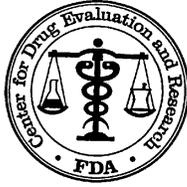


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202880Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA #:** NDA 202-880

**Drug Name:** Zohydro (hydrocodone bitartrate) extended-release capsules

**Indication(s):** management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time

**Applicant:** Zogenix, Inc.

**Date(s):** Submitted: 5/1/2012  
PDUFA due date: 3/1/2013  
Advisory Committee Meeting: 12/7/2012

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics II

**Statistical Reviewer:** Katherine B. Meaker, M.S.

**Concurring Reviewers:** Dionne Price, Ph.D.

**Medical Division:** Division of Anesthesia, Analgesia, and Addiction Products

**Clinical Team:** Robert A. Levin, M.D.  
Ellen Fields, M.D.

**Project Manager:** Dominic Chiapperino

**Keywords:** Single Clinical Study

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## 1 EXECUTIVE SUMMARY

Zohydro ER is a single ingredient capsule with hydrocodone bitartrate in an extended release formulation. Hydrocodone bitartrate, in combination with non-opioid analgesics, has been used to treat pain for decades. A single ingredient hydrocodone product has not been approved in the United States.

The clinical development of this product was discussed with the Division of Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) at an End-of-Phase 2 meeting on June 4, 2008. It was agreed that, given the extensive history of hydrocodone, one study in patients with chronic pain would suffice to support a 505(b)(2) submission. The primary objective of the study was to assess efficacy and safety to support a new drug application

This application includes the results of a clinical study in opioid-experienced patients with moderate-to-severe chronic low back. It was a double-blind, randomized withdrawal study in which patients were converted from prior opioid medication to a stable dose of Zohydro ER, then randomized to the stable dose or placebo (with down-taper) for 12 weeks.

The primary efficacy assessment was the change from baseline to Week 12 in pain intensity. Pain intensity was measured on an 11-point Numeric Rating Scale (NRS). The primary efficacy analysis used an analysis of covariance (ANCOVA) model with terms for treatment, baseline pain score, and screening pain score. The applicant used the following single imputation strategy: patients who discontinued due to opioid withdrawal symptoms had the baseline observation carried forward; patients who discontinued due to adverse events had the screening observation carried forward; and patients who discontinued due to lack of efficacy or other reasons had the last observation carried forward.

The results showed a statistically significant difference between the two treatment groups ( $p=0.008$ ), with a mean reduction in average 24-hour pain intensity of  $0.96 \pm 1.55$  units in the Zohydro arm and  $0.48 \pm 1.56$  units in the placebo arm. Analyses of pre-specified secondary endpoints, including a continuous responder analysis, supported the analgesic efficacy of Zohydro.

A meeting of the Anesthetic and Analgesic Drug Products Advisory Committee was convened December 7, 2012. DAAAP sought the committee's opinion on the safety and efficacy of Zohydro, the risk-benefit profile, and the sufficiency of the risk management tools to address the abuse liability in the post-marketing setting. Although the committee agreed that the applicant had met the standards for efficacy and safety, the majority of the committee did not favor approval of Zohydro based on concerns regarding abuse and misuse.

## 2 INTRODUCTION

### 2.1 Overview

There are currently no hydrocodone single entity products approved. Hydrocodone bitartrate is approved and marketed in combination with non-opioid analgesics (e.g. ibuprofen or acetaminophen [APAP]). Opioid tolerance during chronic use requires increased dosing which has led to safety concerns specifically regarding the APAP-containing combination products because of increased levels of APAP being ingested. As such, the applicant states that the objective of the program is to develop a single entity hydrocodone product which would not have a maximum daily dose and would be regulated as a Schedule II drug to reduce abuse and diversion.

The development program for Zohydro ER was conducted under IND 65,111. The applicant met with DAAAP on June 4, 2008 to discuss the protocol for a Phase 3 clinical study to support efficacy for Zohydro ER. Topics discussed included the design, efficacy endpoint, and analysis strategy. The study submitted incorporated the advice given at that meeting. The results of the study were also presented at the pre-NDA meeting on November 17, 2011.

