CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 13, 2017
From	John Feeney, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	207975
Applicant	Teva Branded Pharmaceutical Products R&D Inc.
Date of Submission	December 23, 2014
PDUFA Goal Date	October 23, 2015
Proprietary Name / Established (USAN) names	Vantrela (hydrocodone bitartrate) Extended-Release Tablets
Dosage forms / Strength	15, 30, 45, 60, and 90 mg strength tablets
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
Recommended:	Approval

Material Reviewed	**Review Team**
Primary Medical Officer Review	Robert Levin, MD
Statistical Review (Clinical)	Bradley McEvoy, DrPH, Freda Cooner, PhD
Secondary Statistical Review (Clinical)	Freda Cooner, PhD, Thomas Permutt, PhD
Audiology Review	Ting Zhang, PhD, Srinivas Nandkumar, PhD
Pharmacology Toxicology Review	Elizabeth Bolan, PhD, Huiqing Hao, PhD, Dan Mellon, PhD
Secondary Pharmacology Toxicology Review	Dan Mellon, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD, Yun Xu, PhD
Chemistry Review, Drug Substance	Erika Englund, PhD, Donna Christner, PhD
Chemistry Review, Drug Product	Christopher Hough, PhD, Ciby Abraham, PhD
Chemistry Review, Process	Haitao Li, PhD, Ubrani Venkataram, PhD
Product Quality Microbiology Review	Haitao Li, PhD, Ubrani Venkataram, PhD
Biopharmaceutics Review	Fang Wu, PhD, John Duan, PhD
Clinical Inspection Summary	John Lee, MD, Janice Pohlman, MD, MPH, Susan Thompson, MD
Proprietary Name Review	Millie Brahmbhatt, PharmD, BCPS, Vicky Borders-Hemphill, PharmD
DMEPA Label and Labeling Review	Millie Brahmbhatt, PharmD, BCPS, Vicky Borders-Hemphill, PharmD
Controlled Substances Staff Review	Katherine Bonson, PhD, Silvia Calderon, PhD, Michael Klein, PhD
Chemistry Review (Category 1 Abuse-Deterrence Studies)	Venkateswara Pavuluri, PhD, RPh, Julia Pinto, PhD
Statistical Review (Abuse-Potential Studies)	Feng Zhou, MS, Qianyu Dang, PhD, Yi Tsong, PhD

1. Introduction

Vantrela (hydrocodone bitartrate) Extended-Release Tablets represent an extended-release (ER) oral formulation of hydrocodone. A 505(b)(2) NDA for Vantrela ER was received on December 23, 2014. During the review cycle, the Sponsor amended the application to convert it to a 505(b)(1) NDA. The proposed indication is for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Vantrela ER has been formulated with the intent that the physicochemical properties of the tablet will provide abuse-deterrent (AD) properties.

Hydrocodone is an opioid-receptor agonist that is relatively selective for the mu-opioid receptor. In the United States, it is available in oral immediate-release (IR) products in combination with aspirin, acetaminophen, and ibuprofen. Recently, it is also available in two oral ER formulations, Zohydro and Hysingla. Zohydro was approved in 2013 and was the first single-entity hydrocodone product approved in the U.S. Hysingla is an ER product with AD properties conferred by the physicochemical properties of the tablets. Those physicochemical properties make attempts to defeat the ER properties for purposes of abuse by cutting or crushing Hysingla more difficult. Currently, Hysingla is the only AD ER formulation of hydrocodone marketed in the U.S.

Vantrela ER was developed to provide a twice-daily (bid) dosing regimen. The formulation incorporates compendial materials in order to both provide the ER profile and to provide physical and chemical barriers to misuse and abuse. Five tablet strengths have been developed, including 15, 30, 45, 60, and 90 mg tablets. All strengths of the tablets contain the (b) (4) . (b) (4) . All tablets are capsule-shaped and differentiated by tablet color.

Initially, the listed product cited for the 505(b)(2) application was Vicoprofen (hydrocodone bitartrate/ibuprofen) Tablets (NDA 020716). Vicoprofen is an immediate-release product indicated for the short-term (generally less than 10 days) management of acute pain. Exposures to hydrocodone are different with Vantrela ER and Vicoprofen and the Sponsor was therefore required to provide the results of an efficacy study along with additional safety data to support the application.

In 2010, public discussions began about initiating a class-wide Risk Evaluation and Mitigation Strategy (REMS) for all Extended-Release/Long-Acting (ER/LA) opioids. The ER/LA REMS was implemented in 2012. Vantrela ER is an ER/LA opioid and would fall under the REMS.

The Sponsor of this NDA is Teva Branded Pharmaceutical Products R&D Inc. Throughout all the reviews, Vantrela ER is sometimes referred to as CEP-33237.

2. Background

Vantrela ER was developed under IND 105587. The IND was opened in 2009 by Cephalon, Inc. The name of the Sponsor changed to Teva Branded Pharmaceutical Products R & D, Inc. in 2012 when Cephalon was acquired by Teva Pharmaceutical Industries Ltd. There were a number of meetings between the Sponsor and DAAAP during the development of Vantrela ER. These are outlined in detail in Dr. Levin's Clinical Review.

To support the 505(b)(2) application, the Sponsor was required to provide an efficacy study and additional safety data. Study 3079 was the first large, randomized, double-blind (DB), placebo-controlled (PC), parallel-group study conducted by the Sponsor to demonstrate the efficacy of Vantrela ER. However, because a statistically-significant difference between Vantrela ER and placebo was not observed on the protocol-specified primary analysis, the Sponsor conducted a second randomized, DB, PC, parallel-group study, Study 3103, that proved to be positive on the primary analysis. Studies 3080 and 3104 were open-label (OL) extension studies of Studies 3079 and 3103, respectively, and were intended to collect additional safety data. Some de novo patients also entered the safety studies.

In addition to the described efficacy and safety studies, the Sponsor also performed Category 1, 2, and 3 AD studies to support labeling. (See guidance for industry: *Abuse-Deterrent Opioids – Evaluation and Labeling* (April 2015) describing Category 1, 2, and 3 AD studies). Additional clinical pharmacology studies were also included in the application.

Vantrela ER was granted Fast Track designation on May 26, 2014 and was eligible for a rolling review. The first section of the NDA was received on September 30, 2014. The final sections were received on December 23, 2014. The filing communication letter issued on February 28, 2015 and did not identify any potential review issues.

During the review cycle for Vantrela ER, the Sponsor became concerned that the exclusivity that attached to prior hydrocodone products would block approval of Vantrela ER. Discussions were held between the Sponsor and DAAAP about the requirements for switching the application from a 505(b)(2) to a 505(b)(1). Specifically, for the efficacy requirement to support a 505(b)(1) application, the Sponsor was told that it would be a review issue whether a reasonable post hoc analysis of Study 3079 could fulfill the requirement for a second study to support a finding of efficacy.

On July 21, 2015, the Sponsor submitted a letter requesting conversion to a 505(b)(1) application. That letter stated, "Based on previous discussions and written communications

with the Division concerning Teva's plan to convert our current 505(b)(2) application to a 505(b)(1) application by obtaining the right of reference to the Vicoprofen NDA (January 15, 2015 Type C Meeting Minutes; e-mail correspondences dated February 9, 2015 between D. Harnish and K. Compton), the Division confirmed for Teva that the Division would not impose any additional requirements for a possible 505(b)(1) application beyond what would have been required if the Sponsor submitted a 505(b)(2) application referencing FDA's findings of safety and/or effectiveness for Vicoprofen as the listed drug. Moreover, Teva obtained the right of reference to Zohydro's carcinogenicity data (NDA 202,880) to support this conversion (SN0012; April 28, 2015)."

In support of the 505(b)(1) application, AbbVie Inc., the sponsor of Vicoprofen, submitted a letter of authorization (LOA) for Teva to reference the Vicoprofen NDA, including all the investigations and underlying raw data, in support of the Vantrela ER NDA. The letter was submitted on June 10, 2015 and a letter with the corrected NDA number was submitted on July 1, 2015.

Vicoprofen is a fixed-dose combination product. Each tablet of Vicoprofen contains 7.5 mg of hydrocodone and 200 mg of ibuprofen. Vicoprofen is indicated for the short-term (generally less than 10 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The recommended starting dose is one tablet every 4 to 6 hours, as necessary.

With the LOA, Study 3079 was no longer critical to support the (b)(1) efficacy requirement, although it remains supportive. With the LOA, Teva could rely on the previous evidence of efficacy of hydrocodone contained in the Vicoprofen NDA. The study of Vantrela ER, coupled with the evidence of IR hydrocodone effectiveness underlying the Vicoprofen NDA, together support the conclusion that the Vantrela ER is effective for chronic pain management.

The need for Vantrela ER to be part of the ER/LA REMS was discussed with the Sponsor and the Sponsor has submitted REMS documents with their application. REMS elements include a MedGuide, prescriber training/certification, and a communication plan.

The following table provides a comparison of the dosage regimens and formulations for the three ER hydrocodone products.

Table: Comparison of Extended-Release Hydrocodone Products

Product	Dosing Regimen	Dosage Form
Zohydro	twice daily	capsule
Hysingla	once daily	tablet
Vantrela ER	twice daily	tablet

Therefore, Vantrela ER triggers the requirements under the Pediatric Research Equity Act (PREA) because it provides 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. This is discussed later in this review.

There were a number of information requests (IRs) from multiple disciplines to obtain clarifications and additional information during the review cycle. The Sponsor supplied the requested information in a timely manner.

