2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Hydrocodone Bitartrate-Acetaminophen (NORCO®)	**Volume:**	
Name of Active Ingredient: Hydrocodone Bitartrate-Acetaminophen	**Page:**	
Title of Study: A Randomized, Multicenter, Double-blind Study Comparing the Analgesic Efficacy and Safety of Immediate-release Hydrocodone/Acetaminophen to Placebo in Subjects with Acute Pain Following Bunionectomy		
Coordinating Investigator: [redacted] redacted information 24Sep2014		
Study Sites: 6 sites in the United States		
Publications: None		
Study Period: First Subject First Visit: 28 Apr 2008 Last Subject Last Visit: 02 Jul 2008	**Phase of Development:** 3b	
Objectives: The primary objective was to examine the analgesic efficacy and safety of an immediate-release hydrocodone/acetaminophen combination product (hydrocodone 10 mg/acetaminophen 325 mg; NORCO), 1 tablet Q4H by mouth for 3 doses, compared to placebo in the treatment of moderate to severe pain on the day following primary, unilateral, first metatarsal bunionectomy surgery. An additional objective was to explore the exposure-response relationship of an immediate-release hydrocodone/acetaminophen in subjects experiencing pain.		
Methodology: This was a randomized, multicenter, double-blind, placebo-controlled study designed to compare the analgesic efficacy and safety of an immediate-release hydrocodone/acetaminophen combination product (NORCO) in the treatment of subjects with moderate to severe pain on the day following, primary, unilateral, first metatarsal bunionectomy surgery under regional anesthesia (Mayo block) and propofol sedation.		
Number of Subjects (Planned and Analyzed): Planned: 75 Analyzed: 71 (46 – NORCO; 25 – placebo)		
Diagnosis and Main Criteria for Inclusion: Subjects who were suitable candidates to undergo primary, unilateral, first metatarsal bunionectomy (no collateral procedures) under regional anesthesia and sedation, and who met all inclusion and no exclusion criteria were eligible to participate in this study.		

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

Hydrocodone and acetaminophen immediate-release (NORCO) tablet (Hydrocodone 10 mg/acetaminophen 325 mg) administered orally; lot number [redacted]

Duration of Treatment: Every 4 hours during the 12 hours post-operation (total of 3 doses)

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

placebo administered orally; lot number [redacted] redacted information 24Sep2014

Criteria for Evaluation

Efficacy: The primary efficacy assessment was the time-interval weighted sum of pain intensity difference (SPID) using a visual analogue scale (VAS; 100 mm, 0 being "no pain" and 100 being "worst pain imaginable") for the 0 to 12 hours following initial study drug administration. SPID is a commonly used summary measure to assess analgesic efficacy over a defined time period that utilizes multiple measurements of pain intensity (PI). Secondary efficacy assessments included the following:

- Time-interval weighted sum of pain relief (TOTPAR);
- SPID using the categorical pain intensity scale;
- Time-interval weighted sum of pain relief and pain intensity difference (SPRID);
- Perceptible pain relief (PR);
- Meaningful pain relief;
- Rescue/supplemental medication use;
- PR;
- PI;
- Subject Global Assessment of Study Drug.

Pharmacokinetic: Values for the pharmacokinetic parameters of hydrocodone and acetaminophen, 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_{0-12}) were estimated using noncompartmental methods.

Safety: Adverse events (AEs), physical examinations, concomitant medications, laboratory data, and vital signs were assessed throughout the study.

Statistical Methods

For efficacy endpoints, efficacy comparisons were between the immediate-release hydrocodone/acetaminophen (NORCO) treatment group and the placebo treatment group.

Analyses of covariance (ANCOVA) were performed with Proc GLM using Type III sums of squares. Model-based means (least square means) and standard errors were obtained from the LSMEANS statement for ANCOVAs. Univariate summary statistics (mean, standard deviation, median, minimum, maximum, first quartile, and third quartile) were obtained using Proc UNIVARIATE. Cochran-Mantel-Haenszel (CMH) and Fisher's Exact tests were performed using Proc FREQ. Log rank statistics were obtained using Proc LIFETEST.

