CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206627Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206627
Priority or Standard	Priority
Submit Date(s)	April 28, 2014
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Division / Office	Anesthesia, Analgesia and Addiction Products
Reviewer Name(s)	Jacqueline A Spaulding, MD
Review Completion Date	July 28, 2014
Established Name	Hydrocodone bitartrate
(Proposed) Trade Name	HYSINGLA ER
Therapeutic Class	Opioid
Applicant	Purdue Pharma L.P.
Formulation(s)	Oral - 20, 30, 40, 60, 80, 100 and 120 mg tablets
Dosing Regimen	Once daily
Indication(s)	Management of pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adult

	patients.
Intended Population(s)	Adults aged ≥ 18 years

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend an approval action for the new drug application, NDA #206627 HYSINGLA ER (hydrocodone bitartrate extended-release) oral tablets, for the management of pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adult patients. This was a 505(b) (2) application relying on vicoprofen (NDA 020716) as the listed drug.

I am recommending approval for only the HYSINGLA ER doses of 20, 30, 40, 60, 80 and 100 mg because of concerns regarding the 120 mg dose:

- The single dose unit of HYSINGLA ER 120 mg contains more active ingredient which may pose a greater risk for overdose and death due to the larger amount of hydrocodone. For chronic pain patients that are appropriately monitored and managed by informed health care providers these concerns may be less of an issue. However, the availability of the HYSINGLA ER 120 mg dose to nondependent users, addicts and persons experimenting with prescription opioids, may compound the risk of accidental overdose, abuse, addiction, diversion, and accidents involving injuries (such as falls and motor vehicle accidents).

- The new once daily dosing regimen of HYSINGLA ER may be confusing to some chronic pain patients and prescribers who may be more familiar with the twice daily dosing schedule offered by the other extended-release hydrocodone product on the market. Because of the higher hydrocodone content in the 120 mg dose unit, there is more potential for harm particular in cases when the recommended dosing schedule is not adhered to by either healthcare providers or patients. For example, one patient from the clinical trial was discontinued due to misuse or abuse of HYSINGLA ER study drug by taking 40 mg twice daily instead of 40 mg once daily. This patient took twice the recommended dose for approximately one month and cited the reason for taking 40 mg twice a day was that the study coordinator had instructed her to increase the dose.

- As an extended-release formulation, HYSINGLA ER is expected to deliver hydrocodone over a period of 24 hours. Pharmacokinetic data shows that in some individuals peak hydrocodone plasma levels were noted at 24 hours to 30 hours following a single dose of Hysingla ER. If the HYSINGLA ER 120 mg dose were approved, the potential for higher amounts of hydrocodone peaking at later than expected times may impair the patient.

In addition, pharmacokinetic data also demonstrates the exposure of hydrocodone resulting from HYSINGLA ER 120 mg tablet administration appears to be highly variable. It is not clear from this data why this variability exists. I believe the applicant should explore the variability in exposure after HYSINGLA ER 120 mg dose tablet administration before approval of this dose is granted.

- In a thorough QT study involving healthy subjects, mild QT prolongation was observed at HYD doses of 120 and 160 mg. The label can provide warnings and cautionary language regarding the use HYSINGLA ER in patients at risk (e.g., cardiac arrhythmias, electrolyte abnormalities) for QT prolongation. However, since QT prolongation was observed at the HYD 120 mg dose in healthy subjects it is unclear how the label would be able to instruct health care practitioners.

One multi-center, randomized, placebo-controlled, 12-week trial in adult patients (opioid–naïve and opioid–experienced) with chronic low back pain did provide evidence for the Applicant's claim that HYSINGLA ER is effective in adults patients for the proposed indication. The overall safety profile of HYSINGLA ER is similar to that of other mu opioids and no unexpected safety findings were observed. There were some study patients who experienced formulation-related gastrointestinal (GI-obstruction adverse events, likely due to the hydrogelling of the tablet). Also, in addition to cases of QT prolongation in clinical trials, a thorough QT study showed mild QT prolongation at the 120 mg dose. There was adequate exposure during clinical trials to inform the safety of HYSINGLA ER and the adverse event profile appeared acceptable in the intended to-be-marketed dosage of up to hydrocodone 100 mg once daily.

An additional hazard posed by opioids concerns the abuse potential inherent to this class of drugs. Throughout the clinical development program of HYSINGLA ER assessments were performed on a routine basis to evaluate for diversion and/or aberrant drug behavior. Incidences of 10% or more in excess of the maximum prescribed study drug dose used or unaccounted for (HYSINGLA ER or rescue medication hydrocodone/APAP) were termed diversion. Diversion was also to be reported if diversion of any amount was suspected. Suspected diversion was reported at eight study sites. Overall, three percent of subjects (47/1827) exposed to HYSINGLA ER in the chronic pain studies were discontinued due to confirmed or subject diversion.

Less than one percent (9/1827) of subjects exposed to HYSINGLA ER experienced adverse events related to aberrant drug behavior (drug abuse, substance abuse, overdose, intentional drug misuse). For three of the nine HYSINGLA-treated patients it appears that their adverse event was related to HYSINGLA ER. One subject experienced a polydrug overdose, and the remaining two subjects misused/abused HYSINGLA ER by taking extra doses.

As a Schedule II opioid, hydrocodone is similar to other opioids and poses risks including: misuse/abuse, overdose, dependency, and tolerance. It is also expected

that diversion behaviors will occur. Because of the adverse effects of prescription opioid abuse to individuals and society as a whole, in recent years the Agency and various sponsors have attempted to address these harms through the development of abuse-deterrent opioids.

Purdue Pharma, LP has developed this new hydrocodone formulation to function as a controlled-release product, with abuse-deterrent features via a polyethylene oxide platform (PEO). The PEO platform purportedly imparts the physicochemical properties of hardness and hydrogelling. The Applicant postulates that these physicochemical features will make the Hysingla tablet difficult to crush, difficult to snort and difficult to inject intravenously. Human abuse potential studies and in vitro physical and chemical manipulation studies have been conducted and the final findings of the Controlled Substance Staff are still pending at this time. However the initial review of the data shows that HYSINGLA ER has abuse-deterrent features that may mitigate abuse by the intravenous and nasal routes. In addition, the extended-release, long-acting (ERLA) opioid analgesic REMS will be required for approval of this drug to mitigate against the potential for misuse and abuse.

HYSINGLA ER tablet formulation strengths proposed for marketing include: 20, 30, 40, 60, 80, 100, and 120 mg. The dosing recommendations are acceptable up to the 100 mg dose; based on the data from the Hysingla clinical development program. However, due to the variability in exposure among subjects administered the HYD 120 mg tablet; internal discussion is ongoing regarding the approvability of the HYD 120 mg tablet. The currently approved and marketed hydrocodone ER formulation has a maximum dosage of 100 mg/day (50 mg twice daily).

1.2 Risk Benefit Assessment

A recent draft review entitled “Effectiveness and Risk of Long-Term Opioid Treatment for Chronic Pain” performed by the United States (US) Agency for Healthcare Research and Quality (AHRQ) states that up to one-third of adults in the US report chronic pain (which is generally defined at pain lasting longer than 3 months). 1 The review also suggests that over the past two decades there has been a substantial increase in the prescribing of opioid medications for chronic pain, yet limited evidence shows long-term beneficial effects. Further, the hazards associated with prescription opioids include: accidental overdose, abuse, addiction, diversion and accidents.

When prescribing opioid analgesics health care providers must always weigh the benefits versus the risks. On one hand, opioids fall into the most potent class of analgesics that treat malignant and nonmalignant types of chronic pain. However, the adverse event profile includes life-threatening respiratory depression along with

1 Kronick RG, Chang S, Chiang YP, Iyer S. Draft Comparative Effectiveness Review. *The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain*. Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. 2014; pp. 1-98

sedation, nausea/vomiting, constipation, hypotension, and pruritis. The additional risk posed by opioids is the abuse potential related to this class of drugs.

Risks

1. Aberrant drug behavior
   The incidence of adverse events related to aberrant drug behavior in HYD-treated subjects was <1%. The standard MedDRA query (SMQ) analysis showed that a total of nine HYD-treated subjects experienced adverse events termed as either: drug abuse, overdose, substance abuse, intentional drug misuse or positive drug screen. Three of the nine events appear to be related to HYSINGLA ER (one patient with polydrug overdose and two patients who took extra doses of HYD study drug). . These cases highlight the already known risk of abuse and misuse associated with the opioid class of drugs.

2. Diversion
   As previously mentioned incidences of 10% or more in excess of the maximum prescribed study drug dose used or unaccounted for (HYSINGLA ER or rescue medication immediate-release oxycodone) were investigated during the HYSINGLA ER clinical development program and termed diversion. All suspected and confirmed diversions, whether or not exceeding the 10% threshold, were to have been reported by the site investigator. These reports occurred at eight study sites.

   The overall incidence of diversion in chronic pain studies was three percent. For details regarding diversion events, refer to Section 7 (Safety Summary). Similar to other opioids, diversion behaviors may be occur when prescribing HYSINGLA ER.

3. HYSINGLA ER formulation specific issues
   a. Polyethylene oxide (PEO) component – As described by Dr. Khairuzzaman, the Biopharmaceutics reviewer, Hysingla is a ““(b) (4)” which utilizes a polyethylene oxide (PEO)-based formulation platform. The PEO platforms serves as the (b) (4) excipient in HYSINGLA ER and it reportedly functions in release rate-control as well as for abuse-deterrence. It is also the PEO excipient that contributes to peak plasma levels of hydrocodone that may occur 14 – 16 hours (Range 6 – 30 hours) after tablet administration.

      Health care providers and patients should be warned regarding the potential for blood levels of hydrocodone, beyond 24 hours after dosing, high enough to impair activities that require alertness, including driving. Patients should also be instructed to take HYSINGLA ER at a consistent time every day to maintain a once every twenty four hour dosing interval. Patients should adhere to the physician prescribed titration regimen. If patients experience breakthrough pain during maintenance therapy dosage adjustment (increase) with HYSINGLA ER, may not alleviate the pain immediately. In case of breakthrough pain, patients may require rescue medication with an

immediate-release opioid or non-opioid analgesic as prescribed by the physician.

Because of the risk of choking and obstruction associated with HYSINGLA ER administration, use caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. HYSINGLA ER should be taken with at least eight ounces of water.

b. The 120 mg HYD dose-tablet

Because HYSINGLA ER is indicated for once daily administration the general expectation would be one that the product that would yield steady plasma concentration over a 24 hour period. In a pharmacokinetics and dose proportionality single-dose study, healthy subjects were evaluated under naltrexone blockade, and HYSINGLA ER was administered to subjects as 4 of 5 treatments (20, 40, 60, 80 or 120 mg) in the fasted state according to the randomization schedule. According to the Clinical Pharmacology review, "it was observed that subjects receiving the 120 mg tablet of HYSINGLA ER had higher variability with respect to both Cmax (Range 28.2 – 199 ng/mL) and AUCinf (305 – 3347 ng.hr/mL). Also, in a multiple-dose PK study HYSINGLA ER 120 mg administered over three days to steady-state showed an average %fluctuation and % swing of 102% and 220%, respectively.

In a thorough QT study, Clinical Pharmacology reviewer, Dr. Nallani remarks "that plasma PK parameters overlap to some extent between 80 mg, 120 mg and 160 mg. In other words, some individuals taking 120 mg may experience plasma levels comparable to average plasma levels noted with 160 mg dose". In a pharmacokinetic study, there was marked variability of the HYD 120 mg tablet, particularly at the low end of absorption. The variability of the HYD 120 tablet exposure in clinical studies raises questions regarding the acceptability of this dose tablet. Internal discussion is ongoing regarding the approvability of the 120 mg tablet.

4. QT Prolongation

In the clinical development program, cases of ECG QT prolongation were observed. In addition, a formal Thorough QT study provided evidence of mild QT prolongation for the HYD 120 mg dose. Language regarding QT prolongation will be included in the label.

5. Hearing Impairment

In clinical trials, acute ototoxicity was not observed, as reviewed by CDRH.

Benefits

1. Effectiveness of HYSINGLA ER treatment
   Efficacy for HYSINGLA ER was demonstrated in one adequate and well-controlled, randomized, double-blind, placebo-controlled study. There was statistically significantly less pain at 12 weeks in adult patients with chronic low back pain that was severe enough in intensity to require around-the-clock long-term opioid treatment and for which alternative treatment options were inadequate. While the treatment effect for HYD compared to placebo is small, it is similar to that of most opioids. Efficacy was also supported by secondary endpoints including: a cumulative responder analysis, patient global assessment of change, and use of medication.

2. First abuse- deterrent once-daily hydrocodone formulation
   HYSINGLA ER has been developed as a once daily, extended-release, abuse-deterrent formulation. The product was designed to release hydrocodone over a 24-hour period. The formulation contains a polyethylene oxide (PEO) excipient which imparts physicochemical properties of hardness and hydrogelling and the PEO component is believed to be the release-controlling polymer as well as the property that deters abuse. The Applicant conducted two abuse-potential studies and one survey. The preliminary findings of the human abuse potential studies show that HYSINGLA ER may deter abuse-related behaviors such as "snorting" and/or "injection", however Refer to the CSS review for details regarding the findings of these studies.

3. Safety
   HYSINGLA ER's clinical development program provided for adequate exposure to HYSINGLA ER in the intended population of patients with chronic pain. Overall, safety findings were consistent with those of the opioid class of drugs. The most common adverse reactions associated with HYSINGLA ER use are similar to those of other mu opioids such as gastrointestinal reactions including nausea, vomiting, and constipation; and nervous system disorders such as dizziness and somnolence.

   There was one death possibly associated with the use of HYSINGLA ER that involved a patient with acute toxicity of HYSINGLA ER, a benzodiazepine and a muscle relaxant. There was inadequate information provided to determine whether this was accidental or intentional. There were other serious adverse reactions associated with Hysingla administration including but not limited to: formulation-related choking and obstruction, overdose, QT prolongation, and drug misuse and abuse. All opioids pose the risk of abuse and misuse.

As an extended-release Schedule II opioid, the risks (including overdose, misuse and abuse) and adverse events associated with the use of HYSINGLA ER appear to be manageable with labeling and the REMS and should not preclude approval. It appears

from preliminary findings that HYSINGLA ER may have potential benefit in the reduction of abuse related via the intranasal and/or intravenous/injection routes.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

HYSINGLA ER as a member of the ER/LA opioid class of drugs would be required to function under the ER/LA opioid analgesics REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

In order to comply with the Pediatric Research Equity Act (PREA), the Applicant submitted a pediatric plan. The proposed pediatric plan was discussed at a Pediatric Review Committee (PeRC) meeting on July 9, 2014. The consensus at that meeting was

1. A partial waiver for pediatric patients ages birth to 11 years is being granted.
    a. The Applicant's rationale for requesting a waiver of the pediatric study in patients aged birth to 6 years is that conducting studies in this pediatric age group would be highly impractical due to the small number of pediatric patients meeting this indication would be too small.

    b. The Applicant's rationale for requesting a waiver of the pediatric study in patients aged 7 to 11 years is due to formulation issues. The dimensions of the tablets for dosing are all round, ~ 12 mm in diameter and (b) (4) mm in thickness. The rate of drug release is controlled by the (b) (4) [i.e. polyethylene oxide (PEO)] polymer (b) (4). The Applicant has attempted to develop and evaluate (b) (4)

2. A deferral of the PK and safety study for pediatric patient ages 12 to less than17 years is acceptable. Since the efficacy of opioids for the management of pain can be extrapolated down to age 2 if systemic exposure is similar, only PK and safety studies would be needed in the age-group (12-17 years). .

The following is the recommended timeline for pediatric development:
<u>PK/safety protocol and study in pediatric patients ages 12 to 17</u>
Protocol Submission: 6 months after NDA approval
Study Completion: 2 ½ years after NDA approval
Final Study Report: 3 years after NDA approval.

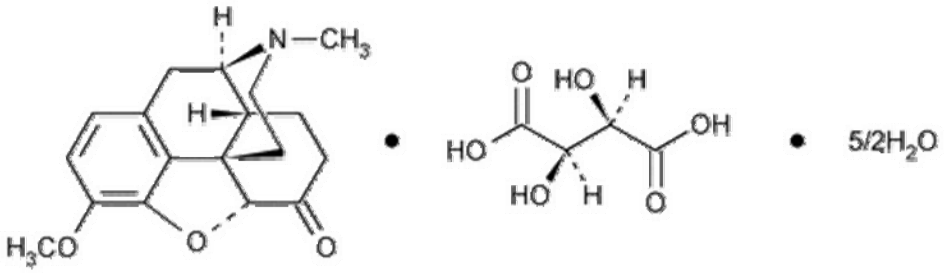
2 Introduction and Regulatory Background

2.1 Product Information

Hydrocodone is a semi-synthetic opioid. The chemical name for hydrocodone is 4,5(alpha)-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5) or morphinan-6-one, 4,5-epoxy-3-methoxy-17-methyl-, (5 alpha)-, [R (R*, R*)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5).

Figure 1 shows the structural formula for hydrocodone bitartrate.

Figure 1: Structural Formula - Hydrocodone bitartrate



Source: Xiaobin Shen CMC Review, pg. 5/86

Product description: Extended-release oral coated tablet
Dosage Strengths: 20, 30, 40, 60, 80, 100 and 120 mg
Dosing regimen: once daily
Pharmacological class: mu opioid agonist
Trade name and established name: HYSINGLA ER (hydrocodone extended-release) tablets

Proposed Indication: management of pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Throughout this review, study drug may be referred to as HYSINGLA ER or HYD interchangeably.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 displays the Applicant's table of currently available opioid drugs indicated for chronic pain conditions severe enough to require around-the-clock, long-term opioid treatment

Table 1: Current Opioid Treatments for Proposed Indication

Drug[a]	Product Description	Indication[b]
Schedule II Products		
Fentanyl	Extended-release fentanyl	Management of persistent, moderate to severe chronic pain in opioid-tolerant patients 2 years of age and older when a continuous, around-the-clock opioid analgesic is required for an extended period of time, and the patient cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids.
Single-entity hydrocodone	Extended-release hydrocodone	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Hydromorphone	Immediate-release hydromorphone	Management of pain in patients where an opioid analgesic is appropriate
	Extended-release hydromorphone	Management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time
Methadone	Extended-release methadone	Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
Morphine sulfate	Immediate-release morphine sulfate	Relief of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate
	Extended-release morphine sulfate	Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
Single-entity oxycodone products	Immediate-release oxycodone	Management of moderate to severe pain where the use of an opioid analgesic is appropriate
	Extended-release oxycodone	Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time
Combination oxycodone-containing products	Oxycodone/ Acetaminophen	Moderate to moderately severe pain
	Oxycodone/ Aspirin	Moderate to moderately severe pain
Oxymorphone	Extended-release oxymorphone	Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.
Tapentadol	Extended-release Tapentadol	Management of moderate to severe chronic pain in adults when a continuous, around-the-clock analgesic is needed for an extended period of time
Schedule III Products[c]		
Combination hydrocodone-containing products	Hydrocodone/ Acetaminophen	Moderate to moderately severe pain

Source: NDA 206627, Clinical Overview, Table 7, pg. 64/70

Reviewer Note: All extended-release/long acting opioid analgesics are indicated for the management of pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The Applicant's table above includes older indications for some of the ERLA opioids that have subsequently been revised.

In addition to opioids, other pharmacological options available for the management of chronic pain severe to require around-the-clock treatment include:

- Nonsteroidal anti-inflammatory drugs (NSAIDS) such as celecoxib, naproxen and ibuprofen
- Acetaminophen. and
- Regional and local anesthetics such as lidocaine

2.3 Availability of Proposed Active Ingredient in the United States

Hydrocodone bitartrate is currently approved and marketed in the United States (US) in combination with the nonopiate analgesic drugs including: acetaminophen, aspirin and ibuprofen. These combination products contain immediate – release hydrocodone at doses of 5, 7.5 or 10 mg and are to be administered every four to six hours as necessary for pain.

Hydrocodone is also available as a single-entity product in an extended-release (ER) formulation. This ER product contains doses of hydrocodone at 10, 15, 20, 30, 40 and 50 mg and is approved for the indication 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.

2.4 Important Safety Issues With Consideration to Related Drugs

Hydrocodone and other mu opioid agonists are associated with known and potentially serious safety events including: respiratory depression (possibly leading to coma and death), withdrawal, physical dependence and abuse, and the risk of overdosage. Similar to other opioids, the hydrocodone label contains a boxed warning which in addition to the above reactions discusses events such as accidental exposure, neonatal opioid withdrawal syndrome and interaction with alcohol.

Concomitant use of hydrocodone with MAO inhibitors or tricyclic antidepressants may increase the effect of either the antidepressant or hydrocodone. Drugs that inhibit CYP3A4 activity may cause decreased clearance of hydrocodone which could lead to an increase in hydrocodone plasma concentrations.

The most common adverse reactions associated with hydrocodone use include: constipation, nausea, somnolence, fatigue, headache, dizziness, dry mouth, vomiting, pruritus, abdominal pain, edema peripheral, upper respiratory tract infection, muscle spasms, urinary tract infection, back pain and tremor.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2 displays the important aspects of the presubmission regulatory activity for this NDA.

Table 2: Summary of Presubmission Regulatory Activity

DATE	REGULATORY ACTIVITY
October 26,1999	**IND Submission**
May 4, 2011	**End-Of-Phase 2 Meeting – The following comments were provided to the Applicant:** • (b) (4) • A 505(b)(2) application for a modified-release formulation that relies upon prior findings of efficacy for an immediate-release product, will require only one adequate and well controlled study to support efficacy. • For a viable 505(b)(2) NDA submission for HYD, an FDA approved immediate-release hydrocodone-containing product which also contains another (one or more) active ingredient (e.g. APAP), could be referenced. The submission must also address relative bioavailability and must reference a product with an approved NDA, rather than an approved ANDA. • Conduct a thorough QTc study in opioid-tolerant patients during Phase 3 clinical development or provide rationale as to why a study would not be needed • Since progressive hearing loss has been associated with the chronic use of hydrocodone/acetaminophen products and the potential exposure to hydrocodone from HYD is higher than the combination product. Hearing will have to be monitored during Phase 3 clinical development • A detailed description of the pediatric plan must be submitted for review and initiation of studies must begin as soon as possible • Safety database: o Should be large enough to provide sufficient exposure data to evaluate potential safety concerns observed with formulations

	that contain polyethylene oxide, such as gastrointestinal problem. Also, the exposure in the safety database must be representative of the range of exposures typical of patients in this setting. o Should consist of at least 300 patients exposed for at least 6 months and 100 patients exposed for at least one year at the maximum labeled dose. • Sponsor proposed that, of the 300 and 100 subjects exposed for 6 months and 1 year, respectively, approximately 1/3 will have received HYD at the upper dose range, 80 and 120 mg/day, representing the dosage levels intended for clinical use. o Division clarified that while it is not necessary for all 300 patients be exposed at the maximum labeled dose (120 mg/day), a fair number of these patients should be appropriate to receive the maximum labeled dose of 120 mg to support the need for such a high dose. • Based on the assumptions, the sample size calculation appears reasonable. However, we notice that the sample size is larger than normally seen in analgesic trials and caution that the magnitude of the beneficial effect will be weighed against risk • Regarding the proposed primary efficacy analysis for Phase 3 efficacy study: o Provide a justification for your assumption, though not explicitly stated, that patients who drop out due to reasons other than AEs have responses similar to the average response at Week 2 and Week 4. o Thoroughly ascertain and document the reason for discontinuation for dropouts and also thoroughly document medications received after discontinuation for retrieved dropouts. o Currently, a patient who discontinues the study treatment due to an AE may be included in the analysis as a completer if Week 12 data is collected after he/she drops out. Thus, your weighted average estimate will implicitly assign the mean pain score at Week 12 to this patient. This strategy is consistent with the intent-to-treat principle. However, concern will arise if the data from the study suggest that the use of subsequent analgesic medications after discontinuation for retrieved dropouts' results in better pain scores at Week 12 compared to those that continue the study treatment.
November 2, 2011	**<u>Advice Letter –</u> The letter contained the following comments:** • Include high frequency audiology or otoacoustic emission (OAE) to

	identify early changes in hearing sensitivity or provide a rationale for not doing so • Include an initial hearing assessment at screening • Institute an improved method to identify, screen and follow-up patients who may be at higher risk for choleotoxicity (e.g. pre-existing hearing loss) • Counsel patients regarding potential effects to hearing and for those patients who have complaints consistent with cochlear/vestibular damage, immediate evaluation and treatment with follow-up to resolution is warranted • Include hearing loss as possible risk in informed consent • Provide qualifications of those conducting audiology assessments
March 13, 2012	**<u>Type C Meeting</u> – the Division made the following comments to the Applicant regarding their Audiology program** • At least 100 subjects will need to be exposed to HYD for at least one year, a sufficient number of subjects will have to be assessed using the new audiometry methodologies to adequately determine the long-term safety of your product on hearing • Schedule monitoring tests at intervals that will enable the earliest possible detection (within reason) of cochleotoxic effects. Consider including an additional air conduction threshold monitoring assessment at 12 weeks during maintenance. Alternatively, provide your rationale for permitting a 24-week maintenance period without auditory testing during this interval. • Provide details about how the central ENT physician determines whether the hearing loss is related to the study drug. • Utilize an alternate tinnitus questionnaire [besides the Dizziness Handicap Inventory] that better achieves your goal by evaluating the severity of the tinnitus, rather than the functional impact of tinnitus.
July 20, 2012	**<u>Advice Letter –</u> The following comments regarding Study HYD3003 were provided to the Applicant:** • Your projection for the number of study subjects exposed to HYD for 12 months is 165-240 subjects, and will include: a. 135-180 existing subjects who will have on-treatment comprehensive audiologic assessment; and b. 35-60 new subjects will have pre-treatment baseline comprehensive audiologic assessment • Projected exposure appears acceptable as part of your ototoxicity

	monitoring program to evaluate the long-term safety of HYD with respect to hearing loss. • Immitance audiometry and speech recognition threshold testing will not be required for "high risk/at-risk subjects." • High frequency threshold audiometry will not be required for subjects in the study protocol.
August 2, 2012	**Applicant submission of 505(b)(2) Plan consisting of:** • Vicoprofen (hydrocodone/ibuprofen) as the proposed listed drug • Phase 3 program will consist of one efficacy trial (HYD3002)and an open-label, long-term safety study (HYD3003) • HYD1016, a relative bioavailability study comparing HYD to Vicoprofen®, the proposed listed drug; • In vitro and in vivo HYD abuse liability studies
July 10, 2013	**Pre-NDA Meeting – the Division made the following comments to the Applicant** • In the absence of clinical data, 3000 mg/day will be used as the Maximum Theoretical Daily Dose (MTDD) for HYD • The drug substance and drug product impurity specification must meet ICH Q3A and ICH Q3B for qualification based on a maximum daily dose of 3 grams or justification must be provided • For the pivotal study HYD3002, provide justification for the assumption that patients who drop out due to reasons other than adverse events (AEs) have responses similar to the average response at Week 3, Week 4, and Week 5. • In addition to conducting a subgroup analyses based on age, also conduct subgroup analyses for gender and race. • The abuse-deterrent properties of HYD would warrant a priority review for the NDA • PREA requirements • Class REMS for ER/LA opioids will apply to HYD • Given the (b) (4) level of PEO in the HYD formulation, provide an analysis of gastrointestinal adverse events (e.g., obstruction, choking, and vomiting) occurring in all clinical studies in order to assess whether the presence of PEO results in an excess of these events • Biowaiver request for 30 and 100 mg HYD tablets is appropriate. • Details of CDER clinical review template found in Manual of Policies and Procedures (MAPP 6010.3R) • Technical instructions for submitting Bioresearch Monitoring (BIMO) clinical data in eCTD format, dataset requirements (e.g., ISS, ISE, AEs,) and PLR requirements

	• Controlled Substance Staff (CSS)comments: o Provide in tabular form information and data related to the abuse potential assessment, including drug diversions and overdose o Provide descriptions of all reports and details of all incidents of abuse, misuse or overdose (intentional or unintentional) or drug that is lost, stolen, missing or unaccounted for in all clinical studies. Include study number, site, type of report, subject identifier and narratives o Provide case narratives of subjects in clinical studies who are discontinued from studies for lack of compliance to study medication or procedures or who discontinue participation without returning the study medication o Provide any data you have regarding abuse of hydrocodone containing products via non-oral routes including inhalation, insufflation and intravenous (IV) injection

Source: IND 059175HYD EOP2 Meeting Minutes, Type C Meeting Minutes, Pre-NDA Meeting Minutes and NDA 206627, Section 1.6, Correspondence Regarding Meetings

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the submission was adequate and reasonable well--organized and paginated to allow for a review. All modules and sections were completed.

3.2 Compliance with Good Clinical Practices

The Applicant has stated that all clinical studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP) and applicable regulatory requirements.

In collaboration with Cynthia Kleppinger, reviewer from the Office of Scientific Investigations (OSI), the GCP Site Selection tool was used to select sites that were involved in both Phase 3 studies so that more coverage would be obtained for inspections

The following recommendations were made:

1. Louise Taber, M.D. - Dr. Taber was ranked #1 for both Phase 3 studies. This investigator was a high enroller (highest for Study HYD3003) and her site reported many adverse events. Her site has also been included in (b) (4) INDs. There has been a prior complaint of backdating recordings but this could not be substantiated. The last clinical inspection of Dr. Taber's site was in 2000.

2. David Hassman, M.D. – Dr. Hassman was involved in both Phase 3 studies. This investigator was ranked #2 for Study HYD3003 and was the second highest enroller for that study. His site has been included in (b) (4) INDs. In 2001, Dr. Hassman was sent a Warning Letter for fabricating data. Dr. Hassman's site was subsequently inspected in 2004 and 2008, for which he received VAIs for both of these inspections.

3. Gary Dawson, M.D. – Dr. Dawson was ranked #4 for Study HYD3002 and his site had many AEs. Dr. Dawson's site also has been included in (b) (4) IND and his site has never been inspected.

4. Michael Harris M.D. – Dr. Harris was ranked #5 for Study HYD3003 (enrolling 16 subjects) and ranked #9 for HYD3002 (enrolling 4 subjects). In 2011, a warning letter was sent to the investigator for submission of false information.

Table 3 displays site number, protocol ID, number of subjects and indication for each study investigator.

Table 3: Clinical Studies' Inspection Sites

(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
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

Source: NDA 206627, Section 5.0; Response to IR and GCP Site Selection Tool v 2.4

At the writing of this review, two site inspections have been completed and two site inspections are on ongoing. The preliminary results of the two completed inspections show:

Dr. Louise Taber's site (#0108A) will be issued an Official Action Indicated (OIA) due to alterations in source documents related to initial audiology assessments (clinic visits 2 and 3). The Agency Inspector found at least five fraudulent records in which one subject's test result was used for other subjects. These deficiencies do not appear to affect the efficacy analyses, and are only pertinent to the hearing assessments.

Dr. David Hassman's site (#0608) will be issued a Voluntary Action Indicated (VAI) secondary to some procedures done out of treatment windows. These deficiencies do not appear to affect efficacy or safety.

3.3 Financial Disclosures

In accordance with 21 CFR 54.4, Certification and Disclosure Requirements; the Applicant has submitted the Financial Certification and Disclosure document as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators and this document is located at the end of the review. The Applicant also submitted a completed Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigators." These were no financial arrangements reported between the Applicant and investigators. At this time it does not appear to be financial conflict of interests related to data integrity.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Chemistry, Manufacturing and Controls (CMC) review was conducted by Xiaobin Shen PhD from the Office of New Drug Quality Assurance (QNDQA).

For a detailed discussion of the CMC aspects of this application, refer Dr. Shen's review.

Drug Product
The Applicant describes the hydrocodone bitartrate extended release tablet as a (b) (4) tablet. (b) (4) . Hydrocodone is a fine white to

almost white crystal or crystalline powder that is soluble in water, slightly soluble in alcohol and has a melting point of ~ 118 – 128°C.

Polyethylene oxide (b) (4). It hydrates rapidly in water and forms a viscous gel when hydrated and it is this property that makes PEO useful as a release-controlling polymer for a (b) (4) tablet. The PEO polymer is also described as thermoplastic because it becomes pliable/ moldable above a specific temperature and returns to a solid state upon cooling. According to the Applicant (b) (4) and ultimately contributes to the hardness and gelling of the tablet. The Applicant believes that is it the hardness and hyrogelling of the HYD tablet that provides the abuse deterrence and controlled release properties of the formulation.

As the dosage strength of HYD increases (from 20 mg to 120 mg) (b) (4).

The HYD formulation contains the following excipients

1. PEO ((b) (4)
2. Microcrystalline Cellulose (MCC) - used as (b) (4).
3. Hydroxypropyl Cellulose (HPC) – used as a (b) (4)
4. Magnesium Stearate – is used as (b) (4)
5. (b) (4) nd the color is dependent on the dosage strength.
6. (b) (4)
7. (b) (4) Black Ink – all coated HYD tablets are printed with this black ink for identification purposes.

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval, pending a satisfactory EES status.

4.2 Clinical Microbiology

The NDA for HYSINGLA ER does not include a Microbial Limits release specification for drug product release or stability. However according to John Metacale, PhD, senior review microbiologist from the New Drug Microbiology Staff; the Applicant has provided a suitable rationale for the exclusion of this testing.

Per the New Drug Microbiology Staff, HYSINGLA ER is recommended for approval from the standpoint of product quality microbiology.

4.3 Preclinical Pharmacology/Toxicology

The Preclinical Pharmacology/Toxicology review was conducted by nonclinical reviewers Beth Bolan and Huiquing Hao and nonclinical supervisor Dan Mellon.

For a detailed discussion of nonclinical pharmacology/toxicology aspects of this NDA, refer to Drs. Bolan, Hao and Mellon's reviews.

Summary of preliminary P/T findings:

Drug Substance
The drug substance impurity specifications (i.e., (b) (4) are acceptable.

Drug Product
The drug product degradants (i.e., (b) (4) and each individual unknown) are acceptable.

Formulation
The levels of all excipients, when calculated for the maximum therapeutic daily dose (MTDD) of hydrocodone, with the exception of PEO are considered acceptable.

Dr. Dan Mellon, Pharmacology/Toxicology supervisor has reviewed the Master File [MF] (b) (4): PEO Safety Assessment, and is in the process of updating it. He has tentatively determined the MTDD of PEO to be 14 grams. The final determination will be reflected in Dr. Bolan's nonclinical review. .

Safety Pharmacology
Central Nervous System (CNS) effects
HYD was administered orally to male and female rats at dose levels of 20, 60, or 200 mg/kg. Functional Observational Battery (FOB) and locomotor assessments were evaluated in rats. Typical opioid effects were observed; and the No Observed Affect Effect Level (NOAEL) was determined to be 200 mg/kg (high-dose) .

Respiratory System
In a dose-ranging study male rats (4/group) received a single oral administration of HYD at a dose of 0, 250, 500, 750 or 1000 mg/kg, or hydrocodone bitartrate/naltrexone hydrochloride combination at a dose of 250/3.125, 500/6.25, 750/9.375 or 1000/12.5 mg/kg. Assessments included respiratory rate and tidal volume. Results showed HYD dose-dependently decreased respiratory rate with no effect on tidal volume.

Cardiovascular System
- hERG channel assay showed no inhibition (367-fold the human dose of 120 mg)
- Purkinje fiber assay showed concentration-dependent increase in APD observed

- The potential cardiovascular effect of single-doses of HYD article at dose levels of 1, 3, and 10 mg/kg was assessed in conscious freely moving beagle dogs. Results showed decreased heart rate (at medium and high-doses); increased QT/ QTc at high-dose of 10 mg/kg (0.7x)

Chronic Toxicology Studies
A nine-month chronic toxicology study in Beagle dogs showed results of decreased body weight and food consumption. The no-observed-adverse-effect-level (NOAEL) was HD (~0.8-fold the high HYD dose of 120 mg/day HC)

A two-year chronic toxicology study in rats (carcinogen bioassay including interim clinical chemistry, hematology and urinalysis assessments) showed decreased body weight and food consumption, increased survival, decreased cholesterol and triglycerides in male rats. Other findings included swollen paws and sores/scabs. There was also increased hypercellularity of the sternum in male rats; this finding was thought to be related to inflammation of paws. The NOAEL was the high dose (~0.1-fold the high dose of 120 mg/day HC)

Reproductive Toxicology
In animal reproduction studies with hydrocodone 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 exposure of a 120 mg/day dose of hydrocodone based on AUC exposure comparisons. HYD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

HYD will labeled as Pregnancy Category C

Genetic Toxicology
Ames, *in vivo* micronucleus and *in vitro* mouse lymphoma assays were all negative.

Carcinogenicity:
Mouse and rat two-year bioassays were both valid and negative.

From a P/T perspective, there may be approvability issues related to the adequacy of the MF; however the review team will attempt to prove these deficiencies are not an approval issue

4.4 Clinical Pharmacology

The Clinical Pharmacology review was conducted by Srikanth Nallani PhD.

For a detailed discussion of the clinical pharmacology aspects of this application, refer to Dr.Srikanth Nallani's review.

4.4.1 Mechanism of Action

Hydrocodone acts as an agonist binding to and activating opioid receptors in the brain and spinal cord, which are coupled to G-protein complexes and modulate synaptic transmission through adenylate cyclase. The pharmacological effects of hydrocodone including analgesia, euphoria, respiratory depression and physiological dependence are believed to be primarily mediated via μ opioid receptors.

4.4.2 Pharmacodynamics

Cardiac Electrophysiology
QTc interval prolongation was studied in a double-blind, placebo- and positive controlled 3-treatment parallel-group, dose-escalating study of HYD in 185 healthy subjects. The maximum mean (SD) (95% upper confidence bound) difference in the QTc interval between HYD and placebo (after baseline-correction) at steady state was 10 (13) milliseconds, 7 (10) milliseconds, and 6 (9) milliseconds at HYD 160 mg, 120 mg and 80 mg respectively.

