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 Study Comparing Hydrocodone/Acetaminophen Extended Release 10/650, Morphine Extended Release, and Acetaminophen to Placebo in Subjects with Acute Pain Following Bunionectomy		
Investigator: [redacted] redacted information 24Sep2014		
Study Sites: Four investigative sites in the United States.		
Publications: None		
Studied Period (Years): First Subject First Visit: 23 December 2009 Last Subject Last Visit: 04 May 2010	**Phase of Development:** 2	

Objectives:

The primary objective of this Phase 2 study was to compare the analgesic efficacy and safety of multiple doses of hydrocodone/acetaminophen extended release 10 mg/650 mg, 1 tablet twice daily, to placebo in the treatment of moderate to severe pain for 48 hours following primary unilateral first metatarsal bunionectomy surgery.

A secondary objective was to evaluate the contribution of morphine extended release and acetaminophen separately relative to the combination of the 2 agents in the treatment of moderate to severe pain for 48 hours following primary unilateral first metatarsal bunionectomy surgery.

This study also was to evaluate the pharmacokinetics and exposure-response relationship of acetaminophen, hydrocodone, morphine, and possible morphine metabolites in the treatment of moderate to severe pain for 48 hours following primary unilateral first metatarsal bunionectomy surgery.

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 (completion of Treatment Period until the Follow-up phone call 30 days [± 2 days] following the last dose of study drug).

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 4:00 AM on the day following surgery, 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 5 treatment arms: hydrocodone/acetaminophen extended release 10 mg/650 mg, 1 tablet every 12 hours; morphine extended release 10 mg, 1 capsule every 12 hours; acetaminophen 325 mg, 1 tablet every 6 hours; morphine extended release 10 mg, 1 capsule every 12 hours, plus acetaminophen 325 mg, 1 tablet every 6 hours; or placebo. In order to maintain the single-blind nature of the study, all subjects were dosed with study drug (active and/or placebo) every 6 hours.

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):

Two hundred fifty subjects were planned (50 in each treatment group), and 250 subjects were randomized and received at least 1 dose of study drug: 51 received placebo; 48 received hydrocodone/acetaminophen extended release 10 mg/650 mg; 50 received acetaminophen; 49 received morphine extended release/acetaminophen; and 52 received morphine extended release.

Diagnosis and Main Criteria for Inclusion:

Males and females 18 to 75 years of age 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 tablet

Packaged lot numbers: [redacted]

Duration of Treatment:

48 hours; 8 doses, study drug (active or placebo) administered every 6 hours

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

Reference Therapy	Dose	Packaged Lot Number
Placebo for hydrocodone/acetaminophen	1 tablet	[redacted]
Morphine sulfate extended release 10 mg	1 tablet	[redacted]
Placebo for morphine sulfate extended release	1 tablet	[redacted]
Acetaminophen 325 mg	1 tablet	[redacted]

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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), 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 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, physical examination, 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 each active treatment group.

The primary efficacy endpoint was the time-interval weighted sum of pain intensity difference (SPID) using the 100 mm VAS for the 0 to 48 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, study center, and VAS Baseline pain intensity score 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 and from 0 to 48 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 first perceptible pain relief, meaningful pain relief, confirmed perceptible 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 post-initial study drug dose were compared using Fisher's exact test.

Pharmacokinetic:

Values for the pharmacokinetic parameters of hydrocodone, acetaminophen, morphine, and possible morphine metabolites, including maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), and the area under the plasma concentration-time curve (AUC) from time 0 to 12 hours (AUC_{12}) and from 36 to 48 hours (AUC_{36-48}) post-initial dose were estimated using noncompartmental methods. Values for the pharmacokinetic parameters of hydrocodone, acetaminophen, morphine, and possible morphine metabolites including apparent oral clearance (CL/F) were to be estimated using population pharmacokinetic modeling procedures.

Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) version 12.1. All treatment-emergent AEs (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. A summary of the severity and relationship to study drug of all treatment-emergent AEs, tabulated by MedDRA preferred term 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.

Statistical Methods

Safety (Continued):

For vital signs, mean changes from baseline to the minimum, maximum, and final values were summarized. Vital sign results meeting the Data Analysis 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 48 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, as well as absolute pain intensity values from 0 to 48 hours following initial study drug dose. To help explore the contributions of morphine extended release and acetaminophen separately relative to the combination of the two agents, the main effects of morphine extended release and acetaminophen were evaluated for each of the time-interval weighted variables. The interaction term was not statistically significant at most intervals; analyses of the main effects showed a significant contribution for acetaminophen for the majority of assessments.