3. Chemistry

The primary Chemistry Review was performed by numerous individuals identified on the first page of this review. The Chemistry Review concludes, "Based on the recommendation from the following disciplines, drug substance, process, microbiology, biopharmaceutics, facilities, and drug product, CMC recommends the approval of Vantrela ER 15, 30, 45, 60, and 90 mg tablets."

The drug substance is manufactured by (b) (4) (Drug Master File (b) (4); last reviewed by Ying Wang, PhD and found adequate on September 19, 2014). The drug product is manufactured by (b) (4). The CMC review includes Dr. Li's evaluation of the drug product process.

Vantrela ER is formulated with hydrocodone bitartrate (b) (4) hypromellose (HPMC), (b) (4) and ethylcellulose (EC) (b) (4) and glyceryl behenate (b) (4)

The quantitative composition of the various tablet strengths is shown in the following table.

Table: Composition of Vantrela, Hydrocodone Bitartrate, Extended Release Tablets

Component	Reference to Standard	15 mg (Light Red)	30 mg (Yellow)	45 mg (White)	60 mg (Light Blue)	90 mg (Light Green)
		mg/tablet	mg/tablet	mg/tablet	mg/tablet	mg/tablet
Hydrocodone bitartrate[a]	USP	15.00	30.00	45.00	60.00	90.00
(b) (4) lactose monohydrate	NF	(b) (4)				
Ethyl cellulose, (b) (4)	NF					
Hypromellose (b) (4)	USP					
Glyceryl behenate	NF					
Magnesium stearate, (b) (4)	NF					
Red ferric oxide	NF					
Yellow ferric oxide	NF					
FD&C Blue #2 aluminum lake	FD&C					
(b) (4)	USP/NF					
Total Weight / Tablet		575	575	575	1150	1150

Source: Clinical Pharmacology Review, page 12.

For potential impurities, Dr. Englund states, (b) (4) currently releases the drug substance with acceptance criteria for the specified impurities at (b) (4)%, and the unspecified impurities at (b) (4)%. The FDA previously informed the applicant that the impurities should be qualified for a (b) (4)g/day dose with the qualification threshold of (b) (4)% in ICH Q3A(R2). The proposed specifications are for NMT (b) (4)% for the unknown related substances, (b) (4) is controlled at NMT (b) (4)0%. (b) (4) are all controlled at (b) (4)%." Therefore, the Sponsor has proposed tighter specifications for potential impurities than the drug substance manufacturer. The proposed specifications are acceptable to the chemistry reviewers.

For the drug product, Dr. Hough states, "All excipients except FD&C blue #2 aluminum lake are compendial. The blue dye is generally regarded as safe. Compatibility of the API with the excipients has been demonstrated." Therefore, there are no added concerns with the drug product. Stability data for the drug product supports a 36-month expiration dating period. Dr. Hough concluded, "This drug product is acceptable overall, pending the resolution of the container and carton labels." Labeling issues have been resolved as discussed later in this review.

Additionally, the Category 1 AD studies were evaluated as part of the Chemistry Review. These included physical manipulation studies, simple extraction studies, and multiple-step extraction studies. Comparators in these studies included Zohydro (original formulation) and

Vicoprofen. These Category 1 results are also discussed in Dr. Bonson's Controlled Substance Staff Review and I will defer summarizing the results to that part of my review.

Biopharmaceutics Review

This was reviewed by Fang Wu, PhD with concurrence from John Duan, PhD. The Biopharmaceutics Review did not identify any issues that would preclude approval of the application. The review focused on the evaluation and acceptability of: 1) the proposed dissolution methodology and acceptance criteria, 2) IVIVC model, 3) bridging BE studies, 4) the ER designation claim, and 5) the alcohol dose-dumping studies.

The dissolution methodology and acceptance criteria were found acceptable. The dissolution method showed discriminating capability on [redacted] The method and the acceptance criteria are deemed adequate for all tablet strengths.

The Sponsor submitted an in vitro-in vivo correlation (IVIVC) analysis in order to support a proposed IVIVC model. The Sponsor's IVIVC model could not be reproduced because of the unavailability of the proper software version. Therefore, Dr. Wu created a new model. The model did not pass the internal and external validations and was deemed unacceptable. Dr. Wu concludes, "However, a rank order exists between the fraction of the in vitro released and the fraction of the in vivo absorbed, which may be used for justification under appropriate circumstances."

Dr. Wu found the BE studies conducted by the Sponsor appropriately bridged the formulations used in different development stages.

The Biopharmaceutics Review includes a steady-state simulation intended to support the ER claim in the proposed label. Concentration-time profiles were generated for Vantrela ER 30 mg bid versus Vicoprofen 15 mg every six hours. The simulations showed the plasma concentrations of hydrocodone after Vantrela ER falling within the range of simulated steady-state concentrations of hydrocodone after Vicoprofen. Based on the data, Dr. Wu concludes the ER claim is supported.

The results of the in vitro dose-dumping studies indicated that the release profiles for the 15 mg and 30 mg tablet strengths differed from the other strengths. The 15 mg tablet appeared to have the greatest susceptibility to dose-dumping in 40% alcohol. According to Dr. Wu, "In 40% alcohol in 0.1 N HCl, average dissolution was 9% at 1 hour, 23% at 2 hours, ranged from 41-42% at 4 hours, and from 53-55% at 6 hours. Drug release in alcohol was more rapid than that seen under normal conditions with roughly 10% of the drug released during the first hour in the presence of alcohol." Therefore, the Sponsor performed an in vivo PK study to further test for the presence of alcohol dose-dumping in vivo. In that study, there did not appear to be an effect of alcohol on the systemic exposure to hydrocodone and hydromorphone from Vantrela ER.

4. Nonclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology Review was performed by Elizabeth Bolan, PhD and Huiqing Hao, PhD. Dan Mellon, PhD wrote a secondary review. Both reviews conclude that the application can be approved if waivers for certain studies are granted as requested by the Sponsor.

The Sponsor submitted waiver requests for the safety pharmacology studies, primary pharmacology studies, secondary pharmacology studies, nonclinical ADME (absorption, distribution, metabolism, and excretion) studies, and chronic toxicology studies in two species (one rodent and one non-rodent). The waiver requests are formally reviewed in Dr. Mellon's secondary review and will be discussed further from a clinical perspective in Dr. Sharon Hertz's Division Director Memo. Dr. Mellon believes the requested waivers for dedicated pharmacology and nonclinical ADME studies are justifiable and I agree. He believes the application can be approved if the clinical team also concludes that the chronic toxicology studies are not necessary. In support of the waiver for chronic toxicology studies, Dr. Mellon notes in his secondary review the limitations on the information that can be collected in chronic toxicology studies with opioids (pp 9-11). This is due to the development of tolerance in the chronic-use clinical setting, resulting in the need for very high doses for some patients. Dr. Mellon states (p10), "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." If the chronic toxicology studies will not be informative, as discussed in Dr. Mellon's secondary review, it follows that the waiver request should be granted.

With the exception of the glyceryl behenate, all of the excipients in this formulation are found in previously-approved drug products. Glyceryl behenate is found in dietary sources including rapeseed (canola) oil and peanut oil. The primary review states, "At the MTDD of HC, (b) (4) of glyceryl behenate would be consumed. Since estimates of the consumption of all added mono- and diglycerides in the diet approximate between 1 to 10 g per person per day, the amount of glyceryl behenate in this product is considered acceptable. We note that this conclusion is consistent with the Select Committee on GRAS Substances (SCOGS) opinion which came to a Type of Conclusion: 1 for mono- and diglycerides of edible fat-forming fatty acids. A Type of Conclusion: 1 states that there is no evidence in the available information that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future."

For a number of the drug substance impurities and drug product degradants, the proposed specifications exceed the ICH Q3A(R2) thresholds. For all of these, the proposed specifications have been adequately qualified and are acceptable from the pharmacology/toxicology perspective.

The Sponsor provided assessments of the genetic toxicology and reproductive/developmental toxicology of hydrocodone bitartrate. DAAAP had previously agreed that carcinogenicity studies could be submitted as post-marketing requirements (PMRs). The carcinogenicity studies were in fact submitted during the review cycle. They were reviewed and found acceptable to support approval.

The primary review summarizes the genetic toxicology studies as follows: "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 test would typically be required to fully characterize the clastogenic potential of HC. However, regardless of the outcome of a fourth genetic toxicology study, a carcinogenicity assessment would provide the definitive answer as to the impact of potential genotoxicity of HC. Carcinogenicity assessments in mice and rats with HC were submitted to this NDA by Teva through a right of reference. Hydrocodone bitartrate was found to be negative for carcinogenic potential in both rat and mouse. Therefore, a fourth genetic toxicology test is not needed."

A full battery of developmental and reproductive toxicology studies were submitted and reviewed. Labeling recommendations based on these studies are provided in the primary review. No teratogenicity was observed, but toxicities consistent with other opioids were observed and will be described in labeling.

