CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206627Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 28, 2014
From	Ellen Fields, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA #	206627
Applicant	Purdue Pharma LP (PPLP)
Date of Submission	April 28, 2014
PDUFA Goal Date	October 28, 2014
Proprietary Name / Established (USAN) names	HYSINGLA ER/hydrocodone extended-release tablets
Dosage forms / Strength	20, 30, 40, 60, 80, 100, 120 mg tablets
Proposed Indication(s)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate
Recommended:	Approval

1. Introduction

This is a 505(b)(2) NDA for hydrocodone bitartrate tablets for oral administration once daily, for the indication, management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. The application relies in part on prior Agency findings of safety and efficacy for NDA 20716, Vicoprofen (hydrocodone bitartrate and ibuprofen). Throughout the review the drug product will be referred to as HYD (the name used during clinical development) or HYSINGLA ER (the tradename).

The Applicant states that HYSINGLA ER has abuse-deterrent properties. It is difficult to crush, break, or dissolve, and has been formulated to form a viscous hydrogel. These attributes are intended to deter, but not totally prevent, abuse of the drug by the oral, intranasal, and intravenous routes. Because this product represents a public health benefit as the first single-entity extended-release, hydrocodone product with abuse-deterrent properties, a Priority Review was granted.

2. Background

HYSINGLA ER contains hydrocodone bitartrate, a mu receptor agonist that is covered by Schedule II of the Controlled Substance Act, and was developed under IND 59175. The Applicant has proposed seven strengths for once-daily administration; 20, 30, 40, 60, 80, 100, and 120 mg. The formulation contains the excipient polyethylene oxide (PEO), which imparts physicochemical properties including hardness and hydrogelling that are intended to deter certain methods of abuse.

At present, there is one approved single-entity, extended-release, hydrocodone product on the market, Zohydro ER. It does not have abuse-deterrent properties, consequently, if approved,

HYSINGLA ER would be the first approved single-entity extended-release hydrocodone product with abuse-deterrent properties.

The Agency met with the Applicant several times during the clinical development of HYSINGLA ER, including an End-of-Phase 2 meeting where the Division agreed that one positive adequate and well-controlled (AWC) clinical trial would be adequate to support efficacy for the proposed 505(b)(2) application, and that a safety database of at least 300 patients exposed for six months and 100 patients exposed for at least one year would be required. A single AWC trial is considered sufficient for a reformulated opioid such as HYSINGLA ER, as hydrocodone is a known opioid analgesic, therefore the purpose of the study is to confirm that the specific HYSINGLA ER formulation given once daily provides durable efficacy throughout the 24-hour dosing period and the 12-week study period.

At that meeting the Division advised the Applicant to monitor hearing during the proposed Phase 3 trials, because hearing loss has been reported in subjects taking hydrocodone/acetaminophen combination products. The Center for Devices and Radiologic Health (CDRH) was consulted to provide guidance regarding ototoxicity assessments, and multiple interactions occurred between the Applicant and the Division regarding this issue. The Applicant was also told that a thorough QT study would be required for the NDA, or in its absence, rigorous scientific data to justify why it would not be necessary.

The Applicant submitted a full CMC package and nonclinical studies that assessed the safety pharmacology, general toxicology, genetic toxicology, developmental and reproductive toxicology and the carcinogenic potential of hydrocodone. The Applicant also conducted two Phase 3 studies and 14 Phase 1 studies in support of the HYSINGLA ER development program. Study HYD3002 is a Phase 3 multicenter, enriched enrollment randomized withdrawal design, 12-week double-blind, placebo controlled study in patients with moderate to severe chronic low back pain, and Study HYD3003 is a Phase 3, 12-month open label safety study in patients with chronic moderate to severe nonmalignant and non-neuropathic pain. The Phase 1 studies assessed the pharmacokinetics and the abuse potential of HYSINGLA ER tablets, as well as the relative bioavailability of HYSINGLA ER to the Listed Drug, Vicoprofen, in order to provide a scientific bridge for reliance on previous findings for Vicoprofen. A thorough QT (TQT) study was also conducted.

3. CMC/Device

The CMC review was conducted by Xiaobin Shen, Ph.D., with secondary concurrence by Julia Pinto, Ph.D. From the CMC perspective, the NDA is recommended for approval. No postmarketing commitments or agreements were recommended.

The drug substance, hydrocodone bitartrate, exists as fine, white crystals or crystalline powder, and is soluble in water. Support for the drug substance is referenced to DMF (b) (4), which was reviewed by Dr. Shen and deemed adequate. The drug substance is manufactured by (b) (4) and the EES status has been deemed acceptable by the Office of Compliance. As stated in Dr. Shen's review:

> Specifications for hydrocodone bitartrate drug substance include both USP and ICH requirements. Collectively they include appearance, identification, specific rotation, pH, assay, impurities, loss on drying, residue on ignition, residual solvents and particle size distribution. The drug substance is packaged in (b) (4) bags inside a (b) (4) drum. The drug substance stability data was referenced to DMF (b) (4), which is adequate to support its use in the NDA. It has a retest date of (b) (4) months.

In an addendum to the original CMC review dated October 23, 2014, Dr. Shen states the following regarding the inspection of the drug substance manufacture site, (b) (4):

> The drug substance manufacturer site inspection was completed on (b) (4). (b) (4) issued Form-483 to the DMF holder post-inspection, and subsequently recommended a "withhold" for this application. On October 16, 2014, Dr. Juandria Williams from Office of Compliance conducted an overall assessment of the inspection findings, listed on the 483, and the firm's response to Form 483 observations. She has recommended a non-concurrence to the (b) (4) recommendation of withhold, based on the firm's responses to the 483. Consequently, the Office of Compliance has given an overall acceptable recommendation for the facilities.

Regarding the drug product Dr. Shen stated:

> The drug product is available as 20, 30, 40, 60, 80, 100 and 120 mg strength (b) (4) tablets. The different strengths are differentiated by the film coating color as well as over print of "HYD 20", where 20 stands for the strength of 20 mg and changes according to the specific product strength. The differentiation is important because all strengths have the same tablet shape, weight and size. The common excipients include Hydroxypropyl Cellulose, Macrogol/PEG 3350, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Oxide (PEO), Polysorbate 80, Polyvinyl Alcohol, Talc, Titanium Dioxide, and Black Ink. Each strength also contains its unique film coating colorants. All excipients are of compendial grades. The magnesium stearate is (b) (4). PEO is used at quantities (b) (4) than used in already approved products. The safety of this excipient is evaluated by the pharm/tox reviewer Dr. Elizabeth Bolan. The tablets are packaged in (b) (4) cc white oblong HDPE bottles at 60 count and closed with a child-resistant closure. Each bottle also contains two oxygen absorbers. The drug product is manufactured and packaged by applicant's site located in (b) (4). The drug product manufacturing and testing sites have satisfactory EES status.
>
> The drug product specifications include appearance, identification, assay, related substances, content uniformity, and dissolution. Microbial limit testing is not included in either release or stability testing. The drug product primary stability studies were conducted on 3 batches for each strength and packaging configuration combinations. Up to 18 months of stability data is provided for the product stored under long term (25°C/60% RH) storage conditions and six months

of stability data is provided for the storage under accelerated conditions (40°C/75% RH). All tested quality attributes (description, assay, degradation products, and dissolution) results remained relatively stable and showed no trend during the time periods studied for all product strength/packaging configuration combinations and under all storage conditions. Overall, the provided stability data supports the applicant's proposed 24 month product expiry.

The CMC team requested a product quality microbiology assessment for HYSINGLA ER because the NDA did not include a Microbial Limits release specification for the drug product release or stability. John Metcalfe, Ph.D. conducted a review with secondary concurrence by Bryan Riley, Ph.D. They found that the Applicant provided a suitable rationale for the exclusion of this testing, and recommended approval from the perspective of product quality microbiology.

4. Nonclinical Pharmacology/Toxicology

Elizabeth Bolan, Ph.D. performed the nonclinical review with secondary concurrence by Dan Mellon, Ph. D. From the nonclinical perspective, this NDA is recommended for approval. No postmarketing commitments or agreements were recommended.

The following is taken from Dr. Bolan's review verbatim:

All impurities in the drug substance and drug product are controlled at acceptable levels. HYSINGLA ER contains excipients that are intended to confer abuse-deterrent properties and resist alcohol-induced dose dumping. The major component of the formulation consists of (b) (4) polyethylene oxides (b) (4) With the exception of the PEO, the levels of the excipients in this product, when calculated for the maximum theoretical daily dose of hydrocodone (HC), are considered acceptable and do not require qualification. The levels of the PEO (b) (4) levels found in previously approved drugs. To support the safety of the levels of the PEO in this product, the Applicant is referencing Master File (MF) (b) (4) . Master File (b) (4) has been found to be inadequate because (b) (4) These (b) (4) entities could include (b) (4) and specifications for these impurities in the excipient master file may be required. However, because of the longstanding history of use of PEO in many products which reference MF (b) (4) this deficiency will not be an approval issue for NDA 206627. The levels of PEO in HYSINGLA ER when used at the maximum theoretical daily dose (MTDD) of hydrocodone are considered acceptable from a pharmacology/toxicology perspective.

The neurobehavioral and respiratory safety pharmacology studies showed results consistent with the known effects of opioids. The cardiac safety pharmacology assessment showed the potential for effects of HC on the heart. Hydrocodone did not show meaningful inhibition of the hERG potassium channel at concentrations >300-fold higher than human exposure at an oral dose of 120 mg. However, the in vitro Purkinje fiber assay showed HC-dependent

> increases in action potential duration and an in vivo single-dose study in conscious, freely moving telemetered dogs showed increases in RR and QRS interval durations as well as increases in QT and QTc intervals with HC. The findings in dog were seen at C_{max} exposures 0.7-fold the human C_{max} exposure of a 120 mg HC dose. No effects on the heart were observed in the toxicology studies with chronic administration of HC to rat and dog. To address the potential for cardiotoxicity in humans, the Applicant has conducted a clinical study to evaluate the effect of HC on the QT/QTc interval.

The highest proposed strength for HYSINGLA ER is 120 mg, therefore the systemic levels at the human dose of 120 mg/day at steady state is used as exposure comparison for the toxicology studies. The results of the general toxicology studies in rat and dog were typical of an opioid agonist and no clinically-relevant toxicities unique to hydrocodone were demonstrated. The standard ICH battery of genetic toxicology studies were conducted with hydrocodone, and suggest that hydrocodone does not have mutagenic or clastogenic potential. Two-year rat and mouse studies were conducted in rat and mouse and no hydrocodone-related neoplasms were observed. A full reproductive and developmental toxicology battery was conducted with hydrocodone. The observed toxicities in these studies are consistent with Pregnancy Category C designation, and the findings will be described in the label.

Refer to Dr. Bolan's review for the recommended labeling changes for sections 8.1 Pregnancy, 8.3 Nursing Mothers, 11 DESCRIPTION, 12.1 Mechanism of Action, and 13 NON-CLINICAL TOXICOLOGY.

5. Clinical Pharmacology/Biopharmaceutics

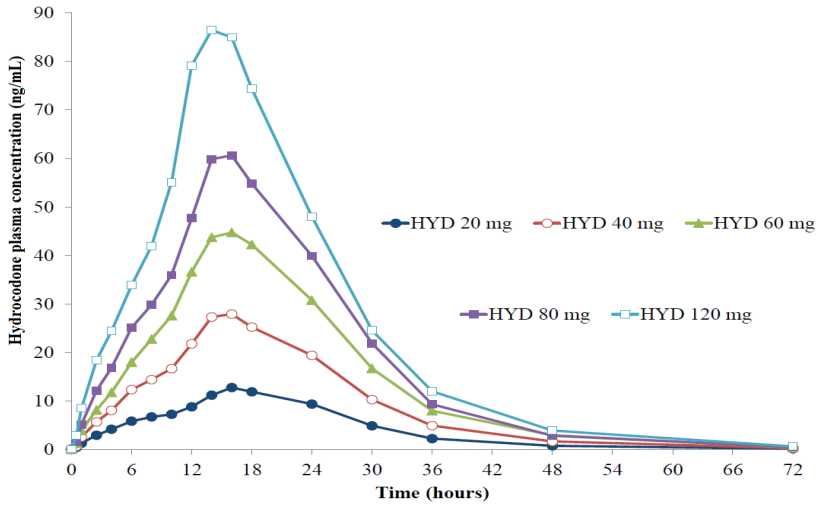
The clinical pharmacology review was conducted by Srikanth Nallani, Ph.D., with secondary concurrence by Yun Xu, Ph.D. They did not identify any issues that would preclude approval.