The application included a randomized, double-blind, multicenter, placebo-controlled clinical study evaluating the efficacy and safety of Zohydro ER in opioid-experienced patients with chronic low back pain. Study ZX002-0801 used a randomized withdrawal design in which eligible patients first entered an open-label conversion and titration phase to convert from their prior opioid medication to a stable, tolerated dose of Zohydro ER which adequately treated their pain. The maximum allowable dose was 200 mg (100 mg BID) per day. Eligible patients were then randomized to receive either the same dose of active treatment or placebo for a 12week double-blind maintenance period.

This application was presented at an Advisory Committee meeting on December 7, 2012. The division sought advice on the potential for abuse and misuse, and risk mitigation, if approved. These issues are not directly assessed by Study ZX002-0801 and are not commented on in my review.

### 2.2 Data Sources

The clinical study report and all datasets were submitted to the electronic document room:

(b) (4) All the necessary documentation to complete my review was provided.

## **3 STATISTICAL EVALUATION**

### **3.1 Data and Analysis Quality**

The data for the efficacy endpoints was submitted in the required format and with sufficient documentation for my review. The derived endpoints were provided by the sponsor in Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model (ADAM) format standardized data sets.

### **3.2 Evaluation of Efficacy**

#### **3.2.1 Study Design and Endpoints**

Study ZX002-0801 (Study 801) was a randomized, double-blind, parallel group, placebo-controlled multicenter trial, conducted at 57 sites in the United States. Eligible patients were adults with low back pain for at least 3 months prior to screening, who had been taking opioid medication for at least 4 weeks and on a stable dose for at least 2 weeks prior to enrollment. After screening, patients were enrolled in an open-label conversion and titration (C/T) phase to convert from their previous opioid medication to Zohydro ER. To be eligible for enrollment in the C/T phase, patients had to report average daily pain intensity of  $\geq 4$  on the 11-point NRS during screening. Patients who achieved a stable dose of 20 mg BID to 100 mg BID of Zohydro ER during the C/T phase, reported at least 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, and had an average 24-hour daily pain intensity score of  $\leq 4$  on the NRS during the last 7 days prior to the baseline visit were randomized in a 1:1 ratio to receive double-blind Zohydro ER (n=151) or placebo (n=151) for the 12-week treatment phase. Patients randomized to placebo were tapered downward in the first two weeks to minimize withdrawal symptoms. Post-treatment follow-up continued for an additional 2 weeks. Efficacy data was collected daily using an electronic diary and averaged weekly. Patients were allowed rescue medication of 5 mg hydrocodone bitrate/500 mg acetaminophen up to 2 tablets per day during the treatment phase.

The primary endpoint was the change from baseline to Week 12 in the average daily pain intensity, measured on a 0-10 NRS. Baseline was defined as the average of the last week on the stable dose during the C/T open-label period. Secondary endpoints included worst pain in last 24 hours, least pain in last 24 hours, and proportion of patients achieving 30% improvement in average daily pain from baseline.

### 3.2.2 Statistical Methodologies

All subjects who were randomized into the 12-week treatment phase of the study and received at least one dose of double-blind study drug were included in the ITT population (n=302).

The primary endpoint was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, baseline pain intensity score, and screening pain intensity score.

For the primary efficacy analyses, the following single-imputation approach was planned for subjects who discontinued prematurely or who had missing Day 85 data for some other reason:

1. If a subject discontinued prematurely in the treatment phase prior to Day 85 due to a lack of efficacy, the last observation carried forward (LOCF) approach was employed.
2. If a subject discontinued prematurely due to opioid withdrawal, the baseline observation carried forward (BOCF) approach was employed.
3. If a subject discontinued due to an AE, the screening observation carried forward (SOCF) approach was employed.
4. If a subject discontinued due to any reason other than indicated above, the LOCF approach was employed.

The protocol did not account for multiplicity for testing secondary endpoints. The following details were included in Section 14.3 of the Statistical Analysis Plan but were not part of the original protocol:

If the primary analysis is statistically significant ( $p < 0.05$ ), then the first key secondary endpoint (30% responder rate) will be evaluated at the 5% level of significance. If the 30% responder rate analysis is statistically significant ( $p < 0.05$ ), then the second key secondary endpoint (change from screening in subject global assessment) will be evaluated at the 5% level of significance.

No multiplicity adjustment will be performed as key secondary analyses will use a gated approach.