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

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

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

Gastrointestinal Tract and Other Smooth Muscle
Hydrocodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic

waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

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

Effect on Hearing
Cases of hearing impairment or permanent hearing loss have been reported for hydrocodone/acetaminophen combination formulations,.

In clinical trials with HYD, comprehensive audiologic assessments, including pure-tone air-conduction audiometry, pure-tone bone conduction audiometry, immittance audiometry, speech reception threshold, word recognition, Dizziness Handicap Inventory and Tinnitus Handicap Inventory, were conducted in 1207 patients with chronic pain by licensed audiologists. No signal of ototoxicity associated with HYD was observed in these clinical trials.

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

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

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

Concentration—Adverse Experience Relationships
There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression.
As with all opioids, the dose of HYD must be individualized. The effective analgesic dose for some patients will be too high to be tolerated by other patients.
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4.4.3 Pharmacokinetics

Absorption
Generally, HYD results in an increase in plasma hydrocodone concentrations with a median Tmax of 14 – 16 hours noted for different formulations ranging from 14-16 hours. Peak plasma levels may occur in the range of 6 -30 hours after single dose HYD administration.

Systemic exposure (AUC and Cmax) increased linearly with doses from 20 to 120 mg. Both Cmax and AUC increased slightly more than dose proportionally. The mean terminal half-life (t1/2) was similar for all [HYD] dose strengths ranging from 7 to 9 hours.

Table 4 shows the mean steady-state hydrocodone PK parameters

Table 4: Mean (SD) Steady-State Hydrocodone Pharmacokinetic Parameters

Regimen	AUC24,ss (ng•h/mL)	Cmax,ss (ng/mL)	Cmin,ss (ng/mL)	%Fluctuation*
IR Hydrocodone Combination Product				
7.5 mg q6h	470 (111)	31.6 (6.6)	13.4 (4.0)	96.3 (56, 193)
HYSINGLA ER				
30 mg q24h	443 (128)	26.4 (7.4)	16.7 (5.2)	61 (6.4,113)
80 mg q24h	1252 (352)	82.6 (25.7)	28.2 (12)	105 (36,214)
120 mg q24h	1938 (729)	135 (50)	63.6 (29)	97.9 (32, 250)

Source: Dr. Srikanth Nallani's NDA Review and Clinical Power Point

Steady state hydrocodone concentrations were confirmed on Day 2 of once daily dosing of HYD. The terminal half-life at steady state was 7 hours. Median Tmax values were 14 hours on both Day 1 and Day 5 following once daily dosing of HYD for five days. Daily fluctuation in peak to trough plasma levels of HYD were higher at the 60 and 120 mg doses compared to the 30 mg dose. In addition, at the 120 mg tablet

Food Effects
The Cmax and AUC of HYD 120 mg tablets were similar under low fat conditions relative to fasting conditions (17% and 9% higher, respectively). Cmax was higher (54%) under high fat conditions relative to fasting conditions; however, the AUC of HYD 120 mg tablets was only 20% higher when co-administered with a high fat meal. HYD may be administered without regard to meals.

Distribution
Following administration of HYD, the typical (70 kg adult) value of apparent volume of distribution (V/F) is 402 L, suggesting extensive tissue distribution. The extent of *in vivo* binding of hydrocodone to human plasma proteins was minimal with a mean % bound at 36%.

Elimination - Metabolism
Hydrocodone exhibits a complex pattern of metabolism, including N-demethylation, O-demethylation, and 6-keto reduction to the corresponding 6-α-and 6-β-hydroxy metabolites. CYP3A4 mediated N-demethylation to inactive norhydrocodone is the primary metabolic pathway of hydrocodone with a lower contribution from CYP2B6 and CYP2C19. The minor metabolite hydromorphone was mainly formed by CYP2D6 mediated O-demethylation of hydrocodone with a smaller contribution by CYP2B6 and CYP2C19. Hydromorphone may contribute to the total analgesic effect of hydrocodone.

Excretion
The percent of administered dose excreted unchanged as hydrocodone in urine 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. Renal clearance (CLr) of hydrocodone in healthy subjects was small (5.3 L/h) compared to apparent oral clearance (CL/F, 83 L/h); suggesting that non-renal clearance is the main elimination route. Ninety-nine percent of the administered dose is eliminated within 72 hours. The mean terminal half-life (t1/2) was similar for all HYD dose strengths ranging from approximately 7 to 9 hours across the range of doses.

Biopharmaceutics Review
The Biopharmaceutics review was conducted by Akm Khairuzzaman PhD.

For a detailed discussion of the Biopharmaceutics aspects of this NDA, refer to Dr. Khairuzzaman's review.

Dr. Khairuzzaman's relevant findings are summarized below;

> [HYSINGLA ER} is a new formulation that is a "(b) (4)" whereby the (b) (4)

(PEO)-based formulation platform which is the (b) (4) excipient in the product ((b) (4) that functions in release rate-control as well as for abuse-deterrence and resistance to alcohol-induced dose dumping purposes.

The Hydrocodone Bitartrate API is very soluble (> 90 mg/mL) across the bio-relevant pH range of pH 1.2 to 8.0. Dissolution was found to be a critical quality attribute for this ER dosage form since three different formulations (fast, slow and medium) of 20 mg prototype tablet having different dissolution rate showed direct impact on Cmax and Tmax from a cross-over bioavailability study. The method is capable of distinguishing significant changes in a composition or manufacturing process and show similar trend of differences between the in vitro and in vivo results.

One of the critical process related attribute for dissolution was found to be (b) (4) . Developmental data showed that significant variability in (b) (4) can lead to dissolution failure. As a result the applicant has developed in process control for (b) (4)). It is to be noted that the applicant will be using a (b) (4)

From the Biopharmaceutics perspective, the NDA 205527 for ER 24-hour hydrocodone tablets (20, 30, 40, 60, 80, 100 and 120mg) is recommended for approval.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5 contains a listing of the 16 clinical studies completed by the Applicant in support of the HYD clinical development program. Two of the 16 studies were Phase 3 trials; 11 of the studies were Phase 1 Clinical Pharmacology trials and the remaining three studies were abuse liability studies.

Table 5: Sixteen Completed HYD Studies

Study #	Phase	Type of Study	Population	HYD Dose (mg)	Total N
HYD3002	Phase 3	Efficacy/Safety	Low Back Pain	20-120	588
HYD3003	Phase 3	Open-Label, Long-term	Nonmalignant and Non-neuropathic chronic pain	20-120	922
HYD1001	Phase 1	Pilot PK	Pilot PK	20, 80, 120	184
HYD1002	Phase 1	Steady State	Healthy subjects under naltrexone block	120	27
HYD1004	Phase 1	Dose-Proportionality	Healthy subjects under naltrexone block	20-120	40
HYD1016	Phase 1	Relative BA compared to Vicoprofen	Healthy subjects under naltrexone block	30	24
HYD1003	Phase 1	Food effect	Healthy subjects under naltrexone block	120	54
HYD1005	Phase 1	DDI of HYD and Paroxetine (CYP2D6 inhibitor)	Healthy subjects	20	24
HYD1006	Phase 1	Effect of age and gender	Healthy male/female elderly (ages 65-77) subjects under naltrexone block	40	50
HYD1007	Phase 1	Hepatic impairment	Subjects with mild, moderate & severe hepatic function matched with healthy subject controls	20	32
HYD1008	Phase 1	Renal impairment	Subjects with mild, moderate and severe renal function & ESRD matched with healthy subject controls under naltrexone block	60	41
HYD1009	Phase 1	Thorough QT study with HYD, PBO, & Moxifloxacin (400 mg)	Healthy subjects	20, 40, 80 & 160	208
HYD1012	Phase 1	DDI with HYD and ketoconazole (CYP3AD4 inhibitor)	Healthy subjects	30	30
HYD1013	N/A	Oral abuse potential	Non-dependent recreational opioid drug users	60	40
HYD1014	N/A	Intranasal abuse potential	Non-dependent recreational opioid drug users	60	31
HYD1015	N/A	Survey for attractiveness for abuse and tampering of HYD	Current recreational opioid users with experience tampering with and administering Rx formulations by alternative routes of administration	N/A	N/A

Source: NDA206627 Clinical Overview, Table 2, pg. 17 of 70

5.2 Review Strategy

The strategy employed in reviewing the NDA involved:

- Evaluation of the overall safety and efficacy of HYD in the management of moderate to pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate and;

- Consultation from the Controlled Substance Staff (CSS) which was obtained to assess the abuse liability studies.

- Consultation from the Interdisciplinary Review Team for QT studies which was obtained to assess the Thorough QT Study and provide recommendations for the HYSINGLA ER Product Insert

5.3 Discussion of Individual Studies/Clinical Trials

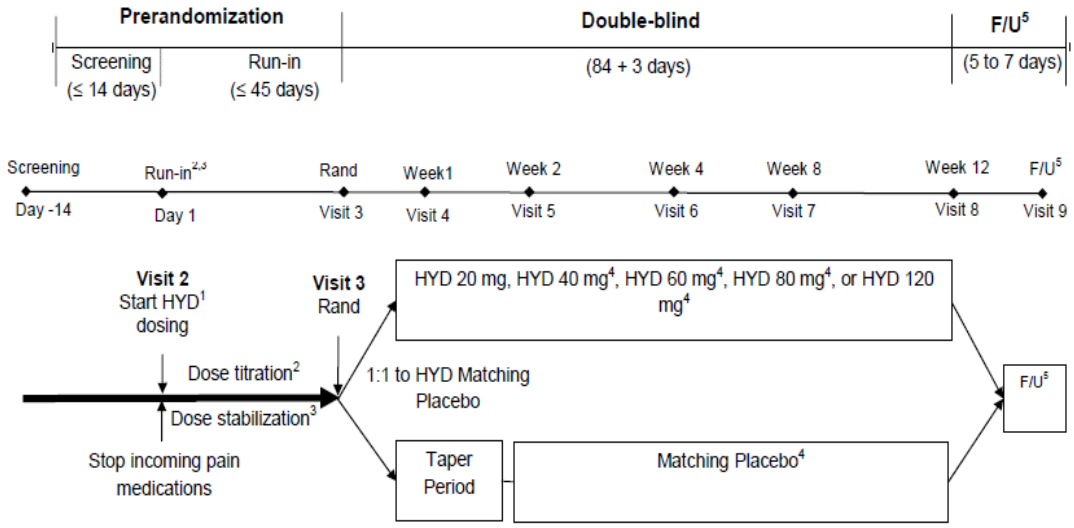
Study HYD3002

Title:
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

Objective:
The objective of the study was to have been to evaluate the analgesic efficacy and safety of hydrocodone bitartrate (HYD) tablets 20 to120 mg once-daily compared to placebo in subjects with moderate to severe chronic low back pain uncontrolled by their current analgesic regimen.

Study Design
This was to have been a multicenter, randomized, double-blind, 12-week, placebo controlled; parallel-group enriched study and an illustration of the design is shown in Figure 3.

Figure 2: Study Design of HYD3002



Source: HYD3002 Protocol Amendment 3 (dated July 11 2012), Section 9.1, Figure 1, pg. 25 of 180

Study Population
The study was to have enrolled a minimum of 600 patients.

Inclusion criteria:
Patients were to have met all of the following criteria to be enrolled.

1. Male and female subjects ≥ 18 years of age with moderate to severe, chronic low back pain (lasting several hours daily) as their predominant pain condition for at least 3 months prior to the screening visit;
2. Subjects' back pain must be related to nonmalignant and nonneuropathic conditions and without radiation or with only proximal radiation (above the knee), i.e., meeting Quebec Task Force Classification 10-12 1 or 2;
3. Subjects whose low back pain is not adequately treated prior to the screening visit with their stable incoming analgesic regimen:
    a. The subjects' "average pain over the last 14 days" score for chronic low back pain must be ≥5 an 11 point numerical rating scale (NRS) at the screening visit, and,
    b. During the 3- to 5-day period when pain scores are recorded in the screening period, subjects must have at least 3 "average pain over the last 24 hours" scores ≥5 on an 11-point NRS, including the scores recorded on the last 2 consecutive days of the 5-day period.
4. Subjects taking opioid analgesic medication equivalent to 0-100 mg (inclusive) of oxycodone per day for their low back pain during the 14 days prior to screening (visit 1);
5. Subjects must be on a stable analgesic regimen prior to the screening visit (visit 1 for their low back pain;
6. Subjects deemed by the investigator/medically qualified designee (must be MD or DO) to be appropriate candidates for the protocol specified, around-the-clock HYD therapeutic regimen
7. Female subjects who are premenopausal or postmenopausal less than 1 year and who have not had surgical sterilization (i.e., tubal ligation, partial or complete hysterectomy) must have a negative serum pregnancy test, be nonlactating, and willing to use adequate and reliable study (e.g., barrier with additional spermicidal foam or jelly, intra-uterine device, hormonal contraception);
8. For subjects receiving adjunct therapy for back pain, such as transcutaneous electrical nerve stimulation (TENS), physical therapy, biofeedback therapy, relaxation therapy, acupuncture therapy, herbal remedies or nutraceuticals, either such treatment should be stopped at screening, or, if continued, the treatment should have been at a stable dose/intensity and frequency for at least 14 days (4 weeks for glucosamine and/or chondroitin sulfate) prior to the screening visit and remain unchanged during the study;
9. If taking oral corticosteroids, subjects must have been on a stable dose for at least 6 weeks prior to the screening visit and be willing to maintain that dose throughout the study;
10. Subjects must have 3 ECGs, a minimum of 20 minutes apart, at the initial screening visit, with average QTcF Interval of the 3 tracings ≤ 470 msec;

11. Subjects who are willing and able to be compliant with the protocol, are capable of subjective evaluation, are able to read and understand questionnaires, are willing and able to use an electronic diary, and are able to read, understand, and sign the written informed consent.
12. Subjects willing to complete audiologic assessments at a predefined secondary location

Exclusion Criteria
Patients who met any of the following criteria were not to have been enrolled.

1. Subjects taking > 100 mg/day oxycodone or equivalent during last 14 days prior to screening visit (visit 1);
2. Subjects with pain with distal radiation (below the knee) with or without neurologic signs, or presumptive or confirmed compression of a spinal nerve root (i.e., Quebec Task Force Classification 10-12 3 to 6);
3. Subjects with radicular symptoms, acute compression fracture, seronegative spondyloarthropathy, cauda equina compression, fibromyalgia, reflex sympathetic dystrophy or causalgia (complex regional pain syndrome), diabetic amyotrophy, meningitis, discitis, or back pain due to secondary infection, tumor, or postherpetic neuralgia, or any neuropathic pain conditions;
4. Subjects with gout (except for subjects with gout who are controlled with diet and/or with stable suppressive treatment with uric acid reducing medication(s) and/or colchicine, not on NSAIDs or COX-2 inhibitors, and who have not had any attack within the past 2 years), pseudogout, psoriatic arthritis, active Lyme Disease, rheumatoid arthritis or other inflammatory arthritis, trochanteric bursitis, or ischial tuberosity bursitis;
5. Subjects who, in the investigator's opinion, have an underlying gastrointestinal condition or other disorder that may predispose them to obstruction;
6. Subjects with any of the following hearing-related conditions and/or who received the following therapies or medications prior to or at baseline (screening period) that would preclude an accurate assessment of hearing function:
    a. History of otologic surgery and/or pre-existing otologic or audiologic diseases/conditions (e.g., asymmetric hearing loss, Meniere's disease, persistent middle ear infections, history of hearing fluctuation, autoimmune inner ear disease; perilymphatic fistula; and/or tumor of the head, neck or auditory system);
    b. History of severe or clinically significant head injury;
    c. Threshold asymmetry > 20 dB at any test frequency including all test frequencies from 250 Hz through 8000 Hz;
    d. Air-bone gaps (i.e., difference between the air-conduction and bone-conduction audiometry) of > 10 dB at any bone conduction test frequency;
    e. Abnormal tympanograms or other indications of middle ear abnormality.

f. Unwilling or unable to avoid excessive noise exposure during the entire study period (e.g., subjects with professions or hobbies that require them to be continuously exposed to loud noise without hearing protection);
g. Any exposure to aminoglycoside during the 6 months prior to visit 1 screening (e.g., streptomycin, neomycin gentamicin, tobramycin, amikacin, kanamycin, paromomycin, netilmicin, and spectinomycin);
h. Any exposure to DFMO-difluoromethylornithine) during the 6 months prior to visit 1 screening;
i. Any exposure to chemotherapy with vincristine and vinblastine, and any exposure to platinum-based chemotherapy agents such as carboplatin, oxaliplatin and cisplatin;
j. Any history of head and neck radiation;

7. Subjects who cannot or will not agree to completely stop all incoming opioid and nonopioid analgesic medications and other medications used for chronic pain, excluding herbal and nutraceutical medications;
8. Subjects who cannot or will not agree to stop local regional pain treatments during the study (nerve/plexus blocks or ablation, neurosurgical procedures for pain control, botulinum toxin injections for control of chronic low back pain, steroid injections in the lower back or inhalation analgesia). The subject must not have had a nerve/plexus block within 4 weeks of the screening visit, neuroablation within 6 months of the screening visit, a botulinum toxin injection in the low back region within 3 months of the screening visit, steroid injections in the lower back within 6 weeks of the screening visit, or intravenous or intramuscular steroid injections within 4 weeks of the screening visit;
9. Subjects who have used any investigational medication within 30 days prior to the first dose of study medication;
10. Subjects with any history of seizures (subjects with history of pediatric febrile seizures may participate in the study) or increase in intracranial pressure;
11. Subjects with current uncontrolled depression or other uncontrolled psychiatric disorder (subjects with controlled depression or other psychiatric disorder must be on a stable medication for
12. Subjects with a history of alcohol, medication, or illicit drug abuse or addiction and/or history of opioid abuse or addiction at any time;
13. Subjects with a positive urine drug screen at the screening visit (visit 1) that is medically unexplainable;
14. Subjects with clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling pacemaker;
15. Subjects with unstable respiratory disease that, in the opinion of the investigator, precludes entry into this study;
16. Subjects with evidence of impaired liver function upon entry into the study (laboratory tests 3 times the upper limit of the laboratory reference (normal) range ULN for aspartate transaminase [AST/SGOT] or alanine transaminase [ALT/SGPT], or values > 2 times the ULN for alkaline phosphatase), or total bilirubin level > 1.5

times the ULN or, in the opinion of the investigator/medically qualified designee (must be MD or DO), liver function impairment to the extent that the subject should not participate in this study;
17. Subjects with evidence of impaired kidney function upon entry into the study (i.e., serum creatinine ≥ 2 mg/dL);
18. Subjects with biliary tract disease, hypothyroidism, adrenal cortical insufficiency, or any other medical condition that, in the opinion of the investigator, is inadequately treated and precludes entry into the study;
19. Subjects who had surgical procedures directed towards the source of chronic low back pain within 6 months of the screening visit (visit 1) or scheduled for surgery of the lower back or any other major surgery during the study conduct period;
20. Subjects with history of malignancy within past 2 years, with exception of basal cell carcinoma that has been successfully treated;
21. Subjects with any condition in which opioids are contraindicated, e.g., severe respiratory depression with hypoxia and/or hypercapnia, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, or paralytic ileus;
22. Subjects who are allergic to hydrocodone or who have a history of allergies to other opioids. This does not include subjects who have experienced common opioid side effects (e.g., nausea, constipation);
23. Subjects receiving monoamine oxidase inhibitors (MAOIs) or who have been taking MAOIs within 2 weeks of the screening visit;
24. Subjects with any medical condition that in the investigators opinion is inadequately treated and precludes entry into the study;
25. Subjects who, in the opinion of the investigator, are unsuitable to participate in this study for any other reason;
26. Subjects with an ongoing Workman's Compensation claim, compensation and/or litigation related to their pain disorder.

Treatments
All eligible patients were to have been randomized in a 1:1 ratio into the following groups:
1. Active treatment (i.e. HYD 20, 40, 60, 80 or 120 mg) one tablet once daily
2. Placebo – one tablet once daily

Prior and Concomitant Therapy
Prior and concomitant therapy was to be defined as all medications (over-the-counter (OTC) and/or prescription, including analgesics), procedures, and significant nonpharmacological therapies that are used to treat the subject, including those used in response to an AE/SAE, during the time periods relevant to study conduct.

Except for potentially ototoxic medications (see below), any medications/therapies received within 30 days of the screening visit, and all medications/therapies taken during study conduct were to have been documented.

History of potentially ototoxic medication use during the 6 months prior to screening was to have been collected at the screening visit (visit 1). These medications include:

- Macrolides - e.g., erythromycin, azithromycin, clarithromycin, dirithromycin, rokitamycin, miokamycin, and telithromycin
- Phosphodiesterase type 5 (PDE5) inhibitors - e.g., avanafil, sildenafil, tadalafil, vardenafil and udenafil
- Nonsteroidal anti-inflammatory drugs (NSAIDs) - e.g., aspirin (acetylsalicylic acid), diflunisal, salsalate, ibuprofen, naproxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin, loxoprofen, indomethacin, sulindac, etodolac, ketorolac, diclofenac, nabumetone, piroxicam, meloxicam, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, celecoxib
- Acetaminophen

Permitted rescue medications
Immediate-release oxycodone was to have been allowed during the open-label run-in period and the double-blind period.

Prohibited medications

1. Opioid analgesics (with the exception of IR oxycodone)
2. Concomitant use of NSAIDs, aspirin, COX-2 inhibitors, and acetaminophen: Medications such as aspirin and other NSAIDs were to be prohibited during the open-label run-in period and the double-blind phase unless they are used for conditions other than chronic pain, including headache, fever, and cardiovascular disease prophylaxis. If treatment with such drugs occurs, the medication (dose, frequency, and reason for ingestion) was to be recorded. Subjects were not to exceed the maximum daily recommended dose for these medications.
3. Any use of platinum-based chemotherapy such as carboplatin, oxaliplatin and cisplatin was to be prohibited throughout the study. Chemotherapy with vincristine and vinblastine, and radiation of the head and neck were also to be prohibited during the course of the study. Other chemotherapy and radiation therapy were to be allowed if treatment, in the opinion of the investigator/medically qualified designee (must be MD or DO), was not expected to substantially alter the subjects analgesic requirements.
4. Concomitant use of monoamine oxidase inhibitors (MAOIs) was to be prohibited throughout the study.

Study Conduct
The study was to have consisted of three phases: a pre-randomization phase, a double-blind phase and a follow-up phase

Pre-randomization Phase (was to have consisted of a screening period and a run-in period)
Screening period (was to have been up to 14 days): The following information was to have been obtained and the following procedures were to have been performed for all

potential subjects at the screening visit: Written informed consent, medical history and conditions, demographic information, pain history and etiology, obtain subject's "average pain over the last 14 days" score for LBP, physical examination, clinical labs, serum pregnancy, urine drug screen, record vital signs, electrocardiogram (ECG), record all concomitant medications, record ototoxic mediations, record subject's responses to Screener Opioid Assessment for Patients with Pain – Revised (SOAPP-R) and assess potential for drug abuse and/or diversion and review subject's eligibility against all inclusion/exclusion criteria

For subjects who did not meet all inclusion criteria or who met any exclusion criteria, the following screen failure procedures were to have been performed:

- Discontinue the subject and provide with post-study instructions as appropriate and record the reason for discontinuation and;
- Contact IWRS to inform subject discontinuation from study

For subjects who meet all inclusion criteria and who do not meet any exclusion criteria (with exception of daily pain scores, lab evaluations, audiology assessments and ECGs), the screening visit was to have continued as followed:

- Obtain 3 ECGs a minimum of 20 minutes apart
- Draw clinical labs (i.e., hematology, serum chemistry and urinalysis) , serum pregnancy test for female subjects of childbearing age, and UDS
- Draw DNA, RNA and protein extraction from subjects who consented to participate in the optional pharmacogenomics portion of study
- Dispense subject diary and instruct on its use, and to record daily "average pain over the last 24 hours" scores for LBP at approximately eight pm every evening starting with visit 1 for up to five days (or until instructed to stop)
- Instruct subjects to maintain incoming analgesic regimen during screening period
- Subject to schedule a comprehensive audiologic assessment at audiologist's office in approximately seven days and remind the subject to avoid exposure to loud noise for at least 48 hours prior to the audiologist visit (this assessment will not be required if study entry criteria are not met)

For a subject to have been considered for the open-label run-in period the following criteria were to have been met:

- The average QTcF value from the 3 ECG tracings during the screening visit is ≤ 470 msec (base on the report from the central ECG provider)
- Results of the clinical laboratory assessments met all study entry criteria
- Results of comprehensive audiologic assessment met all study entry criteria
- During the 3 to 5 day period when pain scores are recorded, the subject was to have had at least 3 days of "average pain over the last 24 hours" scores ≥ 5 (on an 11-point NRS where 0 = no pain and 10 = pain as bad as you can imagine), including the 2 scores recorded on the last 2 consecutive days

Open-label Run-in Period (was to have been up to 45 days):
During this period all subjects were to have been instructed to discontinue all incoming analgesic medications and any medication used for chronic pain and to have been converted to HYD based on the dose of their incoming opioid medication as noted in Table 6.

Table 6: Conversion of Incoming Opioid to HYD during Open-Label Run-In-Period

Incoming Opioid	Starting Dose
Doses equivalent to ≤ 40mg/day of oxycodone*	HYD 20 mg*
Doses equivalent to > 40 but ≤ 60 mg/day of oxycodone	HYD 40 mg
Doses equivalent to > 60mg/day but ≤ 80mg/day of oxycodone	HYD 60 mg
Doses equivalent to > 80mg/day of oxycodone	HYD 80 mg
*Subjects who are not on an opioid regimen will begin treatment with HYD 20 mg.	

Source: HYD3002 Protocol Amendment 3 (dated July 11 2012), Section 9.1, Table 1, pg. 26 of 180

At visit 2 (the start of HYD dosing) the following procedures were to have been performed: review subjects diary for "average pain over the last 24 hours" scores to confirm subject's eligibility for run-in-period, contact IVWR to notify subject is entering open-label run-in period, record all concomitant medications, AEs, subject's vital signs, subject's responses to Current Opioid Misuse Measure (COMM), investigator completes Addiction, Behavior Checklist (ABC), record subjects response to Clinical Opiate Withdrawal Scale (COWS) if incoming opioid medication equivalent to ≥5 mg of oxycodone daily, subject's responses to Oswestry Disability Index (ODI), the Medical Outcomes Study Sleep-Revised (MOS-R) Brief Pain Inventory (BPI), SF-36 Health Survey), Dizziness Handicap Inventory (DHI) and the Tinnitus Handicap Inventory THI), dispense HYD, dispense supplemental analgesic medication,

On the evening of visit 2, subjects were to have recorded daily "average pain over the last 24 hours" scores in their diary every evening at approximately 8 pm. Subjects who tolerated HYD but did not achieve adequate analgesia were to have their HYD doses up titrated to the next HYD dose level until a stable dose was achieved. Before an upward titration was to have been considered, minimum treatment duration of 72 hours was to have been required for subjects on HYD 20, 40, and 60 mg, and minimum treatment duration of 120 hours was to have been required for subjects on HYD 80 mg. Dose up-titration was to have occurred until a "stable dose" was achieved.

Supplemental analgesic medication (IR oxycodone, 10 mg daily) was to have been permitted for breakthrough pain during the run-in period as subjects titrated to their stable HYD dose.

To have been considered stable on a HYD dose, subjects must to have met the following criteria:

- Been on the same HYD dose level during ≥ 7 days preceding the randomization visit (visit 3), and
- Have had "average pain over the last 24 hours" scores on an 11-point NRS of ≤ 4 on each of the 3 days preceding visit 3 (randomization), and
- Have had "average pain over the last 24 hours" scores on an 11-point NRS that are at least 2 points lower than their screening mean pain scores (i.e., average of the last 2 consecutive "average pain over the last 24 hours" scores that qualified the subjects for the open-label run-in period) on each of the 3 days preceding visit 3 (randomization), and
- Have had acceptable tolerability as determined by the investigator/designee's assessment Not have taken > 10 mg of immediate-release oxycodone daily on each of the 3 days preceding visit 3.

Subjects were to have been discontinued if they could tolerate HYD and/or if they did not achieve adequate analgesia after 7 (+ 2) days of exposure to the highest dose level, HYD 120 mg. Subjects who were discontinued from the dose-titration period were to have been converted to an appropriate pain management regimen as deemed medically appropriate by the investigator/medically qualified designee and were to have had follow up phone call/clinic visit.

All subjects stabilized on their HYD doses were to have been randomized to that dose level or matching placebo and enter a double-blind period. Randomization was to have been stratified by:

1. Dose at end of the run-in period (20, 40, 60, 80, or 120 mg) and;
2. Opioid naïve status (naïve or experienced)

Double-Blind Phase (was to have been 84 ± 3 days or 12 weeks)

At visit 3, subjects who tolerated and achieved adequate analgesia with an HYD dose were to have been randomized in a 1:1 ration to their corresponding HYD dose or placebo (PBO). All subject visits were to be scheduled at weeks 1, 2, 4, 8 and 12 of the double-blind phase.

During the first 2 weeks of the double-blind phase, subjects who were randomized to the placebo treatment arm were to be tapered from their titrated HYD dose to placebo in a blinded fashion. Table 7 displays this tapering scheme.

Table 7: Blinded Taper Schedule During the First Two Weeks of Double-Blind Phase

Randomized dose	Visit 3 to Visit 4		Visit 4 to Visit 5	
	Bottle 1*	Bottle 2*	Bottle 3*	Bottle 4*
	(to be taken daily for the first 3 days)	(to be taken daily up to visit 4)	(to be taken daily for the first 3 days)	(to be taken daily up to visit 5)
HYD 120 mg	HYD 120 mg	HYD 120 mg	HYD 120 mg	HYD 120 mg
HYD 80 mg	HYD 80 mg	HYD 80 mg	HYD 80 mg	HYD 80 mg
HYD 60 mg	HYD 60 mg	HYD 60 mg	HYD 60 mg	HYD 60 mg
HYD 40 mg	HYD 40 mg	HYD 40 mg	HYD 40 mg	HYD 40 mg
HYD 20 mg	HYD 20 mg	HYD 20 mg	HYD 20 mg	HYD 20 mg
placebo 120 mg	HYD 80 mg	HYD 60 mg	HYD 40 mg	HYD 20 mg
placebo 80 mg	HYD 60 mg	HYD 40 mg	HYD 20 mg	placebo
placebo 60 mg	HYD 40 mg	HYD 20 mg	placebo	placebo
placebo 40 mg	HYD 20 mg	placebo	placebo	placebo
placebo 20 mg	placebo	placebo	placebo	placebo
* Note: To achieve proper tapering between visits 3 and 5, the scheduling of visit 4 must ensure subjects have opportunity to take at least 3 doses of study medication (1 dose/day) from bottle 1 and at least 2 doses of study medication (1 dose/day) from bottle 2. Similarly, the scheduling of visit 5 must ensure subjects have taken at least 3 doses of study medication (1 dose/day) from bottle 3 and at least 2 doses of study medication (1 dose/day) from bottle 4.				

Source: HYD3002 Protocol Amendment 3 (dated July 11 2012), Section 9.4.1.2.1, Table 2, pg. 39 of 180

After the 2-week taper period, subjects who were randomized to HYD/placebo 40 mg, 60 mg, 80 mg or 120 mg were permitted to have their doses down-titrated once to one level below their randomized dose if the investigator/designee determined that the subjects were not adequately tolerating the double-blind treatment. Upon down-titration, if the investigator/designee determined that subjects were tolerating treatment but were not achieving adequate analgesia, the subjects were to have had their doses up-titrated back to the randomized dose. Only one dose down-titration was to be permitted; and only one subsequent dose up-titration was to be allowed. All dose adjustments were to have taken place at the clinical site during a regularly scheduled visit or during an unscheduled dose adjustment visit. No dose adjustment was to be allowed for subjects randomized to HYD/placebo 20 mg.

During the double-blind phase for visits 4, 5, 6 and 7 (double-blind weeks 1, 2, 4 and 8) subjects were to have been allowed a ± 2 day window for visit 4 and 5, and a ± 3-day window for visits 6 and 7.

The following procedures were to have been performed

- Collect all unused double-blind medication and supplemental analgesic medication

For subjects taking study drug only, the subject's diary was to have been reviewed for the following information to ensure continual compliance:

- Double-blind medication used (date/time/amount taken)
- Daily "average pain over the last 24 hours" scores for LBP pain at approximately 8 PM every evening
- Supplemental pain medication use (i.e., IR oxycodone -date/time/amount taken) with corresponding "pain right now" scores
- Daily SOWS score (Visit 4 and 5 only)
- Re-educate subject as necessary

For retrieved dropout subjects only, the subject's diary was to have been reviewed for the following information to ensure continual compliance:

- Chronic pain medication use (time/date/amount of taken) in chronic pain medication diary
- Daily "average pain over the last 24 hours" scores for his/her low back pain at approximately 8 PM every evening
- Daily SOWS scores (visits 4 and 5 only)

Immediate-release oxycodone was to have been permitted during the DB period. The maximum daily IR oxycodone was to have been determined by the subject's current double-blind dose level as shown in Table 8.

Table 8: Amount of Immediate-Release Oxycodone Permitted Daily

Dose Level during the Double-blind Phase	Maximum **Immediate-Release Oxycodone** Daily Dose*
HYD/Placebo 20 mg	10 mg
HYD/Placebo 40 mg	10 mg
HYD/Placebo 60 mg	15 mg
HYD/Placebo 80 mg	20 mg
HYD/Placebo 120 mg	30 mg
* Immediate-release oxycodone may be administered as 5-10 mg/dose, *as needed*, with a minimum dosing interval of 4-6 hours. The total daily dose must not exceed the daily maximum. The maximum daily immediate-release oxycodone allowed is determined by the subject's current double-blind dose level.	

Source: NDA 202627, Clinical Protocol HYD3002, Amendment #3, Table 3, pp. 41 of180

Follow-up Phase (was to have occurred 5-7 days after the Run-In Failure Visit or End-of-Study/Early Discontinuation Visit)
The follow-up evaluation was to have been performed via a telephone call or at the study site by the investigator/designee if the investigator deemed necessary. Subjects who required follow-up clinical laboratory or ECG assessments were to have returned to the clinical site for this visit

The following procedures were to have been performed for all subjects:

- Record information for all concomitant medications and nondrug therapies
- Record all adverse events

Study Procedures
Table 9 displays the schedule of activities that were to have been for the prerandomization, double-blind and follow-up phases of the study

Table 9: Schedule of Activities

Protocol Activity	Prerandomization Phase							Double-blind Phase							Follow-Up Phase [a]
	Screening Period		Run-in Period												
	Visit 1	TC [b]	Visit 2	TC [b]	DTV [b]	Visit 3		Visit 4	Visit 5	Visit 6	Visit 7	Unsch Dose Adjust	Study Drug DC Visit [b c]	Visit 8 EOS/E DC	Visit 9
						End-of-RI	Rand								
Study Day	≤ 14 Days		≤ 45 Days				Day 1	Wk 1	Wk 2	Wk 4	Wk 8			Wk 12	5-7 days
Informed Consent Form (ICF)	X														
Contact IWRS to Document Subject Status	X	X[d]	X			X[e]	X						X	X	
Inclusion/Exclusion Criteria	X														
Demography	X														
Medical History	X														
Pain History/Pain Etiology	X														
Record "Average Pain Over the Last 14 Days"	X														
Physical Examination	X					X[e]							X	X	
History of Ototoxic medication use	X														
Concomitant Therapies	X	X[f]	X	X	X	X		X	X	X	X	X	X	X	X
Assess Opioid Equivalence	X		X												
Instructions for incoming pain medications	X[g]	X[f]	X				X								
Adverse Events	X	X[f]	X	X	X	X		X	X	X	X	X	X	X	X
Vital Signs	X		X		X	X		X	X	X	X	X	X	X	
Electrocardiogram	X[g]					X				X			X	X	
Draw Blood for Clinical Laboratory Evaluations	X[g]					X							X	X	
Serum Pregnancy Test	X[g]					X							X	X	
Pharmacogenomics Evaluations (optional)	X[g]					X[e]							X	X[h]	
Collect Urine for Clinical Laboratory Evaluations	X[g]					X							X	X	
Review Laboratory Results/ECG Results/Audiologic Assessment results	X[i]	X[i]				X[i]	X[i]			X[i]			X[i]	X[i]	
Comprehensive Audiologic Assessment		X[q]				X[e]							X	X	
Pure-tone Air Conduction Audiometry						X[r]									
Study Drug Dose Adjustment				X	X							X			
Dispense Study Drug as Instructed by IWRS			X[s]		X		X[s]	X[h]	X[h]	X[h]	X[h]	X			

Schedule of Activities (Continued)

Protocol Activity	Prerandomization Phase						Double-blind Phase							Follow-Up Phase [a]
	Screening Period		Run-in Period											
	Visit 1	TC [b]	Visit 2	TC [b]	DTV [b]	Visit 3 End-of-RI	Visit 3 Rand	Visit 4	Visit 5	Visit 6	Visit 7	Unsch Dose Adjust	Study Drug DC Visit [b c]	Visit 8 EOS/EDC	Visit 9
Study Day	≤ 14 Days		≤ 45 Days				Day 1	Wk 1	Wk 2	Wk 4	Wk 8			Wk 12	5-7 days
Dispense Supplemental Analgesic Medication as Instructed by IWRS			X		X		X	X[h]	X[h]	X[h]	X[h]				
Collect Unused Study Drug					X	X		X[h]	X[h]	X[h]	X[h]	X	X	X[h]	
Abuse/Diversion Assessments															
Urine Drug Screen [j]	X														
Conduct Drug Accountability					X	X		X[h]	X[h]	X[h]	X[h]	X	X	X[h]	
SOAPP-R	X														
COMM			X			X		X		X	X		X	X	
ABC			X			X		X		X	X		X	X	
Evaluate Abuse and/or Diversion	X		X		X	X		X	X	X	X	X	X	X	
COWS			X[k]		X[k]	X[k]		X	X				X[l]	X[m]	
Oswestry Disability Index			X				X	X	X	X	X		X	X	
MOS Sleep - R			X				X			X	X		X	X	
Brief Pain Inventory			X				X	X	X	X	X		X	X	
SF-36			X				X			X	X		X	X	
Dizziness Handicap Inventory			X		X	X		X	X	X	X	X	X	X	
Tinnitus Handicap Inventory			X		X	X		X	X	X	X	X	X	X	
PGIC													X	X	

Dispense Subject Diary/Record Visit	X[g]												X		
Diary Entries (for subjects on study drug only)															
Study Medication Intake (date/time/amount taken)			◄--►												
Supplemental Analgesic Use (time/date/amount taken)			◄--►												
Daily "Average Pain over the Last 24 Hours" Score			◄--►												
"Pain Right Now" Score			◄--►												
Modified SOWS Scores [n]			◄--►												
Diary Entries (for retrieved dropout subjects only) [c]															
Daily "Average Pain Over the Last 24 Hours"								◄--►					X		
Chronic Pain Medication Intake (date/time/dose)								◄--►					X		
Modified SOWS Scores							◄--►								
Review Diary/Record Visit			X	X	X	X		X	X	X	X	X	X	X	
Monitor Pain Scores in Diary			◄--►												
Monitor Subject Compliance			◄--►												
Telephone Contact for Tolerability Assessments				◄--►											

Schedule the next visit/telephone call	X[g]	X[r]	X	X	X	X[e]	X	X	X	X	X	X	X	X[o]	
Collect Diary						X[e]								X	
Discontinue the Subject	X[p]	X[q]				X[e]								X	

Source: NDA 202627, Clinical Protocol HYD3002, Amendment #3, Table 9.5.1, pp. 51- 55/180

Discontinuation Criteria (during open-label run-in period)
Subjects were to have been discontinued from the open-label run-in period for the following reasons:

- Adverse event (AE)[if it causes subject to withdraw from the study]
- Subject's choice
- Lost to follow-up (study personnel lose contact with the subject).
- Lack of therapeutic effect
- Confirmed or suspected diversion
- Administrative reason (subject continues from study early for any logistical nonmedical reasons)
- Did not qualify for the double-blind (DB) phase (did not meet all study entry criteria for DB phase)
- In the investigator's opinion, it is not in the best interest of the subject to continue tin the study
- Change in compliance with inclusion/exclusion criteria that in clinically relevant and affects subject safety
- Ingestion of protocol prohibited concomitant medication that might affect subject safety

If the subject discontinues due to subject's choice, administrative, or lost to follow-up reasons, the specific circumstances surrounding the discontinuation were to have been recorded.

