VANTRELA™ ER (HYDROCODONE BITARTRATE) EXTENDED-RELEASE TABLETS

(CEP-33237)

OPEN SESSION

JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

07 JUNE 2016

Advisory Committee Briefing Materials: Available for Public Release

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition or Explanation
ABC	Addiction Behavior Checklist
ADF	Abuse-deterrent formulation
ADT	Abuse-deterrent technology
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AQ	Abuse quotient (C_{max}/t_{max})
ARCI	Addiction Research Center Inventory
AUC	Area under the plasma concentration curve (subscripts that may follow indicate time points [ie, $AUC_{0-\infty}$ means from time zero to infinity])
$AUC_{0-\infty}$	AUC from time 0 to infinity
AUC_{0-t}	AUC from time 0 to the time of the last measurable drug concentration
AUC_{0-tmax}	AUC from time 0 to median t_{max}
$AUC_{0-tmax, CEP (IN)}$	AUC from time 0 to the median t_{max} for VANTRELA ER when manipulated and administered intranasally
$AUC_{0-tmax, ZOHYDRO ER (IN)}$	AUC from time 0 to the median t_{max} for ZOHYDRO ER when manipulated and administered intranasally
AUC_{τ}	AUC over a dosing interval
AUEC	Area under the effect curve (subscripts that may follow indicate time points [ie, 0-xh means from time zero to x hours after the dose])
BID	Twice a day (Bis in die)
BMI	Body mass index
BPI-SF	Brief Pain Inventory – Short Form
CI	Confidence interval
CIMA	CIMA Labs, Inc.
C_{max}	Maximum observed plasma drug concentration
CNS	Central nervous system
COMM	Current Opioid Misuse Measure
COPD	Chronic obstructive pulmonary disease
COWS	Clinical Opiate Measure Withdrawal Scale
DAWN	Drug Abuse Warning Network

Abbreviation	Definition or Explanation
DEA	Drug Enforcement Agency (of the United States)
DLEQ	Drug Liking and Effects Questionnaire
EERW	Enriched-enrolment-randomized withdrawal
E_{max}	Maximum effect
E_{min}	Minimum effect
ER	Extended-release
FDA	Food and Drug Administration (of the United States)
hr	hour
HPLC	High Performance Liquid Chromatography
IN	Intranasal
IND	Investigational New Drug (application)
IR	Immediate-release
ITT	Intent-to-treat
IV	Intravenous
LA	Long acting
LS	Least-squares
LSD	Lysergic Acid Diethylamide
MAR	Missing at random
MBG	Morphine Benzedrine Group
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MNAR	Missing not at random
NDA	New Drug Application
NRS	Numerical rating scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
PCAG	Pentobarbital Chlorpromazine Alcohol Group
PDUFA	Prescription Drug User Fee Act
PMR	Post-Marketing Requirement
PSD	Particle size distribution
PVAQ	Price Value Assessment Questionnaire

Abbreviation	Definition or Explanation
q12h	Every 12 hours
REMS	Risk Evaluation and Mitigation Strategy
RMDQ	Roland Morris disability questionnaire
ROA	Route of administration
SD	Standard deviation
SE	Standard error
SEM	Standard error of least squares mean
SOAPP-R	Screener and Opioid Assessment for Patients with Pain - Revised
SOC	System Organ Class
SOWS	Subjective Opiate Withdrawal Scale
SRAII	Subject-rated Assessment of Intranasal Irritation
$t_{1/2}$	Elimination half-life
t_{max}	Time to C_{max}
US	United States (of America)
VAS	Visual Analog Scale
v/v	Volume/volume
WPI	Worst pain intensity
w/w	Weight/weight

1. EXECUTIVE SUMMARY

As part of the Food and Drug Administration (of the United States [US]) (FDA)'s Opioid Action Plan, the Agency will expand the use of advisory committees. Subsequently, the FDA requested that the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee review data from abuse deterrence studies of VANTRELA™ ER[1] (hydrocodone bitartrate) extended-release (ER) tablets. The committees will be asked to determine whether the data submitted as part of the New Drug Application (NDA) for VANTRELA ER are sufficient to support labeling that VANTRELA ER has properties that are expected to deter abuse.

VANTRELA ER (CEP-33237) is an abuse-deterrent formulation (ADF) of ER single-entity hydrocodone bitartrate tablet with a proposed indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. If approved by FDA, VANTRELA ER will be provided in dosage strengths that contain 15, 30, 45, 60, and 90 mg of hydrocodone bitartrate. VANTRELA ER can be taken twice a day (BID) without regard to food.

