CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	207975
Applicant Name	Teva Pharmaceuticals
Date of Submission	December 23, 2014
PDUFA Goal Date	October 23, 2015
Proprietary Name / Established (USAN) Name	Vantrela ER (hydrocodone bitartrate) Extended-Release Tablets
Dosage Forms / Strength	Oral tablet, 15, 30, 45, 60, and 90 mg
Proposed Indication(s)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Action:	Approval

Material Reviewed/Consulted: OND Action Package, including:	
Medical Officer Review	Robert A. Levin, MD
Statistical Review	Bradley McEvoy, PhD, Freeda Cooner, PhD
Pharmacology Toxicology Review	Elizabeth Bolan, PhD, R Dan Mellon, PhD
CMC Review/OBP Review	Erika Englund, PhD, Donna Christner, PhD, Christopher Hough, PhD, Haitao Li, PhD, Ubrani Venkataram, PhD, Michael Shanks, Peter Qiu, PhD, Mahesh Ramanadham, PharmD, Fang Wu, PhD, John Duan, PhD, Steven Kinsley, PhD, Ciby Abraham, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD, Yun Xu, PhD
OSI	John Lee, MD, Janice Pohlman, MD, MPH, Susan Thompson, MD
CDTL Review	John Feeney, MD
OSE/DMEPA	Millie Brahmbhatt, PharmD, BCPS, Vicky Borders-Hemphill, PharmD
OSE/DEPI II	Joann H Lee, PharmD, Rajdeep Gill, PharmD, LCDR Grace Chai, PharmD
OPDP/DCDP	Koung Lee, Jessica Fox, Olga Salis
OMPI/DMPP	Morgan Walker, PharmD, MBA, CPH, Barbara Fuller, RN, MSN, CWOCN, LaShawn Griffiths, MSHS-PH, BSN, RN
Controlled Substances Staff	Katherine Bonson, PhD, Silvia Calderon, PhD
Statistical Review (Abuse-Potential Studies)	Feng Zhou, MS, Qianyu Dang, PhD, Yi Tsong, PhD
Audiology Review	Ting Zhang, PhD, Srinivas Nandkumar, PhD

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention
DEPI = Division of Epidemiology
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMPI=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

Vantrela ER is a Schedule II single-entity hydrocodone bitartrate tablet (15, 30, 45, 60, and 90 mg) in an extended-release (ER) formulation, with excipients intended to impart physico-chemical properties that will deter some attempts at abusing Vantrela ER by manipulating the tablet. The proposed indication is for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative options are inadequate. The product was studied under IND 105587. Initially submitted as a 505(b)(2) application with reference to the Agency's prior findings of safety and efficacy for Vicoprofen (NDA 020716), the Applicant subsequently obtained right of reference to NDA 020716 and amended the submission to be a 505(b)(1) application.

2. Background

Vantrela ER is novel formulation of hydrocodone extended-release tablets and was developed to have abuse-deterrent properties for the oral, nasal, and intravenous routes of abuse. The value of an AD formulation of extended-release hydrocodone is based on the general problem of prescription opioid abuse, and the fact that as hydrocodone-containing products listed under Schedule II of the Controlled Substance Act, they carry a known risk for abuse. Much has been written about the extent of prescription opioid abuse in the US. The extent of prescription opioid abuse may be greater for immediate-release hydrocodone combination products, perhaps reflective of the greater number of prescriptions, but the consequences of abuse of higher strength single-entity hydrocodone products include a greater risk of fatal overdose. This increased risk has been reflected in data from the now defunct Drug Abuse Warning Network and other databases and has led to the creation of the Extended-Release and Long-Acting Opioid Risk Evaluation and Mitigation Strategy (ERLA REMS)[1].

There has been a growing understanding of the need to re-evaluate the manner in which pain is managed in the US and how the approach of managing chronic pain by prescribing medication in place of a coordinated interdisciplinary approach has contributed to the widespread availability of opioids in medicine cabinets across the country.[2] This is important not only for the sake of the patient with chronic pain, but for society as a whole, as the widespread availability of opioids prescribed by healthcare providers is the source for much of the misuse and abuse of opioids in the US.[3]

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[1] 11http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf

[2] https://prevention.nih.gov/programs-events/pathways-to-prevention/recent-workshop/opioids-chronic-pain/workshop-resources

The primary route of abuse of most opioid analgesics is oral, followed by varying amounts of intranasal and intravenous abuse depending on the specific formulation or opioid. This is true for both immediate-release and extended-release products. Extended-release opioid products are often manipulated to defeat the extended-release characteristics resulting in faster release of the opioid, and an earlier and higher peak drug level when abused by the oral or intranasal routes. In addition, opioid analgesics are manipulated to create material suitable for abuse by the intravenous route. Vantrela ER contains excipients intended to impart physicochemical properties that resist manipulation for the purpose of abuse. The excipients (b) (4) that are intended to impart abuse-deterrent properties to Vantrela ER. The ability of this formulation to resist manipulation has been evaluated in a series of in vitro and in vivo studies discussed in detail below. These studies represent a best effort to predict whether the formulation properties will have an impact on behavior. Note that the methodology for the in vivo studies is borrowed from the human abuse liability studies used to evaluate the abuse potential of a new drug. The important endpoints for an evaluation of abuse potential and for abuse deterrence overlap, but the focus is different. For an abuse liability assessment, the evaluation is intended to determine if the product produces a high and how much it is liked, along with many other important endpoints.[4] However, the property of abuse deterrence is a relative property, and the evaluation of abuse deterrence requires comparison to either a non abuse-deterrent opioid analgesic or an abuse-deterrent opioid analgesic when available.[5] The important endpoints in these studies are patient reported outcomes, with emphasis on drug high, drug liking, and take drug again. The critical information from the study is whether there is a difference in the likelihood that individuals will want to abuse the product were it available. Differences may be reported in the extent of drug high and drug liking, but there are no data to describe what magnitude of difference is clinically relevant and represents a deterrent effect. Therefore, subjects are asked directly whether they would take the drug again, and this endpoint is used to provide context about whether the results of drug liking or drug high are meaningful to the subject. For products that are approved with labeling describing abuse-deterrent properties, additional evaluation of the actual impact on abuse will be required in postmarketing studies.

There are challenges in assessing the impact of an extended-release hydrocodone product on the amount of abuse. There has not been a lot of clinical experience with the extended-release hydrocodone products. As described at the June 7, 2016, advisory committee meeting, there were approximately 150,000 hydrocodone ER prescriptions dispensed in 2015 and hydrocodone ER products accounted for less than 1% of prescriptions dispensed for the ERLA opioid analgesics market.[6] Additionally, because all of the hydrocodone ER products are

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[3]Substance Abuse and Mental Health Services Administration. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings, 2012. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2012. NSDUH Series H-41; HHS publication (SMA) 11-4658.

[4] See Draft Guidance for Industry, Assessment of Abuse Potential of Drugs, http://www fda.gov/downloads/drugs//guidances/ucm198650.pdf

[5] See Guidance for Industry, Abuse-deterrent Opioids – Evaluation and Labeling, http://www fda.gov/downloads/drugs//guidances/ucm334743.pdf

[6] See presentation by Joann H. Lee, Pharm.D., http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm506635 htm

relatively new, there is very little prior experience with non abuse-deterrent formulations against which the effects of this formulation can be compared.

As a decades-old mu agonist, there is much known about hydrocodone and no question that hydrocodone is an analgesic. Hydrocodone is synthesized from codeine, one of the opioid alkaloids found in the opium poppy and was first synthesized nearly 100 years ago. Opioids have been used as analgesics for centuries, and as approved analgesic drugs for decades. The first hydrocodone product was approved in the 1940s; and the analgesic for which Teva has a right of reference, Vicoprofen (hydrocodone bitartrate and ibuprofen) tablets, was approved 19 years ago. In light of the extensive history of clinical use as an opioid analgesic, it is fair to say that it is general knowledge that hydrocodone is an opioid agonist with the analgesic properties and adverse event profile consistent with other mu agonist opioid analgesics. This is reflected by the fact that products in this class have consistent labeling regarding, for example, contraindications, warnings and precautions, drug-drug interactions, and pharmacodynamics properties.[7]

In addition to the right of reference to Vicoprofen, one positive Phase 3 adequate and well-controlled clinical trial was sufficient to support a finding of efficacy and safety, and serve the purpose of confirming that the proposed twice daily dosing is appropriate for the proposed chronic pain indication. Additional safety information was obtained from an analysis of electrocardiogram data and an audiometric evaluation.

The Applicant submitted a full CMC package along with nonclinical studies that assessed the general toxicology, genetic toxicology, developmental and reproductive toxicology, and the carcinogenic potential of hydrocodone. Although the Applicant submitted or had a right of reference for some nonclinical pharmacology and ADME information, the Applicant submitted a request for a waiver for additional nonclinical pharmacology, nonclinical ADME, and chronic toxicology studies. The Applicant conducted studies to characterize the single-dose and multiple-dose pharmacokinetic characteristics of Vantrela, along with the effect of food, dose proportionality of the five strengths, effects of renal impairment and hepatic impairment, and evaluated the effects of sex, age, and race within the studies conducted.

3. CMC/Device

The following has been excerpted from the OPQ summary review (reproduced text here, and throughout this memo, is in Arial font):

[7] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491739.htm

Drug Substance

The drug substance, hydrocodone bitartrate is manufactured by [redacted] (b) (4) . and is referenced in DMF# [redacted] (b) (4) (adequate, last reviewed 9/19/2015). Hydrocodone bitartrate is a white to slightly yellow-white crystalline substance which is water soluble. The drug substance has a [redacted] (b) (4) month retest period when stored [redacted] (b) (4) .

Drug Product

The drug product Vantrela ER is manufactured by [redacted] (b) (4). The extended-release tablets are manufactured in five capsule strengths containing 15, 30, 45, 60, and 90 mg of hydrocodone bitartrate.

Vantrela ER tablets are packaged in 100-count, high-density polyethylene bottles with induction sealed child-resistant closures. The container closure system contains a 1g of desiccant sachet and rayon coil. The 15 mg, 30 mg, and 45 mg tablets are packaged into 150 cc bottles, while the 60 mg and 90 mg tablets are packaged into 250 cc bottles. Based on the stability data provided, an expiry of 36-months will be granted using the storage statement "Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F)." For the in-vitro abuse deterrence studies, the summary of all the studies can be found on page 9.

All excipients are generally recognized as safe. With the exception of FD&C blue #2 aluminum lake (21 CFR 74.102), all meet compendial quality standards. The safety of the excipients was assessed with the FDA-recommended 3 g per day maximum daily dose standard of hydrocodone bitartrate in a toxicology study, DS-2011-037. Excipient compatibility studies were conducted: the API is compatible with all the [redacted] (b) (4) tablet excipients used to manufacture the clinical lots.

The specification assures API identity, strength, purity and drug product quality (which includes bioavailability). The analytical methods proposed are valid and sufficient to detect and quantify the attributes of the specification. The acceptance criteria of the specification are sufficient to ensure adequate manufacture quality from batch to batch

The in-process controls are adequate to ensure manufacture conformity of drug product quality. There is minimal residual risk remaining in the manufacturing processes, and the drug product has been consistently in conformity with the specification from batch to batch.

The contain/closure system is adequate to prevent degradation and contamination beyond acceptance criteria limits over the expiration dating period, as demonstrated by the stability data below.

(b) (4)

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The following has been reproduced verbatim from Dr. Bolan's review (pages 8-9):

All excipients in this product are commonly used and can be found in either previously approved products or have otherwise been adequately justified for safety and are considered acceptable when this product is consumed up to the current maximum theoretical daily dose (MTDD) of HC (3 grams/day).

Specifications for several drug substance impurities and one drug product degradant exceed the ICH Q3A/B qualification thresholds. Impurities and degradants were adequately qualified and the specifications are considered acceptable.

The standard ICH battery of genetic toxicology studies was conducted with HC. Hydrocodone tested negative in the in vitro bacterial reverse mutation assay and the in vivo mouse micronucleus assay. In contrast, HC tested positive for clastogenic activity in the in vitro chromosome aberration assay. Hydrocodone is considered to have clastogenic potential. A fourth genetic toxicology test would typically be required to fully characterize the clastogenic potential. However, regardless of the outcome of a fourth genetic toxicology study, a carcinogenicity assessment would provide the definitive answer as to the genotoxic potential of HC. Teva submitted carcinogenicity studies in mouse and rat via right of reference and HC was found negative for carcinogenic potential in both rat and mouse. These studies will be described in the product labeling.

A full battery of developmental and reproductive toxicology studies with oral administration of HC has been submitted by Teva. The fertility and early embryo-fetal development study in rats showed no effects on overall mating performance (NOAEL 3.2-times the human daily dose of 180 mg based on

body surface area). However, hydrocodone treatment decreased absolute epididymides weight (3.2-times the human daily dose of 180 mg) and increased latency to mate in males (1-times the human daily dose). Hydrocodone decreased uterine weights and implantation sites in females (3.2-times the human daily dose) and decreased the number of corpora luteal (1-times the human daily dose).

Embryo-fetal development studies in rats and rabbits with oral administration of HC were submitted by Teva. Although no teratogenicity was observed in either species, embryo-fetal toxicities were noted in rats. Increases in post-implantation loss and non-viable litters were observed. In a pre- and post-natal development study in rats with oral administration of HC, increased post-implantation loss in the F0 dams and reduced survival of the F1 pups were observed. Reduced body weights from birth through the lactation phase were observed in the F1 generation pups. The toxicities observed in these studies are consistent with other opioids and will be described in the product labeling.

Two 13-week repeat-dose toxicity studies in rats and mice with HC were submitted by Teva. These studies were designed as dose-range finding studies in support of dose selection for carcinogenicity studies. Therefore, the studies used doses designed to define a maximum tolerated dose and predict dosing that will permit survival out to 2 years. They were not designed to characterize the chronic toxicity of HC or define a NOAEL. Although pharmacologic effects of HC were observed (decreases in body weights and food consumption) no findings considered adverse were noted and no target organs were identified. The studies are not of adequate duration or design to serve as support for the chronic use of HC for this product.

As described in Dr. Bolan's review, the Applicant has not conducted chronic toxicology studies and was asked to evaluate whether their rat carcinogenicity study was suitably designed to provide chronic toxicology data. This turned out to not be the case, the rat carcinogenicity study was not designed with an interim sacrifice with the necessary endpoints to provide adequate data on chronic toxicology. However, she notes the following (page 8):

Late in the review cycle, the Applicant submitted a request for a waiver of the pharmacology, ADME (absorption, distribution, metabolism, and excretion) studies, and chronic toxicology studies with HC. Given the timing of the waiver request, this review does not include a detailed assessment of the waiver request. The waiver request is formally reviewed in the secondary pharmacology toxicology review of this NDA by Dr. Daniel Mellon. I concur with Dr. Mellon's assessment of the waiver request. If the waiver request is granted by the Division, the NDA may be approved from a nonclinical pharmacology perspective.

