CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202880Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-880	**Primary Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	1 May 2012		
Division:	Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)	**Secondary Reviewer:** John Duan, Ph.D. **Team Leader:** Angelica Dorantes, Ph.D. **Supervisor:** Richard Lostritto, Ph.D.	
Sponsor:	Zogenix 5858 Horton Street, Suite 455 Emeryville, CA 94608	**Date Assigned:**	20 June 2012
Trade Name:	To be determined. Zohydro ER (proposed)	**GRMP Date:** **PDUFA Date:**	15 January 2013 1 March 2013
		Date of Review:	15 January 2013 (Review #1)
Generic Name:	Hydrocodone bitartrate extended release capsules	**Type of Submission:** Original NDA 505(b)2	
Indication:	Management of moderate-to-severe chronic pain when a continuous around the-clock opioid analgesic is needed for an extended period of time		
Formulation/ strengths	Extended Release Hard Gelatin Capsules/ 10, 15, 20, 30, 40, 50 mg	**Route of Administration**	Oral
Biopharmaceutics Topics: Biowaiver request (15 mg), dissolution test method, IVIVC model, extended-release claim per 21 CFR 320.25(f), in-vitro alcohol dose dumping study, and product shelf-life (dissolution stability only)			

SUBMISSION: This NDA seeks approval of a hydrocodone bitartrate extended release (HC-ER) product formulated as a 12-hour extended release formulation of hydrocodone utilizing Alkermes' patented Spheroidal Drug Absorption System (SODAS®) drug delivery technology and does not contain acetaminophen or another non-opioid analgesic. Although hydrocodone has been approved for many years in immediate-release combination drug products, there is no approved single-ingredient hydrocodone product currently available. Hydrocodone combination products, such as those containing acetaminophen, are widely prescribed, and are often times used inappropriately as chronic pain medication. The HC-ER product under NDA 202-880 therefore can be dosed based exclusively on the opioid component without the limitation and attendant safety issues associated with the non-opioid constituent.

BIOPHARMACEUTICS INFORMATION: Reference was made to DMF (b) (4) for all drug product quality information. Specifically, the DMF included the review information supporting the following.

- Level A IVIVC model
- Dissolution method and acceptance criteria
- Critical process attributes for drug release
- Formulation development
- Dissolution stability

CONCLUSION/RECOMMENDATION:

1. DMF (b) (4) was found adequate, with comments, from the Biopharmaceutics perspective to support NDA approval. An adequate response to the DMF comments is pending; however, based on the outstanding issues noted for the DMF, the following conclusions can be made.

a. The proposed dissolution method and acceptance criteria are acceptable.

Parameter	Criteria
Apparatus	USP 1 (40 mesh baskets)
Paddle Speed	100 rpm
Media	pH 6.8 Phosphate Buffer, 500 mL @ 37°C
Detection	HPLC
Acceptance Criteria	1 hour = NLT (b)(4)% 4 hour = (b)(4)% 8 hour = (b)(4)% 12 hours = NLT (b)(4)%

b. A Level A IVIVC model submitted under DMF (b)(4) is adequate to support future post-approval drug product changes in accordance with the SUPAC-MR guidance (see DMF review for additional details). The IVIVC model described in the NDA is not the same IVIVC model accepted for regulatory purposes.

2. A biowaiver is granted for the 15 mg capsule strength.
3. The proposed HC-ER capsule is susceptible to alcohol induced dose dumping in vitro. The safety implication of this finding is assessed by the assigned Clinical Pharmacology and Clinical reviewers.
4. A major formulation change was noted between product used in a PK food effect study and the product used in the clinical efficacy/safety studies. There were insufficient in vitro dissolution data to bridge the formulation changes; however, the to-be-marketed formulation, including the dose used for the food effect study, was used in the clinical safety and efficacy studies, which included PK assessments. Thus, there may be sufficient in vivo PK data on both formulations to support the adequacy of the food-effect study. The acceptability of the in vivo data is not under Biopharmaceutics purview. Refer to the Clinical Pharmacology review for additional details on the acceptability of the food effect study.
5. The in vitro and in vivo data support an extended release claim, from the Biopharmaceutics perspective.

From the Biopharmaceutics standpoint, NDA 202-880 is recommended for approval.

SIGNATURE BLOCK: *See electronic signature page.*

Minerva Hughes, Ph.D. , Biopharmaceutics Primary Reviewer

John Duan, Ph.D., Biopharmaceutics Secondary Reviewer

BIOPHARMACEUTICS REVIEW NOTES

1.0 GENERAL INFORMATION

1.1 RELEVANT REGULATORY HISTORY

NDA 202-880 seeks approval for the use of hydrocodone bitartrate-extended release (HC-ER) capsules for the treatment of moderate to severe chronic pain. The active moiety hydrocodone (HC) has been commercially available in the United States for several decades in combination products that also contain non-opioid compounds for the treatment of cough (e.g., HC/chlorpheniramine) and pain (e.g., HC/acetaminophen) or HC/ibuprofen formulations). Most of the currently marketed opioid products, including HC, are immediate-release (IR) formulations administered orally every 4 to 6 hours, which result in significant fluctuations in HC plasma levels. Although there are some oral extended-release (ER) formulations of opioids on the market today, such as oxycodone, oxymorphone, morphine, hydromorphone, and tapentadol, there is no ER formulation of HC currently available.

The HC-ER drug product development was conducted under IND 65,111 with guidance from the FDA. NDA 202-288 was submitted in accordance with Section 505(b)(2) of the FD&C act with reference to the listed drug Vicoprofen Tablet (7.5 mg/200 mg), NDA 20-716, for the Agency's previous findings of safety and efficacy. Relevant Biopharmaceutics advice conveyed during the IND are summarized below.

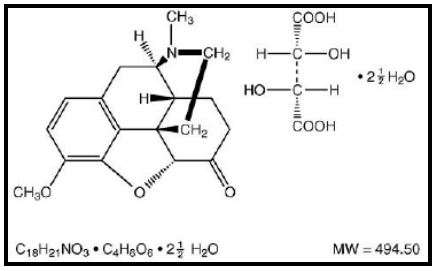
- **4 June 2008 End of Phase 2 Meeting:**
  - (b) (4). FDA requested in-vitro dissolution data in ethanolic media as follows: 0, 4, 20 and 40% EtOH/buffer and 20% EtOH in simulated gastric fluid without enzymes. Low, middle and high strengths should be tested and the quantity of capsules may be determined by the testing method, e.g., n=6 (S1 level testing), n=12 (S2 level testing). If the results of the in vitro alcohol interaction study are positive, the Applicant should consider further evaluation of this interaction in a human pharmacokinetic (PK) study. Specifics were not conveyed to the Applicant on what constituted a positive alcohol effect.
- **17 Nov 2011: Type B pre-NDA Nonclinical/Clinical Meeting:**
  - 505(b)(2) pathway selected. FDA noted the lack of PK information for the 15 mg dosage strength, which implied a biowaiver request for this strength. FDA requested appropriate justification in the NDA to support the biowaiver.
  - The design of the alcohol interaction study, Study ZX002-0901 (A Single-Center, Open-Label, Randomized, Three-Period Crossover, Phase 1 Study to Evaluate the Pharmacokinetics of Hydrocodone Bitartrate Controlled-Release Capsules 50 mg When Co-Administered with Alcohol in Healthy Subjects Under Fasted Conditions), appeared to be sufficient to support

filing the NDA. The adequacy of the study and whether the information will be in the product labeling are review issues.

- **18 Nov 2011: Type B pre-NDA CMC Meeting:**
  - The Applicant should include in the NDA, the data set, dissolution trend, and the complete dissolution method development report. The Agency stated that the extended release claim for their product needed to be supported and noted that the Applicant had not conducted a steady state study comparing their ER product with an IR product. The Applicant was asked to provide the comparative drug plasma fluctuation index (*Cmax to Cmin ratio*) for their HC-ER product compared to that of the IR hydrocodone product (*currently available in the market as a combination product*), as per the requirement described under 21 CFR 320.25 (f) (iii). The Agency recommended that this information be provided for review, prior to NDA submission. The Applicant noted that there is no IR product currently available in the market (*the RLD is a fixed dose combination product*). The Agency and Applicant agreed that the data for this analysis could be pulled from the two different clinical studies.
  - Based on the evaluation of the provided in-vivo PK and clinical data and justification supporting the "extended release claim" for the proposed HC-ER product (7 December 2011 IND Amendment), the Agency agreed that an in-vivo steady-state PK study evaluating the fluctuation index of the proposed HC-ER product vs. a reference IR hydrocodone product was not needed.
  - The in vitro testing design for alcohol induced dose dumping study was reasonable. However, the data showed a trend of dose dumping starting at 10% alcohol.
  - FDA recommended submitting the *in vitro* alcohol assessment report in the NDA for the ease of review and not to the DMF.

1.2 DRUG SUBSTANCE

The drug substance is the tartaric acid salt of hydrocodone or hydrocodone bitartrate. The molecular structure and formula are provided below.



Structure of hydrocodone bitartrate drug substance.

Reference was made to [redacted] (b) (4) DMF [redacted] (b) (4) and [redacted] (b) (4) DMF [redacted] (b) (4) for drug substance chemistry, manufacturing and controls information. A brief summary of

the physicochemical characteristics noted in the NDA is provided in the following table.

Hydrocodone Bitartrate General Properties

Characteristic	Description
Color and Appearance	Fine white to off-white or slightly yellow-white powder
Odor	Odorless
Formula Weight (amu)	494.50
pH	Approx. (b) (4) % aq solution)
Melting Range / Point	(b) (4)
Solubility profile: Water Ethanol (95%) Ether Chloroform	(b) (4)
Specific Rotation	-79° to -84° (a 2 g sample per 100 ml aqueous solution)
Dissociation Constant	pKa (b) (4) C)
Partition Coefficient	Log P ((b) (4)
Chemical Family	Narcotic Alkaloid Salt
DEA Controlled Substance Schedule	II
PBOEL	Category 2

Source: Section 1.3.S.1.3, Table 2.3.S.1-2.

The drug substance specification includes tests for identification, specific rotation, solution pH, loss on drying, residue on ignition, chloride content, assay, impurities, residual solvents, and particle size by sieve testing for the (b) (4) drug substance material only.

Reviewer's Assessment: *The reviewer notes that the drug substance is highly water soluble. A comparability report (ALK-001) was included in the NDA. The Applicant notes that the drug substance specification differed between the (b) (4) and (b) (4) drug substances in terms of the tests for solubility, optical density, UV absorptivities, and particle size. However, these attributes were deemed not critical since the drug substance is used as a solution to manufacture drug product. Given the high solubility and use of the drug as a solution for processing, the reviewer agrees that particle size and optical density (i.e., polymorph) differences are not critical quality attributes from the Biopharmaceutics standpoint.*

1.3 DRUG PRODUCT

The drug product is an extended-release capsule formulation utilizing Alkermes SODAS® technology. This technology is based upon initially coating sugar spheres with the drug substance and selected excipients to form IR multiparticulates. Sustained-release (SR) multiparticulates are then prepared by coating the IR multiparticulates with rate-controlling polymers to obtain a desired dissolution profile.

The target in vitro dissolution rate for the HC-ER product is then achieved by combining IR beads with SR beads in a defined active ratio (20:80) followed by encapsulation to the desired product strength of 10, 15, 20, 30, 40, or 50 mg of hydrocodone bitartrate in hard gelatin capsules. The drug product composition information is summarized in the table below.

Drug Product Components

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

Reference was made to Alkermes DMF (b) (4) for the full details on the drug product chemistry, manufacturing and controls.

Reviewer's Comments: *DMF (b) (4) was reviewed and found adequate, with comments, (review date 2 January 2013) from the Biopharmaceutics perspective.*

1.4 BIOPHARMACEUTICS REVIEW TOPICS

This Biopharmaceutics review evaluates the biowaiver request for the 15 mg strength, the in vitro alcohol dose dumping study, extended release claim, formulation bridging studies using dissolution, and referenced biopharmaceutics information in DMF (b) (4) (IVIVC model, dissolution method and acceptance criteria, process ranges, and dissolution stability). All DMF information is considered proprietary. Therefore, a separate Biopharmaceutics DMF review is filed under the DMF, and a statement of adequacy noted in this report.

2.0 BIOPHARMACEUTICS ASSESSMENT

2.1 BIOPHARMACEUTICS CLASSIFICATION

The Applicant claims a BCS Class 1 designation for the hydrocodone bitartrate drug substance. However, adequate drug solubility and permeability information were not included in the NDA.

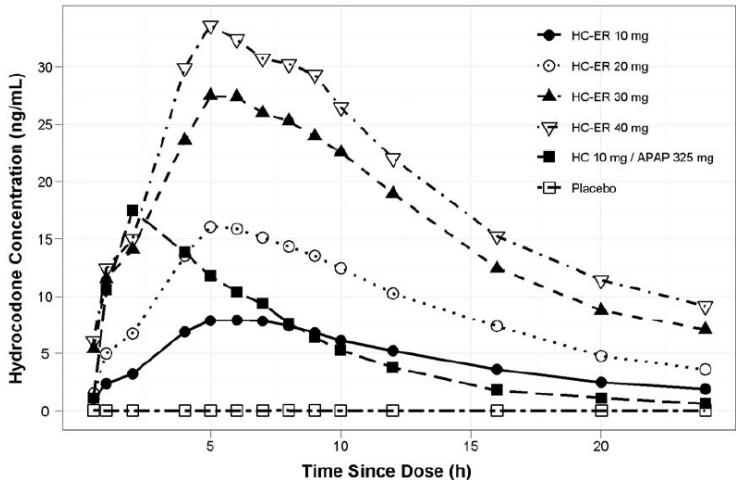
Reviewer's Assessment: *Hydrocodone bitartrate is not listed in the FDA BCS Committee database for approved BCS Class 1 designated drugs. Therefore, FDA can not concur with the Applicant's conclusion. Biowaivers based on a BCS Class 1 designation are not applicable, however, because the drug product is an extended release dosage form.*

2.2 EXTENDED RELEASE CLAIM: 21 CFR 320.25 (F) COMPLIANCE

The proposed dosage from is an extended release hard gelatin capsule. The in vivo PK data supporting the extended release claim are evaluated by the assigned Clinical Pharmacology Reviewer. A brief synopsis follows.

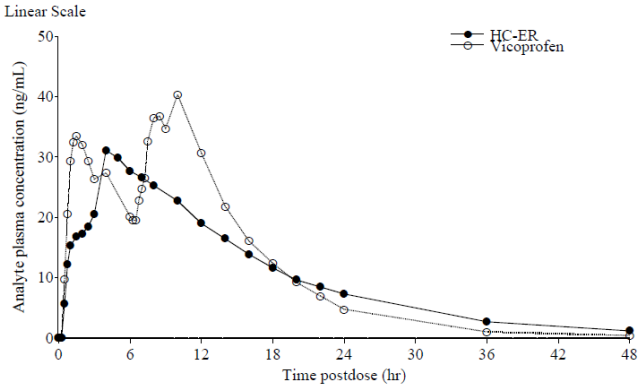
- PK studies showed that the mean Cmax was prolonged for the HC-ER formulations compared with an IR referenced product. The half-life was also longer than that observed for the IR product, which is consistent with a prolonged absorption phase (see figure below)

Figure 2.7.1-13 Mean Plasma Hydrocodone Concentration-Time Profiles for 10, 20, 30 and 40 mg HC-ER from Clinical Study ELN154088 201



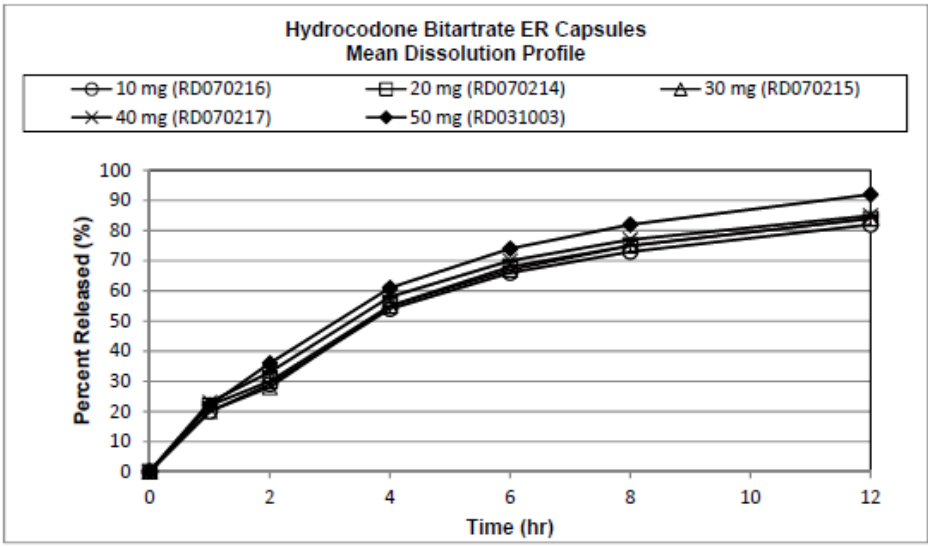
- A bioequivalence analysis of Cmax, AUC0-t, and AUC0-inf derived from hydrocodone concentrations for the ER and referenced IR product showed that the 90% confidence interval (CI) for the least-square (LS) geometric mean ratios (GMR) for overall exposure (AUC0-t, and AUC0-inf) were within the bioequivalence limit of 80%–125% while those for Cmax were not. The LS GMR (90% CI) estimates were 91.1 (82.8–100), 93.2 (84.5–103), and 68.7 (63.2–74.6) for AUC0-t, AUC0-inf, and Cmax, respectively. Thus, the extent of exposure is comparable to the IR product administered at the same dose, although the rate of absorption is slower with HC-ER, which is consistent with the intended ER characteristic.

Figure 2: Mean Hydrocodone Concentrations at Scheduled Time Points, Stratified by Treatment



Source: Section 14, Figure 14.2.1-1a

- The drug product's steady state performance relevant to a currently marketed IR formulation was not addressed in the NDA, as per agreements made under the IND.
- PopPK compartmental modeling showed that the HC-ER capsules provided consistent overall exposure and reliable prolongation of HC concentrations. Absorption profiles were variable across and within subjects, but the variability did not preclude construction of a linear model for elimination.
- Food effect study (Study 0302002) showed no evidence of dose dumping under the fed or fasted condition.
- In vitro dissolution profiles are consistent with an extended release product. Drug release is gradual and requires up to 12 hours for > (b)(4)% drug release from the matrix. Throughout development, the in vitro dissolution profile appeared to follow the same mechanism of release. Representative dissolution profiles for each strength are illustrated below.



Source: Figure 2.7.1-8 of NDA

Reviewer's Assessment: *The in vivo and in vitro drug kinetics are consistent with an extended release product. The observed inter- and intra-subject variation in PK parameters appeared comparable between the IR and ER formulations; however, these review issues are addressed in detail by the assigned Clinical Pharmacology Reviewer. From the Biopharmaceutics standpoint, the data are sufficient to support an extended release claim.*

2.3 BIOWAIVER REQUEST (15 MG CAPSULE) JUSTIFICATION

NDA 202-880 requests approval for HC-ER capsules at the following strengths: 10, 15, 20, 30, 40, and 50 mg. Two phase 3 clinical studies were completed using the 10, 20, 30, 40, and 50 mg capsules administered orally every 12 hour (q12h). Study ZX002-0801 limited the maximum daily dose to 200 mg, while Study ZX002-0802 did not prescribe an upper dose limit. A comparative PK study using the HC-ER 30 mg capsule and the listed drug Vicoprofen (Study ZX002-1102), along with a population PK analysis to support dose proportionally up to the 50 mg strength was completed. However, as noted by FDA during the 17 Nov 2011 pre-NDA meeting, PK was not collected in any study for the 15 mg HC-ER capsule. Therefore, a waiver of in vivo bioavailability studies was required.

The Applicant seeks a waiver of BA/BE studies on the basis of the following claims.

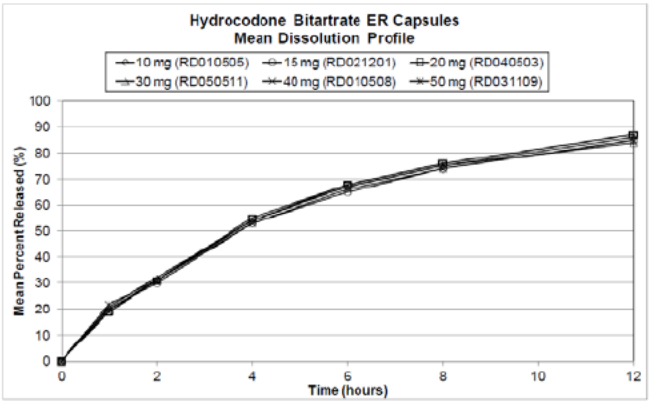
1. Hydrocodone bitartrate is a BCS class 1 (highly soluble, highly permeable) substance.
2. [redacted] (b) (4) of all strengths.
3. All strengths utilize the same drug release mechanism and are manufactured using the same type of equipment, facility, process controls and adhere to the same release specification.
4. Completed clinical studies used HC-ER capsule strengths that bracket the 15 mg capsule at daily doses up to at least 200 mg, with more that 1500 subjects treated with HC-ER capsules in the clinical program.
5. Bioavailability was assessed for a higher strength (30 mg HC-ER capsule)
6. Dose proportionality was demonstrated up to 50 mg.
7. Comparability of the dissolution profiles across all strengths.
    - The in vitro dissolution method used for profile comparisons is summarized below.

Parameter	Criteria
Apparatus	USP 1 (40 mesh baskets)
Paddle Speed	100 rpm
Media	pH 6.8 Phosphate Buffer, 500 mL @ 37°C
Detection	HPLC
Sampling Time	1, 2, 4, 6, 8 and 12 hours

    - Reference was made to DMF [redacted] (b) (4) A008, M3, Report RD-2012-ANL-003 regarding product pH solubility. Since dissolution performance was

considered to be pH independent, the Applicant completed the comparative dissolution study using only one buffer medium (pH 6.8 phosphate buffer). The mean dissolution profile results are summarized in the following figure.

Mean Dissolution Profiles for Hydrocodone Bitartrate ER Capsules 10, 15, 20, 30, 40, and 50 mg (USP 1, pH 6.8 Phosphate Buffer, 100 rpm)



- Similarity f2 values were used to determine profile similarity for the different HC-ER capsules relative to the 15 mg HC-ER capsule. The Applicant's results are summarized in the table below.

Profile Comparison	Calculated F2 Value
15 mg vs 10 mg	91
15 mg vs 20 mg	83
15 mg vs 30 mg	88
15 mg vs 40 mg	96
15 mg vs 50 mg	83

8. Presence of a predictive Level A IVIVC.
   - Reference was made to DMF (b) (4) Amendment 008, Report BC021201 for the HC-ER 15 mg capsule Level A IVIVC predictions to support the biowaiver request. The Applicant concluded that the HC-ER 15 mg capsule will have bioequivalent, dose-normalized plasma concentrations relative to the 50 mg strength because the dissolution profile is essentially the same using the in-vitro method tied to the Level A IVIVC model.

Reviewer's Assessment: *Reference was made to DMF (b) (4) for the product formulation and manufacturing details to support the (b) (4) claim, the complete dissolution data, and justification for comparative dissolution in a single medium. From the Biopharmaceutics standpoint, the DMF data were adequate to support granting a biowaiver.*

Although the Applicant referenced the Level A IVIVC, the Applicant did not use the IVIVC model to predict PK parameters in support of the biowaiver request. However, the IVIVC data are not necessary because of the [redacted] *of the formulation, availability of PK data at a higher strength, demonstration of dose proportionality and acceptable in vitro dissolution performance.*

Conclusion: A biowaiver is granted for the 15 mg strength.

2.4 DISSOLUTION METHOD

The proposed dissolution method and acceptance criteria are as follows.

Dissolution Apparatus	USP Apparatus 1 (40 mesh baskets)	
Media	Phosphate Buffer	
Media pH	6.80 ± 0.05	
Media Volume	500mL per vessel	
Media Temperature	37°C ± 0.5°C	
Basket Speed	100 rpm	
Detection Method	HPLC	
Proposed Dissolution Acceptance Criteria	Time (hr)	Released (%)
	1	[redacted]
	4	
	8	
	12	

Source: Section 2.7 of NDA.

Reference is made to DMF [redacted] for all drug product CMC, including the dissolution method and acceptance criteria.

Reviewer's Assessment: *DMF* [redacted] *was reviewed and found adequate, with comments, (review date 2 Janurary 2013) from the Biopharmaceutics perspective.*

2.5 DRUG PRODUCT STABILITY

Reference is made to DMF [redacted] for the stability data and associated statistical analyses. A variety of components and configurations have been formally studied on stability, however, the Applicant is seeking approval for the following capsule strengths and packaging configurations

- [redacted]
- 24 months expiry for the 100 ct sizes
  - 10, 15, 20, 30, 40, 50 mg: 100 ct, [redacted] cc HDPE bottles

Reviewer's Assessment: *Refer to the CMC Quality review for a final recommendation on the product's shelf life. All dissolution stability issues noted by the reviewer under the DMF were conveyed to Dr. Yong Hu, the assigned CMC Reviewer.*

2.6 IN VITRO ALCOHOL DOSE DUMPING STUDY

The potential for alcohol dose dumping was evaluated both in vitro and in vivo for the HC-ER capsules. Report RD-2009-FOR-001, submitted to the NDA, provided the following details on the in vitro study protocol and results.

Study Design: The dissolution of HC-ER capsules, 10, 40, or 50 mg was evaluated using the USP 1 apparatus at 100 rpm with different media containing various ethanol concentrations:

- 500 mL pH 6.8 phosphate buffer containing 0, 5, 10, 20, or 40% ethanol. Dissolution with 10% ethanol was performed for only the 40 mg strength.
- Two stage buffer (500 mL): medium 1—0.01N HCl and 40% (v/v) ethanol at 1, 2 hours and medium 2—pH 6.8 phosphate buffer at > 4 hours time points), which was used for only the 40 mg capsule.
- 500 mL simulated gastric fluid (SGF) without pepsin and 0 and 20% ethanol for the 40 mg capsule and 900 mL SGF with 20% ethanol for the 10 and 50 mg capsules.
- 900 mL 0.1N HCl with 0, 5, 20, and 50% ethanol, which was used for the 50 mg capsules.

Results: At least 6 samples were used for each tested variable and complete drug release data (individual values, mean, min, max) were provided.

Figure 1a
pH 6.8 Buffer with 0, 5, 20, and 40% (v/v) Ethanol (10 mg)

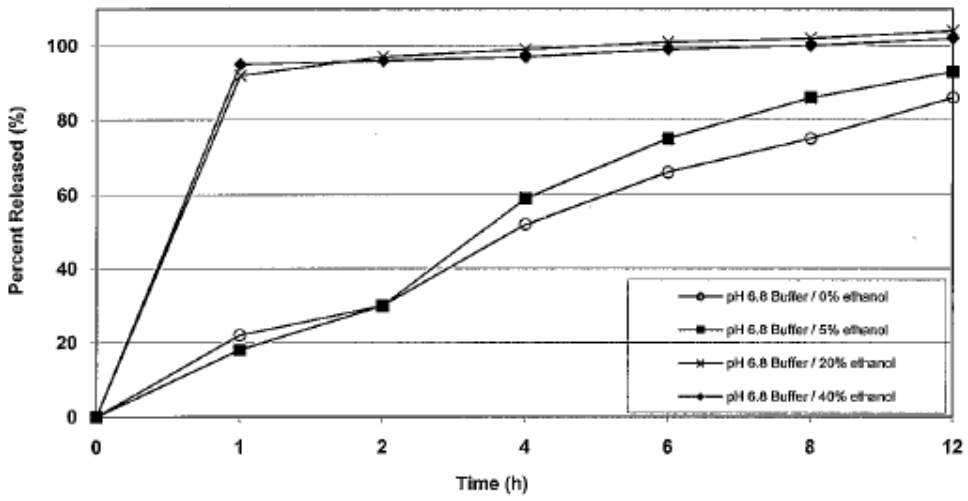


Figure 1b
pH 6.8 Buffer with 0, 5, 10, 20, and 40% (v/v) Ethanol (40 mg)

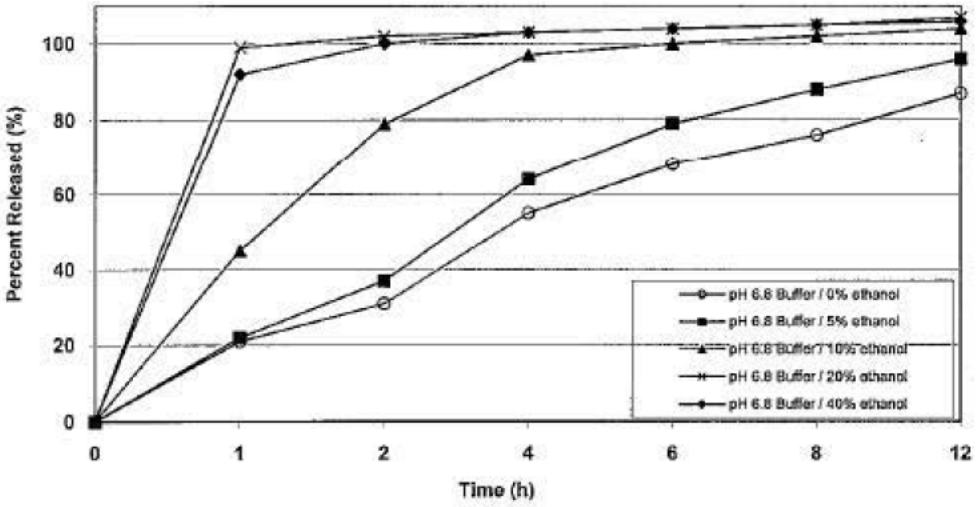


Figure 1c
pH 6.8 Buffer with 0, 5, 20, and 40% (v/v) Ethanol (50 mg)

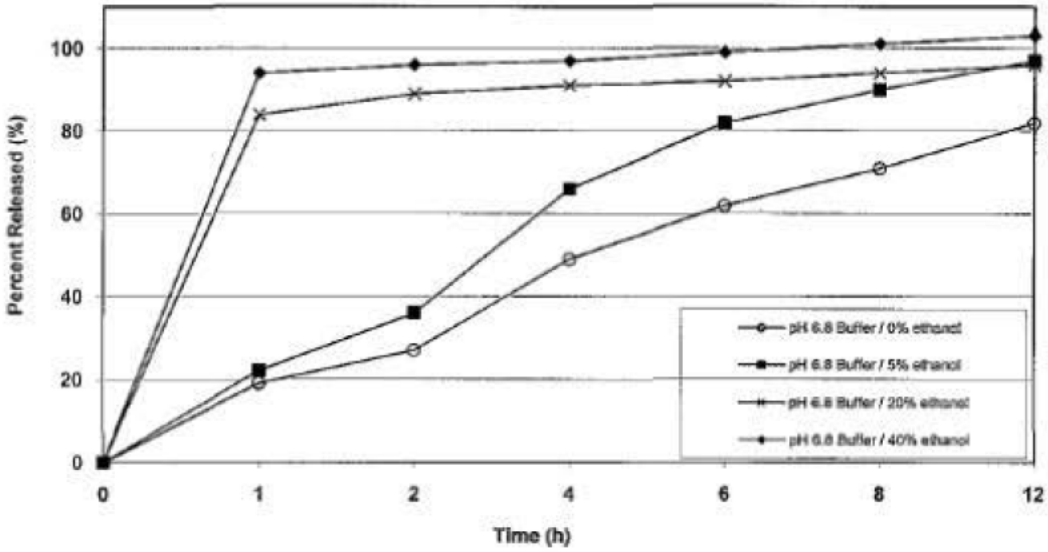


Figure 2
Changeover Dissolution: 0.01N HCl with 0, 5, and 40% (v/v) Ethanol / pH 6.8 Buffer (40 mg)

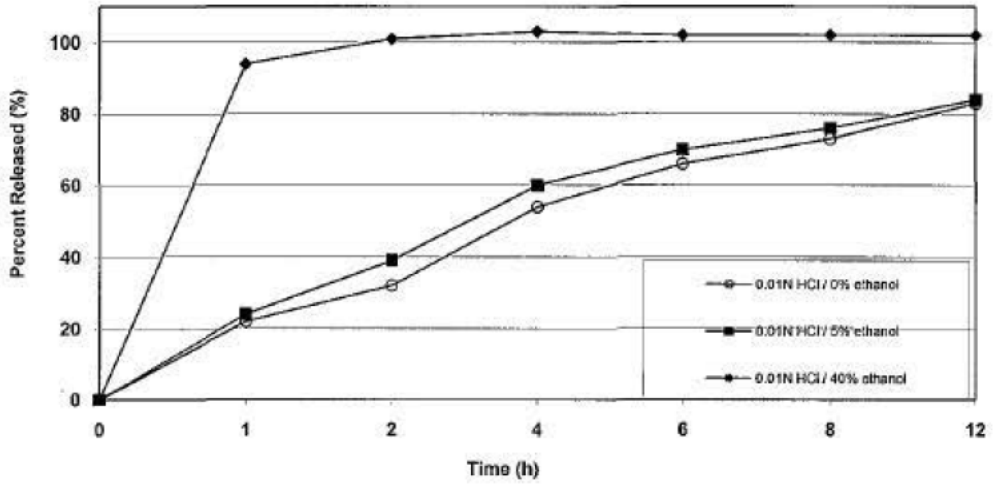


Figure 3
Simulated Gastric Fluid with 0, and 20% (v/v) Ethanol

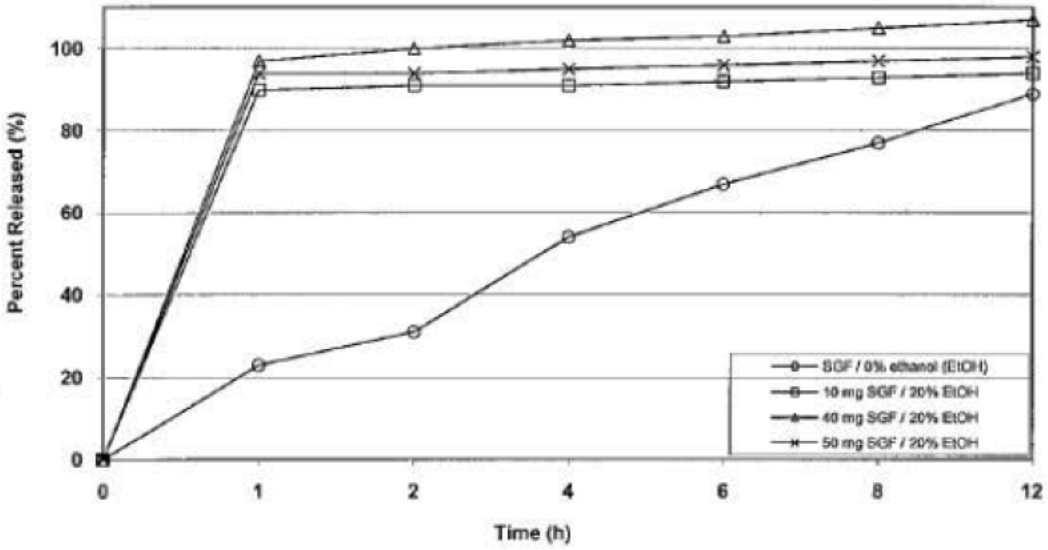
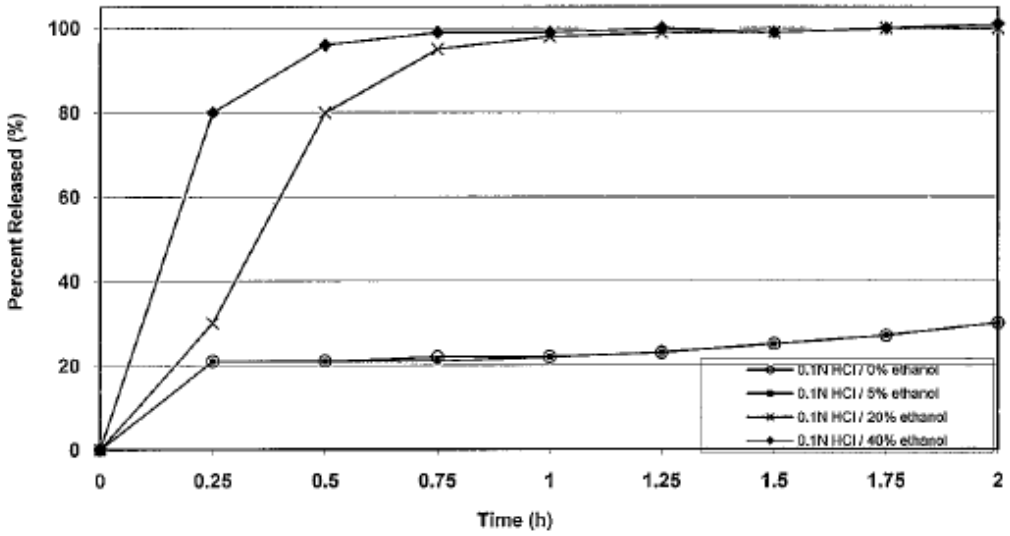


Figure 4
0.1N HCl with 0, 5, 20, and 40% (v/v) Ethanol (50 mg)



Overall, the data show that the controlled-release properties for the HC-ER tablets are compromised in the presence of alcohol (i.e., >5%). Therefore, alcohol induced dose dumping is a potential safety concern, which required further evaluations. To this aim, the Applicant completed Clinical Study ZX002-0901.

