



## 2.0 Synopsis

<b>Abbott Laboratories</b>	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Hydrocodone/Acetaminophen Extended Release		
<b>Name of Active Ingredient:</b> Hydrocodone 10 mg/ Acetaminophen 650 mg Extended Release		
<b>Title of Study:</b> A Phase 2, Randomized Withdrawal Study of the Analgesic Efficacy and Safety of Hydrocodone/Acetaminophen Extended Release Compared to Placebo in Subjects with Chronic Low Back Pain		
<b>Coordinating Investigator:</b> [REDACTED] redacted information 24Sep2014		
<b>Study Sites:</b> Seventeen investigative sites in the United States		
<b>Publications:</b> None		
<b>Studied Period (Years):</b>  First Subject First Visit: 22 June 2011 Last Subject Last Visit: 28 October 2011	<b>Phase of Development:</b> 2	
<b>Objectives:</b> <p>The primary objective of this study was to compare the analgesic efficacy and safety of 1 tablet of hydrocodone/acetaminophen extended release 10 mg/650 mg administered twice daily over 2 weeks to placebo in subjects with moderate to moderately severe chronic low back pain (CLBP).</p> <p>A secondary objective of this study was to explore the population pharmacokinetics of hydrocodone and acetaminophen resulting from administration of hydrocodone/acetaminophen extended release 10 mg/650 mg tablets.</p>		
<b>Methodology:</b> <p>This Phase 2, multicenter, double-blind (DB), placebo-controlled, randomized withdrawal study compared the analgesic efficacy and safety of 1 tablet hydrocodone/acetaminophen extended release 10 mg/650 mg to placebo in subjects with moderate to moderately severe CLBP. Subjects met pre-defined criteria at the conclusion of the Open-Label (OL) Titration Period to proceed to randomization into the DB Maintenance Period of the study.</p> <p>The study included (1) a Screening Period with an analgesic washout, (2) a 2-week OL Titration Period, (3) a stratified, randomized, 2-week DB placebo-controlled Maintenance Period, (4) a 3-day Taper Period, and (5) a Follow-up Visit. A subject's participation in the study lasted approximately 5 weeks.</p>		



**Methodology (Continued):**

Adult male and female subjects were evaluated for a diagnosis of CLBP of at least 6 months duration and were selected for study participation based on the study selection criteria. A sufficient number of opioid-naïve and opioid-experienced subjects, approximately 215, were planned for enrollment in the OL Titration Period to provide approximately 150 subjects for randomization into the 2-week DB Maintenance Period.

Opioid naïve was defined as:

- Subject was taking at least 1 non-opioid analgesic for at least 30 days prior to Screening, OR
- Subject was taking an opioid (single or combination product not to include tramadol, butorphanol, buprenorphine, pentazocine or nalbuphine) with a daily morphine sulfate equivalence of  $\leq 20$  mg for  $< 4$  days per week on a PRN basis for at least 30 days prior to Screening.

Opioid-experienced was defined as:

- Subject was taking an opioid (single or combination product not to include tramadol, butorphanol, buprenorphine, pentazocine or nalbuphine) with a daily morphine sulfate equivalence of  $\leq 20$  mg for  $\geq 4$  days per week on an as needed or regular basis for at least 30 days prior to Screening.

All subjects received hydrocodone/acetaminophen extended release during the OL Titration Period on the following schedule:

- Days 1 to 3: 1 tablet hydrocodone/acetaminophen extended release 10 mg/650 mg once daily (evening).
- Days 4 to 7: 1 tablet hydrocodone/acetaminophen extended release 10 mg/650 mg twice daily (morning and evening).
- Days 8 to 14: 1 tablet hydrocodone/acetaminophen extended release 10 mg/650 mg and 1 tablet hydrocodone/acetaminophen extended release 5 mg/325 mg twice daily (morning and evening).

At the OL Titration Period Baseline visit, subjects completed assessments of pain intensity (100 mm visual analog scale [VAS]) and Subject Global Assessment of Back Pain Status.

At the end of the 2-week OL Titration Period, subjects returned to the study center and were assessed to determine eligibility for entering the 2-week DB Maintenance Period of the study. Subjects' eligibility to continue was based on meeting all of the following randomization criteria:

- Subject was adequately tolerating hydrocodone/acetaminophen extended release.
- Subject answered affirmative to the question:  
*"Has this treatment helped your back pain enough so that you would continue to take this medication?"*
- Subject's Assessment of Chronic Low Back Pain Intensity by VAS was  $\leq 50$  mm.
- Subject's Assessment of Chronic Low Back Pain Intensity by VAS had decreased by at least 15 mm as compared to the assessment performed at the OL Baseline Visit.