Dr. Mellon conducted the secondary pharmacology and toxicology review and has summarized the nonclinical data requirements for a new drug application. The Applicant

submitted a waiver request for certain nonclinical pharmacology and toxicology studies under 21 CFR §314.90[8] stating that pharmacology (primary, secondary, and safety), ADME, and chronic toxicology studies of hydrocodone are not necessary for FDA to make an evaluation on the safety and effectiveness of Vantrela ER. The following has been taken verbatim from Dr. Mellon's review (pages 3-4).

> As per 21 CFR §314.50(d)(2) the nonclinical pharmacology and toxicology section of an NDA should contain the following:
>
> i. Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug or are pertinent to possible adverse effects.
>
> ii. Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute, and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use.
>
> iii. Studies, as appropriate, of the effects of the drug on reproduction and on the developing fetus.
>
> iv. Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.
>
> The nonclinical data recommendations for marketing authorization of a drug product are also outlined in the ICH M3(R2)[9] guidance document. The table below summarizes the information/studies submitted or referenced by TEVA,

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[8] §314.90 Waivers.

(a) An applicant may ask the Food and Drug Administration to waive under this section any requirement that applies to the applicant under §314.50 through 314.81. An applicant may ask FDA to waive under §314.126(c) any criteria of an adequate and well-controlled study described in §314.126(b). A waiver request under this section is required to be submitted with supporting documentation in an application, or in an amendment or supplement to an application. The waiver request is required to contain one of the following:

(1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;

(2) A description of an alternative submission that satisfies the purpose of the requirement; or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds one of the following:

(1) The applicant's compliance with the requirement is unnecessary for the agency to evaluate the application or compliance cannot be achieved;

(2) The applicant's alternative submission satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.

[9] M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

or studies for which a waiver was requested. Discussion of each of these categories with respect to the application follows the table.

Nonclinical Data Category as per M3(R2)	Data Submitted by TEVA
Pharmacology (safety pharmacology and pharmacodynamic studies)	• TEVA submitted right of reference to the Vicoprofen NDA. • TEVA submitted a request for waiver of any additional pharmacology studies.
ADME	• An in vitro metabolism study was submitted. • TEVA submitted right of reference to the Vicoprofen NDA. • TEVA submitted a request for waiver of any additional nonclinical ADME studies.
Toxicology	• TEVA submitted 90-day oral toxicity studies in the dog, rat and mouse • TEVA submitted right of reference to the Vicoprofen NDA. • TEVA submitted a request for waiver for chronic toxicology studies.
Genetic Toxicology	• TEVA conducted the full standard battery of genetic toxicology studies.
Reproductive and Developmental Toxicology	• TEVA conducted the full standard battery of reproductive and developmental toxicology studies.
Carcinogenicity	• TEVA submitted right-of-reference to carcinogenicity studies from Zogenix.

Pharmacology

Dr. Mellon discusses the details of the ICHM3(R2) and other guidance on pharmacology studies and how they relate to the Applicant's request for a waiver of additional pharmacology studies (safety pharmacology, primary pharmacodynamic, and secondary pharmacodynamics studies). His conclusions are reproduced below (Pages 5-7). I have included some additional comments from a clinical perspective where appropriate.

> Reviewer Comment: Safety pharmacology studies are needed to support the first-in-human exposure to drugs or to follow-up on unexpected adverse effects noted in clinical studies. The results of these studies do not appear in labeling and the studies are unnecessary for drugs for which there is an extensive history of clinical use. Teva's request for a waiver of safety pharmacology studies is justified.

The nonclinical safety pharmacology waiver request is further justified from a clinical perspective. As noted in Dr. Mellon's review, Agency guidance states that information from clinical studies can support the safety pharmacology assessment and replace nonclinical safety

pharmacology studies. This is the case here as there were no unexpected adverse effects noted in Teva's clinical studies and the adverse event profile is consistent with the well-known adverse event profile of hydrocodone.

> Reviewer Comment [primary pharmacodynamics studies (studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target)]: The proposed therapeutic indication of hydrocodone is analgesia. As noted in the Vicoprofen labeling [2008[10]]:
>
> > Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opioids is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system.
>
> Therefore, [since Teva has a right of reference to the Vicoprofen NDA,] the NDA contains adequate information to characterize the pharmacological actions of the drug in relation to its proposed therapeutic indication and otherwise define the pharmacologic properties of the drug.
>
> Likewise, the intended effect of hydrocodone is considered general knowledge. As noted in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* chapter on Opioid Analgesics[11], "Morphine and most other clinically used opioid agonists exert their effects through μ opioid receptors." Therefore, no further primary pharmacodynamics studies are necessary to support approval of the application. Teva's request for a waiver of further primary pharmacodynamics studies is justified.

The nonclinical primary pharmacodynamics waiver request is further justified from a clinical perspective. Teva has supported the analgesic effect of hydrocodone for Vantrela ER not only by right of reference to the Vicoprofen NDA (including its analgesic efficacy), but also by conducting an adequate and well-controlled study (Study 3103) as described later in this review.

> Reviewer Comment: Secondary pharmacology studies (receptor binding studies and functional assessments) are conducted for new molecular entities to characterize the potential unintended effects of a drug. The results of these studies can help in the interpretation of general toxicology study results and inform the clinical studies with respect to possible adverse effects.
>
> There is an extensive clinical history of use of hydrocodone and similar mu-opioid receptor agonists such as morphine. As noted in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* chapter on Opioid Analgesics,

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[10] The Vicoprofen product labeling was recently updated and it also indicates that the "principal therapeutic action of hydrocodone is analgesia."

[11] Gutstein HB, Akil H (2001) Opioid Analgesics. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics (Hardman, J. G. et al., eds), pp 569-619 New York: McGraw-Hill.

"The first undisputed reference to opium is found in the writings of Theophrastus in the third century B.C." Morphine was first isolated from opium by Sertürner in 1806 and codeine was isolated by Robiquet in 1832 (Gutstein and Akil, 2001). Hydrocodone is a semi-synthetic opioid that was first synthesized from codeine in Germany in 1920 by Carl Mannich and Helene Löwenheim and was first approved by FDA on March 23, 1943 (NDA 5213; Hycodan, homatropine methylbromide and hydrocodone bitartrate for cough).

Most textbooks do not specifically discuss hydrocodone (or codeine, oxycodone, morphine, oxymorphone, and hydromorphone) separately because these older well-known clinically-used opioids are discussed as a class. As noted in by Gutstein and Akil's chapter on opioid analgesics (Gutstein and Akil, 2001), "Morphine and most other clinically used opioid agonists … affect a wide range of physiological systems. They produce analgesia, affect mood and rewarding behavior (*see also* Chapter 24), and alter respiratory, cardiovascular, gastrointestinal, and neuroendocrine function." As a class, the secondary pharmacodynamics properties of well-understood opioids, like hydrocodone and morphine, are discussed in common textbooks and can be considered to be general knowledge. These unintended effects include alterations in mood (euphoria, tranquility) and rewarding properties, other CNS-mediated effects (temperature, neuroendocrine effects, miosis, convulsions, depression of respiration, depression of the cough reflex, nausea, emesis), cardiovascular effects (peripheral vasodilation), gastrointestinal effects (e.g., decreased peristalsis, constriction of the sphincter of Oddi), other smooth muscle effects (e.g., increased muscle tone of the external sphincters of the urinary bladder, inhibition of micturition), skin effects (e.g., flushing due to dilation of cutaneous blood vessels), immune effects (generally suppressive) and tolerance and physical dependence (Way et al., 1995, Gutstein and Akil, 2001).

Teva claims that based on general knowledge and the fact that the side-effect profile of hydrocodone has been characterized in the clinical studies conducted with Vantrela ER, further secondary pharmacodynamics studies are unnecessary as they would not further contribute to the understanding of the effects of hydrocodone in humans. Given the extensive history of clinical use, I agree that nonclinical secondary pharmacodynamics studies to characterize the adverse effects of hydrocodone would not provide any data that would alter the current clinical use of the drug or inform physicians of potential toxicities that they are not already well aware of. Therefore, a waiver of these studies for hydrocodone based on general knowledge of well-known opioids in this class with extensive human experience is justifiable (refer to the Division Director Review for discussion of the clinical experience).

The nonclinical secondary pharmacodynamics waiver request is further justified from a clinical perspective. As Dr. Mellon notes, there is extensive clinical experience with mu-opioid receptor agonist dating back for centuries and decades of use for hydrocodone in

particular. Mu-opioid receptor agonists include the following moieties - codeine, hydromorphone, morphine, oxycodone, and oxymorphone; and FDA has approved many new drug applications and abbreviated new drug applications over the years. While the precise mechanism of action of hydrocodone and these other opioids is not known, it is believed to relate to the existence of opioid receptors in the central nervous system. It is well-known that full opioid agonists, including hydrocodone, produce not only an analgesic effect, but also certain adverse effects as both are mediated through activation of opioid receptors. In addition, the adverse event profile of hydrocodone has been characterized in the clinical studies conducted by Teva and it is consistent with the clinical experience of hydrocodone and other opioid agonists in this class. In fact, the Division has expected products for this class of opioids to carry consistent labeling regarding the pharmacodynamic effects in the Clinical Pharmacology section of the labeling (e.g., effects on the central nervous system, gastrointestinal tract and other smooth muscle, cardiovascular system, endocrine system, immune system). I agree with Dr. Mellon's assessment, including his view that nonclinical secondary pharmacodynamics studies (such as binding studies or other functional assessments) would not provide any data that would alter the current clinical use of the drug or change the labeling to otherwise inform physicians of potential toxicities of which they are not already aware.

ADME
Dr. Mellon describes the requirements for absorption, distribution, metabolism, and excretion (ADME) information for a NDA (pages 12-13).

> As per 21 CFR §314.50(d)(2) the nonclinical pharmacology and toxicology section of an NDA should contain "**Any** studies of the absorption, distribution, metabolism, and excretion of the drug in animals" (emphasis added). As such, the amount of animal ADME data required for any specific program is determined by the Agency during drug development.
>
> As per ICH M3(R2):
>
> In vitro metabolic and plasma protein binding data for animals and humans and systemic exposure data (ICH S3A, Ref. 7) in the species used for repeated-dose toxicity studies generally should be evaluated before initiating human clinical trials. Further information on pharmacokinetics (PK) (e.g., absorption, distribution, metabolism and excretion) in test species and in vitro biochemical information relevant to potential drug interactions should be available before exposing large numbers of human subjects or treating for long duration (generally before phase 3). These data can be used to compare human and animal metabolites and for determining if any additional testing is warranted.
>
> As noted in the ICH M3(R2) guidance, animal ADME data are used to assure that the nonclinical toxicology studies adequately characterize the safety of human metabolites and assist in the interpretation of the nonclinical toxicology studies. However, because nonclinical toxicology studies for hydrocodone were not necessary to support human studies nonclinical ADME data are also not necessary for this product based on extensive human experience.

> As per 21 CFR 201.57, Section 12 of the labeling, Clinical Pharmacology, "must contain information relating to the human clinical pharmacology and actions of the drug in humans." Animal data are only included in the product labeling if the data are "necessary for the safe and effective use" of the drug and the data "have not been shown by adequate and well-controlled studies" in humans. Given the human experience with hydrocodone, animal data are not necessary for the safe and effective use of the drug and there exists human data that can inform labeling. Teva submitted an in vitro comparative species metabolism study primarily to support their conclusion that hydrocodone N-oxide is a metabolite of hydrocodone (b) (4) [12] Additional animal ADME data are not necessary to support approval of this drug product and a waiver request is justified. The reader is referred to the clinical pharmacology review and Division Director's review for a discussion of the human data submitted by Teva to support Section 12 of their drug product labeling.

ADME for Vantrela ER is supported by Teva's in vitro study, ADME information on the hydrocodone component of Vicoprofen (the NDA for which Teva has a right of reference) as well as Teva's clinical ADME studies. Teva submitted data on the pharmacokinetics and pharmacodynamics of hydrocodone from 19 studies of hydrocodone ER. These findings are described in detail in the clinical pharmacology review and support the clinical ADME findings described in the Clinical Pharmacology/Pharmacokinetics section of the labeling. Additional dedicated nonclinical ADME studies are not necessary to further characterize the absorption, distribution, metabolism, and excretion of hydrocodone for Vantrela ER and a waiver is justified.

Similarly, Dr. Mellon discusses the details of the ICH M3(R2) guidance on toxicology studies and how it relates to the Applicant's request for a waiver of additional toxicology studies. The following has been taken verbatim from his review (pages 7-8).

> As per 21 CFR §314.50(d)(2), the nonclinical pharmacology and toxicology section of an NDA should contain "Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, ***as appropriate***, studies assessing the drug's acute, subacute, and chronic toxicity …" (Emphasis added)
>
> As per the ICH M3(R2) Guidance, to support clinical trials of > 6 months duration and a marketing application for a chronic indication, a 6-month repeat-dose toxicology study in a rodent and a 9-month repeat-dose toxicology study in a nonrodent model should be completed.
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> Chronic toxicology studies are conducted to characterize potentially clinically relevant toxicity in order to inform the design of the long-term clinical studies.

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12 (b) (4)

> For example, if significant adverse effects in the toxicology studies are observed at clinically relevant exposures, the nonclinical study results could indicate the need to impose dosing limitations in proposed clinical studies or inform the need for additional clinical monitoring. For a new molecular entity, these repeat-dose toxicology studies are essential to characterize the potential toxicity of the drug and to support the safety of the proposed doses to be employed in the clinical studies. However, when considerable clinical experience exists, it is not unusual for clinical studies to proceed without repeat-dose toxicology data. For example, there are no GLP chronic general toxicology data for morphine, oxymorphone, or oxycodone, all of which are approved drug products with chronic indications. Likewise, Phase 3 clinical studies for hydrocodone have been allowed to proceed without these data based on extensive clinical experience and our general knowledge of opioids.

As noted by Dr. Bolan, the Applicant has not conducted chronic toxicology studies, nor was their carcinogenicity study designed to provide this information. The Applicant has requested a waiver for conducting chronic toxicology studies which focuses on five general points which were evaluated by Dr. Mellon, as reproduced from Dr. Mellon's review (pages 9-12):

Point Number 1: Repeat-dose toxicology studies of common opioids in animals have demonstrated expected dose-limiting toxicities consistent with exaggerated pharmacology and these effects have been observed in humans.