Reviewer's Assessment: *The in vitro alcohol dose dumping study was appropriately completed with respect to dissolution methodology and ethanolic concentrations tested. The change from 4% to 5% ethanol in solution is acceptable. The study results clearly show that alcohol destroys the extend release properties of the matrix. The effect is probably due to the rapid dissolution of the coating matrix, which acts as the barrier between the solution and API under normal conditions.*

The in vivo alcohol dose dumping study, and associated safety recommendations, should be addressed by the assigned Clinical Pharmacology reviewer and is not covered in this review. However, the reviewer notes that the HC-ER formulation is slightly more resilient to alcohol effects in vivo compared with in vitro. In vitro, the extend release attribute is completely lost in 20% alcohol. However, in vivo, the mean hydrocodone C_{max} was similar in subjects receiving HC-ER + 20% alcohol (51.8 ng/mL) in comparison to those receiving HC-ER + 0% alcohol (46.3 ng/mL). An in vivo alcohol effect was observed at 40%, as the mean hydrocodone C_{max} increased more than two-fold in subjects receiving HC-ER + 40% alcohol (109 ng/mL) in comparison to those receiving HC-ER + 0% alcohol or HC-ER + 20% alcohol.

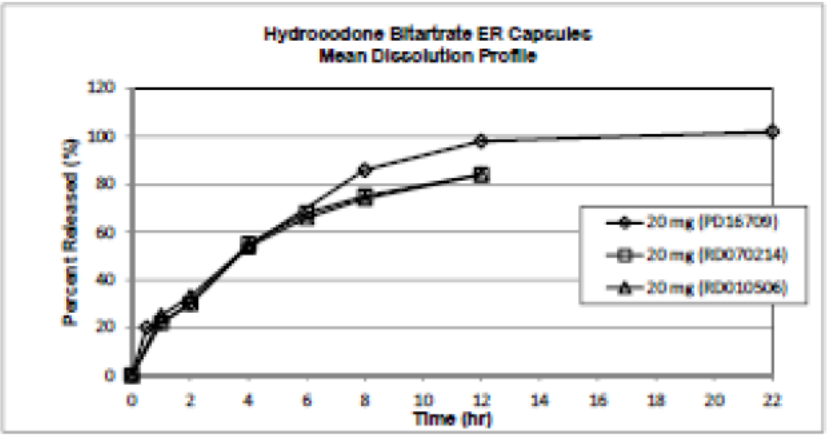
Conclusion: Alcohol induced dose-dumping occurs in vitro and is a potential safety concern for the HC-ER capsules.

2.7 EVALUATION OF BRIDGING STUDIES FOR FORMULATION CHANGES DURING CLINICAL DEVELOPMENT AND THE TO-BE-MARKETED FORMULATION

The relative bioavailability of different investigational formulations was evaluated in the phase 1 PK Study 0901001 and compared PK performance of the HC-ER capsules relative to the approved Vicodin HP tablets (10 mg hydrocordone bitrate/660 mg acetaminophen). The HC-ER formulation with the fastest dissolution profile was selected as optimal and was further evaluated in PK food-effect study 302002 (b) (4) % coating weight). The formulation was further modified to include an (b) (4) This optimized formulation is the to-be-marketed formulation and was used in the pivotal clinical studies ELN154088-201 (bunionectomy surgery) and ELN154088-203 (osteoarthritis) and PK studies on hepatic impairment (ZX002-1001 and ZX002-1002).

Reference is made to DMF (b) (4) for additional details on the formulation changes. The dissolution profile for the early formulation used in the food-effect study and the proposed commercial product used in the clinical efficacy and safety studies is provided below.

Figure 2.7.1-5 Dissolution Profiles Comparing Manufacturing Sites and Scales, HC-ER in Buffer, Lots PD16709 (Athlone, Smaller Scale), RD070214 (Gainesville, Smaller Scale), RD010506 (Gainesville, Larger Scale)



Note: The complete details of the dissolution test method and individual values were not provided.

Reviewer's Assessment: *DMF (b) (4) was reviewed and the submitted in vitro dissolution data were deemed insufficient to establish bioequivalence between the early (b) (4) % formulation used in the food effect study and the formulation used in clinical efficacy/safety studies. The reviewer acknowledges that the dissolution profiles appear similar between the (b) (4) formulation and final formulation, but in vitro dissolution data alone are not adequate for bridging the ER formulation changes when SUPAC-MR principles are applied. The composition of the (b) (4) did not change during develop, just the (b) (4) . Therefore, the mechanism of drug release should be the same. However, the coating weight is a critical attribute for drug*

release and changes in the coating thickness can have a significant impact on the release rate and in vivo kinetics, particularly Cmax values, as noted in Study 0901001. In Study 0901001, there was a rank order relationship in Cmax based on coating weight.

The above dissolution profiles suggest a somewhat faster release profile for the early formulation relative to the clinical formulation, which could translate to differences in the Cmax across the formulations. These differences are not expected to impact the overall conclusion of the food effect study, but this is a review issue to be addressed by the Clinical Pharmacology reviewer.

Biopharmaceutics' findings on the inadequacy of the in vitro dissolution data to support bridging the formulations were communicated to the assigned Clinical Pharmacology Reviewer, Dr. David Lee, for consideration. Since the clinical studies and bioequivalence studies used the proposed to-be-marketed formulation, the reviewer has no concerns regarding the requirement for bioavailability data using the final product. It is also noted that in vivo PK data are available for the final formulation at the same dosage strength (i.e., 20 mg) used in the food effect study. Since in vivo PK data were available for both the early and final formulation to make a risk-based assessment, the reviewer did not request complete in vitro dissolution data to support the formulation. Per communications with Dr. Lee, the in vivo PK data showed acceptable comparability between the (b) (4) *formulation and the final formulation to permit the use of the food-effect study data in the label.*

2.8 IN VITRO/IN VIVO CORRELATION MODEL

Reference was made to DMF (b) (4) for the details on the HC-ER Level A IVIVC model development and validation. The proposed Level A IVIVC model was internally, externally, and cross validated using the in vitro and in vivo data from Clinical Study 0901001 which assessed extended release formulation switch three different in vitro dissolution profiles relative to an immediate release formulation (Vicodin HP) and the proposed commercial formulation employed in Clinical Study ZX002-0901. The robustness of the model was also determined by assessing the lots used for cross-validation using different in vitro release testing methodologies (i.e., comparing USP Apparatus 1 and 2).

Reviewer's Assessment: *DMF* (b) (4) *was reviewed and a Level A IVIVC was found adequate to support post approval formulation changes. However, the reviewer notes that the IVIVC model described in the NDA is not the same IVIVC model accepted for regulatory purposes.*

Refer to the Biopharmaceutics Review No. 1 for DMA (b) (4) *dated 2 January 2013.*

3.0 CONCLUSIONS AND RECOMMENDATIONS

- DMF (b) (4) was found adequate, with comments, from the Biopharmaceutics perspective to support NDA approval. An adequate response to the DMF comments is pending; however, based on the outstanding issues noted for the DMF, the following conclusions can be made.

a. The proposed dissolution method and acceptance criteria are acceptable.

Parameter	Criteria
Apparatus	USP 1 (40 mesh baskets)
Paddle Speed	100 rpm
Media	pH 6.8 Phosphate Buffer, 500 mL @ 37°C
Detection	HPLC
Acceptance Criteria	1 hour = NLT (b) (4)% 4 hour = (b) (4)% 8 hour = (b) (4)% 12 hours = NLT (b) (4)%

b. A Level A IVIVC model submitted under DMF (b) (4) is adequate to support future post-approval drug product changes in accordance with the SUPAC-MR guidance (see DMF review for additional details). The IVIVC model described in the NDA is not the same IVIVC model accepted for regulatory purposes.

- A biowaiver is granted for the 15 mg capsule strength.
- The proposed HC-ER capsule is susceptible to alcohol induced dose dumping in vitro. The safety implication of this finding is assessed by the assigned Clinical Pharmacology and Clinical reviewers.
- A major formulation change was noted between product used in a PK food effect study and the product used in the clinical efficacy/safety studies. There were insufficient in vitro dissolution data to bridge the formulation changes; however, the to-be-marketed formulation, including the dose used for the food effect study, was used in the clinical safety and efficacy studies, which included PK assessments. Thus, there may be sufficient in vivo PK data on both formulations to support the adequacy of the food-effect study. The acceptability of the in vivo data is not under Biopharmaceutics purview. Refer to the Clinical Pharmacology review for additional details on the acceptability of the food effect study.
- The in vitro and in vivo data support an extended release claim, from the Biopharmaceutics perspective.

APPENDIX – SUPPLEMENTAL REVIEW INFORMATION

Table 5a
Effect of Ethanol Concentration in pH 6.8 Buffer (10 mg)

Time (h)	Mean Percent Released (%)				
	0% Ethanol	5% Ethanol	10% Ethanol	20% Ethanol	40% Ethanol
1	22	18	NA	92	95
2	30	30	NA	97	96
4	52	59	NA	99	97
6	66	75	NA	101	99
8	75	86	NA	102	100
12	86	93	NA	104	102

Table 5b
Effect of Ethanol Concentration in pH 6.8 Buffer (40 mg)

Time (h)	Mean Percent Released (%)				
	0% Ethanol	5% Ethanol	10% Ethanol	20% Ethanol	40% Ethanol
1	21	22	45	99	92
2	31	37	79	102	100
4	55	64	97	103	103
6	68	79	100	104	104
8	76	88	102	105	105
12	87	96	104	107	106

Table 5c
Effect of Ethanol Concentration in pH 6.8 Buffer (50 mg)

Time (h)	Mean Percent Released (%)				
	0% Ethanol	5% Ethanol	10% Ethanol	20% Ethanol	40% Ethanol
1	19	22	NA	84	94
2	27	36	NA	89	96
4	49	66	NA	91	97
6	62	82	NA	92	99
8	71	90	NA	94	101
12	82	97	NA	96	103

Table 5d
Effect of Ethanol Concentration in 0.01N HCl / pH 6.8 Buffer (changeover) (40 mg)

Time (h)	Mean Percent Released (%)		
	0% Ethanol	5% Ethanol	40% Ethanol
1	22	24	94
2	32	39	101
4	54	60	103
6	66	70	102
8	73	76	102
12	83	84	102

Table 5e
Effect of Ethanol Concentration in Simulated Gastric Fluid

Time (h)	Mean Percent Released (%)			
	0% Ethanol	20% Ethanol		
	40 mg	10 mg	40 mg	50 mg
1	23	90	97	94
2	31	91	100	94
4	54	91	102	95
6	67	92	103	96
8	77	93	105	97
12	89	94	107	98

Table 5f
Effect of Ethanol Concentration in 0.1N HCl (50 mg)

Time (h)	Mean Percent Released (%)			
	0% Ethanol	5% Ethanol	20% Ethanol	40% Ethanol
0.25	21	21	30	80
0.50	21	21	80	96
0.75	22	21	95	99
1.00	22	22	98	99
1.25	23	23	99	100
1.50	25	25	99	99
1.75	27	27	100	100
2.00	30	30	100	101

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/s/

MINERVA HUGHES
01/15/2013

JOHN Z DUAN
01/15/2013

CLINICAL PHARMACOLOGY REVIEW

NDA: 202880	Submission Date: 5/1/12
Submission Type; Code:	505(b)(2)
Brand/Code Name:	Zohydro Capsules
Generic Name:	Hydrocodone bitartrate extended release capsules
Clinical Pharmacology Primary Reviewer:	David Lee, Ph.D.
Pharmacometric Primary Reviewer:	Joo-Yeon Lee, Ph.D.
Pharmacometric Team Leader:	Venkatesh Atul Bhattaram, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Pharmacometrics and Division of Clinical Pharmacology 2
OND Division:	Division of Anesthesia, Analgesia, and Addiction Products
Sponsor:	Zogenix, Inc
Relevant NDA(s)	-
Relevant IND(s):	65,111
Formulation; Strength(s):	Capsules; 10, 15, 20, 30, 40 and 50 mg
Proposed Indication:	Management of moderate-to-severe chronic pain when a continuous around the clock opioid analgesic treatment is needed for an extended period of time
Proposed Dosage Regimen:	Use low initial doses in patients not already opioid-tolerant; a reasonable starting dose is 10 mg every 12 hours

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application for hydrocodone bitartrate extended release capsules. From a clinical pharmacology perspective, the

information submitted in the NDA is acceptable, pending agreement on the labeling language.

It is noted that a Required Inter-division Level Clinical Pharmacology Briefing for this NDA was held on January 11, 2013, in Office of Clinical Pharmacology, and our recommendations were agreed with in the meeting.

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of CP Findings

Zogenix, Inc. submitted a New Drug Application (NDA) 202880, on 5/1/12, a single entity hydrocodone bitartrate extended release capsules ("HC-ER") (10, 15, 20, 30, 40 and 50 mg capsules), for management of moderate-to-severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time. There is no approved single-ingredient hydrocodone product currently available on the market. Hydrocodone has been approved for many years as an immediate-release, combination drug products, such as those containing acetaminophen and ibuprofen. In theory, the Applicant's drug product can be dosed based on the opioid component without the limitations of the non-opioid constituents, such as safety issues associated with acetaminophen or ibuprofen.

The Applicant's product is a 12-hour extended release formulation of hydrocodone that utilizes Alkermes' patented Spheroidal Drug Absorption System (SODAS®) drug delivery technology. Vicoprofen Tablet (7.5 mg/200 mg), N20-716, is used as a listed drug in this application.

The clinical pharmacology information of hydrocodone after oral administration of the HC-ER has been characterized in 6 Phase 1 studies and 2 Phase 2 studies. Additionally, the Applicant conducted a population pharmacokinetic (PK) analysis using the information observed from conducted studies to support the hydrocodone dose linearity purpose. The information pertinent to the application is presented below.

<u>Relative Bioavailability (Study ZX002-1102)</u>

Study ZX002-1101 was a Phase 1, open-label, randomized, two-dose, two-period cross-over study with minimum 5 day washout between treatments. The study was conducted in 15 healthy subjects between 18 and 45 years of age who received a single dose of 30 mg HC-ER and 2 consecutive doses of 2-tablets of Vicoprofen 6 hours apart for a total of 4 tablets. Subjects were fasted overnight for at least 10 hours before and for at least 3.5 hours post dosing. For Vicoprofen treatment, subjects were provided a light meal, which needed to be consumed within a 30-minute period (3.5–4.0 hours post-dosing), followed by at least four hours of fasting, to allow for 2 hours of fasting before and after the 2nd

dose of Vicoprofen. All doses were administered with 240 mL of ambient temperature water.

Mean hydrocodone Cmax values were 32 ± 7 and 46 ± 7 ng/mL for HC-ER and Vicoprofen treatments, respectively. Mean hydrocodone Cmax were not similar between the two treatments as indicated by the bioequivalence evaluation. This finding is expected since the IR and ER formulation profiles are not similar.

Mean hydrocodone AUC values were 513 ± 92 and 559 ± 122 ng.h/mL for HC-ER and Vicoprofen treatments, respectively. The bioequivalence analysis indicated that the AUC values from the two treatments were equivalent.

Dose linearity

Single dose (Study ELN154088-201)

Study ELN154088-201 was a Phase 2 randomized, single-dose, parallel group, placebo-controlled, active-comparator study. This study also evaluated PKs of hydrocodone from HC-ER capsule. The study was conducted in adult subjects in generally good health requiring primary, unilateral, first-metatarsal bunionectomy surgery, between 18 and 83 years of age who received a single dose of 10, 20, 30 and 40 mg of HC-ER capsules. Over-encapsulated 10-mg hydrocodone/325-mg acetaminophen tablet was used as an active comparator. There were 115 subjects in the PK analysis (17 – 21 subjects per group).

Mean hydrocodone Cmax values were 8.9 ± 2.1, 17.9 ± 5.9, 31.7 ± 8.5 and 37.5 ± 8.8 ng/mL for 10, 20, 30 and 40 mg single dose treatments, respectively.
Mean hydrocodone AUC values were 137 ± 39, 256 ± 89, 481 ± 139 and 596 ± 173 ng.h/mL for 10, 20, 30 and 40 mg single dose treatments, respectively.

Dose-linear increases in hydrocodone Cmax and AUC values were observed over the 10 to 40 mg HC-ER dose range after a single dose administration.

Multiple dose (Study ELN154088-203)

Study ELN154088-203 was a Phase 2, multi-center, open-label, multiple-dose, two-group dose escalation study in patients with moderate-to-severe osteoarthritis designed to assess the safety, tolerability and PK study. The study was conducted in adult subjects in generally good health with osteoarthritis that involved at least one hip or knee joint. The subjects had required pain treatment with NSAID and/or with APAP for at least three months. Additionally, subjects experienced moderate-to-severe arthritis pain on a continuing basis, had received insufficient analgesia from NSAID and APAP therapy, and had used opioids for their arthritis pain on an as-needed basis. The study was divided into 2 groups: Group 1: start at 10 mg BID for 7 days, followed by 20 mg BID for 7 days, followed by 30 mg BID for 7 days. Group 2: start at 20 mg BID for 7 days, followed by 30 mg BID for 7 days, followed by 40 mg BID for 7 days.

Group 1 mean hydrocodone Cmax values were 18 ± 5.2, 39 ± 17, and 63 ± 27 ng/mL for 10, 20, and 30 mg, respectively, at steady state. Group 2 mean hydrocodone Cmax values were 36 ± 10, 56 ± 20, and 78 ± 33 ng/mL for 20, 30, and 40 mg, respectively, at steady state. Mean hydrocodone Cmax values from both groups, 20 and 30 mg doses, were comparable.

Group 1 mean hydrocodone AUC0-12 h values were 169 ± 52, 379 ± 177, and 597 ± 272 ng.h/mL for 10, 20, and 30 mg, respectively, at steady state. Group 2 mean hydrocodone AUC values were 354 ± 103, 549 ± 215, and 738 ± 318 ng.h/mL for 20, 30, and 40 mg, respectively, at steady state. Mean hydrocodone AUC values from both groups, 20 and 30 mg doses, were comparable.

Dose-linear increases in hydrocodone Cmax and AUC values were observed over the 10 to 40 mg HC-ER dose range after multiple dose administration.

Food effect (Study 0302002)

Study 0302002 was a Phase 1, open-label, randomized, two-dose, two-period cross-over study with minimum 7 day washout between treatments. The study was conducted in 12 healthy subjects between 19 and 33 years of age who received a single oral dose of 20 mg HC-ER capsule fasted for at least 10 hours prior to dosing and a single oral dose of 20 mg HC-ER capsule fed 30 minutes prior to dosing and dosed within 5 minutes of consuming the high-fat meal. All subjects remained fasted for at least four hours post dosing. The capsules were administered with 240 mL of water.

Mean hydrocodone Cmax values were 28.8 ± 4.2 ng/mL and 22.7 ± 4.3 ng/mL in fed and fasted states, respectively, after a single dose 20 mg HC-ER post administration. Mean hydrocodone Cmax increased approximately 27% in the fed state compared to the fasted state. However, the extent of absorption (AUC) of hydrocodone was similar between fed and fasted (338 ± 55 ng.h/mL vs. 345 ± 37 ng.h/mL, respectively). The hydrocodone median Tmax were 6 h and 8 h for fasted and fed, respectively. The hydrocodone half-lives were 4.9 ± 1 h and 6.5 ± 0.9 h for fed and fasted states, respectively.

There was no evidence of dose dumping associated with this formulation under fasted and fed conditions. It is noted that a clinical trial formulation ((b) (4)% polymer coated spheres produced at Athlone location) than the to-be-marketed formulation (b) (4)% polymer coated spheres produced at Gainsville location) was used in the food effect study. However, the information obtained from this study is considered adequate and will be included in the Label, based on the facts that 1) formulation between Athlone and Gainsville manufacturing (to-be-marketed formulation) sites are exactly the same, except for the differences in the polymer coating, (b) (4)%, respective, and, that the differences are deemed not to be significant to alter the exposure; and, 2) all strengths, 10 to 50 mg, manufactured from Gainsville manufacturing site are used in clinical studies, including Phase 3 study, ZX002-0801, such that performance aspect of the formulation is not in question (Discussion from Clinical Pharmacology (OCP) Briefing held on January

11, 2013). Additionally, comparison of Cmax across Phase 1 studies indicated, with a caveat that this is a cross-study comparison, that Athlone and Gainsville formulations are not drastically different when 'fasted' treatment from the food study is compared to other 'fasted' treatments, or 'fed' treatment from the food study is compared to other 'fed' treatments (See Section 2.5.3 below). No additional information may be required at this moment regarding food effect on HC-ER formulation.

Alcohol interaction

Study ZX002-0901 was a Phase 1, open-label, randomized, single-dose, three-period crossover study with a 4-5 day washout between doses. The study was conducted in 30 healthy adults between 22 and 44 years of age who received a single dose of HC-CR 50 mg in fasted state with 240 mL solution of 40% alcohol/orange juice, 240 mL solution of 20% alcohol/orange juice, and 240 mL solution of 0% alcohol/orange juice. Commercially available naltrexone (50 mg) was orally administered at approximately 12 (with a light snack) and two hours (fasted) prior to administration, and 10 hours (with a light snack) after administration of HC-ER in each study period.

Mean hydrocodone Cmax values were 109 ± 39, 52 ± 11, and 46 ± 8.6 ng/mL in 40, 20 and 0% alcohol in fasted state, respectively. Mean hydrocodone Cmax increased approximately 2.4-fold in 40% alcohol compared to the 0% alcohol treatments. The greatest increase in Cmax was observed at 3.9-fold (Subject #016). Mean hydrocodone Cmax value for 20% alcohol was comparable to 0% alcohol treatment.

Mean hydrocodone AUC values were comparable for all alcohol treatments (1017 ± 217, 900 ± 243, and 846 ± 225 ng.h/mL in 40, 20 and 0% alcohol in fasted state, respectively). Mean hydrocodone AUC was slightly higher for subjects receiving 40% alcohol. The greatest increase in AUC was observed at 1.7-fold (Subject #007). This difference was not statistically significant (within bioequivalence range).

Mean hydrocodone Tmax values were 2.4 ± 1.1, 5.4 ± 1.5, and 6.2 ± 2.1 h in 40, 20 and 0% alcohol in fasted state, respectively. Tmax decreased less than half the time for subjects receiving 40% alcohol in comparison to those receiving 20% or 0% alcohol.

This study demonstrated that the rate of absorption (Cmax) was affected by co-ingestion with 40% alcohol in the fasted state. However, the greatest individual increase in Cmax was comparable or lower than those of the already approved extended-release opioid products. 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.

Hepatic Impairment

Study ZX002-1001 was a Phase 1, open-label, single-dose, parallel study in subjects with mild or moderate hepatic impairment. Ten healthy control subjects were matched to 20 hepatically-impaired subjects for age (±10 years), and body mass index (BMI) (± 10% of

BMI) with some consideration for race and gender. The hepatically-impaired subjects had a diagnosis of chronic (more than 6 months), stable (no acute episodes of illness within the previous 2 months due to deterioration of hepatic function) hepatic insufficiency with features of cirrhosis due to any etiology. Ten (10) hepatically-impaired subjects were enrolled into one of two Child-Pugh classifications based on their hepatic impairment: mild and moderate, with the expectation of at least 8 evaluable subjects for each severity. All subjects received a single dose of 20 mg HC-ER in a fasted state. All doses were administered with 240 mL of water.

Mean hydrocodone Cmax values were 25 ± 5, 24 ± 5, and 22 ± 3.3 ng/mL for moderately impaired, mildly impaired and normal subjects, respectively. Mean hydrocodone Cmax values were comparable for all groups.

Mean hydrocodone AUC values were 509 ± 157, 440 ± 124, and 391 ± 74 ng/mL for moderately impaired, mildly impaired and normal subjects, respectively. Mean hydrocodone AUC increased approximately 26% for moderately impaired subjects compared to that of normal subjects; this increase in exposure may not be clinically significant and may not warrant a dose adjustment. Severely impaired subjects were not studied. Patients in this population should use low initial dose and be monitored closely.

Renal Impairment

Study ZX002-1002 was a Phase 1, single-dose, parallel study in subjects with mild, moderate, or severe renal impairment per Cockcroft-Gault criteria. Healthy control subjects were matched to renally-impaired subjects for age (±10 years), and body mass index (BMI) (± 10% of BMI) with some consideration for race and gender. The renal-impaired subjects were required to have a diagnosis of chronic (more than 6 months), stable (no acute episodes of illness within the previous 2 months due to deterioration of renal function) renal insufficiency due to any etiology. There were approximately 9 subjects per group. All subjects received a single dose of 20 mg HC-ER in a fasted state. All doses were administered with 240 mL of water.

Mean hydrocodone Cmax values were 26 ± 6.0, 28 ± 7.5, 21 ± 5.1 and 19 ± 4.4 ng/mL for severe, moderate, mild renal impaired and normal subjects, respectively. Mean hydrocodone Cmax values were comparable for all groups.

Mean hydrocodone AUC values were 487 ± 123, 547 ± 184, 391 ± 122 and 343 ± 105 ng.h/mL for severe, moderate, mild renal impaired and normal subjects, respectively.

Data from a study involving 28 patients with varying degrees of renal impairment, matched to 9 subjects with normal renal function, showed that plasma hydrocodone concentrations are higher in patients with renal impairment. Peak plasma HC concentrations 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. On the basis of these findings no routine dose adjustment appears necessary in patients with renal impairment. However, since hydrocodone plasma levels may be increased in

individuals with moderate to severe renal impairment, patients in this population should use low initial dose and be monitored closely.

Pediatric

The Applicant is requesting a waiver and a deferral of the requirement to assess HC-ER in pediatric subjects aged < 7 and > 7 years of age (as a post-marketing commitment), respectively. At the End-of-Phase 2 meeting (6/4/08), the Applicant requested a waiver of the requirement to study HC-ER in pediatric subjects. The Agency responded at that time that analgesia in the pediatric population continues to be an unmet medical need but that a deferral may be requested if supported by an appropriate justification. At the pre-NDA meeting (11/17/11), the Applicant requested a waiver for pediatric subjects (b) (4) years of age and a deferral for (b) (4) - 17 years of age. The Agency indicated that, for opioid analgesics indicated for the treatment of chronic pain, PK and safety data in pediatric subjects aged 7 - 17 years was typically required, but it was agreed that studies in pediatric patients < 7 years of age could be waived. The Agency also indicated that efficacy findings from adults may be extrapolated to the pediatric age group over 7 years of age.

Elderly

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.

Drug Interaction

No drug interaction studies were submitted. It is well known that the formation of the norhydrocodone is mediated by CYP3A4, while the formation of hydromorphone is primarily mediated by CYP2D6. Inhibition or induction of these enzymes due to interacting drugs or genetic predisposition is likely to alter the metabolic profile of hydrocodone. A caution is advised when administering HC-ER in combination with CYP3A4 inhibitors or inducers. The extent of drug interaction could be more pronounced with concomitant use of CYP 2D6 and 3A4 inhibitors.

Gender and Race

No information was submitted.

Analytical Methodology

Liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method was developed and validated to quantify hydrocodone, hydromorphone, and norhydrocodone in human plasma and urine. The typical assay range was from 0.1 to 100 ng/mL for all

analytes. The lower limit of quantitation was 0.1 ng/mL for all analytes. The mean precision and accuracy were less than or equal to approximately 3 to 6 percent. Overall there were no issues identified with analytical information.

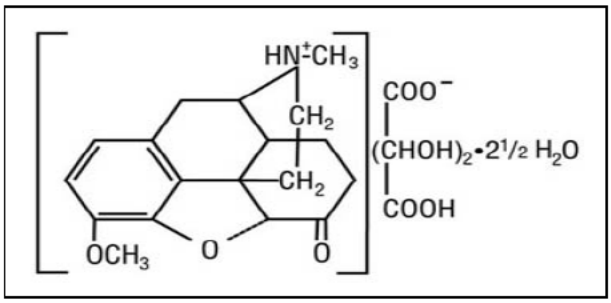
2 QBR

2.1 General Attributes of the Drug and Drug Product

2.1.1 What are known properties of hydrocodone?

Hydrocodone is a semi-synthetic opioid analgesic and anti-tussive with multiple actions qualitatively similar to those of codeine (Per Vicoprofen PI). Most of these involve the central nervous system 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 opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood, and mental clouding. The following figure is a structure of hydrocodone bitartrate (Figure 1).

Figure 1. Hydrocodone bitartrate structure



2.1.2 What is the to-be-marketed formulation?

Hydrocodone bitartrate extended-release capsule is an extended-release capsule formulation utilizing Alkermes SODAS® (Spheroidal Oral Delivery Absorption System) technology. This technology is based upon initially coating sugar spheres with the drug substance and suitable excipients to form immediate-release (IR) spheres. Sustained-release (SR) spheres are prepared by coating the IR spheres with rate-controlling polymers to obtain a desired dissolution profile (final formulation was chosen by (b) (4) were chosen). The target release rate for the HC-ER is achieved by combining IR and SR beads in a defined active ratio (20:80) followed by (b) (4) into the gelatin capsules to the desired dose strength of 10, 15, 20, 30, 40, or 50 mg of hydrocodone bitartrate. The following table (Table 1) contains the drug product components and their functions.

Table 1. Drug product components and function

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

It is noted that the initial formulation utilized in the clinical studies was a (b) (4) polymer coating spheres, manufactured at Athlone, Ireland site. This formulation was used in the food effect study. After optimizing the hydrocodone release characteristics of the formulation, the (b) (4) polymer coated spheres, manufactured at Gainsville, Georgia, were used throughout the clinical development. The (b) (4) polymer coated spheres are proposed as to-be-marketed formulation. The overall snapshot of the formulations used in clinical studies is presented below (Table 2).

Table 2. Summary of formulation and process changes during development; all clinical studies used To-be-marketed formulation.

Description of Clinical Study	Supportive Phase I PK and Safety		Supportive Phase II Safety and Efficacy	Supportive Phase I PK and Safety			Pivotal Phase III
	Bioavailability and IVIVC	Food Effect	Single- and Multi-dose PK and Bioavailability	Alcohol Co-ingestion PK	Renal and Hepatic Impairment PK	Bioavailability Vs Vicoprofen®	Safety and Efficacy
Study	901001	302002	ELN-154088-201 ELN-154088-203	ZX002-0901	ZX002-1001 ZX002-1002	ZX002-1102	ZX002-0801 ZX002-0802
Supporting Stability Study	SP-251	SP-251	STAB-011	STAB-030	STAB-030	STAB-030	STAB-029 STAB-030
Strengths	20mg	20mg	10, 20, 30, 40mg	50mg	20mg	30mg	10, 20, 30, 40, 50mg
Formulation Used	1, 2, 3	1	4				
Site of Manufacture	Athlone, Ireland		Gainesville, GA				
FORMULATION CHANGES DURING DEVELOPMENT							
(b) (4)							

2.1.3 What are the proposed dosage and route of administration?

Zohydro (hydrocodone bitartrate) Extended Release Capsule is proposed to be administered by mouth every 12 hours for the management of moderate-to-severe chronic pain when a continuous around the clock opioid analgesic treatment is needed for an

extended period of time. It is not intended for use on an as-needed basis. Zohydro is not indicated for the management of pain in the immediate postoperative period (the first 12–24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. Zohydro is indicated for postoperative use following the immediate post-operative period only if the patient is already receiving an opioid prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Zohydro is not indicated for pre-emptive analgesia (preoperative administration for the management of postoperative pain). Use low initial doses in patients not already opioid-tolerant; a reasonable starting dose is 10 mg.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials and efficacy measurements?

