CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207975Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207975
Priority or Standard	Standard
Submit Date(s)	23 December 2014
Received Date(s)	23 December 2014
PDUFA Goal Date	23 October 2015
Division / Office	Division of Anesthesia, Analgesia, and Addiction Products/ODE II
Reviewer Name(s)	Robert A. Levin, MD
Review Completion Date	18 December 2015
Established Name	Hydrocodone bitartrate extended-release tablets
(Proposed) Trade Name	Vantrela
Therapeutic Class	Opioid analgesic
Applicant	TEVA
Formulation(s)	15, 30, 45, 60, and 90 mg tablets
Dosing Regimen	Vantrela ER is to be administered orally every 12 hours
Indication(s)	For the management of pain severe enough to require daily,

Intended Population(s)	around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend an Approval action for the subject of the current 505(b)(1) application, Vantrela (hydrocodone bitartrate) Extended-Release Tablets for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The recommendation for Approval is based on the Applicant demonstrating a positive benefit-risk profile in one adequate and well-controlled study and the efficacy of the reference drug, Vicoprofen, which contains hydrocodone as an active moiety.

This application was initially submitted as a 505(b)(2) but Teva changed the application to a 505(b)(1) after they obtained the right of reference to use Vicoprofen as the reference drug. Teva made this change based on concerns that marketing Vantrela would be blocked by exclusivity of the previously approved single entity hydrocodone products Hysingla and Zohydro. The submitted NDA contains sufficient data to establish the safety and efficacy of Vantrela ER and support approval of the application. Additional studies to more completely characterize the drug will be requested as post-marketing requirements (described in Section 1.4).

1.2 Risk Benefit Assessment

Risk Benefit Assessment

The risk-benefit profile of Vantrela is favorable for the proposed indication and the safety data collected in the clinical studies reveal no safety concern unique to this new formulation of hydrocodone.

Benefit

Efficacy for this 505(b)(1) application was supported by one positive adequate and well-controlled Phase 3 trial (Study 3103) and by the reference drug Vicoprofen which contains the active moiety hydrocodone. A second Phase 3 trial (Study 3079) failed to show a statistically significant treatment effect with the primary endpoint but did show efficacy with an important secondary endpoint. Study 3103 was a randomized, double-blind, placebo-controlled, 12 week randomized withdrawal trial in patients with chronic low back pain. Efficacy was demonstrated with the primary endpoint of change from baseline in worst pain intensity (WPI) at week 12. Based on the applicant's prespecified analysis, placebo had a statistically significantly greater mean WPI increase. Compared to placebo, the estimated WPI change was 0.6 units smaller for Vantrela with 95% CI (0.25, 1.00).

The FDA statistical reviewer, Dr. Bradley McEvoy, confirmed the findings of Teva for the primary efficacy endpoint using the prespecified imputation methods but noted, "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 providing greater relief of low back pain than placebo". The potential impact of missing data on WPI change at week 12 was analyzed by Dr. McEvoy using a missing data sensitivity analysis which showed a large number of scenarios in which the difference in average WPI change between treatment groups was no longer statistically significant (Table 22). The results were not impacted in scenarios where the hydrocodone subjects with missing data had slightly more favorable pain values than placebo subjects with missing data. Imputed data were obtained from an imputation model that included assigned treatment, opioid status, baseline and post-baseline WPI values. In the primary analysis subjects assigned to hydrocodone and discontinued study drug due to an adverse event were imputed as if they were assigned to placebo.

The efficacy findings from Study 3103 were reviewed by the statistical team leader, Dr. Freda Cooner, who also considered the study positive. She noted that both the primary analysis and the preferred secondary analysis that included data after discontinuation of study drug for subjects that continued in the study were statistically significant (Table 21). An additional analysis requested by the FDA with all 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 showed statistical significance (Table 21). Treatment efficacy was further supported by the ancillary responder analysis results on the primary endpoint (Figure 1) where all patients missing Week 12 values were treated as non-responders. Dr. Cooner concluded that the results of the primary analysis along with the sensitivity and ancillary analyses provide sufficient evidence on the efficacy of Vantrela. Efficacy was also supported by the important secondary endpoint of average pain intensity change from baseline at Week 12. I concur with Dr. Cooner's conclusion that there is sufficient evidence to support the efficacy of Vantrela in Study 3103.

Efficacy was also supported by the reference drug Vicoprofen which is approved for the treatment of acute pain. Vicoprofen is a fixed combination tablet that contains the opioid analgesic agent, hydrocodone bitartrate with the nonsteroidal anti-inflammatory agent, ibuprofen and is indicated for the short-term management of acute pain. The Division considers the efficacy of Vicoprofen for the treatment of acute pain as supportive evidence of the efficacy of Vantrela since hydrocodone is an active moiety in both products.

Study 3079, a study in chronic low back pain and osteoarthritis failed to demonstrate efficacy with the prespecified primary endpoint of change from baseline in average pain intensity but did show efficacy with an important secondary endpoint of change from baseline in worst pain intensity. Since results from this study were not based on the prespecified primary endpoint the results are not considered statistically significant.

Study 3079 provides additional support of efficacy but was not considered necessary for recommending an Approval action for Ventrela.

Summary of Benefit
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.

Risk
The Vantrela development program provided adequate exposure to assess safety with a total of 1176 patients exposed to at least one dose of hydrocodone ER in the four Phase 3 studies. An additional 788 subjects received at least one dose of study drug in the 19 Phase 1 studies. Overall, 363 patients were treated for at least 6 months and 197 patients were treated for at least 1 year.

There were three deaths reported during the development program. One death occurred prior to the subject receiving any study drug and the other two deaths did not appear to be related to hydrocodone. The serious adverse events and common adverse events reported in the NDA appeared to be consistent with the safety profile of opioids. The following are potential safety concerns related to this NDA submission.

Abuse
The potential for abuse exists with all opioids including Vantrela and therefore the extended-release/long-acting opioid class Risk Evaluation and Mitigation Strategies (ER/LA REMS) will be required for this product to ensure safe use in the target population and mitigate against the potential for misuse and abuse. (b) (4)

Dr. Katherine Bonson from the Controlled Substance Staff (CSS) reviewed the nonclinical and clinical abuse-related data and recommended that, 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. Also, the formulation resists extraction of hydrocodone bitartrate into small volumes that simulate intravenous use, rendering mixtures difficult to filter and pass through a needle.

Hearing loss
Since hearing loss has been associated with the use of hydrocodone/acetaminophen combination products, and the potential exposure to hydrocodone from this product is higher than the labeled doses from combination products, the FDA requested that Teva perform audiometry assessments to monitor for potential hearing loss. Dr. Ting Zhang, from the Center for Devices and Radiological Health (CDRH) concluded the data submitted from Studies 3079 and 3103 showed no significant signal of acute

decrements in hearing or vestibular function from hydrocodone use in the population studied, during the time course of the study, and under the dosage conditions studied.

Systemic exposure in patients with mild and severe hepatic impairment
Teva conducted a study comparing PK of Vantrela ER tablet in patients with moderate hepatic impairment and subjects with normal hepatic function. Results indicated increased exposure in moderate hepatic impairment without any information in mild or severe hepatic impairment. The findings in moderate hepatic impairment are adequate to form the basis for safe labeling. The label will state that patients with moderate hepatic impairment have higher plasma concentrations of hydrocodone than those with normal hepatic function (data obtained from the NDA) and Vantrela should not be used in patients with severe hepatic impairment since no data is available for this group. In patients with mild or moderate hepatic impairment, the recommendation will be to start with one half of the recommended initial dose and to monitor these patients closely for adverse events. Additional information on subjects with mild and severe hepatic impairment will be obtained with a post-marketing requirement to conduct a pharmacokinetics study (described in Section 1.4).

Drug interactions between CYP3A4 inhibitors and Vantrela ER tablets
Hydrocodone is metabolized predominantly by CYP3A4 enzyme, as described in the Vicoprofen label. Although no drug interaction studies were conducted with CYP3A4 inhibitors during the Vantrela development program, appropriate safety information required for prescribing Vantrela based on the Vicoprofen label can be included in the label. The Vantrela label will state that concomitant use of Vantrela ER with a CYP3A4 inhibitor may increase plasma concentrations of hydrocodone and prolong opioid adverse reactions. Information on the effect of CYP3A4 inhibitors on the pharmacokinetics of hydrocodone will be obtained with a post-marketing requirement to conduct an in vivo drug-drug interaction study with a strong CYP3A4 inhibitor.

Risk of QT-prolongation potential of hydrocodone
In the recent Hysingla ER NDA 206627, it was discovered that hydrocodone can prolong QT-interval. In the Vantrela NDA database there was a possible signal for mild QT prolongation. Based on this finding a warning for potential QT prolongation will be included in the label. Since there were no deaths or serious adverse events associated with QT prolongation and the degree of prolongation appeared relatively small with no clear signal based on absolute QTc changes greater than 480 msec, it is reasonable to approve Vantrela with a general warning on potential QT prolongation and require a definitive tQT study as a post-marketing requirement.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

As a long-acting opioid, Vantrela if approved, would be required to be under the class-wide risk evaluation and mitigation strategy (REMS) for extended-release/long-acting

(ER/LA) opioid class of drugs to mitigate the risks of overdose, abuse, misuse, and addiction and to maintain a favorable benefit-risk profile for this product.

1.4 Recommendations for Postmarket Requirements and Commitments

Required Pediatric Assessments

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

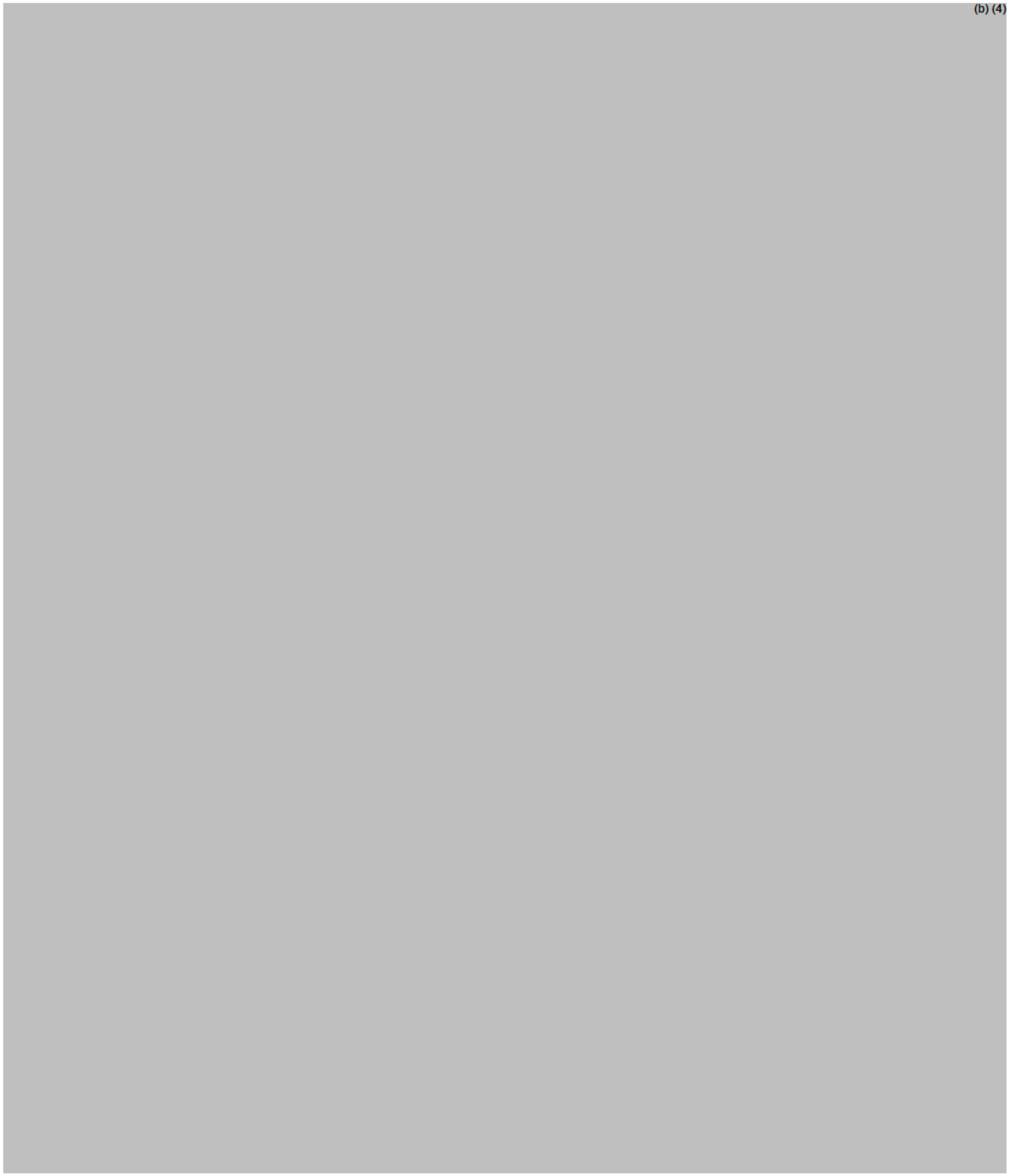
The Division in a letter dated October 9, 2014, confirmed our agreement with Teva's Agreed initial Pediatric Study Plan (iPSP) to conduct a study entitled (b) (4) The Division acknowledged Teva's request to waive studies with CEP-33237 in patients from birth to less than 7 years of age on the basis of the low prevalence of chronic pain in this age group, making studies impossible or highly impractical.

Post-marketing Requirements for Extended-release/Long-acting Opioids

The following class-wide postmarket requirement for ER/LA opioid products will be required for Vantrela:

1. (b) (4)

(b) (4)



Additional Post-marketing Requirements

(b) (4)

3. 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 designed to rule out small changes in QTc interval (i.e., upper bound of 90% confidence interval excludes 10 ms) due to Vantrela ER tablets.

Nonclinical Post-marketing Requirements

Nonclinical post-marketing requirements have not been decided and are still under discussion at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Hydrocodone is a semi-synthetic opioid approved as an analgesic and antitussive agent. Vantrela is a single-agent, extended-release tablet formulation of hydrocodone bitartrate intended for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The extended-release hydrocodone product will be available in strengths of 15, 30, 45, 60, and 90 mg tablets and is intended to be administered orally every 12 hours. Vantrela contains (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Vantrela is a single-agent, extended-release tablet of hydrocodone intended 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. Zohydro and Hysingla are currently approved single-agent, extended-release formulations of hydrocodone available to treat the same indication. Table 1 summarizes the currently available treatments for the management of chronic pain.

Table 1: Available Treatments for Chronic Pain

Product	Route of Administration	Advantages	Disadvantages
NSAIDs	**Oral**	• **Anti-inflammatory activity** • **No respiratory depression** • **No effect on gastric emptying**	• **Increased bleeding due to platlet inhibition** • **GI damage** • **Renal Impairment** • **Poor bone or wound healing** • **Not as effective for severe pain**
Acetaminophen	**Oral**	• **No respiratory depression** • **No effect on gastric emptying** • **No effect on platelet aggregation**	• **No anti-inflammatory activity** • **Possible hepatic impairment from overdose** • **Not as effective for severe pain**
Opioids	**Oral** **Transdermal** **Sublingual** **Patient Controlled Analgesia (PCA)** **Epidural or intrathecal**	• **Effective for severe pain** • **With epidural or intrathecal use the opioid dose can be reduced.**	• **Hypotension** • **Respiratoy depression** • **Nausea and vomiting** • **Delayed gastric emptying and small bowel transit time** • **With epidural/ intrathecal use:** **- Epidural hematoma or Abscess** **- Nerve injury** • **Abuse, misuse, addiction**
Local Anesthetics (Regional and local analgesia)	**Nerve and plexus blocks**	• **Effective for severe pain in a peripheral nerve of nerve root distribution**	• **Nerve injury**
	Epidural or Intrathecal Infusion	• **Effective for severe pain**	• **Epidural hematoma/ abscess** • **Nerve injury**

2.3 Availability of Proposed Active Ingredient in the United States

Hydrocodone is a semi-synthetic opioid that has been utilized as an antitussive agent and analgesic since the 1920s. When the Controlled Substances Act (CSA) was enacted in 1971, hydrocodone was placed in Schedule II, while the products containing hydrocodone in specified amounts with one or more therapeutically active non-narcotic ingredients were placed in Schedule III. Specifically, Schedule III controls applied to hydrocodone combination products containing no more than 300 milligrams per 100 milliliters or not more than 15 milligrams of hydrocodone base per dosage unit, with one or more active non-narcotic ingredients in recognized therapeutic amounts. The Drug Enforcement Administration (DEA) rescheduled hydrocodone combination products from schedule III to schedule II of the Controlled Substances Act effective October 6,

2014. Now all hydrocodone-containing products are currently classified by the DEA as Schedule II controlled substances.

Hydrocodone is available in a number of immediate-release combination products for the short-term management of acute pain conditions. More recently, hydrocodone single-entity products were approved for the indication of the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Hysingla ER (hydrocodone bitartrate) extended-release tablets (NDA 206627) was approved November 20, 2014 and Zohydro ER (hydrocodone bitartrate) extended-release capsules (NDA 202880) was approved October 25, 2013.

2.4 Important Safety Issues With Consideration to Related Drugs

Approved opioids including hydrocodone are all associated with the potentially serious safety issues of misuse, abuse, addiction and respiratory depression.

2.5 Summary of Regulatory Activity Related to Submission

2.5.1 Presubmission Regulatory Activity

Table 2 displays highlights of the regulatory activity that occurred during the clinical development program for Vantrela ER.

Table 2: Presubmission Regulatory Interactions between FDA and the Applicant

Date	Topics
September 29, 2009 IND 105587 opened	• Development program for hydrocodone bitartrate extended-release tablets initiated under this IND by Cephalon, Inc.
July 14, 2010 Type B Meeting	The Division made the following comments to the Applicant during this meeting: As a single entity hydrocodone formulation, the proposed drug product will yield exposures of hydrocodone much greater than seen with previous clinical experience. For a 505(b)(2) NDA, although the extensive clinical experience with hydrocodone combination products and opioids in general can be used to reduce the standard ICH requirements for repeat-dose toxicology, additional toxicology studies will be required for the NDA, including the following: a. 3-month toxicology study b. standard reproductive and developmental toxicology battery for hydrocodone c. standard genetic toxicology battery for hydrocodone d. carcinogenicity assessment in two species

Table 2: Presubmission Regulatory Interactions between FDA and the Applicant	
	• The Division agreed with the clinical pharmacology program of four studies to characterize the single and multiple dose pharmacokinetics of hydrocodone bitartrate; to assess dose proportionality of the tablets; to determine the food effect and to conduct an alcohol interaction study. The Division also said the Sponsor should provide hydrocodone (and its metabolites) exposure information in renal or hepatic impaired patients. • As a 505(b)(2) submission, a single adequate and well-designed clinical trial will be sufficient • Your proposed primary efficacy measure [for Study 3079] will be the change in average pain intensity over the previous 24 hours from the baseline visit (final assessment) to the final visit on Week 12 (or early termination) using the 11 point Numerical Rating Scale (NRS-11). The preferred primary endpoint would be an average of the worst pain intensity in 24 hrs because when patients recall pain, they typically recall their worst pain or recent pain. If you choose to keep change in average pain intensity as the primary endpoint, include an analysis of worst pain for the same time period as a secondary efficacy endpoint. Additionally, to adjust for variability in subjective responses, average pain may be assessed over more than a single or 24 hour duration (an average of up to 7 days). *Reviewer's Note: In response to the FDA's comments the Applicant added worst pain intensity as a secondary outcome measure and planned to assess average pain intensity over the previous 7 days for the primary endpoint.* • Barring unexpected safety findings, your proposal to collect safety data on at least 100 patients with exposure for at least 6 months and at least 50 patients with exposure for at least one year is acceptable. • A safety database of approximately 500 subjects and patients is acceptable. • Auditory function: Since progressive hearing loss has been associated with the abuse of hydrocodone/acetaminophen combination products and the potential exposure to hydrocodone from this product is higher than the labeled doses from combination products, you must monitor hearing during the proposed

Table 2: Presubmission Regulatory Interactions between FDA and the Applicant	
	Phase 3 trials. • The Pediatric Review Committee (PeRC) must review all Pediatric Assessments, Pediatric Plans, and Waiver and Deferral requests.
September 15, 2011 Type B Meeting (Pre-NDA meeting)	The Division made the following comments to the Applicant during this meeting: • We recommend that you continue to evaluate the safety of impurities and excipients based on a 3 gram/day Maximum Theoretical Human Daily Dose (MTDD) which will provide coverage for a broad range of dosage strengths. • The Format for a potential NDA submission was discussed. (Note: NDA was not submitted since Study 3079 failed to show efficacy with its primary endpoint)
March 7, 2012 Name change	• Cephalon, Inc. was acquired by Teva Pharmaceutical Industries Ltd., and the name was changed to Teva Branded Pharmaceutical Products R&D, Inc.
September 6, 2012 Type A Meeting	• The purpose of this meeting was to discuss the failure of pivotal Phase 3 study (Protocol 3079) to meet its primary endpoint on average pain intensity. • The Sponsor stated that the design of Study 3079 contained several deficiencies which reduced assay sensitivity. The Sponsor provided a new Phase 3 study synopsis (Protocol 3103). • The Division made the following comments to the Applicant during this meeting: o Based on the information provided in your briefing packet, the patient population, endpoints, study design, and treatment duration for your proposed study appear suitable for a Phase 3 clinical trial intended to support efficacy for a chronic pain indication. o For eligibility to participate in the Study 3103, patients must have been receiving a stable around-the-clock opioid pain medication equivalent to a minimum total daily dose of 40 mg of oxycodone for at least two weeks. Therefore, enrollment into this study would require patients to be opioid-tolerant and the indication for your product may need to be restricted to an opioid-experienced population. This type of restriction is generally reserved for products that require patients

Table 2: Presubmission Regulatory Interactions between FDA and the Applicant	
	to be opioid-tolerant for safety reasons. (Note: Study 3103 was modified to also enroll opioid naïve patients) o Should you be able to demonstrate efficacy for your product based on the proposed Phase 3 clinical trial (i.e., Study 3103), it may be possible to use this single clinical trial to support submission of an NDA application for a chronic pain indication through the 505(b)(2) regulatory pathway. However, all available data, including the results of your failed clinical trial (i.e., Study 3079), will need to be reviewed during the NDA review cycle, and product labeling may need to reflect the results of the failed study and limitations to the intended population based on the successful study. o Based on the information provided in your briefing packet, it is not possible to determine what contribution the inclusion of opioid-naïve and osteoarthritis patients may have had to the failed efficacy findings. It would be informative to know whether these patients used more rescue, had less pain at baseline, or whether there were other factors that differentiated these patients from patients with low back pain and who were opioid experienced that could explain the difference in response to study drug. *Teva's Response received via email 9-4-2012* *The failure to meet the primary endpoint API appears to be due to a large extent on the lack of expected worsening in the placebo group over time and not necessarily due to the etiology of the pain or the opioid status. The explanation for the lack of placebo worsening is uncertain since no one issue was identified by our subgroup analysis and was likely due to a combination of various assay sensitivity issues that has plagued other opioid analgesic studies. One factor that may have contributed to the failure of the study may be the significant percentage of patients (27%) who achieved stable pain relief at the end of the open-label titration with a dose of only 15 mg of hydrocodone ER bid. Post-hoc analyses performed on the patients who were titrated to more than 15 mg hydrocodone ER bid show that there is an important increase in effect size on both API and WPI as compared to those who were titrated to 15 mg bid only…this is true for the whole population and also when looking at the subgroups of patients based on their opioid status (naïve vs. experienced) or the origin of their pain*

Table 2: Presubmission Regulatory Interactions between FDA and the Applicant	
	(LBP vs. OA).
January 23, 2014 Type C Meeting	• The purpose of this meeting was to ensure that the development program for this product was consistent with the FDA's expectations for abuse-deterrent opioids including in vitro manipulation, particle size distribution and PK studies. • The Division agreed that the abuse liability study conducted seemed to fulfill Category 3 requirements for the oral route. • The Division noted that the Sponsor did not fulfill Category 3 requirements for the intranasal route of abuse and stressed the importance of exploring the intranasal route of abuse through an intranasal liking study.
May 26, 2014 Fast Track designation granted	• Division concluded that the Sponsor's request meets the criteria for Fast Track designation.
July 23, 2014 Type B Meeting (Pre-NDA)	The Division made the following comments to the Applicant during this meeting: • We agree with the rolling submission • Joining the post-marketing requirement (PMR) group that is already working on the extended-release/long-acting (ERLA) opioid PMRs is an acceptable approach for addressing any outstanding PMRs • Although, no integrated efficacy analysis is required for Studies 3079 and 3103, the ISE should contain a discussion of the differences in efficacy findings between the two studies. • The Division agreed with Teva's plan to submit an interim clinical study report for Study 3104 an open-label safety study and the final clinical study report with the 4-month safety update along with an updated ISS. • Include an analysis of adverse events by study-drug dose in the NDA submission.
December 23, 2015 NDA 207975 submitted	Teva Pharmaceutical submitted the final portion of their rolling NDA for Vantrela

2.5.2 Postsubmission Regulatory Activity

Type C Guidance Meeting (January 15, 2015)
The purpose of this meeting was for TEVA to obtain guidance from the Agency on the appropriate regulatory pathway for their NDA application given their uncertainty on the scope of exclusivity granted to Zohydro ER and Hysingla ER.

The Applicant stated that, on October 31, 2014, Zogenix, Inc., announced it had entered into an agreement with Purdue Pharma L.P., under which the two companies exchanged waivers of the three-year marketing exclusivity periods applicable to Zogenix's twice-daily, non-abuse deterrent product, Zohydro ER (hydrocodone bitartrate) extended-release capsules, and Purdue's once-daily product, Hysingla ER (hydrocodone bitartrate) extended-release tablets, which was approved by FDA on November 20, 2014. In light of these developments, TEVA stated that they seek to confirm the regulatory pathway for their NDA.

Specifically, TEVA stated that they request FDA's agreement that the conditions of Zohydro ER's and Hysingla ER's approvals (that is, the scope of any marketing exclusivity periods that may apply to those products) are limited by the products' formulations (including their abuse-deterrence profiles), dosage forms, dosing regimens, and other critical "conditions of approval" and that the conditions of approval for the Sponsor's abuse-deterrent product are significantly different. The Sponsor referenced 21 USC 355(c)(3)(E)(iii) and 21 CFR 314.108(b)(4)(iv) in this regard.

The Applicant stated that they have generated robust data at the Agency's request regarding the abuse-deterrent aspects of their formulation, including the superiority of their product compared to Zohydro ER in in vitro manipulation studies, as well as in a nasal human abuse liability study. The Sponsor would like clarification as to the scope of both Zohydro ER and Hysingla ER's exclusivity-protected conditions of approval to ensure that the Agency understands how Teva's product differs significantly from both. To the extent there remains any uncertainty regarding the differentiation of Teva's product from Zohydro ER and Hysingla ER for purposes of exclusivity, the Sponsor believes one possible approach to overcome this in a timely fashion would be to convert their 505(b)(2) application to a free-standing application under Section 505(b)(1).

