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*APPLICATION NUMBER:*

**202880Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202880
Priority or Standard	Standard
Submit Date(s)	May 1, 2012
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Division / Office	Division of Anesthesia, Analgesia, and Addiction Products/ODE II
Reviewer Name(s)	Robert A. Levin, M.D.
Review Completion Date	January 15, 2013
Established Name	Hydrocodone Bitartrate Extended Release Capsules
(Proposed) Trade Name	Zohydro ER
Therapeutic Class	Opioid
Applicant	Zogenix Inc
Formulation(s)	10, 15, 20, 30, 40 and 50 mg capsules
Dosing Regimen	Zohydro ER is to be administered twice daily
Indication(s)	For the management of moderate-to-severe chronic pain when a continuous,

Intended Population(s)      around-the-clock opioid  
analgesic is needed for an  
extended period of time  
Adults

Template Version: [March 6, 2009](#)

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

I recommend an Approval action for the subject of the current application, Zohydro (hydrocodone bitartrate) Extended-Release Capsules for the indication for the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time in adults. This recommendation for Approval is based on the Applicant demonstrating a positive risk-benefit profile in the intended population when used as directed, along with the inclusion of Zohydro ER in the extended-release/long-acting opioid class REMS (ER/LA REMS). FDA's Anesthetic and Analgesic Drug Products Advisory Committee due to concern about the risk of abuse and misuse and dissatisfaction with the existing risk management of the ERLA opioid class of drugs voted against approval. The committee felt that the sponsor met the current requirements for approval but the addition of Zohydro ER to this class of drugs would not serve the public health unless the class Risk Evaluation and Mitigation Strategies (REMS) program was strengthened for all extended-release opioid products, or an abuse deterrent formulation was used. In reviewing the Zohydro ER NDA, the FDA cannot use different standards than those applied to other drugs in the class, and there is not currently a regulation or Agency policy that prohibits the approval of non-abuse deterrent formulations of extended-release opioids.

Review of the clinical data submitted by the Applicant reveals evidence of efficacy of hydrocodone bitartrate extended-release (HC-ER), an opioid agonist, in the management of moderate-to-severe chronic pain in the adult population. The basis for determining clinical efficacy in this 505(b)(2) application is one principal clinical trial of 12 weeks duration in patients with chronic low back pain, using the primary endpoint of change in pain from baseline to week 12. One Phase 2 single dose study in bunionectomy surgery was reported by the Applicant to demonstrate efficacy but the Division does not consider a single dose study in an acute pain condition as adequate to demonstrate efficacy for treatment of chronic pain.

The safety profile of HC-ER is similar to that of other opioids. No unexpected safety findings were observed. Several cases of abuse and misuse occurred even in the controlled setting of a clinical trial. These cases highlight the already known risk of abuse and misuse associated with the opioid class of drugs. The ER/LA opioid analgesics REMS would be required for this product to mitigate against the potential for misuse and abuse. For a summary of potential safety issues the reader is referred to Section 1.2.

## 1.2 Risk Benefit Assessment

### Benefit

Efficacy for this 505(b)(2) application was demonstrated in one adequate and well-controlled (i.e., randomized, double-blind, placebo-controlled) study (ZX002-0801). There was statistically significantly less pain at 12 weeks in subjects with moderate-to-severe chronic low back pain (CLBP) requiring continuous around-the-clock opioid treatment for an extended period of time. Efficacy was also supported by secondary endpoints including a cumulative responder analysis, subjective global assessment of medication, worst pain intensity and least pain intensity.

While a second efficacy study was not required by the Agency for this application, the Applicant submitted one Phase 2 study (ELN-154088-201), a randomized, single-dose, placebo-controlled, active comparator study in bunionectomy surgery. However, the decision for approving this product was not based on efficacy findings from this study since it was not appropriately designed to demonstrate efficacy for the treatment of chronic pain (i.e., single-dose study in an acute pain model). Therefore the efficacy findings from this study were not reviewed by the FDA statistician. However, the findings as reported by the Applicant for the primary efficacy endpoint, Sum of Pain Intensity Differences (SPID) for the Visual Analog Scale of Pain Intensity (VASPI) for 0 to 12 hours, for HC-ER 40 mg was statistically significantly better than placebo. None of the lower doses of HC-ER were superior to placebo.

### *Summary of Benefit*

The Applicant has demonstrated efficacy for HC-ER for the treatment of moderate-to-severe CLBP requiring continuous around-the-clock opioid treatment for an extended period of time.

### Risk

The HC-ER development program provided adequate exposure to assess safety with a total of 1512 subjects exposed to at least one dose of HC-ER regardless of phase and a total of 332 subjects exposed for greater than or equal to six months and 290 subjects exposed for greater than or equal to one year. There were four deaths reported during the development program and one additional death reported over one year after the end of the study due to an apparent suicide from an overdose. This individual who had participated in the long-term open-label safety study of Zohydro ER (Study ZX002-0802), hoarded at least 40 capsules of the drug, and then opened and ingested all the medication approximately one year after the end of the study. The other four deaths reported in the submission did not appear to be related to HC-ER and occurred in the open-label safety study.

Potential serious or unique safety issues for HC-ER are summarized below. The most serious concern is potential abuse and misuse. If approved, Zohydro ER would be under the ER/LA opioid analgesics REMS as required for all opioids in this class in order to mitigate risk to an acceptable level for approval.

#### Abuse

There is significant concern related to the abuse potential of this product, which is expected to be similar to other marketed, non-abuse deterrent formulations of extended-release opioids. It is noted that in the controlled setting of a clinical study several subjects were found to abuse HC-ER. It is likely that in a clinical setting where subject screening and monitoring is less rigorous the abuse will be even greater. One subject hoarded 40 capsules of the drug which he later intentionally consumed at one time in a suicide.

#### Hearing Loss

Since progressive hearing loss has been associated with the abuse of hydrocodone/acetaminophen combination products, and the potential exposure to hydrocodone from this product is higher than the labeled doses from combination products, the FDA requested that Zogenix perform audiometry assessments to monitor for potential hearing loss. Results of the audiometry evaluations performed on 510 subjects in Study ZX002-0801 were reviewed by James Kane, Ph.D. from the Center for Devices and Radiological Health (CDRH) at the FDA. He concluded that HC-ER appears not to affect hearing sensitivity for the dosages studied (maximum HC-ER dose allowed in Study ZX002-0801 was 200 mg per day).

#### Alcohol Interaction

In alcohol interaction Study ZX002-0901 conducted in healthy adults under naltrexone block, the mean hydrocodone C<sub>max</sub> increased approximately 2.4-fold when Zohydro was ingested concomitantly with 40% alcohol compared to the 0% alcohol treatments. The greatest increase in C<sub>max</sub> was observed at 3.9-fold in one subject. Mean hydrocodone C<sub>max</sub> value for 20% alcohol was comparable to 0% alcohol treatment. Mean hydrocodone AUC values were slightly higher for subjects receiving 40% alcohol (1017 ± 217, 900 ± 243, and 846 ± 225 ng.h/mL in 40, 20 and 0% alcohol in fasted state, respectively). The greatest increase in AUC was observed at 1.7-fold in one subject.

This study demonstrated that C<sub>max</sub> for Zohydro ER was affected by co-ingestion with 40% alcohol in the fasted state. However, the greatest individual increase in C<sub>max</sub> was comparable or lower than those of already approved extended-release opioid products (maximum individual C<sub>max</sub> ratio with 40% alcohol for Exalgo 1.5, Zohydro ER 3.9, Nucynta ER (100 mg) 4.4, Nucynta ER (250 mg) 2.7 and Embeda 5.0). Therefore, the alcohol interaction with the proposed product is not considered as an approvability issue. Warning language on risks with alcohol consumption will be included in the label.

### Discussion of Risks

The risks of opioid use associated with HC-ER are well known for the opioid class of drugs. One of the major safety concerns for this product is the risk for misuse, abuse and addiction. This product will provide large doses of hydrocodone, a product that potentially may be abused, in a non abuse-resistant formulation. Currently hydrocodone is available in limited doses only as combination products that contain acetaminophen or ibuprofen. The number of hydrocodone/acetaminophen tablets that can be taken safely at any one time is limited by acetaminophen toxicity. There is no upper limit to the amount of HC-ER that can be taken since the product does not contain any acetaminophen. However, this risk of misuse, abuse and addiction will be mitigated by requiring the ER/LA opioid analgesics REMS for this product if approved.

### Risk Benefit Analysis

From the data submitted by the Applicant, there is a positive benefit to risk assessment in the intended population for HC-ER for the treatment of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. As previously discussed, the ER/LA opioid analgesics REMS would be required for this product to ensure safe use in the target population and mitigate against the potential for misuse and abuse.

## **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

Zohydro ER as a member of the ER/LA opioid class of drugs, if approved, would be required to be under the ER/LA opioid analgesics REMS.

## **1.4 Recommendations for Postmarket Requirements and Commitments**

Nonclinical carcinogenicity studies are underway and submission of the final results will be required as a Postmarket Requirement.

The Applicant will have to fulfill the requirements of the Pediatric Research Equity Act. The Applicant is requesting a waiver for studies in pediatric patients under the age of 7 years, and deferral of a pharmacokinetic and safety study in pediatric patients ages 7 to 12 years, both of which are acceptable. However, the Applicant is also proposing to

(b) (4)

has been reviewed by the clinical pharmacology team and has been found unacceptable. The Applicant may use (b) (4)

However, they will still need to obtain adequate PK data in this age group to confirm it.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Hydrocodone is a semi-synthetic opioid approved as an analgesic and antitussive agent. Hydrocodone Bitartrate Extended-Release (HC-ER) is an extended-release formulation of hydrocodone intended for the treatment of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. HC-ER capsules contain a blend of immediate release (IR) beads and sustained release (SR) beads of HC (20% IR beads and 80% SR beads).

**Trade Name (established name):** Zohydro (hydrocodone bitartrate) Extended-Release Capsules

#### **Indication**

##### **Approved Indications**

Hydrocodone combination products are approved for use as analgesics and cough suppressants.

##### **Proposed Indication**

Zohydro Extended Release Capsules are indicated for the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 summarizes the currently available treatments for the management of chronic pain.

**Table 1: Available Treatments for Chronic Pain**

Product	Route of Administration	Advantages	Disadvantages
NSAIDs	Oral	<ul style="list-style-type: none"> <li>• Anti-inflammatory activity</li> <li>• No respiratory depression</li> <li>• No effect on gastric emptying</li> </ul>	<ul style="list-style-type: none"> <li>• Increased bleeding due to platelet inhibition</li> <li>• GI damage</li> <li>• Renal Impairment</li> <li>• Poor bone or wound healing</li> <li>• Not as effective for severe pain</li> </ul>
Acetaminophen	Oral	<ul style="list-style-type: none"> <li>• No respiratory depression</li> <li>• No effect on gastric emptying</li> <li>• No effect on platelet aggregation</li> </ul>	<ul style="list-style-type: none"> <li>• No anti-inflammatory activity</li> <li>• Possible hepatic impairment from overdose</li> <li>• Not as effective for severe pain</li> </ul>
Opioids	Oral	<ul style="list-style-type: none"> <li>• Effective for severe pain</li> <li>• With epidural or intrathecal use the opioid dose can be reduced.</li> </ul>	<ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Respiratory depression</li> <li>• Nausea and vomiting</li> <li>• Delayed gastric emptying and small bowel transit time</li> <li>• With epidural/ intrathecal use:               <ul style="list-style-type: none"> <li>- Epidural hematoma or Abscess</li> <li>- Nerve injury</li> </ul> </li> <li>• Abuse, misuse, addiction</li> </ul>
	Transdermal		
	Intramuscular		
	Subcutaneous		
	Intravenous		
	Sublingual		
	Patient Controlled Analgesia (PCA)		
Epidural or intrathecal			
Local Anesthetics (Regional and local analgesia)	Wound infiltration	<ul style="list-style-type: none"> <li>• Postoperative pain</li> <li>• Not effective for chronic pain</li> </ul>	
	Nerve and plexus blocks	<ul style="list-style-type: none"> <li>• Effective for severe pain in a peripheral nerve of nerve root distribution</li> </ul>	<ul style="list-style-type: none"> <li>• Nerve injury</li> </ul>
	Epidural or Intrathecal	<ul style="list-style-type: none"> <li>• Effective for severe pain</li> </ul>	<ul style="list-style-type: none"> <li>• Epidural hematoma/ abscess</li> <li>• Nerve injury</li> </ul>

### 2.3 Availability of Proposed Active Ingredient in the United States

Hydrocodone is a semi-synthetic opioid that has been utilized as an antitussive agent and analgesic since the 1920s. When the Controlled Substances Act (CSA) was enacted in 1971, hydrocodone was placed in Schedule II, while the products containing hydrocodone in specified amounts with one or more therapeutically active non-narcotic ingredients were placed in Schedule III. Specifically, Schedule III controls apply to hydrocodone combination products containing no more than 300 milligrams per 100

milliliters or not more than 15 milligrams of hydrocodone base per dosage unit, with one or more active non-narcotic ingredients in recognized therapeutic amounts. These combination products include marketed and approved analgesic and cough suppressant products. Although not currently available on the market, any product containing single entity hydrocodone would be listed in Schedule II.

Today, hydrocodone products are increasingly utilized for pain management and are the most frequently dispensed opioid pharmaceuticals in the United States. During the year 2011, approximately 136 million prescriptions were dispensed for products containing hydrocodone of which approximately 131 million (96%) were dispensed for hydrocodone analgesic combinations and 5 million (4%) for hydrocodone cough and cold products. Cough suppressant products are marketed containing hydrocodone in combination with the following active ingredients: chlorpheniramine, pseudoephedrine, or homatropine. Numerous combination analgesic products containing hydrocodone and a non-opioid analgesic (e.g., acetaminophen or ibuprofen) exist on the market today. The current combination hydrocodone and acetaminophen analgesic products are limited to a maximum total daily dose of 60 mg of hydrocodone, determined by the dose limiting toxicity associated with the acetaminophen, and not the hydrocodone entity.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Approved opioids including hydrocodone are all associated with the potentially serious safety issues of respiratory depression leading to coma and death, misuse, abuse and addiction. Opioids can also result in a hypotensive effect, constipation, nausea, vomiting, somnolence and alterations in levels of consciousness.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2 displays highlights of the regulatory activity that occurred during the clinical development program for HC-ER.

<b>Table 2: Regulatory Interactions between the FDA and the Applicant</b>	
<b>Date</b>	<b>Topics</b>
June 26, 2002 IND 65111 opened	<ul style="list-style-type: none"><li>• Development program for hydrocodone bitartrate extended-release capsules initiated under this IND by Elan Pharmaceuticals</li></ul>
January 31, 2008 Transfer of sponsorship	<ul style="list-style-type: none"><li>• IND transferred from Elan to Zogenix effective this date</li></ul>

<b>Table 2: Regulatory Interactions between the FDA and the Applicant</b>	
June 4, 2008 Type B Meeting	<p>The Division made the following comments to the Applicant during this meeting:</p> <ul style="list-style-type: none"> <li>• The proposed safety database is acceptable for a 505(b)(2) application.</li> <li>• For a 505(b)(2) submission one study would be acceptable with a single population because this drug is well-known.</li> <li>• The completed Phase 2 trials cannot support a finding of efficacy for an NDA. Study 201, a single-dose trial, does not establish efficacy in a chronic setting. Study 203 was an OL trial with no comparator, and can therefore not establish efficacy.</li> <li>• An enrichment design with a randomized withdrawal is an acceptable study design.</li> <li>• Conversion using the proposed ratios directly to the comparable dose of HC-CR may result in too high an initial dose of HC-CR. Once the morphine equivalents of the patient's prior opioid are calculated, the dose should be cut in half and then converted to HC-CR.</li> <li>• Mean change from baseline to Week 12 in Treatment Phase in the average 24-hr pain intensity rating may be used as the primary endpoint.</li> <li>• The timing and the use of the COWS and SOWS assessments are adequate.</li> <li>• A comprehensive REMS package must be submitted with the NDA application. A Medication Guide will also be needed for this application.</li> <li>• Since progressive hearing loss has been associated with the abuse of hydrocodone/APAP combination products, and the potential exposure to hydrocodone from this product is higher than the labeled doses from combination products, hearing must be monitored during proposed Phase 3 trials.</li> <li>• A pediatric plan must be submitted for review</li> </ul>
September 23, 2010 Advice Letter	<p>The Division made the following comments to the Applicant:</p> <ul style="list-style-type: none"> <li>• Regarding audiology assessment, at-risk subjects should receive baseline evaluations that are as complete as possible.</li> <li>• Monitoring tests should be scheduled at intervals that will enable the earliest possible detection (within reason) of cochleotoxic effects.</li> <li>• A thorough assessment of your data from Study 801 will be</li> </ul>

<b>Table 2: Regulatory Interactions between the FDA and the Applicant</b>	
	<p>necessary in order to determine whether additional (audiology) testing is necessary.</p> <p>When converting the study subjects to HC-ER, after the initial calculation of the daily opioid dose, the subject should be placed on 50%, of the daily opioid requirement, not at 20-30 % less than the previous opioid dose, as noted in the protocol to better account for the possibility of incomplete cross tolerance.</p>
February 17, 2011 Advice Letter	<p>The Division made the following comments to the Applicant:</p> <ul style="list-style-type: none"> <li>• We have reviewed the preliminary results of the Phase 1 pharmacokinetics study that evaluated the effect of co-ingestion of alcohol with HC-CR, and have determined that the findings do not preclude continuing development of HC-CR in Phase 3 trials. During these trials, study subjects must be informed regarding the potential for an alcohol interaction and advised to abstain from alcoholic beverages and alcohol containing medications during the trial.</li> <li>• Upon review of your NDA, if the risk and benefit balance favors approval, the results of the alcohol interaction studies will be included in appropriate sections of the label, along with appropriate Boxed Warning and contraindication regarding the ingestion of alcohol or alcohol containing medication while taking HC-CR.</li> </ul>
November 17, 2011 Pre-NDA Meeting	<p>The Division made the following comments to the Applicant during the Pre-NDA meeting:</p> <ul style="list-style-type: none"> <li>• Based on the information submitted, your nonclinical development plan appears to be adequate to support filing of your NDA. However, final determination of the adequacy of the data cannot be determined until formal review of the NDA.</li> <li>• We note that you wish to file a 505(b)(2) application with (b)(4) as the reference product. A 505(b)(2) application may only rely upon the Agency's previous finding of safety and effectiveness of a drug approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act (i.e., NDAs). As the (b)(4) ANDA was approved under section 505(j) (i.e., ANDAs, generics) there is no Agency previous finding of safety and effectiveness to rely upon.</li> <li>• You must select an approved NDA product listed in the Orange Book as your 505(b)(2) reference and conduct a relative bioavailability study with this product as a scientific</li> </ul>

<b>Table 2: Regulatory Interactions between the FDA and the Applicant</b>	
	<p>bridge to the Agency's prior findings of safety and efficacy for that product.</p> <ul style="list-style-type: none"> <li>• CDRH has reviewed the audiology safety assessments performed in Study ZX002-0801 for monitoring the potential ototoxic effects of HC-ER and has determined that the audiological safety monitoring appears to have been adequate.</li> <li>• Study ZX002-0801, a Phase 3 randomized, double-blind, placebo-controlled efficacy, tolerability and safety study, with the primary endpoint of average NRS from baseline to Day 85 of HC-ER in opioid-experienced patients for a 12-week duration, appears adequately designed to support filing of the NDA.</li> <li>• Pediatric Comments:             <ul style="list-style-type: none"> <li>○ For opioid analgesics indicated for the treatment of chronic pain, the pediatric requirements include PK and safety studies in patients ages 7 to 17 years.</li> <li>○ Efficacy findings in adults may be extrapolated to the pediatric age group over 7 years of age, since the underlying painful conditions and mechanism of action of the opioid class of drugs are similar in adults and pediatric patients in this age group.</li> <li>○ Studies in pediatric patients under the age of 7 years may be waived with acceptable justification, e.g., a small population of pediatric patients in this age group with chronic pain requiring treatment with around-the-clock opioids.</li> <li>○ According to PREA, you are required to develop an age appropriate formulation. If you cannot achieve this, submit documentation regarding your attempts at formulation development.</li> </ul> </li> <li>• The class-wide ER/LA Opioid REMS is anticipated to be approved in early 2012. If approved, it is expected that your product, HC-ER, will be approved with the class-wide ER/LA Opioid REMS program.</li> </ul>
May 1, 2012 NDA Submission	<ul style="list-style-type: none"> <li>• NDA submitted under 505(b)(2) regulatory pathway</li> </ul>

## **2.6 Other Relevant Background Information**

None

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

This NDA was submitted in Electronic Common Technical Document (eCTD) format. All sections/modules were completed appropriately. The submission was reasonably well-organized and paginated to allow for an acceptable review.

### **3.2 Compliance with Good Clinical Practices**

Principal efficacy Study ZX002-0801 was conducted in accordance with Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. Each subject gave informed consent before any study specific procedures were performed.

The Office of Scientific Investigations (OSI) inspected two sites for Study ZX002-0801. The clinical investigator sites chosen for inspection, Site #136 (George S. Walker, MD) and Site #112 (Raymond Tidman, MD) were amongst the highest enrolling centers. In addition, Dr. Tidman, the investigator for Site #112, had a prior Official Action Indicated (OAI) from 2003.

The final inspection report from OSI has not been completed as of the date of this review but the inspections at both sites were reported preliminarily by OSI to have gone well without any issues identified.

### **3.3 Financial Disclosures**

Zogenix, Inc has adequately disclosed financial arrangements with clinical investigators. The Applicant has submitted Debarment Certification and FDA form 3454 certifying that the clinical investigators who supervised Studies in support of this application:

- Did not participate in any financial arrangement with the sponsor, whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study [as defined in 21 CFR 54.2(a)];
- Had no proprietary interest in this product or significant equity interest in the sponsor [as defined in 21 CFR 54.2(b)]; and
- Was not the recipient of significant payments of other sorts [as defined in 21 CFR 54.2(f)]

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

*A detailed discussion of the chemistry issues by Dr. Yong Hu, the chemistry reviewer, is contained in the CMC section.*

From a chemistry, manufacturing and controls (CMC) perspective, there are no outstanding issues impacting on the decision whether to approve this product.

#### Drug Product

Hydrocodone Bitartrate Extended Release (HC-ER) Capsules are an extended-release capsule formulation which uses Alkermes SODAS (Speroidal Oral Drug Absorption System) drug delivery technology. This technology is based on coating sugar spheres with the drug substance and excipients to form immediate-release (IR) beads. These IR beads are then coated with rate-controlling polymers to confer sustained-release characteristics. The target in vitro dissolution rate for HC-ER is achieved by combining IR and SR beads in a defined ratio followed by encapsulation in hard gelatin capsules. Several approved drugs (Verelan, Avinza, Ritalin LA and Focalin XR) utilize SODAS technology. It should be noted that the excipient formulations of these approved products are similar to the formulation used in HC-ER, but not identical. Table 3 contains a summary of the drug product components and their functions. The capsules will be available in strengths of 10, 15, 20, 30, 40, and 50 mg HC per capsule and are intended to be dosed b.i.d.