5. Clinical Pharmacology

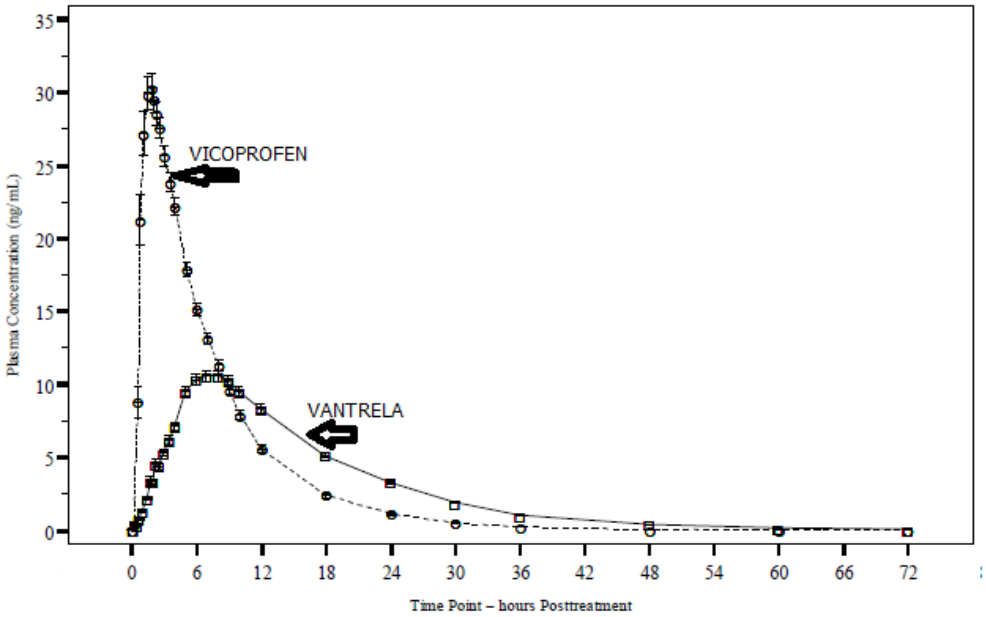
The Clinical Pharmacology Review was completed by Srikanth Nallani, PhD with concurrence from Yun Xu, PhD. They have no outstanding clinical pharmacology issues that would preclude approval of the application and they have made labeling recommendations. They believe there should be three postmarketing requirements: a thorough QT study, a drug-drug interaction study investigating the effect of a strong CYP3A4 inhibitor, and a hepatic impairment study investigating the PK of Vantrela ER in patients with mild and severe hepatic impairment. Submission of these studies after approval does not preclude a determination that this product is safe at the time of approval. Rather, the review of this information post approval would help to further assess the safety risk.

In support of the application, the Sponsor performed a number of clinical pharmacology studies, including comparative bioavailability studies, single-dose PK studies, multiple-dose PK studies, food-effect studies, a renal impairment study, and a hepatic impairment study. Only patients with moderate hepatic impairment were included in the hepatic impairment study.

Dr. Nallani believes the PK of hydrocodone and its metabolite hydromorphone have been well-characterized following single doses of 15 mg through 90 mg. The PK has also been characterized following multiple doses of 45 mg bid and 90 mg bid for 5.5 days. As shown in the Figure below from the Clinical Pharmacology Review, comparable doses of hydrocodone

in Vantrela ER and Vicoprofen result in a Cmax that is three-times higher with Vicoprofen. The Tmax after a single dose of Vantrela ER is 8.5 hours. Hydrocodone and its metabolites are eliminated primarily by the kidney.

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

Systemic exposure to hydrocodone is dose-proportional over the range of 15 mg through 90 mg.

With repeated dosing of Vantrela ER, the Tmax occurs earlier at about 4.5 hours instead of 8.5 hours. Steady state plasma levels of hydrocodone are three-fold higher than levels after a single dose.

Regarding the food effect for Vantrela ER, Dr. Nallani states that the Cmax is about 35-45% higher when Vantrela ER 90 mg is administered with a high-fat meal versus the fasted state. The AUC, however, is unchanged.

Using the single-dose PK data, the Sponsor investigated the effects of age, gender, race, weight, and CYP2D6 metabolizer status on the PK of hydrocodone after Vantrela ER administration. No major impact from any of these variables was observed.

Mild renal impairment had little impact on hydrocodone exposure, but moderate and severe renal impairment increased exposure about 50-70%. Dialysis patients had similar exposures to patients with normal renal function indicating a possible impact of dialysis on elimination.

Patients with moderate hepatic impairment had a 30% higher Cmax and a 70% higher AUC. Therefore, dose adjustment in patients with moderate hepatic impairment will be recommended in labeling and the same dose adjustment will be recommended for patients with mild impairment to reduce the possibility of elevated exposures. Labeling should include a statement to the effect that Vantrela should not be used in patients with severe hepatic impairment.

The Sponsor also conducted a clinical alcohol-interaction study with Vantrela ER 15 mg. The in vitro alcohol dose-dumping study did not suggest dose-dumping but the 15 mg strength showed the most potential for dose-dumping. Therefore, only the 15 mg strength was further studied in a clinical study. Coadministration of Vantrela ER with 20% and 40% alcohol did not significantly change hydrocodone exposure compared to exposure in the fasted state without any alcohol.

Dr. Nallani describes the metabolism of hydrocodone as follows: "…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." Hydromorphone is present in only small levels and the small changes observed in these levels across different polymorphisms of CYP2D6 are not expected to have clinical importance. Hydrocodone levels are only slightly higher in CYP2D6 poor metabolizers.

Dr. Nallani states, "Based on Vicoprofen label, the pharmacokinetics of hydrocodone may be affected by inhibitors and inducers of CYP3A4, with a possible impact on safety and efficacy." To this effect, I believe the label for Vantrela ER should include the following standard Warning, "Initiation of CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of hydrocodone from Vantrela ER."

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The Sponsor submitted the results from two efficacy studies in the application. The primary review of the clinical efficacy data was performed by Robert Levin, MD. The primary statistical review of the efficacy data was performed by Bradley McEvoy, DrPH and Freda Cooner, PhD. A secondary statistical review was performed by Freda Cooner, PhD and Thomas Permutt, PhD "…to clarify the conclusions in the primary [statistical] reviewer's

evaluations of this original NDA submission, and to provide more details on the interpretation of the sensitivity analyses."

The two efficacy studies conducted by the Sponsor were Study 3079 and Study 3103. The designs of the two studies were similar. Both were randomized, double-blind (DB), placebo-controlled (PC), parallel-group studies. Both trials included a randomized-withdrawal design intended to enrich the population of patients studied for responders. In both trials, after screening, all patients were treated in an open-label (OL) titration period for up to six weeks. Responders during the OL period were then randomized to active treatment (at the optimal dose from the titration period) or placebo and followed for 12 weeks.

The two studies differed in three important ways as shown in the table below.

Table: Important Differences Between Study 3079 and Study 3103

	Study 3079	**Study 3103**
Population Studied	Osteoarthritis or low back pain	Low back pain only
Primary Endpoint	Daily average pain intensity	Daily worst pain intensity
Doses Investigated	15 mg bid through 90 mg bid	30 mg bid through 90 mg bid

The Sponsor acknowledged that Study 3079 failed on the protocol-specified primary analysis. During development, the Sponsor intended to submit a 505(b)(2) NDA for Vantrela ER and a single efficacy study was required to support such an application. Because Study 3079 had failed, the Sponsor conducted the second study, Study 3103. Study 3103 was a positive study based on the protocol-specified primary analysis. The two studies will be discussed separately below.

Study 3103

Patients with chronic low back pain (LBP) who met the screening criteria entered the OL titration period. The screening criteria included:

Inclusion Criteria:

1. Moderate to severe chronic low back pain for at least 3 months duration before screening.
2. 18 through 80 years of age at the time of screening.
3. Women of childbearing potential (not surgically sterile or 2 years postmenopausal) must use a medically accepted method of contraception, agree to continue use of this method for the duration of the study and for 30 days after participation in the study, and have a negative pregnancy test at screening.
4. If the patient is receiving interventional therapies, physical therapy, chiropractic treatment, biofeedback therapy, acupuncture therapy, or herbal remedies, these therapies must be completed 2 weeks before the beginning of the open-label titration period.

Exclusion Criteria:

1. The patient is taking a total of more than 135 mg/day of oxycodone, or equivalent, during the 14 days before screening.
2. The patient's primary painful condition under study is related to any source of chronic pain other than low back pain.
3. The patient has radicular (nerve compression) pain or another type of purely neuropathic pain.
4. The patient has any other medical condition or is receiving concomitant medication/therapy (e.g., regional nerve block) that would, in the opinion of the investigator, compromise the patient's safety or compliance.

Each day during the titration period, patients recorded in an electronic diary their worst pain intensity for the day (WPI) and their estimate of their average pain intensity for the day (API). Pain was scored from 0 to 10 on the NRS 11-point scale (0=no pain; 10=worst pain imaginable). To be eligible for randomization, patients had to meet the following criteria:

- Have stable pain relief, defined as 1) an API of 4 or less and a WPI of 6 or less for each of 4 consecutive days, or 2) an API of 4 or less and a WPI of 6 or less for 4 out of 7 consecutive days
- Have no unacceptable adverse events (AEs)
- The dose necessary to achieve the first two criteria, the so-called optimal dose, was at least 30 mg bid and no more than 90 mg bid

Patients were randomized by site and opioid status (naïve versus experienced) in a 1:1 ratio to Vantrela ER or matching placebo bid. The patients assigned to placebo underwent a blinded two-week tapering period intended to minimize withdrawal effects. After randomization, the protocol did not allow any upward or downward dose adjustments of study drug during the study period.

Rescue medication was allowed during both the titration period and the post-randomization period. During the open-label titration period rescue with up to two tablets per day of hydrocodone 5mg/acetaminophen 325 mg was allowed. During the double-blind treatment period up to a total of 12 tablets per day of hydrocodone 5mg/acetaminophen 325 mg were allowed.

Statistical Plan

The primary endpoint was the change from baseline to week 12 in the weekly average of WPI. The weekly average was to be calculated using the daily WPI scores from the previous 7 days for each study visit.

The study was powered to detect a 0.7 difference between the Vantrela ER and placebo groups on the primary endpoint, assuming a standard deviation of at least 2. With 90% power and a two-sided 5% alpha level, the Sponsor calculated that a sample size of 170 patients per treatment arm would be needed.

