CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206627Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 206627	NDA Supplement #: S- Not applicable (n/a)	Efficacy Supplement Type SE- n/a
Proprietary Name: Hysingla ER Established/Proper Name: Hydrocodone bitartrate Dosage Form: extended-release tablets Strengths: 20, 30, 40, 60, 80, 100, and 120 mg		
Applicant: Purdue Pharma LP		
Date of Receipt: April 28, 2014		
PDUFA Goal Date: October 28, 2014	Action Goal Date (if different): Nov 20, 2014	
RPM: Dominic Chiapperino, PhD, DAAAP		
Proposed Indication(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Vicoprofen, NDA 20716	*FDA's previous finding of safety and effectiveness (clinical)*

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant conducted BA/BE study comparing Hysingla ER to the listed drug, Vicoprofen.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Vicoprofen	20716	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

Hysingla ER is for chronic pain, is an extended-release oral tablet formulation for once-daily dosing, and has abuse-deterrent properties, whereas the listed product, Vicoprofen, is an immediate-release tablet for acute pain, and not intended to be an abuse-deterrent formulation.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☒

*If this application relies only on non product-specific published literature, answer **"N/A"***

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): Zohydro ER (hydrocodone bitartarte) extended-release capsules, 10, 15, 20, 30, 40, and 50 mg, 12-hour dosing, i.e., twice-daily [NDA 202880]

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 6348216 (expires 6/10/17) and 6599531 (expires 6/10/17)

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be

infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
Paragraph IV certification applies for both of the above patents, #6348216 and #6599531.

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): *6348216 and 6599531*
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): July 8, 2014

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note *that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information* ***UNLESS*** *the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☒ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

DOMINIC CHIAPPERINO
11/20/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 206627
Product Name: Hysingla ER (hydrocodone extended release tablets)

PMR/PMC Description: Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of Hysingla ER (hydrocodone extended release tablets) actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of Hysingla ER. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance, *Abuse-Deterrent Opioids—Evaluation and Labeling* (January 2013) and proposed comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	10/2015
Study/Trial Completion:	10/2019
Final Report Submission:	04/2020
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☒ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

This PMR requires marketing and use in the community over the long-term in order to assess whether the abuse-deterrent characteristics of Hysingla ER actually deter abuse of the product in "real world" use.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

FDA has determined that the sponsor must conduct individual post-marketing studies of Hysingla ER (hydrocodone extended release tablets) to assess the known serious risks of misuse, abuse, and their consequences, and in particular to assess whether the opioid antagonist properties of Hysingla ER that are intended to deter misuse and abuse actually result in a decrease in misuse and abuse and their consequences.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☒ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The design of the post-marketing study program for Hysingla ER must incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013) and must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of Hysingla ER. In particular, post-marketing studies for Hysingla ER must include individual assessments of all possible routes of abuse and must employ multiple appropriate comparators, including but not limited to 1) immediate and extended release formulations of hydrocodone and other opioid analgesics and 2) both products with and without properties intended to deter abuse. The study program must include geographically diverse populations that include both opioid-dependent and non-dependent individuals and must address all the abuse-related outcomes of interest: misuse, abuse, addiction, overdose, and death.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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

/s/

DOMINIC CHIAPPERINO
11/19/2014

JUDITH A RACOOSIN
11/19/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # Product Name:	ER/LA opioid analgesics, with the addition now of NDA 206627 for Hysingla ER

PMR/PMC Description: Conduct one or more studies to provide quantitative estimates of the risks of misuse, abuse, addiction, overdose and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

I. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

II. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	11/2014
	Study/Trial Completion:	01/2018
	Final Report Submission:	06/2018
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☒ Long-term data needed
☐ Only feasible to conduct post-approval

☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

In order to estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use long-term use of opioids for chronic pain, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  ☐ Accelerated Approval (subpart H/E)
  ☐ Animal Efficacy Rule
  ☐ Pediatric Research Equity Act
  ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  ☒ Assess a known serious risk related to the use of the drug?
  ☐ Assess signals of serious risk related to the use of the drug?
  ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The initial type of study that would be anticipated would be an epidemiological study in large databases to measure the incidences of the adverse outcomes listed above. However, the codes for these outcomes have not been validated. As such, validation studies are required prior to the epidemiological studies (see other PMRs). It may be determined, if the outcome codes do not validate well, that other types of studies or clinical trials are needed.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	ER/LA opioid analgesics, with the addition now of NDA 206627 for Hysingla ER
Product Name:	
PMR/PMC Description:	Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition) , which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	11/2014
	Study/Trial Completion:	08/2015
	Final Report Submission:	11/2015
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The data needed to validate measures of opioid-related adverse events would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

In order to conduct such a study, the outcomes need to be validated, including measures of opioid-related adverse events.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study would likely be conducted that includes identifying patients who fulfill a measure of the opioid-related adverse event, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the case definition.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # Product Name:	ER/LA opioid analgesics, with the addition now of NDA 206627 for Hysingla ER
PMR/PMC Description:	Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	11/2014
	Study/Trial Completion:	08/2015
	Final Report Submission:	11/2015
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The data needed to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the opioid-related adverse events: misuse, abuse, addiction, overdose, and death would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

In order to conduct such a study, the coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify opioid-related adverse events: misuse, abuse, addiction, overdose, and death need to be validated.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study would likely be conducted that includes identifying patients using coded medical terminologies (e.g., ICD9, ICD10, SNOMED) for opioid-related adverse events: misuse abuse, addiction, overdose, and death, and then conducting chart review or a similar activity to determine whether the identified patients actually meet the clinical definition.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # Product Name:	ER/LA opioid analgesics, with the addition now of NDA 206627 for Hysingla ER
PMR/PMC Description:	Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse, and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	11/2014
	Study/Trial Completion:	08/2015
	Final Report Submission:	11/2015
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☒ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

   The data needed to validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse, and/or addiction would optimally be drawn from a source that includes at least some patients who have been taking opioids long-term.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of important adverse effects of opioids, including misuse, abuse, addiction, overdose and death. The goal of the study is to determine those incidences, and identify risk factors for those outcomes.

   In order to conduct such a study, the outcomes need to be validated, including measures of "doctor/pharmacy shopping" which are suggestive of misuse, abuse, and/or addiction.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An observational study would likely be conducted that includes identifying patients who fulfill a measure of "doctor/pharmacy shopping", and then conducting chart review or a similar activity to determine whether the identified patients actually meet the case definition.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	ER/LA opioid analgesics, with the addition now of NDA 206627 for Hysingla ER
Product Name:	

PMR/PMC Description: Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	11/2014
	Study/Trial Completion:	08/2016
	Final Report Submission:	02/2017
	Other:	N/A

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

In order to estimate the risk for the development of hyperalgesia following use of opioid analgesics for at least one year, we must be able to access data from adequate numbers of patients who were treated long-term with opioids.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A recent review of the medical literature conducted by CDER staff indicates gaps in the understanding of the incidence of serious adverse effects of opioids, including hyperalgesia. The goal of the trial is to determine the risk of developing hyperalgesia.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial is needed to determine the risk of hyperalgesia following long-term treatment with opioids because this condition can be distinguished most easily with a randomized withdrawal design.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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

/s/

DOMINIC CHIAPPERINO
11/19/2014

JUDITH A RACOOSIN
11/19/2014

PMR/PMC Development Template

NDA 206627

PMR/PMC Description: Conduct a study to identify and quantify low molecular weight impurities in the (b) (4) polyethylene oxide (PEO) products used to manufacture Hysingla ER. Submit a toxicological risk assessment for the exposure to the impurities taking into consideration the maximum theoretical daily dose of Hysingla ER.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	N/A
Study Completion:	N/A
Final Report Submission:	06/2015
Other: N/A	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The excipient is in FDA-approved drug products, but the daily dose in this product is (b) (4) than any other FDA-approved drug product. Given the long history of use and the likelihood that most individuals will not reach the maximum theoretical daily dose, more definitive characterization of these impurities was considered acceptable to be completed in the postmarketing period.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Although the mean molecular weight of the polymer would restrict the material to the gastrointestinal tract, review of the existing distribution data suggest that 1% of the material is absorbed systemically. At the maximum daily dose, this would result in absorption of up to (b) (4) of material. These are likely lower molecular weight impurities that could include (b) (4) . Once identified, a toxicological risk assessment should be completed for the lower molecular weight impurities. The goal of the PMR is to identify the impurities and determine if potential toxicities related to the impurities warrant the need for specifications to control them, consistent with modern manufacturing quality control methods.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

- **Which regulation?**

  ☐ Accelerated Approval (subpart H/E)
  ☐ Animal Efficacy Rule
  ☐ Pediatric Research Equity Act
  ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

  ☐ Assess a known serious risk related to the use of the drug?
  ☐ Assess signals of serious risk related to the use of the drug?
  ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is a chemical analysis of the excipient. Once the impurities are identified, a toxicological risk assessment should be completed.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

NDA 206627

PMR/PMC Description: Conduct an embryo-fetal development study in the rat model to assess the potential impact of polyethylene oxide (PEO) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Hysingla ER when the product is consumed up to the maximum theoretical daily dose of Hysingla ER.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	02/2016
Study/Trial Completion:	08/2016
Final Report Submission:	02/2017
Other: N/A	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The excipient is in FDA-approved drug products, but the daily dose in this product is higher than any other FDA-approved drug products. Given the long history of use and the likelihood that most individuals will not reach the maximum theoretical daily dose, more definitive characterization of these impurities was considered acceptable to be completed in the postmarketing period.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Embryo-fetal developmental toxicology studies in two species (rat and rabbit models) are generally required to adequately inform the safety of any excipient. Although these studies were not required in the past based on standards at the time, the levels of absorbed material from this Drug Product will exceed that of any other FDA approved drug product. Embryo-fetal development studies are therefore warranted for this drug product. If adverse effects are noted, the labeling would be updated to reflect the added risk.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an in vivo embryo-fetal developmental toxicology study using the rat model.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

NDA 206627

PMR/PMC Description: Conduct an embryo-fetal development study in the rabbit model to assess the potential impact of polyethylene oxide (PEO) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Hysingla ER when the product is consumed up to the maximum theoretical daily dose of Hysingla ER.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	03/2016
	Study/Trial Completion:	12/2016
	Final Report Submission:	06/2017
	Other: N/A	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☒ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

The excipient is in FDA-approved drug products, but the daily dose in this product is higher than any other FDA-approved drug products. Given the long history of use and the likelihood that most individuals will not reach the maximum theoretical daily dose, more definitive characterization of these impurities was considered acceptable to be completed in the postmarketing period.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Embryo-fetal developmental toxicology studies in two species (rat and rabbit models) are generally required to adequately inform the safety of any excipient. Although these studies were not required in the past based on standards at the time, the levels of absorbed material from this Drug Product will exceed that of any other FDA approved drug product. Embryo-fetal development studies are therefore warranted for this drug product. If adverse effects are noted, the labeling would be updated to reflect the added risk.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

- **Which regulation?**

  ☐ Accelerated Approval (subpart H/E)
  ☐ Animal Efficacy Rule
  ☐ Pediatric Research Equity Act
  ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

  ☐ Assess a known serious risk related to the use of the drug?
  ☐ Assess signals of serious risk related to the use of the drug?
  ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an in vivo embryo-fetal developmental toxicology study using the rabbit model.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Description: Conduct a pre- and post-natal development study in the rat model to assess the potential impact of polyethylene oxide (PEO) on development. The study must be designed to adequately qualify the safety of the low molecular weight PEO components (impurities/degradants) in the PEO used to manufacture Hysingla ER when the product is consumed up to the maximum theoretical daily dose of Hysingla ER.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	04/2016
	Study/Trial Completion:	02/2017
	Final Report Submission:	08/2017
	Other: N/A	

6. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The excipient is in FDA-approved drug products, but the daily dose in this product is higher than any other FDA-approved drug products. Given the long history of use and the likelihood that most individuals will not reach the maximum theoretical daily dose, more definitive characterization of these impurities was considered acceptable to be completed in the postmarketing period.

7. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A peri- and post-natal developmental toxicology study is generally required to adequately inform the safety of any excipient. Although these studies were not required in the past based on standards at the time, the levels of absorbed material from this Drug Product will exceed that of any other FDA-approved drug product. Embryo-fetal development studies are therefore warranted for this drug product. If adverse effects are noted, the labeling would be updated to reflect the added risk.

8. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

- **Which regulation?**

  ☐ Accelerated Approval (subpart H/E)
  ☐ Animal Efficacy Rule
  ☐ Pediatric Research Equity Act
  ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

  ☐ Assess a known serious risk related to the use of the drug?
  ☐ Assess signals of serious risk related to the use of the drug?
  ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

9. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an in vivo peri-and post-natal developmental toxicology study using the rat model.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

10. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

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/s/

DOMINIC CHIAPPERINO
11/19/2014

JUDITH A RACOOSIN
11/19/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: NDA 206627/Hysingla ER (hydrocodone bitartrate) extended-release tablets

PMR Description: Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of Hysingla ER tablets in patients from ages 12 to less than 17 years with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

PMR Schedule Milestones:

Final Protocol Submission:	7/2015
Study/Trial Completion:	1/2019
Final Report Submission:	7/2019
Other: N/A	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

We are deferring submission of this required pediatric study (to evaluate the pharmacokinetics and safety of hydrocodone extended-release tablets in patients from ages 12 to less than 17 years) for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

To obtain adequate data to describe the dosing and safety of HYSINGLA ER tablets in pediatric patients from ages 12 to less than 17 years.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study must evaluate the pharmacokinetics and safety of hydrocodone extended-release tablets in patients from ages 12 to less than 17 years

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Pharmacokinetic and safety studies or clinical trials

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

DOMINIC CHIAPPERINO
11/19/2014

JUDITH A RACOOSIN
11/19/2014

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 29, 2014

To: Sharon H. Hertz, M.D., Acting Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: Martin S. Rusinowitz, M.D., Medical Officer
James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: NDA 206627, Hysingla ER (Hydrocodone Bitartrate q24h Film-coated) Tablets.
Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Dosages: 20, 30, 40, 60, 80, 100, and 120 mg hydrocodone bitartrate
Sponsor: Purdue Pharma L.P.

Materials reviewed: Hysingla ER Revised Label, October 20, 2014
Sponsor's Rationale for Retaining Oral Chewed Abuse Study Text, Sequence 0025, October 20, 2014
NDA 206627 CSS Memorandum to DAAAP, September 2, 2014
Analytical Sciences Report: AS-HYD-03/14 003 submitted with original NDA application

This memorandum is an addendum to the Controlled Substance Staff Review of NDA 206627, dated September 2, 2014. (See DARRTS, NDA 206627, Tolliver, James M, CSS Consult Review, 09/02/14) In this review, CSS recommended that:

"The language provided by Sponsor in Section 9.2 of the label for Hysingla ER tablets and pertaining to oral human abuse potential study HYD1013 should be removed from the label. Sponsor provided data showing that treatments of oral intact Hysingla ER 60 mg tablets and chewed Hysingla ER 60 mg tablets produced low scores (Emax) for Drug Liking VAS and Take Drug Again VAS compared to positive comparator of IR hydrocodone bitartrate. The Sponsor

did not include data for the additional treatment of oral milled Hysingla ER 60 mg tablet which produces high Emax of Drug Liking. The omission of these data in the label is understandable, because its inclusion will clearly instruct abusers on the best way to abuse Hysingla. The inclusion of the Emax for Drug Liking values solely for chewed Hysingla ER overstates the oral abuse deterrence properties of the formulation, and could erroneously provide a false sense of security understating the possibility of oral abuse and potential overdose."

On October 20, 2014, the Sponsor submitted a document entitled *Rationale for Retaining Oral Chewed Abuse Study Text* in support of the inclusion of the study results of the oral human abuse potential study (study HYD1013). Sponsor noted the difficulty in crushing Hysingla ER tablets using commonly available household tools. Sponsor showed that a one minute grinding time with one tablet using a Krups coffee grinder could produce a particle size of approximately 60% by weight < 1 mm. However, the coffee grinder was damaged in the process. The in vitro study report (Analytical Sciences Report AS-HYD-03/14 003) documented the cracking of lids on Krups coffee grinders when attempting to mill single Hysingla ER tablets. The more durable, laboratory grade grinder (b) (4)) was used to produce sufficient quantities of ground Hysingla ER (multiple Hysingla ER tablets ground for 1 minute) for use in the in vivo study HYD 1013 and the intranasal study HYD1014 (particle size: about 60% by weight < 1 mm and about 20% by weight < 355 µm). According to Sponsor, the laboratory grinder was selected to produce a similar particle size distribution to that produced by 1 minute grinding with Krup's coffee grinder.

According to Sponsor, the results of study HYD1013, demonstrated that Hysingla ER tablets resist abuse by chewing. Indeed, pharmacokinetic and pharmacodynamic results obtained in study HYD1013 indicate a low abuse potential associated with intentional chewing of Hysingla ER tablets.

The Sponsor also noted that oral abuse of Hysingla ER tablets need to be assessed in light of the difficulty associated with milling the product, as stated above. Results of study HYD 1013 demonstrate that ingestion of the milled Hysingla ER can produce increased hydrocodone blood levels and produce significant subjective reinforcing effects, relative to the intact Hysingla ER tablet. We agree that abuse of milled Hysingla ER is still possible. However, greater effort is needed to obtain milled Hysingla ER than a non-abuse deterrent formulation.

CONCLUSION

The Sponsor has adequately demonstrated that milling of Hysingla ER is difficult. Additionally, in vivo studies predict that intentional chewing is not likely to be a preferred route of abuse.

RECOMMENDATION

CSS agrees with the Sponsor's proposal to include Hysingla ER oral abuse potential study results regarding chewing into Section 9.2 of the label.

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/s/

MARTIN S RUSINOWITZ
10/29/2014

SILVIA N CALDERON
10/29/2014

JAMES M TOLLIVER
10/29/2014

MICHAEL KLEIN
10/29/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 24, 2014

TO: Jacqueline Spaulding, M.D., Clinical Reviewer
Ellen W. Fields, M.D., M.P.H, Clinical Team Leader
Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206627

APPLICANT: Purdue Pharma L.P.

DRUG: Hydrocodone Bitartrate q24h Film-coated Tablets

NME: No

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: The management of pain severe enough to require daily, around-the-

clock, long-term opioid treatment and for which alternative treatment options are inadequate.

CONSULTATION REQUEST DATE: June 3, 2014
CLINICAL INSPECTION SUMMARY GOAL DATE: August 7, 2014 (*delayed due to inspection observations at two of the four initial sites inspected and the need to inspect additional sites*)
DIVISION ACTION GOAL DATE: August 22, 2014 (*delayed due to discipline review and regulatory issues*)
PDUFA DATE: October 28, 2014

I. BACKGROUND

Purdue Pharma L.P. is seeking approval of hydrocodone bitartrate q24h film-coated tablets (HYD) in 20, 30, 40, 60, 80, 100, and 120 mg tablet strengths for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Inspections were requested for the following trials:

- **HYD3002** A Multicenter, Randomized, Double-blind, Placebo-controlled Study with an Open label Run-in to Assess the Efficacy and Safety of Hydrocodone Bitartrate (HYD) Tablets 20 to 120 mg Once Daily in Subjects With Moderate to Severe Chronic Low Back Pain

  This study was conducted at 94 study sites in the United States. The first subject was screened March 23, 2012 and the last subject visit was September 3, 2013. A total of 1927 subjects were enrolled into the study. Of these subjects, 905 subjects qualified for the run-in treatment period, 593 subjects were randomized into the double-blind treatment period and 588 subjects received double-blind treatments (292 randomized to placebo and 296 randomized to HYD). The primary efficacy variable was the mean pain intensity score based on the "average pain over the last 24 hours" scores for chronic low back pain (on an 11- point scale: 0=no pain to 10=pain as bad as you can imagine) recorded in the daily diaries, including all available scores recorded when the subject was on study drug during Week 12. The primary efficacy comparison of HYD vs placebo was based on mean pain intensity at Week 12 of the double-blind period.

- **HYD3003** An Open-label, Multicenter Study to Assess the Long-term Safety of Hydrocodone Bitartrate (HYD) Tablets 20 to 120 mg Once-daily in Subjects with Moderate to Severe Chronic Nonmalignant and Non-Neuropathic Pain

  This study was conducted at 88 study sites in the United States (93 sites screened subjects). The first subject was enrolled July 22, 2011 and the last subject visit was August 26, 2013. There were 1365 subjects enrolled, 922 subjects that entered the dose titration period and 728 subjects that entered the maintenance period. The primary objective was to assess the long-term safety of treatment with HYD 20 to 120 mg once daily in subjects with moderate to severe chronic nonmalignant and nonneuropathic pain. The efficacy assessments included assessments of pain intensity, impact of

treatment on quality of life, and treatment satisfaction.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 206627 in accordance with Compliance Program 7348.811. General instructions were also provided with this assignment.

NOTE: Four sites were initially inspected (b) (4) Therefore, inspections were expanded to four additional sites.

II. RESULTS (by Site):

Name of CI/ Site #	**Protocol # and # of Subjects Randomized**	**Inspection Dates**	**Pending Classification**
Louise Taber Site 0108A	HYD3002 33 Subjects HYD3003 56 Subjects	7/07- 7/18/2014	OAI - Final
Gary Dawson Site 2198A	HYD3002 32 subjects HYD3003 24 subjects	7/16-30/2014 8/04-05/2014	NAI
David Hassman Site 0608A	HYD3002 9 subjects HYD3003 29 subjects	6/25- 7/18/2014	VAI
Michael Harris Site 2059A	HYD3002 4 subjects HYD3003 16 subjects	7/29- 8/29/2014	(b) (5)
Steve Sitar Site 1175A	HYD3002 41 Subjects	9/25- 10/08/2014	VAI
Vrijendra Kumar Site 1194A	HYD3002 33 subjects HYD3003 41 subjects	10/14- 10/22/2014	NAI
Jared Barlow Site 2064A	HYD3002 13 subjects	10/09- 10/23/2014	NAI

	HYD3003 14 subjects		
Robert Buynak Site 2062A	HYD3002 6 subjects HYD3003 32 subjects	10/02- 10/09/2014	VAI

Key to Classifications

NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

1. Louise Taber
2525 W. Greenway Rd
Suite 114
Phoenix, AZ 85023

a. What was inspected: The inspection focused on informed consent documents, credentials and training, IRB correspondence and approvals, handling of lab samples, case report forms (CRFs), delegation of duties, 1572s, financial disclosures, monitoring logs, source documents, and drug accountability records. For Study HYD3002, 13 subject records had full review and three (3) subject records had partial review for audiometry information. For Study HYD3003, 19 subject records had full review.

b. General observations/commentary: Informed consent appeared to be performed as required. All reviewed subject files included initial informed consent on the date of the first visit. Informed consent forms were re-signed as approved; a few deviations from re-signing of the current version appeared to be appropriately reported. The (b) (4) Independent Review Board was the institutional review board (IRB) of record for both studies.

For Study HYD 3002, there were 109 subjects screened, 33 enrolled and 21 who completed the study. For Study HYD 3003, there were 79 subjects screened, 56 subjects enrolled, and 24 subjects who completed the study.

There was no under-reporting of adverse events noted for either study. Subject diaries were generally printed out at each visit and maintained with other source documents for both HYD 3002 and HYD 3003. Select printouts were compared to background and appeared to be accurate. There were some subjects during Study HYD3003 who

recorded their pain scores on paper during the DiaryPro malfunction (Subjects 3045026, 3045012, 3045033, and 3045042). There were multiple instances in Study HYD 3003 where study drug was dispensed manually due to problems with IVRS/IWRS. No issues with drug accountability were noted. It was noted that the site monitor wrote a memo stating that SitePro and DiaryPro was being accessed with the same passwords by multiple employees. This practice at the site has since stopped.

During the inspection, it was discovered that pure tone audiometry test data printouts obtained for the HYD3003 study were altered by blacking-out test dates and/or subject ID numbers and new subject ID numbers and/or dates were handwritten above the blacked-out data for five subjects (Subjects 3045013, 3045005, 3045011, 3045003, and 3045024). These altered printouts were filed with subjects' study records.

Subject ID	Study visit #	Date of study visit	Handwritten notation	Obscured notation/Subject ID	Date assessment data entered into database, if entered
3045013	3	Oct 7, 2011	V3 maintenance ... 3045013	Test Date: 10/31/2011...3045026	December 8, 2011*
	2	Sept 21, 2011	V2 Baseline ... 3045013	Test Date: 10/26/2011...3045026	December 8, 2011*
3045005	3	Sept 21, 2011	V3 maintenance ... 3045005 on 9/21/11	Test Date: 11/13/2011…3045016	December 8, 2011*
	2	Sept 6, 2011	V2 Baseline ... 3045005 on 9/6/11	Test Date: 11/18/2011...3045012	December 8, 2011*
3045011	3	Oct 13, 2011	... 3045011 V3 maintenance on	Test Date: 11/4/2011...3045015	-
	2	Sept 20, 2011	V2 Baseline on 9/20/11 3045011	11/8/2011...3045012	-
3045003	3	Sept 22, 2011	V3 maintenance ... 3045003 on 9/22/11	Test Date: 11/14/2011…3045040	December 8, 2011
	2	Aug 31, 2011	Pt. 3045003 ... 31AUG2011	10/20/2011...3045026	November 16, 2011
3045024	3	Oct 25, 2011	... 3045024 V3 maintenance on 10/25/11	Test Date: 11/12/2011…30450122	January 12, 2012*
	2	Oct 18, 2011	... 3045024 V2 Baseline on 10/18/11	11/4/2011...3045024	November 12, 2011

* data entered into database after query was opened to complete the assessment data.

In addition to the above examples, there were several source documents which contained blacked-out dates on the Visit 2 and/or Visit 3 audiometry printouts with a different date handwritten above the blacked-out date. Pictures of the altered records were taken by the FDA investigator. Of note, after March 2012, audiometry testing was no longer conducted at the site but done off-site by an audiologist.

For Study HYD3003, there were missing audiometry assessments for Subject 3045011 (end of study) and Subject 3045040 (end of study early termination). Review of the source documents show Dr. Taber's assessment of Visit 3 pure tone audiometry results for both subjects as "within normal limits" and then records show that Dr. Taber made late entry corrections up to several months after the supposed pure tone audiometry assessment. (Both of these V3 audiometry assessments had obscured data indicating the V3 tests were from other subjects).

The FDA investigator requested an affidavit of the findings. Dr. Taber stated in an affidavit that several study records contain blacked-out subject IDs and/or test dates

with handwritten subject IDs, subject initials, and/or test dates. Dr. Taber stated that the original printed data under the obscured areas can be viewed by holding the documents under the light and that the subject IDs and corresponding visit dates handwritten on specific pure tone audiometry test study records did not coincide with the obscured printed subject IDs and dates. Dr. Taber specifically identified each of the study records with the falsified information in her affidavit.

Dr. Taber further stated that the handwritten subject information appears to be written by the study coordinator. However, she also noted that the handwriting on both study records for Subject 3045013 and on the Visit 3 study record for Subject 3045011 appears to be hers.

Dr. Taber indicated in the affidavit that her understanding of why the information was obscured was that the sponsor did not want subject identifying information on source documents that they may need to review. Similarly, the previous study coordinator emailed the Director of Arizona Research Center on July 11, 2014 during the inspection and reported that the data was blacked out at the sponsor's request. She further stated that she would assume it was an error on her end when she was trying to make sure that they were all correct and that she had no idea that they were incorrect. However, the information redacted from the study records only contained subject IDs; subject initials were on the forms.

Review of eCRF data for the pure audiometry assessments shows that the pure audiometry data improperly assigned for Subjects 3045013, 3045005, 3045003, and 3045024, as well as for Subject 3045011, were submitted to the sponsor. Review of the files for NDA 206627 shows that the pure audiometry data improperly assigned for Subject 3045003 (Visits 2 and 3) and Subject 3045004 (Visits 2 and 3) were sent subsequently to the FDA.

For Study HYD3002, pure tone air conduction audiometry assessments for Subjects 2033030, 2033034, 2033037, 2033038, 2033043, and 2033044 were not performed at Visit 3 before randomization, but rather were performed late. The protocol indicated that Visit 3 pure tone audiometry assessments were required for subjects, who qualified to continue in the double-blind phase, and must be conducted prior to randomization (< 5 days prior to Visit 3). However, for these six subjects, this Visit 3 assessment was performed after randomization, between 20 and 32 days late.

Subject ID	Date of Visit 3 (Randomization)	Date of "Visit 3" Audiologic Assessment	# of days audiologic assessment was performed after randomization
2033030	September 6, 2012	October 4, 2012	28
2033034	September 18, 2012	October 11, 2012	23
2033037	August 31, 2012	October 2, 2012	32
2033038	August 31, 2012	October 2, 2012	32

2033043	September 12, 2012	October 2, 2012	20
2033044	September 24, 2012	November 6, 2012	43

Upon realization that these Visit 3 assessments were missed for Subjects 2033030, 2033034, 2033037, 2033038, 2033043, and 2033044, the study coordinator notified the sponsor (by email) on September 27, 2012. The sponsor advised to have these performed as soon as possible.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

2. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

OSI Reviewer Comment: Dr. Taber responded to the findings in a letter dated August 1, 2014. She stated that for Study HYD3003, there were numerous problems with the audiology system and, therefore, the test results were not immediately printed out. She also stated that the monitoring CRO told them to black-out the identifying information. (No communication of such instruction was seen during the inspection and none were submitted with the response).

Regarding the late and missing audiograms for Study HYD3002, Dr. Taber stated that the coordinator and she overlooked this protocol requirement.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. The audit indicates serious deviations/findings that would impact the validity and reliability of the submitted data. Based on the inspection findings, OSI recommends that data for pure-tone air conduction audiometry for Protocol HYD3003 for Subjects 3045003, 3045005, 3045011, 3045013, and 3045024 not be used in support of the application because pure-tone air-conduction audiometry reports that were represented as reports for these subjects were originally identified as reports for other subjects. Because these altered records were discovered in five out of 19 records reviewed, we cannot guarantee the accuracy of the remaining 14 audiometry reports for Study HYD3003. Furthermore, although there was no evidence found of other altered records, such actions bring into question the true accuracy of the data and the review division may consider doing separate analyses with the exclusion of all data from this site.

2. Gary N. Dawson, M.D.
5210 Armour Rd.
Suite 400
Columbus, GA 31904*

*Address is previous location where studies took place. New address: Columbus Regional Research Institute, 800 Talbotton Rd., Columbus, GA 31904

a. What was inspected: Records reviewed included staff credentials, licenses, 1572, financial disclosures, drug accountability logs, study enrollment/screening logs, consent forms, case report forms, source documents, sponsor correspondence, monitoring visit correspondence, institutional review board correspondence, and training records. All informed consents for 100% of subjects for both studies were reviewed. For study HYD3002, eight subject records were reviewed. For study HYD3003, seven subject records were reviewed. The ORA field investigator verified that subject demographics, randomization, concomitant medications, protocol deviations, adverse events, study completion, vitals, and pain intensity scores compared favorably to the sponsor supplied data line listings.

b. General observations/commentary: The (b) (4) IRB was the IRB of record for both studies. For study HYD3002, 87 subjects were screened, 32 subjects were enrolled, and 24 subjects completed the study. There was no under-reporting of adverse events and the primary efficacy data was verifiable.

For study HYD3003, 46 subjects were screened, 24 subjects enrolled, and 13 subjects completed the study. There was no under-reporting of adverse events and the primary efficacy data was verifiable.

The mean score calculation was not documented by the site on a source document or eCRF. The ORA field investigator verified the daily diary scores used to calculate the mean pain intensity for the efficacy endpoint.

Audiology testing was initially done at the site and then at (b) (4) .

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was available for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. David Hassman, D.O.
175 Cross Keys Rd.
Building 300B
Berlin, NJ 08009-9263

a. What was inspected: Records reviewed included the 1572s, financial

disclosures, delegation of duties, drug accountability logs, study enrollment/screening logs, consent forms, case report forms, source documents, sponsor correspondence, monitoring visit correspondence, institutional review board correspondence, laboratory credentials and training records. For Study HYD3002, records of nine subjects were reviewed for adherence to selected protocol requirements and data listing accuracy. For Study HYD3003, records of nine subjects were reviewed for adherence to selected protocol requirements and data listing accuracy. All subject records for both studies were reviewed for consent forms.

b. **General observations/commentary:** The (b) (4) Independent Review Board was the institutional review board (IRB) of record for both studies. The records were organized and legible. There was adequate oversight with Dr. Hassman's signature/initials on source records. There were a limited number of missing source documents (laboratory reports, central lab ECG interpretation, one SOAPR-R score) that the site had to find and retrieve.

For Study HYD3002, 23 subjects were screened, nine subjects were enrolled (excludes four run-in failures), and two subjects completed the study. There was no evidence of under-reporting of adverse events. The primary efficacy endpoint identified in the protocol is the mean weekly pain intensity calculated from the diary "average pain over the last 24 hours" score. The "average pain over the last 24 hours" was compared to the data line listings and there were no discrepancies.

For Study HYD3003, 31 subjects were screened, 29 subjects were enrolled, and 21 subjects completed the study. There were two adverse events reported in the source documents (firm generated site visit forms) that were not observed in the sponsor line listings. Subject 3041020 had a diagnosis of pneumonia from 11/29/-12/15/2012. (Levofloxacin used for treatment was also not listed in the concomitant medications list). Subject 3041029 complained of mild sleepiness documented from 7/15- 8/10/12. The "average pain over the last 24 hours" score was compared to the data listings provided. No significant discrepancies were noted.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the investigational plan.

   For several subjects in both trials, the audiology assessments were performed outside of the protocol window (≤ 5 days for HYD3002 and +/-7 days for HYD3003). For example, Subject 3041017 in Protocol HYD3003 had Visit #7 audiology assessment 33 days after the visit.

   For several subjects in both trials, visits occurred outside of the protocol visit windows. For example, Subject 2012020 in Protocol HYD3002 had

Visit #2 occur 20 days after the Screening Visit instead of the protocol required 14 days.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. Michael Harris, D.O.
1215 S. 1680 W.
Orem, UT 84058

a. What was inspected: For Study HYD 3002, all 12 subject records were reviewed for informed consent, adverse events and inclusion/exclusion criteria. Line listings were compared for each of the four enrolled subjects. For Study HYD 3003, all screened and enrolled subjects' records were reviewed for informed consent, adverse events and inclusion/exclusion criteria. Line listings were compared for 10 of the 16 subjects enrolled.

b. General observations/commentary: For Study HYD 3002, there were 12 subjects screened, four subjects enrolled and two subjects that completed the study. For Study HYD 3003, there were 30 subjects screened, 16 subjects enrolled and five subjects that completed the study.

The Clinical Investigator exhibited an overall lack of oversight and control over the studies, which was apparent in data collected and maintained by the site. There were numerous examples of inadequate records, which included the coordinators' and the investigators' progress notes being in conflict with each other. There were occasions in which progress notes, made by the clinical investigator, did not match events of the visit. Throughout the inspection for both studies, the site was deficient for record keeping; on multiple occasions the site had to request copies of documents from the monitors.

There was no apparent under-reporting of adverse events in either study. The primary efficacy endpoints were verifiable based upon subjects' e-diaries uploaded into the sponsor database.

There were multiple instances of failing to follow the protocol as well as multiple instances of failing to maintain adequate and accurate records across both studies HYD 3002 and HYD 3003. Furthermore, the site had submitted false information on both studies to their IRB with regards to the Investigator's inspectional history.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

    a. On two separate occasions, personnel from the clinical site submitted inaccurate/ incorrect information to the Institutional Review Board (IRB) regarding previous FDA inspectional history and issuance of a Form FDA-483. Although a Form FDA-483 had been received several months prior to the communications with the IRB, Dr. Harris denied ever receiving one.

    b. Subjects were dispensed the study's Investigational Product (IP) before the screening procedures were reviewed and signed-off by the principal investigator as required by the protocol.

    c. The subjects' Safety Evaluations were not reported to the Medical Monitor; specifically, Current Opioid Misuse Measure (COMM) scores ≥ 9. Notification of the Medical Monitor, when COMM ≥ 9, was necessary in order for the subject's continued participation in the study. This was observed in three of the fifteen COMM assessments reviewed for Study HYD 3002 and in four of the nineteen COMM assessments for Study HYD 3003.

2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

    a. Source documents were inconsistent and contradictory. For example, for Study HYD 3002, on 04/10/2012, Subject 2016001 was screened against the Inclusion/ Exclusion criteria. On 05/07/2012, the Clinical Coordinator Progress Notes document the subject's refusal of further audiological examinations. On 05/07/2012, the Clinical Investigator Progress Notes cite lack-of-efficacy and refusal of audiological examination during the run-in period. The subject was removed from the study on 05/07/2012. On 06/05/2012, the Clinical Investigator gave his final approval for the subject to be enrolled, randomized and dosed with the IP. For Study HYD 3003, on 05/14/2012, Subject 3021029 was screened and failed to meet two of the initial inclusion criteria. However, the Clinical Investigator signed-off on the inclusion/exclusion worksheet on 05/14/2012. His signature indicated his approval for the subject to continue to the next visit.

    b. Improper signature was applied to source documents. The principal investigator pre-signed blank delegation logs and progress reports. Other delegation logs and progress reports were dated with multiple different dates.

c. All study related documents were not maintained. For example, the site's regulatory files were missing four of the twenty-four Interim Monitor Visit (IMV) follow-up letters. Documentation of communication between the clinical site and the Medical Monitor regarding subjects with COMM scores ≥ 9 were not kept with the source documents.

d. Improper sign-off for determining subjects' eligibility based upon inclusion/ exclusion criteria. Specifically, for Subject 3021019, the principal investigator did not sign off on final screen-fail determination of inclusion/ exclusion criteria; the subject was screen failed by the clinical coordinator.

OSI Reviewer Comment: Dr. Harris submitted a response to the Form FDA-483 in a letter dated September 17, 2014. His response was inadequate in that it did not address all the issues noted and did not have adequate corrective actions put in place.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. The audit indicates serious deviations/findings that would impact the validity and reliability of the submitted data. As the data is considered unreliable, it is recommended that the review team consider doing sensitivity analyses with a set of plausible possibilities regarding the data from this site

5. Steve Sitar, M.D.
Orange County Research Institute
1801 W. Romneya Dr., Suite 409
Anaheim, CA 92801

a. What was inspected: The inspection focused on 100% review of informed consent documents, credentials and training, IRB correspondence and approvals, case report forms (CRFs), delegation of duties, 1572s, financial disclosures, monitoring logs, source documents, and drug accountability records. Review of adverse events and efficacy pain scores were limited to 14 subject charts.

b. **General observations/commentary:** There were 86 subjects screened, 41 subjects enrolled and 25 subjects who completed the study. There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data was verifiable. Drug accountability records were reviewed and significant deviations were not observed. ABC and COMM scores were reviewed for selected subjects and evidence of abuse or diversion was not observed.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the investigational plan.

   Some subjects were enrolled into the study although they had incomplete screening audiology tests or had test results that did not meet enrollment criteria. For example,
   - Subject 2043-002 had audiology screening assessment at baseline on 4/3/12 that indicated air conduction thresholds of 15 dB for the right ear at 2000 Hz and 4000 Hz. Bone conduction audiometry was not performed for those frequencies as required.
   - Subject 2043-025 had audiology screening assessment at baseline on 5/18/12 that indicated air conduction thresholds of 15 dB for the left ear at 250 Hz and for the right ear at 1000 Hz, 2000 Hz and 4000 Hz. Bone conduction audiometry was not performed for those frequencies as required.
   - Subject 2043-047 had audiology screening assessment (Visit 3) on 9/20/12 that indicated air conduction threshold of 15 dB for the left ear at 3000 Hz. Bone conduction audiometry was not performed for that frequency as required.
   - Subject 2043-066 was allowed to enroll although audiology tests on 2/18/13 indicated a threshold asymmetry exceeding 20 dB at 3000 Hz.

   The site monitor discovered the testing errors. There were a total of 34 subjects listed in a Note to File. The incidences were also reported to the medical monitor. After discussing with (b) (4) the sponsor's ENT consultant, the conclusion was that there was no safety risk that resulted from the errors but each instance needed to be captured as a protocol deviation. Dr. Sitar did report the audiology deviations to the IRB.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

6. Vrijendra Kumar, M.D.
Advanced Biomedical Research of America
8420 S. Eastern Ave, Suite 102
Las Vegas, NV 89123

a. What was inspected: The inspection focused on informed consent documents, credentials and training, IRB correspondence and approvals, inclusion/exclusion criteria, adverse event reporting, delegation of duties, 1572s, financial disclosures, monitoring logs, drug accountability records and source document comparison to data line listings. For Study HYD3002, 12 subject records had

full review. For Study HYD3003, 10 subject records had full review.

b. General observations/commentary: For Study HYD 3002, there were 86 subjects screened, 33 subjects enrolled and 23 subjects that completed the study. For Study HYD 3003, there were 72 subjects screened, 41 subjects enrolled and 11 subjects that completed the study.

The subject records were well organized, legible, and complete. The site staff was knowledgeable. There was no under reporting of adverse events. The primary efficacy endpoint data was verifiable for both studies.

During the inspection, it was noted that there was untimely reporting to the sponsor's medical monitor. For Study HYD3002, the protocol states that the medical monitor must be contacted at the time of occurrence if the Current Opioid Misuse Measure (COMM) score was ≥ 9 and/or if the Dizziness Handicap Inventory (DHI) score was ≥ 31. Review of subjects' records indicated that in several occurrences the medical monitor was not contacted at the time of subjects' visits associated with their out-of-range safety assessment scores. Examples are as follows:

Subject No.	Visit No./Date Occurred	Safety Assessment	Date Reported to Sponsor/CRO	Status/Remarks
2030712	V2 – Screening 6/25/12	COMM Score – 15	9/25/12	Run-In Failure
2037008	V2.3 – Dose Titration 7/6/12	DHI Score-50	9/13/12	Early Termination
2037014	V3 – Randomization 7/11/12	DHI Score - 46	10/18/12	Run-In Failure

Subject 2037015 end-of-study audiogram had a significant change from baseline in the high frequency range. The result was flagged by the audiologist 9/27/12 but was not sent to the medical monitor until 11/28/12 for further evaluation. The subject completed the study on 10/26/12.

Baseline (6/29/12)			End of Study (9/27/12)	
Frequency	Left Ear	Right Ear	Left Ear	Right Ear
14000	10	0	40	35
16000	30	30	40	35

For Study HYD3003, Subject 017 had a COMM Score of 10 during V5 (10/17/11), and the result was not reported to medical monitor. Subject was discontinued from the study on 4/2/12.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no significant objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

7. Jared Barlow, M.D.
Upstate Clinical Research Associates
8201 Main Street, Suite 1
Williamsville, NY 14221

a. What was inspected: The inspection focused on informed consent documents, IRB correspondence and approvals, inclusion/exclusion criteria, case report forms (CRFs), delegation of duties, 1572s, financial disclosures, monitoring logs, data transfer, and drug accountability records. Source documents were compared to data line listings. For Study HYD3002, 12 subject records had full review. For Study HYD3003, 12 subject records had full review.

b. General observations/commentary: For Study HYD 3002, there were 27 subjects screened, 13 subjects enrolled and 12 subjects that completed the study. For Study HYD 3003, there were 21 subjects screened, 14 subjects enrolled and 10 who completed the study. The site is under a site management organization (SMO) owned by a previous contract research monitor who hired the principal investigator and the sub-investigator. The IRB of record was (b) (4) IRB.

The site records were well-organized and legible. Source records contained documentation of all visits and communications with the subjects. The site has documented reasons for subject screen failures and for subject discontinuations. There was adequate oversight and monitoring of the site. There was no under-reporting of adverse events noted. The primary efficacy endpoints were primarily collected using electronic pads or diaries, which were then uploaded directly into a sponsor database. The information was not documented in the study records; however, the study site has a CD obtained from sponsor with the collected data. The primary efficacy endpoint data was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

8. Robert Buynak, M.D.
Buynak Clinical Research
55 University Drive, Suite 106
Valparaiso, IN 46383

a. What was inspected: The inspection focused on 100% review of informed consent documents, credentials and training, IRB correspondence and approvals, case report forms (CRFs), delegation of duties, 1572s, financial disclosures, monitoring logs, source documents, and drug accountability records. There was complete record review for seven subject charts for Study HYD3002 and for 10 subject charts for Study HYD3003.

b. **General observations/commentary:** For Study HYD3002, there were 17 subjects screened, six subjects enrolled, and six subjects that completed the study. There was no under-reporting of adverse events noted. The primary efficacy endpoint data was verifiable. For Study HYD 3003, there were 39 subjects screened, 32 subjects enrolled, and 17 subjects that completed the study. There was no under-reporting of adverse events noted. The primary efficacy endpoint data was verifiable. Some COMM scores were initially not reported but later found by the medical monitor.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the signed statement of the investigator.

Fifteen out of 30 subjects for Study HYD3003 and two out of six subjects for Study HYD3002 failed to receive bone conduction audiometry testing when air-conduction pure tone threshold audiometry results were 15 dB or higher at frequencies between 1000Hz-4000Hz. These tests were not conducted in accordance with the protocols.

Twenty-one out of 37 subjects participating in Study HYD3003 had visits out of window, some of which occurred on multiple occasions.

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of eight domestic clinical sites.

Observations noted above for Drs. Taber, Hassman and Dawson are based on the preliminary review of the Establishment Inspection Reports. Observations noted above for Drs. Sitar, Buynak, and Harris are based on communications from the field investigator and review of the Form FDA-483. Observations noted above for Drs. Barlow and Kumar are based on communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

Dr. **Taber** was issued a Form FDA-483 citing inspectional observations and field classification is Official Action Indicated (OAI). Furthermore, headquarters final classification for Dr. Taber is also OAI and a Warning Letter has been communicated. Audiology data from this site for Study HYD3003 are considered not reliable. Altered records were discovered at Dr. Taber's site in five out of 19 audiometry records reviewed for Study HYD3003, and, although there was no evidence found of other altered records, such actions bring into question the true accuracy of the data and the review division may want to consider doing separate analyses with the exclusion of all data from this site.

Dr. **Harris** was issued a Form FDA-483 citing inspectional observations and field classification is (b) (5) . Based on preliminary communications with the field investigator and Form FDA-483 violations, the audit at Dr. Harris' site indicates serious deviations/findings that would impact the validity and reliability of the submitted data for both studies. As the data is considered unreliable, it is recommended that the review team consider doing sensitivity analyses with a set of plausible possibilities regarding the data from this site

Drs. **Hassman**, **Sitar**, and **Buynak** were each issued a Form FDA-483, citing inspectional

observations and preliminary classifications for each of these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above for all sites inspected, they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from these sites is acceptable for use in support of the indication for this application.

Drs. **Dawson, Barlow and Kumar** were not issued a Form FDA 483; the classification for each is NAI (No Action Indicated). Data from these sites is considered reliable based on the available information.

In general, based on the inspections of the eight clinical sites, with the exclusion of the HYD3003 audiology data from the Taber site and all data from the Harris site (based on preliminary communications with the field and Form FDA 483), the inspectional findings of these sites support validity of data as reported by the Sponsor under this NDA.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

CYNTHIA F KLEPPINGER
10/24/2014

JANICE K POHLMAN
10/24/2014

KASSA AYALEW
10/24/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 22, 2014
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 206627
Product Name and Strength:	Hysingla ER (Hydrocodone bitartrate) Extended-release Tablets 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg
Submission Date:	October 21, 2014
Applicant/Sponsor Name:	Purdue Pharma
OSE RCM #:	2014-872-1
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Associate Director:	Irene Z. Chan, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container labels (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised container labels are acceptable from a medication error perspective.

[1] Schlick, J. Label and Labeling Review for Hysingla ER (NDA 206627). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 JUL 18. 8 p. OSE RCM No.: 2014-872

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

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/s/

JAMES H SCHLICK
10/22/2014

IRENE Z CHAN
10/22/2014

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 2, 2014

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team leader
Controlled Substance Staff

From: Martin S. Rusinowitz, M.D., Medical Officer
James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Hysingla ER (Hydrocodone Bitartrate q24h Film-coated) Tablets
Dosages, formulations, routes: 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg hydrocodone bitartrate per tablet for oral administration
NDA/IND Number(s): NDA 206-627, IND 59,175
Indication(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Sponsor: Purdue Pharma L.P.
PDUFA Goal Date: October 28, 2014

Materials Reviewed:

Materials reviewed include the following: Analytical Sciences Report AS-HYD-03/14 (Module 3.2.P.2), Oral Human Abuse Potential Study HYD1013 Report dated March 3, 2014 (Module 5.3.5.4), Intranasal Human Abuse Potential Study HYD1014 Report dated March 14, 2014 (Module 5.3.5.4), Relative Attractiveness Study HYD1015 Report dated March 6, 2013 (Module 5.3.5.4), the Label, and other parts of the NDA submission relevant to abuse potential and assessment of abuse deterrence.

Table of Contents

I. Summary

1. Background

This memorandum responds to a consult request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to evaluate the abuse liability studies and labeling claims submitted by Purdue Pharma L.P. in NDA 206-627 for Hysingla ER (Hydrocodone Bitartrate q24h Film-coated) Tablets. This product is formulated as an abuse deterrent product containing 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg hydrocodone bitartrate per tablet for oral administration. The product is indicated for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Hysingla ER tablets are formulated for oral administration once daily (every 24 hours). Starting dose Hysingla ER for patients who are not opioid tolerant is 20 mg per day. Higher starting doses can be given to opioid tolerant patients. A single dose of Hysingla ER greater than 80 mg, including 100 mg and 120 mg Hysingla ER, or a total daily dose greater than 80 mg are only for patients in whom tolerance to opioid of comparable potency is established.

Hysingla ER tablets is a single entity hydrocodone bitartrate, abuse deterrent product that has not previously been marketed anywhere world-wide. In the United States it was developed under IND 59,175. Hysingla ER tablets are in Schedule II under the federal Controlled Substances Act (CSA).