The investigator/designee was to have documented instances of inability to tolerate treatment as discontinuations due to adverse event and record the specific symptom(s) and/or sign(s) (e.g., nausea, vomiting). Instances of inadequate pain control were to have been documented as lack of therapeutic effect.

Discontinuation Criteria (during the double-blind phase for subjects who continued to participate in the study)
Subjects were to have been discontinued from study drug during the double-blind phase (but continued in the study) for the following reasons:

- AE that causes subject to withdraw from the study
- Subject's choice
- Lack of therapeutic effect
- Administrative reason

If the subject discontinues due to subject's choice, administrative, or lost to follow-up reasons, the specific circumstances surrounding the discontinuation were to have been recorded.

The investigator/designee was to have documented instances of inability to tolerate treatment as discontinuations due to adverse event and record the specific symptom(s) and/or sign(s) (e.g., nausea, vomiting). Instances of inadequate pain control were to have been documented as lack of therapeutic effect.

Discontinuation Criteria (during the double-blind phase for subjects who did continue to participate in the study)

Subjects were to have been discontinued from both study drug and study during the double-blind phase for the following reasons:

- AE that causes subject to withdraw from study
- Subject's choice
- Lost to follow-up
- Lack of therapeutic effect
- Confirmed or suspected diversion
- Administrative reason

If the subject discontinued due to subject's choice, administrative, or lost to follow-up reasons, the specific circumstances surrounding the discontinuation were to have been recorded.

The investigator/designee was to have documented instances of inability to tolerate treatment as discontinuations due to adverse event and record the specific symptom(s) and/or sign(s) (e.g., nausea, vomiting). Instances of inadequate pain control were to have been documented as lack of therapeutic effect.

Outcome Variables

Efficacy

- 11-point Numerical Rating Scale (NRS) where 0=no pain and 10= pain as bad as you can imagine
- Sleep Disturbance Subscale of the Medical Outcome Study (MOS) Sleep Scale
- Patient Global Impression of Change (PGIC)
- Responder to Treatment
- Osewestry Disability Index (ODI)
- Supplemental pain medication for low back pain
- Brief Pain Inventory Short Form (BPI-SF)
- Medical Outcomes Study 36-item Short-Form (SF-36)
- Daily "Pain Right Now" Scores

Safety

- Adverse Events (AEs)
- Vital signs – blood pressure, heart rate, respiratory rate and temperature
- Clinical laboratory tests – chemistry, hematology, and urinalysis, serum pregnancy test for women of childbearing age
- Urine drug screen (UDS)
- Physical examination – including height and weight
- Electrocardiogram (ECG)
- Clinical Opiate Withdrawal Scale (COWS)
- Modified Subject Opiate Withdrawal Scale (SOWS)
- Current Opioid Misuse Measure (COMM) questionnaire
- Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)
- Addiction Behavior Checklist (ABC)
- Dizziness Handicap Inventory (DHI)
- Tinnitus Handicap Inventory (THI)
- Audiologic assessments (pure tone audiometry, bilateral air-conduction pure-tone threshold audiometry, bone conduction pure tone threshold audiometry, tympanometry, speech reception threshold testing and word recognition)

Efficacy Endpoints

Primary

Weekly mean pain intensity score (calculated using the daily diary "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 by the subject during the double-blind phase)

Secondary

- Sleep problems index score
- PGIC score
- Responders analysis

Other endpoints

- Oswestry Disability Index (ODI) score
- Supplemental Medication for Low Back Pain
- Brief Pain Inventory - Short Form score
- Medical Outcomes Study 36-item Short-Form (SF-36) score
- Daily "Pain Right Now" scores

Statistical Analysis Plan (SAP)

Analysis Populations

Enrolled population: was to have consisted of all individuals who signed the informed consent form

Full analysis population (FAP): was to have consisted of the group of subjects randomized and received at least 1 dose of double-blind study drug

Per protocol population (PPP): was to have consisted of a subgroup of the FAP; and was to have excluded subjects with major protocol violations that could affect the primary efficacy analysis

Safety population: was the have consisted of the group of subjects who received at least 1 dose of study drug

Randomized safety population: was to have consisted of subjects who were randomized and received at least 1 dose of double-blind study drug

Causal Estimand

The causal estimand (i.e., primary efficacy parameter) was to have been the difference in weekly mean pain intensity scores at week 12 between the placebo and HYD treatment groups for all subjects in the FAP. Subjects were to have been allowed to continue in the study through week 12 of regardless of whether they discontinue to take their randomized study drug (i.e., the study will allow for retrieved dropouts), however in order to address concerns that no treatment benefit be attributed to retrieved dropout subjects who discontinue study drug due to an adverse event, the primary efficacy analysis was to have included data collected while the subject was receiving double-blind study drug; no retrieved dropout data was to have been used in this primary analysis.

Efficacy Analyses

The primary efficacy analysis was to have been conducted on the full analysis population (FAP). An analysis of the primary efficacy variable for the per-protocol population was to have been performed if more than 20% of the subjects in the FAP were regarded as major protocol deviations that would affect the evaluation of efficacy and excluded from the per protocol population. All hypothesis tests were to have been two-sided at ą=0.05 level.

The analysis of the weekly mean pain intensity scores were to have been performed using a mixed effects model with repeated measures (MMRM). The MMRM was to have treatment (2 levels: HYD or placebo), time (14 levels for weeks -3, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12), and opioid naïve status (naïve or experienced) as fixed effects. The screening and prerandomization mean pain scores were to have been incorporated as the week -3 and 0 values for the dependent variable. Restricted maximum likelihood (REML) was to have been used to estimate the parameters in the model. A pattern mixture model (PMM) framework was to have been used to estimate the week 12 treatment difference while accounting for missing data.

The screening mean pain score was to have been defined as the mean of the diary "average pain over the last 24 hours" scores obtained from the 2 consecutive days of the screening period that qualify the subject for entry into the run-in period. If the subject reported pain scores ≥5 for more than 2 days, the screening main pain score was to have been calculated using the scores from the 2 days closet to the start of the open-label run-in period.

The prerandomization mean pain score was to have been defined as the mean of the "average pain over the last 24 hours" scores obtained from the 3 consecutive days of the open-label run-in period that qualify the subject for entry into the double-blind period. If the subject reported consecutive pain scores that were ≤ 4 for more than three days after HYD exposure; then the prerandomization mean pain score was to have been calculated using the scores from the 3 days closest to the start of double-blind dosing.

The weekly mean pain intensity score was to have been defined as the sum of non-missing daily "average pain over the last 24 hours" scores reported during that week (Days 1-7, Days 8-14, Days 15- 21, … , Days 78-84) divided by the number of days with non-missing scores for that week. If a subject reported less than 3 days of pain scores during a week, the weekly mean pain intensity score was to have been set to missing. Due to scheduling, a subject may have been exposed to double-blind study drug longer than 12 weeks or 84 days; therefore in this case, the "average pain over the last 24 hours" scores was to have been collected after Day 84 was not to have been used in the calculation of the Week 12 mean pain intensity score.

The Kenward-Roger approximation was to have been used to estimate the denominator degrees of freedom. The model was to have been fit using SAS PROC MIXED.38

Data from the double-blind period when subjects were on study drug, as well as the screening and prerandomization pain scores, was to have been included in the linear model. The primary endpoint analysis was to have been based on a treatment contrast at week 12 calculated from this model and taking into account the observed patterns of missing data in each treatment arm.

In the primary efficacy analysis:

1. All observed data collected while subjects were exposed to double-blind treatment was to have been included in the MMRM;
2. The remaining subjects who do not provide week 12 data was to have been categorized into 1 of the following missing data patterns:
    a. Discontinuation of double-blind treatment due to adverse events (AE)
    b. Discontinuations of double-blind treatment due to all other reasons (including lack of efficacy, administrative reasons, etc.) (Other)

Retrieved dropout data was not to have been included in this primary analysis.

Sensitivity Analyses
These analyses were similar to primary efficacy analysis except for:

- The sensitivity analyses were to have included retrieved drop-outs
- The sensitivity analyses were to have analyzed observed data using MMRM, however was not to have included retrieved drop-outs and;
- The sensitivity analyses were to have used the average of prerandomization and screening estimates for subjects who withdraw due to AE or ASHA related event
- The sensitivity analyses were to have used a hybrid BOCF/LOCF for imputation

Safety Analyses
These analyses were to have been performed for all subjects in the safety and randomized safety populations. Safety data that was to be evaluated included: adverse events, clinical laboratory results, vital signs, ECGs, COWS, and modified SOWS.

Missing Values
For the primary analysis of the primary efficacy variable:

- In the calculation of weekly mean pain intensity scores from the daily diary, a weekly mean pain score was to have been calculated provided there were at least 3 non-missing pain scores for that week; otherwise it was to have been set to missing.
- No imputations were to have been used for intermittent missing data (i.e. missing data between visits or days)

For supplemental pain medication for LBP, if the data on the Case Report Form (CRF) indicated supplemental analgesic was used but the dosage information (e.g., dosage, number of tablets) was not reported the missing data point was to have been imputed using linear interpolation between the 2 closest non-missing values. There was to have been no imputation for this variable after study drug discontinuation.

There was to have been no imputation of missing data for the secondary endpoints.

Sample size determination
Assuming a 2- sided significance level of 0.05, a desired detectable treatment difference of 0.70 between treatment means for the week 12 mean pain intensity score, a common within-treatment variance of 6.0 (an assumption which corresponds to a standard deviation of 2.45 and an effect size of 0.7/2.45 = 0.286), a two-sided t-test will have 90% power when the sample size is 259 subjects per treatment group.

The plan was to have been to randomize 300 subjects per treatment arm, for an overall number of 600 subjects to be randomized to double-blind treatment. If the assumptions underlying the simulations should be thought to be substantially different, the sample size may be adjusted to achieve desired statistical power.

Protocol Amendments
The original protocol (dated June 27, 2011) was subsequently followed by three protocol amendments (Amendment #1 dated February 21, 2012, Amendment #2 dated March 26, 2012 and Amendment #3 dated July 11, 2012).

No subjects were enrolled under the original protocol or Amendment #1.

According to the Applicant; the summary of changes for Amendment #3 was to have included:

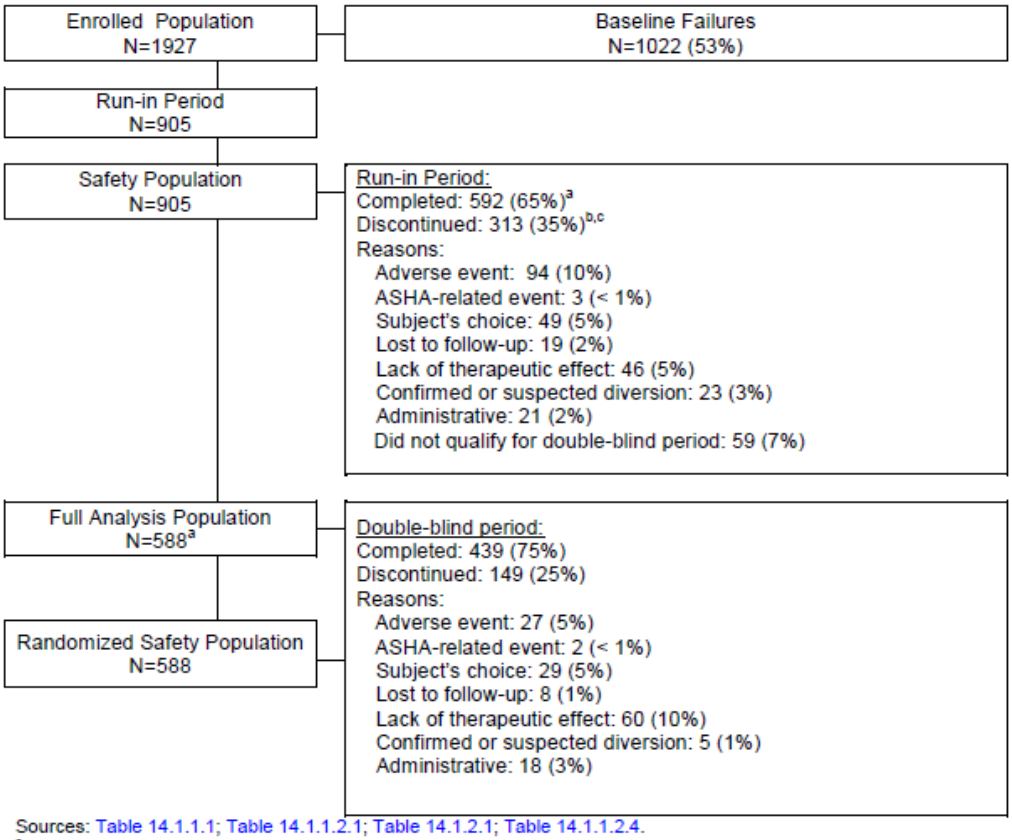
1. Wording was to be added to indicate that doses available for randomization were to be adjusted based on the distribution of subjects in current double-blind doses.
2. The word “compensation” was to have been added to exclusion criterion #26 for clarification purposes.
3. Pharmacogenomics (PG) sample collection was to have been modified – samples were to have been collected at visit 1 and end of study drug treatment only. Subjects being randomized were to no longer have a PG sample collected at the end of the run-in period.
4. The tables for scoring of Dizziness Handicap Inventory and Tinnitus Handicap Inventory were to have been corrected.
5. Wording was to have been added to emphasize that immediate-release oxycodone should be used for breakthrough pain only during the run-in period.
6. GGT was to have been removed from Table 9 (Laboratory Ranges Used to Identify Markedly Abnormal Laboratory Values) because test was not performed for in study.
7. Corrected error in footnote for Nucynta in Opioid Equivalence Chart (Appendix J).

STUDY RESULTS

Subject Disposition
The Applicant reports a total of 102 sites were initiated in the United States, of which 94 sites screened subjects; 89 sites entered subjects into the open-label run-in period and 76 sites entered subjects into the double-blind period.

Figure 3 displays the disposition of study subjects:

Figure 3: Study HYD3002 - Disposition of Subjects



Sources: Table 14.1.1.1; Table 14.1.1.2.1; Table 14.1.2.1; Table 14.1.1.2.4.
[a] Subjects 2047002, 2049010, 2082008 and 2093009 were randomized to Double-blind medication but did not receive any double-blind medication. They are not included in randomized safety or full analysis populations, but they are still regarded as having discontinued study drug during the double-blind period.
[b] Subject 2077008 discontinued the study at the end of the run-in period, but was assigned a randomization number in error.
[c] Subject 2093002 discontinued from the run-in period due to both an AE and an ASHA-related event and was counted once in each category.

Source: NDA 202627, HYD3002 Clinical Study Report (CSR), Figure 2, Pg.176 of 6082

A total of 1927 subjects were enrolled in the study of which 1022 (53%) were screen failures. The Applicant reports the primary reasons for screen failures were: failed inclusion /exclusion criteria (87%), serious adverse event (<1%), adverse event (<1%), subject choice (8%), lost to follow-up (2%), and administrative (3%) 905 were part of the safety population and 588 subjects were considered a part of the full analysis population.

Study subjects who completed the double-blind period represented 75% (n=439/588) of the FAP versus 25% (n=149/588) of subjects who were discontinued during the double-blind period. The Applicant reports that the highest incidence of discontinuations were due to: lack of therapeutic effect (10%, n=60/588), followed by adverse events (5%, n=27/588) and subject's choice (5%, n=29/588).

Of note, during the open-label run-in and double-blind periods, 3% and 1% of study subjects respectively, were reportedly discontinued due to confirmed or suspected diversion of study drug. Discontinuations due to confirmed or suspected diversion will be discussed further in study results and the Summary of Efficacy.

Subject Discontinuations
The Applicant classified reasons for study drug discontinuation or study and study drug discontinuation as follows:

- An AE (if an AE caused a subject to withdraw from the study drug). Note: worsening of the condition (low back pain) for which the subject qualified for study entry was not considered an AE. For these subjects, the reason for discontinuation was to have been recorded as lack of therapeutic effect (see below) or;
- American Society of Hearing Audiology (ASHA) Related Event or;
- Subject's choice (the subject chose for personal reasons to discontinue the study drug) or;
- Lack of therapeutic effect (the subject chose to withdraw from the study drug because he/she did not feel the study drug was effectively treating his/her condition under study or the investigator/medically qualified designee chose to discontinue the subject from the study drug because, in his/her opinion, the study drug was not effectively treating the subject's condition under study; the study staff was to have confirmed that worsening of low back pain, not worsening of other pain, was in fact the cause for discontinuation) or;
- Confirmed or suspected diversion or;
- Administrative reason (the subject discontinued from the study drug early for any logistical, nonmedical reason).

If the subject discontinued due to subject's choice, administrative, or lost to follow-up reasons, the specific circumstances surrounding the discontinuation were to be recorded. The investigator/designee was to have documented instances of inability to tolerate treatment as discontinuations due to AE and recorded the specific symptom(s) and/or sign(s) (e.g., nausea, vomiting). Instances of inadequate pain control were to have been documented as lack of therapeutic effect.

Table 10 shows the Applicant's results for reasons for discontinuations in the safety population and randomized safety population

Table 10: Subject Disposition and Reasons for Discontinuations - Safety Population and Randomized Safety Population

	Run-in Period (N=905)			Double-blind Period (N=592)		
	Non-randomized (NN=312)	Randomized (NN=593)	Overall (NN=905)	Placebo[a] (NN=292)	HYD (NN=296)	Overall (NN=592)
Completed Period on Study Drug[b], n (%)		592 (100)	592 (65)	210 (72)	229 (77)	439 (74)
Discontinued Study Drug - All Cases, n (%)[c]	312 (100)	1 (< 1)	313 (35)	82 (28)	67 (23)	153 (26)
Adverse Event	94 (30)	0	94 (10)	10 (3)	17 (6)	28 (5)
ASHA-Related Event[e]	3 (1)	0	3 (< 1)	1 (< 1)	1 (< 1)	2 (< 1)
Subject's Choice	49 (16)	0	49 (5)	14 (5)	15 (5)	29 (5)
Lost to Follow-up	19 (6)	0	19 (2)	3 (1)	5 (2)	9 (2)
Lack of Therapeutic Effect	46 (15)	0	46 (5)	44 (15)	16 (5)	60 (10)
Confirmed or Suspected Diversion	23 (7)	0	23 (3)	3 (1)	2 (1)	6 (1)
Administrative	20 (6)	1 (< 1)	21 (2)	7 (2)	11 (4)	19 (3)
Did Not Qualify for Double-blind Period	59 (19)	–	59 (7)	–	–	–
Discontinued Study Drug and Study Simultaneously, n (%)				51 (17)	46 (16)	101 (17)
Adverse Event				6 (2)	8 (3)	15 (3)
ASHA-Related Event[e]				0	1 (< 1)	1 (< 1)
Subject's Choice				12 (4)	15 (5)	27 (5)
Lost to Follow-up				3 (1)	5 (2)	9 (2)
Lack of Therapeutic Effect				21 (7)	7 (2)	28 (5)
Confirmed or Suspected Diversion				3 (1)	2 (1)	6 (1)
Administrative				6 (2)	8 (3)	15 (3)
Discontinued Study Drug and Stayed in Study, n (%)[d]				31 (11)	21 (7)	52 (9)
Adverse Event				4 (1)	9 (3)	13 (2)
ASHA-Related Event[e]				1 (< 1)	0	1 (< 1)
Subject's Choice				2 (1)	0	2 (< 1)
Lack of Therapeutic Effect				23 (8)	9 (3)	32 (5)
Confirmed or Suspected Diversion				0	0	0
Administrative				1 (< 1)	3 (1)	4 (1)

Source: NDA 202627, HYD3002 Clinical Study Report (CSR), Table 18, Pg.177 of 6082

The Applicant reports that of the 905 subjects who entered the run-in period, t65% (n=592/905) completed the run-in period and were randomized; and 35% (n=312/905) were discontinued from study and represent nonrandomized subjects. For subjects who were not randomized, the most common reasons for discontinuation were adverse event (30%), did not qualify for double-blind period (19%), subject's choice (16%) and lack of therapeutic effect (15%). The Applicant reports that subjects who did not qualify for the double-blind period were those who completed all of the open-label, run-in period

dosing and procedures but did not meet all of the double-blind period entry criteria which included:

- Meet ECG criteria
- Achieve stable HYD dose and that HYD dose be available in the double-blind period
- Continue to forgo all incoming analgesic medications and other medications used for chronic pain (if applicable)
- No use of any prohibited concomitant medication specified by protocol
- Does not have any audiometric results meeting the American Society of Hearing Audiology (ASHA) criteria. Results must be reviewed by medical monitor before subject randomization

During the double-blind period, 16% of HYD subjects compared to 17% of placebo subjects were reported to have discontinued study drug and study simultaneously. Overall, the most common reasons for discontinuation from study drug and study simultaneously during the double-blind period reportedly were subject's choice (5%) lack of therapeutic effect (5%), adverse event (3%) and administrative reasons (3%). A higher percentage of subjects in the HYD group discontinued the study due to subject's choice compared to placebo subjects (5% vs. 4% respectively) and adverse events (3% versus 2% respectively.

The remainder of discontinuations from HYD study drug and study simultaneously during the double-blind were reportedly due to:

- Lost-to-follow-up (2%)
- Confirmed or suspected diversion (1%)
- ASHA-related AE (<1%)

An information request was sent to the Applicant requesting an additional summary table (HYD versus placebo group) displaying the specific reasons for a subject's choice (e.g. personal reasons, withdrawal of consent) to discontinue study drug and study simultaneously during the open-label run-in period and the double-blind period as listed in the appendix table and subject's case report form.

The Applicant's response follows:

> [Table 1] shows that during the open-label run-in period in study HYD3002, 49 subjects discontinued study drug due to the reason of "subject's choice". For each of these cases, the investigator was required to provide additional details in a free text field captured in the database. Based on these additional details, Purdue has categorized the reasons of "subject choice" into 4 subcategories.

Table 1 Number of HYD3002 Subjects Who Discontinued Study Drug During Open-label Run-in Period Due to the Reason of "Subject's Choice" by Subcategory

	Total
Number of subjects in any sub-category	49
Withdrew consent	33
Family matter	1
Moved away	4
Schedule conflict	11

Source: NDA 206627, Response to Clinical IR, Table 1, pg. 1/32

In addition, the Applicant provided a table of subject listings that included the information contained in the free text field, subcategory assignment, last pain score, last observed AE, and drug accountability issues. Drug accountability along with other pertinent information such as Aberrant Behavior Checklist (ABC), Current Opioid Misuse Measure (COMM), and urine drug screen (at discretion of the investigator) was reviewed by the investigator for potential abuse or diversion at each study visit. The yes/no answer to abuse and diversion question was captured in the CRF.

I performed an additional review of the Applicant's data involving subjects who discontinued study drug and study simultaneously during the open-label, run-in due to the reason of "subject's choice". The discontinuations due to "subject's choice" were reviewed using CRFs and data provided by the Applicant. Table 11 displays the results of this analysis.

Table 11: Discontinuations due to Subject's Choice During the Open-label, Run-in Period

USUBID	DSTERM	Last Pain Score	Subject's choice subcategory	Subject's choice subcategory – (Reviewer's Term)
HYD3002-0562A-2067004	Not satisfied on 20 mg. Thought Rescue Did not help. 40 mg was too high of a dose	5	Withdrew Consent	Lack of Efficacy
HYD3002-0858A-2073012	Subject did not want to titrate up to next dose despite her continued elevated pain scores	7	Withdrew Consent	Lack of Efficacy
HYD3002-1343A-2097001	Subject felt the IP was causing a mental fog and did not want to continue	8	Withdrew Consent	Adverse Event
HYD3002-2050A-2025043	Due to lack therapeutic effect, Subject wishes to withdraw and return to PCP for nerve block	8	Withdrew Consent	Lack of Efficacy
HYD3002-2107A-2046016	Subject withdrew consent due to tolerability	6	Schedule Conflict	Adverse Event
HYD3002-2191A-2054013	Patient refused to come into office for follow-up visit	9	Withdrew Consent	Lack of Efficacy
HYD3002-2142A-2082010	The subject felt that she could not tolerate the product	5	Withdrew Consent	Adverse Event
HYD3002-2681A-2099008	Patient withdrew consent after first dose of study medication	9	Withdrew Consent	Lack of Efficacy
HYD3002-2381A-2076009	Subject had titrated up to HYD 60 mg QD & wasn't getting much relief. She didn't want to continue up titrating & taking "addictive" medication	5	Withdrew Consent	Lack of Efficacy
HYD3002-1194A-2037013	Withdrew Consent due to Personal Reason	9	Withdrew Consent	Lack of Efficacy
HYD3002-1194A-2037067	Withdrew Consent	9	Withdrew Consent	Lack of Efficacy
HYD3002-2043A-2075019	Subject wished to no longer participate in the study due to lack of time. No visit 3 took place	8	Schedule Conflict	Lack of Efficacy
HYD3002-2142A-2082010	Patient felt that she could not tolerate the product	5	Withdrew Consent	Adverse Event
HYD3002-2107A-2046017	Consent withdrawn due to lack of tolerability	3	Withdrew Consent	Adverse Event
HYD2002-2107A-2046026	Lack of efficacy	3	Withdrew Consent	Lack of efficacy

USUBID	DSTERM	Last Pain Score	Subject's choice subcategory	Last Pain Score
HYD3002-1194A-2037058	Withdrew Consent due to Personal Reasons	8	Withdrew Consent	Lack of efficacy
HYD3002-1194A-2037054	Withdrew Consent	6	Withdrew Consent	Adverse Event (Subject had AEs of HA and Somnolence were Ongoing at D/C. Latter AE possibly related to study drug per CSR
HYD3002-1194A-2037069	Withdrew consent	4	Withdrew Consent	Adverse Event (Subject had AEs of abdominal pain, constipation, Disturbance in attention& dry mouth that were ongoing at D/C. Latter two AEs probably related per CSR
HYD3002-2188A-2002003	Withdrew Consent	4	Withdrew Consent	Adverse Event (Subject had AE of dry mouth that was ongoing at D/C and probably related to study drug per CSR
HYD3002-2133A-2055013	Subject does not want to continue	Missing	Withdrew consent	Lack of efficacy
HYD3002-2198A-2034085	Subject stopped taking IP	5	Withdrew consent	Adverse event (Subject had change in hearing sensitivity nausea & HA that was ongoing at D/C. 1st AE was ASHA and possibly related to study drug per CSR

Source: NDA 206627, Response to Clinical IR, Table 1, pp.. 1-8/32

The results of my analysis showed that during the open-label run-in period, 13 subjects discontinued from the study due to lack of efficacy and nine subjects discontinued from the study due to adverse events.

The remaining subjects were discontinued as follows:

- Moving [n=4]
- Work or schedule conflict [n=8]
- A family issue such as death or illness [n=1]

- Withdrawal of consent due to personal reasons and subject's last pain score before discontinuation from was <8 and no recent (within 48 hrs) or ongoing AE{s) [n=6]
- Withdrawal of consent due to other reasons (e.g., didn't want to continue taking opioid, no longer interested, subject's choice, refusal to do audiology test) and subject's last pain score before discontinuation was <8 and no recent (within 48 hours) or ongoing AEs [n=4]
- Withdrawal of consent with no other explanation and last pain score before discontinuation from study was <8 and no recent (within 48 hours) or ongoing AE(s) [n=5]

Of note, one subject (HYD3002-2054A-2022003 was discontinued from study during the open-label, run-period because they were unable to washout of prohibited medication (DS TERM) however they were categorized under the subject's choice subcategory as withdrawing consent. This subject did not withdraw consent but failed to meet one of the criteria for the double-blind period (able to washout from prohibited medications).

In the response to the IR, the Applicant also submitted a summary table for subjects who discontinued study drug and study simultaneously during the double-blind period due to the reason of "subject's choice".

The Applicant's response follows:

> Table 3 shows that during the double-blind period in study HYD3002, 30 subjects discontinued study drug due to the reason of "subject's choice", 16 in the HYD group and 14 in the placebo group. The investigator was required to provide additional details in a free text field captured in the database. Based on these additional details, Purdue has categorized the reasons of "subject choice" into 7 subcategories which are summarized in Table 3. Please note, 3 additional subjects are included. These 3 subjects discontinued the study drug but continued in the study off study drug as "retained dropout". A subject listing is provided in Table 4 that includes the information contained within the DSTERM variable, subcategory assignment, last pain score, last observed AE, and drug accountability issues.

Table 3 Number of HYD3002 Subjects Who Discontinued Study Drug During Double-blind Period Due to the Reason of "Subject's Choice" by Subcategory and by Treatment

	Total	HYD	Placebo
Number of subjects in any sub-category	30	16	14
Withdrew consent	11	7	4
Family matter	4	2	2
Moved away	4	1	3
Schedule conflict	3	2	1
Out of town	3	2	1
Transportation	3	1	2
Wanted to return to prior pain medication	2	1	1

The primary efficacy analysis for the weekly "average pain in the last 24 hours" scores employed a treatment of missing data that depended on a subject's reason for study drug discontinuation.

To ensure an accurate assessment of the subject status at the end of the study, a blinded adjudication review of all early discontinuations occurring during the double-blind period was conducted by an independent third party not involved in the conduct of the study (see section 9.1.2 of HYD3002 protocol). In particular, the adjudication committee reviewed all cases designated as "Subject's Choice" to assess whether they should be re-classified as "adverse event" or "lack of efficacy". In all but 4 cases ……..the adjudication committee agreed with the reason entered by the investigator on the CRF. The primary efficacy analysis was based on the adjudicated reason rather than the CRF reason.

I performed an additional review of the Applicant's data involving subjects who discontinued study drug and study simultaneously during the double-blind period due to the reason of "subject's choice". The discontinuations due to "subject's choice" were reviewed using CRFs and data provided by the Applicant. Table 12 summarizes the results of this analysis.

Table 12: Discontinuations during the Double-Blind Period due to "Subject's Choice"

USUBID	Arm	DSTERM	Last Pain Score	Subject's choice subcategory	Subject's choice subcategory (Reviewer's Term)
HYD3002-1194A-2037005	Placebo	Withdrew consent	4	Withdrew consent	Adverse Event "Mild" Asthma AE started during DB
HYD3002-2164A-2058008	Placebo	Stopped taking med due to misplaced luggage by airline and was later recovered	5	Withdrew consent	Adverse Event (Had Nausea Constipation & Tinnitus, started in Run-In & ongoing into DB ,deemed related to study drug per CSR
HYD3002-2106A-2048012	Placebo	Patient has been experiencing anxiety and does not want to continue	6	Withdrew Consent	Adverse Events Changes in hearing started last day of run-in period and ongoing into DB until D/C, GI virus & diarrhea,
HYD3002-2191A-2054019	Placebo	Patient lived about an hour away from clinic and chose not to return for remaining study visits	6	Transportation	Adverse Events – Tachycardia and changes in hearing sensitivity
HYD3002-2063A-2007006	Placebo	Subject moving out of state	8	Moved away	Lack of efficacy
HYD3002-2197A-2086001	Placebo	Subject wanted to resume his old medication therapy	7	Wanted to return to prior pain medication	Lack of efficacy
HYD3002-0523A-2028020	HYD 80 mg	Subject walked out of unscheduled visit between visits 7-8. He left all IP and diary at the site. Later stating he felt accused (when his IP count was not 100% complaint)	1	Withdrew consent	Suspected diversion
HYD3002-1237A-2039008	HYD 20 mg	Withdrew consent	3	Withdrew consent	Adverse events (Somnolence, Nausea & HA that were deemed possibly

					related to study drug in CSR
HYD3002-0608A-2012003	HYD 120 mg	Subject withdrew consent due to schedule	9	Schedule conflict	Lack of efficacy

Source: NDA 206627 HYSINGLA ER, 2nd IR Response, Tables 3 and 4, pp. 8-12

My additional review showed that during the double-blind period for those subjects who were reported to have discontinued due to "subject's choice"; Table 10 shows two placebo subjects discontinued due to lack of efficacy and four placebo subjects were discontinued due to adverse events. The remaining placebo subjects were discontinued as follows:

- Family matter= n=2
- Moving =n=2
- Schedule conflict = n=1
- Transportation issues = n=1
- Going out of town n=1
- Withdrew consent due subject's doctor would not allow them to participate, n=1

With respect to HYD subjects, Table 12 again shows one HYD was discontinued due to suspected diversion; one subject was discontinued due to AEs) and two HYD subjects were discontinued due to lack of efficacy. The remaining HYD subjects were discontinued due to the following reasons:

- Family matter: n=2
- Going out of town: n=2
- Schedule conflict: n =1
- Transportation issues : n=1
- Moving: n=1
- Withdrawal of consent due to personal reasons and subject's last pain score before discontinuation from was <8 and no recent (within 48 hrs.) or ongoing AE{s); n=1
- Withdrawal of consent due to other reasons (e.g., wants to enter another study, does not want to continue) and subject's last pain score before discontinuation was <8 and no recent (within 48 hrs.) or ongoing AE (s) deemed relevant to study drug; n=3
- Withdrawal of consent (with no other explanation) and last pain score before discontinuation from study was <8 and no recent (within 48 hours) or ongoing AE(s); n=2

With respect to confirmed or suspected diversion, incidences of 10% or more in excess of the maximum prescribed HYD dose or rescue medication (i.e. immediate-release hydrocodone used or unaccounted was termed diversion. Diversion was also to be reported by the investigator if diversion of any amount was suspected.

For study HYD3002, the Applicant in response to another Division IR provided a summary table for subjects who were discontinued during the run-in period and double-blind periods due to confirmed or suspected diversion ((Table 41) located in the Appendix of this review. I was able to confirm the Applicant's results that 7% of subjects during the run-in period were discontinued due to confirmed or suspected diversion.

Table 13 displays a revised summary table showing subject disposition and reasons for discontinuation during the run-in period.

Table 13: Revised Summary Table Showing Subject Disposition and Reasons for Discontinuation from Study Drug during Run-in Period

RUN- IN PERIOD (N=905)			
	Non-Randomized (N=312)	**Randomized (NN=593)**	**Overall (NN=905)**
Completed Period on Study Drug n (%)	**_____**	**592 (100)**	**592 (65)**
Discontinued Study Drug All Cases n (%)	**312 (100)**	**1 (<1)**	**313 (35)**
Adverse Event	103 (33)	0	103 (11)
ASHA-Related Event	3 (1)	0	3 (<1)
Subject's Choice	28 (9)	0	29(3)
Lost to Follow-Up	19 (6)	0	19 (2)
Lack of Therapeutic Effect	58 (19)	0	58 (6)
Confirmed or Suspected Diversion	23 (7)	0	23 (3)
Administrative	20	1 (<1)	21 (2)
Did Not Qualify for Double-Blind Period	60 (19)	_____	60 (7)

Source: NDA 202627, CSR, Study HYD3002, Table 18 pg. 177 of 6082 and Applicant Response to IR #2

The results of the revised summary table shows that during the open-label period, the majority of subjects were discontinued due to AEs (11%), followed by did not qualify for double-blind period (7%) and lack of therapeutic effect (6%).

Table 14 displays a revised summary table showing subject disposition and reasons for discontinuation form study drug and study simultaneously during the double-blind period.