Division's Response
- The Division was unable to comment on the scope of exclusivity periods granted to Zohydro ER and Hysingla ER at the time of the meeting.

- The Division made the following comments regarding the Applicant's question about the NDA submission package being reviewed as a 505(b)(1) application:

    If you plan to pursue a 505(b)(1) regulatory pathway, you must own or have right of reference to all the studies and information you rely upon for approval of your

application, including studies that characterize the basic pharmacology as well as the absorption, distribution, metabolism and excretion (ADME) of hydrocodone in order to support labeling of your product. Chronic toxicology studies in two species are also required. If your carcinogenicity study design included an interim sacrifice group and incorporated all endpoints found in a standard toxicology study (i.e., hematology, clinical chemistry) and established a NOAEL, the data may be used as the chronic toxicology study in the rodent.

The overall clinical pharmacology information in the NDA should contain all data supporting product labeling as indicated below, including, but not limited to:

- ADME of your product
- PK and dosing recommendation in special populations (effect of age, gender, hepatic and renal impairment, etc.)
- Drug-drug interaction potential (in vitro enzyme induction and inhibition properties of your drug)
- There is new evidence that hydrocodone will cause QT prolongation. As a result, a study to evaluate the QT prolongation potential for your product (e.g., a tQT study) must be conducted. Such a study could be conducted as a post marketing requirement (PMR) with proper justification.

We recognize that while Study 3079 did not achieve statistical significance on the protocol-specified primary outcome measure, you have presented several prespecified secondary analyses of the data that are nominally statistically significant. Therefore, whether Study 3079 can fulfill the requirement for a second study to support a finding of efficacy will be a review issue.

If reference to literature is necessary for approval of your application, your application may be deemed a 505(b)(2) application.

Post-Meeting Note (January 22, 2015)
The Applicant provided the following question (italics):

If Teva were able to secure the right of reference to the Vicoprofen NDA, thereby having the right of reference to all studies and data used in the original FDA decision to approve Vicoprofen, would the Division consider our current application supplemented with this data a stand-alone 505(b)(1) NDA?

Division Response
Based on the right of reference described, 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 finding of safety and/or effectiveness for Vicoprofen as the listed drug. The Sponsor would need to confirm that the proposed 505(b)(1) application would not rely on any other data that would make it a 505(b)(2) application.

Meeting follow-up (email dated 2-9-2015)
The Division confirmed that if Teva obtains the right of reference to the Vicoprofen NDA, the combination with Teva's current 207975 NDA application meets the regulatory standard for a 505(b)(1) application.

2.6 Other Relevant Background Information
None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity
This NDA was submitted in Electronic Common Technical Document (eCTD) format. All sections/modules were completed appropriately. There were no issues with the quality of the submission that affected my ability to complete this review.

3.2 Compliance with Good Clinical Practices
Principal efficacy Study 3103 and clinical Study 3079 were conducted in accordance with Good Clinical Practice (GCP) guidelines and in accordance with the Declaration of Helsinki.

The Office of Scientific Investigations (OSI) inspected three sites for Study 3103. The clinical investigator (CI) sites chosen for inspection, Site #10366 (Joseph S. Gimbel, MD) and Site #10388(Jeffrey A. Potts, MD) were amongst the highest enrolling centers and ranked number 1 and 2, by the FDA Site Selection Tool. Site 10390 (Francisco L. Badar III, MD) was selected for inspection due to the low number of discontinuations and high ranking by the FDA Site Selection Tool (ranked #6).

In the OSI review by Dr. John Lee dated 15 September 2015, Dr. Lee reports that at the three inspected sites combined, 94 subjects were enrolled (15% of total study enrollment), of whom case records for all subjects were reviewed, including detailed review for 36 subjects. No significant deficiencies were observed at these sites. Observed GCP deficiencies were limited to minor isolated findings unlikely to be significant to the study outcome. Dr. Lee, concluded the data from the three clinical investigator sites appear reliable as reported in the NDA.

3.3 Financial Disclosures
The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. Teva submitted Debarment Certification and FDA form 3454

certifying that the clinical investigators who supervised pivotal efficacy study 3103 in support of this application:

- Did not participate in any financial arrangement with the sponsor, whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study [as defined in 21 CFR 54.2(a)]:
- Had no proprietary interest in this product or significant equity interest in the sponsor [as defined in 21 CFR 54.2(b)]: and
- Was not the recipient of significant payments of other sorts [as defined in 21 CFR 54.2(f)] except for one investigator ((b) (6))

A copy of the completed Clinical Investigator Financial Disclosure Review form follows.

Clinical Investigator Financial Disclosure
Review Template

Application Number: 207975

Submission Date(s): December 23, 2014

Applicant: Teva

Product: Vantrela (hydrocodone bitartrate extended-release tablets)

Reviewer: Robert A. Levin, MD

Date of Review: September 4, 2015

Covered Clinical Study (Name and/or Number): C33237/3103

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 83		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No X The FDA statistician notes that this site is too small to have any appreciable effect on the primary analysis
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Teva has adequately disclosed financial arrangements with clinical investigators. One investigator ((b) (6)) received payments from Teva Pharmaceutical exceeding $25,000 for consulting. The FDA statistician noted that there were (b) (6) subjects randomized in site (b) (6) (b) (6) this site is too small to have any appreciable effect on the inferences for the primary analysis. The disclosed financial interests/arrangements do not affect the approvability of this application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A detailed discussion of the chemistry issues is contained in the review by Dr. Ciby Abraham, the chemistry reviewer.

From a chemistry, manufacturing and controls (CMC) perspective, there are no outstanding issues impacting on the decision whether to approve this product.

Drug Product

Vantrela is a single-agent, extended-release tablet formulation of hydrocodone bitartrate that contains (b) (4) The extended-release tablet will be available in five strengths containing 15, 30, 45, 60, and 90 mg of hydrocodone bitartrate and is intended to be administered orally every 12 hours. Table 3 contains a summary of the composition for hydrocodone bitartrate extended-release tablets.

Table 3: Quantitative Composition of Hydrocodone Bitartrate Extended Release Tablets

Component	Reference to Standard	Function	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	Active ingredient	15.00	30.00	45.00	60.00	90.00
(b) (4) lactose monohydrate	NF						
Ethyl cellulose (b) (4) (b) (4)	NF						
Hypromellose (b) (4)	USP						
Glyceryl behenate	NF						
Magnesium stearate (b) (4) (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

NA: Not Applicable

[a] (b) (4) hydrocodone bitartrate (b) (4)

Source: Module 2.3.P (Drug Product), Table 2, p7

4.2 Clinical Microbiology
This section is not relevant to this review.

4.3 Preclinical Pharmacology/Toxicology
The Pharmacology/Toxicology review by Dr. Elizabeth Bolan, the pharmacology reviewer, has not yet been finalized.

4.4 Clinical Pharmacology
A detailed discussion of the clinical pharmacology issues is contained in the review by Dr. Srikanth Nallani, the pharmacology reviewer.

4.4.1 Mechanism of Action

Hydrocodone is a semi-synthetic opioid agonist with relative selectivity for the mu-opioid (μ) receptor, although it can interact with other opioid receptors at higher doses. Hydrocodone acts as an agonist binding to and activating opioid receptors in the brain and the spinal cord to produce analgesia. The analgesia, as well as the euphoriant, respiratory depressant and physiologic-dependence properties are believed to be primarily mediated via μ opioid receptors.

4.4.2 Pharmacodynamics

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

Hydrocodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations. In addition to analgesia, the widely diverse effects of hydrocodone include drowsiness, changes in mood, nausea, vomiting, and alterations of the autonomic nervous system.

Gastrointestinal Effects
Hydrocodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric,

biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular Effects
Hydrocodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating and/or orthostatic hypotension.

Caution must be used in hypovolemic patients, such as those suffering acute myocardial infarction, because hydrocodone may cause or further aggravate their hypotension. Caution must also be used in patients with cor pulmonale who have received therapeutic doses of opioids.

A tQT study was not conducted during the Vantrela development program but ECGs were obtained during the clinical studies (refer to Section 7.4.4).

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

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

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

Concentration-Adverse Experience Relationships
There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression.

4.4.3 Pharmacokinetics

As compared to immediate-release hydrocodone combination products, Vantrela ER at similar daily doses results in similar overall exposure but lower maximum concentrations. Mean half-life following administration of Vantrela ER (11-12 hours) is longer than that after administration of immediate-release hydrocodone combination products due to the prolonged duration of absorption.

Steady-state concentrations of hydrocodone were confirmed by day 4 of administration of Vantrela ER every 12 hours. At steady-state, hydrocodone AUC and C_{max} are approximately 3-fold higher than after a single dose. Systemic exposure to hydrocodone following administration of Vantrela ER increases in a dose-proportional manner over the range of 15 mg through 90 mg.

Absorption
Maximum hydrocodone plasma concentrations (t_{max}) are attained gradually with mean t_{max} of approximately 8 hours following a single dose (Table below) and 5 hours at steady state.

Table 4: Mean Single-Dose Pharmacokinetics

Dose Strength (mg)	$AUC_{0\text{-}inf}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)*
15	199 (60)	12.6 (3.5)	7.0 (5.0, 9.0)
30	382 (118)	20.7 (5.5)	8.0 (5.0, 12.0)
45	592 (167)	30.3 (7.5)	8.0 (5.0, 12.1)
60	766 (194)	41.2 (10.1)	8.0 (5.0, 12.0)
90	1189 (341)	62.5 (16.2)	8.0 (5.0, 12.0)

*Median (minimum, maximum)

Food Effects
Administration of a single dose of the hydrocodone ER tablet with a high fat meal increases mean peak plasma drug concentrations (C_{max}) by approximately 34% to 45%. At steady-state, C_{max} was approximately 14% higher with a high fat meal. Food has no notable impact on the area under the plasma drug concentration versus time curve (AUC) either following a single dose or at steady-state.

Distribution
Hydrocodone is well distributed beyond the vascular system with an apparent volume of distribution of approximately 1300-1400 L following administration of Vantrela ER. Although the extent of protein binding of hydrocodone in human plasma was not determined, structural similarities to related opioid analgesics suggest that hydrocodone is not extensively protein bound. As most agents in the 5-ring morphinan group of semi-

synthetic opioids bind plasma protein to a similar degree (range 19% [hydromorphone] to 45% [oxycodone]), hydrocodone is expected to fall within this range.

Metabolism
Hydrocodone is known to undergo N-demethylation, O-demethylation, and 6-ketoreduction. N-demethylation occurs via the CYP3A4 pathway to form norhydrocodone, a metabolite which has not been demonstrated to contribute to the analgesic effects of hydrocodone in humans. The O-demethylation step occurs via the CYP2D6 pathway to form an active metabolite, hydromorphone. Following administration of Vantrela ER, hydromorphone plasma concentrations are approximately 1%-2% of those of hydrocodone. Given the involvement of CYP3A4, drugs known to inhibit or induce this enzyme could alter the metabolic profile of hydrocodone. No formal drug-drug interaction studies (other than alcohol) have been performed with Vantrela ER.

Excretion
Hydrocodone and its metabolites are eliminated primarily in the urine, with a mean apparent plasma half-life after administration of Vantrela ER of approximately 11-12 hours.

Special Populations
Elderly (>65 years)
No dedicated studies to assess the effect of age on pharmacokinetics of Vantrela ER were conducted.

Effect of Hepatic Impairment
Mean Cmax was approximately 30% higher and mean AUC0-∞ was approximately 70% higher in subjects with moderate hepatic impairment than in subjects with normal hepatic function (Table 5). Teva has not evaluated the impact of mild and severe hepatic impairment on Vantrela ER tablet PK.

The label will state that patients with moderate hepatic impairment have higher plasma concentrations of hydrocodone than those with normal hepatic function and Vantrela should not be used in patients with severe hepatic impairment. In patients with mild or moderate hepatic impairment, the recommendation will be to start with one half of the recommended initial dose and to monitor these patients closely for adverse events.

Table 5: Comparison of Primary Pharmacokinetic Parameter Values Following Administration of the 15-mg Hydrocodone ER Tablet to Subjects With Normal Hepatic Function and Subjects with Moderate Hepatic Impairment (Study-Specific Pharmacokinetic Analysis Set)

Parameter (unit)	Normal hepatic function (N=8)	Moderate hepatic impairment (N=8)	Moderate/normal ratio	90% CI
C_{max} (ng/mL)	9.96	12.73	1.277	1.077, 1.515
$AUC_{0-\infty}$ (ng·h/mL)	153	261	1.704	1.415, 2.052

Source: Clinical Pharmacology Review, p 29 (modified from Study 1089, Table 9)
$AUC_{0-\infty}$= area under the plasma drug concentration by time curve from time 0 to infinity; CI=confidence interval; Cmax=maximum observed plasma drug concentration.
Study-Specific Pharmacokinetic Analysis Set
Note: Values presented are geometric mean (SE of the mean).

Effect of Renal Impairment
Mild renal impairment had little impact on hydrocodone exposure. Although the mean increase in Cmax was approximately 50% in the moderately impaired, there was no consistent trend toward an increase in Cmax with increasing severity of renal impairment (Table 6). Overall systemic exposure to hydrocodone (as assessed by AUC0-∞) 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.

The label will state that patients with moderate or severe renal impairment or end stage renal disease have higher plasma concentrations than those with normal renal function. It is recommended that therapy be initiated with one half of the recommended initial dose for patients with moderate or severe renal impairment.

Table 6: PK Parameters for Hydrocodone Following Administration of the 45-mg Bitartrate Extended-Release Tablet to Subjects with Normal Renal Function and Subjects with Moderate Renal Impairment

Parameter	Normal renal function (N=13)	Mild renal impairment (N=8)	Moderate renal impairment (N=9)	Severe renal impairment (N=9)	ESRD (N=9)
C_{max} (ng/mL)	28.60 (5.6704)	33.42 (9.7765)	42.44 (11.5942)	36.48 (12.4442)	31.58 (6.8311)
$AUC_{0-\infty}$ (ng·h/mL)	565 (163.5)	660 (204.8)	973 (227.7)	983 (390.8)	638 (106.1)
AUC_{0-144} (ng·h/mL)	563 (161.5)	658 (204.2)	971 (229.0)	979 (390.1)	634 (108.0)
AUC_{0-t} (ng·h/mL)	561 (161.6)	656 (204.3)	969 (227.9)	975 (390.7)	632 (106.9)
AUC_{0-12} (ng·h/mL)	232 (42.1)	272 (81.7)	345 (111.1)	304 (111.1)	252 (58.4)
t_{max} (h)	8.0 (6.0, 10.0)	6.5 (5.0, 12.0)	10.0 (8.0, 12.0)	9.0 (5.0, 12.1)	8.0 (6.0, 12.0)
$t_{1/2}$ (h)	14.2 (11.08)	17.4 (12.84)	16.1 (9.83)	18.3 (9.92)	22.6 (13.71)
Percentage extrapolation (%)	0.7 (0.57)	0.6 (0.35)	0.5 (0.39)	0.8 (0.52)	1.0 (0.68)
λ_z (1/h)	0.0719 (0.03627)	0.0617 (0.03940)	0.0563 (0.02765)	0.0486 (0.02360)	0.0414 (0.02168)
V_z/F	1694 (1370.22)	1729 (1156.07)	1199 (981.06)	1411 (990.13)	2452 (1730.90)
CL/F	85.3 (22.66)	76.0 (29.38)	48.7 (12.41)	53.0 (21.77)	72.4 (13.09)

Source: Study 1088. Table 9, p60

NOTE: Median (range) is presented for t_{max}.
ESRD=end-stage renal disease; C_{max}=maximum observed plasma drug concentration; $AUC_{0-\infty}$=area under the plasma drug concentration by time curve (AUC) from time 0 to infinity; AUC_{0-144}=AUC from time 0 to144 hours after study drug administration; AUC_{0-t}=AUC from time 0 to the time of the last measurable drug concentration; AUC_{0-12}=AUC from time 0 to 12 hours after study drug administration; t_{max}=time to maximum observed plasma drug concentration; $t_{1/2}$=elimination half-life; % extrapolation=100x($AUC_{0-\infty}$-AUC_{0-t})/$AUC_{0-\infty}$; λ_z=apparent plasma terminal elimination rate constant; V_z/F=apparent volume of distribution of hydrocodone; CL/F=apparent total oral clearance of hydrocodone.

Interactions with Alcohol
Cmax and AUC of hydrocodone were bioequivalent following alcohol treatment (20% and 40%) compared to fasted treatment Vantrela ER 15 mg tablet.

Drug-Drug Interactions
No formal drug-drug interaction studies (other than alcohol) have been performed with Vantrela ER. Given the involvement of CYP3A4, drugs known to inhibit or induce this enzyme could alter the metabolic profile of hydrocodone.

The label will state that concomitant use of Vantrela ER with a CYP3A4 inhibitor or discontinuation of a CYP3A4 inducer may increase plasma concentrations of hydrocodone and prolong opioid adverse reactions.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Vantrela clinical development program includes 23 clinical studies: 19 Phase 1 studies (Table 7) and 4 Phase 3 studies (Table 8).

Table 7: Phase 1 Studies

Study	Title	Number of Subjects/ Dosage Regimen
1089 (PK)	An Open-Label, Single-Dose, Parallel-Group Study to Assess the PK of the Hydrocodone Bitartrate ER Tablet (15 mg) in Subjects With Normal Hepatic Function and Subjects With Moderate Hepatic Impairment	16 adult subjects enrolled: 8 with normal hepatic function and 8 with moderate hepatic impairment Single oral dose of 15 mg hydrocodone bitartrate ER administered
1085 (PK/PD)	A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Assess the Abuse Potential of the Hydrocodone Bitartrate Extended-Release Tablet in Healthy, Nondependent, Recreational Opioid Users	Phase B: 97 nondependent, recreational opioid users treated (92 completed) 2 treatments administered: • 60 mL of flavored beverage • HC bitartrate powder 45 mg reconstituted in 60 mL of flavored beverage Phase C: 49 treated (35 completed) 4 Treatments administered: • 1 crushed 45-mg HC ER tablet • HC powder 45 mg reconstituted in 60 mL of beverage • 1 intact 45-mg HC ER tablet • Placebo
10032 (PK/PD)	A Single-Dose, Double-Blind, Randomized Crossover Study to Assess the Intranasal Pharmacokinetics, Abuse Potential and Safety of CEP-33237 in Healthy, Nondependent, Recreational Opioid	73 healthy nondependent, recreational opioid users treated (34 completed) Treatments administered: • 45 mg CEP-33237 single-dose IN • 45 mg HC API IN

	Users	• PBO powder IN • 45 mg oral • Manipulated Zohydro (one 15 mg and one 30 mg capsule) IN
1071 (PK)	A Randomized, Open-Label, 4-Period Crossover Study to Characterize the Pharmacokinetics and Safety of HC Bitartrate From 3 Extended-Release Prototypes (45-mg Tablet) and From a Commercially Available Immediate-Release HC/APAP Product (10-mg/325-mg Tablet) in Healthy Subjects	39 healthy subjects treated (37 completed) Treatments administered: • 45-mg HC ER tablet single dose • 10 mg HC/325 mg APAP IR q6h until 4 tabs administered
1076 (PK)	A Randomized, Open-Label, 5-Period Crossover Study to Assess the Effect of Food and the Effect of Alcohol on the Pharmacokinetics of Hydrocodone Bitartrate From an Extended-Release Prototype (15-mg Tablet) in Healthy Subjects	39 healthy subjects treated (31 completed) Treatments administered: 15-mg HC ER administered fed, fasted or with 4%, 20%, or 40% alcohol (fasted)
1079 (PK/BA)	A Randomized, Open-Label, 4-Period Crossover Study to Assess the Pharmacokinetics of a Single 15-mg Dose of the Hydrocodone Bitartrate Extended-Release Tablet (Crushed and Intact) and a Single 15-mg/400-mg Dose of a Commercially Available Immediate-Release Hydrocodone/Ibuprofen Tablet (Crushed and Intact) in Healthy Subjects	36 healthy subjects treated (26 completed) 4 treatment periods: • Tablet (intact) 15-mg ER, PO • Tablet (crushed) 15-mg ER, PO • Tablet (intact) two 7.5 mg HC/200 mg ibuprofen, PO • Tablet (crushed) two 7.5 mg HC/200 mg ibuprofen, PO
1081 (PK)	An Open-Label Study to Assess the Pharmacokinetics of Single and Multiple Doses of the Hydrocodone Bitartrate Extended-Release Tablet (45 mg) in Healthy Subjects	40 healthy subjects treated (36 completed) Treatments administered: • Period 1: Single-dose of 45-mg ER • Period 2: 45-mg ER q12h from Days 1 to 6
1082 (PK)	A Randomized, Open-Label, 5-Period Crossover Study to Evaluate the Dose Proportionality of the Hydrocodone Bitartrate Extended-Release Tablet Over the Dose Range of 15 Through 90 mg in Healthy Subjects	78 healthy subjects treated (61 completed) Treatments administered: 5 single doses each separated by 14-day washout period of 15-, 30-, 25-, 60-, or 90 mg HC ER

1088 (PK)	An Open-Label, Single-Dose Study to Assess the Pharmacokinetics of the Hydrocodone Bitartrate Extended-Release Tablet (45 mg) in Subjects With Normal Renal Function and Subjects With Varying Degrees of Renal Impairment	49 subjects (14 with normal renal function, 8 with mild renal impairment, 9 with moderate renal impairment, 9 with severe renal impairment and 9 with ESRD) were treated (48 completed) Single 45 mg HC ER (CEP-33237) dose administered
1090 (PK/BA)	A Randomized, Open-Label, 4-Period Study to Assess the Effect of Food on the Pharmacokinetics of a Single 90-mg Dose of the Hydrocodone Bitartrate Extended-Release Tablet and to Assess Its Relative Bioavailability to the Commercially Available Immediate-Release Hydrocodone/Ibuprofen Tablet in Healthy Subjects	40 healthy subjects treated (35 completed) 4 treatments periods: • Tablet, 90-mg ER (fed) single-dose, PO • Tablet, 90-mg ER (fasted), single-dose, PO • Tablet, two 7.5 mg HC/200 mg ibuprofen (fasted),single-dose • Tablet, placebo (fasted), single-dose, PO
1091 (PK)	An Open-Label Study to Assess the Pharmacokinetics of a Single 90-mg Dose and Multiple 90-mg Doses (Twice Daily) of the Hydrocodone Bitartrate Extended-Release Tablet in Healthy Subjects	40 healthy subjects treated (33 completed) 2 treatment periods: • Period 1: Tablet, 90-mg ER, single-dose, PO • Period 2: Tablet, 45, 60, and 90 mg ER, increasing multiple doses, q12h, PO
1095 (BE)	A Randomized, Open-Label, 2-Period, Crossover Study to Assess the Bioequivalence of Two 30-mg Hydrocodone Bitartrate Extended-Release Tablets Versus One 60-mg Hydrocodone Bitartrate Extended-Release Tablet	36 healthy subjects treated (28 completed) 2 single-dose treatment periods: • Tablet, two 30 mg ER, PO • Tablet, one 60 mg ER, PO
1096 (BE)	A Randomized, Open-Label, 2-Period, Crossover Study to Assess the Bioequivalence of Two 45-mg Hydrocodone Bitartrate Extended-Release Tablets Versus One 90-mg Hydrocodone Bitartrate Extended-	33 healthy subjects treated (28 completed) 2 single-dose treatment periods: • Tablet, two 45 mg ER, PO • Tablet, one 90 mg ER, PO

	Release Tablet	
1097 (BE)	A Randomized, Open-Label, 2-Period, Crossover Study to Assess the Bioequivalence of 30-mg Hydrocodone Bitartrate Extended-Release Tablets Manufactured at 2 Different Facilities	53 healthy subjects treated (47 completed) 2 single-dose treatment periods: • Tablet, 30 mg ER (CIMA), PO • Tablet, 30 mg ER (Cephalon), PO
1098 (BE)	A Randomized, Open-Label, 2-Period, Crossover Study to Assess the Bioequivalence of 45-mg Hydrocodone Bitartrate Extended-Release Tablets Manufactured at 2 Different Facilities	48 healthy subjects treated (44 completed) 2 single-dose treatment periods: • Tablet, 45 mg ER (CIMA), PO • Tablet, 45 mg ER (Cephalon), PO
1099 (BE)	A Randomized, Open-Label, 2-Period, Crossover Study to Assess the Bioequivalence of Two 45-mg and One 90-mg Hydrocodone Bitartrate Extended-Release Tablet	53 healthy subjects treated (43 completed) 2 single dose treatment periods: • Tablet, two 45 mg ER, PO • Tablet, one 90 mg ER, PO
1104 (BE)	A Randomized, Open-Label, 2-Period, Crossover Study to Assess the Bioequivalence of 30-mg Hydrocodone Bitartrate Extended-Release Tablets Manufactured at 2 Different Facilities	52 healthy subjects treated (43 completed) 2 single-dose treatment periods: • Tablet, 30 mg ER (CIMA Labs), PO • Tablet, 30 mg ER (Cephalon), PO
1106 (BE)	A Randomized, Open-Label, 2-Period, Crossover Study to Assess the Bioequivalence of Two 30-mg and One 60-mg Hydrocodone Bitartrate Extended-Release Tablet	53 healthy subjects treated (46 completed) 2 single-dose treatment periods: • Tablet, two 30 mg ER, PO • Tablet, 60 mg ER, PO
10024 (PK)	A Randomized, Open-Label, 2-Period Crossover Study to Assess the Effect of Food on the Pharmacokinetics of the Hydrocodone Bitartrate Extended-Release Tablet at Steady-State	43 healthy subjects treated (30 completed) 2 treatment periods: • Fasted multiple doses x 11 days (90, 45, 60 and 90 mg) of HC ER • Fed state (same dosing as fasted)

Table 8: Phase 3 Studies		
Study	**Title**	**Number of Subjects/ Dosage Regimen**
3079 Efficacy	A 12-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Hydrocodone Bitartrate Extended-Release Tablets (CEP-33237) at 15 to 90 mg Every 12 Hours for Relief of Moderate to Severe Pain in Patients With Osteoarthritis or Low Back Pain Who Require Opioid Treatment for an Extended Period of Time	389 treated:146 hydrocodone and 148 placebo in double-blind period Tablet, 15-, 30-, 45-, 60-, or 90-mg ER q12h, PO
3103 Efficacy	A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study to Evaluate the Efficacy and Safety of Hydrocodone Bitartrate Extended-Release Tablets (CEP-33237) at 30 to 90 mg Every 12 Hours for Relief of Moderate to Severe Pain in Patients With Chronic Low Back Pain Who Require Opioid Treatment for an Extended Period of Time	625 subjects enrolled in the open-label titration period 371 randomized: 191 hydrocodone and 180 placebo Tablet, 15-(open-label period only), 30-, 45-, 60-, or 90-mg ER q12h, PO
3080 Safety	A 12-Month, Open-Label Study to Evaluate the Long-Term Safety of Hydrocodone Bitartrate Extended-Release Tablets (CEP-33237) at 15 to 90 mg Every 12 Hours in Patients Who Require Opioid Treatment for an Extended Period of Time	329 treated with hydrocodone Tablet, 15-, 30-, 45-, 60-, or 90-mg ER q12h, PO
3104 Safety	A 6-Month, Open-Label, Extension Study to Evaluate the Safety of Hydrocodone Bitartrate Extended-Release Tablets (CEP-33237) at 15 to 90 mg Every 12 Hours for Relief of Moderate to Severe Pain in Patients With Chronic Low Back Pain Who Require Opioid Treatment for an Extended Period of Time	181 treated with hydrocodone Tablet, 15-, 30-, 45-, 60-, or 90-mg ER q12h, PO

5.2 Review Strategy

Efficacy

Study 3103 was the principal efficacy study submitted by the Applicant to support the efficacy of Vantrela for the treatment of chronic pain and is reviewed in detail in Section 5.3. Study 3079 failed to demonstrate efficacy with the prespecified primary endpoint of change from baseline in average pain intensity and is briefly summarized in Section 5.3.

