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:**	
Name of Active Ingredient: Hydrocodone 10 mg/ Acetaminophen 650 mg Extended-Release	**Page:**	

Title of Study: A Randomized, Multicenter, Single-blind, Placebo-controlled Study Comparing the Analgesic Efficacy and Safety of Hydrocodone/Acetaminophen Extended-Release Tablets and Hydrocodone/Acetaminophen (NORCO®) to Placebo in Subjects with Acute Pain Following Third Molar Tooth Extraction

Investigator: [redacted] redacted information 24Sep2014

Study Sites: Three investigative sites in the United States

Publications: None

Studied Period (Years):	**Phase of Development:** 2
First Subject First Visit: 03 June 2009 Last Subject Last Visit: 21 August 2009	

Objectives:

The primary objective of this study was to compare the analgesic efficacy and safety of a prototype hydrocodone/acetaminophen extended-release 10 mg/650 mg formulation, administered orally as 1 tablet single-dose, to placebo in the treatment of moderate to severe pain following third molar tooth extraction, as measured by the sum of pain intensity difference (SPID) from 0 to 12 hours after initial study drug dose using a Visual Analog Scale (VAS).

A secondary objective of this study was to compare the analgesic efficacy and safety of NORCO, a hydrocodone/acetaminophen 5 mg/325 mg combination product, administered orally as 1 tablet every 6 hours for 2 doses, to placebo in the treatment of moderate to severe pain following third molar tooth extraction, as measured by SPID from 0 to 12 hours after initial study drug dose using a VAS.

An additional objective was to explore the pharmacokinetics and exposure-response relationship of acetaminophen and hydrocodone in subjects experiencing pain.

Methodology:

This was a Phase 2, randomized, multicenter, single-blind, placebo-controlled study that consisted of 4 periods: Screening, Perioperative (Day of Surgery), Treatment (Day of Dosing until 12 hours following the initial dose of study drug), Follow-up (from the completion of the Treatment Period until the Follow-up Visit 7 days [± 2 days] later).

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 investigative site within 21 days of the Screening Visit. For subjects who continued to meet the selection criteria, designated site personnel were to review the efficacy assessment definitions and procedures for completion of assessments with the subjects prior to surgery and again prior to dosing of study drug.

Subjects were to undergo surgical extraction of two or more third molars, one of which must have been a mandibular third molar requiring bone removal. If only two third molars were removed, they were to have been ipsilateral.

Subjects with pain intensity score of ≥ 40 mm on a 100 mm VAS and moderate or severe pain intensity on the categorical pain intensity scale within the 6 hours following completion of surgery were randomized in an equal ratio to 1 of the following 3 treatments: hydrocodone/acetaminophen extended-release 10 mg/650 mg 1 tablet, NORCO 1 tablet every 6 hours for 2 doses, or placebo. The total dosing period was to be 12 hours. Subjects who did not score ≥ 40 mm on a 100 mm VAS and moderate or severe on a 4-point categorical rating scale during the perioperative period were permitted to repeat the assessment 1 additional time within 6 hours following completion of surgery.

During the Treatment Period, subjects were to complete assessments of pain intensity and of pain relief (PR). Time to perceptible PR (i.e., onset of PR) and time to meaningful PR were to be determined using the 2 stopwatch method. In addition, subjects were to complete a subject global assessment of study drug. Subjects could receive analgesic rescue medication during the Treatment Period if needed; however, rescue medication was to be delayed, if possible, for at least 90 minutes after initial administration of study drug.

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

Number of Subjects (Planned and Analyzed):

Approximately 120 subjects were planned, and 122 subjects were randomized in the study: 43 subjects in the hydrocodone/acetaminophen extended-release 10 mg/650 mg treatment group; 39 subjects in the NORCO treatment group; and 40 subjects in the placebo treatment group. All randomized subjects received at least 1 dose of study drug and were included in the intent-to-treat (ITT) data set.