This change is only pertinent in terms of the inclusion of information in the label, based on the clinical reviewer's opinion of relevance. The applicant's proposed labeling includes a graph of the continuous responder analysis, as shown in other products with the same indication. The applicant is not proposing other endpoints be included in the label.

The applicant provided a graphical display of the percent improvement in average pain intensity from screening to Day 85. All patients who discontinued prior to completing the double-blind treatment period (through Week 12) were classified as failures for the continuous responder analysis.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patients were randomized in a 1:1 ratio to the two treatment arms for the double-blind 12 week treatment phase. The disposition is shown in Table 1. A higher percentage of patients in the placebo group discontinued from the study than in the Zohydro ER arm. The difference is primarily due to lack of efficacy and opioid withdrawal, both of which are not uncommon in this study design. Figure 1 displays the timing of these drop-outs during the double-blind treatment period. Almost all of the drop-outs occurred in the first 3 weeks after randomization, during which patients in the placebo arm were receiving the taper-down dosing. The clinical reviewer's assessment is that return of pain and/or opioid withdrawal symptoms would be expected in that timeframe.

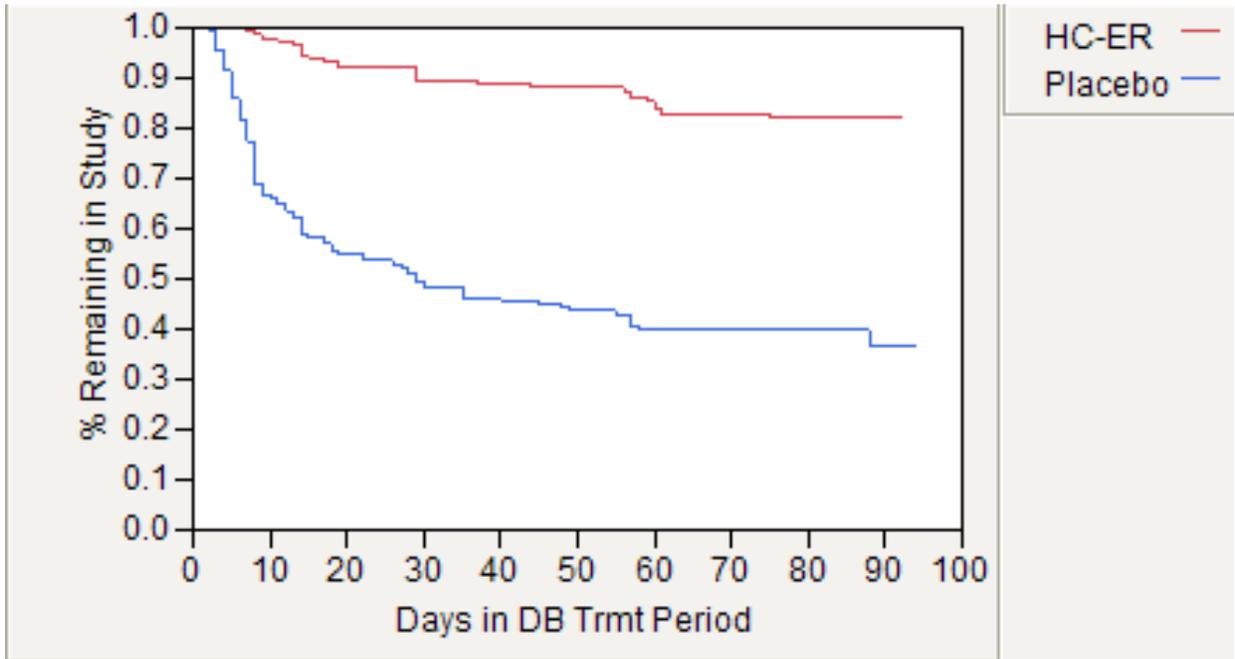
Table 1: Patient Disposition (All Randomized; Study 801)

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%)

HC-ER: Hydrocodone extended release

Source: Clinical Study Report Table 10.2

Figure 1: Patient Disposition over Time in Double-Blind Treatment Period (Study 801)



HC-ER: Hydrocodone extended release

Source: SAS datasets

The two groups were similar in terms of most of the demographic characteristics, screening pain intensity, and baseline pain intensity, as shown in Tables 2. One notable difference was the distribution by gender across the two groups: the Zohydro ER group had a higher proportion of females (62%) than the placebo group (49%). My analyses included a model to investigate potential gender-by-treatment interaction, which found no impact of this imbalance on the results (see Section 4.1 for full details).