Safety

The ISS and Applicant's analyses present data primarily from the four Phase 3 studies. The safety findings for the Phase 1 studies were reviewed separately and not included with the Phase 3 studies due to differences in study design, dosing duration and population (i.e., single-dose or short duration dosing, healthy subjects or recreational opioid users). The safety findings are reviewed and discussed in Section 7 on Safety.

5.3 Discussion of Individual Studies/Clinical Trials

To support efficacy for this 505(b)(1) application, the Applicant submitted Study C33237/3103, hereafter referred to as Study 3103.

5.3.1 Study 3103

The following summary of the design of Study 3103 was derived from the original protocol dated January 3, 2013. There was one amendment to the protocol for this study. Important modifications to the original protocol related to Amendment 1 are shown in italics for additions and strikethrough font for deletions. Amendment 1 was enacted July 15, 2013 at which time 141 patients were enrolled.

Title: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study to Evaluate the Efficacy and Safety of Hydrocodone Bitartrate Extended-Release Tablets (CEP-33237) at 30 to 90 mg Every 12 Hours for Relief of Moderate to Severe Pain in Patients With Chronic Low Back Pain Who Require Opioid Treatment for an Extended Period of Time

Dates Conducted: The first patient enrolled March 8, 2013 and last patient completed February 25, 2014.

Objectives

The primary objective was to have been:

- To evaluate the efficacy of hydrocodone bitartrate extended-release tablets compared with placebo as assessed by the change from baseline in the weekly average of daily worst pain intensity (WPI) scores at week 12, using an 11-point numerical rating scale

The secondary objectives were to have been:

- To evaluate the efficacy of hydrocodone bitartrate extended-release tablets compared with placebo as measured by the following:
    - Change from baseline in the weekly average of daily average pain intensity (API) scores at week 12
    - Time to loss of efficacy, defined as discontinuation of study drug for lack of efficacy
    - Percentage of patients with both a 30% or greater increase in API from baseline to the final on-treatment visit during the double-blind treatment period and an API score of 5 or higher at the final on-treatment visit
    - Change from baseline to the final on-treatment visit in the Roland Morris Disability Questionnaire (RMDQ) score
- To evaluate the safety and tolerability of treatment with hydrocodone bitartrate extended-release tablets, as assessed by the following:
    - Occurrence of adverse events
    - Changes from the titration baseline visit in pure tone audiometry at visit 7 (day 0/baseline), the final on-treatment visit, and the final study visit (week 12 or early termination)
    - Subjective Opiate Withdrawal Scale (SOWS) scores, daily during the first 4 weeks of the double-blind treatment period up to the final on-treatment visit
    - Clinical Opiate Withdrawal Scale (COWS) scores at the visits at weeks 1, 2, and 4 (during the double-blind treatment period) up to the final on-treatment visit
    - Clinical laboratory (chemistry, hematology, and urinalysis) test results
    - Vital signs (blood pressure and pulse) measurements at each visit
    - 12-lead electrocardiogram (ECG) findings at the final on-treatment visit and final study visit (week 12 or early termination)
    - Physical examination findings, including body weight at the final on-treatment visit and final study visit (week 12 or early termination)
    - Concomitant medication usage throughout the study

The exploratory objectives were to have been as follows:

- Rescue medication usage during the double-blind treatment period up to the final on-treatment visit or final study visit (week 12 or early termination)
- Clinical Global Impression of Improvement (CGI-I) ratings (as assessed by the investigator) in regard to pain at the visit at week 4 and the final on-treatment visit
- Medical Outcomes Study Sleep Scale (MOS Sleep Scale) ratings at visit 7 (day 0/baseline) and the final on-treatment visit

Overall Design: Study 3103 was a Phase 3 multicenter, randomized, double-blind, placebo-controlled, randomized-withdrawal study in patients with moderate to severe chronic low back pain who required continuous opioid treatment for an extended period of time. The study consisted of a screening period of approximately 7 to 14 days (visit 1), an open-label titration period of up to 6 weeks (visit 2 [titration baseline] through visit 6), a double-blind treatment period of up to 12 weeks (visit 7 [day 0/baseline] through a

final study visit (visit 12/week 12 [or early termination]). Patients enrolled were opioid-naïve or opioid-experienced. Opioid-naïve patients were defined as those who were taking *tramadol* (Amendment 1 added tramadol) or less than 10 mg per day of oxycodone, or equivalent for the 14 days prior to screening. Opioid-experienced patients were defined as those who were 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.

During the screening period, informed consent and an opioid agreement were obtained, and eligibility to enter the open-label titration period of the study was assessed. During the open-label titration period average pain intensity (API) and worst pain intensity (WPI) scores were recorded daily in patient electronic diaries. If the patient reached a successful dose of study drug they were randomly assigned to the double-blind treatment period of the study. A successful dose was defined as an API score over the previous 24 hours of 4 or less and a WPI score of 6 or less on the NRS 11 point scale for either 4 consecutive days or 4 out of 7 consecutive days, while the same dose of study drug was maintained for up to 7 days. Only patients requiring 30 to 90 mg every 12 hours were randomly assigned to the double-blind treatment period. Pure tone audiometry was obtained before patients could be enrolled in the study, at visit 2 and about 2 weeks before or after visit 7. During the entire study short-acting nonsteroidal anti-inflammatory drugs (NSAIDs) or other adjuvant analgesics were not permitted, except for nonpain symptoms (eg, cardiovascular prophylaxis or fever). Aspirin for cardiovascular prophylaxis was allowed. During the open-label titration period rescue with hydrocodone 5mg/acetaminophen 325 mg up to two tablets per day was allowed and during the double-blind treatment period up to a total of 12 tablets per day were allowed.

Inclusion Criteria:
Patients were to have met all of the following criteria:

1. Moderate to severe chronic low back pain for at least 3 months duration before screening.
2. Able to speak English and willing to provide written informed consent and a written opioid agreement.
3. Able to self-administer the study drug and complete the electronic diary.
4. 18 through 80 years of age at the time of screening.
5. 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.
6. If the patient is receiving interventional therapies, physical therapy, *chiropractic treatment* (added Amendment 1), biofeedback therapy, acupuncture therapy, or herbal remedies, these therapies must ~~remain unchanged during the study~~

(deleted Amendment 1) *be completed 2 weeks before the beginning of the open-label titration period (titration baseline [visit 2])*(added Amendment 1).
Note: I concur with the Applicant's rationale for this revision that ongoing interventional therapies may interfere with assessment of analgesia.

7. The patient must not participate in any other study while enrolled in this study.

Exclusion Criteria:
Patients were to have been excluded if any of the following applied:

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 known or suspected hypersensitivities, allergies, or other contraindications to any ingredient in the study drug.
5. The patient has a recent history (within 5 years) or current evidence of alcohol or other substance abuse, with the exception of nicotine.
6. The patient has medical or psychiatric disease that, in the opinion of the investigator, would compromise collected data.
7. The patient has a history of suicidality.
8. The patient is expected to have surgery during the study.
9. The patient is pregnant or lactating.
10. The patient has active malignancy.
11. The patient has known human immunodeficiency virus (HIV).
12. In the judgment of the investigator, the patient has any clinically significant deviation from normal in the physical examination and/or clinical laboratory tests.
13. The patient has cardiopulmonary disease that would, in the opinion of the investigator, significantly increase the risk of treatment with opioids.
14. The patient has received a monoamine oxidase inhibitor (MAOI) within 14 days before the 1st dose of study drug.
15. 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.
16. The patient is involved in active litigation or has settled litigation or a disability claim *within the past 5 years* (added Amendment 1*)* related to chronic *back* pain. *The patient is receiving workman's compensation in relation to chronic low back pain* (added Amendment 1*).*
17. The patient has a positive urine drug screen that is not medically explainable.
18. The patient has participated in any previous study by the sponsor with hydrocodone bitartrate extended-release tablets.
19. The investigator believes that the patient is not suitable for the study for any reason.

Eligibility Criteria for the Double-blind Period

For entry into the double-blind period subjects were to have met the following criteria:

1. Stable pain relief defined as an API score over the past 24 hours of 4 or less and a WPI score of 6 or less on an 11-point NRS for either 4 consecutive days or 4 out of 7 consecutive days without unacceptable adverse events, while the patient was maintained on the same dose of study drug for up to 7 days. Worst pain intensity and API ratings were recorded daily in each patient's electronic diary.
2. Not exceed the allowed dose of rescue medication of hydrocodone 5 mg/acetaminophen 325 mg tablets, 1 to 2 tablets every 4 to 6 hours as needed, up to a total dosage of hydrocodone (10 mg)/acetaminophen (650 mg) per day.

Study Medication

Hydrocodone bitartrate extended-release tablets: Tablets were to have been self-administered every 12 hours at doses of 15, 30, 45, 60, and/or 90 mg. Opioid-naïve patients were to have started at a dose of 15 mg of hydrocodone bitartrate every 12 hours. Opioid-experienced patients were to have started on a twice-daily dose of hydrocodone bitartrate extended-release tablets that was approximately equivalent to 50% of the dosage of opioid analgesic that they were receiving at screening. Patients were to have been instructed to take hydrocodone extended-release tablets with a glass or water on an empty stomach at least 1 hour before or 2 hours after eating.

Placebo: Matching placebo tablets for each dose of hydrocodone bitartrate extended-release tablets were to have been provided.

Rescue Medication:

Open-label Titration

Rescue medication to have been allowed during the open-label titration period was as follows: hydrocodone (5 mg)/acetaminophen (325 mg) tablets, 1 to 2 tablets every 4 to 6 hours as needed, not to exceed a total of two tablets or a total dosage of hydrocodone 10mg/acetaminophen 650 mg per day. Patients were to have recorded pain intensity ratings before taking rescue medication.

Double-blind Treatment Period

Rescue medication that was to have been allowed during the double-blind treatment period was hydrocodone 5 mg/acetaminophen 325 mg tablets, 1 to 2 tablets every 4 to 6 hours as needed, not to exceed a total of 12 tablets or a total dosage of hydrocodone (60 mg)/acetaminophen (3900 mg) per day. Patients were to have recorded pain intensity ratings before taking the rescue medication. If the patient required rescue medication greater than hydrocodone (60mg)/acetaminophen (3900mg) and the dose of study drug could not be increased to the next higher dose, the patient was to have been discontinued from the study.

Permitted Medications

Aspirin for cardiovascular prophylaxis was to have been allowed if stable throughout the study. Acetaminophen and short-acting NSAIDs were permitted for the treatment of nonpain symptoms (e.g., fever). Patients were allowed to continue their prestudy bowel regimens, such as laxatives and stool softeners or were to have their regimen adjusted, if deemed necessary by the investigators.

Prohibited Medications

The following medications were to have been prohibited:

- Acetaminophen (except as allowed rescue medication), short-acting NSAIDs or other adjuvant analgesics except for the treatment of nonpain symptoms such as fever
- MAOIs within 14 days before the 1st treatment with study drug and during the study
- Opioids other than the patient's study drug

Study Procedures

A schedule of study procedures and assessments is contained in Table 9.

Table 9: Study Procedures and Assessments

	Treatment period (visit number and visit window)												
	Screening	Open-label titration period					Double-blind treatment period						
	V1	V2 (titration baseline)[a]	V3[b]	V4[b]	V5[b]	V6[b]	Day 0 V7 (baseline)[c]	W1 V8	W2 V9	W4 V10	W8 V11	Final on-treatment visit V11.5[d]	Final study visit V12 (W12 or ET)[d]
Procedures and assessments	NA	Days 7-14	3-7 days after V2	3-7 days after V3	3-7 days after V4	3-7 days after V5	4-28 days after V2	5-7 days after V7	4-7 days after V8	11-14 days after V9	25-28 days after V10	NA	21-28 days after V11
Obtain written informed consent/opioid agreement	X												
Inclusion/exclusion criteria review	X	X											
Medical history review and prior medication history[e]	X												
ECG	X											X	X
Clinical laboratory tests[f]	X											X	X
Pregnancy test[g]	X	X					X			X	X	X	X
Vital signs measurements[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine drug screen[i]	X						X			X	X	X	X
Full physical examination[j]	X											X	X
Adverse event inquiry[k]		X	X	X	X	X	X	X	X	X	X	X	X
Detailed pain assessment[l]	X												
API and WPI via NRS-11[m]	X	X	X	X	X	X	X	X	X	X	X	X	X
Schedule pure tone audiometry	X	X[n]									X		
Pure tone audiometry[o]		X					X					X	X
Concomitant medication inquiry		X	X	X	X	X	X	X	X	X	X	X	X
SOWS[p]							X	X	X			X[q]	
COWS								X	X	X[r]		X[q]	
Use of rescue medication		X	X	X	X	X	X	X	X	X	X	X	X
CGI-I (in regard to pain)[s]										X		X	X
Medical Outcomes Study Sleep Scale		X					X					X	X
RMDQ		X										X	X
Dose conversion[t]		X											
Register patients via IRT	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomize patient to treatment via IRT							X						
Analgesia usage review		X	X	X	X	X	X	X	X	X	X	X	X
Provide electronic diary and train patients[u]		X											
Download electronic diary, review data via website			X	X	X	X	X	X	X	X	X	X	X
Schedule telephone or other contacts and next visit[v]	X	X	X	X	X	X	X	X	X	X	X		
Collect and dispense study drug[w]		X	X	X	X	X	X[x]	X[x]	X	X	X	X	X

[a] Visit 2, also referred to as the titration baseline visit, took place within approximately 7 to 14 days after V1. All procedures and assessments were performed before dispensing of study drug.
[b] If a successful dose was confirmed during V3, V4, V5, or V6, the patient may proceed to V7. Patients were instructed to take study drug with a glass of water on an empty stomach at least 1 h before or 2 h after eating.
[c] V7 (day 0), also referred to as the baseline visit, occurred at the end of the open-label titration period and the beginning of the double-blind treatment period.
[d] Patients who discontinued study drug continued to have procedures and assessments performed according to the regular study visits specified in the protocol. Patients who discontinued study drug returned for the final on-treatment visit (also referred to as V11.5), at which study drug and all study-issued rescue medication were returned. If the patient did not discontinue study drug, study drug administration continued until the final study visit (W12). Patients who withdrew from the study had procedures and assessments performed at their final (ET) study visit.
[e] Medical history review included alcohol and caffeine usage. Prior medications included all medications taken within 14 days before the date of consent.
[f] Clinical laboratory tests included serum chemistry, hematology, and urinalysis.
[g] Urine pregnancy tests were performed on women of childbearing potential at screening, V2 (titration baseline), V7 (day 0/baseline), W4 and W8 (during double-blind treatment period), the final on treatment visit, and the final study visit (W12 [or ET]).
[h] Vital signs included seated or supine blood pressure (systolic and diastolic) and pulse.
[i] In addition to those visits specified, the investigators may have ordered, at their discretion, a urine drug screen (UDS) at any time during the patient's participation in the study.
[j] The full physical examination included weight and height (height at screening only).
[k] A blood sample for pharmacokinetic analysis was collected for a serious adverse event or an adverse event leading to study drug discontinuation; at the investigator's discretion, a UDS could be performed. If study center personnel were unable to obtain a blood sample in a timely fashion, this was discussed with the medical monitor to determine whether the sample still needed to be obtained.
[l] The detailed pain assessment included the suspected type of pain, duration of pain, API, WPI, and pain medications taken.
[m] An NRS 11 for API and WPI was recorded in electronic diaries daily throughout the study (starting in the evening of V2). At V1, they were assessed by the clinician during the visit and recorded in the CRF.
[n] At the titration baseline visit (V2), study center personnel should have scheduled the patient's pure tone audiometry appointment for V7. This appointment should be scheduled after V2 and about 2 weeks before or after V7.
[o] Pure tone audiometry was performed by a qualified audiologist within 2 weeks of the start of open-label titration (before the patient was enrolled in the study at V2), about 2 weeks before or after the start (V7 [day 0/baseline]) of double-blind study treatment, within 2 weeks of the final on treatment visit, and within 2 weeks of the final study visit (W12 [or ET]) and was not done at the study center.
[p] Patients recorded SOWS data in their electronic diaries daily, beginning with the evening report in the electronic diary on V7 (day 0/baseline), for the first 4 weeks of the double-blind treatment period up to the final on treatment visit (see footnote "q").
[q] If the patient discontinued study drug before completion of W4 of the double-blind treatment period, the SOWS and COWS were done at the patient's final on treatment visit; if the patient completed W4 of the double-blind treatment period but discontinued study drug after that time, the SOWS and COWS were not done at the final on treatment visit.
[r] If the patient discontinued study drug, this assessment for COWS was done at the final on-treatment visit.
[s] The CGI I ratings were assessed by the investigator. The comparison was from the baseline visit (day 0/V7).
[t] Opioid-naïve patients started at a 15-mg dose of hydrocodone extended-release tablets every 12 h. Opioid-experienced patients were initiated on a twice daily (every 12 h) dose of HER that was approximately equivalent to 50% of the dose of opioid analgesic that they were receiving at screening. Investigators switched patients from previous opioid therapy to HER on the basis of predefined ratios and/or their clinical experiences.
[u] The patient was instructed regarding how and when to perform assessments and to record the results in the electronic patient diary.
[v] Telephone or other contacts were scheduled throughout the study to ensure that study procedures were being followed (ie, dose administration and completion of patient diaries). Study center personnel were to have frequent contacts with patients (minimum of weekly) during the open-label titration period. During the double-blind treatment period, telephone or other contacts were scheduled daily during the first 2 weeks of study drug treatment and then weekly thereafter; in both the open-label titration and double-blind treatment periods, telephone calls or other contacts could be scheduled more frequently as needed.
[w] Partially used and unused bottles of study drug and any study drug supplies were collected. Prescriptions for hydrocodone (5 mg)/acetaminophen (325 mg) tablets were to be provided as needed according to guidelines for rescue medication, as specified in the protocol. Study drug was not dispensed at the final on treatment visit or the final study visit (W12 [or ET]).
[x] A stepwise, double-blind tapering schedule was implemented during the first 2 weeks of the double-blind treatment period to reduce the risk of withdrawal effects in patients randomly assigned to placebo. Starting from visit 9 (the beginning of week 3) and for the remainder of the double-blind treatment period until the final on treatment visit or final study visit (W12 [or ET]), patients received the dose of HER to which they were randomly assigned or matching placebo. The following rescue medication could be taken during the entire double-blind treatment period: hydrocodone (5 mg)/acetaminophen (325 mg) tablets, 1 to 2 tablets every 4 to 6 h (as needed), not to exceed a total of 12 tablets or a total dose of hydrocodone (60 mg)/acetaminophen (3900 mg) per day.
Note: Patients could be permitted to continue participation in the study with visits that were out of the specified windows; however, the medical monitor had to be contacted to grant permission in these cases.
V=visit; W=week; ET=early termination; ECG=electrocardiogram; API=average pain intensity; WPI=worst pain intensity; NRS-11=11-point numerical rating scale; SOWS=Subjective Opiate Withdrawal Scale; COWS=Clinical Opiate Withdrawal Scale; CGI-I=Clinical Global Impression of Improvement; RMDQ=Roland Morris Disability Questionnaire; IRT=interactive response technology; h=hour(s); CRF=case report form; HER=hydrocodone bitartrate extended-release tablet(s); PK=pharmacokinetic; NA=not applicable.

Source: Study 3103 Clinical Study Report. Table 1, p. 31-33

Screening Period

During the screening period (Visit 1), informed consent and an opioid agreement were to have been obtained. Subjects were to have been screened for eligibility to enter the open-label titration period by medical history, physical exam, clinical laboratory tests, 12-lead ECG, pregnancy test, urine drug screen, vital signs measurements, pain assessment, and API and WPI scores via 11-point NRS. In addition, pure tone audiometry was to have been obtained within 2 weeks of starting the open-label titration period. If eligible to enter the open-label titration period of the study, patients were to have continued in the study to visit 2 (titration baseline).

Open-Label Titration Period (Visit 2):

The objective of the open-label titration period was to identify a dose of hydrocodone bitartrate tablets that produced stable pain relief without unacceptable adverse events.

The following procedures were to have been performed at visit 2: review of inclusion/exclusion criteria, urine pregnancy test, vital sign measurements, review of pure tone audiometry results prior to start of open-label titration period, and determine dose conversion.

The starting dose of hydrocodone bitartrate extended-release tablets for opioid-naïve patients was to have been a 15-mg dose every 12 hours. Opioid-experienced patients were to have started on a twice-daily dose of hydrocodone bitartrate extended-release tablets that was approximately equivalent to 50% of the dosage of opioid analgesic that they were receiving at screening. The dose of hydrocodone extended-release tablets to be administered was to have been determined on the basis of predefined equivalencies (Table 10). Investigators were to have been permitted to use their clinical experience to adjust the dose. Patients were to have been instructed to take hydrocodone extended-release tablets with a glass or water on an empty stomach at least 1 hour before or 2 hours after eating.

Table 10: Opioid Dose-Equivalents to Determine Starting Dose for Opioid-Experienced Patients

Medication	Dose-equivalent for hydrocodone extended-release 30 mg/day (mg/day)
Codeine	200
Morphine	30
Hydromorphone	7.5
Oxycodone	20
Oxymorphone	10
Fentanyl transdermal	0.2
Meperidine	300
Methadone	10

Notes: Opioid-experienced patients started with a dose of hydrocodone extended-release tablets that was equivalent to approximately 50% of the dose of opioid analgesic that they were receiving at screening. Patients taking tramadol were considered opioid-naïve.

Source: Study 3103 Clinical Study Report. Table 2, p.37

If the starting dose of hydrocodone extended-release tablets did not provide adequate pain relief, the dose of study drug was to have been titrated up in 15-mg twice-daily increments (i.e., 15 to 30 mg, 30 to 45 mg, and 45 to 60 mg) or a 30-mg twice-daily increment when increasing (60 to 90 mg) every 3 to 7 days until a successful dose was reached. Patients were to return to the study center before each dose adjustment. To enter the double-blind treatment period patients were to have been on a dose of at least 30 mg every 12 hours. Rescue medication was to have been permitted with hydrocodone 5 mg/acetaminophen 325 mg tablets, 1 to 2 tablets every 4 to 6 hours not to exceed a dose of two tablets per day.

Eligibility for participation in the Double-Blind Treatment Period
A patient was supposed to be eligible for entry into the double-blind treatment period if they reached stable pain relief without unacceptable adverse events or exceeding the allowed dose of rescue medication. Stable pain relief was defined as an API score over the past 24 hours of 4 or less and a WPI score of 6 or less for either 4 consecutive days or 4 out of 7 consecutive days without unacceptable adverse events, while the patient was maintained on the same dose of study drug for up to 7 days. The maximum allowed dose of rescue medication was two tablets per day of hydrocodone 5 mg/acetaminophen 325 mg.

12-Week Double-Blind Treatment Period
Baseline (Visit 7; Day 0)
On the day of visit 7, patients were to have taken one scheduled open-label titration dose of study drug in the morning, which was to have been the last dose of study drug in the open-label titration period, before returning to the study center. If eligible to continue, the patient was to have been randomly assigned to study drug treatment in the double-blind treatment period with either hydrocodone bitartrate extended-release tablets or matching placebo, regardless of the API and WPI scores between the time the patient was offered participation in this treatment period and the time of actual randomization (4 days maximum). Starting this same day in the evening, patients were to have started treatment with the double-blind study drug.

2-Week, Double-Blind Tapering Period
A double-blind tapering schedule was to have been implemented during the first two weeks of the 12-week, double-blind, placebo-controlled treatment period to reduce the risk of withdrawal effects in patients randomly assigned to placebo (Table 11). Hydrocodone 5mg/acetaminophen 325 mg tablets, 1 to 2 tablets every 4 to 6 hours, as needed (up to 12 tablets per day) were to be allowed for rescue. Pain intensity ratings were to have been recorded prior to taking rescue medication. If a patient required rescue medication above this amount and the dose of study drug could not be increased to the next higher dose, the patient was to have had study drug discontinued.

Table 11: Tapering Schedule for Study Drug During Double-Blind Treatment Period

	Successful dose (number of tablets)[a]							
	90 mg every 12 hours		60 mg every 12 hours		45 mg every 12 hours		30 mg every 12 hours	
Study visit	PCB	HER	PCB	HER	PCB	HER	PCB	HER
Day 0/ Visit 7 (Baseline)	45-mg HER (1) 45-mg PCB (1)	45-mg HER (2)	30-mg PCB (1) 30-mg HER (1)	30-mg HER (2)	45-mg PCB (1) 30-mg HER (1)	45-mg HER (1) 30-mg PCB (1)	30-mg PCB (1) 15-mg HER (1)	30-mg HER (1) 15-mg PCB (1)
Week 1/ Visit 8	45-mg PCB (2) 15-mg HER (1)	45-mg HER (2) 15-mg PCB (1)	30-mg PCB (2) 15-mg HER (1)	30-mg HER (2) 15-mg PCB (1)	45-mg PCB (1) 15-mg HER (1)	45-mg HER (1) 15-mg PCB (1)	30-mg PCB (1) 15-mg HER (1)	30-mg HER (1) 15-mg PCB (1)

[a] The numbers in parentheses represent the number of bottles to be dispensed. Patients should take 1 tablet from each bottle every 12 hours.
NOTE: During the double-blind treatment period, all patients may take rescue medication, as follows: hydrocodone (5 mg)/acetaminophen (325 mg) tablets, 1 to 2 tablets every 4 to 6 hours (as needed), for up to a total dosage of hydrocodone (60 mg)/acetaminophen (3900 mg) per day.
HER=hydrocodone bitartrate extended-release tablet(s); PCB=matching placebo tablet(s).