Table 14: **Revised Summary Table Showing Subject Disposition and Reasons for Discontinuation from Study Drug and Study Simultaneously during Double-Blind Period**

DOUBLE- BLIND PERIOD (NN= 588)			
	Placebo (NN=292)	**HYD (NN=296)**	**Overall (NN=588)**
Discontinued Study Drug and Study Simultaneously n (%)	51 (17)	46 (16)	97 (17)
Adverse Event	10 (3)	9 (3)	19 (3)
ASHA-Related Event	0	1 (<1)	1 (<1)
Subject's Choice	6 (2)	12 (4)	18 (3)
Lost to Follow-Up	3 (1)	5 (2)	8 (2)
Lack of Therapeutic Effect	24 (8)	7 (3)	31 (5)
Confirmed or Suspected Diversion	3 (1)	3 (1)	6 (1)
Administrative	6 (2)	8 (3)	14 (2)

Source: NDA 202627, CSR, Study HYD3002, Table 18 pg. 177 of 6082 and Applicant Response to IR #2

The Applicant reports that of the 593 subjects randomized into the double-blind treatment period, 588 subjects received double-blind treatments (292 randomized to placebo and 296 randomized to HYD) and 4 subjects did not (subjects 2047002, 2049010, 2082008, and 2093009).

During the double-blind period, similar percentages of HYD and placebo subjects discontinued from study drug and study during the double-blind period due to AEs (3% versus 3% respectively). As expected a higher percentage of placebo subjects compared to HYD subjects discontinued study and study drug during the double-blind period (8% versus 3% respectively). Similar as in the run-in period, I was able to confirm the Applicant's results that showed during the double-blind period 1% of HYD subjects were discontinued from study drug and study simultaneously due to confirmed or suspected diversion.

According to the Applicant, subjects who discontinued study drug (for whatever reason) were encouraged to stay in study to complete all remaining scheduled double-blind visits and procedures. Subjects must have completed a study drug discontinuation visit and then return to their double-blind visit schedule. After study drug discontinuations, subjects were converted to a pain regimen deemed medically appropriate by the study investigator.

Demographics
Table 15 summarizes the demographics and baseline characteristics of the safety population

Table 15: Demographics of Safety Population

Variable	Non-randomized (N=312)	Randomized			Total (N=905)
		Placebo[a] (N=292)	HYD (N=296)	Overall (N=588)	
Age (years)					
n	312	292	296	588	905
Mean (SD)	47.3 (13.40)	47.9 (13.23)	49.2 (13.51)	48.6 (13.38)	48.2 (13.43
Median	47.0	49.0	50.0	50.0	49.0
Min, Max	20, 81	18, 83	18, 81	18, 83	18, 83
Age Group, n (%)					
< 65 years	275 (88)	261 (89)	260 (88)	521 (89)	798 (88)
18 - 39 years	100 (32)	78 (27)	73 (25)	151 (26)	251 (28)
40 - 64 years	175 (56)	183 (63)	187 (63)	370 (63)	547 (60)
≥ 65 years	37 (12)	31 (11)	36 (12)	67 (11)	107 (12)
65 - 74 years	29 (9)	29 (10)	29 (10)	58 (10)	89 (10)
≥ 75 years	8 (3)	2 (1)	7 (2)	9 (2)	18 (2)
Missing	0	0	0	0	0
Sex, n (%)					
Male	121 (39)	126 (43)	124 (42)	250 (43)	373 (41)
Female	191 (61)	166 (57)	172 (58)	338 (57)	532 (59)
Missing	0	0	0	0	0
Race, n (%)					
White	234 (75)	207 (71)	195 (66)	402 (68)	640 (71)
Black or African American	63 (20)	51 (17)	67 (23)	118 (20)	182 (20)
Native Hawaiian or other Pacific Islander	0	0	0	0	0
Asian	5 (2)	29 (10)	25 (8)	54 (9)	59 (7)
American Indian or Alaska Native	3 (1)	1 (< 1)	2 (1)	3 (1)	6 (1)
Other	7 (2)	4 (1)	7 (2)	11 (2)	18 (2)
Missing	0	0	0	0	0
Ethnicity, n (%)					
Hispanic or Latino	37 (12)	45 (15)	58 (20)	103 (18)	140 (15)
Not Hispanic or Latino	275 (88)	247 (85)	238 (80)	485 (82)	765 (85)
Missing	0	0	0	0	0
Baseline Weight (kg)					
n	312	292	296	588	905
Mean (SD)	87.10 (23.423)	90.12 (23.383)	89.77 (22.695)	89.94 (23.020)	88.94 (23.191)
Median	83.90	87.45	88.50	87.75	86.20
Min, Max	45.3, 162.4	41.1, 172.4	45.4, 172.5	41.1, 172.5	41.1, 172.5
Body Mass Index (kg/m^2)					
n	312	292	296	588	905
Mean (SD)	30.483 (7.6596)	31.558 (7.7681)	31.191 (7.6854)	31.373 (7.7222)	31.049 (7.7010)
Median	29.470	31.000	29.890	30.435	30.040
Min, Max	16.26, 61.88	13.72, 57.80	16.56, 64.92	13.72, 64.92	13.72, 64.92
Opioid Experienced[b], n (%)					
Experienced	169 (54)	128 (44)	131 (44)	259 (44)	431 (48)
Naïve	143 (46)	164 (56)	165 (56)	329 (56)	474 (52)
Time since First Diagnosis of Disease/Medical Condition that Qualified Subject for the Study (Months)					
n	312	292	296	588	905
Mean (SD)	132.26 (115.994)	115.96 (108.718)	112.66 (106.241)	114.30 (107.399)	120.42 (110.494)
Median	95.97	79.20	77.57	79.02	82.77
Min, Max	5.8, 641.5	4.1, 680.3	4.2, 640.9	4.1, 680.3	4.1, 680.3

Source: NDA 202627, HYD3002 Clinical Study Report (CSR), Table 20, Pg.183 of 6082

Overall, demographic and baseline characteristics for nonrandomized subjects and randomized subjects are comparable. .

Subjects in the randomized safety population (full analysis population) were reported to have the following demographics:

- The mean age of subjects was 48.6 years
- 57% of the population was female versus 43% male
- 68% of subjects were White, 20% were Black, 8% were Asian and 2% - Other
- 82% of subjects were Non-Hispanic or Latino and;
- The mean BMI of subjects was 31kg/m^2

The demographics of the subjects randomized to the HYD treatment group were comparable to those subjects randomized to the placebo treatment group except for race where 22% of Black subjects were in the HYD group compared to 17% in the placebo.

Screening/Baseline disease characteristics

Overall, subjects in the randomized safety population (full analysis population) were reported to have the following screening and baseline disease characteristics:

- 56% of subjects were opioid-naïve versus 44% opioid-experienced
- The mean time since first diagnosis of disease/medical condition (i.e. LBP) was 114 months or 4.7 years
- The baseline mean average pain over last 14 days reported before the screening visit 7.2 on an 11-point NRS scale
- The baseline mean average baseline over last 24 hours (defined as the “average pain over the last 24 hours” scores obtained from 2 consecutive days of the baseline period that qualified the subject for entry into run-in period) was 7.4 on an 11-point NRS scale

The screening and baseline disease characteristics of the subjects randomized to the HYD treatment group were comparable to those subjects randomized to the placebo treatment group

Protocol Violations

Major protocol violations in the study included: deviations from inclusion/exclusion criteria, deviations from pain score criteria prior to entering the run-in period, deviations from randomization criteria, study drug dosing violations, specific abuse and/or diversion criteria met, ECG violations, noncompliance with supplemental med, and use of prohibited concomitant medication affecting safety and/or efficacy

Table 16 displays the major protocol violations for the full analysis population.

Table 16: Summary of Major Protocol Violations by Treatment (Full Analysis Population)

Protocol Deviations	Placebo* (N=292) n (%)	HYD (N=296) n (%)	Total (N=588) n (%)
Number of Subjects with at Least One Major Protocol Deviation	151 (52)	155 (52)	306 (52)
Number of Subjects with at Least One Major Protocol Deviation which exclude the subjects from per-protocol population	22 (8)	31 (10)	53 (9)
Number of Subjects with at Least One Major Programmed Protocol Deviation	131 (45)	132 (45)	263 (45)
Abuse and/or Diversion	1 (< 1)	0	1 (< 1)
Subject with suspected/confirmed diversion and was not discontinued from the study	1 (< 1)	0	1 (< 1)
Inclusion or Exclusion Criteria Not Met	17 (6)	9 (3)	26 (4)
Baseline Air-bone gaps of >10 dB at any bone conduction frequency	7 (2)	4 (1)	11 (2)
"Average pain over the last 14 days" score <5 at the screening visit	5 (2)	4 (1)	9 (2)
Baseline Abnormal tympanograms	3 (1)	2 (1)	5 (1)
Baseline Threshold asymmetry >20 dB at all test frequency from 250 Hz through 8000 Hz	2 (1)	0	2 (< 1)
Prohibited Medications	60 (21)	72 (24)	132 (22)
Prohibited Concomitant Opioid Analgesic Taken During the Study**	54 (18)	61 (21)	115 (20)

Protocol Deviations	Placebo* (N=292) n (%)	HYD (N=296) n (%)	Total (N=588) n (%)
Prohibited Medications (continued)			
Prohibited Concomitant Nonopioid Analgesic Taken During the Study***	9 (3)	12 (4)	21 (4)
Prohibited Concomitant Nonopioid Analgesic Taken During the Double-blind Period	8 (3)	11 (4)	19 (3)
Prohibited Concomitant Opioid Analgesic Taken During the Double-blind Period	3 (1)	3 (1)	6 (1)
Study Drug Dosing Violation	46 (16)	47 (16)	93 (16)
Study Drug IWRS Compliance <80% or >=110% in Double-blind Period	34 (12)	37 (13)	71 (12)
Subject began HYD treatment on a higher HYD dose than what is permitted by the protocol	7 (2)	6 (2)	13 (2)
Subject was down titrated during the Run-in Period	7 (2)	4 (1)	11 (2)
Subject on <= HYD 60 mg and who up titrated to the next dose level in less than 72 hours on their current dose	5 (2)	3 (1)	8 (1)
Subject on HYD 80 mg and who up titrated to the next dose level in less than 120 hours on their current dose	0	1 (< 1)	1 (< 1)
Supplemental Medication Dosing Violation	17 (6)	7 (2)	24 (4)
Supplemental Analgesic Medication Compliance >=110% in Double-blind Period	17 (6)	7 (2)	24 (4)
Violation of Randomization Criteria	30 (10)	30 (10)	60 (10)
Pain Score Violation at Randomization	22 (8)	29 (10)	51 (9)

Source: HYD3002 Clinical Study Report (CSR), Table 14.1.2.3, pg. 449 of 6082

Results in the Applicant's table shows that 52% of subjects had ≥ 1 major protocol violation during the study. Both HYD and placebo treatment groups experienced the same percentage of subjects with at least one major protocol violation (both 52%). The

most frequently observed protocol violation among treatment groups was taking prohibited medications (24% HYD vs. 21% placebo). The percentage of subjects who took prohibited opioid analgesics during the study was 21% for HYD subjects compared to 18% for placebo subjects. However, during the double-blind period 1% of subjects in both HYD and placebo treatment groups respectively, took prohibited concomitant opioid analgesics.

Primary Efficacy Results

Table 17 shows the Applicant's results for "average pain over the last 24 hours" scores at Baseline and week 12 of the double-blind period and the results of the primary efficacy analysis using a mixed effects model with repeated measures (MMRM) with a pattern mixture model (PMM) approach to account for missing values based on the adjudicated reason for discontinuation. A PMM framework was used to estimate the week 12 treatment difference. Only data observed while subjects were exposed to double-blind study drug were used in the MMRM model.

Table 17: Summary of the "Average Pain over the Last 24 Hours" Scores at Baseline and Week 12 of the Double-blind Period Using Pattern Mixture Model: Full Analysis Population

Study Period/Week Mean Pain Intensity	HYD (n=296)	Placebo (n=292)
Baseline		
N	296	292
Mean (SD)	7.4 (1.13)	7.4 (1.19)
Double-Blind Week 12		
N	218	199
Mean (SD)	3.3 (1.93)	3.7 (2.04)
Repeated Measures Analysis/Least Squares Means (SE) at DB Week 12 from PMM		
LS Mean	3.70 (0.128)	4.23 (0.126)
Difference in LS means from Placebo	-0.53 (0.180)	
P value vs. PBO	0.0016	
95% CI for difference from PBO	(-0.882, -0.178)	

Source: NDA 202627, HYD3002 Clinical Study Report (CSR), Table 26, Pg.196 of 6082

The Applicant's results show that the mean (SD) "average pain over the last 24 hours" scores at baseline were 7.4 (1.13) and 7.4 (1.19) for subjects in the HYD treatment group and placebo treatment group respectively. At week 12, mean (SD) scores were 3.3 (1.93) for the HYD treatment group and 3.7 (2.04) for the placebo treatment group. The primary efficacy analysis, using the MMRM with a PMM approach to account for missing values, estimated the weighted average of least square means for the week 12 "average pain over the last 24 hours" scores to be 3.70 (0.128) for the HYD treatment

group and 4.23 (0.126) for the placebo treatment group, with a HYD minus placebo difference of -0.53 (95% CI, -0.882 to -0.178). This treatment difference was reported to be statistically significant (P = .0016) for the HYD treatment group.

Secondary Efficacy Results
The Applicant did not adjust for the analysis of multiple secondary and exploratory endpoints; therefore all p-values calculated by the Applicant below are only descriptive in nature

Patient Global Impression of Change (PGIC)
The results of PGIC categories at End-of-Study (EOS) for the full analysis population are summarized in Table 18.

Table 18: Summary of Patient Global Impression of Change (PGIC) at End-of-study (EOS) Drug: Full Analysis Population

Category, n (%)	Placebo[a] (N=292)	HYD (N=296)
Total number of subjects responding (n)	267	283
1. Very much improved	49 (18)	61 (22)
2. Much improved	81 (30)	112 (40)
3. Minimally improved	58 (22)	55 (19)
4. No change	59 (22)	44 (16)
5. Minimally worse	12 (4)	10 (4)
6. Much worse	8 (3)	1 (< 1)
7. Very much worse	0	0
Very much improved or much improved	130 (49)	173 (61)
No improvement[b]	137 (51)	110 (39)
P value comparing HYD to placebo[c]		0.0036

Source: NDA 202627, HYD3002 Clinical Study Report (CSR), Table 30, Pg.203 of 6082

The Applicant results show 61% of subjects in the HYD treatment group compared to 49% of subjects in the placebo group reported that their LBP was very much improved or much improved from baseline in PGIC of LBP. This improvement was reported as statistically significant (p-value=0.0036).

Responder Analyses
Responder analyses for subjects with ≥ 30% and ≥ 50% reduction from baseline in "average pain over the last 24 hours" scores for the full analysis population are summarized in Table 19.

Table 19: Subjects with ≥ 30% and ≥ 50% Reduction from Baseline in "Average Pain Over the Last 24 Hours" Scores (Responder Analyses): Full Analysis Population

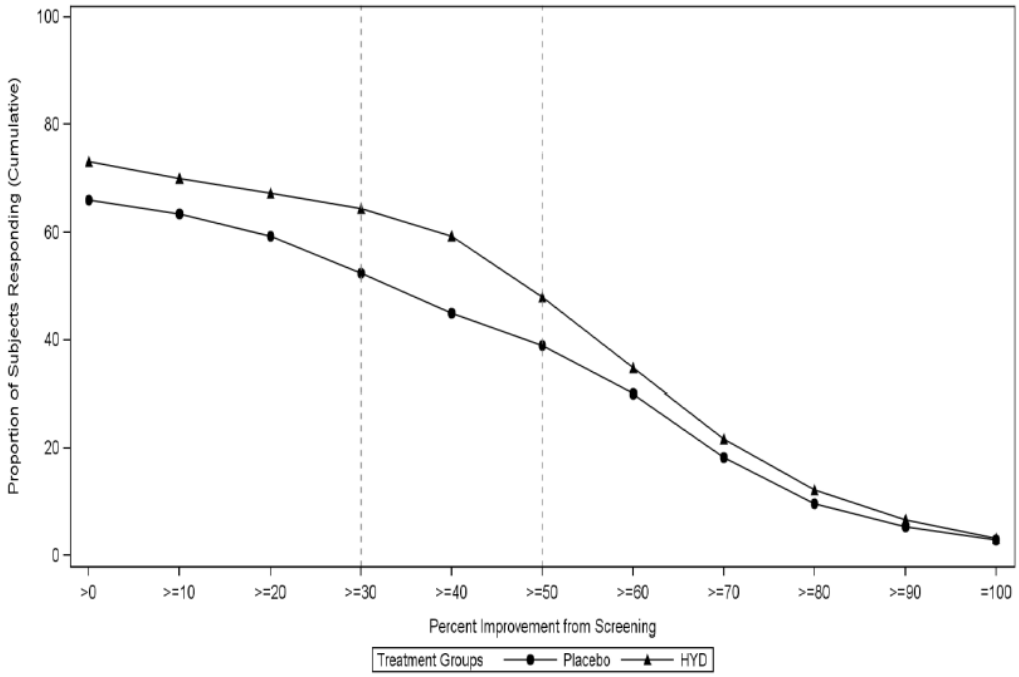
Responder Analysis	Placebo[a] (N=292)	HYD (N=296)
n	280	285
No. of Subjects with ≥ 30% Reduction	147	184
% of Subjects with ≥ 30% Reduction	53	65
Between Group Comparison: *P* value vs Placebo		0.0033
Odds Ratio (95% CI)		1.679 (1.189, 2.370)
n	280	285
No. of Subjects with ≥ 50% Reduction	109	137
% of Subjects with ≥ 50% Reduction	39	48
Between Group Comparison: *P* value vs Placebo		0.0225
Odds Ratio (95% CI)		1.503 (1.059, 2.132)

Source: NDA 202627, HYD3002 Clinical Study Report (CSR), Table 31, Pg.204 of 6082

The Applicant reports that statistically significant differences were seen in the HYD treatment group when compared to the placebo treatment group for the proportion of subjects with a ≥30% reduction in pain (P = .0033 and ≥ 50% reduction in pain (P = 0.0225).

Figure 3 displays the responder curve for the full analysis population

Figure 3: Responder Curve for Full Analysis Population



Source: NDA 202627, HYD3002 Clinical Study Report (CSR), Figure 5, pg. 205/6082

The Applicant's results for the proportion of subjects who experienced ≥30% improvement in pain shows 65% of subjects in the HYD treatment group experienced ≥30% improvement in pain compared to 48%% of placebo patients. There is an appreciable separation of curves between HYD and placebo treatment groups at the ≥30% responder level

Medical Outcome Study Sleep Scale - Revised (MOS Sleep-R) Disturbance Subscale
The Applicant's results of the analysis of the sleep disturbance subscale showed that from baseline to the end of the double-blind period (Week 12) there was no significant difference between HYD and placebo for the sleep disturbance subscale score [Difference from placebo 0.41 (0.431); P value vs placebo 0.3462; 95% CI for difference from placebo (-0.440, 1.252)].

Other "Exploratory" Efficacy Analyses

Supplemental Pain Medication
Table 20 shows the use of supplemental pain medication (i.e. immediate-release oxycodone 5 mg tablet) for LBP during the double-blind period for the full analysis population.

Table 20: Supplemental Pain Medication Use for Low Back Pain during Double-blind Period - Full Analysis Population

	Placebo[a] (N=292)	HYD (N=296)
No supplemental analgesic medication use, n (%)	50 (17)	64 (22)
95% CI of the proportion (%)[b]	(13.0, 21.9)	(17.1, 26.8)
Difference from placebo		0.04
95% CI for difference from placebo		(-0.02, 0.11)
P value[c] vs placebo		0.1677

Source: NDA 202627, HYD3002 Clinical Study Report (CSR), Table 33, pg. 209/6082

The Applicant's results show that during the double-blind period the percentage of subjects that required no supplemental analgesic medication use was 22% for HYD-treated subjects compared to 17% for placebo-treated subjects and this difference was not statistically significant.

The Applicant also conducted an analysis of rescue medication use among individual dose strengths during the double-blind period. Table 21 summarizes the use of rescue medication during the double-period for subjects randomized to placebo.

Table 21: Summary of Mean Daily Number of Immediate-Release Oxycodone Tablets during the Double-blind Period by Randomized Dose-Groups (Full Analysis Population)

	Randomized to Placebo					
	20 mg (N=62)	40 mg (N=86)	60 mg (N=59)	80 mg (N=45)	120 mg (N=40)	Total (N=292)
Mean daily number of tablets for all subjects						
Week 1						
n	62	86	59	45	40	292
Mean (SD)	0.14 (0.394)	0.36 (0.566)	0.62 (0.706)	1.09 (1.259)	1.80 (1.631)	0.67 (1.055)
Median	0.00	0.00	0.29	0.71	1.29	0.14
Min, Max	0.0, 2.4	0.0, 2.0	0.0, 3.0	0.0, 5.4	0.0, 6.0	0.0, 6.0
95% CI for Mean	(0.04, 0.24)	(0.24, 0.48)	(0.44, 0.80)	(0.72, 1.45)	(1.30, 2.31)	(0.55, 0.80)
Week 2						
n	62	86	59	45	40	292
Mean (SD)	0.18 (0.398)	0.40 (0.621)	1.00 (1.047)	1.33 (1.230)	2.31 (2.028)	0.88 (1.277)
Median	0.00	0.07	0.57	1.14	1.71	0.29
Min, Max	0.0, 1.7	0.0, 2.4	0.0, 3.6	0.0, 4.0	0.0, 6.6	0.0, 6.6
95% CI for Mean	(0.08, 0.28)	(0.27, 0.53)	(0.73, 1.27)	(0.97, 1.69)	(1.68, 2.94)	(0.73, 1.03)
Weeks 3-12						
n	62	86	59	45	40	292
Mean (SD)	0.18 (0.413)	0.37 (0.544)	0.92 (0.982)	1.12 (1.279)	1.79 (1.810)	0.75 (1.134)
Median	0.03	0.09	0.46	0.61	1.16	0.13
Min, Max	0.0, 2.0	0.0, 2.0	0.0, 2.9	0.0, 4.0	0.0, 5.7	0.0, 5.7
95% CI for Mean	(0.08, 0.28)	(0.26, 0.49)	(0.67, 1.17)	(0.75, 1.50)	(1.23, 2.35)	(0.62, 0.88)
Overall (Weeks 1-12)						
n	62	86	59	45	40	292
Mean (SD)	0.18 (0.401)	0.44 (0.573)	0.99 (0.912)	1.45 (1.373)	2.30 (1.755)	0.90 (1.218)
Median	0.04	0.13	0.60	1.04	2.36	0.34
Min, Max	0.0, 2.0	0.0, 2.1	0.0, 2.7	0.0, 5.4	0.0, 5.8	0.0, 5.8
95% CI for Mean	(0.08, 0.28)	(0.32, 0.56)	(0.76, 1.23)	(1.05, 1.85)	(1.75, 2.84)	(0.77, 1.04)

Source: NDA 202627, HYD3002 Clinical Study Report, Table 14.2.6.2.2, pp. 1096-1096/6082

Overall, for subjects randomized to placebo during the double-blind period and were previously taking 120 mg HYD; the mean daily number of IR oxycodone tablets taken was 2.3 tablets.

Table 22 summarizes the use of rescue medication during the double-period for subjects randomized to HYD dosage groups

Table 22: Summary of Mean Daily Number of Immediate-Release Oxycodone Tablets during the Double-blind Period by Randomized Dose-Groups (Full Analysis Population)

	Randomized to HYD					
	20 mg (N=63)	40 mg (N=88)	60 mg (N=55)	80 mg (N=48)	120 mg (N=42)	Total (N=296)
Mean daily number of tablets for all subjects						
Week 1						
n	63	88	55	48	42	296
Mean (SD)	0.12 (0.285)	0.29 (0.579)	0.41 (0.687)	0.84 (1.138)	1.81 (1.555)	0.58 (1.024)
Median	0.00	0.00	0.14	0.29	1.79	0.00
Min, Max	0.0, 1.4	0.0, 3.4	0.0, 2.9	0.0, 4.4	0.0, 5.6	0.0, 5.6
95% CI for Mean	(0.05, 0.19)	(0.17, 0.41)	(0.23, 0.59)	(0.52, 1.16)	(1.34, 2.28)	(0.47, 0.70)
Week 2						
n	63	88	55	48	42	296
Mean (SD)	0.12 (0.344)	0.31 (0.621)	0.53 (0.847)	0.87 (1.127)	1.80 (1.623)	0.61 (1.062)
Median	0.00	0.00	0.00	0.36	1.57	0.00
Min, Max	0.0, 2.3	0.0, 3.1	0.0, 3.0	0.0, 4.0	0.0, 5.7	0.0, 5.7
95% CI for Mean	(0.04, 0.21)	(0.18, 0.44)	(0.31, 0.76)	(0.55, 1.19)	(1.31, 2.29)	(0.49, 0.73)
Weeks 3-12						
n	63	88	55	48	42	296
Mean (SD)	0.13 (0.261)	0.30 (0.541)	0.49 (0.839)	0.81 (1.067)	1.66 (1.712)	0.58 (1.030)
Median	0.01	0.05	0.10	0.42	1.14	0.07
Min, Max	0.0, 1.2	0.0, 2.2	0.0, 3.5	0.0, 3.7	0.0, 5.7	0.0, 5.7
95% CI for Mean	(0.07, 0.19)	(0.19, 0.42)	(0.26, 0.71)	(0.51, 1.12)	(1.14, 2.18)	(0.46, 0.69)
Overall (Weeks 1-12)						
n	63	88	55	48	42	296
Mean (SD)	0.13 (0.257)	0.31 (0.523)	0.54 (0.746)	0.93 (1.098)	2.14 (1.704)	0.67 (1.102)
Median	0.02	0.07	0.13	0.51	1.92	0.12
Min, Max	0.0, 1.2	0.0, 2.4	0.0, 3.2	0.0, 3.7	0.0, 5.6	0.0, 5.6
95% CI for Mean	(0.06, 0.19)	(0.20, 0.42)	(0.34, 0.74)	(0.62, 1.24)	(1.62, 2.65)	(0.55, 0.80)

Source: NDA 202627, HYD3002 Clinical Study Report, Table 14.2.6.2.2, pg. 1097- 1098/6082

For subjects randomized to the HYD 20, 40, 60, 80 and 120 mg dosage groups, the mean number of IR 5 mg oxycodone tablets used over Weeks 1-12 were approximately <1, <1, <1, 1 and 2 respectively. Overall, for subjects randomized to HYD during the double-blind period, the use of rescue medication was higher in subjects randomized to higher dose strengths.

Table 23 summarizes the Applicant's results for other "exploratory" efficacy endpoints in the double-blind period including: the Oswetry Disability Index (ODI), Brief Pain Inventory Short Form (BPI-SF), Medical Outcomes Study 36-item Short Form (SF-36), and Medical Outcomes Study Sleep Scale (MOS Sleep)

Table 23: Summary of ODI, BPI, SF-36 and MOS-Sleep during Double-blind period (Full Analysis Population)

	Placebo[a]	HYD	Difference	95% CI	
Other Efficacy Measurements	**LS mean (SE) for Week 4, 8,12**				***P* value**
ODI					
	23.60 (0.482)	22.68 (0.469)	-0.92 (0.671)	-2.238, 0.396	0.1700
BPI-SF					
Severity of pain subscale[b]	3.79 (0.103)	3.39 (0.100)	-0.40 (0.143)	-0.684, -0.123	0.0049
Pain interference[c]	2.34 (0.083)	2.30 (0.081)	-0.04 (0.115)	-0.271, 0.183	0.7031
SF-36					
Physical Component Score[d]	43.26 (0.339)	43.35 (0.327)	0.08 (0.469)	-0.839, 1.002	0.8621
Mental Component Score[e]	56.37 (0.324)	55.98 (0.312)	-0.38 (0.448)	-1.262, 0.497	0.3936
MOS					
Sleep Problem Index II	51.94 (0.314)	51.86 (0.303)	-0.08 (0.435)	-0.938, 0.770	0.8474

Source: NDA 202627, HYD3002 Clinical Study Report (CSR), Table 32, pg. 206/6082

The Applicant's results show that there was no statistically significant improvement for HYD compared to placebo for ODI, BPI – pain interference, SF-36 and MOS-Sleep scores except for the severity of the pain subscale which is consistent with the primary efficacy results. There were very small numerical trends favoring HYD for SF-36 (mental component score only) and MOS, but they do not appear to be clinically significant.

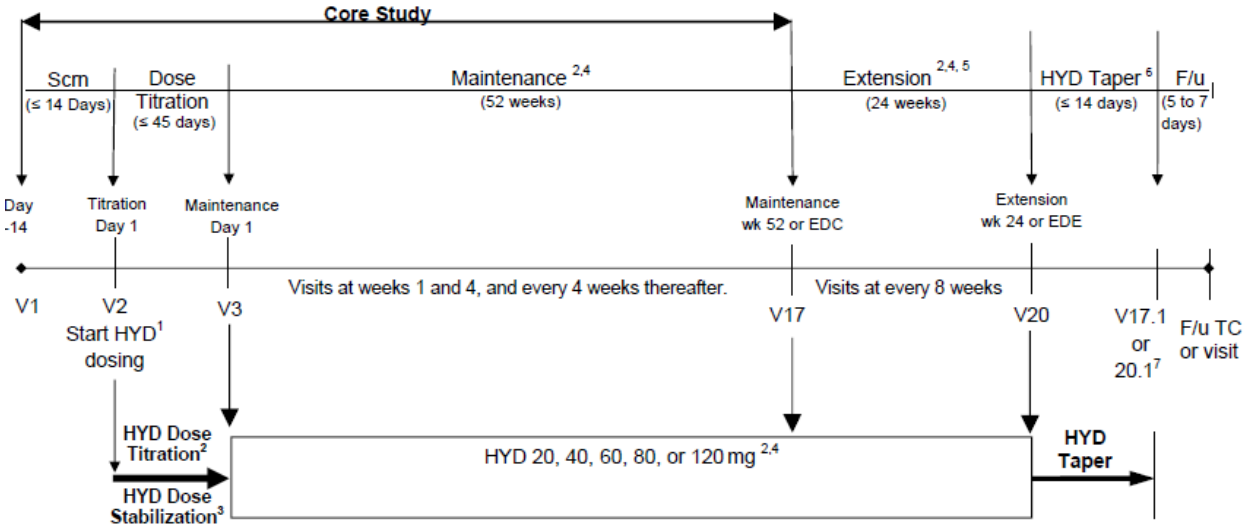
Study HYD3003

Title
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 Nonneuropathic Pain

Objective:
To characterize the long-term safety of Hydrocodone Bitartrate (HYD) tablets 20 to 120 mg once-daily in subjects with chronic nonmalignant and nonneuropathic pain.

Study design
This was to have been an open-label, multi-center, long-term safety study which is illustrated in Figure 4.

Figure 4: HYD3003 Study Design



Source: HYD3003 Protocol Amendment 3 (dated March 8, 2013), Section 9.1, Figure 1, pg. 28 of 180

Study Population
The study was to have enrolled a minimum of 1000 subjects.

Inclusion criteria: Subjects were to have met all of the following criteria to be enrolled.
1. Male and female subjects ≥ 18 years of age with moderate to severe, chronic nonmalignant and nonneuropathic pain (lasting several hours daily) as their predominant pain condition for at least 3 months prior to the screening visit;
2. If the primary pain site is low back, the pain must be related to nonmalignant and nonneuropathic conditions and without radiation or with only proximal radiation (above the knee), i.e., meeting Quebec Task Force Classification5-7 1 or 2;

3. De novo subjects with chronic nonmalignant and nonneuropathic pain that are either:
    a. Currently being controlled with a stable analgesic regimen equivalent to 0 to 120 mg/day of oxycodone with an "average pain over the last 14 days" score ≤ 4 at the screening visit, or,
    b. Currently being uncontrolled with a stable analgesic regimen equivalent to 0 to 100 mg/day of oxycodone with an "average pain over the last 14 days" score ≥ 5 at the screening visit;
4. Subjects must be on a stable analgesic regimen prior to the screening visit (visit 1) for their nonmalignant and nonneuropathic pain;
5. Subjects deemed by the investigator/medically qualified designee (must be MD or DO) to be appropriate candidates for the protocol specified, around-the-clock HYD therapeutic regimen;
6. Subjects from HYD3002 must have completed the double-blind phase either on study drug or on standard of care for chronic pain (i.e., retrieved dropout subjects). Subjects who completed the double-blind phase on study drug must also have completed the follow-up phase of the study. All subjects from HYD3002 must be deemed appropriate by the investigator/medically qualified designee (must be MD or DO) to continue receiving opioid therapies for their chronic low back pain;
7. Female subjects who are premenopausal or postmenopausal less than 1 year and who have not had surgical sterilization (i.e., tubal ligation, partial or complete hysterectomy) must have a negative serum pregnancy test, be nonlactating, and willing to use adequate and reliable contraception throughout the study (egg, barrier with additional spermicidal foam or jelly, intra-uterine device, hormonal contraception);
8. Subjects must have 3 ECGs, a minimum of 20 minutes apart, at the screening visit, with average QTcF value of the 3 tracings ≤ 470 msec;
9. Subjects who are willing and able to be compliant with the protocol, are capable of subjective evaluation (i.e. pain scores), are able to read and understand questionnaires, are willing and able to use an electronic diary, and are able to read, understand, and sign the written informed consent form;
10. Subjects willing to complete audiologic assessments at a predefined secondary location.

Exclusion Criteria: Subjects who met any of the following criteria were not to have been enrolled.

1. Subjects taking opioid analgesic(s) that is/are equivalent to > 120 mg/day of oxycodone during the 14 days prior to the screening visit (visit 1);
2. Subjects with pain with distal radiation (below the knee) with or without neurologic signs, or presumptive or confirmed compression of a spinal nerve root (i.e., Quebec Task Force Classification 3 to 6);

3. Subjects with radicular symptoms, acute compression fracture, seronegative spondyloarthropathy, cauda equina compression, fibromyalgia, reflex sympathetic dystrophy or causalgia (complex regional pain syndrome), diabetic amyotrophy, meningitis, discitis, or back pain due to secondary infection, tumor, or postherpetic neuralgia, or any neuropathic pain conditions;
4. Subjects who, in the investigator's opinion, have an underlying gastrointestinal condition or other disorder that may predispose them to obstruction;
5. Subjects with any of the following hearing-related conditions and/or who received the following therapies or medications prior to or at baseline (screening period) that would preclude an accurate assessment of hearing function:
    a. History of otologic surgery and/or pre-existing otologic or audiologic diseases/conditions (egg, asymmetric hearing loss, Meniere's disease, persistent middle ear infections, history of hearing fluctuation, autoimmune inner ear disease; perilymphatic fistula; and/or tumor of the head, neck or auditory system);
    b. History of severe or clinically significant head injury;
    c. Threshold asymmetry > 20 dB at any test frequency including all test frequencies from 250 Hz through 8000 Hz;
    d. Air-bone gaps (i.e., difference between the air-conduction and bone-conduction audiometry) of > 10 dB at any bone conduction test frequency;
    e. Abnormal tympanograms or other indications of middle ear abnormality.
    f. Unwilling or unable to avoid excessive noise exposure during the entire study period (egg, subjects with professions or hobbies that require them to be continuously exposed to loud noise without hearing protection);
    g. Any exposure to aminoglycoside during the 6 months prior to visit 1 screening (e.g. streptomycin, neomycin gentamicin, tobramycin, amikacin, kanamycin, paromomycin, netilmicin, and spectinomycin);
    h. Any exposure to DFMO (α-difluoromethylornithine) during the 6 months prior to visit 1 screening;
    i. Any exposure to chemotherapy with vincristine and vinblastine, and any exposure to platinum-based chemotherapy agents such as carboplatin, oxaliplatin and cisplatin;
    j. Any history of head and neck radiation;
6. Subjects with gout (except for subjects with gout who are controlled with diet and/or with stable suppressive treatment with uric acid reducing medication(s) and/or colchicine, not on NSAIDs or COX-2 inhibitors, and who have not had any attack within the past 2 years), pseudogout, psoriatic arthritis, active Lyme Disease, rheumatoid arthritis or other inflammatory arthritis, trochanteric bursitis, or ischial tuberosity bursitis;
7. Subjects who previously participated in an investigational hydrocodone study within 90 days prior to the first dose of study medication (except for subjects who have completed the double-blind phase of HYD3002);
8. Subjects who have used any investigational medication other than hydrocodone within 30 days prior to the first dose of study drug;

9. Subjects with any history of seizures (subjects with history of pediatric febrile seizures may participate in the study) or increase in intracranial pressure;
10. Subjects with current uncontrolled depression or other uncontrolled psychiatric disorder (subjects with controlled depression or other psychiatric disorder must be on a stable medication for ≥ 1 month prior to the screening visit (visit 1) to participate in the study);
11. Subjects with a history of alcohol, medication, or illicit drug abuse or addiction and/or history of opioid abuse or addiction at any time;
12. Subjects with a positive urine drug screen at the screening visit (visit 1) that is medically unexplainable;
13. Subjects with clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling pacemaker;
14. Subjects with unstable respiratory disease that, in the opinion of the investigator, precludes entry into this study;
15. Subjects with evidence of impaired liver function upon entry into the study (laboratory test values ≥ 3 times the upper limit of the laboratory reference (normal) range (ULN) for aspartate transaminase [AST/SGOT] or alanine transaminase [ALT/SGPT], or values > 2 times the ULN for alkaline phosphatase), or total bilirubin level > 1.5 times the ULN or, in the opinion of the investigator/medically qualified designee (must be MD or DO), liver function impairment to the extent that the subject should not participate in this study;
16. Subjects with evidence of impaired kidney function upon entry into the study (i.e., serum creatinine ≥ 2.0 mg/dL);
17. Subjects with biliary tract disease, hypothyroidism, adrenal cortical insufficiency, or any other medical condition that, in the opinion of the investigator, is inadequately treated and precludes entry into the study;
18. Subjects with history of malignancy within past 2 years, with exception of basal cell carcinoma that has been successfully treated;
19. Subjects with any condition in which opioids are contraindicated, egg, severe respiratory depression with hypoxia and/or hypercapnia, severe chronic obstructive lung disease, cor pulmonale, severe bronchial asthma, or paralytic ileus;
20. Subjects who are allergic to hydrocodone or who have a history of allergies to other opioids. This does not include subjects who have experienced common opioid side effects (e.g., nausea, constipation);
21. Subjects receiving monoamine oxidase inhibitors (MAOIs) or who have been taking MAOIs within 2 weeks of the screening visit;
22. Subjects with any medical condition that in the investigators opinion is inadequately treated and precludes entry into the study;
23. Subjects who, in the opinion of the investigator, are unsuitable to participate in this study for any other reason;
24. Subjects with an ongoing Workman's Compensation claim and/or litigation related to their pain disorder.