The following is taken verbatim from Dr. Nallani's review:

> After a single dose administration of 20, 40, 60, 80 and 120 mg Hysingla ER tablets, Hysingla ER yields a gradual increase in plasma hydrocodone concentrations with median Tmax ranging from 14 to 18 hours after single and multiple dosing. Systemic exposure (AUC and Cmax) increased linearly with doses from 20 to 120 mg. Both Cmax and AUC increased slightly more than dose proportionally. Mean plasma concentrations of hydrocodone increased slowly after oral administration of Hysingla ER extended-release tablets and reached a maximum concentration at 14 to 16 hours post-dose at all dose levels. However, it should be noted that in some individuals peak plasma levels were noted at 24 hour or up to 30 hours following single dose of Hysingla ER administration.

The figure below from Dr. Nallani's review shows the mean plasma concentration of hydrocodone vs time on a linear scale :

Figure 1

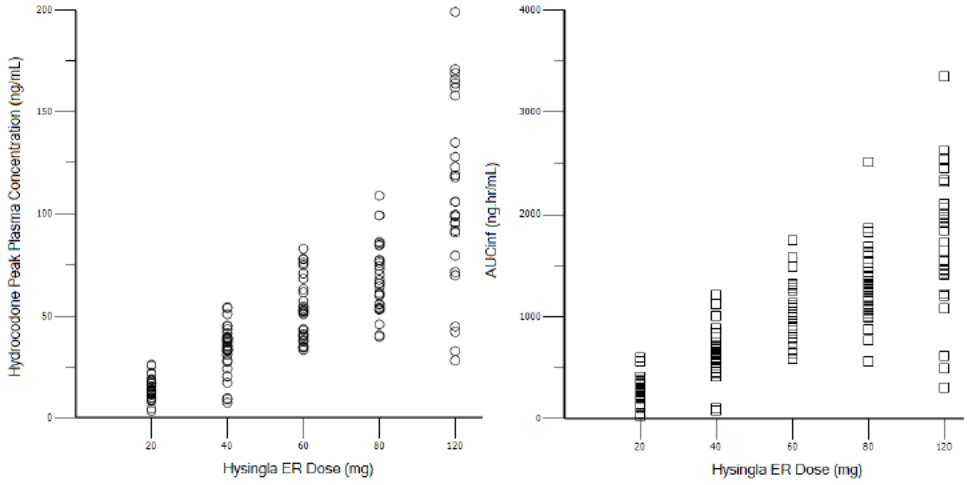


Dr. Nallani noted the following regarding increased variability in PK parameters for the 120 mg dose:

> Upon closer examination of individual data, it was observed that subjects receiving 120 mg tablet of Hysingla ER had higher variability with respect to both Cmax (Range 28.2 – 199 ng/mL) and AUC_{inf} (305 – 3347 ng.hr/mL).

This variability is illustrated in the plots below of the individual data. For both Cmax and AUC, there appears to be increased variability, particularly at the lower end, for subjects taking a single tablet of HYSINGLA ER 120 mg. This has clinical implications in that a reliable systemic exposure to hydrocodone may not be achievable for this dose, and therefore, puts into question the approvability of the 120 mg tablet. However, based on the results of the clinical trials, there did not appear to be any issues regarding efficacy of the 120 mg tablet, therefore there is not a compelling reason to withhold approval of this strength based on the PK variability.

Figure 2: Plot of individual PK parameters (Cmax in the left figure, AUC inf in the right figure).



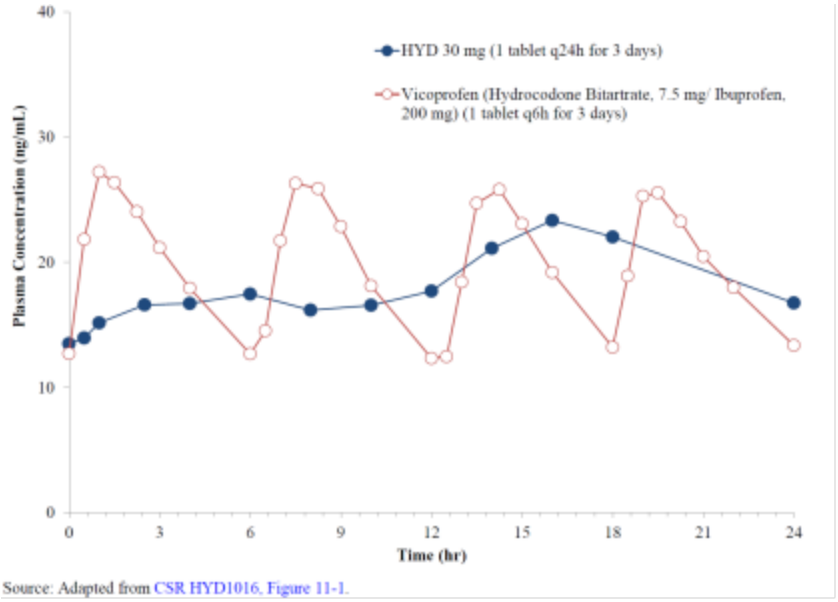
When HYSINGLA ER 120 mg was consumed following a high fat meal, the Cmax overall was 54% higher than under the fasting conditions. Dr. Nallani noted that the hydrocodone AUC with the 120 mg tablets was only 20% higher when co administered with a high fat meal. In the controlled trial HYD3002 and the open-label trial HYD3003, HYSINGLA ER was administered without regard to food, and a titration period was included at the beginning of the each study. Dr. Nallani recommends that it is best if food consumption is consistent at the time of HYSINGLA ER administration, and dose titration or changes should not occur more frequently that every three to five days.

Dose proportionality of the tablet strengths was confirmed in study HYD1001, which showed that the exposure following one tablet of HYSINGLA ER 80 mg was comparable to four tablets of HYSINGLA ER 40 mg.

Hydrocodone is extensively metabolized by CYP3A4, CYP2D6, and 6-keto reduction. Approximately 6.5% of the administered oral dose of HYSINGLA ER is excreted unchanged in the urine. The mean terminal half-life ranged from approximately seven to nine hours in healthy subjects across the range of doses. Steady state plasma concentrations were attained by day two of once-daily dosing of HYSINGLA ER. There was low accumulation (approximately 1.3 fold). The mean half-life at steady state was seven hours.

The Applicant conducted study HYD1016 to demonstrate the relative bioavailability of HYSINGLA ER to the listed drug, Vicoprofen (hydrocodone bitratrate 7.5 mg/ibuprofen 200 mg), in order to provide a scientific bridge to the listed drug. The PK of one tablet of HYSINGLA ER 30 mg was compared to four doses of Vicoprofen at steady state resulting in the following profile from Dr. Nallani's review. The systemic exposure and average plasma concentration of hydrocodone at steady state following the administration of Hysingla ER 30 mg every 24 hours was equivalent to that following Vicoprofen administered every 6 hours for 3 days. The mean hydrocodone exposure following Hysingla ER 30 mg administration was lower (18%) compared to that noted with Vicoprofen 7.5 mg administered four times daily.

Figure 3: Mean Hydrocodone Plasma Concentration Versus Time Profiles for Hysingla ER 30-mg tablet and Vicoprofen (hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg) at Steady State in Study HYD1016



Source: Adapted from CSR HYD1016, Figure 11-1.

The Applicant conducted intrinsic factor PK studies which Dr. Nallani reviewed in detail. Of note, the hepatic impairment study (HYD1007) indicated that on average, patients with mild, moderate and severe hepatic impairment did not show higher plasma concentrations than those with normal hepatic function. However, upon review of the data, Dr. Nallani had the following observations:

> …..four out of eight patients with severe hepatic impairment had received lactulose, a strong laxative also used to manage complications of hepatic encephalopathy. In these subjects systemic exposure of hydrocodone was lower compared to other patients with severe hepatic impairment or with respect to average healthy volunteers. Compared to subjects with normal hepatic function, hydrocodone Cmax values were lower by 6% and higher by 5% and 5% and AUC values were lower by 14%, and higher by 13% and 4% in patients with mild, moderate or severe hepatic impairment, respectively. However, after considering the potential confounding effect of strong laxative on PK Hysingla in severe HI patients, it was observed that AUC and Cmax in severe HI patients without Laxative use were higher by 50%, compared to healthy volunteers.
>
> Taken together, patients with severe hepatic impairment requiring concomitant use of Hysingla with lactulose for the management of constipation or hepatic encephalopathy symptoms, may have lower exposure to hydrocodone.

Dr. Nallani recommended labeling such that prescribers start patients with severe hepatic impairment on a low starting dose of HYSINGLA ER, and monitor closely for adverse events.

There is no dose adjustment recommended for patients with mild or moderate hepatic impairment.

Patients with mild, moderate and severe renal impairment also had higher plasma concentrations (AUC) than those with normal renal function, by 13%, 61%, and 57% respectively, as demonstrated in study HYD1008. Cmax values were also higher. Low initial doses of HYSINGLA ER should be used in these patients with close monitoring for adverse events.

The Applicant conducted CYP3A4 and CYP2D6 interaction studies. Hydrocodone exposure increased 2-fold when coadministered with the strong CYP3A4 inhibitor ketoconazole, and did not change significantly when coadministered with the strong CYP2D6 inhibitor paroxetine. The in vitro CYP inhibition drug interaction potential study revealed that hydrocodone does not inhibit major CYP enzymes.

There was no in vitro evidence of rapid or unexpectedly high rate of hydrocodone release for both 20 and 120 mg HYSINGLA ER tablets in the presence of ethanol. Therefore, an in vivo alcohol interaction study was not conducted.

The Applicant conducted human abuse liability studies to assess the impact of the HYSINGLA ER formulation on oral and intranasal routes of abuse Dr. Nallani reviewed them from the clinical pharmacology perspective, and CSS from the abuse liability perspective. Below is a brief summary of Dr. Nallani's findings. These studies will also be discussed later in this review as part of the CSS evaluation of HYSINGLA ER.

Study HYD1013 evaluated pharmacokinetics and abuse potential in opioid non-dependent abusers by the oral route for intact, chewed, and milled HYSINGLA ER, compared to hydrocodone oral solution. The mean Cmax was highest following the hydrocodone oral solution, followed by milled, chewed, and intact HYSINGLA ER. The median Tmax followed the same trend. The PK results are shown in the figure below from Dr. Nallani's review. The abuse liability assessments generally followed the PK trends. Figure X shows the mean VAS scores over time for drug liking, which are highest for the oral solution and milled HYSINGLA ER, followed by chewed and intact tablets. Although drug liking following chewing is similar to intact HYSINGLA ER, milling the product and ingesting it with water results in drug liking similar to hydrocodone IR solution. The implications of these results in terms of labeling are discussed later in this review.

Figure 4: Mean Hydrocodone Plasma Concentrations Versus Time (Oral Administration) in Study HYD1013.