The primary analysis was to use an ANCOVA model with baseline WPI, randomized treatment, opioid status, and center as covariates. WPI values measured after discontinuation of study drug were excluded from the analysis. Missing week-12 WPI data were imputed based on multiple imputation.

Dr. McEvoy's review describes the imputation process as follows: "Imputed data were obtained from an imputation model that included assigned treatment, opioid status, baseline and post-baseline WPI values. The applicant's results were based on 5 imputed datasets. To minimize the randomness in the estimates that are associated with having a small number of imputed datasets, analyses presented in this review are based on 1000 simulated datasets. This difference is likely to cause differences between the results in my review and the applicant's study report. Patients assigned to HER [hydrocodone ER] and discontinued study drug due to an adverse event were imputed as if they were assigned to placebo; this was achieved by, for the imputation analysis only, recoding their assigned treatment as placebo, not HER."

A number of sensitivity analyses were also planned as described in the Primary Statistical Review.

Demographics of Patients Randomized

The mean age of the patients randomized was about 50 years, with almost 20% of patients greater than 65 years. Males and females were equally represented. About 70% of patients were white and about 20% of patients were black. The mean duration of chronic LBP was about 11 years and the mean duration of opioid therapy was about 3 years.

About half of the opioid-naïve patients had the lowest possible optimal dose, 30 mg bid. As expected, the distribution of optimal doses was more evenly distributed for the opioid-experienced group. There is a suggestion that the optimal doses for the Vantrela ER group tended to be slightly lower than for the placebo group.

Table: Baseline Opioid Status and Dose, Study 3103

	Vantrela ER N=191	**Placebo N=180**
Opioid Status		
Naïve	110 (58%)	105 (58%)
Experienced	81 (42%)	75 (42%)
Optimal Dose		
30 mg	69 (36%)	52 (29%)
45 mg	64 (34%)	57 (32%)
60 mg	32 (17%)	43 (24%)
90 mg	26 (14%)	28 (16%)

Source: Statistical Review, Table 7, page 19.

Patient Disposition

A total of 625 patients were screened in order to achieve 371 randomized. Of those randomized, 191 patients were randomized to Vantrela ER and 180 to placebo. The number of patients who completed 12 weeks of treatment with study drug was 147 (77%) for Vantrela ER and 130 for placebo (72%). The protocol encouraged patients who discontinued study drug early to still stay in the study and complete the study visits. There were 9 such Vantrela ER patients and 11 such placebo patients. In the Vantrela ER group, 35 patients discontinued study drug and withdrew from the study early. In the placebo group, 39 patients discontinued study drug and withdrew from the study early.

Subject disposition differed by opioid status, opioid-naïve versus opioid-experienced, and treatment assignment. In the opioid-naïve group, 25% of patients discontinued study drug in both treatment groups and the reasons for discontinuation are almost identical for the two treatment groups, Vantrela ER and placebo. In the opioid-experienced group, 20% of patients discontinued study drug in the Vantrela ER group and 32% discontinued in the placebo group. In this opioid-experienced group, there is a marked difference between the number who discontinued for lack of efficacy between the Vantrela ER and placebo groups: 3 patients versus 13 patients. The following table from Dr. McEvoy's review demonstrates these differences.

Table: Subject Disposition by Opioid Status, Study 3103

	Experienced		Naïve	
	Hydrocodone n (%†)	**Placebo n (%†)**	**Hydrocodone n (%†)**	**Placebo n (%†)**
Randomized	81	75	110	105
Evaluable for efficacy	81 (100%)	75 (100%)	110 (100%)	104 (99%)
Completed study	68 (84%)	58 (77%)	88 (80%)	83 (79%)
Completed study, but not study treatment	3 (4%)	7 (9%)	6 (5%)	4 (4%)
Withdrawn from study	13 (16%)	17 (23%)	22 (20%)	22 (21%)
Adverse event	2 (2%)	0	7 (6%)	5 (5%)
Lack of efficacy	2 (2%)	6 (8%)	2 (2%)	3 (3%)
Non-compliance: study drug administration	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Non-compliance: study procedures	1 (1%)	3 (4%)	0	0
Consent withdrawn	3 (4%)	1 (1%)	6 (5%)	7 (7%)
Protocol violation	4 (5%)	5 (7%)	3 (3%)	4 (4%)
Lost to follow-up	0	1 (1%)	0	0
Pregnancy	0	0	0	1 (1%)
Other	0	0	1 (1%)	0
Completed study treatment	65 (80%)	51 (68%)	82 (75%)	79 (75%)
Discontinued study treatment	16 (20%)	24 (32%)	28 (25%)	26 (25%)
Adverse event	3 (4%)	2 (3%)	12	7 (7%)
Lack of efficacy	3 (4%)	13 (17%)	2 (2%)	4 (4%)
Non-compliance: study drug administration	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Non-compliance: study procedures	1 (1%)	2 (3%)	0	0
Consent withdrawn	3 (4%)	1 (1%)	6 (5%)	7 (7%)
Protocol violation	4 (5%)	5 (7%)	3 (3%)	4 (4%)
Lost to follow-up	0	0	2 (2%)	1 (1%)
Pregnancy	0	0	0	1 (1%)
Other	1 (1%)	0	2 (2%)	1 (1%)

Source: Statistical Review, Table 4, page 15.

Results

Study 3103 was a positive study based on the protocol-specified primary analysis. The mean change from baseline was 0.1 for the Vantrela ER group and 0.7 for the placebo group, p=0.0012. A sensitivity analysis that mirrored the primary analysis but included the week 12 data for the retrieved dropout patients, n=21, also yielded positive results, p=0.0068.

Based on the hierarchical testing strategy in the protocol, Study 3103 was also positive on the change-from-baseline in API. The next analysis in the hierarchy was time to loss of efficacy or start of excessive rescue medication. The between-group difference for this outcome was not statistically significant, p=0.059, and the remaining study endpoints could therefore not be formally tested.

A categorical responder analysis was performed as a secondary analysis. Responders were defined as completers meeting various % improvement (compared to screening) thresholds. Using thresholds of 15% and 30%, these analyses were nominally statistically significant. Using a threshold of 50%, the analysis was not nominally significant.

In planning the imputation methods, the Sponsor was aware of the potential bias that could be introduced by imputing favorable scores for patients in the active treatment arm who discontinued because of an adverse event (AE). It was for that reason that, in the primary analysis plan, patients assigned to Vantrela ER but who discontinued because of an AE were imputed as if they were assigned to placebo.

Despite the above, Dr. McEvoy expresses the concern in his review that the planned imputation method unduly favored the active treatment arm. His concern arises because of the inclusion of treatment assignment in the imputation model, something he would not have favored if he had reviewed the original protocol and analysis plan. Because the Sponsor did collect retrieved dropout data, Dr. McEvoy was able to investigate his concern by comparing the observed data from retrieved dropouts with the imputed scores for those same patients. When he did this, he found that the nine retrieved dropouts in the active arm had observed scores that were higher (less favorable) than the imputed scores, while the 12 retrieved dropouts in the placebo arm had observed scores that were slightly lower (more favorable/neutral) than the imputed scores. According to Dr. McEvoy, “This suggests the applicant’s primary analysis preserves the treatment difference while on study drug, effectively performing in a similar manner as last observation carried forward.”

Because of the above observation, Dr. McEvoy performed a sensitivity analysis, a so-called tipping-point analysis that investigated the effect of imputation on the sensitivity analysis that mirrored the primary analysis but included the week 12 data for the retrieved dropout patients. Using the primary analysis methods, that latter sensitivity analysis had yielded positive results, p=0.0068. In the tipping analysis, shown on page 24 of the Primary Statistical Review, nominally significant results are only obtained when the scores imputed for the placebo patients are slightly less favorable than the imputed scores for the Vantrela ER patients.

Dr. McEvoy discusses his belief that the categorical analyses might be better at describing a "real-world" drug effect than the primary analysis. However, because the categorical analyses presented only consider completers in the definition of responders, Dr. McEvoy sought to explore the effect of adherence to study drug further. He performed a sensitivity analysis comparing mean scores for active-arm completers (about 80% of those randomized) versus the subset of placebo patients (about 80% of those randomized) chosen because they were the best-performing (missing week 12 data for placebo patients was imputed using a subject's baseline observation). The results were not favorable and he therefore dismisses the categorical results altogether as not supportive. This approach seems inherently biased and overly conservative to me because it is outcome-based and then based only on favorable outcomes among the placebo group. Therefore, I do not agree with him that his negative categorical analyses definitively refute the more favorable categorical analyses.

Because of these findings, Dr. McEvoy believes the results for Study 3103 may not meet the regulatory requirements to support approval. I agree that the inclusion of treatment assignment in the imputation model may not have been optimal, but I do not believe Dr. McEvoy's findings establish that the imputation model provided biased results. I am more persuaded by the results of the categorical analyses than Dr. McEvoy, and by the additional analysis described below.