---

**Methodology (Continued):**

Subjects meeting criteria for entry into the 2-week DB Maintenance Period were randomized and stratified via Interactive Voice Response System/Interactive Web Response System into 2 treatment groups in a 2:1 ratio: hydrocodone/acetaminophen extended release 10 mg/650 mg 1 tablet twice daily or placebo 1 tablet twice daily.

During the DB Maintenance Period, subjects completed assessments of pain intensity (100 mm visual analog scale [VAS]), Subject Global Assessment of Study Drug, and Subject Global Assessment of Back Pain Status.

At the conclusion of the DB Maintenance Period, subjects returned to the study center and entered a 3-day study drug Taper Period. Subjects were contacted via telephone at the conclusion of taper and returned for a Follow-up Visit that was conducted 1 week after the completion of the DB Maintenance Period. In addition, subjects were contacted approximately 30 days after discontinuation of study drug.

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

**Number of Subjects (Planned and Analyzed):**

Approximately 215 were planned for enrollment in the OL Titration Period; 168 subjects were enrolled and analyzed during the OL Titration Period. 150 subjects were planned for the DB Maintenance Period; 146 subjects were randomized into the DB Maintenance Period and 141 were included in the primary efficacy analysis.

**Diagnosis and Main Criteria for Inclusion:**

Adult male and female subjects, 18 to 75 years of age inclusive, with a diagnosis of CLBP (below the 12<sup>th</sup> thoracic vertebrae and above the crease of the buttocks) of at least 6 months duration who were appropriate candidates for around the clock opioid treatment as management of CLBP and who met 1 of the following criteria:

- Currently taking therapeutic doses of at least 1 non-opioid analgesic for at least 30 days prior to Screening, OR
- Currently taking an opioid (single or combination product) with a daily morphine sulfate equivalence of  $\leq 20$  mg/day on a PRN or regular basis for at least 30 days prior to Screening.

Subjects who met these criteria entered an analgesic washout period of 2 to 21 days. They were enrolled into the study and entered the 2-week OL Titration Period if they continued to meet entry criteria, including the following OL Baseline Visit pain criteria:

- Subject's Assessment of Chronic Low Back Pain Intensity as determined by visual analog scale (VAS) was  $\geq 40$  mm.
- Subject's Assessment of Chronic Low Back Pain Intensity (VAS) had increased by at least 10 mm as compared to the assessment performed at the Screening Visit. For those subjects whose screening VAS was  $\geq 85$  mm, a VAS of  $\geq 85$  mm must have been maintained at the OL Baseline Visit.
- Subject's Global Assessment of Back Pain Status was Fair, Poor, or Very Poor.



<p><b>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</b> Hydrocodone/acetaminophen extended release 10 mg/650 mg, 1 oral tablet, lot numbers [REDACTED] [REDACTED] Hydrocodone/acetaminophen extended release 5 mg/325 mg, 1 oral tablet, lot numbers [REDACTED] [REDACTED]</p>
<p><b>Duration of Treatment:</b> Approximately 4 weeks</p>
<p><b>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</b> Placebo for hydrocodone acetaminophen, 1 oral tablet, lot numbers [REDACTED]</p>
<p><b>Criteria for Evaluation</b> <span style="float: right;">redacted information 24Sep2014</span> <b>Efficacy:</b> Efficacy was assessed by determinations of pain intensity (100 mm VAS: 0 mm = no pain and 100 mm = worst pain imaginable), time to premature discontinuation due to lack of efficacy during the DB Maintenance Period, Subject's Global Assessment of Study Drug (excellent, very good, good, fair, poor), Subject Global Assessment of Back Pain Status (very good, good, fair, poor, very poor), and protocol-allowed rescue medication use. <b>Pharmacokinetic:</b> Values for the pharmacokinetic parameters of hydrocodone and acetaminophen were to be estimated. <b>Safety:</b> Adverse events, laboratory data, and vital signs were assessed throughout the study. Physical examination was performed at Screening, Baseline, and during the Taper Period. A 12-lead electrocardiogram (ECG) was performed at Screening.</p>
<p><b>Statistical Methods</b> <b>Efficacy:</b> The primary efficacy variable was the change from DB Baseline to each subject's final assessment during the DB Maintenance Period, as assessed by the Subject's Assessment of Chronic Low Back Pain Intensity VAS using the DB ITT dataset. Treatment group mean differences for the primary efficacy endpoint were evaluated using ANCOVA with factors for treatment group and study center, with DB Baseline pain intensity score as a covariate. Analyses of secondary endpoints were as follows:</p> <ul style="list-style-type: none"><li>• Treatment group differences in the time to premature discontinuation due to lack of efficacy, starting from the beginning of the DB Maintenance Period, were analyzed by log rank statistics from nonparametric survival models.</li><li>• Treatment group differences in the cumulative distribution function for change and percent change from OL baseline, as well as change from DB Maintenance Baseline (immediately prior to entering the DB Maintenance Period) to final assessment using the Subject's Assessment of Chronic Low Back Pain Intensity VAS were assessed using the Monte-Carlo exact Kolmogorov-Smirnov test.</li></ul>