Treatment
All eligible patients were to have received either HYD 20, 40, 60, 80 or 120 mg (one tablet) once daily

Prior and Concomitant Therapy
Prior and concomitant therapy was to be defined as all medications (over-the-counter (OTC) and/or prescription, including analgesics), procedures, and significant nonpharmacological therapies that are used to treat the subject, including those used in response to an AE/SAE, during the time periods relevant to study conduct.

Except for potentially ototoxic medications, any medications/therapies received within 30 days of the screening visit, and all medications/therapies taken during study conduct were to have been documented.

History of potentially ototoxic medication use during the 6 months prior to screening was to have been collected at the screening visit (visit 1). These medications include:

- Macrolides - erythromycin, azithromycin, clarithromycin, dirithromycin, rokitamycin, miokamycin, and telithromycin
- Phosphodiesterase type 5 (PDE5) inhibitors - avanafil, sildenafil, tadalafil, vardenafil and udenafil
- Nonsteroidal anti-inflammatory drugs (NSAIDs) - aspirin (acetylsalicylic acid), diflunisal, salsalate, ibuprofen, naproxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin, loxoprofen, indomethacin, sulindac, etodolac, ketorolac, diclofenac, nabumetone, piroxicam, meloxicam, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, celecoxib
- Acetaminophen

Opioid analgesics: With exception of the study drug, long-acting and controlled-release opioid analgesics were to have been prohibited through the treatment phase (titration, maintenance, extension and optional HYD taper periods). Short-acting opioid analgesics were to have been permitted at the discretion of the investigator/medically qualified designee (must be MD or DO).

Concomitant use of NSAIDs, aspirin, COX 2 inhibitors, and acetaminophen:
Medications such as aspirin and other NSAIDs were to have been allowed provided that subjects do not exceed the maximum recommended daily dose. If treatment with such drugs occurs, the medication (dose, frequency, and reason for ingestion) was to have been recorded.

Concomitant use of Monoamine oxidase inhibitors (MAOI): MAOIs were to have been prohibited throughout the study.

Concomitant use of antibiotics: aminoglycoside antibiotics were to have been prohibited throughout the study. Macrolide antibiotics are permitted during the study.

Chemotherapy and radiation therapy: any use of platinum-based chemotherapy such as carboplatin, oxaliplatin and cisplatin were to have been prohibited throughout the study. Chemotherapy with vincristine and vinblastine, and radiation of the head and neck were also to have been prohibited during the course of the study. Other chemotherapy and radiation therapy was to have been allowed if treatment, in the opinion of the investigator/medically qualified designee (must be MD or DO), is not expected to substantially alter the subjects analgesic requirements.

Concomitant use of α-difluoromethylornithine (DFMO): α-difluoromethylornithine was to have been prohibited throughout the study.

Subjects who need to be treated with the medications or dosage that are prohibited for this study should be discontinued from the study.

Study Conduct
The study was to have consisted of a core study, an optional extension period, an optional HYD taper period and a follow-up period. The core study was to have consisted of three periods: screening, dose-titration and maintenance.

Core Study
Screening Period (up to 14 days)
The following information was to have been obtained and the following procedures/assessments were to have been performed for all potential subjects at the screening visit: written informed consent, medical history and conditions, demographic information, pain history and etiology, concomitant medication, vital signs, physical exam, record subject's "average pain over the last 14 days", record history of potentially ototoxic medication, record AEs, calculate oxycodone equivalence for incoming pain medication, record subject's responses to the SOAAP-R, assess subject's potential for drug abuse and/or diversion, and evaluate inclusion/exclusion criteria

- For subjects not meeting all inclusion and/or meeting any exclusion criteria, the subject was to have been considered a screening failure and the following procedures were to have been completed:
    - Discontinue the subject
    - Record reason for discontinuation
    - Contact IWRS to indicate subject is screen failure and
    - Provide each subject with post-study instructions as medically appropriate
- For subjects meeting all inclusion criteria and not meeting ANY exclusion criteria (with exception of the laboratory evaluations, audiology assessments, and ECGs), the screening visit was to have been continued with the following procedures and assessments:

- Obtain 3 ECGs, a minimum of 20 minutes apart, to determine if the subject is eligible for this study, i.e., average Fridericia-corrected QT Interval (QTcF) of 3 tracings ≤470 msec, with central ECG lab confirmation
- If the average QTcF Interval of 3 tracings is > 470 msec (based on the report from the central ECG provider), the subject will be considered a screen failure; the study site staff will contact any subject with average QTcF Interval of 3 tracings > 470 msec upon receipt of the ECG readings from the central ECG provider.
- Clinical labs (chemistry, hematology, urinalysis) and serum pregnancy for females of childbearing potential, UDS
- Dispense diary and instruct subject to begin recording "average pain over the last 24 hours" scores at 8 pm every evening to be started on Visit 1 and maintain all incoming opioid and nonopioid analgesic medications used for chronic pain
- Schedule a comprehensive audiologic assessment to occur at the audiologist's office in seven days

Dose-titration period (up to 45 days)
At visit 2, de novo subjects were to have been converted to an HYD dose based on their incoming opioid regimen as noted in Table 24. Subjects coming from HYD3002 on a stable opioid regimen (e.g., subjects who stabilized on an opioid regimen after completing HYD3002) were to have been also started on an appropriate HYD dose as described in Table 24. All other subjects from Study HYD3002 were to have been started on HYD 20 mg.

Table 24: Conversion of Incoming Opioid to HYD

Incoming Opioid	HYD Initiation
Doses equivalent to ≤ 40 mg/day of oxycodone*	HYD 20 mg*
Doses equivalent to > 40 to ≤ 60 mg/day of oxycodone	HYD 40 mg
Doses equivalent to > 60 to ≤ 80 mg/day of oxycodone	HYD 60 mg
Doses equivalent to > 80 mg/day of oxycodone	HYD 80 mg
*Subjects who are not on an opioid regimen will begin treatment with HYD 20 mg.	

Source: HYD3003 Protocol Amendment 3 (dated March 8, 2013), Table 1, pg. 26 of 160

The following key procedures and assessments were to have been performed for all eligible subjects: vital signs, review subjects diary for "average pain over the last 24 hours" scores and enter visit information in diary, record AEs, concomitant medications and nondrug therapies, subject to record his/her responses to the COMM, ABC,

Investigator to perform Addiction Behavior Checklist, Medical Outcomes Study – Sleep Revised, Brief Pain Inventory, Short form-36, Dizziness Handicap Inventory and Tinnitus Handicap Inventory; confirm the oxycodone equivalence for the subject's incoming opioid medication, dispense study drug

- If the starting dose was HYD 20 mg, 40 mg, or 60 mg, subjects were to have been dispensed the starting dose plus the next HYD dose level. If the starting dose was HYD 80 mg, subjects were to have been dispensed HYD 80 mg only
- Subject was to have to been instructed to take the first dose of HYD at the study site
- Subject was to have been instructed to take one tablet daily at approximately the same time each day
- Subject was to have recorded in their diary the following: HYD intake (date/time/amount taken), “pain right now “ scores prior to daily HYD dose and approximately 8 pm each evening the following information in the diary and "Average pain over the last 24 hours" score at approximately 8 PM every evening
- Subject was to have scheduled a telephone contact in 2-3 days for tolerability assessment

Subject was to have been considered stable on HYD dose if the following had occurred:

- Been on the same HYD dose level during ≥ 7 days
- Acceptable pain control as determined by the investigator/designee and
- Acceptable tolerability as determined by the investigator/designee’s assessment at least twice a week or every 2 to 3 days via telephone contact or clinic visit until subject is stabilized on HYD dose or discontinued from study

<u>Maintenance Period (up to 52 weeks): Visit 3 – Visit 16</u>

- Visits were to have occurred at weeks 1 and 4, and every 4 weeks thereafter during the maintenance period.
- At the investigator/designee’s discretion, subjects were to be allowed unlimited up- and down-titrations of HYD between 20 mg and 120 mg throughout this period.
- Subjects were to have returned to the clinical site for all dose titrations.
- Safety and pain score assessments were to be performed at every visit.
- In addition, the following assessments and procedures were to have been performed by subjects
    - Record in the diary, their "pain right now" scores twice daily (once immediately prior to HYD dosing and once at approximately 8 pm every evening) until visit 7, and their daily "average pain over the last 24 hours” scores (at approximately 8 PM every evening) until completion of the maintenance period or study drug discontinuation (visit 17).
- Subjects were to have been allowed any supplemental pain medication for nonmalignant and nonneuropathic pain, including short-acting opioids (i.e., IR oxycodone), deemed appropriate by the investigator (long-acting opioids and controlled-release opioid medications were to have been prohibited)

Pharmacokinetic Sampling:
During the maintenance period, sparse PK sampling was to have been performed in approximately 50 subjects before HYD dosing (at visits 3 to 7)

Following completion of the maintenance period or study drug discontinuation, subjects who did not enter the optional extension period were to have been converted to an appropriate pain management regimen as deemed medically appropriate by the investigator. If the investigator/medically qualified designee deemed necessary, subjects on ≥ HYD 40 mg may have been converted to a nonopioid pain regimen by entering the optional HYD taper period.

Optional Open-Label Extension Period (24 weeks) – Visit 17

- Visit 17 was to have been Day 1 of extension period
- To have begun immediately following to completion of ECG visit procedures and all scheduled visit in this period were to have anchored to this Visit
- Only subjects who completed the maintenance period treatment were to have been allowed to participate in this period.
- Subjects who entered the open-label extension period were to have been treated with the same HYD dose they received at the end of the maintenance period or have were to have their HYD dose adjusted at a scheduled visit or an unscheduled visit if deemed necessary by the investigator/medically qualified designee. Dose down-titration was to have occurred anytime for safety or tolerability reasons; however, before an up-titration was to have been considered, a minimum treatment duration of 72 hours is required for subjects on HYD 20, 40, or 60 mg per day, and a minimum treatment duration of 120 hours was to have been required for subjects on HYD 80 mg or higher per day. All dose adjustments were to have been performed at the clinical site during a regularly scheduled visit or during an unscheduled dose adjustment visit.
- Only HYD tablets at dose strengths of 20, 40, and 60 mg were to have been dispensed during the extension period. Subjects requiring doses higher than HYD 60 mg/day were to have taken more than 1 tablet of HYD per day (e.g., HYD 80 mg, subject to have taken 2 tablet of HYD 40 mg daily, one tablet at time of dosing)
- Subjects may have discontinued HYD at any time during the extension period. If such is the case, the subjects should notify the investigator/designee immediately via telephone and record the time and date of their last HYD dose (if not already done so) and their "average pain over the last 24 hours" scores in the subject diary. The pain score to have been captured represented the pain score at time of discontinuation of study drug. The site personnel were to have instructed the subject to return to clinical site to complete all EDE visit (visit 20) procedures.
- At the end of extension or early discontinuation from extension (visit 20) visit, subjects were to have converted from the study drug to an opioid or nonopioid pain regimen as deemed appropriate by the investigator. Subjects converting to a non-opioid regimen were to have been given the option of entering the HYD taper period if they were on HYD 40 mg or higher at visit 20 (EOE/EDE).

Visits 18 and 19 (Extension Period Weeks 8 and 16)

- The following key procedures and assessments were to have performed at this these visits: vital signs, collect unused study drug, review diary for HYD intake and "average pain over the last 24 hours" score at 8 pm, drug accountability, subject to record responses to COMM and BPI, MOS Sleep-R, SF-36, DHI and THI, investigator to complete ABC, evaluate for potential abuse and/or diversion, record concomitant medication and non-drug therapies, record AEs, dispense study drug with instructions on HYD intake and study diary record keeping, and next visit was to have been scheduled in 8 weeks ± 3 days

End of Extension or Early Discontinuation from Extension (EOE/EDE) – Visit 20

- This visit was to have been completed for subjects who had completed the extension period or who had discontinued early from the extension period
- At this visit, subjects were to have been converted from HYD to their individual pain regimen
- Procedures and assessments that were to have been performed at this visit included: vital signs, physical exam, ECG (total of 3 at 20 minutes apart), clinical labs, urinalysis, serum pregnancy for females of reproductive potential, blood for RNA and protein only from subjects who have consented to participate in optional exploratory portion of study, collection of unused study drug, review diary for HYD intake, and "average pain over the last 24 hours", enter visit information in diary, drug accountability, subject to record responses to COMM, investigator to complete ABC, evaluation for potential abuse and/or diversion, record concomitant medications and non-drug therapies, and discontinue subject
    - Subjects discontinued from HYD treatment at this visit were to have been scheduled for a follow-up visit or telephone contact to occur in 5 to 7 days
    - For subjects who were to have been entered in the optional HYD taper period:
        - Visit 20.1 was to have been scheduled to occur in 6 to 9 days if the subject was tapering from HYD 120 mg or 80 mg, or
        - A follow-up visit was to have scheduled to occur 5 to 7 days after the last dose of HYD if the subject was tapering from HYD 60 mg or 40 mg.

Optional HYD Taper Period (up to 14 days)

- Subjects who competed this period were to have returned to study site for follow-up visit 5-7 days after last HYD dose
- Subjects who were to have been tapered for HYD 80 mg or 120 mg were to have been required to return to the study site for Visit 12 or Visit 20 (as applicable)

Follow-Up Period

- For subjects who did not participate in the optional HYD taper period, the follow-up evaluation was to have been performed 5 to 7 days after the last dose of HYD, or 5

to 7 days after visit 17 or visit 20. Evaluation was to have been performed either via telephone or at the study site by investigator or designee

- For subjects who had undergone the optional HYD taper period, the follow-up evaluation was to have been performed at the study site by the investigator or designee
- Procedures that were to have been performed included: collection of unused study medication, drug accountability, evaluation for potential abuse and/or diversion, record of concomitant medications, record of AEs, record responses to Dizziness Handicap Inventor and Tinnitus Handicap Inventory

Study Procedures

Table 25 shows the schedule of procedures that were to have been conducted during the study

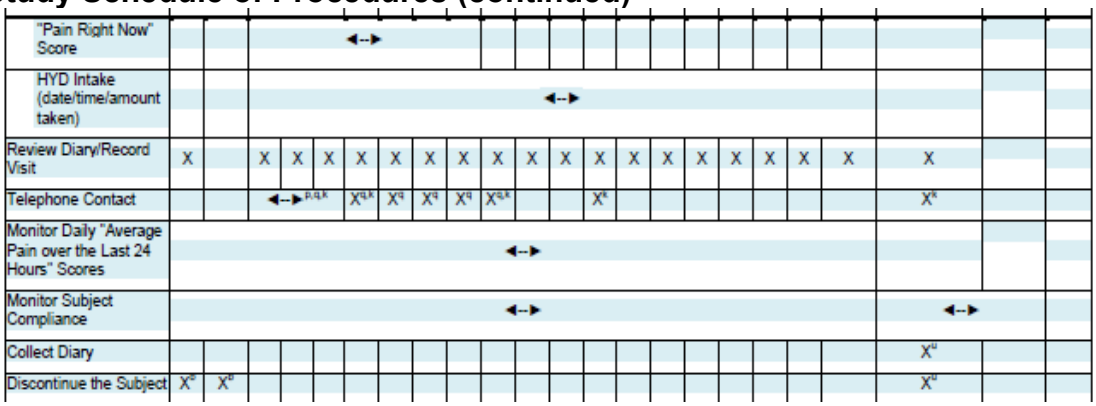
Table 25: Study Schedule of Procedures

	Core Study																				Optional Taper Period[u]	F/U [s,u]
Protocol Activity	Screening		Dose Titration Period			Maintenance Period																
						Maintenance Day 1, Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48														UDA [s]	EOC/EDC [s]		
	Visit 1 [s]	TC	Visit 2	TC [s]	TV [s]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	UDAV [s]	Visit 17[v]	Visit 17.1	F/U [s]
	≤ 14 days		≤ 45 days			Day 1	Wk 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48		Wk 52	≤ 14 days	≤ 7 days
Informed Consent Process	X																						
Contact IWRS to Document Subject Status	X	X[b]	X			X															X		
Inclusion/Exclusion Criteria	X																						
Confirm eligibility for study continuation			X			X																	
Demography	X[c]																						
Medical history	X[f]																						
Pain history/Pain etiology	X[r]																						
Record "Average Pain Over the Last 14 days"	X																						
Physical Examination	X[d]												X								X		
Vital Signs	X[e]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
History of Ototoxic medication use	X[c]																						
Concomitant Therapies	X[r]	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Opioid Equivalence	X		X																				
Adverse Events	X[r]	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram	X[d,g]					X		X		X			X			X			X		X		
Review ECG Results from central ECG provider	X[h]					X[h]		X[h]		X[h]			X[h]			X[h]			X[h]		X[h]		
Draw Blood for Clinical Laboratory Evaluations	X[d,g]							X					X								X		
Serum Pregnancy Test	X[d,g]												X								X		
Draw Blood for PK Sample						X[i]	X[i]	X[i]	X[i]	X[i]													
Pharmacogenomic Evaluations	X[g]					X															X[u]		
Collect Urine for Urinalysis	X[d,g]							X					X								X		
Collect Unused Study Drug					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[x]

Study Schedule of Procedures (continued)

Protocol Activity	Core Study: Screening		Core Study: Dose Titration Period			Core Study: Maintenance Period														Optional Taper Period[w]	F/U [x,y]
						Maintenance Day 1, Weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48													UDA *	EOC/EDC *		
	Visit 1 *	TC	Visit 2	TC *	TV *	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	UDAV *	Visit 17*	Visit 17.1	F/U *
	≤ 14 days		≤ 45 days			Day 1	Wk 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48		Wk 52	≤ 14 days	≤ 7 days
Abuse/Diversion Assessments																							
Urine Drug Screen [i]	X[c]																						
Conduct Drug Accountability					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]
SOAPP-R	X																						
ABC			X			X		X	X	X	X	X	X	X	X	X	X	X			X		
COMM			X			X		X	X	X	X	X	X	X	X	X	X	X			X		
Evaluate Abuse and Diversion	X		X		X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X	X[n]
Review Clinical Laboratory Results	X[k]							X[k]					X[k]								X[k]		
Comprehensive Audiologic Assessment		X[d,r]				X ◄--► *															X		
Pure-tone Air Conduction Audiometry						X				X			X										
Review Audiologic Assessments Results		X[h]				X[h]	◄--►[h]														X[h]		
Dizziness Handicap Inventory			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]
Tinnitus Handicap Inventory			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]
MOS Sleep Scale - Revised			X			X		X	X	X	X	X	X	X	X	X	X	X	X		X		
Brief Pain Inventory			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
SF-36			X			X		X	X	X	X	X	X	X	X	X	X	X	X		X		
Treatment Satisfaction Survey Part I								X													X[m]		
Treatment Satisfaction Survey Part II																					X		
PGIC																					X		
Unscheduled HYD Dose Adjustments				X	X														X				
Dispense Study Drug as Instructed by IWRS			X[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]	X	
Schedule the next visit or phone call	X[d,g]	X[g,s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Subjects Diary /Record Visit	X[g]																						
Diary Entries																							
Daily "Average Pain over the Last 24 Hours" Scores	◄--►																						

Study Schedule of Procedures (continued)



Source: HYD3003 Protocol Amendment 3 (dated March 8, 2013), Table 7, pp. 49-53/180

Outcome Variables

Efficacy

- Daily "Average Pain over the last 24 hours"
- "Pain Right Now" Scores
- Sleep Disturbance Subscale of the Medical Outcome Study (MOS) Sleep Scale
- Brief Pain Inventory Short Form (BPI-SF)
- Medical Outcomes Study 36-item Short-Form (SF-36)
- Patient Global Impression of Change (PGIC)
- Treatment Satisfaction Survey – Part I and Part II

Pharmacokinetic Assessments

- Hydrocodone plasma concentration

Pharmacogenomic Assessments

- RNA, DNA and protein

Safety

- Adverse Events (AEs) including SAEs
- Adverse Events of Special Interest
- Vital signs – systolic and diastolic blood pressure, heart rate, respiratory rate and temperature
- Clinical laboratory tests – chemistry, hematology, and urinalysis, serum pregnancy test for women of childbearing age
- Urine drug screen (UDS)
- Physical examination – including height and weight
- Electrocardiogram (ECG)
- Current Opioid Misuse Measure (COMM) questionnaire
- Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)

- Addiction Behavior Checklist (ABC)
- Dizziness Handicap Inventory (DHI)
- Tinnitus Handicap Inventory (THI)
- Audiologic assessments (pure tone audiometry, bilateral air-conduction pure-tone threshold audiometry, bone conduction pure tone threshold audiometry, tympanometry, speech reception threshold testing and word recognition)

STUDY RESULTS
Results of safety will be discussed in Section 7

6 Review of Efficacy

Efficacy Summary

Efficacy of HYSINGLA ER in the management of moderate to pain severe enough to require around the clock long-term opioid treatment and for which alternative treatment options are inadequate was demonstrated in adults in one principal efficacy study (HYD3002). There was statistically less pain at 12 weeks in subjects with moderate to severe CLBP treated with HYSINGLA ER compared to placebo. Efficacy was also supported by several secondary endpoints including: cumulative responder analysis, and subject global impression.

6.1 Indication

The proposed indication for HYSINGLA ER is:

> "Management of moderate to pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate"

6.1.1 Methods

The Applicant has submitted one principal efficacy study (i.e., HYD3002) to support a finding of efficacy for the indication of HYD for the management of moderate to pain severe enough to require around-the clock, long-term opioid treatment and from which alternative treatment options were inadequate in adults. This clinical trial was an adequate and well-controlled (i.e., randomized, double-blind, placebo-controlled) study in subjects with chronic low back pain. The primary efficacy endpoint was the weekly mean PI score calculated using the daily diary "average pain over the last 24 hours".

The study design and primary endpoint meet the Division's current standards for opioids

6.1.2 Demographics

The overall demographic and baseline characteristic for subjects in the controlled study are summarized in Table 12. The demographic characteristics of randomized HYD-treated subjects were similar to placebo-randomized subjects with respect to age, sex, and BMI.

The demographics of the subjects with respect to race were not comparable across treatment groups. A higher percentage of black subjects (23%) were randomized to the HYD group compared to the placebo group (17%).

6.1.3 Subject Disposition

In the primary efficacy study (HYD3002), overall, 65% of subjects completed the run-in period and 35% were discontinued. The majority of subjects were discontinued from the run-in period due to adverse events (6%).

With respect to subject discontinuation secondary to suspected or confirmed diversion , assessments for diversion were performed throughout clinical studies.

Subsequent to the start of study drug dosing, if ≥ 1 of the following conditions were met, the investigator or diverting drug:

- ≥ 10% of the returned drug (study drug and/or immediate-release oxycodone) was unaccounted for or was used in excess of the maximum prescribed - drug accountability was conducted by site personnel at every scheduled visit and unscheduled dose adjustment visit starting from the first open-label run-in visit until the EOS.

In response to an information request from the Division, the Applicant provided a listing of subjects who were discontinued from the run-in period and the double-blind period because of confirmed or suspected diversion. From the data provided, my review confirms the Applicant's findings that 7% of nonrandomized subjects were discontinued from the run-in period due to confirmed or suspected diversion. Overall, (randomized plus nonrandomized) 3% of subjects were discontinued from the run-in period due to confirmed or suspected diversion.

During the double-blind period of the efficacy study, overall 74% of subjects completed the period on study drug and 26% of subjects were discontinued from study drug. Higher percentages of HYD subjects completed the double-blind compared to placebo subjects (77% versus 72% respectively.

Similar percentages of HYD and placebo subjects were discontinued from both study drug and study simultaneously (16% and 17% respectively). The reasons for discontinuation in HYD-treated subjects in order of decreasing frequency were:

subject's choice (4%), adverse events (3%), lack of therapeutic effect (3%) and administrative reasons (3%), lost-to-follow (2%), confirmed or suspected diversion (1%) and ASHA-related AE (<1%). The reasons for discontinuation of placebo-treated subjects in order of decreasing frequency were: lack of therapeutic effect (8%), adverse events (3%), subject's choice (2%), administrative (2%), confirmed or suspected diversion (1%) and lost-to-up (1%).

Similar to the run-period, based on my review of the IR response, the Applicant's data shows that overall 1% of subjects (1% HYD-treated subjects compared to 1% placebo subjects) were discontinued during the double-blind period secondary to confirmed or suspected diversion. There were no reported discontinuations from study drug and study secondary to hearing related AEs in placebo subjects.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the weekly mean pain intensity score (calculated using the daily diary "average pain over the last 24 hours". This endpoint was discussed with the Applicant at the End-of-Phase 2 guidance meeting held on May 4, 2011.

The primary efficacy analysis involved using an mixed effects general linear model with repeated measures (MMRM) with a pattern mixed model (PMM) approach to account for missing values, and estimating the weighted average of LS means for the week 12 "average pain over the last 24 hours" scores. The Applicant's results for the weighted average of LS means at week 12 (average pain over the last 24 hours' scores) were 4.23 (0.126) (n=292) for the placebo treatment group and 3.70 (0.128) (n=296) for the HYD treatment group, with an HYD minus placebo difference of -0.53 (95% CI, -0.882 to -0.178). This treatment difference showed HYD was statistically significant (P=.0016) compared to placebo. The treatment difference appears to be marginal but is similar to the treatment effect of other ER opioids.

Yan Zhou, statistician from the Division of Biometrics repeated the analyses using the Applicant's datasets. Dr. Zhou confirmed the primary efficacy findings as reported by the Applicant using the prespecified imputation methods and four prespecified sensitivity analyses (not missing at random - all observed data, missing at random - observed data on study drug, not missing at random - partial AE penalty, and hybrid baseline observation carried forward/last observation carried forward).

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy endpoints of HYD for the treatment of chronic pain were generally supportive of the efficacy findings of the primary endpoint with exception of the Medical Outcome Study Sleep Scale – Revised analysis. The Applicant's use of p-

values for the secondary endpoints is descriptive, since there was no correction for multiple endpoints included in the analysis plan.

Responder Analysis
The Applicant defined "Responders to treatment" as subjects with a ≥ 30% reduction in pain compared with baseline and as subjects with a≥ 50% reduction in pain compared with baseline. After 12 weeks of study treatment, a greater percentage of subjects in the HYD treatment group compared to the placebo treatment group showed improvement in the continuous responder analysis across all response rate levels.

Of note, 11 HYD randomized subjects and 12 placebo randomized subjects completed the study on study drug but had a missing week 12 mean pain intensity score. These subjects were excluded from the analysis.

Patient Global Impression of Change (PGIC)
This variable measured the global change of overall status (either improvement or worsening). The proportion of subjects reporting "very much improved" or "much improved" on PGIC rating was higher in HYD-treated subjects compared to placebo-treated subjects (61% versus 49% respectively,).

Medical Outcome Study Sleep Scale – Revised
Results of the MOS Sleep-R sleep disturbance subscale analysis showed no difference between treatment groups at the end of double-blind period.

6.1.6 Other Endpoints

Oswetry Disability Index (ODI), Brief Pain Inventory-Short Form (BPI-SF), and Short Form (SF-36)
At the end of the double-blind period, there were no treatment differences between HYD and placebo subjects in other exploratory endpoints with the exception of the BPI-SF pain severity subscale where HYD subjects showed improvement in the pain severity subscale score only.

Rescue Medication Use
During the double-blind treatment period, subjects could receive IR oxycodone tablets as rescue medication. The maximum daily IR oxycodone dose allowed, determined by the subject's double-blind daily dose level of HYD (or matching placebo), was 10 mg for subjects receiving HYD 20 or 40 mg, 15 mg for subjects receiving HYD 60 mg, 20 mg for subjects receiving HYD 80 mg, and 30 mg for subjects receiving HYD 120 mg.

There was no significant difference in the proportion of HYD subjects compared to placebo subjects that required no rescue medication. However, there is a trend that

shows that for subjects randomized to HYD mean number of supplemental IR oxycodone tablets taken increased with increasing HYD doses.

6.1.7 Subpopulations

Efficacy analyses in subgroups were performed by the Applicant for the primary efficacy study (HYD3002). The weekly mean pain intensity score was calculated using the daily "average pain over the last 24 hours" was examined for consistency across subgroups including sex, age group (< 65 and ≥ 65 years), and race (white and black).

Table 26 summarizes the "average pain over the last 24 hours" scores using all observed data during the double-blind period by sex, age and race for the full analysis population.

Table 26: Summary and Analysis of the Week 12 "Average Pain Over the Last 24 Hours" Scores by Sex, Age and Race; FAP (Study HYD3002)

Study period/week	Sex		Age		Race	
Treatment group LS mean (SE) pain intensity Confidence interval	Male (N=250)	Female (N=338)	< 65 years (N=521)	≥ 65 years (N=67)	White (N=402)	Black (N=118)
Baseline						
Placebo[a]						
LS mean (SE)	7.31 (0.104)	7.46 (0.090)	7.46 (0.072)	6.86 (0.209)	7.29 (0.082)	7.72 (0.166)
95% CI of LS mean	(7.11, 7.52)	(7.28, 7.64)	(7.32, 7.60)	(6.45, 7.27)	(7.13, 7.45)	(7.40, 8.05)
HYD						
LS mean (SE)	7.22 (0.105)	7.53 (0.089)	7.43 (0.072)	7.18 (0.194)	7.27 (0.085)	7.65 (0.145)
95% CI of LS mean	(7.01, 7.43)	(7.35, 7.70)	(7.29, 7.57)	(6.80, 7.56)	(7.10, 7.43)	(7.36, 7.93)
Prerandomization						
Placebo[a]						
LS mean (SE)	2.78 (0.102)	2.86 (0.089)	2.81 (0.071)	2.94 (0.205)	2.92 (0.080)	2.57 (0.161)
95% CI of LS mean	(2.58, 2.98)	(2.68, 3.03)	(2.67, 2.95)	(2.53, 3.34)	(2.76, 3.08)	(2.26, 2.89)
HYD						
LS mean (SE)	2.81 (0.103)	2.75 (0.087)	2.79 (0.071)	2.69 (0.190)	2.87 (0.082)	2.76 (0.140)
95% CI of LS mean	(2.60, 3.01)	(2.58, 2.92)	(2.65, 2.93)	(2.32, 3.07)	(2.71, 3.03)	(2.48, 3.03)
Double-blind week 12						
Placebo[a]						
LS mean (SE)	4.33 (0.204)	4.05 (0.172)	4.18 (0.139)	4.11 (0.401)	4.53 (0.157)	3.62 (0.305)
95% CI of LS mean	(3.93, 4.73)	(3.72, 4.39)	(3.90, 4.45)	(3.33, 4.90)	(4.22, 4.83)	(3.02, 4.22)
HYD						
LS mean (SE)	3.56 (0.200)	3.41 (0.167)	3.55 (0.137)	2.95 (0.355)	3.86 (0.156)	3.00 (0.272)
95% CI of LS mean	(3.16, 3.95)	(3.08, 3.74)	(3.28, 3.82)	(2.25, 3.64)	(3.55, 4.17)	(2.46, 3.53)
P value[b]		0.9789		0.9103		0.4426

Source: NDA 206627, Summary of Clinical Efficacy, Table 9, pg. 30 of 72

Results of the applicant's subgroup analyses shows there were no significant differences between HYD and placebo treatments and each subgroup.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The proposing dosing recommendation for HYD is 20, 30, 40, 60, 80 or 120 mg once daily. .

Pooled chronic pain studies assessed HYD administered at daily doses of 20, 40, 60, 80 or 120 mg. The Applicant did not formally evaluate differences in efficacy between HYD doses. Generally, opioids such as HYD are titrated to effect.

Data from pooled chronic pain studies support the following dosing recommendations:

- For opioid-naïve patients, initiate therapy with HYD 20 mg once daily.
- For opioid-experienced patients being converted to HYD from other oral hydrocodone formulations to HYD, add the patient's current total daily oral hydrocodone dose and convert that sum to HYD dose once daily
- For opioid-experienced patients being converted to HYD from other opioids, the oxycodone equivalent dose of incoming opioid (See Table 4) is used to convert to the starting HYD starting dose. The initial HYD doses as see in Table 4 represents a 25% to 60% reduction of the calculated TDD based on conversion factors provided in pooled chronic pain studies.

Additional information related to dosing was obtained from PK studies evaluating the plasma concentration-time profile of hydrocodone following HYD administration as well as bioavailability and the effects of food, drug interactions (cytochrome P450 CYP 2D6 and CYP3A4 inhibition), age, sex, hepatic impairment, and renal impairment. Please see Dr. Srikanth Nallani's Clinical Pharmacology review for full details regarding these studies as it relates to dosing recommendations under the fed and fasted state, age, sex and for special populations (as applicable).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy was demonstrated at the end of the 12 week treatment phase in the primary efficacy study.

The persistence of efficacy was also evaluated in the open-label, long-term safety study (HYD3003) in which after the dose-titration period subjects were eligible to receive HYD study drug for up to 12 months in the maintenance period. The Applicant reports the mean "average pain over the last 24 hours" score decreased from 6.43 at baseline to 4.10 at the end of the dose-titration period. The overall mean "average pain over the last 24 hours" score during the maintenance period was reported as 3.61.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

The safety profile of HYSINGLA ER was assessed in 2,476 healthy subjects and /or patients with chronic pain of nonmalignant and/or nonneuropathic origin. Of the 2, 476 subjects/patients who received at least one dose of HYD, 364 subjects received HYD for at least 12 months. In addition, 374 subjects were exposed to at least one dose of the proposed maximum labeled HYD dose of 120 mg.

There were a total of seven deaths, six of which occurred in HYD-treated patients in the clinical development program. The death of one HYD-treated subject was possibly related to hydrocodone use (acute hydrocodone, cyclobenzaprine and citalopram toxicity. The overall incidence of nonfatal SAEs was low in HYD-treated subjects compared to placebo-treated subjects in the controlled efficacy study. Various uncommonly SAEs occurred in clinical trials including: QT prolongation, HYD formulation-related obstruction, and adverse events associated with HYD study drug abuse /misuse and/or other opioid misuse/abuse.

Assessments were performed for aberrant drug behavior throughout clinical studies. If one or more of the following conditions were met, the investigator was supposed to contact the medical monitor to evaluate whether the subject was abusing:

- Addiction Behaviors Checklist (ABC) scores ≥ 3.
- Response was “yes” to question #1 and/or question #8 in the first section (‘Addiction behaviors - since last visit’) of the ABC.
- Current Opioid Misuse Measure (COMM) scores ≥ 9.

The SMQ analysis showed the rate of aberrant drug behavior of HYSINGLA ER-exposed subjects was <1%. Nine subjects were reported to have experienced AEs related to overdose, drug abuse, substance abuse, positive UDS, or intentional drug misuse. Three subjects experienced AEs related to aberrant drug behavior that appear to be related to HYD study drug. Please refer to Section 7.3.5 (Submission Specific Primary Safety Concerns) for details regarding all nine subjects.

Incidences of 10% or more in excess of the maximum prescribed study drug dose used or unaccounted for were investigated during the HYD clinical development program and some of these events were considered by investigators to be diversion. Diversion was also to be reported by the investigator if diversion of any amount was suspected.

For study HYD3002, a total of 158 out of 905 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 HYD subjects and 8 placebo

subjects). The remainder (119 subjects) was deemed not to have diverted study drugs by the investigators after their evaluation of the cases. Among them, 6 had study drug stolen (HYD and/or immediate-release oxycodone tablet) or study drug used by people other than study subjects.

For study HYD3003 a total of 176 out of 922 subjects were investigated for possible diversion. Diversion was confirmed or suspected for 24 (2.6%) subjects. No diversion was suspected by the investigators for 152 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 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). Case narratives are summarized for two subjects who discontinued due to confirmed or suspected diversion and can be found in Section 7.3.3 (Dropouts and/or Discontinuations)

In addition, several *in vitro* manipulation and extraction studies, and two clinical abuse liability studies were conducted to support the Applicant's claims of abuse deterrence via intravenous, intranasal abuse of their Hysingla. These studies were reviewed by the Controlled Substances Staff and their findings are still pending.

The most common adverse events associated with HYD use include: nausea, vomiting, constipation, dizziness, insomnia, upper respiratory infection and influenza.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

A total of 16 studies were used in the safety analysis. Refer to Section 5 (Sources of Clinical Data) and Section 7.1.3 (Pooling of Data) for a listing and brief description of the studies included in this submission.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0 (released in March 2013) terminology. An AE dictionary listing sorted by MedDRA System-Organ-Class (SOC), and Preferred Term (PT) was produced by the Applicant including all occurrences of unique verbatim descriptions associated with each PT.