An IR was sent on September 21, 2015, asking the Sponsor to perform the following analysis: "Repeat the primary analysis for Study 3103 on the primary efficacy endpoint of change-from-baseline WPI, but performing multiple imputations for all patients in the active-drug treatment group who discontinue study drug as if these patients are in the placebo group, regardless the reason of discontinuation." The results of that analysis are described in the Secondary Statistical Review. The change-from-baseline was 0.10 for the active arm and 0.70 for the placebo arm, a difference of 0.60 that was statistically significant, p=0.001. Dr. Cooner cautions that this new sensitivity analysis does not address the issues raised about the primary imputation methodology. She views it as a different view of the data providing supportive evidence of the treatment efficacy. The inclusion of treatment assignment in the imputation model for the primary analysis was not optimal. In that case, absent an acceptable pre-specified imputation method, I believe the best approach is to rely on a conservative imputation method that, if biased, biases *against* the active treatment. That is the analysis presented in the Secondary Statistical Review. Relying on the imputation method discussed in that review, I believe it is reasonable to conclude that a treatment effect has been demonstrated in Study 3103. The Secondary Statistical Review states "…the results of such an analysis [the protocol-specified primary analysis] are of potential to support treatment efficacy as this imputation method addresses the usual concern about assigning favorable values to discontinuation due to intolerance of the treatment…" and concludes "…the results of the primary analysis along with the sensitivity and ancillary analyses have provided sufficient evidence on the efficacy of Vantrela in moderate to severe chronic low back pain management, as measured by the change from baseline in the weekly average WPI at week 12."

Findings in Subgroups (Study 3103)

From the Primary Statistical Review, it appears that the opioid-experienced subgroup performed better than the opioid-naïve. Similarly, the group of patients with an optimal dose of 45 mg bid experienced a more favorable outcome than those in the other dose groups (30 mg bid, 60 mg bid, and 90 mg bid). There did not appear to be significant differences in response based on age, gender, or race.

Study 3079

Study 3079 was very similar in design to Study 3103. However, the primary outcome measure was API versus WPI. Also, optimal dose for patients to be randomized was defined only by API, while both API and WPI were used to define optimal dose in Study 3103. Patients with an optimal dose of 15 mg bid could be randomized in Study 3079, while 30 mg bid was the lowest allowed dose for randomization in Study 3103. About a quarter of patients in Study 3079 had an optimal dose of 15 mg bid. The majority of patients randomized (72%) in Study 3079 had a diagnosis of LBP, while the remainder of patients had osteoarthritis pain.

The study failed on its primary analysis. The change from baseline in API was about -0.22 for the active arm and about 0.14 for the placebo arm, p=0.134. For the secondary analysis, change from baseline in WPI, the change was -0.35 for the active arm and 0.20 for the placebo arm, a difference that was nominally statistically significant. The observed between-group difference on WPI was larger when the 15 mg bid dose group was excluded from the analysis, -0.68 versus -0.54.

Efficacy Data for Vicoprofen

As described in the Background section above, Vicoprofen is a fixed-dose combination product. Each tablet of Vicoprofen contains 7.5 mg of hydrocodone and 200 mg of ibuprofen. It is indicated for the short-term (generally less than 10 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The recommended starting dose is one tablet every 4 to 6 hours, as necessary.

Teva has a right of reference to the NDA for Vicoprofen. According to approved labeling, the efficacy of Vicoprofen was established in multiple single-dose studies in which patients with post-surgical pain after abdominal, gynecological, or orthopedic surgery were enrolled. Full-factorial design studies demonstrated that Vicoprofen had a greater effect than hydrocodone alone, ibuprofen alone, and placebo. Those same studies demonstrate that IR hydrocodone provides benefit in the short-term management of pain. The evidence of IR hydrocodone effectiveness underlying the Vicoprofen NDA, together with study 3103, supports the conclusion that Vantrela ER is effective for chronic pain management.

Overall Efficacy Conclusions

Dr. Levin concludes that Study 3103 demonstrates the efficacy of Vantrela ER for the intended indication. He states, "Efficacy findings from Study 3103 along with the efficacy of the reference drug, Vicoprofen, provide adequate evidence of efficacy for Vantrela for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." He believes the results of Study 3079 provide additional support for efficacy, but were not necessary for recommending an Approval action for Vantrela ER. I agree with his overall assessment. While Vicoprofen was studied only for the short-term management of pain and Vantrela will be indicated for chronic pain, this is an example where a single study for chronic use along with independent substantiation from studies in acute use together can provide evidence of effectiveness to support approval for chronic pain management.

Study 3103 established the effectiveness of the doses studied, 30 mg bid through 90 mg bid. During the open-label dose-titration phase of the study, all opioid-naïve patients were started on a dose of 15 mg bid and titrated upward as needed. Only if the optimal dose achieved was 30 mg bid or higher were patients randomized. Patients on 15 mg bid were excluded from randomization in the hope of improving assay sensitivity in the study, but the exclusion of the 15 mg bid dose did not imply that it was ineffective. In fact each tablet of Vicoprofen contains 7.5 mg of hydrocodone and 200 mg of ibuprofen and the recommended starting dose is one tablet every 4 to 6 hours. Therefore, the lowest recommended daily dose of hydrocodone for acute pain, delivered as Vicoprofen (including ibuprofen), is 30 mg. Although not formally studied in Study 3103, a total daily dose of Vantrela of 30 mg (15 mg bid) should be the recommended starting dose for Vantrela in opioid-naïve and opioid non-tolerant patients. This is consistent also with the precautionary instruction in labeling: "Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals."

8. Safety

The primary review of the safety data was performed by Robert Levin, MD.

The safety database submitted in the NDA contains safety data from 19 Phase 1 studies and 4 Phase 3 studies. The Phase 3 studies included Study 3079 and 3103, along with their associated OL extension studies, Studies 3080 and 3104. Study 3080 was a one-year, OL study. It included patients who completed Study 3079 (rollover patients), as well as new patients with chronic pain (including diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, complex regional pain syndrome, back pain, neck pain, osteoarthritis, or rheumatoid arthritis). Study 3104 was a six-month, OL study completed in August, 2014. Study 3104 only allowed enrollment of rollover patients from Study 3103. The initial NDA submission in December, 2014 did not contain all of the safety data from Study 3104 and a 4-month safety update was submitted on April 22, 2015 that included this data. Dr. Levin concluded that the information contained in the 4-month safety update did not significantly change the safety profile for Vantrela ER as presented in the original submission.

A total of 788 volunteers/patients were exposed to at least one dose of Vantrela ER across all Phase 1 studies. A total of 1176 patients were treated in the four Phase 3 studies and this is referred to as the "safety analysis set" in the submission and in Dr. Levin's review. Of these, 363 were treated for at least six months and 197 were treated for at least one year. At the highest dose, 90 mg bid, there were 112 patients exposed, with 67 exposed for at least three months, 42 patients exposed for at least six months, and 20 patients exposed for at least one year.

A total of 663 patients received at least one dose of study drug post-titration in Studies 3079 and 3103 and this group is referred to as the "post-titration analysis set for double-blind (DB) studies" in the submission. Across the two studies, there were 326 patients treated with placebo and 337 patients treated with Vantrela ER. A randomized-withdrawal design was employed in Studies 3079 and 3103 to enrich for responders for the randomized treatment phase. Therefore, the comparison between the Vantrela ER and placebo groups in this post-titration analysis set is confounded by prior active treatment by all patients, including the placebo patients.

For analysis purposes, patients in both the safety analysis set and the post-titration analysis set for DB studies were grouped based on the optimal dose they achieved in the titration phases of the studies. The following table taken from Dr. Levin's review shows the number of patients in each dose group.

Table: 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: Integrated Summary of Safety, Table 7, page 93.
[a]Optimal dose was not achieved due to lack of efficacy, intolerability, or other reasons for discontinuation

Deaths

Dr. Levin describes two patients who died during treatment with Vantrela ER. A third patient died during the screening period before receiving any study medication.

The first death was in a 74-year-old man with multiple medical problems including emphysema and chronic LBP. The exact cause of death is unclear, but the patient had entered hospice care at the time of death. He had been treated for 287 days in an OL safety study.

The second death was in a 54-year-old woman with chronic LBP. She was treated with Vantrela ER in both a controlled trial and in an OL extension study. After 242 days of treatment in the OL extension study, she developed nausea and diarrhea. While waiting for medical evaluation, she had a cardiac arrest and died. She was found to have hyperkalemia. Potassium was 8.6 mmol/L (normal range, 3.5 to 4.9). Her death was attributed to hyperkalemia and cardiac arrest. The hyperkalemia was possibly due to self-medication with potassium supplements for leg cramps.

Neither death seems reasonably-attributable to Vantrela ER.

Serious Adverse Events

There were no SAEs in the Phase 1 studies. In the Phase 3 studies, 57 patients (5%) experienced at least one SAE. Dr. Levin's review discusses the SAEs in general and he specifically summarizes those that either seem reasonably-related to Vantrela ER and/or are of special interest or concern. The following SAEs were observed by more than one patient: deep vein thrombosis (3), pneumonia (3), acute renal failure (4), cellulitis (2), chest pain (2), cholecystitis (2), chronic obstructive pulmonary disease (2), dehydration (2), pancreatitis (2), intestinal obstruction (2) and panic attack (2). Specific narratives for the following SAEs are included in the Clinical Review: spontaneous abortion, accidental overdose (respiratory arrest), pancreatitis, intestinal obstruction, cholecystitis, syncope, sedation, and hypotension.

During the post-randomization periods of Studies 3079 and 3103, the pattern of SAEs shown in the table below was observed.

Table: Serious Adverse Events in the Post-Randomization Period, 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 serious AE	6 (2)	6 (2)
Pancreatitis	0	2[a] (<1)
Panic attack	1 (<1)	1 (<1)
Anaphylactic reaction	0	1 (<1)
Cellulitis	0	1 (<1)
Hernia obstructive	0	1 (<1)
Oesophagitis	0	1 (<1)
Basal cell carcinoma	1 (<1)	0
Bipolar disorder	1 (<1)	0
Bladder cancer recurrent	1 (<1)	0
Hip fracture	1 (<1)	0
Hypernatraemia	1 (<1)	0
Papillary thyroid cancer	1 (<1)	0
Rhabdomyolysis	1 (<1)	0

Source: Clinical Review, Table 32, page 87.