Diagnosis and Main Criteria for Inclusion:

Male and female subjects between 18 and 65 years of age, inclusive, whose pain from third molar tooth extraction was anticipated to require an opioid analgesic and for whom, in the Investigator's clinical judgment, an oral hydrocodone/acetaminophen combination product would be appropriate as part of their pain management, and who met all inclusion criteria and did not meet any of the exclusion criteria were eligible for the study.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:
Hydrocodone/acetaminophen extended-release 10 mg/650 mg, 1 tablet
Packaging Lot number: [redacted] redacted information 24Sep2014

Duration of Treatment: 1 dose

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
Hydrocodone/acetaminophen immediate-release 5 mg/325 mg (NORCO), 1 tablet every 6 hours for 2 doses
Packaging Lot number: [redacted]

Placebo for hydrocodone/acetaminophen extended-release 15 mg/500 mg and NORCO, 1 tablet every 6 hours for 2 doses
Packaging Lot number: [redacted] redacted information 24Sep2014

Criteria for Evaluation

Efficacy:

Efficacy was assessed by determinations of pain intensity, pain relief, and subject global evaluation. These assessments included a 4-point categorical scale (no pain, mild pain, moderate pain, or severe pain) and 100 mm VAS of pain intensity, a 5-point categorical scale of pain relief from baseline (no relief, a little relief, some relief, a lot of relief, or complete relief), 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 via use of 2 stopwatches.

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}), were determined using noncompartmental methods.

Safety:

Adverse events, physical examinations, laboratory data, and vital signs were assessed throughout the study.

Statistical Methods

Efficacy:

For efficacy endpoints, comparisons of primary interest were between the hydrocodone/acetaminophen extended-release 10 mg/650 mg treatment group and the placebo treatment group. Efficacy endpoints also were compared pairwise between the NORCO treatment group and each of the placebo and hydrocodone/acetaminophen extended-release 10 mg/650 mg treatment groups.

The primary efficacy endpoint 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 a 2-way ANCOVA with factors for treatment and study center and VAS pain intensity as the covariate.

Secondary efficacy analyses include the following: SPID (categorical and VAS) for each scheduled evaluation, time interval weighted sum of pain relief (TOTPAR) for each scheduled evaluation, time interval weighted sum of pain relief and pain intensity difference (SPRID) scores for each scheduled evaluation, time to perceptible pain relief and time to meaningful pain relief, time to first analgesic rescue medication, subject global evaluation, and PR, pain intensity (PI), and pain intensity difference (PID) at each scheduled evaluation.

Efficacy (Continued):

The TOTPAR, SPID, and SPRID were calculated through the first 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. Wald statistics from Cox proportional hazards models (with Kaplan-Meier estimates of median time to event) were used to compare the placebo treatment group to each of the other 2 treatment groups (i.e., hydrocodone/acetaminophen extended-release 10 mg/650 mg and NORCO).

The actual scores of the subject global assessment were analyzed at each scheduled evaluation using CMH methodology for equal row means with study centers as the stratification factor.

Absolute PR, PI, PID, and PRID (PR+PID) were analyzed using Fisher's Protected Least Significant Difference (LSD) and ANOVA models. Analyses of mean scores within 12 hours of the initial dose of study drug were completed using 2 ANOVA models (the first being a 2-way ANOVA with treatment and Baseline PI and the second being a 2-way ANOVA with treatment, Baseline PI, and the interaction between them) as well as Fisher's LSD.

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 12.0. All treatment-emergent adverse events (i.e., those which began or worsened in severity after initiation of study drug), as well as adverse events that began in the interval between the end of surgery and time of initial study drug dosing, and adverse events that began after the first dose of rescue medication, 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 adverse events, tabulated by MedDRA preferred term and SOC, was presented. Surgically Related Events were coded using MedDRA and tabulated by MedDRA preferred term.

For laboratory data, mean changes from baseline to final values were analyzed using a one-way ANOVA with treatment as the main effect. 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 analyzed using a one-way ANOVA with treatment as the main effect. Vital sign results satisfying the Criteria for Potentially Clinically Significant Vital Sign Findings were identified.

Summary/Conclusions

Efficacy Results:

For the protocol-specified primary endpoint, each of the hydrocodone/acetaminophen extended-release 10 mg/650 mg and NORCO treatment groups demonstrated statistically significantly superior mean 0 to 12 hour time-interval weighted SPID VAS scores compared to placebo ($P = 0.001$ and $P = 0.009$, respectively), and the difference between the active treatment groups was not statistically significant.

Each of the hydrocodone/acetaminophen extended-release 10 mg/650 mg and NORCO treatment groups demonstrated statistically significantly superior results compared to placebo for the secondary endpoint: time-interval weighted pain assessments of categorical SPID 0 to 12 hours ($P = 0.002$ and $P = 0.025$, respectively) and SPRID 0 to 12 hours ($P = 0.005$ and $P = 0.044$, respectively). The hydrocodone/acetaminophen extended-release 10 mg/650 mg treatment group demonstrated a statistically significantly superior result compared to placebo for the time-interval weighted assessment of total pain relief (TOTPAR) ($P = 0.011$).

