydrocodone/Acetaminophen Extended Release	**Volume:** **Page:**	
Name of Active Ingredient: Hydrocodone 10 mg/ Acetaminophen 650 mg Extended Release		

Title of Study: A Randomized, Multicenter, Study Comparing the Analgesic Efficacy and Safety of Hydrocodone/Acetaminophen Extended Release to Placebo in Subjects with Acute Pain Following Bunionectomy

Investigator: [redacted] redacted information 24Sep2014

Study Sites: Three investigative sites in the United States

Publications: None

Studied Period (Years): First Subject First Visit: 18 April 2011 Last Subject Last Visit: 08 June 2011	**Phase of Development:** 2

Objectives:

The primary objective of this Phase 2 study was to compare the analgesic efficacy and safety of hydrocodone/acetaminophen extended release 10 mg/650 mg, 1 tablet twice daily (BID), to placebo in the treatment of moderate to severe pain for the day following primary unilateral first metatarsal bunionectomy surgery.

The secondary objective was to explore the pharmacokinetics of hydrocodone/acetaminophen extended release 10 mg/650 mg in subjects with moderate to severe pain.

Methodology:

This was a Phase 2, randomized, multicenter, single-blind, placebo-controlled study that consisted of 4 study periods: Screening (≤ 21 days from the Screening Visit to the day of surgery); Perioperative (from the beginning of confinement on the day of surgery until the first dose of study drug on the day after surgery); Treatment (from the first dose of study drug to 48 hours following the first dose of study drug); and Follow-up (from completion of Treatment Period until the Follow-up phone call 30 days [± 2 days] following the last dose of study drug).

Methodology (Continued):

Subjects who met the selection criteria at the Screening Visit were eligible to participate in the study and were to return to the study center within 21 days of the Screening Visit. If subjects continued to meet the selection criteria, pre-operative assessments were performed and confinement at the investigational site began.

The bunionectomy surgery was performed under regional anesthesia using a Mayo block and propofol sedation. Perioperative anesthesia was standardized for all subjects. Upon completion of surgery, designated study personnel ensured continued eligibility per the selection criteria of the protocol.

Beginning at approximately 2:00 AM on the day following surgery through 12:00 PM, subjects who had a pain intensity score of ≥ 40 mm on a 100 mm visual analog scale (VAS) and moderate or severe pain intensity per the categorical pain intensity scale were eligible for randomization, in equal numbers, into 1 of 2 treatment arms: hydrocodone/acetaminophen extended release 10 mg/650 mg, 1 tablet every 12 hours; or placebo.

During the Treatment Period, subjects completed assessments of pain intensity and pain relief. Time to first perceptible pain relief (i.e., onset of pain relief) and time to first meaningful pain relief were determined using the two-stopwatch method. In addition, subjects completed a subject global assessment of study drug.

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

Number of Subjects (Planned and Analyzed):

100 planned; 50 in each treatment group

100 analyzed; 49 in the placebo group and 51 in the hydrocodone/acetaminophen extended release 10 mg/650 mg

Diagnosis and Main Criteria for Inclusion:

Males and females 18 to 75 years of age inclusive who were qualified for enrollment based on the predefined inclusion/exclusion criteria, which were designed to select subjects suitable to undergo bunionectomy surgery and for whom it was appropriate to administer study drug, perioperative medication, and rescue medication

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Hydrocodone/acetaminophen extended release 10 mg/650 mg, 1 oral tablet, lot number [redacted]

Duration of Treatment: 48 hours; 4 doses, study drug (active or placebo) administered every 12 hours

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

Placebo for hydrocodone acetaminophen, 1 oral tablet, lot number [redacted]

redacted information 24Sep2014

Criteria for Evaluation

Efficacy:

Efficacy was assessed by determinations of pain intensity, pain relief, and subject global evaluation of study drug. These assessments included both a 100 mm pain intensity VAS and a 4-point categorical pain intensity scale (no pain, mild pain, moderate pain, or severe pain). They also included a 5-point categorical scale of pain relief from Baseline (no relief, a little relief, some relief, a lot of relief, or complete relief), analgesic rescue medication use, and a subject global evaluation of the study drug for pain (poor, fair, good, very good, excellent). In addition, time to perceptible pain relief and time to meaningful pain relief were determined using the two-stopwatch method.

Pharmacokinetic:

The pharmacokinetic parameters of hydrocodone and acetaminophen, including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), and the area under the plasma concentration-time curve (AUC) from time 0 to 12 hours (AUC_{0-12}) and from 36 to 48 hours were determined using noncompartmental methods.

Safety:

Adverse events (AEs), physical examination, laboratory data, and vital signs were assessed throughout the study.

Statistical Methods

Efficacy:

The primary efficacy variable was the time interval weighted sum of pain intensity difference (SPID) using the 100 mm VAS for the 0 to 12 hours following initial study drug administration. Treatment group mean differences for the primary efficacy endpoint were evaluated using analysis of covariance (ANCOVA) with factors for treatment group and study center and VAS Baseline pain intensity as the covariate.

Secondary endpoints were SPID VAS at 0 to 12 hours, as well as SPID for the categorical pain score, total pain relief (TOTPAR), and the sum of pain relief and pain intensity difference (SPRID) from 0 to 12 hours following initial study drug dosing. The time interval weighted pain scores were analyzed using ANCOVA, utilizing the same analysis model used for the primary efficacy variable. The time to subject's first perceptible and meaningful pain relief, and time to analgesic rescue medication were analyzed using log rank statistics from nonparametric survival models.