There were two cases of pancreatitis reported. One of the cases appears to be due to gallstones. The second case may have been a case of autoimmune pancreatitis, but it may also have been attributable to Vantrela ER.

Overall, the pattern of SAEs that were reasonably-attributable to study drug was consistent with the well-known AE profile of opioids.

Discontinuations

A total of 214 patients (18%) withdrew from treatment because of an AE. The AEs that led to discontinuation for 2% or more of patients were nausea (5%), vomiting (3%), constipation (2%), somnolence (2%), and dizziness (2%), all consistent with the known AE profile of opioids.

During the post-randomization periods of Studies 3079 and 3103, the pattern of AEs leading to discontinuation shown in the table below was observed. Only AEs leading to discontinuation in at least two patients overall are included in the table.

Table: Number of Patients with Adverse Events Leading to Treatment Discontinuation in the Post-Randomization Period, Studies 3079 and 3103.

MedDRA preferred term	**Placebo, N=326 n (%)**	**Hydrocodone ER, N=337 n(%)**
Any Adverse Event	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: Clinical Review, Table 33, page 99.

Dr. Levin notes, "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."

Dr. Levin reviewed the narratives for patients who discontinued for AEs. His findings were "…consistent with the known adverse event profile for opioids."

Common Adverse Events

The common AEs from the pooled Studies 3079 and 3103 are shown in the table below. The observed profile is consistent with other opioid drug products.

Table: Adverse Events Reported in > 2% of Patients, Pooled Studies 3079 and 3103

	Titration Period*	**Double-Blind Treatment Period**	
MedDRA preferred term	**VANTRELA ER N=1012 n (%)**	**Placebo N=326 n (%)**	**VANTRELA ER N=337 n (%)**
Nausea	168 (17)	23 (7)	39 (12)
Constipation	152 (15)	15 (5)	46 (14)
Headache	85 (8)	16 (5)	21 (6)
Somnolence	81 (8)	3 (<1)	9 (3)
Vomiting	64 (6)	11 (3)	17 (5)
Dizziness	55 (5)	5 (2)	5 (1)
Pruritus	50 (5)	3 (<1)	5 (1)
Fatigue	32 (3)	4 (1)	7 (2)
Dry mouth	26 (3)	2 (<1)	5 (1)
Diarrhea	22 (2)	10 (3)	12 (4)
Insomnia	18 (2)	9 (3)	4 (1)
Anxiety	7 (<1)	5(2)	13 (4)

Source: Clinical Review, Table 35, page 101.

Additionally, Dr. Levin reviewed the common AEs for the long-term safety studies and found them consistent with the findings from the controlled trials.

Vital Signs

No clinically significant differences in mean systolic blood pressure, diastolic blood pressure, or pulse were observed between the active and placebo groups in the post-titration analysis set for DB studies. The number of patients with potentially important decreases in systolic blood pressure was slightly greater in the active arm compared to the placebo arm across the post-titration analysis set for DB studies. Dr. Levin notes that this would be consistent with the AE profile for opioids.

Laboratory Findings

Dr. Levin did not find any clinically meaningful trends in mean differences from baseline for any of the chemistry values and the numbers of patients with potentially important chemistry abnormalities were similar between the active and placebo groups in the post-titration analysis

set for DB studies. Similarly, his review of the hematology data did not raise any additional concerns.

QTc Prolongation

Electrocardiograms were performed during Studies 3079 and 3103 at screening and at end-of-study. The Sponsor provided analyses of QTc, using both Bazett (QTcB) and Fridericia (QTcF) corrections, for the post-titration analysis set for DB studies. Mean changes from screening to the end-of-study (EOS) visit did not differ significantly between groups for either QTcB or QTcF.

Only two patients had a QTcB > 500 msec at the EOS visit, one in the active treatment group and one in the placebo group. For both patients, the QTcB was > 500 msec at screening as well. Only one patient had a QTcF > 500 msec at the EOS visit, a patient in the placebo group. That patient's QTcF was 489 msec at screening.

Four patients had a QTcB > 480 msec at the EOS visit as well as an increase in QTcB from screening, two in the active treatment group (optimal doses of 30 mg bid and 45 mg bid) and two in the placebo group. One of the patients on Vantrela ER had a change from screening of 62 msec and the other had a change from screening of only 25 msec. Four patients had a QTcF > 480 msec at the EOS visit as well as an increase in QTcB from screening, two in the active treatment group (optimal doses of 15 mg bid and 30 mg bid) and two in the placebo group. One of the patients on Vantrela ER had a change from screening of 49 msec and the other had a change from screening of 62 msec.

Six patients had a QTcB change-from-screening > 60 msec at the EOS visit, four in the active treatment group (a fifth had an unreliable recording of QTc at screening, 128 msec, and is not included) and two in the placebo group. The Vantrela ER patients had optimal doses of 30 mg bid or 45 mg bid. One of the Vantrela ER patients was a 67-year-old male patient (optimal dose of 30 mg bid) whose QTcB was 498 msec at his early termination visit. Five patients had a QTcF change-from-screening > 60 msec at the EOS visit, four in the active treatment group and one in the placebo group. The Vantrela ER patients again had optimal doses of 30 mg bid or 45 mg bid.

Dr. Levin notes that there was also a trend for changes > 30 msec to occur more frequently in the active arm than the placebo arm (7% versus 4% for QTcB). He did not observe a dose-response for this, but he believes this may be due to the small numbers of patients in the higher dose groups.

An additional notable patient was a 39-year-old male who had a QTcF change-from-screening > 60 msec (78 msec) and a final measurement of 574 msec during the titration phase. His concomitant medications included diflucan which is associated with some risk of QT prolongation.

There were no deaths or serious AEs that were related to QTc prolongation or cardiac arrhythmias. There was one AE of QTc prolongation reported. Patient 10392002 in Study

3103 was a 49-year-old male randomized to Vantrela ER. The patient's QT interval increased by 84 msec during the study, reaching a maximum of 454 msec. There were no associated problems and the patient continued on Vantrela ER during the OL safety study without any additional problems.

Hydrocodone is known to prolong the QTc interval. For example, Hysingla was approved on November 20, 2014. The labeling for Hysingla warns that the drug should be avoided in patients with congenital long QT syndrome and further states that this should be considered when making decisions about monitoring when prescribed to patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. If QTc prolongation is observed in patients, Hysingla labeling advises, "…consider reducing the dose by 33-50%, or changing to an alternate analgesic." This information on Hysingla is included for background purposes only; it was not necessary to rely on Hysingla for purposes of approving the Vantrela NDA as discussed below.

Based on the data presented in the current application from Studies 3079 and 3103, there is a very small signal of QT prolongation in patients treated with study drug. All patients in the study were allowed to use IR hydrocodone as rescue medication and some patients were taking other concomitant medications known to prolong the QTc. While there appears to be a small overall signal for QTc prolongation, the concomitant use of these other medications obscures more detailed information about dose response. A dedicated QT study has not been performed with Vantrela ER.

In the safety database of almost 1200 patients, 112 patients were treated with Vantrela ER 90 mg bid. Half of these were treated for four months or longer and about 30 were treated for eight months or longer. No serious AEs have occurred in the safety database that can be obviously attributed to a cardiac arrhythmia. Dr. Levin concludes that the information provided in the Vantrela ER NDA supports the safety of approving the product with appropriate warnings, while allowing completion of a definitive thorough-QT study as a postmarketing requirement (PMR) to further characterize the effects on the QT interval. Based on the totality of the data presented in the Vantrela ER NDA, there may be a small risk when prescribing Vantrela to patients who are already at risk for QT prolongation. Therefore, labeling should warn prescribers to avoid use in at-risk patients, to use clinical judgment in deciding on monitoring for QT prolongation, and to reduce the dose of Vantrela or use alternative medications if QT prolongation is observed. With such labeling, I agree with Dr. Levin that the product can be approved with a PMR to conduct a definitive QT study.

Concomitant use of hydrocodone with CYP3A4 inhibitors will significantly increase exposure to hydrocodone. While these higher exposures will increase risk of QT prolongation and cardiac arrhythmia, the following standard hydrocodone warning will already be included in the labeling for Vantrela and adequately warns prescribers about the risk of CYP3A4 inhibitors: "Initiation of CYP3A4 inhibitors…can result in a fatal overdose of hydrocodone from Vantrela ER."

Audiology

There have been literature reports that describe a sensorineural hearing loss associated with hydrocodone/acetaminophen combination products and often associated with hydrocodone abuse. The hearing loss is typically sudden in onset or rapidly progressive and is often severe. Therefore, to evaluate the ototoxic potential of hydrocodone in the development program for Vantrela ER, the Sponsor incorporated formal audiology testing in Studies 3079 and 3103. In both studies, pure tone audiometry was performed in a controlled setting before and during the OL titration phase, at the first visit of the randomized treatment period, and at the final visit. Ting Zhang, PhD performed the Audiology Review with concurrence from Srinivas Nandkumar, PhD.

Mean and median changes across both the OL titration phases and the randomized treatment phases were reviewed, as well as the changes across the entire study period. No significant changes were noted and there were no differences between the Vantrela ER and placebo groups. Individual clinically-significant changes were also reviewed. Again, there were no differences between the Vantrela ER and placebo groups. AEs related to vestibular function were also reviewed and found to be similar across treatment groups.

The Audiology Review concludes, "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."

Overall Safety Conclusions

Dr. Levin concludes, "Overall, I agree with the applicant's review of the safety findings that the AEs seen in the safety population…were generally consistent with those of the known safety profile of the opioid." I agree with this assessment.