2. Conclusions

1. The overall results of the in vitro studies (Report AS-HYD-03/14 003) and human abuse potential studies (HYD1013 and HYD1014) indicate that the Hysingla ER formulation provides potential deterrence to abuse of Hysingla ER by chewing, snorting, smoking, and intravenous injection. Hysingla ER tablets are still susceptible to oral abuse (swallowing milled, cut, or intact tablet). Although Hysingla ER tablets are hard and therefore difficult to crush, they can be cut and milled using available tools.

2. The abuse deterrent features of Hysingla ER do not withstand milling. Milling of Hysingla ER tablets results in substantial compromise of the controlled release properties of the formulation as evident by increased rates of release of hydrocodone bitartrate in water (room temperature or elevated temperature) and other solvents. Results of dissolution studies and human abuse potential study HYD1013, in which Hysingla ER was administered as a powder directly to the oral cavity, indicate increased rates of release when milled Hysingla ER tablets are ingested. Thus, Hysingla ER tablets could be abused through the oral route, by milling the tablets and ingesting the resulting powder or by taking the resulting powder into water or any other solvent.
3. The Hysingla ER formulation includes polyethylene oxide (PEO) as a (b) (4) As such, it is expected that reduction in particle size (with concomitant increase in surface area) or exposure to heated solutions, such as water, will result in increased release of hydrocodone bitartrate.
4. Hysingla ER tablets are difficult to crush. Tools such as two spoons, pill crusher, mortar and pestle, hammer, food grater, foot file, and nutmeg shaver were not effective in reducing the particle size of the Hysingla ER tablets. Most effective tools were the Waring spice grinder and the Krups brand coffee grinder. Smallest particle sizes consisting of approximately 70% less than 1000 µm and about 20% less than 355 µm was achieved using the Krups coffee grinder. It was also possible to cut Hysingla ER tablets into various pieces using a knife. In contrast to Hysingla ER tablets, Vicodin tablets (10 mg hydrocodone bitartrate/325 mg acetaminophen) were effectively crushed to a fine powder using a mortar and pestle for 2 minutes.
5. Intact Hysingla ER tablets demonstrate a slow release of hydrocodone bitartrate in water at room temperature as evidenced by a mean percentage of label claim released from 120 mg tablets of 9.22% and 45.23% at 6 and 24 hours, respectively. Increasing water temperature to 95°C causes a modest increased rate of release as evidenced by 11.35% label claim (LC) released at 1 hour. (See Table 1 in Discussion)
6. Milling Hysingla ER 120 mg tablets with a Krups coffee grinder resulted in a substantial compromise of the controlled release properties of the drug product. Following milling, 68% LC of hydrocodone bitartrate was released into water at room temperature at 5 minutes, 77 % LC at 20 minutes and 85 % LC at 1 hour. (See Table 1 in Discussion)
7. When taking the milled tablets in water heated to 95°C, an even greater rate of release occurred, as evidenced by approximately 86% LC and 96% LC extracted in just 5 minutes and 20 minutes, respectively. (See Table 1 in Discussion) This data suggest that one way to abuse Hysingla ER tablets is to consume water containing crushed Hysingla ER tablets.
8. For extraction in water all dosage strengths (20, 30, 40, 60, 80, 100, and 120 mg hydrocodone bitartrate) of Hysingla ER were evaluated. There was little difference in extraction rate for hydrocodone bitartrate from all tablet strengths both intact and milled (data not shown), leading the Sponsor to conclude that extraction rate using water as solvent did not appear to be related to the hydrocodone bitartrate to PEO ratio as found in the formulation of Hysingla ER tablets.
9. Pretreatment by freezing or heating 120 mg Hysingla ER tablets did not change the release profile of hydrocodone bitartrate from milled tablets.
10. Qualitatively similar findings to using water as a solvent for extraction of hydrocodone bitartrate from Hysingla ER tablets (intact and milled) were observed using the solvents:

40% ethanol, saline, Coca-Cola, methanol, 100% ethanol, and buffers of pH 1, 3, 8, and 10. (See Tables 2, 3, and 4 in the Discussion) Solutions of 5% and 10% ethanol were not evaluated in this study. For the solvents tested, increasing temperature produced only modest increases in rates of hydrocodone bitartrate extraction. With milled tablets, rates of extraction were substantially increased as evidenced by extractions in 5 minutes. The most effective solvents as indicated by the highest rates of extraction were saline, Coca-Cola, and pH 1 buffer, each resulting in greater than 70% LC and 80% LC of hydrocodone bitartrate released within 5 minutes and 20 minutes, respectively, under heated conditions. Following just 5 minutes extraction at 25°C, the average %LC extracted was 42% in 40% ethanol. Elevation of solvent temperature further increased the average percentage extraction at 5 minutes to 48.3%. The least effective solvent was 100% ethanol in which less than 35% and 45% LC hydrocodone bitartrate was released from milled 120 mg Hysingla ER tablets with heat.

11. Dissolution analyses, simulating direct ingestion of whole, halved, quartered, sliced (120 pieces), and milled 120 mg Hysingla ER tablets, demonstrated progressive increased rates of hydrocodone bitartrate release with increased fractionation of the tablets. (See Table 14 in the Discussion) With 60 minutes of extraction, only modest increases in rate of extraction were observed for halved (10.75 %LC) and quartered 17.03% LC) tablets compared to intact tablet (4.34% LC). With sliced and milled tablets, release at 60 minutes was further increased to 75.88% LC and 67.69% LC, respectively. Results of this study indicate that direct oral administration of Hysingla ER manipulated to reduce particle size, and thereby increase total surface area, can result in increased exposure to hydrocodone bitartrate. As such, it is a possible means of abuse. In addition, the results suggest a possible safety risk (possible overdose) associated with administration of cut or milled Hysingla ER tablets when placed on food subsequently ingested. Clinical relevance of these in vitro findings are evident from human abuse potential study HYD 1013 in which direct oral administration of milled Hysingla ER 60 mg (not in solution) compared to intact Hysingla ER 60 mg produced a significantly higher maximum plasma concentration (Cmax) of hydrocodone (81.0 ng/mL versus 48.4 ng/mL) and shorter time to Cmax (1.55 hours versus 12.05 hours). This higher hydrocodone plasma level following oral administration of milled Hysingla ER was associated with a maximum visual analog scale (VAS) score of Drug Liking (Emax) (84.6) comparable to the Emax (85.9) achieved with positive control of immediate release (IR) hydrocodone 60 mg oral solution. (See Tables 20 and 22 of the Discussion).
12. Dissolution studies demonstrated that heat (oven temperatures ranging from 130°C to 170°C) exposure of single 120 mg Hysingla ER tablets caused increase rates of release of hydrocodone bitartrate, particularly following 2 to 12 hours of extraction. (See Table 5 in the Discussion). Highest rates were achieved at 130°C and 140°C for various times. For example, for HYD 120 mg tablets at 130° for 8 hours, over 90% LC was released by 8 hours, compared to only about 35% released from controlled HYD 120 mg tablets not exposed to heat. At dissolution of 20 minutes, regardless of the exposure temperature, the %LC of hydrocodone bitartrate was less than 4%. Of the three dosage strengths of Hysingla ER examined in this study (20 mg, 60 mg, and 120 mg), the largest increase in the %LC of hydrocodone bitartrate extracted following heating compared to control (no heat) were observed using the 120 mg strength.

13. Microwaving (1100 W) intact Hysingla tablets (20, 60, and 120 mg) at full power for 5 minutes did not alter the dissolution profile for hydrocodone bitartrate release. (See Table 6 in the Discussion)
14. Syringeability studies performed by Sponsor indicate that it will be difficult to manipulate Hysingla ER tablets (with or without heat) for intravenous injection. (See Tables 7, 9-13 in Discussion). Extraction times were 30 seconds and 5 minutes with continuous agitation. For water (2, 5, and 10 mL) held at room temperature or with initial boiling, the amounts of hydrocodone bitartrate extracted from a single milled or sliced (120 pieces) 120 mg Hysingla tablet was generally too low to produce solutions sufficiently concentrated to be effective at producing subjective reinforcing effects when intravenously injected[1]. A limited number of solutions aspirated using either an 18 gauge needle or a needle gauge in the range of 22-27 were sufficiently concentrated to possibly produce subjective reinforcing effects if more than one mL of solution was injected. Suitable injectable solutions were not produced using intact, halved, or quartered 120 mg Hysingla ER tablets in 5 mL of water.
15. Syringeability studies indicate that a single Vicodin (10 mg hydrocodone bitartrate/325 mg acetaminophen) tablet, in part due to low potency (10 mg hydrocodone bitartrate), most likely cannot be used to produce a suitable intravenous injection. With use of needles in the range of 22-27 gauge, it was difficult to aspirate the solutions (< 40% of volume recovered) resulting in low mean %LC of hydrocodone bitarate (< 34%LC). With use of an 18 gauge need %LC recovered was high (range of 65-91%) but resulting in a low concentration of hydrocodone. (See Table 8 in the Discussion)
16. Simulated smoking studies demonstrated that Hysingla ER tablets (20 mg. 60 mg. or 120 mg strengths) and Vicodin (10 mg hydrocodone bitartrate/325 mg acetaminophen) tablets cannot be directly abused by smoking. For both products, the amount of hydrocodone bitartrate recovered from vapor was very low (> 10% of LC). Sponsor did not examine the possible isolation of hydrocodone base for the products followed by examination for possible smoking.
17. Acid-base extraction of 120 mg Hysingla ER tablets for purposes of isolating hydrocodone base was not effective. With the technique used, only 15-17 mg of hydrocodone free base was obtained representing 20-23% recovery of the total base available in a 120 mg Hysingla ER tablet (74 mg). Recovered base purity was in the range of 18% to 21 %.
18. Liquid phase extraction was effective in isolating hydrocodone base from 120 mg Hysingla tablets in high purity. Use of ethyl acetate or toluene as solvents resulted in recovery of hydrocodone base in the range of 42 to 64 mg with a purity of greater than 89 %. (See Table 15 in the Discussion)
19. As demonstrated under study HYD1013, Hysingla ER 60 mg has a lower oral abuse potential when administered whole or chewed compared to IR hydrocodone bitartrate 60 mg in solution. That is, the primary endpoints of "at the moment" Drug Liking visual analog scale (VAS) and High VAS, were found to be statistically significant when Hysingla ER was administered as an intact or chewed pill as compared with the positive control.
20. Study HYD1013 further showed that oral administration of milled 60 mg Hysingla ER tablets is associated with significant levels of Drug Liking and High, thereby indicating a

[1] Stoop WW, Hatton KW, Lofwall MR, Nuzzo PA, and Walsh SL (2010). Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: abuse potential and relative potencies. Psychopharmacology, 212: 193-203.

potential for abuse of the milled product. The levels of Drug Liking and High for Hysingla ER 60 mg are very similar and only slightly lower than that produced by IR hydrocodone 60 mg solution.

21. In study HYD1013, the secondary endpoint of Take Drug Again VAS was similar for milled Hysingla ER 60 mg and IR hydrocodone 60 mg solution, while both were significantly higher than for placebo. This demonstrates a desire on the part of subjects, after considering the drug's positive and negative effects, to again take either milled Hysingla ER or IR hydrocodone solution. In contrast, Hysingla ER intact and chewed produced lower maximum level of Take Drug Again compared to either milled Hysingla ER or IR hydrocodone solution, but still greater than placebo.
22. Results of study HYD1014 indicate that Hysingla ER 60 mg has a lower intranasal abuse potential compared to hydrocodone bitartrate 60 mg. Intranasal administration of either fine (milled) or coarse (cut with razor blade) Hysingla ER 60 mg powder produced substantially lower levels of maximum Drug Liking and High when compared to hydrocodone bitartrate 60 mg powder but significantly higher levels when compared to placebo. Intranasal administration of finely milled Hysingla ER was associated with similar levels of Drug Liking and High compared to the intranasal administration of coarse Hysingla ER.
23. In study HYD1014, there were statistically significant differences in the secondary endpoint of Take Drug Again VAS. The Take Drug Again VAS was higher for Hysingla ER 60 mg than for placebo, but less than for hydrocodone 60 mg.
24. In an examination of nasal tolerability, intranasal administration of fine and coarse Hysingla ER 60 mg treatments were associated with greater negative intranasal effects, especially nasal congestion and irritation, compared to intranasal IR hydrocodone powder.

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

1. Both the in vitro studies and human abuse potential study HYD 1013 indicate that Hysingla ER tablets may be susceptible to oral abuse particularly when tablets are cut and milled. As such, oral abuse of Hysingla ER tablets should be the subject of post-marketing monitoring.
2. The language provided by Sponsor in Section 9.2 of the label for Hysingla ER tablets and pertaining to oral human abuse potential study HYD1013 should be removed from the label. Sponsor provided data showing that treatments of oral intact Hysingla ER 60 mg tablets and chewed Hysingla ER 60 mg tablets produced low scores (Emax) for Drug Liking VAS and Take Drug Again VAS compared to positive comparator of IR hydrocodone bitartrate. The Sponsor did not include data for the additional treatment of oral milled Hysingla ER 60 mg tablet which produces high Emax of Drug Liking. The omission of these data in the label is understandable, because its inclusion will clearly instruct abusers on the best way to abuse Hysingla. The inclusion of the Emax for Drug Liking values solely for chewed Hysingla ER overstates the oral abuse deterrence properties of the formulation, and could erroneously provide a false sense of security understating the possibility of oral abuse and potential overdose. The x-axis of Figure 1 in Section 9.2 of the label regarding the percentage reduction profile as generated in intranasal study HYD1014 should be modified by replacing ">100" by "≥100." This will necessitate a change to the curve in Figure 1. In addition, the label for the x-axis should be modified to read "Percent Reduction in Emax of Drug Liking

for Manipulated Hysingla ER vs. Powdered Hydrococone Following Intranasal Administration."

II. Discussion

1. Chemistry

1.1 Substance information

(b) (4)

(b) (4)

According to the Sponsor, the PEO in the Hysingla ER tablet formulation is intended to serve several functions including controlling the rate of release hydrocodone bitartrate, abuse-deterrence, and resistance to alcohol-induced dose dumping.

1.3 In vitro manipulation and extraction studies for products with Abuse-Deterrent features

Under Module 3.2.P.2 Sponsor submitted Analytical Sciences Report: AS-HYD-03/14 003 entitled "Assessment of In Vitro Abuse Deterrence for Hydrocodone Bitartrate q24h Film Coated Tablets (HYD): Summary of Physical and Chemical Manipulation Study Results." In these studies, Hysingla ER tablets were referred to as "HYD" tablets. In this review of the in vitro studies the approved product name (Hysingla ER) will be used.

According to the Sponsor, Hysingla ER tablets were designed and formulated to be resistant to chewing and physical crushing, exhibit gelling when attempts are made to extract hydrocodone in small volumes of aqueous solution thereby resisting extraction, and to retain its controlled release properties in the presence of ethanolic media (alcohol does not cause "dose dumping"). These properties were intentionally incorporated into the formulation by using Polyethylene Oxide (PEO) to impart physico-chemical properties such as added hardness and hydrogelling.

Based on consultations with "independent experts in drug abuse and abuser tampering" as well as information provided by the FDA's January, 2013; Guidance for Industry Abuse-Deterrent Opioids – Evaluation and Labeling) for Category 1 studies, the Sponsor conducted a series of Category 1 in vitro physical and chemical manipulation laboratory assessments of Hysingla ER tablets for possible abuse-deterrent properties. Studies were conducted by three contract research organizations (CRO) including

(b) (4) . Studies were generally conducted with replicates ranging from 2 to 6 depending upon the specific study.

Sponsor noted that since a currently marketed comparator (extended release formulation of hydrocodone bitartrate) to Hysingla ER did not exist, generic Vicodin (10 mg hydrocodone bitartrate/325 mg acetaminophen) was used as a comparator with regard to assessing tablet hardness and hydrocodone extraction efficiency. In some cases, the free base and bitartrate salt forms of hydrocodone were used as controls.

In some in vitro studies, the Sponsor used multiple dosage strengths of Hysingla ER tablets. For the purposes of this review, focus was placed on data generated using the 120 mg Hysingla ER table since this strength provided the greater ratio of hydrocodone bitartrate to PEO. A cursory examination of in vitro study data for other dosage strengths did not suggest substantial differences between dosage strengths when examined.

Study 1. Physical Manipulation and Determination of Test Articles

The goal of this study was to evaluate to use of "commonly employed household tools" acquired from pharmacies and kitchenware proprietors to manipulate Hysingla ER tablets and comparator (generic Vicodin) and determine the achievable range of particle size reduction. Both non-pretreated tablets as well as pre-heated and pre-frozen tablets were evaluated in this study. Based on the results, physical manipulation methods were standardized for producing cut (sliced) and ground samples of Hysingla ER tablets and comparators for use in other in vitro studies.

Non-Pretreated Tablets

Specific tools examined included two spoons, mortar and pestle (CoorsTek, Porcelain), pill crusher(Apex, pill pulverizer) , hammer (Tekton, 16 oz), food grater (Microplane), foot file (PedEgg), nutmeg shaver (Peugeot), razor blade (Fisher), spice grinder (Waring Commercial), and coffee grinders (Cuisinart Model DCG-12BC and Krups 203 Electric Spice and Coffee Grinder).

When appropriate, resultant particle size was determined by placing the physically manipulated tablets onto a stack of sieves ranging in size from 4000 µm to 355 µm with the smallest particles collected into a pan. Sieves were subjected to vibration and tapping to segregate the material across the sieves. Percent weight retained on each sieve was used to determine the particle size distribution.

Following 4-5 minutes using either a mortar and pestle or two spoons and following 1.5 minutes using a pill crusher, it was not possible to crush or grind Hysingla ER tablets. In contrast, generic Vicodin tablets were reduced to a powder within 2 minutes with the use of these tools. Using a mortar and pestle for 3 minutes to crush Vicodin tablets resulted in a powder with 89% of the weight of the powder being <355 µm.

The food grater, foot file, and nutmeg shaver were effective following 5 minutes of use in removing some of the coating on Hysingla ER tablets but not in reducing the particle size of the rest of the tablet. Using a hammer, Hysingla ER tablets were flattened with a few broken pieces (> 4000 µm). According

to Sponsor, Hysingla ER tablets could be cut with a knife with difficulty. Following approximately14 minutes of effort, a Hysingla ER tablet was cut into 180 pieces in sizes of 1000 µm to 2000 µm.

Mechanical tools including the spice grinder (Waring) and coffee bean grinders (Cuisinart and Krups) were most effective in reducing the particle size of the tablets. After one minute using these tools, the Hysingla ER tablets were reduced to milled particles the smallest of which were produced using the Krups brand coffee bean grinder (approximately 70% less than 1000 µm and approximately 20% less than 355 µm). Recovery was compromised using these mechanized grinders. Upwards of 13% total weight loss was recorded after milling a single tablet.

Pretreated (Freezing and Heated) Tablets

Pre-freezing Hysingla ER tablets consisted of exposing tablets to -10°C to -25°C for 4 days. Frozen tablets were subjected to manipulation using the hammer (1 minute), razor blade, and Krups coffee grinder (1 minute) followed by particle size determination. Pre-freezing tablets did not result in differences in manipulating the tablets, nor in the resultant particle size distributions as compared to untreated tablets.

Thermal pretreatment consisted of baking in an oven Hysingla ER tablets under the following conditions: 1) 130°C for 8 hours; 2) 170°C for 30 minutes; and 3) 250°C for 10 minutes. Manipulation of the pre-heated tablets was assessed using the hammer, razor blade, and Krups coffee grinder. All three thermal pre-treatments caused some discoloration of the tablets.

Grinding Hysingla ER tablets pretreated at 130°C for 8 hours and 250°C for 10 minutes resulted in large particle sizes compared to ground non-pretreated tablets (2% >2000 µm for untreated tablets compared to 34% >2000 µm for thermally pretreated tablets and 71% >1000 µm compared to 32% >1000 µm, respectively). Thermal pretreatment at 170°C for 30 minutes did not result is a difference in particle size following grinding compared to grinding non-pretreated tablets.

According to Sponsor, Hysingla ER tablets were easier to cut following pretreatment at 170°C for 30 minutes and 250° for 10 minutes. When treated by exposure to 130°C for 8 hours, Hysingla ER tablets became harder, possibly due, according to Sponsor, to additional curing of PEO at this lower temperature.

Standardized Hysingla ER and Vicodin Samples for Use in In Vitro Studies.

In vitro studies were conducted on intact, sliced, and milled Hysingla ER tablets and on intact or crushed generic Vicodin.

Sliced Hysingla ER tablets had a particle size distribution of approximately 50% greater than 2000 µm and 50% greater than 1000 µm. Tablets were sliced using a razor blade.

A batch of Hysingla ER tablets were subjected to a commercial (b) (4) to create a composite milled sample with about 40%, 30%, and 25% having particles sizes of >1000 µm, between 1000 and 355 µm, and <355 µm, respectively. The composite sample was subsequently divided into individual test articles each equivalent to one tablet.

Crushed generic Vicodin (10 mg hydrocodone bitartrate/325 mg acetaminophen) samples for use in the in vitro studies were obtained by grinding into a fine powder between 10 and 20 tablets using a mortar and pestle for 2 minutes. Approximately 89% of the weight of the generic Vicodin powder had a particle size of <355 µm. Samples representing a weight of one tablet were used as necessary.

Study 2. Extraction Studies

Extraction studies were conducted on intact and milled Hysingla ER tablets and generic Vicodin (10 mg/325 mg) tablets using 100 mL of the following solvents: water, Coca-Cola, saline (commercially available), 40% ethanol, methanol, 100% ethanol, 0.1N HCl aqueous solution (pH 1), and "commercially available" buffers of pH 3, 8, and 10. Extractions were conducted using glass jars with solvents held at 25°C and at elevated temperature (50°C or 95°C depending on solvent) with agitation (150 rpm orbital motion). Extraction sample times using whole tablets were 6, 24, and 48 hours with solvents held at 25°C and 1, 6, and 24 hours with solvents held at 50/95°C. When using milled tablets, extraction times were 5, 20, 60, 180, and 300 minutes with solvents held at 25°C and 5, 20, 60, and 180 minutes with solvents held at 50/95°C.

Whole and crushed Generic Vicodin tablets were used as a comparator with extraction times of 5, 20, and 60 minutes.

Study 2A. Extraction Studies on Hysingla ER Tablets in Water.

Extraction studies using water as the solvent were conducted on all strengths (20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 120 mg) of Hysingla ER tablets.

Results of extraction in water using 120 mg Hysingla ER tablets are found in Table 1. Extraction of hydrocodone bitartrate from intact Hysingla ER tablets at room temperature (25°C) was slow as indicated by 9.22% LC and 45.23 %LC extracted at 6 hours and 24 hours, respectively. Full extraction was seen at 48 hours. Increasing the water temperature to 95°C resulted in a partial disruption in the controlled release of hydrocodone bitartrate, as evidenced by a mean 11.35% LC extracted at 1 hour compared to an average of 9.22% LC extracted at 6 hours with water held at 25°C.

A larger disruption of the controlled release of hydrocodone bitartrate was observed with milled Hysingla ER tablets, most likely resulting from an increase of surface area of the milled sample compared to an intact Hysingla ER tablet. Following 5 minutes of exposure to water at 25°C, there was an average of 68.03% LC of hydrocodone bitartrate extracted from milled Hysingla ER tablets. Further disruption of the controlled release of hydrocodone bitartrate was observed using water at 95°C as evidenced by mean extraction of 86.46% LC and 96.94% LC within 5 minutes and 20 minutes, respectively.

There was little difference in extraction rate for hydrocodone bitartrate from all tablet strengths both intact and milled (data not shown) leading the Sponsor to conclude that extraction rate using water as solvent did not appear to be related to the hydrocodone bitartrate to PEO ratio as found in the formulation of Hysingla ER tablets.

Table 1. Mean Percentage of Label Claim (%LC) of Hydrocodone Bitartrate Extracted from Whole and Milled 120 mg Hysingla ER (HYD) Tablets in Water Held at Room Temperature (25°C) and Elevated Temperature (95°C). Numbers in parentheses are percentage standard deviations (%SD).

120 mg Hysingla ER Tablet	Extraction Duration (Hours) in 100 mL Water							
	5 min.	20 min.	1 h	3 h	5 h	6 h	24 h	48 h
	Mean %LC of Hydrocodone Bitartrate Extracted (%SD) (N=4)							
Whole - 25°C						9.22 (12.94)	45.23 (19.50)	91.76 (10.80)
Whole - 95°C			11.35 (3.63)			70.23 (4.22)	88.80 (4.03)	
Milled - 25°C	68.03 (11.65)	77.29 (7.75)	85.63 (7.37)	88.99 (9.64)	89.62 (8.09)			
Milled - 95ºC	86.46 (5.68)	96.94 (9.62)	93.52 (9.64)					

Study 2A (Continued) – Extraction Studies on Generic Vicodin Tablets in Water

Extraction of hydrocodone bitartrate from immediate release generic Vicodin® tablets was not affected by particle size or temperature. Both intact and crushed Vicodin tablets in 100 mL of water released hydrocodone bitartrate completely within 5 minutes regardless of temperature. (Data is not shown).

Study 2B. Extraction in Selected Household Solvents (40% Ethanol, Commercial Saline, Coca-Cola)

Extraction studies using selected household solvents were conducted on 20 mg, 60 mg, and 120 mg strengths of intact and milled Hysingla ER as well as on intact and crushed generic Vicodin 10 mg/325 mg.

Table 2 provides extraction results from Hysingla ER 120 mg tablets using as solvents 40% ethanol, saline (commercially available), and Coca-Cola. Sponsor did not examine the use of 4% or 10% ethanol as solvents. Extraction with these solvents at 25°C was a slow with an average of less than 8% of LC of hydrocodone bitartrate extracted at 6 hours. The least effective solvent was 40% ethanol in which at 48 hours a mean of 50.13% of LC of hydrocodone bitartrate was extracted. Increasing solvent temperature caused a partial disruption of the controlled release of hydrocodone bitartrate from intact Hysingla ER tablets as indicated by mean % LC extracted at 1 hour of 3.48, 14.24, and 14.12 using 40% ethanol, saline, and Coca-Cola as solvents, respectively.

Rates of hydrocodone bitartrate extraction in all three solvents were substantially increased after milling Hysingla ER tablets. Following just 5 minutes extraction at 25°C, the mean %LC extracted were 42.06, 52.52, and 59.36 in 40% ethanol, saline, and Coca-Cola, respectively. Elevation of solvent temperature further increased the average % LC extraction at 5 minutes to 48.30, 73.52, and 82.70 for 40% ethanol, saline, and Coca-Cola, respectively.

The rates of release of hydrocodone bitartrate from intact 20 mg, 60 mg, and 120 mg Hysingla ER tablets were similar using either Coca-Cola or 40% ethanol as solvent. When using saline as solvent, rate of release was faster from intact 120 mg Hysingla ER tablets compared to intact 20 mg or 60 mg Hysingla ER tablets.

Table 2. Mean Percentage of Label Claim (%LC) of Hydrocodone Bitartrate Extracted from Whole and Milled 120 mg Hysingla ER Tablets in 40% Ethanol, Saline, and Coca-Cola Held at Room Temperature (RT) and Elevated Temperature (50°C or 95°C). Numbers in parentheses are percentage standard deviation (%SD).

120 mg Hysingla ER Tablet	Extraction Duration (Hours) in 100 mL of Selected Household Solvents							
	5 min	20 min	1 h	3 h	5 h	6 h	24 h	48 h
	Mean % LC of Hydrocodone Bitratrate Extracted (%SD) (N=4)							
Whole - 25ºC 40% Ethanol						5.03 (5.36)	18.20 (12.32)	50.13 (24.85)
Whole - 50ºC 40% Ethanol			3.48 (2.27)			13.72 (5.40)	64.20 (7.98)	
Milled - 25ºC 40% Ethanol	42.06 (6.47)	52.84 (5.17)	62.66 (4.23)	70.04 (3.08)	72.99 (2.63)			
Milled - 50ºC 40% Ethanol	48.30 (9.34)	54.89 (5.29)	71.10 (6.98)	79.24 (7.39)				
Whole - 25ºC Saline						6.97 (11.20)	35.75 (8.67	777.76 (8.17
Whole - 95ºC Saline			14.24 (12.40)			92.56 (9.29)	93.98 (2.04)	
Milled - 25ºC Saline	52.52 (9.79)	64.61 (6.45)	75.25 (8.20)	78.41 (6.31)	78.38 (7.45)			
Milled - 95ºC Saline	73.52 (6.68)	87.49 (7.89)	83.02 (8.38)	84.86 (5.96)				
Whole - 25ºC Coca-Cola						7.25 (1.58)	30.72 (5.94)	69.89 (4.47)
Whole - 95ºC Coca-Cola			14.12 (15.18)			79.78 (6.08)	98.99 (2.41)	
Milled - 25ºC Coca-Cola	59.36 (9.51)	67.88 (7.83)	75.09 (2.62)	74.89 (7.00)	76.10 (11.92)			
Milled - 95ºC Coca-Cola	82.70 (22.00)	92.66 (14.73)	87.93 (8.11)	90.59 ((8.66)				

According to Sponsor the rate of release of hydrocodone bitartrate from milled 60 mg Hysingla ER tablets was "slightly lower" compared to the same release from 20 mg and 120 mg Hysingla ER tablets. Sponsor suggested that this difference might be an artifact of variability in the milling and sampling procedures. Overall, the effects of milling and solvent temperature on hydrocodone bitartrate release were similar for the three dosage strengths.

With use of generic Vicodin at temperatures of 25°C and 95°C, almost complete release of hydrocodone bitartrate was observed after 5 minutes in Coca-Cola and saline. Complete release of hydrocodone bitartrate was also observed at 25°C in 40% ethanol. The hydrocodone bitartrate release at elevated temperature (50°C) in 40% ethanol was about 70% LC after 5 minutes and >90% LC recovery after the 20-minute extraction time point. (Data not shown).

Extraction in Methanol and 100% Ethanol

Methanol and 100% ethanol, held at 25°C, were not effective solvents for extraction of hydrocodone bitartrate from intact Hysingla ER tablets as evidenced by an average of 17.49% LC and 1.37% of LC extracted at 24 hours (See Table 3). According to Sponsor this low release rate is likely due to the low

solubility of the PEO (rate controlling excipient) in methanol and ethanol, thereby reducing the ability of the tablet matrix to swell and facilitate dissolution.

The release rate varied per tablet strength in methanol and ethanol. More notably in methanol, the 20 mg tablet appeared to release faster followed by 60 and 120 mg strengths (data for three strengths not shown). This may be due to lower solubility of hydrocodone bitartrate in methanol combined with the reduced ability of the tablet matrix to swell. According to Sponsor, lower solubility could result in a similar milligram amount of hydrocodone bitartrate released from all tablet strengths. When these numbers are presented as %LC, the lowest strength would appear to be releasing faster (i.e., 12 mg released would be reported as 60% from the 20 mg tablet and only 10% from the 120 mg tablet).

Increasing solvent temperature to 50°C resulted in an increase in %LC of hydrocodone bitartrate extracted from intact Hysingla ER tablets to 87.34 and 35.03 in methanol and 100% ethanol, respectively, thereby indicating a disruption of the controlled release of hydrocodone bitartrate in these heated solvents.

Milling of Hysingla ER tablets resulted in a disruption of the extended release properties of hydrocodone bitartrate as evidenced by average %LC extracted of 81.61 and 52.04 following exposure.

Table 3. Percentage of Label Claim (%LC) of Hydrocodone Bitartrate Extracted from Whole and Milled 120 mg Hysingla ER Tablets in 100 mL Methanol and Ethanol (100%) Held at Room Temperature (25°C) and Elevated Temperature (50°C). Numbers in parentheses are percent standard deviation (%SD).

120 mg Hysingla ER Tablet	Extraction Duration (Hours) in 100 mL of Selected Solvents							
	5 min	20 min	1 h	3 h	5 h	6 h	24 h	48 h
	Mean % LC of Hydrocodone Bitratrate Extracted (%SD)							
Whole – 25ºC Methanol						6.99 (3.31)	17.49 (2.37)	24.78 (3.07)
Whole - 50ºC Methanol			4.0 (7.01)			22.93 (1.00)	87.34 (4.18)	
Milled – 25ºC Methanol	70.11 (13.05)	81.61 (10.25)	88.09 (9.21)	91.88 (7.85)	90.72 (8.19)			
Milled - 50ºC Methanol	59.08 (6.97)	77.54 (11.50)	74.02 (5.62)	79.74 (4.15)				
Whole - 25ºC Ethanol						0.12 (117.01)	1.37 (30.45)	2.85 (24.01)
Whole - 50ºC Ethanol			0.61 (6.27)			9.87 (1.20)	35.03 (3.97)	
Milled - 25ºC Ethanol	37.97 (6.86)	52.04 (4.46)	65.32 (3.33)	75.32 (2.35)	79.81 (1.83)			
Milled - 50ºC Ethanol	34.83 (37.78)	43.42 (15.89)	56.00 (8.50)	68.62 (6.49)				

for 20 minutes to methanol and 100% ethanol held at 25°C (See Table 3). Increasing the temperature of either solvent to 50°C did not further increase the percentage extraction of hydrocodone bitartrate from milled tablets

The release rate was slowest for the 60 mg HYD milled tablets, compared to 20 mg or 120 mg strengths. There were some differences in the release rate of the tablet strengths. This may be due to a combination of solubility considerations and the variability introduced by the milling and sampling procedures.

The generic Vicodin data in methanol at 25°C showed ≥83% LC of hydrocodone bitartrate released after 5 minutes extraction and a complete release by the 20 minute extraction time point. The 25°C data for ethanol showed about 25% LC released after the 5 minute extraction and maximum recovery of >68% LC after the 60 minute extraction time point. The release for the elevated temperature conditions for methanol and ethanol showed >89%LC after 5 minutes. (Data not shown)

Study 2C – Extraction in of pH Buffers.

The results of extraction of hydrocodone bitartrate from intact and milled 120 mg Hysingla ER tablets into pH 1, 3, 8, and 10 buffers are shown in Table 4. Similar patterns of hydrocodone bitartrate extraction were observed using the four pH buffers.

Slow extraction (<10% LC at 6 hours and >80% LC at 48 hours) of hydrocodone bitartrate from intact Hysingla ER tablets was observed with buffers held at 25°C. With an increase in buffer temperature to 95°C, there was an increase in the average %LC of hydrocodone bitartrate extracted into all buffers from intact tablets of greater than 60% LC at 6 hours of extraction.

Exposure of milled Hysingla ER tablets for 5 minutes to the buffered solutions held at room temperature (25°C) resulted in average %LC extracted in the range of 50% to 62%. For all four buffers at elevated temperature (95°C), there were increases in the %LC of hydrocodone bitartrate extracted into the range of 69%LC to 80% LC following 5 minutes of extraction.

Overall, similar release rates were observed for 20 mg, 60 mg, and 120 mg Hysingla ER tablets (whole or milled) regardless of the buffered solvent used.

The release of hydrocodone bitartrate from generic Vicodin® was complete after 5 minutes for all solutions at room temperature and >86% LC at elevated 95°C conditions. Lower results for API recovery were observed in pH 10 solutions after 1 hour. Significant loss of API is observed after this short exposure to high temperature, high pH solution. According to Sponsor, in addition to the possibility of some degradation, lower recovery may have been due to conversion to, and precipitation of, the free base of hydrocodone under conditions of high pH.

Study 3. Thermal Stressing of Hysingla ER 120 mgTablets

The intent of the thermal stressing studies was to assess the impact of intentional heat pretreatment, using a "laboratory oven" and "common household microwave", on the release rate of hydrocodone bitartrate from intact 20, 60, and 120 mg Hysingla ER tablets. According to Sponsor, "Experts suggest that exposure to elevated temperatures is a method used for manipulating tablets with the intention of misuse and/or abuse of various pharmaceutical formulations." Hysingla ER tablets contain (b) (4) PEO that imparts both a barrier to diffusion and significant viscosity. According to Sponsor, with thermal exposure, the (b) (4)

Table 4. Percentage of Label Claim (%LC) of Hydrocodone Bitartrate Extracted from Whole and Milled 120 mg Hysingla ER Tablets in 0.1N HCl (pH 1) and Commercially Available Buffers of pH 3,8, and 10 Held at Room Temperature (25°C) (RT) and Elevated Temperature (95°C). Numbers in parentheses are percentage standard deviations (%SD).

120 mg Hysingla ER Tablet	Extraction Duration (Hours) in 100 mL of Buffered Solutions							
	5 min	20 min	1 h	3 h	5 h	6 h	24 h	48 h
	Mean % LC of Hydrocodone Bitratrate Extracted (%SD)							
Whole – 25°C pH 1 Buffer						9.16 (11.22)	50.06 (12.72)	87.99 (8.62)
Whole - 95°C pH 1 Buffer			13.86 (11.03)			73.60 (11.91)	98.36 (5.00)	
Milled - 25°C pH 1 Buffer	51.50 (12.95)	66.69 (10.50)	74.29 (10.07)	78.66 (5.80)	81.72 (5.01)			
Milled - 95°C pH 1 Buffer	71.55 (13.72)	82.63 (5.16)	88.45 (16.76)	86.10 (4.09)				
Whole – 25°C pH 3 Buffer						6.56 (3.33)	37.29 (5.82)	82.56 (6.21)
Whole - 95°C pH 3 Buffer			11.39 (7.48)			70.07 (9.28)	96.45 (1.97)	
Milled - 25°C pH 3 Buffer	57.50 (23.70)	60.45 (9.92)	69.36 (9.11)	74.01 (9.78)	76.17 (10.03)			
Milled - 95°C pH 3 Buffer	75.91 (15.38)	76.10 (5.43)	88.46 (17.07)	82.08 (8.22				
Whole – 25°C pH 8 Buffer						7.52 (4.53)	39.41 (7.39)	80.38 (6.43)
Whole - 95°C pH 8 Buffer			11.36 (12.46)			62.62 (16.70)	88.69 (3.03)	
Milled - 25°C pH 8 Buffer	50.86 (8.90)	63.45 (8.86)	71.26 (4.46)	76.80 (11.74)	75.88 (5.47)			
Milled - 95°C pH 8 Buffer	69.92 (11.63)	75.82 (4.28)	73.69 (8.72)	72.25 (7.66)				
Whole – 25°C pH 10 Buffer						7.66 (4.19)	47.14 (1.01)	82.31 (9.09)
Whole - 95°C pH 10 Buffer			36.85 (11.72)			83.96 (1.32)	73.15 (1.85)	
Milled - 25°C pH 10 Buffer	61.45 (18.12)	72.10 (11.01)	77.76 (10.07)	81.95 (9.76)	80.53 (9.45)			
Milled - 95°C pH 10 Buffer	79.78 (12.03)	77.94 (15.27)	73.73 (6.93)	73.37 (6.38)				

(b) (4)

.

Following weighing, intact Hysingla ER tablets (20 mg, 60 mg, and 120 mg strengths) were exposed to laboratory oven temperatures of:

- 90°C for 240 and 480 minutes
- 110°C for 240 and 480 minutes
- 130°C for 120, 240, 360, and 480 minutes
- 140°C for 60, 120, 240, 360 minutes
- 150°C for 30, 60, 120, and 240 minutes
- 170°C for 30, 60, 120 minutes

- 190°C for 10, 30, 60 minutes
- 210°C for 10 and 30 minutes
- 250°C for 10 and 30 minutes

A calibrated thermocouple or thermometer was used to monitor the oven temperature. In the oven, tablets were placed in a single layer in an open glass container.

Controls consisted of intact tablets that were not exposed to heat. Generic Vicodin was not examined in this study.

Following thermal pretreatment, all tablets were kept at room temperature (in ambient conditions) for at least 1 hour and no more than 24 hours before dissolution testing. At approximately 1 hour post-heating, the weight of each tablet was determined.

Dissolution methodology consisted of using a USP dissolution Apparatus I using USP 10 mesh baskets with 900 mL of simulated gastric fluid without enzyme as the dissolution media held at 37°C and 100 rpm. Sampling time points included 20 minutes and at 1, 2, 4, 8, 12, 18, and 24 hours. Hydrocodone bitartrate release was evaluated using HPLC. The number of replicates was six, as required for USP standard Stage 1 dissolution testing. Data were expressed in mean %LC extracted.

The dissolution profiles for hydrocodone bitartrate from controlled (non-heated intact tablets) and heated 120 mg Hysingla tablets are provided in Table 5. Exposing 120 mg HYD tablets to 90°C for 240 or 480 minutes or to 250°C for just 10 minutes did not modify the dissolution profile compared to control. Exposure for 30 minutes to 250°C did suppress the %LC extracted across all sampling time points most likely due to decomposition of hydrocodone bitartrate at this high oven temperature. At this high temperature, tablets were severely discolored. For all thermal pretreatments, average %LC of hydrocodone bitartrate extracted from intact 120 Hysingla ER tablets at 20 minutes was less than 5% and at 1 hour was less than 10% (one exception was 14.33% LC extracted from tablets exposed to 170°C for 120 minutes).

Examination of the dissolution profiles show that pretreatment of 120 mg Hysingla ER tablets with an oven temperature of 130°C for 360 and 480 minutes produced the greatest increases in rates of hydrocodone bitartrate release, particularly at sampling times of 4, 8 and 12 hours. At the 8 and 12 hour time points, greater than 96% of label claim was extracted compared to 34.96%LC and 58.69% LC of hydrocodone bitartrate extracted from control intact Hysingla ER tablets. At the 4 hour sampling time, greater extraction was in the range of 57%LC to 65%LC compared to 14.41%LC extracted from control tablets. Extraction was also high from tablets preheated at 140°C. but less than that observed following exposure to the 130°C.

With exposure of 120 mg Hysingla ER tablets to higher temperatures (150°C, 170°C. and 190°C) for designated times, there was a progressive decrease in the rate of release of hydrocodone bitartrate as compare to that observed from tablets exposed to 130°C and 140°C.

Table 5. Dissolution Profile for Hydrocodone Bitartrate from Intact Hysingla ER 120 mg Tablets Either Not Exposed (Control) or Exposed to Selected Oven Temperatures (Ranging from 90°C to 250°C) for Specified Times. (N = 6) (Percentage standard deviations are not provided but were generally less than 10%)

Oven Termperature	Baking Duration (minutes)	Extraction Duration (Hours) in Simulated Gastric Fluid (SGF) Under Dissolution Conditions							
		0.33	1	2	4	8	12	18	24
		Mean % LC Hydrocodone Bitartrate Extracted from 120 mg Hysingla ER Tablet							
Control		2.01	4.36	7.39	14.41	34.94	58.69	90.49	99.55
90ºC	240	2,07	4.56	7.75	14.99	35.98	59.34	93.47	99.13
	480	2.22	4.73	7.81	14.99	36.39	61.04	95.93	99.03
110ºC	240	2.24	5.06	8.94	19.24	52.86	96.19	99.06	98.84
	480	2.35	5.79	10.68	26.11	86.27	97.70	97.22	96.70
130°C	120	2.60	6.25	11.85	30.49	90.81	99.20	99.61	99.20
	240	3.03	7.84	15.61	44.54	97.28	98.84	97.98	98.06
	360	2.96	8.55	19.38	57.72	97.98	98.33	97.54	97.02
	480	3.16	9.40	22.33	65.30	96.75	96.92	96.17	95.65
140°C	60	2.60	6.32	11.69	27.89	85.10	99.31	98.54	98.44
	120	2.79	7.35	14.94	41.75	94.06	96.18	95.47	95.37
	240	3.32	8.61	19.92	57.28	91.83	92.01	91.34	90.84
	360	2.88	6.21	15.29	37.31	74.73	87.96	88.61	88.32
150°C	30	2.82	6.65	13.54	32.51	67.17	82.24	83.04	83.58
	60	2.98	7.04	13.88	33.52	79.99	92.90	93.44	93.73
	120	3.00	7.81	17.23	41.39	84.32	91.43	91.68	91.87
	240	3.28	9.11	21.04	48.38	81.28	82.38	82.68	82.82
170°C	30	3.08	7.62	14.42	37.26	86.18	94.55	94.45	94.77
	60	2.61	6.16	11.21	25.77	74.65	97.80	98.09	98.05
	120	5.86	14.33	24.80	39.65	58.01	65.64	67.48	67.67
190°C	10	2.64	5.51	9.27	18.09	42.62	73.23	99.99	100.53
	30	2.65	6.05	11.41	24.32	53.89	78.76	89.08	89.52
	60	2.05	5.75	11.42	24.02	49.37	65.54	73.61	54.44
210°C	10	2.75	5.49	8.81	16.03	36.14	59.43	89.82	91.43
	30	1.59	4.61	8.69	17.49	39.02	58.90	73.39	76.21
250°C	10	1.52	4.16	7.71	15.59	37.29	61.41	78.45	81.33
	30	0.14	0.48	1.00	5.11	20.63	38.83	54.71	61.97

When comparing the effect of tablet strengths, a slightly larger difference from control is observed for the 120 mg tablet as compared to the 20 and 60 mg tablets. This is likely the result of slightly lower amounts of PEO in the highest strength tablet.

Microwave Studies of Intact 120 mg Hysingla ER Tablets

The purpose of the microwave study was to determine the effect on release rate of hydrocodone bitartrate from Hysingla ER tablets heated by microwave irradiation. Intact Hysingla ER tablets (20. 60, and 120 mg) were exposed to a 1100W common household microwave oven at full power for periods of

30, 60, 120, and 300 seconds. Following microwave exposure, tablets were allowed to "cool completely." Tablet weight was then determined.

Controls in this study were intact Hysingla ER tablets not exposed to microwave irradiation.

Dissolution methodology consisted of using a USP Apparatus I with basket with 900 mL of simulated gastric fluid without enzyme as the dissolution media held at 37°C and 100 rpm. Samples were taken at 20 minutes and at 1, 2, 4, 8, 12, 18, and 24 hours. Hydrocodone bitartrate release was evaluated using HPLC. The number of replicates was six. Data were expressed in mean %LC extracted.

As can be seen in Table 6, comparison of dissolution profiles of microwave pretreated 120 mg Hysingla ER tablets and that of 120 mg Hysingla ER tablets without treatment demonstrate little change in the release rate of Hysingla ER tablets. Additionally, pretreatment with microwave irradiation did not alter the physical appearance of the tablets. Similar results were found using the 20 mg and 60 mg Hysingla ER tablets (data not shown).

Table 6. Dissolution Profile for Hydrocodone Bitartrate from Intact Hysingla ER 120 mg Tablets Either Not Exposed (Control) or Exposed to Microwave Irradiation (1100 W Microwave Oven at Full Powder) for 30, 60, 120, and 300 Seconds. (N=6)

Duration of Microwave Exposure	Extraction Duration (Hours) in Simulated Gastric Fluid Under Dissolution Conditions							
	.33	1	2	4	8	12	18	24
	Mean % LC Hydrocodone Bitartrate Extracted from 120 mg Hysingla ER Tablet							
None	2.01	4.36	7.39	14.41	34.94	58.69	90.49	99.55
30 sec	1.91	4.36	7.36	14.07	33.65	56.08	84.85	99.60
60 sec	1.90	4.27	7.21	13.62	32.54	54.85	83.39	99.53
120 sec	1.96	4.42	7.43	14.08	34.63	58.03	89.48	103.11
300 sec	2.09	4.65	7.80	14.47	33.87	56.23	85.12	99.36

Study 4. Syringeability

Syringeability studies were conducted to assess the limits of the Hysingla formulation with regard to preparation for abuse via intravenous injection.
Sponsor conducted a variety of syringeability studies. Assessment of the data for these studies was accomplished with the help of a study by Stoops et al (2010)[2] demonstrating that the infusion to non-dependent, opioid experienced users of 10 mg or 20 mg, but not 5 mg, of hydrocodone hydrochloride produced significant levels of drug liking. Notwithstanding the differences in salt forms used (HCl versus bitartrate), solutions capable of delivering at least 10 mg of hydrocodone bitartrate when intravenously injected were considered to possibly produce subjective reinforcing effects (drug liking).

Syringeability studies were conducted using water (2, 5, 10, or 15 mL) on intact, sliced, and milled Hysingla ER tablets with extraction times of 30 seconds and 5 minutes. In the case of milled tablets,

[2] Stoop WW, Hatton KW, Lofwall MR, Nuzzo PA, and Walsh SL (2010). Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: abuse potential and relative potencies. Psychopharmacology, 212: 193-203.

dosage strengths of 20 mg, 60 mg, and 120 mgs were examined. Further characterization of intact, quartered, sliced, and thermally pretreated tablets, was performed using only the highest tablet strength, namely 120 mg. An additional study evaluated the release of hydrocodone bitartrate at just 24 hours (not other extraction durations) from intact 120 mg Hysingla ER tablets in water held at room temperature and without agitation.

Studies were conducted with water held at room temperature (25°C) or initially brought to a boil and with continuous agitation. Boiling was achieved by holding the admixture over a classic Zippo lighter until boiling was achieved, after which the sample was agitated for the allotted time. As such, samples were not boiled for the entire extraction time.

Extraction times were 30 seconds and 5 minutes. In the case of intact tablets, water was held at room temperature, without agitation and sampling continued out to 24 hours.

Additional studies were conducted on 120 mg Hysingla ER tablets thermally pretreated in a laboratory oven with prolonged heating at lower temperature (130°C, 8 hours), mid-range temperature and duration (170°C, 30 minutes), and short duration at high temperature (250°C, 10 minutes).

Syringeability was examined using 18, 27, 25, and 22 gauge needles. Testing was conducted by aspirating the sample through a needle and into a syringe. Aspiration was continuously attempted for 1 minute for each needle gauge tested. Initial testing was performed with an 18 gauge needle. If unsuccessful (< 10% of the preparatory volume aspirated), testing was determined complete, use of additional needle gauges was unnecessary. If successful (≥ 10% of the preparatory volume aspirated), testing continued by repeating the procedure with a newly prepared sample and a 27 gauge needle. If success was obtained with the 27 gauge needle, additional testing was unnecessary and the resulting aspirate was assayed. If aspiration was < 10%, the 27 gauge needle was replaced with a 25 gauge needle and aspiration continued with the same sample. If the cumulative aspirated volume (for the 25 and 27 gauge needles) was ≥ 10%, testing was complete and the sample was assayed. If not, the needle was replaced with a 22 gauge needle and aspiration continued. Success was obtained if the cumulative aspirated volume was ≥ 10% of the volume used to prepare the sample.