## **Statistical Methods (Continued)**

### **Efficacy (Continued):**

- The actual scores for the Subject's Global Assessment of Study Drug and the Subject's Global Assessment of Back Pain Status at each scheduled evaluation following randomization were analyzed using the Cochran-Mantel-Haenszel test for equal row means scores with study centers and DB Maintenance Baseline evaluation score as stratification factors in separate analyses.
- Protocol-allowed rescue medication (acetaminophen) during the OL Titration Period, as well as acetaminophen used for any reason, were summarized separately by weekly intervals (e.g., Study Days 1 through 7, 8 through 14). The proportion of subjects taking rescue medication/acetaminophen was summarized using frequencies and percentages. No statistical comparisons for rescue medication/acetaminophen use were made and missing data were not imputed.

### **Pharmacokinetic:**

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

### **Safety:**

Safety variables were summarized separately for the OL and DB periods of the study. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 14.1. All treatment-emergent adverse events (TEAEs) (i.e., those that began or worsened in severity after initiation of study drug) were summarized by system organ class (SOC) and MedDRA preferred term (PT). For the DB Maintenance Period, treatment group differences were evaluated using Fisher's exact test for the proportion of subjects reporting a particular AE. Summaries of TEAEs by severity and relationship to study drug, by MedDRA PT and SOC, were presented. Treatment-emergent AEs leading to premature discontinuation, serious adverse events (SAEs), possibly or probably drug-related TEAEs, possibly or probably drug-related TEAEs by severity, and TEAEs that met the Standardized MedDRA Query of "Drug Abuse, Dependence, and Withdrawal" also were summarized by SOC and PT.

For laboratory data, changes in continuous laboratory parameters from OL Baseline to the final OL value were summarized. For the DB Maintenance Period, changes in continuous laboratory parameters from the OL Baseline 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, changes from OL Baseline to the final OL value were summarized. For the DB Maintenance Period, changes from the OL Baseline to minimum, maximum, and final values were summarized. Vital sign results meeting the Criteria for Potentially Clinically Significant Vital Sign Findings were identified. The number and percentage of patients with at least one vital sign value that met the Criteria for Potentially Clinically Significant Vital Sign were summarized.



## Summary/Conclusions

### Efficacy Results:

Subjects who were randomized in the DB Maintenance period had a mean change in pain intensity of -52.4 from OL Baseline to end of the OL Titration Period.

For the protocol-specified primary endpoint (mean change in Subject's Assessment of CLBP Intensity by VAS from DB Baseline to Final evaluation during the DB Maintenance Period), the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group had a smaller mean increase in pain compared with the placebo treatment group; however, the difference was not statistically significant. In sensitivity analyses using: 1) the OL Baseline value for final evaluation score for randomized subjects who discontinued prematurely or who did not have any post-randomization assessments in one analysis; and 2) the maximum of each subject's last observed VAS score and the OL Baseline VAS score in another analysis, the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group was statistically significantly superior to the placebo group.

In the secondary efficacy analyses, the difference between treatment groups in time to premature discontinuation due to lack of efficacy was not statistically significant.