**Table 3: Drug Product Components and Function**

Ingredient and Standard	Function
Hydrocodone Bitartrate, USP	Active
Sugar Spheres, NF (b) (4)	(b) (4)
Hypromellose (b) (4) USP	(b) (4)
Ammonio Methacrylate Copolymer (b) (4) NF, (b) (4)	Controlled Release Polymer
Silicon Dioxide, NF	(b) (4)
Talc, USP	(b) (4)

### 4.2 Clinical Microbiology

Zohydro ER is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

### 4.3 Preclinical Pharmacology/Toxicology

*A detailed discussion of the Pharmacology/Toxicology issues is contained in the review by Dr. Elizabeth Bolan, the pharmacology reviewer.*

#### *Carcinogenesis*

Rat and mouse studies are underway to evaluate the carcinogenic potential of hydrocodone. Since hydrocodone is a well known drug substance we agreed to allow these studies to be completed as post marketing requirements.

#### *Mutagenesis*

Hydrocodone bitartrate was genotoxic in an *in vitro* chromosomal aberration assay in the presence of metabolic activation. No evidence of clastogenicity was observed in this assay in the absence of metabolic activation. There was no evidence of genotoxic potential in an *in vitro* bacterial reverse mutation assay (*Salmonella typhimurium* and *Escherichia coli*) or in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay).

#### *Impairment of Fertility*

In a reproductive study, rats were administered once daily by oral gavage the vehicle or hydrocodone bitartrate at doses of 25, 75, and 100 mg/kg/day (equivalent to approximately 4, 12, and 16 times an adult human dose of 80 mg/day, on a mg/m<sup>2</sup> basis). Male and female rats were dosed before cohabitation (up to 28 days), during the cohabitation and until gestation day 7 (females) or necropsy (males; 2-3 weeks post-cohabitation). Hydrocodone bitartrate did not affect reproductive function in males. No NOAEL was established for female fertility parameters in the rat fertility study. Doses of 25 mg/kg/day and greater in females significantly reduced the rate at which females became pregnant which correlated with suppression of estrous cyclicity, thought to be due to increases in prolactin, an effect seen in rats dosed with opioids. In hydrocodone bitartrate treated rats that became pregnant, early embryonic development was unaffected. Unlike humans, prolactin plays a unique role in the estrous cycle in rats and the clinical relevance of the female rat reproductive findings are uncertain.

In rabbit, fetal body weights were significantly decreased in all treated groups. Significant increases in the number of fetal malformations including umbilical hernia and various irregularly shaped bones (ulna, femur, tibia, fibula) were observed in the highest dose group. Significant decreases in the number of ossified hyoid bodies and ossified xiphoid bones were also observed in the highest dose group. The NOAEL for teratogenic effects for this study is the mid dose, 50 mg/kg but the reductions in fetal weight were observed at all doses (no NOAEL could be established for developmental effects).

In the peri- and post-natal study, significant increases in the number of stillborn pups, dams with stillborn pups, and number of pups dying within a week after birth were seen

in the 10 and 25 mg/kg groups. Significant reductions in the number of liveborn pups as well as viability and lactation indices were seen in the 10 and 25 mg/kg groups. The NOAEL for peri- and postnatal toxicity is the lowest dose tested, 5 mg/kg.

#### **4.4 Clinical Pharmacology**

*A detailed discussion of the clinical pharmacology issues is contained in the review by Dr. David Lee, the pharmacology reviewer.*

##### **4.4.1 Mechanism of Action**

Hydrocodone is a semi-synthetic opioid agonist with multiple actions qualitatively similar to those of other opioids such as fentanyl, methadone, morphine, oxycodone, and oxymorphone. Most of these actions involve the CNS and smooth muscle. The precise mechanism of action of hydrocodone and other opioids is not known, although it is believed to relate to the existence of opioid receptors in the CNS and elsewhere. There is convincing evidence for three major classes of opioid receptors in the CNS ( $\mu$  [ $\mu$ ],  $\kappa$  [ $\kappa$ ] and  $\delta$  [ $\delta$ ] receptors). Opioids produce their analgesic effects on the CNS mainly through  $\mu$  receptors. The analgesia, as well as the euphorant, respiratory depressant and physiologic dependence properties of  $\mu$  agonist opioids like hydrocodone, result principally from agonist action at the  $\mu$  receptors.

##### **4.4.2 Pharmacodynamics**

###### Central Nervous System

The principal therapeutic action of hydrocodone is analgesia. In common with other opioids, hydrocodone causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation. Opioids depress the cough reflex by direct effect on the cough center in the medulla.

Hydrocodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations. Other therapeutic effects of hydrocodone include anxiolysis, euphoria and feeling of relaxation.

In addition to analgesia, the widely diverse effects of hydrocodone include drowsiness, changes in mood, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system.

###### Gastrointestinal Tract and Other Smooth Muscle

Hydrocodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

#### Cardiovascular System

Hydrocodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

#### Endocrine System

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

#### Immune System

In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

#### Concentration—Efficacy Relationships

The minimum effective plasma concentration of hydrocodone for analgesia varies widely among patients, especially among patients who have been previously treated with agonist opioids. As a result, individually titrate patients to achieve a balance between therapeutic and adverse effects. The minimum effective analgesic concentration of hydrocodone for any individual patient may increase over time due to an increase in pain, progression of disease, development of a new pain syndrome and/or potential development of analgesic tolerance.

#### Concentration—Adverse Experience Relationships

There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression.

As with all opioids, the dose of Zohydro ER must be individualized. The effective analgesic dose for some patients will be too high to be tolerated by other patients.

#### 4.4.3 Pharmacokinetics

As compared to immediate-release hydrocodone combination products, Zohydro ER at similar daily doses results in similar overall exposure but with lower maximum concentrations. The half-life is also longer due the prolonged duration of absorption. Based on the half-life of hydrocodone, steady-state should be obtained after 3 days of dosing. Following 7 days of dosing, AUC and C<sub>max</sub> increase approximately two-fold as compared to the first day of dosing. The pharmacokinetics of Zohydro ER has been shown to be independent of dose up to a dose of 50 mg.

##### Absorption

Zohydro ER capsules exhibit peak plasma concentrations occurring approximately 5 hours after dose administration.

##### Food Effects

Food has no significant effect on the extent of absorption of hydrocodone from Zohydro ER. Although there was no evidence of dose dumping associated with this formulation under fasted and fed conditions, peak plasma concentration of hydrocodone increased by 27% when a Zohydro ER 20 mg capsule was administered with a high-fat meal.

##### Distribution

Although the extent of protein binding of hydrocodone in human plasma has not been definitely determined, structural similarities to related opioid analgesics suggest that hydrocodone is not extensively protein bound. As most agents in the 5-ring morphinan group of semi-synthetic opioids bind plasma protein to a similar degree (range 19% [hydromorphone] to 45% [oxycodone]), hydrocodone is expected to fall within this range.

##### Metabolism

Hydrocodone exhibits a complex pattern of metabolism, including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6- $\alpha$ - and 6- $\beta$ -hydroxy metabolites. Hydromorphone, a potent opioid, is formed from the O-demethylation of hydrocodone and contributes to the total analgesic effect of hydrocodone. The O- and N-demethylation processes are mediated by separate P-450 isoenzymes: CYP2D6 and CYP3A4, respectively.

Published in vitro studies have shown that N-demethylation of hydrocodone to form norhydrocodone can be attributed to CYP3A4 while O-demethylation of hydrocodone to hydromorphone is predominantly catalyzed by CYP2D6 and to a lesser extent by an unknown low affinity CYP enzyme.

##### Excretion

Hydrocodone and its metabolites are eliminated primarily in the kidneys, with a mean apparent plasma half-life after Zohydro ER administration of approximately 8 hours.

### Interactions with Alcohol

In alcohol interaction Study ZX002-0901 conducted in healthy adults under naltrexone block, the rate of absorption of Zohydro ER 50 mg was affected by co-administration with 40% alcohol in the fasted state, as exhibited by an increase in peak hydrocodone concentrations (on average 2.4-fold increase with maximum increase of 3.9-fold in one subject) and a decrease in the time to peak concentrations. The extent of absorption was increased on average 1.2-fold with a maximum increase of 1.7-fold in one subject with 40% alcohol.

This study demonstrated that C<sub>max</sub> for Zohydro ER was affected by co-ingestion with 40% alcohol in the fasted state. However, the greatest individual increase in C<sub>max</sub> was comparable or lower than those of already approved extended-release opioid products (maximum individual C<sub>max</sub> ratio with 40% alcohol for Exalgo 1.5, Zohydro ER 3.9, Nucynta ER (100 mg) 4.4, Nucynta ER (250 mg) 2.7 and Embeda 5.0). Therefore, the alcohol interaction with the proposed product is not considered as an approvability issue. Warning language on risks with alcohol consumption is proposed in the label.

### Special Populations

#### *Elderly (≥ 65 years)*

No significant pharmacokinetic differences by age was observed based on population pharmacokinetic analysis.

#### *Gender*

No significant pharmacokinetic differences by gender were observed based on population pharmacokinetic analysis.

#### *Hepatic Impairment*

After a single dose of 20 mg HC-ER in 20 patients with mild to moderate hepatic impairment based on Child-Pugh classifications, mean hydrocodone C<sub>max</sub> values were 25 ± 5, 24 ± 5, and 22 ± 3.3 ng/mL for moderate and mild impairment, and, normal subjects, respectively. Mean hydrocodone AUC values were 509 ± 157, 440 ± 124, and 391 ± 74 ng/mL for moderate and mild impairment, and, normal subjects, respectively. Hydrocodone C<sub>max</sub> values were 8-10% higher in patients with hepatic impairment while AUC values were 10% and 26% higher in patients with mild and moderate hepatic impairment, respectively. Severely impaired subjects were not studied.

#### *Renal Impairment*

After a single dose of 20 mg HC-ER in 28 patients with mild, moderate, or severe renal impairment based on Cockcroft-Gault criteria, mean hydrocodone C<sub>max</sub> values were 26 ± 6.0, 28 ± 7.5, 21 ± 5.1 and 19 ± 4.4 ng/mL for severe, moderate, mild renal impairment, and, normal subjects, respectively. Mean hydrocodone AUC values were 487 ± 123, 547 ± 184, 391 ± 122 and 343 ± 105 ng.h/mL for severe, moderate, mild renal impairment, and, normal subjects, respectively. Hydrocodone C<sub>max</sub> values were

15%, 48%, and 41% higher and AUC values were 15%, 57% and 44% higher in patients with mild, moderate and severe renal impairment, respectively.

#### Drug-Drug Interactions

While comprehensive PK drug-drug interaction studies (other than alcohol) have not been performed in humans receiving hydrocodone, published in vitro and human PK studies indicate that conversion of hydrocodone to its primary metabolites, norhydrocodone and hydromorphone, is mediated by the cytochrome p450 enzyme system. N-demethylation of hydrocodone to form norhydrocodone is attributed to CYP3A4 and O-demethylation of hydrocodone to hydromorphone is predominantly catalyzed by CYP2D6 and to a lesser extent by an unknown low affinity CYP enzyme. Inhibition of CYP3A4 and 2D6 due to interacting drugs could alter the metabolic profile of hydrocodone causing a slowing of hydrocodone clearance, and lead to elevated hydrocodone concentrations and effects which could be more pronounced with concomitant use of cytochrome P-450, 2D6 and 3A4 inhibitors.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

The HC-ER clinical development program for the treatment of moderate to severe chronic pain includes 10 clinical studies: 6 Phase 1 studies (Table 4), 2 Phase 2 studies and 2 Phase 3 studies (Table 5). One Phase 1 study (ZX002-1102), a study to evaluate the pharmacokinetics and bioequivalence of hydrocodone bitartrate extended-release 30 mg capsules when compared to Vicoprofen (7.5 mg hydrocodone bitartrate/200 mg ibuprofen) tablets, was submitted after the initial submission, on July 27, 2012.

<b>Table 4: Phase 1 Studies</b>		
<b>Study</b>	<b>Description</b>	<b>Number of Subjects/ Dosage Regimen</b>
<b>ELN-901001</b>	PK/BE study in healthy subjects to assess the bioavailability of hydrocodone from hydrocodone bitartrate formulations relative to Vicodin HP® tablet	18 healthy adult subjects Single oral dose of 20 mg hydrocodone bitartrate Active comparator: 2 doses of Vicodin HP (10 mg HC/660 mg acetaminophen)
<b>ELN-302002</b>	PK/BA study in healthy adult subjects to assess the rate and extent of the absorption of hydrocodone from a 20 mg hydrocodone bitartrate capsule in both fed and fasted states	12 healthy adult subjects Single oral dose of 20 mg HC-ER dosed in both the fed and fasted states

<b>ZX002-0901</b>	PK/PD study in healthy adult subjects to determine the influence of co-ingestion of alcohol on the safety, pharmacokinetics, and relative bioavailability of HC-ER	30 healthy adult subjects Single oral dose of 50 mg HC-ER capsules given with 0%, 20%, and 40% alcohol
<b>ZX002-1001</b>	PK study in healthy adults and adults with mild and moderate hepatic impairment to determine the influence of hepatic impairment on the PK and relative bioavailability of hydrocodone and its metabolites following administration of HC-ER 20 mg under fasted conditions	30 subjects: <ul style="list-style-type: none"> <li>• 10 healthy</li> <li>• 10 mild hepatic impairment</li> <li>• 10 moderate hepatic impairment</li> </ul> Single oral dose of 20 mg HC-ER
<b>ZX002-1002</b>	PK study in healthy adults and adults with mild, moderate and severe renal impairment to determine the influence of renal impairment on the PK and relative bioavailability of hydrocodone and its metabolites following administration of HC-ER 20 mg under fasted conditions	36 subjects: <ul style="list-style-type: none"> <li>• 9 healthy</li> <li>• 9 mild renal impairment</li> <li>• 9 moderate renal impairment</li> <li>• 9 severe renal impairment</li> </ul> Single oral dose of 20 mg HC-ER capsule
<b>ZX002-1102</b>	PK/BE study to compare the PK profile of HC after a single dose of HC-ER to two consecutive doses of Vicoprofen administered 6 hours apart, under fasted conditions	15 healthy adult subjects Single dose of 30 mg HC-ER capsule (Period 1) 2 consecutive doses of 2 Vicoprofen tablets (7.5 mg HC / 200 mg APAP) (Period 2)

**Table 5: Phase 2 and 3 Studies**

Study	Description	Number of Subjects/ Dosage Regimen
<p><b>ELN-154088-201</b> Phase 2 Study</p>	<p>Randomized, single-dose, placebo-controlled, active comparator study to establish a dose response relationship among several capsule strengths of HC-ER, to compare efficacy of HC-ER to placebo, to estimate duration of efficacy, to establish the minimum effective dose and maximum tolerated dose of HC-ER, to evaluate single-dose PK, to compare effectiveness of HC-ER to an IR HC/APAP combination product and to determine the concentration-effect relationship of HC-ER</p>	<p>241 post-operative bunionectomy surgery subjects in safety analysis (39-41 per arm)            115 subjects in PK analysis (17-21 per arm)            Single oral dose of one of the following:</p> <ul style="list-style-type: none"> <li>• 10 mg HC-ER</li> <li>• 20 mg HC-ER</li> <li>• 30 mg HC-ER</li> <li>• 40 mg HC-ER</li> <li>• 10 mg HC / 325 mg APAP</li> <li>• Placebo</li> </ul>
<p><b>ELN-154088-203</b> Phase 2 Study</p>	<p>Multiple dose, open-label dose-escalation study to assess the safety, PK, and tolerability of multiple doses of HC-ER, taken with food at steady state in subjects with chronic, moderate to severe osteoarthritis (OA) pain</p>	<p>37 OA subjects            21 days of treatment of HC-ER 10 mg, 20 mg, 30 mg or 40 mg, taken orally BID</p>
<p><b>ZX002-0801</b> Phase 3 Pivotal Study</p>	<p>Enriched enrollment, randomized withdrawal with an open-label conversion and titration phase and a randomized double-blind, placebo-controlled treatment phase in subjects with moderate to severe chronic low back pain            Study consists of: screening up to 14 days, conversion/titration up to 6 weeks, treatment up to 12 weeks and follow-up 2 weeks</p>	<p>510 subjects enrolled in the conversion/titration (C/T) phase            302 subjects enrolled in the double-blind treatment phase            HC-ER doses of 20 mg to 100 mg BID or placebo</p>
<p><b>ZX002-0802</b> Phase 3 Open-label Study</p>	<p>Open-label study with a conversion/titration phase (up to 6 weeks) followed by a treatment phase (up to 48 weeks) to evaluate the long-term safety and tolerability of HC-ER in subjects with moderate to severe chronic pain</p>	<p>638 subjects enrolled in the C/T phase            424 subjects enrolled in the treatment phase            HC-ER dosed orally BID</p>

## 5.2 Review Strategy

### **Efficacy**

Study ZX002-0801 was the principal study submitted by the Applicant to support the finding of efficacy for HC-ER for the relief of chronic pain in adults. The other studies submitted by the Applicant were not adequately designed to demonstrate efficacy of HC-ER in the treatment of chronic pain (i.e., single-dose study, acute pain model, or no control group).

### **Safety**

Zogenix's safety analyses included safety data from all studies regardless of phase. However, these studies were analyzed separately due to differences in study design and duration of treatment (i.e., single-dose study and no control group). The safety findings are reviewed and discussed in Section 7 on Safety.

## 5.3 Discussion of Individual Studies/Clinical Trials

To support efficacy for this 505(b)(2) application, the Applicant submitted Study ZX002-0801.

### 5.3.1 Study ZX002-0801

The following summary of the design of Study ZX002-0801 was derived from the revised protocol incorporating Amendment # 1 dated January 7, 2010. This amendment was enacted prior to study initiation on March 11, 2010. The original protocol was dated September 29, 2009 and was amended four times. Amendment 2 was added March 29, 2010, Amendment 3 was added June 4, 2010 and Amendment 4 was added November 18, 2010. Relevant changes to the protocol related to Amendments 2, 3 and 4 are included in italics. These protocol amendments are not considered likely to affect the interpretation of the efficacy findings.

**Title:** A randomized double-blind, placebo-controlled trial to evaluate the efficacy, tolerability and safety of Hydrocodone Bitartrate Extended-Release Capsules in opioid-experienced subjects with moderate to severe chronic low back pain

**Dates Conducted:** The study was initiated (first subject screened) March 11, 2010 and completed July 27, 2011.

### **Objectives**

The primary objective was to have been:

- To evaluate the change from Baseline to the end of the Treatment Phase (Day 85) in pain intensity as measured daily by a 0-10 Numerical Rating Scale (NRS) comparing HC-ER with Placebo

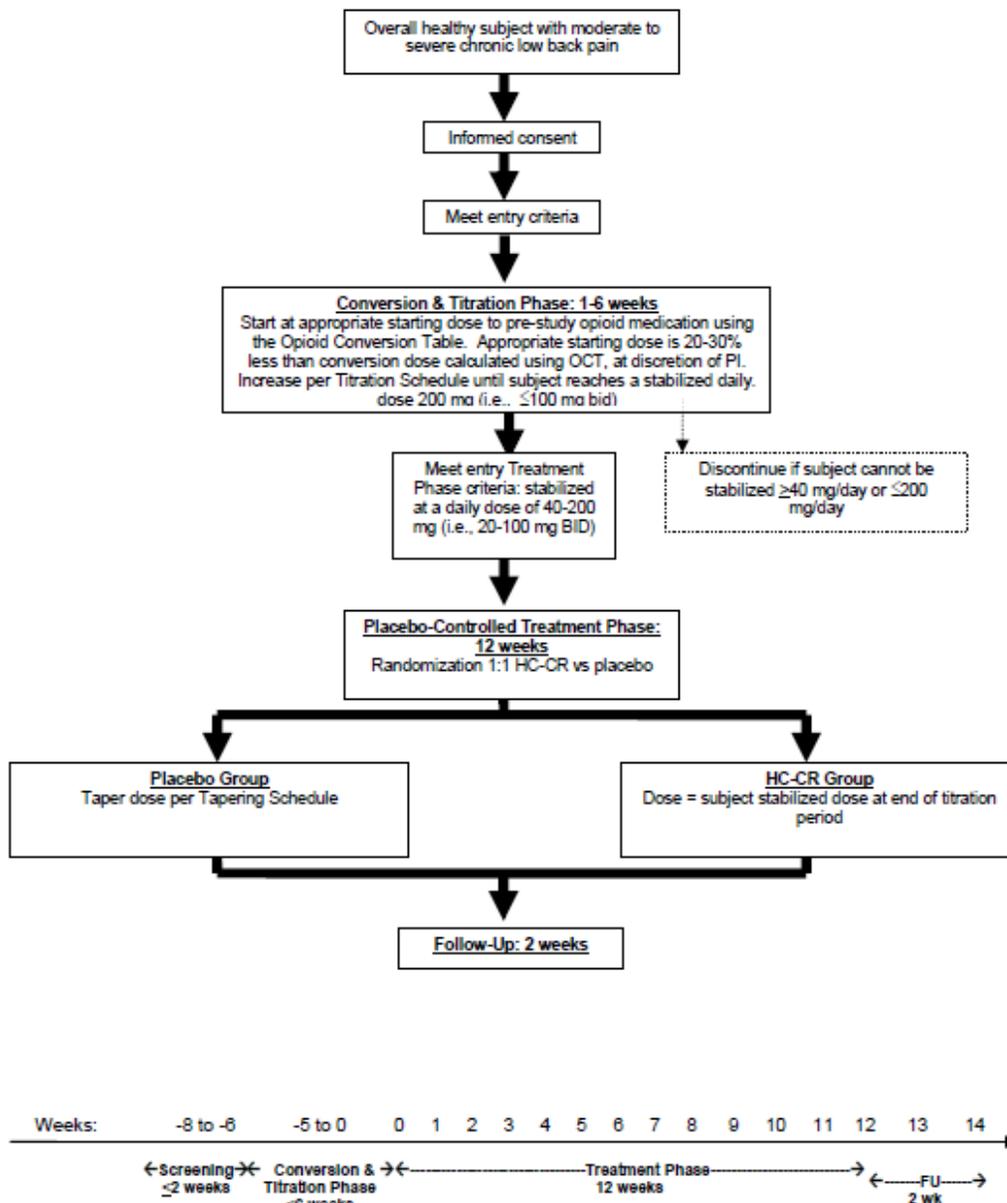
The secondary objectives were to have been:

- To evaluate the change from Baseline to Day 85 in pain intensity as measured in the clinic by a 0-10 Numeric Rating Scale (NRS)
- To evaluate the change from Baseline to Day 85 in daily “worst pain” intensity
- To evaluate the change from Baseline to Day 85 in daily “least pain” intensity
- To compare the response rate of HC-ER to Placebo as defined by the proportion of subjects with a predefined improvement (i.e., 30%, 50%) in pain intensity
- To evaluate the change from Baseline to Day 85 in rescue dose consumption
- To evaluate the therapeutic utility of HC-ER compared to Placebo based on time-to-exit for all causes, time-to-exit due to lack of efficacy, and time-to-exit due to adverse events
- To characterize the results of the Conversion and Titration period with respect to:
  - The proportion of subjects who achieve a stabilized dose
  - The distribution of times and median time to achieve a stabilized dose
  - The safety of the prespecified conversion algorithm
  - The distribution of stabilized doses
  - Pain intensity as measured from Screening to the end of the Conversion and Titration Phase in the clinic by a 0-10 NRS
- To evaluate overall satisfaction with medication
- To evaluate the change from Baseline in physical function as measured by the Oswestry Disability Inventory (ODI)
- To evaluate the impact of HC-ER compared to Placebo on mood using the Hospital Anxiety and Depression Scale (HADS)
- To evaluate the change from Baseline in back-related disability as measured by the Quebec Back Pain Disability Scale
- Safety and tolerability of HC-ER during the Conversion and Titration Phase
- Safety and tolerability of HC-ER during the Treatment Phase

Overall Design: Study ZX002-0801 was a Phase 3 multicenter, randomized, placebo-controlled study with an open-label conversion/titration (C/T) phase of HC-ER followed by a randomized double-blind treatment phase of HC-ER vs. placebo in subjects with moderate-to-severe CLBP requiring continuous, around-the-clock opioid treatment for an extended period of time. The study was to have consisted of a screening phase (up to 14 days), an open-label C/T phase (up to 6 weeks), a 12-week placebo-controlled treatment phase, and a 2-week follow-up phone call (Figure 1). The primary endpoint of the study was to have been change in pain intensity measured daily by NRS from baseline to the end of the treatment phase (Day 85) comparing HC-ER with placebo.