Table 2: Patient Demographics (Study 801)

	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

HC-ER: Hydrocodone extended release  
Source: Clinical Study Report Table 11.1

### 3.2.4 Results and Conclusions

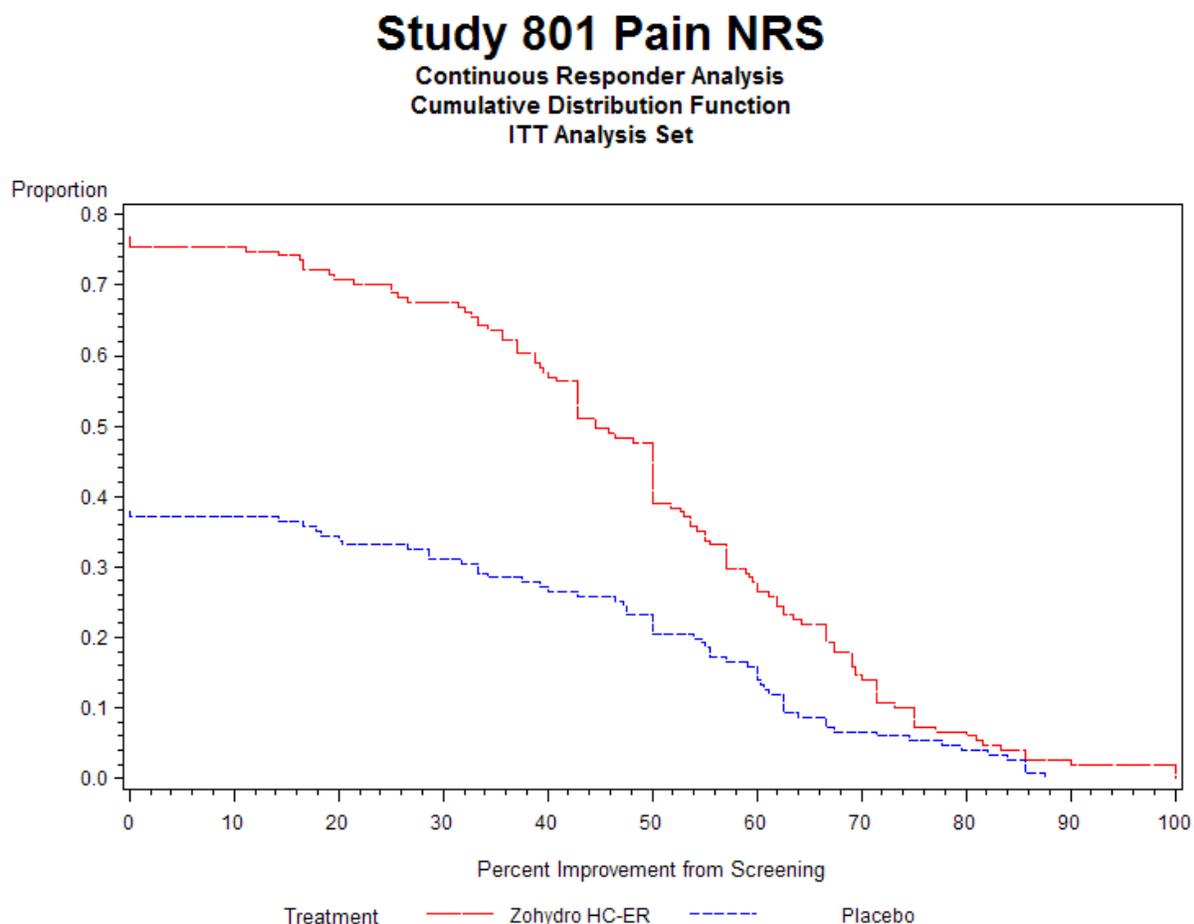
The applicant's efficacy analyses followed the planned protocol. The results of the ANCOVA model are shown in Table 3 below. Note that imputation was only performed for the Day 85 (Week 12) time point. The sample size at intermediate time points reflects the imbalance in the discontinuations across the treatment arms. I confirmed the applicant's results.