> Reviewer Comment: Teva has completed 13-week toxicology studies for hydrocodone in rats, mice, and dogs. The adverse effect profile is consistent with predicted opioid toxicities taking into consideration the known physiological effects of opioids. For example, adverse effects noted in Teva's animals studies include sedation, hypoactivity, ataxia, decreased food intake, tremors, and body weight loss. At higher doses of opioids, respiratory depression and convulsions are well known risks of opioids. The latter two findings are considered to have exceeded the maximum tolerated dose in toxicology studies. All of these findings are known side effects of opioids in humans. One finding in the Teva animal toxicology studies that has not been routinely described in humans is scabs in the skin and self-mutilation. These findings may be due to histamine release and subsequent itching and scratching of the skin by the animals. Although not reported in humans, these findings are well-known and expected to occur in opioid toxicology studies. Overall, I agree with Teva's conclusion that the toxicities noted in animals do appear to be primarily exaggerated pharmacological effects. However, the 13-week studies with hydrocodone they can refer to are not chronic toxicology studies and therefore this point alone does not justify a waiver.

Point Number 2: The nonclinical dose limitations preclude testing of clinically relevant higher doses and humans are the only feasible species to test higher doses of hydrocodone.

Reviewer Comment: Chronic toxicology studies with opioids intending to characterize the safety of opioid exposure levels predicted to be obtained in opioid-tolerant patients are not feasible due to dose limiting toxicities. The design of such a study is extremely complicated.

The study design of a chronic toxicology study should include three different doses of a drug administered daily over the course of the study. The top dose should produce frank toxicity, when feasible, and the low dose should help to define a No Adverse Effect Level (NOAEL). The study is intended to characterize the toxicologic profile of a compound at and above the intended clinical exposures. For opioid agonists, tolerance develops to the analgesic effects following repeated drug administration (Gutstein and Akil, 2001). In order to obtain the same desired analgesic effect, the dose of the drug has to be increased as needed on an individual basis in order to maintain efficacy. In the clinic, a physician may decide to increase the dose when a patient reports that the drug is no longer having the same analgesic effect as it used to. This is far more challenging to do in nonclinical toxicology studies since the animals are not in pain and cannot tell you that the drug is not producing the same effect as it did previously. In order to obtain this type of data, the animals would have to be tested periodically via a physiological assessment of an opioid effect, such as pain sensation (nociception) in order to determine if they are now tolerant to the antinociceptive effects of the drug. If tolerance is detected in the physiological assessment, the dose of the opioid could be increased gradually over time. Dose escalation would have to be done in a manner to avoid producing respiratory depression, a well-known pharmacodynamic effect of opioids which is potentially fatal.

Designing a repeat-dose toxicology study that includes assessment of each animal's development of tolerance to an opioid agonist and includes dose escalation presents considerable challenges. Specifically, a 6-month chronic toxicology study in the rat model typically includes 20 animals per sex per group with additional satellite animals used for toxicokinetic analyses. Therefore, a normal dose-escalation study would include at least 160 animals, 120 of which would require frequent nociception or other physiological assessments to assess tolerance of the opioid agonist and dosing solution adjustments to gradually ramp up the dose. Given the distinct potential for non-uniform tolerance development, a decision to increase the dose for any given treatment group could result in the inadvertent death of some animals from respiratory depression. Not all groups will show tolerance at the same time and each group will have to be considered independently. If too many animals are lost during the course of the study as a result of the adverse events associated with the drug, the study could be compromised and not accomplish the desired objective of characterizing the effect of different doses of the drug over the entire duration of study.

The same challenges would exist for a nonrodent study; however, as the number of animals in a typical nonrodent study is 4-6 per sex per group, loss of even a few animals can compromise the study. In reality, humans tolerate gradual dose-escalation of opioids over the course of chronic therapy in their lifetime that exceeds doses that can be achieved over the course of 6- or 9-month nonclinical studies. As such, to date, the Division has not requested toxicology studies be designed in a manner that includes careful but aggressive dose escalation for a well-understood opioid with considerable clinical experience. Dosing regimens of opioid agonists in chronic toxicology studies are not expected to be able to reach exposures that are comparable to exposures ultimately obtained in humans due to the development of tolerance in humans over time (the maximum theoretical daily dose or MTDD for an opioid-tolerant patient). The animals would likely die from respiratory depression or have to be sacrificed moribund due to some other adverse event (e.g., significant weight loss, self-mutilation) before exposure levels could be reached that would be comparable to exposure levels associated with the MTDD for an opioid-tolerant patient. This is evident in the exposure margins that were obtained in the 13-week dose-range finding studies in rats conducted by Teva to support carcinogenicity studies. As noted in Dr. Bolan's review, doses that produced a dose-limiting suppression of body weight gain and were deemed unacceptable for an ultimate 2-year rat study produced exposures that were at best 1/5th the human AUC following a 90 mg dose of hydrocodone.

That being said, for a novel opioid, the chronic toxicology studies would still be required to determine if the toxicity profile was consistent with what would be expected for an opioid agonist and determine if there were unexpected adverse effects from a new drug for which neither nonclinical nor clinical data exist. When an opioid compound is truly novel, the Agency has discussed the challenge of designing a toxicology program for the compound with sponsors and encouraged them to consider if their compound will develop tolerance and propose methods to characterize the safety of their compound at higher doses.

Unlike a novel opioid, characterizing the chronic toxicity of an opioid analgesic with decades of clinical experience, such as with hydrocodone, is not necessary to support the safety of long-term clinical studies. For example, large-scale Phase 3 clinical studies for hydrocodone, morphine, oxymorphone, and oxycodone drug products have been allowed to proceed without any chronic nonclinical toxicology studies, based an understanding of the safety profile of these compounds due to extensive previous clinical experience.

Collectively, I agree with Teva's statement that opioid toxicology studies are limited in terms of their ability to characterize high doses of the opioid and that the ultimately safety for many of these well-known compounds is derived from human experience.

Point Number 3: The 13-week toxicology studies conducted by Teva demonstrated only expected toxicities for a mu opioid agonist

> Reviewer Comment: As noted above, the 13-week studies did demonstrate effects that are consistent with our understanding of what a morphine-like compound displays in a toxicology study. However, the studies are not chronic toxicology studies. This alone does not justify a waiver request.

Point Number 4: The carcinogenicity studies obtained by right of reference inform the chronic toxicity profile.

> Reviewer Comment: As we have with other Sponsors, we agree to consider the utility of Teva's carcinogenicity studies in the rodent models in lieu of a rodent chronic toxicology study, if the carcinogenicity study design included an interim sacrifice group and incorporated all endpoints found in a standard toxicology study (i.e., hematology, clinical chemistry) and establish a NOAEL. As Teva does not have access to the actual study reports, the company may not be aware that the studies did not include an interim sacrifice or any clinical chemistry or urinalysis endpoints. Nonetheless, the studies do provide histopathological evaluation for non-neoplastic lesions. As noted in Dr. Bolan's review of the rat carcinogenicity study, from a histopathological standpoint, a clear NOAEL for retinal atrophy and pododermatitis was not defined. Likewise, in the mouse study, ulcerative dermatitis was noted in all groups which could be attributed to either overgrowth of endogenous skin flora or histamine release. A clear NOAEL level in a carcinogenicity study is not unusual, as these studies are designed to specifically push the dose to a maximum tolerated dose without resulting in a significant impact on survival to preclude reaching the 2 year planned sacrifice time. Therefore, this alone does not justify a waiver request for chronic toxicology studies.

Point Number 5: Teva's Phase 3 studies did not identify any unexpected safety findings.

> Reviewer Comment: Please see the clinical reviews for a discussion of the adverse event profile of the drug product.

Dr. Mellon's overall conclusions are as follows (page 12):

> Collectively, I agree that it is difficult to design a chronic toxicology study that would be able to fully characterize the toxicologic potential of the exposures to opioids that would occur in opioid tolerant patients who may take up to the maximum theoretical daily dose of hydrocodone (revised to 1500 mg/day). At best, toxicology studies can characterize the effects of lower doses of hydrocodone within the range that most patients will consume.

> For well-known opioids with a long history of clinical use, such as morphine and hydrocodone, general toxicology studies are not likely to provide any data that would alter the current clinical use of the drug or inform physicians of potential toxicities that they are not already well aware of. Therefore, a waiver of chronic toxicology studies for hydrocodone is justifiable based on both the limitations of the existing nonclinical study designs and on extensive human experience with the well-known drugs in this class. The reader is referred to the Division Director's review for a discussion of the clinical experience with hydrocodone and related well-known opioids

Chronic toxicology studies are important to identify those effects of a drug that take time to develop. These studies are difficult to conduct with opioid analgesics. To be informative, chronic toxicology studies should use dosages that include the highest expected exposures in humans, but generally there is no maximum dose for opioids as they have no celling effect for analgesia. Opioid tolerant patients can sometimes require very large doses of an opioid for pain management. Vantrela ER will have a maximum labeled dose of 90 mg twice daily.[13] As noted in Dr. Bolan's review, referenced above, the maximum doses used for the 13-week oral toxicity study in rats were 0.12-fold and 0.08-fold lower than a human hydrocodone dose of 90 mg, for male and female rats, respectively. These doses produced dose-limiting reduction in body weight and were unacceptable for use in a two-year rat study. The range of opioid dosages that can be tolerated in nonclinical studies typically produce a range of findings consistent with an opioid, as demonstrated in the 13-week toxicology studies with full histopathological evaluation of the animals, conducted by the Applicant. The nonclinical acute toxicology and carcinogenicity studies and the clinical studies conducted on Vantrela ER did not reveal any unexpected safety findings and were consistent with the class of opioids. Completion of standard chronic toxicology studies cannot result in exposures that would approach exposures expected to be obtained for a single-entity hydrocodone drug product in an opioid-tolerant individual (and findings for the rat studies suggest that 90 mg may result in unacceptable exposures in animals). For an opioid analgesic with decades of clinical experience, it would be an unreasonable use of laboratory animals. For these reasons and those set forth by Dr. Mellon a waiver of chronic toxicology studies is justified.

Dr. Mellon's final recommendation is as follows (page 14):

> Teva completed the full standard batteries of both genetic toxicology and reproductive and developmental toxicology studies. Teva submitted carcinogenicity studies via a right of reference to studies completed by Zogenix. Teva has requested a waiver of dedicated pharmacology, ADME, and chronic toxicology studies primarily based on the extensive clinical experience with opioids and the clinical studies conducted with their drug product. The reader is referred to the Division Director's review for a discussion of the clinical experience. Teva's request for a waiver for these studies cites decades of clinical use of well-understood opioids as well as their own clinical studies with the Vantrela ER drug product.

[13] This limitation is consistent with the dose used in clinical trials in which QT intervals were analyzed and may be removed once a dedicated QT study is conducted and evaluated as part of the postmarketing requirements.

> Dr. Bolan recommended that the NDA may be approved if the Division grants the waiver request for pharmacology studies, nonclinical ADME data (if needed), and chronic toxicology studies. As discussed above, nonclinical pharmacology and ADME data are not necessary to support approval of a well-understood opioid with extensive clinical experience. The adverse histopathological effects of hydrocodone in animal models are not reported. However, completion of standard chronic toxicology studies will not result in exposures that would approach exposures expected to be obtained for a single-entity hydrocodone drug product in an opioid-tolerant individual. Given the extensive clinical history of use of hydrocodone in combination drug products and the extensive clinical history of use of single-entity morphine-related opioids, results of standard chronic nonclinical general toxicology studies are not expected to provide any new information beyond the general knowledge of dose-limiting opioid adverse effects that would likely impact how this drug product is prescribed or labeled.
>
> Therefore, the NDA may be approved as a 505(b)(1) application if the clinical team concludes, that based on generally accepted scientific knowledge obtained from the extensive human experience with well-understood clinically-used opioid agonists, chronic nonclinical toxicology are not necessary.

I concur with the conclusions reached by Drs. Bolan and Mellon as reflected in their reviews and as further justified from a clinical perspective as discussed herein.[14] There are no outstanding nonclinical issues that preclude approval. In particular, I concur with granting the requested waiver for additional nonclinical pharmacology, nonclinical ADME, and chronic toxicology studies. These waivers are justified either because the Applicant's compliance with the requirement is unnecessary, the applicant's alternative submission satisfies the requirement, or the applicant's submission otherwise justifies the waiver.

5. Clinical Pharmacology/Biopharmaceutics

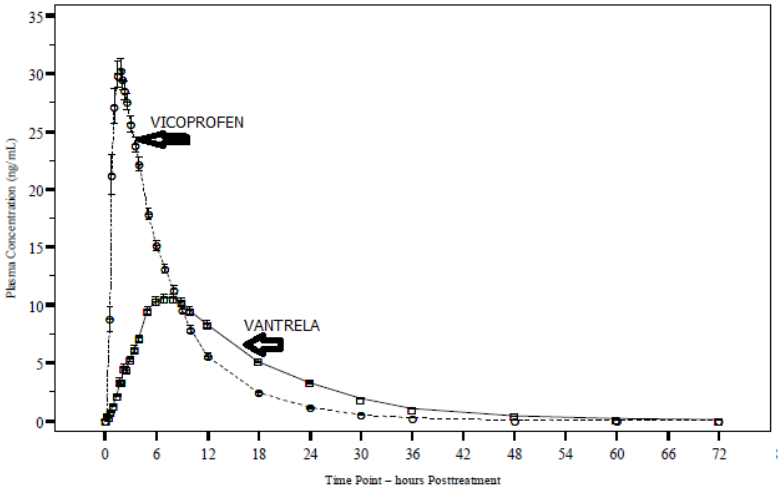
The Applicant conducted 19 pharmacokinetic and pharmacodynamic studies. Sixteen of these studies were conducted in healthy subjects who also received naltrexone to block the effects of hydrocodone. As noted by Dr. Nallani in his review, the Applicant characterized the single-dose pharmacokinetic profile of Vantrela:

> The pharmacokinetics of hydrocodone and its metabolite hydromorphone have been well characterized in healthy subjects following administration of single doses of Vantrela ER tablet (hydrocodone ER tablet) in the dose range of 15 to

[14] As noted elsewhere, Teva's application was initially submitted as a 505(b)(2) NDA; and originally relied, in part, on the agency's finding of safety and effectiveness for Vicoprofen and literature to support approval. Teva obtained a right of reference to the Vicoprofen NDA and amended the application to be a 505(b)(1) NDA. To the extent literature (including text books) is referenced in the reviews it is cited as background or evidence of general knowledge and it was not necessary to rely on literature for approval as a 505(b)(1) NDA.