The Applicant submitted one adequate and well-controlled Phase 3 study (ZX002-0801), and three supportive studies, one Phase 3 open label long term safety study (ZX002-0802) and two Phase 2 studies (ELN-154088-203 an open label 3 week chronic osteoarthritis study and ELN-154088-201 a placebo controlled acute bunionectomy study). The two Phase 2 studies also collected PK information (see below single- and multiple-dose PK information). Study ZX002-0801 was a multicenter study with an open-label conversion/titration (C/T) phase of HC-ER followed by a randomized double-blind treatment phase of HC-ER versus placebo in subjects with moderate to severe chronic low back pain (CLBP). Opioid experienced subjects with a clinical diagnosis of moderate-to severe CLBP, whose pain was present for at least several hours a day for a minimum of 3 months and who qualified for around-the-clock opioid therapy for treatment of their CLBP, were eligible to enroll in the study. Subjects must 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). The primary objective of the study was to evaluate the change from baseline, following the conversion/titration phase, to the end of the treatment phase on Day 85 in pain intensity as measured by a 0-10 numerical rating scale (NRS) comparing HC-ER with placebo. The trial 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. Enrollment included 829 subjects screened with 511 subjects continuing into the C/T phase of which 302 subjects were randomized equally to HC-ER or placebo. The results indicated that the mean change in pain intensity score from baseline to Day 85 was significantly lower ($p=0.008$) in the HC-ER group (arithmetic mean ± standard deviation: 0.48 ± 1.56) than the placebo group (0.96 ± 1.55), indicative of the significant effect HC-ER had on reducing subject-reported average daily pain intensity.

2.2.2 Does hydrocodone prolong the QT interval?

No information was submitted to characterize hydrocodone.

2.2.3 Protein binding, metabolism, enzyme induction/inhibition

The following information was obtained from the Vicoprofen package insert.

Protein Binding:

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-α-and 6-β-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.

2.2.4 What are the single and multiple dose PK parameters?

Dose linearity

Single dose (Study ELN154088-201)

Study ELN154088-201 was a Phase 2 randomized, single-dose, parallel group, placebo-controlled, active-comparator study in adults requiring primary, unilateral, first-metatarsal bunionectomy surgery, between 18 and 83 years of age. Subjects received a single dose of 10, 20, 30 and 40 mg of HC-ER capsules. Over-encapsulated 10-mg hydrocodone/325-mg acetaminophen tablet was used as an active comparator. The primary objective of this study was to establish a preliminary dose-response relationship and to compare the efficacy with that of placebo. This study also evaluated PKs of hydrocodone from HC-ER capsule, estimate the duration of efficacy, assess safety and tolerability, the minimum effective and maximum tolerated dose, and, compare the effectiveness to the over-encapsulated comparator. There were 115 subjects in the PK analysis (17 – 21 subjects per group). Blood samples were drawn at baseline, and at 0.5, 1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 16, 20, 24-hr after dosing. The Sum of Pain Intensity Differences (SPID) for the Visual Analog Scale of Pain Intensity (VASPI) from 0 to 12 hours (at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, and 12 hours after dosing or at the time of rescue) were measured for the primary efficacy variable. The VASPI and hydrocodone concentrations were plotted to see if there exist a concentration-response

relationship. The mean hydrocodone, hydromorphone, and norhydrocodone concentration profiles for each treatment groups are shown below (Figures 2, 3 and 4, respectively).

Figure 2. The mean hydrocodone concentration profiles for each treatment groups after single dose

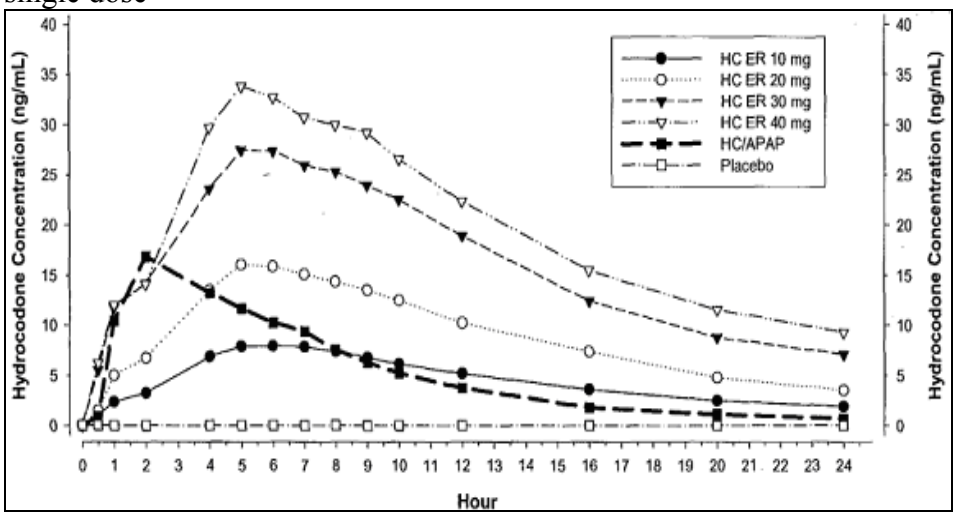


Figure 3. The mean hydromorphone concentration profiles for each treatment groups after single dose

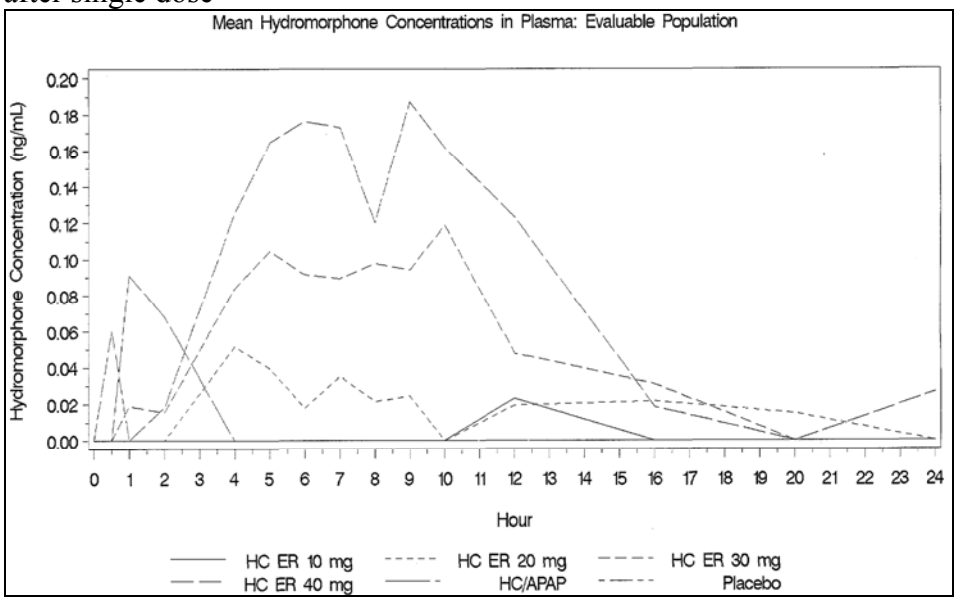
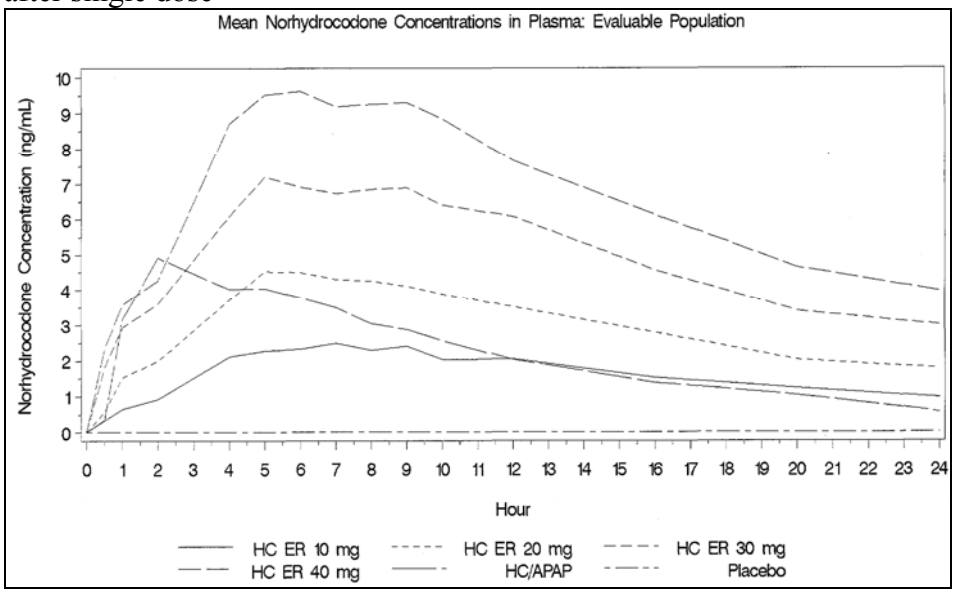


Figure 4. The mean norhydrocodone concentration profiles for each treatment groups after single dose



The mean hydrocodone, hydromorphone, and norhydrocodone PK parameters for each treatment groups are shown below (Tables 3, 4 and 5, respectively).

Table 3. Pharmacokinetic Parameters for hydrocodone after single dose

Parameter Statistic	ELN154088 10 mg N = 21	ELN154088 20 mg N = 19	ELN154088 30 mg N = 19	ELN154088 40 mg N = 17	HC/APAP N = 18	Placebo N = 21
C_{max} (ng/mL)						
n	21	19	19	17	18	21
Mean	8.9	17.9	31.7	37.5	19.5	0.1
SD	2.11	5.85	8.50	8.82	8.69	0.17
Median	9.1	16.3	30.1	34.1	20.2	0.0
Min/Max	5/15	10/27	16/46	28/62	9/45	0/1
T_{max} (h)						
n	21	19	19	17	18	3
Mean	6.3	6.0	6.3	6.1	2.7	8.2
SD	1.46	1.80	1.88	1.62	1.65	13.70
Median	6.1	5.2	6.1	6.0	2.1	0.6
Min/Max	4/9	4/12	4/10	4/10	1/7	0/24
k_{el} (1/h)						
n	21	19	19	17	18	NC[a]
Mean	0.090	0.095	0.086	0.079	0.138	NC
SD	0.0276	0.0289	0.0229	0.0211	0.0297	NC
Median	0.092	0.089	0.083	0.079	0.147	NC
Min/Max	0.02/0.13	0.05/0.16	0.05/0.13	0.05/0.13	0.06/0.18	NC
$t_{1/2}$ (h)						
n	21	19	19	17	18	NC
Mean	9.5	7.9	8.6	9.4	5.3	NC
SD	8.25	2.44	2.32	2.40	1.64	NC
Median	7.6	7.8	8.4	8.8	4.7	NC
Min/Max	5/45	4/15	5/13	5/14	4/11	NC
AUC_{last} (ng h/mL)						
n	21	19	19	17	18	21
Mean	109.0	212.9	392.5	464.6	131.2	0.1
SD	27.25	73.19	117.74	124.01	36.80	0.19
Median	104.2	196.2	367.0	471.0	129.9	0.0
Min/Max	73/179	130/377	177/671	321/712	80/182	0/1
AUC_{inf} (ng h/mL)						
n	21	19	19	17	18	NC
Mean	136.9	255.6	480.7	596.2	137.6	NC
SD	39.48	88.66	138.70	172.73	39.99	NC
Median	128.1	252.7	459.5	578.0	135.4	NC
Min/Max	80/217	151/468	226/756	375/992	83/189	NC

[a] NC = Not Calculated.

Table 4. Pharmacokinetic parameters for hydromorphone after single dose

Parameter Statistics	ELN1544088 10 mg N = 21	ELN1544088 20 mg N = 19	ELN1544088 30 mg N = 19	ELN1544088 40 mg N = 17	HC/APAP N = 18	Placebo N = 21
C_{max} (ng/mL)						
n	21	19	19	17	18	21
Mean	0.0	0.1	0.2	0.3	0.1	0.0
SD	0.09	0.13	0.17	0.21	0.24	0.00
Median	0.0	0.0	0.3	0.3	0.0	0.0
Min/Max	0/0	0/0	0/0	0/1	0/1	0/0
T_{max} (h)						
n	1	3	13	12	5	NC
Mean	12.0	5.7	6.7	6.9	1.4	NC
SD	NC[a]	2.89	2.41	3.23	0.55	NC
Median	12.0	4.1	7.0	6.0	1.0	NC
Min/Max	12/12	4/9	4/10	1/12	1/2	NC
k_{el} (1/h)						
n	NC	1	2	NC	NC	NC
Mean	NC	0.038	0.090	NC	NC	NC
SD	NC	NC	0.0204	NC	NC	NC
Median	NC	0.038	0.090	NC	NC	NC
Min/Max	NC	0.04/0.04	0.08/0.10	NC	NC	NC
$t_{1/2}$ (h)						
n	NC	1	2	NC	NC	NC
Mean	NC	18.3	7.9	NC	NC	NC
SD	NC	NC	1.78	NC	NC	NC
Median	NC	18.3	7.9	NC	NC	NC
Min/Max	NC	18/18	7/9	NC	NC	NC
AUC_{last} (ng*h/mL)						
n	21	19	19	17	18	21
Mean	0.0	0.4	0.9	1.5	0.1	0.0
SD	0.09	1.41	1.24	1.78	0.22	0.00
Median	0.0	0.0	0.3	1.0	0.0	0.0
Min/Max	0/0	0/6	0/4	0/6	0/1	0/0
AUC_{inf} (ng*h/mL)						
n	NC	1	2	NC	NC	NC
Mean	NC	13.3	6.4	NC	NC	NC
SD	NC	NC	2.08	NC	NC	NC
Median	NC	13.3	6.4	NC	NC	NC
Min/Max	NC	13/13	5/8	NC	NC	NC

[a]NC = Not Calculated.

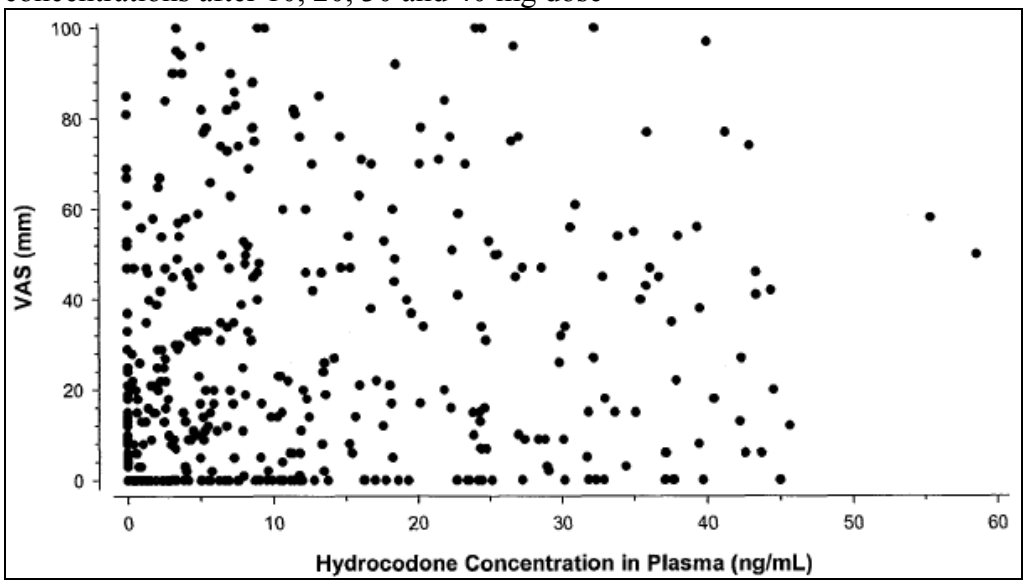
Table 5. Pharmacokinetic parameters for norhydrocodone after single dose

Parameter Statistics	ELN154088 10 mg N = 21	ELN154088 20 mg N = 19	ELN154088 30 mg N = 19	ELN154088 40 mg N = 17	HC/APAP N = 18	Placebo N = 21
C_{max} (ng/mL)						
n	21	19	19	17	18	21
Mean	2.8	5.2	8.3	11.3	5.7	0.0
SD	1.01	1.50	1.44	2.61	2.79	0.00
Median	2.6	5.2	7.9	10.7	4.4	0.0
Min/Max	1/5	3/9	6/12	6/17	3/12	0/0
T_{max} (h)						
n	21	19	19	17	18	NC[a]
Mean	7.7	7.1	7.3	7.0	2.9	NC
SD	2.04	3.08	2.22	1.99	2.18	NC
Median	7.1	5.2	8.0	7.0	2.0	NC
Min/Max	4/12	4/16	5/12	4/10	1/7	NC
k_{el} (1/h)						
n	21	19	19	17	18	NC
Mean	0.073	0.071	0.064	0.060	0.107	NC
SD	0.0223	0.0230	0.0233	0.0194	0.0284	NC
Median	0.066	0.069	0.058	0.061	0.104	NC
Min/Max	0.05/0.14	0.04/0.12	0.02/0.11	0.04/0.10	0.06/0.18	NC
$t_{1/2}$ (h)						
n	21	19	19	17	18	NC
Mean	10.2	10.8	12.5	12.7	6.9	NC
SD	2.46	3.60	5.33	4.08	1.92	NC
Median	10.5	10.0	11.9	11.4	6.6	NC
Min/Max	5/15	6/17	6/29	7/19	4/11	NC
AUC_{last} (ng*h/mL)						
n	21	19	19	17	18	21
Mean	38.2	70.9	118.3	158.1	53.9	0.0
SD	11.48	16.95	19.62	35.58	19.48	0.00
Median	36.4	72.1	118.5	156.1	48.0	0.0
Min/Max	20/58	39/98	85/149	87/241	29/96	0/0
AUC_{inf} (ng*h/mL)						
n	21	19	19	17	18	NC
Mean	52.9	99.2	175.7	233.1	60.1	NC
SD	20.26	28.00	51.21	53.66	22.38	NC
Median	53.2	105.9	167.3	220.0	52.3	NC
Min/Max	22/102	49/153	106/330	127/323	32/104	NC

[a]NC = Not Calculated.

The VASPI and hydrocodone concentrations were plotted (Figure 5) to see if there exists a concentration-response relationship.

Figure 5. Visual Analog Scale Pain Intensity (VASPI) scores vs. hydrocodone concentrations after 10, 20, 30 and 40 mg dose



There was not a significant correlation between VASPI score and hydrocodone (0.31) concentration in plasma. Similar conclusion was derived for norhydrocodone (0.31) and for hydromorphone (0.08).

Mean hydrocodone Cmax values were 8.9 ± 2.1, 17.9 ± 5.9, 31.7 ± 8.5 and 37.5 ± 8.8 ng/mL for 10, 20, 30 and 40 mg single dose treatments, respectively.
Mean hydrocodone AUC values were 137 ± 39, 256 ± 89, 481 ± 139 and 596 ± 173 ng.h/mL for 10, 20, 30 and 40 mg single dose treatments, respectively.

Compared to hydrocodone, hydromorphone and norhydrocodone concentrations were relatively less. The following table (Table 6) contains the relative ratio of the metabolites compared to hydrocodone.

Table 6. Metabolites to drug ratio after single dose

	ELN154088					
Ratio of AUC_{last} Statistics	**10 mg N = 21**	**20 mg N = 19**	**30 mg N = 19**	**40 mg N = 17**	**HC/APAP N = 18**	**Placebo N = 21**
Hydromorphone/ Hydrocodone						
n	21	19	19	17	18	3
Mean	0.000	0.001	0.002	0.003	0.001	0.000
SD	0.0009	0.0038	0.0027	0.0050	0.0012	0.0000
Median	0.000	0.000	0.001	0.002	0.000	0.000
Min/Max	0.00/0.00	0.00/0.02	0.00/0.01	0.00/0.02	0.00/0.00	0.00/0.00
Norhydrocodone/ Hydrocodone						
n	21	19	19	17	18	3
Mean	0.366	0.360	0.327	0.362	0.448	0.000
SD	0.1189	0.1215	0.1243	0.1310	0.2144	0.0000
Median	0.368	0.324	0.297	0.334	0.400	0.000
Min/Max	0.11/0.61	0.17/0.58	0.20/0.76	0.23/0.74	0.22/0.84	0.00/0.00

Dose-linear increases in hydrocodone Cmax and AUC values were observed over the 10 to 40 mg HC-ER dose range after a single dose administration. The following table (Table 7) contains the relative ratio based on 40 mg-dose as a reference.

Table 7. Single dose linearity assessment based on 40-mg dose as a reference

			ELN154088			
Analyte	Dose-Normalized[a] Parameter	Statistics[b]	10 mg N = 21	20 mg N = 19	30 mg N = 19	40 mg N = 17
Hydrocodone	C_{max}	Ratio	0.947	0.929	1.112	1.000
		90% CI[c]	0.816-1.100	0.797-1.082	0.955-1.296	N/A[d]
	AUC_{last}	Ratio	0.942	0.899	1.114	1.000
		90% CI	0.807-1.100	0.768-1.053	0.951-1.305	N/A
Hydromorphone	C_{max}	Ratio	4.330	1.756	1.112	1.000
		90% CI	2.756-6.804	1.327-2.325	0.935-1.323	N/A
	AUC_{last}	Ratio	1.227	1.733	0.678	1.000
		90% CI	0.154-9.786	0.478-6.282	0.305-1.508	N/A
Norhydrocodone	C_{max}	Ratio	0.971	0.918	0.987	1.000
		90% CI	0.836-1.128	0.788-1.070	0.847-1.150	N/A
	AUC_{last}	Ratio	0.945	0.891	1.008	1.000
		90% CI	0.823-1.087	0.773-1.028	0.875-1.163	N/A

[a] Parameters were dose-normalized for comparison (parameter/dose).
[b] Ratio and 90% Confidence Interval were calculated relative to the 40 mg dose.
[c] CI = Confidence Interval.
[d] NA = Not Applicable; ratios were calculated with the 40 mg dose value as the denominator.

Mean hydrocodone Cmax values were 8.9 ± 2.1, 17.9 ± 5.9, 31.7 ± 8.5 and 37.5 ± 8.8 ng/mL for 10, 20, 30 and 40 mg single dose treatments, respectively.
Mean hydrocodone AUC values were 137 ± 39, 256 ± 89, 481 ± 139 and 596 ± 173 ng.h/mL for 10, 20, 30 and 40 mg single dose treatments, respectively.

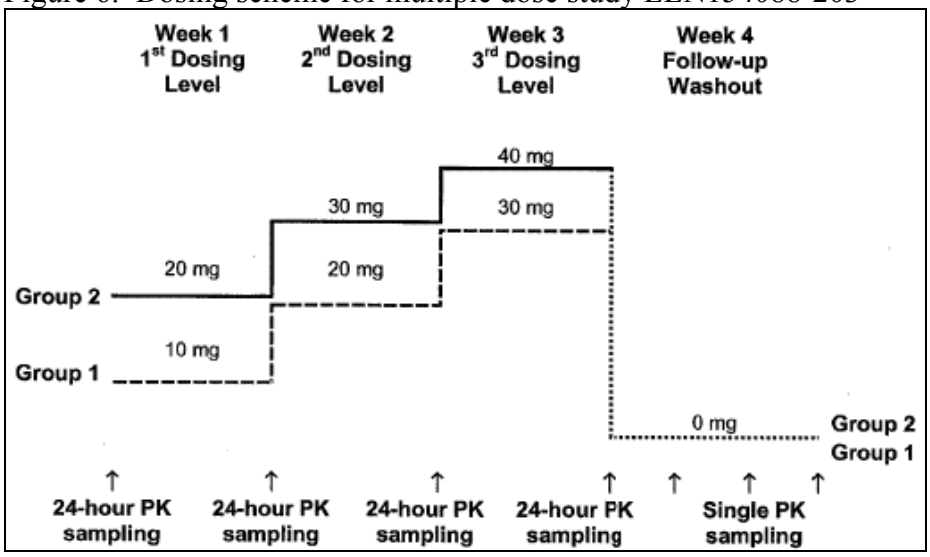
Dose-linear increases in hydrocodone Cmax and AUC values were observed over the 10 to 40 mg HC-ER dose range after a single dose administration.

Multiple dose (Study ELN154088-203)

Study ELN154088-203 was a Phase 2, multi-center, open-label, multiple-dose, two-group dose escalation study in patients with moderate-to-severe osteoarthritis designed to assess the safety, tolerability and PK study. The study was conducted in adult subjects in generally good health with osteoarthritis (OA) that involved at least one hip or knee joint. The subjects had required pain treatment with NSAID and/or with APAP for at least three months. Additionally, subjects experienced moderate-to-severe arthritis pain on a continuing basis, had received insufficient analgesia from NSAID and APAP therapy,

and had used opioids for their arthritis pain on an as-needed basis. The study was divided into 2 groups with increasing 10 mg dose every week for the 3 treatments: Group 1: start at 10 mg BID for 7 days, followed by 20 mg BID for 7 days, followed by 30 mg BID for 7 days. Group 2: start at 20 mg BID for 7 days, followed by 30 mg BID for 7 days, followed by 40 mg BID for 7 days (see below schematic diagram, Figure 6).
Blood samples were taken at 0.5, 1, 2, 3, 4, 6, 8, 12 (14, 16, 20 if possible) and 24 hours on Days 1, 7, 14, and 21. In addition, a PK sample was taken before the evening dose on Days 6, 13 and 20, as well as at the study visits on Days 24, 26, and 28, during the week after their final dose on Day 21. It is noted that there is no concern on food effect on Zohydro capsules, as Study ELN-0302002 showed minimal increase in Cmax (27%) and no changes to AUC values. However, the protocol instructed subjects to take study drug with food, since OA subjects would take the medication with breakfast and dinner. This study also intended to help define the dose range to be used in subsequent efficacy studies. The pain intensity (Visual Analog Scale VAS) were measured at screening, Day -1, Days 6, 13, 20 and follow-up. The VAS and hydrocodone concentrations were plotted to see if there exist a concentration-response relationship.

Figure 6. Dosing scheme for multiple dose study ELN154088-203



The mean hydrocodone concentration profiles from all dose groups at steady state (Day 7 of dosing) for each treatment groups, Groups 1 and 2 (Figures 7 and 8, respectively), are shown below.

Figure 7. The mean hydrocodone concentration profiles from Group 1 at steady state

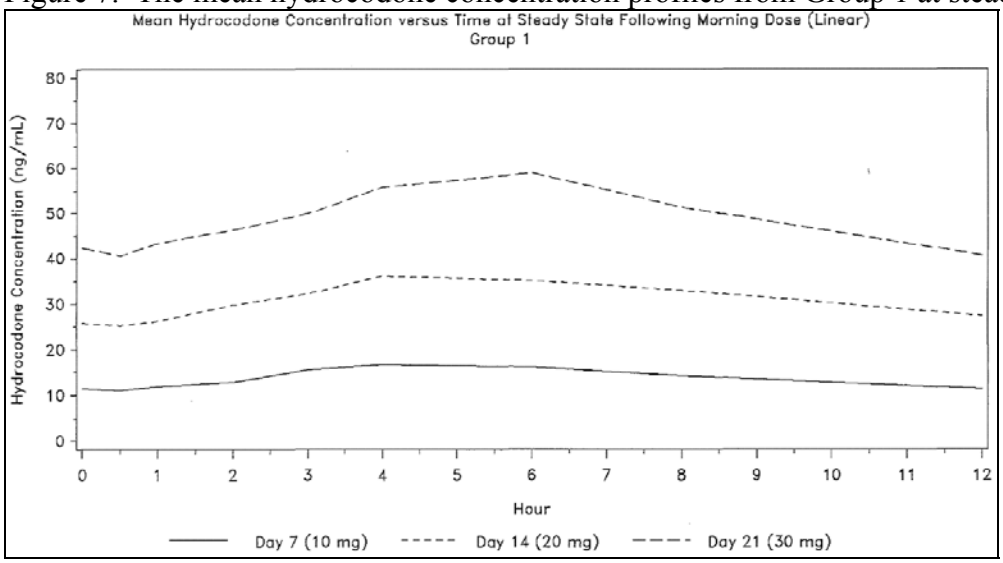
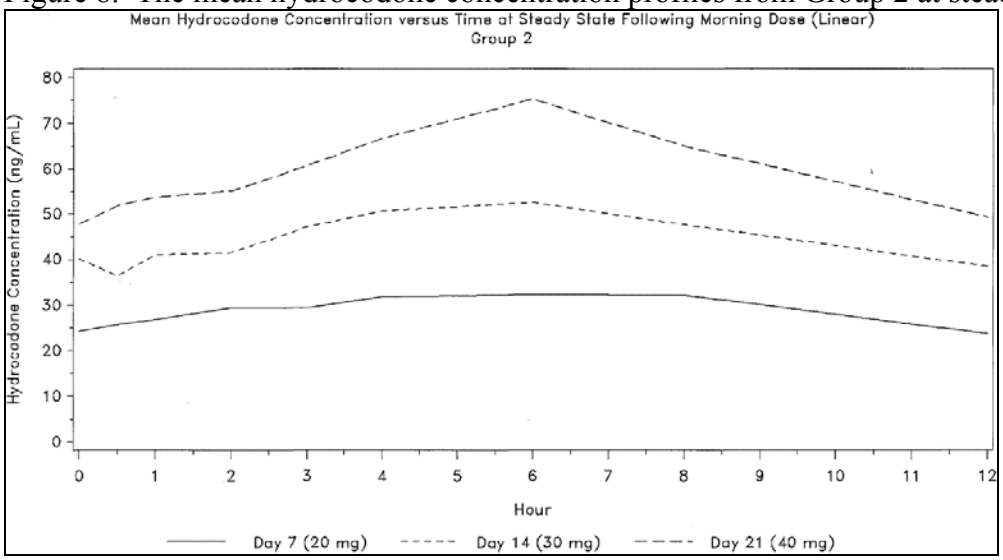


Figure 8. The mean hydrocodone concentration profiles from Group 2 at steady state



The hydrocodone PK parameters (Table 8) at steady-state after the morning dose are presented below.

Table 8. The hydrocodone pharmacokinetic parameters at steady-state after the morning dose

Parameter at Steady State[a]	Statistics	Group 1 N = 18			Group 2 N = 18[b]			Pooled N = 36	
		10 mg	20 mg	30 mg	20 mg	30 mg	40 mg	20 mg	30 mg
t_{max} (h)	n	12	17	18	17	16	15	34	34
	Mean	4.8	5.0	4.8	4.6	4.6	5.1	4.8	4.7
	SD	1.59	2.37	1.50	2.45	1.54	1.79	2.38	1.50
	Median	4.0	4.0	6.0	4.0	4.0	6.0	4.0	4.0
	Min/Max	3/8	2/12	1/6	1/8	2/8	2/8	1/12	1/8
C_{max} (ng/mL)	n	12	17	18	17	16	15	34	34
	Mean	18.3	38.9	62.6	36.3	56.0	78.2	37.6	59.5
	SD	5.19	16.89	26.51	10.02	19.83	32.75	13.73	23.49
	Median	18.8	32.6	57.6	35.0	51.8	66.2	34.8	54.5
	Min/Max	10/27	19/78	25/128	24/59	35/114	41/150	19/78	25/128
C_{min} (ng/mL)	n	12	17	18	17	16	15	34	34
	Mean	9.9	22.4	36.2	21.3	32.0	44.1	21.9	34.2
	SD	3.70	11.57	20.35	7.28	15.97	21.62	9.53	18.27
	Median	9.3	18.6	34.1	19.7	26.8	40.2	19.6	28.0
	Min/Max	4/15	9/53	12/86	13/39	16/79	16/95	9/53	12/86
C_{avg} (ng/mL)	n	12	17	18	17	16	15	34	34
	Mean	14.0	31.6	49.8	29.5	45.7	61.5	30.5	47.8
	SD	4.35	14.79	22.64	8.59	17.89	26.45	11.96	20.34
	Median	13.6	26.2	46.7	29.2	41.7	49.7	28.6	43.1
	Min/Max	7/20	14/66	20/102	18/47	27/98	31/113	14/66	20/102
% Fluctuation	n	12	17	18	17	16	15	34	34
	Mean	62.2	54.9	57.0	52.1	55.1	58.7	53.5	56.1
	SD	17.29	11.77	15.79	11.31	12.94	20.75	11.45	14.34
	Median	63.1	56.6	55.7	51.0	53.7	56.8	52.1	54.5
	Min/Max	35/95	39/78	29/102	31/77	36/80	26/113	31/78	29/102
$AUC_{(0-12)}$ (ng h/mL)	n	12	17	18	17	16	15	34	34
	Mean	168.5	378.9	597.0	353.6	548.5	738.0	366.3	574.2
	SD	52.25	177.46	271.63	103.08	214.69	317.41	143.38	244.06
	Median	163.5	314.8	559.9	350.2	499.9	596.0	343.2	517.0
	Min/Max	81/239	174/789	244/1222	221/559	324/1181	377/1362	174/789	244/1222

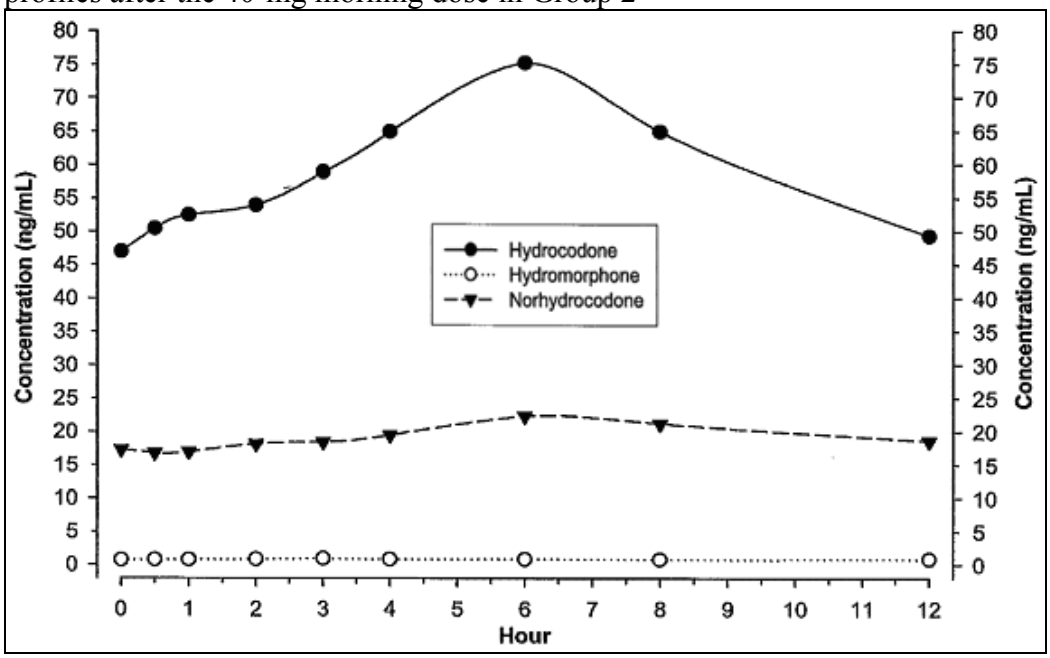
Group 1 mean hydrocodone Cmax values were 18 ± 5.2, 39 ± 17, and 63 ± 27 ng/mL for 10, 20, and 30 mg, respectively, at steady state. Group 2 mean hydrocodone Cmax values were 36 ± 10, 56 ± 20, and 78 ± 33 ng/mL for 20, 30, and 40 mg, respectively, at steady state. Mean hydrocodone Cmax values from groups, 20 and 30 mg doses, were comparable.