In addition, hydrocodone/acetaminophen extended release 10 mg/650 mg treatment was superior to placebo in time to meaningful pain relief and time to confirmed perceptible pain relief. The short time to meaningful pain relief for the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment (median time ~60 minutes compared with 220 minutes for placebo) demonstrates that the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment is appropriate for acute pain.

In addition, the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment was superior to the placebo treatment with regard to time to the first rescue medication use within 12 hours after initial dose (median times = 539 versus 236 minutes for the hydrocodone/acetaminophen extended release 10 mg/650 mg and placebo treatment groups, respectively). From 0 to 12 hours post-initial study drug dose, 63% of subjects in the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group used rescue or supplemental medication compared with 80% of subjects in the placebo treatment group. A statistically significantly smaller proportion of subjects in the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group used rescue or supplemental medication from 0 to 48 hours following the initial study drug dose compared with the placebo treatment group.

The hydrocodone/acetaminophen extended release 10 mg/650 mg treatment also was superior to placebo with regard to the Subject Global Assessment of Study Drug; 88% of subjects who received hydrocodone/acetaminophen extended release 10 mg/650 mg rated the study drug as good or very good compared with 63% of subjects in the placebo treatment group.

Pharmacokinetic Results:

The mean ± SD pharmacokinetic parameters of hydrocodone, acetaminophen, morphine, and morphine-6-glucuronide (M6G) during 0 to 12 hours and 36 to 48 hours after first dose administration are shown in the following 2 tables.

Mean Pharmacokinetic Parameters of Hydrocodone, Acetaminophen, Morphine, and Morphine-6 glucuronide, 0 to 12 Hours After Initial Study Drug Dose

Pharmacokinetic Parameters (units)		Regimens: Hydrocodone/ Acetaminophen 10/650 mg Q12h (N = 48)	Morphine ER Q12h (N = 52)	Acetaminophen 325 mg Q6h (N = 50)	Morphine ER Q12h + Acetaminophen 325 mg Q6h (N = 49)
Hydrocodone					
T_{max}	(h)	4.58 ± 1.70	--	--	--
C_{max}	(ng/mL)	12.0 ± 2.78	--	--	--
AUC_{12}	(ng•h/mL)	99.5 ± 22.1[a]	--	--	--
Acetaminophen					
T_{max}	(h)	1.65 ± 1.23	--	2.70 ± 2.87	3.90 ± 3.88
C_{max}	(ng/mL)	3520 ± 1070	--	3920 ± 899	3840 ± 904
AUC_{12}	(ng•h/mL)	17600 ± 4850[a]	--	23300 ± 6310[b]	23100 ± 6060[c]
Morphine					
T_{max}	(h)	--	7.96 ± 3.16	--	7.96 ± 2.90
C_{max}	(ng/mL)	--	1.45 ± 0.78	--	1.49 ± 0.71
AUC_{12}	(ng•h/mL)	--	9.85 ± 4.77[d]	--	10.0 ± 4.27[c]
Morphine-6-glucuronide					
T_{max}	(h)	--	8.19 ± 2.89	--	7.71 ± 2.74
C_{max}	(ng/mL)	--	9.26 ± 4.74	--	9.38 ± 4.33
AUC_{12}	(ng•h/mL)	--	63.8 ± 28.6[a]	--	62.2 ± 25.7[c]

ER = extended release; Q6h = every 6 hours; Q12h = every 12 hours

a. N = 47.

b. N = 49.

c. N = 48.

d. N = 50.