90 mg and multiple doses of 45 and 90 mg of hydrocodone ER administered every 12 hours for 5.5 days. Following oral administration of intact product, a steady rise in systemic exposure is noted with the extended release product compared to immediate release product which shows a relatively rapid appearance of peak plasma concentrations. Median peak plasma concentrations are noted after 8.5 hours after single dose administration. Since the Sponsor originally planned to submitted the NDA under a 505(b)(2) pathway using Vicoprofen as the listed drug, a relative BA study with Vicoprofen was conducted. While the overall exposure of hydrocodone (AUC) was similar between Vantrela ER tablet 15 mg and Vicoprofen (two tablets of 7.5 mg hydrocodone/200 mg Ibuprofen), peak plasma levels with Vantrela ER tablet 15 mg were 1/3 that noted with IR Vicoprofen (Study 1079).

Figure: **Mean (±SE) Plasma Concentration versus Time Profiles for Hydrocodone Over 72 Hours Following Administration of a Single Dose of Hydrocodone ER (Dose Normalized to 15 mg) and a Single 15 mg Dose of Hydrocodone within VICOPROFEN in Healthy Subjects (Pharmacokinetic Analysis Set, Bioavailability Subset)**



SOURCE: Pharmacokinetic Analysis Set, Bioavailability Subset, Figure 3.1, Summary 10.1

Dr. Nallani also describes the finding of dose proportionality across the proposed dose range, food effect, and information from repeated dosing:

The systemic exposure of hydrocodone increased dose-proportionally over the range of 15 through 90 mg doses of Vantrela ER tablet (Study 1082). The absolute bioavailability of orally administered hydrocodone is unknown.

Table: Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone Following Oral Administration of Vantrela ER tablet (Study 1082).

Variable	A 15 mg (N=60)	B 30 mg (N=60)	C 45 mg (N=60)	D 60 mg (N=60)	E 90 mg (N=60)
C_{max} (ng/mL)	12.6 (3.50)	20.7 (5.47)	30.3 (7.48)	41.2 (10.11)	62.5 (16.19)
$AUC_{0-\infty}$ (ng·h/mL)	198.8 (60.37)	381.6 (117.78)	592.3 (167.20)	765.7 (193.98)	1189.0 (341.31)
AUC_{0-t} (ng·h/mL)	195.8 (60.09)	377.6 (116.47)	585.8 (163.68)	757.2 (190.82)	1178.8 (335.97)
AUC_{0-72} (ng·h/mL)	196.7 (59.98)	378.1 (116.31)	586.0 (163.48)	757.3 (190.66)	1178.8 (335.94)
AUC_{0-12} (ng·h/mL)	99.9 (27.40)	169.5 (45.31)	247.1 (62.94)	334.2 (78.09)	505.6 (129.73)
t_{max} (h)	7.0 (5.0, 9.0)	8.0 (5.0, 12.0)	8.0 (5.0, 12.1)	8.0 (5.0, 12.0)	8.0 (5.0, 12.0)
$t_{1/2}$ (h)	10.4 (4.05)	10.6 (4.06)	10.2 (3.64)	10.8 (4.13)	10.0 (2.94)
Percentage extrapolation (%)	1.4 (0.85)	1.0 (0.72)	1.0 (1.19)	1.1 (1.06)	0.8 (0.83)
λ_z (1/h)	0.08 (0.027)	0.07 (0.024)	0.08 (0.025)	0.07 (0.025)	0.08 (0.020)
V/F	1233.9 (588.91)	1323.4 (797.07)	1206.3 (543.84)	1289.5 (575.27)	1196.2 (584.14)
CL/F	83.4 (29.14)	85.7 (25.31)	81.6 (21.54)	83.0 (19.66)	82.2 (24.93)

SOURCE: Adhoc Summary 15.9.1, Listing 16.2.8.23.
NOTE: Median (range) is presented for t_{max}

With regard to food-effect, overall exposure (both AUC_{0-t} and $AUC_{0-\infty}$) including specific emphasis on first 8 hours (AUC0-8, median t_{max} in the fasted state) met the bioequivalence criteria within the range of (0.800, 1.250), mean C_{max} was approximately 34% to 45% higher (Studies 1076, 1090, and 10024) following administration of a single 90-mg dose of hydrocodone ER with a high-fat meal as compared to when administered in a fasted state (See General Biopharmaceutics section 2.6).

Unlike single dose administration, peak plasma concentrations are noted earlier (Median Tmax ~4.5 hours) with repeated administration. Following twice-daily administration of 90-mg doses (Study 1091) of the Vantrela ER tablet, accumulation of hydrocodone in plasma was observed. The steady-state plasma concentrations are 3-fold higher than that observed with single dose or mean observed accumulation ratio (R_{obs}) was 2.8. Similar observation of accumulation was also made after multiple dose administration of 45 mg Vantrela ER tablet (Study 1081).

Information about distribution and metabolism to support the application were obtained from right of reference to the Vicoprofen NDA (see e.g., Vicoprofen label) and by studies conducted by the Applicant, as described by Dr. Nallani:

Hydrocodone appears to be well distributed beyond the vascular system with a V_z/F of approximately 1300 to 1400 L following administration of the hydrocodone ER tablet (integrated single and multiple-dose PK analysis set Study 1081 and 1091). The extent of protein binding of hydrocodone in human plasma has not been determined.

As described in Vicoprofen product label, hydrocodone exhibits a complex pattern of metabolism, including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6-α-an d 6-β-hydroxymetabolites. Hydromorphone, a potent opioid, is formed from the O-demethylation of

hydrocodone and contributes to the total analgesic effect of hydrocodone. The O-and N-demethylation processes are mediated by separate P-450 isoenzymes: CYP2D6 and CYP3A4, respectively.

Given the partial involvement of CYP2D6 in the metabolism of hydrocodone, the impact of metabolism status (eg, poor or extensive CYP2D6 metabolism) on systemic exposure to hydrocodone and hydromorphone following administration of hydrocodone ER was assessed using the pooled clinical pharmacology database. The results of the subgroup analyses suggest that the mean hydrocodone exposure (as assessed by C_{max} and $AUC_{0-\infty}$) is slightly higher in CYP2D6 poor metabolizers as compared to the rest of the population. A corresponding decrease in exposure (as assessed by C_{max}) to hydromorphone was observed in the poor metabolizers (Section 2.3 Intrinsic factors). However, given the small differences observed, the negligible levels of hydromorphone following administration of hydrocodone ER, and the fact that hydrocodone ER is titrated to a therapeutic dose for the same subject, it is unlikely that these differences in systemic exposure would produce significant differences in safety or efficacy.

Decline from peak plasma concentrations generally occurs in a biphasic manner with a mean half-life of approximately 11 to 12 hours (integrated single- and multiple-dose PK analysis set). Mean apparent total plasma clearance following administration of hydrocodone ER is approximately 70 to 90 L/h.

The effects of specific populations on the pharmacokinetic profile were evaluated in studies conducted by the Applicant, as described by Dr. Nallani:

There is no known information on effect of age, race, sex, BMI, or CYP2D6 metabolizer status on the pharmacokinetics of hydrocodone from Vicoprofen product label. However, the sponsor utilized the single dose PK data (C_{max} and $AUC_{0-\infty}$ data) and generally compared PK of hydrocodone across the following demographic groups and indicates that no major impact is observed:

- Age subgroups (18 to 45 years (n=474), 46 to 65 years (n=14), and >65 years (n=5)).
- White (n=349) vs. Non-white (all other races combined to n=144)
- Male (n=325) vs. female (n=168)
- BMI ≤25 kg/m^2 vs. >25 kg/m^2
- CYP2D6 poor metabolizers (n=21), intermediate metabolizers (n=225) and extensive metabolizers (n=225). Impact of CYP2D6 polymorphisms on hydromorphone, metabolite of hydrocodone, was also evaluated and noted to be significant but may not be clinically relevant because hydromorphone is formed in very small quantities.

Impact of renal impairment on hydrocodone PK following Vantrela ER 45 mg tablet administration was evaluated in Study 1088. Mild renal impairment had little impact on hydrocodone exposure. Although the mean increase in C_{max} was approximately 50% in the moderately impaired, there was no consistent trend toward an increase in C_{max} with increasing severity of renal impairment. Overall systemic exposure to hydrocodone (as assessed by $AUC_{0-\infty}$) in subjects with moderate or severe renal impairment was, on average, up to approximately 70% higher than that in subjects with normal renal function. Subjects with ESRD undergoing dialysis displayed similar exposure as subjects with normal renal function or mild renal impairment indicating possible impact of dialysis on hydrocodone elimination.

Pharmacokinetics of hydrocodone following a single dose administration of Vantrela ER 15 mg tablet was evaluated in patients with moderate hepatic impairment and compared to subjects with normal hepatic function in study 1089. Mean C_{max} was approximately 30% higher and mean $AUC_{0-\infty}$ was approximately 70% higher in subjects with moderate hepatic impairment than in subjects with normal hepatic function. **PK of hydrocodone is unknown in patients with mild or severe hepatic impairment after receiving Vantrela ER tablet.**

While there are no studies of Vantrela ER in mild or severe hepatic impairment, no additional studies are needed. Vantrela ER will be labeled with the information about moderate hepatic impairment and with the following information in Dosage and Administration:

Dosage Modifications in Patients with Mild or Moderate Hepatic Impairment
Patients with hepatic impairment may have higher plasma concentrations of hydrocodone than those with normal function. In patients with mild or moderate hepatic impairment, initiate therapy with one half of the recommended initial dose followed by careful dose titration. Use of alternate analgesics is recommended for patients who require a VANTRELA ER dose of less than 15 mg. Monitor closely for adverse events such as respiratory depression. VANTRELA ER is not recommended in patients with severe hepatic impairment *[see Hepatic Impairment (8.6) and Clinical Pharmacology (12.3)]*.

Dr. Nallani also conducted an analysis to determine whether the PK results of studies with Vantrela ER were impacted by the concurrent use of naltrexone, concluding that this was not a problem.

PK of hydrocodone in single dose studies with and without naltrexone:
As such most of the single dose PK or PK/PD studies, except food-effect studies, recruited either healthy volunteers who received naltrexone to block opioid effects of Vantrela ER tablet or opioid-experienced, non-dependent subjects without naltrexone-block. A cross study comparison was made to generally evaluate hydrocodone systemic exposure following Vantrela ER tablet administration in fasting healthy volunteers. There was no data

available from drug liking studies where Vantrela ER tablet was given with food. As shown in the table below, Cmax and AUC values appear to be similar across different studies. Mean peak plasma concentrations were in the range of 25 – 30 ng/mL, AUCinf was in the range of 565 – 592 ng.hr/mL, and median Tmax was 8 hours (5 -12 hours). Hence, it appears that there is no major difference in hydrocodone PK in different studies that were conducted while fasting with or without naltrexone.

Table: Pharmacokinetics (mean (SD) of hydrocodone following administration of intact Vantrela ER 45 mg tablet to healthy volunteers under fasting condition with or without naltrexone block.

	Study 1082	Study 1081	Study 1088	Study 1085	Study 10032
Parameter (unit)	**Vantrela ER 45 mg (N=60)**	**Vantrela ER 45 mg (N=36)**	**Normal Renal function Arm 45 mg (N=13)**	**Intact Vantrela ER 45 mg Arm (N=40)**	**Intact Vantrela ER 45 mg Arm (N=38)**
	Fasting Arm with Naltrexone-Block			**Fasting Arm without Naltrexone-Block**	
Cmax (ng/mL)	30.3 (7.5)	29 (8.16)	28.60 (5.67)	28.77 (6.088)	25.05 (7.18)
AUC0-∞ (ng·h/mL)	592 (167)	568.3 (142.52)	565 (164)	584 (124.8)	568 (172)
Tmax (h)[a]	8.0 (5.0, 12.1)	8.5 (5, 12)	8.0 (6, 10)	7.1 (6.1, 12.0)	9.11 (4.10, 12.12)
t½ (h)	10.2 (3.6)	11.1 (2.97)	14.2 (11.1)	8.04 (2.194)	9.96 (3.03)
λz (1/h)	0.08 (0.025)	0.07 (0.21)	0.0719 (0.0363)	0.0929 (0.02671)	0.076 (0.024)

[a] Median value and range.

The labeling for Vantrela ER is consistent with previous safety labeling changes or class labeling pertaining to opioids. Potential drug-drug interactions would be based on either pharmacokinetic or pharmacodynamic effects. Although no specific drug-drug interaction studies have been performed with Vantrela ER, Teva has a right of reference to the Vicoprofen NDA and information from the Vicoprofen label provides insight as to the likelihood of pharmacokinetic interactions based on concomitant drugs that are inhibitors or inducers of CYP3A4. The pharmacodynamic interactions for opioids are well described in the Vicoprofen labeling. Additive effects of CNS depressants (e.g., alcohol, benzodiazepines, barbiturates, hypnotics, and muscle relaxants) are labeled for Vicoprofen along with the risk for interactions with serotonergic drugs, mixed/partial agonist opioids, MAO inhibitors, anticholinergic drugs, and diuretics. Therefore, no additional studies of drug-drug interactions are required in order to label Vantrela ER for safe use.

An in vitro study by the Applicant demonstrated a lack of dose-dumping when Vantrela ER is exposed to different concentrations of alcohol.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The finding of efficacy for Vantrela ER is supported by one adequate and well-controlled study and reference to the analgesic efficacy of Vicoprofen. Study 3103 was a 12-week, randomized, double-blind, placebo-controlled, randomized-withdrawal study of 60 to 180 mg per day of Vantrela ER in patients with moderate to severe chronic low back pain for at least six months, considered suitable candidates for around-the-clock treatment with an opioid analgesic. The patient population included patients defined as opioid-naïve, taking tramadol or less than 10 mg per day of oxycodone or equivalent for the 14 days prior to screening, and patients defined as opioid-experienced, taking 10 mg per day or more of oxycodone or equivalent for the 14 days prior to screening. Opioid-experienced patients requiring more than 135 mg/day of oxycodone or equivalent were excluded from the study. Patients with radicular pain or other neuropathic pain symptoms were excluded from the study. The details of the inclusion and exclusion criteria are available in Dr. Levin's review.