Source: Protocol 3103. Table 4, p68

Double-Blind Treatment Period After Tapering

Starting at visit 9 (beginning of week 3) and for the remainder of the double-blind treatment period patients were to have received the dose of hydrocodone bitartrate extended-release tablets at the successful dose identified during the open-label titration period or matching placebo. Patients were to have returned to the study center for visits at weeks 1, 2, 4, 8, and 12 or early termination. Telephone contacts were to have been scheduled weekly starting from week 3 during the double-blind treatment period.

Dose Adjustment

Amendment 1 removed the allowance for a dose adjustment.

~~A single up adjustment of study drug was to have been permitted to the next highest dose as long as the adjusted dose remained at or below 90 mg every 12 hours.~~
(Amendment 1 removed allowance for 1 dose increase)

~~In the case of any safety concern, one down adjustment to the next lower dose was to have been allowed as long as the adjusted dose remained between 30 and 90 mg every 12 hours. If a patient had an up adjustment, the patient was not to be allowed to have a down adjustment of study drug. If the patient had one up adjustment of study drug and then required a down adjustment, the patient was to have had study drug discontinued.~~
(Amendment 1 removed allowance for one dose decrease)

Rescue Medication

Patients were to have been permitted to receive the same dosage of rescue medication as allowed during the first two weeks of the double-blind treatment period, as follows: hydrocodone 5 mg/acetaminophen 325 mg tablets, 1 to 2 tablets every 4 to 6 hours as needed, not to exceed a total of 12 tablets per day.

Efficacy Assessments/Endpoints

The following efficacy assessments were to have been performed:

Primary Efficacy Assessment/Endpoint

The primary efficacy variable was to have been 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 WPI score was to have been calculated by averaging the available daily WPI scores for the last 7 days before randomization.

Secondary Efficacy Assessments/Endpoints

The following efficacy assessments/endpoints were to have been measured:

- Change from baseline in the weekly average of daily API scores at week 12, based on an 11-point NRS
- Time to loss of efficacy, defined as discontinuation of study drug for lack of efficacy or the start of excessive rescue medication use. Excessive rescue medication was defined as 10 or more days of rescue medication usage in any 14 consecutive days at a total of 15 mg (hydrocodone-equivalent) or higher each day during the post 2-week tapering period of the double-blind treatment period.
- Percentage of patients with both a 30% or greater increase in API from baseline to the final on-treatment visit and an API score of 5 or higher at week 12.
- Change from baseline to the final on-treatment visit in the Roland Morris Disability Questionnaire (RMDQ) score.

Exploratory Efficacy Assessments

The following exploratory efficacy endpoints were to have been measured:

- Rescue medication usage during the double-blind treatment period up to the final on-treatment visit or week 12.
- Clinical Global Impression of Improvement (CGI-I) ratings as assessed by the investigator in regard to pain at the visit at week 4 and the final on-treatment visit.
- Medical Outcomes Study (MOS) Sleep Scale ratings at visit 7 (day 0/baseline) and the final on-treatment visit.

Safety Assessments

Safety was to have been assessed by the following: adverse events, clinical laboratory test results, vital signs, 12-lead ECG, pure tone audiometry findings, SOWS and COWS scores, physical examination, and concomitant medication usage.

Clinical Laboratory Tests

Clinical laboratory test results outside of the reference range were to have been interpreted using the following categories:

- Abnormal but not a clinically significant worsening
- Abnormal and a clinically significant worsening

A laboratory test result that had significantly worsened (according to medical judgment) compared with the baseline result was to have been recorded as an adverse event.

Clinical laboratory tests to assess safety of the study drug were to have been performed at screening, final on-treatment visit a or early termination. The specific laboratory tests performed to assess safety are listed below.

Serum Chemistry*:* sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, uric acid, alanine aminotransferase (ALT) aspartate aminotransferase (AST), lactic dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, creatine phosphokinase, total bilirubin

Hematology: Hemoglobin, hematocrit, red blood cell (RBC) count, platelet count, white blood cell (WBC) count with differential if clinically indicated

Urinalysis: appearance, bilirubin, color, protein, glucose, ketones, leukocytes, blood (hemoglobin), pH, nitrite, microscopic (if leukocytes, nitrite, blood, or protein are positive)

Vital Signs
Vital signs were to have been obtained at screening (visit 1); titration baseline (visit 2); visits 3 through 6 during the open-label titration period; baseline (day 0/visit 7); weeks 1, 2, 4, and 8 (visits 8, 9, 10, and 11) during the double-blind treatment period, and final study visit (visit 12 or early termination). Vital signs included pulse and seated *or supine* (added Amendment 1) blood pressure.

Electrocardiography
A 12-lead ECG was to have been obtained at screening (visit 1) and final study visit or early termination. Any ECG finding that was judged by the investigator as a clinically significant change (worsening) compared with a baseline value was to have been considered an adverse event.

Pure Tone Audiometry
Pure tone audiometry was to have been performed within 2 weeks of the start of open-label titration (visit 2), within 2 weeks before or after the start of double-blind study treatment (day 0/visit 7 [baseline]) and within 2 weeks of the final study visit (visit 12) or early termination. The testing was to have been performed by a qualified audiologist.

Subjective Opiate Withdrawal Scale
Subjective Opiate Withdrawal Scale (SOWS) data was to have been recorded by patients in their electronic diaries daily for the first 4 weeks of the double-blind treatment period up to the final on-treatment visit. If the patient discontinued study drug before completion of week 4 of the double-blind treatment period, the SOWS was to have been done at the patient's final on-treatment visit; if the patient completed week 4 of the

double-blind treatment period but discontinued study drug after that time, the SOWS did not have to be done at the final on-treatment visit. The SOWS scale contains 16 symptoms, the intensity of which was to have been rated by the patient on a scale of 0 (not at all) to 4 (extremely).

Clinical Opiate Withdrawal Scale

The Clinical Opiate Withdrawal Scale (COWS) was to have been performed for the first 4 weeks of the double-blind treatment period up to the final on-treatment visit. If the patient discontinued study drug before completion of week 4 of the double-blind treatment period, the COWS was to have been completed at the patient's final on-treatment visit; if the patient completed week 4 of the double-blind treatment period but discontinued study drug after that time, the COWS did not have to be done at the final on-treatment visit. The COWS is a clinician-rated scale used to measure a patient's signs and symptoms of withdrawal from opiates with the following scale of severity: 5 to 12=mild; 13 to 24=moderate; 25 to 36=moderately severe; and more than 36=severe withdrawal.

Urine Pregnancy Test (HCG) was to have been obtained at screening (Visit 1), titration baseline (Visit 2), start of the double-blind treatment period (Visit 7), weeks 4 and 8, and final study visit.

Urine Drug Screen (UDS) was to have been performed at screening (visit 1), at baseline (day 0/visit 7), weeks 4 and 8 (visits 10 and 11), final study visit or early termination. Patients were to have agreed to unannounced UDSs as part of the opioid agreement. The UDS includes measuring for the presence of prohibited drugs including cannabinoids, alcohol, cocaine, amphetamines, barbiturates, benzodiazepine, and opiates.

Analysis Sets/Populations

Enrolled Patients

The set of enrolled patients included all patients who were enrolled in the open-label titration period, regardless of whether or not a patient took any study drug.

Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) analysis set was defined as all randomized patients. This analysis set included all patients in the treatment group they were randomly assigned to, regardless of which treatment they actually received.

Safety Analysis Set

The safety analysis set included all enrolled patients who received at least one dose of study drug. In this analysis set, patients were included in the treatment group for the study drug treatment they actually received, regardless of which study drug they were randomly assigned to.

Full Analysis Set
The full analysis set included all patients in the ITT population who received at least one dose of study drug and had at least one postbaseline efficacy observation.

Statistical Analysis
The primary efficacy endpoint was the change from baseline in weekly average of daily WPI scores at week 12, based on an 11-point NRS obtained from an electronic diary. The WPI over the past 24 hours was to have been collected daily by electronic diary. The weekly WPI scores from the previous 7 days were to be calculated for each study visit. The baseline WPI score was calculated by averaging the available daily WPI scores for the last 7 days before randomization (when the successful dose of hydrocodone bitartrate extended-release tablets was confirmed). The primary efficacy analysis was with the ITT population. For the primary efficacy analysis, the Applicant analyzed change in WPI from baseline to week 12 using 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 on-treatment data using multiple imputation. Subjects assigned to hydrocodone and discontinued study drug due to an adverse event were imputed as if they were assigned to placebo.

Protocol Amendments:
Original Protocol, January 3, 2013

Amendment #1, July 15, 2013
Amendment 1 was issued after 141 patients were enrolled into the study. Protocol Amendment 1 is not considered likely to affect the interpretation of the efficacy findings. The following were major changes made in Amendment 1 and the rationale as reported by the Applicant:

- The allowance for a dose adjustment during the double-blind treatment period was removed in order to facilitate data analysis.
- Patients were no longer permitted to receive interventional therapies, physical therapy, chiropractic treatment, biofeedback therapy, acupuncture therapy, or herbal remedies during study, and all such therapies had to be completed at least 2 weeks before the beginning of the open-label titration period. In addition, chiropractic treatment was added to the list of forbidden therapies.
- Patients who previously settled litigation or a disability claim were no longer excluded if the activity occurred more than 5 years previously. In addition, the claim had to be for chronic back pain, not just chronic pain. Patients receiving workman's compensation in relation to chronic low back pain were excluded from the study.
- The planned enrollment and target number of evaluable patients was increased by less than 10%, as allowed by Teva standard operating procedure, due to a

potential unintentional unblinding of treatment assignments in the current study relating to the titration scheme used in Study 3104. When the issue was discovered, 26 patients who had completed Study 3103 had enrolled in Study 3104. Enrollment in Study 3104 was temporarily suspended on 17 September 2013 so that the titration scheme could be revised and the blind would be maintained. Therefore, the planned enrollment of 570 patients and target number of 340 evaluable patients were increased to 596 patients and 366 evaluable patients, respectively. A sensitivity analysis was done of the primary efficacy variable that excludes the first 26 patients enrolled in Study 3104.

Changes in the Planned Analyses

- The definition for time to loss of efficacy was revised to include addition of the start of excessive rescue medication after consideration that use of excessive rescue medication could be a factor in loss of efficacy. A definition for excessive rescue medication use was implemented for the analysis of data. Excessive rescue medication use was defined as 10 or more days of rescue medication use in any 14 consecutive days at a total of 15 mg (hydrocodone-equivalent) or higher each day during the post 2-week tapering period of the double-blind treatment period.

Enrollment/Randomization
Of the total 845 patients screened for enrollment in this study, 625 patients were enrolled in the open-label titration period and 371 (60%) of these patients achieved a successful dose and were randomly assigned to receive hydrocodone extended-release tablets (191 patients) or placebo (180 patients) during the double-blind treatment period.

Subject Disposition
Of the 845 patients screened, 220 patients were not enrolled for the following reasons: 147 were excluded on the basis of inclusion/exclusion criteria, 33 patients withdrew consent, 8 patients were lost to follow-up before the baseline visit, 1 patient had adverse events (10432008, motor vehicle accident and broken left tibia), 1 patient died (10439001, unknown cause), and 30 patients were not enrolled for reasons that were not otherwise specified.

A total of 41% (254/625) of subjects enrolled in the open-label titration phase discontinued. Two of the patients that discontinued withdrew consent before receiving study drug. The reasons for discontinuation from the open-label titration period are summarized in Table 12. The primary reasons for early discontinuation from the open-label titration period were not otherwise specified 12%, adverse event 11%, lack of efficacy 5%, consent withdrawn 5%, and protocol violation 3%. By opioid status discontinuation of study drug due to adverse events were slightly higher for opioid-naïve patients 12% versus opioid-experienced patients 9% as would be expected.

Table 12: Reasons for Discontinuation from Open-label Titration Phase

Reason for Discontinuation	**Number (%) of Patients**		
	Opioid-naïve (N=370)	**Opioid-experienced (N=255)**	**Total (N=625)**
Adverse event	46 (12)	22 (9)	68 (11)
Lack of efficacy	15 (4)	16 (6)	31 (5)
Consent withdrawn	19 (5)	12 (5)	31 (5)
Protocol violation	9 (2)	9 (4)	18 (3)
Pregnancy	1 (<1)	1 (<1)	2 (<1)
Lost to follow-up	3 (<1)	2 (<1)	5 (<1)
Noncompliance	11 (3)	10 (4)	21 (3)
Other	49 (13)	27 (11)	76 (12)

Source: Reviewer-generated based on Table 8 from CSR

A total of 59% (371/625) of subjects enrolled in the open-label titration period were randomized to either hydrocodone (191 subjects) or placebo (180 subjects) in the double-blind treatment period. Table 13 shows the disposition of the 371 subjects randomized to treatment: 277 subjects (75%) completed study drug treatment: 147 subjects (77%) in the hydrocodone group and 130 subjects (72%) in the placebo group. During the double-blind treatment period 25% (93/371) of subjects discontinued study drug treatment. Also one patient in the placebo group withdrew consent before receiving double-blind study drug. Within the hydrocodone group, 23% (44/191) of subjects discontinued study drug early for the following reasons: adverse event 8% (15/191) of subjects, lack of efficacy 3% (5/191) of subjects, consent withdrawn 5% (9/191) of subjects and protocol violation 4% (7/191) of subjects. Within the placebo group, 28% (50/180) of subjects (including one subject who discontinued before receiving study drug) discontinued study drug early for the following reasons: adverse event 5% (9/180) of subjects, lack of efficacy 9%(17/180) of subjects, consent withdrawn 4% (8/180) of subjects and protocol violation 5% (9/180) of subjects. As expected there were slightly more discontinuations due to adverse events in the hydrocodone group and more discontinuations due to lack of efficacy in the placebo group. Table 13 also shows subjects who discontinued study drug but remained in the study.

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

Protocol Violations

A total of 34% (212/625) of enrolled subjects had a protocol violation. The incidence was similar in opioid-naïve and opioid-experienced patients. During the double-blind treatment period 130 (35%) subjects had a protocol violation with 62 (32%) subjects in the hydrocodone treatment group and 68 (38%) in the placebo treatment group (Table 14). The most frequent protocol violations were not compliant with GCP guidelines, not compliant with study drug administration, and took an excluded concomitant medication. Among patients who were not compliant with GCP guidelines, the most frequent violations were related to failure to return study drug bottles or rescue medication bottles at study visits and failure to complete all protocol-specified study procedures at each visit.

Table 14: Protocol Violations for Enrolled Patients by Opioid Status and by Treatment Group During the Double-blindTreatment Period

	Number (%) of patients[a]					
	Enrolled patients			ITT Population		
Violation classification	Opioid-naïve (N=370)	Opioid-experienced (N=255)	Total (N=625)	Placebo (N=180)	Hydrocodone (N=191)	Total (N=371)
Patients with a protocol violation	**120 (32)**	**92 (36)**	**212 (34)**	**68 (38)**	**62 (32)**	**130 (35)**
Inclusion criteria	3 (<1)	0	3 (<1)	0	1 (<1)	1 (<1)
Exclusion criteria	1 (<1)	1 (<1)	2 (<1)	0	0	0
Primary endpoint criteria	7 (2)	4 (2)	11 (2)	4 (2)	6 (3)	10 (3)
GCP guidelines	55 (15)	51 (20)	106 (17)	28 (16)	33 (17)	61 (16)
Noncompliance with study drug	45 (12)	31 (12)	76 (12)	28 (16)	24 (13)	52 (14)
Excluded concomitant medication/treatment	27 (7)	23 (9)	50 (8)	20 (11)	10 (5)	30 (8)

Source:CSR. Table 18, p93

Discontinuations due to protocol violations during the double-blind treatment occurred in 7 (4%) patients receiving hydrocodone and 9 (5%) patients receiving placebo (Table 15). The most frequent protocol violations that led to discontinuation of study treatment during the double-blind period were noncompliance with GCP guidelines for the hydrocodone treatment group (2%) and excluded concomitant medication/treatment for the placebo treatment group (4%).

Table 15: Protocol Violations Leading to Discontinuation for Enrolled Patients and by Treatment Group During the Double-blind Treatment Period

	Number (%) of patients[a]			
	Enrolled patients		ITT population	
Violation classification	Opioid-naïve (N=368)	Opioid-experienced (N=255)	Placebo (N=180)	Hydrocodone (N=191)
Patients with a protocol violation leading to discontinuation of study drug treatment	**16 (4)**	**18 (7)**	**9 (5)**	**7 (4)**
Inclusion criteria	1 (1)	0	0	0
Primary endpoint criteria	3 (<1)	1 (<1)	1 (<1)	2 (1)
GCP guidelines	1 (<1)	6 (2)	1 (<1)	3 (2)
Noncompliance to study drug	8 (2)	5 (2)	1 (<1)	1 (<1)
Excluded concomitant medication/treatment	4 (1)	10 (4)	7 (4)	2 (1)

Source:CSR. Table 19, p94

Demographics

The overall demographic characteristics for opioid-naïve and opioid-experienced enrolled subjects were similar with respect to body mass index (BMI) and sex (Table 16). Opioid-naïve subjects were slightly younger (mean age 50.3) compared with opioid-experienced patients (53.8 years).

Table 16: Demographic Information by Opioid Status

Demographic Characteristic	Opioid-naïve (N=370)	Opioid-experienced (N=255)	Total (N=625)
Age (years)			
n	370	255	625
Mean (SD)	50.3 (13.5)	53.8 (12.4)	51.7 (13.1)
Min, max	19, 80	23, 80	19, 80
Gender			
Male	167 (45)	118 (46)	285 (46)
Female	203 (55)	137 (54)	340 (54)
Race			
White	256 (69)	204 (80)	460 (74)
Black	84 (23)	42 (16)	126 (20)
Asian	19 (5)	5 (2)	24 (4)
American Indian or Alaskan Native	3 (<1)	1 (<1)	4 (<1)
Native Hawaiian or Pacific Islander	1 (<1)	0	1 (<1)
Other	7 (2)	3 (1)	10 (2)
Ethnicity			
Hispanic or Latino	62 (17)	17 (7)	79 (13)
Non-Hispanic	308 (83)	237 (93)	545 (87)
Unknown	0	1 (<1)	1 (<1)
BMI, kg/m^2			
N	369	255	624
Mean	31.7	31.0	31.4
Median	29.7	30.4	29.9
Min, max	17.4, 75.2	14.8, 66.9	14.8, 75.2

BMI=body mass index
Source: Protocol 3103 CSR. Table 10, p.81

The demographic characteristics for the hydrocodone and placebo treatment groups were similar with respect to age, sex, BMI and opioid status (Table 17). In both treatment groups the majority of subjects were white (72% for the placebo group and 70% for the hydrocodone group). Screening and baseline worst pain intensity (WPI) scores were similar for the hydrocodone and placebo treatment groups.

Table 17: Demographic Information for the Hydrocodone and Placebo Treatment Groups

Demographic Characteristic	Placebo (N=180)	Hydrocodone (N=191)	Total (N=371)
Age (years)			
Mean (SD)	51.8 (12.5)	51.7 (13.5)	51.8 (13.0)
Min, max	23, 80	20, 80	20, 80
Median age group			
≤53 years	95 (53)	104 (54)	199 (54)
>53 years	85 (47)	87 (46)	172 (46)
Age group			
≤65 years	154 (86)	156 (82)	310 (84)
>65 years	26 (14)	35 (18)	61 (16)
Gender			
Male	88 (49)	94 (49)	182 (49)
Female	92 (51)	97 (51)	189 (51)
Race			
White	129 (72)	133 (70)	262 (71)
Black	41 (23)	39 (20)	80 (22)
Asian	8 (4)	13 (7)	21 (6)
Ethnicity			
Hispanic or Latino	23 (13)	24 (13)	47 (13)
Non-Hispanic	156 (87)	167 (87)	323 (87)
Unknown	1 (<1)	0	1 (<1)
BMI, kg/m^2			
N	180	191	371
Mean	31.5	31.3	31.4
Median	29.7	30.2	29.9
Min, max	14.8, 59.5	18.5, 57.2	14.8, 59.5
Opioid Status			
Opioid-naïve	105 (58)	110 (58)	215 (58)
Opioid-experienced	75 (42)	81 (42)	156 (42)
Worst Pain Intensity, mean			
Screening	8.23	8.13	
Baseline (end of open-label titration)	4.47	4.45	

Source: Protocol 3103 CSR. Table 11, p.82-83

Subjective Opiate Withdrawal Scale

During week 1 the mean SOWS scores were slightly higher for the placebo group compared to the hydrocodone group but at all other timepoints the placebo group was similar or slightly lower than the hydrocodone group:

- Week 1: 6.9 in the placebo group and 6.6 in the hydrocodone group
- Week 2: 5.1 in the placebo group and 5.1 in the hydrocodone group
- Week 4: 5.0 in the placebo group and 5.5 in the hydrocodone group

- Endpoint: 5.7 in the placebo group and 6.1 in the hydrocodone group

In analyzing the severity of SOWS scores for week 1 the difference between groups was limited to the mild withdrawal group with no increase in placebo compared to hydrocodone in the moderate withdrawal or above category (Normal 93 (52%) placebo, 112 (59%) hydrocodone; mild withdrawal 65 (36%) placebo, 54 (28%) hydrocodone; moderate withdrawal 14 (8%) placebo, 17 (9%) hydrocodone; moderately severe withdrawal 2 (1%) placebo, 3(2%) hydrocodone; severe withdrawal 0 placebo, 0 hydrocodone). Overall, the findings in the two groups appear similar. The study design allowed up to 60 mg/day of immediate-release hydrocodone as rescue medication which could mask evidence of withdrawal.

Clinical Opiate Withdrawal Scale

The Clinical Opiate Withdrawal Scale (COWS) was performed for the first 4 weeks of the double-blind treatment period up to the final on-treatment visit. If the patient discontinued study drug before completion of week 4 of the double-blind treatment period, the COWS was completed at the patient's final on-treatment visit; if the patient completed week 4 of the double-blind treatment period but discontinued study drug after that time, the COWS was not done at the final on-treatment visit. The COWS is a clinician-rated scale used to measure a patient's signs and symptoms of withdrawal from opiates with the following scale of severity: 5 to 12=mild; 13 to 24=moderate; 25 to 36=moderately severe; and more than 36=severe withdrawal.

Table 18 shows that the majority of patients in both treatment groups had no evidence of opioid withdrawal symptoms, as assessed at weeks 1, 2, and 4 (87% to 94% of hydrocodone-treated patients and 82% to 91% of placebo-treated patients) and at endpoint (95% and 93%, respectively). The remaining patients in both treatment groups exhibited only mild opioid withdrawal symptoms (3% or less of hydrocodone-treated patients and 4% or less of placebo-treated patients at all time points). No patients had scores corresponding to greater than mild withdrawal.

Table 18: Clinical Opiate Withdrawal Assessment Study 3103

Visit	Category	Placebo (N=179)	Hydrocodone (N=191)
Week 1	n	170	181
	Mean	0.9	0.8
	Normal, n (%)	163 (91)	176 (92)
	Mild withdrawal, n (%)	7 (4)	5 (3)
	Moderate withdrawal, n (%)	0	0
	Moderately severe withdrawal, n (%)	0	0
	Severe withdrawal, n (%)	0	0
Week 2	n	161	181
	Mean	0.8	0.7
	Normal, n (%)	154 (86)	179 (94)
	Mild withdrawal, n (%)	7 (4)	1 (<1)
	Moderate withdrawal, n (%)	0	0
	Moderately severe withdrawal, n (%)	0	0
	Severe withdrawal, n (%)	0	0
Week 4	n	149	167
	Mean	0.8	0.6
	Normal, n (%)	146 (82)	166 (87)
	Mild withdrawal, n (%)	3 (2)	1 (<1)
	Moderate withdrawal, n (%)	0	0
	Moderately severe withdrawal, n (%)	0	0
	Severe withdrawal, n (%)	0	0
Endpoint	n	174	185
	Mean	0.9	0.7
	Normal, n(%)	167 (93)	182 (95)
	Mild withdrawal, n(%)	7 (4)	3 (2)
	Moderate withdrawal, n (%)	0	0
	Moderately severe withdrawal, n (%)	0	0
	Severe withdrawal, n (%)	0	0

Source: Clinical Study Report. Table 77, p.196-7

Efficacy Results
A detailed discussion of the efficacy results is presented in Section 6.

Primary Endpoint
Based on the prespecified analysis, patients in the hydrocodone ER treatment group had a statistically significantly lower increase from baseline to week 12 in the primary endpoint of weekly average of daily WPI scores compared to placebo. The difference as confirmed by the FDA statistician, Dr. Bradley McEvoy, was 0.6 (p=0.0012). Table 19 prepared by the FDA statistician shows both the primary analysis and the preferred FDA secondary analysis that included data after discontinuation of study drug for subjects that continued in the study. An additional analysis requested by the FDA with

all 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 also showed statistical significance (Table 21). Treatment efficacy was further supported by the ancillary responder analysis results on the primary endpoint (Figure 2). For this responder analysis, all patients missing Week 12 values were treated as non-responders. Based on the primary analysis along with the sensitivity and ancillary analyses, Study 3103 is considered positive even though there were interpretation issues related to missing data (discussed in Section 6)

Table 19: Analysis of Change in WPI from Baseline to Week 12

	HER	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	

** Number of subjects with week 12 data included in the analysis; Analysis based on the 1000 imputed datasets*
Source: Table 8 from FDA Statistical Review

Secondary Efficacy Endpoints

Weekly Average Pain Intensity Change from Baseline at Week 12

Patients in the hydrocodone treatment group had a statistically significantly lower change from baseline in the weekly average of daily API scores at week 12 compared to placebo-treated patients (treatment difference of 0.58, p-value<0.001) (Table 24). The FDA statistician confirmed the positive findings for this endpoint.

Time to loss of efficacy or start of excessive rescue medication use

The proportion of patients with loss of efficacy, defined as discontinuation of study drug due to lack of efficacy or use of excessive rescue medication, was lower for the hydrocodone treatment group (23%) compared with the placebo treatment group (30%) but did not reach statistical significance. Due to the failed secondary endpoint of time to loss of efficacy the remaining study endpoints could not be formally tested for statistical significance based on the prespecified testing strategy.

Proportion of patients with a 30% increase in average pain intensity

Although the proportion of patients with an increase in pain intensity, defined as a 30% or greater increase in weekly API and an API of 5 or greater at week 12, was lower for the hydrocodone treatment group (12.5%) compared with the placebo group (18.8%), these results were not considered statistically significant based on the prespecified testing strategy.

Roland Morris Disability Questionnaire Score Change from Baseline
No meaningful differences in the change from baseline to end of treatment in RMDQ score were observed between the hydrocodone and placebo treatment groups.