Eligibility criteria were to have included a clinical diagnosis of moderate-to-severe CLBP, a baseline pain score of at least 4 out of 10, pain present for at least several hours a day for a minimum of 3 months, and receiving opioid therapy for treatment of CLBP. Subjects were to have been taking opioids for at least 5 days/week for the 4 weeks prior to study entry at the equivalent of at least an average daily dose of HC 30 mg (45 mg oral morphine equivalents per day).

**Figure 1: Study Flowchart**



Note: Amendment 2 revised the number of days of the Screening Phase from (b) (4) 14 days

OCT = opioid conversion table

Source: Study Flowchart, Protocol ZX002-0801 Version 5, p. 291

**Inclusion Criteria:**

Patients were to have met all of the following criteria:

1. Male or non-pregnant, non-lactating female
2. Subjects aged 18-75 years, inclusive
3. Clinical diagnosis of moderate to severe chronic low back pain (CLBP) that must have been present for at least several hours a day for a minimum of 3 months. The pain must occur in an area with boundaries between the lowest rib and the crease of the buttocks.
4. Subjects must be classified as non-neuropathic (Class 1 and 2), neuropathic (Class 3, 4, 5 and 6), or symptomatic for more than 6 months after LBP surgery (Class 9) based on the Quebec Task Force Classification of Spinal Disorders
5. Subjects must in the Investigator's opinion qualify for around-the-clock opioid therapy for treatment of their CLBP
6. Subjects must have been taking opioids for at least 5 days/week for the past 4 weeks at the equivalent of at least an average daily dose of 30 mg hydrocodone (45 mg oral morphine equivalents per day).
7. Subjects must have an average clinic pain score  $\geq 4$  on the 11-point NRS as an average for the last 24 hours of Screening, prior to entry into the Conversion and Titration Phase. Any adjunctive therapy must have been at stable levels for at least 2 weeks.
8. Subjects must be in generally good health based upon the results of a medical history, physical examination, laboratory profile and 12-lead ECG.
9. Subjects must be able to speak, read, write and understand English.
10. Female subjects of childbearing potential must have a negative urine pregnancy test at the Screening Visit, and must use a medically acceptable method of contraception.
11. Subjects must provide written informed consent.
12. Subjects must be able to complete study procedures

**Exclusion Criteria:**

Patients were to have been excluded if any of the following applied:

1. Any clinically significant condition that would preclude study participation or increase the risk of opioid-related adverse events (e.g., respiratory depression, chronic constipation, gastroparesis, inflammatory bowel disease, or active seizure disorder).
2. Any medical condition that would compromise the subject's ability to swallow, absorb, metabolize or excrete the study drug.

3. Diagnosis of fibromyalgia, complex regional pain syndrome, neurogenic claudication due to spinal stenosis, spinal cord compression, acute nerve root compression, severe or progressive lower extremity weakness or numbness.
4. A surgical procedure for back pain within 6 months prior to the Screening Visit.
5. A nerve or plexus block, including epidural steroid injections or facet blocks, within 1 month prior to the Screening Visit or botulinum toxin injection in the lower back region within 3 months of the Screening Visit.
6. History of chemotherapy or confirmed malignancy within the past 2 years
7. Any other chronic pain condition other than CLBP that would interfere with the assessment of LBP
8. Uncontrolled blood pressure, i.e., sitting systolic blood pressure >180 mmHg or <90 mmHg, and/or a sitting diastolic blood pressure >120 mmHg or <50 mmHg at Screening.
9. Body Mass Index (BMI) > 45 kg/m<sup>2</sup>
10. HADS index score of >12 in either depression or anxiety subscales or a history of major depressive disorder that is poorly controlled with medication.
11. Clinically significant abnormality in clinical chemistry, hematology or urinalysis, including aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 times the upper limit of the reference range or a serum creatinine >2 mg/dL at Screening.
12. Workman's compensation, insurance claim or litigation related to back pain. *An active or pending workman's compensation or litigation related to back pain (i.e., primary claim is back pain). (added in Amendment 4)*
13. Allergy or hypersensitivity to opioids
14. History of clinically significant intolerance to hydrocodone
15. History of intolerance to acetaminophen
16. Have taken any investigational drug within 30 days of the Screening visit
17. Have used a monoamine oxidase inhibitor within 14 days prior to the start of study medication
18. History of any illicit substance or alcohol abuse in the past 5 years or any history of opioid abuse
19. Positive urine drug screen for illicit drugs, or non-prescribed controlled substances

### **Treatment Phase Inclusion Criteria**

For entry into the Treatment Phase subjects were to have met all of the following criteria.

1. Stabilized on at least 20 mg BID but not more than 100 mg BID of HC-ER
2. Reached a stabilized dose within 6 weeks of entry into the Conversion and Titration Phase
3. A 2 point reduction on the NRS in the average pain intensity over the last 7 days prior to the Baseline Visit compared to the Screening score

4. Tolerable side effects and be willing to stay on the medication for the duration of the study
5. Compliant with diary completion and drug accountability during the Conversion and Titration Phase
6. Average 24-hour daily Average Pain Score of  $\leq 4$  on the NRS during the last 7 days prior to the Baseline Visit

### **Study Medication**

**HC-CR:** Supplied as 10, 20, 30, 40, and 50 mg capsules; subjects to be dosed twice a day (BID), at fixed doses. Dosing for the Conversion and Titration Phase was to have been 10-100 mg BID. Dosing for the Treatment Phase was to have been 20-100 mg BID. Capsules were to have been supplied in blister packages.

**Placebo:** Matching placebo capsules dosed as the test drug BID during the Treatment Phase.

**Rescue Medication:** 5 mg hydrocodone bitartrate /500 mg acetaminophen tablets, 2 tablets BID (up to 4 tablets during the C/T phase and 2 tablets during the treatment phase)

### **Concomitant Therapy**

#### **Rescue Analgesia**

Acetaminophen was to have been allowed occasionally for headache, fever, or other indications aside from CLBP, for no more than 3 consecutive days and at a maximum daily dose of no more than 2-3 g. Total daily consumption of acetaminophen, including that contained within the rescue medication was not to have exceeded 4 g/day.

#### **Permitted Medications**

Other analgesics were to have been allowed but subjects were to have been on a stable dose for at least 2 weeks prior to enrollment. Anti-constipation medications were to have been allowed and were to have been appropriately adjusted during the study.

The following medications and therapies were to have been permitted provided they remained stable throughout the duration of the study:

- CNS depressants
- Muscle relaxants
- Sedatives
- Antidepressants
- Anticonvulsants
- Benzodiazepines
- Physical Therapy
- Biofeedback therapy

- Acupuncture therapy
- Herbal remedies

Aspirin at doses  $\leq 325$  mg/day for cardiovascular prophylaxis was to have been allowed.

**Prohibited Medications**

The following medications were to have been prohibited:

- Any opioid or non-opioid pain medication including NSAIDs, except those specified in this protocol
- Aspirin except for cardiovascular prophylaxis at dosages  $\leq 325$  mg per day
- Cough syrups containing opioids
- Monoamine oxidase inhibitors
- Another investigational drug
- Alcohol and alcohol-containing products such as over-the-counter cold preparations

**Study Procedures**

A schedule of assessments is contained in Table 6.

**Table 6: Schedule of Procedures**

	Screening	Conversion & Titration Phase			Baseline	Treatment Phase (visits <sup>a</sup> )					Follow-Up Phone Call
	Visit 1 (Day -56 to -43)	Visit 2 Day -42±1	Visits 3-7 Days -35±3, -28±3, -21±3, -14±3, -7±3		Visit 8 Day 1	Visit 9 Day 8±3	Visit 10 Day 15±3	Visit 11 Day 29±3	Visit 12 Day 57±3	Visit 13 <sup>b</sup> Day 85±3	2 weeks after Visit 13 <sup>b</sup> Day 99±3
Informed Consent	X										
Entry Criteria	X <sup>c</sup>				X <sup>d</sup>						
Medical History	X	X <sup>e</sup>									
Physical Examination	X										X
ECG	X										
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Audiometry	X				X						X
Pregnancy Test	X	X	X (Visit 6 only)	X				X	X	X	
Drug Screen	X		X (Visit 4) <sup>f</sup>								
Blood Chemistry/Hematology/Urinalysis	X <sup>g</sup>			X						X	
Randomize Subject				X <sup>h</sup>							
Subject Diary		D	C/R/D	C/R/D	C/R/D	C/R/D	C/R/D	C/R/D	C/R/D	C/R	
Study Medication (inc. rescue)		D	C/R/D	C/R/D	C/R/D	C/R/D	C/R/D	C/R/D	C/R/D	C/R	
Study Drug Administration		HC-CR titration <sup>i</sup>			HC-CR at stabilized dose or placebo						
Clinic NRS	X	X	X	X	X	X	X	X	X	X	X
Daily Diary (NRS/study medication)		←-----X-----→									
Oswestry Disability Index	X			X							X
Subject Global Assessment of Medication	X			X							X
Quebec Back Pain Disability Scale	X			X							X
Hospital Anxiety & Depression Scale	X			X							X
COWS	X			X	X	X					X <sup>g</sup>
SOWS	X			X	X	X					X <sup>g</sup>
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X <sup>h</sup>
Enroll subject in extension study (ZX002-0803), if appropriate										X	

C=collect; D=Dispense; R=Review  
 a. Each visit should be scheduled based on the Baseline Visit 8 date.  
 b. Or Early Termination Visit.  
 c. Entry criteria specific for the Conversion & Titration Phase.  
 d. Entry criteria specific for the Treatment Phase.  
 e. Update medical history with any new medical conditions noted since the Screening Visit.  
 f. Randomize subject to HC-CR or placebo (1:1 ratio) after verifying that the subject meets the entry criteria for the Treatment Phase.  
 g. Only performed in the case of early termination.  
 h. All subjects will have a follow-up phone call unless they are enrolled in the extension study (ZX002-0803).  
 i. At Screening under fasting condition.  
 j. Subjects who are stable and ready for randomization at Visit 4 or earlier will undergo urine drug screening at Baseline.

Source: Schedule of Procedures, Protocol ZX002-0801 Amendment 2, p. 76

The study was to have included an open-label Conversion and Titration Phase of HC-ER followed by a randomized double-blind Treatment Phase of HC-ER vs. placebo in subjects with moderate to severe chronic low back pain. The trial was to have consisted of a Screening Phase (up to 14 days, (b) (4) 14 days in Amendment 2), an open-label Conversion and Titration Phase (up to 6 weeks), a 12-week placebo-controlled Treatment Phase, and a 2-week Follow-Up Phone Call.

**Screening Phase:** Subjects were to have been screened for eligibility for study participation by medical history, physical exam, clinical laboratory studies, urine drug screen, pregnancy tests, audiometry and ECG. Subjects who met all eligibility criteria at the Screening visit were to have been enrolled into the open-label Conversion and Titration Phase. Subjects were to have been required to report average pain intensity over the last 24 hours of the Screening Phase (at Visit 2) of at least 4 out of 10 to enter the Conversion and Titration Phase.

**Conversion and Titration Phase (Visits 2-7):**

The Conversion and Titration Phase was to have been an open-label design and start after subjects successfully completed all Screening procedures. Subjects were to have been converted from previously used opioid medication to HC-ER using the opioid conversion table (OCT) provided in Table 7 and the calculation method outlined in Table 8. The starting dose of HC-ER was to have been approximately 20-30% less than the calculated conversion dose. Study medication was to have been increased by 20 mg (i.e., 10 mg BID) every 3 to 7 days until a stabilized dose was reached (up to a maximum daily dose of 200 mg (100 mg BID)). A stabilized dose was defined as one that subjects tolerate well for at least 7 days with an average 24-hour daily Average Pain Score of  $\leq 4$  on the NRS during the last 7 days prior to the Baseline Visit and a reduction of 2 points on the NRS compared to Screening (Visit 1), and no more than 2 doses of rescue medication on any day (i.e., no more than 2 tablets/day of hydrocodone 5 mg/acetaminophen 500 mg). Subjects were to have been permitted to take 1-2 hydrocodone 5 mg/acetaminophen 500 mg tablets every 4-6 hours as rescue medication for up to a maximum of 4 tablets per day.

**Table 7: Opioid Conversion Table to Morphine Equivalent Dose**

<b>Prior Opioid</b>	<b>Equianalgesic Oral Dosage for Chronic Use (mg)</b>	<b>Conversion Factor</b>
Morphine	30	1
Hydrocodone	20	1.5
Hydromorphone	7.5	4
Methadone	20	1.5
Oxycodone	20	1.5
Levorphanol	4	7.5
Oxymorphone	10	3
Meperidine	300	0.1
Codeine	200	0.2
Fentanyl (transdermal) (Duragesic®)*	25 ug/hr ptach	0.5
Tramadol	100	0.3
Propoxyphene	130	0.2

\*Duragesic® patch package insert = 25 µg/hr patch equivalent to 60 mg morphine/day

Reference: Katz NP, McCarberg BH, Reisner L. Managing Chronic Pain with Opioids in Primary Care. ApotheCom Associates LLC, Wakefield MA. 2007.

Reference: Appendix H: Opioid Conversion Table, Protocol ZX002-0801 Version 2, p. 125

**Table 8: Calculation to Determine Starting Dose of HC-CR**

1. Write in total daily use of all Opioids used.
2. Write in Conversion Factor for each opioid from OCT.
3. Convert to morphine equivalents by multiplying total daily dose by conversion factor.
4. Add up all total daily morphine equivalents.
5. Divide total daily morphine equivalents by 1.5 to get total daily Hydrocodone-CR dose.
6. Divide total daily Hydrocodone-CR dose by 2 to get converted BID dose.
7. Decrease converted dose of Hydrocodone-CR dose by 20-30% depending on current total daily opioid dose to get starting BID dose.

Prior Opioid	Total Daily Dose (mg)	Conversion Factor	Total Daily Oral Morphine Equivalent (mg)
Total Daily Morphine equivalents (mg) (Sum of individual Opioids)			
Total Daily Hydrocodone Equivalents (mg) (divide by 1.5; e.g. 60 mg Morphine = 40 mg Hydrocodone)			
Reduce converted HC-CR dose by approximately 20-30%, at the discretion of the investigator			
Starting dose BID (mg) (Total Dose divided by 2; e.g. 40 mg/day = 20 mg BID)			

**NOTES:**

- 1) For Duragesic<sup>®</sup> patch indicate 60 mg morphine as daily dose for 25 mg/hr patch. For other strengths use equivalent ratios.
- 2) Subjects on less than 45 mg of morphine equivalents /day (30 mg hydrocodone/day) are excluded from the study.
- 3) Subjects on 45 mg of Morphine equivalents /day (30 mg hydrocodone/day) to less than 60 mg of morphine equivalents /day (<40 mg hydrocodone/day) are to be started on 10 mg/BID HC-CR BID.

Source: Protocol ZX002-0801 Version 2, p. 126

*Amendment 2 added, "Consult the Medical Monitor before screening subjects who are on fentanyl products or other opioids not listed." The sponsor reports that this requirement was added to provide guidance to the Investigator on an appropriate conversion factor for fentanyl products.*

*Dose Escalation:* Study medication was to have been increased by 10 mg BID every 3-7 days up to a maximum dosage of 100 mg BID or until a stabilized dose had been identified.

*Dose Reduction:* Subjects were to have been allowed one optional down titration of their dose for reasons of tolerability.

*Study Termination:* Subject who could not be stabilized at a dose of  $\geq 20$  mg and  $\leq 100$  mg BID by the end of the Conversion and Titration Phase were to have been discontinued from the study.

*Rescue Medication:* During the Conversion and Titration Phase subjects were to have been allowed to take 1 to 2 hydrocodone 5 mg/acetaminophen 500 mg tablets every 4-6 hours as rescue medication for up to a maximum of 4 tablets per day.

## **Treatment Phase**

### Baseline Visit (Visit 8; Day 1)

Entry criteria were to have been reviewed to verify that subjects were stabilized at a dose of HC-ER of at least 40 mg/day ( $\geq 20$  mg BID) and not to exceed 200 mg/day ( $\leq 100$  mg BID). Subjects were to have been randomized at a ratio of 1:1 to either their fixed stabilized dose of HC-ER or a matching placebo for 12 weeks.

### Treatment Phase (Visits 9-12)

During the Treatment Phase, no change in dose was to have been permitted. The following procedures were to have been performed during the treatment visits: vital signs, pregnancy test (Visits 11 and 12 only), clinic NRS, COWS and SOWS at Visits 9 and 10 only, record AEs, collect all unused study medication and empty blister packs, dispense next assigned blister pack, dispense hydrocodone 5 mg/acetaminophen 500 mg (rescue medication) and record concomitant medications. In addition to HC-ER, subjects were to have been permitted to take a maximum of 2 doses/day of hydrocodone 5 mg/acetaminophen 500 mg tablets every 4-6 hours for rescue medication up to a maximum of 2 tablets per day.

### Day 85 of Treatment Phase (Visit 13) or Early Termination

The following procedures were to have been performed at Visit 13 or early termination: physical examination, vital signs, audiometry, pregnancy test (urine), laboratory analyses, clinic NRS, collect diary and review for completion, Oswestry Disability Inventory, Subject Global Assessment of Medication, Quebec Back Pain Disability Scale, Hospital Anxiety and Depression Scale, COWS and SOWS only for subjects who

terminate early, record concomitant medications, record AEs, collect all returned study drug and empty blister packs and complete drug accountability.

*Amendment 3 deleted,* (b) (4)

*Amendment 3 added since subjects would no longer be enrolled in the planned extension study, "Upon subject completion or discontinuation from the study, Investigators should treat subjects according to their individual institution's standard of care. This may include, but not be limited to, appropriate conversion of subjects back to their pre-study opioid regimen with titration to a dose that provides an acceptable balance of analgesia and side effects."*

#### Follow-up Phone Call (Day 99±3)

Site personnel were to have contacted subjects who completed the study and did not enter the extension study or those who discontinued the study early, 14 days after the end of the study or early termination to collect information on AEs that were ongoing at the end of the study and any new SAEs that occurred.

#### Drug Accountability

At each visit, the study drug and rescue medication dispensed and returned were to have been recorded by the clinical staff. If a difference of greater than 10% occurred, compliance was to have been discussed with the Applicant. Subject compliance was to have been monitored by counting the capsules of study drug and rescue medication dispensed and returned at each visit compared to diary entries.

#### Efficacy Assessments/Endpoints

The following efficacy assessments were to have been performed:

##### Primary Efficacy Assessment/Endpoint

The primary efficacy endpoint was to have been the mean change from Baseline to Day 85 in the Treatment Phase in the average 24-hour pain intensity ratings

- Pain intensity over the past 24 hours was to have been recorded daily (i.e., at bedtime) in an electronic diary using the 0-10 NRS.
- Baseline was to have been the average of the last 7 days on stabilized dosing prior to randomization into the treatment Phase.
- Day 85 measurement was to have been the average of the last 7 days prior to the Day 85 visit.

##### Secondary Efficacy Assessments/Endpoints

The following efficacy assessments/endpoints were to have been measured:

- Proportion of responders who have a 30% and 50% improvement in pain intensity scores from Baseline to Day 85 among study completers
- Change from Screening to the end of the Conversion and Titration Phase in average pain intensity scores
- Oswestry Disability Inventory (ODI) change in physical function from Baseline to Day 85
- Quebec Back Pain Disability Scale change from Baseline to Day 85 in back-related disability
- Rescue medication consumption measured by the average number of rescue doses taken per day and proportion of days rescue medication was taken for both the Conversion and Titration Phase and the Treatment Phase
- Time-to-exit due to lack of efficacy measured in the number of days from Baseline to the time the subject is discontinued from the study
  - Subjects who complete the study were to have been censored at Day 85
  - Subjects who discontinue for reasons other than lack of efficacy were to have been censored at their day of last dose of study medication
- Time-to-exit due to adverse events measured in the number of days from Baseline to the time subject is discontinued from the study due to an adverse event
  - Subjects who complete the study were to have been censored at Day 85
  - Subjects who discontinue for reasons other than adverse event were to have been censored at their day of last dose of study medication
- Time-to-exit due to all causes measured in the number of days from Baseline to the time subject is discontinued from the study due to an adverse events, lack of efficacy, lost to follow-up, withdrawal of consent, etc.
  - Subjects who complete the study were to have been censored at Day 85
- Hospital Anxiety and Depression Scale (HADS) change from Baseline to Day 85 in mood
- Subject Global Assessment of Medication at Day 85
- Conversion and Titration Phase characterization with respect to:
  - Proportion of subjects who achieve a stabilized dose
  - Distribution of times and median time to achieve a stabilized dose
  - Safety of the prespecified conversion algorithm
  - Distribution of stabilized doses
  - Pain intensity measured from Screening to the end of the Conversion and Titration Phase

### **Safety Assessments**

The following pre-specified safety assessments were to have been performed:

- Adverse Events were to have been recorded in the eCRF beginning at the Treatment and Conversion Phase through 14 days after the last treatment administration (Day 99)
- Physical Examinations at Screening (Visit 1) and Visit 13 (Day 85 or Early Termination)
- Vital Signs (i.e., blood pressure, heart rate, respiratory rate, and body temperature) measurements after the subject has been sitting quietly for at least 5 minutes at all clinic visits (Visits 1 through 13)
- Laboratory measurements

Urine Pregnancy Test at Screening (Visit 1) and Visits 2, 6, 8, 11, 12, and 13 (Day 85)

Urine Drug Screen at Screening (Visit 1) and at Visit 4 or Visit 8 depending on when the subject stabilizes and is ready for randomization

Chemistry, hematology and urinalysis at Screening (Visit 1), Baseline (Visit 8) and Visit 13 (Day 85)

*Chemistry Panel:* ALT, AST, alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, creatinine, amylase, blood urea nitrogen (BUN), sodium, potassium, chloride, bicarbonate, calcium, total cholesterol, uric acid, glucose, total protein, and albumin. Serum alcohol will be collected at Screening (Visit 1) only.

*Hematology Panel:* Hemoglobin, hematocrit, red cell count, red cell indices, white blood cell count (with differential) and platelet count

*Urinalysis:* Total urinalysis including a microscopic examination

- Electrocardiogram at Screening (Visit 1)
- Opioid withdrawal was to have been measured at Screening (Visit 1), Baseline (Visit 8), Visits 9 and 10, and Visit 13 (for early discontinuation only) using the Clinical Opioid Withdrawal Scale (COWS) and the Subjective Opioid Withdrawal Scale (SOWS)
- Audiometric evaluations were to have been performed at Screening (Visit 1), Baseline (Visit 8), and at the end of the study (Day 85; Visit 13). Changes in hearing thresholds from the baseline values at the various frequencies were to have been evaluated.