The actual scores of the subject global assessment of study drug were analyzed for the 0- to 48-hour period using Cochran Mantel Haenszel methodology for equal row means, with study center as the stratification factor. The proportion of subjects reporting at least good and at least very good responses at 48 hours post-initial study drug dose were compared using Fisher's exact test.

Pharmacokinetic:

Individual hydrocodone and acetaminophen plasma concentrations and pharmacokinetic parameter values were tabulated for each subject and treatment group and summarized with appropriate statistical methods.

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 14.0. All treatment-emergent adverse events (i.e., those that began or worsened in severity after initiation of study drug) were tabulated by system organ class (SOC) and MedDRA preferred term (PT). A summary of the severity and relationship to study drug of all treatment-emergent adverse events, tabulated by MedDRA PT and SOC, was presented. Surgically related events were summarized.

For laboratory data, mean changes from Baseline to final values were summarized. Laboratory results that satisfied the Data Analysis Criteria for Potentially Clinically Significant Laboratory Findings were identified. Additionally, 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 normal ranges to define categories (low, normal, high and missing) were summarized.

For vital signs, mean changes from Baseline to the average, minimum, maximum, and final values were summarized. Vital sign results meeting the Criteria for Potentially Clinically Significant Vital Sign Findings were identified.

Summary/Conclusions

Efficacy Results:

For the protocol-specified primary endpoint (SPID VAS score for 0 to 12 hours following initial study drug dose), the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment was superior to placebo. The hydrocodone/acetaminophen extended release 10 mg/650 mg treatment also was superior to placebo for most secondary analyses involving differences in categorical pain intensity and pain relief from 0 to 48 hours following initial study drug dose.

Statistically significantly greater proportions of subjects in the hydrocodone/acetaminophen extended release 10 mg/650 mg experienced perceptible, meaningful, and confirmed perceptible pain relief within 12 hours of initial study drug dose compared with the placebo treatment group. In addition, the distributions of times to onset of perceptible, meaningful, and confirmed perceptible pain relief within 12 hours after the initial study drug dose were statistically significantly different for the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group versus placebo.

A statistically significantly greater proportion of subjects in the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group (73%; 37 subjects) reported a good, very good, or excellent response on the Global Assessment of Study Drug compared with the placebo treatment group (33%; 16 subjects) at 48 hours post-initial study drug dose.

A statistically significantly smaller proportion of subjects (63%; 32 subjects) in the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group used rescue/supplemental medication from the time of initial study drug dose to 12 hours compared with the proportion of subjects (96%; 47 subjects) in the placebo treatment group. The distribution of time to the first rescue medication/supplemental use within 12 hours after initial dose was statistically significantly different for the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group compared with the placebo treatment group.

Pharmacokinetic Results:

Following hydrocodone/acetaminophen extended release 10 mg/650 mg administration, mean hydrocodone C_{max} was 16.0 ± 4.1 ng/mL and AUC_{0-12} was 127 ± 32 ng●h/mL during the first dosing interval. Mean hydrocodone C_{max} increased to 21.9 ± 5.3 ng/mL, and AUC_{0-12} was 189 ± 48 ng●h/mL following multiple BID doses. Mean acetaminophen C_{max} was 3850 ± 1140 ng/mL and AUC_{0-12} was 24700 ± 7870 ng●h/mL during the first dosing interval. Mean acetaminophen C_{max} increased to 4500 ± 1380 ng/mL, and AUC_{0-12} was 25500 ± 7060 ng●h/mL following multiple BID doses.

Safety Results:

The safety profile of hydrocodone/acetaminophen extended release 10 mg/650 mg demonstrated an AE profile consistent with a *mu*-opioid-receptor-agonist/acetaminophen containing agent.

A greater proportion of subjects in the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group reported at least 1 AE, at least 1 possibly or probably study drug-related AE, and at least 1 severe AE compared with the placebo treatment group. No deaths or other serious AEs (SAEs) were reported, and no subjects discontinued as a result of an AE. Among subjects who reported at least 1 AE, the majority of subjects reported events assessed by the Investigator as possibly related to study drug and mild or moderate in severity. Three subjects in the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group reported severe vomiting, 1 reported severe nausea, and 1 subject reported severe headache. In the placebo treatment group, 1 subject had a severe headache, and 1 subject had a severe treatment-emergent AE of the PT: post-traumatic pain. Treatment-emergent AEs reported by ≥ 5% of subjects in any treatment group were nausea, vomiting, dizziness, headache, somnolence, cellulitis, alanine aminotransferase (ALT) increased, and aspartate aminotransferase (AST) increased.

Two subjects in the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group had both potentially clinically significant ALT and AST values (≥ 3 × ULN). One other subject in the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group had a potentially clinically significant ALT value. All 3 subjects had AEs involving one or more of the following parameters: ALT, AST, total bilirubin, alkaline phosphatase. Most values returned to normal by the last measurement time point. Criteria for Hy's Law were not met at any point in time in these subjects.

There were no other notable clinical laboratory findings and no notable vital signs findings.

Conclusions:

This study demonstrated the efficacy of hydrocodone/acetaminophen extended release 10 mg/650 mg in the treatment of moderate to severe pain for 48 hours following primary unilateral first metatarsal bunionectomy surgery compared with placebo. The safety profile of hydrocodone/acetaminophen extended release 10 mg/650 mg demonstrated an AE profile consistent with a *mu*-opioid-receptor-agonist/acetaminophen containing agent.

The pharmacokinetic profiles of hydrocodone and acetaminophen for hydrocodone/acetaminophen extended release 10 mg/650 mg in subjects with acute pain following bunionectomy were similar to those observed in previous Phase 1 studies in healthy subjects.