Rescue Medication Usage
During the double-blind treatment period, 71% of patients in the hydrocodone treatment group and 81% of patients in the placebo group took rescue medication. Rescue medication use was significantly lower for the hydrocodone treatment group compared with the placebo group at week 2 and week 4, but not at week 1, week 8 or week 12 (Table 27).

Safety Results
A detailed discussion of the safety findings is presented in Section 7.

5.3.2 Study 3079

Study 3079 was a Phase 3, 12-week, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of hydrocodone ER at 15 to 90 mg q12h for relief of moderate to severe pain in patients with osteoarthritis or low back pain who required opioid treatment for an extended period of time. Patients were categorized as either opioid-naïve (ie, those taking less than 10 mg/day of oxycodone, or equivalent, for 14 days before screening) or opioid-experienced (ie, those taking 10 mg/day or more but not more than a total of 135 mg/day of oxycodone or equivalent for 14 days before screening).

Open-label titration period
During the open-label titration period the optimal dose of hydrocodone ER was identified that produced successful pain relief (defined as an API score of 4 or less on an 11-point NRS for either 3 consecutive days or 3 out of 5 consecutive days while the patient was maintained on the same dose of study drug for up to 7 days). In the open-label titration period the starting dose of hydrocodone ER was 15 mg q12h for 3 to 7 days. Four dose increases were allowed until the dose that produced successful pain relief was reached, as follows: 15 mg q12h to 30 mg q12h, 30 mg q12h to 45 mg q12h, 45 mg q12h to 60 mg q12h, and from 60 mg q12h to 90 mg q12h. Nonsteroidal anti-inflammatory drugs (NSAIDs) were allowed as rescue medication, during the open-label titration period for a maximum duration of 10 consecutive days.

Double-blind treatment period
Patients who met the criterion of an optimal dose were randomized into the 12-week, double-blind, placebo-controlled treatment period on the final day of the open-label titration period (baseline visit). Patients began treatment with double-blind study drug at the optimal dose of hydrocodone ER achieved during the titration period or matching placebo. Rescue medication was permitted in addition to the study drug during the double-blind treatment period. Patients were allowed to take 5 mg/325 mg of

hydrocodone/acetaminophen tablets up to a maximum of 10 mg of hydrocodone per day. However, patients who required 7 days of continuous rescue medication usage at the dose of 10 mg/day during the double-blind treatment period were withdrawn from the study. Also patients who increased the daily dose of rescue medication above the allowed dose of 10 mg/day of hydrocodone on two occasions were withdrawn from the study. Patients were allowed to continue taking NSAIDs during the double-blind treatment period.

Results
Of the 519 patients screened, 391 patients were enrolled and 389 patients were treated with study drug during the open-label titration. The mean age of patients in the study was 53.5 years, and there were more women (56%) than men (44%). A higher percentage of patients had low back pain (72%) than osteoarthritis (28%) as their primary pain condition. A total of 294 patients were randomly assigned to receive hydrocodone ER (146 patients) or placebo (148 patients) (1 placebo patient did not receive study drug); 196 (67%) patients completed the double-blind treatment period. Ninety four (94; 64%) subjects in the hydrocodone ER group completed 12 weeks of Vantrela ER treatment, which was less than the 102 (69%) in the placebo group. Most subjects (27%) achieved stable pain relief with the 15 mg dose. Of those subjects that entered the double-blind treatment period, approximately half were opioid experienced, and the majority primary pain diagnosis was low back pain 72%. At baseline, the average API was 3.8 and the average WPI was 4.5. In total, 100 subjects (34%) had their API value imputed in the primary analysis, with proportion relatively similar across treatment arms (hydrocodone: 34%; Placebo: 33%).

Efficacy
The prespecified primary endpoint was the difference between the hydrocodone ER and placebo groups for the change from baseline to week 12 in mean weekly average pain intensity (API) score. The findings were not statistically significant (b) (4) A statistically significant difference in favor of hydrocodone was demonstrated with the secondary endpoint of mean weekly average of WPI change from baseline to week 12. The difference (hydrocodone ER - placebo) was -0.54 with 95% CI (-1.02, -0.07). The FDA statistician noted that although the difference between groups on WPI was statistically significant at a nominal 5% significance level, this finding can only be interpreted as being “hypothesis generating” since the trial failed on the primary endpoint.

A post-hoc analysis of the primary efficacy variable (weekly API) without the 15-mg dose group (which comprised approximately 27% of randomized patients [43 patients in the hydrocodone ER and 36 patients in the placebo groups]) demonstrated a statistically significant difference in favor of hydrocodone (0.59 p=0.03).

Study 3079 Efficacy Summary
Based on the Applicant's prespecified analysis of the primary endpoint, hydrocodone ER failed to demonstrate a statistically significant difference in weekly API compared to placebo at week 12. Compared to placebo, the API change was 0.35 units smaller for hydrocodone ER (p=0.13). A statistically significant difference in favor of hydrocodone was demonstrated with the secondary endpoint of mean weekly average of WPI change from baseline at week 12 with a difference of 0.54. Due to the failed primary endpoint Study 3079 is considered a failed study.

6 Review of Efficacy

Efficacy Summary

The efficacy of Vantrela in the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate was demonstrated in one principal efficacy study (3103). There was statistically significantly less pain as measured by worst pain intensity (WPI) at 12 weeks in subjects with chronic low back pain treated with hydrocodone ER compared to placebo. Based on the prespecified analysis for the primary endpoint, the treatment difference was 0.6 (p=0.012). Although the statistician, Dr. Bradley McEvoy, considered Study 3103 to be positive he commented that the amount of missing data coupled with the marginal effect in those with week 12 data does not lead to robust evidence of Vantrela providing greater relief of low back pain than placebo. The statistical team leader, Dr. Freda Cooner, also reviewed the data and concluded that the results of the primary analysis along with the sensitivity and ancillary responder analyses provide sufficient evidence on the efficacy of Vantrela.

Efficacy of Vantrela is also supported by the reference drug Vicoprofen which is approved for the treatment of acute. Hydrocodone is the active moiety in both Vicoprofen and Vantrela. The efficacy findings from Study 3103 along with the efficacy of the reference drug, Vicoprofen, provide adequate evidence of efficacy for Vantrela for the proposed indication.

6.1 Indication

Proposed Indication
Teva's proposed indication is the following:

> Vantrela (hydrocodone bitartrate) Extended-Release Tablets are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

6.1.1 Methods

The Applicant submitted one principal efficacy study (Study 3103) to support a finding of efficacy for the indication of Vantrela ER 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. This study was an adequate and well-controlled (i.e., randomized, double-blind, placebo-controlled) study in subjects with chronic low back pain. The primary efficacy endpoint was change from baseline at week 12 in weekly average of daily WPI scores based on an 11-point NRS. The study design and primary endpoint meet the Division's standards.

Study 3079 conducted by Teva in the past is considered a failed study since it did not demonstrate a statistically significant treatment effect of hydrocodone ER tablets using the primary efficacy endpoint of average pain intensity. Therefore, this study was not reviewed in detail by the statistician and not relied upon for supporting the approval recommendation for Vantrela.

6.1.2 Demographics

The demographic characteristics for the hydrocodone and placebo treatment groups were similar with respect to age, sex, BMI and opioid status (Table 17). In both treatment groups the majority of subjects were white (72% for the placebo group and 70% for the hydrocodone group). Screening and baseline worst pain intensity (WPI) scores were similar for the hydrocodone and placebo treatment groups.

The overall demographic characteristics for opioid-naïve and opioid-experienced enrolled subjects were similar with respect to body mass index (BMI) and sex (Table 16). Opioid-naïve subjects were slightly younger (mean age 50.3) compared with opioid-experienced patients (53.8 years).

6.1.3 Subject Disposition

Of the 845 patients screened, 220 patients were not enrolled for the following reasons: 147 were excluded on the basis of inclusion/exclusion criteria, 33 patients withdrew consent, 8 patients were lost to follow-up before the baseline visit, 1 patient had adverse events (10432008, motor vehicle accident and broken left tibia), 1 patient died (10439001, unknown cause), and 30 patients were not enrolled for reasons that were not otherwise specified.

A total of 41% (254/625) of subjects enrolled in the open-label titration phase discontinued. Two of the patients that discontinued withdrew consent before receiving study drug. The reasons for discontinuation from the open-label titration period are summarized in Table 12. The primary reasons for early discontinuation from the open-label titration period were not otherwise specified 12%, adverse event 11%, lack of

efficacy 5%, consent withdrawn 5%, and protocol violation 3%. By opioid status discontinuation of study drug due to adverse events were slightly higher for opioid-naïve patients 12% versus opioid-experienced patients 9% as would be expected.

A total of 59% (371/625) of subjects enrolled in the open-label titration period were randomized to either hydrocodone (191 subjects) or placebo (180 subjects) in the double-blind treatment period. Table 13 shows the disposition of the 371 subjects randomized to treatment: 277 subjects (75%) completed study drug treatment: 147 subjects (77%) in the hydrocodone group and 130 subjects (72%) in the placebo group. During the double-blind treatment period 25% (93/371) of subjects discontinued study drug treatment. Also one patient in the placebo group withdrew consent before receiving double-blind study drug. Within the hydrocodone group, 23% (44/191) of subjects discontinued study drug early for the following reasons: adverse event 8% (15/191) of subjects, lack of efficacy 3% (5/191) of subjects, consent withdrawn 5% (9/191) of subjects and protocol violation 4% (7/191) of subjects. Within the placebo group, 28% (50/180) of subjects (including one subject who discontinued before receiving study drug) discontinued study drug early for the following reasons: adverse event 5% (9/180) of subjects, lack of efficacy 9%(17/180) of subjects, consent withdrawn 4% (8/180) of subjects and protocol violation 5% (9/180) of subjects. As expected there were slightly more discontinuations due to adverse events in the hydrocodone group and more discontinuations due to lack of efficacy in the placebo group. Table 13 also shows subjects who discontinued study drug but remained in the study.

6.1.4 Analysis of Primary Endpoint(s)

Choice of Primary Endpoint for Study 3103

The protocol-specified primary efficacy endpoint for Study 3103 was the change from baseline to week 12 in the weekly average of daily WPI scores, based on an 11-point NRS collected daily from an electronic diary. The baseline WPI score was calculated by averaging the available daily WPI scores for the last 7 days before randomization into the double-blind treatment period. The Applicant's choice of primary endpoint is consistent with the Division's current standard.

Efficacy Results

Primary Endpoint:

Based on the Applicant's prespecified analysis, patients in the hydrocodone ER treatment group had a statistically significantly lower increase in mean WPI from baseline in the weekly average of daily WPI scores at week 12 compared to placebo-treated patients. Table 20 based on Teva's analysis shows a treatment difference of 0.63 (95% CI:0.26, 1.00), p-value<0.001. Baseline WPI scores were similar for the hydrocodone ER and placebo treatment groups (4.45 and 4.47, respectively), and mean scores at week 12 were 4.52 for the hydrocodone ER treatment group and 5.18 for the placebo treatment group. The weekly averages of WPI scores remained relatively

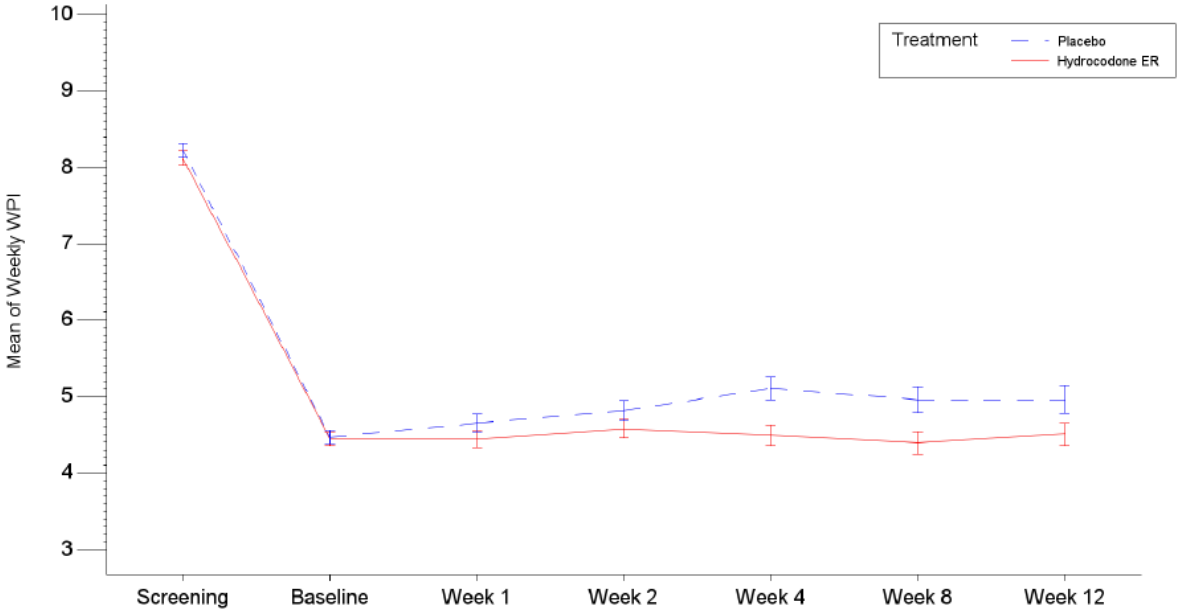
steady through 12 weeks of treatment for the hydrocodone ER treatment group while they increased for the placebo treatment group as shown in Figure 1.

Table 20: Change From Baseline to Week 12 in Weekly Average of Daily Worst Pain Intensity (Study 3103)

Time Point Statistic	**Placebo (n=179)**	**Hydrocodone (n=191)**
Screening		
n	179	191
Mean (SD)	Mean 8.23 (1.24)	Mean 8.13 (1.29)
Median	8.00	8.00
Baseline [a]		
n	179	191
Mean (SD)	4.47 (1.15)	4.45 (1.19)
Median	4.57	4.45
Week 12		
n	179	191
Mean [b]	5.18	4.52
SE of mean [b]	0.156	0.145
Change from baseline to week 12		
n	179	191
Mean [b]	0.71	0.07
SE of mean [b]	0.145	0.134
LS mean (SE) [c]	0.74 (0.147)	0.11 (0.138)
Difference (95% CI) placebo-hydrocodone	0.63 (0.26, 1.00)	
p-value	<0.001	

Source: CSR. Modified from Table 22, p. 97
[a] Baseline values were obtained at the end of the open-label titration period, before patients were randomly assigned to study drug treatment in the double-blind treatment period.
[b] The statistics were based on 5 sets of imputed data from PROC MI for which the mean was the average of the means from the 5 data sets, and the SE of the mean was adjusted based on the within-imputation variances estimates and the between-imputation variance.
[c] All statistics were adjusted for multiple imputations using PROC MIANALYZE. Details are included in the Statistical Analysis Plan
CI=confidence interval; LS=least squares; max=maximum, min=minimum; n=number; SD=standard deviation; SE=standard error.

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



Source: ISE. Figure 2, p.40

Notes: For the hydrocodone treatment group, samples sizes at each visit were as follows: baseline (n=191), week 1 (n=191), week 2 (n=182), week 4 (n=176), week 8 (n=166), and week 12 (n=152).
For the placebo treatment group, sample sizes at each visit were as follows: baseline (n=179), week 1 (n=178), week 2 (n=169), week 4 (n=163), week 8 (n=145), and week 12 (n=133).

The FDA statistical reviewer, Dr. Bradley McEvoy, confirmed the findings of Teva for the primary efficacy endpoint using the prespecified imputation methods (Table 21) and calculated a treatment difference of 0.6 (p=0.0068). Imputed data were obtained from an imputation model that included assigned treatment, opioid status, baseline and post-baseline WPI values. Patients assigned to hydrocodone ER and discontinued study drug due to an adverse event were imputed as if they were assigned to placebo; this was achieved by recoding their assigned treatment as placebo, not hydrocodone ER. 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, Dr. McEvoy's analyses are based on 1000 simulated datasets. This difference is likely to cause some differences between the results in his review and the applicant's study report.

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

Dr. McEvoy concluded that the study demonstrated efficacy but in his review commented, "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 providing greater relief of low back pain than placebo". The potential impact of this missing data on WPI change at week 12 was analyzed by Dr. McEvoy using a missing data sensitivity analysis (Table 22) which showed a large number of scenarios in which the difference in average WPI change between treatment groups was no longer statistically significant. The conclusions were not impacted in scenarios where the hydrocodone subjects with missing data had slightly more favorable pain values than placebo subjects with missing data.

Table 22: Missing data sensitivity analysis results: Estimates of the difference in mean WPI change for Hydrocodone ER (HER)-Placebo (Upper 95% CI) assuming a given WPI change for the group with missing data in the treatment groups

HER sensitivity parameter: Week 12 WPI change from baseline in the group with missing data	Placebo sensitivity parameter: Week 12 WPI change from baseline in the group with missing data															
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5
0	-.3 (.05)	-.32 (.03)	-.34 (.01)	-.36 (-.01)	-.38 (-.03)	-.4 (-.05)	-.42 (-.07)	-.44 (-.09)	-.46 (-.11)	-.48 (-.13)	-.5 (-.15)	-.51 (-.16)	-.53 (-.18)	-.55 (-.2)	-.57 (-.22)	-.59 (-.24)
0.1	-.29 (.06)	-.31 (.04)	-.33 (.02)	-.35 (0)	-.36 (-.02)	-.38 (-.04)	-.4 (-.05)	-.42 (-.07)	-.44 (-.09)	-.46 (-.11)	-.48 (-.13)	-.5 (-.15)	-.52 (-.17)	-.54 (-.19)	-.56 (-.2)	-.58 (-.22)
0.2	-.27 (.08)	-.29 (.06)	-.31 (.04)	-.33 (.02)	-.35 (0)	-.37 (-.02)	-.39 (-.04)	-.41 (-.06)	-.42 (-.08)	-.44 (-.1)	-.46 (-.11)	-.48 (-.13)	-.5 (-.15)	-.52 (-.17)	-.54 (-.19)	-.56 (-.21)
0.3	-.26 (.09)	-.27 (.07)	-.29 (.05)	-.31 (.04)	-.33 (.02)	-.35 (0)	-.37 (-.02)	-.39 (-.04)	-.41 (-.06)	-.43 (-.08)	-.45 (-.1)	-.47 (-.12)	-.49 (-.14)	-.5 (-.15)	-.52 (-.17)	-.54 (-.19)
0.4	-.24 (.11)	-.26 (.09)	-.28 .07)	-.3 (.05)	-.32 (.03)	-.33 (.01)	-.35 (-.01)	-.37 (-.02)	-.39 (-.04)	-.41 (-.06)	-.43 (-.08)	-.45 (-.1)	-.47 (-.12)	-.49 (-.14)	-.51 (-.16)	-.53 (-.17)
0.5	-.22 (.13)	-.24 (.11)	-.26 (.09)	-.28 (.07)	-.3 (.05)	-.32 (.03)	-.34 (.01)	-.36 (-.01)	-.38 (-.03)	-.4 (-.05)	-.41 (-.07)	-.43 (-.08)	-.45 (-.1)	-.47 (-.12)	-.49 (-.14)	-.51 (-.16)
0.6	-.21 (.14)	-.23 (.12)	-.24 (.1)	-.26 (.08)	-.28 (.07)	-.3 (.05)	-.32 (.03)	-.34 (.01)	-.36 (-.01)	-.38 (-.03)	-.4 (-.05)	-.42 (-.07)	-.44 (-.09)	-.46 (-.1)	-.47 (-.12)	-.49 (-.14)
0.7	-.19 (.16)	-.21 (.14)	-.23 (.12)	-.25 (.1)	-.27 (.08)	-.29 (.06)	-.31 (.04)	-.32 (.02)	-.34 (.01)	-.36 (-.01)	-.38 (-.03)	-.4 (-.05)	-.42 (-.07)	-.44 (-.09)	-.46 (-.11)	-.48 (-.12)
0.8	-.17 (.18)	-.19 (.16)	-.21 (.14)	-.23 (.12)	-.25 (.1)	-.27 (.08)	-.29 (.06)	-.31 (.04)	-.33 (.02)	-.35 (0)	-.37 (-.02)	-.38 (-.03)	-.4 (-.05)	-.42 (-.07)	-.44 (-.09)	-.46 (-.11)
0.9	-.16 (.19)	-.18 (.17)	-.2 (.15)	-.22 (.13)	-.23 (.12)	-.25 (.1)	-.27 (.08)	-.29 (.06)	-.31 (.04)	-.33 (.02)	-.35 (0)	-.37 (-.02)	-.39 (-.04)	-.41 (-.05)	-.43 (-.07)	-.45 (-.09)
1.0	-.14 (.21)	-.16 (.19)	-.18 (.17)	-.2 (.15)	-.22 (.13)	-.24 (.11)	-.26 (.09)	-.28 (.07)	-.29 (.06)	-.31 (.04)	-.33 (.02)	-.35 (0)	-.37 (-.02)	-.39 (-.04)	-.41 (-.06)	-.43 (-.07)
1.1	-.13 (.23)	-.14 (.21)	-.16 (.19)	-.18 (.17)	-.2 (.15)	-.22 (.13)	-.24 (.11)	-.26 (.09)	-.28 (.07)	-.3 (.05)	-.32 (.03)	-.34 (.02)	-.36 (0)	-.37 (-.02)	-.39 (-.04)	-.41 (-.06)
1.2	-.11 (.24)	-.13 (.22)	-.15 (.2)	-.17 (.18)	-.19 (.17)	-.2 (.15)	-.22 (.13)	-.24 (.11)	-.26 (.09)	-.28 (.07)	-.3 (.05)	-.32 (.03)	-.34 (.01)	-.36 (0)	-.38 (-.02)	-.4 (-.04)
1.3	-.09 (.26)	-.11 (.24)	-.13 (.22)	-.15 (.2)	-.17 (.18)	-.19 (.16)	-.21 (.14)	-.23 (.13)	-.25 (.11)	-.27 (.09)	-.28 (.07)	-.3 (.05)	-.32 (.03)	-.34 (.01)	-.36 (-.01)	-.38 (-.02)
1.4	-.08 (.28)	-.1 (.26)	-.12 (.24)	-.13 (.22)	-.15 (.2)	-.17 (.18)	-.19 (.16)	-.21 (.14)	-.23 (.12)	-.25 (.1)	-.27 (.09)	-.29 (.07)	-.31 (.05)	-.33 (.03)	-.34 (.01)	-.36 (-.01)
1.5	-.06 (.29)	-.08 (.28)	-.1 (.26)	-.12 (.24)	-.14 (.22)	-.16 (.2)	-.18 (.18)	-.19 (.16)	-.21 (.14)	-.23 (.12)	-.25 (.1)	-.27 (.08)	-.29 (.07)	-.31 (.05)	-.33 (.03)	-.35 (.01)

Shaded boxes correspond to scenarios where the 95% CI for the difference in average WPI change from baseline (HER-Placebo) includes 0.

Source: FDA Statistical Review, p24

The statistical team leader, Dr. Freda Cooner, was aware of the issue of missing data potentially impacting on the study results but concluded the study showed efficacy. She noted that both the primary analysis and the preferred FDA analysis that included data after discontinuation of study drug for subjects that continued in the study were both statistically significant (Table 21). An additional analysis requested by the FDA with all 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 showed statistical significance (Table 21). Treatment efficacy was further supported by the ancillary responder analysis results on the primary endpoint (Figure 2). For the responder analysis, all patients missing Week 12 values were treated as non-responders. Dr. Cooner concluded that the results of the primary analysis along with the sensitivity and ancillary analyses provide sufficient evidence on the efficacy of Vantrela. Efficacy was also supported by the secondary endpoint of average pain intensity change from baseline at Week 12. I concur with Dr. Cooner's conclusion that there is sufficient evidence to support the efficacy of Vantrela in Study 3103.

Applicant's sensitivity analysis

One of the Applicant's sensitivity analysis for the primary efficacy endpoint excluded data from 26 subjects that rolled over into long-term safety study 3104 and were

potentially unblinded during the double-blind treatment period of study 3103. To investigate the impact of potential unblinding the applicant repeated the primary analysis excluding these 26 subjects. Results from this analysis were consistent with the primary analysis, suggesting that the conclusion was not impacted by the potential unblinding.

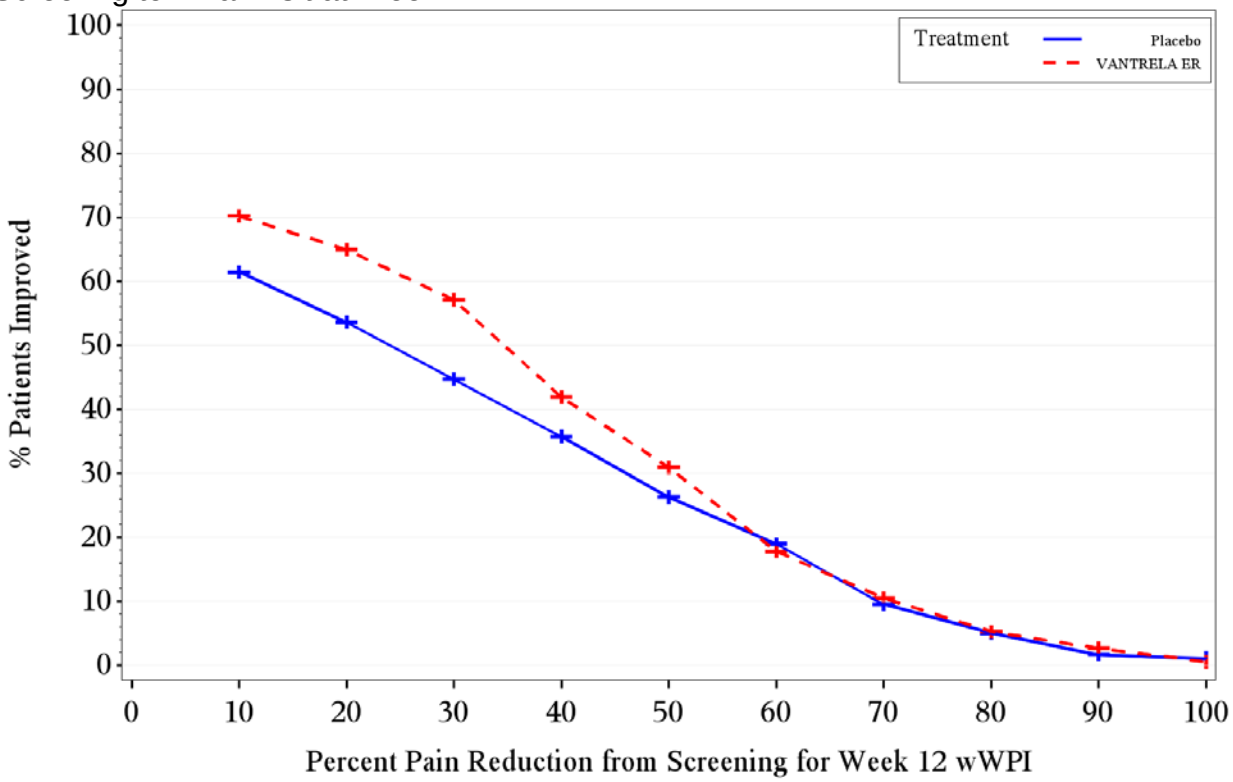
Cumulative Responder Analysis

The FDA statistician determined the proportions of subjects that stayed on treatment to week 12 and had a change of at least 15%, 30% and 50% in WPI from screening to week 12 (Table 23). For the 15% and 30% threshold the difference between hydrocodone and placebo was statistically significant at a nominal 5% significance level. For the 50% threshold the difference did not reach statistical significance. Subjects who did not complete the study treatment were classified as non-responders. The percentage of subjects in each group who demonstrated improvement in their average WPI score at week 12, as compared to Screening is shown in Figure 2.