## **Statistical Methods**

### **Analysis Populations**

#### Intent-to-Treat Population

The Intent-to-Treat (ITT) Population was defined as all subjects who were randomized into the 12-week treatment Phase of the study and received at least one dose of double-blinded study medication after randomization.

#### Per-Protocol Population

The Per Protocol (PP) Population was defined as all subjects in the ITT population minus subjects considered to be major protocol violators. Excluded subjects were to have been identified prior to unblinding of the database by the Applicant.

#### Safety Population

The Safety Population was to have been all subjects that received at least one dose of study medication. Analyses of safety data was to have been performed on subjects administered HC-ER during the Conversion and Titration Phase and on subjects receiving at least one dose of study medication after randomization in the Treatment Phase.

### **Statistical Analysis**

#### Primary Efficacy Analysis

The primary efficacy analysis was to have been the mean change from Baseline to Day 85 in the Treatment Phase in the average 24-hour pain intensity ratings from daily electronic diaries. Baseline was to have been the average of the last 7 days on stabilized dosing prior to randomization into the Treatment Phase. Day 85 was to have been the average of the last 7 days prior to the Day 85 study visit.

The primary efficacy analysis population was to have been the ITT population. The following data imputation methods were to have been used. If a subject discontinues prematurely due to a lack of efficacy, the last observation carried forward (LOCF) was to have been used. In this case, the last 24-hour pain score from the electronic diary was to have been used to impute the Day 85 result.

If a subject discontinues prematurely due to opioid withdrawal, the Baseline observation carried forward (BOCF) was to have been used. In this case, the average of the last 7 days prior to the Baseline Visit was to have been used.

If a subject discontinues prematurely due of treatment-related AEs, the Screening observation carried forward approach was to have been used. In this case, the clinic average 24-hour pain intensity score from Screening Visit was to have been used.

If a subject discontinues due to any other reason than indicated above, the LOCF approach was to have been used. In this case, the last 24-hour pain score from the daily diary prior to discontinuation was to have been used to impute the Day 85 result.

An analysis of covariance model was to have been used to analyze the primary endpoint using the mean change from Baseline to Day 85 as the dependent variable. The model was to have included treatment group as a factor and Baseline pain score, Screening pain score, and stabilized dose as covariates. Least square means of change from Baseline was to have been summarized and compared between treatment groups to assess statistical significance using a 2-sided, 2-sample t-test.

#### Secondary Efficacy Analyses

The secondary efficacy analyses were to have been the following:

1. Mean change from Baseline to Day 85 visit of the clinic 0-10 NRS pain intensity in the past 24 hours
2. Mean change from Baseline to Day 85 visit of the "worst pain" 0-10 NRS pain intensity in the past 24 hours
3. Mean change from Baseline to Day 85 visit of the "least pain" 0-10 NRS pain intensity in the past 24 hours
4. Proportion of responders, defined as randomized subjects who complete the 12-week treatment period and who experience 30% and 50% changes from Screening to Day 85 in pain scores will be summarized across treatment groups and compared using Fisher's exact test.
5. Average number of rescue doses taken per day and proportion of days rescue medication was taken will be summarized using descriptive statistics across treatment groups for both the Conversion and Titration Phase and the Treatment Phase.
6. Time to treatment discontinuation due to lack of efficacy, adverse events, and overall time to exit for any reason will be analyzed using time to event (Kaplan-Meier) analysis and compared using the log-rank test.

All remaining secondary endpoints were to have been summarized using descriptive statistics and compared between treatment groups. Study drug accountability was to have been provided for all phases, and by treatment group for the Treatment Phase.

#### Safety Analyses

Safety analyses were to have included descriptive statistical summaries of shifts in vital signs, audiometry, and laboratories by treatment group. The number and percentage of subjects with AEs were to have been displayed by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

The proportion of subjects with a clinically significant change from Baseline hearing thresholds (b) (4)

-deleted in Amendment 2 to the end of the Treatment Phase (Day 85) was to have been summarized. *Amendment 2 added that significant changes from Baseline were to have been defined as:*

- 20 dB decrease at any one test frequency

- 10 dB decrease at any two adjacent test frequencies
- A loss of response at three consecutive test frequencies where responses were previously obtained (refers specifically to the highest frequencies tested, where earlier responses cannot be obtained at the limits of the audiometer).
- Repeat testing must be conducted to confirm changes in hearing levels.

#### **Protocol Amendments:**

##### **Original Protocol, September 29, 2009**

No subjects were enrolled under this protocol.

##### **Amendment #1, January 7, 2010**

The preceding protocol review was based on Protocol Amendment 1. The first subject was screened under this amended protocol. Amendment 1 provided the following changes:

- Revised the numbering of study days such that Day 0 was removed and the first day of the double-blind period was Day 1
- Clarified the amount of rescue medication permitted when determining if a subject had reached a stable dose of HC-ER during the Conversion\Titration Period
- Revised urine drug screening exclusion criteria to allow qualitative results and deleted requirement for quantitative urine drug screen
- Provided clarification to timing of urine drug screening, added fasted condition to Screening laboratory assessments and added preliminary results form an alcohol interaction study
- Added requirement that subjects must not consume alcohol or alcohol-containing products such as OTC cold preparations while taking hydrocodone

##### **Amendment #2, March 29, 2010**

Amendment 2 included the following changes:

- Revised the number of days of the Screening Phase from (b) (4) 14 days
- Clarified the criterion for a stabilized dose regarding the average 24-hour daily Average Pain Score of  $\leq 4$  on the NRS during the last 7 days prior to the Baseline Visit and added clarification that for stabilized dose no more than 2 tablets/day of hydrocodone 5 mg/acetaminophen 500 mg should be taken.
- Revised the audiometry safety analyses
- Added the Day 85 assessment for resolution and relatedness of ongoing AEs prior to breaking the blind. Any clinically significant laboratory abnormalities resulting form the Day 85 laboratory analyses will be assessed as related to HC-ER.
- Included requirement that the Medical Monitor should be consulted prior to screening subjects who are on fentanyl products. This requirement was added to

provide guidance to the Investigator on an appropriate conversion factor for fentanyl products.

**Amendment #3, June 4, 2010**

Amendment 3 included the following changes:

- Removal of all references to the unblinding procedures prior to subjects being enrolled in the planned extension study, since that study would no longer be conducted for subjects completing the current study on active study drug.
- Clarification that the Screening NRS score is the score noted by the subjects at Visit 1

**Amendment #4, November 18, 2010**

Amendment 4 included a revision to exclusion criteria #12 that clarified subjects should be excluded for a workman's compensation claim or litigation related to back pain.

**Study Results**

**Enrollment/Randomization**

Of the total 510 subjects enrolled, 302 subjects (59%) completed the conversion/titration (C/T) phase and were randomized to treatment and 208 subjects (41%) discontinued the C/T phase early. Of the 302 subjects randomized, 151 subjects (30%) were randomized to receive HC-ER and 151 subjects (30%) were randomized to receive placebo.

**Subject Disposition**

A total of 41% (208/510) of subjects discontinued early from the C/T phase. The reasons for discontinuation from the C/T phase are summarized in Table 9. The primary reasons for early discontinuation from the C/T phase were protocol violation 13% (67/510) of subjects, non-compliance with study drug 9% (47/510) of subjects, adverse event 9% (46/510) of subjects and lack of efficacy 3% (17/510) of subjects.

**Table 9: Summary of Subject Disposition for the C/T Phase**

Disposition	Not Randomized (N=208)	Total (N=510)
Subjects who completed the C/T phase	0 (0.0%)	302 (59.2%)
Subjects who discontinued early from the C/T phase	208 (100.0%)	208 (40.8%)
Reasons for discontinuation from the C/T phase		
Protocol violation	67 (32.2%)	67 (13.1%)
Non-compliance with study drug	47 (22.6%)	47 (9.2%)
Adverse event: other	46 (22.1%)	46 (9.0%)
Withdrawal by subject	23 (11.1%)	23 (4.5%)
Lack of efficacy	17 (8.2%)	17 (3.3%)
Lost to follow-up	5 (2.4%)	5 (1.0%)
Physician decision	2 (1.0%)	2 (0.4%)
Adverse event: opioid withdrawal	1 (0.5%)	1 (0.2%)

Source: Protocol ZX002-0801 Clinical Study Report, p. 59

Of the 302 subjects randomized to the treatment phase, 183 subjects (61%) completed that phase (Table 10): 124 subjects (82%) in the HC-ER group and 59 subjects (39%) in the placebo group. Within the HC-ER group, 27 subjects (18%) discontinued early for the following reasons: lack of efficacy 9% (14/151 subjects), withdrawal by subject 3% (5/151 subjects), non-compliance with study drug 3% (4/151) and adverse event 1% (2/151 subjects). No subjects were reported to have discontinued due to an AE related to opioid withdrawal.

Within the placebo group, 92 subjects (61%) discontinued early for the following reasons: lack of efficacy 42% (64/151 subjects), non-compliance with study drug 5% (7/151 subjects), adverse event related to opioid withdrawal 5% (7/151 subjects) and adverse event 3% (5/151 subjects). Of interest, a higher proportion of subjects in the placebo group withdrew due to adverse events than in the study drug group.

**Table 10: Summary of Subject Disposition for the Treatment Phase**

Disposition	HC-ER (N=151)	Placebo (N=151)	Total (N=302)
Subjects Who Completed the Treatment Phase	124 (82.1%)	59 (39.1%)	183 (60.6%)
Subjects Who Discontinued Early from the Treatment Phase	27 (17.9%)	92 (60.9%)	119 (39.4%)
Reasons for Discontinuation from Study in the Treatment Phase			
Lack of efficacy	14 (9.3%)	64 (42.4%)	78 (25.8%)
Non-compliance with study drug	4 (2.6%)	7 (4.6%)	11 (3.6%)
Withdrawal by subject	5 (3.3%)	5 (3.3%)	10 (3.3%)
Adverse event: opioid withdrawal	0 (0.0)	7 (4.6%)	7 (2.3%)
Adverse event: other	2 (1.3%)	5 (3.3%)	7 (2.3%)
Protocol violation	1 (0.7%)	2 (1.3%)	3 (1.0%)
Lost to follow-up	1 (0.7%)	0 (0.0)	1 (0.3%)
Other	0 (0.0)	1 (0.7%)	1 (0.3%)
Physician decision	0 (0.0)	1 (0.7%)	1 (0.3%)

Source: Protocol ZX002-0801 Clinical Study Report, p. 60

### Protocol Violations

Major protocol violations for the ITT population were reported for 14 subjects (9%) in the HC-ER group and for 10 subjects (7%) in the placebo group. These protocol violations included deviations from inclusion/exclusion criteria where the subject did not meet treatment phase eligibility criteria due to either: a) the subject not experiencing a 2-point decrease in NRS pain score, and/or b) the subject's average daily NRS pain score in the 7 days prior to Baseline was  $\geq 5$ .

### Demographics

The overall demographic and baseline characteristics for subjects in the C/T phase and treatment phase are summarized in Table 11. The demographic characteristics of the subjects randomized to HC-ER were similar to those subjects randomized to placebo with respect to age, race, and baseline average pain score. The HC-ER group and placebo group were different based on gender. In HC-ER group, 38% of subjects were male and 62% were female and in the placebo group 51% of subjects were male and

49% were female. The majority of the subjects were White in both the group randomized to HC-ER (82%) and the group randomized to placebo (80%).

In the C/T phase, the randomized and not randomized groups were different based on age. In the C/T phase, the mean age of subjects was 50.6 years  $\pm$  11.7 years for the randomized group and 47.8 years  $\pm$  11.7 years for the not randomized group. This difference in age does not appear to be clinically relevant.

**Table 11: Demographic and Baseline Characteristics C/T and Treatment Phases**

	C/T Phase		Treatment Phase	
	Not Randomized (N=208)	Randomized (N=302)	HC-ER (N=151)	Placebo (N=151)
Age (years)				
n	208	302	151	151
Mean (SD)	47.8 (11.72)	50.6 (11.66)	50.4 (10.94)	50.8 (12.37)
Range	18 – 75	21 – 74	21 – 74	24 – 74
Gender				
Male	102 (49.0%)	135 (44.7%)	58 (38.4%)	77 (51.0%)
Female	106 (51.0%)	167 (55.3%)	93 (61.6%)	74 (49.0%)
Race				
White	161 (77.4%)	243 (80.5%)	123 (81.5%)	120 (79.5%)
Black or African American	40 (19.2%)	51 (16.9%)	26 (17.2%)	25 (16.6%)
Native Hawaiian or other Pacific Islander	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	2 (1.0%)	2 (0.7%)	0 (0.0%)	2 (1.3%)
American Indian or Alaska Native	1 (0.5%)	3 (1.0%)	1 (0.7%)	2 (1.3%)
Other	3 (1.4%)	3 (1.0%)	1 (0.7%)	2 (1.3%)
Ethnicity				
Hispanic or Latino	8 (3.8%)	14 (4.6%)	5 (3.3%)	9 (6.0%)
Not Hispanic or Latino	200 (96.2%)	288 (95.4%)	146 (96.7%)	142 (94.0%)
Screening Average Pain Score				
n	208	302	151	151
Mean (SD)	7.0 (1.41)	6.9 (1.38)	7.0 (1.30)	6.9 (1.45)
Range	4 – 10	4 – 10	4 – 10	4 – 10
Baseline Average Pain Score (in-clinic)				
n	—	—	150	148
Mean (SD)	—	—	3.0 (1.12)	2.9 (1.03)
Range	—	—	0 – 8	0 – 7
Missing	—	—	1	3

Source: Protocol ZX002-0801 Clinical Study Report, p. 64

## **Efficacy Results**

### ***Primary Endpoint:***

The primary efficacy endpoint for Study ZX002-0801 was the mean change from Baseline to Day 85 in the Treatment Phase in the average 24-hour pain intensity scores (based on subject diaries). The change in pain intensity score from baseline to Day 85 was statistically significantly lower in the HC-ER group than the placebo group using an analysis of covariance model in the intent to treat population (Table 12). The mean change in pain intensity score from baseline to Day 85 was  $0.48 \pm 1.56$  in the HC-ER group, and  $0.96 \pm 1.55$  in the placebo group ( $p=0.008$ ). The following data imputation methods were used. If a subject discontinued prematurely due to a lack of efficacy, the last observation carried forward (LOCF) was used. If a subject discontinued prematurely due to opioid withdrawal, the baseline observation (end of C/T phase) carried forward was used. If a subject discontinued prematurely due to treatment-related adverse events, the screening observation (prior to C/T phase) carried forward approach was used. If a subject discontinued due to any other reason than indicated above, the LOCF approach was used. The statistical team was able to replicate the Sponsor's findings of efficacy.

**Table 12: Summary of Change from Baseline of Average Daily Pain Intensity Score for the ITT Population**

Time Point	HC-ER (N=151)	Placebo (N=151)
<b>Day 8</b>		
n	147	98
Mean (±SD)	0.07 (0.757)	0.12 (0.740)
Min, Max	-1.9, 4.1	-2.3, 3.1
LS Mean	0.07	0.12
p-value	0.621	—
<b>Day 15</b>		
n	140	83
Mean (±SD)	0.08 (0.885)	0.24 (1.038)
Min, Max	-1.9, 3.6	-2.7, 3.1
LS Mean	0.09	0.23
p-value	0.268	—
<b>Day 29</b>		
n	134	72
Mean (±SD)	0.10 (1.061)	0.37 (1.231)
Min, Max	-2.3, 5.3	-2.0, 5.3
LS Mean	0.10	0.37
p-value	0.098	—
<b>Day 57</b>		
n	122	60
Mean (±SD)	0.25 (1.314)	0.35 (1.300)
Min, Max	-2.6, 5.2	-2.0, 4.1
LS Mean	0.25	0.35
p-value	0.591	—
<b>Day 85</b>		
n	151	151
Mean (±SD)	0.48 (1.563)	0.96 (1.550)
Min, Max	-3.0, 5.3	-2.4, 6.7
LS Mean	0.48	0.95
p-value	0.008	—

Source: Protocol ZX002-0801 Clinical Study Report, p. 71

## Secondary Efficacy Endpoints

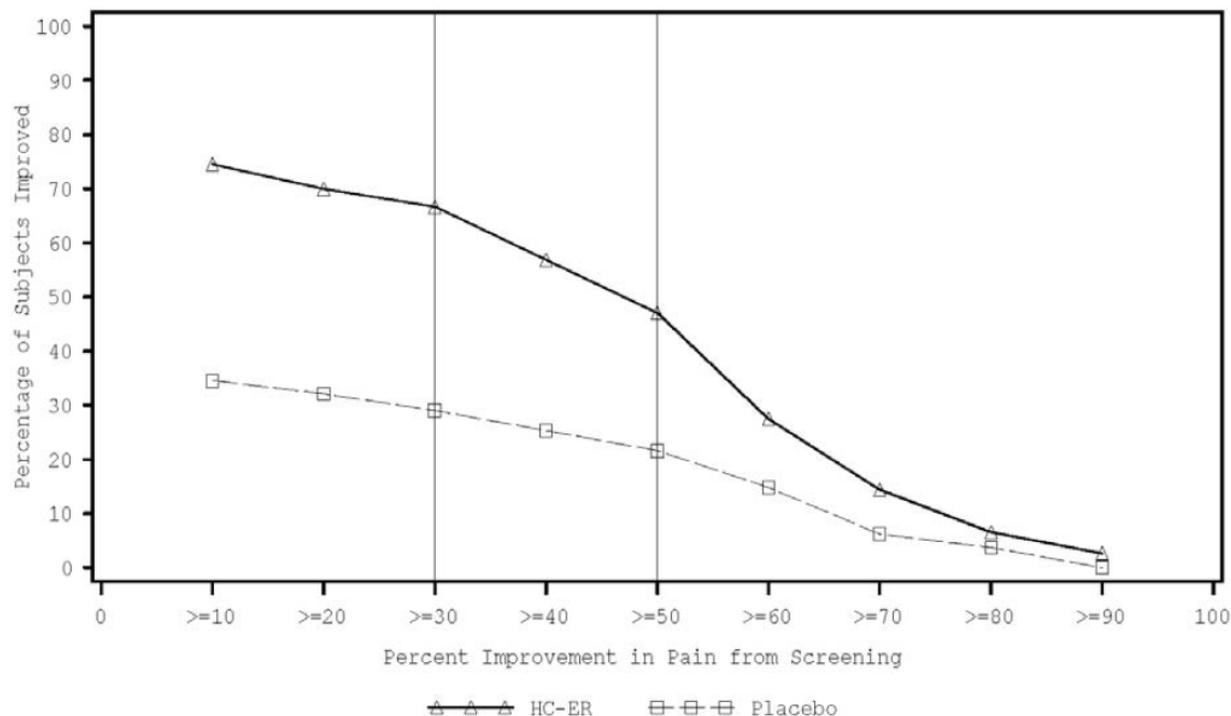
The Sponsor's use of p-values for the secondary endpoints is merely descriptive, since there was no correction for multiple endpoints included in the statistical analysis plan.

### *Responder Analysis*

The Applicant defined a responder as a randomized subject who completed the 12-week treatment period and who experienced at least a 30% or 50% improvement from

the screening 24-hour average pain intensity score to the average daily pain intensity score at Day 85 (Figure 2). A greater percentage of subjects in the HC-ER group compared to placebo group showed improvement in the continuous responder analysis across all response rate levels.

**Figure 2: Percent Improvement in Average Pain from Screening to Final Visit**



Source: Protocol ZX002-0801 Clinical Study Report, p. 73

**Subject Global Assessment of Medication (SGAM)**

Change from screening to Day 85 in satisfaction with treatment was graded as “not at all”, “a little bit”, “moderately”, “very much”, and “completely” corresponding to scores of 1, 2, 3, 4, and 5 respectively. A higher score indicated greater satisfaction with treatment. At Day 85, the number of subjects at least moderately satisfied with treatment was 85% (122 subjects) in the HC-ER group compared with 61% (90 subjects) in the placebo group. According to the Applicant, the mean change from screening to Day 85 in SGAM score was  $0.8 \pm 1.3$ , with a range of -3 to 4, for the HC-ER group, compared with  $0.0 \pm 1.4$ , with a range of -3 to 3, for the placebo group ( $p < 0.001$ ).

**Worst Pain Intensity**

HC-ER had a greater effect on worst pain intensity than did placebo with the increase in daily worst pain intensity score from baseline to Day 85 significantly less in the HC-ER

group than placebo group. According to the Applicant, the mean change in daily worst pain intensity score from baseline to Day 85 was  $0.42 \pm 1.76$  in the HC-ER group, and  $1.03 \pm 1.79$  in the placebo group ( $p=0.002$ ).

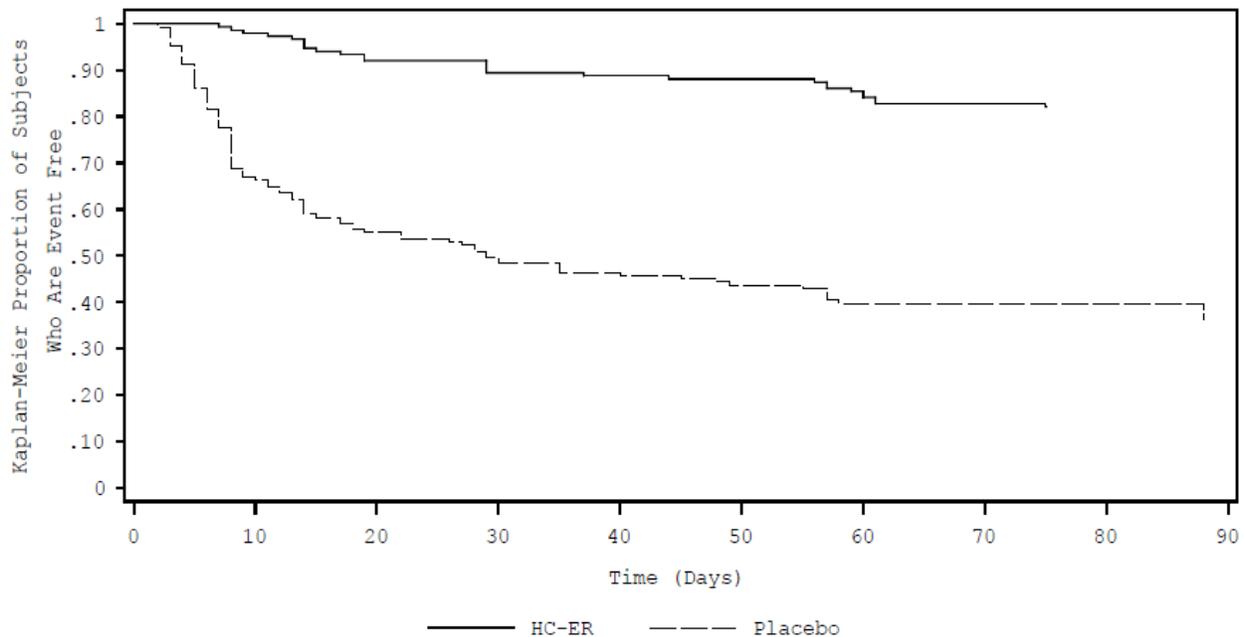
#### *Least Pain Intensity*

The increase in daily least pain intensity score from baseline to Day 85 was significantly less in the HC-ER group than the placebo group. The Applicant reported that the mean change in daily least pain intensity score from baseline to Day 85 was  $0.50 \pm 1.43$  in the HC-ER group and  $0.98 \pm 1.47$  in the placebo group ( $p=0.004$ ).