Retrievable samples were analyzed by HPLC to determine the %LC of hydrocodone bitartrate recovered. Number of replicates varied from 2 to 4 depending upon the particular study conditions.

Syringeability results for milled and sliced non-thermally stressed 120 mg Hysingla ER tablets are shown in Table 7. In the case of milled tablets, use of 5 mL of water did not result in retrievable amounts of fluid aspirated. With use of 10 mL of water (room temperature or boiled) and an 18 guage needle, aspiration volumes were in the range of 3.8 to 5.4 mL with a range of 12.18%LC to 26.49% LC hydrocodone bitartrate recovered. Concentrations on a per mL basis for these solutions are small; however, with injection of multiple milliliters it might be expected to achieve some subjective effects. Again, with the use of 10 mL of water, aspirated volumes along with %LC of hydrocodone bitartrate recovered were small using 22-27 gauge needles making such solutions unlikely to be useful for intravenous injection. With use of 15 mL of water (room temperature or initially boiled) and an 18 gauge needle, the ranges of aspirated fluid and %LC recovered were 9 to 10 mL and 22.90 to 25.85% LC, respectively. Concentrations of such solutions would be too low to be useful for intravenous abuse.

Solutions resulting from use of 22-27 gauge needles also would not likely be effective for intravenous abuse.

Table 7 also provides results for syringability studies on sliced 120 mg Hysingla ER tablets using 2, 5, and 10 mL of water. Use of 2 mL water with any gauge needle did not result in suitable solutions for

Table 7. Syringeability/Injectability Results for Milled (N = 4) and Sliced (120 pieces) (N=2) 120 mg Hysingla ER Tablets. (Data is expressed in terms of mean mL of fluid recovered and mean % LC of hydrocodone bitartrate recovered.)

Extraction Time (Min)	Water Volume (mL)	Boiling (B) or Room Temp. (RT)	18 G		22 – 27 G	
			Mean mL Recovered	Mean %LC Recovered	Mean mL Recovered	Mean %LC Recovered
Milled 120 mg Hysingla ER Tablets (N = 4)						
0.5	5	B	0.5	7.27	0	n/a
	10	B	5.1	20.39	1.1	3.01
	15	B	9.8	24.94	2.5	6.55
5	5	B	0	n/a		
	10	B	3.8	17.71	1.4	3.73
	15	B	9.0	22.90	2.4	4.71
0.5	5	RT	0	n/a	0	n/a
	10	RT	4.3	12.18	1.1	4.36
	15	RT	9.8	24.67	2.4	6.44
5	5	RT	0	n/a	0	n/a
	10	RT	5.4	26.49	1.5	5.46
	15	RT	10.0	25.85	4.1	12.40
Sliced (120 pieces) 120 mg Hysingla ER Tablets (N = 2)						
0.5	2	B	0.9	5.47	0.6	3.51
	5	B	3.3	12.57	2.0	9.10
	10	B	8.1	17.35	3.8	8.14
5	2	B	0	n/a	n/a	n/a
	5	B	1.8	16.82	0.8	7.47
	10	B	7.0	31.16	1.8	7.67
0.5	2	RT	0.7	2.19	1.4	3.30
	5	RT	3.6	4.40	3.0	2.53
	10	RT	8.5	3.92	6.0	2.28
5	2	RT	0.6	2.95	0.4	2.33
	5	RT	3.2	7.81	1.5	3.92
	10	RT	8.3	5.51	6.3	3.61

intravenous injection. Use of 5 mL of water initially boiled and extracted for 5 minutes resulted in a solution of 1.8 mL with 16.82 % LC recovered as aspirated using an 18 gauge needle. Such a solution might produce subjective effects if the 1.8 mL were injected. Solutions recovered using 22-27 gauge needles would not be acceptable for intravenous abuse. Resulting solutions using 10 mL of water and 18 to 27 gauge needles mostly likely would be too dilute to be effective for intravenous injection.

Sponsor used generic Vicodin 10/326 mg tablets as a comparator. No analysis of acetaminophen was conducted in this study. Table 8 provided syringeability data using 2 mL and 5 mL of water. With use of an 18 gauge needle, more than 80% of water was recovered following extraction times of either 0.5 minutes or 5 minutes. Recovery of hydrocodone bitartrate was also high, being in the range of 65%LC to 74%LC for 2 mL of water and 86%LC to 91% LC for 5 mL of water. Considering the low strength

(10 mg hydrocodone bitartrate) obtained, the resulting solutions from use of an 18 gauge needle would not likely be effective for intravenous injection. Of particular interest were the low aspirated volumes resulting from use of 22-27 gauge needles, suggesting some viscosity associated with the solutions. With use of the higher gauge needles, the resulting solutions also would be useful for intravenous injection. Under the conditions examined, Vicodin 10/325 mg tablets were not useful in producing a solution suitable for intravenous abuse.

Table 8. Syringeability/Injectability Studies with Generic Vicodin (10mg hydrocodone bitartraate/300 mg acetaminophen) (N=3). Data is expressed in terms of mean mL of fluid recovered and mean % LC of hydrocodone bitartrate recovered.)

Extraction Time (Min)	Water Volume (mL)	Boiling (B) or Room Temp (RT)	18 G		22 – 27 G	
			Mean mL Recovered	Mean %LC Recovered	Mean mL Recovered	Mean %LC Recovered
0.5	2	B	1.9	73.90	NA	NA
	5	B	4.7	90.28	1.0	26.87
5	2	B	1.9	74.66	0.4	6.79
	5	B	4.7	90.78	1.9	34.00
0.5	2	RT	1.8	65.92	NA	NA
	5	RT	4.6	86.58	1.1	20.64
5	2	RT	1.8	73.53	0.2	6.33
	5	RT	4.6	91.11	1.7	32.01

Table 9 provides syringeability results using milled 120 mg Hysingla ER tablets pretreated by baking in a laboratory oven at 130°C for 8 hours. Water volumes included 2 mL, 5 mL, and 10 mL. Due to low recovery of hydrocodone bitartrate, a 2 mL volume of water was not useful to produce an intravenous

Table 9. Syringeability/Injectability Results for Milled Hysingla ER 120 mg Tablets Pretreated by Baking at 130ºC for 8 Hours. Data is expressed in terms of mean mL of fluid recovered and mean % LC of hydrocodone bitartrate recovered. (N=4)

Extraction Time (Min)	Water Volume (mL)	Boiling (B) or Room Temp (RT)	18 G		22 – 27 G	
			Mean mL Recovered	Mean %LC Recovered	Mean mL Recovered	Mean %LC Recovered
0.5	2	RT	0.7	5.92	0.6	6.33
	5	RT	3.4	18.92	2.0	12.34
	10	RT	8.4	26.50	6.0	14.15
5	2	RT	0.4	4.97	0.3	2.31
	5	RT	3.4	31.30	1.9	12.09
	10	RT	8.4	33.51	3.1	9.62
0.5	2	B	0.6	7.38	0.6	6.49
	5	B	3.3	25.91	1.2	16.00
	10	B	8.5	45.20	2.8	15.24
5	2	B	0.3	3.69	0.2	2.98
	5	B	3.8	44.76	0.7	8.2
	10	B	6.4	45.50	2.0	15.71

solution. With use of 5 mL of water and aspiration via a 22-27 gauge needles, several solutions possibly suitable for intravenous injection were obtained assuming that subjects would be willing to inject more than 1 mL. For example, 30 second extraction in 5 mL of water initially boiled resulted in an aspirated

volume of 1.2 mL and mean % LC recovery of 16.00. Such a solution would contain 19.2 mg hydrocodone bitartrate which if injected (1.2 mL) could possibly produce subjective effects. With use of an 18 gauge needle several solutions were obtained that might produce subjective effects if intravenously injected, again assuming injection of more than 1 mL of solution. For example, 5 minute extraction at room temperature followed by aspiration with an 18 gauge needle resulted in a 3.4 mL solution containing 37.56 mg hydrocodone bitartrate (11.05 mg/mL). Another example is 5 minutes extraction in boiled water followed by aspiration with an 18 gauge needle providing 3.8 ml solution containing 53.71 mg hydrocodone bitartrate (14.13 mg/mL). Generally speaking, with the use of 10 mL of water, the resulting solutions were too dilute to use for intravenous injections. It might, however, be possible to use for intravenous abuse solutions aspirated using the 18 gauge and 22-27 gauge needle following 5 minutes of extraction with initial boiling, provided several mL of solution would be injected.

Syringeability results using sliced 120 mg Hysingla ER tablets pretreated by heating at 130°C for 8 hours are provided in Table 10. Use of water (2 mL, 5 mL, or 10 mL) held at room temperature was not effective in producing solutions for possible intravenous abuse. In addition, due to low concentrations

Table 10. Syringeability/Injectability Studies on Sliced 120 mg Hysingla ER Tablets Pretreated By Heating at 130ºC for 8 Hours. Data is expressed in terms of mean mL of fluid recovered and mean % LC of hydrocodone bitartrate recovered. (N = 2)

Extraction Time (Min)	Water Volume (mL)	Boiling (B) or Room Temp (RT)	18 G		22 – 27 G	
			Mean mL Recovered	Mean %LC Recovered	Mean mL Recovered	Mean %LC Recovered
0.5	2	RT	1.4	4.19	1.5	3.77
	5	RT	4.3	5.35	4.2	4.95
	10	RT	9.4	4.47	8.3	3.65
5	2	RT	1.1	7.27	0.9	7.30
	5	RT	4.1	11.14	4.2	10.03
	10	RT	9.1	9.31	7.6	9.50
0.5	2	B	1.2	9.17	1.2	9.75
	5	B	3.8	18.74	4.1	21.00
	10	B	8.5	24.41	7.5	24.97
5	2	B	0.8	10.13	0.8	10.57
	5	B	4.1	28.42	2.0	20.36
	10	B	8.8	46.63	5.8	31.69

of hydrocodone bitartrate it is not likely that solutions produced using 10 mL of water initially boiled would be usable for intravenous abuse unless abusers were willing to evaporate most of the excess liquid. Five minutes extraction in 5 mL of water initially boiled, followed by aspiration using a 22-27 gauge needle resulted in 2.0 mL of recoverable liquid containing 20.36%LC (24.43 mg hydrocodone bitartrate). Injection of the 2 mL might be expected to produce subjective effects.

Syringeability data are provided in Table 11 for milled 120 mg Hysingla ER tablets pretreated by heating at 170°C for 30 minutes and using 5ml or 10 mL of water held at room temperature or initially boiled. With water held at room temperature, no suitable intravenous solutions were obtained using 22-27 gauge needles of aspiration. Aspiration with an 18 gauge needle resulted in solutions that could possibly produce subjective effects providing that more than 1 mL was injected. In the case of using

water at boiling, at least some solutions obtained using either the 18 gauge or 22-27 gauge needles could potentially produce subjective effects providing, again, that more than 1 mL was injected.

Table 11. Syringeability/Injectability Studies on Milled 120 mg Hysingla ER Tablets Pretreated By Heating at 170ºC for 30 Minutes. Data is expressed in terms of mean mL of fluid recovered and mean % LC of hydrocodone bitartrate recovered. (N = 4)

Extraction Time (Min)	Water Volume (mL)	Boiling (B) or Room Temp (RT)	18 G		22 – 27 G	
			Mean mL Recovered	Mean %LC Recovered	Mean mL Recovered	Mean %LC Recovered
0.5	5	RT	1.0	6.41	0.8	4.23
	10	RT	5.5	18.59	3.4	7.41
5	5	RT	1.8	10.11	NA	NA
	10	RT	5.7	21.91	1.5	4.65
0.5	5	B	1.6	11.60	1.0	6.03
	10	B	5.7	30.17	4.8	21.97
5	5	B	1.4	12.88	0.8	7.99
	10	B	5.1	28.72	2.4	13.56

Syringeability data using sliced 120 mg Hysingla ER tablets pretreated by heating at 170°C for 30 minutes is provided in Table 12. Water volume was 5 mL and 10 mL held either at room temperature or initially boiled. Data suggest that due to limited extraction of the hydrocodone bitartrate, use of water at room temperature under the conditions used would not produce suitable intravenous solutions for abuse. With the use of water initially brought to a boil, some conditions might produce a usable solution for intravenous injection, assuming that more than one mL is injected. For example, with use of boiled water and 22-27 gauge needles for aspiration, a solution was obtainable with a mean volume of 2.0 mL with a mean recovery of 17.71% LC of hydrocodone bitartrate (21.25 mg of hydrocodone bitartrate from 120 mg tablet). Injection of the 2 mL solution might be expected to produce significant levels of drug liking.

Table 12. Syringeability/Injectability Studies on Sliced 120 mg Hysingla ER Tablets Pretreated By Heating at 170ºC for 30 Minutes. Data is expressed in terms of mean mL of fluid recovered and mean % LC of hydrocodone bitartrate recovered. (N = 2).

Extraction Time (Min)	Water Volume (mL)	Boiling (B) or Room Temp (RT)	18 G		22 – 27 G	
			Mean mL Recovered	Mean %LC Recovered	Mean mL Recovered	Mean %LC Recovered
0.5	5	RT	4.0	6.95	3.5	6.79
	10	RT	8.9	7.21	6.8	6.05
5	5	RT	3.4	16.76	1.1	4.86
	10	RT	5.7	13.49	4.0	7.88
0.5	5	B	3.4	21.95	3.3	14.32
	10	B	8.2	30.66	4.5	16.78
5	5	B	2.9	26.65	2.0	17.71
	10	B	7.8	42.52	5.5	30.44

Table 13 provides syringeability data on milled and sliced 120 mg Hysingla ER tablets pretreated at 250°C for 10 minutes and subjected to extraction in 10 mL of water. Due to very low extraction in 2

mL and 5 mL of water, data are not provided. Extraction of hydrocodone bitartrate was higher with use of 10 mL of water; however, due to low concentrations, the resulting solutions would not likely be useful for intravenous injection.

Table 13. Syringeability/Injectability of Milled (M) (N=4) or Sliced (S) (N-2) 120 mg Hysingla ER Tablets Pretreated With Heat (250ºC) and Extracted in 10 mL of Water (Room Temperature and Boiling). Data is expressed in terms of mean mL of fluid recovered and mean % LC of hydrocodone bitartrate recovered.

Extraction Time (Min)	Milled (M) or Sliced (S)	Boiling (B) or Room Temp (RT)	18 G		22 – 27 G	
			Mean mL Recovered	Mean %LC Recovered	Mean mL Recovered	Mean %LC Recovered
0.5	M	RT	3.8	5.07	1.2	3.50
5	M	RT	5.2	11.95	1.6	4.11
0.5	M	B	2.6	9.41	1.8	8.19
5	M	B	4.8	20.69	1.8	6.65
0.5	S	RT	8.9	3.29	6.3	1.72
5	S	RT	6.3	7.64	4.0	4.12
0.5	S	B	8.0	15.22	6.8	12.49
5	S	B	7.5	25.36	3.5	11.55

To evaluate the possible effects of ionic strength on hydrocodone bitartrate extraction, 5 mL of 10% sodium chloride (NaCl) held at either room temperature or initially boiled was used in an attempt to make a suitable intravenous solution from milled 120 mg Hysingla ER tablets. With 5 minute extraction time under either room temperature or boiled conditions, no recoverable solution was obtained. With 30 seconds of extraction, using 22-27 gauge needles recoverable fluid was less than 1 mL and %LC of hydrocodone bitartrate was less than 5%. Use of an 18 gauge needle and 30 seconds of extraction under initial boiling conditions, a mean of 0.8 mL recovered with a mean 10.39% of label claim hydrocodone was extracted. With the 10% NaCl solution held at room temperature, aspiration with an 18 gauge needle resulted in a mean of 1.5 mL of recovered liquid and a mean of 9.42% LC of hydrocodone bitartrate extracted. Specific data is not shown.

Sponsor evaluated the use of 120 mg Hysingla ER tablets cut into 4 pieces (quartered) to produce a suitable intravenous solution. Cut tablets were extracted with 5 mL of water and 10% NaCl solution (both held at room temperature and initially boiled) for 30 seconds and 5 minutes. Due to the low extraction (< 9% LC) of hydrocodone bitartrate, no solutions were recovered suitable for intravenous abuse. Data is not shown.

Sponsor also examined the use of intact 120 mg Hysingla ER tablets to produce a suitable intravenous solution. Individual intact tablets were extracted with 5 mL of either water or 10% NaCl (room temperature and initial boiling) for 30 seconds and 5 minutes. Additional individual tablets were extracted with water held at room temperature for 24 hours. Under all these conditions, due to low extraction (< 8% LC) of hydrocodone bitartrate, no solutions were recovered suitable for intravenous abuse. Data is not shown.

Study 5. Simulated Smoking (Vaporization)

The goal of this study was to assess the limits of Hysingla ER tablet susceptibility to inhalation abuse. The experiment was designed to simulate abuse via smoking and inhalation by determining the heat dependent vaporization and recoverable hydrocodone bitartrate from milled Hysingla ER tablets.

Inhalation was simulated with a gel Sep-Pak® (solid phase extraction cartridge) apparatus. This apparatus uses standard bonded silica column technology and solid phase extraction to trap the vapors generated after heating and vaporizing milled Hysingla ER tablets (20 mg. 60 mg. and 120 mg strengths). Milled samples of Hysingla ER tablets were exposed to temperatures of 250ºC, 280ºC, and 300ºC for 30 and 45 minutes. These selected temperatures were higher than the hydrocodone bitartrate melting point and approached the ignition temperature of PEO, thus providing for the possible vaporization of hydrocodone under these conditions. According to Sponsor, shorter heating times and lower temperatures were studied during development and found to result in less effective vaporization. Upon completion of the experiment, the Sep-Pak® cartridge was removed and extracted with solvent to recover the total amount of trapped API. The residue left behind after pyrolysis was extracted with water and assayed.

Comparator data was generated from manipulated generic Vicodin® tablets exposed for 5 minutes and 10 minutes to 250ºC, 280ºC or 300ºC. Hydrocodone free base and hydrocodone bitartrate salt were used as control samples to ensure the integrity of the experiments.

Heating milled Hysingla ER tablets (20 mg, 60 mg, or 120 mg) to temperatures in the range of 250ºC to 300ºC resulted in less than 10% of LC of hydrocodone bitartrate in vapor. At the selected temperatures, extending the exposure time from 30 minutes to 45 minutes did not increase hydrocodone bitartrate in vapor. At a temperature of 250ºC, %LC of hydrocodone bitartrate remaining in the residue ranged from approximately 35% for milled 20 mg Hysingla ER tablets to 60% from milled 120 mg Hysingla ER tablets. These values of hydrocodone bitartrate in residue decreased somewhat at a temperature of 280ºC. At the highest temperature of 300ºC, the average %LC of hydrocodone bitartrate in residue was in the range of 10% from 20 mg HYD to 35% from 120 mg Hysingla ER tablets, thereby indicating significant levels of degradation of hydrocodone bitartrate.

Less than 3% LC of hydrocodone bitartrate was found in vapor following exposure of generic Vicodin for 5 or 10 minutes to either 250ºC, 280ºC, or 300ºC. For these same temperatures average %LC of hydrocodone bitartrate recovered in residue was 63, 33, and 3%, respectively. The % LC of hydrocodone recovered from vapor + residue from crushed generic Vicodin exposed to 300ºC for just 5 minutes was less than 4%, indicating extensive degradation of the hydrocodone bitartrate.

The base form of hydrocodone was most easily volatilized as evidenced by approximate average percentage recovery in vapor in the range of 50% to 60% following 5 minutes exposure to heat (range of 250ºC to 300ºC). By contrast, similar exposure for hydrocodone bitartrate API, resulted in approximate average percentage recovery in vapor in the range of 30% to 40%.

Overall, the results of this study indicate that neither milled Hysingla ER tablets or crushed generic Vicodin tablets are likely to be abused by inhalation (smoking).

Study 6. Dissolution of Physically Manipulated Hysingla ER Tablets in Simulated Gastric Fluid

This in vitro dissolution study evaluated the effects on dissolution rate of halved, quartered, sliced (approximately 120 pieces), and milled Hysingla ER (20, 60, 120 mg) tablets. This study simulated the ingestion of physically manipulated Hysingla ER tablets for purposes of abuse or misuse. Cutting and slicing of tablets was performed with a standard razor blade.

Dissolution was carried out in a USP apparatus I vessel with a 10 mesh basket with 900 mL of simulated gastric fluid maintained at 37ºC and agitated at 100 rpm. When using intact and halved Hysingla ER tablets, assay time points were 10, 30, and 60 minutes, and 2, 4, 8, 12, 18, and 24 hours. When using quartered, sliced, and milled tablets, assay time points included 10, 30, and 60 minutes, and 2, 4, 8, and 24 hours. Samples were assayed by HPLC for hydrocodone bitartrate release. When using intact or manipulated Hysingla ER tablets, the number of replicants was six. This methodology was reviewed and determined to be "reasonable" by the Office of Biopharmaceutics (DARRTS, NDA 206627, July 31, 2013, Author: Akm Khairuzzaman, Ph.D.).

Generic Vicodin, whole or crushed, served as comparator involving three replicants. Vicodin tablets were crushed with a mortar and pestle for approximately 2 minutes.

The effect of cutting, slicing, and milling a 120 mg Hysingla ER tablet on hydrocodone release is seen in Table 14. Similar findings were found for the 20 mg and 60 mg Hysingla ER tablets (data not shown). As the number of tablet pieces increases from 2 to 4 to 120, there is an increase in the rate of release of hydrocodone bitartrate. This can be seen for example at a sampling time of 60 minutes in which the mean %LC of hydrocodone bitartrate extracted from whole, halved, quartered, and sliced (120 pieces) Hysingla ER tablet is 4.34, 10.75, 17.03, and 75.88, respectively. This may be explained by the fact that Hysingla ER tablets are a solid matrix formulation that when cut into an increasing number of pieces results in an increased surface area from which extraction can take place. Of note, it was observed that, at later time points there was a trend in the direction of reduced hydrocodone bitartrate extraction from milled Hysingla ER tablet compared to sliced (120 pieces) Hysingla ER tablet.[3] This reduction may be the result of gelling of the powdered material, resulting in a single mass in about 30 minutes. The solid mass would reflect some decrease in total surface area from which extraction can take place.

Table 14. Dissolution Study – Extraction of Hydrocodone Bitartrate from Whole and Physically Manipulated (Halved, Quartered, Sliced into 120 Pieces, and Milled) Hysingla ER 120 mg Tablets. (Data Expresed in Terms of %LC Extracted)

120 mg Hysingla ER Tablet	Dissolution Sampling Times (Minutes)								
	10	30	60	120	240	480	720	1080	1440
	Mean % of Label Claim (LC) of Hydrocodone Bitartrate Extracted								
Whole	1.09	2.65	4.34	7.21	13.30	32.27	55.10	83.86	99.42
Halved	3.16	6.78	10.75	17.62	31.18	60.19	82.30	98.12	100.45
Quartered	5.36	10.84	17.03	27.26	46.93	77.84			100.39
Sliced	31.40	57.77	75.88	89.29	97.45	100.57			101.31
Milled	44.42	57.93	67.69	76.28	84.36	90.24			93.32

[3] Except at the 10 minute time point, there was a further increase in hydrocodone bitartrate release.

Overall, this dissolution study demonstrates that cutting Hysingla ER tablets into pieces followed by ingestion results in increased rates of release of hydrocodone bitartrate. Such increased rates could potentially result in increased subjective reinforcing effects and possible overdose effects. Direct ingestion of Hysingla ER tablets cut into pieces may be a mode of abuse of Hysingla ER tablets.

Exposure of whole or crushed (mortar and pestle) generic Vicodin for just 5 minutes to simulated gastric fluid under dissolution conditions resulted in greater than 90% release of hydrocodone bitartrate reflecting the fact that Vicodin is an immediate release formulation.

Study 7A. Free Base Isolation – pH Mediation

The goal was to determine whether hydrocodone base isolation from Hysingla ER milled tablets through pH mediation is feasible. The desired outcome was to define the conditions under which hydrocodone base could be isolated with maximum recovery and purity. Sponsor noted that the free base form of drugs, including hydrocodone, might be more amenable to certain types of abuse such as smoking.

Studies used only the highest strength (120 mg) Hysingla tablets since this strength had the highest hydrocodone bitartrate to PEO ratio and therefore was considered to be the worst case example for possible isolation of the hydrocodone freebase. Hydrocodone bitartrate (120 mg) was equivalent to 74 mg hydrocodone free base.

Designs of these studies were based on known differences in the solubility of hydrocodone bitartrate salt verses hydrocodone freebase in acidic and alkaline media. Hydrocodone bitartrate is soluble (about 100 mg/ml) in aqueous solutions with neutral pH. In basic solutions with high pH, those greater than the pKa of hydrocodone bitartrate, the salt form converts to the free base form. This form has low solubility (about 1 mg/ml) in aqueous solutions with pH greater than 11. Hence, hydrocodone free base will precipitate at high pH when the solution concentration reaches certain levels.

Sponsor noted that procedures for isolation of hydrocodone free base from Hysingla ER 120 mg tablets using pH mediated precipitation with filtration and centrifuge were developed internally.

Milled samples of Hysingla ER 120 mg tablet were dissolved in 60 mL of water for 20 minutes resulting in a viscous solution. The sample was heated in a microwave (1100W) for 30 seconds to aid in filtration through a coffee filter. During this filtration step, hydrocodone tartrate was partially lost in the undissolved solid phase. The pH of the viscous solution collected from filtration was adjusted to greater than 11 to ensure the tartrate salt was converted to the free base. Sodium chloride was added to the solution to facilitate precipitation by increasing the ionic strength of the solutions. Initially, there was no obvious precipitation; over time the solution began to turn murky and cloudy. Precipitation was allowed to proceed overnight, after which some white solid was observed at the bottom of the container. A second filtration was attempted to separate the solid from the viscous solution without success. Instead, the sample was centrifuged twice to aid in separation of the solid and liquid phases. The clear supernatant was removed and the solid was dried in the oven at 100°C for 30 minutes. This technique was conducted twice.

The water absorption and swelling properties of the PEO made it difficult to precipitate hydrocodone free base from basic solution resulting in poor recovery and low purity of the hydrocodone free base.

Utilizing the above described technique only 15-17 mg of hydrocodone free base was obtained, representing 20-23% recovery of the total base available in a 120 mg Hysingla ER tablet (120 mg hydrocodone bitartrate is equivalent to 74 mg hydrocodone free base). Recovered base purity was in the range of 18% to 21%.

Study 7B. Free Base Isolation – Liquid Phase Extractions

This study evaluated whether liquid phase extraction using a water immiscible organic solvent could isolate hydrocodone free base from milled 120 mg Hysingla ER tablets. Although possibly not available to everyday abusers, a range of organic solvents, including dichloromethane, ethyl acetate and toluene, were studied to represent a worst case with regard to successful conversion and isolation of the free base.

Milled Hysingla ER tablets were added to 60 ml distilled water and stirred for 20 minutes. Filtration of the solution was then attempted to separate insoluble components of the formulation. The PEO in the formulation produces a highly viscous solution; therefore, filtration of the solution is very slow at room temperature. A microwave (1100W) was used to heat the solution for 30 seconds to aid in filtration. The pH of the filtrate was adjusted to pH >11 with sodium hydroxide. An additional 50 ml of water was added, along with 50 ml of dichloromethane. Extraction was accomplished by shaking the mixture in a separatory funnel for two minutes and resting for 40 minutes to separate the layers. Two additional extractions were performed on the same solution. All three organic layers were combined and evaporated by rotary evaporator to collect the solids. For the ethyl acetate and toluene extractions, eight grams of sodium chloride were added to the aqueous solution before adding the solvent. As conducted for dichloromethane, the solution was extracted three times and evaporated. The recovered solids from each solvent were reconstituted with an extraction solvent [2:1, acetonitrile (ACN): simulated gastric fluid (SGF)] and assayed using a previously validated method for the quantitation of hydrocodone.

Table 15. Hydrocodone (API) Loss, Recovery, and Purity Following Liquid Phase Extractions of Hysingla ER Tablets Using Selected Solvents. (Percent base recovered is label claim converted from bitartrate to free base with 120 mg of hydrocodone bitartrate being equivalent to 74 mg hydrocodone free base.)

Solvent	Sample	API Lost During Filtration (mg)	Base Recovered in Aqueous Phase (mg)	Base Recovered in Organic Phase (mg)	Base Recovered in Organic Phase (%)	Recovered Base Purity (%)
Dichloromethane	1	23	0	41	58	15
	2	25	0	37	52	25
Ethyl Acetate	1	26	1	30	42	94
	2	23	1	46	64	98
Toluene	1	35	0	36	50	89
	2	30	0	37	52	95

Results of the liquid phase extraction studies utilizing dichloromethane, ethyl acetate, and toluene are provided in Table 15. Filtration of the initial viscous aqueous solution resulted in a loss of hydrocodone bitartrate (API) in the range of 23 to 35 mg. Subsequent multiple (2 times) extractions with the three organic solvents resulted in recovery of hydrocodone base in the range of 42 to 64 mg. Use of ethyl acetate and toluene resulted in high purity (>89%) of the hydrocodone base. In contrast, use of

dichloromethane, in which PEO is somewhat soluble, resulted in much lower purity (15 to 25%) of the hydrocodone base.

Benchtop Comparison of Hysingla ER Tablets to Reformulated OxyContin Tablets Regarding Difficulty in Manipulation.

Within Analytical Sciences Report: AS-HYD-03/14 003, Sponsor described a study comparing Hysingla ER tablets to reformulated OxyContin with respect to the difficulty of physical manipulation.

Four "experienced laboratory technicians" were recruited to conduct physical manipulations of both formulations using the following tools:

- Spoons – Venice®, 18/10 stainless steel teaspoons
- Mortar/pestle – CoorsTek®, Porcelain Ceramic Mortar and Pestle # 60313
- Pill crusher – Apex®, pill pulverizer #70029
- Hammer – Tekton®, 16 oz wood claw hammer
- Food grater – Microplane®, 5100506, 18/8 gauge stainless steel blade
- Foot file – PedEgg®, pedicure foot file
- Razor blade – GEM®, stainless steel uncoated single edge industrial blades, thickness 0.0009in, Fisher Cat # 62-0167
- Spice grinder – Waring® Commercial, Model WSG30
- Coffee grinder – Cuisinart®, Model DCG-12BC
- Coffee grinder – Krups®, 203 electric spice and coffee grinder

Following attempted manipulations with each tool, subjects were required to assess difficulty using an "ALERRT Visual Analog Scale" consisting of a 100 mm horizontal line, anchored on the left side with the descriptor "very easy" and on the right side with "extremely difficult."

Overall results for all 10 tools are provided in Table 16. According to Sponsor, these results demonstrate that it is more difficult to physically manipulate either Hysingla ER tablets or reformulated OxyContin compared to manipulating generic Vicodin and that generally it was more difficult to manipulate Hysingla ER than reformulated OxyContin. With respect to individual tools, the greatest differences in VAS scores between Hysingla ER and reformulated OxyContin were seen with the food grater (32 point difference) and the razor blade (28 point difference) suggesting, according to Sponsor, that Hysingla ER tablets are more difficult to grate and to cut compared to reformulated OxyContin tablets.

Table 16. Descriptive Statistics (N = 40) ALERT VAS Scale – Overall Results for All Ten Tools. (100 mm VAS scale with zero respresenting low difficulty to manipulate and 100 representing extreme difficulty in manipulating.)

Formulation	Mean (SE)	Median	Range
Hysingla ER	70.98 (3.99)	72.5	10 - 100
Generic Vicodin	9.40 (1.89)	5	0 - 63
Reformulated OxyContin	55.85 (4.04)	52.5	6 - 100

The use of this study in this review to assess Hysingla ER tablets for abuse deterrent properities is problematic. The validity of the ALERT VAS has not been established. In addition, for each tool the number of attempts was small (N=4, one attempt for each of the four subjects).

Relative Attractiveness Study HYD1015

As part of the NDA submission, Sponsor submitted a relative attractiveness study entitled "Relative Attractiveness of Controlled Release Hydrocodone Tablets (HYD): Comparative Assessment of Tampering Potential and Recreational Drug User Preferences for Different Opioid Formulations". Study was initiated on September 4, 2012, and completed on September 18, 2012. Date of final report was March 6, 2013. Study was conducted by the independent contract research organization, (b) (4) All subjects were enrolled and interviewed on site.

(b) (4)

(b) (4)

Based on the following reason, these reviewers have elected not to consider the results of this study in the review of NDA 206-627.

1. The Agency has not encouraged or endorsed the use of attractiveness studies in the assessment of abuse-deterrent formulations

(b) (4)

4. Clinical Studies

4.1 Human abuse potential studies

Several extended release (ER) formulations of opioids are available. Enhanced compliance is more feasible with (ER) formulations over immediate release (IR) formulations. Unfortunately, ER formulations are often tampered with, since they contain higher amounts of the active drug compared to the IR formulations. These two Human Abuse Potential (HAP) studies attempt to demonstrate that the abuse deterrent formulation of Hysingla ER, using polyethylene oxide (PEO) as the (b) (4) excipient, will help mitigate this abuse potential.

The Phase 1 clinical pharmacology studies included two abuse potential studies, HYD1013 and HYD1014, completed in Canada. See Table 17.

Clinical Study HYD1013 entitled "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetcis, and Safety of Oral Crushed and Intact Controlled Release Hydrocodone Tablets in Recreational Opioid Users." (Study Initiation: June 10, 2013; Study Completion: September 25, 2013)

Clinical Study HYD1014 entitled "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Crushed and Intranasally Administered Controlled Release Hydrocodone in Recreational Opioid User." (Study Initiation: June 7, 2013; Study Completion: October 22, 2013)

These two protocols, submitted in IND 059175, reflect the Protocol Amendment-Change in Protocol Serial #0236, submitted on May 15, 2013, to address the review division's comments in their advice letter dated April 12, 2013. This included stricter qualification entry criteria, reporting of missing data, sample size determination and analysis populations for HYD1013 as well as further characterization of Hysingla ER fine and coarse powders in HYD1014.

Table 17. Summaries of Two Abuse Liability Studies Performed on ER Hydrocodone Product

Study	Design	Objectives	Details of Treatment	Details of Subjects
HYD1013	Single-center, double-blind, placebo-controlled randomized crossover study	Evaluate oral abuse potential and PD effects, PK and safety of intact HYD, milled and chewed tablets compared to hydrocodone API solution and placebo	HYD 60mg intact, milled and chewed tablet, po Hydrocodone bitartrate API 60mg, po Placebo HYD, po	40 (33M/7F) Ages 36.3y (21-54) Healthy nondependent recreational opioid users
HYD1014	Single-center, double-blind, placebo controlled Randomized 4-way crossover study	Evaluate intranasal abuse potential, PD effects, PK and safety of fine and coarse particle size HYD compared to hydrocodone API and placebo	HYD 60mg fine or coarse particle size, intranasal Hydrocodone bitartrate API 60mg, intranasal Placebo, intranasal	31 (28M/3F) Ages 38.9y (21-54) Healthy nondependent recreational opioid users with a hx of intranasal abuse

Summary and Conclusions from HYD 1013 and HYD 1014

Study HYD 1013 demonstrates a lower subjective drug effect (when Hysingla ER was compared to hydrocodone API) when administered by the oral route as intact or chewed. Unfortunately, similar findings were not observed for the milled Hysingla ER. In fact, these data suggest that Hysingla ER 60 mg milled and hydrocodone 60 mg solution have similar drug abuse ability.

In study HYD 1014, intranasal administration of fine or coarse particle size Hysingla ER demonstrated significantly lower subjective and physiological effects and greater intranasal irritation compared with hydrocodone API powder. Increased nasal irritation may contribute to a lower intranasal abuse potential compared with hydrocodone 60 mg API.

Clinical Study HYD1013

This study was designed to evaluate the abuse potential, pharmacokinetic profile, and safety of orally administered Hysingla ER tablets when crushed (milled and chewed) as well as intact in subjects with a history of recreational opioid use.

Study Objective:

1. Evaluate the oral abuse potential and pharmacodynamics (PD) effects of intact Hysingla ER, milled (produced using an industrial mill) Hysingla ER, and chewed Hysingla ER 60 mg tablets compared to hydrocodone API 60 mg solution and placebo. The primary PD endpoints were the "at the moment" Drug Liking VAS and the High VAS.

2. Evaluate the safety and tolerability of orally administered intact, milled, and chewed Hysingla ER, and to determine the pharmacokinetic (PK) profile of orally administered intact, milled, and chewed Hysingla ER compared to hydrocodone API solution. The PK endpoints included plasma concentrations over time, Cmax, Tmax, AUClast, AUCinf, t1/2, CL/F and V/F. Safety endpoints included type, incidence and severity of adverse events (AEs), vital signs, clinical laboratory assessments, 12-lead ECG and physical examination.

Study Design

The study consisted of 4 phases: Screening, Qualification, Treatment, and Follow-up. The treatment phase consisted of 5 visits, each lasting 3 days (2 overnight stays). Subjects received each of the treatments outlined below in a randomized, double-blind, quadruple-dummy fashion (1 per treatment visit):

- Treatment A: 60 mg tablet, intact
- Treatment B: Hysingla ER 60 mg tablet, milled
- Treatment C: Hysingla ER 60 mg tablet, chewed
- Treatment D: Hydrocodone API 60 mg in oral solution
- Treatment E: Placebo

The Screening Phase included two visits: a Screening visit (Visit 1), conducted within 28 days of the first study drug administration of the Qualification Phase, and a Naloxone Challenge visit lasting 1 day (Visit 2). All subjects completed the Naloxone Challenge test at least 12 hours prior to drug administration in the Qualification Phase, to confirm that subjects are not opioid-dependent.

Hydrocodone API was selected as an IR reference compound for oral abuse potential. Administration of hydrocodone alone was used to validate the study and confirm that the hydrocodone dose selected has detectable subjective effects. Because of its delayed Tmax, the abuse potential of intact Hysingla ER was evaluated, in addition to determining the effect of crushing and chewing the tablets on the abuse potential of Hysingla ER 60 mg (crushed and intact) and hydrocodone 60 mg.

Study Population

Forty healthy female and male subjects aged 18 to 55 years (inclusive) who were nondependent recreational drug users with moderate opioid experience were randomized into the Treatment Phase.

The most important Inclusion Criteria for this abuse potential study included:

1. Moderately experienced opioid users who met the following criteria: 1) have used opioids for nontherapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions in the past year and 2) have used opioids at least 3 times in the 12 weeks prior to Screening.

2. Must have experienced at least 3 occasions of chewing an opioid medication for the purpose of recreational oral abuse/misuse in the last 12 months.

3. Must report taking an opioid equivalent to 60 mg hydrocodone (e.g., 40 mg oxycodone, 60 mg morphine, etc.) (by any route of administration) or higher on at least one occasion in their lifetime.

Subject Completion

Subjects were considered as have completed the study if they had undergone all screening procedures, received all study drug treatments, and finished all follow-up evaluations. Any subject who received at least one treatment of study drug was considered valid for clinical safety and tolerability evaluations.

Out of the 40 randomized patients, 35 (87.5%) completed all 4 treatment periods and only 5 (12.5%) discontinued prior to completing all 5 treatment periods. Of those 5 subjects, 2 (5.0%) did not complete treatment period 2; one withdrew consent and the other was discontinued for non-compliance. An additional 2 subjects (5.0%) did not complete treatment period 3; one because of an AE (non-conductive P wave on ECG) and one was discontinued for undocumented administrative reasons. The last of the 5 discontinuations was for an unexplained withdrawal of consent. See Table 18.

Table 18. Patient Disposition Study HYD 1013

Number of Subjects in the Randomized Population	40 (100%)
Completed Treatment Period 1 (visit 4)	40 (100%)
Completed Treatment Period 2 (visit 5)	38 (95.5%)
Completed Treatment Period 3 (visit 6)	36 (90.0%)
Completed Treatment Period 4 (visit 7)	36 (90.0%)
Completed Treatment Period 5 (visit 8)	35 (87.5%)
Subjects Who Completed the Study	35 (87.5%)
Subjects Who Withdrew Early	5 (12.5%)
Subjects in Safety Population	40 100%)
Subjects in PK Population	40 (100%)
Subjects in PD Population	35 (87.55)

The Qualification Phase results for hydrocodone 60 mg oral solution and placebo oral solution demonstrated an acceptable placebo response for Drug Liking VAS and High VAS. See Table 19.

Table 19. Study HYD 1013 Qualification Phase Results

	Placebo (n=35)	Hydrocodone 60 mg solution (n=35)
Drug Liking VAS Emax Mean (SD) Range	50.6 (0.65) 50-53	96.4 (6.28) 79-100
High VAS Emax Mean (SD) Range	4.9 (14.25) 0-51	98.9 (3.72) 86-100

Milling was accomplished by pulsating the mill for 15 seconds using an up-and-down motion. After a wait time of 15 seconds, 2 additional cycles of milling were performed for a total time of 45 seconds. The mill was allowed to stand for approximately 2 minutes so that the material could settle. The material was transferred to a clean weighing paper by inverting the mill chamber and then using an anti-static clean brush and gently tapping the mill and mill chamber to remove any residual milled material. Following weighing of the milled tablet, the percent recovery was calculated. The milled tablet was administered only if the percent recovery was ≥90%.

Chewing included instructions to chew the tablet for 2 to 3 minutes with his or her molars without swallowing. A mouth check was performed by staff to ensure the tablet had been chewed sufficiently. If the tablet remained unchewed, the subject was instructed to chew for approximately 1 more minute without swallowing. Another mouth check was performed to ensure that the tablet was chewed. Subjects were instructed to swallow the tablet pieces with any remaining water.

The majority of subjects were unable to break the pill up into more than one piece with vigorous chewing; instead, they were able to flatten the pill. On average this took subjects approximately 3 minutes of continuous chewing. As a result, the study specific procedure *was* amended July 19, 2013 to increase the chewing duration to approximately 2-3 minutes. When subjects indicated that they wanted to stop chewing, they were instructed to continue chewing to the best of their ability until the 3 minute mark was reached.

Results and Conclusions of Study HYD 1013:

Pharmacokinetic Results

Mean plasma concentrations of hydrocodone increased rapidly following oral administration of the hydrocodone solution, with a maximum plasma concentration (Cmax) observed around 1 hour post-dose. Cmax were reached later following oral administration of Hysingla ER milled (approximately 1.5 hours post-dose) and chewed (6 to 8 hours post-dose), and the latest was for Hysingla ER intact (approximately 15 hours post-dose). Mean hydrocodone concentrations were highest following the hydrocodone solution. Lower concentrations were observed following Hysingla ER chewed or intact than following Hysingla milled.

The median time to reach Cmax (Tmax) of hydrocodone was 1.05 hours following the hydrocodone solution, and was observed later following Hysingla ER milled (1.55 hours) and chewed (8.04 hours). The longest Tmax was observed following oral Hysingla ER intact (15.1 hours). The mean AUClast values of hydrocodone were similar for Hysingla ER intact (885.7 h*ng/mL), chewed (913.4 h*ng/mL), and the hydrocodone solution (951.4 h*ng/mL). Mean AUClast values were lower following Hysingla ER milled (647.8 h*ng/mL). The results were similar for AUCinf.

The mean Cmax, Tmax and AUCinf are summarized in Table 20.

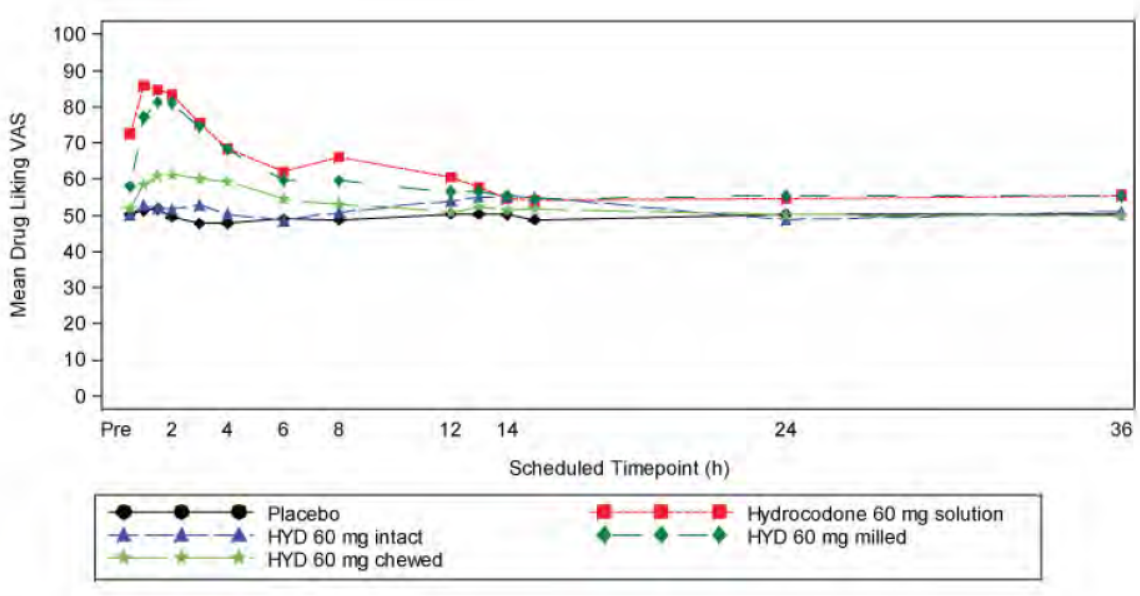
Table 20. Summary of Mean PK Parameters Hydrocodone and Hysingla ER Preparations

	Hydrocodone 60 mg Solution	Hysingla ER 60 mg Intact	Hysingla ER 60 mg Milled	Hysingla ER 60 mg Chewed
C max (ng/mL)	127.1	48.38	81.0	67.6
T max (h)	1.050	12.05	1.55	8.042
AUCinf (hng/mL)	971.4	1059	655.8	942.5

Pharmacodynamics Results

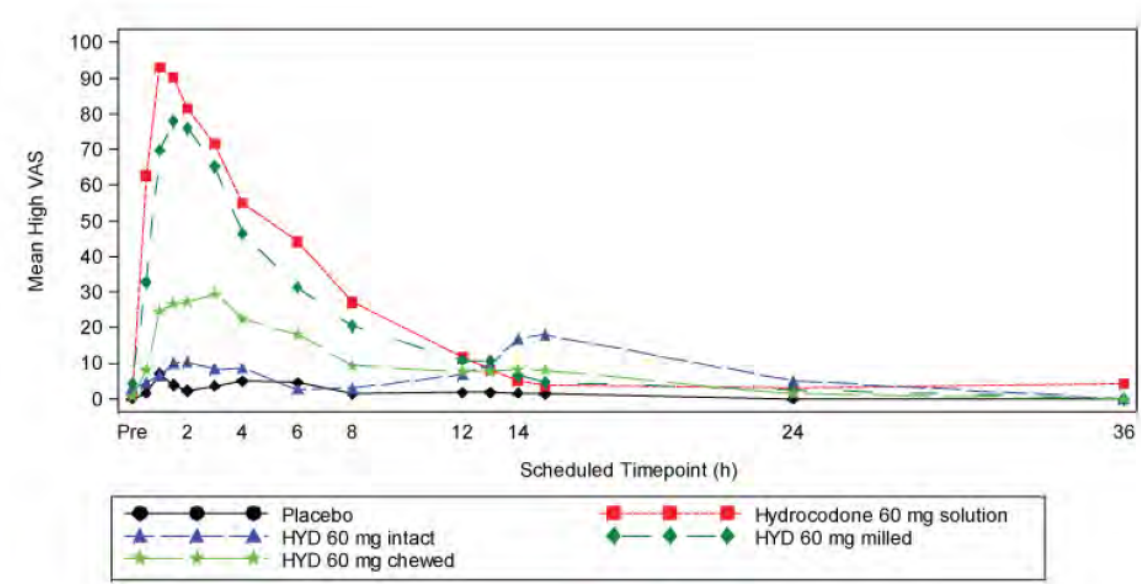
Drug Liking VAS scores of placebo and Hysingla ER intact administration had very similar profiles, showing little change across time points, generally around the neutral mark. On the other hand, both hydrocodone solution and Hysingla ER milled had mean scores that were much higher than placebo and Hysingla ER intact. In general, mean peak effects were slightly delayed with Hysingla ER treatments relative to hydrocodone solution. Hysingla ER chewed showed a relatively small increase (~10 points) in Drug Liking VAS scores.

The Treatment Phase results are demonstrated in the Sponsor's plots of mean scores over time on the primary measures of Drug Liking VAS. See the Sponsor's Figure 1.



Sponsor's Figure 1. Mean Scores Over Time for Drug Liking VAS (Oral Administration: Chewed, Milled and Intact) VAS=visual analog scale. Drug Liking VAS is a bipolar scale. At this moment, my liking for this drug is "where responses range from 0 (strong disliking) to 100 (strong liking) and 50 (neither like nor dislike) is the neutral point.

The Treatment Phase results are demonstrated in the Sponsor's plots of mean scores over time on the primary measures of High VAS. See the Sponsor's Figure 2.



Sponsor's Figure 2. Mean Scores Over Time for High VAS (Oral Administration; Chewed, Milled and Intact) HYD=hydrocodone bitartrate q24h film coated tablet; Hydrocodone 60 mg solution=hydrocodone bitartrate, USP powder, administered as a 240 mL oral solution; PD=pharmacodynamic; VAS=visual analog scale High VAS is a unipolar scale:"I am feeling high," where responses range from 0 (Definitely not) to 100 (Definitely so).