Unless otherwise specified, categorical data were summarized by frequencies and percentages;

summaries of continuous data displayed the univariate mean, standard deviation, model-based mean, standard error, 95% confidence interval limits of the model-based mean, median, minimum, maximum, first quartile, and third quartile. The number of non-missing values was given. For time to event analyses, Kaplan Meier estimates for each quartile (i.e., first quartile, median, and third quartile) and corresponding 95% confidence interval limits were presented.

Efficacy: Treatment group mean differences for the primary efficacy measure were evaluated using ANCOVA with factors for treatment group, study center, and the Baseline VAS PI score as a covariate. Heterogeneity of treatment effects across study centers was also evaluated. For the primary efficacy analysis, all data obtained after subjects received any rescue/supplemental medication were excluded from the analysis. For subjects who received rescue/supplemental medication within 12 hours after initial study drug dosing or who did not complete all of the scheduled pain evaluations within 12 hours after initial study drug dosing, the missing pain scores were imputed using LOCF methodology.

Efficacy was also assessed for the following secondary variable types:

Analysis of time-interval weighted variables

- SPID, TOTPAR, SPID categorical, and SPRID
- Treatment group mean differences in time-interval weighted variables were evaluated using ANCOVA with factors for treatment group, study center, and the Baseline PI score as a covariate.

Analysis of scheduled pain assessments

- PI VAS, pain intensity difference (PID) VAS, PI categorical, PID categorical, PR, and PRID
- Treatment group mean differences in pain scores at each scheduled evaluation were analyzed using ANCOVA models. The ANCOVA analyses were conducted using two models. Mean differences in treatment group effects were analyzed using an ANCOVA model with factors for treatment group and Baseline PI as a covariate (no interaction). Treatment-by-Baseline PI interaction was analyzed using an ANCOVA model with factors for treatment group, Baseline PI, and the interaction term as a covariate.

Analysis of time to event variables

- Perceptible PR, Meaningful PR, Confirmed perceptible PR, and First rescue medication use
- Log-rank statistics from nonparametric survival models (with Kaplan Meier estimates of median time to onset or first use) were used to compare treatment groups for time to perceptible PR, time to meaningful PR, time to confirmed perceptible PR, and time to first rescue/supplemental medication use.
- Time to perceptible PR was censored at the time of withdrawal (time of last completed pain assessment prior to withdrawal), at 12 hours for subjects who either rescued prior to experiencing perceptible relief during the 12 hour interval after the initial dose of study drug, or who remained in the study but did not experience perceptible relief over the 12 hour interval after the initial dose of study drug. Time to meaningful PR was handled similarly. Time to confirmed perceptible PR is defined as the time to perceptible relief if the subject also subsequently experiences meaningful relief; time to confirmed relief was set equal to 12 hours for subjects who experienced perceptible relief but not meaningful relief, and other situations were handled similarly to time to perceptible relief. Time to

rescue was considered censored at the time of withdrawal (time of last completed pain assessment prior to withdrawal) or at the time of last completed pain assessment, whichever was earliest, if rescue did not occur prior to these times.

Analysis of proportion variables

- Proportion of subjects experiencing perceptible PR, Proportion of subjects experiencing meaningful PR, Proportion of subjects experiencing confirmed perceptible PR, and Proportion of subjects receiving rescue/supplemental medication
- Treatment differences in the proportion of subjects receiving rescue/supplemental medication, the proportion of subjects experiencing perceptible, meaningful, and confirmed perceptible PR, within 12 hours after the first dose of study drug, were compared using Fisher's Exact test.
- Treatment group differences in the proportion of subjects responding to treatment as measured by the VAS for the change from Baseline to the peak PID within the 0 to 12 hours following initial study drug dosing were assessed by a CMH test for equal row mean scores with study center as a stratification factor.