Group 1 mean hydrocodone AUC0-12 h values were 169 ± 52, 379 ± 177, and 597 ± 272 ng.h/mL for 10, 20, and 30 mg, respectively, at steady state. Group 2 mean hydrocodone AUC values were 354 ± 103, 549 ± 215, and 738 ± 318 ng.h/mL for 20, 30, and 40 mg, respectively, at steady state. Mean hydrocodone AUC values from both groups, 20 and 30 mg doses, were comparable.

Metabolites:

Mean hydromorphone and norhydrocodone concentrations were less than that of the hydrocodone at steady state in all doses. The hydrocodone, hydromorphone and norhydrocodone steady state concentration profiles are shown below after the 40-mg morning dose in Group 2 (Figure 9). All doses from both Groups showed similar profiles.

Figure 9. Hydrocodone, hydromorphone and norhydrocodone steady state concentration profiles after the 40-mg morning dose in Group 2



The following table (Table 9) contains the AUC ratios of metabolite to hydrocodone. Hydromorphone and norhydrocodone levels were consistently less than that of the hydrocodone.

Table 9. Ratio of metabolite vs. hydrocodone AUC0-12 at steady-state

		Group 1 N = 18			Group 2 N = 18[a]		
$AUC_{(0-12)}$ Ratio	**Statistics**	**10 mg**	**20 mg**	**30 mg**	**20 mg**	**30 mg**	**40 mg**
Hydromorphone/ Hydrocodone	n	6	12	14	11	14	13
	Mean	0.021	0.017	0.015	0.020	0.016	0.016
	SD	0.0126	0.0099	0.0096	0.0109	0.0090	0.0087
	Median	0.021	0.018	0.015	0.016	0.016	0.015
	Min/Max	0.00/0.04	0.00/0.04	0.00/0.03	0.01/0.04	0.00/0.03	0.00/0.03
Norhydrocodone/ Hydrocodone	n	12	17	18	17	16	15
	Mean	0.348	0.325	0.316	0.380	0.370	0.380
	SD	0.2314	0.2337	0.2164	0.2122	0.1999	0.2165
	Median	0.250	0.244	0.220	0.296	0.291	0.340
	Min/Max	0.16/0.89	0.14/1.09	0.16/1.03	0.15/0.81	0.13/0.77	0.10/0.85

Steady state assessment:

With respect to assessing steady-state, the trough hydrocodone concentrations after the morning dose on Days 6, 13, 20 compared to morning dose on Days 7, 14 and 21, were compared. There was no trend of trough concentration increase on Days 7, 14 and 21,

implying that steady-state has been reached. See following table for trough concentrations (Table 10).

Table 10. Trough hydrocodone concentrations after the morning dose on Days 6, 13, 20 compared to morning dose on Days 7, 14 and 21

		Time After Morning Dose (hours)			
		Day 6	Day 7		
Dose	Statistics[a]	12	0	12	24
10 mg (Group 1)	n	18	12	12	12
	Mean	12.72	11.37	11.40	11.04
	SD	11.58	3.76	4.96	4.71
	Geom Mean Ratio	1.000	1.125	1.092	1.066
	90% CI[b]	NA[c]	1.002-1.264	0.972-1.227	0.949-1.197
		Time After Morning Dose (hours)			
		Day 6 or 13	Day 7 or 14		
Dose	Statistics	12	0	12	24
20 mg (pooled)	n	35	34	34	34
	Mean	22.70	24.95	25.53	25.31
	SD	13.34	11.21	11.62	10.76
	Geom Mean Ratio	1.000	1.153	1.173	1.164
	90% CI	NA	1.075-1.237	1.093-1.258	1.085-1.249
		Time After Morning Dose (hours)			
		Day 13 or 20	Day 14 or 21		
Dose	Statistics	12	0	12	24
30 mg (pooled)	n	33	34	34	34
	Mean	34.51	41.22	39.64	37.02
	SD	17.07	18.94	20.00	17.51
	Geom Mean Ratio	1.000	1.241	1.165	1.119
	90% CI	NA	1.130-1.362	1.061-1.279	1.020-1.229
		Time After Morning Dose (hours)			
		Day 20	Day 21		
Dose	Statistics	12	0	12	24
40 mg (Group 2)	n	15	15	15	15
	Mean	41.89	47.82	49.34	49.05
	SD	21.75	24.17	24.05	28.69
	Geom Mean Ratio	1.000	1.130	1.174	1.125
	90% CI	NA	1.003-1.274	1.042-1.324	0.998-1.269

[a] Ratios and confidence intervals were calculated relative to the concentration values on Days 6, 13, and 20.

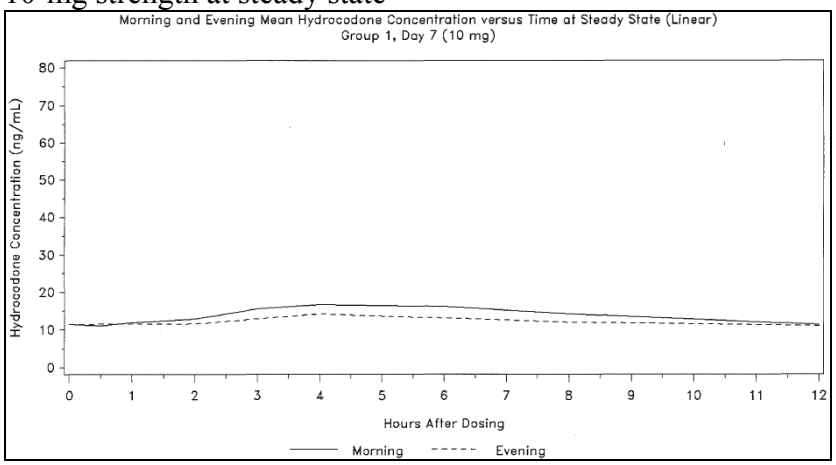
[b] CI = Confidence interval.

[c] N/A = Not applicable.

Comparison of morning and evening doses:

Comparison of hydrocodone concentration profiles of morning and evening doses are presented below for Group 1, 10-mg strength at steady state (Figure 10). There were no differences in hydrocodone concentrations between morning and evening doses at Day 7.

Figure 10. Hydrocodone profile comparison of morning and evening doses for Group 1, 10-mg strength at steady state



Comparison of morning and evening dose Cmin values are presented below for Groups 1 and 2 below (Tables 11 and 12). There were no differences in hydrocodone concentrations (Cmin) between morning and evening doses at Day 7.

Table 11. Hydrocodone morning and evening doses for Group 1 at steady-state

Morning versus Evening Pharmacokinetic Parameters of Hydrocodone at Steady State
Group 1

		10 mg N = 18		20 mg N = 18		30 mg N = 18	
Parameter	Statistics	Morning	Evening	Morning	Evening	Morning	Evening
Cmin (ng/mL)	n	12	12	17	17	18	18
	Mean	9.9	10.2	22.4	24.0	36.2	34.8
	Std. Dev.	3.70	4.16	11.57	13.02	20.35	18.36
	Median	9.3	9.8	18.6	18.2	34.1	33.9
	Min/Max	4/15	4/17	9/53	8/54	12/86	11/89
	P-Value (a)	0.4654		0.3119		0.6018	

(a) P-Value for difference between morning and evening using ANOVA with a randomized block model.
(b) Group 2, Subject 2-S012 did not have PK samples collected while receiving 30 mg.

Table 12. Hydrocodone morning and evening doses for Group 2 at steady-state

Morning versus Evening Pharmacokinetic Parameters of Hydrocodone at Steady State
Group 2

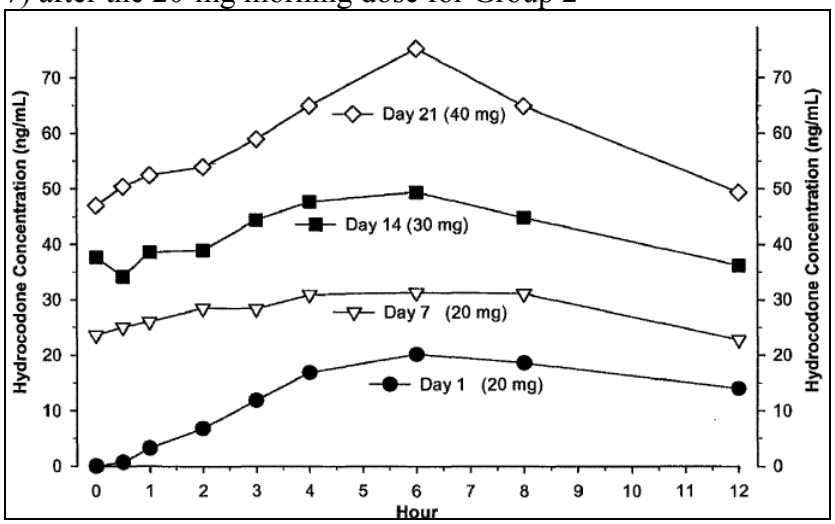
		20 mg N = 18		30 mg N = 17 (b)		40 mg N = 18	
Parameter	Statistics	Morning	Evening	Morning	Evening	Morning	Evening
Cmin (ng/mL)	n	17	17	16	16	15	15
	Mean	21.3	22.6	32.0	30.6	44.1	44.8
	Std. Dev.	7.28	7.70	15.97	9.36	21.62	24.40
	Median	19.7	21.0	26.8	28.2	40.2	38.6
	Min/Max	13/39	12/38	16/79	16/45	16/95	18/104
	P-Value (a)	0.1462		0.6814		0.5843	

(a) P-Value for difference between morning and evening using ANOVA with a randomized block model.
(b) Group 2, Subject 2-S012 did not have PK samples collected while receiving 30 mg.

Accumulation assessment:

With respect to accumulation, the mean hydrocodone concentration profiles on Day 1 and at steady-state (Day 7) after the 20-mg morning dose for Group 2 shown below.

Figure 11. Mean hydrocodone concentration profiles on Day 1 and at steady-state (Day 7) after the 20-mg morning dose for Group 2



The following table (Table 13) contains Cmax and AUC0-12 for 10- and 20-mg hydrocodone concentration values on Day 1.

Table 13. Hydrocodone Cmax and AUC0-12 for 10- and 20-mg hydrocodone concentration values on Day 1

Pharmacokinetic Parameters on Day 1 Following Morning Dose

		Group 1 (10 mg) N = 18			Group 2 (20 mg) N = 19		
Parameter	Statistics	Hydrocodone	Hydromorphone	Norhydrocodone	Hydrocodone	Hydromorphone	Norhydrocodone
Tmax (hr)	n	18	NC (a)	18	18	4	18
	Mean	6.1	NC	9.1	6.6	5.3	8.6
	Std. Dev.	1.88	NC	2.76	2.03	2.25	2.45
	Median	6.0	NC	8.0	6.0	5.0	8.0
	Min/Max	4/12	NC	6/12	3/12	3/8	4/12
Cmax (ng/mL)	n	18	18	18	18	18	18
	Mean	10.5	0.0	2.3	21.6	0.1	5.0
	Std. Dev.	3.49	0.00	0.85	4.16	0.14	2.39
	Median	10.2	0.0	2.3	21.1	0.0	4.1
	Min/Max	6/21	0/0	1/4	16/32	0/0	3/10
AUC (0-12) (ng*hr/mL)	n	18	18	18	18	18	18
	Mean	82.3	0.0	18.9	171.0	0.4	41.0
	Std. Dev.	29.05	0.00	8.85	28.48	0.77	17.78
	Median	82.1	0.0	17.1	169.4	0.0	33.4
	Min/Max	42/170	0/0	8/39	121/222	0/2	19/84

(a) NC = Not Calculated

It appears that approximately 2-fold accumulation was observed for hydrocodone, based on Day 1 (Table 13) and at steady-state PKs (Table 8), when 10- and 20-mg doses were compared.

Multiple dose linearity assessment:

With respect to assessing linearity after multiple administrations, the following table (Table 14) contains the relative ratio based on 40 mg-dose as a reference. Dose-linear increases in hydrocodone Cmax and AUC values were observed over the 10 to 40 mg HC-ER, as the ratio is approximately 1 or near 1.

Table 14. Linearity assessment after multiple administrations based on 40 mg-dose as a reference

Substance	Dose-Normalized Parameter[a]	Statistics[b]	10 mg	20 mg	30 mg	40 mg[b]
Hydrocodone	C_{max}	Ratio	1.024	0.945	0.994	1.0
		90% CI	0.904-1.160	0.864-1.033	0.909-1.086	NA[c]
	$AUC_{(0-12)}$	Ratio	1.029	0.982	1.022	1.0
		90% CI	0.907-1.168	0.897-1.075	0.934-1.119	NA
Hydromorphone	C_{max}	Ratio	1.084	1.003	1.080	1.0
		90% CI	0.848-1.385	0.855-1.177	0.932-1.253	NA
	$AUC_{(0-12)}$	Ratio	0.680	0.924	0.974	1.0
		90% CI	0.520-0.891	0.775-1.101	0.828-1.146	NA
Norhydrocodone	C_{max}	Ratio	1.043	0.996	1.010	1.0
		90% CI	0.953-1.142	0.933-1.062	0.946-1.078	NA
	$AUC_{(0-12)}$	Ratio	1.036	1.021	1.039	1.0
		90% CI	0.957-1.121	0.965-1.080	0.982-1.099	NA

[a] Parameters were dose-normalized for comparison (parameter/dose).
[b] Ratio and CI were calculated relative to the 40-mg dose.
[c] NA = Not applicable because the 40-mg dose was used as the denominator.

Overall, the mean peak-to-trough fluctuation was approximately 50 to 60% for hydrocodone at steady state. The mean AUC of each of the 2 metabolites was lower than that of hydrocodone, with hydromorphone at 1.1% to 1.4%, and, norhydrocodone at 31.6% to 38.0% of the hydrocodone AUC over all dose levels. Based on the concentration-time profiles, no apparent difference in morning versus evening PKs was observed for hydrocodone or its metabolites.

VAS scores vs. hydrocodone concentrations:

With respect to VAS and hydrocodone concentration relationship, the following bar graphs summarize mean VAS scores at each dose level for Groups 1 and 2 (Figures 12 and 13).

Figure 12. VAS scores vs. pain intensity and other adverse events for Group 1 at steady state

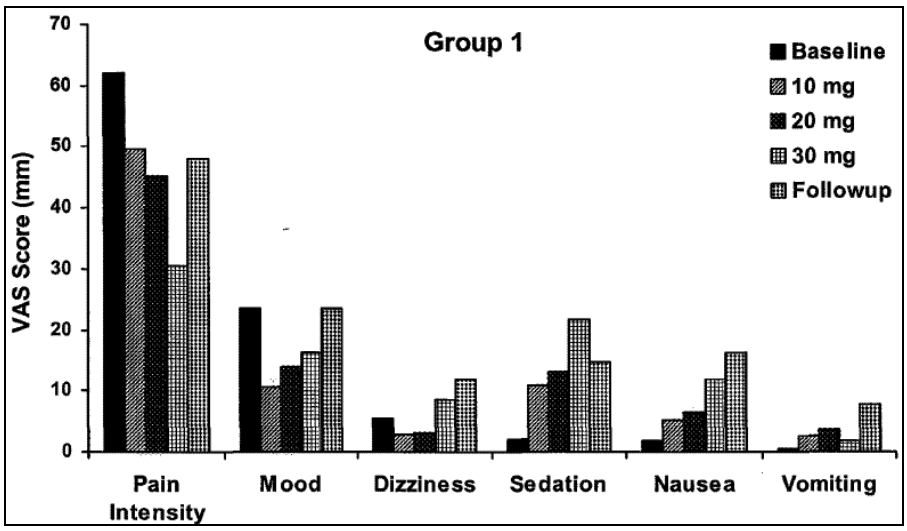
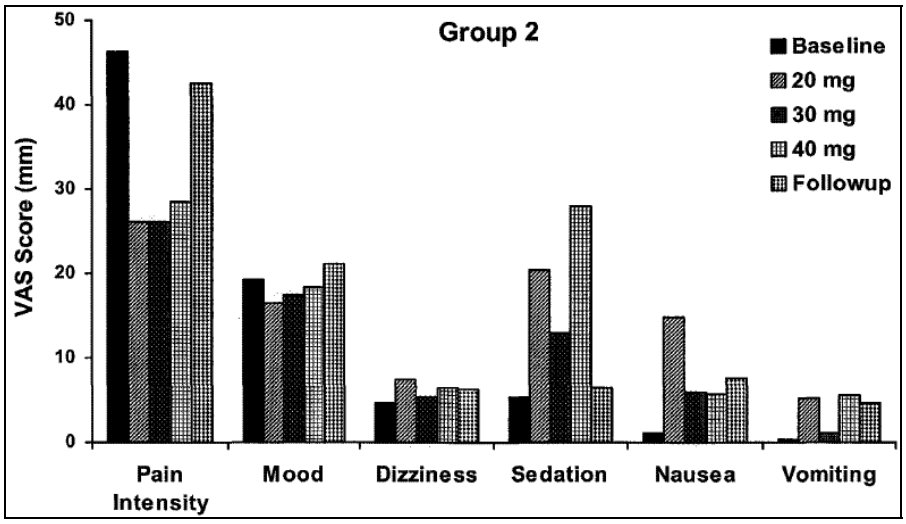


Figure 13. VAS scores vs. pain intensity and other adverse events for Group 2 at steady state



The following table (Table 15) contains mean VAS scores for pain intensity by dose received.

Table 15. VAS scores for pain intensity by dose for both Groups 1 and 2 at steady state

	Dose Level (mg)					
	(Before Study)					(After Study)
Group	0	10	20	30	40	0
1	62.1 ± 17.08	49.7 ± 24.22	45.1 ± 30.29	30.4 ± 30.23	NA [a]	48.0 ± 33.20
2	46.3 ± 20.08	NA [a]	26.1 ± 21.51	26.1 ± 26.93	28.6 ± 23.38	42.6 ± 32.88

[a] NA = Not applicable because this group did not receive this dose level.

There was not a significant correlation between VAS scores and hydrocodone dose levels, although the Group 1 showed decrease in VAS scores with increasing doses, implying a dose response. However, the similar trend was not observed in Group 2. Looking at the individual data, there was no significant correlation can be seen (Figures 14 – 19 for individual VAS scores versus pain intensity, mood, dizziness, sedation, nausea and vomiting , respectively, for Group 1; Figures 20 – 25 for individual VAS scores versus pain intensity, mood, dizziness, sedation, nausea and vomiting , respectively, for Group 2).

Figure 14. Individual VAS score vs. pain intensity for Group 1

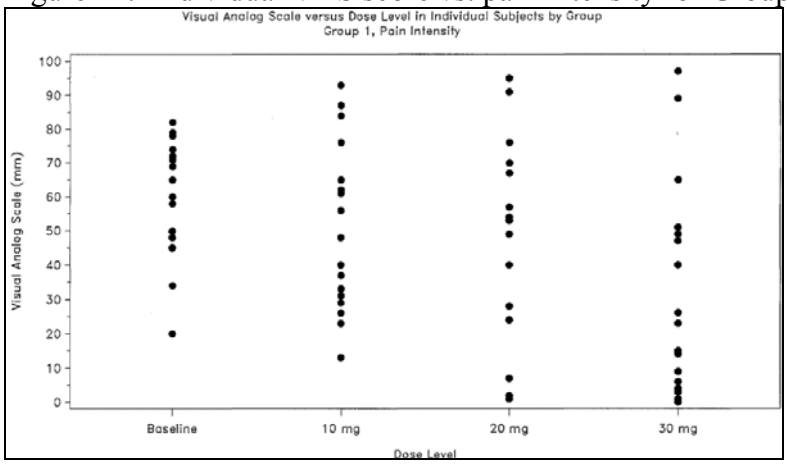


Figure 15. Individual VAS score vs. mood for Group 1

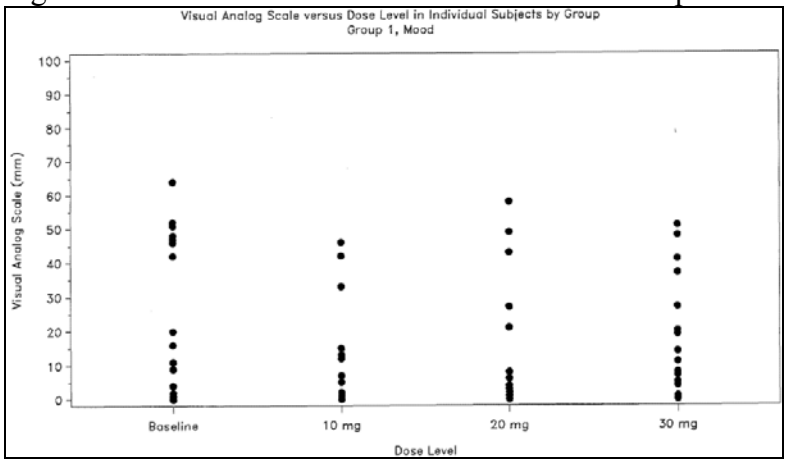


Figure 16. Individual VAS score vs. dizziness for Group 1

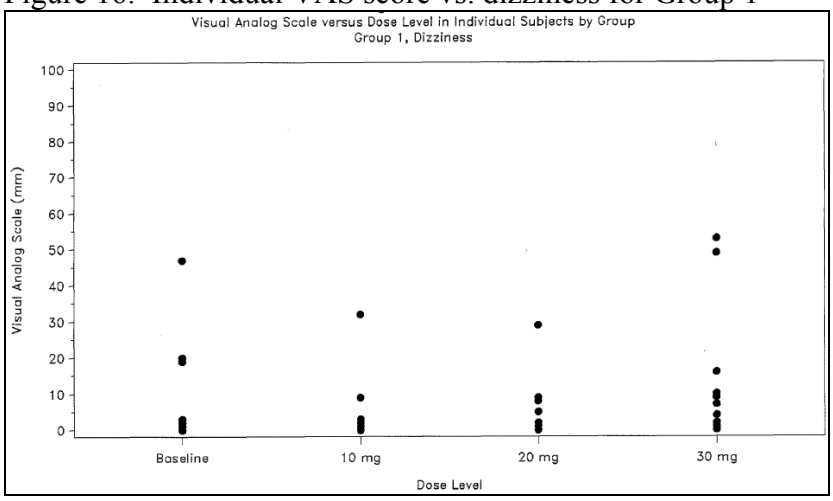


Figure 17. Individual VAS score vs. sedation for Group 1

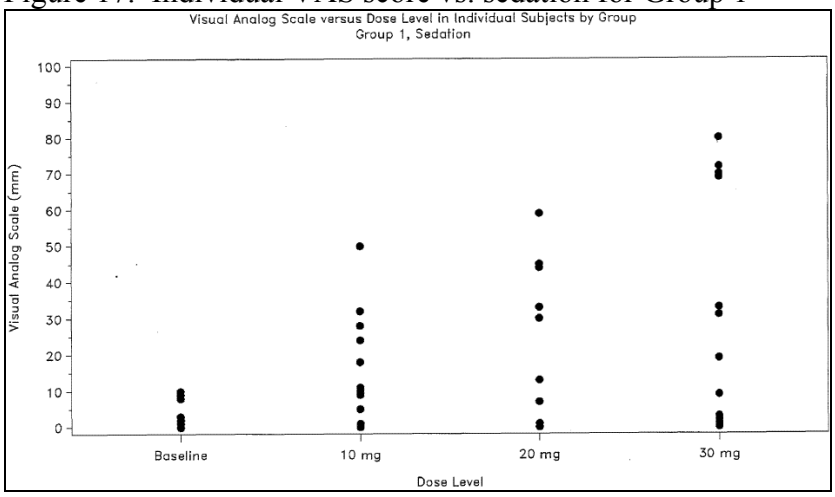


Figure 18. Individual VAS score vs. nausea for Group 1

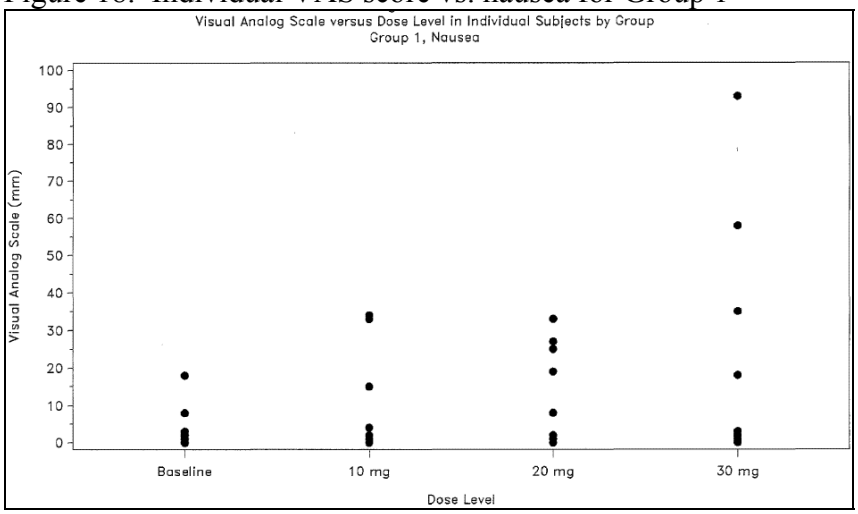


Figure 19. Individual VAS score vs. vomiting for Group 1

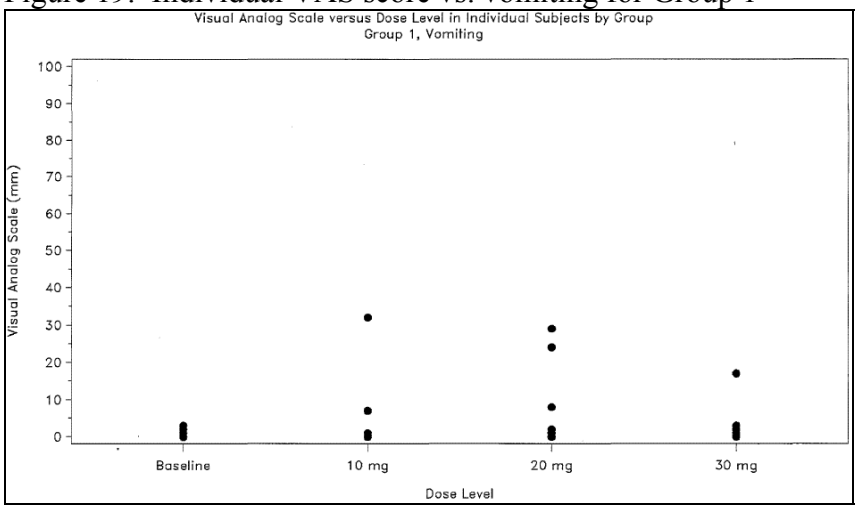


Figure 20. Individual VAS score vs. pain intensity for Group 2

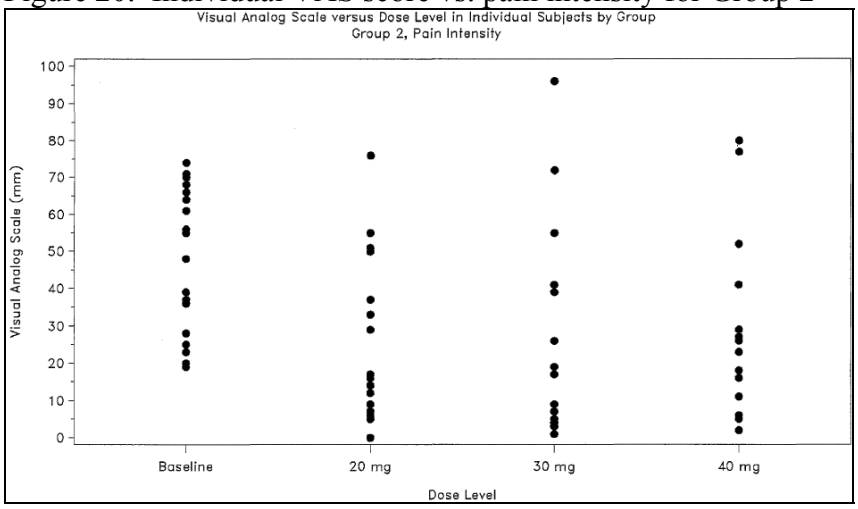


Figure 21. Individual VAS score vs. mood for Group 2

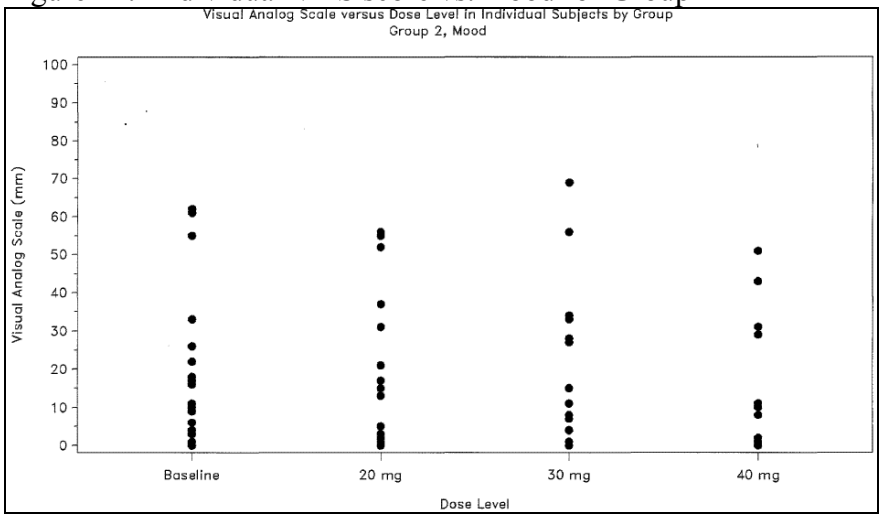


Figure 22. Individual VAS score vs. dizziness for Group 2

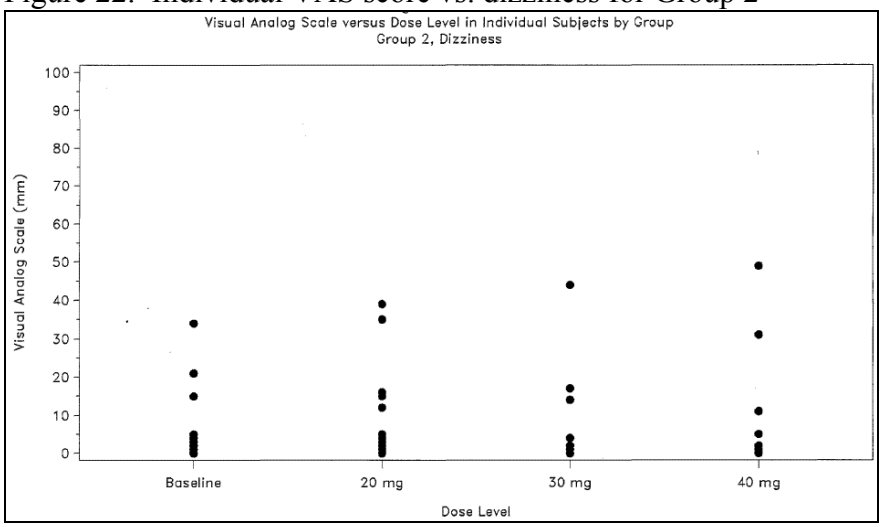


Figure 23. Individual VAS score vs. sedation for Group 2

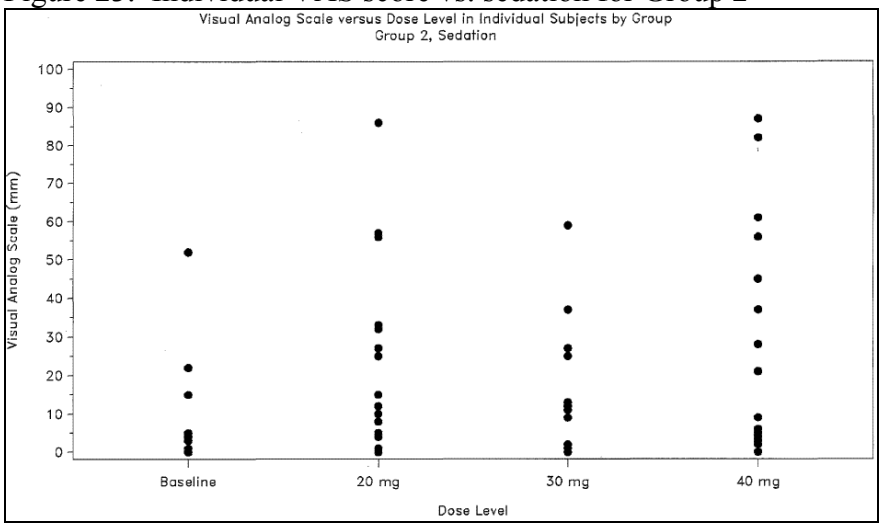


Figure 24. Individual VAS score vs. nausea for Group 2

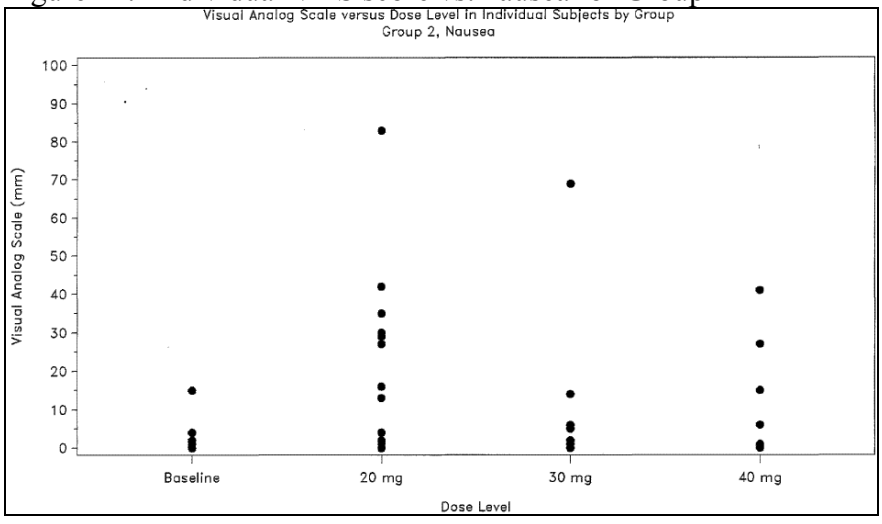
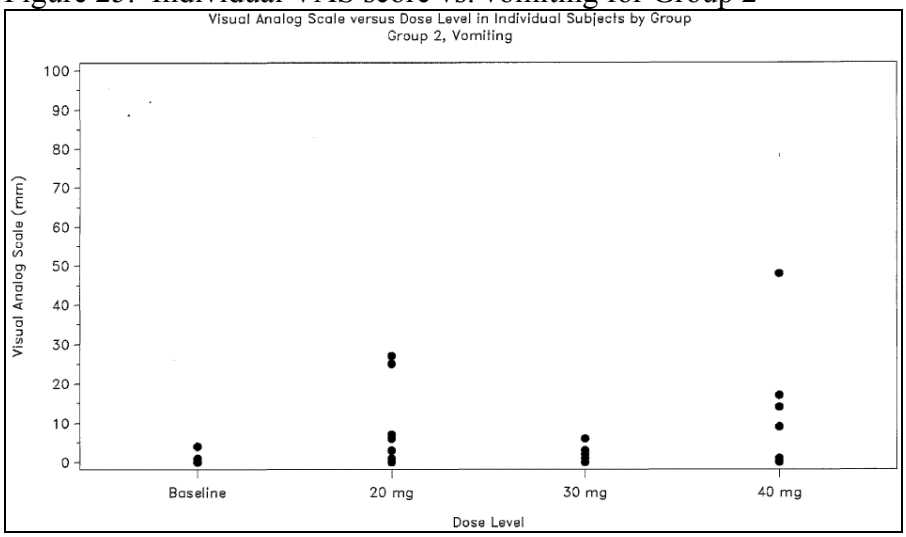


Figure 25. Individual VAS score vs. vomiting for Group 2



2.3 Intrinsic Factors

No information was submitted to characterize HC-ER in race, gender and elderly population.