Pharmacokinetic Results (Continued):

Mean Pharmacokinetic Parameters of Hydrocodone, Acetaminophen, Morphine, and Morphine-6 glucuronide, 36 to 48 Hours After Multiple Dosing

Pharmacokinetic Parameters (units)		Regimens: Hydrocodone/ Acetaminophen 10/650 mg Q12h (N = 46)	Morphine ER Q12h (N = 49)	Acetaminophen 325 mg Q6h (N = 48)	Morphine ER Q12h + Acetaminophen 325 mg Q6h (N = 47)
Hydrocodone					
T_{max}[a]	(h)	4.30 ± 1.88	--	--	--
C_{max}	(ng/mL)	19.1 ± 5.26	--	--	--
AUC_{12}	(ng•h/mL)	179 ± 52.5	--	--	--
Acetaminophen					
T_{max}[a]	(h)	2.52 ± 1.15	--	2.54 ± 1.15[b]	2.21 ± 0.95[b]
C_{max}	(ng/mL)	3820 ± 1300	--	3480 ± 1230[b]	3400 ± 914[b]
AUC_{12}	(ng•h/mL)	28800 ± 11200	--	13900 ± 5430[b,c]	13600 ± 3850[b,c]
Morphine					
T_{max}[a]	(h)	--	6.61 ± 3.30	--	7.02 ± 4.19
C_{max}	(ng/mL)	--	3.23 ± 1.42	--	2.87 ± 1.10
AUC_{12}	(ng•h/mL)	--	29.9 ± 12.6[d]	--	25.6 ± 8.17
Morphine-6-glucuronide					
T_{max}[a]	(h)	--	7.27 ± 3.36	--	7.96 ± 4.08
C_{max}	(ng/mL)	--	19.5 ± 5.67	--	19.6 ± 5.59
AUC_{12}	(ng•h/mL)	--	187 ± 56.3[d]	--	176 ± 45.4

BID = twice daily; ER = extended release; Q6h = every 6 hours; Q12h = every 12 hours

a. T_{max} is given relative to the last previous dose.

b For acetaminophen, T_{max}, C_{max}, and AUC_{12} were calculated from 36 to 42 hours.

c. N = 46.

d. N = 48.

Safety Results:

A greater proportion of subjects in the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group reported at least 1 treatment-emergent AE and at least 1 severe treatment-emergent AE compared with each of the other treatment groups. The proportion of subjects who reported at least 1 possibly or probably study drug-related treatment-emergent AE (as assessed by the Investigator) was similar among the active treatment groups and lower in the placebo group. Among subjects who reported at least 1 treatment-emergent AE, the majority reported events that were assessed by the Investigator as mild or moderate in severity and possibly related to study drug. No SAEs or deaths were reported.

Treatment-emergent AEs reported by ≥ 5% of subjects in any treatment group were nausea, headache, vomiting, dizziness, constipation, somnolence, diarrhoea, alanine aminotransferase (ALT) increased, and dehydration.

One subject, Subject [redacted], in the morphine/acetaminophen treatment group, discontinued from the study due in part to an AE of decreased blood pressure (Preferred Term: blood pressure decreased). The onset of the event was 6 hours after dosing; the event was considered by the Investigator to be mild and possibly related to study drug.

Adverse events were reported for 8 subjects involving increased ALT and/or aspartate aminotransferase (AST) or liver function test abnormalities. Potentially clinically significant (PCS) elevated ALT and/or AST values (criteria were ≥ 3 × ULN) were reported in 2 subjects in the acetaminophen treatment group, 2 subjects in the morphine treatment group, and 3 subjects in the morphine/acetaminophen treatment group. Two subjects in the placebo group had post-Baseline PCS decreased calcium values (criterion was ≤ 1.8 mmol/L), as did 1 subject in the morphine/acetaminophen treatment group.

Five subjects had post-Baseline hematology values (hemoglobin and/or hematocrit, and/or red blood cell count) that met the predefined PCS criteria; however, no subjects in the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group had PCS post-Baseline hematology values.

From 2 to 8 subjects in each treatment group, including the placebo treatment group, experienced predefined PCS decreases in systolic and/or diastolic blood pressure. Other than an AE of decreased blood pressure in Subject [redacted], who discontinued due in part to that AE, no AEs were reported for PCS vital signs values.

No key differences between the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group and the placebo treatment group were observed for mean changes from Baseline to final assessment for hematology, clinical chemistry, or urinalysis parameters. The morphine/acetaminophen treatment group exhibited numerically greater mean increases from Baseline to final assessment in ALT and AST compared with the placebo treatment group.

Surgically related events were similar for all treatment groups.

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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.

Systemic exposures (C_{max} and AUC) of hydrocodone, acetaminophen, morphine, and M6G were consistent with exposures observed in previous Phase 1 studies and published data. Acetaminophen, morphine, and M6G exposure were comparable between acetaminophen and morphine administered alone and coadministration.