The distributions of times to perceptible PR and confirmed perceptible PR were comparable for the NORCO and HC/APAP ER treatment groups (median times were 22 to 24 minutes for perceptible PR and 24 to 40 minutes for confirmed perceptible PR for the NORCO and hydrocodone/acetaminophen extended-release 10 mg/650 mg treatment groups, respectively) and were significantly different from the distribution of times to perceptible PR for the placebo treatment group (median time to perceptible PR was 48.5 minutes; confirmed perceptible PR could not be estimated with the model). Treatment group differences for the distribution of time to perceptible, meaningful, and confirmed perceptible PR were statistically significant for each active treatment group versus placebo.

Similar proportions of subjects in each treatment group received rescue medication; however, the hydrocodone/acetaminophen extended-release 10 mg/650 mg treatment group had the longest median time to rescue medication, 442 minutes, followed by a median time of 205 minutes for the NORCO treatment group, and 124 minutes for the placebo treatment group. The difference in time to first rescue medication use between each active treatment group and the placebo treatment group was statistically significant.

Pharmacokinetic Results:

Mean ± standard deviation (SD) pharmacokinetic parameters of hydrocodone after administration of hydrocodone/acetaminophen extended-release 10 mg/650 mg and NORCO are listed in the following table.

Pharmacokinetic Parameters (units)		Mean ± SD Pharmacokinetic Parameters of Hydrocodone and Acetaminophen Regimens HC/APAP extended-release 10 mg/650 mg AC-270 Formulation (N = 43)	NORCO 5/325 Q6H × 1 (N = 21)	NORCO 5/325 Q6H × 2 (N = 16)
Hydrocodone				
C_{max}	(ng/mL)	10.7 ± 2.5	11.6 ± 3.4	15.8 ± 3.1
T_{max}	(h)	4.09 ± 1.48	1.42 ± 0.59	6.63 ± 2.89
AUC_{0-12}	(ng•h/mL)	90.8 ± 21.2	60.9 ± 14.9	112 ± 25
Acetaminophen				
C_{max}	(ng/mL)	3330 ± 1190	3630 ± 1140	3780 ± 1090
T_{max}	(h)	1.11 ± 0.63	0.99 ± 0.46	2.80 ± 3.11
AUC_{0-12}	(ng•h/mL)	15800 ± 4970	12700 ± 3100	21700 ± 6990

HC/APAP = hydrocodone/acetaminophen

The pharmacokinetic profiles of hydrocodone and acetaminophen for hydrocodone/acetaminophen extended-release 10 mg/650 mg Formulation AC-270 and NORCO 5 mg/325 mg (2 doses) in subjects with acute dental pain were similar to those observed in a Phase 1 study (M10-918) in healthy subjects. The ratios of mean hydrocodone and acetaminophen C_{max} for hydrocodone/acetaminophen extended-release 10 mg/650 mg versus NORCO 5 mg/325 mg (2 doses) in the current parallel design study were also close to those observed in the same study (M10-918).

Safety Results:

Similar proportions of subjects in each treatment group experienced at least 1 treatment-emergent AE: 33%, 31%, and 35% of subjects in the hydrocodone/acetaminophen extended-release 10 mg/650 mg, NORCO, and placebo treatment groups, respectively. Treatment-emergent AEs occurring in ≥ 5% of subjects in any treatment group were nausea, headache, dizziness, vomiting, chills, and diarrhea.

No subject experienced an SAE, and no subject discontinued study drug prematurely due to an AE.

No clinically significant changes from Baseline or differences between groups were observed for any laboratory measurement, vital sign assessment, or surgically related events.

Conclusions:

This study demonstrated the efficacy of hydrocodone/acetaminophen extended-release 10 mg/650 mg treatment and NORCO in treatment of moderate to severe pain due to third molar tooth extraction. The safety profile of hydrocodone/acetaminophen extended-release 10 mg/650 mg and NORCO demonstrated an AE profile consistent with a *mu*-opioid-receptor-agonist containing agent.

The pharmacokinetic profiles of hydrocodone and acetaminophen for hydrocodone/acetaminophen extended-release 10 mg/650 mg Formulation AC-270 and NORCO 5 mg/325 mg (2 doses) in subjects with acute dental pain were similar to those observed in a Phase 1 study in healthy subjects.