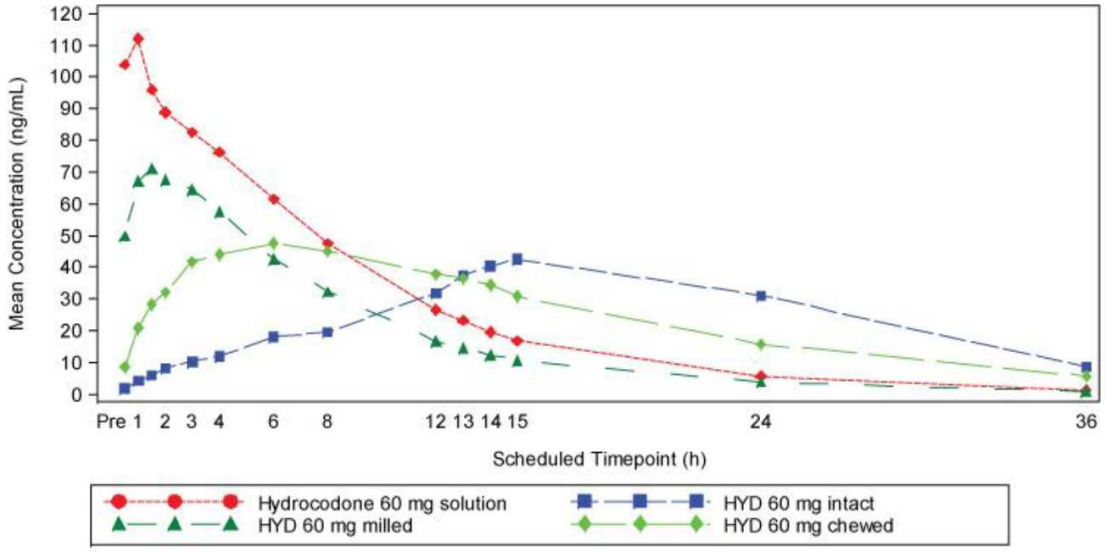
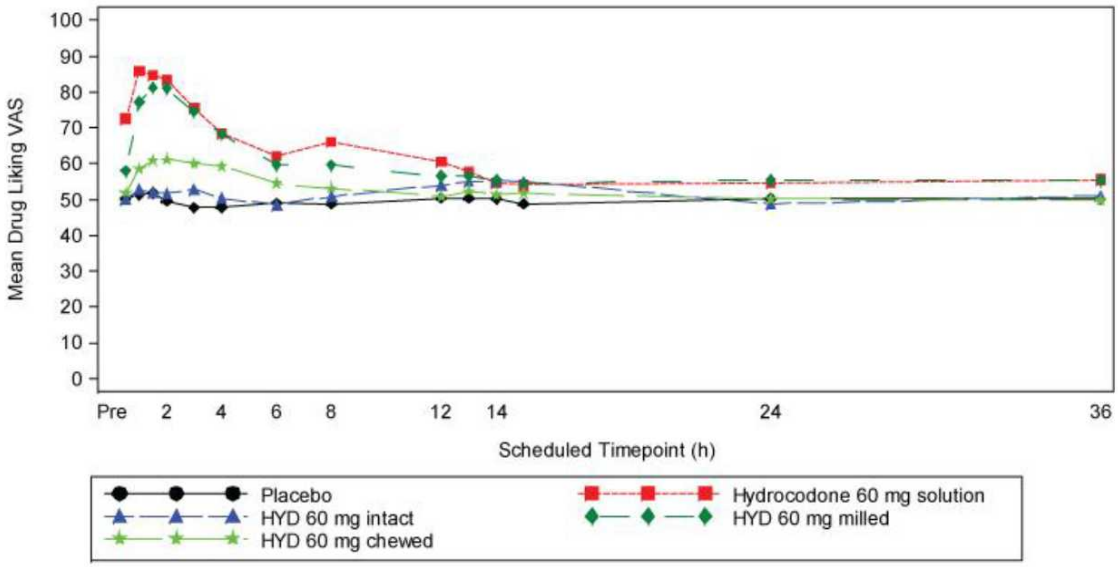


Figure: Mean Scores Over Time for Drug Liking VAS (Oral Administration, Chewed, Milled and Intact) in Study HYD1013.



Study HYD1014 evaluated abuse potential and pharmacokinetics of crushed (fine and coarse), IN administered HYSINGLA ER in non-dependent opioid abusers with a history of intranasal abuse. Mean Cmax values of hydrocodone were lower following HYSINGLA ER fine and coarse powder administered IN than following hydrocodone IR powder. This may have been related, at least in part, to the lower percentage of the dose observed to have been inhaled for coarse and fine ground HYSINGLA ER compared to hydrocodone IR powder. Median Tmax was also later following both ground preparations compared to IR powder. The AUCs for the ground HYSINGLA ER were both lower than the IR powder. The drug liking VAS scores followed the same trends

predicted by the PK profiles. As shown in Figure X below from Dr. Nallani's review, the IR powder median drug liking VAS was much higher compared either ground preparation of HYSINGLA ER administered IN.

Figure 5: Mean Hydrocodone Plasma Concentrations Versus Time following Intranasal Administration of Hysingla ER fine powder (Squares), coarse powder (Triangles) compared to hydrocodone powder (Circles) in Study HYD1014

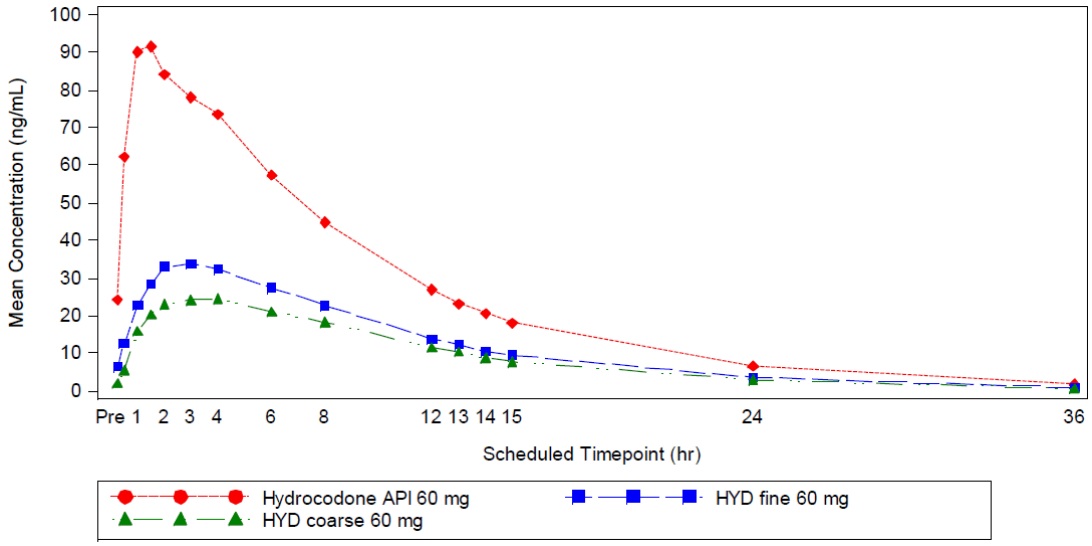
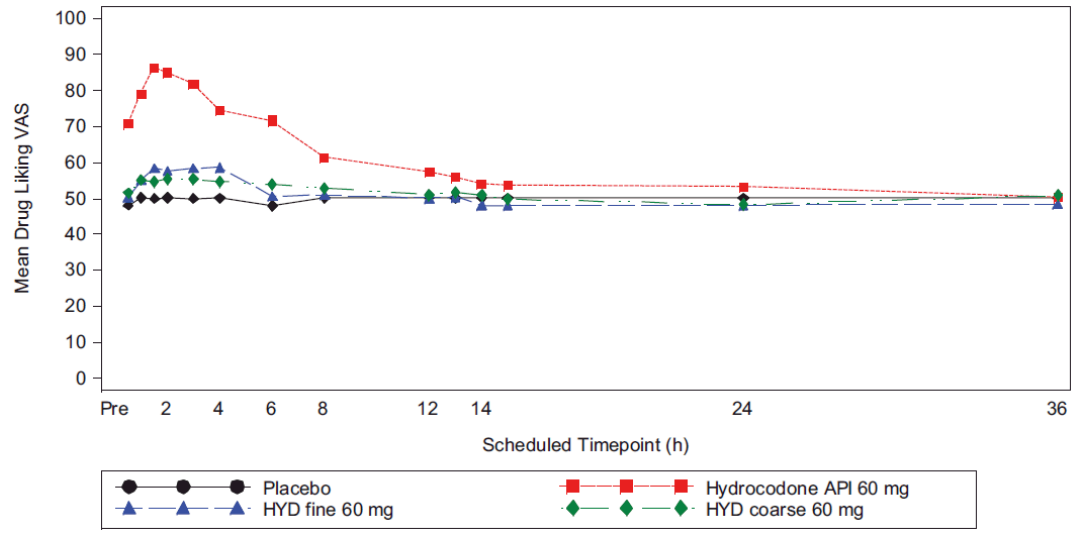


Figure 6: Mean Scores Over Time for Drug Liking VAS following Intranasal Administration of Fine Hysingla ER (Triangle) and Coarse Particle Size Hysingla ER (Diamond) compared to hydrocodone powder (Squares) and placebo (Circles) in Study HYD1014.



Dr. Nallani has recommended labeling regarding the following issues. Refer to his review and the final label for details:

- Because the peak plasma levels of hydrocodone may occur more than 14-16 hours following administration of HYSINGLA ER, patients should be made aware that plasma levels may be high enough after 24 hours to impair activities that require

alertness. Additionally, HYSINGLA ER should be taken at a consistent time each day to maintain 24-hour dosing interval.

- Patients should following the prescriber's titration instructions, and not attempt to increase HYSINGLA ER dose on their own.
- Patients with any degree of renal impairment and severe hepatic impairment should be started on a low dose of HYSINGLA ER and monitored closely for adverse events.
- Patients taking CYP3A4 inhibitors may require lower doses of HYSINGLA ER and should be monitored for adverse events
- The effect of lactulose on the HYSINGLA ER PK should be described in the label

The Biopharmaceutics review was conducted by Akm Khairuzzaman, Ph.D. with secondary concurrence by Tapash Ghosh, Ph.D. They recommended approval of this NDA from the Biopharmaceutics perspective.

The Biopharmaceutics team found that the dissolution method and limit proposed by the Applicant are acceptable. They identified a potential problem regarding the manufacturing process which was resolved during the review cycle. The drug product is manufactured using (b) (4) and the finished tablet ha (b) (4) . The final tablet is called a " (b) (4) The concern was that the (b) (4) , and affect the dissolution characteristics of the final product. The Applicant provided acceptable processes and control for the (b) (4) in the commercial machine to ensure uniformity of the finished product. Refer to Dr. Khairuzzaman's review for details.

Thorough QT Study

The Applicant conducted a thorough QT study as required by the Agency (conveyed to the Applicant at the EOP 2 meeting). The Interdisciplinary Review Team for QT studies (QT-IRT) reviewed the protocol prior to the conduct of the study, and the study report was submitted on May 28, 2014. The QT-IRT reviewed the study report and provided advice to the Division regarding labeling. The following is a summary of their findings taken verbatim from their review.

> This randomized study administrated of multiple doses (once daily for 3 days) of HYD titrated from 20 to 160 mg. A central tendency analysis of the individual corrected QT (QTcI) interval data at steady-state demonstrated that the maximum mean (90% upper confidence bound) difference in QTcI from placebo after baseline-correction was 9.9 (12.7) ms, 6.9 (10.2) ms, and 5.6 (8.5) ms at HYD 160 mg, 120 mg and 80 mg respectively. The largest 90% upper confidence bound for the mean differences at HYD 160 mg and 120 mg was above 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 7, indicating that assay sensitivity was established.
>
> In this randomized, double-blind, placebo-and positive-controlled, multiple-dose escalation, parallel-design study, 208 subjects received HYD 80 mg, HYD 120 mg, HYD

160 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for HYD (80mg, 120 mg and 160 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment Group	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
HYD 80 mg (Day 9)	24	5.6	(2.7, 8.5)
HYD 120 mg (Day 12)	24	6.9	(3.6, 10.2)
HYD 160 mg (Day 15)	10	9.9	(7.1, 12.7)
Moxifloxacin 400 mg (Day 9)*	3	11.6	(8.8, 14.5)
Moxifloxacin 400 mg (Day 12)*	3	9.7	(6.2, 13.2)
Moxifloxacin 400 mg (Day 15)*	4	8.7	(5.5, 11.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points are 7.7 ms, 4.9 ms, and 4.3 ms on Days 9, 12 and 15; respectively.

The HYD dose (160 mg) produces mean steady state exposure 2-fold that of the therapeutic dose (80 mg) for both parent drug and major metabolites. There was no evident exposure-response relationship for change in QTcI based on hydrocodone concentration. However, it seems there are positive trends in exposure-response relationships for change in QTcI based on HYD metabolite norhydrocodone or hydromorphone concentration.

Overall, the QT-IRT determined that while there was some QT effect, it was mild, not apparently dose related, and not associated with any clinically significant adverse events. The team suggested the following language for the label Sections 5 and 12.6. Labeling discussions are ongoing at this time. Please see the approved label for the exact wording. (b) (5)

[redacted]

5.x QT INTERVAL PROLONGATION

QT prolongation has been observed with [TRADENAME]. [TRADENAME] should be avoided in patients with congenital long QT syndrome. In patients with congestive heart failure, bradyarrhythmias electrolyte abnormalities or who are taking medications that are known to prolong the QT interval, consider periodic monitoring with electrocardiograms and electrolytes. In patients who develop QTc prolongation, consider dose reduction *[see Clinical Pharmacology (12.6)]*.

12.6 CARDIAC ELECTROPHYSIOLOGY

QTc interval prolongation was studied in a double-blind, placebo- and positive controlled 3-treatment parallel-group, dose-escalating study in 185 healthy subjects. A central tendency analysis of the QTcI data at steady-state demonstrated that the maximum mean (95% upper confidence bound) difference in QTcI from placebo after baseline-correction was 10 (13) ms, 7 (10) ms, and 6 (9) ms at [TRADENAME] 160 mg, 120 mg and 80 mg respectively.

6. Clinical Microbiology

This product is not an antimicrobial therefore this section is not applicable.