Hydrocodone solution showed High VAS scores that were markedly higher than placebo. Hysingla ER milled also showed relatively high scores compared to placebo, although these were slightly lower than for hydrocodone. Placebo and Hysingla ER intact had similar profiles, with High VAS scores only slightly above neutral.

As might be expected, hydrocodone solution showed significantly higher Emax for High VAS than placebo, confirming study validity (P<0.001). Table 21 demonstrates the analysis results for High VASmax. Emax treatments were significantly lower compared to those of hydrocodone solution (P≤0.019), but were significantly greater than those of placebo (P≤0.003). Hysingla ER milled also had significantly greater High VAS Emax values than those of Hysingla ER chewed and intact (P<0.001 for both).

Table 21. The Analysis Results for High VAS Emax

Pair Comparisons	Median Difference	P value
Hydrocodone Solution vs Placebo	99.0	<0.001
Hysingla ER intact vs Hydrocodone Solution	-50.0	<0.001
Hysingla ER milled vs Hydrocodone Soln.	0.0	<0.001
Hysingla ER chewed vs Hydocodone Soln.	-50.0	<0.001
Hysingla ER intact vs Placebo	16.0	0.003
Hysingla ER milled vs Placebo	77.0	<0.001
Hysingla ER chewed vs Placebo	39.0	<0.001
Hysingla ER milled vs Hysingla ER intact	42.0	<0.001
Hysingla ER chewed vs Hysingla ER intact	1.0	0.483
Hysingla ER chewed vs Hysingla ER milled	-33.0	<0.001

Emax=maximum effect; HYD=hydrocodone bitartrate q24h film coated tablet; Hydrocodone solution=hydrocodone bitartrate, USP powder, administered as a 240 mL oral solution; VAS=visual analog scale Overall Treatment Effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences.

The Take Drug Again VAS provided a measure of the balance of drug effects and indicated the subject's willingness to take the drug again. The Take Drug Again VASs were administered using a unipolar format. In contrast to the Drug Liking VAS, these scales, administered at least 8 hours after study drug administration, had the advantage of the subject being relatively less affected or unaffected by study drug effects (if any) by the time of the assessment. Its disadvantage is that it requires the subject to be able to recall the drug's effects at a later time, and therefore, it may not be as reliable as Drug Liking (at the moment).

Drug Liking VAS results at 12 and 24 hours post-dose were approximately 25 to 35 points higher for hydrocodone solution and Hysingla ER milled and in the "liking" range of the scale compared to placebo, Hysingla ER intact, and chewed, which were all within the neutral range of the scale (between 48 and 58 points).

For the Take Drug Again VAS, mean scores for hydrocodone solution and Hysingla ER milled were approximately 75 to 85 points higher than placebo and approximately 45 to 60 points higher than Hysingla ER intact. Mean scores for Hysingla ER chewed were also higher (~10 to 20 points) than Hysingla ER intact but still approximately 40 points lower than for hydrocodone solution and Hysingla ER milled. See Table 22.

Table 22. Take Drug Again VAS vs Drug Liking VAS Emax

	Placebo	Hydrocodone 60 mg Solution	Hysingla ER 60 mg Intact	Hysingla ER 60 mg Milled	Hysingla ER 60 mg Chewed
Drug Liking VAS mean (SD)	49.7 (10.0)	85.9 (17.6)	59.4 16.2	84.6 (17.6)	59.2 (27.9)
Take Drug Again VAS mean (SD)	3.9 (15.9)	89.7 (21.2)	34.3 (36.0)	84.1 (28.1)	44.3 (40.8)

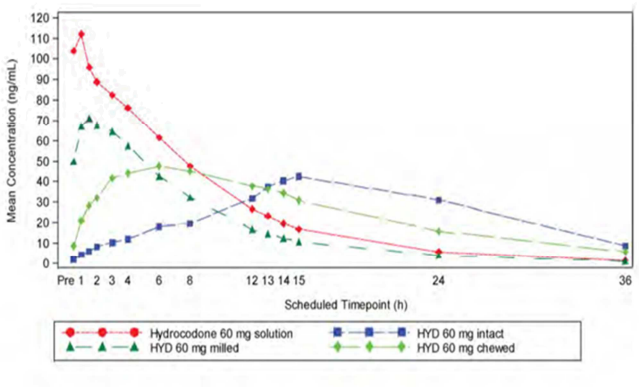
Overall Summary of Pharmacodynamic Results Study HYD 1013

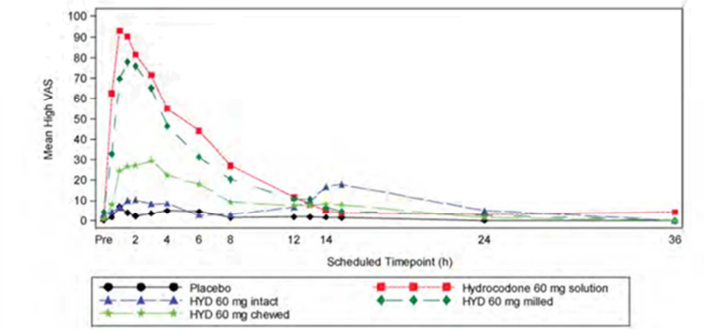
This clinical study was designed to investigate the subjective and objective effects of oral Hysingla ER, when intact, milled, or chewed, compared with oral hydrocodone solution. Overall, it succeeded in demonstrating that Hysingla ER intact and chewed showed significantly lower abuse potential compared to hydrocodone solution across the majority of endpoints. When Hysingla ER was milled for oral ingestion, a smaller reduction in abuse potential was observed.

Hysingla ER intact and chewed treatments were associated with significantly lower effects for most subjective measures, with a delayed onset of effects relative to hydrocodone solution. The differences were most pronounced with the Hysingla ER intact treatment, but in most cases the Hysingla ER intact and chewed treatments were not statistically different. The majority of subjects (>50%) showed at least a 30% reduction in Drug Liking scores (responders) following administration of Hysingla ER chewed and at least a 50% reduction in Drug Liking scores following administration of Hysingla ER intact.

Pharmacokinetic–Pharmacodynamic Conclusions

Study HYD 1013 demonstrates that the High VAS PD findings are reasonably consistent with the serum concentrations of hydrocodone and Hysingla ER for 36 hours. These findings suggest that the abuse potential of Hysingla ER (and hydrocodone) is directly proportional to the serum concentrations of these drugs. These PD and PK parameters are compared in the Sponsor's Figure 3.





Sponsor's Figure 3 Mean Drug Plasma Concentration versus Time Compared with Mean High VAS vs Time

Clinical Study HYD 1014

This study was designed to evaluate the abuse potential, PK profile and safety of intranasally administered Hysingla ER (fine and coarse powder), compared to hydrocodone API and placebo, in recreational opioid users with a history of intranasal abuse. The objectives of the study were to evaluate the intranasal abuse potential and PD effects of intranasally administered fine and coarse particle size Hysingla ER 60 mg (produced using an industrial mill and razor blade, respectively) compared to hydrocodone API 60 mg powder and placebo. Additionally, the study evaluated the safety and tolerability of intranasally administered Hysingla ER and determined the PK of intranasally administered HYD compared to hydrocodone API powder.

Study Objectives

1. To evaluate intranasal abuse potential and PD effects of intranasally administered Hysingla ER compared to hydrocodone Active Pharmaceutical Ingredient (hydrocodone API) and placebo in recreational opioid users with a history of intranasal abuse.

2. To evaluate the safety and tolerability of intranasally administered fine and coarse Hysingla ER powder in recreational opioid users with a history of intranasal abuse.

3. To determine the PK profile of intranasally administered fine and coarse Hysingla ER powder

compared to hydrocodone API in recreational opioid users with a history of intranasal abuse.

Study Design

The study consisted of 5 phases: Screening, Dose Selection, Qualification, Treatment, and Follow-up. The Screening Phase included 2 visits: a standard medical screening visit (visit 1) conducted within 28 days of the first study drug administration of the Qualification Phase, and a naloxone challenge visit lasting 1 day (visit 2).

A subject was eligible for the Treatment Phase if the following eligibility criteria were met in the qualification phase:

1. Peak scores (Emax) in response to hydrocodone greater than that of placebo on 'at this moment' Drug Liking VAS (difference of at least 15 points, or 30%, on this bipolar scale) and Overall Drug Liking VAS (difference of at least 10 points, or 20%, on this bipolar scale), and High VAS (difference of at least 30 points, or 30%, on this unipolar scale). A peak score of ≥75 must have been indicated on 'at this moment' Drug Liking VAS, ≥70 on Overall Drug Liking VAS, and ≥40 on High VAS in response to hydrocodone.

2. Acceptable responses to placebo on at the moment Drug Liking VAS and Overall Drug Liking VAS, defined as a peak score between 40 to 60, inclusive, and on High VAS, defined as a peak score between 0 to 10, inclusive.

The treatment phase consisted of 4 visits (visit 4 to visit 7), each lasting 3 days with 2 overnight stays. Subjects self-administered each of the following 4 treatments (1 treatment per visit) intranasally in a double-blind, randomized order:

- Treatment A: 60 mg hydrocodone API powder
- Treatment B: 60 mg Hysingla ER, fine particle size
- Treatment C: 60 mg Hysingla ER, coarse particle size
- Treatment D: Placebo

All subjects were discharged from each visit after completion of the final post-dose procedures. Each study drug administration was separated by 5 to 7 days (if needed, rescheduling may have occurred up to a maximum of 14 days). The Follow-up phase (visit 8) was conducted approximately 3 to 7 days after the last drug administration or after early withdrawal from the study. Subjects participated in the study for approximately 8 weeks, from screening to follow-up. Single doses of study drugs in the treatment phase were separated by a washout interval of 5 to 7 days (if needed, rescheduling may have occurred up to a maximum of 14 days).

Study Population

A sufficient number of subjects were screened and entered into the Qualification Phase to ensure that approximately 32 healthy male and female subjects 18 to 55 years of age, inclusive, were eligible to enter the treatment phase in order to complete approximately 24 recreational opioid users with a history of intranasal abuse.

The Inclusion Criteria included:

1. Moderately experienced opioid users who met the following criteria: 1) had used opioids for non-therapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions in the past year and 2) had used opioids at least 3 times in the 12 weeks prior to screening.

2. Experienced at least 3 occasions of intranasal opioid drug use for the purpose of recreational abuse/misuse in the last 12 months.

3. Reported having taken a dose of opioid equivalent to 40 mg hydrocodone (by any route of administration) or higher on at least 1 occasion in the past year.

Subjects were excluded if the presented symptoms of withdrawal following administration of the naloxone challenge test, OOWS score ≥3, unless in the opinion of the medical investigator the symptoms present were not related to opioid withdrawal.

Study Completion

Among the 32 randomized subjects, there were 25 (78.1%) subjects who completed all 4 treatment periods and were included in the PD population. A total of 7 (21.9%) subjects discontinued prior to completing all 4 treatment periods. One (3.1%) subject (Subject 01095) was withdrawn prior to receiving any study drug in the treatment phase due to AEs of bradycardia and presyncope on day 1 of treatment period 1. Four (12.5%) subjects did not complete treatment period 2: Subject 01061 experienced an AE of ventricular tachycardia after dosing in treatment period 1 and was withdrawn from the study. Subjects 01122, 01127, and 01128 were discontinued for administrative reasons (i.e., study discontinued) after dosing in treatment period 1. Two (6.3%) subjects did not complete treatment period 4. Subject 01118 was discontinued due to poor venous access, and Subject 01119 was discontinued for administrative reasons after dosing in treatment period 3. See Table 23.

Table 23. Patient Disposition Study HYD 1014

Number of Subjects in the Randomized Population	32 (100%)
Completed Treatment Period 1 (Visit 4)	31 (96.9%)
Completed Treatment Period 2 (Visit 5)	27 (84.4%)
Completed Treatment Period 3 (Visit 6)	27 (84.4%)
Completed Treatment Period 4 (Visit 7)	25 (78.1)
Subjects Who Completed the Study	25 (78.1%)
Subjects Who Withdrew Early	7 (21.9&)
Subjects in Safety Population	31 (96.9%)
Subjects in PK Population	30 (93.8%)
Subjects in PD Population	25 (78.1%)

Results and Conclusions of Study HYD 1014

Pharmacokinetic Results

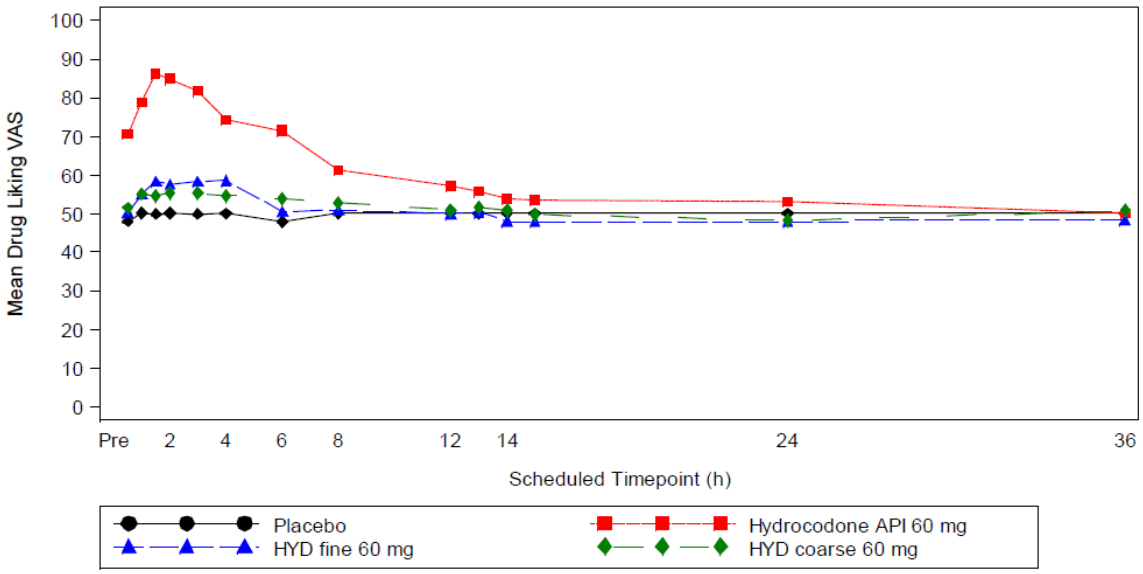
Mean plasma concentrations were considerably lower following Hysingla ER fine (36.49 ng/mL) and coarse (27.49 ng/mL) than following hydrocodone API (105.8 ng/mL). These lower values may be partly due to the lower insufflation percentage for Hysingla ER fine and coarse compared to hydrocodoneAPI. Median Tmax was observed later following Hysingla ER fine (3.07 hours) and coarse (4.05 hours) than following hydrocodone API (1.57 hours). The mean AUClast values following Hysingla ER fine and coarse were considerably lower than the AUClast value for hydrocodone API (902.3 h*ng/mL). The results were similar for AUCinf. The mean Cmax, Tmax and AUCinf are summarized in Table 24.

Table 24. Summary of Mean PK parameters Hydrocodone and Hysingla ER Preparations

	Hydrocodone 60 mg Solution	Hysingla ER 60 mg Fine	Hysingla ER 60 mg Chewed
Cmax (ng/mL)	0.8010	0.1832	0.1856
Tmax (h)	1.57	6.05	6.05
AUCinf (h ng/mL)	7.603	5.926	6.123

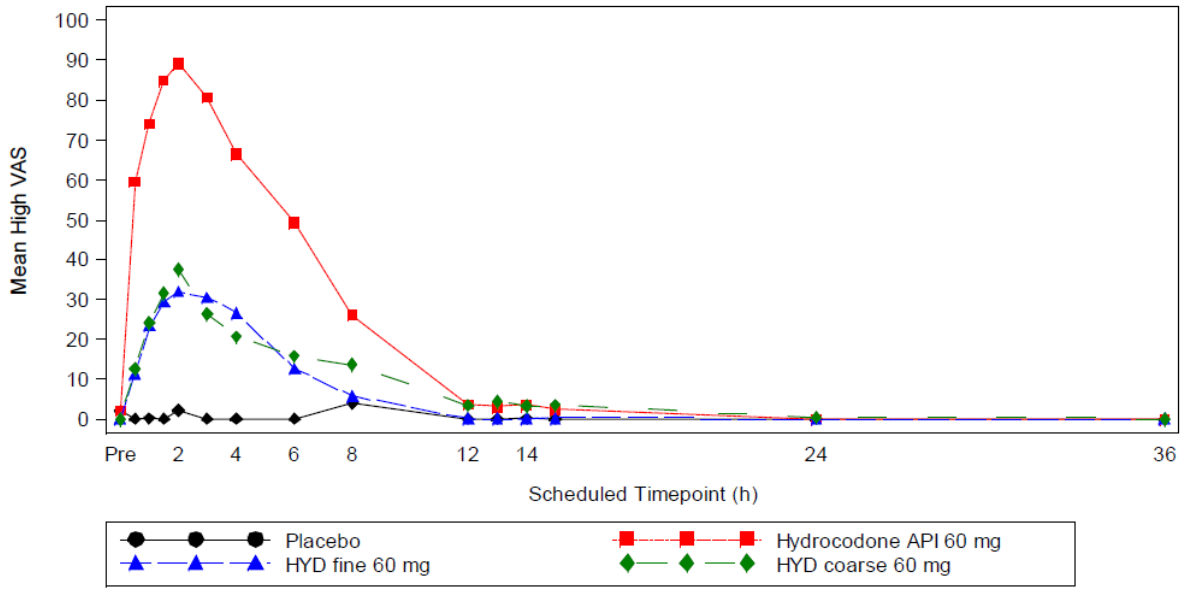
Pharmacodynamic Results

In the Treatment Phase hydrocodone API had mean scores that were much higher than all other treatments. Scores were in the "liking" range (>50) between 0.5 and 8 hours post-dose, after which they returned to just above neutral (50). Both Hysingla ER treatments (fine and coarse) showed a minimal increase in scores on Drug Liking VAS between 1 and 4 hours post-dose, after which scores returned to neutral. Placebo scores remained close to the neutral mark (50), showing very little change through the sampling period. These Treatment Phase results are demonstrated in the Sponsor's plots of mean scores over time on the primary measures of Drug Liking VAS and High VAS. See the Sponsor's Figure 9.



Sponsor's Figure 9. Mean Score Over Time for Drug Liking VAS (Intranasal Administration; Fine and Coarse Particle Size) API=active pharmaceutical ingredient; HYD=hydrocodone bitartrate q24h film coated tablet; PD=pharmacodynamic; VAS=visual analog scale; Drug Liking VAS item: "At this moment, my liking for this drug is," where values can range from 0 (Strong disliking) to 100 (Strong liking), and 50 (Neither like nor dislike) is the neutral point

Hydrocodone API showed High VAS scores that were markedly higher than placebo from 0.5 to 8 hours post-dose, with the highest mean scores observed between 1.5 and 3.0 hours post-dose. Mean scores for Hysingla ER treatments (fine and coarse) showed similar time course profiles with a 25- to 37-point increase in scores (relative to pre-dose) from approximately 1 to 4 hours post-dose before gradually returning to neutral at approximately 8 hours post-dose. Mean scores for both Hysingla ER treatments were higher than placebo but much lower than hydrocodone API; however, peak scores for Hysingla ER coarse were slightly higher than for fine. Placebo scores remained around neutral for the entire sampling period. See the Sponsor's Figure 10.



Sponsor's Figure 10. Mean Score Over Time for High VAS VAS (Intranasal Administration; Fine and Coarse Particle Size) API=active pharmaceutical ingredient; HYD=hydrocodone bitartrate q24h film coated tablet; PD=pharmacodynamic; VAS=visual analog scale High VAS item: "I am feeling high," where responses range from 0 (Definitely not) to 100 (Definitely so)

Hydrocodone API had the highest mean and median scores for Emax compared to all other treatments. Mean High VAS Emax values were similar for the two Hysingla ER treatments; however, median Emax scores for Hysingla ER coarse were higher than for fine. There was greater variability in mean High VAS Emax scores for both Hysingla ER treatments when compared to hydrocodone API. Mean and median High VAS Emax scores were neutral for placebo. See Table 25.

Table 25. The Analysis Results for High VAS Emax

Pair Comparisons	Median Difference	P value
Hydrodocone 60 mg vs Placebo	100.0	<0.001
Hysingla ER fine 60 mg vs Hydrocodone 60 mg	-65.0	<0.001
Hysingla ER coarse 60 mg vs Hydrocodone 60 mg	-40.0	<0.001
Hysingla ER fine vs Placebo	16.0	0.001
Hysingla ER coarse 60 mg vs Placebo	37.0	<0.001
Hysingla ER coarse 60 mg vs Hys ER fine 60 mg	0.0	0.640

Observer-Rated Assessment of Intranasal Irritation (ORAII) was measured over time. Mean pre-dose ORAII scores were similar for all treatments. Mean and median ORAII Emax scores for hydrocodone API were low and not notably different from placebo. Mean and median Emax values of all ORAII measures were higher for Hysingla ER treatments (fine and coarse) compared to placebo and hydrocodone API. ORAII Emax scores were similar for both Hysingla ER treatments, although mean and median Emax of Nasal Irritation were lower for coarse Hysingla ER. Mean ORAII scores (pre-dose and Emax) are presented in Table 26.

Table 26. Selected Descriptive Statistics of Emax for ORAII

	Placebo (N=25)	Hydrocodone 60 mg (N=25)	Hysingla ER fine 60 mg (N=25)	Hysingla ER coarse 60 mg (N=25)
Nasal Congestion Mean (SD) Median	 0.8 (1.03) 0.0	 1.3 (1.17) 1.0	 4.3 (0.54) 4.0	 3.6 (1.44) 4.0
Nasal Irritation Mean (SD) Median	 0.3 (0.63) 0.0	 0.9 (1.01) 1.0	 3.6 (1.29) 4.0	 2.5 (1.78) 2.0
Nasal Discharge Mean (SD) Median	 0.5 (0.87) 0.0	 0.5 (0.77) 0.0	 2.8 (1.05) 3.0	 2.4 (1.38) 3.0

The Take Drug Again VAS provided a measure of the balance of drug effects and indicated the subject's willingness to take the drug again. In contrast to the Drug Liking VAS, these scales, administered at least 8 hours after study drug administration, had the advantage of the subject being relatively less affected or unaffected by study drug effects (if any) by the time of the assessment. See Table 27.

Table 27. Take Drug Again VAS with Drug Liking VAS Emax

	Placebo	Hydrocodone 60 mg Solution	Hysingla ER 60 mg Fine	Hysingla ER 60 mg Coarse
Drug Liking VAS mean (SD)	50.2 (0.47)	89.4 (13.56)	62.2 (21.68)	61.2 (16.44)
Take Drug Again VAS mean (SD)	2.0 (10.00)	85.2 (24.86)	40.7 (38.39)	36.4 (41.02)

Overall Summary of Pharmacodynamic Results HYD 1014

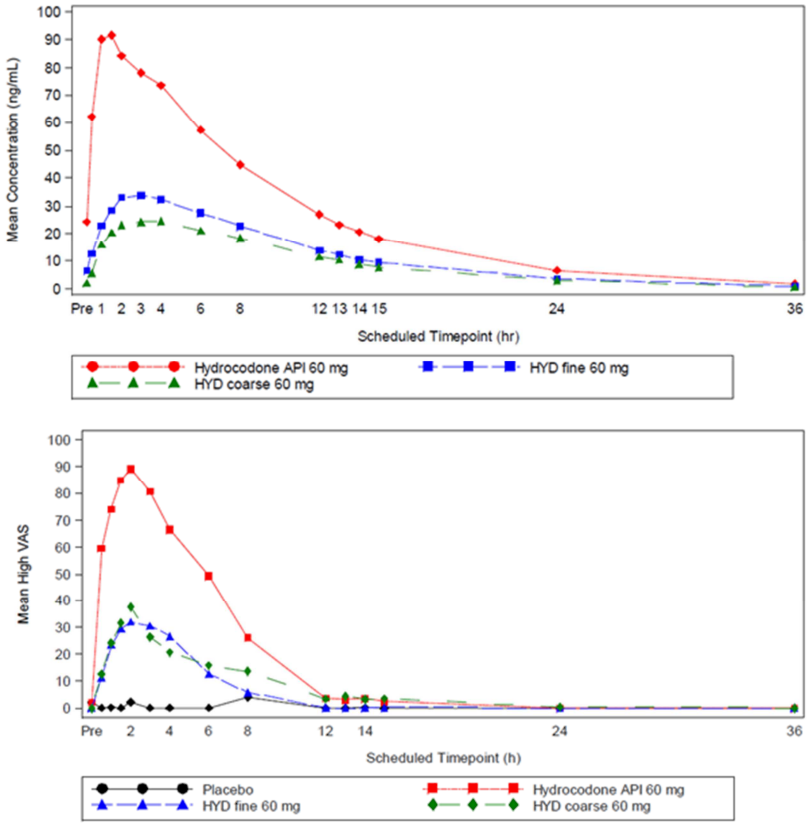
This study was conducted to investigate the subjective and objective effects of Hysingla ER, when milled into fine particles or cut into coarse particles and administered intranasally (via insufflation), in comparison to hydrocodone API and placebo administered intranasally. The results indicated that Hysingla ER, whether insufflated as fine or coarse particles, showed significantly less abuse potential than hydrocodone API on almost all endpoints, including both primary endpoints of Drug Liking VAS and High VAS.

There were statistically significant differences between placebo and hydrocodone API for the primary measures of Drug Liking VAS and High VAS. Hydrocodone API was also associated with small but statistically significant negative effects, including increased nasal irritation and congestion in comparison to placebo. Relative to hydrocodone API, Hysingla ER coarse and fine were associated with significantly lower effects on all subjective and objective measures, including both primary endpoints, and both Hysingla ER treatments were associated with greater intranasal effects, especially measures of nasal congestion and irritation. Hysingla ER fine was associated with greater nasal

congestion compared to coarse, but on most other outcome measures, the two treatments were not statistically different. The majority of subjects (>50%) showed at least a 30% reduction in Drug Liking VAS scores (responders) following administration of Hysingla ER coarse and at least a 40% reduction in Drug Liking VAS scores following administration fine.

Pharmacokinetic–Pharmacodynamic Conclusion

Study HYD 1014 demonstrates that the High VAS PD findings are reasonably consistent with the serum concentrations of hydrocodone from positive control and Hysingla ER for 36 hours. These findings suggest that the abuse liability of hydrocodone in both products is directly proportional to the serum concentrations produced in these drugs. These PD and PK parameters are compared in the Sponsor's Figure 11.



Sponsor's Figure 11. Mean Drug Plasma Concentration versus Time Comparison with High VAS versus Time

4.2 Adverse event profile through all phases of development

The total number of study patients exposed to at least one dose of Hysingla ER was 2,476 (364 for more than 12 months).

The incidence of AEs associated with potential abuse during Hysingla ER exposure (titration, post titration, taper, and overall) were assessed, by AE group, for the pooled chronic pain studies (HYD3002

and HYD3003), and the clinical pharmacology studies. The AEs considered strongly associated with abuse potential were:

- Dependence, Withdrawal, and Substance-Related Disorders
- Euphoria
- Central Nervous System Depressant Effects
- Stimulation and Anxiety Symptoms
- Perception Disturbances/Psychotomimetic Effects
- Mood Disorders and Disturbances
- Mental and Cognitive Impairment

See Sponsor's Table 28.

Sponsor's Table 28. Number (%) of Subjects with Treatment-Emergent Adverse Events Associated with Drug Abuse Potential

	Number (%) of Subjects			
	Pooled chronic pain studies - HYD exposure	HYD3002 – double-blind period		Pooled clinical pharmacology studies – HYD exposure
Category	HYD (N=1827)	Placebo[a] (N=292)	HYD (N=296)	HYD (N=584)
Drug abuse, dependence, withdrawal and substance-related disorders	26 (1)	4 (1)	3 (1)	1 (< 1)
Euphoria-related adverse-events	186 (10)	5 (2)	9 (3)	82 (14)
CNS depressant effects	296 (16)	4 (1)	8 (3)	80 (14)
Stimulation and anxiety symptoms	68 (4)	5 (2)	5 (2)	16 (3)
Perceptual disturbances/psychotomimetic effects	72 (4)	0	3 (1)	12 (2)
Mood disorders and disturbances	41 (2)	3 (1)	1 (< 1)	1 (< 1)
Mental and cognitive impairment	32 (2)	0	1 (< 1)	3 (1)

Source: ISS Appendix 10.2, Tables 6.13.1, 6.13.2, 6.13.3.
CNS=central nervous system.
Note: N=number of subjects in the group. Percentages are based on N.
[a] The placebo column represents subjects randomized to placebo but who may have had exposure to HYD during the taper period in the double-blind period.

In addition to the AEs there were 120 nonfatal treatment-emergent SAEs reported in 84 subjects; 12 of these SAEs were considered by the investigator to be definitely, probably, or possibly related to study drug. The most common AEs (≥ 5%) were nausea, constipation, vomiting, dizziness, fatigue, upper respiratory tract infection, headache, and somnolence. There were no dose-response relationships observed for any AEs and none leading to discontinuation or SAEs.

4.3 Safety profile

A total of 7 deaths were reported, all of which occurred in the Phase 3 chronic pain studies. Of the total number of deaths reported, 6 were considered treatment emergent (5 subjects died while receiving

Hysingla ER, 1 subject died while receiving placebo). Of the 6 treatment-emergent deaths, 5 deaths were considered not related to the study drug (respiratory failure, profound metabolic acidosis/thrombocytopenic embolic purpura, hypoxia, squamous cell carcinoma of the lung, brain aneurysm) and 1 death was considered definitely related to study drug (accidental acute hydrocodone, citalopram, and cyclobenzaprine toxicity). There did not appear to be any trend with regard to study period, organ system or length of exposure to study drug. The incidence of nonfatal SAEs during exposure to Hysingla ER was relatively low considering the large numbers of patients exposed in the pooled chronic pain studies, HYD3002 and HYD3003. The most common nonfatal SAEs in Hysingla ER treated subjects were chest pain (6 [< 1%] subjects), drug abuse (5 [< 1%] subjects), and osteoarthritis (4 [< 1%] subjects). See Sponsor's Table 29.

Sponsor's Table 29. Incidence of Treatment-Emergent Nonfatal Serious Adverse Events During Hysingla ER Exposure Occurring in ≥ 2% of All Hysingla ER Treated Subjects

System organ class Preferred term	Number (%) of HYD treated subjects (N=1827)
Any AE	83 (5)
Cardiac disorders	8 (< 1)
Myocardial ischemia	3 (< 1)
General disorders and administration site conditions	7 (< 1)
Chest pain	6 (< 1)
Infections and infestations	14 (1)
Diverticulitis	2 (< 1)
Pneumonia	2 (< 1)
Musculoskeletal and connective tissue disorders	11 (1)
Osteoarthritis	4 (< 1)
Arthralgia	2 (< 1)
Psychiatric disorders	10 (1)
Drug abuse	5 (< 1)
Renal and urinary disorders	4 (< 1)
Nephrolithiasis	2 (< 1)
Respiratory, thoracic and mediastinal disorders	9 (< 1)
Asthma	3 (< 1)
Chronic obstructive pulmonary disease	2 (< 1)
Pulmonary embolism	2 (< 1)
Surgical and medical procedures	2 (< 1)
Abortion induced	2 (< 1)

Source: ISS Appendix 10.2 Table 6.6.2.1.
Note: N=the number of subjects exposed to HYD. Percentages are based on N. Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 16.0.

The safety of Hysingla ER in the pediatric population was not assessed; there were no reports of accidental pediatric exposure. Suicidal ideation and accidental overdose were rare treatment emergent AEs reported in < 0.1% of the Hysingla ER treated subjects in the pooled chronic pain studies. There were no reports of homicidal ideation.

4.4 Evidence of abuse, misuse and diversion in clinical trials

The incidences of AEs related to aberrant drug behavior were: drug abuse (5 [< 1%] subjects), drug screen positive (1 [< 1%] subject), substance abuse (1 [< 1%] subject), intentional drug misuse (1 [< 1%] subject), and overdose (1 [< 1%] subject). There were no cases of diversion reported in the clinical pharmacology studies since the subjects did not have access to the study drug.

For the HYD3002 study, a total of 158 subjects were investigated for possible diversion. Diversion was confirmed for 39 (4.3%) subjects: 28 subjects during the run-in period and 11 subjects during the

double-blind period (3 Hysingla ER subjects and 8 placebo subjects). Among the cases of suspected diversion, 6 had study drug stolen (Hysingla ER and/or immediate-release oxycodone tablet) or study drug used by people other than study subjects.

For the HYD3003 study, a total of 176 subjects were investigated for possible diversion. Diversion was confirmed or suspected for 24 (2.6%) subjects. Among them, 10 subjects had study drug stolen or study drug used by people other than study subjects; of these, 4 subjects reported that the study drug was stolen by a family member or roommate; 6 reported that the study drug was stolen by non-family member(s).

Suspected diversion was reported at 8 investigative sites (5 sites in study HYD3002 and 3 sites in study HYD3003).

4.5 Tolerance and physical dependence studies in humans

The 8 AEs related to aberrant drug behavior included: drug abuse (5 [< 1%] subjects), drug screen positive (1 [< 1%] subject), substance abuse (1 [< 1%] subject), intentional drug misuse (1 [< 1%] subject), and overdose (1 [< 1%] subject). One event occurred while the subject was taking Hysingla ER 40 mg, 2 events at 80 mg, and 5 events at 120 mg. All 8 events occurred in study HYD3003. All 8 subjects were withdrawn from the study. These cases included subjects taking extra doses of Hysingla ER, filling narcotic prescriptions from other physicians, and cases of poly drug use and overdoses (cannabinoids and non-prescription opioids).

5. Regulatory issues and assessment

There are no scheduling issues, disposal issues, REMS or Advisory Committee recommendations. There are ongoing discussions between CSS, the Review Division (DAAAP) and the Sponsor regarding Hysingla ER's abuse deterrent claims and designations. CSS has determined that the drug does not have any significant "abuse deterrence" when ingested orally after fine milling. On the other hand, when Hysingla ER is taken whole, chewed, or inhaled it does demonstrate abuse deterrence.

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/s/

JAMES M TOLLIVER
09/02/2014

MARTIN S RUSINOWITZ
09/02/2014

SILVIA N CALDERON
09/02/2014

MICHAEL KLEIN
09/02/2014

Office of Prescription Drug Promotion

Internal Consult

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Joan Blair, Health Communications Analyst, DRISK

From: Eunice Chung-Davies, Regulatory Review Officer

CC: Sam Skariah, Team Leader
Vaishali Jarral, RPM, OSE
Kimberly Lehrfeld, Team Leader, DRISK
Jamie Wilkins-Parker, Senior Risk Management Analyst, DRISK
Carole Broadnax
CDER-OPDP-RPM
Michael Wade

Date: August 15, 2014

Re: **HYSINGLA ER (hydrocodone) extended-release tablets, for oral use, CII**
Comments on the addition of Hysingla ER to the draft SSS Risk Evaluation and Mitigation Strategies (REMS) Materials

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Materials Reviewed

OPDP has reviewed the following proposed ER/LA SSS REMS materials for Hysingla ER

- Healthcare Provider (HCP) REMS Materials:

- Patient Counseling Document (PCD) on Extended Release/Long Acting Opioid Analgesics
- FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics
- Prescriber Letter 1
- Prescriber Letter 2
- Prescriber Letter 3
- Professional Organization/Licensing Board Letter 1
- Professional Organization/Licensing Board Letter 2
- ER/LA Opioid Analgesic REMS SSS website (screen shots for www.ER-LA-opioidREMS.com)

The version of the draft REMS materials used in this review, entitled, "1-16-risk-mang-rems-and-materials-clean-Hysingla.doc", were sent from DRISK via email (Joan Blair, Health Communication Analyst) on August 6, 2014 and they are attached to the end of this review.

General Comment

Please remind the sponsors that REMS materials are not appropriate for use in a promotional manner.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Patient Counseling Document (PCD) on Extended Release/Long Acting Opioid Analgesics
- FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics
- Prescriber Letter 1
- Prescriber Letter 2
- Prescriber Letter 3
- Professional Organization/Licensing Board Letter 1
- Professional Organization/Licensing Board Letter 2
- ER/LA Opioid Analgesic REMS SSS website (screen shots for www.ER-LA-opioidREMS.com)

Specific Comments

OPDP considers recommends revision for the following:

- FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics (blueprint)

- Section VI. Specific Drug Information for ER/LA Opioid Analgesic Products includes a table entitled “Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)

  Hysingla ER

  - The “Key Instructions” row states (emphasis added), “During titration, dose adjustments may occur as early as **every 2 days**.” We acknowledge that the Highlights section of the PI (Dosage and Administration section) states, “Dose titration of HYSINGLA ER may occur every 2 days.” However, according to the Dosage and Administration section in the Full Prescribing Information, it states (emphasis added), “Adjust the dose of HYSINGLA ER in increments of 10-20 mg **every 3 to 5 days** as needed to achieve adequate analgesia.” Therefore, revision may be necessary depending on clarification from the Review Division.

  - The “Key Instructions” row includes (emphasis added), “Use a **low initial dose** and monitor closely for adverse events, such as respiratory depression and sedation, when administering HYD to patients with severe hepatic impairment or patients with moderate to severe renal impairment.” However, we note that Dosage and Administration sections (Sections 2.4 and 2.5) of the Full Prescribing Information state (emphasis added), “Initiate therapy **with ½ the initial dose of HYSINGLA ER** in these patients and monitor closely for respiratory depression and sedation.” We recommend revising to include the specific recommendation to use “1/2” the initial dose.

  - We note that section 7 of the Full Prescribing Information appears to include drug interactions for strong laxatives and potentially antiarrhythmic medications. As such, we recommend revising the “Specific Drug Interactions” row to include this information.

  - We note that the PI for Hysingla ER includes a warning for QT prolongation. Similar to the Butrans “Drug-Specific Safety Concerns” Row, we recommend adding this risk information to the “Product-Specific Safety Concerns” row.

- Prescriber Letters #1 and #2, Professional Organization/Licensing Board Letters #1 and 2
  - We note that the these letters state (emphasis added), “Extended-release and long-acting (ER/LA) opioid analgesics are approved for the

management of chronic moderate-to-severe pain in the U.S.,..." We recommend revising to language that is consistent with the currently approved ER/LA products. For example, we would not object to revising in a manner consistent with Prescriber letter #3 (i.e., "ER/LA opioid analgesics are used for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate...")

- Prescriber Letter #1 and Professional Organization/Licensing Board Letter #1

    - Please consider adding "hydrocodone" to the following, if appropriate:,

    "The branded and generic drug products subject to this REMS include *all*:
    - extended-release, oral-dosage forms containing
    - hydromorphone,
    - morphine,
    - oxycodone,
    - oxymorphone, or
    - tapentadol; …"

- ER/LA Opioid Analgesic REMS SSS website (www.ER-LA-opioidREMS.com)

    We note the presence of a yellow button with the text "Looking for Accredited REMS CME/CE? Click Here" (we note that this link currently exists on the active shared REMS website). This button links to a list of available REMS CME/CE programs. As previously discussed on May 7, 2014, we are concerned that it may appear that the Agency is endorsing these sites. Therefore, please ensure that the linked content is appropriate and that the FDA is comfortable with the content of each CE program listed on the CME/CE site. Please also check with the Office of Communications to see if they have any policies on linking to external sites.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

Enclosures:
Proposed REMS Materials for Hyingla ER

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/s/

EUNICE H CHUNG-DAVIES
08/15/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 07, 2014

To: Dominic Chiapperino, Ph.D.
Senior Regulatory Project Manager
Division Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Eunice Chung-Davies, Pharm.D.
Regulatory Review Officer
Office of Professional Drug Promotion (OPDP)

Subject: NDA 206627
OPDP labeling comments for HYSINGLA ER (hydrocodone) extended-release tablets, for oral use, CII

In response to DAAAP's May 6, 2014 consult request, OPDP has reviewed the draft Prescribing Information, Medication Guide, and carton and container labeling for HYSINGLA ER (hydrocodone) extended-release tablets, for oral use, CII

The review of the Prescribing Information (PI) is based on the proposed SCPI, entitled "Hysingla ER 4-28-3014 label with FDA revisions as of 7-28-2014 (CLEAN distributed as CPPI) emailed on July 28, 2014 from the DAAAP RPM. Please see the comments on the marked up version attached below.

The review of the carton and container labeling is based on the carton and container labeling obtained from the EDR (submission dated 8/1/14). We do not have any comments on the carton and container labeling at this time.

OPDP Comments on the proposed Medication Guide will be sent in collaboration with comments from the DMPP Patient Labeling Group.

If you have any questions for OPDP, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov .

Enclosure:
Marked up Prescribing Information

Carton and container labeling

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/s/

EUNICE H CHUNG-DAVIES
08/07/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 7, 2014
To:	Robert Rappaport, MD Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Eunice Chung-Davies, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name) Dosage Form and Route:	HYSINGLA ER (hydrocodone) extended-release tablets, for oral use, CII
Application Type/Number:	NDA 206627
Applicant:	Purdue Pharma L.P.

1 INTRODUCTION

On April 28, 2014, Purdue Pharma L.P. submitted for the Agency's review a 505 (b)(2) New Drug Application (NDA) 206627 for HYSINGLA ER (hydrocodone) extended-release tablets with the proposed indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which the alternative treatment options are inadequate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on May 6, 2014 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for HYSINGLA ER (hydrocodone) extended-release tablets.

2 MATERIAL REVIEWED

- Draft HYSINGLA ER (hydrocodone) extended-release tablets MG submitted on April 28, 2014, and received by DMPP and OPDP on May 6, 2014.
- Draft HYSINGLA ER (hydrocodone) extended-release tablets Prescribing Information (PI) submitted on April 28, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 28, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the class language for extend-release long-acting (ER/LA) products

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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

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/s/

MORGAN A WALKER
08/07/2014

EUNICE H CHUNG-DAVIES
08/07/2014

BARBARA A FULLER
08/07/2014

LASHAWN M GRIFFITHS
08/07/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
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M E M O R A N D U M

From: Donna L. Snyder, MD, Medical Officer
Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD, Team Leader
Lynne Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff (PMHS)

To: Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

NDAs: 206627

Sponsor: Purdue Pharma L.P.

Drug: Hysingla ER® (extended-release hydrocodone bitartrate) 20, 30, 40, 60, 80, 100 and 120 mg tablets

Proposed Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adult patients.

Division Consult Request:
The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Pediatric and Maternal Health Staff (PMHS) to review the Pediatric Use subsection in Hysingla ER® (hydrocodone bitartrate) labeling.

Background:
Purdue Pharma L.P. submitted a 505(b)(2) application for an abuse-deterrent, once daily, extended-release formulation of hydrocodone bitartrate (Hysingla ER®) for use in adult patients on April 28, 2014. The application relies on the Vicoprofen® (7.5 mg

hydrocodone bitartrate/200 mg ibuprofen) as the listed drug. The proposed indication is for the management of moderate to severe pain in adult patients when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The PDUFA date for this application is October 28, 2014, however this is a high priority review and DAAAP plans to take early action on the application.

Pediatric Review:
Under the Pediatric Research Equity Act (PREA), all applications for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must include a pediatric assessment that is adequate to assess the safety and effectiveness of the product and to support dosing and administration for all relevant pediatric populations, unless requirement is waived, deferred, or inapplicable. The application triggers PREA as a new dosing regimen.

The sponsor has requested a partial waiver for pediatric patients from birth to 7 years of age because studies are impossible or highly impractical. This is because the number of pediatric patients with the indication of chronic pain needing treatment for an extended period of time is too small. A partial waiver in this age group is consistent with other opioid narcotics such as Zohydro ER® (hydrocodone bitartrate) extended-release capsules and Exalgo® (hydromorphone HCL) extended-release tablets.

The sponsor has requested a partial waiver for pediatric patients ages 7 to 12 years of age on the grounds that a pediatric formulation cannot be developed for this age range. The tablets are (b) (4) in size. The rate of release of the drug is controlled by the (b) (4) tablet design and the dimension of the tablet. If the size of the tablet is reduced, the rate of release will be increased and duration of release will be reduced. The sponsor has attempted to develop a once-daily formulation with the same release profile that would be appropriate for this age range, but has been unsuccessful. Additionally the product swells and becomes a "viscous hydrogel" when exposed to water or other fluids and may be a choking hazard in this younger pediatric population. In the adult clinical studies, several patients reported difficulty swallowing the tablet, with one patient requiring medical intervention to remove the tablet.

The sponsor has requested a deferral of studies in pediatric patients 12 years of age and older because the product is ready for approval in adults and studies in this pediatric population have not been completed.

Reviewer comment: DAAAP met with the Pediatric Review Committee (PeRC) on July 9, 2104. PeRC agreed with the partial waivers in pediatric patients less than 12 years of age and deferral for the product, including that adequate attempts have been made to develop an age appropriate formulation for pediatric patients between 7 and 12 years of age. Information documenting the sponsor's failed attempts to develop a pediatric formulation must be posted on FDA's website.[1] *PeRC also recommended that labeling should include information on the choking risk in the Pediatric Use subsection.*

[1] Draft Pediatric Review Committee (PeRC) Meeting Minutes dated July 9, 2014.

Pediatric Use Labeling:
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

Discussion:
PMHS – Pediatrics Team recommended changes to Hysingla ER® (hydrocodone bitartrate extended-release tablets) Pediatric Use labeling to include information on overdose and risk of choking because of the size of the tablet and because the tablet becomes a "viscous hydrogel" when exposed to water or other fluids. PMHS participated in labeling meetings and reviewed the final proposed labeling for this product.

Recommendations from the PMHS-Maternal Health Team related to Neonatal Opioid Withdrawal Syndrome (NOWS) will be conveyed in another document.

PMHS-PEDIATRIC TEAM RECOMMENDATIONS FOR LABELING
Note: these labeling recommendations are based on draft labeling from April 28, 2014. Refer to approval letter for final approved labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

---------- WARNINGS AND PRECAUTIONS ----------

- Risk of Choking/GI Obstruction: Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. (5.9, 5.10)

5 WARNINGS AND PRECAUTIONS

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of HYSINGLA ER, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with HYSINGLA ER and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of HYSINGLA ER are essential *[see Dosage and Administration (2)]*. Overestimating the HYSINGLA ER dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone.

5.9 Gastrointestinal Obstruction, Dysphagia, and Choking

In the clinical studies, some subjects reported difficulty swallowing HYSINGLA ER tablets described as esophageal obstruction, dysphagia, and choking. This may require medical intervention to remove the tablet. [*see Adverse Reactions (6)*]

Instruct patients not to pre-soak, lick, or otherwise wet HYSINGLA ER tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth [*see Patient Counseling Information (17)*].

Patients with underlying gastrointestinal disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying gastrointestinal disorders resulting in a small gastrointestinal lumen.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of HYSINGLA ER in pediatric patients have not been established.

Accidental ingestion of a single dose of HYSINGLA ER in children can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*.

HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) when exposed to water or other fluids. Pediatric patients may be at increased risk of esophageal obstruction, dysphagia, and choking because of a smaller gastrointestinal lumen if they ingest HYSINGLA ER *[see Warnings and Precautions (5.9)]*.

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/s/

HARI C SACHS
07/25/2014
I am signing on behalf of Donna Snyder and concur with these recommendations.

LYNNE P YAO
07/31/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
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Pediatric and Maternal Health Staff – Maternal Health Review

Date:	July 29, 2014 **Consult Received:** July 11, 2014
From:	Carol H. Kasten, MD, Medical Officer Pediatric and Maternal Health Staff, Maternal Health Team
Through:	Melissa S. Tassinari, Ph.D. DABT, Senior Clinical Advisor, Pediatric and Maternal Health Staff, Maternal Health Team Lynne P. Yao, MD, OND IO Associate Director Pediatric and Maternal Health Staff
To:	Division of Anesthesia, Analgesia and Addiction Products
Drug:	Hydrocodone Bitartrate (HYSINGLA ER) NDA 206627
Subject:	Labeling Review
Sponsor:	Purdue Pharma LP
Consult Request:	"DAAAP needs input from PMHS for appropriately labeling the product, including risk summary for specific population (maternal, pregnancy category, etc.)"

INTRODUCTION

On July 11, 2014 the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Pediatric and Maternal Health Staff - Maternal Health Team (PMHS-MHT) to review and revise relevant sections of the labeling for Hysingla ER (hydrocodone bitartrate extended release).

On April 18, 2014 Purdue Pharma submitted a 505(b)(2) application for hydrocodone formulated as abuse deterrent, film-coated tablets for oral administration every 24 hours. The NDA was granted Priority Review status. The proposed indication for Hysingla ER is for "the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time."

The reference listed drug (RLD) for this 505(b)(2) application is Vicoprofen (NDA 20716) which contains hydrocodone bitartrate and ibuprofen. The bioavailability data submitted for Hysingla ER have been accepted by the Division as comparable to that of hydrocodone in Vicoprofen. The abuse deterrence is derived from the excipient polyethylene oxide (PEO) which both imparts hardness and forms a viscous hydrogel when attempts are made to dissolve a Hysingla ER tablet in water. These characteristics are intended to make it more difficult to crush, chew, snort or inject the dissolved Hysingla ER tablet.

BACKGROUND

Hydrocodone

Hydrocodone is an opioid analgesic drug product which is biotransformed to the opioid hydromorphone. Its analgesic effect is attributable to both hydrocodone and hydromorphone. Both CYPs 3A4 and 2D6 metabolize hydrocodone, the first cytochrome to the inactive metabolite norhydromorphone; the second cytochrome to hydromorphone, a more potent opioid.