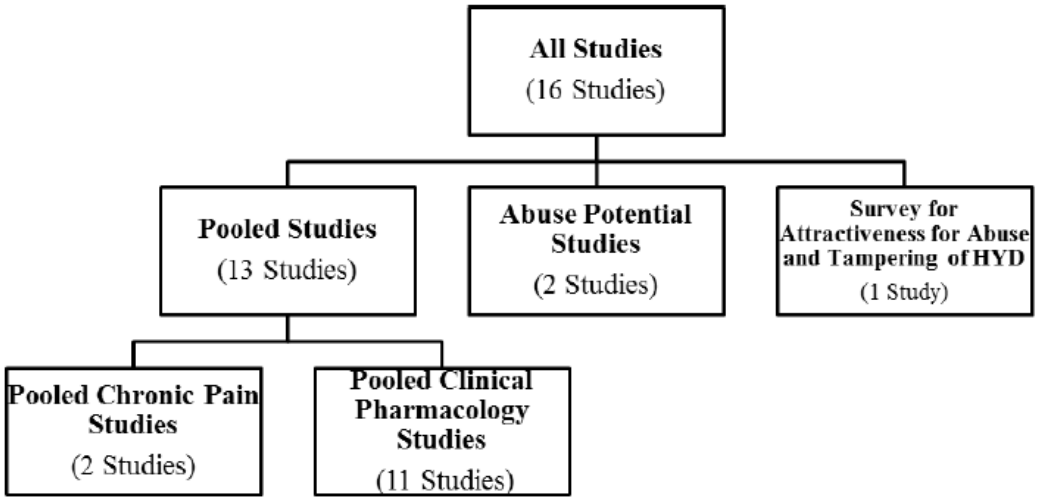
Adverse events were analyzed by treatment-emergent signs and symptoms.
The Applicant defined treatment emergent adverse events (TEAEs) as AEs that either:

- Emerge during treatment, having been absent at pre-treatment;
- Re-emerge during treatment, having been present at pre-treatment but stopped before treatment; or
- Worsen in severity during treatment relative to the pre-treatment state (when the AE is continuous).

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

Figure 5 illustrates the Applicant's pooling scheme.

Figure 5: Applicant Pooling Strategy Across Clinical Studies



Source: NDA 206627, Summary of Clinical Safety, Figure 1, pg. 18/115

Five analysis groups were defined by the Applicant:

1. Pooled studies (n=13): consisting of 11 Phase 1 studies and 2 Phase 3 studies
2. Pooled chronic pain studies (n=2) : consisting of an efficacy/safety study and an open-label, long-term safety study
3. Efficacy/safety study (n=1): HYD3002
4. Open-label, long-term safety study (n=1): HYD3003
5. Pooled clinical pharmacology studies (n=11)

Pooling of data across clinical trials to estimate and compare incidence was limited due to two chronic pain studies: one controlled study (HYD3002) and one uncontrolled open-label long-term safety study (HYD3002).

7.2 Adequacy of Safety Assessments

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

Overall, the exposure to HYD in terms of numbers of subjects, dose and duration, and demographics appears adequate.

Exposure

A total of 2476 subjects were exposed to at least one dose of HYD ranging from 20 to 160 mg during the entire clinical development program.

Table 27 shows the cumulative exposure of HYD by dose for pooled chronic pain studies.

Table 27: Cumulative Extent of Exposure to HYD by Dose (Pooled Chronic Pain Studies)

	HYD dose					
Exposure category	20 mg (N=1569)	40 mg (N=1305)	60 mg (N=957)	80 mg (N=655)	120 mg (N=374)	Any dose (N=1827)
Subjects by cumulative extent of exposure, n (%)						
Any exposure	1569 (100)	1305 (100)	957 (100)	655 (100)	374 (100)	1827 (100)
< 1 week[a]	630 (40)	424 (32)	246 (26)	98 (15)	27 (7)	106 (6)
≥ 1 week	939 (60)	881 (68)	711 (74)	557 (85)	347 (93)	1721 (94)
≥ 2 weeks	317 (20)	404 (31)	342 (36)	304 (46)	266 (71)	1561 (85)
≥ 1 month	214 (14)	293 (22)	247 (26)	232 (35)	216 (58)	1206 (66)
≥ 3 months	154 (10)	198 (15)	165 (17)	153 (23)	160 (43)	798 (44)
≥ 6 months	86 (5)	104 (8)	87 (9)	83 (13)	104 (28)	500 (27)
≥ 9 months	77 (5)	78 (6)	57 (6)	60 (9)	84 (22)	450 (25)
≥ 12 months	53 (3)	37 (3)	26 (3)	30 (5)	46 (12)	364 (20)
Cumulative number of days on HYD						
Mean	32.2	43.5	47.8	64.1	121.0	132.3
SD	79.53	86.90	88.43	103.36	135.68	144.99
Median	7.0	8.0	9.0	11.0	52.5	57.0
Min, Max	1, 396	1, 381	1, 396	1, 461	1, 389	1, 517

Source: NDA 2062, ISS, Table 6, pg. 73 of 339

In the pooled chronic pain studies:

- A total of 1827 subjects were exposed to at least one dose of HYD. ranging from 20 to 120 mg
- A total of 364 subjects received ≥12 months exposure
- A total of 374 subjects were exposed to at least one dose of 120 mg HYD
    - 12% of subjects who took the 120 mg HYD were exposed for ≥12 months

Demographics
Overall, the mean age of subjects receiving HYD in pooled chronic pain studies was 50.0 years. There were more female subjects than male subjects (58% versus 42% respectively,). The racial makeup of the study population was predominantly White [77%] followed by Blacks [18%]) and Asians [4%]; all other races were represented at ≤1%. The mean BMI was 31.4 kg/m2; and 52% of subjects were in the ≥ 30 kg/m2 category. There were more opioid-experienced subjects than opioid-naïve subjects (56% versus 44% respectively,).

7.2.2 Explorations for Dose Response

As with other opioid analgesics, HYSINGLA ER is titrated to effect and tolerability. There was no specific dose-response studies conducted.

7.2.3 Special Animal and/or In Vitro Testing

The Applicant's preclinical and *in vitro* testing appears to be adequate to have explored potential AEs.

Please refer to Drs. Bolan, Qui and Mellon's toxicology reviews for a completed discussion of this testing.

7.2.4 Routine Clinical Testing

The Applicant's routine collection of clinical laboratory tests (hematology and serum chemistry) and urinalysis appeared adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to Section 4.4 of this review and Dr. Srikanth Nallani's Clinical Pharmacology Review.

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

Generally, the opioid drug class is associated with potential serious adverse events including: overdose, abuse and misuse, addiction, and fatal respiratory depression. and the product insert for drug in this class contains a boxed warning describing these potential adverse events The most commonly reported AEs for similar opioids are: constipation, nausea, vomiting, somnolence, dizziness, and pruritus.

7.3 Major Safety Results

7.3.1 Deaths

A total of seven deaths occurred during Phase 3 clinical studies (6- HYD group and 1-placebo). Information including case narratives, case report forms and data listings for each death were reviewed. Summary narratives for patient deaths in the HYD treatment group follow.

Subject 3002051: was a 41-year-old white female participating in study HYD3003 who reportedly began treatment with HYD 40 mg and the dose was titrated to HYD 80 mg per protocol. At the time of study entry the subject's medical history included: chronic LBP, asthma, hypertension, morbid obesity, hypercholesterolemia, gastroesophageal reflux (GERD), methicillin resistant staphylococcus aureus (MRSA), migraines, history of blood transfusion, history of shingles, depression, anxiety, history of insomnia sinus allergies, seasonal allergies, and history of sinus cyst. Prior surgical history included: gastric by-pass, caesarean section, abdominalplasty, and abdominal wound debridement. Concomitant medications included: hydrocodone /acetaminophen, citalopram hydrobromide, propranolol, cyclobenzaprine, furosemide, alprazolam, levabuterol hydrochloride, rizatriptan benzoate, azithromycin, diphenhydramine, potassium, calcium, omega-3 fish oil, guaifenesin pseudoephrine hydrochloride, sodium sulfacetamide ophthalmic solution, ciprofloxacin, methylprednisolone, decadron,

One hundred forty days after the start of HYD, the subject reportedly died due to accidental acute hydrocodone, citalopram, and cyclobenzaprine toxicity (accidental overdose). According to the subject's death certificate, other significant conditions contributed to the subject's death which included dilated cardiomyopathy and morbid obesity. Per the Applicant, after submission of the death cert

Reviewer Comment: The SAE of death due to acute hydrocodone, citalopram and cyclobenzaprine toxicity was possibly related to study drug.

Subject 2043041 was a 56-year-old white female participating in study HYD3002 who reportedly began treated with HYD 20 mg. The subject took the last dose of study drug on day 24 of study drug dosing during the run-in period, 1 day before the occurrence of the event. At the time of study entry, the subject's medical history included: chronic LBP, osteoarthritis of the lumbosacral spine, obesity and seasonal allergies. Concomitant medications: IR oxycodone per study investigator

On day 25 of study drug dosing, the subject was found unconscious in bed, biting down on her tongue and snoring loudly. The subject was taken to the hospital by paramedics and was subsequently diagnosed with brain aneurysm (intracranial aneurysm) by

report. At the time of hospitalization there was no reported bleeding. The subject underwent two brain surgeries and the aneurysm subsequently bled and the subject died due to the serious adverse event (SAE) of brain aneurysm (intracranial aneurysm). The Applicant reports the study site was unable to get consent for the subject's power of attorney to obtain medical records. No additional information was reported on this subject

Reviewer Comment: The SAE of death due to brain aneurysm was not related to HYD study drug.

Subject 3081005: was a 62-year-old white male participating in study HYD3003 who reportedly began treatment with HYD 40 mg and the dose was titrated to HYD 120 mg per protocol. At the time of study entry, the subject's medical history included: uncontrolled hypertension, cardiovascular disease, tobacco abuse, coronary artery disease, Prior surgical history included multiple stent placement, acute renal failure, angioplasty, congestive heart failure, hyperlipidemia, MI, and uncontrolled hypertension. At screening, the baseline ECG assessment showed an inferior wall myocardial infarction, flat T waves, non-specific intraventricular conduction delay, sinus bradycardia, and premature ventricular complex.

On day 28 of the study, HYD 120 mg was discontinued due to AEs of sleepiness and disorientation. At the early discontinuation visit, the subject's ECG assessment continued to show inferior wall myocardial infarction, nonspecific intraventricular conduction delay, and premature ventricular complex. That same day, the subject reportedly began taking hydrocodone /APAP (Vicodin) for chronic back pain.

Approximately 10 days after early discontinuation from study, the subject's physician was reported to have changed the subject's pain medication from hydrocodone /APAP to methadone. The subject's spouse reported that after he began taking methadone, the subject complained of sweats, weakness, and shaking. Approximately 1 week after starting methadone, the subject began losing his appetite and complained of not feeling well. The next day the subject experienced vomiting and shortness of breath. The subject refused to go to the emergency room; however, at approximately noon that same day, the subject became weak with shortness of breath. The subject's spouse called the Emergency Medical Service and the subject had a cardiac arrest while sitting on the stretcher. The subject arrived at the emergency room in asystole and was pronounced dead 10 minutes later. The cause of death was acute myocardial infarction.
.
Reviewer Comment: The SAE of death due to MI was not related to HYD study drug.

Subject 3041007 was a 54-year-old white female participating in study HYD3003 who reportedly began taking HYD 20 mg. At the time of study entry the subject's medical history included: chronic LBP, thrombotic thrombocytopenia purpura, degenerative disc disease, history of tubo-ovarian adhesions, allergy to penicillin, allergy to Motrin and tobacco use. Prior surgical history included: appendectomy, total abdominal hysterectomy, and surgery for degenerative disc disease. No reported concomitant medications.

A few days prior to starting HYD treatment, the subject was reported to have experienced fever, malaise, and anorexia. Three days after the start of HYD 20 mg, the subject presented to the emergency room with altered mental status and acute flare of thrombotic thrombocytopenic purpura. The subject was reported to be somnolent but arousable. Later the same day, the subject was diagnosed with thrombocytopenic embolic purpura (thrombotic thrombocytopenic purpura) and profound metabolic acidosis. The subject was intubated and treated with IV normal saline IV methylprednisolone sodium succinate, and sodium bicarbonate. Blood gas analysis revealed a pH of 6.94 after receiving bicarbonate. The subject was also transfused with 2 units of platelets and packed red blood cells.

A plasmapheresis was planned; however, that same day, the subject reportedly experienced cardiac arrest and expired. The cause of death was reported as thrombocytopenic embolic purpura (thrombotic thrombocytopenic purpura) and profound metabolic acidosis (metabolic acidosis).

Reviewer Comment: The SAE of death due to of TTP and metabolic acidosis was not related to HYD study drug

Subject 3045014 was a 57-year-old white female participating in study HYD3003 who reportedly began treatment with HYD 20 mg and the dose was titrated to HYD 60 mg per protocol. At the time of study entry, the subject's medical history included: history of asthma, chronic obstructive pulmonary disease, mediastinal adenopathy, pulmonary fibrosis, and a 30-year history of smoking. Approximately 1 month after starting study drug, the subject was seen by the investigator, and by report did not appear to have any respiratory difficulty, and her HYD dose was increased to HYD 80 mg. However, at a later time that day, the subject was hospitalized due to the SAEs of emphysema exacerbation and interstitial pneumonia.

The subject recovered from these events and was later discharged from the hospital and continued on HYD 80 mg. Approximately 2 weeks later, the subject was again hospitalized with dyspnea, hypoxia, and cough, and her chest X-ray revealed coarse moderate interstitial lung markings throughout the lungs, suggesting either acute pulmonary infiltrates or pulmonary fibrosis. The subject was diagnosed again with the

SAE of emphysema exacerbation and respiratory failure-multifactorial (respiratory failure). The subject was treated with endotracheal intubation and mechanical ventilation. However, her condition continued to deteriorate and her course was complicated by subcutaneous emphysema, pneumomediastinum, progressive hypoxemia, and acute renal failure. After approximately 1 month in the hospital, consent was obtained from the subject's family and the subject was disconnected from ventilator support. The subject reportedly died due to the SAE of respiratory failure-multifactorial (respiratory failure).

Reviewer Comments: This subject had a complicated pulmonary history particularly. In the 2nd month prior to her death, the subject experienced serious AEs which may have been sequelae of her three decade history of smoking. The SAE of death due to respiratory failure (multi-factorial) was not related to HYD study drug.

Subject 3065030: was a 54-year-old white female participating in study HYD3003 who reportedly began treatment with HYD 20 mg on and was titrated up to HYD120 mg per protocol. Medical history included: bilateral knee OA, chronic obstructive pulmonary disease, morbid obesity (431 lbs.), hypothyroidism, hypertension, restless leg syndrome, depression, , hemorrhoids, gastritis, diverticulosis, obstructive sleep apnea, edema, constipation, congestive heart failure (CHF) and gastrointestinal esophageal reflux disease (GERD).

Concomitant medications included: amlodipine, furosemide, ropinirole, levothyroxine, fluozetine, Advair,, hydrocodone/APAP, docusate, skelaxin, modafinil, fluticasone, ferrous sulfate, metoclopramide, acetazolamide, chlorthalidone, lisinopril, potassium chloride,

Approximately two months prior to her death the subject was reported to have experienced three SAEs events (i.e., bronchospasm, worsening anemia and acute renal failure) that required hospitalization: On day 186 of study drug dosing, the subject reportedly experienced hypoxia (hypoxia) that led to her death.

No autopsy was performed however the Applicant submitted a copy of the death certificate issue which states the cause of death was due to hypoxia.

Reviewer Comment: Due to this subject's complex medical history it cannot be completed ruled out the contribution of HYD to the SAE of death due to hypoxia.

7.3.2 Nonfatal Serious Adverse Events

A total of 120 nonfatal SAEs were reported in 84 HYD-treated subjects in pooled studies (119 of these AEs reported for pooled chronic pain studies and one nonfatal SAE reported for pooled clinical pharmacology studies. Table 43 (located in Appendix A of

this review) displays the treatment emergent nonfatal SAEs during HYD treatment occurring in ≥ 2 of HYD-treated subjects for pooled chronic pain studies

Table 28 summarizes the incidence of nonfatal SAEs occurring during the double-blind period for subjects participating in study HYD3002.

Table 28: Incidence of Treatment-Emergent Nonfatal Serious Adverse Events During the Double-Blind Period: Randomized Safety Population (Study HYD3002)

System Organ Class Preferred Term	Placebo[a] (N=292) n (%)	HYD (N=296) n (%)
Any AE	4 (1)	2 (1)
Cardiac disorders	1 (< 1)	0
Atrial fibrillation	1 (< 1)	0
Endocrine disorders	0	1 (< 1)
Hypothyroidism	0	1 (< 1)
General disorders and administration site conditions	0	1 (< 1)
Chest pain	0	1 (< 1)
Hepatobiliary disorders	1 (< 1)	0
Cholecystitis	1 (< 1)	0
Infections and infestations	1 (< 1)	0
Lobar pneumonia	1 (< 1)	0
Injury, poisoning and procedural complications	1 (< 1)	0
Concussion	1 (< 1)	0
Musculoskeletal and connective tissue disorders	1 (< 1)	0
Musculoskeletal chest pain	1 (< 1)	0
Psychiatric disorders	0	1 (< 1)
Major depression	0	1 (< 1)
Respiratory, thoracic and mediastinal disorders	1 (< 1)	0
Emphysema	1 (< 1)	0
Respiratory failure	1 (< 1)	0

Source: NDA 206627, ISS, Table 31, pg. 129/339

The overall incidence of nonfatal SAEs was low for both treatment groups (1% respectively,). No unusual or unexpected nonfatal SAEs were noted.

During my review of NDA, the majority of nonfatal SAEs cases and corresponding CRFs were reviewed. Summary narratives were written for non-fatal SAEs that were either casually associated or related to HYD study drug; that are uncommonly reported AEs for mu opioids and/or either nonfatal SAEs that involved QT prolongation, formulation-related obstruction, or HYD study drug abuse and/or misuse.

Subject 3020017 was a 53-year-old white female participating in study HYD3003 who reportedly began treatment with HYD 20 mg and was titrated up to HYD 40 mg per protocol. At the time of study entry, the subject's medical history included:: chronic

LBP, asthma, hypothyroidism, hypertension, hypercholesterolemia, cholelithiasis, GERD, history of drug-induced constipation, herpes genitalis, recurring UTI, seasonal allergies, bipolar disorder and depression.

Concomitant medications included: acetaminophen, albuterol inhalation, levothyroxine, clonazepam, fluoxetine, simvastatin, pantoprazole, valaciclovir, xolair, cyclobenzaprine, diltazem, doxazosin, quetiapine, azelastine, montelukast, digoxin, and carbidopa/levodopa.

Reportedly, after approximately 191 days (6 months) on HYD treatment the subject complained of abdominal fullness, nausea and voting. She was subsequently hospitalized for egigastric pain, diarrhea, nausea and vomiting. A CT scan of the abdomen revealed small bowel obstruction versus ileus (resolving). The subject was subsequently diagnosed with nonfatal SAE of gastroparesis (impaired gastric emptying) and AE of ileus, and was discontinued from HYD study drug that same day. The subject was treated with metoclopromide, IV fluids, carafate, omeprazole and IV levofloxacin. The SAE was reported to have resolved.

Reviewer Comments: The subject's medical history included hypothyroidism and history of drug-induced constipation which are risk factors for SBO. However, the nonfatal SAE of gastroparesis was possibly related to HYD study drug.

Subject 3051016 was a 69-year-old black female participating in study HYD3003 who reportedly began treatment with HYD 20 mg which was subsequently increased to 80 mg per protocol. At the time of study entry the subject's medical history included: low back pain, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, emphysema, gastroesophageal reflux, hypercholesterolemia, hypertension, history of myocardial infarction, cholelithiasis, insomnia, carpal tunnel and anxiety. Prior surgical history included: spinal fusion surgery, nasal reconstruction, carpal tunnel decompression and cholecystectomy.

Concomitant medications included: seretide, albuterol, zolopidem, clonidine, pantoprazole, simvastatin, trazodone, estrogen conjugated, valproate, busiprone, carvedilol, cyproheptadine, and transdermal nicotine patch.

At screening, an ECG examination revealed QTcF values of 402, 414, and 423 msec (average of 413 msec). Table 29 shows the ECG results from screening to end of study. At visit 5, the subject presented to the ED for SOB and nonproductive cough. An arterial blood gas shoed pH of 7.34, pC02 of 57 and p02 of 76 and an ECG examination revealed QTcF values of 477, 508, and 509 msec (average of 498.0 msec), a mean change of 85.0 msec from the mean baseline value. Subject was hospitalized for SAEs of COPD exacerbation and tracheobronchitis. On that same day, an AE of change in ECG QTcF > 480 msec with a >60 msec increase from screening (electrocardiogram

QT prolonged) was reported. Table 29 summarizes the ECG values for Subject 3051016.

Table 29: ECG Results for Subject 3051016

Date	Time	QT (msec)	QTcB (msec)	QTcF (msec)	HR (bpm)	PR (msec)	RR (msec)	QRS (msec)	ECG Findings
Screening 14-Nov-2011	14:08:45	372	418	402	75	127	790	80	Normal
	14:28:21	380	432	414	77	125	771	72	Normal
	14:48:07	395	438	423	73	123	811	80	Normal
Visit 3 04-Jan-2012	10:26:33	399	419	412	66	132	903	77	Normal
	10:54:38	408	425	419	65	135	923	76	Normal
	11:37:57	408	416	413	62	129	961	73	Normal
Visit 5 02-Feb-2012	13:17:46	446	493	477	73	122	816	87	Abnormal: T-wave inversion, ST depression
	13:38:42	497	514	508	64	132	935	88	Abnormal: T-wave inversion, prolonged QTc, ST depression
	13:57:50	502	513	509	62	114	958	94	Abnormal: T-wave inversion, prolonged QTc, ST depression
Visit 17 14-Feb-2012	11:08:10	406	413	410	62	124	965	80	Abnormal: T-wave inversion
	11:28:50	398	411	406	64	128	936	76	Abnormal: T-wave inversion
	11:52:21	410	432	425	66	118	897	87	Abnormal: T-wave inversion

Abbreviations: ECG = electrocardiogram; QT = QT interval (ECG); QTcB = QT data corrected for heart rate using the Bazett formula; QTcF = QT data corrected for heart rate using the Fridericia formula; PR = PR interval (ECG); RR = RR interval (ECG); HR = heart rate; QRS = QRS interval (ECG); msec = millisecond; bpm = beats per minute

Source: NDA 206627, HYD3003 CSR, Table 1, pg. 3738/9013

The subject was discontinued from the study. At Visit 17 (early discontinuation visit), an ECG examination revealed QTcF values of 410, 406, and 425 msec (average of 413.7 msec).

Reviewer's comment: The nonfatal SAE of change in ECG QTcF > 480 msec with a >60 msec increase from screening (electrocardiogram QT prolonged) was possibly related to HYD study drug. None of the reported concomitant medications cause prolonged QT.

Subject 3017010 was a 70-year-old white male participating in Study HYD3003 who reportedly began treatment with HYD 20 mg on (b) (6). At the time of study entry, the patient's reported medical history included: bilateral knee osteoarthritis, low back pain, left ear basal cell carcinoma, left thigh meralgia paresthetica, right shoulder muscle injury, left hand fracture, right wrist fracture, and episodes of reflux and difficulty swallowing meds. . Prior surgical history included: right should muscle transplant, left hand reconstruction and discectomy.

Concomitant medications included: Aleve (naproxen sodium), calcium, vitamin D (ergocalciferol) and Lortab (hydrocodone, paracetamol)

On (b) (6) after taking his 3rd dose of HYD study medication, the patient reported that he was not able to get the pill to "go down" . Subsequently, the subject reported experiencing pain and difficulty swallowing fluids or liquids. After discussion of his complaints and additional symptoms of "choking sensations" with the study investigator, the patient was instructed to go the emergency room (ER). In the ER, the patients was described as alert and appearing well, with the following vital signs: temperature of 98° Fahrenheit, heart rate of 59, blood pressure of 140/71 and pulse oximetry of 98%. On physical exam; the patient's throat exam was clear and his respiratory status was described as in no respiratory distress and normal breath sounds. ECG showed normal sinus rhythm, and incomplete right bundle branch block.

A gastroenterologist was consulted due to inability to dislodge study medication. Endoscopy was performed and revealed a tablet in "glue-like form" found stuck in the esophagus. The material was advanced along with the endoscope into the stomach. Endoscopy also revealed a proximal esophageal stricture at around 23 cm. The patient was discharged home the same day (b) (6) with the following diagnoses: 1) Proximal esophageal obstruction with a pill (appearing to contain a hygroscopic material) and expanding beyond its normal limits causing an obstruction with a glue-like gelatinous material and; 2) Proximal esophageal stricture, requiring dilation in the near future.

Reviewer's Comment: The SAE of proximal esophageal obstruction was related to HYD study drug. It is likely that the esophageal stricture found on endoscopy predisposed this patient to obstruction caused by HYD.

7.3.3 Dropouts and/or Discontinuations

Pooled chronic pain studies
The overall incidence of TEAEs leading to discontinuation of study drug during HYD exposure for pooled chronic pain studies was 17%. The system-organ-classes (SOCs)

with the highest frequency of TEAEs leading to discontinuations were the Gastrointestinal disorder SOC and Nervous System disorder SOC (7% and 6% respectively,).

HYD3002 (double-blind period)
Table 30 summarizes the incidence of AEs occurring in ≥1% of subjects leading to discontinuation of study drug by SOC and preferred term (PT) for the randomized safety population study HYD3002.

Table 30: Incidence of TEAES Occurring in ≥ 1% of Subjects Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term: Randomized Safety Population

	Double-blind Period (N=588)		
MedDRA System Organ Class Preferred Term	Placebo[a] (NN=292) n (%)	HYD (NN=296) n (%)	Overall (NN=588) n (%)
Any TEAE leading to discontinuation of study drug[c]	8 (3)	13 (4)	21 (4)
Gastrointestinal disorders	0	3 (1)	3 (1)
Nausea	0	3 (1)	3 (1)
Vomiting	0	2 (1)	2 (< 1)
Constipation	0	0	0
Abdominal pain upper	0	0	0
General disorders and administration site conditions	0	2 (1)	2 (< 1)
Fatigue	0	0	0
Nervous system disorders	2 (1)	2 (1)	4 (1)
Dizziness	0	1 (< 1)	1 (< 1)
Somnolence	0	0	0
Headache	0	1 (< 1)	1 (< 1)

Source: NDA 206627, HYD3002 CSR, Table 40, pg. 227

The overall incidence of TEAEs leading to discontinuation of study treatment during the double-blind period was 4% (4% in HYD-treated subjects and 3% in placebo subjects). Similar to pooled chronic pain studies, the Gastrointestinal disorder SOC and the Nervous system disorder SOC while relatively low had the highest percentage of AEs leading to study drug discontinuation. The highest incidences of TEAEs leading to discontinuation of study drug in HYD treated subjects were nausea, vomiting, and upper abdominal pain.

Study HYD3003
Overall, 21% of subjects in the long-term safety study had TEAEs leading to discontinuation of study treatment. The incidence of AEs leading to discontinuation of

study drug was highest in the Gastrointestinal disorder SOC (8%) and Nervous System disorder SOC (7%).

Case Narratives

Subject 2011010 was a 39 year-old white female participating in study HYD3002 who reportedly began treatment with HYD 20 mg and the dose was titrated up to HYD 40 mg per protocol. At the time of study entry, the subject's relevant medical history included: CLBP, neck pain, migraine headache, anxiety, basal cell carcinoma of cheek, basal cell carcinoma on left arm, and lumbar degenerative disc disease.

Concomitant medications included: acetaminophen, ferrous sulfate, alprazolam, hydrocodone/acetaminophen and Benadryl cold and flu.

During the run-in period, the subject took supplemental immediate-release oxycodone2 for breakthrough pain. Approximately one month after start of study drug the subject visited the study site and was short two tablets of study drug and returned only 17 tablets out of 30 oxycodone rescue tablets and she reported that the bottle had opened in her bag. The subject returned 1 whole tablet of 40 mg hydrocodone and 1 tablet that had been cut in half. The subject was discontinued from the study due to confirmed or suspected diversion.

Reviewer Comments: The subject was discontinued from the study due to confirmed or suspected diversion. She return less rescue medication that was unaccounted for and one HYD study drug tablet that was cut in half.

Subject 2071009 was a 50-year-old black female participating in study HYD3002 who reportedly began treatment with HYD 20 mg and remained on this dose until discontinuation. At the time of study entry, the subject's relevant medical history included: history of LBP, OA of the right knee, hypertension, GERD, migraine headache and insomnia.
Concomitant medications included: acetaminophen, nonsteriodal anti-inflammatory drugs, diphenhydramine, benazepril hydrochlorothiazide, meloxicam, and lansoprazole.

The subject's screening urinalysis test results were positive for hydrocodone, hydromorphone, and opiates. During the run-in period, the subject took supplemental IR oxycodone for breakthrough pain. Approximately one month after start of HYD study drug the subject returned for a dose titration visit. The subject reported to have been unclear about the dosing instructions. The subject returned with missing HYD study drug from the assigned HYD dose. In addition, the subject was reported to have returned with missing doses of rescue medication (IR oxycodone). The subject reported that she spilled the medication and that the medication was not recoverable. Since the

container of HYD study drug, as well as the container of the rescue medication had missing tablets, the investigator suspected diversion of HYD study drug and rescue medication. Subsequently, the investigator reported confirmed or suspected diversion and the subject was discontinued from the study. That same day, the total ABC and

Reviewer Comments: The subject was discontinued from the study due to confirmed or suspected diversion of HYD study drug and rescue medication (IR oxycodone).

7.3.4 Significant Adverse Events

Pease refer to Sections 7.3.2 and & 7.3.3 for a detailed discussion of significant AEs.

7.3.5 Submission Specific Primary Safety Concerns

Adverse Events of Special Interest

The Applicant discussed adverse events of special investigation (AESI) in a section by AESI category. These categories included the events of hearing impairment, related choking and obstruction risks, QT prolongation/cardiac repolarization events, aberrant drug behavior events, accidents and injuries, acute central respiratory depression, AE pregnancy outcome reproductive toxicity, cardiac failure, cardiac arrhythmias, dementia, hepatic disorders and renal and urinary disorders).

Hearing impairment and vestibular disorders
Audiology assessments were incorporated into the Phase 3 clinical studies to assess the potential for HYD to cause hearing impairment.

The number and percentage of subjects with confirmed TEAEs related to hearing impairment and vestibular disorders during HYD exposure in HYD-treated subjects for the pooled chronic pain studies are summarized in Table 31.

Table 31: Number and Percentage of HYD Subjects with Confirmed TEAEs Related to Hearing Impairment and Vestibular Disorders during HYD Exposure – 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: NDA 206627, Audiology Report, Table 43, Pg.95/121

Overall, three percent of HYD subjects experienced an AE related under the SMQ categories related to hearing impairment and vestibular disorder for pooled chronic studies. The most frequently reported hearing impairment and vestibular disorder AEs were tinnitus (3%) and dizziness (1%) respectively.

Overall, HYD subjects experiencing TEAEs related to hearing impairment and vestibular disorders during the double-blind of study HYD3002 was 2% compared to 1% in placebo subjects. The commonly reported TEAES in HYD treated subjects were dizziness and tinnitus (1% each) compared to zero placebo-treated subjects experiencing these AEs.

The Applicant reports no increased risk for hearing impairment or vestibular disorders with HYD.

The Center for Radiological Health (CDRH) – Audiology team was consulted to review the Applicant's Audiology Report and the review was completed by clinical reviewers in Audiology, Cherish Giusto AuD and Ting Zhang PhD.

Please refer to review of Dr. Gusto and Dr. Zhang for a detailed discussion regarding the Applicant's audiology program,

CDRH's overall conclusion and recommendations is summarized below:

From an 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

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 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." 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.

Of note, the Office of Scientific Investigations will be issuing an Official Action Indicated to Dr. Louise Taber (one of the sites selected for inspection) due to fraudulent audiology data. The audiology data from this site will not be adequate for review. The removal of audiology data from the audiology analyses would not change the findings.

The additional recommended analyses from CDRH are not likely to reveal additional useful data, as the studies were not designed as "outcome" trials for adverse events related to hearing. The label will include language regarding the overall finding of a lack of signal for hearing events, and will also state the data provided by the sponsor has some limitations.

Formulation-related choking and obstruction

A known consequence of the PEO excipient contained in the HYD formulation is that the tablet can swell with moisture. The Applicant analyzed formulation-related choking and obstruction under AEs of special investigation (AESI) which was based on Standardized MedDRA Queries (SMQs). The search terms were pre-specified in the ISS SAP. The SMQ categories and preferred terms which the Applicant deemed pertinent to formulation-related choking are listed in Table 44 (located in the Appendix of this review).

In the pooled chronic pain studies, there were eight reports of formulation-related choking and GI obstruction AEs in HYD-treated subjects.. Two subjects reported dysphagia, two reported esophageal obstruction and two reported vomiting. One subject reported choking and one subject reported intestinal obstruction.

A case summary narrative for a subject (#3017010) reported to have experienced nonfatal SAE related to HYD formulation-relating choking/ obstruction is discussed in Section 7.3.2. A case summary narrative review of a subject who had AEs of HYD formulation-related choking and obstruction follows.

Subject 2046019 was a 66 year-old white female who was participating in study HYD3002 who reportedly began treatment with HYD 20 mg and was not titrated up due to the AE occurring with first dose administration.

At the time of study entry, the subjects pertinent past medical history included: chronic LBP, cholelithiasis, gastroesophageal reflux disease. Concomitant medications: none reported.

While taking the first dose of HYD study drug at the beginning of the run-in period, the subject reportedly took study drug with a carbonated beverage, subsequently burped and got study drug obstructed in the esophagus. The subject experienced chest discomfort with shortness of breath; reportedly panicked and was unable to swallow the study drug. The investigator reported that the subject was able to speak and breathe throughout the event. The subject was taken to the ER where vomiting was induced and the study drug came out. That same day, the subject took the last dose of study drug before it was stopped permanently due to the AE of esophageal obstruction. The subject reportedly underwent upper GI endoscopy three days after the event with normal results. The subject was discontinued from the study nine days after the event due to the SAE of esophageal obstruction.

Reviewer's Comment: The SAE of esophageal obstruction was related to HYD study drug. This subject had a history of GERD and also reportedly took the initial dose of study drug with soda instead of water as per patient instructions. It is possible that the subject's history of GERD and taking 1st dose of HYD study drug with soda contributed to the obstruction.

QT prolongation AEs

Table 32 shows the incidence of HYD-treated subjects with QT prolongation /cardiac repolarization related TEAES for pooled chronic pain studies

Table 32: Number and Percentage of HYD-Treated Subjects with QT Prolongation/Cardiac Repolarization Related TEAEs during HYD Exposure (Pooled Chronic Pain Studies)

SMQ category Preferred term	Number (%) of HYD treated subjects (N=1827)
All SMQ category/preferred term	7 (< 1)
QT prolongation	7 (< 1)
[B] Syncope	4 (< 1)
[N] Electrocardiogram QT prolonged	3 (< 1)

Source: NDA 206627, ISS, Table 45, pg. 156/339

A total of seven in HYD-treated subjects were reported to have QT prolongation in pooled chronic pain studies. Four of these seven subjects reportedly experienced syncope and the remaining three subjects had ECG findings of prolonged QT. All of the case narrative summaries and corresponding CRFs were reviewed.

Aberrant drug behaviors

The Applicant listed abuse, overdose, and misuse/abuse and medications error under aberrant drug behavior events. The Applicant analyzed aberrant drug behaviors under AEs of special investigation (AESI) which was based on SMQs. The search terms were pre-specified in the ISS SAP. The SMQ categories and preferred terms which the Applicant deemed pertinent to aberrant drug behaviors are listed in Table 45 (located in the Appendix of this review)

In addition, the Applicant search under the database under preferred term using the different SMQ (i.e. additional medical concept and drug abuse and dependence) and found nine subjects with TEAEs related to aberrant drug behavior during HYD exposure. The case summary narratives for all these subjects are discussed below.

Table 33 shows the incidence of AEs related to aberrant drug behavior for HYD treated subjects for the pooled chronic pain studies.

Table 33: Number and Percentage of HYD-treated Subjects with TEAEs Related to Aberrant Drug Behavior During HYD Exposure by SMQ Term (Pooled Chronic Pain Studies)

SMQ category Preferred term	Number (%) of HYD treated subjects (N=1827)
All SMQ category/preferred term	9 (< 1)
Additional medical concept	2 (< 1)
Intentional drug misuse	1 (< 1)
Overdose	1 (< 1)
Drug abuse and dependence	7 (< 1)
[N] Drug abuse	5 (< 1)
[B] Drug screen positive	1 (< 1)
[N] Substance abuse	1 (< 1)

Source: NDA 206627, ISS, Table 46 pg. 159/339

The Applicant's results show overall a low percentage (<1%. N=9) of HYD-treated subjects experienced TEAEs related to aberrant drug behavior for pooled chronic pain studies. All of these cases were reviewed. The summary case narratives for HYD-treated subjects with AEs related to aberrant drug behavior for pooled chronic pain studies are discussed in this section.

Intentional Drug Misuse

Subject 2054015 was a 26-year-old white male participating in study HYD3002 and reportedly began treatment with study drug HYD 20 mg and IR oxycodone 5 mg tablets as rescue.

At the time of study entry, the subject's relevant medical history included: history of lumbar degenerative disc disease, craniosynstosis, chronic headaches, hypertension, and gastroesophageal reflux. No prior history of aberrant drub behavior was reported.

Concomitant medications included: none reported.

On day 3 of study drug dosing, an AE of overuse of rescue medication (intentional drug misuse) was reported. Per the investigator, the subject took more than 2 tablets of IR oxycodone per day because of increased pain. No treatment was given for the AE and no action was taken with study drug in response to this event. The investigator did not consider this event as abusing the study medication. Reportedly, one day after onset of the event, study drug dose was increased to HYD 40 mg. This AE of overuse of rescue medication (intentional drug misuse) was resolved 5 days later. The subject was otherwise compliant with study medications and completed the study per protocol.

Reviewer's Comment: The AE of intentional drug misuse (overuse of rescue medication) was not related to HYD study drug. It appears that the subject used more IR oxycodone because of increased pain, although by protocol instructions and criteria he misused rescue medication. Of note, the subject had been taking sublingual buprenorphine prior to study entry but discontinued on day of screening.