7. Clinical/Statistical- Efficacy

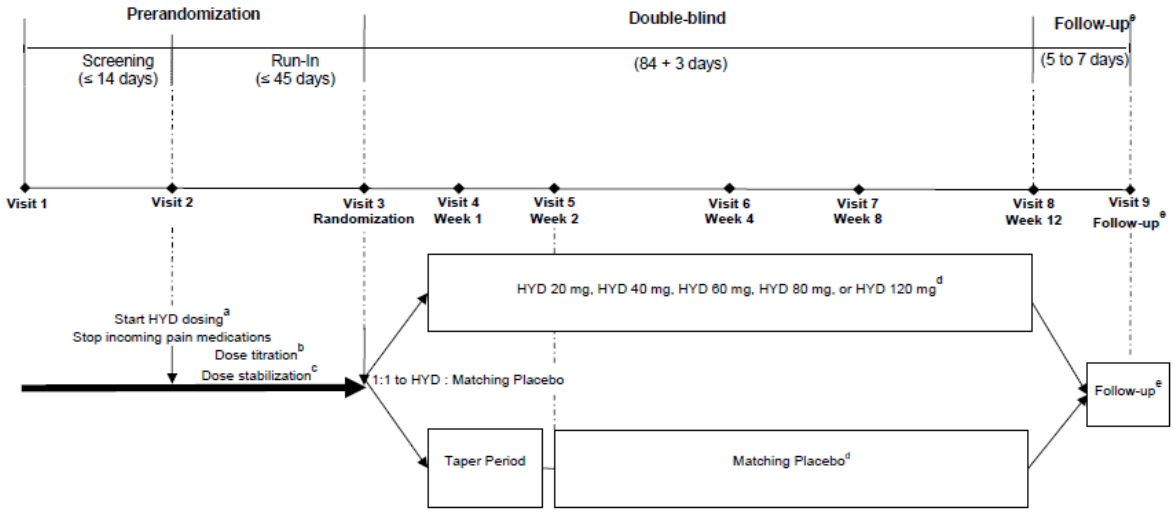
The clinical review was conducted by Jacqueline Spaulding M.D., and the statistical review was conducted by Yan Zhou, Ph.D., with secondary concurrence by Janice Derr, Ph.D. Neither review team noted any issues that would preclude approval.

One adequate and well-controlled (AWC) Phase 3 clinical trial was submitted to support the efficacy of HYSINGLA ER for the proposed indication. One AWC trial is considered sufficient for a reformulated opioid such as HYSINGLA ER, as hydrocodone is a known opioid analgesic, therefore the purpose of the study is to confirm that the specific HYSINGLA ER formulation given once daily provides durable efficacy throughout the 24-hour dosing period and the 12-week study period.

Study HYD3002 was a multicenter, double-blind, placebo-controlled, randomized-withdrawal design study of the safety and efficacy of HYSINGLA ER in patients with moderate-to-severe non-neuropathic, non-malignant, chronic low back pain (CLBP) for at least three months, whose pain was not controlled by their incoming analgesic regimen. Subjects were converted from their previous opioid to HYSINGLA ER based on their prior opioid therapy. Those who had not been treated with opioids were started on HYSINGLA ER 20 mg/day. During the open-label run-in period, the dose of HYSINGLA ER could be increased up to once every three to five days until a stable and tolerable dose was identified. Rescue was allowed up to 10 mg per day of IR oxycodone. Subjects who tolerated and achieved adequate analgesia with HYSINGLA ER by the end of the 45-day, open-label run-in period were then randomized 1:1 to either continue treatment with HYSINGLA ER or take placebo for 12-weeks. The HYSINGLA ER doses included 20, 40, 60, 80, and 120 mg once daily.

Study visits occurred at weeks 1, 2, 4, 8 and 12 of the double-blind (DB) period. In order to minimize opioid withdrawal symptoms, subjects who were randomized to the placebo treatment group were tapered from their run-in HYSINGLA ER dose to placebo in a prespecified, blinded manner during the first 2 weeks of the DB period. For tolerability reasons, one down titration was permitted subsequent to the 2-week taper period for subjects randomized to HYD 40 mg, 60 mg, 80 mg, 120 mg, or the corresponding matching placebo. If after a down titration subjects did not achieve adequate analgesia, one up titration back to the randomized dose was allowed. Rescue medication, oxycodone immediate-release was allowed during the double-blind period study based on the subject's HYSINGLA ER dose, and ranged from 10 to 30 mg per day.

Figure 7: Study Design HYD3002



Source: HYD3002 Study Report p. 58

The primary efficacy variable was the weekly mean PI score using the daily diary "average pain over the last 24 hours" scores recorded by the subject (on an 11-point NRS) each evening during the DB period. Secondary efficacy endpoints included medical outcome study sleep scale, patient global impression of change, responder analysis, and others. Subjects who discontinued study drug during the double-blind period were encouraged to remain in the study to complete all remaining scheduled double-blind visits and procedures.

Nine-hundred and five subjects entered the run-in period, of whom 592 were randomized into the DB period. Of the 592 subjects randomized to the DB phase, 588 received treatment (292 placebo and 296 HYSINGLA ER). The table below from Dr. Zhou's review shows the number randomized to each dosage group.

Table 5: Number of randomized subjects in each dosage group

	optimal dose at the end of run-in period					total
	20 mg	**40 mg**	**60 mg**	**80 mg**	**120 mg**	
Hysingla ER	63	88	55	48	42	296
placebo	62	86	59	45	40	292
total	125	174	114	93	82	588

The majority of subjects were white (68%) and female (57%) and the mean age was 49 years. The demographic and baseline characteristics were generally balanced between the two treatment groups.

According to the Applicant the most common reason for discontinuation during the run-in period was adverse event (30%), followed by subject's choice (16%), lack of therapeutic effect (15%), and confirmed or suspected diversion (7%). During the DB period, 5% of subjects discontinued study drug due to adverse (3% placebo, 6% HYSINGLA ER), 10% due to lack of efficacy (15% placebo, 5% HYSINGLA ER), and 5% in each treatment group due to subject's choice. In the DB phase, 7% of HYSINGLA ER-treated subjects and 11% of placebo-treated subjects who discontinued study drug stayed in the study as "retrieved dropouts."

Due to the high discontinuation rate coded as subject's choice, the Applicant was requested to provide additional data on these subjects in order for the reviewer to determine whether these discontinuations were actually due to adverse events, lack of efficacy, or some other specific reason. The following is Dr. Spaulding's reanalysis of discontinuations. Overall, there was not a large difference between the Applicant's categorization compared to Dr. Spaulding's, as shown in the tables below from her review.

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

*ASHA = American Speech and Hearing Association

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

Dr. Spaulding reviewed the protocol deviations that occurred during the study and found that neither the rate nor the types of deviations were likely to affect the efficacy analyses.

Analysis and Results of Primary Efficacy Endpoint

Dr. Zhou was able to replicate the Applicant's results for the primary efficacy analysis. In her review she details the statistical methodologies. Briefly, the Applicant utilized a mixed effects model with repeated measures (MMRM) analysis of the primary efficacy variable incorporating a pattern mixture model (PMM) framework to account for missing data. The following is taken verbatim from her review:

> The method can be described as the following four steps: (1) all observed data collected while subjects were exposed to the DB treatment were firstly analyzed using a MMRM model. The MMRM model included treatment, time and prior opioid experience status as fixed effects. The baseline and pre-randomization mean PI scores were incorporated as the dependent variables; (2) within each treatment, subjects were categorized into three patterns: completing the study; discontinuing the DB treatment due to an AE or American Speech and Hearing Association (ASHA) related event; or discontinuing the DB treatment due to all other reasons. For each pattern, the mean PI score at week 12 was then estimated differently. For subjects discontinuing the DB treatment due to an AE or ASHA related event, missing mean PI score was replaced with the least square (LS) mean PI score at the screening baseline that was estimated from the MMRM model. For subjects discontinuing due to other reasons, missing mean PI score was replaced with an arithmetic mean of the weekly LS mean PI scores at week 4, 5, 6, 7 and 8 that were estimated from the MMRM model. For completers, the estimated LS mean at week 12 was used; (3) within each treatment, the week 12

treatment estimate was a weighted average of the estimated mean PI scores for subjects categorized by the three patterns, while weight was the proportion of each group of subjects within a treatment; (4) Finally, the week 12 treatment estimates between two treatment groups were compared.

Dr. Zhou notes in her review that this statistical approach is acceptable because it does not attribute a treatment benefit to subjects who could not tolerate or remain on treatment. The primary efficacy analysis as conducted by the Applicant and replicated by Dr. Zhou is shown below.

Table 6: Primary efficacy analysis

Study Period/Week **Mean Pain Intensity**	**Placebo[a]** **(N=292)**	**HYD** **(N=296)**
Baseline		
n	292	296
Mean (SD)	7.4 (1.19)	7.4 (1.13)
Prerandomization		
n	291	296
Mean (SD)	2.8 (1.15)	2.8 (1.16)
Double-blind Week 12		
n	199	218
Mean (SD)	3.7 (2.04)	3.3 (1.93)
Pattern 1: Completed Week 12**		
n (%)	210 (72)	229 (77)
LS Mean (SE)	4.17 (0.131)	3.47 (0.128)
Pattern 2: Discontinued Study Drug due to Adverse Event or ASHA Related Event**		
n (%)	11 (4)	18 (6)
LS Mean (SE)	7.40 (0.048)	7.40 (0.048)
Pattern 3: Discontinued Study Drug due to Other Reasons**		
n (%)	71 (24)	49 (17)
LS Mean (SE)	3.90 (0.114)	3.38 (0.112)
Repeated Measures Analysis/Least Squares Means (SE) at Double-blind Week 12 from PMM		
LS Mean (SE)	4.23 (0.126)	3.70 (0.128)
Treatment Comparison at Double-blind Week 12		
Difference in LS means from Placebo (Mean (SE))		-0.53 (0.180)
P value vs Placebo		0.0016
95% CI for difference from Placebo		(-0.882, -0.178)

Source: Clinical Study Report Table 14.2.1.1.1 and Table 14.2.1.1.2.

The primary efficacy results demonstrated that HYSINGLA ER is statistically significantly superior to placebo, however the treatment difference is relatively small, 0.53 on a pain intensity scale of 0-10. It is common to see such small treatment effects in clinical trials of analgesics, even for products like opioids that are known to provide analgesia, and this is an area of interest for researchers in this field. The Division has historically accepted these statistically significant but small treatment effects as clinically meaningful, especially when supported by the findings of relevant secondary outcomes, as is the case with HYSINGLA ER.

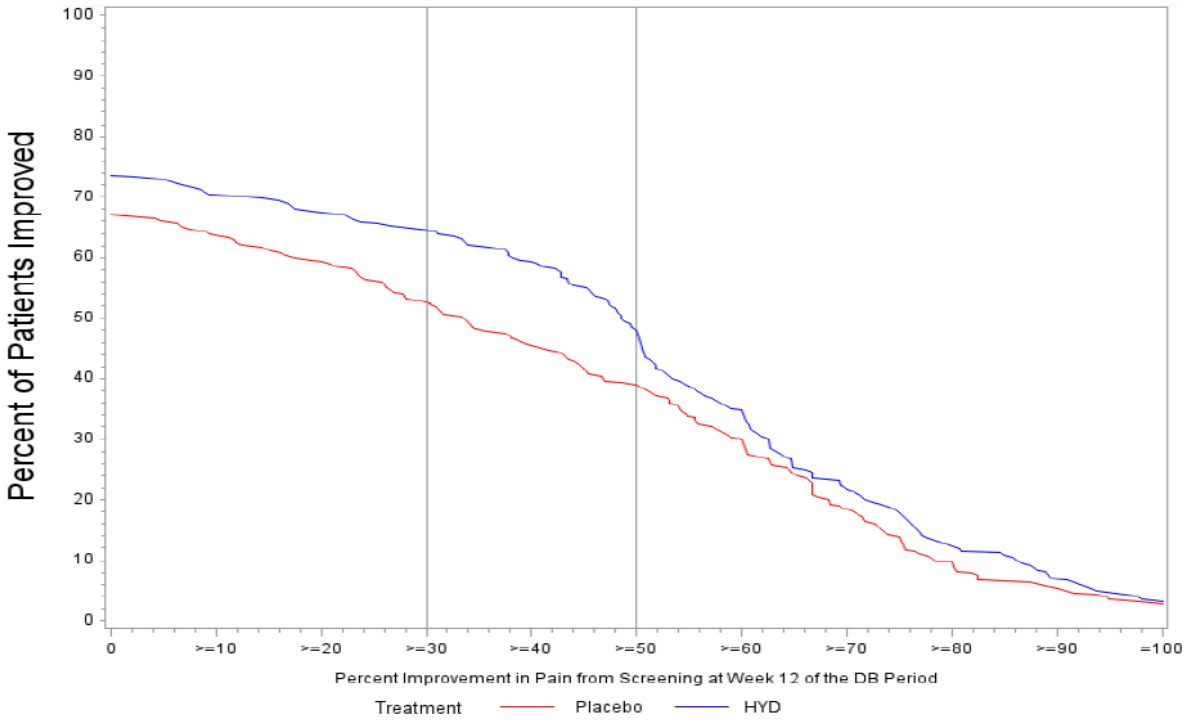
Refer to Dr. Zhou's review for the sensitivity analyses she conducted using alternate approaches to handling missing data, and including retrieved dropouts. The results were similar to the primary analysis.