Opioid Analgesic Drug Products' Class Labeling

Newly required class labeling for opioid analgesic drug products have been issued which apply to Schedule II controlled substances with extended release or long acting (ER/LA) formulations.[1] As part of the class labeling, boxed warnings are required for addiction, abuse and misuse, respiratory depression that can lead to overdose and death and Neonatal Opioid Withdrawal Syndrome (NOWS) which may be life threatening in neonates whose mothers required prolonged opioid therapy while pregnant. In addition to the boxed warnings, there is class labeling in several sections and sub-sections. In April, 2014 PMHS-MHT recommended specific labeling for NOWS as part of a response to a Citizen's Petition on NOWS. The basis for the NOWS class labeling is contained in the PMHS-MHT consult review.[2]

[1] *Draft Guidances for Industry: Analgesic Indications: Developing Drug and Biological Products (February 2014); and, Abuse Deterrent Opioids-Evaluation and Labeling (January 2013).*
[2] Ref ID: 3488324

Literature and Databases Review
There are no adequate and well controlled studies on the use of Hysingla ER in pregnant women.

Pregnancy
A review of TERIS[3] states that a small risk for congenital anomalies cannot be excluded with prenatal exposure to hydrocodone but concludes this is unlikely. Reprotox[4] notes that there are small cohorts of hydrocodone exposed pregnancies which showed no increase in congenital malformations. Reprotox also comments on a small retrospective study which found an increase in several malformations[5] but cautions that the study's conclusions were based on a small number of affected children.

Lactation
LACTMED®[6] reports that use of oral narcotics during nursing "can cause infant drowsiness, CNS depression and even death." The report also notes that neonates are sensitive to even small doses of opioid analgesic drug products taken by the nursing mother.[6] A variety of factors may place neonates at particular risk of opioid toxicity.[7]

CYP3A4, which metabolizes hydrocodone to the inactive metabolite norhydrocodone, is only present in small quantities at birth and increases slowly over many months. This may delay the inactivation of hydrocodone which may persist at high levels.[7,8] The function of CYP2D6 which metabolizes hydrocodone to the more potent opioid hydromorphone, is low at birth[7]; however, the quantity of CYP2D6 protein rises quickly after birth such that its concentration reaches about one half to two-thirds that of the adult concentration by one month of age.[9] As a result, neonates and infants may biotransform increasing quantities of hydrocodone to hydromorphone putting them at increasing risk for the adverse effects of hydrocodone. Additionally, an ultra-rapid metabolizer variant of CYP2D6 exists which is capable of biotransforming hydrocodone to hydromorphone very rapidly.[7] Hendrickson and McKeown suggest it is the interplay of maturational and pharmacogenomic factors, particularly that of the CYP2D6 variant,

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[3] TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. Accessed July 15, 2014 http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/

[4] www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed July 15, 2014.

[5] Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, and Honein MA (2011) Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol 204 (4):314-11

[6] LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed Record Number: 990; Accessed July 15 2014. Last Revision Date:

[7] Hendrickson RG and McKeown NJ (2012) Is maternal opioid use hazardous to breast-fed infants? Clin Toxicol (Phila) 50 (1):1-14.

[8] Hysingla ER labeling

[9] Treluyer JM, Jacqz-Aigrain E *et al*. Expression of CYP2D6 in developing human liver. Eur J Biochem 1991;202, 583-588.

which may have played a role in the two reports of serious adverse events following human milk exposure to hydrocodone.[7,10,11]

In addition to LACTMED, the publication by Sauberan, Anderson *et al*[12] was reviewed. This publication is also is referenced in the labeling for Zohydro ER (NDA 202880), another extended-release hydrocodone bitartrate product. In the Sauberan, Anderson *et al* publication, the levels of hydrocodone and hydromorphone reported in breast milk were highly variable. Of the thirty women in the study, only twelve had measurable levels of the drug and its metabolite. The authors note that there is a risk of toxic quantities of hydrocodone and hydromorphone in human milk for neonates with mothers are administered high hydrocodone doses. The authors also emphasize that maternal doses of hydrocodone should not exceed standard postpartum doses nor should they be used for a prolonged period.[12]

DISCUSSION

As part of the review of labeling language for Hysingla ER, PMHS-MHT reviewed labeling for Zohydro ER (hydrocodone bitartrate) and the RLD Vicoprofen. The applicant conducted reproductive toxicology studies for its product Hysingla ER, the results of which were comparable to Zohydro ER and the RLD at comparable doses. Therefore, the data reported in the labeling reflect the reproductive toxicology studies conducted specifically for this product, and not those of Zohydro ER or the RLD. In studies with hydrocodone for Hysingla in rats and rabbits no embryotoxicity or teratogenicity was observed. However, reduced pup survival rates and fetal/pup body weights were observed at doses causing maternal toxicity. In all of the studies conducted, the exposures in animals were less than the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons.

Labeling for subsection 8.3 Nursing Mothers was based on the information provided above. Given there have been reports of serious adverse events in neonates following exposure to hydrocodone which had been administered to their mother postnatally, either Hysingla ER should be discontinued or nursing of the neonate or infant should be discontinued.

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May, 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the

[10] Bodley V, Powers D. Long-term treatment of a breastfeeding mother with fluconazole-resolved nipple pain caused by yeast: a case study.J Hum Lact 1997;13:307 – 311.
[11] Meyer D, Tobias JD. Adverse effects following the inadvertent administration of opioids to infants and children. Clin Pediatr 2005;44:499 – 503.
[12] Sauberan JB, Anderson PO et al. Breast milk hydrocodone and hydromorphone levels in mothers using hydrocodone for postpartum pain. Obstet Gynecol 2011; 117:611 – 617.

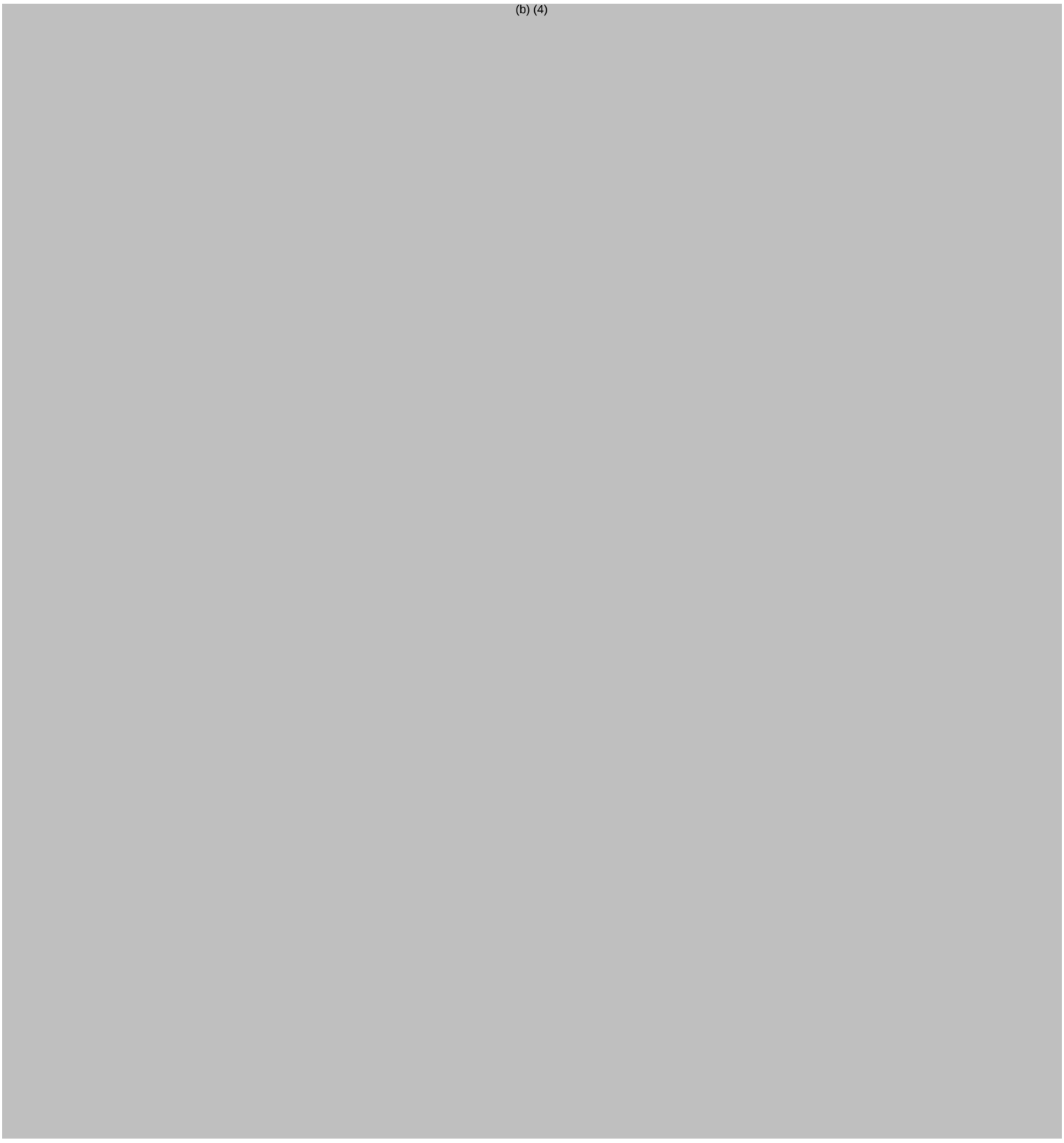
available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

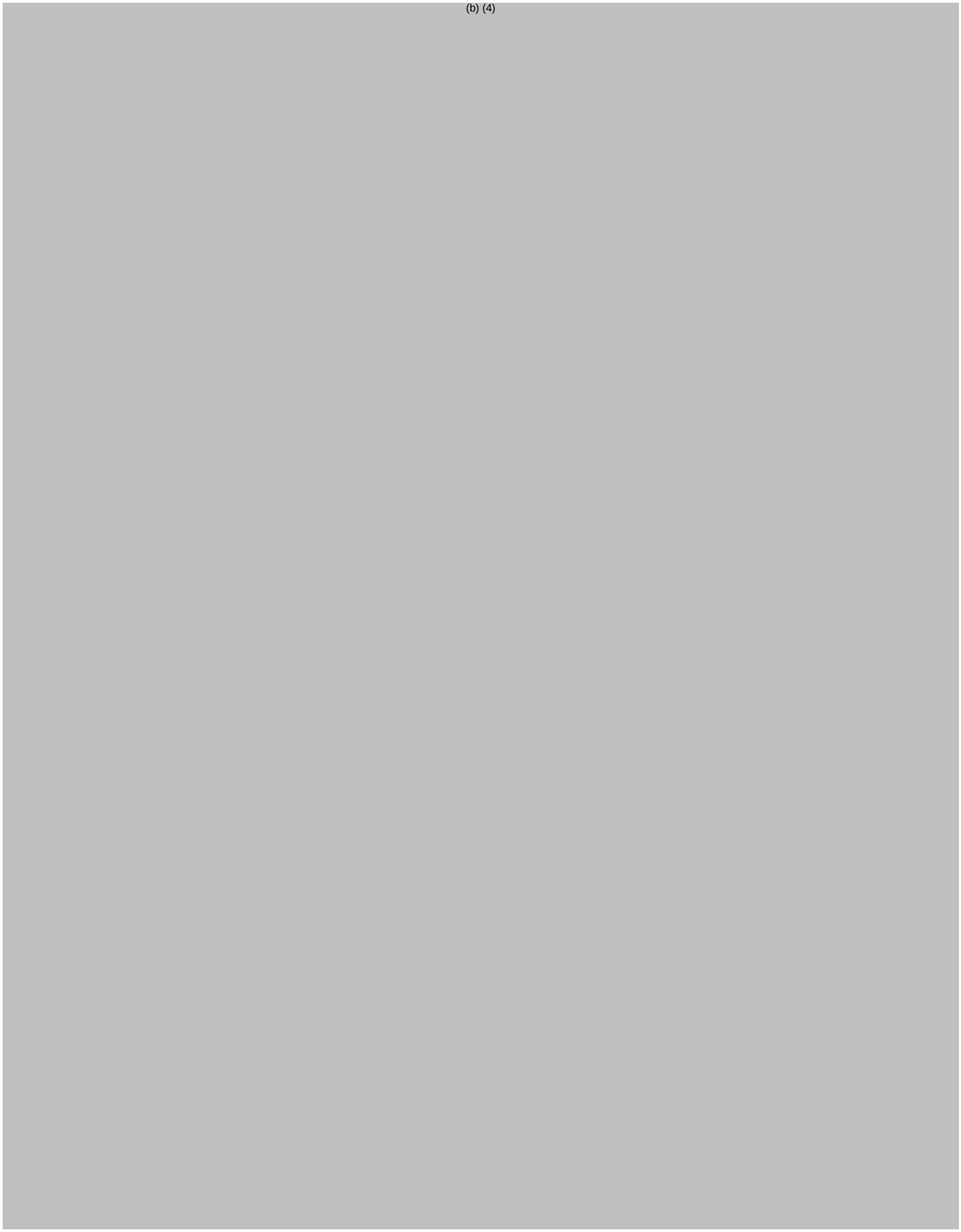
RECOMMENDATIONS

PMHS-MHT attended labeling meetings with the Division on July 16 and 24, 2014. The following are the PMHS Maternal Health Team recommendations for the proposed labeling for Hysingla ER. For the Pregnancy and Nursing Mothers sections, the information was re-formatted to conform to the structure outlined in the proposed PLLR.

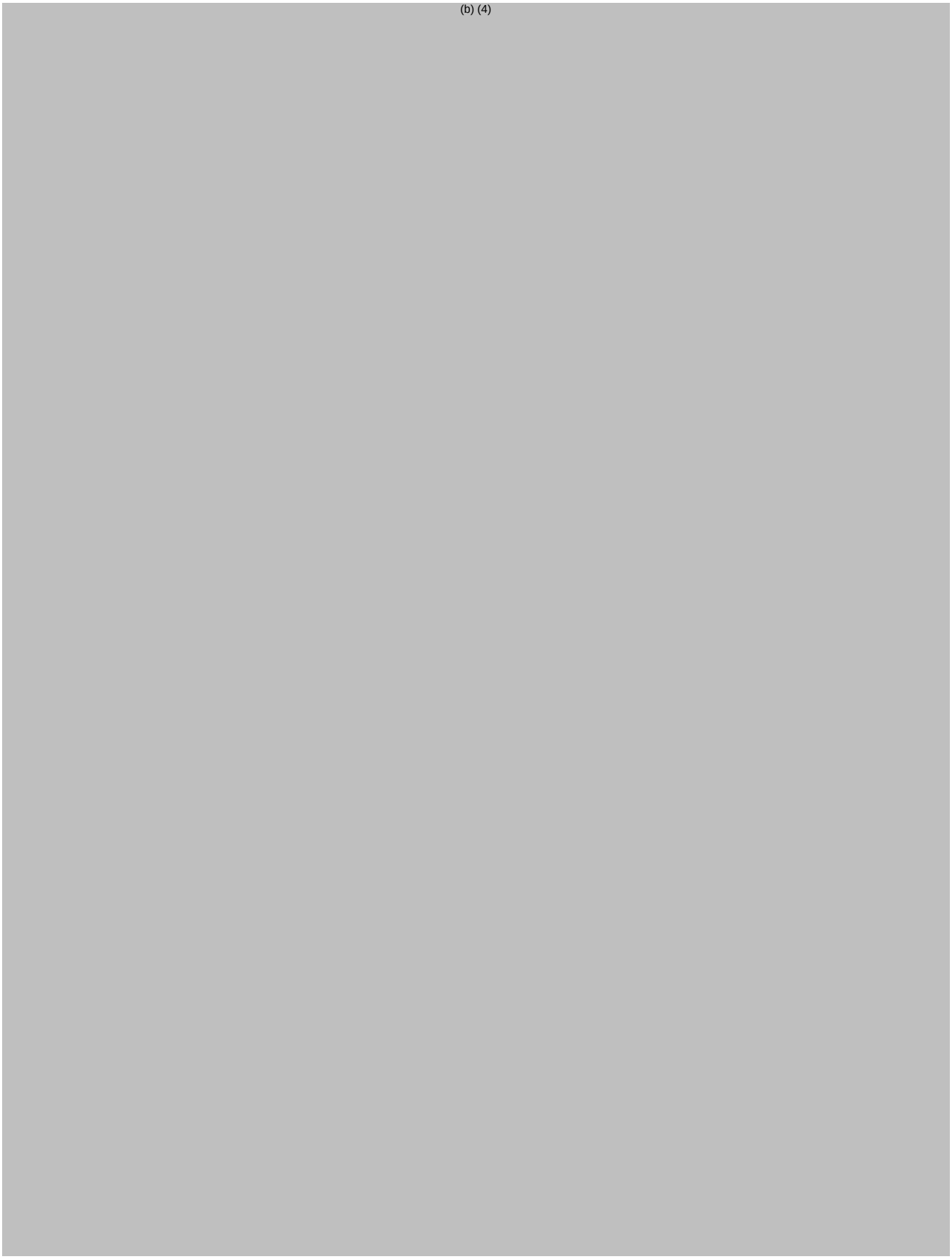
Language was provided in the following sections of the Hysingla ER labeling:

(b) (4)


(b) (4)


(b) (4)

(b) (4)



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/s/

CAROL H KASTEN
07/29/2014

MELISSA S TASSINARI
07/29/2014

LYNNE P YAO
07/31/2014

Center for Devices and Radiological Health

(ODE/DOED/ENTB)

Audiology Review

To**:** Jackie Spaulding, M.D. (CDER, WO22, Rm. 3231)

From: Cherish Giusto, Au.D.

Thru: Srinivas "Nandu" Nandkumar, Ph.D., Chief, ENTB

Date: June 26, 2014

Re: NDA 206627 (Purdue Pharma, L.P., HYD)

Thank you for your request of a consultative review of NDA 206627 submitted by Purdue Pharma, L.P. for HYD (hydrocodone bitartrate) ER tablets. I have reviewed the study report entitled: "Audiology Report for Hydrocodone Bitartrate Once-Daily, Extended-Release Tablets." The following memo presents a summary of the audiology report and an evaluation of the information provided in that report for the assessment of potential ototoxic effects from the study drug from the audiology perspective. Dr. Ting Zhang (audiology reviewer) also provided input that was incorporated into this review of the audiology report.

I. Purpose & Background

Purdue Pharma LP (Purdue) has developed Hydrocodone Bitartrate q24h Film-Coated Tablets (HYD) as a once-daily, abuse-deterrent, extended-release formulation of single-entity hydrocodone for treating moderate to severe chronic pain. HYD reportedly has the following indications:

Intended use: treatment of chronic pain
Proposed indication: "indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate"

There have been reports in the literature of hearing loss associated with the use of hydrocodone, usually with a hydrocodone/acetaminophen combination. These reports describe a sensorineural hearing loss that is typically sudden or rapidly progressive in nature, and often severe in degree. Currently, there is no clear consensus on the extent of hydrocodone's risk for ototoxic effects on hearing and vestibular function. Factors that contribute to the unclear nature of hydrocodone-associated hearing loss include: drug dosage, drug use period, patient risk factors (e.g., existing hearing loss, history of noise exposure) that may make them more susceptible to ototoxic effects, and the use of hydrocodone in conjunction with other agents (e.g., acetaminophen, NSAIDS,

aspirin). Since progressive hearing loss has been associated with the chonic use of hydrocodone/acetaminophen combination products and the potential exposure to hydrocodone from this HYD product is higher than the labeled doses from combination products, it was important to monitor for any potential cochleo-vestibular ototoxicity from the use of HYD during the Phase 3 clinical trials for this product.

Dr. Cherish Giusto (audiology reviewer), Dr. James Kane (audiology reviewer), and Dr. Srinivas Nandkumar participated with DAAAP in a Type C sponsor teleconference to discuss plans to monitor for ototoxicity on March 13, 2012. Dr. Giusto then provided a consult review and guidance for a Pre-NDA industry meeting held July 10, 2013, to advise whether the planned audiology assessments and resulting data would be a complete reviewable package for the NDA to assess ototoxicity.

The sponsor implemented an agreed upon protocol for audiological ototoxicity monitoring. Comprehensive audiology evaluations in the HYD phase 3 studies (study HYD3002 and study HYD3003) included assessment of air-conduction pure-tone audiometry, bone-conduction pure-tone audiometry, speech reception threshold, immittance audiometry (tympanometry), DHI, and THI.

The sponsor (Purdue Pharma, L.P.) recently submitted the results of their ototoxicity assessment as part of NDA 206627, and CDRH (ENTB) has been consulted to evaluate the resulting audiology report. Specifically, CDRH (ENTB) has been asked to answer the following question: Do you concur with sponsor's conclusion that there is not an increased risk for hearing impairment or vestibular disorders with HYD?

II. Review of Audiology Report

Purdue Pharma LP (PPLP) is submitting a 505(b)(2) New Drug Application (NDA) for a once-daily, abuse-deterrent, extended-release formulation of single-entity hydrocodone bitartrate tablets (HYD) for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

The following 2 Phase 3 studies, both of which were conducted in the United States, have been completed in support of the HYD program:

- Study HYD3002 was a Phase 3 multicenter, enriched-enrollment, randomized-withdrawal-design, double-blind, placebo-controlled study conducted in 905 subjects to compare HYD once daily (20 to 120 mg) with matching placebo in the treatment of subjects with moderate to severe chronic low back pain during a 12-week double-blind treatment period.
- Study HYD3003 was a Phase 3 open-label, multicenter study to assess the long-term (12-month) safety of HYD 20 to 120 mg once daily in 922 subjects with moderate to severe nonmalignant and nonneuropathic pain.

Audiology data and hearing impairment and vestibular disorders AE data from the 2 Phase 3 studies, pooled and for each individual study, were examined for a total of 1827 subjects (Table 3).

The numbers of subjects exposed to study treatment are summarized by dose in Table 3 for the safety population, audiology safety populations 1 and 2, study HYD3002, and cohorts 1 and 2A of study HYD3003.

Table 3 Enumeration of Subjects in This Integrated Audiology Analysis

		HYD						
	Placebo	20 mg	40 mg	60 mg	80 mg	120 mg	Any HYD	Total
Pooled Chronic Pain Studies	277	1569	1305	957	655	374	1827	1827
Audiology safety population 1	277	1046	860	604	401	225	1207	1207
Audiology safety population 2	277	1135	940	671	449	256	1308	1308
Study HYD3002 safety population	277	839	660	425	259	125	905	905
Study HYD3003 cohort 1	NA	207	200	179	142	100	302	302
Study HYD3003 cohort 2A	NA	89	80	67	48	31	101	101

Source: ISS Appendix 10.2 Table 1.1; HYD3003 CSR Table 14.1.4.1.1.2; and HYD3003 CSR Table 14.1.4.1.1.5.
NA=not applicable.
Notes: Audiology safety population 1 includes subjects in the safety population of study HYD3002 and subjects in cohort 1 of study HYD3003. Audiology safety population 2 included subjects in the safety population of study HYD3002 and subjects in cohorts 1 and 2A of study HYD3003. In study HYD3002 and study HYD3003, up-titration and down-titration of dose was permitted during specified study periods; if a subject received multiple treatments or HYD doses during a study, the subject was counted once in each treatment group or HYD dose level.

In audiology safety population 1 (see section 3.2.1.1), subjects who had a comprehensive audiology baseline prior to HYD treatment performed by licensed audiologists, 1207 subjects were exposed to HYD, including 187 (15%) subjects with exposure ≥ 6 months and 144 (12%) subjects with exposure ≥ 12 months. In audiology safety population 2 (see section 3.2.1.1), the above study population plus an additional subset of subjects (N=101) in study HYD3003 who had already been exposed to HYD but had a normal on-treatment baseline, 1308 subjects were exposed to HYD, including 283 (22%) subjects with exposure ≥ 6 months and 206 (16%) subjects with exposure ≥ 12 months (see Table 6). These numbers represent an adequate database for evaluation of ototoxicity.

There were 1827 subjects exposed to HYD in the safety population from the pooled chronic pain studies, including 798 (44%) subjects with exposure ≥ 3 months, 500 (27%) subjects with exposure ≥ 6 months, and 364 (20%) subjects with exposure ≥ 12 months.

Demographics, medical history, prior medications, and concomitant medications data demonstrated that the audiology safety populations were similar to the safety population (including those without appropriate audiology assessments but all other safety assessments).

3.2.1.1 Audiology Assessments

Two analysis populations from the pooled chronic pain studies were used in the analysis of the audiology data:

- **Audiology safety population 1:** This is the primary analysis population and includes subjects in study HYD3002 and subjects in cohort 1 of study HYD3003 who received ≥ 1 dose of study drug during the study.
- **Audiology safety population 2:** Includes subjects in study HYD3002 and subjects in cohort 1 and cohort 2A of study HYD3003 who received ≥ 1 dose of study drug during the study.

For the above audiology safety populations, the study HYD3003 cohorts were defined as follows:

- Cohort 1 consisted of subjects enrolled in study HYD3003 after implementation of protocol amendment 1 (protocol version 2: 21-Feb-2012). Additionally, these subjects

must have had a predose comprehensive audiology assessment performed ≤ 7 days prior to visit 2 (the start of HYD treatment).

- Cohort 2 consisted of subjects enrolled in study HYD3003 under the original protocol. Cohort 2A included subjects in cohort 2 who had a normal on-treatment baseline audiology assessment. A normal on-treatment baseline was defined as one meeting the following criteria:
    - Air conduction threshold ≤ 25 dB (applicable only to conventional frequencies of 250 through 8000 Hz)
    - Air-bone gap ≤ 10 dB
    - Normal tympanogram
    - Air conduction threshold asymmetry ≤ 20 dB at all test frequencies (applicable only to conventional frequencies of 250 through 8000 Hz).

3.2.1.2 Safety Populations

- The safety population of the pooled chronic pain studies includes all subjects who received ≥ 1 dose of study drug in study HYD3002 and study HYD3003.
- The randomized safety population of study HYD3002 includes all subjects who received ≥ 1 dose of the double-blind treatment.

Reviewer's Comments: From a clinical perspective, these numbers represent an adequate database for an acute evaluation of ototoxicity. Generally speaking, we would expect to see ototoxic drug effects on hearing and vestibular function (especially as measured by pure-tone audiometry) within 12 months of treatment with the drug. Furthermore, the type of hearing loss most typically reported in association with hydrocodone use is sudden in onset and/or rapid in progression. Therefore, these numbers/data from a 12 month post-treatment period are reasonable for an assessment of potential hydrocodone-associated hearing loss.

In summary: From an audiology perspective, we believe that 12-18 months is a sufficient time interval for assessing audiological effects from this drug. Please note that we defer to the CDER review team and statistical reviewers to determine if these exposure numbers will suffice for an adequate assessment of the long-term risk of HYD-associated hearing loss.

III. Review of Audiology Report

Sponsor's Summary and Conclusions from the analyses of the Audiological data:

This section presents pooled audiology assessment results for audiology safety populations 1 and 2 and audiology analyses results from study HYD3002 that compared HYD treatment and placebo treatment. These include the primary analyses (air-conduction pure-tone audiometry at conventional frequencies) and supportive and supplemental analyses.

Although variability in the data was observed, overall no signal of ototoxicity with HYD was identified in the analyses of the data from the comprehensive and extensive audiology testing conducted in the HYD phase 3 studies. The data patterns observed in the analyses are not consistent with a drug that is potentially ototoxic. The following is a summary of key findings for the primary analyses results.

- In the primary analysis based on air-conduction pure-tone audiometry at conventional frequencies (250 to 8000 Hz) in audiology safety population 1, similar number of subjects (99[11%]), if not more subjects, had improvement in hearing sensitivity compared to the number of subjects (71 [8%]) with decreased hearing sensitivity (American Speech-Language-Hearing Association (ASHA) event [ASHA events]). No dose-response was observed.
- Of subjects with ASHA events who had a subsequent pertinent audiology assessment, all either no longer met ASHA criteria or stabilized; no subjects were identified to have progressive hearing loss in this analysis.
- Few ASHA events (2 [<1%] subjects) were classified as CTCAE toxicity grade 2 or higher; no subjects had CTCAE grade 4 ASHA events.
- Baseline hearing status (normal v abnormal hearing) did not appear to increase the risk of experiencing ASHA events regardless of treatment (HYD or placebo).
- Air-conduction pure-tone audiometry conducted at ultra-high frequencies (10000 to 16000 Hz) provided a more sensitive evaluation of hearing sensitivity changes, but at the expense of increased variability. Nonetheless, the conclusions drawn from that data are similar to those based on conventional frequencies.
- Mean changes in air-conduction pure-tone audiometry threshold values from baseline were small and bidirectional, and not clinically remarkable.
- Threshold category shifts in air-conduction pure-tone audiometry between baseline and the end of HYD exposure were not clinically notable.
- Data patterns in speech reception threshold, bone-conduction pure-tone audiometry, word recognition, immittance audiometry, THI, and DHI do not suggest ototoxicity with HYD and support the primary analysis conclusions.

Reviewer's Comments: Essentially an equal amount of subjects experienced a significant improvement in hearing as experienced a significant decrease in hearing during the course of the audiological evaluation (see bullet point #1). The first bullet point reflects the variability that is inherent in the measurement of pure-tone air-conduction thresholds. Although measurement of these thresholds uses a well-established procedure with a documented +/- 5dB test-retest reliability, it is not uncommon to see +/- 10 dB test-retest fluctuations in hearing thresholds in clinical practice, especially in the high frequencies. Patient factors contributing to this including fatigue, attention, motivation, etc. play a role in the measurement variability, in addition to all of the typical psychoacoustic measurement factors. If there were a signal for ototoxicity, we would expect the data to be more skewed towards the amount of decrease in hearing sensitivity observed. We would also expect to see a greater magnitude of change in the decreases in hearing. Therefore, given these pure-tone air-conduction outcomes in the conventional frequencies, we agree that the data do not suggest any signal of adverse effects on hearing sensitivity.

The sponsor did not include ultra-high frequency audiometry as part of the primary analyses. Although we typically expect to see ototoxic medication effects first in the ultra-

high frequencies, it is also reasonable to assume that if there is no impact on conventional frequencies after 6-12 months of treatment with the drug, then there likely are not ototoxic effects on hearing function, particularly for speech understanding. Given the variability noted in the results from conventional audiometry, we would expect there equal or even greater variability in the ultra-high frequency data. It is reasonable to use the ultra-high frequency data as supplemental support. And in fact, a review of these ultra-high frequency data revealed a similar pattern to the conventional frequencies, with both improvement and decrements in hearing observed equally. Overall, the ultra-high frequency data did not suggest any significant signal of treatment-emergent hearing loss.

Please see comments below for more details about the sponsor's conclusions conveyed in the remaining bullet points not discussed here.

Sponsor's Summary and Conclusions from the ASHA Events:

71 (8%) of the subjects in audiology safety population 1 experienced a decrease in hearing as defined by the criteria by the American Speech and Hearing Association (ASHA). Subjects experiencing a significant threshold shift are described as having an "ASHA event."

5.1.3.3 American Speech-Language-Hearing Association Events by Magnitude of Change

The magnitude of change from baseline in air-conduction pure-tone audiometry results for subjects meeting ASHA criteria for conventional frequencies is summarized for audiology safety population 1 in Table 20.

During overall HYD exposure, 33 (46%) subjects had a ≥ 10 to < 15 dB change and 32 (45%) subjects had a ≥ 15 to < 30 dB change, while 4 (6%) subjects had ≥ 30 to < 50 dB change and 2 (3%) subjects had a ≥ 50 dB change. Results for during the study period were similar overall.

The magnitude of change from baseline in air-conduction pure-tone audiometry for subjects meeting ASHA criteria during the double-blind period for conventional frequencies for the randomized safety population of study HYD3002 is summarized in Table 21.

Of subjects in the HYD group who met ASHA criteria during double-blind treatment (13 subjects), 7 subjects had a ≥ 10 to < 15 dB change and 5 subjects had a ≥ 15 to < 30 dB change; 1 subject had a ≥ 30 to < 50 dB change, and no subject had a ≥ 50 dB change.

Of subjects receiving placebo who met ASHA criteria during double-blind treatment (9 subjects), 6 subjects had a ≥ 10 to < 15 dB change and 2 subjects had a ≥ 15 to < 30 dB change; no subject had a ≥ 30 to < 50 dB change. However, 1 subject had a ≥ 50 dB change. Overall, in the placebo group the number of subjects with changes in each of the specified magnitude categories was generally similar to those in the HYD group.

Reviewer's Comments: We agree that for the patients who experienced ASHA changes, overall the magnitude of changes were relatively small. These types of (relatively small) changes in hearing sensitivity are not consistent with the typical reports of rapid onset severe degrees of hearing loss associated with hydrocodone use.

5.1.3.4 Status of American Speech-Language-Hearing Association Events at Follow-up

AUDIOLOGY SAFETY POPULATION 1

The status of subjects meeting ASHA criteria based on air-conduction pure-tone audiometry during HYD exposure for conventional frequencies for audiology safety population 1 is summarized in Table 22.

Of 71 subjects who originally met ASHA criteria, subsequently 21 (30%) subjects no longer met ASHA criteria and 9 (13%) subjects stabilized, while no subject had progressive hearing loss. The remaining 41 subjects did not have a follow-up test while taking HYD.

Table 22 Status of Subjects Meeting American Speech-Language-Hearing Association Criteria Based on Air Conduction Pure-Tone Audiometry during HYD Exposure – Conventional Frequencies: Audiology Safety Population 1

	Overall HYD (N=1207)				
Frequency (Hz)	Number of subjects originally meeting ASHA n	Number of subjects no longer meeting ASHA n (%)	Number of subjects who stabilized n (%)	Number of subjects with progressive hearing loss n (%)	Number of subjects without subsequent audiometry assessment n (%)
250	11	4 (36)	0	0	7 (64)
500	13	5 (38)	0	0	8 (62)
1000	10	3 (30)	0	0	7 (70)
2000	13	3 (23)	1 (8)	0	9 (69)
3000	25	10 (40)	2 (8)	0	13 (52)
4000	31	11 (35)	5 (16)	0	15 (48)
6000	31	13 (42)	3 (10)	0	15 (48)
8000	42	12 (29)	5 (12)	0	25 (60)
Total	71	21 (30)	9 (13)	0	41 (58)

Source: ISS Appendix 10.2 Table 10.1.5.1a.
ASHA=American Speech-Language-Hearing Association; N=number of subjects in the period; n=number of subjects with data.

PIVOTAL STUDY HYD3002

The status of subjects meeting ASHA criteria based on air-conduction pure-tone audiometry during the double-blind period for conventional frequencies for the randomized safety population of study HYD3002 is summarized in Table 23.

Of 13 subjects who received HYD who originally met ASHA criteria during the double-blind period, subsequently 1 subject no longer met ASHA criteria and 1 subject stabilized, while no subject had progressive hearing impairment. Results were generally similar for subjects who received placebo. The remaining subjects did not have a follow-up test during double-blind treatment.

Reviewer's Comments: The sponsor concludes that no subjects with ASHA events had progressive hearing impairment in both the Audiology Safety Population 1 and the HYD3002 cohort. However, 41 out of 71 (58%) subjects in the Audiology Safety Population 1, and 11 out of 13 subjects who received HYD in the safety population for HYD 3002 who originally

met ASHA criteria for threshold shift did not have a follow-up test. This is a large amount of missing data. These missing data are significant enough to impact the ability to draw conclusions about progressive hearing loss. That is, we do not know if there was any progressive hearing loss in the majority of the subjects who experienced an ASHA event. Therefore, conclusions and claims about a finding of no progressive hearing loss observed during this study should be limited. See comment in "Conclusions" section below.

5.1.3.5 American Speech-Language-Hearing Association Events Time Course

AUDIOLOGY SAFETY POPULATION 1

Table 24 summarizes the time course of subjects meeting ASHA criteria based on air-conduction pure-tone audiometry during HYD exposure for the conventional frequencies for audiology safety population 1.

Of HYD-treated audiology safety population 1 subjects who originally met ASHA criteria at any frequency, the total number meeting ASHA criteria (conventional frequencies) based on air-conduction pure-tone audiometry during HYD exposure by time course was 5 subjects at ≤ 1 month, 8 subjects at > 1 to 3 months, 5 subjects at > 3 to 6 months, and 3 subjects at > 6 months.

Table 24 Time Course of HYD-Treated Subjects Meeting American Speech-Language-Hearing Association Criteria Based on Air-Conduction Pure-Tone Audiometry during HYD Exposure – Conventional Frequencies: Audiology Safety Population 1

	Overall HYD (N=1207)					
	Number of subjects originally meeting ASHA	1-month n/NN (%)	>1-3-months n/NN (%)	>3-6-months n/NN (%)	>6-months n/NN (%)	Total n/NN (%)
Left ear	45	4/10 (40)	6/21 (29)	4/13 (31)	3/9 (33)	10/30 (33)
Right ear	41	1/10 (10)	3/21 (14)	2/13 (15)	1/9 (11)	5/30 (17)
Unilateral	56	5/10 (50)	7/21 (33)	4/13 (31)	2/9 (22)	11/30 (37)
Bilateral	15	0/10	1/21 (5)	1/13 (8)	1/9 (11)	2/30 (7)
Total	71	5/10 (50)	8/21 (38)	5/13 (38)	3/9 (33)	13/30 (43)

Source: ISS Appendix 10.2 Table 10.1.8a.
ASHA=American Speech-Language-Hearing Association; N = number of subjects exposed to HYD. n = number of subjects who continue to meet ASHA at subsequent assessments in the specific time interval. NN = population at risk (subjects with a follow-up audiology assessment in that time interval). Percentages are based on NN. .
Notes: Audiology safety population 1 includes subjects in safety population of HYD3002 and cohort 1 of HYD3003.

The number and percentage of subjects with a post-treatment result for air-conduction pure-tone audiometry meeting ASHA criteria are summarized for audiology safety population 1 in ISS Appendix 10.2 Table 10.1.9a. The results of this analysis showed that for subjects meeting the ASHA criteria, the percentages of those subjects for each of the time course categories (ie, 1 month, > 1 to 3 months, > 3 to 6 months, and > 6 months [and total]) were within a range of approximately 25% to 60%, with gradual increases with longer durations noted (ie, 26.9%, 38.2%, 40.9%, and 56.3% [and 29.8%], respectively). This is as expected as only subjects whose ASHA events did not resolve were followed up further, with the subjects having longer follow up representing a higher risk group.

Reviewer's Comments: The ASHA events occurred at time intervals spread out between <1 month to > 6 months. The sponsor notes that the percentages for each time period ranged from 25 to 60% and showed a gradual increase in events with longer durations of HYD-use. Equally importantly, the above table shows that there were relatively few numbers of events (9-21) at each time interval, with the majority of events (21) occurring at 1-3 months. As the sponsor notes, the subjects whose ASHA events did not resolve were followed-up longer and represent a higher risk group. There is no overwhelming skew of the frequency of ASHA events towards any one time point.

Sponsor's Summary of Narratives from the ASHA Adverse Events related to Hearing Impairment and Vestibular Function:

A narrative was written for each subject with ≥ 1 ASHA event either at conventional frequencies or at ultra-high frequencies. Full narratives are provided in section 14.3.3 of study HYD3002 CSR and study HYD3003 CSR. A listing of the subjects with narratives is provided in Audiology Report Appendix 11.1.

Each hearing impairment and vestibular disorder-related event was first identified using SMQs for hearing impairment and vestibular disorders. Then these AEs were further evaluated by the investigators to determine if they were potentially related to hearing or vestibular systems. For example, a number of dizziness events were identified by the vestibular disorder SMQ, but most of these events were deemed to be opioid-related AEs and not associated with vestibular symptoms; narratives were only written for those dizziness events (a small subset) determined to be associated with vestibular symptoms.

ISS Appendix 10.2 Table 10.3 presents a listing of subjects in the safety population who discontinued from study treatment due to an ASHA-related event.

Brief case summaries are provided in this section for those events that occurred after the implementation of protocol amendment 1 for both study HYD3002 and study HYD3003 (after the audiologist performed audiology assessment was implemented).

Reviewer's Comments: Most of the ASHA events were unilateral. This is not consistent with hearing loss resulting from systemic ototoxicity or reports of hydrocodone-associated hearing loss that typically manifests in a bilateral hearing loss. There is nothing inherently alarming in the narratives to suggest ototoxicity from HYD use in this study.

We note that subjects #3070010, #3073004, #3031006, #3006016 all have history of noise exposure. We believe that additional analyses (such as those described on page 70 of the audiology report for baseline hearing level) would be useful to determine if the data suggest that noise exposure increases the risk of experiencing ASHA events. See comment in the "Conclusions" section below.

Sponsor's Discussion of Additional Risk Factors:

Events by Baseline Hearing Status

ASHA events by baseline hearing status were summarized for audiology safety population 1 and for study HYD3002.

A logistic regression analysis was conducted on subjects in the randomized safety population of study HYD3002 who met ASHA criteria for conventional frequencies during the double-blind period. The analysis model included terms for treatment group, age group (< 65 and >= 65 years), audiology baseline (normal v abnormal [defined as > 25 dB at frequencies of 250 through 8000 Hz]), sex, and prior use of ototoxic drugs (defined as ototoxic medication use prior to double-blind period) as covariates and treatment by audiology baseline and treatment by prior ototoxic use interaction terms. The logistic regression model included subject with ASHA event during the double blind period (Yes v No) as response variable. The exact method was used to estimate model parameters. P-values to test effects of each covariate and treatment interactions were presented.

These analyses were performed for conventional frequencies only. These analyses were not performed for audiology safety population 2. The study HYD3002 analyses are included in this report only (they are not part of the study HYD3002 CSR).

5.1.3.6 American Speech-Language-Hearing Association Events by Baseline Hearing Status

The percentages of subjects meeting ASHA criteria during HYD exposure or during the study were slightly higher for the subgroup with abnormal baseline hearing levels.

During overall HYD exposure, 32 (7%) subjects from the normal baseline subgroup (N=653), compared with 39 (9%) subjects from the abnormal baseline subgroup (N=549), had an ASHA event.

Similarly, during the study (postbaseline), 37 (7%) subjects from the normal baseline subgroup (N=653), compared with 46 (10%) subjects from the abnormal baseline subgroup (N=549), had an ASHA event.

Table 25 Number (%) of Subjects with American Speech-Language-Hearing Association Events by Baseline Hearing Level (Normal v Abnormal) during Overall HYD Exposure and during Study – Conventional Frequencies: Audiology Safety Population 1

	NN	Left ear n (%)	Right ear n (%)	Unilateral n (%)	Bilateral n (%)	Total n (%)
Normal baseline						
Overall HYD exposure[a] (N=653)	480	21 (4)	16 (3)	27 (6)	5 (1)	32 (7)
During study (postbaseline)[b] (N=653)	542	25 (5)	19 (4)	30 (6)	7 (1)	37 (7)
Abnormal baseline						
Overall HYD exposure[a] (N=549)	415	24 (6)	25 (6)	29 (7)	10 (2)	39 (9)
During study (postbaseline)[b] (N=549)	469	28 (6)	31 (7)	33 (7)	13 (3)	46 (10)

The slight difference in the incidence of ASHA events in the 2 subgroups may be attributable to differences in their demographic and baseline characteristics, as well as the use of potential ototoxic medications. Demographic and baseline characteristics are summarized by audiology baseline (normal *v* abnormal) for audiology safety population 1 in ISS Appendix 10.2 Table 4.1.1c. For the normal *v* abnormal groups, the following differences were observed: mean (SD) age 42.8 (11.41) *v* 56.3 (11.47) years; number (percentage) of males 227 (34.8%) *v* 273 (49.7%); and number (percentage) of opioid experienced subjects 322 (49.3%) *v* 318 (57.9 %) subjects. Prior and concomitant potential ototoxic medications are summarized by baseline hearing status (normal *v* abnormal) for audiology safety population 1 in ISS Appendix 10.2 Tables 5.1.2aa and 5.3.1.3b2a, the following differences were observed: there was more concomitant use of ototoxic medications in subjects with abnormal baseline hearing (43.2%) than in subjects with normal baseline hearing (36.1%); the prior use of ototoxic medications was similar between the 2 subgroups.

A logistic regression analysis was performed (see section 3.2.7.1) to examine the impact of baseline hearing status. After adjusting for baseline hearing status (normal *v* abnormal), age groups (< 65, >= 65 years), sex, the use of prior potential ototoxic medications, the results of the logistic regression showed that, compared to placebo, HYD did not show a statistically significant difference in ASHA events (p = .454), and the interaction between study treatments and baseline hearing status was not significant (p= >.999). In addition, prior use of potential ototoxic medications was not a significant factor (p= >.999). (ISS Appendix 10.2 Table 10.1.11)

Reviewer's Comments: We concur with the sponsor's analyses and conclusions regarding baseline hearing status with respect to ASHA events. There does not appear to be a significant difference in the rate of ASHA threshold shifts in those with normal versus abnormal baseline (pre-treatment) hearing assessments. Therefore, existing hearing loss does not appear to pose an increased risk for any ototoxic effects from the use of HYD under the conditions studied.

3.2.5 Prior and Concomitant Medications

Collection of data regarding ototoxic agent use within 6 months prior to screening was not included in the original protocols for either study HYD3002 or study HYD3003 but was subsequently instituted with protocol amendment 1 (dated 21-Feb-2012) for both studies.

As all subjects enrolled in study HYD3002 were screened under protocol amendment 1 or later, data regarding ototoxic agent use within 6 months prior to screening were to have been obtained for all subjects in this study. In study HYD3003, however, 483 subjects were enrolled under the original protocol, and thus information regarding prior ototoxic agent use within 6 months prior to screening was not collected for these subjects. As a result, analyses of ototoxic agent use within 6 months prior to screening involves study HYD3002 subjects screened under all protocol versions and study HYD3003 subjects screened under protocol amendment 1 or later (cohort 1).

Subjects in both chronic pain studies took concomitant medications (allowed in the studies), including some analgesics for their pain conditions, that are potentially ototoxic. This information is relevant to the analyses of audiology data and the assessment of AEs associated with hearing impairment or vestibular disorders. These potentially ototoxic medications include medications in the following 4 categories: macrolides, phosphodiesterase 5 (PDE5) inhibitors, NSAIDs, and acetaminophen.

The use of known ototoxic medications (eg, certain chemotherapeutic agents, aminoglycosides) was exclusionary after protocol amendment 1 for both study HYD3002 and study HYD3003 (see study HYD3002 protocol and study HYD3003 protocol). Subjects in cohort 2A of study HYD3003 were enrolled before protocol amendment 1; any ototoxic medications taken by these subjects are noted in the study HYD3003 CSR.

Prior medications were defined as medications taken within 30 days of screening. Prior medications were summarized by pharmacological class, pharmacological sub-class, and preferred term by enrollment status (ie, for subjects entering the post-titration period and for subjects not entering the post-titration period) and overall, and specifically for the following:

- Potentially ototoxic medications (ISS Appendix 10.1 SAP) taken within 30 days before screening
  - For audiology safety populations 1 and 2 and the safety population of the pooled chronic pain studies
- Potentially ototoxic medications taken within 6 months before screening
  - For the audiology safety population 1
- Incoming oxycodone-equivalent daily dose at screening (as reported by the investigator)
  - For the audiology safety populations 1 and 2 and the safety population of the pooled chronic pain studies

Concomitant medications and concomitant ototoxic medications were defined as the medications after the first HYD dose and were summarized by pharmacological class, pharmacological sub-class, and preferred term by study period for the audiology safety populations 1 and 2 and the safety population of the pooled chronic pain studies. The primary analysis for concomitant medications and concomitant ototoxic medications was based on concomitant medications excluding overlapped medications which are defined as prohibited medications stopped on the same day as the first study drug dose date and/or start the prohibited medications on/after the day they discontinued study drug.

4.4.3 Concomitant Potential Ototoxic Medications

4.4.3.1 Audiology Safety Populations

ISS Appendix 10.2 Tables 5.3.1.3b1, 5.3.1.3b2, 5.3.1.3c1, and 5.3.1.3c2 present summaries of the concomitant ototoxic medications taken by subjects exposed to HYD for audiology safety populations 1 and 2.

For subjects in audiology safety population 1 (excluding overlapped medications) overall, 373 (31%) subjects took NSAIDs, 192 (16%) subjects took acetaminophen, 35 (3%) subjects took macrolides, and 16 (1%) subjects took PDE5 inhibitors. For subjects in audiology safety population 2 (excluding overlapped medications) overall, 446 (34%) subjects took NSAIDs, 243 (19%) subjects took acetaminophen, 42 (3%) subjects took macrolides, and 18 (1%) subjects took PDE5 inhibitors.

4.4.3.2 Study HYD3002

Discussions of concomitant ototoxic medications for study HYD3002 are presented in study HYD3002 CSR section 11.2.3.2.1 and study HYD3002 CSR Table 14.1.6.1.4. For these subjects, overall 338 (37%) subjects took NSAIDs, 260 (29%) subjects took acetaminophen, 18 (2%) subjects took macrolides, and 9 (1%) subjects took PDE5 inhibitors during HYD exposure. Their use was balanced between subjects assigned to the different double-blind treatments (30% for placebo *v* 34% for HYD). The most frequently used concomitant ototoxic medications (used in ≥ 10% of subjects) were NSAIDs (21%) and acetaminophen (14%), which were prohibited to be used during the study for pain. However, very few subjects (2%) actually had more than 1 day overlapping use of these medications with the study treatment. Some subjects took NSAIDs (up to 15%) and acetaminophen (up to 4%) for non-pain conditions in both treatment groups.

The rate of the concomitant use of NSAIDs and acetaminophen (excluding overlapped medications) varied somewhat between the audiology safety populations, study HYD3002, and the safety population, although the variation was not greater than approximately 15% of subjects between any 2 populations. NSAIDs were used by 31% of subjects in audiology safety population 1, by 34% of subjects in audiology safety population 2, by 37% of subjects in study HYD3002, and by 42% of subjects in the safety population. Acetaminophen was used by 16% of subjects in audiology safety population 1, by 19% of subjects in audiology safety population 2, by 29% of subjects in study HYD3002, and by 26% of subjects in the safety population.