Drug Abuse

Subject 3060007 was a 34-year-old white female participating in study HYD3003 who reportedly began study treatment with HYD 40 mg and was titrated up to HYD 120 mg per protocol.

At the time of study entry, the subject's relevant past medical history included: history of LBP, cardiac arrhythmia, anxiety, and cervical dysplasia

Concomitant medications included: paroxetine hydrochloride, omeprazole, medinite, acetaminophen and Advil PM.

At the first dose titration visit 1, the subject reportedly brought an empty bottle stating one study drug tablet was left at home. The study coordinator gave the empty bottle back to the subject requesting that the missing tablet be put back in the bottle to be returned at the next visit.. At the next titration visit, the study coordinator dispensed a new bottle of study drug and following this visit it was discovered that the subject inadvertently took one study drug tablet from the wrong bottle when her diary alarm went off because of being extremely tired and not paying attention to which bottle she was taking the tablet from. At the next dose, the subject reported taking another tablet from the correct bottle, therefore taking two tablets of study drug instead of one. Per the advice of the medical monitor for the study, the subject was allowed to continue I n the study providing that she was retrained on how to take the study drug and the study site would not dispense two different dose strength bottles to the subject. Approximately one month after the first dose titration visit 1, the investigator was notified that the subject had been prescribed and receiving acetaminophen 325 mg/hydrocodone 10 mg tablets which was not provided by the study site. The subject was subsequently discontinued from the study with an SAE of suspected drug abuse of rescue medication hydrocodone/acetaminophen. No treatment was given for this SAE

Reviewer's Comments: The SAE of suspected drug abuse of rescue medication hydrocodone/acetaminophen was not related to HYD study drug. While it is not unusual for chronic pain patients to become tolerant to opioid, for subjects participating in study HYD3003 the access to rescue medication was determined by the investigator.

Subject 3016006 was a 59-year-old white female participating in study HYD3003 and who reportedly began study treatment with HYD 40 mg and increased to HYD 120 mg per protocol.

At that time of study entry, the subject's relevant medical history included: history of LBP, left brachial plexus paralysis, osteoarthritis of bilateral knees and bilateral hips, hypertension, diverticulitis, and irregular heartbeat.

Concomitant medications included: acetaminophen, naproxen, lisinopril/hydochlorothiazide, and docusate.

At screening, the subject's urinalysis test results were positive for hydrocodone, hydromorphone, and opiates. Approximately, two months after starting study med, the subject the subject began taking supplemental hydrocodone/APAP for breakthrough low back pain. That same day, during study visit 6, the subject reported that she dropped one pill down the drain. She also reported that one pill fell down and rolled under the dresser, which she would be returning to the site during her next study visit which was study visit 7 at which time the subject returned the missing pill. Approximately, after eight months after taking study drug, the investigator received a Medco report, which showed that the subject was prescribed acetaminophen/hydrocodone by several providers. That same day, the SAE of excess opioid medication acquisition (abuse) (drug abuse) was reported and the subject was discontinued from study.

Reviewer's Comment: The SAE of drug abuse (excess opioid medication acquisition (abuse) was not related to HYD study drug.

Subject 3001017 was a 47-year-old, black female participating in study HYD3003 who reportedly began study treatment with HYD 40 mg and was titrated up to HYD 80 mg per protocol.

At the time of study entry, the subject's relevant medical history included: history of chronic LBP, hypertension, upper extremity bilateral arthritis, lumbar radiculopathy carpal tunnel syndrome lumbar spondylosis lumbar spinal stenosis, facet joint syndrome, mild ulnar nerve entrapment, hypercholesterolemia, and anxiety.

Concomitant medications included: alprazolam, calcium, hydromorphone, folic acid, amlodipine, prednisone, estrogens conjugated, and simvastatin.
The subject's screening urinalysis test results were positive for morphine and opiates.

Approximately, one month after starting study drug SAE of controlled medication abuse (drug abuse) was reported. Per investigator, the subject had signed a pain management agreement stating that she would not receive or fill any prescriptions other than the ones given by practice. The subject broke this agreement by filling

prescriptions from two other physicians. The subject was subsequently discontinued from study. At the early discontinuation visit, the subject stated that she had not ingested the controlled medications she received from other providers; however, she could not locate the prescriptions. The outcome of the event was unknown as the subject was lost to follow-up.

Reviewer's Comments: The SAE of drug abuse (controlled medication abuse) was not related to HYD study drug.

Subject 3044018 was a 48-year-old white female participating in Study HYD3003 who reportedly began treatment with HYD 20 mg and the dose was titrated up to HYD 120 mg per protocol. At the time of study entry the subject's medical history included: low back pain, lower lumbar spine fracture, hypertension, dyslipidemia, history of stroke, migraine headaches, right ovarian tumor, intermittent hematuria and allergies to ibuprofen (Motrin) and celecoxib. Prior surgical history included right oophorectomy. No prior history of abuse was reported. The subject's urine drug screen at screening reportedly was negative

Concomitant medications included acetaminophen, aspirin, gemfibrozil, carisoprodol, lisinopril, amlodipine, nitrofurantoin and acetaminophen/caffeine/axotal.

On multiple visits, the subject did not report any dosing information. Also, the site reported drug accountability issues on multiple occasions between visit 9 and visit 17. When the subject was questioned regarding unreturned HYD tablets, the subject reported that she had been taking extra doses of HYD due to severe pain. As a result, an SAE of investigational product (IP) abuse (drug abuse) was reported and the study drug was stopped permanently due to the IP abuse (drug abuse).

Reviewer Comment: The SAE of IP drug abuse was related to HYD study drug

Subject 3098002 was a 44-year-old black female with a participating in study HYD3003 who reportedly began study treatment with HYD 20 mg and was titrated up HYD 40 mg per protocol.

At the time of study entry, the subject's relevant medical history included: chronic LBP, osteoarthritis, and obesity.

Concomitant medications: hydrocodone.

At screening, the subject's urine drug screen test results were positive for hydrocodone, hydromorphone, and opiates. Per investigator, subject was taking hydrocodone as prescribed (although hydrocodone was not reported as the subject's concomitant

medication), and the positive hydromorphone result was due to “false positive”. Approximately after one month on HYD study drug, the subject began taking HYD 40 mg two times a day. That same day, the SAE of abuse-investigation product taken twice a day instead of once daily (drug abuse) was reported. No treatment was given the SAE. The investigator reported that the subject stated that she “has been taking two 40 mg tablets daily since the last visit” and insisted that the study coordinator had instructed her to increase the dose. The investigator and the medical monitor for the study thought it very unlikely that those instructions were given (and the coordinator denied giving those instructions), since no subject ever took more than one tablet daily in this study. As a result of taking excess study drug, the subject ran out of the study drug about 5-6 days prior to the scheduled visit. It was noted that the subject’s pain scores did not improve while taking 80 mg daily and she experienced little or no withdrawal symptoms after she ran out of the study drug. The subject was discontinued from the study.

Reviewer Comments: The SAE of drug abuse (IP taken twice instead of once daily) was related to HYD study drug. It is not clear from the Applicant’s case summary narrative if this subject continued “previously prescribed” hydrocodone and/or any other opioid as rescue medication.

Subject 3045007 was a 64-year-old white female participating in study HYD3003 who reportedly began treatment with HYD 20 mg and was titrated up to HYD 60 mg per protocol.

At the time of study entry, the subject’s relevant medical history included: history of chronic LBP, L4-L5 intervertebral disc degeneration, intermittent bilateral hip pain, sensory loss in bilateral feet, hypertension, obesity, irritable bowel syndrome with diarrhea, Type 2 diabetes mellitus, hepatic steatosis, right knee arthralgia, cholelithiasis, deep vein thrombosis, ophthalmic migraine, and tobacco smoking history.

Concomitant medications: acetaminophen, NSAIDs, metformin, atenolol, glipizide, ASA, lisinopril, triamterene/hydrochlorthiazide, calcium, and hydrocodone/APAP. .

Approximately three months after being on HYD study drug, the subject took various amounts of hydrocodone/APAP for LBP over a period of approximately two weeks (i.e., hydrocodone 15/APAP 1500 mg four times per day for one day, then hydrocodone 25/APAP 2500 mg twice a day for three days; then hydrocodone 10 mg/APAP 1000 mg four time a day for two days; then hydrocodone 15 mg/APAP 1500 mg two times a day was decreased to hydrocodone 10 mg/APAP 1000 mg four time per day over the course of four day.

Approximately four months after start of HYD study drug, an AE of marijuana use (drug abuse) was reported. Per the investigator, the subject reported that she used

marijuana while she was attending a funeral because of an ophthalmic migraine. The investigator reported that this was a one-time use and that the subject had been 100% compliant with study drug. The event was considered by the investigator as not related to study drug and the subject was allowed to complete the study per protocol. Thus, this event was not included in Table 31 as an event pertaining to drug abuse**.**

Reviewer Comments: The SAE of drug abuse (THC) was not related to HYD study drug. This subject had a complicated medical history with an uncertain reported amount of rescue medication use (i.e. hydrocodone/APAP) while on the study followed by use of THC. This subject should have been discontinued from study per protocol instructions despite the investigator's rationale for allowing the subject to continue study drug and complete the study.

Substance Abuse

Subject 3005020 was a 28-year-old, white male participating in study HYD3003 who reportedly began study treatment with HYD 60 mg and titrated up to HYD 120 mg per protocol.

At the time of study entry, the subject's relevant medical history included: history of chronic LBP, anxiety and history of right shoulder musculoskeletal pain.

Concomitant medications include: acetaminophen, macrolides, NSAIDS, ASA and cyclobenzaprine.

At screening, the subject's screening urinalysis test results were positive for hydrocodone, hydromorphone, and opiates. Per the investigator, the subject was taking opioids as prescribed

Approximately seven months after taking HYD study drug, drug accountability was performed and showed six unaccounted study drug tablets. The subject claimed that these tablets were in his locker at work and he had lost his keys to the locker since a visit to the ER one month prior (for complaints of chest pain, shortness of breath and confusion.). The study site received the subject's medical records from the ER and the results of the urine drug screen (UDS) were positive for tetrahydrocannabinol (THC) and amphetamines. he subject was contacted and he denied that the results of the UDS were possible. As a result an SAE of polysubstance abuse (substance abuse) the subject was discontinued from the study however was allowed to continue a taper period. No treatment was given for the SAE of polysubstance abuse (substance abuse).

Reviewer Comments: This subject had an SAE of substance abuse (polysubstance abuse). Per the Applicant this event was not a prescription opioid medication abuse and therefore was not included in Table 31.

Overdose

Subject 3044015 was a 67-year-old white male participating in study HYD3003 and reportedly began study treatment with HYD 60 mg and was titrated up to HYD 80 mg per protocol.

At the time of study entry, the subject's relevant medical history included: history of LBP, bilateral knee OA, carpal tunnel syndrome, COPD, asthma, hypertension, sleep apnea, hypothyroidism, GERD, chronic bronchitis, status-post (S/P) left knee arthroplasty and S/P left shoulder arthroplasty, insomnia, generalized weakness secondary to use of multiple muscle relaxers, use of narcotics and sleeping aid, and chronic pain syndrome

Concomitant medications included: dutasteride, cyclobenzaprine, diazepam, gabapentin, ibuprofen, zolpidem, Azor, tamsulosin, levothyroxine, ovastatin duloxetine, propranolol and famotidine

Approximately 10 days after start of HYD study treatment, the subject's wife thought he appeared disoriented. The next morning, the subject's wife noted that his level of consciousness was decreased and he was unable to get out of bed. The subject was subsequently transferred to the ER and on exam the subject was noted to be awake but lethargic, oriented to self and place only, and able to follow few commands. The subject's BP was 114/84 mmHg, RR was 18 breaths per minute, temperature was 98.4oF, and oxygen saturation was 93% on room air. He was placed on a cardiac monitor and a 12-lead ECG showed atrial fibrillation at a rate of 103 bpm and there were no acute ST or T-wave abnormalities. Blood gases revealed CO2 retention and mild respiratory acidosis. CT of the brain was negative. The subject was treated with IV 0.4 mg of naloxene hydrochloride without any improvement in his alertness or lethargy and was subsequently admitted to the hospital. Overdose of any individual drug could not be confirmed and the subject and his wife denied overdose of a single drug. HYD study drug was withdrawn due to subject's hospitalization. The SAEs of poly drug overdose (overdose), altered level of consciousness (altered state of consciousness), and carbon dioxide retention (hypercapnia) were reported.

Reviewer Comments: The SAE of polydrug overdose was possibly related to HYD study drug. This subject was on several drugs zolipidem (sleeping aid), diazepam (benzodiazepine), cyclobenzaprine (muscle relaxant) and gabapentin.(anti-seizure medication) that may have led to symptoms as well as his state of health. The contribution of HYD to the SAEs of polydrug overdose, hypercapnia, and altered state of consciousness cannot be completed ruled out.

Drug Screen Positive

Subject 3035002 was a 57-year old white male participating in HYD3003 and reportedly began treatment with HYD 20 mg and was titrated up to HYD 60 mg per protocol.

At the time of study entry, the subject's relevant medical history included: history of LBP, and right hip arthralgia.

Concomitant medications included: ASA.

At screening, UDS was negative. Approximately 10 months after HYD study treatment an unscheduled urine drug screen was positive for THC (drug screen positive). Per the investigator the subject admitted to using THC. The subject was discontinued from the study due to UDS positive for THC and entered the taper period.

Reviewer Comments: The AE of UDS positive for THC was not related to study drug.

Pooled Clinical Pharmacology Studies

In addition, there were subjects with AEs related to aberrant drug behavior in HYD treated subjects with naltrexone block in the pooled clinical pharmacology studies. Brief summary case narratives for these three subjects follow.

Subject 000128 was a 21-year-old Hispanic female participating in study HDY1001 who reportedly had no relevant medical history and was taking no medications at the time of study entry.

After screening, the subject completed the naltrexone challenge test, was randomized and received all planned naltrexone doses for period 1. She received HYD 20 mg, medium-release tablet, fasted and one week later she experienced an AE of positive UDS for benzodiazepines. The subject reportedly discontinued the study because of administrative reasons ("unreliable subject –did not return for day 4 blood PK draw") in period one.

Reviewer Comments: This subject had an AE of positive UDS (benzodiazepine) that was not related to HYD study drug.

Subject 0001042 was a 26-year-old while male participating in study HYD1001 who reportedly had no relevant medical history (outside of seasonal allergies) and was taking to medications at the time of study entry.

After screening, the subject completed the naltrexone challenge test, was randomized and received all planned naltrexone doses for periods one and two. He received a single dose of HYD 120 mg twice separated by a seven-day washout period. Prior to period 3 dosing, the subject experienced the AE of positive UDS for cotinine. The subject was discontinued due to this AE in period two.

Reviewer Comments: This subject had a AE of positive UDS (cotinine) that was not related to HYD study drug..

Subject 0001024 (HYD1003) was a 21-year-old white male participating in study HYD1003 who reportedly receive a single dose of HYD 120 mg on study day 1.

The subject's past medical history included substance abuse that started in 2003 and was currently ongoing. However, the past medical history of substance abuse was not reported by the subject at screening

On study day 7, the subject experienced an AE of positive drug screen test result for cannabinoids (drug abuse). After the positive drug screen result, the subject was questioned and admitted to prior substance abuse. The subject's medical history was updated to include substance abuse and the subject was discontinued from the study for the AE of drug abuse on study day 7.

Reviewer Comments: This subject had a AE of positive UDS (cannabinoids) that was not related to HYD study drug. This subject had a prior history of drug abuse that was not disclosed to investigators.

In summary, during pooled chronic pain studies and clinical pharmacology studies there were cases of aberrant drug behavior related to misuse and/or abuse of HYD study drug, rescue medication (IR oxycodone), other opioids and drug screens that were positive for illicit drugs (THC). There was also a case of reported overdose. One subject (#3005020) involving an AE of drug abuse was not included in Table 31 because according to the Applicant the case did not involve prescription opioid medication abuse.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events reported in ≥ 2% of HYD subjects compared to placebo subjects for study HYD3002 are described in Table 34

Table 34: Incidence of TEAEs Occurring in ≥2% of Subjects by System Organ Class and Preferred Term: Safety Population and Randomized Safety Population

	Run-in Period (N=905)			Double-blind Period (N=588)			
MedDRA System Organ Class Preferred Term	Non-randomized (NN=312) n (%)	Randomized (NN=593) n (%)	Overall (NN=905) n (%)	Placebo[a] (NN=292) n (%)	HYD (NN=296) n (%)	Overall (NN=588) n (%)	HYD Total[b] (NN=905) n (%)
Any TEAE [c]	184 (59)	247 (42)	431 (48)	103 (35)	136 (46)	239 (41)	499 (55)
Ear and labyrinth disorders	14 (4)	10 (2)	24 (3)	5 (2)	8 (3)	13 (2)	31 (3)
Tinnitus	9 (3)	8 (1)	17 (2)	2 (1)	7 (2)	9 (2)	24 (3)
Gastrointestinal disorders	109 (35)	130 (22)	239 (26)	33 (11)	54 (18)	87 (15)	282 (31)
Nausea	77 (25)	67 (11)	144 (16)	16 (5)	24 (8)	40 (7)	166 (18)
Constipation	26 (8)	59 (10)	85 (9)	7 (2)	10 (3)	17 (3)	99 (11)
Vomiting	38 (12)	28 (5)	66 (7)	9 (3)	18 (6)	27 (5)	84 (9)
Diarrhoea	8 (3)	8 (1)	16 (2)	8 (3)	6 (2)	14 (2)	31 (3)
General disorders and administration site conditions	28 (9)	34 (6)	62 (7)	13 (4)	17 (6)	30 (5)	91 (10)
Fatigue	15 (5)	21 (4)	36 (4)	2 (1)	2 (1)	4 (1)	40 (4)
Infections and infestations	27 (9)	48 (8)	75 (8)	38 (13)	52 (18)	90 (15)	141 (16)
Upper respiratory tract infection	4 (1)	10 (2)	14 (2)	11 (4)	10 (3)	21 (4)	28 (3)
Influenza	2 (1)	5 (1)	7 (1)	3 (1)	9 (3)	12 (2)	17 (2)
Nasopharyngitis	1 (< 1)	5 (1)	6 (1)	10 (3)	3 (1)	13 (2)	11 (1)
Metabolism and nutrition disorders	7 (2)	11 (2)	18 (2)	4 (1)	12 (4)	16 (3)	32 (4)
Decreased appetite	5 (2)	6 (1)	11 (1)	2 (1)	6 (2)	8 (1)	19 (2)
Musculoskeletal and connective tissue disorders	16 (5)	26 (4)	42 (5)	22 (8)	18 (6)	40 (7)	65 (7)
Back pain	7 (2)	5 (1)	12 (1)	10 (3)	2 (1)	12 (2)	17 (2)
Nervous system disorders	93 (30)	83 (14)	176 (19)	18 (6)	29 (10)	47 (8)	204 (23)
Dizziness	39 (13)	25 (4)	64 (7)	5 (2)	9 (3)	14 (2)	74 (8)
Headache	26 (8)	33 (6)	59 (7)	5 (2)	6 (2)	11 (2)	66 (7)
Somnolence	20 (6)	21 (4)	41 (5)	2 (1)	3 (1)	5 (1)	45 (5)
Psychiatric disorders	18 (6)	24 (4)	42 (5)	12 (4)	16 (5)	28 (5)	64 (7)
Insomnia	7 (2)	7 (1)	14 (2)	5 (2)	8 (3)	13 (2)	25 (3)
Skin and subcutaneous tissue disorders	26 (8)	30 (5)	56 (6)	4 (1)	6 (2)	10 (2)	64 (7)
Pruritus	10 (3)	15 (3)	25 (3)	1 (< 1)	0	1 (< 1)	25 (3)

Sources: Table 14.3.1.1.1; Appendix 16.2.7.1.

AE=adverse event; HYD=hydrocodone bitartrate; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event. Note: TEAEs were assigned to study drug according to their onset date. AEs that started after a subject's last dose but within 4 days of dosing were considered TEAEs and were assigned to the last treatment administered. AEs that started > 4 days after the last dose of study drug were considered nonTEAEs. Multiple occurrences of the same AE in 1 individual were counted only once in the period of onset of the AE. Categories were based on MedDRA, version 16.0. N=number of subjects in the safety population in that period. NN=number of subjects in the treatment group. n=number of subjects with data. Percentages were based on NN.

[a] The placebo column includes subjects randomized to placebo but may had exposured to HYD during the taper period in the double-blind period.

[b] The HYD total column presents the AEs for all subjects while exposed to HYD, including those during the taper period for subjects randomized to placebo.

[c] This table includes TEAEs that occurred in ≥ 2% of the subjects in the run-in period overall column, placebo and HYD columns in double-blind period.

Source: NDA 206627, HYD3002 CSR, Table 25, pg. 216/6082

Overall, the incidence of TEAEs reported during the double-blind period was 41%. A higher percentage of HYD subjects compared to placebo subjects experienced any TEAE (46% versus 35% respectively,). The Gastrointestinal disorders and Infections and Infestations SOCs had the highest frequency of TEAEs reported for HYD subjects (18% each respectively) followed by the Nervous System disorders SOC at 10%.

The most commonly reported AEs for HYD-treated subjects during the double-blind period were: nausea (8%), vomiting (6%), constipation (3%), dizziness (3%), insomnia (3%), upper respiratory infection (2%) and influenza (2%).

I performed a check of the applicant's dataset using Jump and found no substantial differences that would affect my perception of the adverse event profile.

In summary, the review of common adverse events showed that HYD treated subjects experienced events usual for the opioid drug class, and the Applicant's analysis of these events appears acceptable.

7.4.2 Laboratory Findings

Overview of laboratory testing in the development program
Laboratory assessments performed in chronic pain studies were obtained at baseline and at various post-baseline time points. Clinical laboratory assessments included hematology, chemistry and urinalyses.

The Applicant provided laboratory values and change from baseline for each hematologic and blood chemistry parameter

- Shifts from baseline in hematology, blood chemistry, and urinalysis tests: The normal reference range for each parameter was used to create categories of low, normal, or high for hematology and blood chemistry tests, and normal or abnormal for urinalysis tests
- Number and percentage of subjects in each category of shift from baseline to an abnormal postbaseline peak value in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase (ALP) during HYD exposure for the pooled chronic pain studies and during study for the pooled clinical pharmacology studies.

While results from pooled chorionic pain studies, study HYD3002 (double-blind only) and study HYD3003 individually were reviewed only data from efficacy/safety study HYD3002 which had the placebo group are displayed.

7.4.2.3 Hematology

Shifts from baseline in hematologic values for the safety population of the pooled chronic pain studies were evaluated. The incidences of subjects with shifts in hematologic values were generally small and not clinically meaningful. .

Those hematologic values that had a shift of 5% or more from normal to abnormal included the following:
Shifts from normal to high included:

- neutrophils (fraction) [10% of subjects who had shifts from baseline],
- eosinophils (fraction) [7%],
- absolute monocytes (5%)

Shifts from normal to low included:

- lymphocytes (fraction) (13%),
- hematocrit (fraction) (7%).

Shifts from baseline in hematologic values for the end of the run-in period to the end of the double-blind period for the randomized safety population of study HYD3002 were generally small and not clinically meaningful. . The incidence of shifts in hematologic values from normal at the end of the run-in period to abnormal at the end of the double-blind period was similar between the placebo and HYD treatment groups with the following exceptions: hematocrit (4% v 7%, normal to low), neutrophils absolute (<1% v 4%, normal to low), eosinophils (fraction) (4% v 7%, normal to high), and neutrophils (fraction) (4% v 7%, normal to high).

The hematologic values that had a shift of 5% or more from normal to abnormal included the following:

Shifts from normal to high in the placebo and HYD treatment groups, respectively included:

- White blood cells (6% v 5%),
- Eosinophils (fraction) (4% v 7%),
- Lymphocytes (fraction) (5% v 5%),
- Absolute monocytes (3% v 5%),
- Neutrophils (fraction) (4% v 7%), and
- Absolute neutrophils (3% v 5%)

The shifts from baseline in hematologic values for the safety population of the long-term safety study HYD3003 were small and not clinically meaningful. The hematologic values that had a shift of 5% or more from normal to abnormal included the following:

Shifts from normal to high included:

- neutrophils (fraction) (11% of subjects who had changes from baseline) and
- Eosinophils (fraction) (8%)

Shifts from normal to low included:

- Lymphocytes (fraction) (14%),
- Hematocrit (8%),
- Hemoglobin (5%), and
- White blood cells (5%).

7.4.2.4 Chemistry

Shifts from baseline in blood chemistry values for the safety population of the pooled chronic pain studies were evaluated and generally the incidence of HYD subjects with shifts outside of the normal range was small and not clinically meaningful. Blood chemistry values that shifted by from normal at baseline to abnormal at the end of HYD exposure in ≥ 5% of subjects were:

Shifts from normal to high values included: triglycerides (21%), total cholesterol (10%), ALT (7%), lactate dehydrogenase (7%), uric acid (6%), AST (6%), blood glucose (6%), phosphorus/inorganic phosphate (6%), bicarbonate/carbon dioxide (5%), potassium (5%), and creatinine (5%)

Shifts from normal to low values included: total bilirubin (10%) and total protein (7%).

Shifts from baseline in blood chemistry values for the end of the run-in period to the end of the double-blind period for the randomized safety population in study HYD3002 were small and not clinically meaningful. The blood chemistry values that had a shift of 5% or more from normal to abnormal included the following:

Shifts from normal to high values in the placebo and HYD treatment groups, respectively included: triglycerides (24% v 19%), total cholesterol (15% v 12%), uric acid (8% v 8%), phosphorus/inorganic phosphate (4% v 7%), ALT (4% v 6%), AST (6% v 7%), lactic dehydrogenase (6% v 6%), potassium (5% v 4%), and creatinine (3% v 5%)

Shifts from normal to low values in the placebo and HYD treatment group respectively, included: BUN (2% v 7%) and total bilirubin (13% v 10%).

Similar to the pooled chronic pain studies, the shifts from baseline in blood chemistry values for the safety population of the long-term safety study (HYD3003) were small and not clinically meaningful during HYD treatment. The blood chemistry values that had a shift in ≥ 5% of subjects included
:
Shifts from normal to high values: triglycerides (22%), total cholesterol (11%), ALT (8%), AST (7%), bicarbonate/carbon dioxide (7%), lactic dehydrogenase (7%), blood glucose (6%), phosphorus/inorganic phosphate (6%), ALP (5%), potassium (5%), and uric acid (5%)

Shifts from normal to low values: total bilirubin (10%) and total protein (8%).

7.4.3 Vital Signs

Vital sign assessments included systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR), and temperature (T). Weight was also included in some summary tables for vital sign values.

This section presents mean change of vital sign values from baseline, incidence of outliers, and clinically significant vital sign findings for the pooled chronic pain studies, the double-blind period study HYD3002 and long-term safety study HYD3002.

The Applicant defined outliers in the aforementioned studies by the following criteria:

- HR: ≤ 50 (bpm) or ≥ 120 bpm and change from baseline > 30%
- SBP: ≤ 90 mm Hg or ≥ 180 mm Hg & change from baseline > 30%
- DBP: ≤ 50 mm Hg or ≥ 105 mm Hg & change from baseline > 30%
- RR < 12 breaths/min or > 20 breaths/min

The Applicant defined clinically significant decreases in BP (i.e., hypotension) for the pooled chronic pain studies, study HYD3002, and study HYD3003, by the following criteria:

- Systolic blood pressure: < 100 mm Hg and difference from baseline of ≥ 30 mm Hg
- Diastolic blood pressure: < 60 mm Hg and difference from baseline of ≥ 15 mm Hg
- Hypotension: either or both of the above.

Pooled chronic pain studies

Mean Vital Sign Changes, Baseline to End of HYD Exposure for HYD-Treated Subjects

The mean changes in SBP, DBP, HR, RR and T were -0.3 mm Hg, -0.3 mm Hg, -0.2 beats/min, 0 breaths/min and 0.02 Celsius respectively. These changes were small and not clinically meaningful.

Incidence of Outliers

The vital sign with the highest percentage of outliers was high respiration rate (> 20 breaths per minute), which was observed in five percent of HYD treated subjects in pooled chronic pain studies

Clinically significant vital sign findings

Overall, five percent of HYD subjects experienced hypotension for pool chronic pain studies

Study HYD3002

Mean Vital Sign Changes, Baseline to End of HYD Exposure for HYD-Treated Subjects

The mean change in vital sign values from the end of the run-in period to the end of the double- blind period for the randomized safety population of study HYD3002 are displayed in Table 35

Table 35: Mean Vital Sign Changes from End of Run-In Period to End of Double-blind Period for Randomized Safety Population (Study HYD3002)

	Placebo[a] (N=292)		HYD (N=296)	
Vital sign parameter (unit)	NN, Mean at EORI	NN, Mean change from EORI to EODB (SD)	NN, Mean at EORI	NN, Mean change from EORI to EODB (SD)
Systolic blood pressure (mm Hg)	292, 124.4	288, 0.2 (11.31)	295, 124.0	292, 0.8 (11.49)
Diastolic blood pressure (mm Hg)	292, 77.2	288, 1.0 (8.06)	295, 77.9	292, 0.7 (9.08)
Heart rate (beats/min)	292, 73.3	288, 1.1 (10.22)	295, 73.1	292, 0.4 (10.02)
Respiratory rate (breaths/min)	292, 16.6	288, 0.1 (1.93)	295, 16.6	292, -0.2 (1.97)
Temperature (				

Source: NDA 206627, ISS, Table 80, pg. 232/339

During the double-blind period, mean changes in vital signs were small and not clinically meaningful and mean changes were similar between the HYD and placebo treatment groups.

Incidence of Outliers

Table 36 summarizes the percentage of HYD-treated subjects that experienced outlier vital signs as defined by the Applicant.

Table 36: Number and Percentage of HYD-Treated Subjects with Clinically Notable Vital Signs During the Double-Blind Period: Randomized Safety Population (Study HYD3002)

	Placebo[a] (N=292) n/NN (%)	HYD (N=296) n/NN (%)
Systolic Blood Pressure (mm Hg)		
High: Obs ≥ 180 and IFB of ≥ 20	3/288 (1)	2/293 (1)
Low: Obs ≤ 90 and DFB of ≥20	0/288	1/293 (< 1)
Diastolic Blood Pressure (mm Hg)		
High: Obs ≥ 105 and IFB of ≥ 15	2/288 (1)	4/293 (1)
Low: Obs ≤ 50 and DFB of ≥ 15	0/288	0/293
Heart Rate (beats/min)		
High: Obs ≥ 120 and IFB of ≥ 15	0/288	0/293
Low: Obs ≤ 50 and DFB of ≥ 15	0/288	1/293 (< 1)
Respiratory Rate (breaths/min)		
High: Obs > 20	4/288 (1)	7/293 (2)
Low: Obs < 12	7/288 (2)	4/293 (1)

Source: NDA 206627, ISS, Table 82, pg. 235/339

Vital sign outliers as defined by the Applicant occurred at a higher frequency in HYD-treated subjects compared to placebo subjects during the double-blind period of study HYD3002. A relatively small number of HYD-treated experienced events of hypertension, hypotension, and bradycardia. Of note, the highest incidence of vital sign outliers occurred HYD-treated subjects who experienced an increased respiratory rate (2%)

Clinically significant vital sign findings (i.e. hypotension)
Clinically significant blood pressure decreases as defined by the Applicant for the HYD treatment group included 1% of subjects with low SBP, 2% of subjects with low DBP and 2% of subjects with hypotension. The incidences were similar in the placebo group, with 0 subjects with low SBP, 3% of subjects with low DBP and 3% of subjects with hypotension.

Study HYD3003
Mean Vital Sign Changes ,Baseline to End of HYD Exposure for HYD-Treated Subjects
Similar to the pooled chronic pain studies, there were no clinically meaningful changes in vital sign values between baseline and the end of HYD exposure.

Incidence of Outliers
The overall incidence of hypotension was 1% of HYD subjects with low SBP and < 1% of HYD subjects with low DB.

Clinically significant vital sign findings (i.e. hypotension)
Overall, clinically significant blood pressure decreases as defined by the Applicant for HYD exposure in study HYD3003 included 1% of subjects with low SBP and < 1% of subjects with low DBP.

Oxygen Saturations (Pulse Oximetry)
Respiratory depression is a serious and sometime fatal adverse event associated with opioid use. The Applicant reports that pulse oximetry tests were performed at various time points during the 11 clinical pharmacology studies. Of note, seven of the 11 clinical pharmacology studies were conducted under naltrexone block.

No clinically meaningful changes from baseline in SpO2 were reported during these studies, none of the individual Sp02 measurements were reported to be clinically significant, and no Sp02 results were reported as AEs.

7.4.4 Electrocardiograms (ECGs)

ECGs were conducted at screening, the end of run-in period, Week four visit, and study drug discontinuation visit and/or end-of study/early discontinuation visit in the primary efficacy/safety study (HYD3002).

In the open-label, long-term safety study (HYD3003), ECGs were conducted at screening, Day 1 and Weeks 4, 12, 24, 36, 48 and 52/EOC/ECD visit of the maintenance period.

ECG evaluation by the Applicant included: RR, PR, QRS, and QT interval durations as well as corrected QT measurements using both Bazett's (QT/√RR) and Frederica's (QT/RR1/3) formulas (denoted as QTcB and QTcF, respectively). The analyses (mean changes from baseline and shifts from baseline) for ECG parameters were reported for pooled chronic pain studies, study HYD3002 individually, study HYD3003 individually and clinical pharmacology studies.

An additional analysis performed by the Applicant for pooled chronic pain studies, study HYD3002 DB only, HYD3003 only and clinical pharmacology studies was cardiac repolarization outlier results. Outliers were categorized by:

- Treatment-emergent QTcB /QTcF interval values > 500 msec or > 480 msec with a concurrent change from baseline > 60 msec (averaged over 3 ECG tracings obtained at each visit; ≤ 500 msec at baseline)
- Treatment-emergent QTcB /QTcF mean changes in interval values > 30 but ≤ 60 msec from baseline
- Treatment-emergent QTcB /QTcF mean changes in interval values > 60 msec from baseline.

ECG results showed:

- For pooled chronic pain studies, the mean changes from baseline to the end of HYD exposure in QT interval, QTcB, QTcF and heart rate values (-3.7 msec, 1.5 msec, -0.4 msec and 1.9 beats/min respectively) were small and did not appear to be clinically meaningful.
    - Small changes from baseline for ECG parameters were seen in HYD-treated subjects and these small changes were similar to those of placebo-treated subjects during the randomized period of study HYD3002 (DB period). Similar results were reported for study HYD3003 as those for pooled chronic pain studies.
- For pooled chronic pain studies, one subject (#3051016 in study HYD3003) had a mean QTcF >500 msec or >480 msec with a concurrent change from baseline of ≥60 msec that was reported as an AE of ECG QT prolongation The case narrative for this subject is described in Section 7.3.2

The incidence of AEs related to QT prolongation or cardiac repolarization in HYD-treated subjects in the pooled chronic pain studies is presented in Table 37.

Table 37: Number and Percent of HYD-Treated Subjects with QT Prolongation/Cardiac Repolarization - Related TEAEs During HYD Exposure (Pooled Chronic Pain Studies)

SMQ category Preferred term	Number (%) of HYD treated subjects (N=1827)
All SMQ category/preferred term	7 (< 1)
QT prolongation	7 (< 1)
[B] Syncope	4 (< 1)
[N] Electrocardiogram QT prolonged	3 (< 1)

Source: ISS Appendix 10.2 Table 6.9.1.2.
[B]=broad search; [N]=narrow search; SMQ=standard MedDRA query.
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.

Source: NDA 206627 Hydrocodone ER, ISS Appendix, Tablet 6.9.1.2

A total of 7 subjects were reported to have QT prolongation in pooled chronic pain studies. Four subjects reportedly experienced episodes of syncope and three subjects had ECG findings consistent with QT prolongation. The case narratives and CRFs for all seven subjects were reviewed. The case narrative of one subject with confirmed ECG prolongation is discussed in Section 3.7.2

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT (TQT) Study
The Applicant performed a Thorough QT study, which evaluated the effect of multiple doses (once daily for 3 days) of HYSINGLA ER at 80, 120 and 160 mg in a double-blind, randomized, placebo and positive-controlled (moxifloxacin 400 mg), 3-treatment parallel-group, dose escalating study in 185 healthy male and female subjects aged 18 to 55 years. The dose escalation and taper sequence for once daily dosing for three days of each HYSINGLA ER dose strength was: 20, 40, 80, 120, 160, 80 and 120 mg. "

The QTc evaluation for HYSINGLA ER consisted of 14 measurements during the third day of 80, 120 and 160 mg HYSINGLA ER dosing, when the plasma concentrations of hydrocodone and its metabolites, hydromorphone and norhydrocodone were at steady state. The QTc effects of placebo and moxifloxacin treatments were evaluated at each of the corresponding time points

The Applicant's interpretation of the TQT study includes:
- There was no clinically meaningful effect on mean QTc at either 80 or 120 mg [HYSINGLA ER] doses at steady state
- The maximum tested dose of 160 mg [HYSINGLA ER} administered once daily for 3 days without naltrexone blockade was adequately tolerated in healthy male and female subjects. This [HYSINGLA ER] dose prolonged time-matched, placebo-

adjusted change from baseline mean QTcI by a maximum of 9.85 (two-sided 90% CI: 6.73 – 12.97) msec.

- The magnitude of QTcI prolongation at [HYSINGLA ER] 160 mg was similar to the prolongation following each of the three successive moxifloxacin evaluations in the study.

IRT Committee Interpretation of Thorough QT Study
Overall summary of their findings is presented in Table 38.

Table 38: Point Estimates and the 90% CI Corresponding to the Largest Upper Bounds for HYD (80 mg, 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.
Source: IRT Consult Response

The IRT Committee reports the following:

> 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) msec, 6.9 (10.2) msec, and 5.6 (8.5) msec 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 msec, 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 msec, and the moxifloxacin profile over time is adequately demonstrated …..indicating that assay sensitivity was established.
>
> 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.