As discussed in Section 11 below, two study sites for HYD3002 (Taber and Harris) had serious deficiencies noted during their OSI inspections. The clinical review team requested that Dr. Zhou reanalyze the primary efficacy endpoint omitting these two study sites. She conducted these analyses and concluded that the efficacy results were not affected and HYSINGLA ER was consistently superior to placebo.

Dr. Zhou generated a continuous responder curve by treatment group, shown below. All non-completers were classified as non-responders. Her results confirmed the Applicant's results and showed that HYSINGLA ER-treated subjects had consistently higher responder rates than placebo-treated subjects. The two curves are significantly different when non-parametric tests were applied (Wilcoxon rank sums test: p-value = 0.023); Van der Warden test: p-value = 0.026).

Figure 8

Figure 3: Percent improvement in pain from screening baseline at week 12 of the DB period

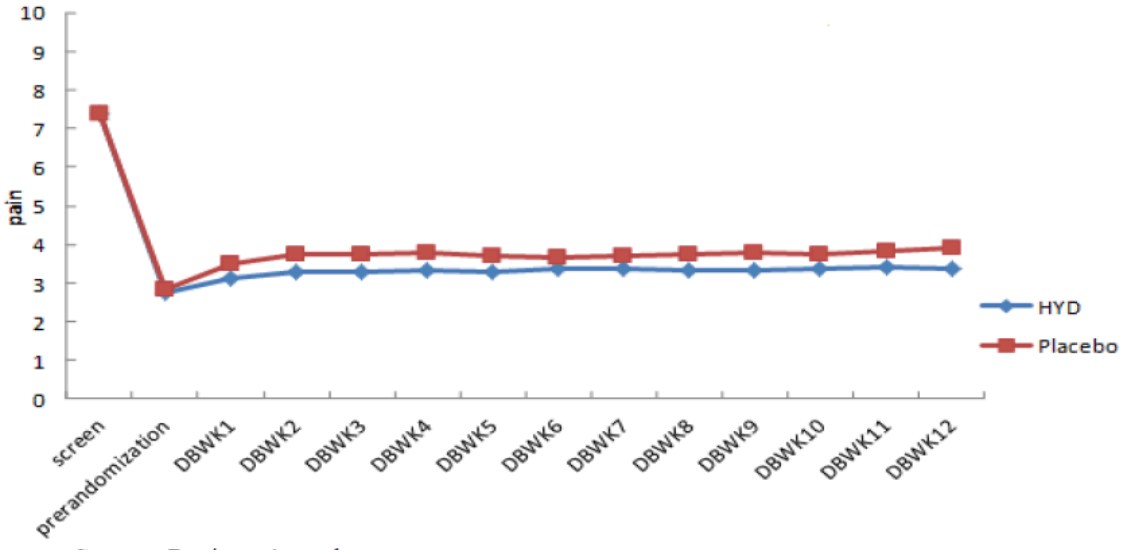


Source: Dr. Zhou's review, p. 16

Dr. Zhou also did an analysis of observed pain scores over time for each treatment group with and without retrieved dropouts. The overall trend is a plateau after randomization and the pain curves of the two treatment groups show a small separation for both scenarios.

Figure 9

Figure 2: Average pain over time (observed pain scores with retrieved dropouts)



Other secondary endpoints, including Patient Global Impression of Change (PGIC), Brief Pain Inventory (BPI), and rescue medication use generally supported the superiority of HYSINGLA ER over placebo, with the exception of the Medical Outcome Sleep Scale which showed no difference between the treatment groups. A slightly higher percentage of subjects treated with HYSINGLA ER did not use any rescue medication (22%) compared to placebo-treated subjects (17%), although the use of rescue in the HYSINGLA ER treated-group increased with increasing doses of study drug.

Subjects were allowed to take immediate-release oxycodone 10 mg tablets as rescue medication, and the maximum amount allowed was based on the subject's randomized dose of HYSINGLA ER, as follows:

Table 3. Amount of Immediate-release Oxycodone Permitted Daily

Dose Level During the Double-blind Period	Maximum Immediate-release Oxycodone Daily Dose[a]
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

Source: Protocol Amendment 3 (11-Jul-2012)

[a] Immediate-release oxycodone could have been administered as 5 to 10 mg/dose, as needed, with a minimum dosing interval of 4 to 6 hours. The total daily dose was not to exceed the daily maximum. The maximum daily immediate-release oxycodone dose allowed was determined by the subject's current double-blind dose level.

The mean daily number of oxycodone 10 mg tablets taken was higher in the placebo group compared to HYSINGLA ER. During Week 1 the mean daily number of tablets for the placebo group was 0.67 tablets for compared to 0.58 tablets for the HYSINGLA ER group. For Week 2, the mean use was 0.88 tablets vs 0.61 tablets, and for Weeks 3-12, the mean use was 0.75 vs 0.58 tablets. For Weeks 0-12 the mean daily number of tablets for the placebo

group was 0.90 compared to 0.67 for the HYSINGLA ER group. Trends were the same for median rescue use for all time periods. The amount of rescue taken was consistently higher for the placebo group compared to those taking HYSINGLA ER.

In summary, HYSINGLA ER appears superior to placebo over a 12-week double-blind treatment period, based on the results of a single AWC clinical trial in patients with CLBP not successfully treated by their pre-study analgesic. The analysis of the primary endpoint showed a statistically significant, but small treatment effect. This is commonly seen in clinical trials of opioid analgesics known to be efficacious, and the Division has generally accepted such small treatment effects as clinically meaningful, particularly when supported by secondary analyses such as the cumulative responder analysis and rescue medication use.

8. Safety

The safety database for this application was made up of subjects from 11 Phase 1 studies and two Phase 3 studies of HYSINGLA ER, and consisted of 2,476 subjects who were exposed to at least one dose ranging from 20 to 160 mg. The Phase 3 studies included HYD3002, the AWC efficacy and safety study in patients with chronic low back pain, and HYD3003, an open-label, multicenter study to assess the long-term safety of HYSINGLA ER in patients with chronic nonmalignant, nonneuropathic pain. Subjects in this study were treated with HYSINGLA ER for up to 76 weeks. Dr. Spaulding focused her safety review primarily on the data from the two Phase 3 studies, which is summarized here. Safety issues related to the Phase 1 studies are also noted in this review as appropriate. In many of the Phase 1 studies, subjects received naltrexone block to prevent serious opioid-related adverse reactions, so that safety findings in those studies do not reflect the true safety profile of HYSINGLA ER.

In the pooled Phase 3 studies, a total of 1827 subjects were exposed to at least one dose of HYSINGLA ER ranging from 20 to 120 mg. A total of 364 subjects were exposed for at least 12 months, and a total of 374 were exposed to at least one dose of 120 mg. Twelve percent of subjects who took 120 mg were exposed for at least 12 months. Overall, the mean age of subjects receiving HYSINGLA ER in pooled chronic pain studies was 50 years. There were more female subjects than male subjects (58% versus 42%). 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%).

Deaths

There were a total of seven deaths that occurred during the Phase 3 trials, six in the HYSINGLA ER group and one in the placebo group. There were no deaths in the Phase 1 studies. Refer to Dr. Spaulding's review for detailed narratives of the deaths. In summary, the causes of death in the HYSINGLA ER-treated subjects included an overdose (multiple drugs including HYSINGLA ER, citalopram, and cyclobenzaprine), brain aneurysm, myocardial infarction, thrombotic thrombocytopenic purpura and metabolic acidosis, respiratory failure (in a patient with underlying COPD), and hypoxia (in a patient with underlying COPD). There was insufficient data provided to determine whether the overdose was intentional or accidental. Both patients with respiratory failure had complex and serious

medical histories. Contribution of HYSINGLA ER to the overdose, and two deaths due to respiratory failure/hypoxia cannot be ruled out.

Nonfatal Serious Adverse Events

A total of 120 nonfatal serious adverse events (SAEs) were reported in 84 (5%) of exposed HYSINGLA ER-treated subjects, one of which was in a Phase 1 study, and 119 in the Phase 3 studies. The SAE that occurred during the Phase 1 study was in Study HYD1008, a PK study in patients with renal impairment. The event was reported as sepsis syndrome in a 48 year old black male subject with severe renal impairment. The investigator determined that the event was unlikely related to study drug, and I concur.

The most common nonfatal SAEs in HYSINGLA ER-treated subjects in the pooled Phase 3 studies were chest pain (6 [< 1%] subjects), drug abuse (5 [< 1%] subjects), and osteoarthritis (4 [< 1%] subjects). SAEs related to GI disorders (abdominal pain, GI hemorrhage, impaired gastric emptying, esophageal obstruction, rectal fissure, vomiting) were experienced by one subject each. Nonfatal SAEs considered possibly related to the study drug occurred in 10 subjects (total of 12 events) and included asthma, esophageal obstruction, impaired gastric emptying, lethargy, sedation, drug abuse, and overdose, each occurring in < 1% of subjects. Drug abuse-related AEs will be discussed later in this section.

There was one SAE of QT prolongation that is of note given the positive TQT study conducted by the Applicant. There were also two reports of esophageal obstruction associated with HYSINGLA ER , one in a patient with a preexisting esophageal stricture (endoscopy showed a glue-like mass lodged in the esophagus after three doses of HYSINGLA ER), and one in a patient with no apparent structural abnormality of the GI tract.

Adverse Events Leading to Discontinuation

The overall incidence of treatment emergent adverse events (TEAEs) in HYSINGLA ER-treated subjects leading to discontinuation of study drug in the pooled Phase 3 studies was 17%. The gastrointestinal and nervous system disorders (7% and 6%) were the most commonly reported system organ classes. The incidence of discontinuation due to adverse events in the double-blind study HYD3002 was 10% during the open-label run in phase, and during the double-blind phase was 4% in HYSINGLA ER-treated subjects versus 3% in placebo-treated subjects. Again the most common adverse events were GI and CNS related, including nausea, vomiting, dizziness, and headache, as would be expected for an opioid analgesic.

Common Adverse Events

Common adverse events reported in at least 2% of HYSINGLA ER-treated subjects compared to placebo-treated subjects for Study HYD3002 are described in the Applicant's table below for the run-in period as well as the double-blind period. The following is paraphrased from Dr. Spaulding's review:

> Overall, the incidence of TEAEs reported during the double-blind period was 41%. A higher percentage of HYSINGLA ER-treated subjects compared to placebo subjects experienced any TEAE (46% versus 35% respectively). The

Gastrointestinal Disorders and Infections and Infestations system organ classes (SOCs) had the highest frequency of TEAEs reported for HYSINGLA ER subjects (18% each) followed by the Nervous System Disorders SOC at 10%. The most commonly reported preferred terms for HYSINGLA ER-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%).

Table 1: 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: Study report HYD3002 Table 25, pg. 216

The TEAEs that occurred during HYSINGLA ER exposure at a rate of at least 2% in the pooled Phase 3 chronic pain studies were similar in nature to those in Study HYD3002. The most common TEAES were nausea (21%), constipation (16%), vomiting (10%), dizziness (10%), headache (8%), and somnolence (8%). There were no new or unexpected common TEAEs reported. Review of the common TEAEs in the Phase 1 studies in subjects who were not naltrexone blocked did not reveal any new or unexpected events.

Overall, the common TEAEs reported for HYSINGLA ER during its development are those typically associated with opioid analgesics.

Laboratory, Vital Sign, and ECG Findings

Dr. Spaulding reviewed the laboratory findings and determined there were no clinically important findings for hematology and chemistry assessments in the study population.

Vital sign changes were also reviewed and noted to be not clinically meaningful. A small number of subjects experienced small changes in blood pressure, none of which required treatment.

ECG findings are discussed below with AEs of special interest/QT prolongation.