#### *Time to Treatment Discontinuation*

A total of 27 subjects (18%) discontinued due to all causes in the HC-ER group, compared with 92 subjects (61%) in the placebo group. The probability of discontinuing due to any reason in the HC-ER group was 11% at Day 30, 16% at Day 60 and 18% at Day 85, while in the placebo group same the probability was 52% at Day 30, 60% at Day 60 and 60% at Day 85. Subjects in the HC-ER group had a lower probability of discontinuing from treatment due to any cause than did those in the placebo group ( $p<0.001$ ). A Kaplan-Meier plot of time to discontinuation due to all causes is presented in (Figure 3).

**Figure 3: Time to Discontinuation Due to All Causes**



Discontinuations due to lack of efficacy occurred in a total of 14 subjects (9%) in the HC-ER group, compared with 64 subjects (42%) in the placebo group. According to the Applicant's calculations, the probability of discontinuing due to lack of efficacy was 7% at Day 30, 9% at Day 60 and 10% at Day 85 in the HC-ER group, while the probability was 41% at Day 30, 47% at Day 60 and 47% at Day 85 in the placebo group.

#### *Rescue Medication Use*

##### *Conversion/Titration Phase*

The amount of allowed rescue medication during the C/T phase was limited to a maximum of four tablets per day of hydrocodone 5 mg/acetaminophen 500 mg. In the randomized group, the mean total daily dose (TDD) of rescue medication (for the hydrocodone component only) during the C/T phase was 9.1 mg  $\pm$  5.2 mg, with a range from 0.1 mg to 19.6 mg. In the not randomized group, the mean TDD of rescue medication was 12.1 mg  $\pm$  6.3 mg, with a range from 0.3 mg to 32.5 mg. The lower TDD of rescue medication in the randomized group likely reflects more effective pain control with HC-ER in this group.

##### *Treatment Phase*

As specified in the protocol, the amount of allowed rescue medication during the treatment phase was limited to a maximum of two tablets per day of hydrocodone 5 mg/acetaminophen 500 mg. The mean TDD of rescue medication (for the hydrocodone component only) during the treatment phase in the HC-ER group was 6.0 mg  $\pm$  3.4 mg, with a range from 0.1 mg to 12.5 mg. In the placebo group, the mean TDD of rescue medication was 7.5 mg  $\pm$  3.9 mg, with a range from 0.1 mg to 20 mg. Although, the TDD of rescue medication was lower in the HC-ER group than placebo group, the difference did not appear to be clinically significant. The small difference in use of rescue medication may have been related to the relatively low limit on the amount of rescue medication subjects were allowed to use.

## **6 Review of Efficacy**

### **Efficacy Summary**

Efficacy of HC-ER in the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time was demonstrated in adults in one principal efficacy study (ZX002-0801). There was statistically significantly less pain at 12 weeks in subjects with moderate-to-severe CLBP treated with HC-ER compared to placebo. Efficacy was also supported by secondary endpoints including a cumulative responder analysis, subjective global assessment of medication, worst pain intensity and least pain intensity.

The finding of efficacy was supported by one additional Phase 2 study (ELN-154088-201) a randomized, single-dose, placebo-controlled, active comparator study in bunionectomy surgery. Study ELN-154088-201 was not considered adequate to

support a finding of efficacy on its own due to the study design (i.e., single-dose study in an acute pain model). Therefore the efficacy findings from this study were not reviewed by the FDA statistician. However, the efficacy findings as reported by the Applicant were supportive of the findings in Study ZX002-0801. For study ELN-154088-201, the Applicant reported that the primary endpoint, Sum of Pain Intensity Differences (SPID) for the Visual Analog Scale of Pain Intensity (VASPI) for 0 to 12 hours, for HC-ER 40 mg was statistically significantly better than placebo. None of the lower doses of HC-ER were superior to placebo.

## 6.1 Indication

### Proposed Indication

Zogenix's proposed indication is the following:

Zohydro Extended Release Capsules are indicated for the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

#### 6.1.1 Methods

The Applicant has submitted one principal efficacy study to support a finding of efficacy for the indication of Zohydro ER for the management moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed in adults. This study was an adequate and well-controlled (i.e., randomized, double-blind, placebo-controlled) study in subjects with chronic low back pain. The primary efficacy measure and the pre-specified primary endpoint was change from baseline to end of treatment (Day 85) in the average 24-hour pain intensity based on an 11-point NRS. The study design and primary endpoint meet the Division's standards.

#### 6.1.2 Demographics

The overall demographic and baseline characteristics for subjects in the C/T phase and treatment phase are summarized in Table 11. The demographic characteristics of the subjects randomized to HC-ER were similar to those subjects randomized to placebo with respect to age, race, and baseline average pain score. The HC-ER group and placebo group were different based on gender. In HC-ER group, 38% of subjects were male and 62% were female and in the placebo group 51% of subjects were male and 49% were female. The majority of the subjects were White in both the group randomized to HC-ER (82%) and the group randomized to placebo (80%).

In the C/T phase, the randomized and not randomized groups were significantly different based on age. In the C/T phase, the mean age of subjects was 50.6 years  $\pm$

11.7 years for the randomized group and 47.8 years  $\pm$  11.7 years for the not randomized group. This difference in age does not appear to be clinically relevant.

### 6.1.3 Subject Disposition

A total of 41% (208/510) of subjects discontinued early from the C/T phase. The reasons for discontinuation from the C/T phase are summarized in Table 9. The primary reasons for early discontinuation from the C/T phase were protocol violation 13% (67/510) of subjects, non-compliance with study drug 9% (47/510) of subjects, adverse event 9% (46/510) of subjects and lack of efficacy 3% (17/510) of subjects.

Of the 302 subjects randomized to the treatment phase, 183 subjects (61%) completed that phase (Table 10): 124 subjects (82%) in the HC-ER group and 59 subjects (39%) in the placebo group. Within the HC-ER group, 27 subjects (18%) discontinued early for the following reasons: lack of efficacy 9% (14/151 subjects), withdrawal by subject 3% (5/151 subjects), non-compliance with study drug 3% (4/151) and adverse event 1% (2/151 subjects). No subjects were reported to have discontinued due to an AE related to opioid withdrawal.

Within the placebo group, 92 subjects (61%) discontinued early for the following reasons: lack of efficacy 42% (64/151 subjects), non-compliance with study drug 5% (7/151 subjects), adverse event related to opioid withdrawal 5% (7/151 subjects) and adverse event 3% (5/151 subjects).

### 6.1.4 Analysis of Primary Endpoint(s)

#### Choice of Primary Endpoint for ZX002-0801

The protocol-specified primary efficacy endpoint for Study ZX002-0801 was the mean change from Baseline to Day 85 in the Treatment Phase in the average 24-hour pain intensity ratings as measured by a 0-10 Numerical Rating Scale (NRS) from daily electronic diaries. Baseline was defined as the average of the last 7 days on stabilized dosing prior to randomization into the Treatment Phase. Day 85 was defined as the average of the last 7 days prior to the Day 85 study visit. If a subject had fewer than 7 scores in the last 7 days, the mean of the available scores was used. The Applicant's choice of primary endpoint is consistent with the Division's current standard.

#### Efficacy Results

##### **Primary Endpoint:**

The primary efficacy endpoint for Study ZX002-0801 was the mean change from Baseline to Day 85 in the Treatment Phase in the average 24-hour pain intensity scores. The change in pain intensity score from baseline to Day 85 was statistically significantly lower in the HC-ER group than the placebo group using an analysis of covariance model in the intent to treat population (Table 12). The mean change in pain

intensity score from baseline to Day 85 was  $0.48 \pm 1.56$  in the Zohydro ER group, and  $0.96 \pm 1.55$  in the placebo group ( $p=0.008$ ). The following data imputation methods were used. If a subject discontinued prematurely due to a lack of efficacy, the last observation carried forward (LOCF) was used. If a subject discontinued prematurely due to opioid withdrawal, the baseline observation (end of C/T phase) carried forward was used. If a subject discontinued prematurely due to treatment-related adverse events, the screening observation (prior to C/T phase) carried forward approach was used. If a subject discontinued due to any other reason than indicated above, the LOCF approach was used. The FDA statistician confirmed the primary efficacy findings as reported by the Applicant using the prespecified imputation methods and also using alternative imputation methods.

### 6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoints of HC-ER for the treatment of chronic pain were supportive of the efficacy findings of the primary endpoint. The Sponsor's use of p-values for the secondary endpoints is merely descriptive, since there was no correction for multiple endpoints included in the analysis plan.

#### *Responder Analysis*

The Applicant defined a responder as a randomized subject who completed the 12-week treatment period and who experienced at least a 30% or 50% improvement from the screening 24-hour average pain intensity score to the average daily pain intensity score at Day 85 (Figure 2). A greater percentage of subjects in the HC-ER group compared to placebo group showed improvement in the continuous responder analysis across all response rate levels. However, since dropouts were considered not responders and there were many more dropouts in the placebo group, the responder curve reflects more the disparity in dropouts than the percent improvement.

#### *Subject Global Assessment of Medication (SGAM)*

Change from screening to Day 85 in satisfaction with treatment was graded as "not at all", "a little bit", "moderately", "very much", and "completely" corresponding to scores of 1, 2, 3, 4, and 5 respectively. At Day 85, the majority of subjects reporting in the HC-ER group (122 subjects or 85%) were at least moderately satisfied with treatment, compared with 90 subjects (61%) in the placebo group.

#### *Worst Pain Intensity*

HC-ER had a greater effect on worst pain intensity than did placebo with the increase in daily worst pain intensity score from baseline to Day 85 significantly less in the HC-ER group than placebo group. According to the Applicant, the mean change in daily worst pain intensity score from baseline to Day 85 was  $0.42 \pm 1.76$  in the HC-ER group, and  $1.03 \pm 1.79$  in the placebo group ( $p=0.002$ ).

#### *Least Pain Intensity*

HC-ER had a greater effect on least pain intensity than did placebo with the increase in daily least pain intensity score from baseline to Day 85 significantly less in the HC-ER group than the placebo group. The Applicant reported that the mean change in daily least pain intensity score from baseline to Day 85 was  $0.50 \pm 1.43$  in the HC-ER group and  $0.98 \pm 1.47$  in the placebo group ( $p=0.004$ ).

#### *Time to Treatment Discontinuation*

Subjects in the HC-ER group had a lower probability of discontinuing from treatment due to any cause than did those in the placebo group. A total of 27 subjects (18%) discontinued due to all causes in the HC-ER group, compared with 92 subjects (61%) in the placebo group. The probability of discontinuing due to any reason in the HC-ER group was 11% at Day 30, 16% at Day 60 and 18% at Day 85, while in the placebo group the probability was 52% at Day 30, 60% at Day 60 and 60% at Day 85. A Kaplan-Meier plot of time to discontinuation due to all causes is presented in (Figure 3). Discontinuations due to lack of efficacy occurred in a total of 14 subjects (9%) in the HC-ER group, compared with 64 subjects (42%) in the placebo group.

#### *Rescue Medication Use*

##### *Conversion/Titration Phase*

The amount of allowed rescue medication during the C/T phase was limited to a maximum of four tablets per day of hydrocodone 5 mg/acetaminophen 500 mg. In the randomized group, the mean total daily dose (TDD) of rescue medication (for the hydrocodone component only) during the C/T phase was  $9.1 \text{ mg} \pm 5.2 \text{ mg}$ , with a range from 0.1 mg to 19.6 mg. In the not randomized group, the mean TDD of rescue medication was  $12.1 \text{ mg} \pm 6.3 \text{ mg}$ , with a range from 0.3 mg to 32.5 mg.

##### *Treatment Phase*

As specified in the protocol, the amount of allowed rescue medication during the treatment phase was limited to a maximum of two tablets per day of hydrocodone 5 mg/acetaminophen 500 mg. The mean TDD of rescue medication (for the hydrocodone component only) during the treatment phase in the HC-ER group was  $6.0 \text{ mg} \pm 3.4 \text{ mg}$ , with a range from 0.1 mg to 12.5 mg. In the placebo group, the mean TDD of rescue medication was  $7.5 \text{ mg} \pm 3.9 \text{ mg}$ , with a range from 0.1 mg to 20 mg. Although, numerically the TDD of rescue medication was lower in the HC-ER group than placebo group, the difference was small and did not appear to be clinically significant. This small separation in the use of rescue medication between the two groups may be related to the relatively limited amount of rescue medication allowed.

#### 6.1.6 Other Endpoints

Not applicable.

### 6.1.7 Subpopulations

The FDA statistician verified that the efficacy findings in Study ZX002-0801 were not significantly affected by age, sex or race. There were no clinically meaningful treatment-by-subgroup interactions.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendation

There did not appear to be a clinically significant difference in efficacy between the doses of HC-ER studied. This finding would not be unexpected since subjects were titrated to effect.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy was demonstrated at the end of the 12 week maintenance phase.

### 6.1.10 Additional Efficacy Issues/Analyses

None.

## 7 Review of Safety

### 7.1 Methods

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The overall HC-ER clinical development program for the treatment of chronic pain included 10 clinical studies: 6 Phase I studies (Table 4), 2 Phase 2 studies and 2 Phase 3 studies (**Error! Reference source not found.**). In supporting the safety and tolerability of HC-ER the Applicant presented the study data organized as follows in the Integrated Summary of Safety:

- *All Treated Population*

The All Treated Population is comprised of 1553 subjects who were enrolled in 9 studies (ELN-302002, ELN-901001, ZX002-0901, ZX002-1001, ZX002-1002, ELN-154088-201, ELN-154088-203, ZX002-0801, and ZX002-0802) and includes 1512 subjects in the HC-ER group and 192 placebo group subjects. Most subjects (74%) in the All Treated Population were in Study ZX002-0801 (principal efficacy study) or Study ZX002-0802 (open-label, long-term safety study). Subjects from Study ZX002-0801 who were randomized to placebo in the treatment phase were included in the HC-ER total for the C/T phase assignment and included in the placebo total for the treatment phase assignment in the ISS. Of the 192 subjects in the All Treated

Population placebo group, 151 (78.6%) received HC-ER during the treatment phase of Study ZX002-0801 and the remaining placebo group subjects (21.4%) were in Study ELN154088-201 (single-dose bunionectomy study) and did not receive HC-ER.

The Applicant did not integrate safety data from Study ZX002-0901 (alcohol safety study) in the All Treated Population because of the concomitant use of naltrexone but summaries of demographics, disposition, and exposure were included in the All Treated Population. Results of Study ZX002-1102 (HC-ER and Vicoprofen PK study) were not pooled with data from other studies as agreed with the FDA at the pre-NDA meeting (17 Nov 2011).

- *Chronic Population*

The Chronic Population was comprised of subjects enrolled in Studies ZX002-0801 (the Phase 3 efficacy study) and ZX002-0802 (the long-term safety study) and included a total of 1148 subjects in the C/T phase and 726 subjects in the treatment phase. Summaries for this population are displayed by study and overall. Subjects who received HC-ER in the C/T phase and placebo in the treatment phase are included in both treatment summaries (HC-ER and placebo).

- *Controlled Acute Population*

Study ELN-154088-201 is the only study in the Controlled Acute Population and is comprised of 241 subjects. Results presented in the ISS were obtained from the Study ELN-154088-201 Clinical Study Report.

- *Healthy Volunteers Population*

The Healthy Volunteers Population was comprised of 79 subjects enrolled in five studies (ELN-302002, ELN-901001, ZX002-0901, ZX002-1001, and ZX002-1002). Safety data from Study ZX002-0901 was not integrated in the Healthy Volunteers Population because of the concomitant use of naltrexone.

- *Impaired Volunteers Population*

The Impaired Volunteers Population was comprised of 48 subjects of whom 20 were hepatically impaired and 28 were renally impaired enrolled in Studies ZX002-1001 and ZX002-1002. Summaries for this population were displayed by study and overall.

- *Study ZX002-1102*

Study ZX002-1102, comprised of 15 healthy adults, was ongoing at the time of the ISS submission but results obtained from the CSR were presented in the Updated ISS. These data were not pooled with other studies.

### 7.1.2 Categorization of Adverse Events

Adverse events were categorized by system organ class (SOC) and preferred term coded according to the Medical Dictionary for Regulatory Activities (MedDRA) v12.1 dictionary for the All Treated, Impaired Volunteers, Chronic C/T phase, Chronic treatment phase, and Healthy Volunteers populations. An AE was considered treatment-emergent if the event occurred on or after the first dose of study drug. For any AEs for which an onset time relative to the first dose of study drug could not be determined, the AE was considered treatment-emergent. All AEs that changed in severity or relationship to study drug were assigned a new start date and captured as a new record.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling data across studies to estimate and compare incidence of adverse events was of limited value since there were only two chronic studies: one controlled study (ZX002-0801) and one uncontrolled open-label safety study (ZX002-0802).

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The HC-ER development program provided adequate exposure to assess safety, with a total of 1512 subjects exposed to at least one dose of HC-ER regardless of phase and a total of 332 subjects exposed for 6 months or more and 290 subjects exposed for one year or more. For Study ZX002-0801 the maximum dose of HC-ER was 200 mg/day with 22 subjects stabilized at this dose. For Study ZX002-0802 the maximum dose used was up to 600 mg/day in one subject with 62 subjects stabilized at a dose greater than 200 mg/day.

In the HC-ER group in the Chronic Population, 802 subjects were Caucasian, 173 were African American, and 22 were of other races. In the placebo group, 120 subjects were Caucasian, 25 were African American, and 6 were of other races.

### 7.2.2 Explorations for Dose Response

A summary of the number of subjects in the chronic studies exposed to various doses of HC-ER for various durations is shown in Table 13.

**Table 13: Dose and Duration Chronic Population**

Duration (days)	<40 mg N=64	40-80 mg N=400	>80-120 mg N=236	>120-160 mg N=184	>160-200 mg N=158	>200 mg N=106
1-7	30 (46.9%)	87 (21.8%)	34 (14.4%)	24 (13.0%)	12 (7.6%)	6 (5.7%)
>7-14	29 (45.3%)	124 (31.0%)	51 (21.6%)	33 (17.9%)	40 (25.3%)	8 (7.5%)
>14-21	3 (4.7%)	31 (7.8%)	23 (9.7%)	13 (7.1%)	11 (7.0%)	3 (2.8%)
>21-31	2 (3.1%)	8 (2.0%)	7 (3.0%)	6 (3.3%)	8 (5.1%)	2 (1.9%)
>31-85	0	26 (6.5%)	14 (5.9%)	21 (11.4%)	17 (10.8%)	14 (13.2%)
>85-168	0	58 (14.5%)	51 (21.6%)	49 (26.6%)	41 (25.9%)	31 (29.2%)
>168-252	0	15 (3.8%)	29 (12.3%)	23 (12.5%)	15 (9.5%)	22 (20.8%)
>252-365	0	51 (12.8%)	26 (11.0%)	15 (8.2%)	14 (8.9%)	20 (18.9%)
>365	0	0	1 (0.4%)	0	0	0

Summary includes data from Studies ZX002-0801 and ZX002-0802  
 Source: ISS (June 14, 2012), p.82

### 7.2.3 Special Animal and/or In Vitro Testing

Not applicable

### 7.2.4 Routine Clinical Testing

The routine clinical testing performed during the development of HC-ER appears adequate.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to Section 4.4 and the Clinical Pharmacology Review.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The opioid class of drugs have been associated with abuse, addiction, and fatal respiratory depression and contain a boxed warning describing these potential adverse events in the label.

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were a total of five deaths among the 575 subjects in the chronic population and the 1512 subjects in the all treated population exposed to HC-ER. Four deaths occurred during Study ZX002-0802 (long-term open-label safety study) as follows: completed suicide (carbon monoxide poisoning), drug toxicity (methadone and oxycodone), non-small cell lung cancer, and coronary artery arteriosclerosis. The fifth death, an apparent suicide from an overdose, occurred after completion of Study

ZX002-0802 in a subject who hoarded HC-ER capsules and then opened and ingested all the medication approximately one year after the end of the study.

### **Individual Patient Death Summaries**

#### **Subject 106-15 (Study ZX002-0802)**

*Serious Event: Death due to suicide*

Subject 106-15 was a 52 year old woman with a history of depression, anxiety, head injury and hypothyroidism. She committed suicide on Drug Day 59 from leaving the car motor running in the garage. She was started on HC-ER 80 mg and titrated up to 240 mg over approximately 5 weeks. The subject experienced worsening anxiety starting on Drug Day 50 (considered possibly related to treatment), which was ongoing on Drug Day 59 when she died. Her medication was reduced to 200 mg on Drug Day 57. The investigative site did not receive an autopsy report. Concomitant medications included levothyroxine, meloxicam, citalopram, trazodone, clonazepam, omeprazole, echinacea, senna alexandrina, psyllium, multivitamins, ascorbic acid and vitamin D.

#### *Impression*

It appears unlikely that this subject's suicide was related to HC-ER given her history of depression and anxiety.

#### **Subject 134-07 (Study ZX002-0802)**

*Serious Event: Death due to mixed drug toxicity*

Subject 134-07 was a 33-year-old woman with a history of fibromyalgia, depression, anxiety, and back pain. The subject was found dead in her bed on Drug Day 236. An autopsy revealed that mixed drug (methadone and oxycodone) toxicity was the cause of the death. Toxicological analysis of postmortem (aortic) blood revealed the presence of caffeine, methadone, oxycodone, diazepam 0.18 mg/L, nordiazepam 0.45 mg/L, oxazepam < 0.050 mg/L, and temazepam <0.020 mg/L. Blood from a femoral vessel revealed methadone level of 0.83 mg/L, oxycodone 0.08 mg/L, and trace HC. Analysis of postmortem liver revealed methadone 4.3 mg/kg.

Prior to study enrollment, the subject had been prescribed tramadol for pain, but not methadone or oxycodone. The subject's family was unable to locate any of the study medication bottles or diary. Concomitant medications included zolpidem, acetaminophen, methylprednisolone, alprazolam, levocetirizine, pseudoephedrine, carisoprodol, and pregabalin.

During the study the subject experienced insomnia from Drug Day 153 to 236. From Drug Day 178 to 191, the subject experienced moderate sciatica secondary to a fall. On Drug Day 233, the subject began to experience an influenza-like illness. A chest X-ray showed mild nonspecific basilar coarsening without focal infiltrate. The impression was mild hypoventilation. The subject was found dead in her bed on Drug Day 236.

*Impression*

This subject's death from mixed drug toxicity (methadone and oxycodone) does not appear to be related to HC-ER by postmortem blood analysis. However, the case does illustrate the potential use of multiple opioids by subjects even when enrolled in a study where presumably there is extensive monitoring.

**Subject 211-24 (Study ZX002-0802)**

*Serious Event: Death due to non-small cell lung cancer*

Subject 211-24 was a 68 year old woman with a history of smoking admitted to the hospital on Drug Day 110 for evaluation of nausea and vomiting. She underwent computed tomography scan of the chest that revealed bilateral lung masses and extensive mediastinal and periaortic adenopathy consistent with bilateral malignant lung disease. The subject declined treatment for her cancer. A bronchoscopy showed an obstruction of the posterior segment of the left upper lobe. Biopsies were positive for poorly differentiated non-small cell lung cancer. The subject remained in the study and died from her lung cancer on Drug Day 262.

*Impression*

This subject's death from lung cancer was not related to use of HC-ER.