2.3.1 What is the hydrocodone exposure in pediatric subjects?

The Applicant is requesting a waiver and a deferral of the requirement to assess HC-ER in pediatric subjects aged < 7 and > 7 years of age (as a post-marketing commitment), respectively. The Applicant submitted following rationale to address requesting a waiver and a deferral:

Waiver for Subjects < 7 Years

While pediatric acute pain continues to be an unmet need, chronic pain is much less common in very young pediatric patients than in adult patients and is typically associated with a co-morbid condition (e.g. cancer, cystic fibrosis, sickle-cell anemia) (American Medical Association 2010). These subjects and their families are more likely to seek out and participate in clinical trials for medications aimed at addressing their underlying disease state, making them ineligible for a trial evaluating opioid analgesia. Combined with the very small patient population of pediatric subjects suffering from chronic pain, this has posed an extreme obstacle to product sponsors wishing to study opioid analgesics in children under 7 years of age. While still extremely difficult, there is more opportunity to study opioid analgesics for acute pain in these very young subjects. However, HC-ER is an extended-release form of hydrocodone bitartrate and has not been adequately studied in adult subjects for the management of acute pain. As such, the Applicant believes that it has been adequately demonstrated that studies of opioid analgesics for chronic pain in pediatric subjects under 7 years of age are not practical to conduct and

would provide little value to physicians for the prescription of HC-ER. The Applicant wishes to request a waiver of the requirement to conduct studies in this pediatric population.

Deferral for Subjects > 7 Years

The Applicant proposes to conduct an open-label safety study with HC-ER in opioid-experienced pediatric subjects with chronic pain, including PK evaluation. The study will enroll subjects aged 7-12 years of age, and the Applicant intends to (b) (4) This is consistent with the feedback to the FDA's Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting held on 14 March 2012. The Applicant is requesting a deferral to be able to conduct this study as a post-approval commitment.

It is noted that after discussion with the clinical team, the Division will request the Sponsor to conduct PKs and safety study in patients from 7-17 years of age to fulfill PREA. The Sponsor may extrapolate the efficacy in this age group by comparing PKs data to adults.

Development of an Age-Appropriate Dosage Form

The Applicant anticipates converting subjects from their current opioid dose to HC-ER on an equianalgesic basis, with an initial dose step down of approximately 20-30% for safety, and then titrating them to a dose at which their pain is adequately controlled. This procedure is consistent with that used for the Phase 3 HC-ER studies. It is anticipated that some subjects may require doses lower than the current lowest developed dosage strength of HC-ER (10 mg). While the six (10, 15, 20, 30, 40, and 50 mg) current dosage strengths of HC-ER represent (b) (4) cannot be produced using the current manufacturing process (b) (4) The Applicant proposes to develop (b) (4)

HC-ER Proposed Post-Approval Milestones for Pediatric Deferral

The Applicant agrees to conduct a pediatric study with HC-ER (proposed study design to be agreed to by FDA) as a post-approval commitment. Upon approval of HC-ER for adults, the applicant will undertake the development and manufacturing of an age-appropriate dosage form for the intended pediatric population. The development, manufacturing, testing, release, and packaging of this formulation is expected to take (b) (4) months, and is reflected in the proposed milestone timing below.

- Protocol Submission: 12 months following NDA approval
- Study Start: 24 months after NDA approval (12 months after Protocol Submission, above)
- Final Report Submission: 72 months after NDA approval (4 years after, Study Start, above)

2.3.1.1 Renal impairment

Study ZX002-1002 was a Phase 1, single-dose, parallel study in subjects with mild, moderate, or severe renal impairment per Cockcroft-Gault criteria. Healthy control subjects were matched to renally-impaired subjects for age (±10 years), and body mass index (BMI) (± 10% of BMI) with some consideration for race and gender. The renal-impaired subjects were required to have a diagnosis of chronic (more than 6 months), stable (no acute episodes of illness within the previous 2 months due to deterioration of renal function) renal insufficiency due to any etiology. There were approximately 9 subjects per group. All subjects received a single dose of 20 mg HC-ER in a fasted state. All doses were administered with 240 mL of water. Blood samples were collected at time 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 30, 36, 48, 60, and 72 hours after administration of each HC-ER 20-mg capsule. Urine samples were collected at (time 0) and during intervals of 0-12, 12-24, 24-48 and 48-72 hours after administration of HC-ER 20 mg administration. Urine volumes were measured and recorded for each timepoint following time zero. Subjects were required to empty their bladders at time zero, prior to drug administration. The following table describes the study population (Table 16).

Table 16. Demographics for renal impairment subjects

Demographic / Statistic	Mild Renal Impairment N (%)	Moderate Renal Impairment N (%)	No Renal Impairment N (%)	Severe Renal Impairment N (%)	All Subjects N (%)
No. of Subjects	9	10	9	9	37
Sex					
Male n (%)	7 (77.8%)	6 (60.0%)	5 (55.6%)	8 (88.9%)	26 (70.3%)
Female n (%)	2 (22.2%)	4 (40.0%)	4 (44.4%)	1 (11.1%)	11 (29.7%)
Age (years)					
Mean (SD)	67.6 (7.99)	64.2 (9.05)	59.2 (12.07)	61.7 (7.86)	63.2 (9.50)
Median	67.0	65.5	61.0	62.0	64.0
Min / Max	53, 79	52, 78	40, 76	50, 70	40, 79
Age Group					
18 – < 65 years	3 (33.3%)	5 (50.0%)	7 (77.8%)	5 (55.6%)	20 (54.1%)
≥ 65 – < 75 years	4 (44.4%)	3 (30.0%)	1 (11.1%)	4 (44.4%)	12 (32.4%)
≥ 75 years	2 (22.2%)	2 (20.0%)	1 (11.1%)	0 (0%)	5 (13.5%)
Weight (kg)					
Mean (SD)	80.03 (11.65)	70.36 (10.67)	72.08 (15.66)	83.09 (12.54)	76.23 (13.32)
Median	79.60	71.95	66.00	82.80	75.00
Min / Max	59.2, 100.1	49.2, 85.6	55.2, 99.2	68.7, 103.2	49.2, 103.2
Height (cm)					
Mean (SD)	172.67 (8.20)	165.60 (5.64)	166.56 (10.17)	174.44 (9.57)	169.70 (9.01)
Median	174.00	166.00	167.00	175.00	170.00
Min / Max	158.0, 184.0	156.0, 173.0	152.0, 178.0	158.0, 186.0	152.0, 186.0
BMI (kg/m^2)					
Mean (SD)	26.81 (3.21)	25.52 (2.89)	25.82 (4.32)	27.19 (2.22)	26.31 (3.18)
Median	26.80	26.40	23.80	27.00	26.80
Min / Max	20.4, 31.7	20.1, 30.3	20.7, 33.1	23.6, 31.6	20.1, 33.1
BMI Classification[1]					
Underweight: < 18.50 kg/m^2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal: 18.50 – 24.99 kg/m^2	2 (22.2%)	3 (30.0%)	5 (55.6%)	1 (11.1%)	11 (29.7%)
Overweight: ≥ 25.00 kg/m^2	7 (77.8%)	7 (70.0%)	4 (44.4%)	8 (88.9%)	26 (70.3%)
Obese: ≥ 30.00 kg/m^2	1 (11.1%)	1 (10.0%)	2 (22.2%)	1 (11.1%)	5 (13.5%)
Ethnicity					
Hispanic or Latino n (%)	3 (33.3%)	4 (40.0%)	4 (44.4%)	4 (44.4%)	15 (40.5%)
Not Hispanic or Latino n (%)	6 (66.7%)	6 (60.0%)	5 (55.6%)	5 (55.6%)	22 (59.5%)
Race					
American Indian or Alaskan Native n (%)	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)	1 (2.7%)
Black, African American or of African Heritage n (%)	2 (22.2%)	1 (10.0%)	1 (11.1%)	0 (0%)	4 (10.8%)
White n (%)	6 (66.7%)	9 (90.0%)	8 (88.9%)	9 (100%)	32 (86.5%)

Hydrocodone individual plasma concentration profiles from all groups (Figure 26) are presented below followed by hydrocodone median concentration profiles (Figure 27).

Figure 26. Individual hydrocodone concentration profiles for renal impairment subjects

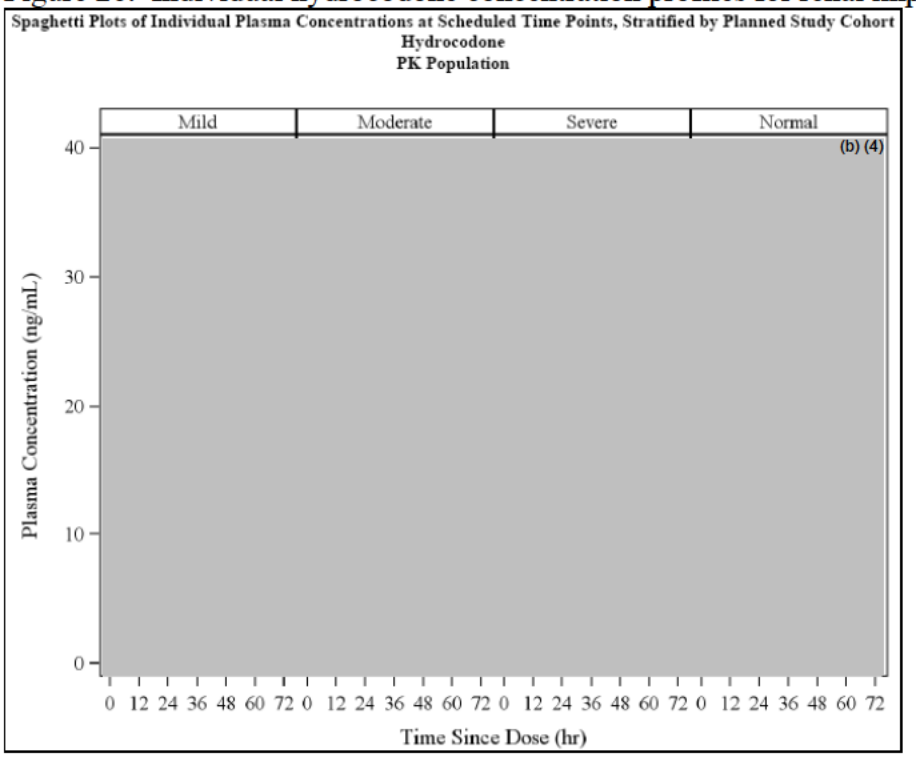
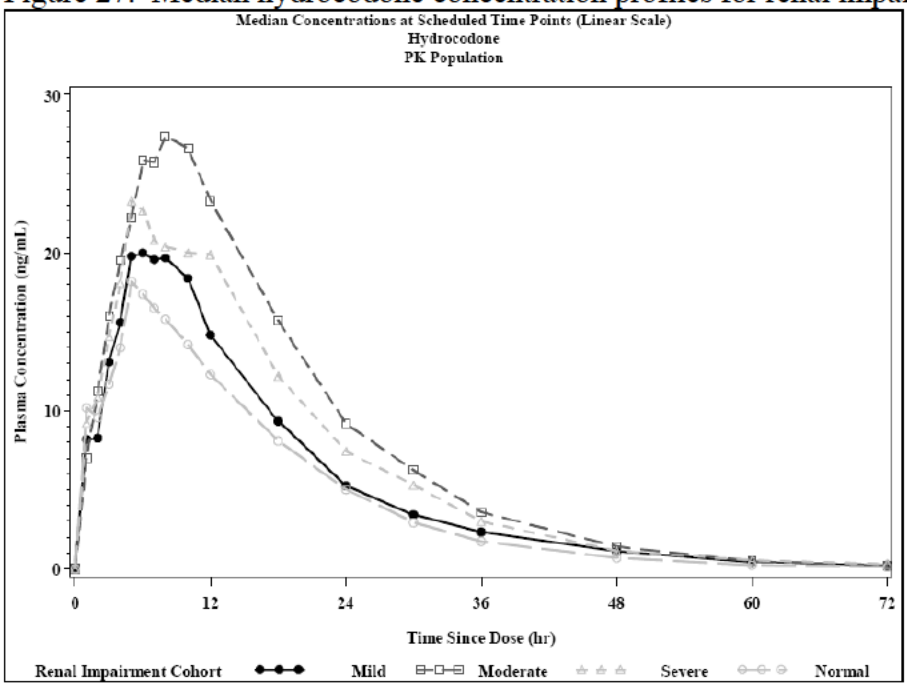


Figure 27. Median hydrocodone concentration profiles for renal impairment subjects



Hydromorphone individual plasma concentration profiles (Figure 28) from all groups are presented below followed by hydromorphone median concentration profiles (Figure 29).

Figure 28. Individual hydromorphone concentration profiles for renal impairment subjects

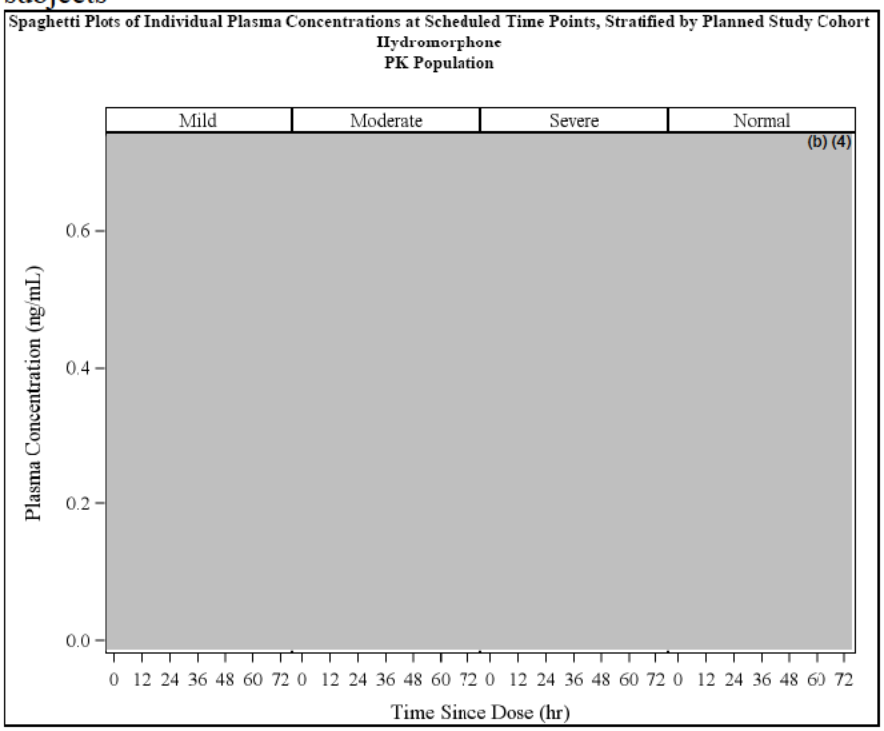
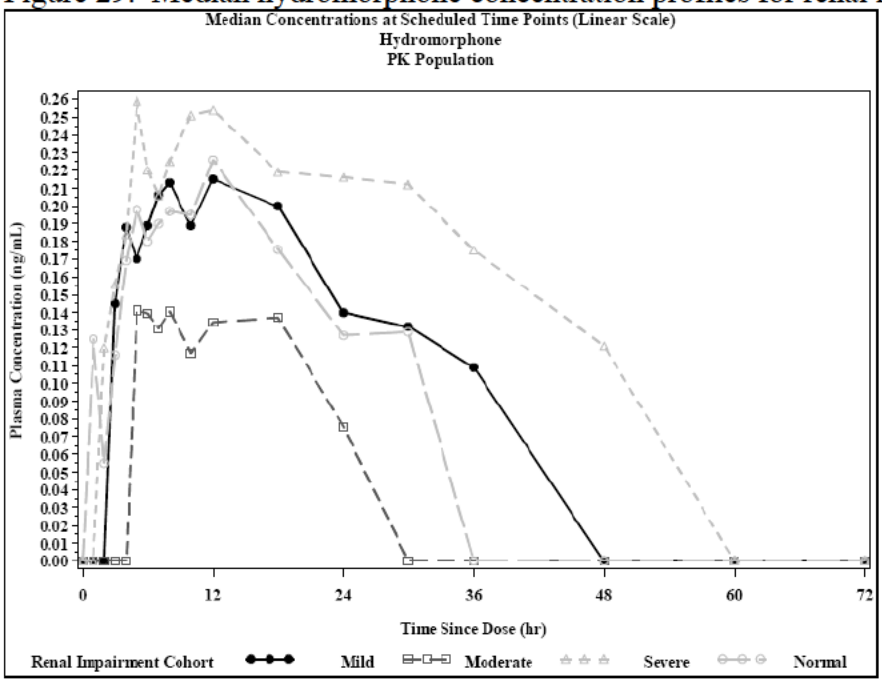


Figure 29. Median hydromorphone concentration profiles for renal impairment subjects



Norhydrocodone individual plasma concentration profiles (Figure 30) from all groups are presented below followed by norhydrocodone median concentration profiles (Figure 31).

Figure 30. Individual norhydrocodone concentration profiles for renal impairment subjects

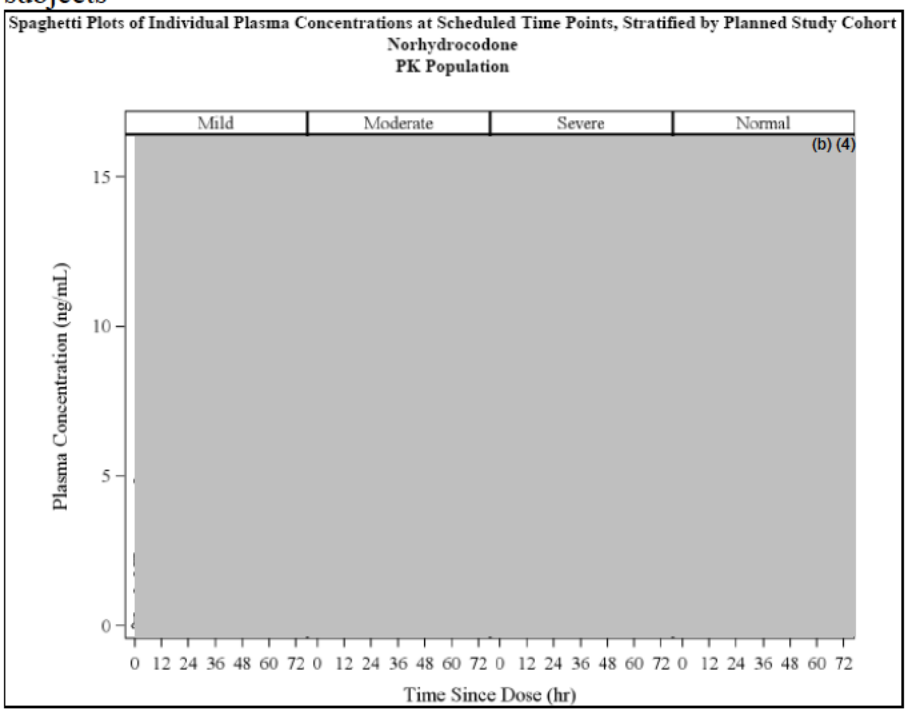
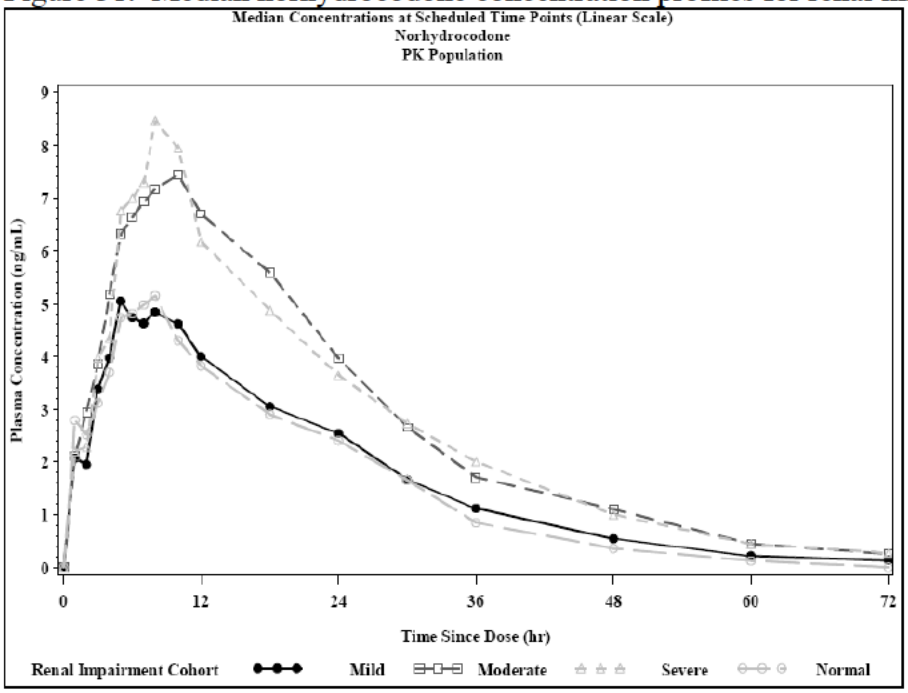


Figure 31. Median norhydrocodone concentration profiles for renal impairment subjects



PK parameters are presented below for renal impairment subjects (Table 17).

Table 17. PK parameters for renal impairment subjects

Renal Impairment Group				
Pharmacokinetic Parameters	**Renal Impairment Cohort**			
	Mild	**Moderate**	**Severe**	**Normal**
PK Subjects	**9 (24.3%)**	**10 (27.0%)**	**9 (24.3%)**	**9 (24.3%)**
Hydrocodone				
C_{max} (ng/mL)	21.3 (5.11)	27.5 (7.49)	25.8 (6.01)	18.5 (4.43)
T_{max} (hr)	5 (5 – 7)	6 (5 – 10)	6 (4 – 12)	6 (5 – 7)
$AUC_{0\text{-}inf}$ (ng*h/mL)	391 (122)	547 (184)	487 (123)	343 (105)
AUC Extrapolated % (ng*h/mL)	0.9 (0.2)	0.9 (0.71)	0.9 (0.34)	0.8 (0.47)
$T_{1/2}$ (hr)	10.3 (1.87)	9 (2.20)	10 (1.74)	8.3 (1.38)
% Dose Excreted	5.2 (1.98)	5 (2.38)	3.1 (1.52)	7.2 (2.04)
% Dose Excreted, Combined[2]	14.8 (3.95)	14.7 (4.88)	7.5 (3.62)	19.4 (2.43)
Norhydrocodone				
C_{max} (ng/mL)	5.5 (2.05)	7.9 (3.38)	8.1 (3.46)	5.1 (1.43)
T_{max} (hr)	8 (5 – 10)	9 (6 – 12)	10 (5 – 18)	6 (5 – 10.1)
$AUC_{0\text{-}inf}$ (ng*h/mL)	134 (45.9)	223 (92.1)	222 (97.1)	113 (29.3)
AUC Extrapolated % (ng*h/mL)	2.3 (0.87)	2.3 (1.76)	2.3 (0.92)	1.8 (0.89)
$T_{1/2}$ (hr)	11.2 (1.02)	10.9 (2.94)	11.2 (1.75)	9.2 (0.92)
% Dose Excreted	9.3 (2.83)	9.6 (4.28)	4.3 (2.42)	11.9 (2.91)
Hydromorphone				
C_{max} (ng/mL)	0.3 (0.08)	0.2 (0.09)	0.3 (0.16)	0.2 (0.08)
T_{max} (hr)	10 (6 – 12)	6 (5 – 24)	12 (5 – 30)	7 (5 – 12)
$AUC_{0\text{-}inf}$ (ng*h/mL)	14.7 (5.31)	11.6 (0.57)	21.3 (15.7)	11.9 (4.33)
AUCExtrapolated % (ng*h/mL)	42.5 (21.2)	38.9 (24.7)	34.2 (18.6)	47.3 (28.6)
$T_{1/2}$ (hr)	33 (20.1)	24.4 (14.1)	35.6 (32.8)	41.2 (41.1)
% Dose Excreted	0.2 (0.17)	0.1 (0.09)	0.1 (0.05)	0.3 (0.16)

Mean hydrocodone Cmax values were 26 ± 6.0, 28 ± 7.5, 21 ± 5.1 and 19 ± 4.4 ng/mL for severe, moderate, mild renal impaired and normal subjects, respectively. Mean hydrocodone Cmax values were comparable for all groups. Mean hydrocodone AUC values were 487 ± 123, 547 ± 184, 391 ± 122 and 343 ± 105 ng.h/mL for severe, moderate, mild renal impaired and normal subjects, respectively.

Box-and-Whisker plots of hydrocodone Cmax and AUC0-inf parameters for the renally impaired subjects are presented below (Figures 32 and 33, respectively).

Figure 32. Box-and-Whisker plots of hydrocodone Cmax parameters for renal impairment subjects

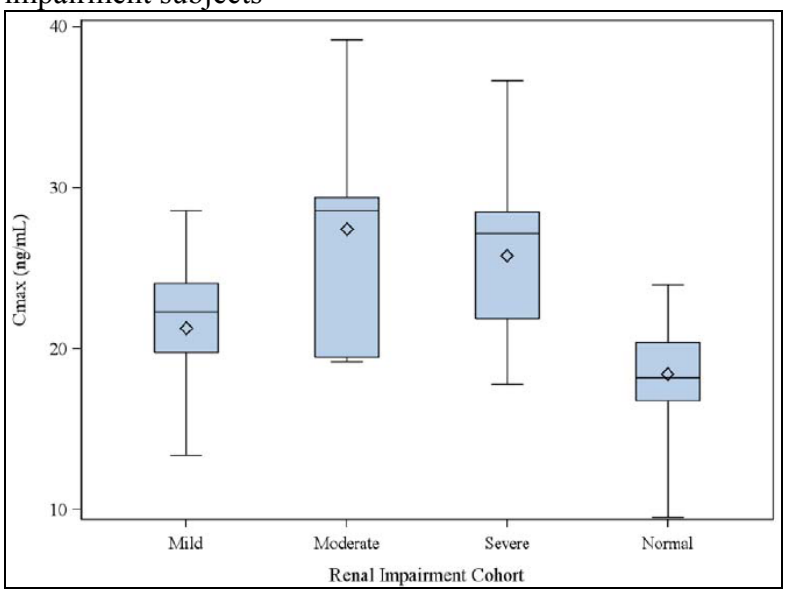
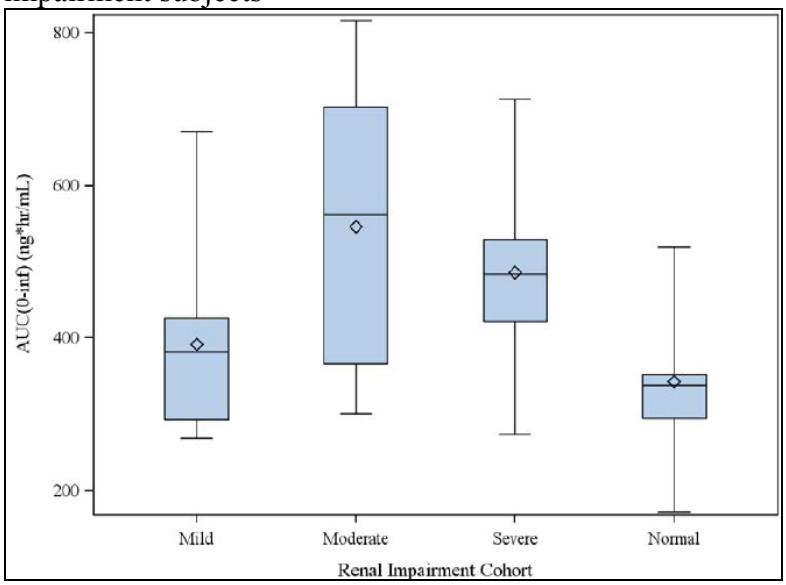


Figure 33. Box-and-Whisker plots of hydrocodone AUC0-inf parameters for renal impairment subjects



Comparison of Cmax and AUC values (Table 18) are presented below for renally impaired subjects.

Table 18. Comparison of Cmax and AUC values for renal impairment subjects

	Subject Cohort		
	Mild Renal Impairment vs. No Renal Impairment	Moderate Renal Impairment vs. No Renal Impairment	Severe Renal Impairment vs. No Renal Impairment
PK Subjects	9/9	10/9	9/9
$AUC_{0\text{-}inf}$ (ng*h/mL)			
Geometric Mean Ratio (%)	1.15	1.57	1.44
90% Confidence Interval	(0.90, 1.47)	(1.20, 2.07)	(1.13, 1.83)
C_{max} (ng/mL)			
Geometric Mean Ratio (%)	1.15	1.48	1.41
90% Confidence Interval	(0.92, 1.44)	(1.19, 1.85)	(1.14, 1.74)

Data showed that plasma hydrocodone concentrations are higher in patients with renal impairment. Peak plasma HC concentrations 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. On the basis of these findings no routine dose adjustment appears necessary in patients with renal impairment. However, since HC plasma levels may be increased in individuals with moderate to severe renal impairment, patients in this population should be monitored closely.

Approximately 19.4%, 14.8%, 13.4% and 7.5% of the administered dose was excreted via the urine over 72 hours as hydrocodone, hydromorphone, or norhydrocodone in subjects with no renal impairment, mild, moderate, and severe renal impairment, respectively.

2.3.1.2 Hepatic impairment

Study ZX002-1001 was a Phase 1, open-label, single-dose, parallel study in subjects with mild or moderate hepatic impairment. Ten healthy control subjects were matched to 20 hepatically-impaired subjects for age (±10 years), and body mass index (BMI) (± 10% of BMI) with some consideration for race and gender. The hepatically-impaired subjects had a diagnosis of chronic (more than 6 months), stable (no acute episodes of illness within the previous 2 months due to deterioration of hepatic function) hepatic insufficiency with features of cirrhosis due to any etiology. Ten (10) hepatically-impaired subjects were enrolled into one of two Child-Pugh classifications based on their hepatic impairment: mild and moderate, with the expectation of at least 8 evaluable subjects for each severity. All subjects received a single dose of 20 mg HC-ER in a fasted state. All doses were administered with 240 mL of water. Blood samples were taken at the following time points: 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 30, 36, 48, 60, and 72 hours after dose administration. Urine samples were collected during intervals of 0-12, 12-24, 24-48 and 48-72 hours after administration of HC-ER 20 mg administration. Urine volumes were measured and recorded for each time point following the time zero.

The following table describes the study population:

Table 19. Demographics for hepatic impairment subjects

Demographic / Statistic	Mild Hepatic Impairment N (%)	Moderate Hepatic Impairment N (%)	No Hepatic Impairment N (%)	All Subjects N (%)
No. of Subjects	10	10	10	30
Sex				
Male n (%)	7 (70.0%)	8 (80.0%)	7 (70.0%)	22 (73.3%)
Female n (%)	3 (30.0%)	2 (20.0%)	3 (30.0%)	8 (26.7%)
Age (years)				
N	10	10	10	30
Mean (SD)	56.1 (11.02)	56.6 (4.60)	56.8 (7.58)	56.5 (7.89)
Median	56.5	58.5	57.5	58.0
Min / Max	36, 75	47, 61	41, 65	36, 75
Age Group				
18 – < 65 years	8 (80.0%)	10 (100%)	7 (70.0%)	25 (83.3%)
≥ 65 – < 75 years	1 (10.0%)	0 (0%)	3 (30.0%)	4 (13.3%)
≥ 75 years	1 (10.0%)	0 (0%)	0 (0%)	1 (3.3%)
Weight (kg)				
N	10	10	10	30
Mean (SD)	80.68 (16.15)	87.89 (18.31)	83.46 (13.60)	84.01 (15.86)
Median	79.65	86.75	84.00	82.15
Min / Max	58.8, 112.5	59.2, 113.6	65.5, 101.2	58.8, 113.6
Height (cm)				
N	10	10	10	30
Mean (SD)	170.20 (8.53)	172.20 (9.33)	169.80 (8.60)	170.73 (8.59)
Median	169.00	173.50	171.00	171.00
Min / Max	159.0, 187.0	162.0, 188.0	156.0, 183.0	156.0, 188.0
BMI (kg/m^2)				
N	10	10	10	30
Mean (SD)	28.07 (6.02)	29.75 (6.31)	28.89 (3.54)	28.90 (5.29)
Median	26.75	30.40	29.15	29.15
Min / Max	19.0, 38.9	22.0, 37.7	23.3, 34.6	19.0, 38.9
BMI Classification[1]				
Underweight: < 18.50 kg/m^2	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Normal: 18.50 – 24.99 kg/m^2	5 (50.0%)	4 (40.0%)	2 (20.0%)	11 (36.7%)
Overweight: ≥ 25.00 kg/m^2	5 (50.0%)	6 (60.0%)	8 (80.0%)	19 (63.3%)
Obese: ≥ 30.00 kg/m^2	4 (40.0%)	5 (50.0%)	4 (40.0%)	13 (43.3%)
Ethnicity				
Hispanic or Latino n (%)	6 (60.0%)	2 (20.0%)	5 (50.0%)	13 (43.3%)
Not Hispanic or Latino n (%)	4 (40.0%)	8 (80.0%)	5 (50.0%)	17 (56.7%)
Race				
American Indian or Alaskan Native n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asian n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Black, African American, or of African Heritage n (%)	1 (10.0%)	1 (10.0%)	2 (20.0%)	4 (13.3%)
Native Hawaiian or Other Pacific Islander n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
White n (%)	9 (90.0%)	9 (90.0%)	8 (80.0%)	26 (86.7%)
Multiple Races Checked n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Child-Pugh score and classification (Table 20) at baseline for the patient population is described below.