Table 3: Applicant's Results - Change from baseline of average daily pain intensity score (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	—

HC-ER: Hydrocodone extended release  
Source: Clinical Study Report Table 11-4

Figure 2 shows the cumulative distribution for the continuous responder analysis. The separation of the curves is driven initially by the imbalance in the number of drop-outs in the placebo arm (see Section 3.2.3). I conducted the Van der Waerden nonparametric test on the distribution. The test showed a significant difference between the curves ( $p < 0.001$ ).



### 3.3 Evaluation of Safety

Dr. Levin completed the review of the safety data, with no addition requests for me. According to Dr. Levin, the safety findings were consistent with the known opioid adverse event profile.

The main safety concern discussed at the Advisory Committee meeting was the potential for misuse and abuse of this extended release formula, if approved. Patients were carefully monitored for compliance with study medication and rescue medication (HC-ER/APAP)

throughout the development program; therefore, this issue was not directly assessable from the submitted safety data.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

There were no differences in the efficacy results across subgroups for age, race or gender. All sites in this study were in the United States, so no subgroup analysis by region was performed.

As mentioned in Section 3.2.3, there was an imbalance by gender across the two treatment arms. To check if this imbalance had any impact on the results or conclusions, I repeated the ANCOVA model with terms for treatment group, gender, and the treatment-by-gender interaction. The results indicated that the change from baseline in average pain intensity was higher for males in both arms, but the between-gender difference was the same for both treatment arms.

Table 5: Treatment-by-Gender Subgroup Results (Study 801)

Change from baseline to Week 12: Average Pain Intensity N (row %) Mean (Std Error)	Zohydro ER (n=151)	Placebo (n=151)	Difference
Males (n=135)	58 (43%) 0.69 (0.20)	77 (57%) 1.13 (0.18)	0.44
Females (n=167)	93 (56%) 0.34 (0.16)	74 (44%) 0.78 (0.18)	0.44

Source: SAS Datasets

The randomized treatment arms were balanced with regard to race and age subgroups. The results were consistent across those subgroups, as shown in Table 6.

Table 6: Race and Age Subgroups (Study 801)

Change from baseline to Week 12: Average Pain Intensity				
N (row %) Mean (Std Error)		Zohydro ER (n=151)	Placebo (n=151)	Difference
Race	White (n=243)	123 (51%) 0.47 (0.14)	120 (49%) 0.95 (0.14)	0.48
	Non-White (n=59)	28 (47%) 0.52 (0.29)	31 (53%) 0.93 (0.28)	0.41
Age	18-64 (n=271)	140 (52%) 0.52 (0.13)	131 (48%) 1.02 (0.13)	0.50
	65-75 (n=31)	11 (35%) -0.07 (0.46)	20 (65%) 0.49 (0.34)	0.56

Source: SAS Datasets

## 4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

There was an imbalance in the drop-outs between the two treatment arms during the double-blind treatment phase. Such an imbalance can cause concern in chronic pain trials when a large proportion of the drop-outs are due to adverse events in the treatment arm. However, the clinical reviewers confirmed that the higher rate of discontinuations in the placebo arm due to lack of efficacy and opioid withdrawal were not uncommon in this study design. These were opioid-experienced patients with chronic low back pain titrated to a stable effective dose, so it is not unexpected that pain control on placebo was insufficient. In addition, the dose of rescue medication (at most two tablets of 5 mg hydrocodone/500 mg acetaminophen per day) was minimal relative to the dose level of opioid medication prior to enrollment.

The imputation plan for discontinuations was discussed with DAAAP prior to initiating the study and prior to the National Academy of Sciences report recommending consideration of alternative methods in preference to the single imputation approach used here. The following advice was given to the applicant at the pre-NDA meeting in November, 2011 “At this time, we are recommending that all sponsors consider the NAS report when planning, conducting, and analyzing clinical trials. We understand that study ZX002-0801 is complete and has been analyzed and unblinded; therefore, the NDA may be submitted without additional analyses.”