Adverse Events of Special Interest

Gastrointestinal obstruction/choking/sticking

HYSINGLA ER contains PEO, which is known to make tablets containing it swell and become sticky when they come in contact with moisture, and result in the tablets sticking in the GI tract, choking, and possible GI obstruction, particularly in patients with prior GI surgery or structural abnormality that result in a small gastrointestinal lumen. Subjects in the clinical trials were to have been advised to avoid wetting the tablets prior to swallowing and to swallow the tablet with sufficient water. Both the placebo and active drug product contained PEO.

A total of 11 (<1%) of subjects in the HYSINGLA ER clinical development program experienced formulation-related choking or GI obstruction AEs. The label will include language for prescribers to consider the risk of GI obstruction and choking when prescribing HYSINGLA ER.

Dr. Spaulding reviewed the Applicant's analysis based on an SMQ consisting of prespecified terms related to choking and GI obstruction of the incidence of these events. In the pooled chronic pain studies there were eight reports, two dysphagia, two esophageal obstructions, two vomiting, one choking, and one intestinal obstruction. Seven of the eight events appear to have been related to study drug. The case of intestinal obstruction was apparently not related, as this patient had a complication of his ostomy stoma in that it had grown together. One of the esophageal obstructions occurred in a subject without any known GI structural abnormality, and one occurred in a subject with an esophageal stricture. There were also two reports of dysphagia and one "pill stuck in throat" in the Phase 1 studies.

I concur with the above analysis and agree that the label must include appropriate language for safe prescribing in patients at risk for choking and obstruction.

QT prolongation

The Applicant assessed the incidence of QT prolongation or cardiac repolarization events in subjects treated with HYSINGLA ER in the pooled chronic pain studies. A total of seven in HYSINGLA ER-treated subjects were reported to have QT prolongation or syncope, all during the open-label HYD3003 study. Four of these seven subjects reportedly experienced syncope

and the remaining three subjects had ECG findings of prolonged QT (HYSINGLA ER doses were 40 mg in one subject and 80 mg in two). Two of the cases prolonged QT resolved when drug was discontinued, and one while still taking study drug. The two cases of syncope were not associated with QT prolongation on ECGs.

Given the finding of mild QT prolongation in the thorough QT study, it is possible the QT prolongations in the clinical trial were associated with HYSINGLA ER. The label will include appropriate language regarding the results of the QT study.

Adverse events associated with drug abuse potential and aberrant drug behavior
As a Schedule II opioid analgesic, HYSINGLA ER administration is associated with the risks of addiction, abuse, and misuse. As well as collecting and analyzing adverse events related to drug abuse and aberrant drug behavior, the Applicant conducted an analysis of aberrant drug behavior events (abuse, overdose, misuse, and medication errors) that occurred in the HYSINGLA ER clinical development program, utilizing an SMQ to search the database.

The Applicant assessed the incidence of AEs associated with drug abuse potential that occurred in subjects exposed to HYSINGLA ER in the pooled chronic pain studies (N=1827). These AEs were not necessarily associated with actual drug abuse. The most common AEs reported were euphoria (10%) and CNS depression (16%), both commonly associated with the use of opioids. AEs of drug abuse, dependence, withdrawal and substance-related disorders occurred in 1% of exposed subjects in the pooled chronic pain studies.

In the pooled chronic pain studies there were nine subjects (<1%) for whom aberrant drug behavior was reported as follows: drug abuse (5 [< 1%]), drug screen positive (1 [< 1%]), substance abuse (1 [< 1%]), intentional drug misuse (1 [< 1%]), and overdose (1 [< 1%]). Dr. Spaulding reviewed the narratives for these subjects: three subjects obtained hydrocodone/apap IR tablets from sources other than the investigators, one subject took extra rescue medication on one day due to increased pain (aberrant drug behavior according to the protocol, however would not be labeled as abuse), one subject had a positive urine drug screen for THC, another admitted to using THC, and one subject had a nonfatal polydrug overdose involving benzodiazepine, zolpidem, cyclobenzaprine, gabapentin, and HYSINGLA ER. It was not clear if this was intentional. One subject took a single extra dose of HYSINGLA ER, and another took the HYSINGLA ER twice daily for several days and said she had been instructed to do so. She did not have any reported associated adverse events.

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 investigated during the HYSINGLA ER clinical development program and termed diversion. These reports occurred at 8 study sites. Sixty three cases of diversion (39 [4.3%] cases in HYD3002, and 24 cases [2.5%] in HYD3003) were confirmed by investigators. Of the 39 cases in HYD3002, 28 occurred during the run-in period and 11 during the double-blind period (3 HYSINGLA ER subjects and 8 placebo subjects). Six subjects reported that their study drug was stolen or used by someone other than themselves. Of the 24 reports of diversion in open-label study HYD3003, 10 subjects reported study drug stolen.

The SMQ analysis showed rate of aberrant drug of <1% of HYSINGLA ER-exposed subjects, and three of the events appear to have been directly related to HYSINGLA ER (two subjects who took extra doses, and the polydrug overdose). The incidence of diversion in the pooled chronic pain studies was approximately 3%. Aberrant drug behaviors and diversion are commonly seen in clinical trials of opioids, and the incidence and types of behaviors reported during this development program do not appear unusual.

Audiological adverse events
CDRH, Division of Ophthalmic, and Ear, Nose, and Throat Devices, Ear, Nose, and Throat Branch (ENTB) was consulted during the IND phase of HYSINGLA ER, to provide advice to the Applicant regarding audiological assessments during clinical trials, and during the NDA review, to assess the Applicant's findings. Cherish Giusto, Au.D. provided a review of the data to the Division on June 26, 2014, with secondary concurrence from Srinivas Nankumar, Ph.D., Chief, ENTB.

As stated in the CDRH review:

> There have been reports in the literature of hearing loss associated with the use of hydrocodone, usually with a hydrocodone/acetaminophen combination. These reports describe a sensorineural hearing loss that is typically sudden or rapidly progressive in nature, and often severe in degree. Currently, there is no clear consensus on the extent of hydrocodone's risk for ototoxic effects on hearing and vestibular function. Factors that contribute to the unclear nature of hydrocodone-associated hearing loss include: drug dosage, drug use period, patient risk factors (e.g., existing hearing loss, history of noise exposure) that may make them more susceptible to ototoxic effects, and the use of hydrocodone in conjunction with other agents (e.g., acetaminophen, NSAIDS, aspirin). Since progressive hearing loss has been associated with the chonic use of hydrocodone/acetaminophen combination products and the potential exposure to hydrocodone from this HYD product is higher than the labeled doses from combination products, it was important to monitor for any potential cochleo-vestibular ototoxicity from the use of HYD during the Phase 3 clinical trials for this product.

The Applicant implemented an agreed upon protocol for audiological toxicity monitoring. Comprehensive audiology evaluations in the phase 3 studies included assessment of air-conduction pure-tone audiometry, bone-conduction pure-tone audiometry, speech reception threshold, immittance audiometry (tympanometry), Dizziness Handicap Inventory (DHI), and Tinnitus Handicap Inventory (THI). The Applicant submitted results of their ototoxicity assessments as part of the NDA. CDRH was asked to review the data and determine whether they agreed with the Applicant's conclusion that there is not an increased risk for hearing impairment or vestibular disorders with HYSINGLA ER.

Of note, the Office of Scientific Investigations determined that the audiology data from one study site (Taber) was not reliable. The Sponsor was aware of these issues and did not include audiologic data from that site in the analyses.

The following are the conclusions and recommendations noted in the CDRH review.

IV. Conclusions & Recommendations:

Overall, the sponsor has provided appropriate data analyses to evaluate the ototoxicity of hydrocodone in their study. The sponsor followed the agreed upon ototoxicity monitoring protocol from the audiology perspective. Given the nature of a typical hydrocodone-associated hearing loss (i.e., sudden onset, rapidly progressing severe sensorineural hearing loss) from reports in the literature, we believe that 12-18 months is a sufficient time interval for assessing audiological effects from this drug.

From a clinical audiology perspective, the audiology report submitted as part of this NDA reveals no significant signal of acute decrements in hearing or vestibular function in the population studied, during the time course of the study, and under the dosage conditions studied. The overall treatment-emergent adverse event rate related to hearing and vestibular disorders during HYD use for the pooled chronic pain studies was 3% (59 out of 1827). It was noted that

the overwhelmingly most frequently occurring event in the safety population was tinnitus (37 out of 59 events, or 2% of the population).

We defer to the CDER review team regarding the adequacy of the exposure numbers/sample size and the primary data break down of subjects with significant changes in hearing into dose-response and toxicity grade analyses. We also defer to the CDER review team and statistical reviewers to determine if these exposure numbers will suffice for an adequate assessment of the long-term risk of HYD-associated hearing loss.

In summary, the data submitted in this audiology report adequately addresses our concerns about the potential for ototoxic effects from HYD use. There was no signal of any significantly increased risk for hearing loss or vestibular impairment in this study population with the HYD treatment protocol that was used. We have some additional comments for your consideration regarding progressive hearing loss and additional potential patient risk factors for hearing loss.

Question for CDRH (ENTB): Do you concur with sponsor's conclusion that there is not an increased risk for hearing impairment or vestibular disorders with HYD?

Answer: In general, we agree that the audiology data provides a reasonable assurance that there is not a significantly increased risk for hearing impairment or vestibular disorders with the use of HYD in the doses and time periods investigated during these Phase 3 trials from a clinical audiology perspective. However, we defer to the CDER review team regarding the significance of the treatment-emergent adverse event rates related to hearing and vestibular disorders, particularly the rate of tinnitus which occurred in 2% of the pooled chronic pain studies population (see Section 6.1 of the audiology report).

CDRH found that there is not a signal for hearing loss in the HYSINGLA ER database. They have suggested possible additional analyses to further asses the audiology findings (see CDRH review). However, the Phase 3 clinical trials were not designed as outcome studies to assess audiology endpoints, and therefore additional analyses may not be worthwhile.

Because the findings are negative, and the audiology assessments conducted would identify a signal only if it was common (due to the relatively small number of patients assessed), language regarding these findings will not appear in the label.

Safety Summary

The adverse event profile for HYSINGLA ER is similar to that of other extended-release opioids, in that the common adverse events include mostly CNS (dizziness, somnolence) and GI (nausea, vomiting, constipation, and abdominal pain) related reactions. Due to the PEO in the HYSINGLA ER formulation and the stickiness and swelling of the tablets when exposed to moisture, a small number of events of choking, dysphagia, and GI obstruction occurred during the clinical trials. The Applicant conducted a TQT study that showed the potential for mild QT prolongation, and in fact three subjects in the database experienced mild QT prolongation. Of note, there were no adverse events associated with these QT findings. Hearing associated adverse reactions have been reported during the use of hydrocodone/acetaminophen combination products, and the Applicant performed audiological assessments and collected adverse events related to hearing. Review of this data by CDRH showed no signal for hearing associated events, although there were some limitations to the data. Finally, there were a small number of subjects for whom aberrant drug behavior was reported. This is a common finding in clinical trials of opioid analgesics, and the reports in this study are consistent with those from other opioid trials.

The 120-day safety update was submitted to the NDA on August 25, 2014. It was not reviewed by Dr. Spaulding as her review was completed prior to the submission of the update. The submission includes the following additional safety data collected between December 13, 2013 (cutoff date for original NDA) and April 28, 2014 (cutoff date for 120-day safety update):

- Safety data on 106 subjects who participated in the extension period of the open-label long-term study HYD3003. The core study was from Weeks 1-52, and the extension period was 24 weeks in duration from Weeks 52-74.
- Safety reports from literature published between 03-Dec-2013 (cutoff date for the ISS) and 30-Apr-2014 (the cutoff date for Safety Update)
- ECG data from Studies HYD3002 and HYD3003 that was not included in the original NDA submission. During the database lock for the extension period for HYD3003, the Applicant discovered that some ECG data collected during the conduct of these studies were not transmitted from the sites to the ECG vendor and were not included in the final analyses submitted in the NDA. Upon discovery, the missing ECG tracings were retrieved and analyzed, and the results of the evaluation are included in the safety update.

Safety data from extension period of HYD3003

Safety data for 106 subjects who participated in the extension period of Study HYD3003, consisting of exposure to study treatment, demographics, medical history, prior and concomitant medications, adverse events (AEs), clinical laboratory parameters, vital sign evaluations, electrocardiogram (ECG) evaluations, audiologic evaluations, and safety evaluations in special groups and conditions, were submitted in the safety update. There were no deaths, 4 (4%) SAEs, and 2 (2%) discontinuations due to adverse events during the extension period. There were two reports of formulation-related choking and obstruction, and no reports related to either QT prolongation, aberrant drug behavior, or hearing impairment. No diversion was reported in this period of the study. Review of the data showed no new or

unexpected safety signals, and a similar safety profile to that noted in the original NDA submission.