Patients on prior opioids were converted to a dose of Vantrela ER equivalent to approximately 50% of their prior analgesic dose. All patients who were able to titrate to a dose of Vantrela ER between 30 mg twice a day and 90 mg twice a day with a 24-hour average pain intensity score of 4 or less and a 24-hour worst pain intensity score of 6 or less on an 11-point numeric rating scale, and who tolerated the dose were continued in the study. During titration, up to two hydrocodone 5 mg/acetaminophen 325 mg tablets were permitted as rescue medication, and up to 12 tablets per day were permitted during the double-blind treatment phase. Patients who were successfully titrated onto Vantrela ER were then randomized to stay on Vantrela ER or to placebo with a two-week blinded taper for those randomized to placebo and patients were monitored for signs or symptoms of opioid withdrawal. Patients were not permitted any dose adjustment during the 12-week blinded period. At the end of the 12 weeks, patients were tapered off study drug.

A total of 845 patients were screened and 625 patients were enrolled. A total of 254 (41%) patients did not successfully complete the open-label titration period, primarily due to adverse events or lack of efficacy. Of the 371 patients that went on to the double-blind period, 277 (75%) completed the full 12-weeks. The disposition of the patients in the double-blind treatment period is shown in the following table from page 55 of Dr. Levin's review:

Table 13: Subject Disposition (Study 3103)

	Hydrocodone ER n (%†)	Placebo n (%†)
Randomized	191	180
Evaluable for efficacy	191 (100%)	179 (99%)
Completed study drug treatment	147 (77%)	130 (72%)
Discontinued study drug	44 (23%)	50 (28%)
Adverse event	15 (8%)	9 (5%)
Lack of efficacy	5 (3%)	17 (9%)
Non-compliance: study drug administration	2 (1%)	2 (1%)
Non-compliance: study procedures	1 (1%)	2 (1%)
Consent withdrawn	9 (5%)	8 (4%)
Protocol violation	7 (4%)	9 (5%)
Lost to follow-up	2 (1%)	1 (1%)
Pregnancy	0	1 (1%)
Other	3 (2%)	1 (1%)
Completed study	156 (82%)	141 (78%)
Completed study, but not study drug	9 (5%)	11 (6%)
Withdrawn from study	35 (18%)	39 (22%)
Adverse event	9 (5%)	5 (3%)
Lack of efficacy	4 (2%)	9 (5%)
Non-compliance: study drug administration	2 (1%)	2 (1%)
Non-compliance: study procedures	1 (1%)	3 (2%)
Consent withdrawn	9 (5%)	8 (4%)
Protocol violation	7 (4%)	9 (5%)
Lost to follow-up	2 (1%)	2 (1%)
Pregnancy	0	1 (1%)
Other	1 (1%)	0

Source: Modified from Table 3 of Statistical Review
† Percent of randomized subjects

Most of the early discontinuations were due to lack of efficacy, adverse events, consent withdrawn, and protocol violations. Consent is generally withdrawn as a result of lack of efficacy or adverse events. The types of protocol violations were similar in both treatment groups, including failure to return study drug bottles or rescue medication bottles, failure to complete all protocol-specified study procedures at each visit, and taking excluded concomitant medication. The overall demographic characteristics and baseline pain scores were balanced across the two treatment group

The primary efficacy assessment was the change from baseline in weekly average of daily WPI scores at week 12, based on an 11-point NRS collected daily from an electronic diary. The baseline scores were calculated by averaging the available daily WPI scores for the last 7 days before randomization. The placebo group had a statistically significantly greater change in pain intensity, characterized by a worsening of pain, while the Vantrela ER group had nearly no change in pain score from baseline to end of the treatment period. The Applicant's analysis was confirmed by statistical reviewer, Dr. McEvoy. Sensitivity analyses by Dr. McEvoy were consistent with the primary analysis. These results are summarized in the following table from Dr. Levin's review.

Table 21: Analysis of Change in WPI from Baseline to Week 12

	Vantrela ER	Placebo
Applicant's primary analysis		
N*	152	133
Adj. mean change from baseline	0.1	0.7
HER – Placebo	-0.6	
(95% CI)	(-1.00, -0.25)	
p-value	0.0012	
Sensitivity analysis 2 (preferred FDA analysis)		
N*	161	145
Adj. mean change from baseline	0.1	0.7
HER – Placebo	-0.5	
(95% CI)	(-0.90, -0.14)	
p-value	0.0068	
FDA Requested Sensitivity analysis*		
N	191	179
Adj. mean change from baseline	0.1	0.7
HER – Placebo	-0.6	
(95% CI)	(-0.97, -0.24)	
p-value	0.001	

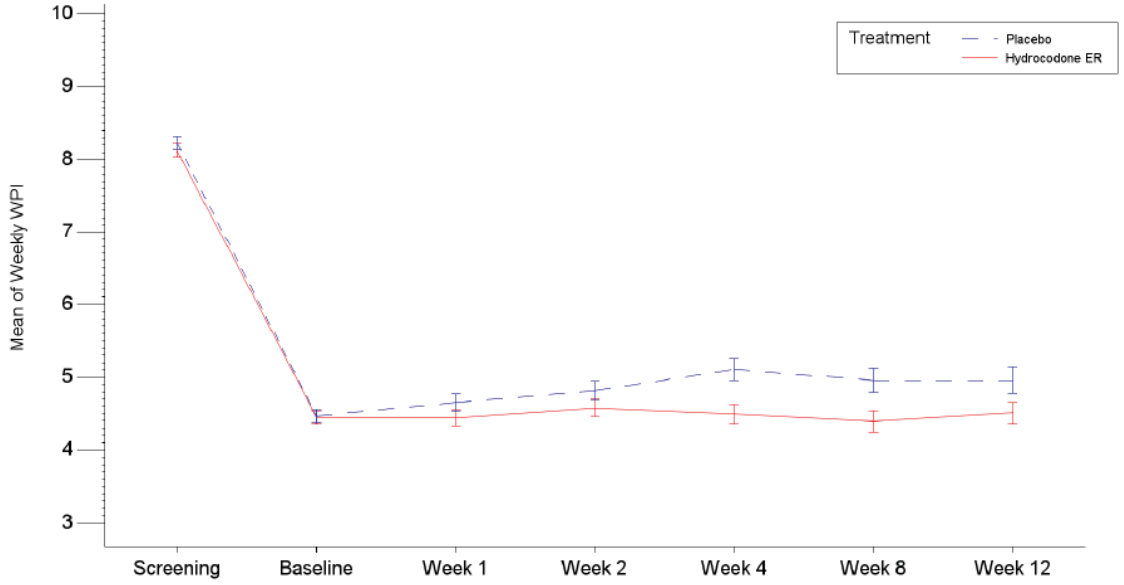
Source: Modified from statistical team leader review. Table 1, p2

* Number of subjects with week 12 data included in the analysis; Analysis based on the 1000 imputed datasets

** Subjects in the active-drug treatment group who discontinued study drug treated as if they were in the placebo group and their missing data imputed based on the observed placebo subjects' data regardless of the discontinuation reasons

The mean average of worst pain intensity data for each treatment group is shown in the following graph from Dr. Levin's review.

Figure 1: Plot of Weekly Average of Daily Worst Pain Intensity by Analysis Visit in Study 3103



There were numerous secondary endpoints including change from baseline in average pain intensity which favored Vantrela ER over placebo. The placebo group also had greater use of rescue medication as shown in the following table from Dr. Levin's review. While not separating statistically, the trend for greater use of rescue in the placebo group was consistent throughout the trial.

Table 27: Rescue Medication Usage (Daily Number of Tablets) by Visit

Time point	Daily number of tablets		Difference (95% CI) (Placebo-hydrocodone)	p-value
	Placebo (n=179)	Hydrocodone (n=191)		
Week 1				
n	178	191		
Mean	1.2	0.8		
LS mean (SE)	1.17 (0.148)	0.78 (0.144)	0.39 (-0.01, 0.79)	0.055
Week 2				
n	168	182		
Mean	1.6	1.2		
LS mean (SE)	1.55 (0.153)	1.13 (0.147)	0.42 (0.01, 0.83)	0.044
Week 4				
n	156	176		
Mean	1.9	1.3		
LS mean (SE)	1.81	1.30	0.50 (0.08, 0.92)	0.019
Week 8				
n	142	164		
Mean	1.9	1.5		
LS mean (SE)	1.83 (0.166)	1.47 (0.155)	0.36 (-0.08,0.80)	0.105
Week 12				
n	131	150		
Mean	1.7	1.6		
LS mean (SE)	1.69 (0.173)	1.56 (0.161)	0.13 (-0.33, 0.59)	0.576

Source: CSR, Table 32, p.114

There was no difference in the change from baseline in the Roland Morris Disability Questionnaire score.

As described in Dr. McEvoy's review:

> The subgroup analysis was performed on WPI change at week 12 using an ANCOVA model within each subgroup. The model included as covariates baseline WPI, treatment, center and opioid status (except for the analysis by opioid status).
>
> Results from different subgroups were reasonably in-line with the estimate from the overall analysis. The greatest difference between levels for the subgroups explored was for opioid status, with the effect being more pronounced for the opioid experienced group (-0.82) than for the opioid naïve group (-0.28). These differences, as with all subgroup comparisons, should be interpreted cautiously for several reasons including multiplicity considerations and the fact that the trials were not designed to detect differences across levels of the subgroups.

Dr. McEvoy concluded that "the amount of missing data in Study 3103 coupled with the marginal effect in those with week 12 data does not lead to robust evidence in favor of Vantrela ER providing greater relief of low back pain than placebo, as measured by the change from baseline in the weekly average WPI at week 12." However, I disagree with this conclusion. The ability to demonstrate efficacy for an opioid analgesic over a blinded 12-week period is challenging due to a number of issues, including some particular to opioid analgesic clinical trials. These include: 1) to reduce the number of patients who discontinue study participation early due to untreated pain, clinical analgesic trials must include rescue medication for the active and placebo treatment groups and 2) there is traditionally a high placebo response in analgesic studies. Both of these issues reduce the size of the treatment effect of the study drug relative to placebo. In addition, the number of early discontinuations is frequently high and treatment-related in opioid analgesic studies of chronic pain. Some patients in the active treatment group fail to tolerate the side effects of the opioid drug and discontinue the study because of adverse events (e.g. nausea, sleepiness), while a subgroup of patients in the placebo group have more pain than they are willing to tolerate, even with the available rescue medication and discontinue the study for lack of efficacy. This leads to a problem with missing data. Sensitivity analyses were conducted by both the Applicant and the FDA statistics team to evaluate the effects of the method of imputation on the efficacy outcome and, as described by Dr. Cooner in her secondary statistics memo, the sensitivity analysis, "renders a different perspective of the data and the results provide supportive evidence of the treatment efficacy ." Dr. Cooner concluded that "the results of the primary analysis along with the sensitivity and ancillary analyses have provided sufficient evidence on the efficacy of Vantrela ER in moderate to severe chronic low back pain management, as measured by the change from baseline in the weekly average WPI at week 12." I concur with Dr. Cooner's analysis of the study results.

A second adequate and well-controlled clinical trial, Study 3079 evaluated pain in patients with chronic low back pain or osteoarthritis. While the study failed to meet a statistically significant difference in treatment groups for the prespecified primary endpoint of change from baseline in average pain intensity, there was evidence of efficacy including the secondary endpoint of change from baseline in worst pain intensity. Additional details of Study 3079 can be found in Dr. McEvoy's review.

The final titrated dose for the two Phase 3 studies is summarized in the following table from Dr. Levin's review. Note that Study 3079 permitted dosing at the 15 mg twice a day dosage.

Table 30: Optimal Dose (Safety Analysis Set)

Optimal dose (q12)	Total N=1176 n (%)
Not achieved[a]	385 (33)
15 mg	108 (9)
30 mg	218 (19)
45 mg	204 (17)
60 mg	149 (13)
90 mg	112 (10)

Source: ISS. Table 7, p93
[a]Optimal dose was not achieved due to lack of efficacy, intolerability, or other reasons for discontinuation.

This table shows that the titrated dose to achieve the randomization criteria was distributed across the full range of dosing options, from 15 mg twice a day to 90 mg twice a day.

8. Safety

Sections of this review are paraphrased from Dr. Levin's review. The primary clinical evaluation of the safety of Vantrela ER is based on data from the four Phase 3 studies (double-blind, placebo-controlled studies [3103, 3079] and open-label, long-term safety studies [3104, 3080]). Sixteen of the 19 clinical pharmacology studies included naltrexone to block the effects of hydrocodone and do not contribute substantial data about the safety of Vantrela ER.

The safety database consisted of a total of 1176 patients who took at least one dose of Vantrela ER in the Phase 3 studies. The safety analysis set included 389 patients from Study 3079, 164 new patients from Study 3080, and 623 patients from Study 3103. Rollover patients who entered Studies 3080 and 3104 were included in the safety analysis as part of the number of patients in Studies 3079 and 3103.

The Applicant defined a post-titration analysis set from the two double-blind, placebo-controlled trials, Studies 3079 and 3103 (N=663), that included patients from the double-blind, post-titration treatment period, 293 patients from Study 3079 (147 patients who received

placebo and 146 patients who received Vantrela ER) and 370 patients from Study 3103 (179 patients who received placebo and 191 patients who received Vantrela ER).

The duration of exposure is summarized in the following table from Dr. Levin's review.

Table 29: Duration of Exposure for 90 mg Dose

Duration of Treatment	Total (N=112) n (%)
≥ 1 month	83 (74%)
≥ 3 months	67 (60%)
≥ 6 months	42 (38%)
≥ 9 months	22 (20%)
≥ 12 months	20 (18%)

Source: ISS, Adhoc Summary 6

The safety database was somewhat diverse, as described by Dr. Levin, although not fully representative of the diversity of the US population. The following is from Dr. Levin's review:

> In the post-titration analysis set for the double-blind Studies (3079 and 3103), 299 subjects(45%) were male and 364 subjects (55%) were female; 567 subjects (86%) were less than or equal to 65 years and 96 subjects (14%) were greater than 65 years; 480 subjects (72%) were Caucasian, 149 subjects (22%) were African American, 24 subjects (4%) were Asian and 10 subjects (2%) were of other races. With respect to opioid status, 360 subjects (54%) were opioid-naïve and 303 subjects (46%) were opioid-experienced.