Table 23: Results from FDA composite of treatment adherence up to week 12 and 15%, 30% and 50% difference in WPI from screening to week 12 (Study 3103)

Threshold	HER	Placebo	Difference: HER – Placebo (95% CI)
15%	68%	56%	11% (0, 21)
30%	56%	45%	12% (1, 22)
50%	27%	25%	1% (-7, 10)

Figure 2: Percentage Improvement in Average Worst Intensity (WPI) Score From Screennng to Final Visit at Week 12



Source: Vantrela label (prepared by Teva)

6.1.5 Analysis of Secondary Endpoints(s)

Change from Baseline in Weekly Average Pain Intensity

Patients in the hydrocodone treatment group had a statistically significant lower change from baseline in the weekly average of daily API scores at week 12 compared to placebo-treated patients (treatment difference of 0.58 [95% CI 0.25, 0.91], p-value<0.001) (Table 24). Baseline API scores were similar for the hydrocodone and placebo treatment groups (3.31 and 3.41, respectively). Mean scores at week 12 were 3.33 for the hydrocodone treatment group and 3.98 for the placebo treatment group. The FDA statistician confirmed the positive findings for this endpoint.

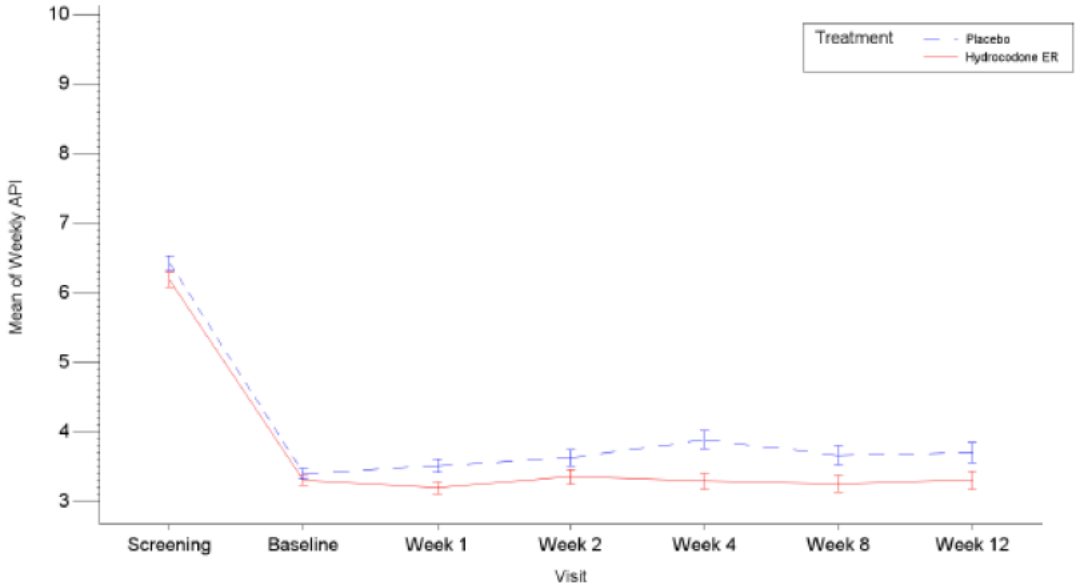
Table 24: Change from Baseline to Week 12 in Weekly Average Pain Intensity

Time point	Placebo (N=179)	Hydrocodone (N=191)
Screening		
Mean pain score	6.43	6.19
Baseline		
Mean pain score	3.41	3.31
Week 12		
Mean pain score	3.98	3.33
Change from baseline to week 12		
Mean	0.57	0.02
SE of mean	0.126	0.116
LS mean (SE)	0.55 (0.135)	-0.03 (0.121)
Difference (95%CI) placebo-hydrocodone	0.58 (0.25, 0.91) p-value <0.001	

Source: CSR 3103. Table 27, p107
Multiple imputation method used. Population full analysis set.

The weekly averages of API scores remained relatively steady through 12 weeks of treatment for the hydrocodone treatment group while they increased for the placebo treatment group (Figure 3).

Figure 3: Weekly Average of Average Pain Intensity Scores by Visit and Treatment Group



Source: Protocol 3103 Clinical Study Report, Figure 6, p. 107

Time to loss of efficacy or start of excessive rescue medication use
The proportion of patients with loss of efficacy, defined as discontinuation of study drug due to lack of efficacy or use of excessive rescue medication, was lower for the

hydrocodone treatment group (23%) compared with the placebo treatment group (30%) but did not reach statistical significance (Table 25). Excessive rescue medication use was defined as 10 or more days of rescue medication use in any 14 consecutive days at a total of 15 mg (hydrocodone-equivalent) or higher each day during the post 2-week tapering period of the double-blind treatment period. The FDA statistician noted that due to the failed secondary endpoint of time to loss of efficacy the remaining study endpoints cannot be formally tested for statistical significance based on the prespecified testing strategy.

Table 25: Time to Loss Of Efficacy (Full Analysis Set)

Category	Placebo (N=179)	Hydrocodone (N=191)
Number (%) of patients with loss of efficacy	54 (30)	43 (23)
Number (%) of patients censored	125 (70)	148 (77)
Hazard ratio (95% CI)	0.68 (0.45, 1.01)	
p-value[a]	0.059	

Source: CSR, Table 28, p110
[a] The p-value for the hazard ratio is based on the Wald chi-square test from PROC PHREG for the hazard ratio using the Cox proportional hazards model with treatment, baseline WPI, opioid status, and study center in the model.
CI=confidence interval; WPI=worst pain intensity.
Note: All quartile estimates were based on the Kaplan-Meier method. Patients terminated due to lack of efficacy or patients who took excessive rescue medication are considered to have had loss of efficacy.

Proportion of patients with a 30% increase in average pain intensity

Although the proportion of patients with an increase in pain intensity, defined as a 30% or greater increase in weekly API and an API of 5 or greater at week 12, was lower for the hydrocodone treatment group (12.5%) compared with the placebo group (18.8%) (Table 26), these results were not considered statistically significant based on the prespecified testing strategy due to the failed secondary endpoint for time to loss of efficacy.

Table 26: Proportion of Patients with a 30% or Greater Increase in Weekly Average Pain Intensity Increase and an Average Pain Intensity Score of at Least 5 at Week 12 (Multiple Imputation Method) (Full Analysis Set)

Variable	Treatment group[a]		Odds ratio (95% CI)[b] (hydrocodone/placebo)	Nominal p-value[b]
	Placebo (N=179)	Hydrocodone (N=191)		
API increase from baseline ≥30% and API ≥5	**25/133 (18.8%)**	**19/152 (12.5%)**	**0.67 (0.47, 0.96)**	**0.0293**
API increase from baseline ≥30%	48/133 (36.1%)	32/152 (21.1%)	0.61 (0.45, 0.83)	
API ≥5	32/133 (24.1%)	25/152 (16.4%)	0.68 (0.50, 0.92)	

Source: Protocol 3103 Clinical Study Report, Table 30, p112
[a] Counts and percentages included only the patients who had observed weekly average API for week 12.
[b] Odds ratios (95% CI) and p-values were based on multiple imputation method using logistic regression stratified by center with treatment, opioid status and baseline API in the model.
API=average pain intensity; CI=confidence interval.

Roland Morris Disability Questionnaire Score Change from Baseline

No meaningful differences in the change from baseline to end of treatment in RMDQ score were observed between the hydrocodone and placebo treatment (nominal p-value=0.557). The estimated difference (hydrocodone-placebo) was 0.28 with 95% CI (-0.65, 1.20). The RMDQ is a patient-rated 24-question evaluation used to assess acute disability associated with low back pain. Scores on the RMDQ range from 0 to 24, with higher scores indicating greater disability.

Exploratory Endpoints

Rescue Medication Usage

During the double-blind treatment period, 136 (71%) patients in the hydrocodone treatment group and 145 (81%) patients in the placebo treatment group took rescue medication. The daily mean number of tablets of rescue medication ranged from 0.8 to 1.6 tablets for the hydrocodone treatment group and from 1.2 to 1.9 tablets for the placebo treatment group during the double-blind treatment period. Table 28 shows the use of rescue medication by visit. Rescue medication use was significantly lower for the hydrocodone treatment group compared with the placebo treatment group at week 2 and week 4, but at week 12 the number of tablets used appeared similar between the two treatment groups.

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

6.1.7 Subpopulations

The FDA statistician, Brad McEvoy, analyzed WPI change at week 12 within subgroup populations. Data collected after a subject discontinued treatment was included in the analysis. The subgroups explored were the following:

- Sex (females; males)
- Age (≤ 65 years; > 65 years)
- Race (white; non-white)
- Opioid status (naïve; experienced)
- Stable hydrocodone dose (30 mg; 45 mg; 60 mg; 90 mg)

Table 28 summarizes results from the subgroup analyses. Results from different subgroups were reasonably in-line with 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, should be interpreted cautiously because of multiplicity considerations and the fact that the trials were not designed to detect differences across levels of the subgroups.

Table 28: Subgroup Analysis of WPI Change at Week 12 (Study 3103)

	Adj. mean change	Difference: HER - Placebo (95% CI)	Adj. mean change	Difference: HER - Placebo (95% CI)
Sex	**Males**		**Females**	
HER	0.07		0.20	
Placebo	0.44	-0.37 (-0.89, 0.15)	0.80	-0.59 (-1.18, -0.01)
Age	**≤ 65 years**		**> 65 years**	
HER	0.31		-0.36	
Placebo	0.69	-0.38 (-0.80, 0.04)	0.50	-0.86 (-1.90, 0.17)
Race	**White**		**Non-white**	
HER	0.47		-0.42	
Placebo	0.98	-0.51 (-0.98, -0.04)	0.03	-0.45 (-1.08, 0.18)
Opioid Status	**Naïve**		**Experienced**	
HER	0.02		0.22	
Placebo	0.30	-0.28 (-0.81, 0.26)	1.04	-0.82 (-1.35, -0.28)
Stable dose	**30 mg**		**45 mg**	
HER	0.07		0.10	
Placebo	-0.19	-0.26 (-0.99, 0.46)	1.05	-0.95 (-1.61, -0.30)
	60 mg		**90 mg**	
HER	0.72		0.72	
Placebo	1.14	-0.42 (-1.27, 0.44)	0.92	-0.19 (-1.46, 1.07)

Source: FDA Statistical Review. Table 15, p29
HER=hydrocodone ER. 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 the analysis by opioid status).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In the subgroup analysis of the primary efficacy variable by stable pain relief dose group, numerical treatment differences from placebo in favor of hydrocodone extended-release tablets were noted for all dose groups, with the largest difference being observed for the 45-mg dose group (Table 28). Baseline WPI scores were similar for patients in the hydrocodone and placebo treatment groups whose stable pain relief dose was 45 mg (4.54 and 4.50, respectively), and scores at week 12 were 4.58 for the hydrocodone treatment group and 5.38 for the placebo treatment group. In clinical practice, individual patients would be titrated to efficacy.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy was demonstrated with the primary endpoint of WPI at the end of the 12 week double-blind treatment period. The weekly averages of WPI scores remained relatively steady through 12 weeks of treatment for the hydrocodone ER treatment group while they increased for the placebo treatment group as shown in Figure 1.

6.1.10 Additional Efficacy Issues/Analyses

Efficacy was also supported by the reference drug Vicoprofen which is approved for the treatment of acute pain. Vicoprofen is a fixed combination tablet that contains the opioid analgesic agent hydrocodone bitartrate with the nonsteroidal anti-inflammatory agent ibuprofen and is indicated for the short-term management of acute pain. The Division considers the efficacy of Vicoprofen for the treatment of acute pain as supportive evidence of the efficacy of Vantrela since hydrocodone is an active moiety in Vicoprofen.

Study 3079, a study in chronic low back pain and osteoarthritis failed to demonstrate efficacy with the prespecified primary endpoint of change from baseline in average pain intensity but did show efficacy with an important secondary endpoint of change from baseline in worst pain intensity. Since the positive results from this study were not based on the prespecified primary endpoint the findings are not considered statistically significant. Study 3079 provides additional support of efficacy but was not relied upon for recommending an Approval action for Ventrela.

Summary of Benefit
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.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety information reviewed for this section includes information from the Integrated Summary of Safety and the 4-month safety update. The safety of hydrocodone ER is supported by data from 23 completed clinical studies: 19 Phase 1 studies (Table 7) and 4 Phase 3 studies (Table 8). The initial NDA submission of 23 December 2014 did not contain all of the safety data from Study 3104, a long-term safety study, which has since been completed and included in the safety update.

The 4-month safety update submitted April 22, 2015 contains five new adverse drug reactions: pyrexia, contusion, neck pain, lethargy, and tremor. There was no new information presented in the 4-month safety update that would significantly change the safety profile of hydrocodone ER based on the information contained in the original submission.

The primary clinical evaluation of the safety of hydrocodone ER is based on data from the following 4 Phase 3 studies (2 double-blind placebo-controlled studies [3103, 3079] and 2 open-label, long-term safety studies [3104, 3080]):

- Study 3079, a double-blind, placebo-controlled study in patients with osteoarthritis or low back pain was completed on 22 August 2011. The study consisted of up to a 6-week open-label titration period, followed by a randomized, double-blind, 12-week treatment period.
- Study 3080, a long-term (12-month), open-label extension of Study 3079 completed on 14 September 2012. The study 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 3103, a double-blind, placebo-controlled study in patients with chronic low back pain was completed on 25 February 2014. The study consisted of up to a 6-week open-label titration period, followed by a randomized, double-blind, 12-week treatment period.
- Study 3104, a long-term (6-month), open-label safety extension of Study 3103 was completed on 18 August 2014. A total of 182 patients were enrolled and dosed in this study.

The Applicant presented the safety data of hydrocodone ER in the Integrated Summary of Safety as follows:

Safety Analysis Set
The safety analysis set (N=1176) included all patients who took at least 1 dose of hydrocodone 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 set as part of the number of patients in Studies 3079 and 3103.

Post-titration Analysis Set (Studies 3079, 3080, 3103, and 3104)
All 4 studies (Studies 3079, 3080, 3103, and 3104) included a titration period after which subjects entered either double-blind treatment (Studies 3079 and 3103) or open-label treatment (Studies 3080 and 3104). The post-titration analysis set (N=625) included all patients who took at least 1 dose of hydrocodone ER in either a double-blind (Studies 3079 and 3103) or long-term open-label phase (Studies 3080 and 3104).

Post-titration Analysis Set for the Double-blind Studies (Studies 3079 and 3103)
The post-titration analysis set for double-blind Studies 3079 and 3103 (N=663) included all patients in the double-blind, post-titration treatment period from the 2 double-blind, placebo-controlled studies. The post-titration analysis set for double-blind Studies 3079 and 3103 included 293 patients from Study 3079 (147 patients who received placebo and 146 patients who received hydrocodone ER) and 370 patients from Study 3103 (179 patients who received placebo and 191 patients who received hydrocodone ER).

The ISS and my review primarily presents data from the safety analysis set and the post-titration analysis set for the double-blind studies (Studies 3079 and 3103). The post-titration analysis set allows for a comparison of hydrocodone to placebo.

Patient Population Subsets
The following subgroups were evaluated: age group (≤65 years, >65 years), sex (men, women), race, body mass index (BMI) (<30 kg/m2, ≥30 kg/m2), opioid status (opioid-naïve, opioid-experienced, primary pain diagnosis (low back pain, osteoarthritis, other), optimal dose (for AEs only). For the ISS, optimal dose is defined as the pain relief dose strength found to be both effective and tolerable during the titration treatment period.

7.1.2 Categorization of Adverse Events

All adverse events were coded by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.0. The Applicant provided summaries for all adverse events, serious adverse events, adverse events causing withdrawal from the study, and nonserious adverse events. The incidence of adverse events was summarized using descriptive statistics by system organ class (SOC), high-level term (HLT), and preferred term (PT). Adverse events that were ongoing in Study 3080 but

started in Study 3079 and adverse events that started in Study 3103 and continued in Study 3104 were counted only once.

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

Data was pooled for the post-titration analysis set for double-blind Studies 3079 and 3103 since the study design was similar for both studies and the placebo treatment arm allowed for a comparison of incidence to hydrocodone.

7.2 Adequacy of Safety Assessments

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

The Vantrela development program provided adequate exposure to assess safety, with a total of 1176 patients exposed to at least one dose of hydrocodone ER in the four Phase 3 studies. An additional 788 subjects received at least one dose of study drug in the 19 Phase 1 studies. Overall, 363 patients were treated for at least 6 months and 197 patients were treated for at least 1 year. A total of 112 patients received 90 mg twice daily (highest dose) with 83 patients for at least 1 month, 42 patients for at least 6 months and 20 patients for at least 12 months (Table 29).

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

An adequate number of subjects were exposed to Vantrela in various demographic subsets (i.e., gender, opioid status (naïve versus experienced), race, and age. 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. Table 16 provides demographic information by opioid status and Table 17 provides demographic information by age, gender and race for Study 3103.

7.2.2 Explorations for Dose Response

A summary of the optimal dose for the 1176 patients enrolled in Phase 3 studies is shown in Table 30. This data is of limited value in assessing the optimal dose for an individual patient since opioids should be titrated to efficacy for each individual patient.

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.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the development of Vantrela appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to Section 4.4 and the Clinical Pharmacology Review.

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

The opioid class of drugs have been associated with abuse, addiction, and fatal respiratory depression and contain a boxed warning describing these potential adverse events in the label.

7.3 Major Safety Results

7.3.1 Deaths

There were three deaths during the Phase 3 studies. Two deaths were reported in Study 3080 and one death occurred prior to the subject receiving any study drug during the screening period of Study 3103. There were no deaths during the Phase 1 studies. The three deaths reported during the Vantrela development program are reviewed below and do not appear to be related to hydrocodone.

Individual Patient Death Summaries

Patient Number: 026111
Study Number: 3080 (Hydrocodone)
Death: Cause unknown

Patient 026111 was an opioid-experienced, 74-year-old white man with chronic back pain. At study entry, the patient was taking clopidogrel and clonazepam (for a heart attack in 1999); digoxin for congestive heart failure; acetylsalicylic acid for heart health; simvastatin for elevated lipids; ranitidine for heartburn; salbutamol and salmeterol xinafoate for chronic obstructive pulmonary disease and emphysema; prednisone for emphysema and rheumatoid arthritis; hydroxychloroquine for rheumatoid arthritis; and hydrocodone/acetaminophen as rescue medication. Other relevant medical history included angina, coronary artery bypass graft, coronary artery disease, peripheral vascular disease, basal cell carcinoma, edema, asthma, and obstructive sleep apnea.

The patient began the open-label titration period with hydrocodone 15 mg every 12 hours on (b) (6) (day 1). The patient achieved a successful dose of 30 mg every 12 hours, and he began the open-label treatment period on day 13. On day 40, the patient did not feel well, had a cough, and was confused. The patient was hospitalized the next day with severe pneumonia. The patient was treated with salbutamol, ipratropium, prednisone, and levofloxacin. The patient was discharged on day 42 with the pneumonia improved and the pneumonia resolved with no residual effect by day 85. On day 185, the patient had shortness of breath, was not feeling well, and was having problems staying awake. The patient was hospitalized with severe pulmonary edema (verbatim: cardiogenic pulmonary edema). Treatment with the study drug was interrupted on days 185 to 194. The pulmonary edema resolved with no residual effect by day 195. On day 267, the patient was hospitalized with urosepsis, which resolved with no residual effect by day 270. On day 270, the patient was started on azathioprine for rheumatoid arthritis, and he had mild depression, which was reported as an adverse event. He was treated with bupropion. On day 287, the patient was admitted to hospice, and there was no further information regarding how the study drug was taken. The patient died on day 304. Attempts to ascertain the cause of death

by the Applicant were unsuccessful. At the time of his death, the patient was undergoing testing for cancer.

Impression
The cause of death is unclear for this patient but appears unlikely that this subject's death was related to hydrocodone ER given that he was admitted to hospice care on day 287 of treatment.

Patient Number: 026002
Study Number: 3080 (Hydrocodone)
Death: Cardiac arrest and hyperkalemia

Patient 026002 was a 54-year-old white woman in the rollover group with chronic low back pain. At study entry, the patient was taking levothyroxine for thyroid disease, hydroxyzine for anxiety, diphenhydramine hydrochloride and pseudoephedrine hydrochloride as needed for sinus pressure, diphenhydramine hydrochloride as needed for insomnia, esomeprazole magnesium for acid reflux, acetaminophen/aspirin/caffeine for headache, and 200 mg of ibuprofen as needed. Other relevant medical history included gastric bypass, hysterectomy, anemia, failed back surgery syndrome, neck pain, sacroiliac joint pain, left ankle swelling, hypertension, and depression. The patient participated in study 3079 ((b) (6)), and during that study had been randomly assigned to the hydrocodone treatment group during the double-blind treatment period, receiving a dose of 90 mg every 12 hours. After completion of study 3079, the patient entered study 3080 on (b) (6) and began the open-label titration period with hydrocodone 30 mg every 12 hours. On day 1, the patient started 5 mg/325 mg of hydrocodone/acetaminophen as rescue medication and pregabalin for pain; on day 4, the patient's dose of rescue medication was increased to 10 mg/325 mg of hydrocodone/acetaminophen. On day 15, the patient was started on furosemide for swelling. The patient achieved a successful dose of 90 mg every 12 hours, and began the open-label treatment period on day 21. On day 237, the patient had moderate vomiting and diarrhea, which were reported as adverse events. On day 242, she went to the doctor's office with complaints of symptoms of a urinary tract infection, vomiting, and diarrhea of 5 days duration. While waiting in the examination room, the patient developed respiratory distress and stopped breathing. Cardiopulmonary resuscitation was initiated; breathing and pulse were reestablished, but stopped several minutes later. The patient was intubated, defibrillated, and transported to the hospital, arriving in full cardiac arrest. The patient did not recover.

Laboratory results showed the patient's potassium was 8.6 mmol/L (normal range, 3.5 to 4.9). The patient's daughter reported the patient had been self-medicating with an unknown dose of potassium from a previous prescription for leg cramps. The cause of death was cardiac arrest secondary to severe hyperkalemia, both events were reported as serious adverse events with a fatal outcome. The investigator considered the cardiac

arrest and hyperkalemia not related to study drug treatment. The last dose of study drug was taken on day 242.

Impression
Hyperkalemia can cause cardiac arrest and this patient's reported potassium of 8.6 mmol/L was at a dangerous level that could have caused a cardiac arrest.

Patient Number: 10439001
Study Number: 3031 (no hydrocodone given)
Death: Cause unknown (during screening period)

Patient 10439001 was a 46-year-old man who died during the screening period. The patient's relevant medical history included chronic low back pain (treated with hydrocodone/acetaminophen), spontaneous pneumothorax (1980), type 2 diabetes mellitus (treated with metformin), sleep apnea, insomnia (treated with zolpidem), depression, and obesity. He was found dead at his cabin; cause and exact time of death were unknown. No study drug had been dispensed to the patient.

Impression
Cause of death is unknown but unrelated to study drug which had not been dispensed to the patient.

Summary of Deaths
The two deaths that occurred in subjects treated with hydrocodone ER during the development program do not appear to be related to study drug.

7.3.2 Nonfatal Serious Adverse Events

Serious Adverse Events
Of the 1176 patients who were enrolled in the Phase 3 studies and received at least 1 dose of hydrocodone ER, 57 (5%) patients reported at least one serious adverse event (Table 31). There were no serious adverse events reported during the Phase 1 studies. The only SAEs observed by more than one patient were: pneumonia (4), renal failure acute (4), deep vein thrombosis (3), cellulitis (2), chest pain (2), cholecystitis (2), chronic obstructive pulmonary disease (COPD) (2), dehydration (2), pancreatitis (2), intestinal obstruction (2) and panic attack (2).