Reviewer's Comments: Although the sponsor included prior ototoxic medication use in their logistic regression analysis (e.g. age, hearing status, noise exposure) as described on page 29 of the audiology report, this concomitant ototoxic medication use is not analyzed to the same extent as baseline hearing status in the audiology report (i.e., we cannot locate additional analyses related this variable in the audiology report). We believe that the effects of use of prior or concomitant ototoxic medications, as well as prior opioid use, are important to inform labeling, since much of the intended population for your HYD product will be likely to use other ototoxic medications. We recommend that if the sponsor has not adequately analyzed this variable elsewhere in this NDA (e.g., in HYD3002 CSR section 11.2.3.2.1, or CSR Table 14.6.1.4), then the sponsor should perform additional analyses, similar to those performed to determine if baseline hearing level was a risk factor for ototoxic effects from HYD in your study (see page 70), with prior and concurrent ototoxic medication use as a factor. We defer to the CDER review team to make this judgment.

Sponsor's Summary and Conclusions from the Adverse Events related to Hearing Impairment and Vestibular Function:

The incidence of hearing impairment and vestibular disorder-related events was low. Overall, 59 (3%) subjects in the safety population (pooled chronic pain studies) experienced a TEAE related to hearing impairment and vestibular disorders during HYD exposure; the most frequently occurring events were tinnitus in 37 (2%) subjects, dizziness in 13 (1%) subjects, and vertigo in 4 (<1%) subjects. The AE data do not suggest an increased risk for hearing impairment or vestibular disorders with HYD.

The sponsor provides the following table presenting a cumulative summary of the percentage of subjects with confirmed treatment-emergent AEs related to hearing and balance in the pooled chronic pain studies population:

Table 43 Number (%) of Subjects with Confirmed Treatment-Emergent Adverse Events Related to Hearing Impairment and Vestibular Disorders during HYD Exposure in HYD-Treated Subjects: Pooled Chronic Pain Studies

SMQ category Preferred term	Number (%) of HYD treated subjects (N=1827)
All SMQ Category/Preferred Term	59 (3)
Hearing impairment	42 (2)
[N] Tinnitus	37 (2)
[N] Deafness transitory	3 (<1)
[N] Deafness	1 (<1)
[N] Deafness bilateral	1 (<1)
[N] Eustachian tube dysfunction	1 (<1)
[N] Hyperacusis	1 (<1)
[N] Hypoacusis	1 (<1)
[N] Tympanic membrane perforation	1 (<1)
Vestibular disorder	19 (1)
[B] Dizziness	13 (1)
[N] Vertigo	4 (<1)
[B] Vestibular disorder	1 (<1)
[N] Vertigo positional	1 (<1)
[N] Vestibular neuronitis	1 (<1)

Source: ISS Appendix 10.2 Table 6.9.1.1 and Table 6.9.1.13.

The sponsor provides the following table presenting a cumulative summary of the percentage of subjects with confirmed treatment-emergent AEs related to hearing and balance in the randomized safety population:

Table 44 Number (%) of Subjects with Confirmed Treatment-Emergent Adverse Events Related to Hearing Impairment and Vestibular Disorders during Double-blind Period: Randomized Safety Population (Pivotal Study HYD3002)

System organ class Preferred term	Placebo (N=292) n (%)	HYD (N=296) n (%)
All SMQ category/preferred	2 (1)	5 (2)
Related to hearing impairment or vestibular disorder	2 (1)	5 (2)
Dizziness	0	2 (1)
Tinnitus	0	2 (1)
Vestibular disorder	0	1 (<1)
Deafness unilateral	1 (<1)	0
Vertigo positional	1 (<1)	0

Source: HYD3002 CSR Table 14.3.1.5.1.3

Reviewer's Comments: The overall treatment-emergent adverse event rate for the pooled chronic pain studies was 3% (59 out of 1827). It was noted that the overwhelmingly most frequently occurring event in the safety population was tinnitus (37 out of 59 events, or 2% of the population). The sponsor reported that there were "no notable overall changes from

baseline in THI subscales." This suggests that overall, patients did not perceive an increase in tinnitus handicap during the course of the study. Very few vestibular disorders were noted in the entire population, suggesting no significant signal of vestibular dysfunction related to HYD use. In general, these data provide a reasonable assurance that there is not a significantly increased risk for hearing impairment or vestibular disorders with the use of HYD in the doses and time periods investigated during these Phase 3 trials from a clinical audiology perspective. However, we defer to the CDER review team regarding the significance of the treatment-emergent adverse event rates, particularly the rate of tinnitus which occurred in 2% of the pooled chronic pain studies population. We also defer to the CDER review team and statistical reviewers to determine if these exposure numbers will suffice for an adequate assessment of the long-term risk of HYD-associated hearing loss.

Sponsor's Report from Expert Opinions:

Three external subject matter experts assisted the sponsor in the evaluation of ototoxicity with HYD. They are:

(b) (4) Independent ENT Consultant

(b) (4) Independent Audiology Consultant

(b) (4) Independent Audiology Consultant

The consultants provided guidance on the development of the audiology testing methodology and the data analysis plan, conducted ongoing review of subject data, and reviewed this report and all subject narratives included in this report. They submitted the following opinion on the overall results:

Hearing loss has been reported with high dose and long-term use of hydrocodone/acetaminophen combination analgesics. The hearing loss has been described as rapid (occurring within days to weeks), severe to profound, and often bilateral. Many patients require a cochlear implant due to the severity of hearing loss. However, despite the widespread abuse of hydrocodone/acetaminophen combination analgesics, the reported incidence of hearing loss is extremely low. An in vitro mouse model study by Yorgason et al. suggests that acetaminophen, and not hydrocodone, is the component more likely causing ototoxicity.[2,3,4,6,11] However, since it is not definitively known whether or not hydrocodone is ototoxic, comprehensive audiologic testing was performed for both conventional and ultra-high frequency thresholds during the phase 3 studies of HYD.

Significant variability in thresholds was measured when compared to baseline during both the HYD 3002 and HYD 3003 studies. Threshold variability was similar in both directions with more subjects showing an improvement in thresholds. The variability may be due to multiple factors including less reliable audiologic testing due to decreased concentration or fatigue from analgesic use or from ongoing pain and discomfort. The changes seen in both studies appear to be variability and not indicative of ototoxicity.

In subjects with ASHA changes, most changes were of small magnitude and either resolved or persisted. No subjects in either study were found to have progressive changes. The literature regarding hydrocodone/acetaminophen ototoxicity describes a rapidly progressive and severe hearing loss. This pattern of hearing loss was not seen in either study. Also, most ototoxic medications affect the ultra-high frequencies and progress towards the conventional frequencies. This pattern was not seen in either study, and there was no identifiable pattern of ASHA changes in either group. For those subjects with ASHA changes, most changes showed variability over time. Finally, most ototoxic medications are dose dependent, but there was no dose dependent change in hearing thresholds seen with HYD.

Few subjects had greater than a CTCAE toxicity grade 1 change in hearing. In subjects that had CTCAE toxicity grade 2 or 3 change, most resolved or improved, and none progressed. None of these subjects progressed to severe to profound hearing loss as has been described in the literature regarding hydrocodone/acetaminophen ototoxicity. In addition, most of the changes were isolated to a single or a few frequencies and were unilateral, which is not a feature typical for drug-induced ototoxicity.

In summary, although there was a great deal of variability in hearing thresholds, there is no clear evidence of HYD ototoxicity at the dosages and time periods investigated in either study. It cannot be determined from these studies whether higher doses of hydrocodone could be ototoxic, especially with the concurrent use of acetaminophen. Finally, even if a potentially ototoxic dose exists, the abuse deterrent formulation may make it less likely that such a dose might be taken.

Reviewer's Comments: In general, we agree with the expert opinion's assessment of the audiological outcomes from these Phase 3 trials, as reflected in reviewer's comments above. We also agree with the expert opinion that "It cannot be determined from these studies whether higher doses of hydrocodone could be ototoxic, especially with the concurrent use of acetaminophen." It is important to note that we can only draw conclusions with respect to the specific population and treatment conditions studied in these trials.

IV. Conclusions & Recommendations:

Overall, the sponsor has provided appropriate data analyses to evaluate the ototoxicity of hydrocodone in their study. The sponsor followed the agreed upon ototoxicity monitoring protocol from the audiology perspective. Given the nature of a typical hydrocodone-associated hearing loss (i.e., sudden onset, rapidly progressing severe sensorineural hearing loss) from reports in the literature, we believe that 12-18 months is a sufficient time interval for assessing audiological effects from this drug.

From a clinical audiology perspective, the audiology report submitted as part of this NDA reveals no significant signal of acute decrements in hearing or vestibular function in the population studied, during the time course of the study, and under the dosage conditions studied. The overall treatment-emergent adverse event rate related to hearing and vestibular disorders during HYD use for the pooled chronic pain studies was 3% (59 out of 1827). It was noted that

the overwhelmingly most frequently occurring event in the safety population was tinnitus (37 out of 59 events, or 2% of the population).

We defer to the CDER review team regarding the adequacy of the exposure numbers/sample size and the primary data break down of subjects with significant changes in hearing into dose-response and toxicity grade analyses. We also defer to the CDER review team and statistical reviewers to determine if these exposure numbers will suffice for an adequate assessment of the long-term risk of HYD-associated hearing loss.

In summary, the data submitted in this audiology report adequately addresses our concerns about the potential for ototoxic effects from HYD use. There was no signal of any significantly increased risk for hearing loss or vestibular impairment in this study population with the HYD treatment protocol that was used. We have some additional comments for your consideration regarding progressive hearing loss and additional potential patient risk factors for hearing loss.

Question for CDRH (ENTB): Do you concur with sponsor's conclusion that there is not an increased risk for hearing impairment or vestibular disorders with HYD?

Answer: In general, we agree that the audiology data provides a reasonable assurance that there is not a significantly increased risk for hearing impairment or vestibular disorders with the use of HYD in the doses and time periods investigated during these Phase 3 trials from a clinical audiology perspective. However, we defer to the CDER review team regarding the significance of the treatment-emergent adverse event rates related to hearing and vestibular disorders, particularly the rate of tinnitus which occurred in 2% of the pooled chronic pain studies population (see Section 6.1 of the audiology report).

In addition, we have the following comments for your consideration:

1. The sponsor provides an analysis of the status of subjects meeting ASHA (American Speech and Hearing Association) criteria for threshold shift based on air-conduction pure-tone audiometry during HYD exposure for conventional frequencies for audiology safety population 1 (Section 5.1.3.4 of the audiology report). They state "Of 71 subjects who originally met ASHA criteria, subsequently 21 (30%) subjects no longer met ASHA criteria and 9 (13%) subjects stabilized, while no subject had progressive hearing loss." However, they also note that 41 out of 71 (58%) subjects in audiology safety population 1 who originally met ASHA criteria did not have a follow-up test. This is a large amount of missing data regarding the status of these subjects at follow-up; therefore, we do not know if there was any progressive hearing loss in the majority of the subjects who experienced an ASHA event. We acknowledge that reports of hydrocodone-associated hearing loss in the literature usually describe a sudden or rapidly progressive, severe sensorineural hearing loss. Thus, there is less concern about delayed onset or gradual progressive hearing loss from the use of hydrocodone. However, given the missing follow-up data for subjects who experienced a threshold shift (ASHA event) and relatively smaller

sample of subjects followed out to > 12 months, conclusions or claims about progressive hearing loss may be limited.

2. In Section 3.2.7.1 of the audiology report, the sponsor state "A logistic regression analysis was conducted on subjects in the randomized safety population of study HYD3002 who met ASHA criteria for conventional frequencies during the doubleblind period. The analysis model included terms for treatment group, age group (< 65 and >= 65 years), audiology baseline (normal *v* abnormal [defined as > 25 dB at frequencies of 250 through 8000 Hz]), sex, and prior use of ototoxic drugs (defined as ototoxic medication use prior to double-blind period) as covariates and treatment by audiology baseline and treatment by prior ototoxic use interaction terms." We believe that the effects of prior opioid use, and use of prior or concomitant ototoxic medications in conjunction with HYD use, are important to inform labeling, since much of the intended population for this HYD product will be likely to use other ototoxic medications. We recommend that if the sponsor has not adequately analyzed these variables elsewhere in this NDA (e.g., in HYD3002 CSR section 11.2.3.2.1, or CSR Table 14.6.1.4), then the sponsor should perform additional analyses, similar to those analyses performed to determine if baseline hearing level was a risk factor for ototoxic effects from HYD (see page 70 of the audiology report), to determine if prior opioid use and prior or concurrent ototoxic medication use increase the risk of experiencing an ASHA event.

3. In the brief case studies for subjects with select ASHA events from study HYD3003 (Section 7.2 of the audiology report), we note that subjects #3070010, #3073004, #3031006, #3006016 all had history of noise exposure. We believe that additional analyses would be useful to determine if the data suggest that noise exposure increases the risk of experiencing ASHA events. We recommend that the sponsor perform additional analyses with history of noise exposure as a factor, similar to those analyses performed to determine if baseline hearing level was a risk factor for ototoxic effects from HYD (see page 70 of the audiology report), particularly to inform their labeling.

Cherish Giusto, Au.D.
Clinical Reviewer in Audiology

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/s/

DOMINIC CHIAPPERINO
07/22/2014
Archiving the 6/26/14 review finalized by Cherish Giusto and Srinivas Nandkumar in CDRH/ENTB

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	206627
Brand Name	To be determined
Generic Name	Hydrocodone bitartrate extended-release tablets
Sponsor	Purdue Pharma L.P.(Stamford, CT)
Indication	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Dosage Form	Extended-release tablet 20, 30, 40, 60, 80, 100, and 120 mg
Drug Class	Mu (μ) receptor agonist opioid
Therapeutic Dosing Regimen	For opioid-naïve patients, initiate with 20 mg tablets orally every 24 hours For opioid-tolerant patients, no specified maximum therapeutic daily dose
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	160 mg
Submission Number and Date	001 /May 28, 2014
Review Division	DAAAP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

This randomized study administrated of multiple doses (once daily for 3 days) of HYD titrated from 20 to 160 mg. A central tendency analysis of the individual corrected QT (QTcI) interval data at steady-state demonstrated that the maximum mean (90% upper confidence bound) difference in QTcI from placebo after baseline-correction was 9.9 (12.7) ms, 6.9 (10.2) ms, and 5.6 (8.5) ms at HYD 160 mg, 120 mg and 80 mg respectively. The largest 90% upper confidence bound for the mean differences at HYD 160 mg and 120 mg was above 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 7, indicating that assay sensitivity was established.

In this randomized, double-blind, placebo-and positive-controlled, multiple-dose escalation, parallel-design study, 208 subjects received HYD 80 mg, HYD 120 mg, HYD

160 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for HYD (80mg, 120 mg and 160 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment Group	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
HYD 80 mg (Day 9)	24	5.6	(2.7, 8.5)
HYD 120 mg (Day 12)	24	6.9	(3.6, 10.2)
HYD 160 mg (Day 15)	10	9.9	(7.1, 12.7)
Moxifloxacin 400 mg (Day 9)*	3	11.6	(8.8, 14.5)
Moxifloxacin 400 mg (Day 12)*	3	9.7	(6.2, 13.2)
Moxifloxacin 400 mg (Day 15)*	4	8.7	(5.5, 11.8)

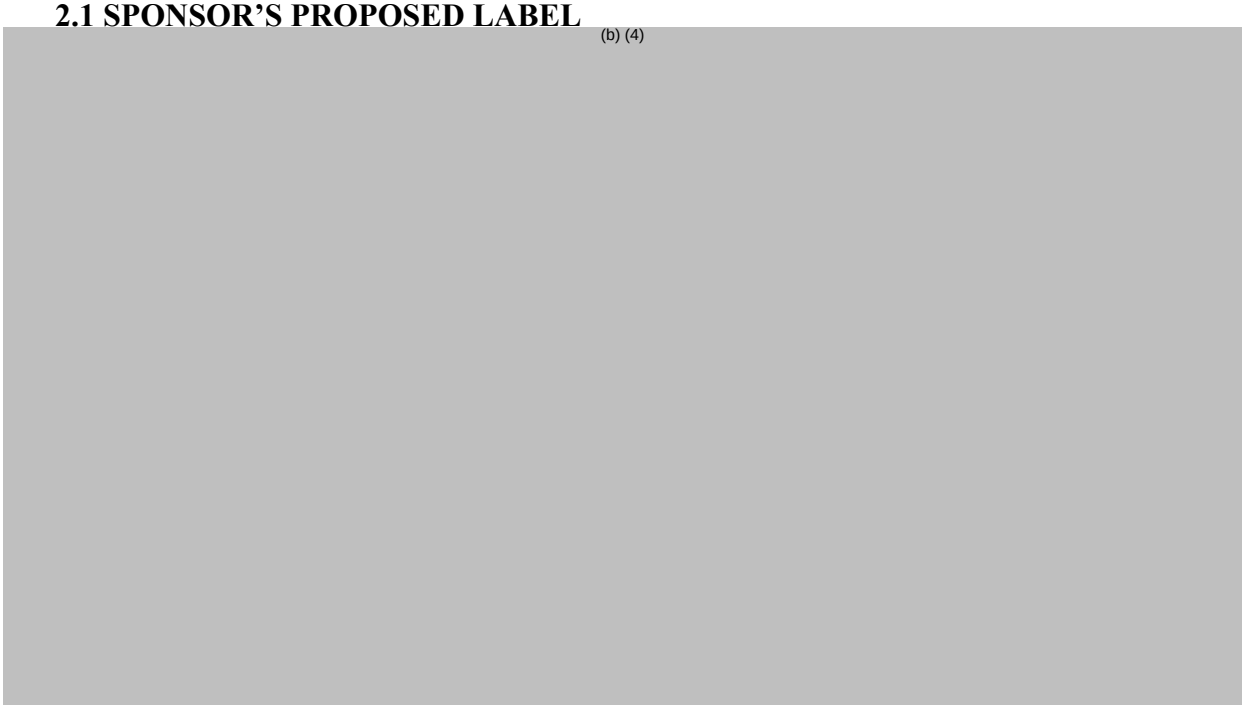
* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points are 7.7 ms, 4.9 ms, and 4.3 ms on Days 9, 12 and 15; respectively.

The HYD dose (160 mg) produces mean steady state exposure 2-fold that of the therapeutic dose (80 mg) for both parent drug and major metabolites. There was no evident exposure-response relationship for change in QTcI based on hydrocodone concentration. However, it seems there are positive trends in exposure-response relationships for change in QTcI based on HYD metabolite norhydrocodone or hydromorphone concentration.

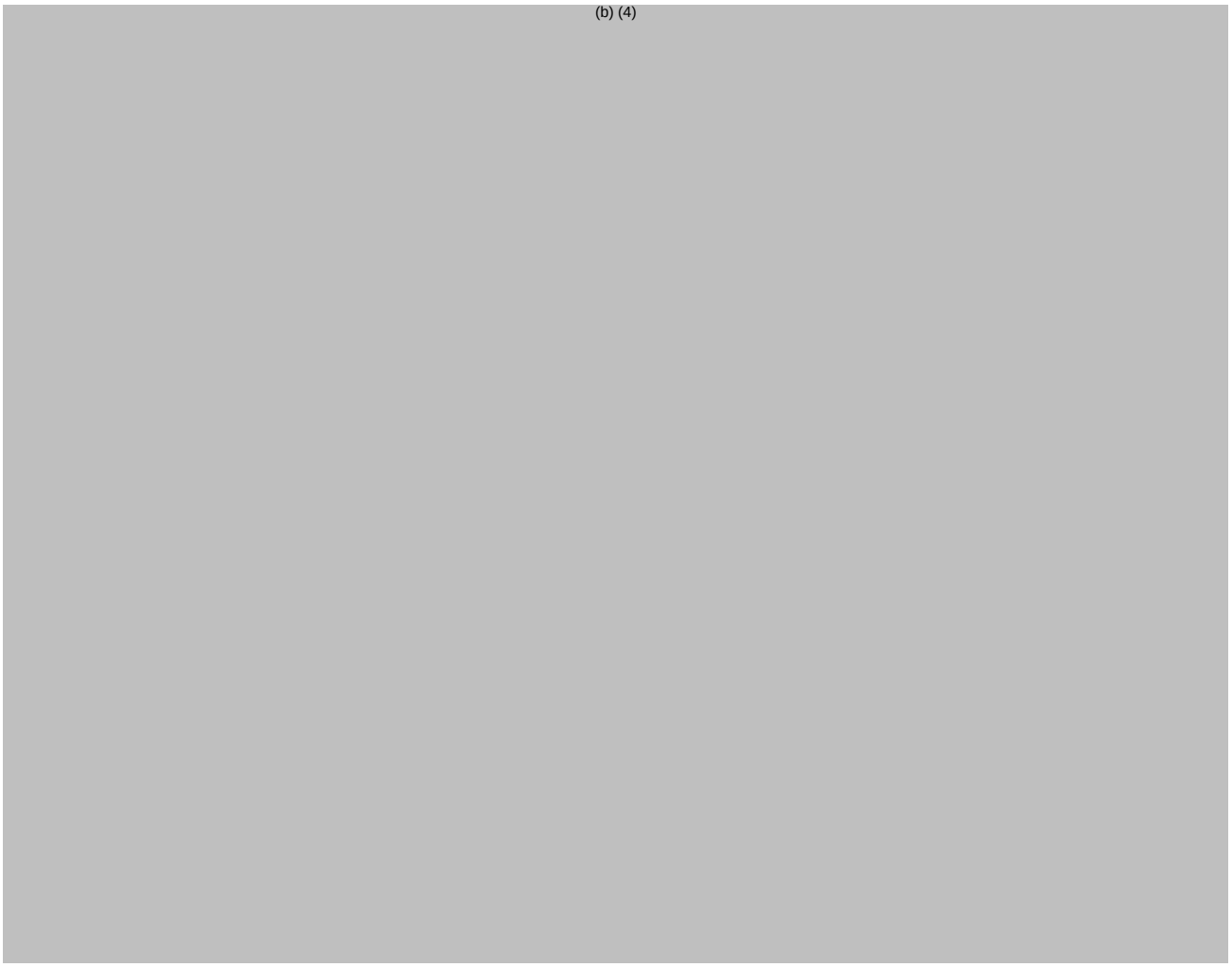
2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

(b) (4)



(b) (4)



2.2 QT-IRT RECOMMENDED LABEL

Our recommendations are suggestions only. We defer final labeling decisions to the review division.

5.x QT INTERVAL PROLONGATION

QT prolongation has been observed with [TRADENAME]. [TRADENAME] should be avoided in patients with congenital long QT syndrome. In patients with congestive heart failure, bradyarrhythmias electrolyte abnormalities or who are taking medications that are known to prolong the QT interval, consider periodic monitoring with electrocardiograms and electrolytes. In patients who develop QTc prolongation, consider dose reduction *[see Clinical Pharmacology (12.6)]*.

12.6 CARDIAC ELECTROPHYSIOLOGY

QTc interval prolongation was studied in a double-blind, placebo- and positive controlled 3-treatment parallel-group, dose-escalating study in 185 healthy subjects. A central tendency analysis of the QTcI data at steady-state demonstrated that the maximum mean (95% upper confidence bound) difference in QTcI from placebo after baseline-correction was 10 (13) ms, 7 (10) ms, and 6 (9) ms at [TRADENAME] 160 mg, 120 mg and 80 mg respectively.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Hydrocodone is a semisynthetic mu-receptor opioid agonist that is being developed by Purdue Pharma L.P. for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The product is available as once-daily, extended-release tablets with dose strength of 20, 30, 40, 60, 80, 100, and 120 mg.

3.2 MARKET APPROVAL STATUS

Hydrocodone, as the bitartrate form, is currently marketed in the United States in combination with nonopioid analgesic drugs (eg, acetaminophen, aspirin, and ibuprofen). The currently developed product by Purdue Pharma L.P. is a single-entity extended-release hydrocodone bitartrate (HYD) tablet formulation for use in moderate to severe chronic pain. The product has not been approved in any countries.

3.3 PRECLINICAL INFORMATION

Experimental assessment for the risk of hydrocodone on QT prolongation using human ether-a-go-go-related gene (hERG) assay has shown that the half maximal inhibitory concentration for HYD inhibition of hERG-mediated potassium repolarization was 40.2 μM (13.4 mcg/mL). In an *in vitro* isolated Purkinje fiber (dog) assay, HYD concentrations of 10 and 100 μM produced concentration-related, reverse-rate dependent prolonged action potential duration to a maximum extent of 17.3%; there was no effect at ≤ 2 μM (0.67 mcg/mL). In a dog telemetry study, HYD produced a very mild QT data corrected for heart rate (QTc) prolongation (approximately 5% above the control group) at 0.4 μM (0.097 mcg/mL)

3.4 PREVIOUS CLINICAL EXPERIENCE

Not provided.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of HYD's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND (b) (4)
The sponsor submitted the study report HYD1009 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Double-blind, Placebo- and Positive-Controlled, Parallel Group, Dose Escalating Study of the Effect of Hydrocodone Bitartrate (HYD) Extended-Release Tablets at Doses up to 160 mg on QT/QTc in Healthy Adult Subjects

4.2.2 Protocol Number

HYD1009

4.2.3 Study Dates

First Subject First Visit: 05-Nov-2012
Last Subject Last Visit: 03-May-2013

4.2.4 Objectives

The primary objective of this study was:

- To evaluate the effect of hydrocodone bitartrate (HYD) extended-release tablets (HYD 80, 120, and 160 mg) on the QT/QTc.

The secondary objectives of this study were:

- To assess moxifloxacin (400-mg tablet) relative to placebo (assay sensitivity) on the QT/QTc interval.
- To characterize the safety of HYD at doses up to 160 mg in healthy adult subjects.

4.2.5 Study Description

4.2.5.1 Design

This was a single-center, randomized, double-blind, placebo- and positive-controlled, 3-treatment parallel study with digital ECGs collected for evaluation of QT/QTc intervals from healthy adult subjects.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms and the positive (moxifloxacin) control were administered blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

HYD was administered orally once every 24 hours (q24h). A dose titration (20, 40, 80, 120, and 160 mg) and taper (80 and 20 mg) scheme were used.

The subjects were randomly assigned to 1 of 3 treatment groups:

- HYD 20, 40, 80, 120, and 160 mg
- Placebo (placebo control)
- Moxifloxacin (positive control)

The sequence of administration of active or placebo forms of HYD and moxifloxacin for each of the 3 treatments is summarized in the study design table below:

Treatments Administered:

Treatment Group	Titration period					Taper period	
	Days 1 to 3	Days 4 to 6	Days 7 to 9[a]	Days 10 to 12[a]	Days 13 to 15[a]	Days 16 to 18	Days 19 to 21
HYD (mg)	1 × HYD 20	1 × HYD 40	1 × HYD 80	1 × HYD 120	HYD 160 (1 × HYD 120 and 1 × HYD 40)	1 × HYD 80	1 × HYD 20
			1 × PboMOX[b]	1 × PboMOX[b]	1 × PboMOX[b]		
Pbo	1 × PboHYD	1 × PboHYD	1 × PboHYD	1 × PboHYD	2 × PboHYD	1 × PboHYD	1 × PboHYD
			1 × PboMOX[b]	1 × PboMOX[b]	1 × PboMOX[b]		
MOX	1 × PboHYD	1 × PboHYD	1 × PboHYD	1 × PboHYD	2 × PboHYD	1 × PboHYD	1 × PboHYD
			1 × MOX[b]	1 × MOX[b]	1 × MOX[b]		

[a] 24-hour digital Holter electrocardiogram recordings were collected beginning just prior to MOX/PboMOX dosing on days 9, 12, and 15

[b] MOX/PboMOX doses were administered on the morning of days 9, 12, and 15 only

HYD = hydrocodone bitartrate (HYD) extended-release tablets administered every 24 hours.
PboHYD = matching placebo for HYD administered every 24 hours.
MOX = moxifloxacin 400 mg.
PboMOX = matching placebo for moxifloxacin.

4.2.6.2 Sponsor's Justification for Doses

Hydrocodone, like other opioids, does not have an anticipated maximum therapeutic daily dose. Therefore, a clear maximum therapeutic daily dose basis for defining a therapeutic and supratherapeutic dose for HYD is not available. In addition, for the present study, there was a safety and tolerability issue associated with administering high doses of HYD to an opioid-naïve healthy subject population. Based on safety and tolerability experience titrating other opioids and HYD to date in the sample population, HYD 160 mg was the anticipated maximum tolerable dose that can be achieved. Based on these observations and PK/PD considerations, HYD 80 mg was selected as the low dose and HYD 160 mg was selected as the high dose to examine the effect of HYD on the QT/QTc interval.

Reviewer's Comment: Acceptable.

4.2.6.3 Instructions with Regard to Meals

Each subject received study drug with 240 mL of water. Drug administration was preceded by an overnight fast (i.e., at least 10 hours) from food (not including water) and followed by a 2-hour or 4-hour fast (water was allowed).

Reviewer's Comment: Acceptable. Hydrocodone should not be administered with food because high fat food increases hydrocodone C_{max} and AUC by 50% and 20%, respectively, in comparison to fasting conditions.

4.2.6.1 ECG and PK Assessments

ECG Assessments:

Three successive individual digital 12-lead ECG recording were extracted from the 24-hour digital Holter ECG recordings. These extractions were obtained at the following nominal time points:

Baseline and Day -1: -24, -23.5, -23, -22, -21 -20, -18, -14, -12, -10, -8, and -6 hours predose;

Dose titration period, day 9 (HYD 80 mg), Day 12 (120 mg) and day 15 (HYD 160 mg); predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 10, 12, 14, 16, 18, and 24 hours postdose.

Pharmacokinetic assessments:

Blood samples were collected to determine plasma concentrations of hydrocodone, its metabolites, and moxifloxacin at the following time points:

Dose titration period, day 9 (HYD 80 mg), day 12 (HYD 120 mg), and day 15 (HYD 160 mg): predose and at 0.5, 1, 1.5. 2, 3, 4, 6, 10, 12, 14, 16, 18, and 24 hours postdose.

Reviewer's Comment: The ECG and PK sampling schedule is acceptable. The chosen time points are matching and covered the T_{max} (time to maximum plasma concentration) of both parent drug and the metabolites (~14-16 hours).

4.2.6.2 Baseline

The sponsor used time-matched pre-dose QTc values on Day -1 as baselines.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Two hundred and eight subjects (118 males and 90 females) were randomly enrolled and 196 subjects (94.2%) completed the study. Twelve (5.8%) discontinued due to adverse events (AEs) with 7 subjects from HYD 80 mg, 2 subjects from Moxifloxacin and 3 subjects from Placebo groups.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was time-matched baseline-adjusted mean differences between HYD (80 mg, 120 mg and 160 mg) and placebo in ΔQTcI. The sponsor used a mixed model and the results were presented in Table 2. The model included baseline values as a covariate; time, treatment, time-by-treatment interactions, gender, and treatment-by-gender interactions as fixed effect; and subjects as random effect. The upper limits 2-sided 90% CI of HYD 80 mg was 9.14 ms at 3 hours was below 10 ms. The upper limits

2-sided 90% CI for HYD 120 mg and HYD 160 mg were 10.7 ms at 24 hours and 12.97 ms at 10 hours, respectively.

Table 2: Sponsor Results ΔΔQTcI for HYD 80 mg, HYD 120 mg and HYD 160 mg

	HYD 80 mg Day 9 (N = 77)			HYD 120 mg Day 12 (N=73)			HYD 160 mg Day 15 (N=73)		
Time (h)	Estimate	Lower Bound	Upper Bound	Estimate	Lower Bound	Upper Bound	Estimate	Lower Bound	Upper Bound
Predose	3.46	0.57	6.35	4.35	1.21	7.49	8.60	5.48	11.71
0.5	2.38	–0.52	5.27	5.06	1.93	8.20	7.09	3.97	10.21
1	1.85	–1.05	4.75	3.80	0.67	6.94	5.05	1.93	8.16
1.5	3.63	0.74	6.52	4.83	1.69	7.97	6.62	3.50	9.74
2	5.51	2.62	8.40	6.42	3.29	9.56	9.61	6.49	12.74
3	6.25	3.35	9.14	6.02	2.86	9.17	7.97	4.84	11.09
4	4.79	1.90	7.69	4.77	1.61	7.93	6.88	3.76	10.00
6	5.26	2.36	8.15	4.53	1.39	7.67	8.40	5.29	11.52
10	5.63	2.73	8.53	6.02	2.88	9.16	9.85	6.73	12.97
12	3.62	0.72	6.52	6.16	3.02	9.31	9.56	6.44	12.68
14	3.57	0.67	6.48	4.58	1.43	7.72	6.49	3.36	9.61
16	1.67	–1.23	4.57	2.16	–0.97	5.30	1.49	–1.64	4.61
18	–1.12	–4.02	1.79	0.31	–2.83	3.46	0.03	–3.09	3.16
24	5.49	2.59	8.39	7.55	4.41	10.70	9.28	6.15	12.40
Time averaged	3.72	1.52	5.91	4.75	2.19	7.31	6.93	4.58	9.27

Abbreviations: ECG, electrocardiogram; HYD, hydrocodone bitartrate; msec, millisecond; QTcI, individual correction.

Note: Mixed-model analysis of variance was fit for placebo-corrected change from baseline and included terms for treatment, gender, time-by-treatment interaction, and treatment-by-gender interaction.

The lower/upper bound = the lower/upper 2-sided 90% model-based confidence limit.

The *P* values for gender effects were gender main effect day 9 = 0.0588, day 12 = 0.0449, and day 15 = 0.9870.

Source: Clinical Study Report No., Table 11-2, page 86/7184

Reviewer's Comments: We will provide our independent analysis result in Section 5.2. Our analysis results are similar with the sponsor's results of QTcI. The upper limits 2-sided 90% CI of HYD 80 mg was below 10 ms. However, for HYD 120 mg and HYD 160 mg were greater than 10 ms.

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the ΔQTcI effect for moxifloxacin on Days 9, 12 and 15. The results were presented in Table 3. The lower bounds of the 90% CI were greater than 5 ms. Thus, assay sensitivity in this thorough QTcI study was established.

Table 3: Sponsor's analysis ΔΔQTcI for Moxifloxacin

	Moxifloxacin Day 9 (N = 62)			Moxifloxacin Day 12 (N=61)			Moxifloxacin Day 15 (N=62)		
Time (h)	Estimate	Lower Bound	Upper Bound	Estimate	Lower Bound	Upper Bound	Estimate	Lower Bound	Upper Bound
Predose	–0.22	–3.27	2.83	0.33	–3.00	3.66	0.52	–2.51	3.56
0.5	0.39	–2.66	3.45	1.29	–2.05	4.62	0.33	–2.71	3.36
1	6.66	3.60	9.71	6.37	3.04	9.71	6.59	3.55	9.62
1.5	9.25	6.20	12.30	8.97	5.63	12.32	6.90	3.87	9.94
2	9.69	6.64	12.74	9.36	6.02	12.69	7.44	4.41	10.48
3	12.64	9.59	15.70	11.57	8.22	14.91	9.60	6.57	12.64
4	11.82	8.76	14.88	10.26	6.91	13.61	9.50	6.46	12.54
6	10.91	7.86	13.96	9.02	5.69	12.35	8.94	5.90	11.99
10	8.63	5.57	11.68	8.64	5.31	11.97	6.72	3.68	9.76
12	7.92	4.86	10.97	7.82	4.49	11.15	5.58	2.55	8.62
14	7.81	4.75	10.88	4.62	1.28	7.96	3.73	0.68	6.78
16	8.23	5.17	11.29	8.02	4.68	11.36	4.00	0.95	7.06
18	8.05	4.98	11.11	7.33	4.00	10.66	4.55	1.52	7.59
24	6.06	3.01	9.12	5.37	2.04	8.70	2.48	–0.57	5.52
Time averaged	7.69	5.40	9.98	7.05	4.42	9.67	5.48	3.08	7.88

Abbreviations: ECG, electrocardiogram; msec, millisecond; QTcI, individual correction.

Note: Mixed-model analysis of variance was fit for placebo-corrected change from baseline and included terms for treatment, gender, time-by-treatment interaction, and treatment-by-gender interaction.
The lower/upper bound = the lower/upper 2-sided 90% model-based confidence limit.
The *P* values for gender effects were gender main effect day 9 = 0.0588, day 12 = 0.0449, and day 15 = 0.9870.

Source: Clinical Study Report No., Table 11-3, page 87/7184

Reviewer's Comments: We will provide our independent analysis result in Section 5.2.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's absolute QTc > 500 ms and ΔQTc >60 ms.

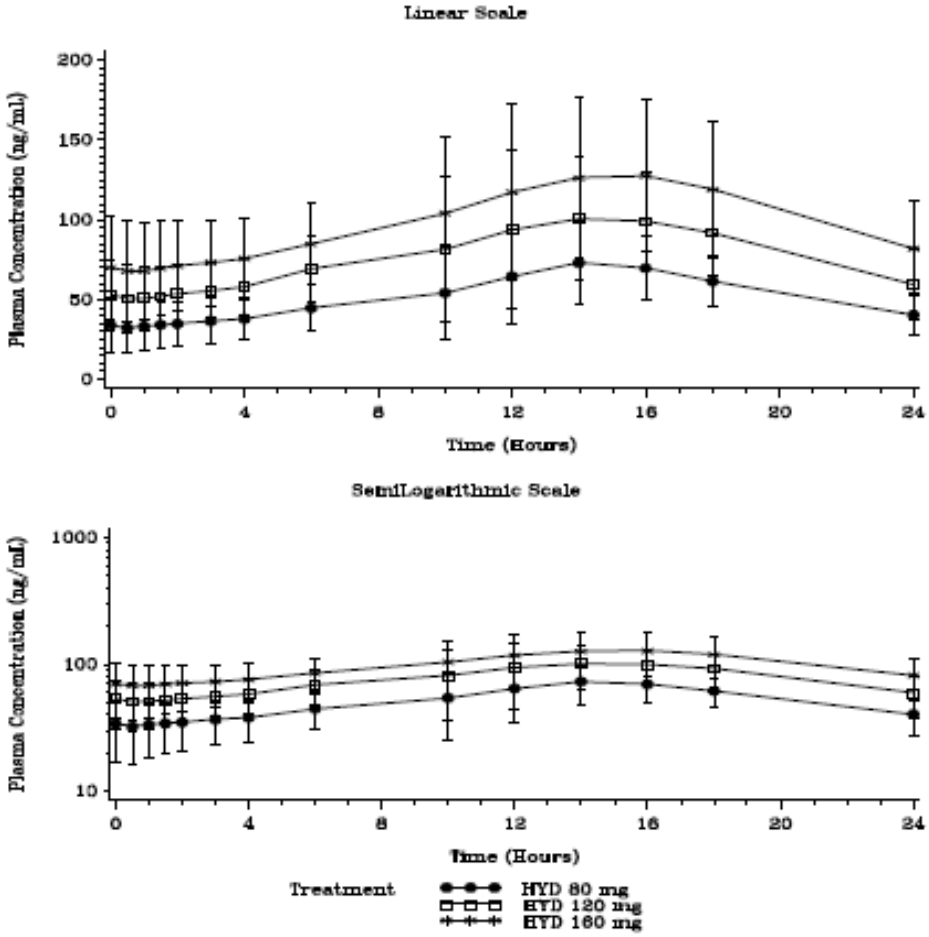
4.2.8.3 Safety Analysis

No concerning cardiovascular events were reported.

4.2.8.4 Clinical Pharmacology

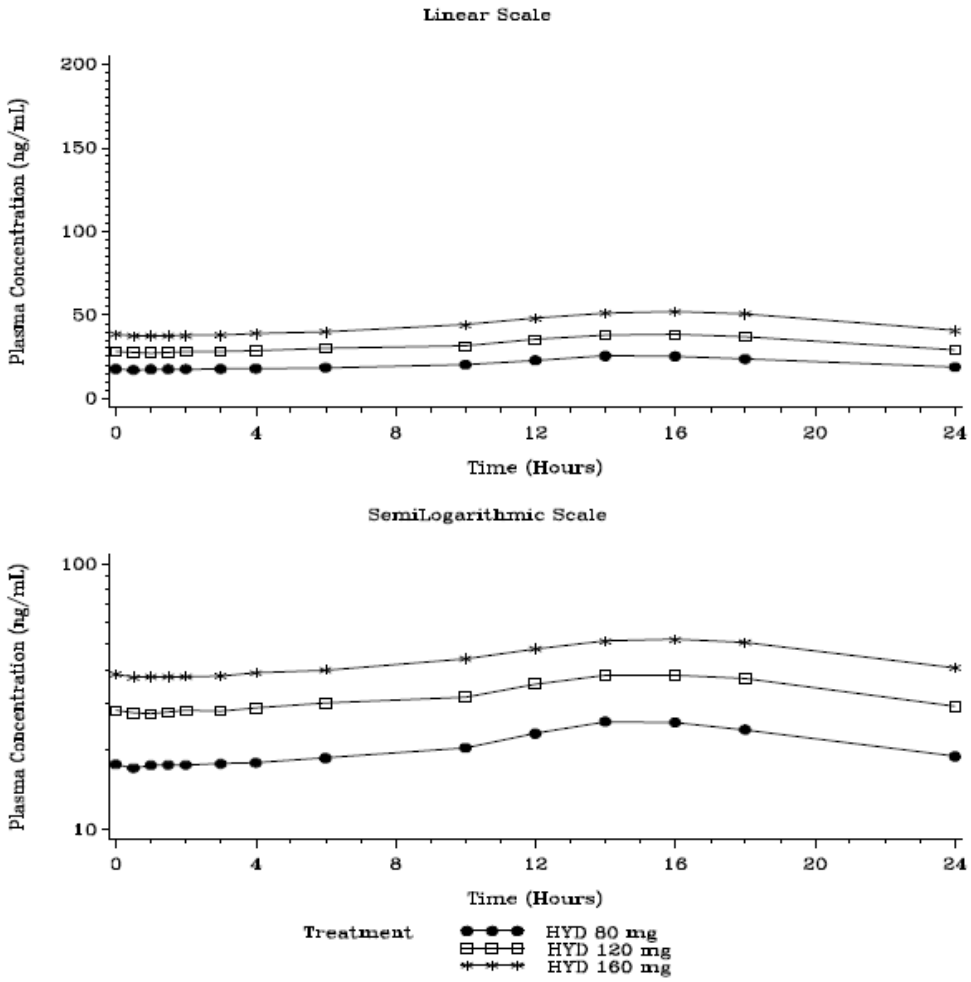
The PK results for HYD, its major metabolites norhydrocodone and hydromorphone, as well as moxifloxacin are presented in Figure 1 to Figure 4, and summarized in Table 4 to Table 6. $C_{max,ss}$ and AUC_{inf} values of HYD were 80% and 90% higher, respectively, following administration of 160 mg hydrocodone Supra compared with hydrocodone 80 mg, the intended clinical dose.

Figure 1: Mean Plasma Concentrations of Hydrocodone versus Time on Linear and Semi-logarithmic Scale (Full Analysis for Pharmacokinetic Population)



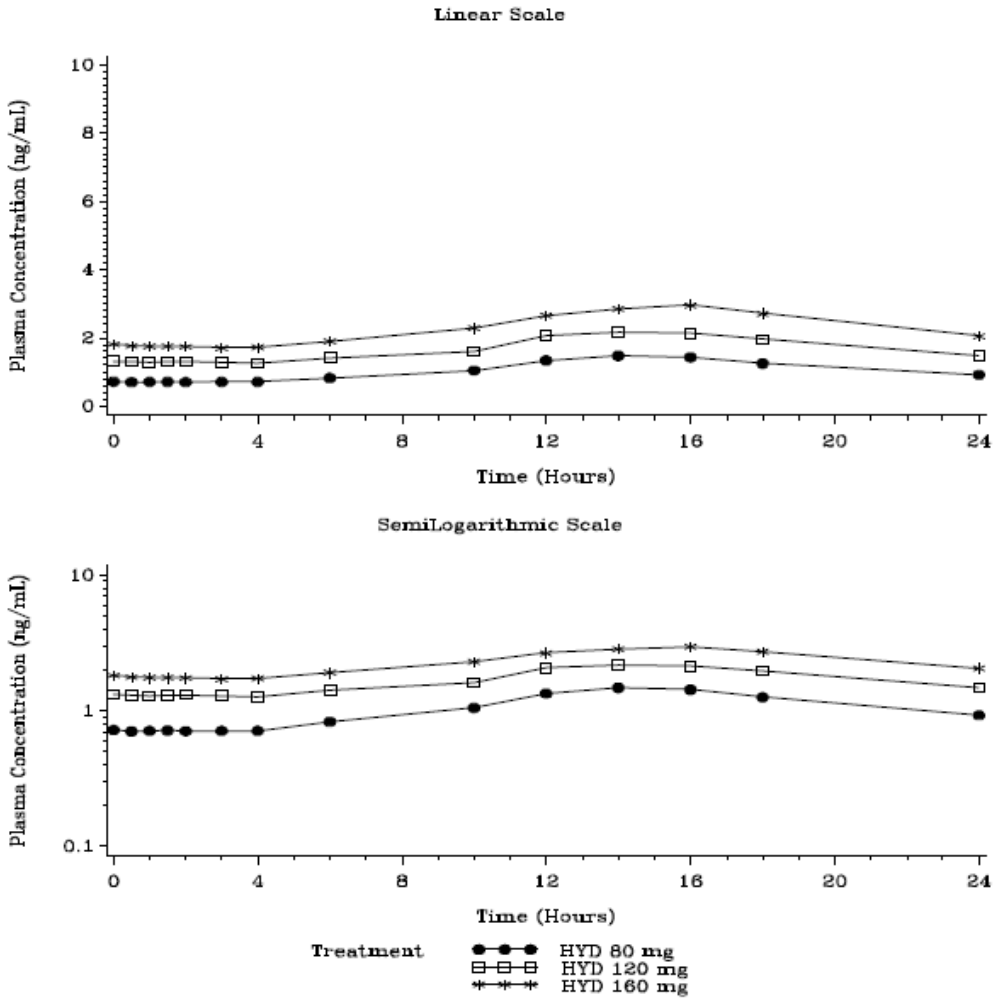
Source: Adapted from Figure 11-13 on page 108 of sponsor's report

Figure 2: Mean Plasma Concentrations of Norhydrocodone versus Time on Linear and Semi-logarithmic Scale (Full Analysis for Pharmacokinetic Population)



Source: Figure 11-14 on page 109 of sponsor's report

Figure 3: Mean Plasma Concentrations of Hydromorphone versus Time on Linear and Semi-logarithmic Scale (Full Analysis for Pharmacokinetic Population)



Source: Figure 11-15 on page 110 of sponsor's report

Table 4: Summary of Mean Plasma Pharmacokinetic Metrics of Hydrocodone (Full Analysis for Pharmacokinetic Population)

Metric (Unit)	HYD 80 mg Day 9 (N = 77)	HYD 120 mg Day 12 (N = 75)	HYD 160 mg Day 15 (N = 73)
AUC0-24,ss (ng•h/mL)			
Mean	1252.49	1844.10	2380.47
SD	352.038	542.945	733.371
%CV	28.1	29.4	30.8
Minimum, Maximum	637.51, 2358.64	842.31, 3358.29	1282.06, 4764.17
Cmax,ss (ng/mL)			
Mean	82.62	122.12	151.05
SD	25.732	43.259	52.393
%CV	31.1	35.4	34.7
Minimum, Maximum	37.50, 175.00	51.70, 312.00	66.90, 337.00
Tmax,ss (h)			
Mean	14.96	14.51	14.67
SD	3.321	3.945	4.169
%CV	22.2	27.2	28.4
Median	14.00	14.00	14.00
Minimum, Maximum	10.00, 23.92	0.00, 23.97	0.00, 23.92
Cmin,ss (ng/mL)			
Mean	28.21	43.51	57.79
SD	12.041	17.479	26.261
%CV	42.7	40.2	45.4
Minimum, Maximum	4.05, 59.90	0.48, 94.10	7.65, 132.00
Cavg,ss (ng/mL)			
Mean	52.19	76.84	99.19
SD	14.668	22.623	30.557
%CV	28.1	29.4	30.8
Minimum, Maximum	26.56, 98.28	35.10, 139.93	53.42, 198.51

Abbreviations: %CV, coefficient of variation; HYD, hydrocodone bitartrate; SD, standard deviation.

Source: Table 11-9 on page 113 of sponsor's report

Table 5: **Summary of Mean Plasma Pharmacokinetic Metrics of Norhydrocodone (Full Analysis for Pharmacokinetic Population)**

Metric (Unit)	HYD 80 mg Day 9 (N = 77)	HYD 120 mg Day 12 (N = 75)	HYD 160 mg Day 15 (N = 73)
AUC0-24,ss (ng•h/mL)			
Mean	503.20	780.55	1064.11
SD	143.841	258.192	286.196
%CV	28.6	33.1	26.9
Minimum, Maximum	220.57, 861.08	348.84, 1625.11	508.96, 2036.02
Cmax,ss (ng/mL)			
Mean	28.14	43.79	59.05
SD	7.884	15.583	17.851
%CV	28.0	35.6	30.2
Minimum, Maximum	13.50, 46.20	22.60, 124.00	26.50, 111.00
Tmax,ss (h)			
Mean	14.43	14.10	15.17
SD	4.824	4.947	4.934
%CV	33.4	35.1	32.5
Median	14.10	14.00	16.00
Minimum, Maximum	0.00, 23.92	0.00, 23.97	0.00, 23.92
Cmin,ss (ng/mL)			
Mean	14.99	23.52	31.92
SD	5.385	8.954	9.667
%CV	35.9	38.1	30.3
Minimum, Maximum	1.53, 29.00	0.25, 48.50	8.37, 56.20
Cavg,ss (ng/mL)			
Mean	20.97	32.52	44.34
SD	5.993	10.758	11.925
%CV	28.6	33.1	26.9
Minimum, Maximum	9.19, 35.88	14.53, 67.71	21.21, 84.83

Abbreviations: %CV, coefficient of variation; HYD, hydrocodone bitartrate; SD, standard deviation.