Literature reports
The Applicant conducted a literature search regarding the safety of hydrocodone between the dates December 3, 2013 and April 30, 2014. In ten relevant publications discussing single-entity hydrocodone products, no new or unexpected safety signals were detected.

Retrieved ECG data for Studies HYD3002 and HYD3003 after original NDA submission
The Applicant states that when the database was locked for the extension period of the open label safety study in April 2014, they discovered that 19/8658 (0.2%) of ECG tracings for 11/905 (1.2%) subjects in study HYD3002 and 45/15573 (0.3%) tracings for 16/923 subjects (1.7%) in Study HYD3003 were missing, had not been sent to the Applicant's independent cardiologist for review and were not included in the original NDA submission analyses. The Applicant subsequently sent them for review and provided an analysis in the 120 day update.

There were no abnormal findings related to QT prolongation in the retrieved ECGs. There was no clinically meaningful difference between the ECG data submitted with the original NDA and the ECG data that integrated the previously missing tracings.

Safety Conclusions
The safety issues and risks associated with HYSINGLA ER are those related to the opioid drug class, and the HYSINGLA ER formulation. These can be adequately managed by labeling and the inclusion of HYSINGLA ER in the ERLA REMS, and do not preclude approval of this product.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. Advisory committee meetings have been convened in the past for extended-release opioid products with potential abuse-deterrent properties. The Agency has had experience reviewing and labeling these types of products, and a draft guidance issued in 2013, *Abuse Deterrent Opioids, Evaluation and Labeling,* is now available to sponsors. Consequently the Agency determined that we have had sufficient experience labeling these products and an advisory committee meeting was not necessary.

10. Pediatrics

The pediatric study plan was discussed and agreed upon with the Pediatric Research Committee on July 9, 2014.

This application triggered PREA because it is a new dosing regimen for hydrocodone. The Applicant submitted a pediatric study plan requesting a waiver for studies in pediatric patients from birth to less than 7 years of age because studies of chronic pain in this age group would be impossible or highly impracticable due to the small population of patients in this age group. They also requested a waiver of studies in patients ages 7 to less than 12 years because they have failed to develop an age appropriate pediatric formulation with abuse-deterrent and extended-release characteristics. The PeRC agreed with both waiver requests, and stated that

the Applicant must submit a summary of their attempts to develop an age appropriate formulation to be posted on the FDA website.

The Applicant requested and the PeRC agreed to a deferral for pediatric patients ages 12 to less than 17 years because adult studies have been completed and the product is ready for approval. For opioid analgesics intended to treat chronic pain, efficacy from adult studies can be extrapolated to this age group. The required study or studies, therefore, must include pharmacokinetic and safety data to support the dosing and safety of the product. The following study and goal dates have been proposed by the Applicant and are acceptable.

> Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of hydrocodone extended-release in patients from ages 12 to less than 17 years with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
>
> Final Protocol Submission: July 31, 2015
> Study Completion: January 31, 2019
> Final Report Submission: July 31, 2019

11. Other Relevant Regulatory Issues

- At this writing, the Offices of Regulatory Policy and Chief Counsel are reviewing the scope of exclusivity for Zohydro ER and whether Zohydro ER's exclusivity will block the approval of HYSINGLA ER. Based on their findings, HYSINGLA ER may receive a tentative approval. Please refer to the decisional memo for the outcome of this issue.
- Financial disclosure: The Applicant has submitted the Financial Certification and Disclosure document. There were no financial agreements reported between the Applicant and investigators.

- The Office of Scientific Investigations (OSI) was initially asked to inspect four study sites that participated in both Phase 3 studies (HYD3002 and HYD 3003) (b) (5) [redacted] one site (Hassman) was issued a Voluntary Action Indicated (VAI), and one (Dawson), No Action Indicated (NAI). (b) (5) [redacted] an additional four sites were inspected.

  Dr. Louise Taber's site (#0108A) was issued an OAI due to alterations in source documents related to initial audiology assessments. 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. There did not appear to be any underreporting of adverse events. The Applicant was aware of problems at this site, and did not include audiologic data obtained there in the analyses. In their review, OSI stated that the audit

indicated serious deviations/findings that would impact the validity and reliability of the submitted data, and recommended that data for audiometry assessments for Protocol HYD3003 for the five records noted to be fraudulent not be included in support of audiology findings, and went on to state that because these altered records were discovered in five of 19 records reviewed, they cannot guarantee the accuracy of the remaining 14 audiometry reports.

The Applicant conveyed to the Division that they omitted this site's data in the audiometry assessments. Additionally, due to the unreliability of data at this site, the primary efficacy endpoint was reanalyzed by the Agency statistician without data from the Taber site, and the results were similar to those that included this site.

Dr. Michael Harris's (#2059A) site (b) (5) exhibited an overall lack of oversight and control over the studies, which was apparent in data collected and maintained by the site. Four subjects were randomized in study HYD3002 and 156 in HYD3003. As stated in the OSI review:

> There were numerous examples of inadequate records, which included the coordinators' and the investigators' progress notes being in conflict with each other. There were occasions in which progress notes, made by the clinical investigator, did not match events of the visit. Throughout the inspection for both studies, the site was deficient for record keeping; on multiple occasions the site had to request copies of documents from the monitors.
>
> There was no apparent under-reporting of adverse events in either study. The primary efficacy endpoints were verifiable based upon subjects' e-diaries uploaded into the sponsor database.
>
> There were multiple instances of failing to follow the protocol as well as multiple instances of failing to maintain adequate and accurate records across both studies HYD 3002 and HYD 3003. Furthermore, the site had submitted false information on both studies to their IRB with regards to the Investigator's inspectional history.

The OSI reviewer stated the audit indicates serious devaiations/findings that would impact the validity and reliability of the submitted data. The Agency statistician reanalyzed the primary efficacy endpoint without data from this site, and the results were similar to those obtained when this site's data were included.

Of the additional four sites inspected after the inspection results of the first four were reported, two received VAI's and two NAI's. The OSI review stated that data from these four sites appear acceptable, and no serious deviations/findings were noted that would impact the validity or reliability of the submitted efficacy and safety data. Refer to the OSI review for details regarding these inspections.

Of the eight study sites inspected, the data from six sites was determined to be acceptable for review based on the OSI inspections. It does not appear that there is a systemic problem of data reliability in all study sites, and therefore the data from the study sites (b) (5) are acceptable for support of this NDA.

- The Controlled Substance Staff (CSS) reviewed the in vitro and in vivo studies relevant to the abuse liability of HYSINGLA ER. The primary review was conducted by James Tolliver, Ph.D. and Martin Rusinowitz, MD, with secondary concurrence by Silvia Calderon, Ph.D. and Michael Klein, Ph.D. Refer to the CSS review for details regarding the studies performed by the Applicant. The following summarizes CSS's initial findings.

  The Applicant conducted a series of in vitro physical and chemical manipulation laboratory assessments of HYSINGLA ER tablets in order to assess possible abuse-deterrent properties. At the time these studies were conducted, there was not an approved single-entity extended-release formulation of hydrocodone on the market, therefore immediate-release hydrocodone/APAP was used as a comparator with regard to assessing tablet hardness and extractability of hydrocodone. The in vitro studies included the following:

  1. Physical manipulation of HYSINGLA ER and the comparator IR hydrocodone/APAP using commonly employed household tools (two spoons, morter and pestle, pill crusher, hammer, food grater, foot file, nutmeg shaver, razor blade, spice grinder, and coffee grinder) to determine the achievable range of particle size reduction.
  2. Extraction studies on intact and milled HYSINGLA ER tablets and IR hydrocodone/APAP using the following solvents: water, coca cola, saline, 40% ethanol, methanol, 100% ethanol, , 0.1N HCl aqueous solution (pH 1), and commercially available buffers of pH 3, 8, and 10, to determine extraction times and amounts for hydrocodone.
  3. Thermal stressing of HYSINGLA ER tablets to assess the impact of intentional heat pretreatment, using a laboratory oven and common household microwave, on the release rate of hydrocodone bitartrate from intact 20, 60, and 120 mg HYSINGLA ER tablets and IR hydrocodone/APAP
  4. Syringeability studies to assess the limits of the HYSINGLA ER formulation compared to IR hydrocodone/APAP with regard to preparation for abuse via intravenous injection. They were conducted using heated and room temperature water and a variety of extraction time on intact, sliced, and milled HYSINGLA ER tablets and assessing syringeability with a number needle gauge sizes.
  5. Simulated smoking was studied to assess the limits of HYSINGLA ER tablets susceptibility to abuse by inhalation compared to IR hydrocodone/APAP. Inhalation was simulated with a gel Sep-Pak apparatus. Milled samples of HYSINGLA ER tablets were exposed to temperatures of 250ºC, 280ºC, and 300ºC for 30 and 45 minutes. These selected temperatures were higher than

the hydrocodone bitartrate melting point and approached the ignition temperature of PEO thus providing for the possible vaporization of hydrocodone under these conditions

6. In vitro dissolution in simulated gastric fluid was studied to evaluate the effects on the dissolution rate of halved, quartered, sliced, and milled HYSINGLA ER compared to IR hydrocodone/APAP. This study simulated the ingestion of physically manipulated HYSINGLA ER tablets for purposes of abuse or misuse.
7. Free base isolation was studied to determine whether hydrocodone base isolation from HYSINGLA ER milled tablets through pH mediation is feasible.
8. A bench-top study was conducted comparing HYSINGLA ER to OxyContin in order to assess the difficulty of physical manipulation. The Agency has not encouraged or endorsed the use of bench-top studies of this kind in the assessment of abuse-deterrent formulations.

The Applicant conducted a study (HYD1015) comparing the relative attractiveness of HYSINGLA ER to other opioid formulations to determine whether its properties reduce attractiveness for abuse, diversion and tampering. The opinions of experienced opioid drug abusers, who had knowledge and experience tampering pharmaceutical opioid products was sought. No drugs were administered in this study. The Agency has not encouraged or endorsed the use of attractiveness studies in the assessment of abuse-deterrent formulations.

Two clinical human abuse potential studies were conducted in support of this NDA. The PK data from these studies is discussed in Section 5 of this review.

1. Study HYD1013, "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Oral Crushed and Intact Controlled Release Hydrocodone Tablets in Recreational Opioid User." This study evaluated the oral abuse potential and pharmacodynamic (PD) effects, PK and safety of intact, milled, and chewed HYSINGLA ER 60 mg tablets compared to hydrocodone API solution and placebo in healthy non-dependent opioid abusers.

2. Study HYD1014, "A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Crushed and Intranasally Administered Controlled Release Hydrocodone in Recreational Opioid Users." This study evaluated intranasal abuse potential, PD effects, PK and safety of fine and coarse particle size HYSINGLA ER 60 mg tablets compared to hydrocodone API and placebo

As demonstrated in Study HYD1013, a lower subjective drug effect (Drug Liking VAS) was shown when HYSINGLA ER 60 mg tablets were compared to hydrocodone API administered orally either intact or chewed. The milled HYSINGLA ER 60 mg had a mean drug liking VAS similar to IR hydrocodone solution, which suggests that HYSINGLA ER 60 mg milled and hydrocodone 60 mg solution have similar drug abuse ability. The Take Drug Again VAS

was also similar between milled HYSINGLA ER and IR hydrocodone solution, while both were significantly higher than for placebo. In contrast, HYSINGLA ER intact and chewed produced substantially lower maximum levels of Take Drug Again VAS compared to either milled HYSINGLA ER or IR hydrocodone solution, but still above placebo. The results are shown in the table below adapted from the CSS review.

Table X. Study HYD1013 Take Drug Again VAS vs Drug Liking VAS Emax

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

As demonstrated in Study HYD1014 significantly lower subjective and physiological effects were noted for intranasal abuse in terms of Drug Liking and Take Drug Again compared to hydrocodone API powder. These results are shown below in a table adapted from the CSS review. Also, in an examination of nasal tolerability, both HYSINGLA ER 60 mg treatments (fine and coarse) were associated with greater negative intranasal effects, especially nasal congestion and irritation compared to IR hydrocodone powde

Table X. Study 1014 Take Drug Again VAS with Drug Liking VAS Emax

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

The following briefly summarizes CSS's conclusions regarding the in vivo and in vitro studies conducted by the Applicant. Refer to the CSS review for additional details:

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

2. The abuse deterrent features of Hysingla ER do not withstand milling. Milling of Hysingla ER tablets results in substantial compromise of the controlled release properties of the formulation as evident by increased rates of release of hydrocodone bitartrate in water (room temperature or elevated temperature) and other solvents. Results of dissolution studies and human abuse potential study HYD1013, in which Hysingla ER was administered as a powder directly to the oral cavity, indicate increased rates of release when milled Hysingla ER tablets are ingested. Thus, Hysingla ER tablets could be abused through the oral route, by milling the tablets and ingesting the resulting powder or by taking the resulting powder into water or any other solvent.