9. Advisory Committee Meeting

A Joint Advisory Committee Meeting of the Anesthetic/Analgesic Drug Products and Drug Safety/Risk Management Advisory Committees was held on June 7, 2016. A closed session, in which the methodology for the Sponsor's Category 1 AD studies was discussed, was followed by an open session.

The committee was asked to discuss whether there are sufficient data to support a finding that Vantrela has properties that can be expected to deter abuse, commenting on support for AD effects for oral, nasal, and intravenous abuse. The committee was asked to vote on the following questions:

1. 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?

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

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

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

Data supporting the AD claims proposed for labeling were reviewed as part of both the Chemistry and CSS Reviews and are discussed further in Section 11 below.

Committee members were generally persuaded by the results of the Category 1, 2, and 3 AD studies. The committee voted to approve Vantrela for the proposed indication (14-to-3) and to approve Vantrela with AD language for the oral (14-to-3), nasal (14-to-3), and intravenous (16-to-1) routes.

10. Pediatrics

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 $\geq$ 7 years. PeRC agreed with the planned deferral for that study.

11. Other Relevant Regulatory Issues

Clinical Site Inspections

The Clinical Inspection Summary was prepared by John Lee, MD with concurrence from Janice Pohlman, MD, MPH, and Susan Thompson, MD.

Inspections were performed at three sites involved in Study 3103. Together, the three sites accounted for 15% of the total enrollment in the study. The inspections were performed June 3-24, 2015.

Name	Number Enrolled	Final Classification
Joseph Gimbel, MD Arizona Research Center Phoenix, Arizona	48 patients	Preliminary NAI
Jeffrey Potts, MD Great Lakes Research Group Bay City, Michigan	25 patients	VAI
Francisco Badar, MD Skyline Research Cerritos, California	21 patients	Preliminary NAI

Key to Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable
Preliminary results based on communication with field investigator

No significant deficiencies were observed and a Form 483 was not issued at the first and third sites. A Form FDA 483 was issued at Dr. Potts' site, with only one finding listed, stating, "Of the nine subjects randomized at this CI site, three (Subjects 20, 28, and 33) may have been incorrectly stratified with respect to their previous opioid exposure, as opioid-experienced when actually opioid-naive (inadequate documentation of exposure history), and the potential imbalance in subject enrollment across the two opioid exposure strata was not rigorously minimized as intended in the study protocol."

Even with the deficiencies noted for Dr. Potts' site, the Clinical Inspection Summary states, "All audited endpoint data were verifiable among source records, CRFs, and NDA data listings…The data from this study site appear reliable."

The overall assessment of the Inspection Summary states, "No significant deficiencies were observed at all CI sites. Observed GCP deficiencies were limited to minor isolated findings

unlikely to be significant to the study outcome, typically discussed with the CI or cited on Form FDA 483 (inspector discretion). Study conduct appeared adequate, including IRB and sponsor oversight of study conduct. All audited data were verifiable among source records, CRFs, and NDA data listings. The data from the three CI sites appear reliable as reported in the NDA."

The two human abuse liability studies, discussed later in the review, were both performed at Lifetree Clinical Research in Salt Lake City, Utah. The principal investigator in Study 1085 was Lynn Webster, MD. The principal investigator in Study 10032 was Shawn Searle, MD. While Lifetree was not formally inspected for the Vantrela ER application, (b) (4)

Controlled Substances Staff (CSS)

Data supporting the AD claims proposed for labeling were reviewed as part of both the Chemistry and CSS Reviews. Katherine Bonson, PhD and Silvia Calderon, PhD provided the CSS review with concurrence from Michael Klein, PhD. Venkateswara Pavuluri, PhD, RPh reviewed the Category 1 studies in the Chemistry Review with concurrence from Julia Pinto, PhD. Dr. Bonson summarized these Category 1 results in her review. The supporting statistical review of the oral and nasal Category 2/3 human abuse liability (HAL) studies was performed by Feng Zhou, MS with concurrence from Qianyu Dang, PhD and Yi Tsong, PhD.

In Vitro Studies

The in vitro studies were performed to investigate various methods of defeating the ER properties of Vantrela ER with the intent to abuse the product by various methods of administration, including intravenous, oral, and nasal. The active controls in these studies included Zohydro (original formulation), hydrocodone drug substance, and Vicoprofen tablets. Dr. Bonson's review provides a comprehensive description of these studies.

Dr. Bonson notes that the to-be-marketed formulations for the 45 mg and 90 mg tablets of Vantrela ER were used in these studies, but that the final formulations of the lower strength tablets were not used in a number of studies. Therefore, at the request of the reviewers, the Sponsor conducted a series of in vitro studies with the lower strength tablets to validate the prior study results.

The Sponsor evaluated a number of tools to comminute the tablets. The use of a coffee mill for 30 seconds and the use of a rotary abrasion tool to complete the comminution were selected as the best methods to manipulate tablets. This is the method used in the oral and intranasal HAL studies described later.

Large volume extraction in water was reasonably good and depended primarily on increased temperature and increased duration of agitation. Mechanical reduction in particle size did not

seem to alter extraction. Interestingly, the proportion extracted was somewhat greater for the 15 mg tablets than the 90 mg tablets. Vantrela ER may represent an incremental improvement over Zohydro in that longer time, higher temperatures, and more agitation are required to attain similar extractions with Vantrela ER than for Zohydro (original formulation).

Altering the pH does not seem to improve extraction with Vantrela ER.

When heated and subjected to agitation in 30 mL of either 20% or 40% alcohol, Vantrela ER retained its ER properties. Zohydro did not. However, when Vantrela ER tablets were comminuted and subjected to the same conditions, about 70-80% extraction was attained after 30 minutes. Similar extraction from Zohydro was attained within 5 minutes.

Organic solvents were also studied. When using relatively large volumes (30 mL) of organic solvents, hydrocodone can be readily extracted from both comminuted Vantrela ER tablets and manipulated Zohydro tablets.

Vantrela ER was studied for producing small volume solutions suitable for intravenous injections. Extraction from the lower strength tablets was found to be inefficient under most of the conditions tested. Under specific conditions, 90 mg tablets could produce a solution that could potentially be abused.

Oral Abuse Potential Study, Study C-1085

The Sponsor conducted a category 2/3 oral HAL study in non-dependent recreational opioid users to investigate the AD properties of Vantrela ER following oral administration. The study was a randomized, DB, triple-dummy, active- and placebo-controlled, crossover study. The primary objective of the study was to determine the abuse potential of comminuted Vantrela ER 45 mg administered orally versus intact Vantrela ER, IR hydrocodone powder 45 mg, and placebo.

A total of 100 subjects were screened with 97 entering the qualification phase. After a Naloxone Challenge Test and a Drug Discrimination Test, there were ultimately 45 subjects that received at least one treatment in the Treatment Phase of the study, with 35 completing. The study was a 4-way crossover study with the following treatment groups:

- Treatment A: crushed Vantrela ER; intact placebo; 60 mL flavored beverage
- Treatment B: hydrocodone powder; intact placebo; 60 mL flavored beverage
- Treatment C: intact Vantrela ER; crushed placebo; 60 mL flavored beverage
- Treatment D: intact placebo; crushed placebo tablet; 60 mL flavored beverage

PK parameters were determined and the following measures of drug-liking were obtained: Drug Liking Visual Analog Scale (VAS), Overall Drug Liking VAS, Take Drug Again Assessment (TDAA), and the Price Value Assessment Questionnaire (PVAQ). There were other secondary measures, including the Addiction Research Center Inventory (ARCI) and pupil diameter measurement. The primary endpoint was the Emax for the Drug Liking VAS.

The primary treatment comparison of interest was Treatment A versus Treatment B. A hierarchy was determined by the statistical analysis plan. First, the comparison between Treatments B and D was to be assessed. If significant, the comparison between Treatments B and C was to be assessed. If that was significant, the comparison of interest between Treatments B and A was to be assessed.

Results

Pharmacodynamic

The Sponsor's analysis dataset included subjects with adequate PD data to contribute to at least one of the planned comparisons, n=45. The FDA Statistical Review analysis dataset included completers, n=35. According to the Statistical Review, the results were similar based on these two populations.

All three of the comparisons in the pre-specified hierarchy were highly statistically significant for the Drug Liking VAS Emax based on the completers analysis in the Statistical Review, n=35, with higher scores for Treatment B in all three comparisons. Similarly, they were all statistically significant in the Sponsor's pre-specified analysis, n=45. In these analyses, the Emax for the Drug Liking VAS was almost identical for the intact Vantrela ER and placebo groups. Although not part of the hierarchy outlined in the prespecified analysis, a comparison of the Drug Liking VAS between Vantrela ER intact (53.9) and Vantrela ER crushed (66.9) was nominally statistically significant , $p<0.001$.

A similar ordering of the other secondary outcome measures was seen in the study as discussed in the CSS Review. The results support an AD effect of Vantrela ER to oral abuse.

Pharmacokinetic

The pharmacokinetic results are consistent with the observed pharmacodynamic results. The PK results were supportive of the Drug Liking results, with the following ordering of plasma hydrocodone levels for the different treatment groups: IR hydrocodone powder > crushed CEP-33237 > intact CEP-33237.

Table: Pharmacokinetic Results, Study C-1085

	Vantrela ER 45 mg Intact N=40	**Vantrela ER 45 mg Crushed N=41**	**Hydrocodone Powder 45 mg N=39**
Cmax (ng/ml)	29 $\pm$ 1	41 $\pm$ 2	91 $\pm$ 3
AUC (0-inf) (ng*hr/ml)	584 $\pm$ 22	586 $\pm$ 22	625 $\pm$ 22
Tmax (hours)	7.7 $\pm$ 0.2	4.0 $\pm$ 0.2	1.1 $\pm$ 0.1

Source: CSS Review, Table 6, page 21.