**Subject 229-10 (Study ZX002-0802)**

*Serious Event: Death due to atherosclerotic coronary artery disease*

Subject 229-10 was a 59 year old man with a history of extremity pain since 1980, anxiety, depression, constipation, cholelithiasis, and hepatitis C. On Drug Day 158, while on 440 mg of HC-ER per day, the subject was admitted to the hospital with confusion and altered mental status. A family member reported the subject had experienced occasional disorientation and forgetfulness (e.g., names and dates) during the 4 months prior to admission with more pronounced symptoms in the 2 days prior to admission. The subject started the conversion/titration phase on 140 mg and over the next three months up-titrated to his current dose of 440 mg per day on Drug Day 129. On admission his vital signs were: blood pressure 114/60 mmHg, heart rate 65 bpm, temperature 98.4°F, and respiratory rate 16 breaths/min. He denied any headache, nausea, or vomiting. Confusion diminished in the hospital, but the subject was not at his baseline state. The subject's son denied any possibility of withdrawal or drug overdose as the study medications were in his possession. The subject had sleep apnea, which was also suspected of causing the confusion.

On Drug Day 159, the event of disorientation was considered resolved and the subject was discharged from the hospital. The investigator considered the mental impairment possibly related to study drug and his HC-ER dose was decreased on Drug Day 160 to

100 mg BID. Alprazolam and citalopram were co-suspect medications, and sleep apnea was also considered to be a contributing cause of his mental impairment.

On Drug Day 207, the subject began again experiencing mental impairment. The event resolved on Drug Day 208. The study drug was withdrawn on Drug Day 208 due to the event of mental impairment. On Drug Day 214, the subject died suddenly in bed. The family refused an autopsy; however the cause of death was provided as atherosclerotic coronary artery disease. Toxicology was reported as negative.

#### *Impression*

Although the basis for classifying his death as due to atherosclerotic coronary artery disease is unclear, it is unlikely that HC-ER contributed directly to his death since the medication was discontinued approximately 6 days earlier. This subject's initial hospitalization for confusion may have been related to HC-ER and apparently resolved with a reduction in dose.

#### **Subject 122-010 (Study ZX002-0802)**

*Serious Event: Death due to suicide form HC-ER overdose*

This subject was a 47 year old man with a past medical history significant for a right tibia/fibula fracture, post traumatic arthritis, colon resection, panic attacks (2003, treated with Xanax), attention deficit disorder, anxiety (since 2006), insomnia, depression (since 2008), diabetes, hypertension, diverticulitis, joint pain, chronic low back pain, fibromyalgia, shoulder pain, paralyzed right hemidiaphragm, constipation, elevated CPK, high triglycerides, and elevated lipids.

The patient began study treatment on [REDACTED] (b) (6) with HC-ER 80 mg. At the time of study screening, the patient's Hospital Anxiety and Depression Scale (HADS) anxiety score was 9, and depression score was 12 (0-7 normal, 8-10 mild, 11-15 moderate, and 16-21 severe). The dose was gradually titrated up and on Study Day 115, the total daily dose was 200 mg. On 23 May 2011, the patient was diagnosed with anterior inferior labral tear and underwent shoulder surgery. During the study, the patient was found to be reliable. Non-compliance was not suspected since the patient's accountability with the study drug was correct. On July 1, 2011, the patient completed the study and his HADS anxiety score was 11 and depression score was 12. The patient was referred on 30 Jun 2011 to the pain management office for follow up care.

The patient's family reported that on [REDACTED] (b) (6), the patient entered rehabilitation, where he seemed to improve for awhile, but evidentially relapsed and started taking multiple drugs again. The patient's family did not believe that the patient had chronic pain, but rather the pain medications gave him relief from a bad relationship with his spouse. The patient's family noted that he had a photograph of a large plate filled with piles of labeled pills, and a note in the center of the plate which stated "Heaven".

The patient's family reported that on a date not reported, the patient was taken to the emergency room due to taking 30 pills of Xanax. The patient told his wife about plans regarding funeral arrangements and a cemetery. On Thanksgiving Day, the patient was noted to have fallen asleep in a chair which was presumed to be due to medication. On [REDACTED] (b) (6), the patient went to bed at 20:00, as he was sleepy after reportedly drinking 4 beers and taking 3 Trazodone pills. At 22:20, the patient was found by his wife. The patient's hands and face were blue. The patient could not be resuscitated and was pronounced dead on [REDACTED] (b) (6).

According to the patient's family, after the patient's death, a family member found a bottle of extended-release Xanax in the house, along with a Ziploc bag containing a yellow powdered substance, and a mortar and pestle. The patient had apparently ground up hydrocodone, since empty and open capsules of the study drug were found. The patient's family noted that during the study, the patient had "hoarded 40 capsules" of study drug. No Xanax was found in the patient's system postmortem (although it was unclear whether the toxicology panel included alprazolam). The drugs that were found in the patient postmortem were: hydromorphone (0.12 ug/mL), hydrocodone and dihydrocodeine and Trazodone (0.99 ug/mL). Ethanol was also present. A detective, who was investigating the patient's death, reported to the patient's family that the patient's death was caused by an "overdose of hydrocodone." Other medications confiscated from the patient's home by the detective were Cymbalta, Rapaflo, Benicar, metformin, and zolpidem.

Concomitant medications administered during the study included Adderall, alprazolam XR, Amitiza, Amrix, Benicar, Cozaar, Colace, Seroquel, Cymbalta, Fentanyl patch, trazodone, metformin, curcumin, Flexeril, Nexium, Percocet, Lovaza, Miralax, Obetrol, Toradol, and monthly Vitamin B-12 injections.

### *Impression*

This subject's suicide from an overdose of HC-ER provided one year earlier illustrates the potential for this drug to be misused and abused even in a supervised setting.

### Overall Summary of Deaths

The deaths of all five subjects taking HC-ER were reviewed. Four of the deaths did not appear directly related to HC-ER but the death due to multiple-drug toxicity illustrates the potential for HC-ER to be used by individuals abusing drugs even in the setting of a controlled study. The drug death due to a suicide from an overdose that occurred after completion of the study in a subject who hoarded HC-ER capsules and then opened and ingested all the medication again demonstrates the potential for HC-ER to be misused and abused.

### 7.3.2 Nonfatal Serious Adverse Events

In the HC-ER development program, 81 subjects reported a total of 118 nonfatal medical SAEs. During the C/T phase, 22 subjects reported a total of 32 nonfatal SAEs. During the treatment phase, 56 subjects (9.7%) reported a total of 83 nonfatal SAEs. Three cases of drug misuse in Study ELN-154088-203 were classified as medical SAEs based on the sponsor's definition of a medical SAE in this protocol. Review of these cases was not consistent with a SAE since in all three cases the subjects took only one extra dose of study drug after they apparently forgot they had previously taken a dose. No significant medical event (i.e., death, life threatening AE, inpatient hospitalization, persistent disability, congenital anomaly or important medical event that might jeopardize the patient) occurred as a result of the extra dose of study medication. No SAEs were reported in the 151 patients receiving placebo, but it is noted that the majority of SAEs occurred in the long-term chronic pain study where there was no placebo group.

#### *Chronic Population - Conversion/Titration (C/T) Phase*

A total of 22 subjects (1.9%) in the Chronic Population experienced a medical SAE during the C/T phase, including 6 subjects (1.2%) in the Study ZX002-0801 and 16 subjects (2.5%) in Study ZX002-0802. The only medical SAEs observed in more than 1 subject in the Chronic Population during the C/T phase were non-cardiac chest pain, which was observed in 3 subjects (0.3%), and COPD, which was observed in 2 subjects (0.2%).

#### *Chronic Population - Treatment Phase*

A total of 9.7% of subjects in the HC-ER group experienced a medical SAE during the treatment phase (3.3% in Study ZX002-0801 and 12.0% in Study ZX002-0802). No placebo group subject experienced an SAE during the treatment phase. The medical SAEs observed most frequently in the Chronic Population during the treatment phase were COPD (0.9%), OA (0.7%), and pneumonia (0.5%). All other SAE preferred terms were reported for  $\leq 0.3\%$  of subjects (not more than 2 subjects each) in the total Chronic Population during the treatment phase. A summary of subjects in the Chronic Population who experienced a medical SAE during the treatment phase of the study in more than one subject is provided in Table 14.

**Table 14: Medical Serious Adverse Events Observed in More than One Subject Chronic Population, Treatment Phase**

Preferred term <sup>a</sup>	HC-ER			ZX002-0801
	ZX002-0801	ZX002-0802	Total	Placebo
	N=151	N=424	N=575	N=151
Subjects with at least 1 medical SAE	5 (3.3%)	52 (12.0%)	56 (9.7%)	
Chronic obstructive pulmonary disease	0	5 (1.2%)	5 (0.9%)	0
Osteoarthritis	0	4 (0.9%)	4 (0.7%)	0
Pneumonia	0	3 (0.7%)	3 (0.5%)	0
Dehydration	0	2 (0.5%)	2 (0.3%)	0
Small intestinal obstruction	0	2 (0.5%)	2 (0.3%)	0
Intentional overdose	0	2 (0.5%)	2 (0.3%)	0
Hypokalaemia	1 (0.7%)	1 (0.2%)	2 (0.3%)	0
Anaemia	1 (0.7%)	1 (0.2%)	2 (0.3%)	0
Non-cardiac chest pain	1 (0.7%)	1 (0.2%)	2 (0.3%)	0
Depression	1 (0.7%)	1 (0.2%)	2 (0.3%)	0

Percentages are based on the number of subjects in each column.

Subjects were counted once within each preferred term.

<sup>a</sup>All investigator adverse event terms were coded using MedDRA dictionary version 12.1.

Source: ISS (June 14, 2012), p.133

The narratives of all subjects with medical SAEs on HC-ER in the development program were reviewed. All subjects who experienced an SAE were in the Chronic Population. Since the adverse event profile of opioids is well known given the experience with other opioids, SAEs that appeared reasonably related to HC-ER are summarized below and include the following: anxiety (1), mental impairment (2), small bowel obstruction (2) and abdominal distension/constipation (3). Review of three events coded as a SAE due to an overdose were reviewed and determined not to be an SAE or overdose. The events were coded as SAE and overdose due to the definition of overdose in Protocol ELN154088-203 which defined an overdose as taking more pills than prescribed whether or not there were any clinical sequelae. Three additional SAEs that did not appear related to HC-ER but are of special interest due to their seriousness are also summarized below: depression and homicidal ideation (1), intentional overdose with quetiapine (1) and intentional overdose and cutting wrists (1).

### **Individual Patient Nonfatal Serious Adverse Events Summaries**

#### **Subject 101-02 (Study ZX002-0801)**

*Nonfatal Serious Adverse Event: Anxiety*

Subject 101-02 was a 60 year old woman with a history of chronic low back pain, type II diabetes mellitus, arthritis, hypertension, gastroesophageal reflux disease, respiratory disorder, and multiple drug hypersensitivities. The subject began the C/T phase on HC-ER 10 mg BID. The subject started receiving HC-ER 50 mg BID on Drug Day 18 and was on this dose on Drug Day 22 when she was brought to the ER about 2 hours after experiencing sudden onset of shortness of breath, chest tightness, and anxiety. The anxiety was reported by the subject to have started 30-45 minutes after taking study drug. The subject reported chronic shortness of breath secondary to asthma, which had worsened on the morning of the day of the ER visit. The subject was admitted to the hospital for telemetry and further testing. Chest x-ray was negative for any acute cardiopulmonary process. The ECG revealed normal sinus rhythm and no acute ST or T-wave abnormalities. A ventriculogram showed an ejection fraction of 60% with normal wall motion. There was mild 20% plaque in the right coronary artery (RCA), left anterior descending (LAD) artery, and circumflex. Cardiac catheterization revealed non-obstructive coronary artery disease.

The SAE of anxiety was considered resolved 4 days after it began. The subject was discharged from the hospital with acetylsalicylic acid, montelukast, cetirizine, hydrochlorothiazide, potassium chloride, metformin, NPH insulin 70/30, and furosemide. The subject was discontinued from the study due to the SAE on Drug Day 37. After discontinuation from study, the subject was prescribed escitalopram 10 mg/day to treat the anxiety.

#### *Impression*

This subject had several confounding factors that make it difficult to determine whether her anxiety was related to HC-ER but study medication cannot be excluded given the reported onset of her anxiety 30 to 45 minutes after taking the medication.

#### **Subject 121-11 (Study ZX002-0801)**

##### *Nonfatal Serious Adverse Event: Abdominal Distention (Constipation)*

Subject 121-11 was a 67 year old woman with a history of chronic low back pain, hypertension, hyperlipidemia, hypothyroidism, fatigue, mood swings, arthritis and depression. The subject began the C/T phase on HC-ER 20 mg BID. On Drug Day 26, the subject began receiving HC-ER 90 mg BID. She received the last dose of study drug on Drug Day 42. On Study Day 45, the subject was seen in the ER for constipation, which had begun 2 days earlier. The subject had an abdominal x-ray that showed partial small bowel obstruction and laboratory results were significant for an elevated WBC  $14.2 \times 10^3/\mu\text{L}$  ( $4.5\text{-}10.5 \times 10^3/\mu\text{L}$ ) and low potassium  $3.0 \text{ mmol/L}$  ( $3.5\text{-}5.1 \text{ mmol/L}$ ). The subject was treated with an enema and she was discharged with polyethylene glycol electrolyte solution. After taking the polyethylene glycol electrolyte solution, the subject experienced nausea, diffuse abdominal distention, and diarrhea. The subject was admitted to the hospital for close observation and fluid replacement.

An abdominal x-ray revealed abnormal bowel loops in the left upper abdomen mildly distended with air fluid levels. The abdominal discomfort resolved and diet was advanced from clear liquids to regular diet with no problems. The subject was discharged home on Drug Day 48. This subject also had an SAE of diarrhea that led to the discontinuation of the study drug and SAE of hypokalemia.

*Impression*

The SAE of abdominal distention (constipation) may have been due to or exacerbated by the HC-ER. The SAEs of diarrhea and hypokalemia do not appear to be directly related to the HC-ER but were likely related to the treatment for her constipation.

**Subject 204-13 (Study ZX002-0802)**

*Nonfatal Serious Adverse Event: Ileitis (Small Bowel Obstruction)*

Subject 204-13 was a 47 year old woman with a history of hypochondroplasia, asthma, diabetes mellitus, hypertension, neck pain, back pain, anxiety and insomnia. There was no history of Crohn's disease or ulcerative colitis. She began C/T phase on 40 mg and up-titrated to 60 mg on Drug Day 7. She began the treatment phase on 60 mg on Drug Day 15 and up-titrated to 80 mg on Drug Day 71. The subject reported beginning to feel ill around Drug Day 60 and on Drug Day 83 experienced nausea, vomiting and diarrhea. On Drug Day 90, the subject presented to the emergency room and was admitted to the hospital with weakness, dehydration, abdominal pain, nausea, vomiting and diarrhea. Examination revealed fluid-filled stomach as well as small bowel loops suggestive of ileus or partial small bowel obstruction.

The study drug was interrupted from Drug Day 90 to 95. On Drug Day 91, there was no evidence of bowel obstruction. A computed tomography CT scan of the abdomen (with and without) contrast and CT scan of the pelvis (with contrast) revealed circumferential thickening of mid-to-distal small bowel loops. Mild to moderate distension of small bowel loops was seen, as were fatty changes of the liver with mild hepatomegaly. On Drug Day 92, the subject had a fever up to 99.7°F. A small bowel series revealed fold thickening consistent with inflammatory changes. On Drug Day 94, the SAE of ileitis was considered resolved and the subject was discharged from the hospital. The investigator considered the SAE of ileitis to be moderate in intensity and not related to study drug. The subject completed the study (last dose of study drug on Drug Day 350).

*Impression*

HC-ER cannot be excluded as a contributing cause of this subject's small bowel obstruction.

**Subject 217-01 (Study ZX002-0802)**

*Nonfatal Serious Adverse Event: Lethargy and Mental Deterioration*

Subject 217-01 was a 49 year old woman with a history of asthma, coronary artery disease, depression, anxiety, constipation, diabetes mellitus and chronic back and knee pain. She began the C/T phase on 20 mg and up-titrated to 40 mg on Day 6, 80 mg on Day 10, 100 mg on Day 13, 120 mg on Day 17, 140 mg on Day 21, 160 mg on Day 23 and 180 mg on Day 24.

On Day 26, the subject presented to an emergency room with lethargy and mental deterioration. Computed tomography scan of the head was clinically unremarkable. Study drug was permanently discontinued on Drug Day 27 and the subject's symptoms improved. The mental deterioration and lethargy resolved within a couple of days. Concomitant medications taken included quetiapine, moxifloxacin, methylprednisolone, alprazolam, clonazepam, escitalopram, amitriptyline, naproxen, estradiol (cream), nicotinic acid, clopidogrel, enalapril, rosuvastatin, metoprolol, acetylsalicylic acid, oxycodone, montelukast, cetirizine, budesonide with formoterol, metformin, insulin, gabapentin, pantoprazole, senna alexandrina and oxycodone/APAP.

*Impression*

The SAEs of lethargy and mental deterioration are probably related to HC-ER and responsible for her discontinuing the drug. It is noted that the up-titration was rather rapid with an increase from 20 mg to 180 mg in less than a month which may have contributed to her symptoms.

**Subject 228-02 (Study ZX002-0802)**

*Nonfatal Serious Adverse Event: Constipation*

Subject 228-02 was a 51 year old woman with a history of fibromyalgia, hypertension, depression, GERD, systemic lupus erythematosus and chronic constipation. She began the C/T phase on 40 mg and up-titrated to 60 mg on Day 4, 80 mg on Day 9, 100 mg on Day 15, 120 mg on Day 18, 160 mg on Day 29, 180 mg on Day 32, and 200 mg on Day 36. She began the treatment phase on 200 mg on Day 45 and her last dose of study drug was on Day 61

On Drug Day 62, the subject presented to the emergency room with abdominal and rectal pain. She reported no bowel movement for 3 days. The subject received laxatives and an enema. The subject also reported mild nausea and was found to have gastritis and worsening of GERD. The subject underwent an abdominal X-ray series that was negative for free air, but nonspecific bowel gas pattern was present with a few air-fluid levels in non-dilated loops of small bowel. On Drug Day 64, an upper gastrointestinal exam with air and small bowel follow-through revealed the pylorus as slightly widened possibly due to prior pyloroplasty or the result of peptic ulcer disease. Otherwise, the

examination was unremarkable with normal small bowel follow-through. On Day 64, lipase was elevated at 106 U/L (13-60), which prolonged the subject's hospitalization. On Day 65, the constipation and rectal pain were considered resolved, but the subject remained hospitalized. On the same day, laboratory exams revealed elevated lipase 170 U/L. On Drug Day 66, the subject underwent an esophagogastroduodenoscopy with biopsy that revealed esophagitis, diffuse gastritis, and a small hiatal hernia. The biopsy ruled out *Helicobacter pylori*. The following day, the subject underwent an abdominal magnetic resonance imaging without contrast. It was noted that the subject underwent a previous cholecystectomy. Dilatation of the common hepatic and common bile ducts, which may have resulted from prior cholecystectomy was also noted. No other significant abnormality was found. Laboratory examinations revealed lipase 122 U/L. The subject did not receive any treatments for elevated lipase. On Drug Day 68, the SAE of elevated lipase was considered resolved and the subject was discharged home.

Concomitant medications included acetazolamide, dietary fibers, cetirizine, clindamycin, cyclobenzaprine, diazepam, fleet enema, furosemide, glycerol, guaifenesin, ketorolac, lactulose, pethidine, liquid paraffin, macrogol, simethicone, naproxen, sodium chloride, omeprazole, ondansetron, pantoprazole, phentermine, sorbitol, topiramate, hydromorphone (on Drug Day 62), oxycodone/APAP (on Drug Day 65) and HC/APAP (on Drug Day 66 to 68).

#### *Impression*

The SAE of constipation was possibly related to HC-ER but the SAE of elevated lipase does not appear related to study drug. HC-ER was discontinued due to the SAE of constipation.

#### **Subject 229-10 (Study ZX002-0802)**

##### *Nonfatal Serious Adverse Event: Mental Impairment*

This patient is described in the section on deaths. His death was reported to be related to arteriosclerotic coronary artery disease but the basis for this diagnosis is unclear. His SAE of mental impairment described in the section on deaths may have been related to HC-ER.

#### **Subject 235-21 (Study ZX002-0802)**

##### *Nonfatal Serious Adverse Event: Small Intestinal Obstruction*

Subject 235-21 was a 61 year old man with a history of back pain, hypertension, irritable bowel syndrome, GERD, anxiety, diverticulosis, hyperlipidemia, esophagitis, sleep apnea and hyperhidrosis. He began the C/T phase on 80 mg and up-titrated to 100 mg on Day 5, and 120 mg on Day 12. He began the treatment phase on 120 mg on Day 22 and up-titrated to 140 mg on Day 49 and 160 mg on Day 188. The last dose of study drug was on Day 355.

On Day 133, the subject was admitted to the hospital with worsening upper right-sided abdominal pain and some nausea and vomiting. Physical examination revealed a soft abdomen, with some tenderness into his upper quadrant. Computed tomography scan (with contrast) of the abdomen and pelvis revealed abnormal dilation of the small bowel, consistent with mid-to-distal small bowel obstruction. Final diagnosis included small bowel obstruction and dehydration. A nasogastric tube was placed and he was treated with IV fluids, pain medications and antiemetics. On Day 134, the SAE of small intestinal obstruction was considered resolved.

This subject was also reported as having SAEs of worsening degenerative disc disease, joint instability and deep vein thrombosis (following a right knee arthroplasty). None of these SAEs was related to HC-ER.

#### *Impression*

The SAE of small bowel obstruction may have been related or exacerbated by the HC-ER.

#### **Subject 104-10 (Study ZX002-0802)**

##### *Nonfatal Serious Adverse Event: Coded Gastroenteritis (constipation)*

Subject 104-10 was a 49 year old woman with a history of diabetes, diabetic peripheral neuropathy, anxiety and depression. She began the C/T phase on 60 mg and up-titrated to 80 mg on Day 4, 100 mg on Day 12, 160 mg on Day 23 and began treatment phase on 160 mg on Day 48. She up-titrated to 180 mg on Day 138 and 200 mg on Day 245. The last dose of study drug was on Day 385.

From Drug Day 342 to 374, the subject suffered from constipation which was initially mild, but then severe and considered probably related to study drug. On Drug Day 374, the subject experienced acute gastroenteritis and was admitted to the hospital. The pain was mostly located in the epigastric region with some radiation to the right upper quadrant. The pain was associated with nausea, vomiting, and diarrhea, but not fever. The study drug was interrupted due to the event. The subject had dehydration and hypokalemia that required intravenous fluid and potassium replacement. An abdominal and pelvis computed tomography scan (with contrast) revealed some mildly distended loops of small bowel in the left mid abdomen, with diffuse mesenteric edema suggestive of enteritis versus early bowel obstruction. There was trace ascites in the abdomen and pelvis. An abdominal ultrasound confirmed the liver and biliary system were normal. On Drug Day 378, the event was considered resolved and the subject was discharged from the hospital. The study drug was interrupted from Drug Day 374 to 377. The investigator considered the SAE of gastroenteritis not related to study drug and the subject completed the study with the last dose of study drug on Day 385.

*Impression*

This subject was coded with an SAE of gastroenteritis but the exact etiology of this subject's abdominal pain with nausea, vomiting and diarrhea is unclear. Clinical findings and abdominal CT exam are also suggestive of possible small bowel obstruction. HC-ER cannot be excluded as a cause or exacerbating factor of her symptoms.