There were three deaths, one prior to study drug administration. One of the remaining two deaths was a 74 year old man with a history of coronary artery disease and coronary artery bypass graft, congestive heart failure, hypercholesterolemia, chronic obstructive pulmonary disease and emphysema, rheumatoid arthritis, and obstructive sleep apnea. Following titration to a Vantrela ER dose of 30 mg twice a day, the patient developed a cough and confusion on Day 40, and was admitted with a diagnosis of pneumonia that resolved with treatment. On Day 185, the patient was short of breath and appeared sedated. Study drug was interrupted for Days 185 to 194. The patient was diagnosed and treated for pulmonary edema. The patient was hospitalized on Day 267 with a diagnosis of urosepsis, resolved by Day 270. That same day he was started on azathioprine for his rheumatoid arthritis. Bupropion was begun for mild depression. The patient was admitted to hospice on Day 287 and died on study day 304. The cause of death could not be ascertained by the Applicant. It seems unlikely that the death could be attributed to study participation after the patient had been on study drug for at least 287 days. The second of the remaining two deaths was a 54 year old woman with a history of hypothyroidism, anxiety, insomnia, headache, gastric bypass, anemia, hypertension, depression, and chronic low back pain following failed back pain surgery. The patient completed the randomized, double-blind study treatment on Vantrela ER 90 mg twice a day and began participation in the open-label extension study. Pregabalin was added for pain management. On Day 237 of the open-label study, the patient had moderate vomiting and

diarrhea, still present along with symptoms of a urinary tract infection on Day 242. The patient had a cardiopulmonary arrest while waiting to be seen by her physician in the office waiting room and could not be revived. Her potassium was found to be 8.6 mmol/L (normal range 3.5 to 4.9). Her daughter reported the patient was taking potassium left over for the treatment of leg cramps. This death was unlikely associated with study drug participation.

Serious adverse events occurred in 57 (5%) patients, all during Phase 3 studies. The only SAEs observed by more than one patient were: pneumonia (4), renal failure acute (4), deep vein thrombosis (3), and each of the following were reported in two patients: cellulitis, chest pain, cholecystitis, chronic obstructive pulmonary disease, dehydration, pancreatitis, intestinal obstruction, and panic attack. A full listing of serious adverse events can be found in Dr. Levin's review who also reviewed the case report forms. Of note, there was a case of accidental overdose and respiratory arrest in a 70 year old man two days following titration to 90 mg twice a day, who was also known to have opioid prescriptions from a number of providers prior to the study. It is unclear if the overdose was due solely to exposure to Vantrela ER and the details of drug levels or number of doses was not provided by the Applicant.

Dr. Levin conducted a review of early discontinuations as noted in the following from his review.

> In the four Phase 3 studies, a total of 1176 patients received at least one dose of study drug and 214 (18%) patients discontinued from the study because of an adverse event. The most common adverse events reported by 2% or more of patients causing discontinuation were nausea (5%), vomiting (3%), constipation (2%), somnolence (2%), and dizziness (2%).
>
> During the open-label titration period for the double-blind studies, adverse events leading to discontinuation occurred more often in opioid-naïve patients (15%) compared with opioid-experienced patients (8%) which would be expected.
>
> During the post-titration period for the double-blind studies (Studies 3079 and 3103) 20(6%) patients in the hydrocodone ER group and 10 (3%) patients in the placebo group reported adverse events causing discontinuation from the study (Table 33). In the hydrocodone ER group abdominal pain, anxiety, and headache were reported by 3(<1%) patients each and nausea, somnolence, vomiting, constipation, drug withdrawal syndrome, and pancreatitis were reported by 2 (<1%) patients each. In the placebo group, nausea was reported by 2 (<1%) patients. The interpretation of these findings is complicated by the study design, where all subjects were on hydrocodone ER prior to randomization and those that did not tolerate hydrocodone may have dropped out in the open-label phase and would not be captured in the controlled, double-blind phase.

Therefore it is likely that the difference in discontinuations due to adverse events between hydrocodone and placebo would have been even greater in the hydrocodone group than observed in the double-blind portion of the study.

Table 33: Adverse Events in at Least 2 Patients Causing Discontinuation During the Post-titration Treatment Period in Studies 3079 and 3103

MedDRA 16.0 preferred term	Placebo, N=326 n (%)	Hydrocodone ER, N=337 n(%)
Number of patients with at least 1 AE causing discontinuation	10 (3)	20 (6)
Abdominal pain	0	3 (<1)
Anxiety	0	3 (<1)
Headache	0	3 (<1)
Nausea	2 (<1)	2 (<1)
Somnolence	1 (<1)	2 (<1)
Vomiting	1 (<1)	2 (<1)
Constipation	0	2 (<1)
Drug withdrawal syndrome	0	2 (<1)
Pancreatitis	0	2 (<1)

Source: ISS. Table 31, p145

A summary of subject disposition during the double-blind treatment period (post titration) for the double-blind studies (Studies 3079 and 3103) is provided in Table 34. As expected a larger percentage of placebo group subjects discontinued due to lack of efficacy compared with HC-ER group (8% vs 3%) and a larger percentage of HC-ER group subjects discontinued due to an adverse event compared with placebo group (6% vs 3%). The narratives were reviewed for the discontinuations due to adverse events and consistent with the known adverse event profile for opioids. Major causes of discontinuation were nausea/vomiting, somnolence, and pruritus.

Table 34: Patient Disposition by Treatment Group During the Double-blind Treatment Period of Controlled Studies 3079 and 3103

Analysis Group	Placebo N=328 n(%)	Hydrocodone ER N=337 n(%)	Total N=665 n(%)
Patients entered post-titration	328 (100)	337 (100)	665 (100)
Patients entered post-titration, not treated	2 (<1)	0	2 (<1)
Post-titration analysis set	326 (>99)	337 (100)	663 (>99)
Completed study	243 (74)	250 (74)	493 (74)
Discontinued study	85 (26)	87 (26)	172 (26)

Adverse event	9 (3)	19 (6)	28 (4)
Lack of efficacy	26 (8)	9 (3)	35 (5)
Withdrawal by subject	11 (3)	14 (4)	25 (4)
Protocol violation	18 (5)	21 (6)	39 (6)
Lost to follow-up	2 (<1)	2 (<1)	4 (<1)
Non-compliance to study procedures	5 (2)	3 (<1)	8 (1)
Non-compliance to study medication	11 (3)	13 (4)	24 (4)
Other	2 (<1)	6 (2)	8 (1)
Pregnancy	1 (<1)	0	1 (<1)

Source: ISS. Table 4, p87
N=number of patients; n=number of patients in subgroup.
Note: The denominator for calculating percentages is the number of patients who entered post-titration in double-blind Studies 3079 and 3103.

The most frequent common adverse events were 5% or more patients were constipation 23%, nausea 23%, headache 12%, somnolence 10%, vomiting 10%, dizziness 7%, pruritus 6%, fatigue 5%, and diarrhea 5%.

Overall, there were no unexpected findings in the review of deaths, serious adverse events, adverse events leading to early discontinuation, or common adverse events.

A thorough QT study was not conducted by the Applicant. However, electrocardiograms (ECGs) were recorded at baseline and endpoint and evaluated for evidence of a QT effect. The following is from Dr. Levin's review.

> At the Division's request, the Applicant prepared a summary of QTcB and QTcF change from screening to endpoint greater than 30 msec (Table 41) and greater than 60 msec (Table 42) for patients in Studies 3079 and 3103. The results showed a trend for changes greater than 30 msec occurring more often in the hydrocodone ER treatment group compared to the placebo treatment group (QTcB: 7% versus 4%, respectively; QTcF: 5% versus 2%, respectively). There was no clear dose relationship observed but this may have been due to the small number of subjects in the higher dose groups. The increased number of patients with QTcB and QTcF prolonged greater than 30 msec in the hydrocodone ER group compared to placebo group was consistent with an analysis of patients in the double-blind phase of Studies 3079 and 3103 performed by Dr Ana Szarfman from the FDA Office of Translational Sciences Data Mining Team using the ECG analysis module of the Empirca program. Only a few patients had QTc changes greater than 60 msec, but there was still a numerically higher incidence observed in the hydrocodone ER group compared to the placebo group (QTc B; 1.2% versus 0.6%, respectively; QTcF 1.2% versus 0.3%, respectively. Again no clear dose relationship was apparent but this may have been related to the small number of subjects.

Table 41: Number of Patients with QTcB and QTcF Change from Screening >30 msec Pooled Data from Study 3079 and Study 3103

Optimal dose[a] from the open-label titration phase	QTcB Change >30 msec		QTcF Change >30 msec	
	Hydrocodone ER group N=337 x/y (%)	Placebo group N=326	Hydrocodone ER group N=337 x/y (%)	Placebo group N=326
15 mg	3/36 (8)	1/43 (2)	4/36 (11)	1/43 (2)
30 mg	6/104 (6)	2/93 (2)	3/104 (3)	2/93 (2)
45 mg	10/103 (10[b])	3/80 (4)	8/103 (8)	1/80 (1)
60 mg	2/53 (4)	4/66 (6)	1/53 (2)	3/66 (5)
90 mg	3/41 (7)	3/44 (7)	2/41 (5)	1/44 (2)
All doses	24/337 (7)	13/326 (4)	18/337 (5)	8/326 (2)

Source: Teva provided analysis
[a] every 12 hours
[b] The 10% incidence for the pooled dataset, QTcB at the 45 mg dose hydrocodone ER should have been 9% as 1 case was reported in error (Patient 3103_10398001).
x/y: x is the number of patients with a change >30 msec, and y is the number of patients in that optimal dose.

Table 42: Number of Patients with QTcB and QTcF Change from Screening >60 msec- Pooled Data from Study 3079 and Study 3103

Optimal dose[a] from the open-label titration phase	QTcB Change >60 msec		QTcF Change >60 msec	
	Hydrocodone ER group N=337 x/y (%)	Placebo group N=326	Hydrocodone ER group N=337 x/y (%)	Placebo group N=326
15 mg	0/36 (0)	0/43 (0)	0/36 (0)	0/43 (0)
30 mg	2/104 (2)	0/93 (0)	2/104 (2)	1/93 (1)
45 mg	3/103 (3[b])	0/80 (0)	2/103 (2)	0/80 (0)
60 mg	0/53 (0)	1/66 (2)	0/53 (0)	0/66 (0)
90 mg	0/41 (0)	1/44 (2)	0/41 (0)	0/44 (0)
All doses	5/337 (1.5[c])	2/326 (0.6)	4/337 (1.2)	1/326 (0.3)

Source: Teva provided analysis
[a] every 12 hours
[b] The 3% incidence for the pooled dataset, QTcB at the 45 mg dose hydrocodone ER should have been 2% as 1 case was reported in error (Patient 3103_10398001).
[c] The 1.5% incidence for the pooled dataset, QTcB at the all doses should have been 1.2% as 1 case was reported in error (Patient 3103_10398001).
x/y: x is the number of patients with a change >60 msec, and y is the number of patients in that optimal dose.

Analysis of Absolute QTc >500 msec and >480 msec.
Absolute QTc >500 msec

There were three patients in the posttitration analysis set for double-blind studies that had QTc >500 msec. Two of the patients (Patients 3079_050003 and 3079_052002) had QTcB baselines greater than 500 msec and one patient (Patient 3103_10357009) on placebo had a change in QTcF from 489 msec at baseline to 503 msec. During the titration phase, Patient 3103_10404002 had a QTcF of 574 msec which represents a change from baseline of 78 msec (baseline, 496 msec). This patient was also receiving diflucan which can cause QT prolongation.

In summary, QTc >500 msec was infrequent and all occurred in patients with QTc values close to or exceeding 500 msec at baseline. One patient with QT prolongation was also on diflucan.

Absolute QTc >480 msec in Safety Analysis Set

In the safety analysis set, there were 12 patients with the reported QTcB value >480 msec. In 2 patients (patient 3079_019001 and 3103_10419006), the reported QTcB values on treatment were actually lower than those at baseline. In another patient (patient 3079_050003), the reported QTcB values when on treatment were lower on 2 occasions (decrease of -9 and -16 msec) and higher on 1 occasion (increase of +1 msec) than those at baseline. In the remaining 9 patients, the reported QTcB values meeting this criterion represented an increase from baseline and ranged from an 11 to 68 msec increase, and occurred either during titration or on treatment with hydrocodone ER at 30 or 45 mg every 12 hours doses.

There were 6 patients with the reported QTcF >480 msec. In 2 patients, the reported QTcF values were lower than those at baseline. In the remaining 4 patients the reported QTcF values represented an increase from baseline and ranged from 38 to 78 msec, and occurred in 1 patient each during titration, on treatment with hydrocodone ER at 15, 30 or 60 mg every 12 hours doses.

Absolute QTc >480 msec in Posttitration Analysis Set For Double-Blind Studies

QTcB >480 msec

There were 7 patients with reported QTcB values >480 msec. In 3 patients, the reported QTcB values when on treatment were actually lower than those at baseline. In the remaining 4 patients the reported QTcB values meeting this criterion represented an increase from baseline and 2 occurred when receiving placebo (increase of 7 and 72 msec) and 2 occurred when receiving hydrocodone ER at doses of 30 mg every 12 hours (increase of 62 msec) or 45 mg every 12 hours (increase of 25 msec).

QTcF >480 msec

There were 6 patients with the reported QTcF >480 msec. In 2 patients, the reported QTcF values meeting this criterion when on treatment were actually lower than those at baseline. In the remaining 4 patients the reported QTcF values meeting this criterion represented an increase from baseline and 2

> occurred when receiving placebo (increase of 14 and 48 msec) and 2 occurred when receiving hydrocodone ER at doses of 15 mg e every 12 hours (increase of 49 msec) or 30 mg every 12 hours (increase of 62 msec). For QTc greater than 480 msec and 500 msec the number of cases was low and comparable between hydrocodone ER and placebo treatment groups.

Dr. Levin notes that there were more increases in QTc interval in patients treated with Vantrela ER than placebo suggesting a potential association. He recommends further assessment with a thorough QT study. Given the changes noted were relatively small, Dr. Levin concludes a thorough QT study can be conducted postmarketing. The information provided in the Vantrela ER NDA supports the safety of approving the product with appropriate warnings and limitation of a maximum dose of 90 mg every 12 hours, while allowing completion of a definitive thorough-QT study as a postmarketing requirement to further characterize the effects on the QT interval.

Because the evaluation of the effects of Vantrela ER on the QT interval are limited by the maximum dosing in clinical studies, until the thorough QT study is conducted and analyzed, dosing should not exceed that permitted during clinical trials, 90 mg twice a day.