Table 20. Child-Pugh score and classification at baseline for the hepatic impairment subjects

Child-Pugh / Category	Mild Hepatic Impairment N (%)	Moderate Hepatic Impairment N (%)	Total N (%)
No. of Subjects	10	10	20
Encephalopathy			
Grade 0	5 (50.0%)	1 (10.0%)	6 (30.0%)
Grade 1 or 2	5 (50.0%)	9 (90.0%)	14 (70.0%)
Grade 3 or 4	0 (0%)	0 (0%)	0 (0%)
Ascites			
Absent	9 (90.0%)	1 (10.0%)	10 (50.0%)
Slight	1 (10.0%)	6 (60.0%)	7 (35.0%)
Moderate	0 (0%)	3 (30.0%)	3 (15.0%)
Total Bilirubin			
< 2 mg / dL (< 34 µmol/L)	10 (100%)	9 (90.0%)	19 (95.0%)
2 – 3 mg / dL (34 – 50 µmol/L)	0 (0%)	1 (10.0%)	1 (5.0%)
> 3 mg / dL (> 50 µmol/L)	0 (0%)	0 (0%)	0 (0%)
Albumin			
> 3.5 g / dL (> 35 g/L)	10 (100%)	9 (90.0%)	19 (95.0%)
2.8 – 3.5 g / dL (28 – 35 g/L)	0 (0%)	0 (0%)	0 (0%)
< 2.8 mg / dL (< 28 g/L)	0 (0%)	1 (10.0%)	1 (5.0%)
INR			
< 1.7	10 (100%)	10 (100%)	20 (100%)
1.7 – 2.2	0 (0%)	0 (0%)	0 (0%)
> 2.2	0 (0%)	0 (0%)	0 (0%)
Classification Score			
A (Child-Pugh Score 05–06: Mild Hepatic Impairment	10 (100%)	0 (0%)	10 (50.0%)
B (Child-Pugh Score 07–09: Moderate Hepatic Impairment	0 (0%)	10 (100%)	10 (50.0%)

Reference: Synteract Table 14-3 and Listing 16.5.
Encephalopathy Grades:
Grade 0: Normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.
Grade 2: Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
Grade 3: Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: Unrousable coma, no personality/behavior, decerebrate, slow 2–3 cps delta activity time.

Hydrocodone individual and median plasma concentration profiles (Figures 34 and 35, respectively) are shown below.

Figure 34. Individual hydrocodone concentration profiles for hepatic impairment subjects

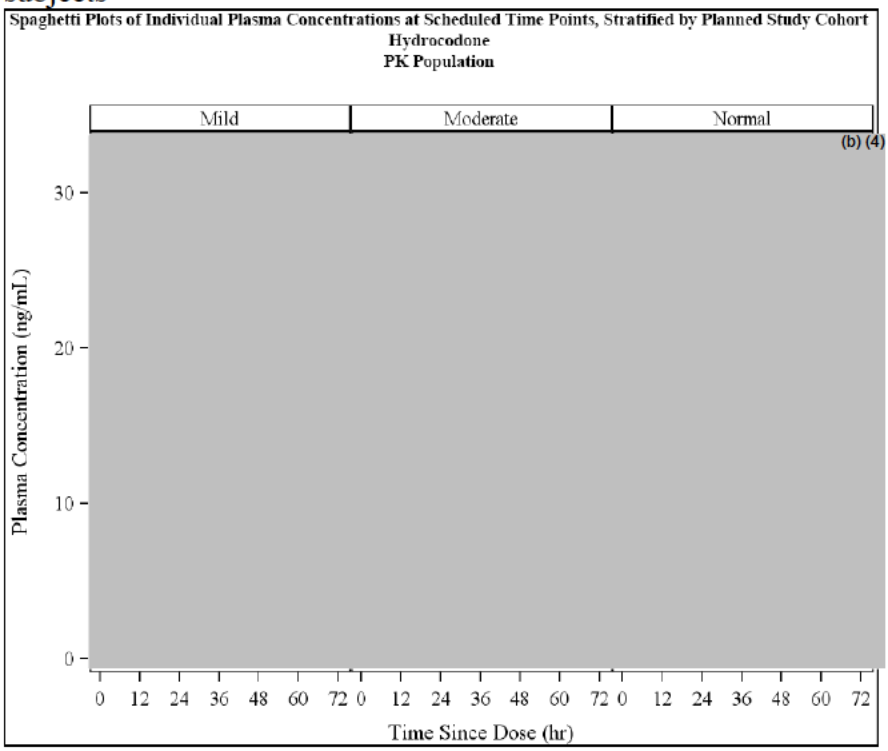
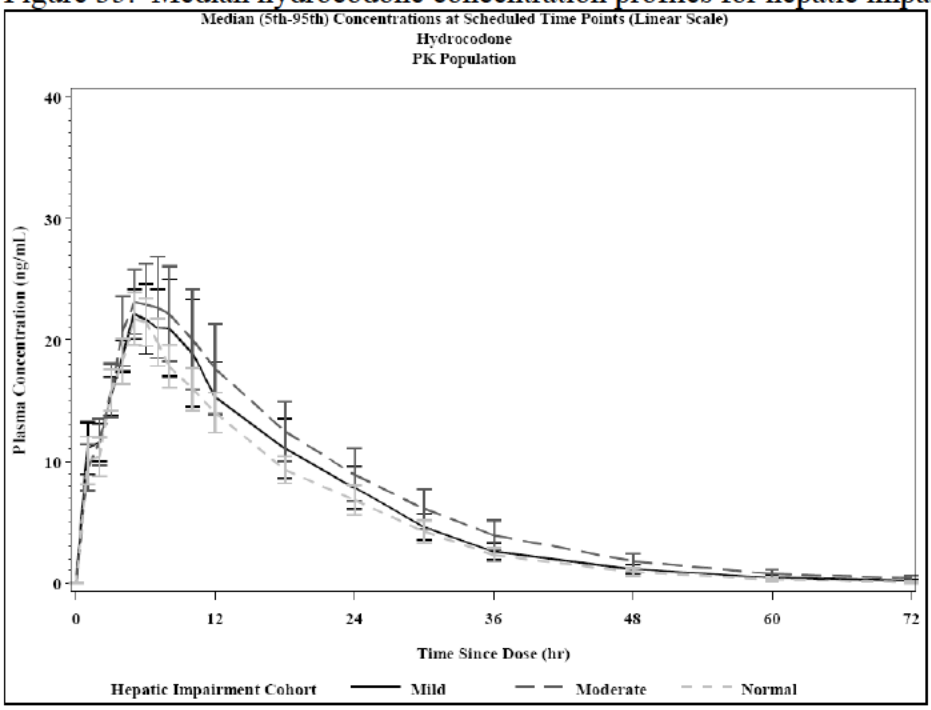


Figure 35. Median hydrocodone concentration profiles for hepatic impairment subjects



Hydromorphone individual and median plasma concentration profiles (Figures 36 and 37, respectively) are shown below.

Figure 36. Individual hydromorphone concentration profiles for hepatic impairment subjects

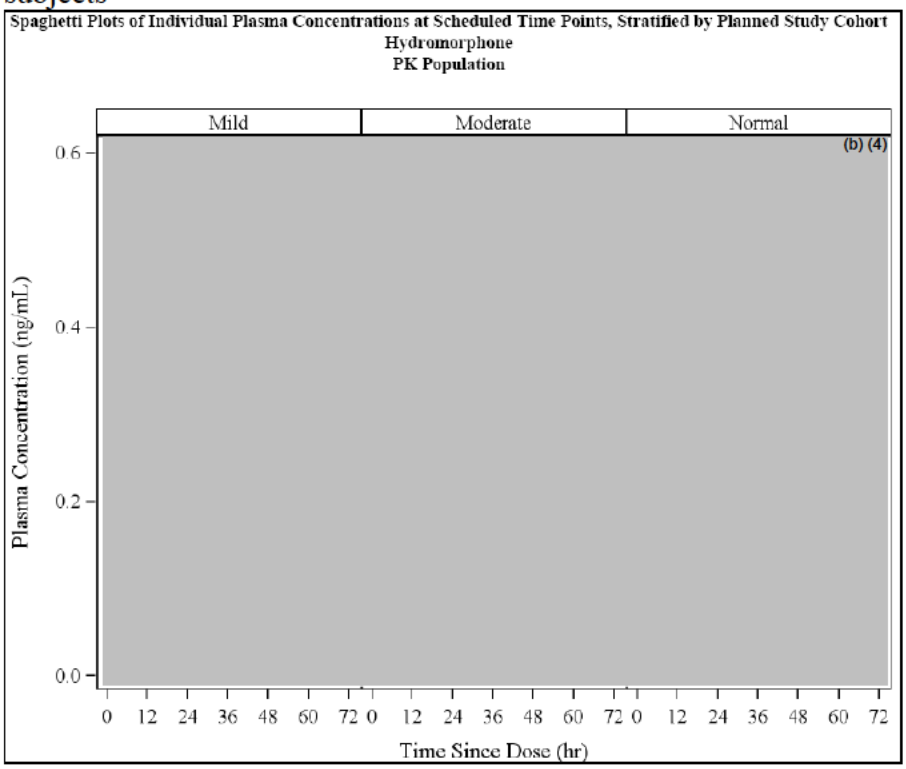
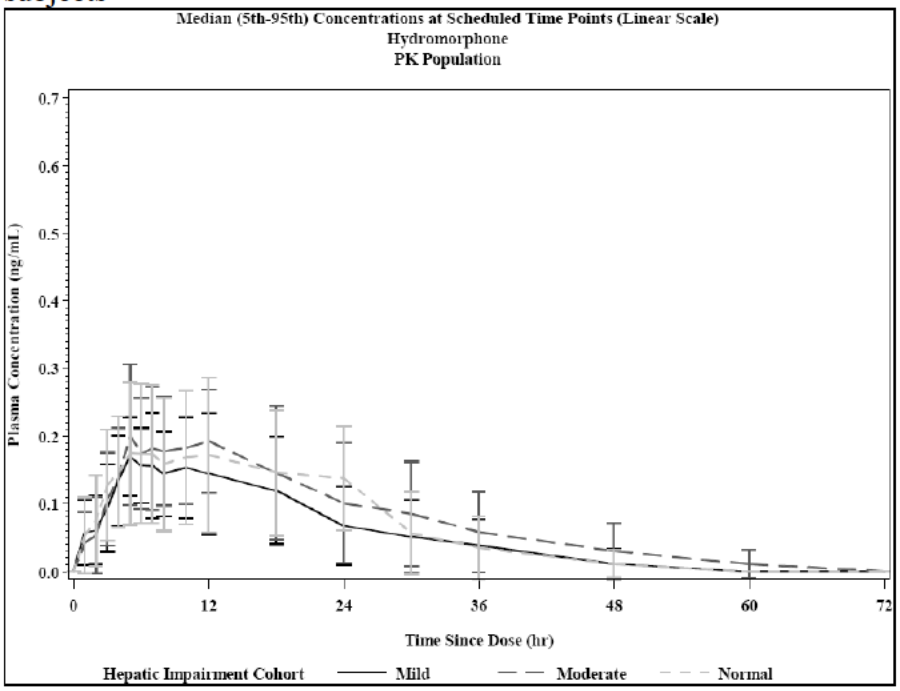


Figure 37. Median hydromorphone concentration profiles for hepatic impairment subjects



Hydromorphone individual and median plasma concentration profiles (Figures 38 and 39, respectively) are shown below.

Figure 38. Individual norhydrocodone concentration profiles for hepatic impairment subjects

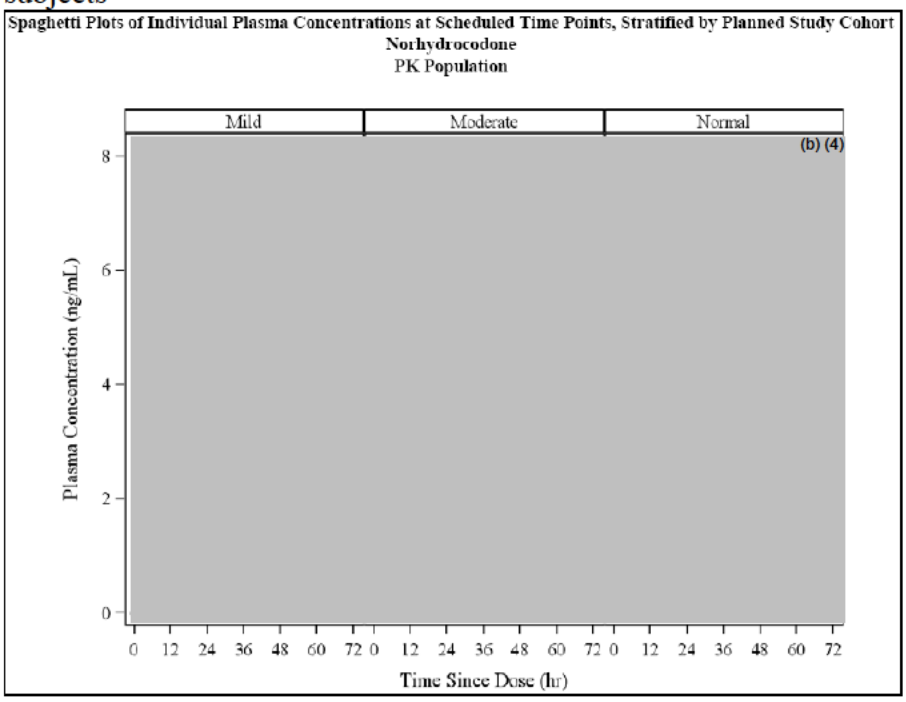
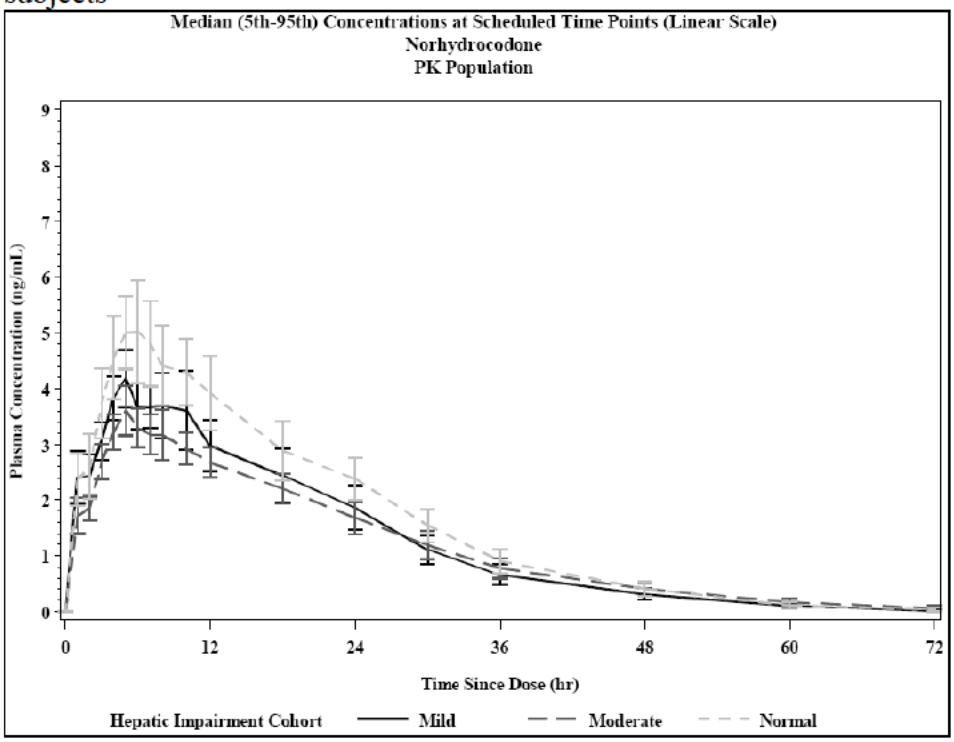


Figure 39. Median norhydrocodone concentration profiles for hepatic impairment subjects



PK parameters (Table 21) are described below for the hepatically impaired subjects.

Table 21. PK parameters for hepatic impairment subjects

Pharmacokinetic Parameters	Subject Cohort		
	Mild Hepatic Impairment	Moderate Hepatic Impairment	No Hepatic Impairment
PK Subjects	10	10	10
Hydrocodone			
C_{max} (ng/mL)	24.0 (5.07)	24.5 (5.03)	22.1 (3.36)
T_{max} (hr) [1]	6 (5–10)	6 (5–8)	6 (5–7)
$AUC_{0\text{-}inf}$ (ng*h/mL)	439.6 (123.59)	508.8 (156.94)	391.3 (74.36)
AUC Extrapolated (%)	0.9 (0.5)	1.1 (0.72)	0.7 (0.31)
$T_{1/2}$ (hr)	9.1 (1.55)	9.9 (2.1)	7.9 (1.54)
% Dose Excreted	8.3 (2.36)	9.5 (2.52)	7.4 (2.46)
% Dose Excreted, Combined [2]	17.8 (5.26)	18.3 (3.29)	18.2 (4.9)
Norhydrocodone			
C_{max} (ng/mL)	4.5 (0.82)	3.7 (0.65)	5.3 (1.37)
T_{max} (hr) [1]	5 (4–10)	5 (4–10)	5.5 (4–10)
$AUC_{0\text{-}inf}$ (ng*h/mL)	92.7 (22.92)	87.7 (16.42)	115.9 (28.41)
AUC Extrapolated (%)	2.3 (0.93)	3 (0.91)	1.9 (0.67)
$T_{1/2}$ (hr)	9.2 (1.79)	11.4 (2.25)	9 (1.45)
% Dose Excreted	9.1 (3.3)	8.4 (1.5)	10.5 (3.61)
Hydromorphone			
C_{max} (ng/mL)	0.2 (0.09)	0.3 (0.15)	0.3 (0.16)
T_{max} (hr) [1]	6 (4–12)	10 (5–24)	12 (5 – 24)
$AUC_{0\text{-}inf}$ (ng*h/mL)	8.3 (3.34)	11.2 (4.63)	14.4 (6.51)
AUC Extrapolated (%)	52.1 (23.77)	42.1 (26.08)	40.5 (28.2)
$T_{1/2}$ (hr)	25.3 (12.54)	25.1 (19.77)	28.6 (26.35)
% Dose Excreted	0.4 (0.18)	0.4 (0.23)	0.3 (0.2)

Box-and-Whisker plots of hydrocodone Cmax and AUC0-inf parameters for the hepatic impairment subjects are presented below (Figures 40 and 41, respectively).

Figure 40. Box-and-Whisker plots of hydrocodone Cmax parameters for hepatic impairment subjects

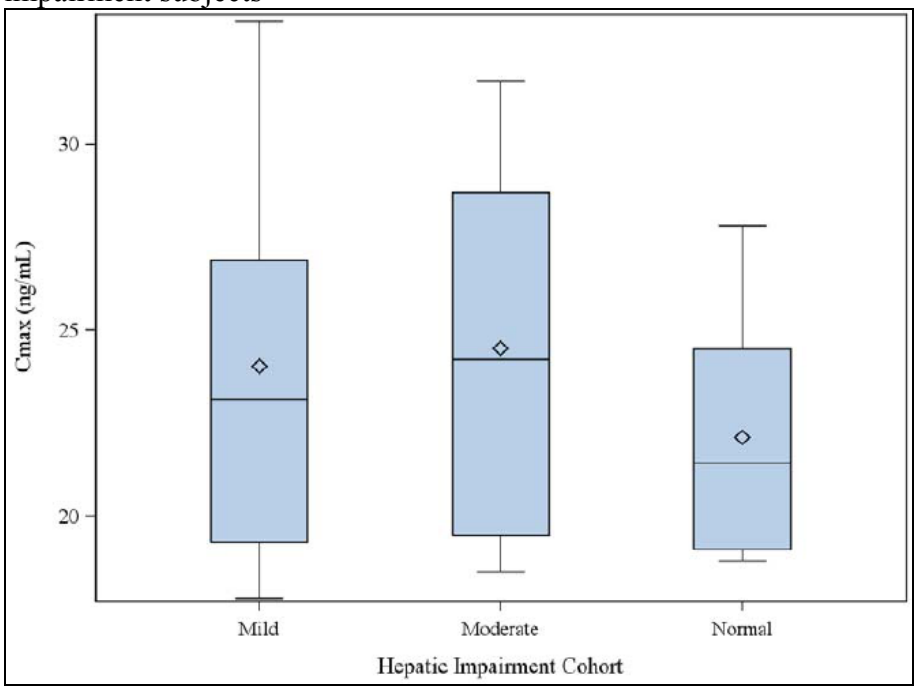
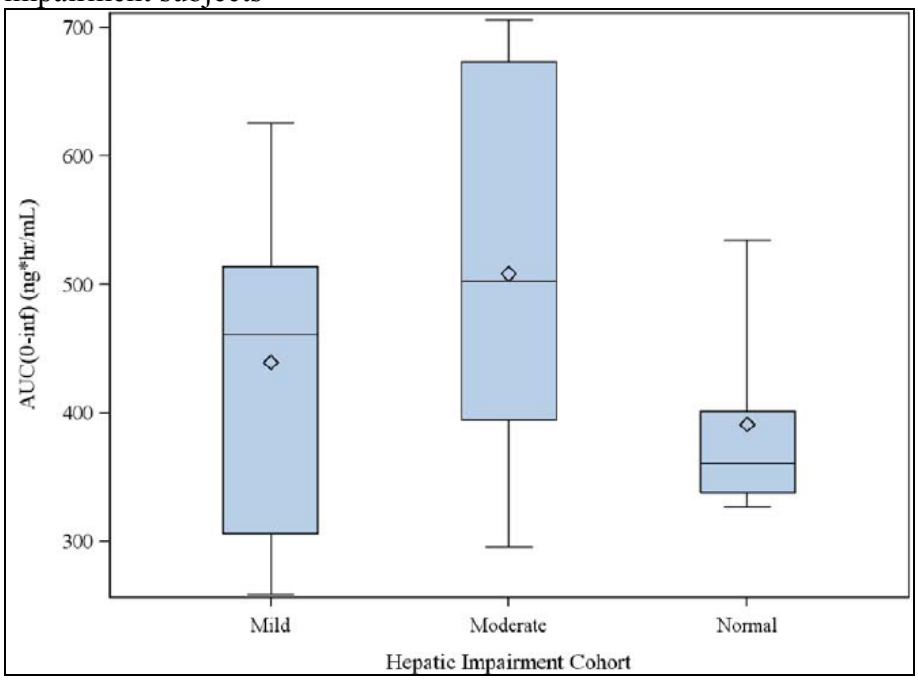


Figure 41. Box-and-Whisker plots of hydrocodone AUC0-inf parameters for hepatic impairment subjects



Comparison of AUC and Cmax (Table 22) across hepatic impairment cohorts are presented below.

Table 22. Comparison of Cmax and AUC across hepatic impairment subjects

Analyte / Parameter	Subject Cohort		
	Mild Hepatic Impairment vs. No Hepatic Impairment	Moderate Hepatic Impairment vs. No Hepatic Impairment	Moderate Hepatic Impairment vs. Mild Hepatic Impairment
PK Subjects	**10**	**10**	**10**
Hydrocodone			
$AUC_{0\text{-}inf}$ (ng*h/mL)			
Geometric Mean Ratio (%)	1.10	1.26	1.15
90% Confidence Interval	(0.91, 1.33)	(1.03, 1.55)	(0.90, 1.46)
C_{max} (ng/mL)			
Geometric Mean Ratio (%)	1.08	1.10	1.02
90% Confidence Interval	(0.94, 1.24)	(0.95, 1.26)	(0.87, 1.20)
Norhydrocodone			
$AUC_{0\text{-}inf}$ (ng*h/mL)			
Geometric Mean Ratio (%)	0.80	0.77	0.96
90% Confidence Interval	(0.65, 0.98)	(0.64, 0.92)	(0.79, 1.16)
C_{max} (ng/mL)			
Geometric Mean Ratio (%)	0.87	0.70	0.81
90% Confidence Interval	(0.73, 1.02)	(0.60, 0.83)	(0.71, 0.92)
Hydromorphone			
$AUC_{0\text{-}inf}$ (ng*h/mL)			
Geometric Mean Ratio (%)	0.59	0.79	1.34
90% Confidence Interval	(0.35, 0.99)	(0.45, 1.37)	(0.88, 2.03)
C_{max} (ng/mL)			
Geometric Mean Ratio (%)	0.75	0.90	1.21
90% Confidence Interval	(0.50, 1.11)	(0.56, 1.45)	(0.80, 1.83)

Mean hydrocodone Cmax values were 25 ± 5, 24 ± 5, and 22 ± 3.3 ng/mL for moderately impaired, mildly impaired and normal subjects, respectively. Mean hydrocodone Cmax values were comparable for all groups.

Mean hydrocodone AUC values were 509 ± 157, 440 ± 124, and 391 ± 74 ng/mL for moderately impaired, mildly impaired and normal subjects, respectively. Mean hydrocodone AUC increased approximately 26% for moderately impaired subjects compared to that of normal subjects; this increase in exposure may not be clinically significant and may not warrant a dose adjustment. Severely impaired subjects were not studied.

Approximately 18% of the administered dose was excreted via the urine over 72 hours as hydrocodone, norhydrocodone or hydromorphone regardless of hepatic impairment.

2.4 Extrinsic Factors

The PK interaction between HC-ER and other drugs has not been studied in this submission. Hydrocodone is metabolized by CYP2D6 and CYP3A4. Therefore, use with caution when using hydrocodone with other drugs which may alter the activity of CYP2D6 and CYP3A4 enzymes.

2.4.1 What is the hydrocodone exposure if co-administered with alcohol?

Study ZX002-0901 was a Phase 1, open-label, randomized, single-dose, three-period crossover study with a 4-5 day washout between doses. The study was conducted in 30 healthy adults between 22 and 44 years of age who received a single dose of HC-CR 50 mg in fasted state with 240 mL solutions of 40% alcohol/orange juice, 20% alcohol/orange juice, and 0% alcohol/orange juice (Everclear 190 proof was used as an alcohol solution). Commercially available naltrexone (50 mg) was orally administered at approximately 12 (with a light snack) and two hours (fasted) prior to administration, and 10 hours (with a light snack) after administration of HC-ER in each study period. Blood samples were obtained at the following time points: pre-dose, 0.25, 0.5, 0.75, 1.0, 1.25, 1.50, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 h after administration of each HC-CR 50 mg capsule. If a subject experienced productive vomiting (an emetic episode involving the voiding of gastric contents) within 4 h following dosing, the subject was deemed not eligible for PK evaluation; however, PK blood draws were continued per schedule at the discretion of the Investigator to allow for review of drug levels in the case of a safety event (compared to subjects who were *eligible* for PK evaluation, defined as the subjects who completed the full 12-h treatment period; PK evaluable subjects are defined as no emesis within 4 h post dosing). The alcohol solution was prepared as follows (Table 23):

Table 23. Alcohol solution preparation

Study Treatment	Alcohol % (V:V)	Everclear 190 Proof (mL)	Orange Juice (pulp-free)(mL)	Total volume (mL)
A	40	101	139	240
B	20	50	190	240
C	0	0	240	240

The following table contains the demographics of subjects (Table 24) who participated in this study.

Table 24. Alcohol demographics

Demographic / Statistic	Result
No. of Subjects	30
Gender	
Male n (%)	28 (93.3%)
Female n (%)	2 (6.7%)
Age (years)	
Mean (SD)	32 (7.1)
Median	33
Min / Max	22 / 44
Weight (kg)	
Mean (SD)	87.2 (9.88)
Median	86.1
Min / Max	67.3 / 111.5
Height (cm)	
Mean (SD)	175.0 (6.52)
Median	174.5
Min / Max	161.3 / 192.7
BMI (kg/m^2)	
Mean (SD)	28.5 (3.08)
Median	28.3
Min / Max	22.4 /34.3
Ethnicity	
Hispanic or Latino n (%)	11 (36.7%)
Not Hispanic or Latino n (%)	19 (63.3%)
Race	
White n (%)	22 (73.3%)
Black or African American n (%)	6 (20.0%)
American Indian / Alaskan Native n (%)	1 (3.3%)
Other: American Indian and White n (%)	1 (3.3%)

Mean hydrocodone, hydromorphone and norhydrocodone concentration profiles (Figures 42 – 44, respectively) are presented below for all groups.

Figure 42. Mean hydrocodone concentration profiles for 0, 20 and 40% alcohol cohorts

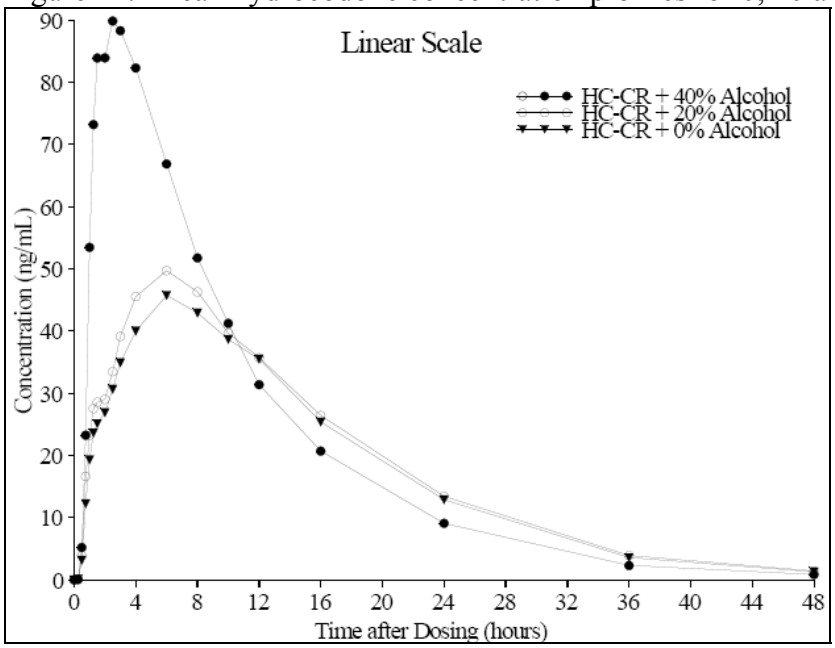


Figure 43. Mean hydromorphone concentration profiles for 0, 20 and 40% alcohol cohorts

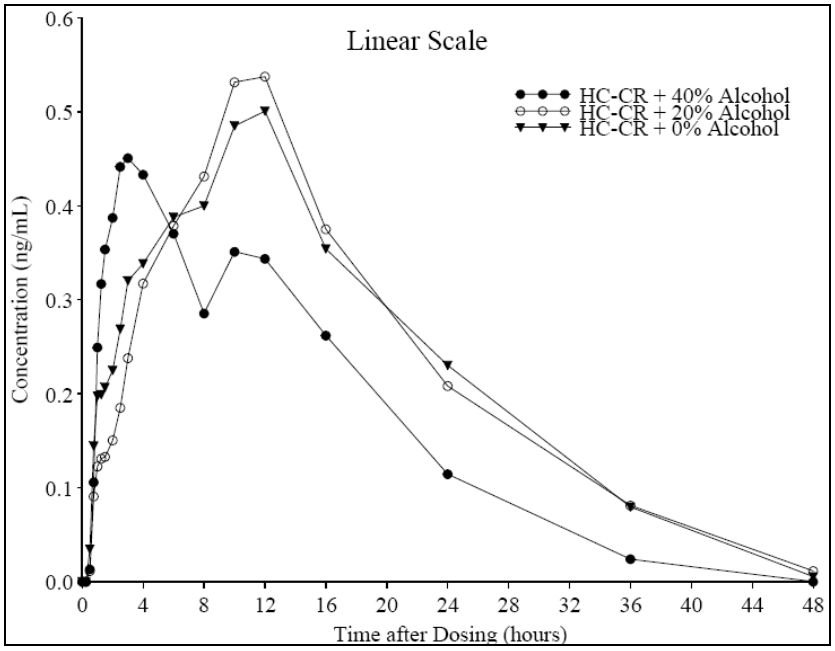
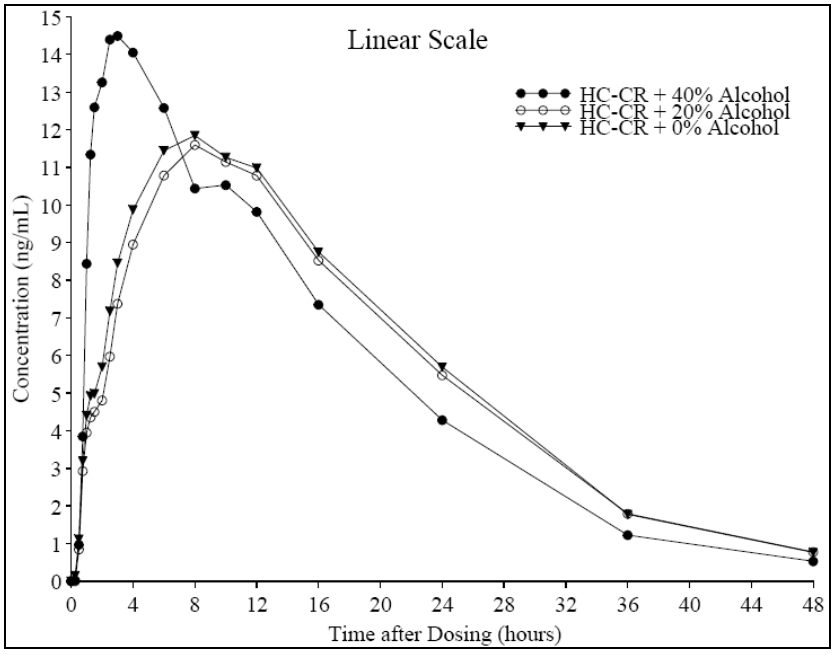


Figure 44. Mean norhydrocodone concentration profiles for 0, 20 and 40% alcohol cohorts



Mean hydrocodone, hydromorphone and norhydrocodone PK parameters (Table 25) are presented below.