3. The Hysingla ER formulation includes polyethylene oxide (PEO) as a (b) (4) serving as the release-controlling polymer for hydrocodone bitartrate. As such, it is expected that reduction in particle size (with concomitant increase in surface area) or exposure to heated solutions, such as water, will result in increased release of hydrocodone bitartrate.

4. Syringeability studies indicate that it will be difficult to manipulate HYSINGLA ER tablets (either non-thermally stressed or thermally stressed) for purposes of intravenous injection. When exposed to an aqueous environment, HYSINGLA ER gradually forms a viscous hydrogel (gelatinous mass) that resists passage through a hypodermic needle. Syringeability studies also indicate that a single IR hydrocodone/acetaminophen tablet, in part due to low potency (10 mg hydrocodone) most likely cannot be used to produce a suitable intravenous injection

5. Simulated smoking studies demonstrated that neither HYSINGLA ER tablets or IR hydrocodone/APAP tablets can be directly abused by smoking. For both products, the amount of hydrocodone recovered from vapor was very low

CSS's initial finding regarding an oral abuse claim was that although HYSINGLA ER tablets are resistant to chewing and grinding, they could be milled into particles small enough to allow compromise of the extended release properties when the particles were placed in water and swallowed. Therefore an oral abuse claim would not be appropriate for the label. On October 20, 2014 the Applicant submitted their rationale for inclusion of the oral abuse claim in the label, which was reviewed by CSS and the Division. The Applicant stated that milling of HYSINGLA ER that would compromise it's ER properties could only be accomplished with laboratory-grade milling machines and not the type used by consumers. This combined with the Applicant's findings that it is very difficult to chew or grind HYSINGLA ER by other means supports the inclusion of the Oral Abuse Potential Study in the label. CSS agreed with this rationale and has recommended inclusion of this study in Section 9.2. At this writing, CSS is in the process of writing an addendum to their original review to update their original conclusions.

In summary, the in vitro and human abuse potential studies support labeling for abuse-deterrence by the intravenous, intranasal, and oral routes of abuse. Please refer to the approved label for the exact wording of Section 9.2.

12. Labeling

- The Division of Medication Error Prevention and Analysis (DMEPA) conducted a review of the proprietary name, HYSINGLA ER, and found it acceptable from both a promotional and safety perspective.

- Physician labeling
    - The Maternal Health Team of the Pediatric and Maternal Health Staff (PMHS) provided recommendations for the Section 8.1 Pregnancy, Section 8.3 Nursing Mothers, Section 17 Patient Counseling Information, and the Medication Guide. Refer to the final label for details.
    - PMHS also provided recommendations for Section 8.4 Pediatric Use (added Accidental ingestion of a single dose of HYSINGLA ER in children can result in a fatal overdose of hydrocodone , and HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) when exposed to water or other fluids. Pediatric patients may be at increased risk of esophageal obstruction, dysphagia, and choking because of a smaller gastrointestinal lumen if they ingest HYSINGLA ER)
    - The QT-IRT recommended labeling regarding the positive TQT study. See Section 5 of this review for details.
    - The Office of Prescription Drug Promotion (OPDP) provided recommendations for modification of labeling language determined to be promotional in the absence of support from the NDA submission.
    - Section 9.2 Abuse will include information regarding the formulation's abuse-deterrent properties for the intravenous, intranasal, and oral routes of abuse.

- The Division of Medical Policy Programs (DMPP), Patient Labeling Team, provided input on the Medication Guide.
- HYSINGLA ER is a member of the ERLA class, and therefore a Medication Guide is required.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend an Approval action for NDA 206627 for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate, because the benefits of HYSINGLA ER outweigh the risks in the intended population. My approval recommendation is for dosage strengths 20, 30, 40, and 60 mg tablets, and not for the 80, 100, and 120 mg tablets, the reasons for which are explained in the risk-benefit assessment below. HYSINGLA ER is the first extended-release hydrocodone product with abuse-deterrent properties that may mitigate abuse of hydrocodone by the intravenous, intranasal, and oral routes of abuse, and thereby may make an incremental positive public-health impact on the abuse of hydrocodone by these routes. This NDA may receive a Tentative Approval pending the outcome of ORP's review of the exclusivity issues related to Zohydro ER.

- Risk Benefit Assessment

Efficacy of HYSINGLA ER was demonstrated in one AWC clinical trial conducted in patients with chronic low back pain where HYSINGLA ER was shown to be statistically significantly superior to placebo for analgesia over a 12-week double-blind treatment period. Although the treatment effect was relatively small, this is often seen in clinical studies of opioids known to be analgesics, and is acceptable. The Applicant also demonstrated via in vitro and in vivo studies, that HYSINGLA ER has opioid-deterrent properties that warrant inclusion in the label. Due to physicochemical properties of the formulation that result from the inclusion of the excipient PEO, when exposed to an aqueous environment, HYSINGLA ER gradually forms a viscous hydrogel (e.g., gelatinous mass) that resists passage through a hypodermic needle, making it unsuitable for intravenous abuse. A human abuse potential study conducted in non-dependent opioid abusers showed that HYSINGLA ER had significantly lower subjective and physiological effects for intranasal abuse in terms of Drug Liking and Take Drug Again compared to hydrocodone API powder. HYSINGLA ER may therefore incrementally impact the abuse of hydrocodone by the IV and IN routes, however, abuse of HYSINGLA ER is still possible by these as well as the oral route, and it is subject to misuse, abuse and addiction, similar to other opioids.

The overall safety profile for HYSINGLA ER is similar to other products in the ERLA opioid class, however there are some safety issues unique to this product. The most commonly reported adverse events in this NDA are the class-wide events seen for ERLA opioids, including nausea, vomiting, constipation, abdominal pain, dizziness, and somnolence. A small number of reports of diversion and aberrant drug behavior were reported during the clinical trials, and are of concern. However, these types of events are reported in most clinical trials of opioid analgesics, and as Schedule II drugs, the events can be expected, even in the controlled setting of a trial. The Applicant conducted audiologic assessments due to the concern that there have been reports of hearing loss associated with hydrocodone/APAP combination products. A signal for hearing associated adverse events was not detected in this safety database.

A safety issue unique to this product (compared to other ERLA opioids) is the potential for mild QT prolongation demonstrated in the TQT study, and supported by a small number of mild QT prolongation reports in the safety database. The QT-IRT recommended labeling in the WARNINGS and PHARMACODYNAMICS sections of the label to advise the prescriber regarding safe administration of HYSINGLA ER. A contraindication for use was not recommended. The recommended labeling should adequately mitigate the risk of QT prolongation in patients.

Due to the presence of PEO in HYSINGLA ER, it becomes sticky when wet and forms a gelatinous mass when exposed to an aqueous environment. This attribute contributes to HYSINGLA ER's abuse-deterrent properties, but also increases the risk of sticking, choking, and GI obstruction, particularly in patients with small GI lumens. There were two reports of esophageal obstruction in the safety database, one in a patient with an esophageal stricture, and one in a patient with no prior esophageal abnormality. The label will include dosing and administration instructions to take one pill at a time with ample water to ensure complete swallowing immediately after placement in mouth, as well as a warning to not pre-soak, lick,

or otherwise wet HYSINGLA ER tablets prior to placing in mouth, and to consider an alternative analgesic in patients who have difficulty swallowing and those at risk for underlying GI disorders resulting in a small GI lumen. Labeling should mitigate the risk, and the Division will continue to monitor for these events via routine pharmacovigilance.

The Applicant's proposed dosages for HYSINGLA ER are 20, 30, 40, 60, 80, 100, and 120 mg. I recommend not approving the three highest strength tablets (80, 100, and 120 mg). These contain more hydrocodone per tablet than is currently marketed (Zohydro highest strength is 50 mg administered BID). Although the clinical trials included doses of HYSINGLA ER up to 120 mg per day, and these were found to be safe and effective, and acknowledging that HYSINGLA ER is to be administered once daily, and subjects titrated up to 120 mg in the clinical trial, the concern for these dosage strengths is two-fold; 1) the fact that there is both a once daily and twice daily extended-release hydrocodone formulation on the market may result in confusion for prescribers and subsequent medical errors, and 2) the large amount of hydrocodone in a single tablet may increase the risks of serious adverse events including death if HYSINGLA ER is incorrectly prescribed as twice daily, or if it is abused or misused such that the extended-release properties of the product are defeated. I recommend that only the 20, 30, 40, and 60 mg tablets be approved at this time. Once the product is on the market for a period of time, the Agency can review the postmarketing adverse event profile, and if it is acceptable, the higher dosage units may then be approved via a CMC supplement. This has been discussed with the Applicant and they disagree, do not intend to withdraw the higher strengths from consideration. While this is my recommendation for approval, discussions with Agency upper management stated that because HYSINGLA ER was shown to be safe and effective in the clinical at doses up to 120 mg, there is no regulatory basis for not approving the higher doses.

Overall the benefits of HYSINGLA ER outweigh the risks for use in the intended population. The abuse-deterrent properties related to IV and IN abuse will hopefully mitigate the abuse of ER hydrocodone by these routes. Postmarketing epidemiologic investigations will be required to address whether the properties intended to deter misuse and abuse of HYSINGLA ER extended release tablets actually result in a significant and meaningful decrease in misuse and abuse, and their consequences addiction, overdose, and death in the community. HYSINGLA ER will be included in the ERLA REMS as well.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

As a member of the ERLA class of opioid analgesics, a REMS is required for this product.

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, FDA has determined that a REMS is necessary for HYSINGLA to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that HYSINGLA ER poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of HYSINGLA ER. FDA has determined that HYSINGLA ER is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use HYSINGLA ER. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed HYSINGLA ER.

Pursuant to 505-1(f)(1), we have also determined that HYSINGLA ER can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risk of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse that are listed in the labeling. The elements to assure safe use will inform and train healthcare providers about the potential risks and the safe use of HYSINGLA ER.

- Recommendation for other Postmarketing Requirements and Commitments

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of misuse, abuse, addiction, hyperalgesia, overdose, and death associated with the long-term use of ER/LA opioid analgesics, of which HYSINGLA ER is a member. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

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

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

psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

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

The following timetable proposes the schedule by which you will conduct these studies:

Final Protocol Submission: (b) (4) /2014
Study Completion: 01/2018
Final Report Submission: 06/2018

2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: (b) (4) 2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: (b) (4) /2014
Study Completion: 08/2015
Final Report Submission: 11/2015

2065-4 Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

The following timetable proposes the schedule by which you will conduct this study:

Final Protocol Submission: (b) (4) /2014
Study Completion: 08/2015
Final Report Submission: 11/2015

Please note the following considerations regarding the postmarketing requirements detailed above. Given that misuse, abuse, addiction, overdose, and death are serious risks associated with the use of opioids as a class, FDA recommends that sponsors capture all opioid use among studied patient populations, rather than limit their efforts to specific products. However, specific product information should also be captured so as to better understand the role of specific product characteristics as risk factors for misuse, abuse, addiction, overdose, and death, as appropriate. Because many of the risk factors for misuse, abuse, addiction, overdose, and death cannot be captured using administrative databases alone, FDA is unlikely to find adequate protocols or strategies that evaluate administrative databases only as meeting the objectives outlined above.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia associated with the class of ER/LA opioids, of which HYSINGLA ER is a member.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2065-5 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

The following timetable proposes the schedule by which you will conduct this trial:

Final Protocol Submission: (b) (4) 2014
Trial Completion: 08/2016
Final Report Submission: 02/2017

FDA has determined that, in addition to participation in the PMR studies required of all ER/LA opioid analgesic application holders listed above, you are required to conduct the following individual post-marketing studies of HYSINGLA ER extended release tablets.

XXXX-1: Conduct epidemiologic investigations to address whether the properties intended to deter misuse and abuse of HYSINGLA ER (Hydrocodone bitartrate) extended release tablets actually result in a significant and meaningful decrease in misuse and abuse, and their consequences addiction, overdose, and death in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of HYSINGLA ER. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance Abuse-Deterrent Opioids—Evaluation and Labeling (January 2013)[1], and proposed study populations and drug comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.

The following timetable proposes the schedule by which you will conduct this study:

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

- Recommended Comments to Applicant

None

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

/s/

ELLEN W FIELDS
10/28/2014