The question of whether chronic exposure to hydrocodone is associated with hearing loss is based on predominantly anecdotal reports with hydrocodone/acetaminophen products. As a result, the Applicant was asked to include formal audiometric assessments to the development program for Vantrela ER. The following is from Dr. Levin's review:

> Results of the audiometry evaluations and clinically significant hearing changes for clinical studies3103 and 3079 were reviewed by Ting Zhang, Ph.D. from the Center for Devices and Radiological Health (CDRH) at the FDA. Dr Zhang provided the following conclusions in her review dated September 25, 2014.
>
> > The data submitted in the audiology report and follow-up response has adequately addressed our concerns about the potential for ototoxic effects from HYD use. There is 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.

Extended-Release and Long-Acting REMS

Vantrela ER will be added to the ERLA REMS and will have all of the postmarketing requirements from the ERLA REMS.

9. Advisory Committee Meeting

A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held on June 7, 2016. The following section has been reproduced from the meeting minutes.[15]

Questions to the Committee:

1. DISCUSSION: Please discuss whether there are sufficient data to support a finding that Vantrela ER (hydrocodone bitartrate extended-release tablets) has properties that can be expected to deter abuse, commenting on support for abuse-deterrent effects for each of the three possible routes of abuse:
   a. Oral
   b. Nasal
   c. Intravenous

Committee Discussion: It was the general consensus of the committee that Vantrela ER has sufficient data to support a finding of abuse-deterrent characteristics for the oral, nasal and intravenous routes of administration. The committee stated that data presented for all three routes of administration show at least a moderate amount of reduction in the possibility of abuse. It was also noted that although the reduction is incremental, the committee found the data to be compelling at the present time. Please see the transcript for details of the committee discussion.

2. VOTE: Should Vantrela ER be approved for the proposed indication, management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate?

Vote Result: Yes: 14 No: 3 Abstain: 0

Committee Discussion: The majority of the committee voted "Yes," agreeing that Vantrela ER should be approved for the proposed indication. Those members who voted "Yes" stated that the clinical development program met the standard for demonstrating efficacy. Those members who voted "No" stated that they were concerned with how opioid products are regulated and approved, as well as the potential effect this process has on the opioid epidemic. Please see the transcript for details of the committee discussion.

[15] See http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM512757.pdf

3. VOTE: If approved, should Vantrela ER be labeled as an abuse-deterrent product by the oral route of abuse?

Vote Result: Yes: 14 No: 3 Abstain: 0

Committee Discussion: The majority of the committee voted "Yes," agreeing that Vantrela ER should be labeled as an abuse-deterrent product by the oral route of abuse. Those members who voted "Yes" stated that there were sufficient data provided to label the drug as abuse deterrent. Those members who voted "No" stated that they were unconvinced as the data was not compelling and felt the abuse-deterrent properties of Vantrela ER would not be significant in clinical practice. Please see the transcript for details of the committee discussion.

4.VOTE: If approved, should Vantrela ER be labeled as an abuse-deterrent product by the nasal route of abuse?

Vote Result: Yes: 14 No: 3 Abstain: 0

Committee Discussion: The majority of the committee voted "Yes," stating that Vantrela ER should be labeled as an abuse-deterrent product by the nasal route of abuse. Those members who voted "Yes" agreed that the data provided moderately convincing evidence that Vantrela ER was formulated with abuse-deterrent properties and was a step forward in making opioids safer for patients. Those members who voted "No" stated that they were unimpressed with the small margin of change. Please see the transcript for details of the committee discussion.

5.VOTE: If approved, should Vantrela ER be labeled as an abuse-deterrent product by the intravenous route of abuse?

Vote Result: Yes: 16 No: 1 Abstain: 0

Committee Discussion: The majority of the committee voted "Yes," stating that Vantrela ER should be labeled as an abuse-deterrent product by the intravenous route of abuse because the studies show that Vantrela ER has a high viscosity and low syringability (sic). The member who voted "No" stated that there was no evidence that Vantrela ER was safer than other products that still get injected and abused despite their high viscosity. Please see the transcript for details of the committee discussion.

As can be seen, the committee members found the data to support approval of Vantrela ER adequate, and agreed the data provided were sufficient to support labeling to describe the abuse-deterrent properties for the oral, nasal and intravenous routes of abuse.

10. Pediatrics

The following has been reproduced from Dr. Feeney's review (page 26):

> The application triggers the requirements of PREA because it is a new dosage form and a new dosing regimen. No pediatric data have been submitted as part of this NDA, but the Sponsor did submit a Pediatric Study Plan (PSP) in the NDA.
>
> In a letter dated October 9, 2014, DAAAP confirmed agreement with the Sponsor's initial PSP (iPSP). The Sponsor had requested a waiver for studies with Vantrela ER in patients from birth to less than 7 years of age on the basis of the low prevalence of chronic pain in this age group, making studies impossible or highly impractical. DAAAP agreed with the waiver. The Sponsor did propose a PK and safety study in pediatric patients 7 years to less than 17 years.
>
> The PSP was discussed at the Pediatric Review Committee (PeRC) on September 9, 2015. The PeRC noted that development of this AD product in patients less than 7 years would almost certainly require different formulation development which would defeat the AD properties. For that reason, PeRC agreed with the waiver for patients less than 7 years. PeRC believes that "…pediatric patients should have access to drugs which have been appropriately studied to provide accurate dosing, efficacy and safety information." For that reason, PeRC agreed with the planned PK and safety study in pediatric patients ≥ 7 years. PeRC agreed with the planned deferral for that study.

11. Other Relevant Regulatory Issues

Abuse Deterrence

Oral Abuse Liability, Study 1085

This was a randomized, double-blind, triple-dummy, placebo-controlled crossover study that evaluated the oral abuse potential, safety, tolerability, and PK of intact and crushed Vantrela ER compared to placebo and hydrocodone powder in healthy nondependent recreational opioid users. The study consisted of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase) and a Follow-Up Visit.

Study treatment groups were:

- Vantrela ER 45 mg intact and placebo intact
- Vantrela ER 45 mg crushed and placebo intact
- Hydrocodone bitartrate powder 45 mg and placebo crushed
- Placebo intact and placebo crushed

A total of 100 nondependent, recreational opioid users were enrolled in the Qualification Phase. The subjects were from 18 to 43 years of age, 79 were men and 21 women. A total of 45 subjects passed a naloxone challenge test and the qualification phase and 35 completed the study.

As noted by Dr. Nallani, the pharmacokinetic parameters for Vantrela ER from this study were similar to other studies. Crushed Vantrela ER 45 mg tablet had a 42% higher Cmax compared to intact Vantrela ER 45 mg tablet as shown in the following table from Dr. Nallani's review

Table : Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone After Administration of Immediate- and Extended-Release Hydrocodone (Pharmacokinetic Analysis Set)

Variable	45-mg IR (N=39)	45-mg ER crushed (N=41)	45-mg ER intact (N=40)
C_{max} (ng/mL)	91.46 (16.817)	40.78 (10.204)	28.77 (6.088)
t_{max} (h)	0.8 (0.3, 4.1)	4.0 (1.8, 7.0)	7.1 (6.1, 12.0)
$AUC_{0-\infty}$ (ng·h/mL)	625 (137.3)	586 (138.5)	584 (124.8)
$AUC_{0-0.75}$ (ng·h/mL)	29 (13.5)	3 (1.7)	1 (0.3)
AUC_{0-4} (ng·h/mL)	246 (42.9)	103 (25.0)	34 (9.0)
AUC_{0-7} (ng·h/mL)	377 (60.2)	212 (47.1)	104 (22.6)
AUC_{0-t} (ng·h/mL)	623 (135.5)	584 (138.6)	581 (124.5)
Extrapolation (%)	0.26 (0.098)	0.40 (0.200)	0.61 (0.497)
λ_z (1/h)	0.1384 (0.02176)	0.0933 (0.02519)	0.0929 (0.02671)
$t_{1/2}$ (h)	5.13 (0.804)	7.97 (2.132)	8.04 (2.194)
AQ (ng/mL/h)	108.59 (58.789)	10.97 (3.997)	3.88 (1.056)

SOURCE: Summary 15.9.1, Listing 16.2.5.03.

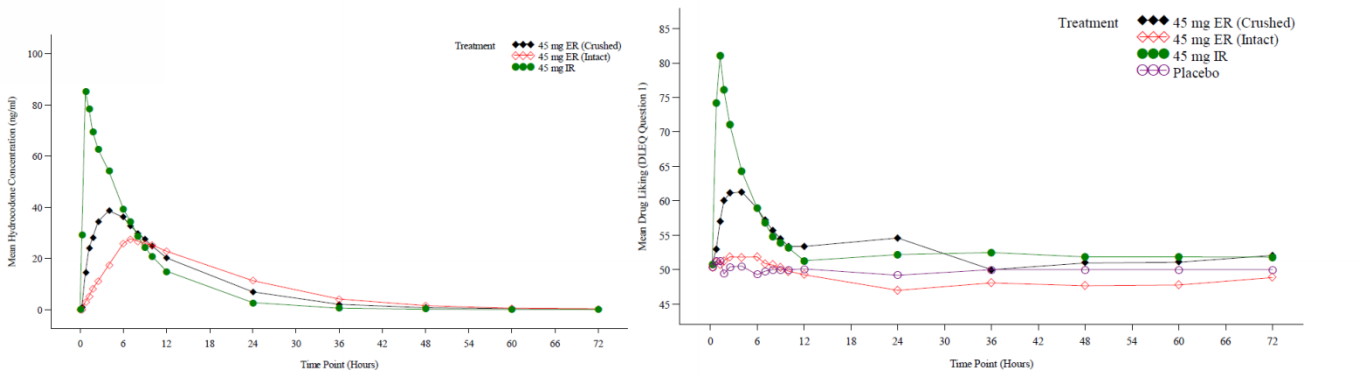
As noted by Dr. Bonson, the subjective responses produced by the three treatment conditions reflected the plasma levels of hydrocodone produced by these conditions, as shown in the following table, modified from her review. (Vantrela ER was named CEP-33237 during development). Mean drug liking for intact Vantrela ER tablet was low (~50 or neither like nor dislike) followed by crushed Vantrela ER tablet, and the highest drug liking noted with crushed hydrocodone IR.

Table 7: Effects of Oral Placebo, CEP-33237 (Intact and Crushed) and Hydrocodone Powder on Subjective Measures (VAS and ARCI)

Measure	Placebo N = 35	CEP-33237 45 mg intact N = 35	CEP-33237 45 mg crushed N = 35	hydrocodone 45 mg powder N = 35
Drug Liking VAS bipolar	53 ± 2	54 ± 1	66 ± 3	85 ± 2
Overall Drug Liking VAS bipolar	51 ± 1	51 ± 1	58 ± 4	74 ± 3
Take Drug Again VAS	47 ± 2	46 ± 3	59 ± 3	75 ± 3
PVAQ VAS ($0.25-50.00)	1 ± 1	1 ± 1	7 ± 2	12 ± 1
Good Drug Effects VAS	9 ± 3	11 ± 3	33 ± 5	73 ± 4
ARCI-MGB Euphoria (0-16)	2.5 ± 0.5	2.8 ± 0.4	5.7 ± 0.7	8.6 ± 0.7
Pupil Diameter	5.5 ±0.1	3.2 ±0.1	4.0±0.1	3.2 ± 0.1

The results of mean drug liking and the pharmacokinetic profiles are displayed below in a figure from Dr. Nallani's review.

Figure: Mean Plasma Concentration-Time Profiles and Mean Drug Liking (DLEQ Question 1) Over Time in Healthy, Nondependent, Recreational Opioid Users Administered Single Doses of Hydrocodone Extended-Release Tablets (Crushed or Intact) or an Immediate-Release Formulation or Placebo



SOURCE: Section 15, Figure 1.1.1.A, Adhoc Figure 1.1.0.A.
ER=hydrocodone bitartrate extended-release tablet; IR=immediate-release hydrocodone; DLEQ=Drug Liking and Effects Questionnaire.

The following conclusions are from Dr. Bonson's review:

- The study was validated by the statistically significant increase in Drug Liking VAS in response to hydrocodone powder (immediate release) compared to placebo. Hydrocodone powder similarly statistically significantly increased scores on other positive subjective responses (Overall Drug Liking, Take Drug Again, Subjective Drug Value, Good Effects, and Euphoria), as well as on negative subjective scales (Bad Effects, Dysphoria, Nausea), Sedation and Any Effects.

- In general, crushed CEP-33237 produced statistically significantly lower responses on all subjective measures compared to hydrocodone powder,

but the crushed CEP-33237 produced statistically significantly greater responses compared to intact CEP-33237 and to placebo. Intact CEP-33237 was often statistically equivalent on subjective measures to placebo.

Study 10032 was a single-dose, randomized, double-blind, quadruple-dummy, active- and placebo-controlled crossover study designed to assess the abuse potential of manipulated intranasal Vantrela ER in healthy, nondependent recreational opioid users. The study consists of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase) and a Follow-Up Visit.

Study treatment groups were:

- Vantrela ER 45 mg, manipulated, intranasal
- Hydrocodone API 45 mg, intranasal
- Vantrela ER 45 mg, intact, oral
- Zohydro 45 mg (original formulation), manipulated, intranasal
- Placebo

A total of 73 nondependent, recreational opioid users (ages 18 to 50 years, 52 men and 21 women) were enrolled into the Qualification Phase after passing a naloxone challenge test. There were 34 subjects who completed the Treatment Phase.

The peak plasma concentration of hydrocodone and maximum drug liking were highest and achieved rapidly (Tmax 1.5 h) following intranasal administration of API and crushed Zohydro as summarized in the following table from Dr. Nallani's review.

Table: Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone After Intranasal Administration of Crushed Vantrela ER (IN CEP-33237), Hydrocodone API or Crushed Zohydro™, or Oral Administration of Intact Vantrela ER (OR CEP-33237) at 45 mg Dose (Study 10032).