Table 25. Mean hydrocodone, hydromorphone and norhydrocodone PK parameters from 0, 20 and 40% alcohol cohorts

Pharmacokinetic Parameters	Treatment			
	HC-CR + 0% Alcohol N=30	HC-CR + 20% Alcohol N=29	HC-CR + 40% Alcohol Primary[a] Analysis N=30	HC-CR + 40% Alcohol Secondary[a] Analysis N=30
Evaluable Subjects	**29**	**28**	**21**	**20**
Hydrocodone				
C_{max} (ng/mL)	46.3 (8.63) Min: 32.6 Max: 61.0	51.8 (10.7) Min: 33.9 Max: 78.8	104 (43.8) Min: 8.18 Max: 196	109 (38.8) Min: 66.9 Max: 196
T_{max} (hr)	6.16 (2.06) Min: 0.750 Max: 12.0	5.44 (1.54) Min: 0.750 Max: 8.00	2.45 (1.11) Min: 1.00 Max: 6.00	2.43 (1.14) Min: 1.00 Max: 6.00
AUC_{0-t} (ng . hr/mL)	832 (216) Min: 452 Max: 1190	878 (231) Min: 512 Max: 1356	963 (291) Min: 65.1 Max: 1456	1008 (212) Min: 690 Max: 1456
AUC_{0-inf} (ng . hr/mL)	846 (225) Min: 454 Max: 1217	900 (243) Min: 520 Max: 1368	972 (296) Min: 67.4 Max: 1491	1017 (217) Min: 693 Max: 1491
$t_{1/2}$ (hr)	7.16 (1.18) Min: 5.34 Max: 9.46	7.38 (1.35) Min: 5.16 Max: 10.3	6.69 (1.13) Min: 4.78 Max: 9.69	6.79 (1.07) Min: 5.27 Max: 9.69
k_{el} (1/hr)	0.0993 (0.0165) Min: 0.0733 Max: 0.130	0.0969 (0.0177) Min: 0.0671 Max: 0.134	0.106 (0.0173) Min: 0.0716 Max: 0.145	0.104 (0.0152) Min: 0.0716 Max: 0.131
Hydromorphone				
C_{max} (ng/mL)	0.537 (0.249)	0.580 (0.280)	0.542 (0.288)	0.563 (0.278)
T_{max} (hr)	10.8 (2.00)	11.3 (1.41)	4.79 (3.66)	4.90 (3.71)
AUC_{0-t} (ng . hr/mL)	9.76 (5.35)	9.79 (6.20)	6.78 (4.13)	7.11 (3.93)
AUC_{0-inf} (ng . hr/mL)	16.6 (4.83)	16.2 (5.72)	12.1 (2.05)	12.1 (2.05)
$t_{1/2}$ (hr)	13.0 (3.30)	11.5 (2.80)	9.68 (1.84)	9.68 (1.84)
k_{el} (1/hr)	0.0565 (0.0140)	0.0638 (0.0161)	0.0746 (0.0172)	0.0746 (0.0172)
Norhydrocodone				
C_{max} (ng/mL)	12.4 (2.61)	12.0 (3.14)	16.2 (6.63)	16.9 (5.90)
T_{max} (hr)	8.16 (2.29)	8.40 (1.89)	3.01 (2.38)	3.01 (2.44)
AUC_{0-t} (ng . hr/mL)	270 (81.0)	258 (86.0)	247 (103)	258 (92.0)
AUC_{0-inf} (ng . hr/mL)	280 (87.9)	270 (93.8)	253 (109)	265 (97.9)
$t_{1/2}$ (hr)	7.99 (1.37)	8.38 (1.59)	7.80 (1.31)	7.90 (1.27)
k_{el} (1/hr)	0.0565 (0.0140)	0.0854 (0.0152)	0.0909 (0.0132)	0.0896 (0.0121)

[a]Subject 005 was found to have anomalously low hydrocodone and hydrocodone metabolite values, and, based on the Sponsor's request, secondary PK statistical analyses were conducted (the secondary analyses were intended to correct for an underestimate of the effect of 40% alcohol in the Evaluable Population). Therefore, the only difference between the primary and secondary analyses was the exclusion of Subject 005 from the secondary analyses.

Mean hydrocodone Tmax values were 2.4 ± 1.1, 5.4 ± 1.5, and 6.2 ± 2.1 h in 40, 20 and 0% alcohol in fasted state, respectively. Tmax decreased less than half the time for subjects receiving 40% alcohol in comparison to those receiving 20% or 0% alcohol.

Mean hydrocodone Cmax values were 109 ± 39, 52 ± 11, and 46 ± 8.6 ng/mL in 40, 20 and 0% alcohol in fasted state, respectively. Mean hydrocodone Cmax increased approximately 2.4-fold in 40% alcohol compared to the 0% alcohol treatments. Mean hydrocodone Cmax value for 20% alcohol was comparable to 0% alcohol treatment. Mean hydrocodone AUC values were comparable for all alcohol treatments (1017 ± 217, 900 ± 243, and 846 ± 225 ng.h/mL in 40, 20 and 0% alcohol in fasted state, respectively). Mean hydrocodone AUC was slightly higher for subjects receiving 40% alcohol. The following table compares the mean Cmax and AUC values (Table 26).

Table 26. Comparison of mean Cmax and AUC value across alcohol cohorts

PK Parameters	Treatments[a] and Comparisons							
	N[b]	Treatment A (LS Mean)	N[b]	Treatment B (LS Mean)	N[b]	Treatment C[c] (LS Mean)	Treatment A vs. C[d] (90% CI)[e]	Treatment B vs. C[d] (90% CI)[e]
Hydrocodone - Primary Analyses[e]								
C_{max} (ng/mL)	21	92.3	28	51.0	29	45.6	**202%** (170.71, 139.99)	**112%** (95.93, 139.39)
AUC_{0-t} (ng . hr/mL)	21	859	28	849	29	806	**107%** (91.21, 124.58)	**105%** (91.65, 121.21)
AUC_{0-inf} (ng . hr/mL)	21	867	28	868	29	819	**106%** (90.88, 123.54)	**106%** (92.43, 121.70)
Hydrocodone - Secondary Analyses[e]								
C_{max} (ng/mL)	20	105	28	51.2	29	45.9	**229%** (209.22, 251.10)	**112%** (102.96, 120.94)
AUC_{0-t} (ng . hr/mL)	20	970	28	848	29	809	**120%** (114.74, 125.24)	**105%** (100.85, 108.83)
AUC_{0-inf} (ng . hr/mL)	20	979	28	867	29	823	**119%** (113.87, 124.38)	**105%** (101.47, 109.56)

Source: Tables 14.2.3-1a and 14.2.3-1b (Section 14).

[a]Treatment A was HC-CR + 40% alcohol, Treatment B was HC-CR + 20% alcohol, and Treatment C was HC-CR + 0% alcohol.

[b]N was the number of observations used in the model.

[c]Treatment C (HC-CR + 0% alcohol) was the reference treatment used for comparison with Treatment A and Treatment B.

Additionally, the following tables (Tables 27 – 30) contain individual fold-differences, as the magnitudes of the differences in each of the subjects tested were of an interest in each of the alcohol groups.

Table 27. Cmax comparison: 0 vs. 40% alcohol in descending ratio

Subj. ID	Cmax		Ratio 40 %/0 %
	0% alcohol	40% alcohol	
016	43.6	170	3.90
017	38	137	3.61
010	59	196	3.32
012	50.7	160	3.16
022	54.9	164	2.99
008	53	140	2.64
011	41.1	103	2.51
029	34	83.3	2.45
026	49	107	2.18
018	37.2	79.9	2.15
020	42.3	89.4	2.11
007	35.6	74.5	2.09
002	32.6	68.2	2.09
013	57	117	2.05
009	46.2	87.8	1.90
025	37.7	70.5	1.87
003	53.5	99.8	1.87
021	51.6	92	1.78
030	41.1	66.9	1.63
015	55.8	76.4	1.37

Table 28. Cmax comparison: 0 vs. 20% alcohol in descending ratio

Subj. ID	Cmax		Ratio 20 %/0 %
	0% alcohol	20% alcohol	
017	38	58.9	1.55
014	51.9	78.8	1.52
006	38.8	51.7	1.33
025	37.7	49	1.30
029	34	43.8	1.29
002	32.6	41.2	1.26
004	61	73.6	1.21
013	57	68.3	1.20
027	33.9	40.4	1.19
021	51.6	60.8	1.18
009	46.2	54.3	1.18
030	41.1	48.2	1.17
007	35.6	41.2	1.16
026	49	55.6	1.13
022	54.9	61.5	1.12
019	54.5	60.1	1.10
012	50.7	55.6	1.10
011	41.1	45	1.09
020	42.3	45.8	1.08

005	47.3	51	1.08
016	43.6	45.5	1.04
003	53.5	55.3	1.03
015	55.8	52.5	0.94
018	37.2	33.9	0.91
023	59.1	53.4	0.90
001	40.5	34.3	0.85
008	53	43.5	0.82
010	59	47.8	0.81

Table 29. AUC0-inf comparison: 0 vs. 40% alcohol in descending ratio

Subj. ID	AUC0-inf		Ratio 40 %/0 %
	0% alcohol	40% alcohol	
007	454	757	1.67
017	683	1106	1.62
021	1036	1491	1.44
029	483	693	1.43
002	595	840	1.41
025	634	887	1.40
010	904	1228	1.36
011	762	1004	1.32
020	709	886	1.25
030	702	819	1.17
022	1183	1362	1.15
018	699	804	1.15
003	1175	1341	1.14
026	922	987	1.07
016	811	860	1.06
009	881	930	1.06
013	1052	1091	1.04
012	1217	1190	0.98
015	1067	1026	0.96
008	1095	1043	0.95

Table 30. AUC0-inf comparison: 0 vs. 20% alcohol in descending ratio

Subj. ID	AUC0-inf		Ratio 20 %/0 %
	0% alcohol	20% alcohol	
006	661	947	1.43
002	595	799	1.34
019	876	1144	1.31
014	874	1098	1.26
021	1036	1243	1.20
029	483	579	1.20
017	683	808	1.18
030	702	825	1.18
007	454	520	1.15

004	1202	1368	1.14
011	762	857	1.12
003	1175	1300	1.11
016	811	887	1.09
009	881	957	1.09
012	1217	1301	1.07
026	922	979	1.06
005	756	794	1.05
015	1067	1116	1.05
010	904	904	1.00
018	699	679	0.97
025	634	606	0.96
023	1137	1083	0.95
020	709	647	0.91
027	620	563	0.91
022	1183	974	0.82
013	1052	862	0.82
008	1095	846	0.77
001	709	525	0.74

Looking at the individual Cmax and AUC values, the greatest increase in Cmax was observed at 3.9-fold (Subject #016). The greatest increase in AUC was observed at 1.7-fold (Subject #007). This difference was not statistically significant (within bioequivalence range). This study demonstrated that the rate of absorption (Cmax) was affected by co-ingestion with 40% alcohol in the fasted state. However, the greatest individual increase in Cmax was comparable or lower than those of the already approved extended-release opioid products (e.g. 2.7-fold for OPANA ER, 4.38-fold for NUCYNTA ER, 5-fold for EMBEDA ER); and much lower than that of PALLADONE (16-fold). Therefore, the alcohol interaction with the proposed product is not considered as an approvability issue.

2.5 General Biopharmaceutics

2.5.1 Relative Bioavailability

Study ZX002-1101 was a Phase 1, open-label, randomized, two-dose, two-period cross-over study with minimum 5 day washout between treatments. The study was conducted in 15 healthy subjects between 18 and 45 years of age who received a single dose of 30 mg HC-ER and 2 consecutive doses of 2-tablets of Vicoprofen 6 hours apart for a total of 4 tablets. Subjects were fasted overnight for at least 10 hours before and for at least 3.5 hours post dosing. For Vicoprofen treatment, subjects were provided a light meal, which needed to be consumed within a 30-minute period (3.5–4.0 hours post-dosing), followed by at least four hours of fasting, to allow for 2 hours of fasting before and after the 2nd dose of Vicoprofen. All doses were administered with 240 mL of ambient temperature water. For HC-ER, blood samples were collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 36, and 48 h after dose administration. For Vicoprofen, blood samples were collected at pre-dose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2,

2.5, 3, 4, 6, 6.25, 6.5, 6.75, 7, 7.25, 7.5, 8, 8.5, 9, 10, 12, 14, 16, 18, 20, 22, 24, 36, and 48 h after administration of the first Vicoprofen dose. The following table (Table 31) contains the demographics of the subjects participated in the study.

Table 31. Relative bioavailability study demographics

Demographic / Statistic	All Subjects
No. of Subjects	15
Age (years)	
Mean (SD)	33 (5.3)
Median	31
Min / Max	27 / 43
Sex	
Male n (%)	8 (53.3%)
Female n (%)	7 (46.7%)
Race	
White n (%)	9 (60.0%)
Black, African American, or of African Heritage n (%)	3 (20.0%)
Other n (%)	3 (20.0%)
Ethnicity	
Hispanic or Latino n (%)	8 (53.3%)
Not Hispanic or Latino n (%)	7 (46.7%)
Weight (kg)	
Mean (SD)	79.0 (14.90)
Median	83.7
Min / Max	55.6 / 107.0
Height (cm)	
Mean (SD)	169.5 (11.48)
Median	171.9
Min / Max	146.8 / 187.2
BMI (kg/m^2)	
Mean (SD)	27.3 (3.12)
Median	28.0
Min / Max	21.1 / 33.2

Mean hydrocodone, hydromorphone, and, norhydrocodone concentration profiles (Figures 45 – 47, respectively) are presented below from comparing HC-ER and Vicoprofen.

Figure 45. Mean hydrocodone concentration profiles for HC-ER and Vicoprofen.

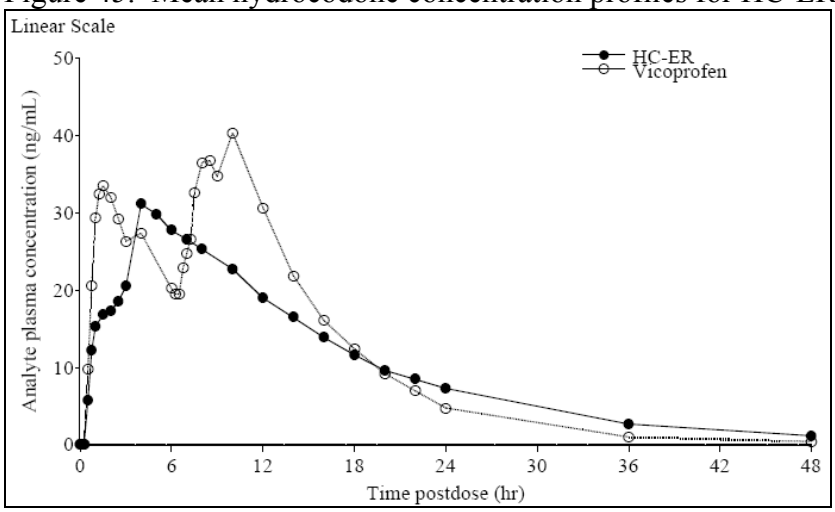


Figure 46. Mean hydromorphone concentration profiles for HC-ER and Vicoprofen.

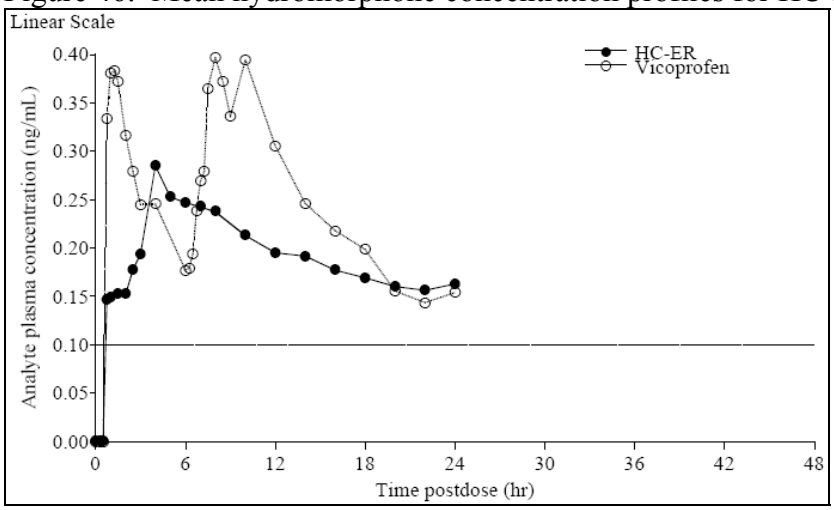
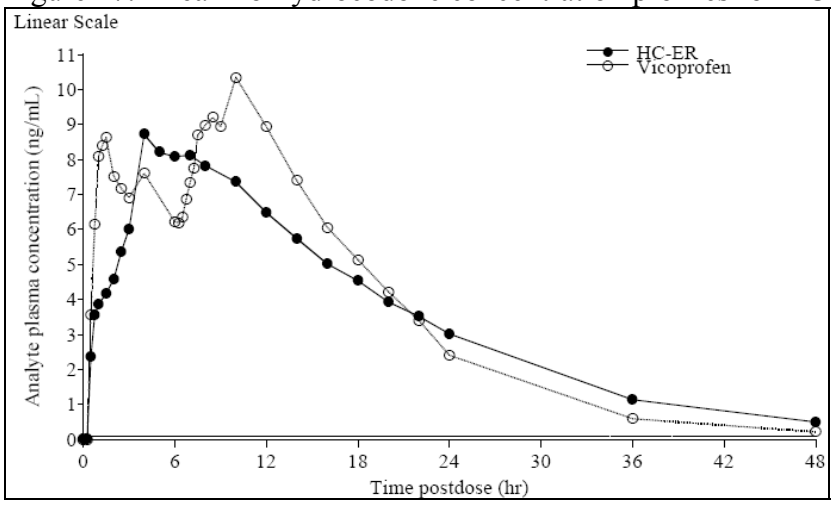


Figure 47. Mean norhydrocodone concentration profiles for HC-ER and Vicoprofen.



Mean hydrocodone PK parameters are presented below (Table 32), followed by comparison of hydrocodone Cmax and AUC parameters (Table 33).

Table 32. Mean hydrocodone PK parameters for HC-ER and Vicoprofen

Pharmacokinetic Parameters	Geometric Mean	Geometric CV%	Arithmetic Mean (SD)	Median	Min, Max
HC-ER (N = 14)					
AUC_{0-t} (ng*h/mL)	491	16.6	497 (83.0)	489	384, 654
AUC_{0-inf} (ng*h/mL)	506	17.7	513 (91.5)	505	390, 706
C_{max} (ng/mL)	31.5	21.9	32.2 (7.08)	30.5	22.4, 44.6
T_{max} (hr)	NC	NC	4.93 (1.54)	5.00	4.00, 10.0
$T_{1/2}$ (hr)	8.46	23.8	8.67 (2.01)	8.22	5.78, 12.4
Vicoprofen (N = 13)					
AUC_{0-t} (ng*h/mL)	542	22.7	555 (121)	590	397, 728
AUC_{0-inf} (ng*h/mL)	546	22.8	559 (122)	594	399, 736
C_{max} (ng/mL)	45.8	16.3	46.3 (7.17)	46.6	31.9, 59.0
T_{max} (hr)[1]	NC	NC	8.65 (1.21)	8.00	7.00, 10.0
$T_{1/2}$ (hr)	6.54	28.7	6.91 (2.52)	6.59	4.23, 14.7

[1] T_{max} is calculated from the time of the first Vicoprofen dose; a median T_{max} of 8 hours is approximately 2 hours after the administration of the second dose of Vicoprofen 15 mg.

Table 33. Comparison of hydrocodone Cmax and AUC parameters for HC-ER and Vicoprofen.

Analyte / Parameter	HC-ER vs. Vicoprofen
PK-Bioequivalence Population (N = 13)	
AUC_{0-t} (ng*h/mL)	
Geometric Mean Ratio (%)	91.1
90% Confidence Interval	82.8, 100
AUC_{0-inf} (ng*h/mL)	
Geometric Mean Ratio (%)	93.2
90% Confidence Interval	84.5, 103
C_{max} (ng/mL)	
Geometric Mean Ratio (%)	68.7
90% Confidence Interval	63.2, 74.6

Mean hydrocodone Cmax values were 32 ± 7 and 46 ± 7 ng/mL for HC-ER and Vicoprofen treatments, respectively. Mean hydrocodone Cmax were not similar between the two treatments as indicated by the bioequivalence evaluation. This finding is expected since the IR and ER formulation profiles are not similar.

Mean hydrocodone AUC values were 513 ± 92 and 559 ± 122 ng.h/mL for HC-ER and Vicoprofen treatments, respectively. The bioequivalence analysis indicated that the AUC values from the two treatments were equivalent.

2.5.2 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

To-Be-Marketed formulation ("Gainesville site formulation") was used in all of the clinical pharmacology and Phase 3 trials, except for the food effect study (ELN-0302002 study utilized 20 mg dose; see below), which was labeled as a pilot PK study ("Athlone site formulation"). The applicant claimed that that both formulations from the two different sites are similar based on dissolution profiles and IVIVC analysis. Biopharmaceutics Team, ONDQA is evaluating the IVIVC information and will report the findings.

2.5.2.1 What data support a waiver of in vivo BE data?

The Applicant is requesting a waiver for 15 mg strength. This request will be assessed by Biopharmaceutics Team, ONDQA. The Applicant presented the following reasons in the Application for a waiver request:

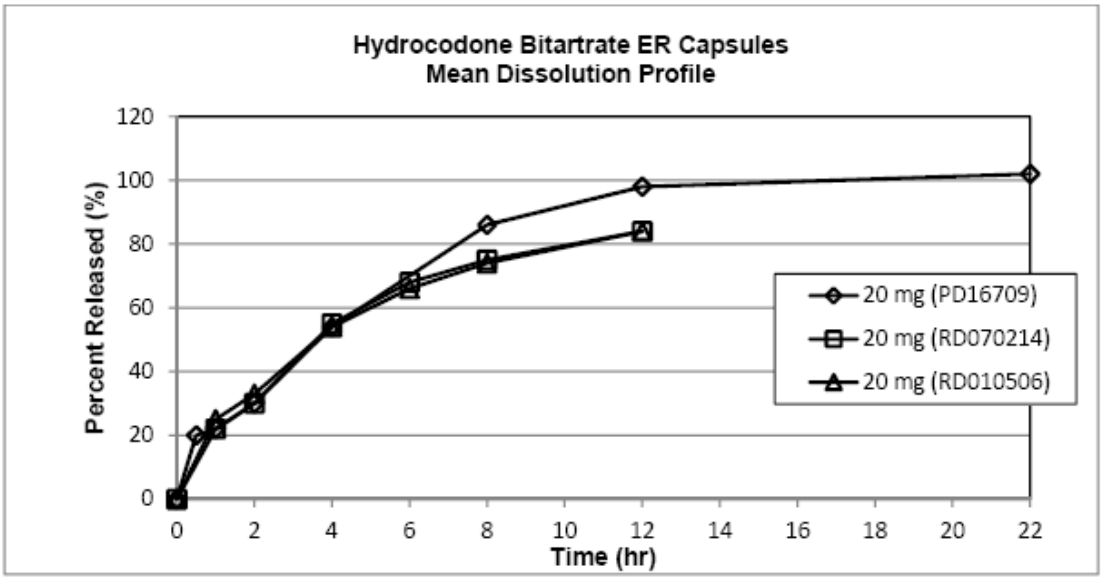
(1) Hydrocodone bitartrate is a Biopharmaceutics Classification System Class I, highly soluble, highly permeable substance.
(2) All dosage strengths are (b) (4) differing only in (b) (4) /capsule size.
(3) All dosage strengths have the same release mechanism and are manufactured using the same type of equipment and the same process at the same manufacturing site, and have the same release specifications.
(4) Safety and efficacy with HC-ER (dosage strengths of 10, 20, 30, 40, and/or 50 mg administered orally q12h up to a maximum daily dose of 200 mg) have been demonstrated in a Phase 3 efficacy study (ZX002-0801), and in a Phase 3 safety study (Study ZX002-0802) in which the upper dose was not limited. Overall, more than 1500 patients have been exposed to HC-ER in the clinical development program.
(5) A Phase 1 study (ZX002-1102) evaluating the PK profile of hydrocodone after a single dose of HC-ER 30 mg relative to two consecutive doses of two tablets of Vicoprofen (7.5 mg hydrocodone bitartrate/200 mg ibuprofen) administered 6 hours apart is ongoing - This study has been conducted and submitted
(6) Dose proportionality has been demonstrated for this ER drug product up to a 50 mg dose (Section 1.12.15.1 of this document).
(7) *In vitro* dissolution profiles of all strengths are similar, which indicates that the absorption profile is expected to be similar.
(8) Presence of a predictive Level A IVIVC.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Study ELN-0302002 was a Phase 1, open-label, randomized, two-dose, two-period cross-over study with minimum 7 day washout between treatments. The study was conducted in 12 healthy subjects between 19 and 33 years of age who received a single oral dose of 20 mg HC-ER capsule fasted for at least 10 hours prior to dosing and a single oral dose of 20 mg HC-ER capsule fed 30 minutes prior to dosing and dosed within 5 minutes of consuming the high-fat meal. All subjects remained fasted for at least four hours post dosing. The capsules were administered with 240 mL of water. Blood samples were taken at pre-dose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 30, and 36 h postdose.

It is noted that this study utilized a formulation from "Athlone manufacturing site" rather than "Gainesville manufacturing site," the designated to-be-marketed manufacturing site. This study was also labeled as a 'pilot' study. The applicant claimed that formulations from the two different sites are similar based on dissolution profiles and IVIVC analysis. Biopharmaceutics Team, ONDQA is evaluating the IVIVC information and will report the findings. Briefly, the Applicant presented the dissolution profiles comparing the Athlone and Gainsville formulations (Figure 48), and stated that the dissolution profiles are similar between the two formulations.

Figure 48. Dissolution Profiles Comparing Manufacturing Sites and Scales, HC-ER in Buffer, Lots PD16709 (Athlone, Smaller Scale), RD070214 (Gainesville, Smaller Scale), RD010506 (Gainesville, Larger Scale)



With respect to the 20-mg tested strength, it is also noted that during the End-of-Phase-2 Meeting conducted on June 4, 2008, the Agency conveyed to the Applicant that food effect information obtained with 20-mg strength may suffice if a dose-linearity is demonstrated up to 80-mg strength. In the current Application, however, the highest

proposed dose-strength is 50 mg, as the Applicant (b) (4) Nevertheless, the information obtained using 20-mg strength is acceptable since the Applicant has provided dose-linearity information up to 50-mg dose (40-mg single and multiple dose PKs and 50-mg dose using population PKs and dissolution).

Mean hydrocodone and hydromorphone concentration profiles (Figures 49 and 50, respectively) from the food effect study are presented below.

Figure 49. Mean hydrocodone concentration profiles from the food effect study

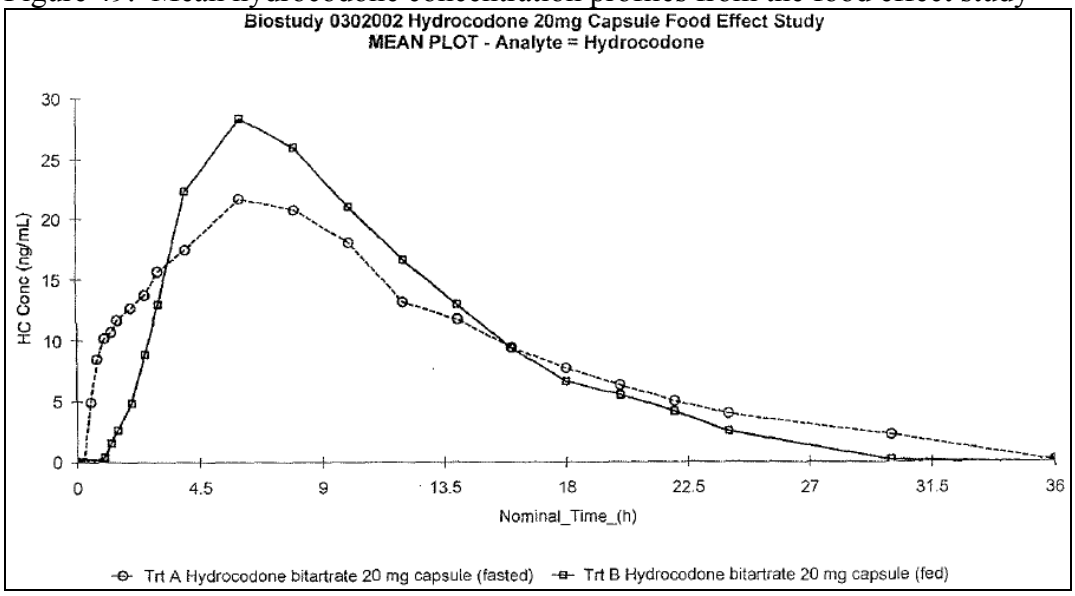
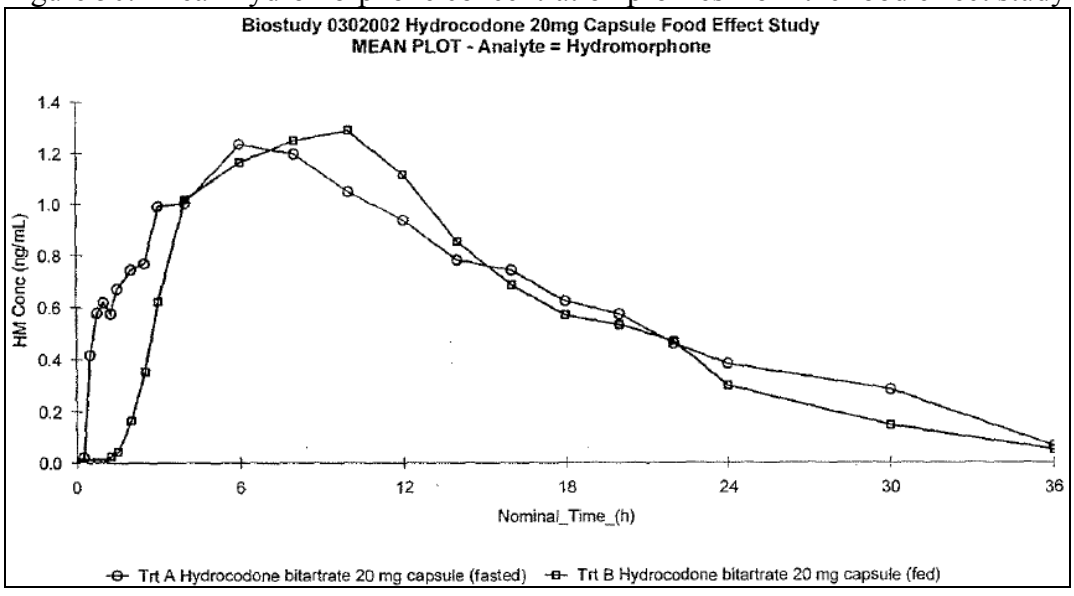


Figure 50. Mean hydromorphone concentration profiles from the food effect study



Mean hydrocodone and hydromorphone parameters (Table 34 and 35, respectively) are presented below from the food effect study.

Table 34. Mean hydrocodone parameters from the food effect study

PK Parameters	Trt A HCER hydrocodone bitartrate 20 mg capsule (fasted) PO *N=12*	Trt B HCER hydrocodone bitartrate 20 mg capsule (fed) PO *N=12*
Relative Bioavailability AUCinf (%)	-	99.96 ± 9.57*
%CV	-	9.6
Relative Bioavailability AUClast (%)	-	101.74 ± 11.74
%CV	-	11.5
AUCinf (ng/mL.h)	345.01 ± 36.74*	338.43 ± 55.00
%CV	10.6	16.3
AUClast (ng/mL.h)	311.94 ± 45.57	316.14 ± 53.75
%CV	14.6	17.0
Cmax (ng/mL)	22.74 ± 4.31	28.76 ± 4.16
%CV	19.0	14.5
tmax (h)	7.01 ± 1.35	6.34 ± 0.78
%CV	19.2	12.3
Median	8.00	6.01
Range	4.00-8.02	5.99-8.01
thalf (h)	6.48 ± 0.86*	4.94 ± 1.07
%CV	13.3	21.7
Lambda_z (h^{-1})	0.11 ± 0.01*	0.15 ± 0.03
%CV	12.9	21.3

*=n11

Table 35. Mean hydromorphone parameters from the food effect study

PK Parameters	Trt A HCER hydrocodone bitartrate 20 mg capsule (fasted) PO *N=12*	Trt B HCER hydrocodone bitartrate 20 mg capsule (fed) PO *N=12*
AUClast (ng/mL.h)	21.32 ± 6.18	19.74 ± 8.89
%CV	29.0	45.1
Cmax (ng/mL)	1.29 ± 0.35	1.39 ± 0.57
%CV	27.0	41.0
tmax (h)	7.09 ± 2.15	8.50 ± 2.28
%CV	30.4	26.8
Median	7.01	9.01
Range	3.01-12.01	4.00-12.00

Mean hydrocodone Cmax values were 28.8 ± 4.2 ng/mL and 22.7 ± 4.3 ng/mL in fed and fasted states, respectively, after a single dose 20 mg HC-ER post administration. Mean hydrocodone Cmax increased approximately 27% in the fed state compared to the fasted state. However, the extent of absorption (AUC) of hydrocodone was similar between fed and fasted (338 ± 55 ng.h/mL vs. 345 ± 37 ng.h/mL, respectively). The hydrocodone median Tmax were 6 h and 8 h for fasted and fed, respectively. The hydrocodone half-lives were 4.9 ± 1 h and 6.5 ± 0.9 h for fed and fasted states, respectively. The hydromorphone Cmax and AUC values appear similar between fasted and fed states.

With respect to utilizing the information obtained from this study in the Label despite the fact that food study was conducted with Athlone formulation, a discussion was carried out in the Office of Clinical Pharmacology (OCP) Briefing held on January 11, 2013. It was concluded in the meeting that the information obtained from this study was acceptable and should be included in the Label based on the fact that 1) formulation between Athlone and Gainsville manufacturing (to-be-marketed formulation) sites are exactly the same, except for the differences in the polymer coating, (b) (4) and (b) (4)%, respective, and, that the differences are deemed not to be significant to alter the exposure; and, 2) all strengths, 10 to 50 mg, manufactured from Gainsville manufacturing site are used in clinical studies, including Phase 3 study, ZX002-0801, such that performance aspect of the formulation is not in question. Additionally, comparison of Cmax across Phase 1 studies indicated, with a caveat that this is a cross-study comparison, that Athlone and Gainsville formulations are not drastically different when 'fasted' treatment from Food study is compared to other 'fasted' treatments, or 'fed' treatment from Food study is compared to other 'fed' treatments as presented below (Table 36). Therefore, it is concluded that two formulations performed similarly, and, that the food effect information obtain from using the Athlone manufacturing site is acceptable. No additional information may be required at this moment regarding food effect on HC-ER formulation.

Table 36. Cross study comparison of Cmax values from Phase 1 studies

Study	20 mg dose Cmax (ng/mL)		Comment – Single dose Normal subjects
	Mean	Range	
Food study	28.8 ± 4.16	-	Fed
	22.7 ± 4.31	-	Fasted
Osteoarthritis	21.6 ± 4.16	16 - 32	Fed; Day 1 Cmax value
Hepatic	22.1 ± 3.36	-	Fasted
Renal	18.5 ± 4.43	-	Fasted
Bunionectomy	17.9 ± 5.85	10 - 27	Fasted

2.5.4 How do the dissolution conditions and specifications assure in vivo performance and quality of the product, especially for 50-mg dose?