Individual Nonfatal Serious Adverse Events Coded as Overdose

In Protocol ELN154088-203 an overdose, whether or not there were any clinical sequelae, was included in the definition of SAE.

**Subject 1-S006 (ELN154088-203)**

*Serious Adverse Event: Accidental Overdose*

Subject 1-S006 was a 64 year old woman who received HC-ER 10 mg BID for 7 days, 20 mg BID for 7 days, and 30 mg BID for 7 days. On Day 17, her third day at the 30-mg dose, she could not remember whether she had taken her study drug dose and therefore took another dose. This event was reported as an accidental overdose of study drug of mild severity but due to the definition of SAE in the protocol was considered a SAE. Later the day she developed mild chills, moderate pruritus, and moderate nervousness which the investigator judged to be related to study drug. It is noted that this subject did not require treatment or any change in dosage and completed the study according to the protocol.

*Impression:*

Although this event was listed as a SAE for accidental overdose due to the protocol definitions, review of the case does not support that there was an overdose or SAE.

**Subject 2-S011 (ELN154088-203)**

*Serious Adverse Event: Accidental Overdose*

Subject 2-S011 was a 55 year old man who received HC-ER 20 mg BID for 7 days, 30 mg BID for 7 days, and 40 mg BID for 7 days. On Day 10, of his third day at the 30-mg dose, he could not remember whether he had taken his morning dose and therefore took another dose. No treatment or change in dose was required for this event.

*Impression:*

Although this event was listed as a SAE for accidental overdose due to the protocol definitions, review of the case does not support that there was an overdose or SAE.

**Subject 3-S0018 (ELN154088-203)**

*Serious Adverse Event: Accidental Overdose*

Subject 3-S018 was a 64 year old woman who received HC-ER 20 mg BID for 7 days, 30 mg BID for 7 days, and 40 mg BID for 7 days. On Day 12, her fifth day at the 30-mg dose, she could not remember whether she had taken her study drug dose and therefore took another dose. This event was reported as an accidental overdose of study drug.

*Impression:*

Although this event was listed as a SAE for accidental overdose due to the protocol definition, review of the case does not support that this event was an overdose or SAE.

Individual Nonfatal Serious Adverse Events of Special Interest

**Subject 237-18 (Study ZX002-0802)**

*Nonfatal Serious Adverse Event: Intentional Overdose, Pulmonary Embolism*

Subject 236-18 was a 57 year old woman with a history of headache, anxiety, depression, deep vein thrombosis, back and leg pain, restless legs syndrome and hypothyroidism. She began the C/T phase on 40 mg and up-titrated to 60 mg on Day 4, 80 mg on Day 13, 100 mg on Day 16, 140 mg on Day 31, 160 mg on Day 36 and began treatment phase on 160 mg on Day 45. She up-titrated to 180 mg on Day 67, 200 mg on Day 116, 220 mg on Day 173 and 240 mg on Day 326. The last dose of study drug was on Day 386.

On Drug Day 375, the subject's family member was unable to rouse her from sleep over the course of a day. After 36 hours of sleep, the unresponsive subject was taken to the emergency room, where she experienced a brief seizure. She was intubated, given fluid, and put on mechanical ventilation. She was hypothermic and hypernatremic with a Glasgow coma scale score of 3. The subject's urine drug screen was positive for benzodiazepines. It was discovered that the subject took quetiapine fumarate (2700 to 3000 mg), a drug for which she did not have a prescription, because she was having difficulty sleeping. The subject denied attempting suicide. On Drug Day 376, a computed tomography angiogram with contrast of the subject's chest revealed acute, small peripheral pulmonary artery emboli of the lower lungs. The subject was extubated on Day 378. The psychiatry department was consulted and the subject was cleared to go home. The subject completed the study with last dose of study drug on Day 386.

*Impression*

This subject's intentional overdose with quetiapine which she reports was to help with sleep does not appear to be related to HC-ER. The SAE pulmonary embolus is not related to HC-ER.

**Subject 225-04 (Study ZX002-0802)**

*Nonfatal Serious Adverse Event: Suicide Attempt (cutting wrists and intentionally overdosing)*

Subject 225-04 was a 62 year old man with a history of chronic low back pain, sleep disturbance, intermittent depression, restless legs syndrome, bipolar disorder and anxiety. He began the C/T phase on 40 mg and up-titrated to 80 mg and began treatment phase on Day 28. The last dose of study drug was on Day 93.

On Day 93, the subject attempted suicide by cutting his wrists and intentionally overdosing (by taking all his study medication at one time). The subject was found in a pond and transported to the hospital. On admission, he presented with hypothermia. He was admitted to the intensive care unit for several days and then transferred to the hospital crisis center. On Day 97, the subject was discharged home and the event of attempted suicide was considered resolved.

Concomitant medications included diphenhydramine, ibuprofen, clonazepam, lamotrigine, lovastatin, gabapentin, carbidopa-levodopa, trazodone, diazepam, hydroxyzine, sertraline, olanzapine and APAP.

The subject had longstanding diagnoses of depression (25 years), bipolar disorder (13 years), and anxiety (5 years). The subject's psychiatric disorders had been successfully managed with medication (clonazepam, lamotrigine, sertraline, and carbidopa/levodopa). Because of loss of health insurance coverage, the subject had not been taking his medications for approximately 2 months prior to the suicide attempt.

*Impression*

This subject's attempted suicide was not related to HC-ER but likely due to stopping his psychiatric medications following loss of insurance coverage.

**Subject 103-10 (Study ZX002-0801)**

*Nonfatal Serious Adverse Event: Depression and Homicidal Ideation*

Subject 103-10 was a 47 year old man with a medical history of chronic low back pain, hypertension, chronic obstructive pulmonary disease, gastroesophageal reflux disease, anxiety, depression, and insomnia. Additional medical history included traumatic brain injury, mood disorder, chronic mental illness, heroin drug abuse, codeine allergy, sleep apnea, asthma, panic attacks, diabetes type II, and coronary atherosclerosis.

The subject began the C/T phase on HC-ER 20 mg BID and the dose was up-titrated during this phase. On Day 25, the subject was randomized and began receiving HC-ER 70 mg BID. On Day 57 while on 70 mg BID he was admitted to the hospital for worsening of depressive disorder and homicidal ideation. The subject had obsessive thoughts of shooting his mother's boyfriend. The subject reported that voices were urging him to act on his anger and kill the man. The subject also reported hearing

doorbells ringing and voices telling him to kill people who hurt animals. The subject reported these phenomena were all new to him and they had been increasing in intensity. The subject requested an inpatient program to prevent him from acting on his homicidal thoughts.

The subject was oriented to time, place, and person. He did not display any memory deficit. He had homicidal and suicidal preoccupations and was depressed. A urine drug screen was positive for benzodiazepine and opiates. According to the subject, he had not used marijuana, amphetamine, or excessive alcohol within the past five years. Treatment for the event included individual and group work and medication, including paliperidone, risperidone, and carbamazepine. The subject also received hydrocodone/acetaminophen for CLBP beginning on the day of hospitalization. Concomitant medications taken at the time of the event included amlodipine, esomeprazole, clonazepam, duloxetine, metoprolol, atorvastatin, trazodone, tizanidine, diphenhydramine, paliperidone, albuterol, ipratropium/albuterol, fluticasone/salmeterol, and acetylsalicylate. The subject was discharged on Drug Day 66.

#### *Impression*

This subject's worsening depression and homicidal ideation do not appear to be related to HC-ER given his long history of psychiatric problems. However, it is impossible to completely exclude study drug as a contributing factor although it is considered unlikely.

### 7.3.3 Dropouts and/or Discontinuations

All subjects in the Chronic Population received HC-ER for the C/T phase. A summary of subject disposition in the Chronic Population is provided in Table 15. The majority of subjects in the Chronic Population completed the C/T phase (63.2%). Successful stabilization on HC-ER was slightly higher in Study ZX002-0802 vs Study ZX002-0801 (66.5% vs 59.2%). The Applicant speculates that the higher stabilization rate in Study ZX002-0802 may be related to the flexibility of using higher doses of HC-ER.

**Table 15: Subject Disposition - Chronic Population, C/T Phase**

Disposition	HC-ER		Total N=1148
	ZX002-0801 N=510	ZX002-0802 N=638	
Subjects who completed	302 (59.2%)	424 (66.5%)	726 (63.2%)
Subjects who discontinued early	208 (40.8%)	214 (33.5%)	422 (36.8%)
Reasons for discontinuation			
Protocol violation	67 (13.1%)	68 (10.7%)	135 (11.8%)
Adverse event			
Other	46 (9.0%)	56 (8.8%)	102 (8.9%)
Opioid withdrawal	1 (0.2%)	3 (0.5%)	4 (0.3%)
Non-compliance with study drug	47 (9.2%)	53 (8.3%)	100 (8.7%)
Withdrawal of consent by subject	23 (4.5%)	26 (4.1%)	49 (4.3%)
Lack of efficacy	17 (3.3%)	0	17 (1.5%)
Lost to follow-up	5 (1.0%)	3 (0.5%)	8 (0.7%)
Physician decision	2 (0.4%)	5 (0.8%)	7 (0.6%)

Note: Percentages are based on the total number of subjects in each column.

Source: ISS (June 14, 2012), p.50

A summary of subject disposition in the Chronic Population for the treatment phase is provided in Table 16. In Study ZX002-0801, 82.1% of HC-ER group subjects and 39.1% of placebo group subjects completed the treatment phase. In Study ZX002-0802, 67.2% of subjects (all of whom received HC-ER) completed the treatment phase. In Study ZX002-0801, a larger percentage of placebo group subjects discontinued prematurely (60.9%) compared with HC-ER group subjects (17.9%). As expected a larger percentage of placebo group subjects discontinued due to lack of efficacy compared with HC-ER group (42.4% vs 9.3%). In Study ZX002-0801, 4.6% of placebo group subjects and no HC-ER group subject discontinued due to opioid withdrawal. Two subjects (0.5%) in Study ZX002-0802 discontinued due to opioid withdrawal. Discontinuations due to AEs not related to opioid withdrawal were comparable for HC-ER group and placebo group subjects in the treatment phase of Study ZX002-0801 (1.3% vs 3.3%). The rate of discontinuations due to adverse events in Study ZX002-0802 was higher (9.4%). The Applicant speculates that the difference between the two studies is likely attributable to the longer treatment period used in Study ZX002-0802.

Subjects withdrew consent from the Study ZX002-0801 in an equal proportion (3.3%) for HC-ER and placebo groups, which was comparable to the proportion of subjects who withdrew consent from Study ZX002-0802. Protocol violations led to the discontinuation of approximately 1% of subjects in Study ZX002-0801 and approximately 2% of subjects in Study ZX002-0802.

**Table 16: Subject Disposition - Chronic Population, Treatment Phase**

Disposition	HC-ER		Total	ZX002-0801 Placebo
	ZX002-0801	ZX002-0802		
	N=151	N=424	N=575	N=151
Subjects who completed	124 (82.1%)	285 (67.2%)	409 (71.1%)	59 (39.1%)
Subjects who discontinued early	27 (17.9%)	139 (32.8%)	166 (28.9%)	92 (60.9%)
Reasons for discontinuation				
Non-compliance with study drug	4 (2.6%)	48 (11.3%)	52 (9.0%)	7 (4.6%)
Adverse event				
Other	2 (1.3%)	40 (9.4%)	42 (7.3%)	5 (3.3%)
Opioid withdrawal	0	2 (0.5%)	2 (0.3%)	7 (4.6%)
Withdrawal of consent by subject	5 (3.3%)	27 (6.4%)	32 (5.6%)	5 (3.3%)
Lack of efficacy	14 (9.3%)	-	14 (2.4%)	64 (42.4%)
Protocol violation	1 (0.7%)	9 (2.1%)	10 (1.7%)	2 (1.3%)
Lost to follow-up	1 (0.7%)	8 (1.9%)	9 (1.6%)	0
Other	0	2 (0.5%)	2 (0.3%)	1 (0.7%)
Physician decision	0	3 (0.7%)	3 (0.5%)	1 (0.7%)

Note: Percentages are based on the total number of subjects in each column.

Source: ISS (June 14, 2012), p.52

All narratives of subjects discontinuing due to adverse events were reviewed. The most common adverse events leading to study discontinuation were not unexpected for an opioid and included nausea, somnolence, constipation, vomiting, lethargy, fatigue, and cognitive changes. A summary of the adverse events that led to discontinuation during the C/T phase in the Chronic Population is provided in Table 17.

**Table 17: Adverse Events that Led to Discontinuation of More Than One Subject in the Chronic Population, C/T Phase**

Preferred term <sup>a</sup>	HC-ER		
	ZX002-0801 N=510	ZX002-0802 N=638	Total N=1148
Subjects with at least 1 TEAE that led to discontinuation	55 (10.8%)	66 (10.3%)	121 (10.5%)
Nausea	15 (2.9%)	10 (1.6%)	25 (2.2%)
Somnolence	4 (0.8%)	9 (1.4%)	13 (1.1%)
Headache	3 (0.6%)	7 (1.1%)	10 (0.9%)
Constipation	7 (1.4%)	3 (0.5%)	10 (0.9%)
Vomiting	6 (1.2%)	4 (0.6%)	10 (0.9%)
Lethargy	2 (0.4%)	7 (1.1%)	9 (0.8%)
Insomnia	2 (0.4%)	7 (1.1%)	9 (0.8%)
Dizziness	2 (0.4%)	2 (0.3%)	4 (0.3%)
Oedema peripheral	1 (0.2%)	3 (0.5%)	4 (0.3%)
Pruritus allergic	2 (0.4%)	2 (0.3%)	4 (0.3%)
Fatigue	3 (0.6%)	0	3 (0.3%)
Abdominal pain	2 (0.4%)	1 (0.2%)	3 (0.3%)
Agitation	2 (0.4%)	0	2 (0.2%)
Depression	2 (0.4%)	0	2 (0.2%)
Anxiety	1 (0.2%)	1 (0.2%)	2 (0.2%)
Non-cardiac chest pain	1 (0.2%)	1 (0.2%)	2 (0.2%)
Pain in extremity	1 (0.2%)	1 (0.2%)	2 (0.2%)
Haematochezia	1 (0.2%)	1 (0.2%)	2 (0.2%)
Hyperhidrosis	1 (0.2%)	1 (0.2%)	2 (0.2%)
Drug withdrawal syndrome	0	2 (0.3%)	2 (0.2%)
Feeling jittery	0	2 (0.3%)	2 (0.2%)
Irritability	0	2 (0.3%)	2 (0.2%)
Arthralgia	0	2 (0.3%)	2 (0.2%)

Percentages are based on the number of subjects in each column.

Subjects were counted once within each preferred term.

All investigator adverse event terms were coded using MedDRA dictionary version 12.1.

Drug diversion events are not included in this table.

Source: ISS (June 14, 2012), p.137

A summary of the adverse events that led to discontinuation in the Chronic Population during the treatment phase is provided in Table 18. The most common causes in the HC-ER group were not unexpected and included gastrointestinal and cognitive changes. In the placebo group, not unexpectedly, the most common cause was opioid withdrawal syndrome in six subjects (4%).

**Table 18: Adverse events that Led to Discontinuation of More than One Subject in the Chronic Population, Treatment Phase**

	HC-ER			ZX002-0801
	ZX002-0801	ZX002-0802	Total	Placebo
Preferred term <sup>a</sup>	N=151	N=424	N=575	N=151
Subjects with at least 1 TEAE that led to discontinuation	3 (2.0%)	34 (8.0%)	37 (6.4%)	16 (10.6%)
Abdominal pain upper	0	2 (0.5%)	2 (0.3%)	0
Constipation	0	2 (0.5%)	2 (0.3%)	0
Cognitive disorder	0	2 (0.5%)	2 (0.3%)	0
Back pain	1 (0.7%)	1 (0.2%)	2 (0.3%)	2 (1.3%)
Withdrawal syndrome	1 (0.7%)	0	1 (0.2%)	6 (4.0%)
Insomnia	0	1 (0.2%)	1 (0.2%)	2 (1.3%)

Percentages are based on the number of subjects in each column.

Subjects were counted once within each preferred term.

All investigator adverse event terms were coded using MedDRA dictionary version 12.1.

Drug diversion events are not included in this table.

Source: ISS (June 14, 2012), p.138

### 7.3.4 Significant Adverse Events

Discussed in Section 7.3.2

### 7.3.5 Submission Specific Primary Safety Concerns

Not applicable

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The most common adverse events in HC-ER treated subjects from Study ZX002-0801 are listed in Table 19. The most common adverse events were consistent with the opioid class of drugs and include constipation, nausea, somnolence, fatigue, headache and dizziness.

**Table 19: Adverse Events in ≥2% of Subjects in ZX002-0801**

	Open-Label Titration Period	Double-Blind Treatment Period	
	Zohydro	Zohydro	Placebo
<b>Preferred Term</b>	<b>(N = 510)</b>	<b>(n = 151)</b>	<b>(n = 151)</b>
Constipation	56 (11.0%)	12 (7.9%)	0 (0.0%)
Nausea	50 (9.8%)	11 (7.3%)	5 (3.3%)
Somnolence	24 (4.7%)	1 (0.7%)	0 (0.0%)
Fatigue	21 (4.1%)	1 (0.7%)	2 (1.3%)
Headache	19 (3.7%)	0 (0.0%)	2 (0.7%)
Dizziness	17 (3.3%)	3 (2.0%)	1 (0.7%)
Dry Mouth	16 (3.1%)	0 (0.0%)	0 (0.0%)
Vomiting	14 (2.7%)	7 (4.6%)	1 (0.7%)
Pruritus	13 (2.5%)	0 (0.0%)	0 (0.0%)
Abdominal Pain	8 (1.6%)	4 (2.6%)	0 (0%)
Edema peripheral	7 (1.4%)	4 (2.6%)	0 (0.0%)
Upper respiratory tract infection	7 (1.4%)	5 (3.3%)	1 (0.7%)
Muscle spasms	6 (1.2%)	4 (2.6%)	2 (1.3%)
Urinary Tract Infection	4 (0.8%)	8 (5.3%)	3 (2.0%)
Back Pain	4 (0.8%)	6 (4.0%)	5 (3.3%)
Tremor	1 (0.2%)	4 (2.6%)	1 (0.7%)

Source: Tables 14.3.9.3.1 and 14.3.9.3.2 in the ISS (June 14, 2012)

For the long-term open-label safety study (ZX002-0802), the common adverse events were reviewed and found to be similar to Study ZX002-0802. The most common adverse events during the C/T Phase in ZX002-0802 were: constipation (11.3%), nausea (10.7%), somnolence (7.7%), headache (7.5%), vomiting (4.1%), insomnia (3.8%), fatigue (3.6%), diarrhea (3.1%), dizziness (2.8%), dry mouth (1.9%) and pruritus (1.7%). In the treatment phase the most common adverse events were: constipation (12.5%), back pain (11.1%), nausea (9.9%), vomiting (9.7%), arthralgia (7.8%), headache (6.8%), urinary tract infection (6.6%), upper respiratory tract infection (5.9%), fall (5.9%), anxiety (5.4%), nasopharyngitis (5.7%), sinusitis (5.4%), insomnia (5.0%). Additional adverse events reported that are often associated with opioids included somnolence (4.2%), fatigue (3.5%), confusion (3.3%), and dizziness (3.1%).

#### 7.4.2 Laboratory Findings

Clinical laboratory tests were performed in the chronic population in Studies ZX002-0801 and ZX002-0802. The Applicant provided shifts from normal at Screening to abnormal in laboratory values and changes in mean values. Results from both studies were reviewed but only data from Study ZX002-0801 which had a placebo group as a control are displayed.

##### Hematology

Table 20 provides a summary of hematology shifts for Protocol ZX002-0801. No clinically significant shifts in hematology values were identified. Review of the mean changes in hemoglobin, hematocrit, leukocytes, platelets, eosinophils, basophils, neutrophils and monocytes from screening to Day 85 showed no apparent clinically meaningful differences between HC-ER and placebo.

<b>Table 20: Shift Summary of Hematology Results for Protocol ZX002-0801</b>					
		HC-ER (N=151)		Placebo (N=151)	
		Screening Result		Screening Result	
<i>Parameter</i>	<i>Time</i>	<i>Normal</i>	<i>Abnormal</i>	<i>Normal</i>	<i>Abnormal</i>
Hemoglobin	Day 85				
	Normal	126 (86.9%)	5 (3.4%)	127 (90.1%)	6 (4.3%)
	Abnormal	3 (2.1%)	11 (7.6%)	3 (2.1%)	5 (3.5%)
Hematocrit	Day 85				
	Normal	98 (67.6%)	11 (7.6%)	103 (73.0%)	9 (6.4%)
	Abnormal	14 (9.7%)	22 (15.2%)	12 (8.5%)	17 (12.1%)
Leukocytes	Day 85				
	Normal	116 (80.0%)	6 (4.1%)	111 (78.7%)	11 (7.8%)
	Abnormal	13 (9.0%)	10 (6.9%)	14 (9.9%)	5 (3.5%)
Platelets	Day 85				
	Normal	140 (96.6%)	2 (1.4%)	129 (94.9%)	2 (1.5%)
	Abnormal	1 (0.7%)	2 (1.4%)	3 (2.2%)	2 (1.5%)

Source: Table 14.3.4.4.1 in the CSR ZX002-0801

Chemistry

Table 21 provides a summary of shifts in chemistry results from screening to Day 85/Early Termination for Protocol ZX002-0801. There did not appear to be any clinically significant shifts in chemistry findings between the HC-ER and placebo groups.