Variable	45 mg IN API (N=38)	45 mg IN Zohydro™ (N=39)	45 mg IN CEP-33237 (N=41)	45 mg OR CEP-33237 (N=38)
C_{max} (ng/mL)	71.28 (30.48)	80.27 (29.29)	56.84 (15.07)	25.05 (7.18)
t_{max} (h)	1.38 (0.60, 7.07)	1.12 (0.55, 6.17)	2.62 (1.33, 7.02)	9.11 (4.10, 12.12)
$AUC_{0-\infty}$ (ng·h/mL)	579 (163)	639 (179)	572 (150)	568 (172)
AUC_{0-t} (ng·h/mL)	576 (161)	637 (178)	568 (149)	531 (152)
$AUC_{0-tmax, API}$ (ng·h/mL)	57.5 (28.3)	66.5 (28.3)	24.9 (13.4)	1.9 (0.8)
$AUC_{0-tmax, CEP (IN)}$ (ng·h/mL)	125.9 (51.8)	142.4 (51.5)	78.5 (28.6)	9.4 (2.7)
$AUC_{0-tmax, CEP (Oral)}$ (ng·h/mL)	380.0 (112.3)	416.3 (108.8)	336.4 (75.1)	127.5 (34.9)
$AUC_{0-tmax, Zohydro}$ (ng·h/mL)	39.3 (20.9)	46.4 (21.2)	15.1 (8.7)	1.0 (0.5)
Extrapolation (%)	0.60 (0.94)	0.38 (0.24)	0.73 (0.72)	6.04 (3.94)
λ_z (1/h)	0.124 (0.023)	0.127 (0.021)	0.114 (0.015)	0.076 (0.024)
$t_{1/2}$ (h)	5.78 (1.06)	5.58 (0.86)	6.16 (0.76)	9.96 (3.03)
AQ (ng/mL/h)	59.6 (55.2)	75.4 (54.0)	22.6 (12.2)	3.1 (1.2)

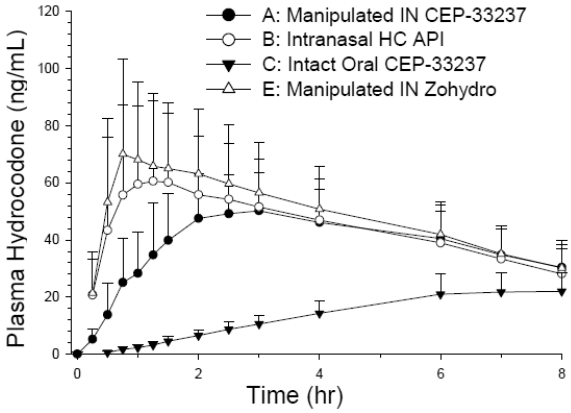
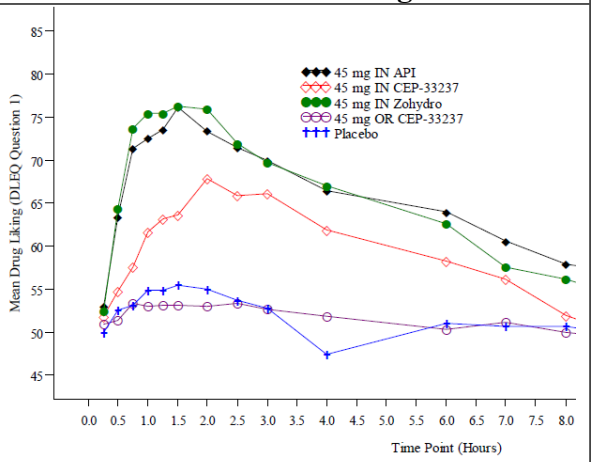
Source: Summary 15.9.1.
API=active pharmaceutical ingredient; AQ=abuse quotient (C_{max}/t_{max})

The subjective responses produced by the three treatment conditions reflect the plasma levels of hydrocodone produced by these conditions, as shown in the pharmacokinetic data above. A two-fold increase in systemic exposure is noted following intranasal administration of Vantrela ER tablet which was associated with a significant increase in drug liking. The pharmacodynamic responses are summarized in the following table, modified from Dr. Bonson's review.

Table 11: Effects of Intranasal Placebo, API hydrocodone, Zohydro and CEP-33237 (IN and Oral) on Subjective Measures (VAS and ARCI)

Measure	**Placebo N=34**	**45 mg IN API N=34**	**45 mg IN Zohydro N=34**	**45 mg IN CEP-33237 N=34**	**45 mg Oral Zohydro N=34**
Drug Liking VAS bipolar	59 ± 2	80 ± 2	83 ± 2	73 ± 2	57 ± 2
Overall Drug Liking VAS bipolar	58 ± 2	77 ± 3	80 ± 3	69 ± 3	58 ±3
Take Drug Again VAS	56 ± 12	76 ± 15	79 ± 17	68 ± 20	56 ± 14
PVAQ VAS ($0.25-50.00)	3 ± 6	11 ± 8	13 ± 10	9 ± 8	3 ± 7
Good Drug Effects VAS	16 ± 23	59 ± 28	68 ± 24	44 ± 27	13 ± 23
ARCI-MGB Euphoria (0-16)	3.9 ± 3.4	7.1 ± 4.3	6.8 ± 4.2	6.3 ± 4.6	3.0 ± 2.5
Bad Drug Effects VAS	5 ± 10	15 ± 18	19 ± 24	23 ± 28	8 ± 14
Nausea VAS	4 ± 8	15 ± 22	16 ± 23	15 ± 23	6 ± 14
Pupil Diameter (mm)	5.5 ±0.8	3.3 ±0.7	3.0±0.5	3.4 ± 0.6	4.0 ± 0.8

As shown in the following side by side figures from Dr. Nallani's reviews, the subjective responses produced by the three treatment conditions reflect the plasma levels of hydrocodone produced by these conditions, as shown in the pharmacokinetic data above.

Mean hydrocodone PK profile following intranasal abuse of different hydrocodone preparations (45 mg) vs. intact oral Vantrela ER 45 mg tablet.	Mean drug liking (question 1) vs. time following intranasal abuse of different hydrocodone preparations (45 mg) vs intact oral Vantrela ER 45 mg tablet.
 Source: Summary 15.8.1. Note: Concentration-time profile to 8 hours is shown as an inset.	

The order of plasma hydrocodone levels, from highest to lowest, produced by each of these conditions was IN Zohydro, IN hydrocodone powder, IN crushed CEP-33237, oral intact CEP-33237, which also reflects the order of subjective measures response.

The postmarketing requirements to evaluate the effects of the abuse-deterrent formulation of Vantrela ER currently in place for other abuse-deterrent formulations will be required.

As described by Dr. Levin, there were no concerns that financial interests have played a role in the outcome of studies intended to support this application.

There are no other unresolved relevant regulatory issues

12. Labeling

The proposed proprietary name, Vantrela ER, was found acceptable. Carton and container labels were reviewed and the final labels found acceptable from a medication error prevention perspective. Labeling recommendations from the patient labeling team were implemented. OPDP has provided comments that were incorporated into the package insert and had no comments on the carton and container labeling.

The labeling will include information from the pharmacokinetic and human abuse potential studies that describe the abuse-deterrent properties of Vantrela ER. The following is the summary that will be included in the package insert:

Summary
The in vitro data demonstrate that VANTRELA ER has physical and chemical properties that are expected to make intravenous abuse difficult. The data from the in vitro studies and clinical abuse potential studies indicate that VANTRELA ER has physicochemical properties that are expected to reduce abuse via the oral route and the intranasal route. However, abuse of VANTRELA ER by the intravenous, nasal, and oral routes is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of VANTRELA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

VANTRELA ER contains hydrocodone bitartrate, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. VANTRELA ER can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)]*.

Because the evaluation of the effects of Vantrela ER on the QT interval are limited by the maximum dosing in clinical studies, 90 mg twice a daily, this will be the maximum labeled dose in the package insert.

Moderate hepatic injury results in greater exposure to hydrocodone from Vantrela ER. Therefore, labeling will reflect the importance of starting with a lower dose of Vantrela ER than in patients with normal hepatic function in patients with moderate impairment as well as mild. As the effects of severe hepatic impairment were not evaluated, labeling will reflect that Vantrela ER should not be used in these patients. Labeling will also include the data from the study. The following is from Section 2, Dosage and Administration, of the proposed label:

2.3 Dosage Modifications in Patients with Mild or Moderate Hepatic Impairment

Patients with hepatic impairment may have higher plasma concentrations of hydrocodone than those with normal function. In patients with mild or moderate hepatic impairment, initiate therapy with one half of the recommended initial dose followed by careful dose titration. Use of alternate analgesics is recommended for patients who require a VANTRELA ER dose of less than 15 mg. Monitor closely for adverse events such as respiratory depression. VANTRELA ER is not recommended in patients with severe hepatic impairment *[see Hepatic Impairment (8.6) and Clinical Pharmacology (12.3)]*.

Similarly, the increased exposure of hydrocodone in renal impairment will be conveyed in labeling as follows:

> **2.4 Dosage Modifications in Patients with Moderate or Severe Renal Impairment or End Stage Renal Disease**
>
> Patients with moderate or severe renal impairment or end stage renal disease may have higher plasma concentrations than those with normal renal function. Initiate therapy with one half of the recommended initial dose of VANTRELA ER and titrate carefully. No adjustment in starting dose is required for patients with mild renal impairment. Use of alternate analgesics is recommended for patients who require a VANTRELA ER dose of less than 15 mg. Monitor all patients with renal impairment closely for adverse events such as respiratory depression *[see Renal Impairment (8.7) and Clinical Pharmacology (12.3)]*.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval
- Risk Benefit Assessment

In this NDA, the Applicant has provided adequate chemistry, manufacturing, and controls and biopharmaceutics data to support approval. The Applicant has provided a combination of new nonclinical studies, right of reference to a carcinogenicity study by another sponsor, right of reference for the Vicoprofen NDA, and a request for a waiver of nonclinical pharmacology studies, nonclinical ADME studies, and chronic toxicology studies. The Applicant has conducted clinical pharmacology studies that describe the single-dose and multiple-dose pharmacokinetic profile, including absorption and elimination, effect of administration with food, and dose proportionality across the five strengths of Vantrela ER tablets. The Applicant is relying on the metabolism and distribution information through right of reference to the Vicoprofen NDA. The Applicant has conducted studies in patients with renal and hepatic impairment. While specific drug-drug interaction studies have not been performed with Vantrela ER, information from the Vicoprofen label provides insight as to the likelihood of interactions based on concomitant drugs that are inhibitors or inducers of CYP3A4, and on the risks of concomitant use with other CNS depressants, including benzodiazepines, and the risk for interactions with anticholinergic drugs, mixed/partial agonist opioids, and MAO inhibitors. The in vitro effects of alcohol on the dissolution of Vantrela ER demonstrated no dose dumping precluding the need for a clinical study of the risk for dose dumping. Efficacy has been demonstrated in an adequate and well-controlled clinical trial of Vantrela, with supportive evidence from a clinical trial that trended positively, but failed to reach statistical significance for the prespecified primary analysis. Efficacy is also supported by right of reference for the Vicoprofen NDA. The safety of Vantrela ER is supported by the data from the clinical trials of Vantrela, and right of reference for the Vicoprofen NDA. Safety studies include an assessment of the effects of hydrocodone on hearing. The effects of Vantrela ER on the QT interval for the range of doses in clinical trials, have been assessed by an analysis of ECG data from clinical trials. Because the evaluation of the effects of Vantrela ER on the QT

interval are limited by the maximum dosing in clinical studies, until the study is conducted and analyzed, dosing should not exceed that permitted during clinical trials, 90 mg twice a day.

In vitro studies of the physicochemical properties of Vantrela ER and human abuse liability studies of intact and manipulated Vantrela ER support the finding that Vantrela ER has abuse-deterrent properties expected to make abuse by the intravenous route difficult and to deter abuse by the intranasal and oral routes of administration.

The Applicant submitted a full battery of certain nonclinical studies either by conducting, sponsoring, or submitting a right of reference to them (genetic toxicology, reproductive and developmental toxicology, and carcinogenicity). The Applicant also submitted a right of reference to the Vicoprofen NDA to support aspects of nonclinical pharmacology and ADME and conducted an in vitro study to support the latter; and submitted a request for a waiver of additional nonclinical pharmacology, ADME, and chronic toxicity studies. The waivers are justified and granted either because the applicant's compliance with the requirement is unnecessary, the applicant's alternative submission satisfies the requirement, or the applicant's submission otherwise justifies the waiver.

There is much known about hydrocodone and no question about whether it has the analgesic properties and adverse event profile expected of a mu opioid agonist. Opioid analgesics, as a class, have many common effects, which is reflected by the fact that the labeling for these products is consistent across the class in certain respects.[16] Drug specific concerns about possible hearing loss, and to a limited extent, the effects on the QT interval have been addressed through clinical studies conducted by the Applicant.

Therefore, Vantrela ER may be approved as a 505(b)(1) application with the labeling described above. The additional information requested in the post marketing requirements below will provide useful information for prescribers, but are not required to support approval with the proposed labeling.

- Recommendation for Postmarketing Risk Management Activities

Vantrela ER will be part of the ERLA REMS.

The following postmarketing requirements have been agreed to by the Applicant.

2981-1 Deferred pediatric study under PREA: Conduct a pharmacokinetic and safety study of an age-appropriate formulation of Vantrela ER in patients from ages seven 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.

2981-2 In order to provide the baseline data to support the hypothesis-testing studies required under PMR 2981-3, conduct a descriptive study that analyzes data on the following:

[16] http://www fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491739.htm

1) Utilization of Vantrela ER (hydrocodone bitartrate) extended-release tablets and selected comparators. Reports should include nationally-projected quarterly retail dispensing, overall and by age group and census region; AND

2) Abuse of Vantrela ER (hydrocodone bitartrate) extended-release tablets and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for Vantrela ER (hydrocodone bitartrate) extended-release tablets as well as mutually agreed-upon, selected comparators to provide context.

   - Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.

   - Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.

   - Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g., 95% confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.

2981-3 Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of Vantrela ER (hydrocodone bitartrate) extended-release tablets actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of Vantrela ER (hydrocodone bitartrate) extended-release tablets and should incorporate recommendations contained in Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry (April 2015). Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA's Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.

2981-4 A multiple ascending dose thorough QT (tQT) clinical trial in adults to determine the maximum tolerated dose of hydrocodone bitartrate without co-administration of naltrexone (b) (4)

(b) (4)

3033-1 A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.

This study must address at a minimum the following specific objectives:

a. Estimate the incidence of misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain. 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, and addiction.

b. Evaluate and quantify other risk factors for misuse, abuse, and addiction associated with long-term use of opioid analgesics 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.

3033-2 An observational study designed to measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records, insurance claims, and death records.

This study must address at a minimum the following specific objectives:

a. Estimate the incidence of abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain. Stratify 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 abuse/addiction, overdose, and death.

b. Evaluate and quantify other risk factors for abuse/addiction, overdose, and death associated with long-term use of opioid analgesics 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 overdose by intentionality wherever possible.

3033-3 A prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.

3033-4 An observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.

3033-5 An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioid analgesics for chronic pain.

3033-6 An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.

3033-7 An observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.

3033-8 An observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.

3033-9 An observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.

3033-10 An observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.

3033-11 Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy

- Recommendation for other Postmarketing Study Commitments

None

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

/s/

SHARON H HERTZ
01/17/2017