Conclusions from Study C-1085

The CSS Review concludes that the results of this oral HAL study suggest that Vantrela ER has AD properties when it is physically manipulated and ingested orally. It is true that drug-liking is less when crushed Vantrela ER is ingested compared to when IR hydrocodone powder is ingested. However, the increased drug-liking observed with crushed Vantrela ER compared to intact Vantrela ER suggests that the AD properties can be at least partially defeated for oral abuse.

Nasal Abuse Potential Study, Study C-10032

Additionally, the Sponsor conducted a category 2/3 nasal HAL study in non-dependent recreational opioid users to investigate the AD properties of Vantrela ER following nasal administration. The study was a randomized, DB, quadruple-dummy, active- and placebo-controlled, crossover study. The primary objective of the study was to determine the abuse potential of comminuted Vantrela ER 45 mg tablets administered intranasally versus IN Zohydro 45 mg (originally-approved formulation), IR hydrocodone powder 45 mg, and intact Vantrela ER 45 mg administered orally.

After screening, 73 subjects entered the qualification phase. After a Naloxone Challenge Test and a Drug Discrimination Test, there were 45 subjects that were randomized in the Treatment Phase of the study, with 34 completing. The study was a 5-way crossover study with the following treatment groups:

Treatment	Intranasal Treatment	Oral Treatment
A	Vantrela ER	Placebo
B	Hydrocodone powder	Placebo
C	Placebo	Vantrela ER
D	Placebo	Placebo
E	Zohydro	Placebo

Each subject received about 575 mg of intranasal material to insufflate. The Vantrela ER 45 mg tablet alone weighs 575 mg. In contrast, 45 mg of hydrocodone powder and Zohydro each weigh less. Therefore, the total amount insufflated for the different treatment arms needed to be balanced with the addition of inactive ingredients to include lactose and crushed sugar spheres to Treatments B, C, D, and E. Each total intranasal treatment was then divided into 3 separate containers with a straw inserted in each to facilitate administration.

All tablets were comminuted with a rotary blade blender. Category 1 studies identified the blender as an efficient means of grinding Vantrela ER. Note that the particle size distribution differed for the comminuted Vantrela ER tablets and the Zohydro tablets. The addition of matching placebo was intended to help blind these differences.

PK parameters were determined and the following measures of drug-liking were obtained: Drug Liking Visual Analog Scale (VAS), Overall Drug Liking VAS, Take Drug Again Assessment (TDAA), and the Price Value Assessment Questionnaire (PVAQ). There were other secondary measures, including the Addiction Research Center Inventory (ARCI) and pupil diameter measurement. The primary endpoints were both the Emax for the Drug Liking VAS and the Emax for the Overall Drug Liking VAS.

To establish study validity, Treatment B (IN hydrocodone powder) was required to beat Treatment D (placebo). The following treatment comparison was to be between Treatment A (IN Vantrela ER) and Treatment B (IN hydrocodone powder). Other planned comparisons included: Treatment A (IN Vantrela ER) versus Treatment C (oral Vantrela ER), and Treatment A (IN Vantrela ER) versus Treatment E (IN Zohydro).

Results

Pharmacodynamic

With the exception of one subject who insufflated only about a third of the IN hydrocodone powder, subjects were able to successfully insufflate the study treatments.

All of the treatment comparisons described above were found to be statistically significant for both Drug Liking and Overall Drug Liking. The results showed that the mean and median Drug Liking Emax scores and Overall Drug Liking Emax scores for subjects treated with IN hydrocodone powder and IN Zohydro were relatively high (about 79 or higher), while the means and medians for the same two endpoints for the IN Vantrela ER patients were about 73 or lower. Significantly higher scores were observed for patients treated with IN Vantrela ER compared to patients treated with oral Vantrela ER.

A similar ordering of the other secondary outcome measures was seen in the study as discussed in the CSS Review. The results support a lower abuse potential for IN Vantrela ER compared to IN hydrocodone powder and IN Zohydro.

Pharmacokinetic

The PK results were generally consistent with the Drug Liking results, with the following ordering of plasma Cmax for the different treatment groups: Zohydro > IR hydrocodone powder > crushed CEP-33237 > intact oral CEP-33237.

Table: Pharmacokinetic Results, Study C-10032

Measure	Placebo N=34	Hydrocodone Powder N=34	Zohydro 45 mg crushed N=34	Vantrela ER 45 mg crushed N=34	Vantrela ER 45 mg Oral N=34
Percent Dose Insufflated	98%	97%	98%	97%	Oral, 100%
Cmax (ng/ml)	--	71 ± 31	80 ± 29	57 ± 15	25 ± 7
AUC (0-inf) (ng*hr/ml)	--	579 ± 163	639 ± 179	572 ± 150	568 ± 172

Source: CSS Review, Table 10, page 35.

Conclusions from Study C-10032

The results support an AD effect of Vantrela ER to intranasal abuse compared to IN hydrocodone powder and IN Zohydro (originally-approved formulation). At the same time, the significantly higher scores with IN Vantrela ER compared to IN placebo and oral Vantrela ER indicates a significant abuse potential.

Overall Recommendations from the CSS Review

The CSS Review includes the detailed conclusions of Drs. Bonson and Calderon after review of the Category 1-3 data. Based on those conclusions, their review states:

a) Based on the study results from human abuse potential studies, Vantrela should be allowed a label claim that it has abuse deterrence with regard to oral and intranasal abuse of manipulated tablets.
b) Based on the study results from the large extraction studies aimed to characterize the extraction of hydrocodone in small volume of ingestible solvents, CSS recommends not accepting the statement proposed by the Sponsor under the abuse deterrent section of the label that claims that (b) (4)

For abuse by injection, based on the Category 1 studies, the CSS Review states, "Syringeability/injectability studies show that a solution for injection could be obtained under very specific conditions of extraction using the high strength 90 mg tablets, though the extraction of hydrocodone bitartrate may not be very efficient in that a small percentage of the active ingredient was extracted and abusers would have to inject volumes of 5-7 ml to feel the reinforcing effects of the opioid."

Schedule
Vantrela ER tablets will be in Schedule II of the Controlled Substances Act.

Financial Disclosures

According to Dr. Levin's review, "Teva has adequately disclosed financial arrangements with clinical investigators…The disclosed financial interests/arrangements do not affect the approvability of this application." One investigator received significant payments for consulting services, but only (b) (4) patients were enrolled at that investigator's site. This small number of patients would not have any appreciable effect on the overall study results.

REMS

Vantrela ER will be part of the ER/LA REMS.

12. Labeling

Proprietary Name

The proposed proprietary name, Vantrela ER, was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and found acceptable from both a promotional and a safety perspective (review dated February 24, 2015). The Sponsor was notified that the name was acceptable in a letter dated March 2, 2015.

Carton and Container Labeling

The DMEPA reviewer for Vantrela ER was Millie Brahmbhatt, PharmD, BCPS with concurrence from Vicky Borders-Hemphill, PharmD. The review dated March 12, 2015 evaluated the carton and container labels for Vantrela ER to assess risk for medication errors. The review identified several items to improve readability and increase prominence of important information. I agree with their proposals for the container labels. The proposals were shared with the Sponsor and the Sponsor submitted revisions. DMEPA found the revised container labels for Vantrela ER acceptable in a review dated September 30, 2015.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action
At this time, I recommend Approval for the Vantrela ER application.

There will be postmarketing study requirements as described below.

Risk Benefit Assessment

Vantrela ER has physicochemical properties that are expected to reduce, but not totally prevent, abuse of the drug. 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. The development of opioids with AD properties is a valuable component of the broader approach to reducing abuse and misuse, while still making appropriate treatments available for patients. Currently, Hysingla represents the only AD ER formulation of hydrocodone marketed in the U.S. Hysingla was approved in 2014.

The efficacy of Vantrela ER is supported by the results of Study 3103, a 12-week, DB, PC, parallel-group study comparing Vantrela ER with placebo in patients with chronic low back pain. Efficacy is further supported by the efficacy of hydrocodone for acute pain demonstrated in support of the Vicoprofen NDA. A signal of QT-prolongation was observed in the safety database, but without any related serious adverse events. Labeling will describe this potential and a thorough-QT study should be required as a PMR. The data across the Category 1, 2, and 3 AD studies supports AD labeling for the product.

Recommendation for Postmarketing Risk Management Activity

Vantrela ER will be part of the ER/LA REMS.

Recommendation for Postmarketing Study Requirements

The following three PMRs are recommended by the clinical and clinical pharmacology reviews: 1) a thorough-QT study, 2) a drug-drug interaction study investigating the effect of a strong CYP3A4 inhibitor, and 3) a hepatic impairment study investigating the PK of Vantrela ER in patients with either mild or severe hepatic impairment.

The application triggers the requirements of PREA because it is a new dosage form and a new dosing regimen. There will be a PMR for the planned PK and safety study in pediatric patients $\geq$ 7 years. PeRC has agreed with the planned deferral for that study.

Postmarketing studies of Vantrela ER will be needed to assess the effects of the AD features on the risk for abuse of Vantrela ER and the consequences of that abuse in the community.

In addition, Vantrela ER is part of the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS), which requires companies to make available to health care professionals educational programs on how to safely prescribe ER/LA opioid analgesics and to provide Medication Guides and patient counseling documents containing information on the safe use, storage, and disposal of ER/LA opioids. The postmarketing study requirements under the ER/LA REMS will apply for Vantrela ER.

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/s/

JOHN J FEENEY
01/13/2017