<b>Table 21: Shift Summary of Chemistry Results for Protocol ZX002-0801</b>					
		HC-ER (N=151)		Placebo (N=151)	
		Screening Result		Screening Result	
<i>Parameter</i>	<i>Time</i>	<i>Normal</i>	<i>Abnormal</i>	<i>Normal</i>	<i>Abnormal</i>
ALT	Day 85				
	Normal	135 (94.4%)	5 (3.5%)	126 (88.7%)	5 (3.5%)
	Abnormal	2 (1.4%)	1 (0.7%)	2 (1.4%)	9 (6.3%)
Albumin	Day 85				
	Normal	139 (96.5%)	1 (0.7%)	136 (95.8%)	3 (2.1%)
	Abnormal	3 (2.1%)	1 (0.7%)	2 (1.4%)	1 (0.7%)
Alkaline Phosphatase	Day 85				
	Normal	134 (93.1%)	0 (0%)	134 (94.4%)	1 (0.7%)
	Abnormal	3 (2.1%)	7 (4.9%)	3 (2.1%)	4 (2.8%)
Amylase	Day 85				
	Normal	132 (91.7%)	4 (2.8%)	120 (84.5%)	4 (2.8%)
	Abnormal	1 (0.7%)	7 (4.9%)	9 (6.3%)	9 (6.3%)
AST	Day 85				
	Normal	134 (93.7%)	4 (2.8%)	125 (88.0%)	6 (4.2%)
	Abnormal	5 (3.5%)	0 (0%)	3 (2.1%)	8 (5.6%)
Bicarbonate	Day 85				
	Normal	91 (63.6%)	15 (10.5%)	94 (66.2%)	24 (16.9%)
	Abnormal	26 (18.2%)	11 (7.7%)	16 (11.3%)	8 (5.6%)
Bilirubin	Day 85				
	Normal	103 (71.5%)	5(3.5%)	107 (75.4%)	9 (6.3%)
	Abnormal	19 (13.2%)	17 (11.8%)	19 (13.4%)	7 (4.9%)
Calcium	Day 85				
	Normal	140 (97.2%)	3 (2.1%)	140 (98.6%)	1 (0.7%)
	Abnormal	1 (0.7%)	0 (0%)	0 (0%)	1 (0.7%)
Chloride	Day 85				
	Normal	134 (93.1%)	1 (0.7%)	127 (89.4%)	5 (3.5%)
	Abnormal	8 (5.6%)	1 (0.7%)	9 (6.3%)	1 (0.7%)
Cholesterol	Day 85				
	Normal	62 (43.1%)	31 (21.5%)	64 (45.1%)	22 (15.5%)
	Abnormal	15 (10.4%)	36 (25.0%)	18 (12.7%)	38 (26.8%)

Creatinine	Day 85				
	Normal	134 (93.1%)	4 (2.8%)	131 (92.3%)	2 (1.4%)
	Abnormal	3 (2.1%)	3 (2.1%)	6 (4.2%)	3 (2.1%)
Gamma Glutamyl Transferase	Day 85				
	Normal	91 (63.2%)	14 (9.7%)	93 (65.5%)	11 (7.7%)
	Abnormal	6 (4.2%)	33 (22.9%)	5 (3.5%)	33 (23.2%)
Glucose	Day 85				
	Normal	83 (57.6%)	30(20.8%)	78 (55.3%)	32 (22.7%)
	Abnormal	6 (4.2%)	25 (17.4%)	12 (8.5%)	19 (13.5%)
Potassium	Day 85				
	Normal	138 (96.5%)	2 (1.4%)	133 (94.3%)	3 (2.1%)
	Abnormal	2 (1.4%)	1 (0.7%)	5 (3.5%)	0 (0%)
Protein	Day 85				
	Normal	137 (95.1%)	2 (1.4%)	128 (90.1%)	7 (4.9%)
	Abnormal	2 (1.4%)	3 (2.1%)	3 (2.1%)	4 (2.8%)
Sodium	Day 85				
	Normal	142 (98.6%)	1 (0.7%)	136 (95.8%)	1 (0.7%)
	Abnormal	1 (0.7%)	0 (0%)	5 (3.5%)	0 (0%)
Blood Urea Nitrogen	Day 85				
	Normal	130 (90.3%)	9 (6.3%)	127 (90.1%)	3 (2.1%)
	Abnormal	2 (1.4%)	3 (2.1%)	4 (2.8%)	7 (5.0%)
Urate	Day 85				
	Normal	133 (92.4%)	5 (3.5%)	123 (86.6%)	9 (6.3%)
	Abnormal	5 (3.5%)	1 (0.7%)	8 (5.6%)	2 (1.4%)

Source: Table 14.3.4.2.1 in the CSR ZX002-0801

### 7.4.3 Vital Signs

Vital signs in the chronic population were monitored at each study visit. The vital signs were reviewed for Studies ZX002-0801 and ZX002-0802 but only data from Study ZX002-0801 which had a placebo group for comparison are displayed (Table 22). No clinically significant unexpected changes in any of the parameters monitored (i.e., blood pressure, pulse, temperature and respiratory rate) were observed. Changes in blood pressure were consistent with a mild hypotensive effect which is known to occur with opioids. There did not appear to be any clinically relevant change in pulse, temperature or respiratory rate in the chronic population.

In Study ELN-154088-201, the single-dose post-bunionectomy study, hypoxia was reported as an adverse event in four subjects and oxygen desaturation was reported in an additional three subjects. The oxygen saturation values for the four subjects reported to have hypoxia were all greater than 90%. Two of the subjects were on HC-ER (10 mg and 30 mg), one subject was on 10 mg HC/APAP and one subject was on

placebo. There were three subjects with oxygen saturation below 90% (87%, 89% and 89%). Two subjects were on HC-ER (10 mg and 20 mg) and one subject on 10 mg HC/APAP. There did not appear to be a dose response with HC-ER and hypoxia or desaturation (i.e., no case on the highest dose 40 mg and only one case on the next highest dose, 30 mg). This finding of oxygen desaturation during the post-operative period is not unexpected. The label specifically notes that HC-ER is not indicated in the immediate postoperative period.

<b>Table 22: Summary of Change in Vital Signs for Protocol ZX002-0801 from Screening to Day 85/Early Termination</b>			
Parameter		HC-ER (N=147)	Placebo (N=147)
Systolic BP (mmHg)	Mean	-2.9	-2.7
	Min	-56	-34
	Max	35	28
Diastolic BP (mmHg)	Mean	-3.7	-0.7
	Min	-32	-26
	Max	17	28
Pulse (Beats/Min)	Mean	1.2	3.2
	Min	-35	-29
	Max	44	38
Temperature (C)	Mean	0.01	0.07
	Min	-1.0	-1.3
	Max	1.0	0.9
Respiratory Rate (Breaths/Min)	Mean	0.01	0.07
	Min	-1.0	-1.3
	Max	1.0	0.9

Source: Table 14.3.5 in the CSR ZX002-0801

#### 7.4.4 Electrocardiograms (ECGs)

ECGs were collected at screening and end of study in the following four studies: ELN-302002, ELN-901001, ELN-154088-201, and ELN-154088-203. A total of 159 subjects received HC-ER in these four studies. The data for P-R interval, QRS interval and QT interval were reviewed for all these studies. No clinically meaningful changes were identified in these parameters. However, interpretation of the findings were limited because ECGs were not collected at Cmax and the highest dose of HC-ER administered was only 40 mg. ECGs were collected only at screening in studies ZX002-0901, ZX002-1001, ZX002-1002, ZX002-0801, ZX002-0802 and ZX002-1102.

### **Study ELN-302002**

This was a single-dose pharmacokinetic study of HC-ER 20 mg administered fasted and fed in 12 healthy subjects. 12-lead ECGs were obtained at screening and at the poststudy assessment. The mean QTc change was 5.4 msec and maximum change in QTc was 45 msec. The maximum QTc at end of study was 425 msec.

### **Study ELN-901001**

This was a bioavailability study of a single-dose of different formulations of HC 20 mg in 18 healthy subjects. Resting 12-lead ECGs were conducted at screening and at the poststudy assessment. The mean QTc change was 6.6 msec and maximum change in QTc was 48 msec. The maximum QTc at end of study was 440 msec.

### **Study ELN-154088-201**

This was a single-dose efficacy and safety study in subjects following bunionectomy surgery. 241 subjects were randomly assigned to 1 of 6 treatment groups: 10, 20, 30 or 40 mg of HC-ER, active comparator (10 mg hydrocodone/325 mg APAP) or placebo. ECGs were obtained at screening and discharge. There was no evidence of a dose relationship with QT interval. The mean QTc intervals at screening and discharge were the following: HC-ER 10 mg - screening 417.6, discharge 426.4; HC-ER 20 mg - screening 421.8, discharge 421.6; HC-ER 30 mg - screening 420.4, discharge 417.5; HC-ER 40 mg – screening 416.5, discharge 417.3; HC/APAP - screening 420.9, discharge 416.9 and placebo - screening 418.9, discharge 422.4.

### **Study ELN-154088-203**

This was a multiple-dose open-label study in 37 patients with chronic, moderate to severe osteoarthritis pain treated with HC-ER for 21 days. Subjects were started on 10 or 20 mg BID and the dose was increased weekly up to 40 mg BID. ECGs were obtained at screening and follow-up. The mean QTc at follow-up was less than at screening. The greatest change in QTc was 45 msec in one patient where QTc was 434 msec at screening and 479 msec at Day 28.

## **7.4.5 Special Safety Studies/Clinical Trials**

### Audiology Evaluations

Since progressive hearing loss has been associated with the abuse of hydrocodone/acetaminophen combination products, and the potential exposure to hydrocodone from this product is higher than the labeled doses from combination products, the FDA requested that Zogenix perform audiometry assessments to monitor for potential hearing loss. Results of the audiometry evaluations performed on 510 subjects in Study ZX002-0801 were reviewed by James Kane, Ph.D. from the Center for Devices and Radiological Health (CDRH) at the FDA. He concluded that HC-ER appears not to affect hearing sensitivity for the dosages studied (maximum HC-ER dose allowed in Study ZX002-0801 was 200 mg per day).

Excerpts from Dr. Kane's review of Protocol ZX002-0801 are reproduced below:

A medical history specifically for hearing issues was collected from each subject including information regarding exposure to noise levels (occupational or otherwise). Subjects were categorized at screening as "low risk" or "high risk" for the purposes of analyzing the audiometry data. High-risk subjects were those who had at least one of the following at screening: tinnitus, a medical history of hearing loss, or evidence of impairment in the pure-tone audiometry test. All other subjects were categorized as low risk. Prior to the audiology testing an otologic physical examination was conducted to rule out active pathological conditions and excessive cerumen.

Subjects received pure tone audiometry testing at the Screening Visit (Visit 1) prior to enrollment into the Conversion Titration Phase (which consisted of up to 6 weeks of HC-CR treatment for all subjects), at Baseline (Visit 8) (when subjects were randomized to HC-CR or placebo in a ratio of 1:1), and at End of Study (Visit 13) (up to 3 months of blinded treatment or early termination). Subjects were to be retested within 2 weeks if results suggest any clinical significant change (using prespecified criteria) in hearing levels from the Screening Visit and were to be referred for further evaluation by an external specialist if the results on retest remained clinically significantly abnormal. A clinically significant change from the Screening Visit (baseline value) was determined as 1) a 20 dB decrease at any one test frequency; or 2) a 10 dB decrease at any two adjacent test frequencies; or 3) a loss of response at three consecutive test frequencies where responses were previously obtained. The audiometers were supplied from the instrumentation provider fully calibrated and then were calibrated on an annual basis. Calibration was password protected to ensure the integrity of data.

Clinical staff from each site received appropriate centralized training to use the audiometer and perform the testing under the supervision of a responsible physician (per 29 CFR 1910.95 (g)(4)). Testing took place in a designated room at each site, under similar circumstances at each visit (same room, same noise level, i.e., quiet).

Of the one hundred twenty-one (23.7%) subjects who had an on-study clinically significant abnormal audiometric finding based on the predetermined criteria, 83 (68.6%) subjects were retested; 70/83 (84.3%) returned to their "baseline" on retest. The remaining 38 subjects were not retested and no reason was provided for not doing so. The large percentage of subjects who were identified as having hearing loss occurring during the study, but who returned to normal upon retesting (i.e., false positives), indicates a lack of control either in the test procedure or in the ambient noise in the test environment. This conclusion is supported by the review comments of Dr Charles Frankhauser in his Summary Review (see Section 16.1.13). In addition, Dr. Frankhauser noted "poor site compliance with retesting."

Of the 83 subjects who were retested, 13 subjects again had clinically significant abnormal results, and these subjects were referred for a full audiology evaluation. Only six (6) of these 13 subjects received the latter work-up; the remaining seven (7) subjects refused further evaluation. None of the six subjects were found to have clinically significant hearing loss based on comprehensive audiological assessment.

In conclusion, of the 510 subjects who had audiometric data 45 subjects may or may not have experienced a potential change in their hearing sensitivity related to the study drug (38 subjects were not retested after initial identification of potential change in hearing sensitivity and 7 subjects refused a complete audiological evaluation). However, based on the outcomes of the additional assessments conducted on 76 subjects (70 subjects retested at the study sites and six subjects who had comprehensive audiological evaluation), the likelihood of the 45 subjects having a drug related change in hearing sensitivity is very unlikely. The study drug, Hydrocodone Bitartrate

Extended-Release (HC-ER) Capsules, appears not to effect hearing sensitivity for the dosages studied.

#### 7.4.6 Immunogenicity

This product does not raise concerns regarding immunogenicity.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

The percentages of subjects in the HC-ER group who experienced an adverse event tended to be higher at higher dose levels.

#### 7.5.2 Time Dependency for Adverse Events

In general, the percentages of subjects who experienced an adverse event were higher earlier in the C/T phase (i.e. first week) especially for gastrointestinal symptoms.

#### 7.5.3 Drug-Demographic Interactions

No formal studies evaluated differences in hydrocodone PK between young and elderly subjects. However, elderly subjects are more likely to have compromised renal function and theoretically experience higher hydrocodone exposures as compared to younger subjects with normal renal function. Therefore, elderly patients generally should be started on low dose and observed closely. In the all treated population only 13 subjects (0.9%) were greater than 75 years of age and 138 subjects (9.1%) were 65 to 75 years old.

#### 7.5.4 Drug-Disease Interactions

The reader is referred to Section 4.4.3 for information on hepatic impairment and renal impairment.

#### 7.5.5 Drug-Drug Interactions

The reader is referred to Section 4.4.3 for information on drug-drug interactions

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

No studies done

### 7.6.2 Human Reproduction and Pregnancy Data

No subject became pregnant while in the HC-ER clinical trial program.

No formal clinical trials in humans have been conducted assessing the effects of HC-ER on reproduction, pregnancy or lactation.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies have been performed to date with HC-ER. The requirement under the Pediatric Research Equity Act for pediatric studies was deferred.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Cases of potential abuse, misuse and diversion in the clinical development program of HC-ER were reviewed by Dr. Lori Love from the Controlled Substance Staff (CSS). Her review is not yet final, however she communicated the following concerns during the wrap-up meeting for this NDA. She noted that because data were not collected and evaluated systematically during clinical development for abuse, misuse and diversion, it was not possible to provide an accurate independent assessment of these events occurring in clinical trials. Specific limitations she encountered in reviewing the study data included:

- The Applicant did not provide definitions of abuse, misuse, diversion, noncompliance, or what constitutes mild, moderate, or severe diversion.
- There was no evidence that the investigators received training to recognize, report, and classify cases of abuse, misuse, diversion, noncompliance, so that consistent data were obtained and reported.
- There was difficulty navigating PDF copies of the electronic case report forms (CRFs) for studies ZX002-0801 and -0802. In general the CRFs were not informative related to abuse, misuse and study drug diversions.
- No detailed narratives of cases related to abuse, misuse, diversion and noncompliance were provided.
- Multiple instances of missing drug/drug accountability were discovered after the fact indicating problems with study site record keeping and oversight.
- There were differences in the numbers or amounts of 'missing' drug reported in different records.

The concerns noted above by Dr. Love are still being assessed by the CSS and the Division. There is not a regulatory requirement that CRFs have specific information regarding abuse, misuse, or diversion, nor is there a requirement for subject narratives of cases related to abuse, misuse and diversion to be included in the NDA submission. The concern noted in the fifth bullet above may be the result of coding on the CRF, i.e., missing drug may be coded on the CRF as a study compliance issue (as per the

protocol), however on further investigation by CSS, it is determined that this is a case of abuse/misuse/diversion. This would not be considered a data integrity issue. The sixth bullet regarding differences in numbers or amounts of “missing” drug reported in different records is of potential concern. If on further review there appear to be issues related to data integrity, a for cause inspection of some or all of the following will be initiated: study sites, CRO, or Sponsor.

Although Dr. Love notes that it is impossible to provide an accurate assessment of the number of cases of abuse, misuse and diversion that occurred during the development program for HC-ER, the following cases were identified that are indicative of drug abuse:

Subject 143-24 (ZX002-0801): 29 year old man with history of chronic low back pain, muscle spasms and anxiety. He presented overmedicated and/or intoxicated with slurring speech, glazed red eyes, and pinpoint pupils. In addition to HC-ER 30 mg bid, he had consumed 36 rescue medication tabs in the previous 6 days. The subject was found tampering with his urine sample and was immediately discontinued from the study.

Subject 140-19 (ZX002-0801): 27 year old man with a history of chronic low back pain, LBP surgery, depression, adult ADHD, anxiety, left sciatica, migraine, hip pain, early degenerative disc disease L1-3, and herniated nucleus pulposus. He was randomized to placebo after stabilizing on HC-ER 80 mg BID. Forty-four days after randomization, he was misusing rescue medication (ranging from 4-14 tablets/day) over a 4-day period. The subject was subsequently discontinued from the study due to noncompliance. At the termination visit the subject stated that he thought he was switched over to placebo and was in a lot of pain. The subject knew that taking a lot of acetaminophen was bad, so he extracted the acetaminophen out of the rescue medication tablets. He crushed the tablets, put them in water, and froze them so that he could strain them to separate the hydrocodone from the acetaminophen. Then he ingested the hydrocodone portion of the rescue medication.

Subject 244-14 (ZX002-0802): 42 year old woman started the C/T phase on HC-ER 10 mg bid. She was dispensed 90 caps of study drug and 30 rescue medication tabs. She didn't return for visit 3. The site contacted the subject, leaving several voicemails with no call back. A certified letter was sent and was declined by the subject. On a later date, the subject was seen at the site's private practice. She stated that she went to Indiana and lost her study medication. On an unknown date, the subject was terminated due to further investigation that showed she was getting numerous pain medications (Vicodin ES filled by multiple pharmacies and two different providers). A certified letter was sent to inform the subject that she was terminated from the investigator's practice.

Subject 230-02 (ZX002-0802): 55 year old woman with osteoarthritis, fibromyalgia, anxiety, and SVT, started the C/T phase on HC-ER 10 mg bid. She was titrated to 40 mg bid on 28-Oct-2010. On 21-Oct-2010, the urine drug screen was reported as positive for propoxyphene. On 01-Nov-2010, the subject was permanently withdrawn from the study. 60 caps of study medication and 30 tabs of rescue medication were not returned by the subject at discontinuation.

Subject 202-12 (ZX002-0802): The investigator was informed that the subject's drug was seized by police as there was evidence of drug dealing. The subject had numerous previous narcotics convictions and currently was on parole.

Subject 211-06 (ZX002-0802): The subject discontinued on Day 78 due to a protocol violation (positive urine drug screen for oxycodone). The subject failed to return one bottle of study medication (10 mg – 30 caps) at the termination visit.

In study ELN-154088-203 (open-label study in osteoarthritis), there were two events where diversion by family members was suspected. Subject 1-S004 discovered 3 capsules from her 30-mg bottle were missing at day 20, and subject 2-S013 returned 2 capsules too few at day 6 and 7 capsules too few on day 13. He suspected that his adult daughter had stolen the missing capsules.

The above cases illustrate the risk for misuse, abuse, and diversion that can occur with all opioids. Although, it is impossible to determine from the clinical trials conducted in the development program whether the risk of abuse and misuse for HC-ER will be greater than with other opioids, it is clear that abuse, misuse and diversion will occur. If approved this product would be under the ER/LA opioid analgesics REMS as required for all opioids in this class in order to mitigate risk to an acceptable level for approval.

## **7.7 Additional Submissions / Safety Issues**

The Applicant submitted the 120-day safety update on July 27, 2012. The update included results from Study ZX002-1102 which was not previously submitted. Study ZX002-1102 was a pharmacokinetics and bioequivalence study of hydrocodone bitartrate extended-release 30 mg capsules compared to Vicoprofen (7.5 mg hydrocodone bitartrate/200 mg ibuprofen) tablets. Review of the safety information for this study revealed no new safety issues. No other new information was contained in the 120-day safety update.

## **8 Postmarket Experience**

There is no postmarket experience with Zohydro.

## 9 Appendices

### 9.1 Literature Review/References

Not applicable

### 9.2 Labeling Recommendations

The labeling review is still ongoing by the Division. The boxed warning is being updated to include language about abuse potential, life threatening respiratory depression and interaction with alcohol. The product name Zohydro has been changed to Zohydro ER throughout the label. The section on initiating therapy with Zohydro ER and converting from oral opioids to Zohydro ER is being revised to emphasize that relative potency data are approximations and as such, it is safer to underestimate a patient's hydrocodone requirement. Modification to the clinical studies section includes (b) (4)

### 9.3 Advisory Committee Meeting

The Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration met on December 7, 2012 to discuss the new drug application 202880, hydrocodone bitartrate extended-release capsules for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The committee was asked to determine whether the benefit/risk assessment of this product favors its approval for marketing. In their application, Zogenix submitted data to provide sufficient evidence that their product is safe and effective when used according to the proposed product labeling, which includes a risk evaluation and mitigation strategy, or REMS. As the FDA review of these data did not raise any different conclusion from that of the sponsor regarding the efficacy and the general safety findings, the applicant presented both the efficacy findings from their phase 3 study and the overall safety profile from the Zohydro ER development program.

One extremely important issue before the committee was this product's potential for abuse and misuse and their consequences (i.e., addiction, overdose, and death) and how this potential may compare to the already-approved products in the class. The committee voted 11-2 against approval with one abstention on the

question, “Based on the data presented and discussed today, do the efficacy, safety and risk-benefit profile of Zohydro ER support the approval of this application?” The vote reflected the panel’s dissatisfaction with risk management of the ER/LA opioid class of drugs. The Committee chairman, said the Committee felt the Sponsor met the current requirements for approval but the addition of Zohydro ER to this class of drugs would not serve the public health unless the REMS program is strengthened for the entire drug class or an abuse-deterrent formulation is proposed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ROBERT A LEVIN  
01/15/2013

ELLEN W FIELDS  
01/16/2013  
See CDTL memo for issues pending at the time of this review



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1: ZX002-0801 Indication: Management of moderate-to-severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			OL conversion /titration phase followed by a randomized DB withdrawal phase
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Change in pain from baseline to end of treatment (day 85) measured on an 11-point NRS
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	All the studies were conducted in the United States except for 2 Phase 1 studies (ELN-302002 and ELN-901991) were conducted in Ireland
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?  The Division did not request that the Applicant conduct a TQT study.		X		The Applicant has not submitted a TQT study and the ECG data collected during clinical studies were not at maximum or supramaximal doses. Although QT prolongation has not been a problem with approved HC combination products and the Applicant reports that no subject had a QTc >450 ms or change from baseline. greater than 50 ms in healthy volunteers
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	HC-ER has not been marketed in the United States or in any country
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be	X			Adequate exposure based on Division's request for a (B)(2):

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

File name: Clinical Filing Checklist for NDA 202880

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	efficacious?				over 300 subjects treated for 6 months and over 100 subjects treated for 1 year
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?		X		Cannot find but the Applicant reports that across the clinical development program, medications and adverse events are consistently coded to WHO-DDE Ver. 2009 Mar01 and MedDRA 12.1, respectively
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Narratives for deaths, adverse dropouts and SAEs are in Module 5 Clinical Study Reports
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Audiometry assessments were conducted in study ZX002-0801 in 510 subjects.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Requested waiver for subjects (b) (4) years and deferral for subjects ages (b) (4) to 17
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?		X		No human abuse liability study was requested or done. The Applicant believes that the abuse liability will be addressed by the REMS and the fact that this is a Schedule

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: Clinical Filing Checklist for NDA 202880

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					II product
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	All the studies were conducted in the US except for 2 Phase 1 studies (ELN-302002 and ELN-901991) conducted in Ireland
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			CRFs link to subject in Clinical Study Report CRFs are legible but not presented in a manner that allows easy review due to their length. Also, some information contained in narratives not in CRF but obtained from the MedWatch forms
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?  CRFs were requested for all instances of addiction, abuse, misuse, overdose, drug diversion, discrepancies in amount of the clinical supplies, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up and any other reasons why subjects dropped out of the study.	X			CRFs were provided for suspected diversions and dropouts not due to AEs
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			Form 3454 included
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Controlled efficacy studies Pivotal Study and ELN154088-201 were conducted in accordance with GCP. IRB approval and informed consent obtained

File name: Clinical Filing Checklist for NDA 202880

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

## IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Robert A. Levin, MD	July 6, 2012
Reviewing Medical Officer	Date
Frank Pucino, PharmD, MPH	July 6, 2012
Clinical Team Leader	Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ROBERT A LEVIN  
08/10/2012

FRANK PUCINO  
08/10/2012