Source: Table 11-10 on page 114 of sponsor's report

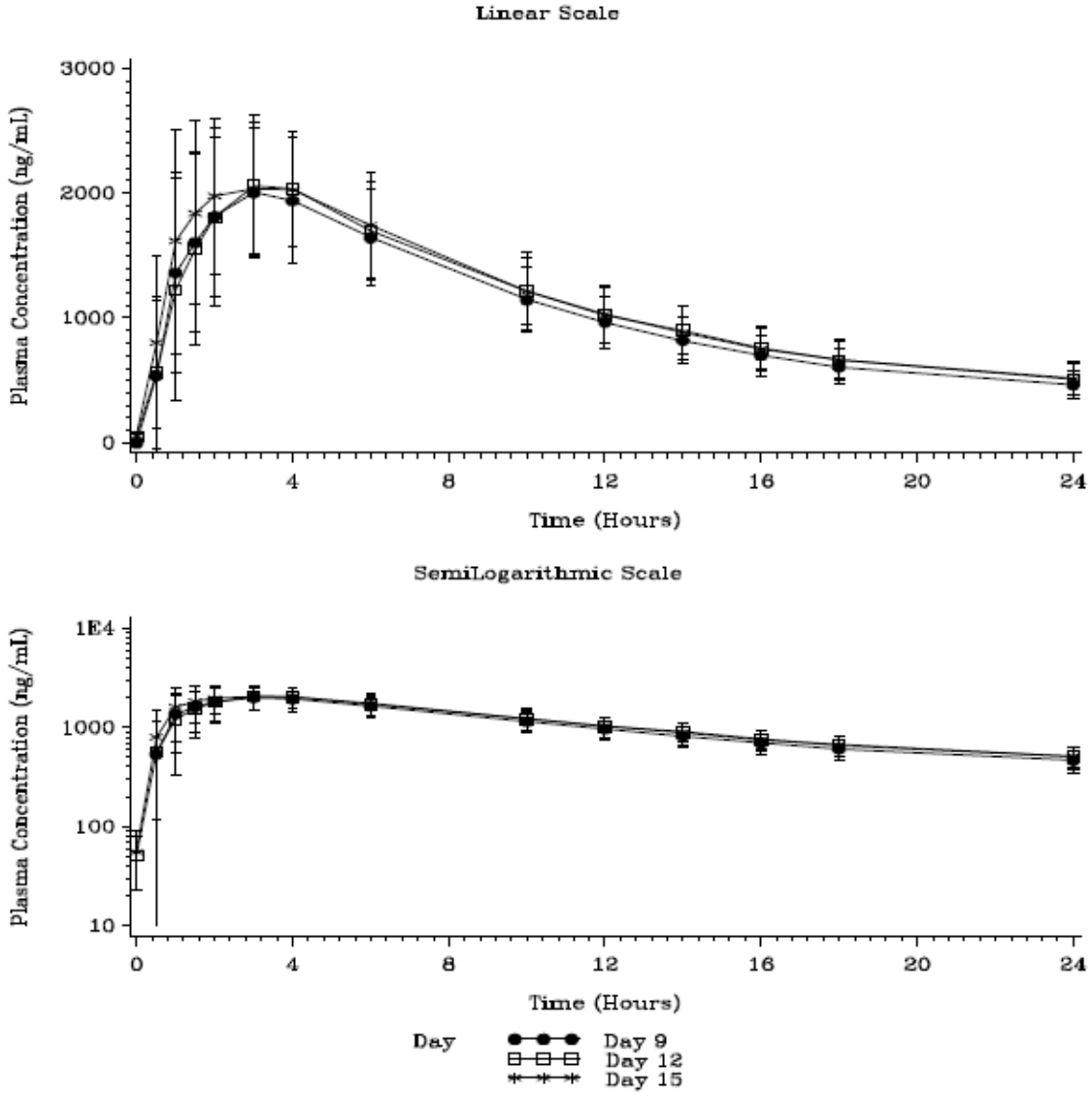
Table 6: **Summary of Mean Plasma Pharmacokinetic Metrics of Hydromorphone (Full Analysis for Pharmacokinetic Population)**

Metric (Unit)	HYD 80 mg Day 9 (N = 77)	HYD 120 mg Day 12 (N = 75)	HYD 160 mg Day 15 (N = 73)
AUC0-24,ss (ng•h/mL)			
Mean	25.39	40.35	55.11
SD	11.681	19.403	25.851
%CV	46.0	48.1	46.9
Minimum, Maximum	3.63, 65.46	4.20, 96.92	8.89, 131.45
Cmax,ss (ng/mL)			
Mean	1.65	2.54	3.38
SD	0.789	1.300	1.617
%CV	47.9	51.2	47.8
Minimum, Maximum	0.22, 4.23	0.35, 7.28	0.48, 7.42
Tmax,ss (h)			
Mean	15.11	14.24	15.03
SD	3.139	4.080	3.959
%CV	20.8	28.7	26.3
Median	14.00	14.00	16.00
Minimum, Maximum	10.00, 23.92	0.00, 23.97	1.00, 23.97
Cmin,ss (ng/mL)			
Mean	0.62	1.07	1.52
SD	0.298	0.555	0.814
%CV	47.8	51.7	53.6
Minimum, Maximum	0.09, 1.44	0.09, 2.72	0.22, 3.97
Cavg,ss (ng/mL)			
Mean	1.06	1.68	2.30
SD	0.487	0.808	1.077
%CV	46.0	48.1	46.9
Minimum, Maximum	0.15, 2.73	0.18, 4.04	0.37, 5.48

Abbreviations: %CV, coefficient of variation; HYD, hydrocodone bitartrate; SD, standard deviation.

Source: Table 11-11 on page 115 of sponsor's report

Figure 4: Mean (±SD) Plasma Concentrations of Moxifloxacin Versus Time on Linear and Semi-logarithmic Scales

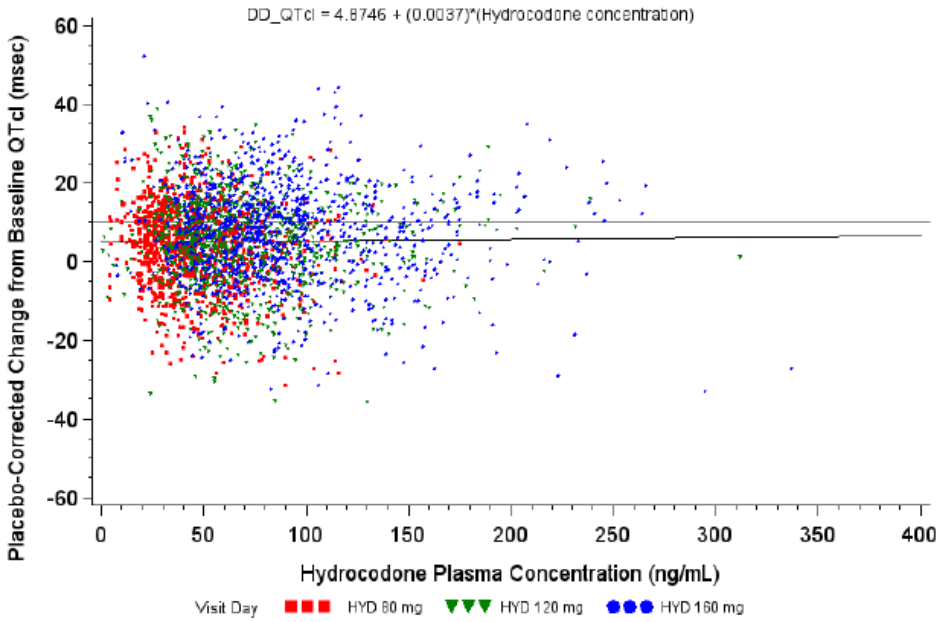


Source: Figure 11-16 on page 111 of sponsor's report

Exposure-Response Analysis

Relationship between hydrocodone exposure (plasma concentration of hydrocodone) and the effect (placebo-corrected change from baseline in QTcI) was explored by the sponsor. The results are shown in Figure 5, with no evident exposure-response relationship observed.

Figure 5: Placebo-corrected Change from Baseline QTcI Versus Mean Hydrocodone Plasma Concentration-Estimates from the Mixed-Effects Model Regression



Source: Figure 11-17 on page 120 of sponsor's report

Reviewer's Analysis: The reviewer conducted independent exposure-response analysis. Plots of ΔΔQTcI vs. HYD or its metabolites concentration by the reviewer are presented in Figure 10, Figure 11, and Figure 12.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

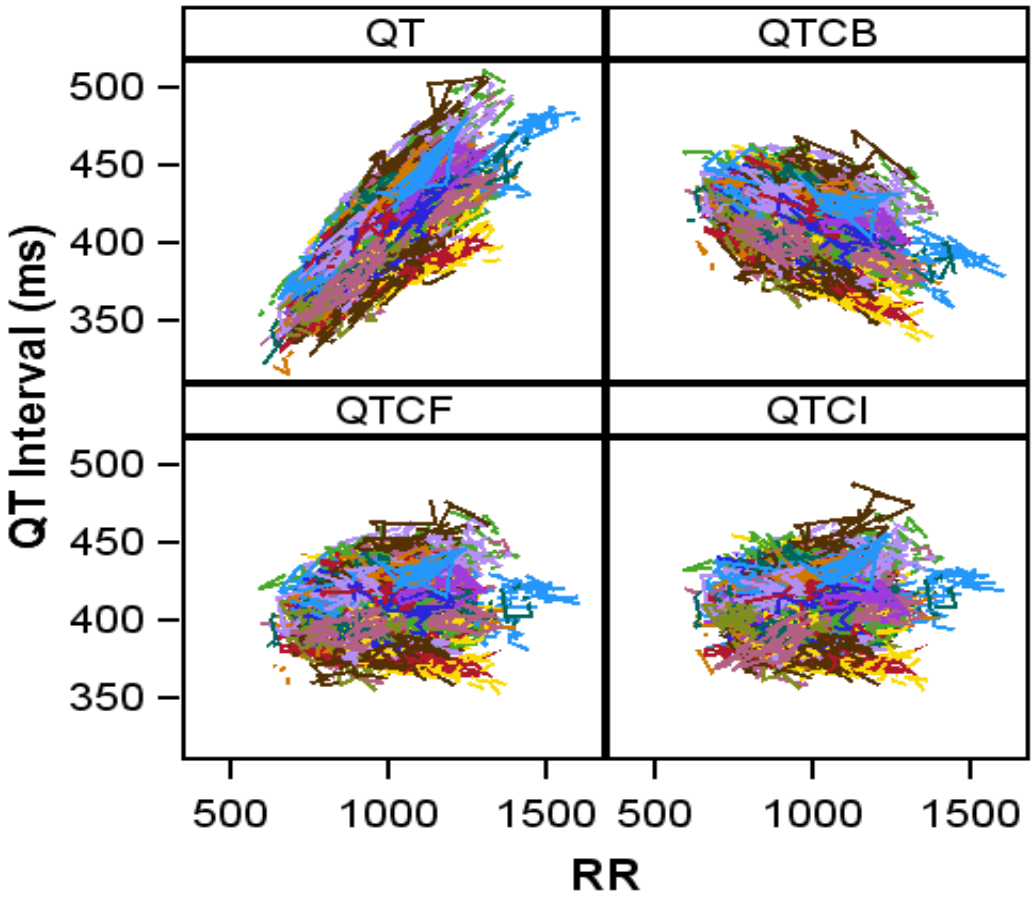
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 7, it appears that QTcF and QTcI are similar better than QTcB. To be consistent with the sponsor's analyses, we choose to present QTcI results.

Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	QTcB		QTcF		QTcI	
Treatment Group	**N**	**MSSS**	**N**	**MSSS**	**N**	**MSSS**
Placebo	61	0.00235	61	0.00124	61	0.00150
Moxifloxacin	62	0.00365	62	0.00080	62	0.00125
HYD 80 mg	77	0.00506	77	0.00205	77	0.00189
HYD 120 mg	73	0.00558	73	0.00155	73	0.00182
HYD 160 mg	73	0.00557	73	0.00168	73	0.00159
All	200	0.00367	200	0.00102	200	0.00119

The QT-RR interval relationship between different correction methods and RR is presented in Figure 6.

Figure 6: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcI effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 8, Table 9 and Table 10. The largest upper bounds of the 2-sided 90% CI for the mean differences between HYD 80 mg and placebo, between HYD 120 and placebo, and between HYD 160 mg and placebo are 8.5 ms, 10.2 ms and 12.7 ms, respectively. The upper bounds of HYD 120 and HYD 160 mg which are higher than 10 ms of the regulatory concern as described in ICH E14 guidelines.

Table 8: Analysis Results of ΔQTcI and ΔΔQTcI for HYD 80 mg and Moxifloxacin 400 mg on Day 9

		Treatment Group								
		HYD 80 mg				Moxifloxacin				
	Placebo	ΔQTcI		ΔΔQTcI		ΔQTcI		ΔΔQTcI		
Time(h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
0.5	-6.9	76	-5.1	1.8	(-1.2, 4.8)	61	-7.5	-0.6	(-3.7, 2.5)	(-4.9, 3.7)
1	-5.1	77	-3.7	1.4	(-1.6, 4.5)	62	0.6	5.8	(2.6, 9.0)	(1.4, 10.1)
1.5	-4.5	77	-1.5	3.0	(0.1, 5.9)	62	3.6	8.1	(5.0, 11.2)	(3.9, 12.3)
2	-6.2	77	-1.7	4.5	(1.6, 7.4)	62	2.3	8.5	(5.5, 11.6)	(4.4, 12.7)
3	-5.5	77	0.1	5.6	(2.8, 8.3)	61	6.1	11.6	(8.8, 14.5)	(7.7, 15.6)
4	-4.6	77	-0.5	4.1	(1.0, 7.2)	60	6.1	10.7	(7.4, 14.0)	(6.2, 15.2)
6	-5.7	76	-1.1	4.6	(1.9, 7.3)	62	4.2	9.9	(7.1, 12.7)	(6.1, 13.8)
10	-5.3	77	-0.0	5.3	(2.4, 8.1)	62	2.6	7.9	(4.9, 10.9)	(3.8, 12.0)
12	-3.6	77	-0.7	2.9	(0.2, 5.7)	62	3.3	6.9	(4.0, 9.9)	(3.0, 10.9)
14	-4.7	77	-1.5	3.2	(0.5, 6.0)	62	2.4	7.1	(4.3, 10.0)	(3.2, 11.0)
16	-1.5	74	-0.3	1.2	(-1.8, 4.2)	61	5.9	7.3	(4.3, 10.4)	(3.1, 11.6)
18	-0.9	76	-2.6	-1.7	(-4.7, 1.2)	61	6.1	7.0	(3.9, 10.1)	(2.8, 11.3)
24	-3.6	75	2.0	5.6	(2.7, 8.5)	61	1.6	5.3	(2.3, 8.3)	(1.2, 9.4)

Table 9: Analysis Results of ΔQTcI and ΔΔQTcI for HYD 120 mg and Moxifloxacin 400 mg on Day 12

		Treatment Group								
		HYD 120 mg				Moxifloxacin				
	Placebo	ΔQTcI		ΔΔQTcI		ΔQTcI		ΔΔQTcI		
Time(h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
0.5	-8.2	73	-3.9	4.3	(1.0, 7.5)	61	-8.0	0.1	(-3.2, 3.5)	(-4.5, 4.7)
1	-6.3	73	-3.2	3.1	(-0.2, 6.4)	61	-1.0	5.3	(1.9, 8.7)	(0.6, 9.9)
1.5	-4.4	73	-0.5	3.9	(0.5, 7.3)	59	2.7	7.2	(3.6, 10.7)	(2.3, 12.0)
2	-5.6	73	-0.4	5.2	(1.8, 8.5)	61	2.5	8.0	(4.6, 11.5)	(3.3, 12.8)
3	-5.4	71	-0.9	4.5	(1.1, 7.9)	60	4.3	9.7	(6.2, 13.2)	(4.9, 14.5)
4	-4.0	72	-0.3	3.7	(0.5, 6.9)	60	4.9	8.9	(5.6, 12.2)	(4.4, 13.4)
6	-3.9	72	-0.1	3.8	(0.9, 6.7)	61	4.1	8.0	(5.0, 10.9)	(3.9, 12.0)
10	-4.4	72	1.3	5.6	(2.8, 8.5)	61	3.5	7.9	(4.9, 10.8)	(3.8, 11.9)

		Treatment Group								
		HYD 120 mg				Moxifloxacin				
	Placebo	ΔQTcI		ΔΔQTcI		ΔQTcI		ΔΔQTcI		
Time(h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
12	-3.4	71	1.8	5.2	(2.2, 8.2)	61	3.5	6.9	(3.9, 9.9)	(2.8, 11.1)
14	-3.8	73	0.3	4.1	(1.3, 6.8)	61	0.0	3.8	(0.9, 6.6)	(-0.1, 7.7)
16	-1.1	73	0.3	1.4	(-1.7, 4.5)	61	6.1	7.2	(4.0, 10.5)	(2.8, 11.7)
18	-0.2	72	-0.3	-0.0	(-3.5, 3.4)	61	6.0	6.2	(2.7, 9.7)	(1.4, 11.0)
24	-2.9	72	4.0	6.9	(3.6, 10.2)	61	0.9	3.7	(0.4, 7.1)	(-0.9, 8.4)

Table 10: Analysis Results of ΔQTcI and ΔΔQTcI for HYD 160 mg and Moxifloxacin 400 mg on Day 15

		Treatment Group								
		HYD 160 mg				Moxifloxacin				
	Placebo	ΔQTcI		ΔΔQTcI		ΔQTcI		ΔΔQTcI		
Time(h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
0.5	-8.0	73	-1.4	6.7	(3.5, 9.8)	62	-8.8	-0.7	(-4.0, 2.6)	(-5.2, 3.8)
1	-5.3	73	-0.4	4.9	(1.7, 8.1)	62	0.4	5.7	(2.4, 9.0)	(1.2, 10.2)
1.5	-4.2	73	1.9	6.1	(2.7, 9.5)	62	1.4	5.6	(2.1, 9.2)	(0.8, 10.5)
2	-6.2	72	2.8	8.9	(5.7, 12.1)	62	0.1	6.3	(3.0, 9.5)	(1.8, 10.7)
3	-4.9	73	2.5	7.4	(4.2, 10.5)	62	3.6	8.5	(5.3, 11.7)	(4.1, 12.9)
4	-4.7	73	1.9	6.6	(3.5, 9.6)	61	4.0	8.7	(5.5, 11.8)	(4.3, 13.0)
6	-5.8	73	2.3	8.2	(5.4, 11.0)	61	2.2	8.1	(5.2, 10.9)	(4.1, 12.0)
10	-5.2	73	4.7	9.9	(7.1, 12.7)	61	0.9	6.1	(3.2, 9.0)	(2.1, 10.0)
12	-4.6	73	4.7	9.3	(6.4, 12.2)	62	0.2	4.8	(1.8, 7.7)	(0.7, 8.8)
14	-5.3	73	1.4	6.6	(4.0, 9.3)	61	-2.1	3.2	(0.4, 5.9)	(-0.6, 6.9)
16	-0.9	73	0.6	1.6	(-1.8, 4.9)	61	2.5	3.4	(-0.0, 6.9)	(-1.3, 8.2)
18	-0.6	73	-0.6	-0.0	(-3.2, 3.1)	62	3.0	3.5	(0.3, 6.8)	(-0.9, 8.0)
24	-3.3	73	6.0	9.4	(6.4, 12.3)	62	-2.2	1.2	(-1.9, 4.2)	(-3.0, 5.3)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 8,
Table 9, and Table 10. The largest unadjusted 90% lower confidence interval for HYD 80 mg, HYD 120 mg and HYD 160 mg are 8.5 ms, 10.2 ms, and 12.7 ms, respectively. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval for HYD 80 mg, HYD 120 mg and HYD 160 mg are 7.7 ms, 4.9 ms, and 4.3 ms, respectively. These indicate that an at least 5-ms QTcI effect of moxifloxacin can be detected from the study.

5.2.1.3 Graph of ΔΔQTcI Over Time

Figure 7, Figure 8 and Figure 9 display the time profile of ΔΔQTcI for different treatment groups and moxifloxacin 400 mg corresponding to the treatment dose groups.

Figure 7: Mean and 90% CI ΔΔQTcI Time Course for HYD 80 mg and Moxifloxacin on Day 9

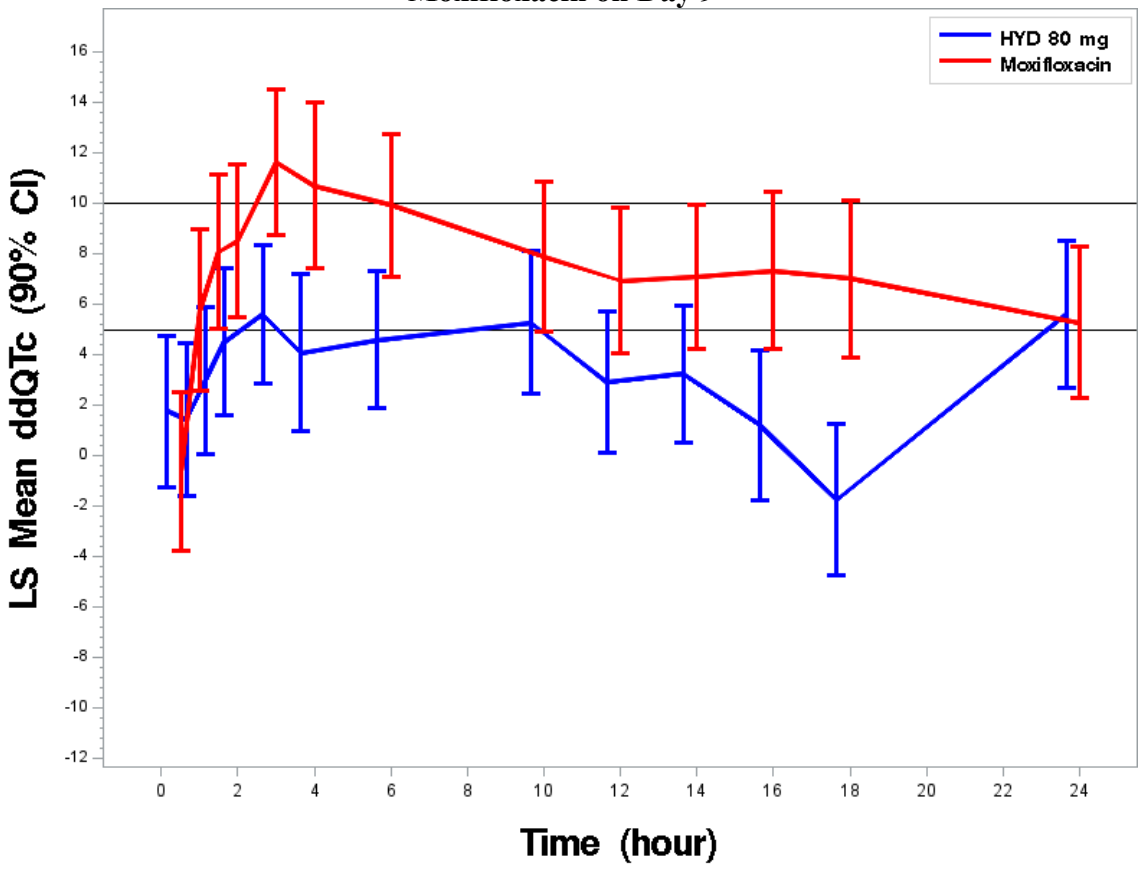


Figure 8: Mean and 90% CI ΔΔQTcI Time Course for HYD 120 mg and Moxifloxacin on Day 12

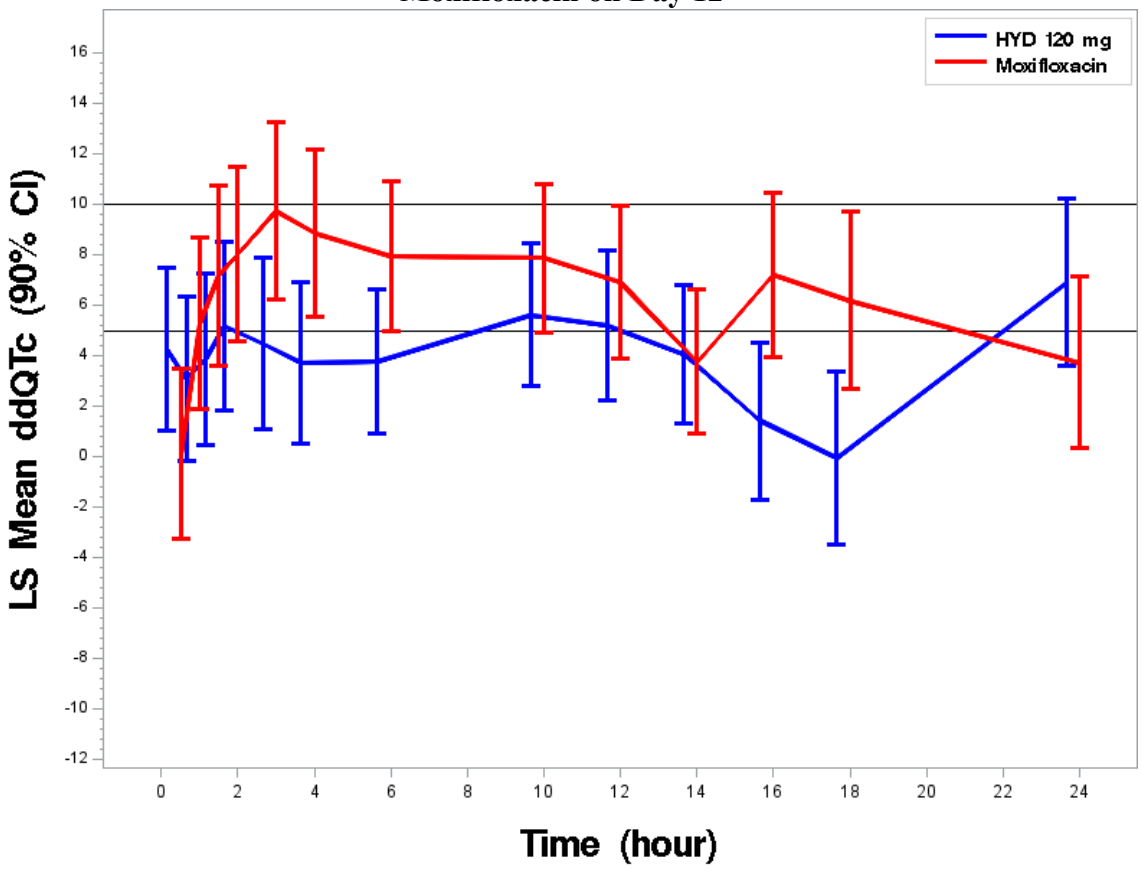
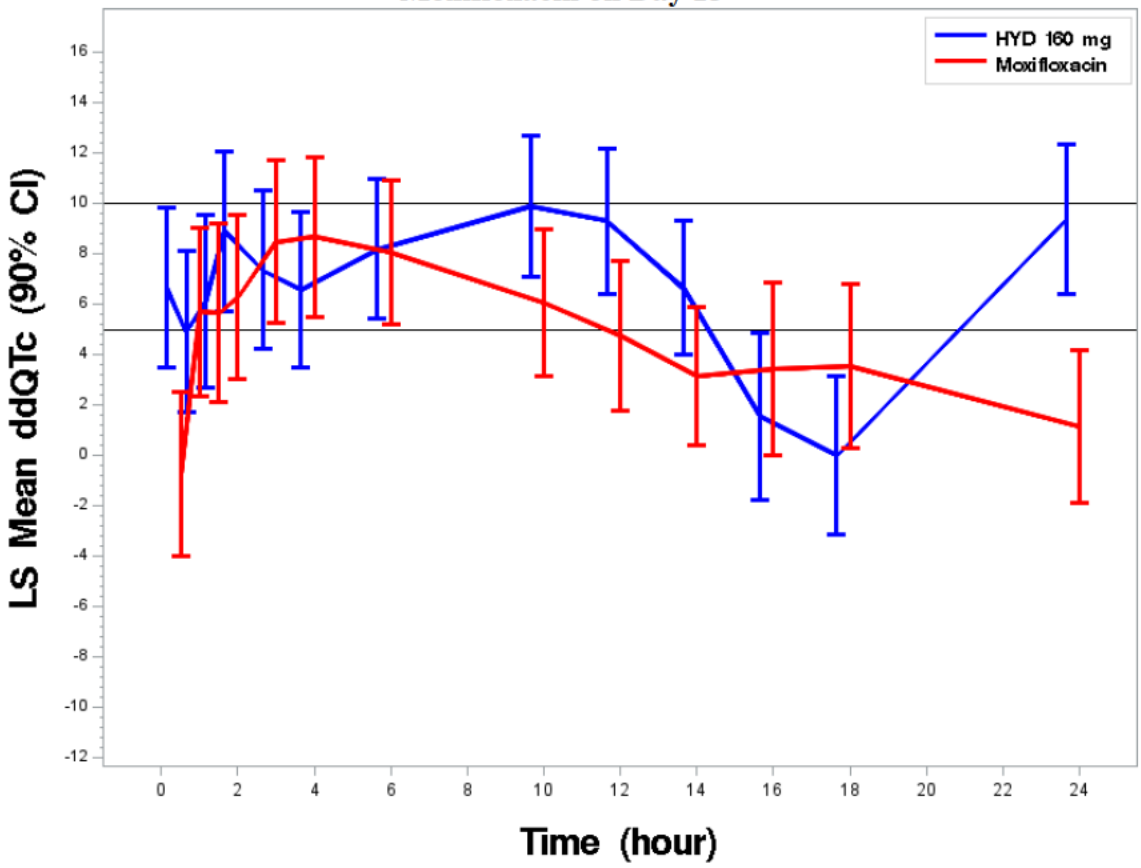


Figure 9: Mean and 90% CI ΔΔQTcI Time Course for HYD 160 mg and Moxifloxacin on Day 15



5.2.1.4 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms. No subject's QTcI is above 500 ms.

Table 11: Categorical Analysis for QTcI

Treatment Group	Total N	Value<=450 ms	450ms<Value<=480 ms	480ms<Value<500 ms
HYD 80 mg	77	76 (98.7%)	1 (1.3%)	0 (0.0 %)
HYD 120 mg	73	68 (93.2%)	5 (6.9%)	0 (0.0%)
HYD 160 Mg	73	71 (97.3%)	2 (2.7%)	0 (0.0%)
Moxifloxacin on Day 9	62	57 (92%)	5 (8.1%)	0 (0.0%)
Moxifloxacin on Day 12	61	55 (90.2%)	5 (8.2%)	1 (1.6%)
Moxifloxacin on Day 15	62	59 (95.2%)	2 (3.2%)	1 (1.6%)
Placebo	61	57 (93.4%)	4 (6.6%)	0 (0.0%)

Table 12 lists changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's change from baseline was above 60 ms.

Table 12: Categorical Analysis for ΔQTcI

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
HYD 80 mg	77	77 (100%)	0 (0.0%)
HYD 120 mg	72	70 (98.6%)	1 (1.4%)
HYD 160 Mg	71	68 (94.4%)	4 (5.6%)
Moxifloxacin on Day 9	62	59 (95.2%)	3 (4.8%)
Moxifloxacin on Day 12	61	57 (93.4%)	4 (6.6%)
Moxifloxacin on Day 15	62	60 (96.8%)	2 (3.2%)
Placebo	61	60 (98.3%)	1 (1.6%)

5.2.2 HR Analysis

The statistical reviewer used the same mixed model to analyze the ΔHR effect. The model includes treatment as fixed effect and baseline values as a covariate. The results are presented in Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between HYD 80 mg and placebo, between HYD 120 and placebo, and between HYD 160 mg and placebo are 5.7 bpm, 5.3 bpm and 5.1 bpm, respectively. No subject who experienced HR interval greater than 100 bpm is in HYD group.

Table 13: Analysis Results of ΔHR and ΔΔHR for HYD 80 mg, HYD 120 mg and HYD 160 mg

	Treatment Group											
	HYD 120 mg				HYD 160 mg				HYD 80 mg			
	ΔHR		ΔΔHR		ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time (h)	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	73	2.0	1.9	(-0.1, 3.9)	73	2.8	2.6	(0.4, 4.8)	76	0.7	0.5	(-1.4, 2.3)
1	73	3.0	2.2	(0.1, 4.3)	73	3.4	2.1	(-0.1, 4.4)	77	1.9	0.8	(-1.1, 2.6)
1.5	73	2.2	1.9	(-0.1, 3.9)	73	2.6	1.8	(-0.2, 3.8)	77	3.2	3.6	(1.4, 5.7)
2	73	2.2	1.8	(-0.1, 3.8)	72	2.9	2.4	(0.2, 4.7)	77	1.5	1.6	(-0.2, 3.3)
3	71	2.1	2.5	(0.4, 4.5)	73	2.1	1.2	(-0.8, 3.1)	77	2.6	2.4	(0.5, 4.3)
4	72	1.6	0.4	(-1.6, 2.4)	73	2.0	1.3	(-0.6, 3.2)	77	1.9	2.2	(0.4, 3.9)
6	72	-1.0	-1.3	(-3.3, 0.7)	73	-0.6	-0.9	(-2.9, 1.2)	76	-0.6	-0.9	(-3.0, 1.2)
10	72	-0.9	-0.8	(-2.8, 1.2)	73	-1.0	-0.9	(-3.1, 1.4)	77	-1.0	-1.6	(-3.8, 0.6)
12	71	-2.3	-1.9	(-3.8, 0.1)	73	-1.7	-2.5	(-4.8, -0.2)	77	-2.2	-2.2	(-4.2, -0.2)
14	73	1.1	1.4	(-0.4, 3.2)	73	2.7	1.8	(-0.4, 4.0)	77	1.6	1.0	(-0.8, 2.8)
16	73	2.9	3.4	(1.5, 5.3)	73	3.6	3.0	(0.9, 5.1)	74	1.5	1.0	(-0.9, 2.9)
18	72	2.1	2.3	(0.4, 4.3)	73	2.8	1.4	(-0.7, 3.5)	76	0.9	-0.0	(-2.0, 1.9)
24	72	-1.2	-0.0	(-2.1, 2.1)	73	-0.3	1.0	(-1.2, 3.2)	75	-1.3	-1.8	(-3.7, 0.2)

5.2.3 PR Analysis

The statistical reviewer used the same mixed model to analyze the ΔPR effect. The model includes treatment as fixed effect and baseline values as a covariate. The results are presented in Table 14. The largest upper bounds of the 2-sided 90% CI for the mean differences between HYD 80 mg and placebo, between HYD 120 and placebo, and between HYD 160 mg and placebo are 4.0 ms, 1.7 ms and 2.8 ms, respectively. Table 15 presents the categorical analysis of PR. Nineteen subjects who experienced PR interval greater than 200 ms are in HYD groups.

Table 14: Analysis Results of ΔPR and ΔΔPR for HYD 80 mg, HYD 120 mg and HYD 160 mg

	Treatment Group											
	HYD 120 mg				HYD 160 mg				HYD 80 mg			
	ΔPR		ΔΔPR		ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time(h)	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	73	1.2	-3.5	(-6.7, -0.3)	73	0.2	-4.5	(-7.8, -1.2)	76	1.1	-1.2	(-4.0, 1.7)
1	73	3.0	-1.1	(-4.3, 2.2)	73	1.9	-2.3	(-5.6, 1.0)	77	2.9	-0.2	(-2.8, 2.4)
1.5	73	0.9	-2.7	(-6.0, 0.5)	73	1.4	-2.2	(-5.5, 1.2)	77	1.1	-0.3	(-3.2, 2.6)
2	73	0.8	-2.7	(-5.5, 0.2)	72	0.0	-2.4	(-5.6, 0.8)	77	2.4	1.5	(-1.1, 4.0)
3	71	1.7	-2.5	(-5.5, 0.5)	73	2.0	-1.2	(-4.4, 2.0)	77	2.4	-0.1	(-2.6, 2.5)
4	72	1.7	-3.3	(-6.1, -0.5)	73	2.4	-2.1	(-5.3, 1.1)	77	3.0	-0.2	(-2.6, 2.3)
6	72	3.3	-1.0	(-3.4, 1.3)	73	3.1	-2.1	(-4.7, 0.4)	76	2.5	-1.0	(-3.4, 1.3)
10	72	0.3	-1.3	(-3.9, 1.2)	73	0.3	-2.0	(-4.9, 0.8)	77	0.9	-0.2	(-2.4, 2.0)
12	71	1.5	-1.1	(-3.9, 1.7)	73	3.5	-0.1	(-3.1, 2.8)	77	3.9	0.5	(-2.2, 3.2)
14	73	-1.6	-3.4	(-6.4, -0.4)	73	-1.0	-4.6	(-7.6, -1.7)	77	-0.1	-3.3	(-6.1, -0.5)
16	73	-2.3	-5.7	(-8.6, -2.9)	73	-1.6	-6.0	(-9.0, -3.0)	74	1.6	-0.2	(-3.0, 2.6)
18	72	-2.4	-5.9	(-8.9, -3.0)	73	-2.9	-5.8	(-9.0, -2.6)	76	-0.5	-3.5	(-6.3, -0.7)
24	72	0.1	-3.5	(-6.5, -0.4)	73	0.3	-4.4	(-7.3, -1.4)	75	3.1	0.6	(-1.9, 3.2)

Table 15: Categorical Analysis for PR

Treatment Group	Total N	PR <= 200 ms	PR >200 ms
HYD 80 mg	77	70 (90.9%)	7 (9.1%)
HYD 120 mg	73	68 (93.2%)	5 (6.9%)
HYD 160 Mg	73	67 (91.8%)	7 (9.1%)
Moxifloxacin on Day 9	62	59 (95.2%)	3 (4.8%)
Moxifloxacin on Day 12	61	58 (95.1%)	3 (4.9%)
Moxifloxacin on Day 15	62	59 (95.2%)	3 (4.8%)
Placebo	61	60 (98.3%)	1 (1.6%)

5.2.4 QRS Analysis

The statistical reviewer used the same mixed model to analyze the ΔQRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The results are presented in Table 16. The largest upper bounds of the 2-sided 90% CI for the mean differences between HYD 80 mg and placebo, between HYD 120 and placebo, and between HYD 160 mg and placebo are 1.4 ms, 1.1 ms and 0.8 ms, respectively. Table 17

presents the categorical analysis of QRS. Three subjects who experienced QRS interval greater than 110 ms are in HYD groups.

Table 16: Analysis Results of ΔQRS and ΔΔQRS for HYD 80 mg, HYD 120 mg and HYD 160 mg

	Treatment Group											
	HYD 120 mg				HYD 160 mg				HYD 80 mg			
	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time(h)	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	73	0.2	-0.6	(-1.8, 0.6)	73	0.1	-1.1	(-2.3, 0.1)	76	-0.3	-0.1	(-1.4, 1.1)
1	73	-0.5	-1.6	(-2.9, -0.3)	73	-0.4	-1.7	(-2.9, -0.5)	77	-0.6	-0.7	(-2.0, 0.6)
1.5	73	0.5	-0.6	(-1.7, 0.6)	73	0.1	-1.1	(-2.3, 0.1)	77	-0.2	-0.5	(-1.7, 0.7)
2	73	0.8	-0.4	(-1.7, 0.8)	72	0.3	-1.4	(-2.5, -0.2)	77	-0.3	-0.8	(-1.9, 0.4)
3	71	0.6	-0.5	(-1.7, 0.7)	73	-0.2	-1.4	(-2.6, -0.2)	77	-0.3	-0.1	(-1.2, 1.1)
4	72	0.8	-0.0	(-1.2, 1.1)	73	-0.1	-1.1	(-2.2, -0.0)	77	-0.5	-0.2	(-1.3, 0.9)
6	72	0.3	-0.4	(-1.5, 0.7)	73	-0.5	-1.8	(-2.9, -0.6)	76	-0.4	-0.0	(-1.3, 1.2)
10	72	0.6	-0.2	(-1.3, 0.9)	73	0.3	-0.7	(-1.8, 0.5)	77	-0.0	0.2	(-0.9, 1.4)
12	71	0.2	-0.1	(-1.3, 1.0)	73	-0.0	-0.4	(-1.6, 0.8)	77	-0.7	0.0	(-1.1, 1.1)
14	73	-0.1	-0.8	(-1.9, 0.4)	73	-0.7	-1.1	(-2.3, 0.0)	77	-0.6	-0.3	(-1.5, 0.9)
16	73	0.2	-0.3	(-1.5, 0.9)	73	-0.3	-1.2	(-2.5, 0.0)	74	-0.7	-0.2	(-1.4, 1.0)
18	72	0.2	-0.2	(-1.4, 0.9)	73	-0.4	-0.8	(-1.9, 0.4)	76	-1.1	-0.5	(-1.8, 0.8)
24	72	0.6	-0.5	(-1.7, 0.7)	73	0.1	-1.9	(-3.1, -0.7)	75	-0.3	0.1	(-1.0, 1.2)

Table 17: Categorical Analysis for QRS

Treatment Group	Total N	QRS <= 110 ms	QRS > 110 ms
HYD 80 mg	77	76 (98.7%)	1 (1.3%)
HYD 120 mg	73	72 (98.6%)	1 (1.4%)
HYD 160 Mg	73	72 (98.6%)	1 (1.4%)
Moxifloxacin on Day 9	62	62 (100%)	0 (0.0%)
Moxifloxacin on Day 12	61	61 (100%)	0 (0.0%)
Moxifloxacin on Day 15	62	62 (100%)	0 (0.0%)
Placebo	61	60 (98.3%)	1 (1.6%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationships between ΔΔQTcI and hydrocodone concentration, as well as its major metabolites norhydrocodone and hydromorphone concentration were investigated by linear mixed-effects modeling.

The following three linear models were considered:

- Model 1 is a linear model with an intercept;
- Model 2 is a linear/ model with mean intercept fixed to 0 (with variability);
- Model 3 is a linear model with no intercept.

Table 18 to Table 20 summarizes the results of the hydrocodone and its metabolites concentration -ΔΔ QTcI analyses. Model 1 was used for further analysis since the model with intercept was found to fit the data best.

Scatter plots between **ΔΔ**QTcI and hydrocodone, as well as its major metabolites norhydrocodone and hydromorphone concentration, are visualized in Figure 10, Figure 11, and Figure 12. The placebo-corrected QTcI change from baseline (**ΔΔ**QTcI) was observed slightly increase with increasing concentrations of norhydrocodone, and hydromorphone.

Table 18. Exposure-Response Analysis of Hydrocodone associated ΔQTcI Prolongation.

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ΔQTcI = Intercept +slope * Hydrocodone Concentration		
Intercept (ms)	4.893 (3.03, 6.75) <0.0001	8.97
Slope (ms per ng/mL)	0.004396 (-0.00936, 0.0182) 0.5953	0.05
Residual Variability (ms)	11.51	-

Table 19. Exposure-Response Analysis of Norhydrocodone associated ΔQTcI Prolongation.

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ΔQTcI = Intercept +slope * Norhydrocodone Concentration		
Intercept (ms)	3.971 (2.146, 5.795) 0.0005	8.39
Slope (ms per ng/mL)	0.0414 (0.00437, 0.0784) 0.0666	0.12
Residual Variability (ms)	11.51	-

Table 20. Exposure-Response Analysis of Hydromorphone associated ΔQTcI Prolongation.