## **5.2 Collective Evidence**

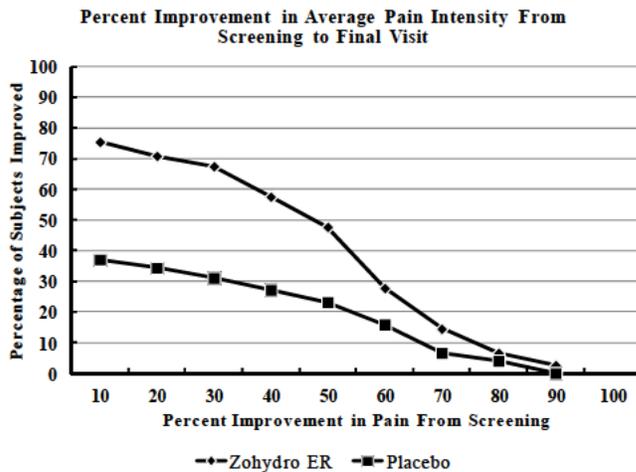
A single placebo-controlled, randomized-withdrawal study in opioid-experienced patients with chronic low back pain was submitted in support of this application. There was a statistically significant difference in pain intensity among patients receiving Zohydro ER compared to those receiving placebo.

## **5.3 Conclusions and Recommendations**

There is sufficient evidence to conclude that Zohydro ER reduces pain in patients with chronic low back pain.

## 5.4 Labeling Recommendations

In the Clinical Studies section of the proposed label, the applicant describes the study design appropriately. The results are presented as:



The figure presents the information in the cumulative responder curves. I suggest the following changes to the text:

1. The primary efficacy endpoint should be reported clearly and without the p-value. Replace the first paragraph with “Zohydro ER provided superior analgesia compared to placebo. There was a significant difference in the mean changes from Baseline to Week 12 in average weekly pain intensity Numeric Rating Scale (NRS) scores between the two groups. “

2. The second paragraph describes Figure 1. The last sentence should be changed to take out the word superior and the p-value. I propose “Treatment with Zohydro ER produced a greater number of responders, defined as subjects with at least a 30% improvement, as compared to placebo (67.5% vs. 31.1%)”.
  
3. The protocol did not plan for testing multiple endpoints. Global patient satisfaction was planned as a secondary endpoint. It is not appropriate to include a (b) (4)  so the paragraph after Figure 1 should be deleted.

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KATHERINE B MEAKER  
01/25/2013

DIONNE L PRICE  
01/25/2013  
concur

**Statistics Filing Checklist New NDA  
Division of Biometrics II**

Date: 8/10/12

NDA #: 202-880

Priority Classification: S

Trade Name:

Applicant: Zogenix, Inc.

Generic Name: Hydrocodone Bitartrate  
Extended Release (HC-ER) Capsules

Date of Submission: 5/1/12

Indication: treatment of chronic pain

No. of Controlled Studies: 1

User Fee Goal Date: 3/1/2013

Date of Filing Meeting: 6/19/2012

Medical Officer: Robert Levin, M.D.

Project Manager: Dominic Chiapperino

Statistical Reviewer: Kate Meaker, M.S.

Statistical sections: Sections 2.5, 2.7, 3.5

Anticipated Review Completion Date: 1/1/2013

**Comments:**

It is fileable for statistics review.

CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Yes
Designs utilized appropriate for the indications requested	Yes
Endpoints and methods of analysis spelled out in the protocols	Yes
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Sufficient data listings and documentation for statistical review	Yes
Data from primary studies submitted electronically	Yes
Intent-to-treat analysis	Yes
Effects of dropouts on primary analyses investigated	Yes
Safety and efficacy for gender, racial, and geriatric subgroups investigated	Yes

## BRIEF SUMMARY OF CONTROLLED CLINICAL TRIALS

<b>Study Number (Dates Conducted)</b>	<b>Number of Centers (Locations)</b>	<b>Total Sample Size</b>	<b>Design</b>	<b>Duration of Treatment</b>
ZX002-0801 (3/10 – 7/11)	57 centers (US)	Zohydro (HC-ER) n=151  Placebo n=151	Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel arm	6-week open-label conversion/titration phase;  12-week double- blind treatment phase

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Katherine B. Meaker  
Mathematical Statistician

Concur: Dionne Price Ph.D.  
Team Leader

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/s/  
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KATHERINE B MEAKER  
10/12/2012