### Pharmacokinetic Results:

The mean  $\pm$  SD plasma concentrations of hydrocodone and acetaminophen after administration of hydrocodone/acetaminophen extended release 10 mg/650 mg are shown below. Due to the time variation in collecting each sample, there is large variability in the hydrocodone and acetaminophen concentrations at each study visit. Before subjects were randomized to the DB Maintenance Period, the mean hydrocodone and acetaminophen concentration values appeared to be similar for subjects who were later randomized to the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group and those randomized to the placebo treatment group.

Mean  $\pm$  SD Plasma Concentrations of Hydrocodone and Acetaminophen

Treatment Group	Open-Label Period	Double-Blind Maintenance Period	
	Visit 3 (Day 8 of OL Period) (N = 143)	Visit 4 (Baseline [Day 15] of DB Period) (N = 143)	Visit 5 (Day 29) (N = 134)
	<b>Hydrocodone (ng/mL)</b>		
Hydrocodone/ Acetaminophen Extended Release 10 mg/650 mg <sup>a</sup>	12.2 $\pm$ 8.17	18.3 $\pm$ 12.6	12.6 $\pm$ 10.8
Placebo <sup>b</sup>	12.9 $\pm$ 9.54	16.6 $\pm$ 11.2	--
	<b>Acetaminophen (ng/mL)</b>		
Hydrocodone/ Acetaminophen Extended Release 10 mg/650 mg <sup>a</sup>	2527 $\pm$ 2107	3479 $\pm$ 2869	2316 $\pm$ 2045
Placebo <sup>b</sup>	2324 $\pm$ 1803	2959 $\pm$ 2172	--

a. N = 97 for Visits 3 and 4; N = 92 for Visit 5.

b. N = 46 for Visits 3 and 4; N = 42 for Visit 5.



## Summary/Conclusions (Continued)

### Safety Results:

Of the 168 subjects who received at least 1 dose of study drug during the OL Titration Period, 50.6% (85/168) experienced at least 1 TEAE, including 68.2% (15/22) of nonrandomized subjects and 47.9% (70/146) of randomized subjects. Treatment-emergent AEs with onset after the start of the OL Titration Period occurring in  $\geq 5\%$  of subjects in either randomization group were constipation, nausea, dizziness, somnolence, pruritus, and headache. Of the 85 subjects who had TEAEs during the OL Titration Period, the majority had TEAEs that were mild in severity and that were assessed by the Investigator as possibly related to study drug. No deaths or other SAEs were reported during the OL Titration Period. Premature discontinuation due primarily to a TEAE was reported in 4.2% (7/168) of all subjects who received at least one dose of study drug; 31.8% (7/22) of nonrandomized subjects discontinued prematurely primarily due to a TEAE.

Of the 146 subjects who received at least 1 dose of study drug during the DB Maintenance Period, 32.9% (48/146) experienced at least 1 TEAE with onset after the start of the DB Maintenance Period, including 28.3% (28/99) of subjects in the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group and 42.6% (20/47) of subjects in the placebo group. Treatment-emergent AEs with onset after the start of the DB Maintenance Period occurring in  $\geq 5\%$  of subjects in either randomization group were nausea and headache. Of the 48 subjects who had TEAEs with onset after the start of the DB Maintenance Period, the majority had events that were mild in severity and that were assessed by the Investigator as not related or probably not related to study drug. One subject (placebo treatment group) reported an SAE of chest pain on Day 33, 1 day after the last dose of study drug (post-DB Maintenance Period). The event was severe and was assessed by the Investigator as probably not related to study drug. It was treated with medication and resolved the same day. One subject (placebo treatment group) had a TEAE that led to premature discontinuation during the DB Maintenance Period. No deaths occurred during the DB Maintenance Period.

No subject reported a TEAE that met the Standardized MedDRA Query of "Drug Abuse, Dependence, and Withdrawal."

No clinically meaningful patterns of changes over time or incidence of potentially clinically significant values were observed in clinical laboratory measurements or vital signs.

### Conclusions:

Administration of hydrocodone/acetaminophen extended release 10 mg/650 mg for treatment of moderate to moderately severe CLBP during a DB Maintenance Period following an OL Titration Period resulted in a smaller mean increase in pain compared with placebo; however, the difference was not statistically or clinically significant.

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 mean hydrocodone and acetaminophen concentrations values were similar at each study visit. Before subjects were randomized to the DB Maintenance Period, the mean hydrocodone and acetaminophen concentration values appeared to be similar for subjects who were later randomized to the hydrocodone/acetaminophen extended release 10 mg/650 mg treatment group and those randomized to the placebo treatment group.