The clinical PK studies evaluated doses up to 50 mg strength (alcohol interaction study). Additionally the pivotal Phase 3 study, ZX002-0801 and a long-tern, open-label, safety study, ZX002-0802, utilized 50-mg dose strength. According to the population PK analysis (reviewed by Dr. Joo-Yeon Lee; see Appendix 4.3) HC-ER exhibited dose linear PK up to a dose of 50-mg. In addition, the Applicant presented dissolution profiles comparing 10 to 50 mg dose strengths and data indicated (two different lots per dose strength) that all strengths released hydrocodone at a similar rate (Figures 51 and 52), although the final assessment will be conducted by the Biopharmaceutics Team, ONDQA.

Figure 51. Dissolution Profiles of 10 mg, 20 mg, 30 mg, 40 mg and 50 mg HC-ER in Buffer (pH 6.8), Lots RD070216, RD070214, RD070215, RD070217 and RD031003

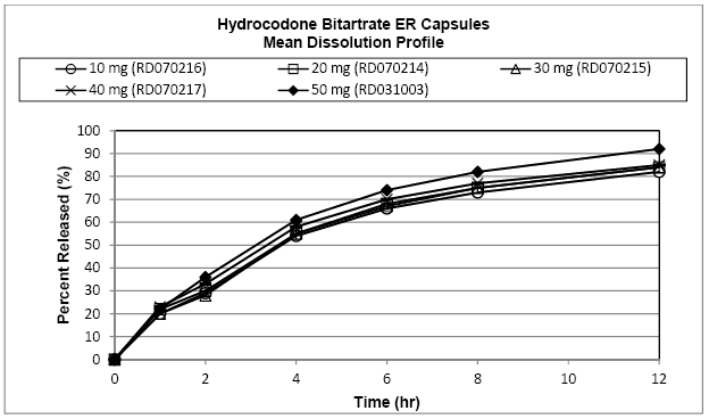
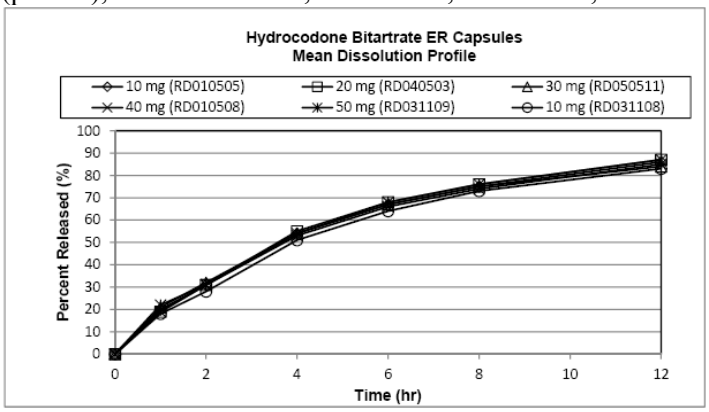


Figure 52. Dissolution Profiles of 10 mg, 20 mg, 30 mg, 40 mg and 50 mg HC-ER in Buffer (pH 6.8), Lots RD010505, RD040503, RD050511, RD010508, RD031109 and RD031108



2.6 Analytical Section

2.6.1 How are hydrocodone and its metabolites measured in plasma?

Liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method was developed and validated to quantify hydrocodone, hydromorphone, and norhydrocodone

in human plasma and urine. Typical plasma and urine analytical assay values are presented below (Tables 37 and 38, respectively).

Table 37. Plasma bioanalytical method and validation summary

Attribute	Hydrocodone	Hydromorphone	Norhydrocodone
Analytical Method: Covance Test Method 2100-360 HCHP (for all analytes)			
Method Description	Protein precipitaton followed by LC-MS/MS using turbo-ion spray		
Internal Standard	Hydrocodone- D6	Hydromorphone- D3	Norhydrocodone- D3
QC Standard Concentrations (ng/mL)	LQC: 0.300 MQC: 5.00 HQC: 75.0	LQC: 0.300 MQC: 5.00 HQC: 75.0	LQC: 0.300 MQC: 5.00 HQC: 75.0
Metabolite Determination	MRM transitions *m/z* 300.3 → 199.1	MRM transitions *m/z* 286.0 → 185.2	MRM transitions *m/z* 286.0 → 199.2
Standard Determination	MRM transitions *m/z* 306.3 → 202.1	MRM transitions *m/z* 289.1 → 185.3	MRM transitions *m/z* 289.1 → 202.2
Validation Report 2100-360			
Linearity Standard Concentrations (ng/mL)	0.100, 0.200, 1.00, 5.00, 25.0, 50.0, 80.0, 100	0.100, 0.200, 1.00, 5.00, 25.0, 50.0, 80.0, 100	0.100, 0.200, 1.00, 5.00, 25.0, 50.0, 80.0, 100
Linear Range (ng/mL)	0.100 - 100	0.100 - 100	0.100 - 100
Correlation Coefficient	0.9962 to 0.9984	0.9956 to 0.9998	0.9974 to 0.9993
LLOQ (ng/mL)	0.100	0.100	0.100
Accuracy: Standard (all batches)	0.100 ng/ml: 100.0% 0.200 ng/ml: 99.5% 1.00 ng/ml: 101.0% 5.00 ng/ml: 103.8% 25.0 ng/ml: 100.8% 50.0 ng/ml: 101.0% 80.0 ng/ml: 93.0% 100 ng/ml: 101.0%	0.100 ng/ml: 100.0% 0.200 ng/ml: 99.0% 1.00 ng/ml: 99.1% 5.00 ng/ml: 97.8% 25.0 ng/ml: 102.4% 50.0 ng/ml: 102.4% 80.0 ng/ml: 102.9% 100 ng/ml: 95.7%	0.100 ng/ml: 96.4% 0.200 ng/ml: 106.5% 1.00 ng/ml: 105.0% 5.00 ng/ml: 99.8% 25.0 ng/ml: 97.6% 50.0 ng/ml: 97.0% 80.0 ng/ml: 99.3% 100 ng/ml: 98.9%
Intra-assay Accuracy range (% of nominal)	LQC: 99.7% - 100.0% MQC: 100.0% - 103.2% HQC: 93.1% - 102.3%	LQC: 96.3% - 94.0% MQC: 98.8% - 105.4% HQC: 97.4% - 100.0%	LQC: 96.0% - 107.0% MQC: 101.8% - 104.2% HQC: 99.8% - 100.3%
Intra-assay Precision range (% RSD)	LQC: 5.8% - 6.7% MQC: 3.4% - 7.1% HQC: 4.4% - 5.9%	LQC: 3.8% - 4.8% MQC: 2.0% - 8.0% HQC: 4.5% - 6.8%	LQC: 4.0% - 4.9% MQC: 2.3% - 3.9% HQC: 4.8% - 7.3%
Inter-assay Mean Accuracy (% of nominal)	LQC : 100.0% MQC: 102.2% HQC: 97.9%	LQC : 101.0% MQC: 102.2% HQC: 98.7%	LQC : 101.3% MQC: 102.8% HQC: 99.7%
Inter-assay Precision (% RSD)	LQC : 5.7% MQC: 5.4% HQC: 6.3%	LQC : 5.3% MQC: 6.1% HQC: 5.4%	LQC : 6.2% MQC: 2.9% HQC: 6.1%
Recovery of analyte from human plasma (% of target)	LQC: 116.3% MQC: 143.6% HQC: 126.2%	LQC: 121.1% MQC: 120.7% HQC: 112.9%	LQC: 116.3% MQC: 143.6% HQC: 126.2%
Recovery of standard from human plasma (% of target)	LQC: 119.6% MQC: 150.8% HQC: 119.6%	LQC: 114.4% MQC: 124.7% HQC: 112.9%	LQC: 119.6% MQC: 150.8% HQC: 119.6%
Specificity	No interference between analytes or internal standard (all)	No interference between analytes or internal standard (all)	No interference between analytes or internal standard (all)
Stability (solutions, standards and samples)			
Freeze and Thaw	5 cycles at -20 and -70 degrees C (all analytes)		
Short-Term Stability	At least 24 hours at room temperature (all analytes)		
Long-Term Stability	At least 109 days at both -20 and -70 degrees C (all analytes)		

LLOQ = Lower limit of quantitation; LOD = Limit of Detection; mL = milliliter; ng = nanogram; QC = quality control

Table 38. Urine bioanalytical method and validation summary

Attribute	Hydrocodone	Hydromorphone	Norhydrocodone
Analytical Method: Covance Test Method 82410-51 HYBHUP (for all analytes)			
Method Description	Supported Liquid extraction followed by LC-MS/MS using turbo-ion spray		
Internal Standard	Hydrocodone-D6	Hydromorphone-D3	Norhydrocodone-D3
QC Standard Concentrations (ng/mL)	LQC: 0.300 MQC: 10.0 HQC: 80.0	LQC: 3.00 MQC: 100 HQC: 800	LQC: 0.300 MQC: 10.0 HQC: 80.0
Metabolite Determination	MRM transitions *m/z* 300.3 → 199.1	MRM transitions *m/z* 286.0 → 185.2	MRM transitions *m/z* 286.0 → 199.2
Standard Determination	MRM transitions *m/z* 306.3 → 202.1	MRM transitions *m/z* 289.0 → 185.3	MRM transitions *m/z* 289.1 → 202.2
Validation Report 82410-51			
Standard Concentrations (ng/mL)	0.100, 0.200, 1.00, 5.00, 25.0, 50.0, 85.0, 100	1.00, 2.00, 10.0, 50.0, 250, 500, 850, 1000	0.100, 0.200, 1.00, 5.00, 25.0, 50.0, 80.0, 100
Linear Range (ng/mL)	0.100 - 100	1.00 - 1000	0.100 - 100
Correlation Coefficient	0.9964 to 0.9995	0.9962 to 0.9993	0.9983 to 0.9996
LLOQ (ng/mL)	0.100	1.00	0.100
Accuracy: Standard (all batches)	0.100 ng/ml: 101.0% 0.200 ng/ml: 98.5% 1.00 ng/ml: 97.5% 5.00 ng/ml: 103.2% 25.0 ng/ml: 101.6% 50.0 ng/ml: 97.8% 85.0 ng/ml: 99.9% 100 ng/ml: 100.0%	1.00 ng/ml: 99.3% 2.00 ng/ml: 101.0% 10.0 ng/ml: 102.0% 50.0 ng/ml: 104.4% 250 ng/ml: 102.8% 500 ng/ml: 98.6% 800 ng/ml: 100.0% 1000 ng/ml: 91.9%	0.100 ng/ml: 103.0% 0.200 ng/ml: 94.0% 1.00 ng/ml: 97.7% 5.00 ng/ml: 104.8% 25.0 ng/ml: 102.4% 50.0 ng/ml: 99.4% 80.0 ng/ml: 99.1% 100 ng/ml: 99.1%
Intra-assay Accuracy range (% of nominal)	LQC: 101.0% - 108.7% MQC: 109.0% - 111.0% HQC: 103.0% - 105.8%	LQC: 101.7% - 104.7% MQC: 104.0% - 109.0% HQC: 98.9% - 101.0%	LQC: 102.3% - 107.0% MQC: 107.0% - 108.0% HQC: 102.0% - 103.5%
Intra-assay Precision range (% RSD)	LQC: 2.8% - 4.2% MQC: 0.9% - 1.8% HQC: 1.2% - 2.4%	LQC: 4.0% - 5.6% MQC: 1.7% - 3.6% HQC: 1.0% - 2.2%	LQC: 1.9% - 3.5% MQC: 1.8% - 3.0% HQC: 1.3% - 3.5%
Inter-assay Mean Accuracy (% of nominal)	LQC : 104.7% MQC: 110.0% HQC: 104.4%	LQC : 102.7% MQC: 106.0% HQC: 100.0%	LQC : 105.3% MQC: 108.0% HQC: 102.6%
Inter-assay Precision (% RSD)	LQC : 4.5% MQC: 1.4% HQC: 2.1%	LQC : 4.6% MQC: 3.4% HQC: 1.7%	LQC : 3.5% MQC: 2.5% HQC: 2.5%
Recovery of analyte from human urine (% of target)	LQC: 80.5% MQC: 77.9% HQC: 78.5%	LQC: 110.3% MQC: 118.6% HQC: 119.4%	LQC: 71.8% MQC: 70.6% HQC: 75.2%
Recovery of standard from human urine (% of target)	LQC: 83.2% MQC: 85.0% HQC: 85.5%	LQC: 114.6% MQC: 115.5% HQC: 119.5%	LQC: 73.3% MQC: 71.8% HQC: 76.8%
Specificity	No interference between analytes or internal standard (all)	No interference between analytes or internal standard (all)	No interference between analytes or internal standard (all)
Stability (solutions, standards and samples)			
Freeze and Thaw	5 cycles at -20 and -70 degrees C (all analytes)		
Short-Term Stability	At least 24 hours at room temperature (all analytes) At least 72 hours at 2 to 8 degrees C (all standards) At least 6 hours at room temperature (all standards)		
Long-Term Stability	At least 98 days at both -10 to -30 degrees C (all analytes)		

LLOQ = Lower limit of quantitation; mL = milliliter; ng = nanogram; QC = quality control

3 Detailed Labeling Recommendations

There are changes recommended for the Clinical Pharmacology section of the label, as below. The package insert is modified by strikeouts of the existing texts and addition of new texts, in RED fonts, where appropriate.

(b) (4)

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

4.2 Individual study review – Not applicable

4.3 Consult Review (including Pharmacometric Reviews)

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OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1. Summary of Findings
1.1 Key Review Questions
1.1.1 Is the labeling claim of dose proportionality of Hydrocodone Bitartrate ER (hereafter HC-ER) reasonable?

Yes, the fact that a linear elimination model was able to describe the observed data supports the conclusions from previous two Phase II studies (ELN154088-201, ELN154088-203) regarding the dose proportionality of hydrocodone PK.

2 Pertinent regulatory background

The dose proportionality of HC-ER has been examined in two Phase 2 studies: ELN154088-201 and ELN154088-203. The results of both studies support that the PK of HC-ER is not dependent on dose. In ELN154088-203, the increase in hydrocodone PK exposure was linearly dose proportional over the entire dose range of 10 to 40 mg.
The primary aim of population PK analysis was to characterize the PK of hydrocodone following the administration of HC-ER in a broad range of subjects and to determine if the PK of HC-ER was dose proportional over the entire dose range (up to 50 mg) by incorporating richer data than the previous studies.

3 Results of Sponsor's Analysis

The data from four Elan studies, two Phase 1 (ELN-0901001 and ELN-0302002) and two Phase 2 (ELN154088-201 and ELN154088-203), and three Phase 1 Zogenix studies (ZX002-0901, ZX002-1001, and ZX002-1002) were included in the population PK analyses.
The primary assessment of dose proportionality was based on the structure of the final population model. If a linear mechanism of drug elimination was adequate to obtain an acceptable fit of the data, the PK of hydrocodone was considered to be dose proportional. If a nonlinear mechanism of drug elimination (i.e., concentration-dependent clearance) was required to obtain an adequate fit of the data, the PK of hydrocodone was considered to not follow dose proportionality.

The most robust fit to the data was obtained using a two-compartment model with linear elimination and a complex absorption model. The absorption model involved two sequential first-order absorption processes with the delay in the first process accomplished by means of multiple transit compartments. Inter-individual variability was estimated for absorption rate constants, apparent oral total clearance, and apparent oral volume of the central compartment. Models incorporating concentration-dependent

clearance failed to provide an improvement in fit over those with linear clearance. The forward selection of covariates resulted in two statistically significant relationships: 1) between CLcr and apparent oral clearance (CL/F) and 2) between BSA and apparent oral volume of distribution (Vc/F). Table 1 presents the parameter estimates from the sponsor's final model.

Table 1. The parameter estimates from the sponsor's final population PK model.

errors

Parameter[a]	Population mean		Magnitude of interindividual variability (%CV)	
	Final estimate	%SEM	Final estimate	%SEM
CL/F (L/hr)	64.4	2.25	32.4[a]	10.1
Vc/F (L)	714	2.83	30.2[a]	12.1
K_{a1} (hr^{-1})	2.27	15.5	115	18.3
Lag (hr)	2.39	1.53	NE	NA
F1	0.382	3.61	NE	NA
K_{a2} (hr^{-1})	0.434	6.31	31.8	32.6
Vp/F	151	34.8	NE	NA
CLd/F	0.910	18.2	NE	NA
K_{tr} (hr^{-1})	8.52	10.9	81.7	21.3
Coefficient of power relationship between CLcr and CL/F	0.223	12.9	NE	NA
Coefficient of power relationship between BSA and Vc/F	0.486	23.9	NE	NA
Residual variability (SD)	0.112	15.4	NE	NA
Minimum value of the objective function = -13978				

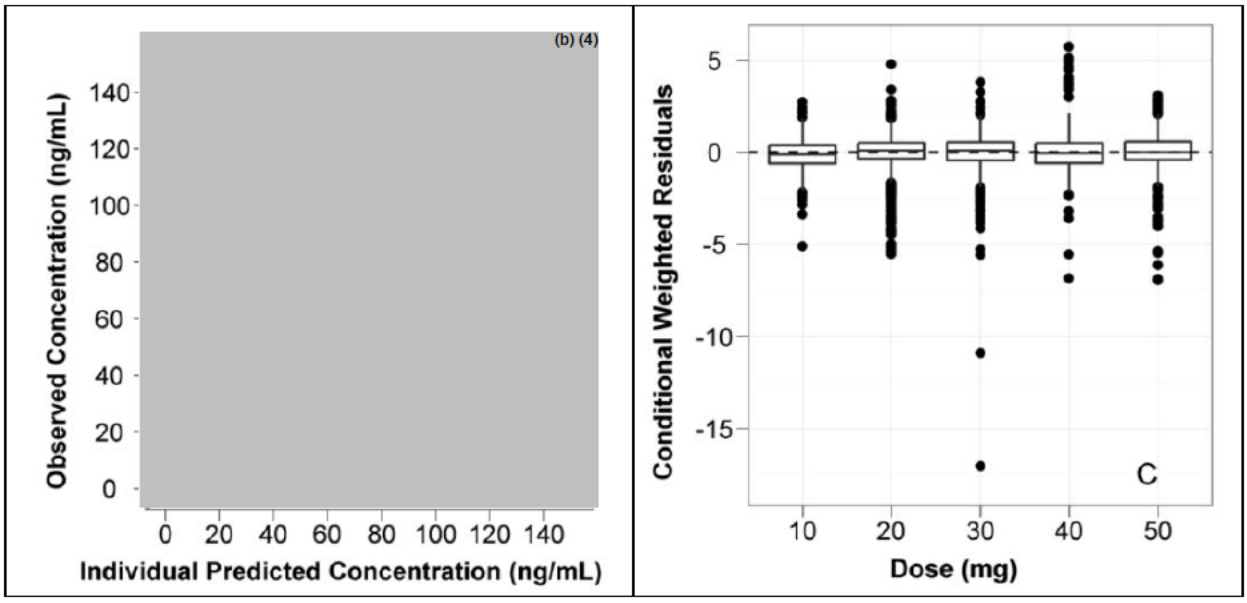
a. Covariance between IIV CL/F and IIV Vc/F= 0.0780

Source: the sponsor's report, page 49

As shown in Figure 1 there were no trends for bias in the fit of the model when evaluated by dose administered, supporting the robustness of the linear elimination model and the dose proportionality of hydrocodone PK.
Given that the highest dose of HC-ER (50 mg) was only administered in the study ZX002-0901, the use of population PK methods allowed a more direct examination of the potential for dose-dependent PK up to a dose of 50 mg.

In conclusion, the fact that a linear elimination model provided an excellent fit to the observed data supports conclusions from previous studies of HC-ER regarding the dose proportionality of hydrocodone PK. Furthermore, it suggests that the range of dose proportional PK can be extended up to HC-ER doses of 50 mg.

Figure 1. The model diagnostics plots: The left panel shows observed vs. predicted concentration: The right panel is conditional weighted residuals by dose which shows no specific trend.



Source: the sponsor's report, page 51-52.

4 Reviewer's Analysis

The reviewer did not conduct the independent analysis of the data since the sponsor's analysis method and conclusion are acceptable.

==========

4.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information			**Information**
NDA/BLA Number	**202880**	**Brand Name**		**Zohydro Capsules**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**		**Hydrocodone bitartrate ER capsules**
Medical Division	**DAAAP**	**Drug Class**		**Opioid**
OCP Reviewer	**David Lee, Ph.D.**	**Indication(s)**		**Analgesia**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**		**10, 15, 20, 30, 40 and 50 mg capsules**
Pharmacometrics Reviewer	-	**Dosing Regimen**		**BID**
Date of Submission	**May 1, 2012**	**Route of Administration**		**Oral**
Estimated Due Date of OCP Review	**January 1, 2013**	**Sponsor**		**Zogenix, Inc.**
Medical Division Due Date	**February 1, 2013**	**Priority Classification**		**Standard**
PDUFA Due Date	**March 1, 2013**			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**

STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**	**1**		**Formulation selection study**
multiple dose:				
Patients-				
single dose:	**x**	**1**		
multiple dose:	**x**	**1**		
Dose proportionality -				
fasting / non-fasting single dose:	**x**			**Part of single dose**
fasting / non-fasting multiple dose:	**x**			**Part of multiple dose**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**x**	**1**		
hepatic impairment:	**x**	**1**		
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**x**	**1**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**x**	**1**		
Bioequivalence studies -				
traditional design; single / multi dose:				**Sponsor requests a biowaiver.**
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**1**		
Bio-waiver request based on BCS	**x**			**Waiver request for 15 mg**
BCS class				
In vivo alcohol induced dose-dumping	**x**	**1**		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**			**Deferral (7-(b)(4) yrs) and waiver (0-7 yrs)**
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			All of the studies are conducted with the TBM, except food effect study; this will be a review issue
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			Sponsor requests a biowaiver for 15 mg strength.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			

14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____yes___

If the NDA/BLA is not fileable from the clinical pharmacology 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.

---

1. This NDA is recommended for filing from a clinical pharmacology perspective.

2. You need to submit the relative bioavailability study with Vicoprofen as soon as the study report is ready to allow sufficient review time.

3. The food effect study was conducted using the Athlone formulation. You stated that the Athlone formulation and the proposed commercial formulation (Gainesville formulation) are equivalent based on the *in vitro* dissolution, Level A IVIVC, and the successful inclusion of PK data from the study conducted with

Athlone and Gainesville formulations. The adequacy of the food effect data will be a review issue.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Zogenix, Inc. submitted a New Drug Application (NDA) for Hydrocodone Bitartrate Extended-Release (HC-ER) Capsules under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The Applicant has developed a single-entity, extended-release formulation (HC-ER) for the management of moderate-to-severe pain in patients requiring continuous around-the-clock opioid therapy for an extended period of time. The proposed dosage strengths of HC-ER are 10, 15, 20, 30, 40, and 50 mg. The HC-ER capsules will be administered twice daily based on a Spheroidal Drug Absorption System (SODAS®) drug delivery technology from Alkermes, Inc.

The listed drug is Vicoprofen (hydrocodone bitartrate/ibuprofen) Tablets (7.5 mg/200 mg), NDA 20-716. For this 505(b)(2) NDA submission, the Applicant is currently conducting a relative bioavailability study using Vicoprofen Tablets. During the pre-NDA meeting, it was agreed that the Applicant can submit the relative bioavailability study when the results become available.

Additionally, the following studies are submitted in the NDA: ELN-901001 (a pilot study to select a formulation); ELN-302002 (Food Effect Study); ZX002-0901 (alcohol interaction); ZX002-1001(hepatic impairment); ZX002-1002 (renal impairment); ELN-154088-201 (Phase 2 Safety/efficacy/PK); ELN-154088-203 (Open label multi-dose safety/efficacy/PK); ZX002-0801 (Pivotal Safety & Efficacy); and, ZX002-0802 (Long-term chronic safety). Information on the bioanalytical methods appear to be adequately presented in the submission. The food effect study was conducted using the Athlone formulation, prior to moving the manufacturing site to Gainesville (proposed commercial formulation). The Applicant stated that the two formulations are equivalent based on the in vitro dissolution, Level A IVIVC, and the successful inclusion of PK data from the study conducted with Athlone and Gainesville formulations. The adequacy of the food effect data will be a review issue.

Conclusion:

From a clinical pharmacology perspective, the application is recommended for filing. However, the results from Study ZX002-1102, a relative bioavailability study comparing HC-ER to Vicoprofen, need to be submitted as soon as information is available.

APPEARS THIS WAY ON ORIGINAL.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID J LEE
01/15/2013

JOO YEON LEE
01/15/2013

VENKATESH A BHATTARAM
01/15/2013

YUN XU
01/15/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**202880**	**Brand Name**	**Zohydro Capsules**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Hydrocodone bitartrate ER capsules**
Medical Division	**DAAAP**	**Drug Class**	**Opioid**
OCP Reviewer	**David Lee, Ph.D.**	**Indication(s)**	**Analgesia**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**10, 15, 20, 30, 40 and 50 mg capsules**
Pharmacometrics Reviewer	**-**	**Dosing Regimen**	**BID**
Date of Submission	**May 1, 2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**January 1, 2013**	**Sponsor**	**Zogenix, Inc.**
Medical Division Due Date	**February 1, 2013**	**Priority Classification**	**Standard**
PDUFA Due Date	**March 1, 2013**		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**	**1**		**Formulation selection study**
multiple dose:				
Patients-				
single dose:	**x**	**1**		
multiple dose:	**x**	**1**		
Dose proportionality -				
fasting / non-fasting single dose:	**x**			**Part of single dose**
fasting / non-fasting multiple dose:	**x**			**Part of multiple dose**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**x**	**1**		
hepatic impairment:	**x**	**1**		
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Population Analyses -				
Data rich:				
Data sparse:	**x**	**1**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**x**	**1**		
Bioequivalence studies -				
traditional design; single / multi dose:				**Sponsor requests a biowaiver.**
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**1**		
Bio-waiver request based on BCS	**x**			**Waiver request for 15 mg**
BCS class				
In vivo alcohol induced dose-dumping	**x**	**1**		
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**			**Deferral (7-(b)(4) yrs) and waiver (0-7 yrs)**
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	**x**			All of the studies are conducted with the TBM, except food effect study; this will be a review issue
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			Sponsor requests a biowaiver for 15 mg strength.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____yes___

If the NDA/BLA is not fileable from the clinical pharmacology 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.

---

1. This NDA is recommended for filing from a clinical pharmacology perspective.

2. You need to submit the relative bioavailability study with Vicoprofen as soon as the study report is ready to allow sufficient review time.

3. The food effect study was conducted using the Athlone formulation. You stated that the Athlone formulation and the proposed commercial formulation (Gainesville formulation) are equivalent based on the *in vitro* dissolution, Level A IVIVC, and the successful inclusion of PK data from the study conducted with Athlone and Gainesville formulations. The adequacy of the food effect data will be a review issue.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Zogenix, Inc. submitted a New Drug Application (NDA) for Hydrocodone Bitartrate Extended-Release (HC-ER) Capsules under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The Applicant has developed a single-entity, extended-release formulation (HC-ER) for the management of moderate-to-severe pain in patients requiring continuous around-the-clock opioid therapy for an extended period of time. The proposed dosage strengths of HC-ER are 10, 15, 20, 30, 40, and 50 mg. The HC-ER capsules will be administered twice daily based on a Spheroidal Drug Absorption System (SODAS®) drug delivery technology from Alkermes, Inc.

The listed drug is Vicoprofen (hydrocodone bitartrate/ibuprofen) Tablets (7.5 mg/200 mg), NDA 20-716. For this 505(b)(2) NDA submission, the Applicant is currently conducting a relative bioavailability study using Vicoprofen Tablets. During the pre-NDA meeting, it was agreed that the Applicant can submit the relative bioavailability study when the results become available.

Additionally, the following studies are submitted in the NDA: ELN-901001 (a pilot study to select a formulation); ELN-302002 (Food Effect Study); ZX002-0901 (alcohol interaction); ZX002-1001(hepatic impairment); ZX002-1002 (renal impairment); ELN-154088-201 (Phase 2 Safety/efficacy/PK); ELN-154088-203 (Open label multi-dose safety/efficacy/PK); ZX002-0801 (Pivotal Safety & Efficacy); and, ZX002-0802 (Long-term chronic safety). Information on the bioanalytical methods appear to be adequately presented in the submission. The food effect study was conducted using the Athlone formulation, prior to moving the manufacturing site to Gainesville (proposed commercial formulation). The Applicant stated that the two formulations are equivalent based on the in vitro dissolution, Level A IVIVC, and the successful inclusion of PK data from the study conducted with Athlone and Gainesville formulations. The adequacy of the food effect data will be a review issue.

Conclusion:

From a clinical pharmacology perspective, the application is recommended for filing. However, the results from Study ZX002-1102, a relative bioavailability study comparing HC-ER to Vicoprofen, need to be submitted as soon as information is available.

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/s/

DAVID J LEE
06/18/2012

YUN XU
06/18/2012

BIOPHARMACEUTICS FILING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-880	**Reviewer:** Akm Khairuzzaman, Ph.D.	
Submission Date:	05/01/2012		
Division:	Division of Antiviral Products	**Team Leader:** Angelica Dorantes, Ph.D.	
Sponsor:	Zogenix, Inc. 5858 Horton Street, Emeryville, CA 94608		
Trade Name:	Not proposed	**Date Assigned:**	05/20/2012
Generic Name:	Hydrocodone Bitartrate Extended Release (HC-ER) Capsule	**Date of Review:**	06/14/2012
Indication:	Pain management	**Type of Submission:** Original NDA 505(b)2	
Formulation/strengths	Capsule/ 10 mg, 15 mg, 20 mg, 30 mg, 40 mg and 50 mg		
Route of Administration	Oral		

SUBMISSION: This NDA is submitted under the Section 505(b)(2) of the Food, Drug and Cosmetic Act. The drug product contains a controlled drug substance namely, hydrocodone which is a semisynthetic opoid (narcotic) derived from either of two naturally occurring opiates: codine and thebine. The drug is well known in the pain management treatment for a long period of time and was actually first approved by the agency on March 23rd, 1943 with a brand name of Hycodan (NDA # 005213)[1]. The NDA was submitted using the electronic common technical (eCTD) format. The reference listed drug product used under this NDA is Vicoprofen Tablet (7.5 mg/200 mg), NDA 20-716.

It is to be noted, that although this drug has been in the market for a long time, it exists as a combination drug product with another drug. The drug product being developed by this Applicant is a sustained release formulation (bead coating technology) of hydrocodone only and its formulation includes a combination of immediate release beads (IR) and sustained release beads in a capsule at a ratio of 20:80. The beads are filled into the capsule (b) (4) the different strengths.

BIOPHARMACEUTIC INFORMATION: In support of its approval, this NDA includes the following biopharmaceutics data for review and evaluation:

- Proposed dissolution method and acceptance criteria, with justification
- Dissolution method development report
- Dissolution method validation report
- Comparative dissolution data
- Drug product stability data, including multi-point sampling data.
- In vitro alcohol dose dumping potential study followed by an in vivo study (study # ZX002-0901)
- A biowaver request is present in the NDA for the 15 mg strength

[1] Drugs@FDA—Approval History: Hycodan. FDA. Retrieved 2006-01-07.

- PK data to support extended release claim
- IVIVC to support biowaver and future changes pertain to SUPAC-MR (Scale-Up and Post Approval Changes)

It is to be noted that all major biopharmaceutics related information such as IVIVC, dissolution method development and method validation, dissolution limits, and dissolution data on stability are submitted in a DMF – (b) (4) A check list of all biopharmaceutics related information is provided in the appendix A.

RECOMMENDATION: From a biopharmaceutics perspective, the NDA is considered fileable. There are sufficient biopharmaceutics data to permit a substantive review.

Akm Khairuzzaman, Ph.D.
Product Quality Reviewer, ONDQA

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader, ONDQA

APPENDIX A: BIOPHARMACEUTICS				
	Parameter			**Comment**
1.	Is the QTPP (Quality Target Product Profile) defined for drug release? (3.2.P.2)	**Yes** ☒	**No** ☐	A list of QTTP has been provided which includes target PK profile. The drug products quality attributes included Dissolution.
2.	Has the risk assessment been performed to evaluate the criticality of the in vitro release? (3.2.P.2/3.2.P.5)	**Yes** ☒	**No** ☐	
3.	Is there any manufacturing parameter evaluated using in vitro release as an end point?	**Yes** ☒	**No** ☐	
4.	Is there any design space proposed using in vitro release as an end point?	**Yes** ☐	**No** ☒	
5.	Is the control strategy related to in vitro drug release? (3.2.P.2/3.2.P.5)	**Yes** ☐	**No** ☐	
6.	Solubility (3.2.S.1)	**High** ☒	**Low** ☐	
7.	Permeability (2.7.1)	**High** ☐	**Low** ☐	**Not Reported** ☒
8.	BCS Class	**I** ☐ **II** ☐	**III** ☐ **IV** ☐	Unknown
9.	Is the study report included for the development of the in vitro release method? (3.2.P.2/3.2.P.5)	**Yes** ☒	**No** ☐	The dissolution method development report is provided in DMF- (b) (4)
10.	In the study report, are the individual data, the mean, the standard deviation and the plots provided?	**Yes** ☒	**No** ☐	
11.	Has the discriminating ability been shown for the in vitro release methodology using formulation variants? (3.2.P.2/3.2.P.5)	**Yes** ☒	**No** ☐	
12.	Is the justification provided for the acceptance criteria of the in vitro release? (3.2.P.2/3.2.P.5)	**Yes** ☒	**No** ☐	.
13.	Are the proposed acceptance criteria adequate? (3.2.P.5)	**Yes** ☒	**No** ☐	Acceptance criteria appear to be reasonable. However, it requires further review in order to make a final decision
14.	Is the to-be-marketed formulation the same as that used in pivotal clinical trials?	**Yes** ☐	**No** ☒	The proposed commercial formulation (identified as Formulation 4 in application) was used for all of the clinical studies, following the initial phase I pharmacokinetic studies
15.	Are all the to-be-marked strengths used in the pivotal clinical trials?	**Yes** ☐	**No** ☒	For 15 mg strength there is a biowaver request in the application
16.	Have any biowaivers been requested? (1.12/2.7.1)	**Yes** ☒	**No** ☐	
17.	Is there any IVIVC information submitted? (5.3.1)	**Yes** ☒	**No** ☐	
18.	If the IVIVC information presented, are the study report and data provided?	**Yes** ☒	**No** ☐	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AKM KHAIRUZZAMAN
06/15/2012
This NDA is fileable from Biopharmaceutics point of view.

ANGELICA DORANTES
06/17/2012