Analysis of subject global evaluation of study drug

- Global evaluation of study drug and Proportion of subjects reporting at least good and at least very good response
- Treatment group comparisons for the subject global evaluation score were made using a CMH test for equal row mean scores with study center as the stratification factor. The proportion of subjects reporting at least good and at least very good responses at each evaluation 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: All safety analyses were performed using an ITT dataset. All randomized subjects who receive at least 1 dose of study drug were included in the ITT analyses.

Baseline for all safety variables was the last measurement obtained prior to the subject receiving the first dose of blinded study drug.

For continuous safety variables, treatment group differences for mean changes from Baseline (laboratory and vital signs data) were analyzed using a one-way ANOVA with treatment as the main effect.

Fisher's Exact test was used to analyze treatment group differences for qualitative categorical variables. Analyses of variance were performed using Proc GLM; Fisher's Exact test was performed using Proc FREQ. Univariate summary statistics (mean, standard deviation, median, minimum, maximum, first quartile, and third quartile) were obtained using Proc UNIVARIATE. Categorical data were summarized by frequencies and percentages. The number of non-missing values was also given.

Data collected more than 2 days after the last dose of study drug were excluded from all safety summaries, except summaries of AEs and surgically-related events.

Missing safety data were not imputed.

Summary/Conclusions

Efficacy Results: The NORCO treatment group demonstrated statistically significantly superior mean 0-12 hour time-interval weighted SPID VAS scores as compared to the placebo treatment group. Other key measures in which NORCO was superior were:

- The time to meaningful PR was statistically significantly shorter in the NORCO treatment group compared to the placebo treatment group.
- The time to first rescue medication use was statistically significantly longer in the NORCO treatment group compared to the placebo treatment group.
- A statistically significantly greater proportion of subjects in the NORCO treatment group experienced meaningful PR and confirmed perceptible PR compared to the placebo treatment group.
- A statistically significantly smaller proportion of subjects in the NORCO treatment group received rescue/supplemental medication compared to the placebo group.
- For the subject's global assessment of study drug, a statistically significantly greater proportion of subjects in the NORCO treatment group reported ratings of at least good and at least very good compared to the placebo treatment group.

Pharmacokinetic Results: Systemic exposures (C_{max} and AUC_{0-12}) of hydrocodone and acetaminophen for the NORCO treatment group were consistent with exposures observed in previous Phase 1 and Phase 2 studies.

Safety Results: Thirty-eight subjects reported at least one AE during the study. Statistically significantly greater proportions of subjects in the NORCO treatment group reported at least one AE and experienced an AE that was at least possibly related to study drug compared to the placebo treatment group. No serious AEs were reported during the study. The majority of reported AEs were mild to moderate in nature. There were no deaths, AEs that led to discontinuation of study drug, or surgically-related AEs during the study. The most commonly reported AEs (occurring in ≥ 5% of subjects in either treatment group) were nausea, vomiting, headache, dizziness, and pyrexia. These AEs occurred in a greater percentage in the NORCO treatment group with nausea and vomiting occurring statistically significantly more frequently in the NORCO treatment group.

The majority of subjects had hematology, chemistry, and urinalysis values within the normal range at the Baseline and Final Visits. Few subjects experienced shifts from normal to low or normal to high in hematology or chemistry values, and the majority of these shifts were not considered clinically significant and were not associated with treatment-emergent AEs. One subject, [redacted] who was a 44 year old White female, had elevations of liver enzymes on treatment Day 1 that were considered clinically significant and were recorded as AEs. This subject had normal AST and ALT at Screening and Baseline, and on Day 20, all chemistry values were normal.

The majority of subjects had vital signs values and ECGs within the normal range. Any differences observed in vital signs were transient and not considered clinically meaningful.

Conclusions: The NORCO treatment group demonstrated statistically significantly superior mean 0-12 hour time-interval weighted SPID VAS scores as compared to the placebo treatment group. Adverse events occurred in a greater percentage in the NORCO treatment group, with nausea and vomiting occurring statistically significantly more frequently in the NORCO treatment group.

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