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ΔQTcI = Intercept +slope * Hydromorphone Concentration		
Intercept (ms)	4.36 (2.64, 6.08) <0.0001	8.20
Slope (ms per ng/mL)	0.7215 (0.1055, 1.3375) 0.0557	1.76
Residual Variability (ms)	11.48	-

Figure 10: ΔΔ QTcI vs. Hydrocodone Concentration

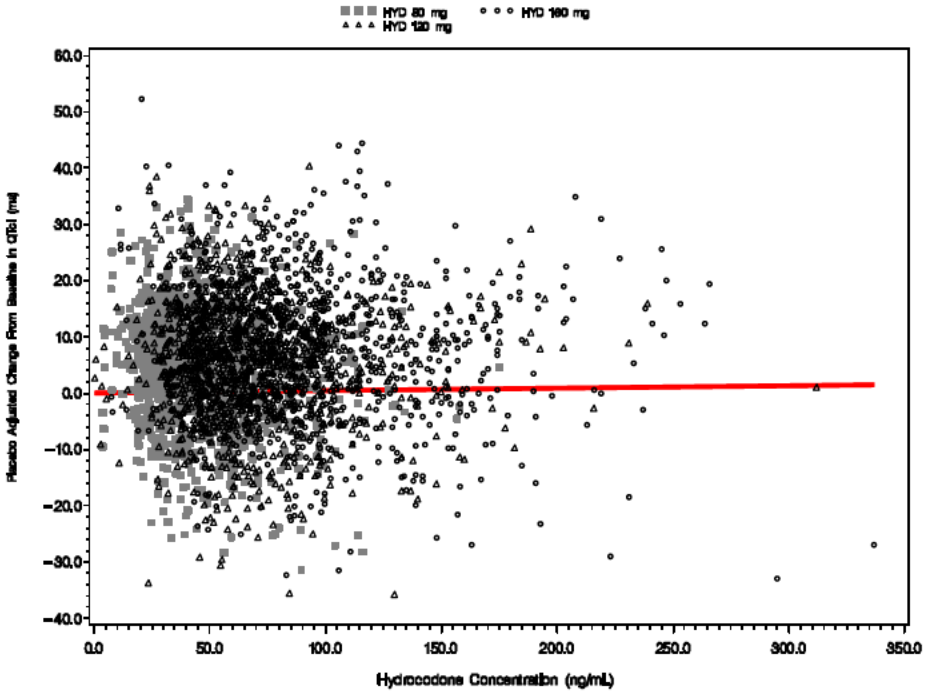


Figure 11: ΔΔ QTcI vs. Norhydrocodone Concentration

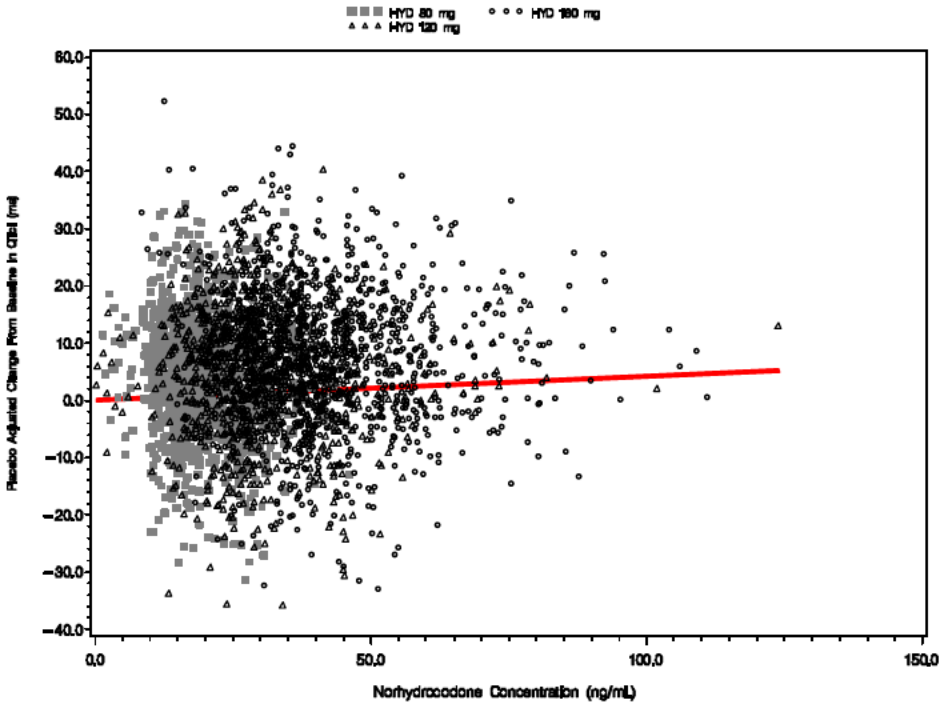
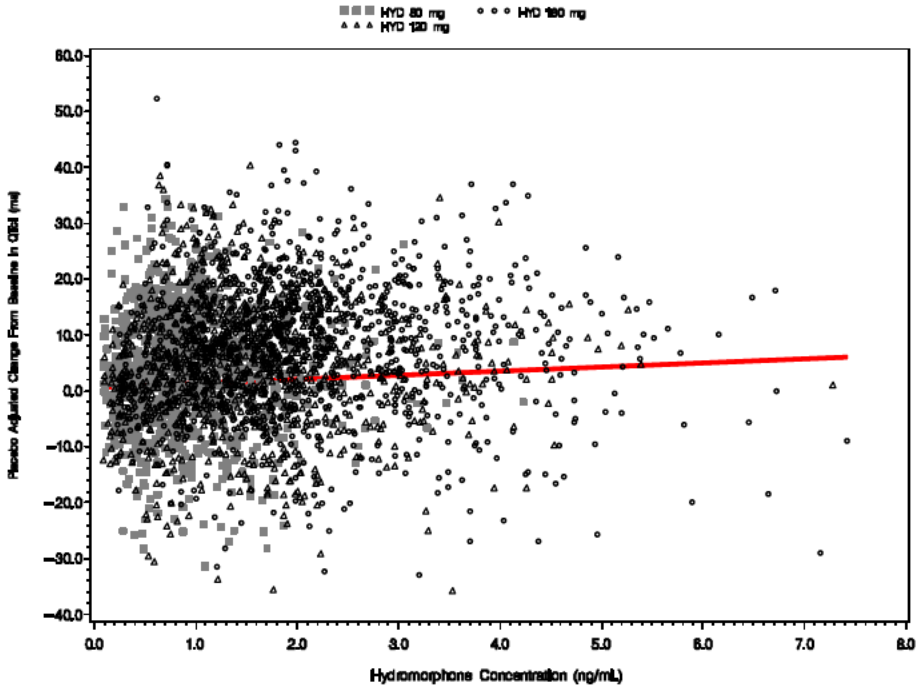


Figure 12: ΔΔ QTcI vs. Hydromorphone Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant effects on PR or QRS were seen.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

<table>
<tr><td>Therapeutic dose</td><td colspan="2">Include maximum proposed clinical dosing regimen
Hydrocodone Bitartrate Controlled-Release Tablets (HYD) will allow dosing once every 24 hours (q24h). The HYD tablet strengths are 20 mg, 30 mg, 40 mg , 60 mg, 80 mg, 100 mg, and 120 mg. HYD dosing will not be limited by a nonopioid component permitting treatment of chronic pain requiring higher total daily opioid doses. The multiple tablet strengths planned for HYD will allow easy titration to effective pain control. The maximum dosing regimen being evaluated in the ongoing Phase 3 clinical trials is HYD 120 mg q24h.</td></tr>
<tr><td>Maximum tolerated dose</td><td colspan="2">Include if studied or NOAEL dose
No maximum tolerated dose has been established for HYD. In healthy subjects, the highest single and multiple dose studied to date is HYD 120 mg. This dose was adequately tolerated in healthy subjects under naltrexone blockade once daily for 5 days. This is also the highest dose studied in the Phase 3 studies. In addition, a maximum tested dose of 160 mg HYD once-daily for 3 days, without naltrexone blockade was well tolerated in the recently completed thorough QTc study.</td></tr>
<tr><td>Principal adverse events</td><td colspan="2">Include most common adverse events; dose limiting adverse events
The AEs which occurred in ≥ 2% of healthy subjects under naltrexone blockade were: nausea, headache, dizziness, somnolence, abdominal pain, vomiting, constipation, diarrhea, euphoric mood, and fatigue. All TEAEs were of mild or moderate intensity and they were those generally associated with opioid analgesics.</td></tr>
<tr><td rowspan="3">Maximum dose tested</td><td>Single Dose</td><td>Specify dose HYD 120 mg under naltrexone blockade</td></tr>
<tr><td>Multiple Dose</td><td>Specify dosing interval and duration
HYD 120 mg q24 for 5 days under naltrexone blockade</td></tr>
<tr><td>Multiple Dose Escalation</td><td>HYD 20, 40, 80, 120, and 160 mg (dose escalation [titration] q24h every 24 hours for 3 days of each HYD dose)</td></tr>
<tr><td>Exposures Achieved at Maximum Tested Dose</td><td>Single Dose</td><td>Mean (%CV) Cmax and AUC
Dose Proportionality
<table>
<tr><th>Hydrocodone</th><th colspan="5">Mean (%CV)</th></tr>
<tr><th>PK Metric (unit)</th><th>HYD 20 mg N = 29</th><th>HYD 40 mg N = 31</th><th>HYD 60 mg N = 28</th><th>HYD 80 mg N = 30</th><th>HYD 120 mg N = 29</th></tr>
<tr><td>C_{max} (ng/mL)</td><td>15 (38)</td><td>34 (35)</td><td>54 (29)</td><td>69 (25)</td><td>110 (40)</td></tr>
<tr><td>AUC_t (ng•h/mL)</td><td>281 (45)</td><td>618 (41)</td><td>1004 (29)</td><td>1298 (29)</td><td>1759 (38)</td></tr>
<tr><td>AUC_{inf} (ng•h/mL)</td><td>284 (45)</td><td>622 (41)</td><td>1009 (29)</td><td>1304 (29)</td><td>1787[a] (38)</td></tr>
</table>
a: n = 28.</td></tr>
</table>

<table>
<tr><td></td><td>Multiple Dose</td><td>Mean (%CV) Cmax and AUC
HYD 120 mg q24h for 5 days
<table><tr><th>Hydrocodone</th><th colspan="2">Mean (%CV)</th></tr><tr><th>PK Metric (unit)</th><th>Day 1
N=24</th><th>Day 5 (steady state)
N=25</th></tr><tr><td>C_{max} (ng/mL)</td><td>128 (23)</td><td>135 (37)</td></tr><tr><td>AUC_{tau} (ng*h/mL)</td><td>1541 (22)</td><td>1938 (38)</td></tr></table>HYD 80, 120, 160 mg q24h for 3 days
<table><tr><th>Hydrocodone</th><th colspan="3">Mean (%CV)</th></tr><tr><th>PK Metric (unit)</th><th>HYD 80
Day 9
N=77</th><th>HYD 120
Day 12
N=75</th><th>HYD 160
Day 15
N=73</th></tr><tr><td>Cmax,ss (ng/mL)</td><td>83 (31)</td><td>122 (35)</td><td>151 (35)</td></tr><tr><td>AUC0-24,ss (ng*h/mL)</td><td>1252 (28)</td><td>1844 (29)</td><td>2380 (31)</td></tr></table></td></tr>
<tr><td>Range of linear PK</td><td colspan="2">Specify dosing regimen
Single doses of HYD 20, 40, 60, 80, and 120 mg. AUC and Cmax increased linearly with dose from 20 to 120 mg. Both Cmax and AUC increased slightly more than dose proportionally. This deviation from dose proportionality was minimal.</td></tr>
<tr><td>Accumulation at steady state</td><td colspan="2">Mean (%CV); specify dosing regimen
HYD 120 mg q24 for 5 days (N=23)
<table><tr><th colspan="3">Hydrocodone</th></tr><tr><th></th><th colspan="2">Accumulation Ratio</th></tr><tr><th>PK Metric (unit)</th><th>Mean</th><th>CV%</th></tr><tr><td>C_{max}[a] (ng/mL)</td><td>1.1</td><td>28</td></tr><tr><td>AUC_{tau}[b] (ng*h/mL)</td><td>1.3</td><td>39</td></tr></table>a: Cmax ss/Cmax single dose, b: AUC 0-24, ss/AUC 0-24 single dose</td></tr>
<tr><td>Metabolites</td><td colspan="2">Include listing of all metabolites and activity
In humans, hydrocodone undergoes CYP2D6 mediated O-demethylation yielding hydromorphone (minor active metabolite, representing up to 3% of systemic exposure of hydrocodone), and CYP3A4 mediated N-demethylation yielding norhydrocodone (major inactive metabolite, representing approximately 40% of systemic exposure to hydrocodone). CYP2D6 and CYP3A4 are believed to be compensatory mechanisms.</td></tr>
<tr><td>Absorption</td><td>Absolute/ Relative Bioavail-ability</td><td>Mean (%CV) Cmax and AUC
The absolute BA of HYD has not been studied.
The relative BA of multiple vs. single HYD tablets has been studied:
<table><tr><th>Hydrocodone</th><th colspan="2">Mean (%CV)</th></tr><tr><th>PK Metric (unit)</th><th>4 x HYD 20 mg
N = 24</th><th>1 x HYD 80 mg
N =24</th></tr><tr><td>C_{max} (ng/mL)</td><td>55 (34)</td><td>66 (25)</td></tr><tr><td>AUC_t (ng•h/mL)</td><td>1137 (27)</td><td>1213 (21)</td></tr><tr><td>AUC_{inf} (ng•h/mL)</td><td>1144 (27)</td><td>1236 (20)</td></tr></table></td></tr>
</table>

<table>
<tr>
<td></td>
<td>Tmax</td>
<td>
Median (range) for parent and metabolites
<table>
<tr><th>Hydrocodone</th><th colspan="5">Median (range)</th></tr>
<tr><th>PK Metric (unit)</th><th>HYD 20 mg N = 29</th><th>HYD 40 mg N = 31</th><th>HYD 60 mg N = 28</th><th>HYD 80 mg N = 30</th><th>HYD 120 mg N = 29</th></tr>
<tr><td>Tmax (h)</td><td>16 (6.0, 24)</td><td>16 (6.0, 24)</td><td>14 (10, 30)</td><td>16 (10, 24)</td><td>14 (6.0, 30)</td></tr>
</table>
<table>
<tr><th>Norhydrocodone</th><th></th></tr>
<tr><th>PK Metric (unit)</th><th>HYD 40 mg N = 24</th></tr>
<tr><td>Tmax (h)</td><td>16 (6.1, 24)</td></tr>
</table>
<table>
<tr><th>Hydromorphone</th><th></th></tr>
<tr><th>PK Metric (unit)</th><th>HYD 40 mg N = 24</th></tr>
<tr><td>Tmax (h)</td><td>16 (6.1, 24)</td></tr>
</table>
</td>
</tr>
<tr>
<td rowspan="2">Distribution</td>
<td>Vd/F or Vd</td>
<td>
<table>
<tr><th colspan="2">Hydrocodone</th></tr>
<tr><th>Typical PK Parameter (Unit)</th><th>Mean (95%CI)</th></tr>
<tr><td>Vc/F (L)</td><td>402 (380, 424)</td></tr>
</table>
</td>
</tr>
<tr>
<td>% bound</td>
<td>The mean plasma protein binding (% bound) of hydrocodone in subjects with normal hepatic function and mild, moderate, and severe hepatic impairment was low and similar at 36%, 37%, 33%, and 34%, respectively.</td>
</tr>
<tr>
<td>Elimination</td>
<td>Route</td>
<td>Primary route; percent dose eliminated
Other routes
Hydrocodone and its metabolites are excreted primarily in the urine. CLr of hydrocodone in healthy subjects was small (5.3 L/h) compared to apparent clearance (CL/F, 83 L/h); suggesting that nonrenal CL is the main elimination route. Following the administration of a single HYD 60-mg dose, total %Ae of unchanged hydrocodone in urine was low for all groups. The %Ae was 6.5% in subjects with normal renal function, and 5.0%, 4.8%, and 2.3% in subjects with mild, moderate, and severe renal impairment, respectively.</td>
</tr>
</table>

	Terminal t½	**Mean (%CV) for parent and metabolite** **Hydrocodone** **Mean (%CV)** **PK Metric (Unit)** / **HYD 20 mg N = 29** / **HYD 40 mg N = 31** / **HYD 60 mg N = 28** / **HYD 80 mg N = 30** / **HYD 120 mg N = 29** t1/2 (h): 7.6 (34) / 7.7 (28) / 8.1 (29) / 8.2 (29) / 8.7[a] (40) [a] n = 28. **Norhydrocodone** **PK Metric (Unit)** / **HYD 40 mg N = 24** t1/2 (h): 8.1 (22) **Hydromorphone** **PK Metric (Unit)** / **HYD 40 mg N = 24** t1/2 (h): 14.2 (33)
	CL/F	**Hydrocodone** **Typical PK Parameter (Unit)** / **Mean (95%CI)** CL/F (L/hour): 63 (60.3, 66.8)
Intrinsic Factors	Age	**Specify mean changes in Cmax and AUC** Exposures increased by 16% in elderly subjects compared to young subjects. HYD 60 mg **Group Comparison** / **Parameter** / **Ratio of geometric means** / **Lower 90% CI** / **Upper 90% CI** elderly/young: C_{max} 1.16 / 90.0 / 149; AUC_{inf} 1.14 / 87.5 / 149
	Sex	**Specify mean changes in Cmax and AUC** No meaningful exposure differences were observed between male and female subjects. HYD 60 mg **Group Comparison** / **Parameter** / **Ratio of geometric means** / **Lower 90% CI** / **Upper 90% CI** Female/Male: C_{max} 0.959 / 74.5 / 123; AUC_{inf} 1.05 / 80.6 / 137
	Race	**Specify mean changes in Cmax and AUC** No studies to date have assessed the pharmacokinetics of HYD by race.

	Hepatic & Renal Impairment	**Specify mean changes in Cmax and AUC** Renal Impairment – HYD 60 mg under naltrexone blockade

Group Comparison	Parameter	Ratio of geometric means	Lower 90% CI	Upper 90% CI
Mild/Healthy	C_{max}	1.14	80.7	161
	AUC_{inf}	1.13	75.8	167
Moderate/Healthy	C_{max}	1.23	90.2	167
	AUC_{inf}	1.61	126	205
Severe/Healthy	C_{max}	1.11	87.6	140
	AUC_{inf}	1.57	119	206
End-stage renal disease[a]/Healthy	C_{max}	0.87	59.2	129
	AUC_{inf}	1.04	62.4	175

[a] initiation of hemodialysis session at 90 minutes after dosing.

Hepatic Impairment – HYD 20 mg

Group Comparison	Parameter	Ratio of geometric means	Lower 90% CI	Upper 90% CI
Mild/Healthy	C_{max}	0.94	69.5	128
	AUC_{inf}	0.86	67.1	111
Moderate/Healthy	C_{max}	1.05	77.8	143
	AUC_{inf}	1.13	99.1	129
Severe/Healthy	C_{max}	1.05	68.3	161
	AUC_{inf}	1.04	65.5	165

Extrinsic Factors	Drug interactions	**Include listing of studied DDI studies with mean changes in Cmax and AUC** Effect of ketoconazole on HYD pharmacokinetics

Group Comparison	Parameter	Ratio of geometric means	Lower 90% CI	Upper 90% CI
HYD 20 mg + Ketoconazole 200 mg q12h / HYD 20 mg +Placebo	C_{max}	1.78	162	196
	AUC_{inf}	2.33	217	251

Effect of paroxetine on HYD pharmacokinetics

Group Comparison	Parameter	Ratio of geometric means	Lower 90% CI	Upper 90% CI
HYD 20 mg + Paroxetine 20 mg / HYD 20 mg + Placebo	C_{max}	1.06	92.7	121
	AUC_{inf}	1.06	97.8	115

<table>
<tr><td></td><td>Food Effects</td><td>Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Cmax and AUC were not affected when co-administered with a low fat meal, approximately 16% and 9%, respectively.

Cmax was approximately 50% higher under high fat conditions in comparison to fasting conditions. However, AUC of HYD 120 mg tablets was not affected when co-administered with a high fat /high caloric meal.

No dose dumping was observed from HYD 120 mg tablets in the presence of a high fat / high caloric or low fat / low caloric meal.

HYD 120 mg
<table>
<tr><th>Group Comparison</th><th>Parameter</th><th>Ratio of geometric means</th><th>Lower 90% CI</th><th>Upper 90% CI</th></tr>
<tr><td>High-fat meal/Fasted</td><td>C_{max}</td><td>1.54</td><td>138</td><td>173</td></tr>
<tr><td></td><td>AUC_{inf}</td><td>1.20</td><td>106</td><td>137</td></tr>
<tr><td>Low-fat meal/Fasted</td><td>C_{max}</td><td>1.17</td><td>104</td><td>131</td></tr>
<tr><td></td><td>AUC_{inf}</td><td>1.09</td><td>95.8</td><td>124</td></tr>
</table></td></tr>
<tr><td>Expected High Clinical Exposure Scenario</td><td colspan="2">Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.
Hydrocodone, like other opioids, does not have an anticipated maximum therapeutic daily dose. Therefore, a clear basis for defining a therapeutic and supratherapeutic dose for HYD is not available. Based on safety and tolerability experience in titrating other opioids and HYD experience to date in the same population, HYD 160 is the anticipated maximum tolerable dose that can be achieved. Based on these observations and PK/PD considerations, we have selected HYD 80 mg as the low dose and HYD 160 mg as the high dose to examine the effect of HYD on the QT/QTc interval. In the recently completed thorough QTc study, HYD doses up to 160 mg without naltrexone blockade were well tolerated.</td></tr>
</table>

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

/s/

MOH JEE NG
06/30/2014

QIANYU DANG
06/30/2014

FANG LI
06/30/2014

JIANG LIU
06/30/2014

NORMAN L STOCKBRIDGE
07/01/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 206627	NDA Supplement #: n/a	Efficacy Supplement Type: n/a
Proprietary Name: Hysingla ER [alternate (b) (4) ER] Established/Proper Name: hydrocodone bitartrate Dosage Form: extended-release oral tablets Strengths: 20, 30, 40, 60, 80, 100, and 120 mg		
Applicant: Purdue Pharma L.P. Agent for Applicant (if applicable): n/a		
Date of Application: April 26, 2014 Date of Receipt: April 28, 2014 Date clock started after UN: n/a		
PDUFA Goal Date: October 28, 2014	Action Goal Date (if different): August 15, 2014	
Filing Date: June 27, 2014	Date of Filing Meeting: May 22, 2014	
Chemical Classification: 3		
Proposed indication(s)/Proposed change(s): Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products

	☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): IND 059175

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒	☐	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒	☐	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☒	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☒	☐	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 202880	Zohydro ER	**NP (new product)**	Oct. 25, 2016

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 years, via reference to CFR 314.108(b)(4) ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the	n/a

application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	Some deficiencies identified, which have been corrected by the sponsor
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**

For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*: 4/29/14	☐	☐	☐	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☒	☐	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☒	☐	☐	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☒	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☒	☐	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	Consulted to PLT
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted?	☐	☐		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** ***CDRH consulted on 5/2/14*** ***QT-IRT Team consulted on 4/29/14*** ***OB/DB-IV consulted 4/28/14***	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** May 4, 2011 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** July 10, 2013 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** SPA-1, stability protocol, agreement on 8/12/11 ***If yes, distribute letter and/or relevant minutes before filing meeting***	☒	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 22, 2014

NDA #: 206627

PROPRIETARY NAME: Hysingla ER

ESTABLISHED/PROPER NAME: hydrocodone bitartrate

DOSAGE FORM/STRENGTH: extended-release tablets, 20, 30, 40, 60, 80, 100 and 120 mg

APPLICANT: Purdue Pharma L.P.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

BACKGROUND: Purdue Pharma has developed an extended-release oral tablet formulation for 24-hour dosing of hydrocodone in strengths ranging from 20 to 120 mg per tablet, with proposed proprietary name, Hysingla ER (and alternate proposed proprietary name, (b) (4) ER). Hysingla ER is purported to have abuse deterrent properties and the proposed package insert contains labeling claims to describe those properties. Given that the formulation may well have abuse deterrent properties, based on the similarity of the formulation to Purdue's oxycodone-containing approved product, OxyContin, we will be granting a priority review of this NDA. The application appears to comply with guidance offered during the pre-NDA meeting, held July 10, 2013. Also for consideration during the review cycle, another hydrocodone-containing extended-release product (Zohydro ER/NDA 202880, ER hydrocodone bitartrate in 10, 15, 20, 30, 40, and 50 mg capsule strengths for twice-daily dosing) was approved by FDA on Oct. 25, 2013, and was granted 3 years of marketing exclusivity for the new clinical study conducted to support its approval. The two formulations may be considered pharmaceutical alternatives by the definition of CFR 320.1, although Hysingla ER has the proposed strength, 120 mg (over a 24-hour dosing period), that is not achievable by Zohydro ER's maximum labeled strength of 50 mg twice daily. Also of significance, Zohydro ER is not an abuse deterrent formulation. It will be for the Exclusivity Board to determine during the review period for NDA 206627 whether the scope of Zohydro ER's granted exclusivity may prevent approval of NDA 206627. However, based on CFR 314.101, the unexpired 3-year exclusivity for Zohydro ER (NDA 202880) does not preclude the filing and review of Purdue's NDA 206627 for Hysingla ER.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dominic Chiapperino	Y
	CPMS/TL:	Parinda Jani	N

Cross-Discipline Team Leader (CDTL)	Ellen Fields		Y
Clinical	Reviewer:	Jacqueline Spaulding	Y
	TL:	Ellen Fields	Y
Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Yun Xu	N
Biostatistics	Reviewer:	Yan Zhou	Y
	TL:	Janice Derr	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Elizabeth Bolan Huiqing (Karen) Hao	Y N
	TL:	Dan Mellon	Y
Product Quality (CMC)	Reviewer:	Xiaobin Shen	Y
	TL:	Julia Pinto	Y
Quality Microbiology *(for sterile products)*	Reviewer:	John Metcalfe	Y
	TL:	Bryan Riley	N
Facility Review/Inspection	Reviewer:	Juandria Williams	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	James Schlick	Y
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:	Joan Blair	Y
	TL:	Jamie Wilkins Parker	Y

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	James Tolliver Martin Rusinowitz	Y Y
	TL:	Silvia Calderon	N
Other reviewers	Eunice Chung-Davies (OPDP) Catherine Dormitzer (DEPI) Cynthia Kornegay (TL, DEPI) Akm Kairuzzaman (Biopharm, ONDQA)		Y Y Y Y
Other attendees	Bob A. Rappaport Sharon Hertz Kimberly Lehrfeld Jamie Wilkins Parker Tara Arguwal Vaishali Jarral Brantley Dorch		

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	☐ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	BA/BE study
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: Some fixes/links are needed but no filing issues	☐ Not Applicable
CLINICAL	☐ Not Applicable ☒ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: FDA now has experience in reviewing abuse-deterrent claims and advice from the Committee is not necessary. ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**: See CSS filing review, for one comment for the 74-day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments: See separate filing review from clinical pharmacology team.	☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: No comments for 74-day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: No comments for 74-day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: See separate filing reviews from CMC and Biopharm teams, both with comments for 74-day letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: Consult not needed.	 ☐ YES ☐ NO ☒ YES ☐ NO ☐ YES ☒ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: See separate filing review from	☐ Not Applicable ☒ YES ☐ NO

microbiology reviewer with comment for 74-day letter.	
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Bob A. Rappaport, Director, DAAAP

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): n/a

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: Review of this application will be attempted on accelerated timelines (even beyond "Priority Review"). Wrap-up meeting is scheduled for July 26, 2014.

REGULATORY CONCLUSIONS/DEFICIENCIES

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be suitable for filing.

Review Issues:

☐ No review issues have been identified for the 74-day letter.

☒ Review issues have been identified for the 74-day letter. List (optional):

From Filing/74-day letter:

"Chemistry, Manufacturing, and Controls

1. We have reviewed DMF (b) (4) in support of NDA 206627 and found that it is deficient. The deficiencies were communicated to the DMF holder on May 30, 2014. Be advised that the outcome of the CMC review of your NDA is dependent upon satisfactory resolution of the identified deficiencies in DMF (b) (4)
2. (b) (4)
3.

4. (b) (4)

5.

6.

Microbiology

7. You propose waiving microbial enumeration release testing for your drug product. This proposal may be acceptable provided that adequate upstream controls are established and documented. We acknowledge your summary of both (b) (4) and microbial limits testing data in module 3.2.P.2. However, a release program that does not include microbial enumeration testing necessitates adequate microbiological controls of both incoming raw materials and the manufacturing process, in addition to the product's (b) (4) Provide the following information for your process:

   a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.

      i. (b) (4)

      ii.

   b. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

   c. Describe activities taken when microbiological acceptance criteria are not met at control points.

   d. At a minimum, perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing. In lieu of providing this information, amend the drug product release and stability specifications with microbial enumeration testing of every

batch.

Biopharmaceutics

8. Based on insufficient data and information submitted thus far, your proposed specifications and process controls related to (b) (4) and dissolution cannot likely be deemed acceptable. Provide the following information:

   a. (b) (4)

   b.

   c.

   d. In your submitted dissolution method development report, we could not locate information for the method's discriminating capability that can distinguish a "bad batch." Provide the exact location in the application where this information can be found or submit a study report that demonstrates the method's capability to detect any faulty batch as a result for unacceptable variation in either material attributes (such a (b) (4)) or manufacturing process deviation or both.

Clinical

9. In your oral human abuse potential study, HYD1013, we note the absence of information regarding how subjects chewed the test drug. There is no indication that a "vigorous" chewing arm was included in the Treatment Phase. This is important as we note the prior findings from Study OTR1016 that evaluated the pharmacokinetics of reformulated OxyContin and demonstrated substantially higher

plasma levels of oxycodone following "vigorous" chewing compared to "normal" chewing of the reformulated product. Therefore, it must be determined whether "vigorous" chewing of HYD tablets could result in significantly higher plasma levels of hydrocodone, and, therefore, possibly higher levels of subjective reinforcing effects (i.e., Drug Liking) compared to when HYD tablets are subjected to "normal" chewing. We recommend that you conduct a pharmacokinetic study examining plasma levels of hydrocodone following "normal" and "vigorous" chewing of HYD tablets to potentially bridge to study HYD1013."

"During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

1. The "Initial U.S. Approval" date in the Highlights (HL) section is currently left blank, perhaps because you believe the year shown here identifies the approval year of this product (which is not known). However, the year shown here would be for the first FDA approval of the hydrocodone bitartrate moiety, which is 1943, and should be included.

2. Under the ADVERSE REACTIONS heading of the HL section, the required bolded statement, "To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [manufacturer's U.S. phone number] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch." should be revised so that the phrase "SUSPECTED ADVERSE REACTIONS" is in all-caps font.

3. The revision date statement included at the end of the HL statement, i.e., "**Revised: xx/xxxx**," should be right-justified in that column.

The above labeling comments, based on the SRPI checklist, are fairly minor and, therefore, we will not request submission of revised labeling at this time.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances."

{End of 74-day letter comments}

Review Classification:

☐ Standard Review

☒ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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/s/

DOMINIC CHIAPPERINO
06/30/2014

CSS Filing Checklist for NDA/BLA or Supplement

NDA Number: 206-627 **Applicant: Purdue Pharma** **Date: June 27, 2014 (Filing)**
Drug Name: Hydrocodone **IND Number: 59,175**
Reviewers: James Tolliver, Ph.D. **Team Leader: Silvia Calderon,**
Martin Rusinowitz, M.D. **Ph.D.**

	Checklist	Yes	No	NA	Comment
	What is the regulatory history of this application?	x			Prior CSS reviews: DARRTS, IND 59175, Love Lori A, dated 12/2012
	Abuse potential assessment is required if any of the following are true for a drug[1,2]:				
	It affects the CNS	x			
	It is chemically or pharmacologically similar to other drugs with known abuse potential	x			
	It produces psychoactive effects such as sedation, euphoria, and mood changes	x			
	Is the drug a new molecular entity?		x		
	Is this a new or novel drug formulation?	x			
	Content of NDA abuse potential section:				
	Module 1: Administrative Information and Prescribing Information 1.11.4 Multiple Module Information Amendment contains:				
	• A summary, interpretation, and discussion of abuse potential data provided in the NDA.	x			
	• A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.	x			
	• A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA		x		Hydrocodone product is in Schedule II of CSA. Sponsor has not proposed scheduling changes.
	Module 2: Summaries 2.4 Nonclinical Overview - includes a brief statement outlining the nonclinical studies performed to assess abuse potential.				
		x			
	Module 3: Quality				
	3.2.P.1 Description and Composition of the Drug Product - describes any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).	x			
	Is there an assessment of extractability/formulation release characteristics of intact and manipulated product?	x			
	3.2.P.2 Description and Composition of the Drug Product - describes the development of any components of the drug product that were included to address accidental or intentional misuse.	x			
	Is this an extended release or abuse-resistant formulation?	x			
	Module 4: Nonclinical Study Reports				
	4.2.1 Pharmacology	x			

1 21 CFR 314.50(d)(5)(vii): If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.
2 21USC811(f) Abuse potential:If, at the time a new-drug application is submitted to the Secretary for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, it appears that such drug has an abuse potential, such information shall be forwarded by the Secretary to the Attorney General.

CSS Filing Checklist for NDA/BLA or Supplement

	Checklist	Yes	No	NA	Comment
	4.2.1.1 Primary Pharmacodynamics - contains study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.				
	Are in vitro receptor binding studies included?	x			
	Are functional assays included?		x		
	4.2.3.7.4 Dependence – section includes:				
	• A complete discussion of the nonclinical data related to abuse potential. • Complete study reports of all nonclinical abuse potential studies.		x		
	Animal Behavioral and Dependence Pharmacology: note all primary data need to be included in the NDA				
	Was a self administration study conducted?		x		
	Was a conditioned place preference study conducted?		x		
	Was a drug discrimination study conducted?		x		
	Was a physical dependence study conducted?		x		
	Module 5: Clinical Study Reports 5.3.5.4 Other Study Reports - section contains complete study reports of all clinical abuse potential studies.				
	Human abuse potential study:				
	Was a human abuse potential study conducted?	x			Two human abuse potential studies were conducted in non-dependent opioid experienced abusers. Studies HYD1013 and HYD1014 examine PK profiles, PD parameters and safety following following oral administration of intact and crushed formulation and following intranasal administration, respectively. Both studies evaluate Drug Liking, High, Overall Drug Liking, and Take Drug Again. Percentage reduction analyses of PD measures were also provided.
	Are all the primary data included in the NDA?	x			
	Is a Statistics consult necessary?	x			Office of Biostatistics has been involved during the IND for the oral but not intranasal HAP study. CSS has already placed a consult for the review of two HAP studies
	Other Clinical trials:				
	Is there evidence of drug accountability issues or overt evidence of misuse, abuse, or diversions?	x			
	Are all abuse/misuse Case Report Forms submitted [addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study]?	x			AEs involving abuse/misuse are documented with detailed descriptions provided for specific subjects.
	Does Compliance need to be consulted re: site inspection for data integrity or other issues?		x		
	5.3.6.1 Reports of Postmarketing Experience - includes information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product				This product has not been previously marketed. No post-marketing experience

CSS Filing Checklist for NDA/BLA or Supplement

	Checklist	Yes	No	NA	Comment
	Did you review the scientific literature?	x			
	Did you conducted a search of databases and other information related to misuse, abuse, and addiction?	x			
	Is there evidence for any of the following:				
	Accidental overdose in the patient population and vulnerable populations	x			Overdose data are provided
	Overdose associated with misuse and abuse		x		"polydrug overdose" p137
	Unintended pediatric exposures to product			x	
	Labeling issues				Proposed Label is provided.
	Drug disposal issues?		x		Review Issue
	Postmarketing activities [PMRs, PMCs, REMS]	x			
	Scheduling activities			x	

Is NDA FILEABLE from a CSS perspective? _____YES_____

If the Application is not fileable, 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.

A potential review issue regarding oral human abuse potential study HYD1013 is the absence of information regarding how subjects chewed the test drug. There is no indication that a "vigorous" chewing arm was included in the Treatment Phase. This is significant considering that previously a pharmacokinetic study (designated OTR1016) involving reformulated OxyContin and submitted under IND 29,038 demonstrated substantially higher plasma levels of oxycodone following "vigorous" chewing compared to that following "normal" chewing of reformulated OxyContin. In consideration of this study, the question arises whether "vigorous" chewing of HYD tablets might result in significantly higher plasma levels of hydrocodone, and therefore possibly higher levels of subjective reinforcing effects (i.e., Drug Liking) compared to when HYD tablets are subjected to "normal" chewing. One way to address this issue might be a pharmacokinetic study examining plasma levels of hydrocodone following "normal" and "vigorous" chewing of HYD tablets to bridge to study HYD1013.

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

/s/

JAMES M TOLLIVER
06/11/2014

MARTIN S RUSINOWITZ
06/11/2014

SILVIA N CALDERON
06/11/2014

MICHAEL KLEIN
06/11/2014

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: 5/22/2014

To: Ni Khin, Acting Division Director, DGCPC
Kassa Ayalew, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
CDEROCDSIPMOs@fda.hhs.gov
Cynthia Kleppinger, M.D.
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance/CDER

Through: *Jacqueline Spaulding, M.D., Medical Officer, DAAAP*
Ellen Fields, M.D.,M.P.H., Clinical Team Leader, DAAAP

From: *Dominic Chiapperino, Ph.D., RPM, DAAAP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: 206627
IND#:59175
Applicant: Purdue Pharma L.P.
Phone: (203) 434-7360
Email: RegulatorySubmissions@pharma.com
Regulatory Point of Contact: Edward Liao, Pharm.D., Director Regulatory Affairs
Regulatory Point of Contact Phone: (203) 588-7558
Regulatory Point of Contact Email: edward.liao@pharma.com

Drug Proprietary Name: Pending
Generic Drug Name: Hydrocodone Bitartrate q24h Film-coated Tablest
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): The management of pain severe enough to require daily, around-the-clock, lon-term opiod treatment and for which alternative treatment options are inadequate.

PDUFA: October 28, 2014
Action Goal Date: August 11, 2014

Inspection Summary Goal Date: July 28, 2014

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table ***(Note: All items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).***

(Name,Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Dawson, Gary 5210 Armour Rd. Suite 400 Columbus, GA 31904 USA United States phone:706-321-0495 fax:706-321-0477 email:dawsong@rcrss.com	2198A	HYD3002	32	A Multicenter, Randomized, Double-blind, Placebo-controlled Study with an Open-label Run-in to Assess the Efficacy and Safety of Hydrocodone Bitartrate (HYD) Tablets 20 to 120 mg Once-daily in Subject
Harris, Michael 1215 S. 1680 W. Orem, UT 84058 USA United States phone:801-356-5555 fax:801-224-6010 email:iand@aspenclinicalresearch.com	2059A	HYD3003	16	An Open-label, Multicenter Study to Assess the Long-term Safety of Hydrocodone Bitartrate (HYD) Tablets 20 to 120 mg Once-daily in Subjects with Moderate to Severe Chronic Nonmalignant and Nonneuropat
Hassman, David 175 Cross Keys Rd. Building 300B Berlin, NJ 8009 USA United States phone: fax: email:	0608A	HYD3003	29	An Open-label, Multicenter Study to Assess the Long-term Safety of Hydrocodone Bitartrate (HYD) Tablets 20 to 120 mg Once-daily in Subjects with Moderate to Severe Chronic Nonmalignant and Nonneuropat
Hassman, David 175 Cross Keys Rd. Building 300B Berlin, NJ 8009 USA United States phone: fax: email (b) (6)	0608A	HYD3002	9	A Multicenter, Randomized, Double-blind, Placebo-controlled Study with an Open-label Run-in to Assess the Efficacy and Safety of Hydrocodone Bitartrate (HYD) Tablets 20 to 120 mg Once-daily in Subject

(Name,Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Taber, Louise 2525 W. Greenway Rd Suite 114 Phoenix, AZ 85023 USA United States phone: fax: email:	0108A	HYD3003	56	An Open-label, Multicenter Study to Assess the Long-term Safety of Hydrocodone Bitartrate (HYD) Tablets 20 to 120 mg Once-daily in Subjects with Moderate to Severe Chronic Nonmalignant and Nonneuropat
Taber, Louise 2525 W. Greenway Rd Suite 114 Phoenix, AZ 85023 USA United States phone: fax: email:ltaber@azresearchcenter.com	0108A	HYD3002	33	A Multicenter, Randomized, Double-blind, Placebo-controlled Study with an Open-label Run-in to Assess the Efficacy and Safety of Hydrocodone Bitartrate (HYD) Tablets 20 to 120 mg Once-daily in Subject

III. Site Selection/Rationale

Site Information

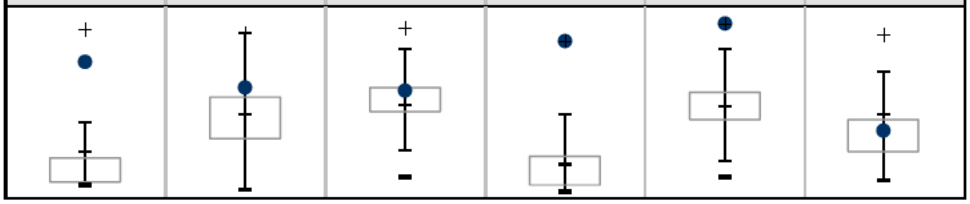
STUDY:	HYD3002	SITEID:	0108A

NAME	Taber, Louise
LOCATION	2525 W. Greenway Rd Suite 114 Phoenix, AZ, USA 85023
PHONE/FAX	/
EMAIL	ltaber@azresearchcenter.com

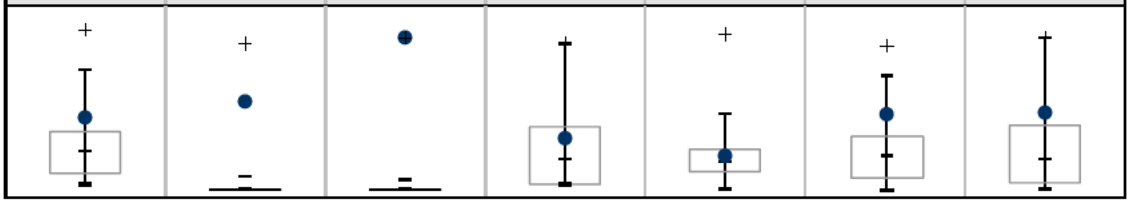
RANK	1	FINLDISC	-1	COMPLAINT	1
SITE RISK	27.1	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	41	7.19	6.86	153.25	22.50	80%
Study Rate	8	3.44	-0.31	26.80	-0.50	39%
Min	1	0.00	-6.86	0.00	-20.42	5%
Site	33	4.64	1.07	153.25	22.50	30%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	11.0	0.3	3%	100%	16.0	11.7	26
Study Rate	2.4	0.0	0%	19%	2.7	2.8	5
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	4.8	0.2	3%	33%	3.5	6.2	13



Site Memo

Taber. High enroller. Many adverse events compared to other sites. Death at site. Last inspected 2000- VAI. Older complaint of backdating records but could not be subtantiated. (b) (4) *INDs.*

Site Information

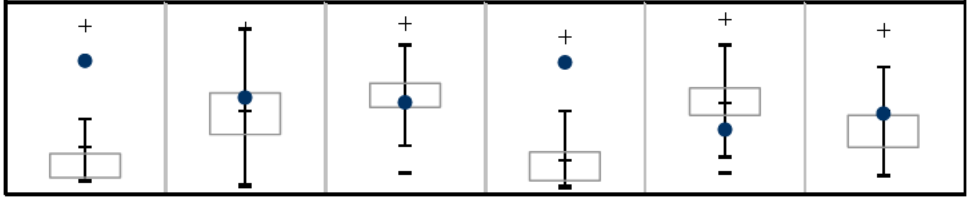
STUDY:	HYD3002	SITEID:	2198A

NAME	Dawson, Gary
LOCATION	5210 Armour Rd. Suite 400 Columbus, GA, USA 31904
PHONE/FAX	706-321-0495 / 706-321-0477
EMAIL	dawsong@rcrss.com

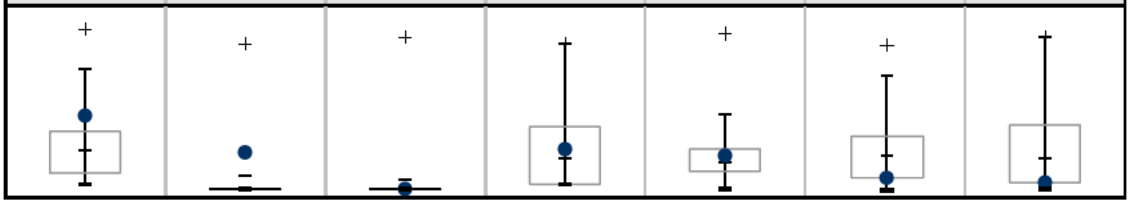
RANK	4	FINLDISC	-1	COMPLAINT	0
SITE RISK	12.9	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	41	7.19	6.86	153.25	22.50	80%
Study Rate	8	3.44	-0.31	26.80	-0.50	39%
Min	1	0.00	-6.86	0.00	-20.42	5%
Site	32	3.99	-0.46	127.77	-8.22	37%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	11.0	0.3	3%	100%	16.0	11.7	26
Study Rate	2.4	0.0	0%	19%	2.7	2.8	5
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	4.9	0.1	0%	25%	3.3	1.0	1



Site Memo

Dawson. Involved in both studies. High enroller for 002. Many adverse events reported. Never been inspected. (b) INDs.

Site Information

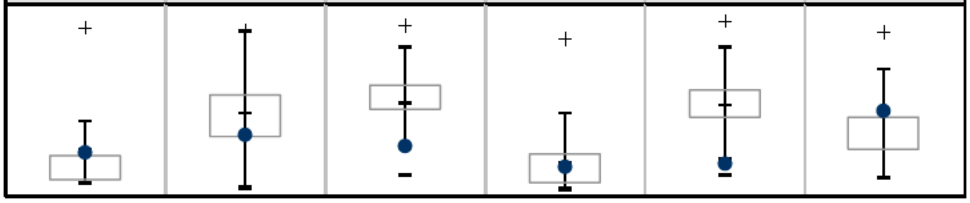
STUDY:	HYD3002	SITEID:	0608A

NAME	Hassman, David
LOCATION	175 Cross Keys Rd. Building 300B Berlin, NJ, USA 8009
PHONE/FAX	/
EMAIL	(b) (4)

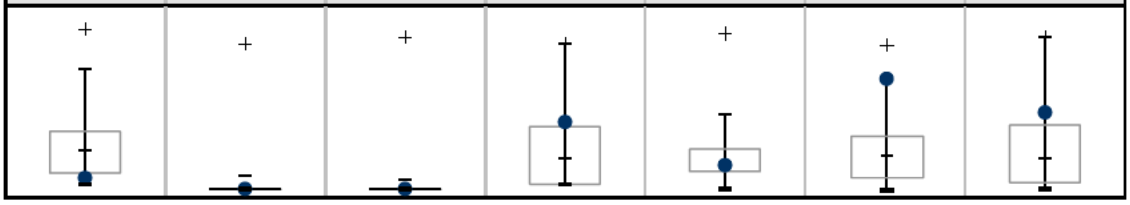
RANK	5	FINLDISC	-1	COMPLAINT	1
SITE RISK	12.9	OAI	(b) (4)	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	41	7.19	6.86	153.25	22.50	80%
Study Rate	8	3.44	-0.31	26.80	-0.50	39%
Min	1	0.00	-6.86	0.00	-20.42	5%
Site	9	2.38	-4.29	21.43	-17.14	39%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	11.0	0.3	3%	100%	16.0	11.7	26
Study Rate	2.4	0.0	0%	19%	2.7	2.8	5
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	0.6	0.0	0%	44%	2.4	8.9	13



Site Memo

Hassman. Ranked high in both studies. (2 and 5) Inspcted in 2001 and received WL for fabricating data. Inspected 2004-VAI. Inspected 2008- VAI. (b) (4) *NDs.*

Site Information

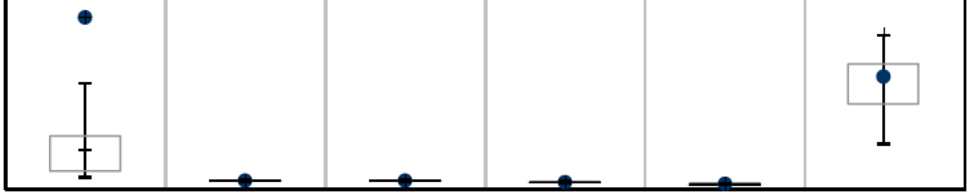
STUDY:	HYD3003	SITEID:	0108A

NAME	Taber, Louise
LOCATION	2525 W. Greenway Rd Suite 114 Phoenix, AZ, USA 85023
PHONE/FAX	/
EMAIL	0

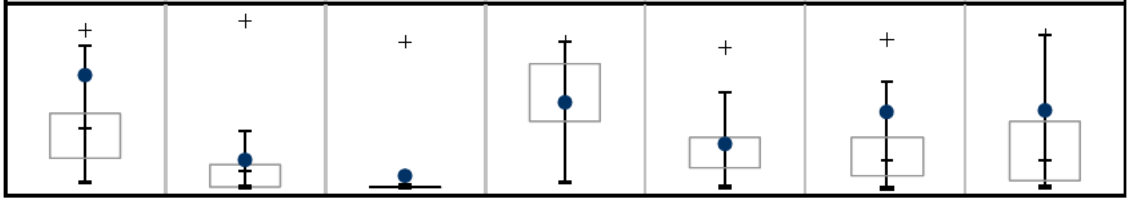
RANK	1	FINLDISC	-1	COMPLAINT	1
SITE RISK	21.3	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	56	0.00	0.00	0.00	0.00	100%
Study Rate	10	0.00	0.00	0.00	0.00	71%
Min	1	0.00	0.00	0.00	0.00	25%
Site	56	0.00	0.00	0.00	0.00	71%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	12.5	1.3	25%	100%	20.0	12.0	26
Study Rate	4.5	0.1	1%	56%	5.8	2.3	4.5
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	8.9	0.2	2%	57%	6.0	6.2	13



Site Memo

Taber. Ranked #1 both studies. High enroller, Many AEs.

Site Information

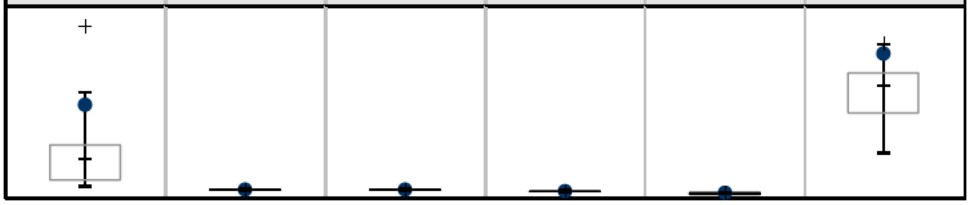
STUDY:	HYD3003	SITEID:	0608A

NAME	Hassman, David
LOCATION	175 Cross Keys Rd. Building 300B Berlin, NJ, USA 8009
PHONE/FAX	/
EMAIL	0

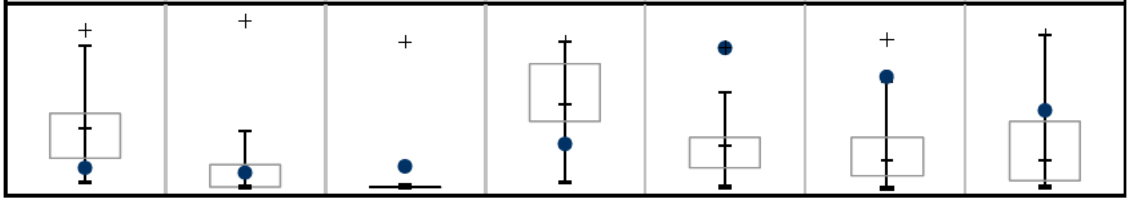
RANK	2	FINLDISC	-1	COMPLAINT	1
SITE RISK	17.2	OAI	(b) (4)	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	56	0.00	0.00	0.00	0.00	100%
Study Rate	10	0.00	0.00	0.00	0.00	71%
Min	1	0.00	0.00	0.00	0.00	25%
Site	29	0.00	0.00	0.00	0.00	94%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	12.5	1.3	25%	100%	20.0	12.0	26
Study Rate	4.5	0.1	1%	56%	5.8	2.3	4.5
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	1.3	0.1	3%	28%	20.0	8.9	13



Site Memo

Hassman. Ranked high (2 and 5) in both studies. Fairly high enroller in study 003. Had WL in 2001 for fabricating data. Inspetected 2004 -VAI. Inspected 2008- VAI. (b) (4) *INDs.*

Site Information

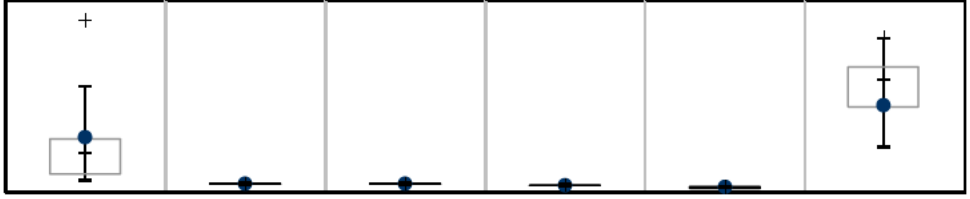
STUDY:	HYD3003	SITEID:	2059A

NAME	Harris, Michael
LOCATION	1215 S. 1680 W. Orem, UT, USA 84058
PHONE/FAX	801-356-5555 / 801-224-6010
EMAIL	iand@aspenclinicalresearch.com

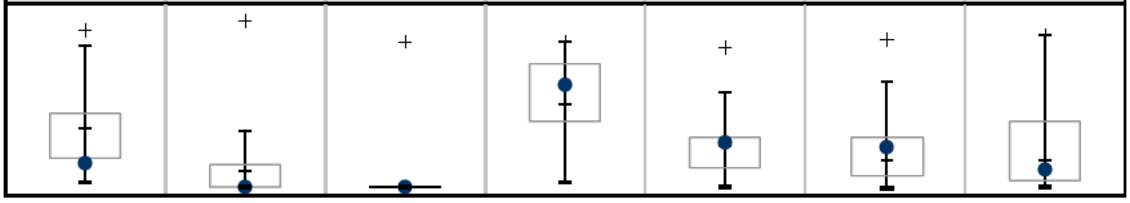
RANK	5	FINLDISC	-1	COMPLAINT	1
SITE RISK	11.7	OAI	(b) (4)	TSLI	2

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	56	0.00	0.00	0.00	0.00	100%
Study Rate	10	0.00	0.00	0.00	0.00	71%
Min	1	0.00	0.00	0.00	0.00	25%
Site	16	0.00	0.00	0.00	0.00	53%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	12.5	1.3	25%	100%	20.0	12.0	26
Study Rate	4.5	0.1	1%	56%	5.8	2.3	4.5
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	1.7	0.0	0%	69%	6.3	3.3	3



Site Memo

Harris. Ranked #5 for study 003 and ranked #9 for study 002. Had a Warning Letter in 2011 for submission of false information. Enrolled 16 subjects in 003 but only 4 in 002. There was an assignment that went out in January 2014 for him to be re-inspected post WL. Will combine with this inspection.

Summarize the reason for requesting OSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for OSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

  *See*** at end of consult template for OSI's thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

- ✓ Enrollment of large numbers of study subjects
- ____ High treatment responders (specify):
- ____ Significant primary efficacy results pertinent to decision-making
- ✓ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- ___ There are insufficient domestic data
- ___ Only foreign data are submitted to support an application
- ___ Domestic and foreign data show conflicting results pertinent to decision-making
- ___ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ___ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites*.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DGCPC.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact at 301-796-1183 (DChiap) or at 301-796-2248 (JSpaulding).

Concurrence: (as needed)

Ellen Fields, MD, MPH, Medical Team Leader (signed electronically)
Jacqueline Spaulding, MD, Medical Reviewer (signed electronically)

n/a Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for OSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
    - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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

/s/

DOMINIC CHIAPPERINO
06/02/2014

JACQUELINE A SPAULDING
06/02/2014

ELLEN W FIELDS
06/03/2014