Table 31: Serious adverse events of subjects who took at least one dose of hydrocodone ER by system organ class and preferred term in the safety analysis set

System Organ Class/Preferred Term	**Total (N=1176)**
Number of patients with SAE (%)	57 (5)
Blood and lymphatic system disorders	*1 (<1)*
Thrombocytopenia	1 (<1)
Cardiac disorders	*4 (<1)*

Acute coronary syndrome	1 (<1)
Acute myocardial infarction	1 (<1)
Coronary artery disease	1 (<1)
Cardiac arrest [a]	1 (<1)
Gastrointestinal disorders	*6 (<1)*
Pancreatitis	2 (<1)
Intestinal obstruction [b]	2 (<1)
Gastritis	1 (<1)
Esophagitis	1 (<1)
Abdominal adhesions	1 (<1)
General disorders and administration site conditions	*4 (<1)*
Chest pain	2 (<1)
Death (unknown cause)[c]	1 (<1)
Hernia obstructive	1 (<1)
Hepatobiliary disorders	*3 (<1)*
Cholecystitis[d,e]	2(<1)
Cholestasis	1 (<1)
Immune system disorders	1 (<1)
Anaphylactic reaction	1 (<1)
Infections and infestations	15 (1)
Pneumonia (includes lobar pneumonia)	4 (<1)
Device related infection	1 (<1)
Infected cyst	1 (<1)
Postoperative abscess	1 (<1)
Appendicitis perforated	1 (<1)
Gastroenteritis	1 (<1)
Cellulitis	2 (<1)
Clostridium difficile infection	1 (<1)
Pneumonia cryptococcal	1 (<1)
Listeria sepsis	1 (<1)
Urosepsis	1 (<1)
Subcutaneous abscess	1 (<1)
Staphylococcal infection	1 (<1)
Urinary tract infection	1 (<1)
Injury and Poisoning	3 (<1)
Tracheal injury	1 (<1)
Road traffic accident	1 (<1)
Accidental overdose [f]	1 (<1)
Laceration	1 (<1)
Investigations	1 (<1)
ECG T wave inversion	1 (<1)
Metabolism and nutrition disorders	4 (<1)
Dehydration	2 (<1)

Diabetic ketoacidosis	1 (<1)
Hyperkalemia	1 (<1)
Musculoskeletal	1 (<1)
Osteoarthritis	1 (<1)
Neoplasm	4 (<1)
Breast, colon, prostate, thyroid (4 separate patients)	4 (<1)
Nervous system disorders	4 (<1)
Sedation	1 (<1)
Syncope	1 (<1)
Lumbar radiculopathy	1 (<1)
Hemiparesis	1 (<1)
Hypoaesthesia	1 (<1)
Speech disorder	1 (<1)
Tremor	1 (<1)
Pregnancy and perinatal conditions	1 (<1)
Abortion spontaneous	1 (<1)
Psychiatric disorders	4 (<1)
Panic attack	2 (<1)
Depression	1 (<1)
Impulsive behavior	1 (<1)
Renal and urinary disorders	5 (<1)
Renal failure acute	4 (<1)
Renal failure	1 (<1)
Respiratory, thoracic and mediastinal disorders	7 (<1)
Chronic obstructive pulmonary disease	2 (<1)
Asthma	1 (<1)
Dyspnea	1 (<1)
Respiratory arrest [f]	1 (<1)
Pulmonary edema	1 (<1)
Pulmonary embolism	1 (<1)
Vascular disorders	4 (<1)
Deep vein thrombosis 3	3 (<1)
Hypotension	1 (<1)

[a] Patient 026002 (Study 3080) discussed in section on deaths
[b] SAEs of small intestinal obstruction in subject 016004 (Study 3080) and intestinal obstruction in subject 10385011 (Study 3104) were combined under term intestinal obstruction
[c] Patient 026111 (Study 3080) discussed in section on deaths
[d] SAEs of cholecystitis, cholangitis and cholelithiasis all occurred in Patient 10357010 (Study 3104)
[e] The SAEs of cholecystitis acute in subject 011109 (Study 3080) and cholecystitis in subject 10357010 (Study 3104) were combined under the term cholecystitis
[f] SAEs of accidental overdose and respiratory arrest occurred in Patient 10388023 (Study 3103)

SAEs during the post-titration treatment of the double-blind studies

The design of the Phase 3 clinical studies limits the ability to compare the incidence of SAEs between placebo and Vantrela since in the open-label, long-term safety studies (Studies 3014 and 3080) there was no placebo group and in the randomized, double-blind studies (Studies 3013 and 3079) all patients initially received Vantrela during the open-label titration period prior to randomization. Table 32 shows the SAEs that occurred during the post-titration period in the double-blind studies. Six (2%) patients in the hydrocodone ER group and 6 (2%) patients in the placebo group reported serious adverse events. In the hydrocodone ER group, there were two patients with pancreatitis. One of the cases appeared to be due to gallstones and autoimmune pancreatitis was the possible cause for the other case. The proposed label lists pancreatitis as a rare (<1%) adverse drug reaction.

Table 32: Serious Adverse Events During the Post-titration Treatment Period for Double-blind 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: ISS, Table 29, p 141
[a] Reported as related to study drug treatment by the investigator
AE=adverse event; ER=extended release; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in subgroup.
Note: Patients are counted only once in each preferred term category.

The narratives of all subjects with nonfatal SAEs in the development program were reviewed. Since the adverse event profile of opioids is well known, only SAEs that appeared reasonably related to hydrocodone ER and/or of special interest or concern

are summarized below and include: spontaneous abortion, accidental overdose (respiratory arrest), pancreatitis, intestinal obstruction, cholecystitis, syncope, sedation and hypotension.

Individual Patient Nonfatal Serious Adverse Events Summaries

Subject Number: 10385007 (Hydrocodone ER)
Study Number: 3103
Serious Adverse Event: Abortion Spontaneous

Patient 10385007 was an opioid-experienced, 43-year-old white woman with low back pain. At study entry, the patient was taking fluoxetine hydrochloride and bupropion for depression, sumatriptan for migraines, orphenadrine citrate as a muscle relaxant, methylphenidate hydrochloride for attention-deficit hyperactivity disorder, lidocaine patch for pain (discontinued on day –14), 10 mg/500 mg of hydrocodone/acetaminophen (discontinued on day –1) and morphine sulfate (discontinued on day–1). Other relevant medical history included hyperlipidemia, lumbar back pain, osteoarthrosis, anxiety, insomnia, and kidney stones. The patient began the titration period with hydrocodone ER 45 mg every 12 hours on 20 September 2013 (day 1), and the dose was titrated to 60 mg every 12 hours by day 5. On day 6, the patient had mild nausea and headache which resolved the same day. On day 7, the patient had mild diarrhea, which was treated with loperamide hydrochloride. On day 8 the last dose of study drug was taken and the patient was discontinued from the study due to a positive pregnancy test. On day 10, the patient had a spontaneous abortion. She reported that she had a miscarriage and had started cramping and bleeding throughout the day. The patient did not go to the hospital.

Impression
Spontaneous abortion is common and the patient was on multiple medications at the time of her miscarriage. No conclusions about the use of hydrocodone and spontaneous abortion can be made from this case.

Subject Number: 10388023 (Hydrocodone ER)
Study Number: 3103
Serious Adverse Event: Accidental overdose, respiratory arrest

Patient 10388023 was an opioid-experienced, 70-year-old white man with low back pain on the following medications terazosin hydrochloride for enlarged prostate, simvastatin for hypercholesterolemia, fluticasone propionate and cetirizine hydrochloride for seasonal allergies, omeprazole for gastroesophageal reflux disease, zolpidem tartrate and diphenhydramine hydrochloride for insomnia, bisacodyl and docusate sodium for constipation, and gabapentin for carpal tunnel syndrome. Other relevant medical history included obesity (screening BMI=32.8 kg/m^2). The patient began the titration period with hydrocodone ER 30 mg every 12 hours on (b) (6) (day 1). On day 7, the

patient had dry mouth, headache, chills, hyperhidrosis, and nausea that resolved by day 10. On day 17, the patient had mild chills and mild diaphoresis. The dose was titrated to 90 mg every 12 hours by day 21. The patient did not reach a successful pain relief dose, and was not randomized to the double-blind period of the study. On day 23, the patient had an accidental overdose (verbatim: unintentional opiate overdose) and respiratory arrest. That day, the patient was found unresponsive by his wife and was taken by ambulance to the hospital. Prior to arrival of emergency medical services, the patient's respirations were assisted with bag-valve-mask ventilation by fire rescue and naloxone hydrochloride was given. Admitting history revealed that the patient had multiple providers for opiates. Per the discharge summary, the patient had 1) acute renal failure due to rhabdomyolysis, likely due to the statin (simvastatin); 2) altered mental status due to toxic metabolic encephalopathy; 3) increased liver function tests due to rhabdomyolysis. ALT, AST creatinine and CPK were all elevated but by time of discharge had improved significantly. Creatinine was as high as1.9 mg/dL but at discharge 1.1 mg/dL. A renal ultrasound on day 24 showed no evidence of hydronephrosis. An ultrasound of the liver showed cholelithiasis with gallbladder wall thickening and fatty infiltrate of the liver, which were most likely chronic. The patient did not take any further doses of the study drug after day 23.

Impression
This case of overdose and respiratory depression appears related to hydrocodone ER but insufficient information has been provided to exclude concomitant use of other sources of opioids as a contributing factor. It is also possible that renal impairment due to rhabdomyolysis from simvastatin may have resulted in higher hydrocodone levels which contributed to his overdose. However, insufficient details and timing of events were provided to reach a definitive understanding of the exact contribution of each factor to his overdose. It is also noted that this patient was titrated to hydrocodone ER 90 mg twice daily, the highest dose allowed in the study. Overdose and respiratory depression are known dose dependent serious complications of opioid use.

Subject Number: 10420016 (Hydrocodone ER)
Study Number: 3103
Serious Adverse Event: Pancreatitis

Patient 10420016 was an opioid-experienced, 46-year-old white man with low back pain. The patient's screening BMI was 32.2 kg/m^2. At study entry, the patient was taking loperamide hydrochloride for irritable bowel syndrome, lisinopril for hypertension, bupropion hydrochloride for mood instability, and 5 mg/325 mg of hydrocodone/acetaminophen (discontinued on day 1). Other relevant medical history included ulcerative colitis, migraines, nephrocalcinosis, large colon resection (1994), lithotripsy (1998), and borderline diabetes (2006). The patient began the titration period with hydrocodone ER 15 mg every 12 hours on (b) (6) (day 1), and the dose was titrated to 30 mg every 12 hours by day 8. The patient began the double-blind period at a hydrocodone ER dose of 30 mg every 12 hours on day 15. On day 81, the

patient reported having abdominal pain, which gradually increased in severity, and the patient was admitted to the hospital on day 86. After admission to the hospital, the patient was found to have elevated levels of transaminases, bilirubin (11.2 mg/dL), lipase (>400 µ/L), and alkaline phosphatase (321 IU/L); and blood cell and absolute neutrophil counts were increased (20.1 k/mL and 18.6 k/mL, respectively). Ultrasound and magnetic resonance imaging revealed that the patient had gallbladder sludge, gallstones, and gallbladder polyps. The patient was diagnosed with the serious adverse event of acute pancreatitis (verbatim: gallstone pancreatitis). Bilateral nonobstructive renal stones and cysts, ulcerative diverticulitis, primary sclerosing cholangitis, and primary biliary stenosis were also diagnosed. Study drug treatment was interrupted while the patient was hospitalized (no study drug was taken on days 88-93). The patient was discharged from the hospital on day 92, and he resumed taking study drug on day 94. The pancreatitis resolved by day 99. The patient completed the study, and the last dose of study drug was taken on day 102.

Impression
The pancreatitis may have been related to the patient's gallstones which are known to cause pancreatitis. Opioids also are associated with pancreatitis but this appears less likely. He was able to resume taking his hydrocodone for an additional week after his symptoms improved.

Subject Number: 035007 (Hydrocodone ER)
Study Number 3079
Serious Adverse Event: Pancreatitis (2 episodes),
Anaphylactic reaction (to CT contrast)

Patient 035007 was a 59-year-old opioid-naïve obese (BMI=39.5 kg/m2) white woman with low back pain. At study entry, the patient was taking spironolactone for edema, acetylsalicylic acid for cardiac prophylaxis, and meloxicam (NSAID). Other relevant medical history included cholelithiasis/cholecystectomy, broken back, osteoarthritis, gastroesophageal reflux disease, anxiety, and depression. The patient was a smoker with no history of alcohol abuse. The patient began the open-label titration period with hydrocodone at 15 mg every 12 hours on (b) (6) (day 1). The patient achieved a successful dose of 15 mg every 12 hours and on day 9 was randomly assigned to the hydrocodone treatment group during the double-blind treatment period. The patient also received 5 mg/325 mg of hydrocodone/acetaminophen as a rescue medication beginning on day 9. On day 61, the patient was hospitalized with severe pancreatitis. Study drug treatment (hydrocodone) was discontinued. On day 62, the patient had a moderate anaphylactic reaction due to administration of the computed tomography scan contrast. The anaphylactic reaction was treated with methylprednisolone, ranitidine and diphenhydramine. Both pancreatitis and the anaphylactic reaction resolved with no residual effect by day 64. Study drug treatment (hydrocodone and rescue medication) was restarted on day 66. On day 71, the patient was hospitalized a second time for severe pancreatitis, which was reported as a serious adverse event. The patient was

treated for pancreatitis pain with morphine, 5 mg/500 mg of hydrocodone/acetaminophen (days 71 to 77), and nalbuphine (days 72 to 77). A computed tomography scan of the abdomen and pelvis was suspicious for minimal acute pancreatitis after cholecystectomy. Pancreatitis resolved with residual effect on day 77. The patient withdrew her consent because of the adverse event and study drug treatment was discontinued (last dose was taken on day 70). The patient was withdrawn from the study on day 87 because of pancreatitis. Subsequent to the acute episodes of pancreatitis, the patient developed chronic pancreatitis and was seen by a pancreas specialist who conducted multiple procedures and felt the patient might have autoimmune pancreatitis. ERCP evaluation from (b) (6) showed moderate pancreatitis with skip strictures and irregular side branches in the body and tail of the pancreas suggestive of autoimmune pancreatitis. She was evaluated by another specialist who felt she had idiopathic chronic pancreatitis and doubted that the initial inciting event was the hydrocodone, but could not exclude that. She was identified with a pancreatic duct stricture and underwent a distal pancreatectomy and splenectomy for pancreatic duct stricture on (b) (6). The pathology report from that date showed:

> Benign pancreatic parenchyma with chronic inflammation and acinar atrophy and acute inflammation within peripancreatic adipose tissue. Chronic sclerosing pancreatitis. Sections from the pancreas show diffuse fibrosis and acinar extinction. There is periductal and perineural inflammation including both lymphocytes and plasma cells. Duct infiltrating lymphocytes present IgG4 immunostain highlights as many as 20 IgG4 positive plasma cells in a single high power field. Taken with morphologic features displayed; this degree of IgG4 positivity is suggestive of autoimmune sclerosing pancreatitis.

Impression
Hydrocodone cannot be excluded as the cause of this patient's pancreatitis but the etiology may also be due to autoimmune chronic pancreatitis/autoimmune sclerosing pancreatitis.

Subject Number: 10385011 (Hydrocodone ER)
Study Number: 3104
Serious Adverse Event: Intestinal Obstruction

Patient 10385011 was an opioid-experienced, 74-year-old white man with chronic low back pain. At entry into the study, the patient was taking warfarin sodium for hypercoagulation disorder, amiodarone hydrochloride for atrial fibrillation, and metformin for type 2 diabetes. Other relevant medical history included obesity (BMI = 41.3 kg/m^2), abdominal hernia, hypertension, pulmonary embolism, intestinal obstruction, diverticulitis, intestinal resection, arthralgia, intervertebral disc protrusion, osteoarthritis, and sleep apnea. He was randomized to hydrocodone bitartrate extended-release tablets in Study 3103. In Study 3104, the patient began the open-label adjustment period with hydrocodone 60 mg every 12 hours on (b) (6) (day 1) and was adjusted down to 45 mg every 12 hours on day 5. The patient did not reach a

successful pain relief dose. On day 18, the patient was hospitalized with severe intestinal obstruction. The intestinal obstruction was diagnosed as secondary to an abdominal wall hernia; the associated pain was treated with morphine. On the same day, the patient had an adverse events of diabetic neuropathy, vomiting, electrolyte imbalance, insomnia, gastroesophageal reflux disease, hypoglycemia, and anxiety. All of these events resolved within 5 days. Study drug treatment was discontinued because he could not keep anything down; his last dose of study drug was taken on day 18. The intestinal obstruction resolved by day 23. The patient was withdrawn from the study on day 34.

Impression
Hydrocodone may have been the cause or contributing factor for this patient's intestinal obstruction. However, the patient had a history of intestinal resection and prior intestinal obstruction which could have caused or exacerbated the obstruction.

Subject Number: 015006 (Hydrocodone ER)
Study Number: 3080
Serious Adverse Event: Small Intestinal Obstruction (abdominal adhesions)

Patient 015006, a rollover patient from Study 3079, was a 44-year-old white woman with osteoarthritis as her primary chronic pain condition. She did not use caffeine or alcohol. At study entry, the patient was taking sertraline for depression, simvastatin for hyperlipidemia, meloxicam,fludrocortisone acetate for hypotension, and hyoscyamine sulfate as needed for abdominal pain. Other relevant medical history included hyperlipidemia, hypoglycemia, obesity, gastric bypass surgery, hiatal hernia, hysterectomy, intermittent kidney infections, tubal ligation, degenerative disc disease, insomnia, and panic attacks. The patient began the open-label titration period with hydrocodone 15 mg every 12 hours on (b) (6) (day 1). The patient achieved a successful dose of 30 mg every 12 hours, and she began the open-label treatment period on day 8. On day 313, the patient had nausea and dehydration and abdominal adhesions (verbatim: abdominal wall adhesions) and small intestinal obstruction (verbatim: small bowel obstruction) reported as serious adverse events. The patient was hospitalized and underwent an exploratory laparotomy with lysis of adhesions and small bowel resection with primary anastomosis. Final diagnosis was bowel obstruction in the right lower quadrant secondary to abdominal wall adhesions. Treatment with study drug was interrupted on day 313. The abdominal adhesions and small intestinal obstruction resolved with no residual effect on day 317. Study drug was restarted on day 329. The patient completed the study on day 429. The investigator considered the events not related to study drug treatment.

Impression
The small bowel obstruction in this patient appears to be due to abdominal adhesions which required surgery. Her small bowel obstruction resolved following surgery and she was able to resume study drug without any reported problems.

Subject Number: 011109 (Hydrocodone ER)
Study Number: 3080
Serious Adverse Event: Cholecystitis acute

Patient 011109 was an opioid-naïve, 47-year-old white man with back pain as his primary chronic pain condition. The patient consumed caffeine and alcohol. At study entry, the patient was taking amphetamine/dextroamphetamine for attention deficit-hyperactivity disorder, carisoprodol for low back pain and muscle spasms, ibuprofen, amlodipine besilate for hypertension, 25 mg of tramadol 4 times daily, and alprazolam for insomnia. Other relevant medical history included hearing loss, spinal stenosis, insomnia, and anxiety. The patient began the open-label titration period with hydrocodone 15 mg every 12 hours on (b) (6) (day 1). The patient achieved a successful dose of 45 mg every 12 hours, and he began the open-label treatment period on day 7. On day 132, the patient had acute cholecystitis, which was reported as a serious adverse event, and a gallbladder abscess. On day 151, the patient was hospitalized with chest pain, epigastric pain, right upper quadrant discomfort, diarrhea, chills, low-grade fever, black stools, and a poor appetite. A chest x-ray revealed mild bibasilar atelectasis, mild emphysema, and moderate renal cysts. A computed tomography (CT) scan of the abdomen and pelvis revealed gallbladder wall thickening, no gallstones, and mild intrahepatic biliary ductal dilation; the presence of a hepatic abscess could not be excluded. A magnetic resonance cholangiopancreatography scan showed a suspected hepatic abscess with gallbladder sludge. The patient underwent an urgent cholecystectomy with purulent fluid drainage of the gallbladder abscess. The patient was treated with enoxaparin sodium, pantoprazole sodium, ciprofloxacin, metronidazole, piperacillin/tazobactam, atorvastatin, acetylsalicylic acid, ciprofloxacin, and metronidazole. The acute cholecystitis and gallbladder abscess resolved with no residual effect by day 154. Study drug treatment was not interrupted while the patient was hospitalized; however, treatment was interrupted on days 157 and 158 because the patient ran out of medication. The patient completed the study on day 387. The investigator considered the events not related to study drug treatment.

Impression
The patient's acute cholecystitis and gallbladder abscess were of unclear etiology. However, the patient tolerated and continued treatment with hydrocodone throughout the time of his cholecystitis.

Subject Number: 10357010 (Hydrocodone ER)
Study Number: 3104
Serious Adverse Event: Cholecystitis, cholangitis, cholelithiasis, acute renal failure

Patient 10357010 was a 65-year-old opioid experienced man enrolled in Study 3103 with diagnosis of chronic low back pain. At study entry the patient was taking hydrochlorothiazide, metoprolol, and lisinopril for hypertension; omeprazole and ondansetron for gastrointestinal reflux disease (GERD); and simvastatin for hyperlipidemia. In Study 3103 he was randomized to hydrocodone and his dosage was increased from 45 to 60 mg on day 8 which he stayed on for the remainder of the study. In Study 3104, the patient's dosage was increased to 90 mg and the patient began the open-label treatment period at a dosage of 90 mg twice daily on day 22. On day 78, the patient had adverse events of vomiting, abdominal pain, and nausea that were considered by the investigator to not be related to study drug treatment. The patient had serious adverse events of cholecystitis, cholangitis, cholelithiasis, and acute renal failure. The patient was hospitalized as a result of these events on day 83 and underwent a sphincterectomy and common bile duct stone removal for a large distal bile duct stone of 1 cm. Following these procedures, the patient underwent laparoscopic cholecystectomy with choleangiogram. All adverse events resolved within 1 week. The patient was withdrawn from the study on day 127 due to the adverse events.

Impression
This patient had a common bile duct stone which is a known cause of cholecystitis.

Subject Number: 10366046 (Hydrocodone ER)
Study Number: 3104
Serious Adverse Event: Cholestasis

Patient 10366046 was a 75-year-old opioid naïve man enrolled in Study 3103 with a diagnosis of chronic low back pain. At study entry, the patient was taking metaprolol and enalapril maleate for hypertension, digoxin for atrial fibrillation, dilitiazem for atrial flutter, aspirin for cardiac prophylaxis, pravastin for hypercholesterolemia, trazodone for insomnia, brimonidine for glaucoma, and indomethacin for gout. Other medical history included obesity, coronary artery disease, cardiomegaly, pancreatitis, gastrointestinal reflux disease (GERD), splenic granuloma, chronic renal failure, renal mass, venous insufficiency, urinary tract infections, and elevated gamma glutamyltransferase (GGT). He was randomly assigned to receive placebo in Study 3103. In Study 3104, the patient began the open-label adjustment period with 60-mg hydrocodone bitartrate extended-release tablets twice daily on day 1. His dosage was increased to 90 mg twice daily on day 7. The patient began the open-label treatment period at a hydrocodone dosage of 90 mg twice daily on day 20 and continued at that dosage for the remainder of the study. The patient went to the emergency room on day 171 due to exhaustion and a loss of appetite. The patient was admitted to the hospital and endoscopic ultrasound and endoscopic retrograde cholangiopancreatography showed cholestasis. On day 172, the serious adverse event of cholestasis was reported, which was considered by the investigator not related to treatment with study drug. The patient underwent surgery for cholestasis. The events of cholestasis and jaundice cholestatic resolved within 3 days. The patient was discharged from the hospital on day 175. The patient had 2 associated

laboratory values that were potentially clinically significant during the study. The patient's GGT level was 258 U/L (screening value was 116 U/L), which met the criteria for significance of ≥3 x ULN (normal range 0 to 75 U/L). At the final assessment on day 181, the patient's GGT level had elevated further to 1176 U/L. On that day, the patient also had an alkaline phosphatase value of 708 U/L that met the criteria for significance (≥3 x ULN, normal range 20 to 125 U/L). On return visit 11 days later both the GGT and alkaline phosphatase values remained elevated (803 and 422 U/L, respectively) but less than previously. Total bilirubin was normal at baseline but mildly elevated at the final assessment (1.6 mg/dL [normal range is 0 to 1.3 mg/dL). Other relevant laboratory values (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] remained normal throughout the study. No further laboratory tests were performed and the patient completed the study.

Impression
This patient's cholestasis dose not appear to be related to study drug and resolved with surgery.

Subject Number: 019101 (Hydrocodone ER)
Study Number: 3080
Serious Adverse Event: Syncope

Patient 019101 was an opioid-experienced, 69-year-old white man with osteoarthritis identified as his primary chronic pain condition. The patient consumed caffeine but not alcohol. At study entry, the patient was taking acetylsalicylic acid as a cardioprotective; atorvastatin calcium for dyslipidemia; exenatide, and insulin for type 2 diabetes mellitus; fexofenadine/pseudoephedrine for environmental (dust and mold) allergies; terazosin for benign prostatic hypertrophy; lisinopril for hypertension; acetaminophen/codeine as an around-the-clock opioid; meloxicam for osteoarthritis; omeprazole for gastroesophageal reflux disease; and lubiprostone for constipation. Other relevant medical history included chronic constipation, gastroesophageal reflux disease, hiatal hernia, recurrent back pain, diabetic neuropathy, and numbness of feet and hands. The patient began the open-label titration period with hydrocodone 15 mg every 12 hours on (b) (6) (day 1). The patient also received 5 mg/325 mg of hydrocodone/acetaminophen as rescue medication, beginning on day 7. The patient achieved a successful dose of 60 mg every 12 hours, and he began the open-label treatment period on day 22. On day 35, the patient went to the hospital reporting that 3 days prior he had fallen on the ice and hit the back of his head, but did not lose consciousness or change his normal activity. However, after strenuous lifting, he lost movement of his body and lost consciousness, which was assessed as syncope and reported as a serious adverse event. Treatment with study drug was interrupted on day 35 and was restarted on day 38. The syncope resolved with no residual effect on day 37. It was concluded that the event was a vasovagal response to strenuous lifting. The patient was withdrawn from the study on day 401 (last dose was taken on day 371)

because the patient felt the study drug was not working and he did not want to increase the dose.

Impression
The SAE of syncope was attributed to a vasovagal response from lifting. There was no evidence to suggest an arrhythmia or QT prolongation but limited details and no ECG findings were provided.

Subject Number: 017001 (Hydrocodone ER)
Study Number: 3080
Serious Adverse Event: Sedation, lumbar radiculopathy

Patient 017001, a rollover patient, was a 54-year-old white woman with low back pain. At study entry, the patient was taking montelukast sodium for allergic rhinitis, phenytoin for seizure disorder, ibuprofen for pain, and rabeprazole sodium for *Helicobacter pylori* infection. Other relevant medical history included atrial enlargement, hyperlipidemia, diverticulosis, dysphagia, gastroesophageal reflux disease, hiatal hernia, anterior cervical spinal fusion, S1 radiculopathy, lumbar spinal fusion, spinal stenosis, tingling in legs, chronic cough, and sleep apnea. The patient began the open-label titration period with hydrocodone 15 mg every 12 hours on (b) (6) (day 1). The patient also received 5 mg/325 mg of hydrocodone/acetaminophen as rescue medication, beginning on day 1. The patient achieved a successful dose of 45 mg every 12 hours, and she began the open-label treatment period on day 22. On day 217, the patient was hospitalized with the serious adverse event of bilateral L3 radiculopathy. On day 222, the patient underwent posterior spinal fusion, and she was treated with morphine sulfate for prophylaxis of surgical pain. On day 223 the patient was placed on 30 mg oxycodone every 12 hours and patient-controlled analgesia (unspecified medication) for breakthrough pain. As a result of the pain medications, the patient had acute mental status changes and the serious adverse event of severe sedation (verbatim: over narcotization). The patient was found to be oxygenating properly, was hemodynamically stable, but over-narcotized. The patient was treated with naloxone hydrochloride, and the patient's mental status/sedation markedly improved and resolved the same day with no residual effect. Treatment with the study drug was interrupted on day 218 and restarted on day 229. The patient completed the study on day 386. The investigator considered the events not related to study drug treatment.

Impression
This patient's sedation was unrelated to hydrocodone which had been temporarily discontinued at the time she developed her symptoms. However, the use of other opioids during her hospitalization resulted in sedation which is a known side effect of opioids.