Overall, there was mild prolongation of the QT interval with the HYD 120 mg dose. Per discussion with the IRT Committee, Please see Section 9.2 for labeling recommendations.

7.4.6 Immunogenicity

No human immunogenicity studies were conducted to support this NDA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Applicant evaluated dose-dependency for AEs by number and percentage of subjects with AEs for the pooled chronic pain studies, the pivotal study HYD3002 double-blind period alone, and the maintenance period of study HYD3003. These latter two analyses were to be representative of a stable HYD dose.

In the pooled chronic pain studies, a dose-response relationship was observed between AEs and HYD exposure with an increase in the frequency of AEs corresponding with increasing doses of HYD. In the double-blind period of study HYD3002 there was no dose- response relationship observed for AEs and randomized HYD doses. Also, during the maintenance period of study HYD3003 a dose-response relationship was not observed between AEs and increasing HYD doses.

7.5.2 Time Dependency for Adverse Events

To evaluate time dependency for AEs, the Applicant provided Kaplan-Meier estimates of time to first occurrence of any AE, any severe AE, and any AE leading to discontinuation of study in HYD-treated subjects in the pooled chronic pain studies.

Generally, for any AE and AEs commonly reported with the use of opioid analgesics (i.e.,, nausea, vomiting, dizziness and somnolence) the rate of increase in AEs was highest up to the first two months of HYD treatment and after that time the rate of AEs gradually slowed (months 2 – 6) and reached a plateau (after 6 months). For AEs leading to discontinuation a similar pattern to that of any AE of time dependency was observed. However, for severe AE the rate of increase in AEs appeared to steady over the course of approximately 13 months.

7.5.3 Drug-Demographic Interactions.

Please refer to Dr. Srikanth Nallani's Clinical Pharmacology review for a full discussion of drug-demographics interactions and recommendations for labeling.

Age and Gender

Study HYD1006 was a single-center, open-label, and parallel-group, study that evaluated the effects of age and gender on the PK, safety and tolerability of a single-dose of 40 mg A total of 50 subjects were randomized into one of 4 four cohorts based on their age and gender:

- Cohort A – 12 young adult healthy female subjects (ages 20-45),
- Cohort B - 12 young adult healthy male subjects (ages 20-45)
- Cohort C – 12 elderly female subjects (ages 65-77 years)
- Cohort D – 13 elderly male subjects (ages 65- 77 years)

Each subject received a single-dose of HYD 40 mg under fasting conditions and with naltrexone blockade. Subjects were categorized into four cohorts: Standard PK parameters were calculated for hydrocodone and its metabolites norhydrocodone and hydromorphone.

Standard PK parameters were calculated for hydrocodone and its metabolites, norhydrocodone and hydromorphone. Statistical analysis of the age and gender effects on the pharmacokinetics of hydrocodone and its metabolites was performed using an analysis of variance model (ANOVA) on the natural logarithms of $AUC_{inf,}$ AUCt, and Cmax with age, gender, and age-by-gender interaction as fixed effects. If the age-by-gender interaction was not significant at the 0.10 level of significance ($\alpha>0.10$), then the model was re-run without the age-by-gender interaction term and the comparison of young versus elderly included both males and females. If interaction was significant ($\alpha\leq0.10$), the comparison of young versus elderly was made separately for males and females. The same approach was taken for the comparison of females versus males. The 90% CIs for the ratio of the means was computed (elderly/young and female/male) from this model.

Study Results
Pharmacokinetic results

- Age-related mean differences in AUCinf and Cmax of hydrocodone were reported as 16%
- Gender-related mean differences in AUCinf and Cmax of hydrocodone were reported as 5%.

Safety results
A total of 98% of subject completed the study. One subject (26 year-old female in Cohort A) was discontinued from the study due to AEs of dizziness, headache, nausea and vomiting. There were no SAEs (including deaths) or severe AEs reported in the study. Overall, 40% of subject experienced at least one AE. The majority of AEs were reported as mild (39%) and 9% were moderate. The percentage of subjects in each cohort that experienced any TEAE (in order of decreasing frequency) were; elderly male (19%), young female (18%), elderly female (10%) and young male (1%). Cohort D consisting of elderly male subjects appeared to experience AEs common to opioids including: vomiting, headache, nausea, and decreased appetite.

In summary, in a controlled PK study elderly subjects (≥ 65 years of age) compared to young adult subjects had similar hydrocodone exposure. Generally, dose adjustments based on age or gender will not be required for HYD. However, observe caution in HYD dose selection for debilitated, opioid-naïve or non-opioid tolerant elderly subjects starting at the lower end of the dosing range.

Controlled Trials
In pooled chronic pain studies, of the 1827 subjects exposed to HYD, 13% (241/1827) were ≥65 years of age and 2% (42/1827) were ≥75 years of age.

Adverse Events Categorized by Gender
The incidence of AEs in ≥ 2% of subjects treated with HYD in the pooled chronic pain studies was analyzed to determine if there was a difference in AE profiles between male and female subjects. The overall incidence of AEs was higher in female subjects (73%) compared with male subjects (65%).

The incidence of AEs (≥ 2% in either subgroup) for which the percentage was higher in female subjects than in male subjects (≥ 2%) were reported for: nausea (24% v 17%), vomiting (12% v 7%), edema peripheral (3% v 1%), Upper respiratory tract infection (7% v 4%), urinary tract infection (6% v 1%), sinusitis (4% v 2%), bronchitis (3% v 1%), fall (3% v 1%), back pain (4% v 2%), headache (10% v 6%), and somnolence (9% v 7%).

Adverse Events Categorized by Age
The incidence of AEs in ≥ 4% of subjects treated with HYD in the pooled chronic pain studies was analyzed to determine if there was a difference in AEs when analyzed by age. There was an increase in the incidence of AEs with increasing age (< 65 years versus ≥ 65 years versus ≥ 75 years), especially for AEs associated with the use of systemic opioid analgesics, including constipation, dizziness, dry mouth, lethargy, insomnia, anxiety, and rash.

Race
The Applicant did not formally study the effect of race on HYD PK. However, the Applicant did evaluate AEs categorized by race. The incidence of AEs in ≥ 2% of

subjects treated with HYD in the pooled chronic pain studies was analyzed to determine if there was a difference among races in the incidence of AEs. As previously mentioned, the racial group with the greatest proportion of subjects in the pooled chronic pain studies was white (76.7%), followed by black (17.7%) and subjects of other races (5.6%).

Overall, the incidence of AEs was 73% for white subjects, 62% for black subjects, and 49% for subjects of other races. For individual AEs, white subjects had the highest incidence of AEs, followed by black subjects and then by subjects of other races for the following AEs: tinnitus (4% v 3% v 2%), constipation (17% v 12% v 9%), diarrhea (5% v 3% v 2%), dry mouth (3% v 2% v 0), fatigue (6% v 5% v 4%), headache (9% v 8% v 6%), insomnia (5% v 3% v 2%), hyperhidrosis (3% v 2% v 1%), and bronchitis (2% v 1% v 0).

Black subjects had the highest incidence of AEs, followed by white subjects and subjects of other races for nausea (23% v 21% v 15%), vomiting (11% v 10% v 8%), and peripheral edema (3% v 2% v 1%). Subjects of other races had the highest incidence of dizziness (12% v 11% v 9%), followed by black subjects and white subjects

In summary, elderly subjects (≥65 years of age) experienced more TEAEs (specifically AEs associated with opioid use) compared to young adult subjects (<65 years of age) during clinical trials. There were no appreciable differences between male and female HYD subjects with respect to TEAEs reported during clinical trials. Similarly, no clinically meaningful differences were noted among racial groups being treated with HYD..

7.5.4 Drug-Disease Interactions

Please refer to Dr. Srikanth Nallani's Clinical Pharmacology review for a full discussion of drug-disease interactions and labeling recommendations.

The safety of HYD was formally evaluated in patients with hepatic impairment and renal impairment. A brief summary of these studies and Applicant results follows.

Hepatic Impairment

Study HYD1007 was a multicenter, open-label, single-dose, parallel-group study conducted in 32 male and female subjects, aged 18 to 80 years, with hepatic impairment as defined by the Child-Pugh classification system (mild [group A], moderate [group B], or severe [group C]), and in subjects with normal hepatic function (group D, healthy) to evaluate the effect of hepatic impairment on the PK of a single dose of HYD 20 mg

Following a 10-hour overnight fast, study subjects received a single oral dose of HYD 20-mg tablet under fasting conditions. All 32 randomized subjects (100%) completed the study: 8 with mild, 8 with moderate, and 8 with severe hepatic impairment, and 8 with normal hepatic function.

Study Results
The Applicant reports hydrocodone exposure in subjects with mild hepatic impairment and normal hepatic function was similar. The (AUCinf) of hydrocodone increased by 14% and 21% in subjects with moderate and severe hepatic impairment, respectively, compared with subjects who had normal hepatic function. Cmax was reported to be similar across all hepatic function groups.

There were no SAEs (including deaths), or discontinuations due to AEs.
Overall, 34% of subjects experienced at least one AE. Adverse events were reported by 3 subjects with mild hepatic impairment (38%), 3 subjects with moderate hepatic impairment (38%), 3 subjects with severe hepatic impairment (38%), and 2 subjects with normal hepatic function (25%).

In summary, there may be a higher systemic exposure of HYD in severe hepatic impairment patients. A low initial dose of HYD in these subjects is warranted and close monitoring for adverse events is critical.

Please see Dr. Srikanth Nallani's review for a full discussion of the effect of HYD on PK and safety in subjects with mild, moderate and severe hepatic impairment compared to subjects with normal renal function and labeling recommendations

Renal Impairment

Study HYD1008 was a multicenter, open-label, single-dose, parallel-group study conducted in41 adult male and female subjects, aged 18 to 80 years, with renal impairment categorized based on estimated glomerular filtration rate (eGFR) (mild [group B], moderate [group C], severe [group D], and end-stage renal disease [ESRD] [group E]), and in subjects with normal renal function (group A, healthy) to evaluate the effect of renal impairment on the PK and safety of HYD 60 mg

Subjects in groups A-D were administered a single HYD 60-mg tablet. Subjects with ESRD were administered a HYD 60-mg tablet on 2 occasions, once in each of 2 periods separated by a 14-day washout period: once 90 minutes before hemodialysis (E1, with dialysis), and once 90 minutes after hemodialysis (E2, without dialysis). Naloxone was first administered as a challenge test, and then naltrexone HCl was administered with study drug to minimize opioid-related AEs.

Study Results
All 41 randomized subjects (100%) completed the study: nine with mild, eight with moderate, and eight with severe renal impairment, eight with ESRD, and eight with normal renal function.

Hydrocodone exposure in subjects with mild renal impairment was similar to subjects with normal renal function, whereas in moderate and severe renal impairment subjects respectively, the AUC increased 63% and 58% and Cmax increased 23% and 11% respectively compared with subjects with normal renal function.

Subjects with ESRD reportedly had increases in hydrocodone AUC (5%) with dialysis and area under the plasma concentration time-curve from 0 hrs. to 72 hrs. after dosing (AUC0-72) (46%) without dialysis compared with subjects with normal renal function. The corresponding Cmax was 13% lower and 22% higher, respectively.

Overall, 63% of subjects experienced at least 1 AE including 38%with normal renal function, 56% with mild renal impairment, 75% with moderate renal impairment, 75% with severe renal impairment, 63% with ESRD during period 1, and 75% with ESRD during period 2. One severe renal impairment subject was reported to have experienced an SAE of sepsis syndrome that was associated with clinically notable changes in vital sign values and resulted in hospitalization. The AEs that were reported in at least 2 subjects in any group were GI disorders (i.e., constipation, nausea, and vomiting), nervous system disorders (i.e., dizziness and headache), metabolism and nutrition disorders (i.e., decreased appetite), and general disorders and administration site conditions (i.e., fatigue).

In summary, subjects with moderate or severe renal impairment or end stage renal disease have higher plasma concentrations of HYD than those with normal renal function. A low initial dose of HYD in these subjects is warranted and close monitoring for adverse events is critical.

Please see Dr. Srikanth Nallani's review for a full discussion of the effect of on the PK and safety in subjects with mild, moderate and severe renal impairment, and ESRD compared to subjects with normal renal function.

7.5.5 Drug-Drug Interactions

Please refer to Dr. Srikanth Nallani's review for a full discussion of HYD drug-drug interactions and labeling recommendations.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were performed using HYD.

7.6.2 Human Reproduction and Pregnancy Data

There were no studies conducted using HYD during pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

No studies were performed in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

HYSINGLA ER contains hydrocodone bitartrate, a Schedule II controlled substance with a known potential for abuse, overdose and tolerance issues. The increased content of hydrocodone in the ER formulation adds to the risk of adverse outcomes such as overdose, drug abuse and misuse.

Overdose
One subject death due to acute hydrocodone, cyclobenzaprine and citalopram toxicity was reported in the clinical development program. Please refer to Section 7.3.2 for the subject case narrative.

Drug Abuse Potential
The Applicant conducted *in vitro* testing, two human abuse potential studies and one survey evaluating the attractiveness of HYD for abuse and tampering.

The Controlled Substances Staff (CSS) was consulted to evaluate results of *in vitro* testing and HAP studies. The CSS review of these studies is ongoing.

In Vitro Studies
In *vitro* physical and chemical tablet manipulations studies were performed to evaluate the success of different extraction methods in defeating the controlled-release properties of HYD. These methods included:
Study 1: Physical Manipulation and Determination of Test Articles
Study 2: Solvent Extraction
Study 3: Thermal Stressing
Study 4: Syringeability
Study 5: Simulated Smoking (Vaporization)

Study 6: Dissolution of Physically Manipulated Tablets in Simulated Gastric Fluid
Study 7: Free Base Isolation Techniques

The comparator in these studies was generic hydrocodone (10 mg)/acetaminophen 325 mg (10 mg HC/325 mg APAP) since extended-release hydrocodone was not yet available. Studies were conducted by independent laboratories.

Human Abuse Potential (HAP) Studies

Study HYD1013 was a single-center, randomized, double-blind, 5-way crossover study conducted in male and female nondependent recreational drug users with moderate opioid experience, ages 18 to 55 years, to evaluate the oral abuse potential, PD effects, PK, and safety of intact HYD, milled HYD, and chewed HYD tablets compared to hydrocodone active pharmaceutical ingredient (API) oral solution and placebo.

Forty subjects were randomized to receive each of the following as a single dose and separated by a washout period of five to seven days.
1. Oral intact HYD 60 mg
2. Oral milled HYD 60 mg
3. Oral chewed HYD 60 mg
4. Oral hydrocodone API solution and
5. Oral placebo

Study HYD1004 was single-center, randomized, double-blind, placebo-controlled, 4-way crossover study conducted in male and female nondependent recreational opioid users with moderate opioid experience and a history of intranasal abuse, ages 18 to 55 years, to evaluate the intranasal abuse potential, PD, PK, and safety profile of intranasally administered HYD (fine and coarse particle size) compared with hydrocodone API powder and placebo.

Thirty-two subjects were randomly assigned to receive each of the following as a single dose and separated by a washout period of five to seven days:
1. Intranasal HYD 60 mg API powder
2. Intranasal milled HYD 60 mg in fine particle size
3. Intranasal HYD60 mg in coarse particle size and
4. Placebo

The preliminary findings of CSS demonstrate that HYSINGLA ER has abuse-deterrent features that may mitigate abuse by the intravenous and nasal routes. Please refer to the CSS review for their final determination and recommendations regarding the in vitro studies and HAP studies.

Survey Evaluation Attractiveness of HYD for Abuse and Tampering

Study HYD1015 was a noninterventional (no treatment), single-session, interview-based investigation of the attractiveness of HYD for abuse and tampering compared with other opioid formulations. A (b) (4)

Incidence of Adverse Events Associated with Drug Abuse Potential

The Applicant evaluated the incidence of AEs associated with drug abuse potential. The Applicant reports that any AE possibly associated with substance abuse was included regardless of whether a subject was found to have actually abused study drug or another substance. Table 39 displays the Applicant's data involving incidence of AEs associated with drug abuse potential that occurred in subjects exposed to HYD in the pooled chronic pain studies, the double-blind period of study HYD3002 and pooled clinical pharmacology studies.

Table 39: Number and Percent of Subjects with TEAES Associated with Drug Abuse Potential (Safety Population and Randomized Safety Population)

	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: NDA 206627, ISS, Table 109, pg. 316/339

There was a higher incidence of euphoria-related AEs and CNS depressant effects in HYD-treated subjects during pooled chronic pain studies and pooled clinical pharmacology studies. Because HYSINGLA ER is a mu opioid, it would be expected that CNS effects would occur in subjects being treated with HYSINGLA ER.

Withdrawal

The Applicant summarized AEs associated with opioid withdrawal according to definitions for withdrawal using DSM-IV term (PT), and definitions for withdrawal using Standardized MedDRA Query (SMQ drug withdrawal) term (PT). Based on DSM-IV criteria, opioid withdrawal syndrome was defined as having AEs during the titration period in at least 3 of the following categories: dysphoric mood (dysphoria); nausea or vomiting; muscle aches (myalgia); lacrimation (lacrimation increased) or rhinorrhea; pupillary dilation (mydriasis), piloerection, or sweating (hyperhidrosis); diarrhea; yawning; fever (pyrexia); and insomnia.

The incidence of AEs associated with opioid withdrawal, as defined by DSM-IV term (preferred term) and SMQ term by previous opioid experience in the pooled chronic pain studies is summarized in Table 40.

Table 40: Number and Percent of HYD-Treated Subjects with TEAEs Related to Opioid Withdrawal During HYD Exposure by DSM-IV Term, SMQ/Preferred Term, and Previous Opioid Experience (Pooled Chronic Pain Studies)

	Opioid Naïve (N=810) n (%)	Opioid Experienced (N=1017) n (%)	Overall (N=1827) n (%)
Subjects with at least 3 symptoms with OW by DSM-IV criteria[a]	21 (3)	34 (3)	55 (3)
Subjects with any AE related to opioid withdrawal	248 (31)	300 (29)	548 (30)
DSM-IV term [preferred term]			
Nausea [nausea]	197 (24)	187 (18)	384 (21)
Vomiting [vomiting]	90 (11)	94 (9)	184 (10)
Diarrhea [diarrhea]	34 (4)	53 (5)	87 (5)
Insomnia [insomnia]	22 (3)	60 (6)	82 (4)
Sweating [hyperhidrosis]	17 (2)	30 (3)	47 (3)
Fever [pyrexia]	7 (1)	14 (1)	21 (1)
Muscle aches [myalgia]	9 (1)	10 (1)	19 (1)
Rhinorrhoea [rhinorrhea]	3 (< 1)	8 (1)	11 (1)
Lacrimation [lacrimation increased]	0	7 (1)	7 (< 1)
Yawning [yawning]	0	1 (< 1)	1 (< 1)
SMQ preferred term			
Drug withdrawal syndrome (narrow)	3 (< 1)	13 (1)	16 (1)
Withdrawal syndrome (broad)	0	1 (< 1)	1 (< 1)

Source: NDA 206627, ISS, Table 110, pg. 320/339

Overall, 30% of HYD-treated subjects experienced an AE possibly related to opioid withdrawal for pooled chronic pain studies. Opioid-naïve subjects had higher incidence of an AE related to withdrawal compared to opioid-experienced (31% versus 29% respectively,). It appears that gastrointestinal symptoms (e.g., nausea, vomiting and diarrhea) were the most frequently reported symptoms possibly related to opioid withdrawal, however these are also common symptoms associated with the use of opioids, and the fact that the rate was higher in opioid naïve subjects, a group that would be less likely to experience opioid withdrawal, implies that these GI events were more likely related to opioid use. It would be expected that withdrawal symptoms would occur in subjects who abruptly stopped treatment with HYSINGLA ER, rather than tapering. .

7.7 Additional Submissions / Safety Issues

During the review cycle, the review team had multiple communications with the Applicant via email for Information Requests and clarifications.

8 Postmarket Experience

There is no postmarket experience associated with HYSINGLA ER. .

9 Appendices

9.1 Literature Review/References

Non-applicable

9.2 Labeling Recommendations

The labeling review is ongoing.

Per the IRT Committee, the following recommendations have been made regarding tQT Prolongation:

> **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) msec, 7 (10) msec, and 6 (9) msec at [TRADENAME] 160 mg, 120 mg and 80 mg respectively.

The Clinical Pharmacology review team has made the following recommendations regarding the label with respect to drug-disease interaction, drug-drug interactions and drug-demographic interactions.

SECTION 7 DRUG INTERACTIONS

7.7 Strong Laxatives

Concomitant use of HYSINGLA ER with strong laxatives (e.g., Lactulose) that increase GI motility rapidly may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. If adequate pain relief is not achieved, rescue medication (opioid/non-opioid) may be necessary before the next dose of Hysingla ER. It is not advisable to start and stop treatment with drugs that markedly decrease GI transit time during treatment with HYSINGLA ER, as this may result in clinically significant changes in systemic exposure to hydrocodone. HYSINGLA ER is not recommended for use in these patients, and alternative treatment should be considered, such as an opioid analgesic that can be administered at least twice daily and can be titrated more effectively as needed.

Section 12 PATIENT COUNSELING INFORMATION

Constipation: Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Proposal to add - Concomitant use of HYSINGLA ER with laxatives or drugs that increase GI motility may decrease hydrocodone absorption resulting in decreased plasma levels. If adequate pain relief is not achieved, rescue medication (opioid/nonopioid) may be necessary before the next dose of HYSINGLA ER.

9.3 Advisory Committee Meeting

There was no advisory committee meeting associated with this NDA.

Section 9.4 Clinical Investigator Financial Disclosure Review Template

Clinical Investigator Financial Disclosure
Review Template

Application Number: 206627

Submission Date(s): April 28, 2014

Applicant: Purdue Pharma

Product: Hysingla ER (hydrocodone extended-release) tablets

Reviewer: Jacqueline Spaulding MD

Date of Review: August 1, 2014

Covered Clinical Study (Name and/or Number): HYD3002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **102**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): **All of the following sections are not applicable** Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from applicant)

The Applicant submitted the Financial Certification and Disclosure in accordance with: 21 CFR 54.4. According to the form, Purdue certified that as the sponsor of the submitted studies, they acknowledged that they did not enter into any financial arrangement with the listed clinical investigators and that the value of compensation to the investigator could not have been affected by the outcome of the study as defined in 21 CFR 54.2(a). They also certified that each listed clinical investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) and that no investigators disclosed any such interests. Further, Purdue certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)

The Applicant also included a statement that no investigator was a full or part-time employee of Purdue.

Appendix A

Table 41: Subjects Discontinued during the Run-In Period and Double-Blind Period Due to Confirmed or Suspected Diversion - Safety and Randomized Safety Population (Study HYD3002)

Subject Number	Study Period	Reason for Discontinuation	Dose at Discontinuation
2010017	Run-in	Confirmed or Suspected Diversion	120 mg
2011010	Run-in	Confirmed or Suspected Diversion	40 mg
2014001	Run-in	Confirmed or Suspected Diversion	20 mg
2017007	Run-in	Confirmed or Suspected Diversion	40 mg
2025014	Run-in	Confirmed or Suspected Diversion	20 mg
2025040	Run-in	Confirmed or Suspected Diversion	60 mg
2034057	Run-in	Confirmed or Suspected Diversion	80 mg
2048008	Run-in	Confirmed or Suspected Diversion	20 mg
2051008	Run-in	Confirmed or Suspected Diversion	80 mg
2052021	Run-in	Confirmed or Suspected Diversion	20 mg
2057001	Run-in	Confirmed or Suspected Diversion	80 mg
2057006	Run-in	Confirmed or Suspected Diversion	80 mg
2065005	Run-in	Confirmed or Suspected Diversion	40 mg
2071009	Run-in	Confirmed or Suspected Diversion	20 mg
2071013	Run-in	Confirmed or Suspected Diversion	40 mg
2073009	Run-in	Confirmed or Suspected Diversion	40 mg
2080002	Run-in	Confirmed or Suspected Diversion	60 mg
2082001	Run-in	Confirmed or Suspected Diversion	120 mg
2085005	Run-in	Confirmed or Suspected Diversion	20 mg
2087021	Run-in	Confirmed or Suspected Diversion	60 mg
2087036	Run-in	Confirmed or Suspected Diversion	40 mg
2087049	Run-in	Confirmed or Suspected Diversion	20 mg
2092017	Run-in	Confirmed or Suspected Diversion	40 mg
2070014	Double-blind	Confirmed or Suspected Diversion	Placebo
2087029	Double-blind	Confirmed or Suspected Diversion	Placebo
2023001	Double-blind	Confirmed or Suspected Diversion	Placebo
2022004	Double-blind	Confirmed or Suspected Diversion	80 MG
2077007	Double-blind	Confirmed or Suspected Diversion	60 MG
2047002	Double-blind	Confirmed or Suspected Diversion	Placebo
2064014*	Double-blind	Administrative: SUSPECTED DRUG DIVERSION	Placebo
2059002*	Double-blind	Administrative: SUSPECTED DIVERSION	60 mg

* These 2 subjects were discontinued from study treatment due to diversion, but were retained in the study as "retained dropout subjects". Both subjects switched to nonopioid analgesics after discontinuation of study treatment.

Source: Clinical Response to IR July 21, 2014, pp. 1-2/3

Table 42: Subjects Discontinued Due to Confirmed or Suspected Diversion - Safety Population (Study HYD3003)

Subject Number	Study Period	Reason for Discontinuation	Dose at Discontinuation
3035016	Titration	Confirmed or Suspected Diversion	120 mg
3038010	Titration	Confirmed or Suspected Diversion	120 mg
3038023	Titration	Confirmed or Suspected Diversion	80 mg
3080005	Titration	Confirmed or Suspected Diversion	120 mg
3001001	Maintenance	Confirmed or Suspected Diversion	80 mg
3004020	Maintenance	Confirmed or Suspected Diversion	20 mg
3014003	Maintenance	Confirmed or Suspected Diversion	40 mg
3017007	Maintenance	Confirmed or Suspected Diversion	20 mg
3035004	Maintenance	Confirmed or Suspected Diversion	40 mg
3038016	Maintenance	Confirmed or Suspected Diversion	120 mg
3044002	Maintenance	Confirmed or Suspected Diversion	120 mg
3061035	Maintenance	Confirmed or Suspected Diversion	60 mg
3065011	Maintenance	Confirmed or Suspected Diversion	120 mg
3067006	Maintenance	Confirmed or Suspected Diversion	120 mg
3070004	Maintenance	Confirmed or Suspected Diversion	120 mg
3076010	Maintenance	Confirmed or Suspected Diversion	40 mg
3076026	Maintenance	Confirmed or Suspected Diversion	60 mg
3076033	Maintenance	Confirmed or Suspected Diversion	120 mg
3085003	Maintenance	Confirmed or Suspected Diversion	80 mg
3098003	Maintenance	Confirmed or Suspected Diversion	40 mg

Source: Clinical Response to IR, July 21, 2014, pp. 2-3/3

Table 43: Incidence of Treatment Nonfatal SAES during HYD Exposure Occurring in ≥2 HYD-treated Subjects (Pooled Chronic Pain Studies)

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.

Source: NDA 206627, ISS, Table 30, pg. 128/130

Table 44: Adverse Event of Special Investigations/SMQ Category/Search Method and Preferred Term – Formulation-Related Choking

AE of Special Investigation Category	SMQ Category/Sub Category	Search	Preferred Term
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	GASTRIC STENOSIS
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	GASTROINTESTINAL STENOSIS
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	ILEAL STENOSIS
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	IMPAIRED GASTRIC EMPTYING
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	INTESTINAL STENOSIS
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	JEJUNAL STENOSIS
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	LARGE INTESTINAL OBSTRUCTION REDUCTION
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	LARGE INTESTINAL STRICTURE
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	OESOPHAGEAL STENOSIS
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	PREPYLORIC STENOSIS
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	RECTAL OBSTRUCTION
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	RECTAL STENOSIS
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	SMALL INTESTINAL OBSTRUCTION
Formulation-Related Choking	Gastrointestinal Obstruction	Narrow	SMALL INTESTINAL STENOSIS

Source: NDA 206627, ISS SAP, Appendix D, pg. 93/244

Table 45: Adverse Events of Special Investigation Category/SMQ Category/Search Method and Preferred Term – Aberrant Drug Behavior

AE of Special Investigation Category	SMQ Category/Sub Category	Search	Preferred Term
Aberrant Drug Behavior	Additional Medical Concept		ACCIDENTAL DRUG INTAKE BY CHILD
Aberrant Drug Behavior	Additional Medical Concept		ACCIDENTAL EXPOSURE
Aberrant Drug Behavior	Additional Medical Concept		CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR
Aberrant Drug Behavior	Additional Medical Concept		COUNTERFEIT DRUG ADMINISTERED
Aberrant Drug Behavior	Additional Medical Concept		DOCUMENTED HYPERSENSITIVITY TO ADMINISTERED DRUG
Aberrant Drug Behavior	Additional Medical Concept		DRUG ADMINISTERED AT INAPPROPRIATE SITE
Aberrant Drug Behavior	Additional Medical Concept		DRUG ADMINISTERED IN WRONG DEVICE
Aberrant Drug Behavior	Additional Medical Concept		DRUG ADMINISTRATION ERROR
Aberrant Drug Behavior	Additional Medical Concept		DRUG DISPENSING ERROR
Aberrant Drug Behavior	Additional Medical Concept		DRUG DOSE OMISSION
Aberrant Drug Behavior	Additional Medical Concept		DRUG EXPOSURE VIA BREAST MILK
Aberrant Drug Behavior	Additional Medical Concept		DRUG LABEL CONFUSION
Aberrant Drug Behavior	Additional Medical Concept		DRUG LEVEL ABOVE THERAPEUTIC
Aberrant Drug Behavior	Additional Medical Concept		DRUG NAME CONFUSION
Aberrant Drug Behavior	Additional Medical Concept		DRUG PRESCRIBING ERROR
Aberrant Drug Behavior	Additional Medical Concept		DRUG TOXICITY
Aberrant Drug Behavior	Additional Medical Concept		EXPIRED DRUG ADMINISTERED
Aberrant Drug Behavior	Additional Medical Concept		INAPPROPRIATE SCHEDULE OF DRUG ADMINISTRATION
Aberrant Drug Behavior	Additional Medical Concept		INCORRECT DOSE ADMINISTERED
Aberrant Drug Behavior	Additional Medical Concept		INCORRECT DOSE ADMINISTERED BY DEVICE
Aberrant Drug Behavior	Additional Medical Concept		INCORRECT DRUG ADMINISTARATION DURATION
Aberrant Drug Behavior	Additional Medical Concept		INCORRECT DRUG ADMINISTARTION RATE
Aberrant Drug Behavior	Additional Medical Concept		INCORRECT DRUG DOSAGE FORM ADMINISTERED
Aberrant Drug Behavior	Additional Medical Concept		INCORRECT ROUTE OF DRUG ADMINISTATION
Aberrant Drug Behavior	Additional Medical Concept		INCORRECT STORAGE OF DRUG
Aberrant Drug Behavior	Additional Medical Concept		INTENTIONAL DRUG ABUSE
Aberrant Drug Behavior	Additional Medical Concept		INTENTIONAL OVERDOSE
Aberrant Drug Behavior	Additional Medical Concept		INTERCEPTED DRUG ADMINISTRATION ERROR
Aberrant Drug Behavior	Additional Medical Concept		INTERCEPTED DRUG DISPENSING ERROR
Aberrant Drug Behavior	Additional Medical Concept		INTERCEPTED MEDICATION ERROR
Aberrant Drug Behavior	Additional Medical Concept		LABELED DRUG-DISEASE INTERACTION MEDICATION ERROR
Aberrant Drug Behavior	Additional Medical Concept		LABELED DRUG-DRUG INTERACTION MEDICATION ERROR
Aberrant Drug Behavior	Additional Medical Concept		LABELED DRUG-FOOD INTERACTION MEDICATION ERROR

NDA 206627, ISS SAP, Appendix D, pp. 93-96/244

Table 45 (continued)

AE of Special Investigation Category	SMQ Category/Sub Category	Search	Preferred Term
Aberrant Drug Behavior	Additional Medical Concept		MEDICATION ERROR
Aberrant Drug Behavior	Additional Medical Concept		MULTIPLE DRUG OVERDOSE
Aberrant Drug Behavior	Additional Medical Concept		MULTIPLE DRUG OVERDOSE ACCIDENTIAL
Aberrant Drug Behavior	Additional Medical Concept		MULTIPLE DRUG OVERDOSE INTENTIONAL
Aberrant Drug Behavior	Additional Medical Concept		NARCOTICINTOXICATION
Aberrant Drug Behavior	Additional Medical Concept		OVERDOSE
Aberrant Drug Behavior	Additional Medical Concept		POOR QUALITY DRUG ADMINISTERED
Aberrant Drug Behavior	Additional Medical Concept		RADIATION EXPOSURE
Aberrant Drug Behavior	Additional Medical Concept		RADIATION OVERDOSE
Aberrant Drug Behavior	Additional Medical Concept		RADIATION UNDERDOSE
Aberrant Drug Behavior	Additional Medical Concept		RUG LEVEL INCREASED
Aberrant Drug Behavior	Additional Medical Concept		THERAPEUTIC AGENT TOXICITY
Aberrant Drug Behavior	Additional Medical Concept		UNDERDOSE
Aberrant Drug Behavior	Additional Medical Concept		VACCINATION ERROR
Aberrant Drug Behavior	Additional Medical Concept		WRONG DRUG ADMINISTERED
Aberrant Drug Behavior	Additional Medical Concept		WRONG TECHNIQUE IN DRUG USAGE PROCESS
Aberrant Drug Behavior	Additional Medical Concept		INTENTIONAL DRUG MISUSE
Aberrant Drug Behavior	Drug Abuse and Dependence	Broad	DEPENDENCE
Aberrant Drug Behavior	Drug Abuse and Dependence	Broad	DISTURBANCE IN SOCIAL BEHAVIOUR
Aberrant Drug Behavior	Drug Abuse and Dependence	Broad	DRUG DETOXIFICATION
Aberrant Drug Behavior	Drug Abuse and Dependence	Broad	DRUG SCREEN
Aberrant Drug Behavior	Drug Abuse and Dependence	Broad	DRUG SCREEN POSITIVE
Aberrant Drug Behavior	Drug Abuse and Dependence	Broad	DRUG TOLERANCE
Aberrant Drug Behavior	Drug Abuse and Dependence	Broad	DRUG TOLERANCE DECREASED

NDA 206627, ISS SAP, Appendix D, pp. 93-96/244

Table 45 (continued)

AE of Special Investigation Category	SMQ Category/Sub Category	Search	Preferred Term
Aberrant Drug Behavior	Drug Abuse and Dependence	Broad	DRUG TOLERANCE INCREASED
Aberrant Drug Behavior	Drug Abuse and Dependence	Broad	NEEDLE TRACK MARKS
Aberrant Drug Behavior	Drug Abuse and Dependence	Narrow	DRUG ABUSE
Aberrant Drug Behavior	Drug Abuse and Dependence	Narrow	DRUG ABUSER
Aberrant Drug Behavior	Drug Abuse and Dependence	Narrow	DRUG DEPENDENCE
Aberrant Drug Behavior	Drug Abuse and Dependence	Narrow	DRUG DEPENDENCE, ANTEPARTUM
Aberrant Drug Behavior	Drug Abuse and Dependence	Narrow	DRUG DEPENDENCE, POSTPARTUM
Aberrant Drug Behavior	Drug Abuse and Dependence	Narrow	MATERNAL USE OF ILLICIT DRUGS
Aberrant Drug Behavior	Drug Abuse and Dependence	Narrow	NEONATAL COMPLICATIONS OF SUBSTANCE ABUSE
Aberrant Drug Behavior	Drug Abuse and Dependence	Narrow	POLYSUBSTANCE DEPENDENCE
Aberrant Drug Behavior	Drug Abuse and Dependence	Narrow	SUBSTANCE ABUSE
Aberrant Drug Behavior	Drug Abuse and Dependence	Narrow	SUBSTANCE ABUSER

NDA 206627, ISS SAP, Appendix D, pp. 93-96/244

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

/s/

JACQUELINE A SPAULDING
08/14/2014

ELLEN W FIELDS
08/14/2014

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 206627 **Applicant: Purdue Pharma** **Stamp Date: 4/28/14**

Drug Name: Hydrocodone bitartrate) Extended -Release **NDA/BLA Type: NDA**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	**X**			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	**X**			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	**X**			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	**X**			
5.	Are all documents submitted in English, or are English translations provided when necessary?	**X**			
6.	Is the clinical section legible so that substantive review can begin?	**X**			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	**X**			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	**X**			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	**X**			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	**X**			
11.	Has the applicant submitted a benefit-risk analysis for the product?	**X**			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				**505(b)(2) Reference drug - vicoprofen**
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			**X**	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1-**HYD 3002 (Efficacy/Safety study)** Indication: Management of moderate to pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adult	**X**			

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 – **HYD3003 (Open-label safety)** Indication: Management of moderate to pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adult				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	**X**			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	**X**			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			**X**	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	**X**			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	**X**			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	**X**			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	**X**			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			**X**	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	**X**			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	**X**			

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

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

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	**X**			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	**X**			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			**X**	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	**X**			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	**X**			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			**X**	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	**X**			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	**X**			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	**X**			
34.	Are all datasets to support the critical safety analyses available and complete?	**X**			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	**X**			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	**X**			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	**X**			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	**X**			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	**X**			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

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

File name: 4_Clinical Filing Checklist for a New NDA_BLA110207

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

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

Jacqueline A. Spaulding MD, MPH	6/0314
Reviewing Medical Officer	Date
Ellen Fields MD, MPH	6/03/14
Clinical Team Leader	Date

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

/s/

JACQUELINE A SPAULDING
06/03/2014

ELLEN W FIELDS
06/04/2014