Subject Number: 017114 (Hydrocodone ER)
Study Number: 3080

Serious Adverse Event: Hypotension, thrombocytopenia, renal failure acute, dehydration, Listeria sepsis

Patient 017114 was a new opioid-naive, 75-year-old white man with diabetic peripheral neuropathy identified as his primary chronic pain condition. The patient consumed caffeine and alcohol. At study entry, the patient was taking latanoprost for glaucoma, acetylsalicylic acid for cardiac prophylaxis, olmesartan medoxomil/hydrochlorothiazide for hypertension, nebivolol hydrochloride for supraventricular tachycardia, glipizide and insulin aspart for diabetes, gabapentin for diabetic peripheral neuropathy, rosuvastatin calcium for hyperlipidemia, furosemide for lower extremity edema, potassium for hypokalemia prophylaxis, allopurinol for hyperuricemia, and tadalafil as needed for erectile dysfunction. Other relevant medical history included stable kidney disease, bilateral cataracts (removal of left and right cataract), edema of the lower extremities, macrocytic anemia, thrombocytopenia, osteoarthritis, and osteoporosis. The patient began the open-label titration period with hydrocodone 15 mg every 12 hours on (b) (6) (b) (6) (day 1). The patient achieved a successful dose of 15 mg every 12 hours, and began the open-label treatment period on day 8. On day 180, the patient was hospitalized with thrombocytopenia (verbatim: worsening thrombocytopenia), acute renal failure, dehydration, and severe Listeria sepsis, which were reported as serious adverse events. It was reported that since the patient had begun an extremely restrictive low-carbohydrate diet and was taken off of insulin, he was experiencing increased fatigue and lethargy and generalized joint discomfort. Treatment with the study drug was interrupted on day 181 and was restarted on day 185. The patient was treated with dextrose, sodium chloride, and sodium bicarbonate for dehydration; sultamicillin and ampicillin for Listeria sepsis; pregabalin for diabetic peripheral neuropathy; pioglitazone hydrochloride, insulin glargine, and insulin for diabetes mellitus; and zolpidem tartrate for insomnia; and he was given oxygen therapy. The events resolved with no residual effect by day 185. On day 224, the patient was hospitalized for the serious adverse event of hypotension (possibly due to dehydration). The patient was treated with dextrose and sodium chloride for dehydration, zolpidem tartrate for insomnia prophylaxis, lorazepam for anxiety prophylaxis, heparin for coagulation prophylaxis, allopurinol for hyperuricemia, and ampicillin for urinary tract infection. The hypotension resolved with no residual effect on day 226. The patient completed the study on day 463.
The investigator considered the events not related to study drug treatment.

Impression
The patient's SAEs of thrombocytopenia, renal failure, dehydration and Listeria sepsis do not appear related to study drug. Hydrocodone ER cannot be completely excluded as a contributing factor of this patient's hypotension but this appears unlikely since the patient was on study drug for 224 days prior to developing hypotension and once his symptoms resolved was able to continue on study drug for over an additional 200 days until the end of the study.

Overall Summary of Serious Adverse Events

Most of the SAEs were not related to hydrocodone. Two subjects had an SAE of pancreatitis. One of the cases appeared to be due to gallstones and autoimmune pancreatitis was a possible cause for the other case. There were three reports of cholecystitis or cholestasis. One case (Subject #10357010) appeared to be related to a common bile duct stone, another case (Subject 10366046) resolved with surgery and the third case (Subject #011109) was of unclear etiology but the patient remained on hydrocodone throughout the episode of actue cholecystitis and tolerated treatment with hydrocodone ER for over an additional 150 days after resolution of his acute cholecystitis. There is no clear evidence that any of the cases of pancreatitis or biliary tract disease was due to hydrocodone. The currently approved opioid label for hydrocodone products and the proposed Vantrela label contains the following statement, "Hydrocodone may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis." The proposed label lists pancreatitis as a rare (<1%) adverse drug reaction.

The SAE of accidental overdose and respiratory arrest (Subject #10388023) was related to use of hydrocodone but due to this subject's complicated medical history of rhabdomyolysis and renal failure it is difficult to assess the contributory role of his underlying medical condition on the overdose. This patient was also receiving hydrocodone ER 90 mg twice daily, the highest dose allowed in the study. Overdose and respiratory depression are known dose dependent complications of opioid use.

7.3.3 Dropouts and/or Discontinuations

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.

7.3.4 Significant Adverse Events

Discussed in Section 7.3.2

Standard MedDRA Query (SMQ)
No cases were identified for severe cutaneous adverse reactions SMQ and for possible drug-related hepatic disorders SMQ.

7.3.5 Submission Specific Primary Safety Concerns

Not applicable

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Of the 1176 patients who were enrolled in the Phase 3 studies, 864 (73%) patients reported at least 1 adverse event. Adverse events reported by ≥5% of patients were constipation 23%, nausea 23%, headache 12%, somnolence 10%, vomiting 10%, dizziness 7%, pruritus 6%, fatigue 5%, and diarrhea 5%.

During the double-blind studies, the adverse drug reactions (reported in ≥2% of patients) during the titration period and/or the post-titration treatment period are shown in (Table 35). The most common adverse events in the hydrocodone treatment group were consistent with the opioid class of drugs and included nausea, constipation, headache, somnolence and vomiting.

Table 35: Adverse Drug Reactions (Reported in ≥2% of Patients) by Preferred Term and Treatment Group During the Titration Period and/orDouble-Blind Post-Titration Treatment Period in Studies 3079 and 3103

	Titration Period*	Double-Blind Treatment Period	
MedDRA 16.0 preferred term	**VANTRELA ER N=1012 n (%)**	**Placebo N=326 n (%)**	**VANTRELA ER N=337 n (%)**
Number of patients with at least 1 AE	540 (53%)	179 (55)	199 (59)
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)

Patients are counted only once in each preferred term category.
* Titration Period includes all patients who started the open-label titration for the 2 double-blind studies (Studies 1 and 2), regardless if they entered the Double-Blind Treatment Period or not.

7.4.2 Laboratory Findings

For the Phase 3 studies, routine laboratory measurements were obtained at the beginning and end of the study. There did not appear to be any clinically meaningful trends in mean changes from baseline for any of the chemistry laboratory tests. In the double-blind studies (Studies 3079 and 3103), 30 patients had potentially clinically important abnormal serum chemistry values, 16 (5%) patients in the hydrocodone ER group and 14 (4%) patients in the placebo group (Table 36). The number of patients with potentially clinically important serum chemistry abnormalities and the types of abnormalities appeared similar between the treatment groups. No clinically significant

difference in the shifts in clinical laboratory values from normal range at baseline to outside the normal range at end of study was apparent between the hydrocodone ER and placebo groups in the double-blind studies (Table 37). No patients met criteria for drug-induced liver injury.

Table 36: Chemistry Laboratory Tests Potentially Clinically Important Abnormal Results, Post-titration Analysis Set for the Double-blind Studies (3079 and 3103)

Test	Significance criteria	Placebo N=326 n/N' (%)	Hydrocodone ER N=337 n/N' (%)
Patients with at least 1 abnormality		14/316 (4)	16/322 (5)
Blood urea nitrogen (mmol/L)	≥10.71	4/316 (1)	5/322 (2)
Creatinine (µmol/L)	≥177	0/316	1/322 (<1)
Uric acid (µmol/L)	Male ≥625 Female ≥506	5/316 (2)	9/322 (3)
Alanine aminotransferase (SGPT) (U/L)	≥3 × ULN	1/316 (<1)	2/321 (<1)
Gamma-glutamyl transpeptidase (U/L)	≥3 × ULN	6/171 (4)	5/178 (3)

Source: ISS. Table 34, p159
N=number of patients; n=number of patients in subgroup; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of the normal range.
Note: The denominator (N') for calculating the percentage of patients with at least 1 abnormality is the number of patients with a postbaseline chemistry laboratory result. The denominator (N') for calculating the percentage of patients with at least 1 abnormality for each test is the number of patients with a postbaseline result for that test.

Table 37: Shift Summary of Chemistry Results from Baseline to Endpoint by Treatment Group for Posttitration Double-Blind Studies 3079 and 3103

		Placebo (N=326)			Hydrocodone ER (N=337)		
		Baseline			Baseline		
Parameter	Endpoint	Low	Normal	High	Low	Normal	High
Sodium	Low	2 (<1%)	3 (1%)	0	1 (<1%)	2 (<1%)	0
	Normal	3 (<1%)	297 (91%)	8 (3%)	2 (<1%)	302 (90%)	9 (3%)
	High	0	3 (1%)	0	0	5 (1.5%)	0
Potassium	Low	1 (<1%)	5 (1.5%)	0	0	2 (<1%)	0
	Normal	4 (1%)	294 (90%)	6 (2%)	2 (<1%)	312 (93%)	1 (<1%)
	High	0	5 (1.5%)	0	0	4 (1%)	0
Chloride	Low	1 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0
	Normal	1 (<1%)	305 (94%)	2 (<1%)	0	307 (91%)	6
	High	0	4 (1%)	2 (<1%)	0	5 (1.5%)	1 (<1%)
Bicarbonate	Low	3 (1%)	13 (4%)	0	3 (1%)	5 (1.5%)	0
	Normal	12 (7%)	287 (88%)	1(<1%)	18 (5%)	294 (87%)	0
	High	0	0	0	0	0	0

		Placebo (N=326)			Hydrocodone ER (N=337)		
		Baseline			Baseline		
Parameter	Endpoint	Low	Normal	High	Low	Normal	High
Glucose	Low	1 (<1%)	3 (1%)	0	2(<1%)	5 (1.5%)	2(<1%)
	Normal	6 (2%)	188 (58%)	32 (10%)	5 (1.5%0	192 (6%)	23 (7%)
	High	2 (<1%)	28 (9%)	56 (17%)	3 (1%)	48 (14%)	41 (12%)
Blood Urea Nitrogen	Low	0	2 (<1%)	0	2 (<1%)	4 (1%)	0
	Normal	4 (1%)	287 (88)	13 (4%)	2 (<1%)	294 (87)	10 (3%)
	High	0	7 (2%)	3 (1%)	0	6 (2%)	4 (1%)
Creatinine	Low	19 (6%)	13 (4%)	0	14 (4%)	7 (2%)	0
	Normal	10 (3%)	250 (77%)	8 (3%)	10 (3%)	270 (80%)	3 (1%)
	High	1(<1%)	7 (2%)	8 (3%)	0	10 (3%)	8 (2%)
Calcium	Low	0	0	0	0	0	0
	Normal	0	136 (42%)	3 (1%)	0	132 (39%)	3 (1%)
	High	0	4 (1%)	2 (<1%)	0	6 (2%)	3 (1%)
Albumin	Low	0	0	0	0	0	0
	Normal	2 (<1%)	143 (44%)	0	0	142 (42%)	1 (<1%)
	High	0	0	0	0	0	0
Uric Acid	Low	2 (<1%)	1 (<1%)	0	1 (<1%)	2 (<1%)	0
	Normal	3 (1%)	282 (87%)	12 (4%)	2 (<1%)	279 (83%)	17 (5%)
	High	0	5 (1.5%)	11 (3%)	0	7 (2%)	14 (4%)
SGOT (AST)	Low	0	2 (<1%)	0	0	0	0
	Normal	0	289 (89%)	8 (3%)	0	296 (88%)	7 (2%)
	High	0	10 (3%)	5 (1.5%)	0	11 (3%)	3 (1%)
SGPT (ALT)	Low	0	1 (<1%)	0	0	0	0
	Normal	1 (<1%)	280 (86%)	11 (3%)	0	278 (82%)	18 (5%)
	High	0	12 (4%)	11 (3%)	0	14 (4%)	10 (3%)
Alk Phos	Low	0	0	0	0	1 (<1%)	0
	Normal	1(<1%)	296 (91%)	4 (1%)	0	295 (88%)	7 (2%)
	High	0	6 (2%)	9 (3%)	0	7 (2%)	11(3%)
Total Bilirubin	Low	2 (<1%)	7 (2%)	0	3 (<1%)	7 (2%)	0
	Normal	10 (3%)	294 (90%)	2 (<1%)	12 (4%)	297 (88%)	0
	High	0	1 (<1%)	0	0	1 (<1%)	1 (<1%)
Cholesterol	Low	25 (8%)	9 (3%)	0	33 (10%)	16 (5%)	0
	Normal	10 (3%)	90 (28%)	6 (2%)	5 (1%)	84 (25%)	3 (<1%)
	High	0	4 (1%)	1 (<1%)	0	3 (<1%)	0

Source: Data from ISS, Summary 9.3.0.4

Hematology

In Studies 3079 and 3103 during the double-blind period, shifts from normal to abnormal values in placebo and hydrocodone ER groups are shown in (Table 38). Shifts for hemoglobin, hematocrit, WBC, and platlet count appeared similar between the placebo and hydrocodone ER groups. Review of the mean changes in hemoglobin, hematocrit, WBCs and platlets from screening to endpoint in the posttitration analysis set of the double-blind studies showed no apparent clinically meaningful differences between hydrocodone ER and placebo groups.

Table 38: Shift Summary of Hematology Results from Baseline to Endpoint for Posttitration Double-Blind Studies 3079 and 3103

		Placebo (N=326)			Hydrocodone ER (N=337)		
		Baseline			Baseline		
Parameter	**Endpoint**	Low	Normal	High	Low	Normal	High
Hemoglobin	Low	25 (8%)	10 (3%)	0	18 (5%)	17 (5%)	0
	Normal	17 (5%)	255 (78%)	6 (2%)	10 (3%)	264 (78%)	3 (1%)
	High	0	1 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)
Hematocrat	Low	15 (5%)	7 (2%)	0	6 (2%)	12 (4%)	0
	Normal	12 (4%)	264 (81%)	5 (2%)	6 (2%)	274 (81%)	7 (2%)
	High	0	4 (1%)	6 (2%)	0	5 (1%)	4 (1%)
WBC	Low	0	3 (1%)	0	0	7 (2%)	0
	Normal	1 (<1%)	281 (86%)	12 (4%)	3 (1%)	271 (80%)	9 (3%)
	High	0	12 (4%)	4 (1%)	0	17 (5%)	7 (2%)
Platlets	Low	3 (1%)	0	0	3 (1%)	1 (<1%)	0
	Normal	2 (<1%)	299 (92%)	5(2%)	0	287 (85%)	6 (2%)
	High	0	2 (<1%)	4 (1%)	0	8 (2%)	10 (3%)

7.4.3 Vital Signs

Vital signs for double-blind Studies 3079 and 3103 were reviewed during the posttitration period since there was a placebo group for comparison. No clinically significant differences in mean systolic or diastolic blood pressure, or pulse, were observed between placebo and hydrocodone treatment groups (Table 39). Table 40 shows the differences in the number of potentially clinically important abnormal vital signs for the hydrocodone ER group compared to the placebo group during the posttitration period for the double-blind studies. There were a total of 23 patients that had potentially clinically important abnormal vital signs values, 16 (5%) patients in the hydrocodone ER group and 7 (2%) patients in the placebo group. Due to the small number of patients with potentially clinically important abnormal vital signs it was difficult to interpret the significance of small differences between treatment groups. There did not appear to be any clinically meaningful differences except for possibly decreased blood pressure which was more common in the hydrocodone than placebo group (i.e., decreased systolic BP ≤90 and ≥ 15% decrease from baseline occurred in 2% of hydrocodone patients and less than 1% of placebo patients). This would not be unexpected clinically, since a mild hypotensive effect is known to occur with opioids. It was also noted that slightly more patients in the hydrocodone group had increased diastolic BP which clinically appears unlikely and is probably related to the small number of subjects.

Table 39:Summary of Mean Changes in Vital Signs From Baseline to Endpoint for Posttitration Analysis Set For Double-Blind Studies 3079 and 3103			
Parameter		Placebo (N=326)	Hydrocodone (N=337)
Systolic BP (Sitting) (mmHg)	Mean	-1.3	-0.7
	Min	-50	-44
	Max	39	53
Diastolic BP (Sitting) (mmHg)	Mean	-0.6	-0.4
	Min	-45	-24
	Max	29	42
Heart Rate (Sitting) (beats/min)	Mean	0.6	0.0
	Min	-34	-35
	Max	34	36

Source: ISS, Summary 10.3.0.1

Table 40: Vital Signs Potential Clinically Important Abnormal Values by Treatment **Group, Post-titration Analysis Set for the Double-blind Studies (Studies 3079 and 3103)**

Test	Significance criteria	Placebo N=326 n/N' (%)	Hydrocodone ER N=337 n/N' (%)
Patients with at least 1 abnormality		7/324 (2)	16/331 (5)
Heart rate (bpm)	≥120 and ≥15 increase from baseline	2/324 (<1)	1/331 (<1)
	≤50 and ≥15 decrease from baseline	1/324 (<1)	1/331 (<1)
Sitting systolic BP (mmHg)	≥180 and ≥20 increase from baseline	2/324 (<1)	2/331 (<1)
	≤90 and ≥20 decrease from baseline	3/324 (<1)	6/331 (2)
Sitting diastolic BP (mmHg)	≥105 and ≥15 increase from baseline	0/324	5/331 (2)
	≤50 and ≥15 decrease from baseline	0/324	3/331 (<1)

Source: ISS. Table 38, p169

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms (ECGs) were recorded at baseline and endpoint. Mean changes from baseline to endpoint by treatment group for the posttitration analysis set for double–blind studies 3079 and 3103 did not reveal any clinically significant differences between the placebo and the hydrocodone ER groups in heart rate, PR interval, or QRS interval. The mean changes from baseline to endpoint for QTcB (placebo 0.1 versus hydrocodone ER 2.9) and QTcF (placebo -1.9 versus hydrocodone ER 2.3) do not appear to be clinically meaningful. A thorough QT study was not done to characterize the QT-prolongation potential of hydrocodone. Therefore the following additional analyses for QTc were examined.

Change from baseline in QTc >60 msec and >30 msec

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 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.

ECG adverse event of QT prolongation
Patient Number: 10392002
Study Number: 3104 (rollover from Study 3103)
Adverse Event: Prolonged QT interval

Patient 10392002 was a 49 year old man with chronic low back pain enrolled in Study 3103 and randomly assigned to receive hydrocodone ER, titrated to 45 mg twice daily. At screening for Study 3103 (day –107), the patient's QT interval was 370 msec. At the final assessment for Study 3103, the QT interval was 454 msec, which was the adverse event reported as prolonged QT interval. The patient continued in Study 3104 on a hydrocodone ER dose of 45 mg twice daily. The patient had an unscheduled ECG on day 41 of Study 3104, at which time it was noted that the patient had borderline 1st degree atrioventricular block, but that the QT interval was 420 msec (improved from previously). At the final assessment of Study 3104 (day 167), the QT interval was 420 msec and the ECG showed borderline 1st degree atrioventricular block. The patient was permitted to continue participation and completed the study.

At study entry, the patient was taking sertraline hydrochloride, clonazepam, and lorazepam for anxiety; risperidone for bipolar disorder; lisinopril and dyazide for hypertension; topiramate for migraines; and various dietary supplements. Other medical history included borderline atrioventricular block 1st degree, gastroesophageal reflux disease, peripheral edema, dyslipidemia, obesity; asthma, chronic obstructive, and pulmonary disease.

Summary of Adverse Event
This patient's QT interval increased by 84 msec from the start of Study 3103 (QT interval 370 msec) until the end of the study (QT interval 454 msec). The patient continued on the same dose of hydrocodone ER in Study 3104 for an additional 167 days without any apparent problem. QT interval while in study 3104 was 420 msec on both day 41 and at the end of the study on day 167. The cause of this patient's prolonged QT interval is unclear but hydrocodone ER cannot be excluded as a cause or contributing factor.

QT Prolongation Summary
In conclusion, there was a trend for QTc changes from baseline greater than 30 msec and 60 msec to occur more frequently in the hydrocodone ER treatment group compared to the placebo treatment group. This evidence of a potential association with QTc prolongation and use of hydrocodone ER requires further assessment with a tQT study. The relatively small increases in QTc and lack of a clear signal based on absolute QTc changes greater than 480 msec support the safety of approving this product with an appropriate warning and allowing completion of a definitive tQT study as a postmarketing requirement.

7.4.5 Special Safety Studies/Clinical Trials

Audiology Evaluations
Since hearing loss has been associated with the use of hydrocodone/acetaminophen combination products, and the potential exposure to hydrocodone from this product is higher than the labeled doses from combination products, the FDA requested that Teva perform audiometry assessments to monitor for potential hearing loss. Results of the audiometry evaluations and clinically significant hearing changes for clinical studies 3103 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.

7.4.6 Immunogenicity

Not assessed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects and respiratory depression.

7.5.2 Time Dependency for Adverse Events

In general, the percentages of subjects who experienced common adverse events were higher during the titration period of the controlled studies than in the double-blind period, suggesting that more adverse events occur early on in therapy.

7.5.3 Drug-Demographic Interactions

No formal studies were conducted to evaluate the effect of age on the pharmacokinetics of Vantrela ER. However, elderly subjects are more likely to have compromised renal function and theorectically experience higher hydrocodone exposures as compared to younger subjects with normal renal function.

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not assessed.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies (other than alcohol) have been performed with Vantrela ER.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

No formal clinical trials in humans have been conducted assessing the effects of HC-ER on reproduction, pregnancy or lactation. There were four pregnancies reported during the development program with three occurring in Study 3103 and one in Study 3104. Patient 10358005 (Study 3103) reported a pregnancy during the open-label titration period and delivered a healthy baby. Patient 10391004 (Study 3103) reported a pregnancy during the double-blind treatment period (placebo group) and delivered a healthy baby. Patient 10385007 (Study 3103) discussed in the section on SAEs reported a pregnancy during the open-label titration period and had a spontaneous abortion. Since spontaneous abortion is common during pregnancy and the patient was on multiple medications, it is difficult to draw any conclusions from this one case. Patient 10408002 (Study 3104) was a 34 year old woman who reported that she was pregnant on day 50 (28 October 2013) of treatment with hydrocodone 60 mg every 12 hours. The date of her last menstrual period was 12 August 2013. The patient was

withdrawn from the study as a result of the pregnancy. Upon follow-up, it was reported that the patient had an elective abortion in November 2013. No additional information was provided.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies have been performed to date with Vantrela. The requirement under the Pediatric Research Equity Act for pediatric studies was deferred.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose
In Phase 3 studies, there was one report of an accidental overdose. A complete discussion of this SAE (Subject 10388023/Study 3103) is provided in Section 7.3.2. Briefly, this was a 70 year old man who was taking a statin and had an accidental overdose and respiratory arrest. The overdose and respiratory depression appear related to hydrocodone but insufficient information was provided to exclude concomitant use of other opioids as a contributing factor and a complicated medical history may have also contributed to the overdose. Renal impairment due to rhabdomyolysis from statin use may have led to both liver and kidney dysfunction, which had the potential to impair the metabolism of hydrocodone. The complexity of this case makes it difficult to draw any firm conclusions about this case except that overdose and respiratory depression are potential known serious complications of opioid use.

Drug Abuse Potential
Vantrela extended-release tablets, 15 mg, 30 mg, 45 mg, 60 mg and 90 mg contain [redacted] (b) (4) . Vantrela tablets do not contain polyethylene oxide (PEO).

Dr. Katherine Bonson from the Controlled Substance Staff (CSS) reviewed the nonclinical and clinical abuse-related data submitted in the NDA and recommended that 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. Also, the formulation resists extraction of hydrocodone bitartrate into small volumes that simulate intravenous use, rendering mixtures difficult to filter and pass through a needle. However, Dr. Bonson states in her review that 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. The study results show that extraction from lower strength tablets was inefficient under most of the conditions tested, and that only under specific conditions of extraction, comminuted 90 mg tablets afforded a solution that could potentially be abused by injection.

Diversion During Clinical Studies
Dr. Bonson noted that in Studies 3079 and 3080 the overall rate of study drug loss was < 9% for Study 3079, and 11% for Study 3080. Most occurrences for study drug loss with either CEP-33237 or rescue medication was for 10 or fewer tablets. The overall rate of possible diversion of study drug was 1% in the 12-week study (Study 3079) and 2% in the 12-month study (Study 3080). However, the Sponsor notes that more patients reported diversion of rescue medication than CEP-33237 tablets in Study #3079 (3 rescue; 1 CEP-33237) and in Study #3080 (4 rescue; 3 CEP-33237; 1 patient had both stolen).

Summary for Study #3103 and Study #3104
In Studies 3103 and 3104, Dr. Bonson, reported that the overall rate of study drug loss was approximately 3% in Study 3103 with CEP-33237 being lost by more patients than either rescue medication or placebo. There was no study drug loss reported in Study 3104. The overall rate of diversion of study drug was < 2% in the 12-week study (Study 3103) and <1% in the 6-month study (Study 3104). In Study 3103, 5 patients diverted CEP-33237, 4 patients diverted rescue medication (hydrocodone/ acetaminophen IR tablets), and 2 patients diverted both medications. In Study 3104, one patient diverted both CEP-33237 and rescue medication.

7.7 Additional Submissions / Safety Issues
The Applicant submitted the 4 month safety update on April 22, 2015. The update included five new adverse drug reactions: pyrexia, contusion, neck pain, lethargy, and tremor. Overall, the information presented in the safety update does not change the safety profile of hydrocodone ER based on the initial NDA submission.

8 Postmarket Experience

There is no postmarket experience with Vantrela.

9 Appendices

9.1 Literature Review/References
Not applicable

9.2 Labeling Recommendations
The labeling review is still ongoing by the Division.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held for this product

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

/s/

ROBERT A LEVIN
12/18/2015

JOHN J FEENEY
12/18/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 207975 **Applicant:** TEVA **Stamp Date:** 12-23-14

Drug Name: Hydrocodone Bitartrate Extended-release Tablets (CEP-33237) **NDA Type:** Standard

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505(b)(2) Reference Drug: Vicoprofen (NDA 20716)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			x	Opioids are titrated to effect. The PK profile is consistent with q12 hour dosing
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study # 3103	x			

File name: Clinical Filing Checklist for NDA 207975

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			Study 3103 was a 12-week, randomized, double-blind, placebo-controlled, randomized-withdrawal study in moderate to severe chronic LBP.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			The primary efficacy variable was the change from baseline to week 12 in weekly average of daily worst pain intensity.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	Pivotal Study 3103 was conducted in the U.S.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			ECGs were obtained at baseline and end of study in double-blind studies 3079 and 3103
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	The Applicant reports that this abuse-deterrent formulation of hydrocodone ER is not yet marketed in any country.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	Since the safety of hydrocodone has been established in previously approved combination products, the Division in a meeting with the Applicant on July 14, 2010 agreed to a safety database of at least 100 patients treated for 6 months and 50 patients treated

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
					for 12 months. The Applicant has exceeded this requirement with 243 patients treated for at least 6 months and 197 patients treated for at least 1 year.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		x		A coding dictionary was created from the dataset that contained the preferred terms that the verbatim terms were mapped to
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Yes
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			Hearing monitored during the Phase 3 trials as requested by the Division
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Proposed pediatric study plan provided in Module 1.9.6
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?				Module 1.11.4
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Robert Levin, MD	February 19, 2015
Reviewing Medical Officer	Date
John, Feeney, MD	February 19, 2015
Clinical Team Leader	Date

File name: Clinical Filing Checklist for NDA 207975

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

/s/

ROBERT A LEVIN
02/19/2015

JOHN J FEENEY
02/19/2015