CIMA Labs, Inc. (CIMA), a corporate affiliate of Teva Branded Pharmaceutical Products R&D, Inc., used a new and unique abuse-deterrent technology (ADT) consisting of 3 complementary formulation layers to develop an ER hydrocodone bitartrate tablet designed to release the drug substance over a 12-hour period when administered orally as instructed and to retain its ER properties when manipulated. The CIMA ADT™[2] formulation does not rely on tablet hardness as a physical barrier to deter abuse. Accordingly, VANTRELA ER tablets are not exceptionally hard and are not intended to be physically difficult to manipulate. They are, however, designed to maintain an ER profile even when reduced to a fine powder through both common and advanced manipulation techniques.

Throughout development, FDA provided significant input, particularly in design of the studies to evaluate abuse potential. In accordance with FDA guidance, the abuse-deterrent properties of VANTRELA ER were tested in Category 1 in vitro manipulation studies of intact and manipulated drug product, Category 2 human pharmacokinetic studies, and Category 3 human abuse potential studies. Drug diversion, drug loss, and other measures potentially related to abuse potential were also assessed in the Phase 3 clinical efficacy/safety studies. While the Category 1, 2, and 3 studies were conducted based upon an earlier draft FDA Guidance (FDA 2013), the overall study designs are consistent with the final FDA Guidance for the development of abuse-deterrent opioid formulations (FDA 2015).

This briefing document has been prepared to support the open session of the advisory committee meeting requested by FDA, to discuss the abuse deterrent data for VANTRELA ER. As such, the extent of efficacy and safety data from the Phase 3 studies with VANTRELA ER has been limited herein to support evaluation of the potential impact of ADT on efficacy and safety.

[1] VANTRELA™ ER is a trademark of Cephalon, Inc., an affiliate of Teva Branded Pharmaceutical Products R&D, Inc.
[2] CIMA ADT is a trademark of CIMA Labs, Inc., an affiliate of Teva Branded Pharmaceutical Products R&D, Inc.

1.1. Unmet Need in the Treatment of Pain Requiring Around-the-Clock Opioid Treatment

Pain is the most common symptom accompanying, to some degree, almost every medical condition humans experience. When it is severe enough, it interferes with a patient's ability to function and with his/her quality of life. While numerous efforts are underway to find new safe and effective non-opioid analgesic drugs, currently ER/long acting (LA) opioids are one of the key components of the armamentarium for the treatment of moderate to severe pain. Many patients in the US suffer from refractory chronic pain as existing therapies often provide inadequate relief and poor tolerability.

The risks of abuse and the potential sequelae of overdose and death associated with prescription opioids pose a serious and growing public health risk and constitute a serious unmet medical need. There has been a 542% increase in the non-medical use of prescription opioids since 1992 (Lourenço et al 2013). Abuse of prescription opioids lead to serious medical complications including but not limited to addiction, physical dependence, overdose, withdrawal symptoms, drug-related suicide, drug-related car crashes, spreading of serious diseases via shared drug paraphernalia, and death. In 2008, prescription opioids were involved in more overdose deaths than heroin and cocaine combined (CDC Policy Impact 2011). As sales of prescription opioids in the US increased by over 300% from 1999 to 2008 (CDC Policy Impact 2011), overdose deaths involving these products increased proportionally over the same period to 19,000 in 2014 (Califf et al 2016).

The FDA has strongly supported the development of ADFs and will continue to support ADFs and encourage development of more effective abuse-deterrent features as one of several ways to combat the abuse epidemic (Califf et al 2016). Further limiting access to potential treatments is not the answer when new treatments are critically needed (FDA 2013).

Drug abusers often seek the maximum plasma drug concentration (C_{max}) in the shortest time (high C_{max}/short t_{max}). Accordingly, ER opioids are often manipulated by drug abusers to transform conventional ER dosage forms to immediate-release (IR) forms for the purposes of abuse by the oral, intranasal, or intravenous (IV) routes of administration (ROA). In general, opioid abusers seek to break down the ER opioid into the smallest possible particle size to defeat the ER mechanism and achieve the most rapid release of the drug product. As a result, many abuse deterrent products rely on hardness as a physical barrier to resist particle size reduction and therefore deter abuse. Subsequently, abusers are becoming more sophisticated in their attempts to defeat these formulations which rely on hardness for abuse-deterrence, with multiple manipulation-attempt recipes available on drug-user internet forums (McNaughton et al 2014).

Common manipulations focusing on particle size reduction include breaking, splitting, crushing, milling, and grinding the tablet. Although less common, some abusers will use solvents to extract the active ingredient. While the most uncommon, the most successful techniques involve multi-step liquid extraction, which requires time, sophisticated chemistry knowledge, and expensive equipment.

Balancing the benefits of prescription opioid analgesics against their abuse liability can be challenging for clinicians. Thus, the development of ADFs of prescription opioid analgesics is an important step toward reducing abuse and diversion of these medications, while ensuring access to these drugs for patients with legitimate medical need. Following distribution of an ER

oxycodone ADF in place of original ER oxycodone in August 2010, it was shown that 8 outcome measures of abuse were lower than those for original ER oxycodone historically, particularly through non-oral ROAs that require tampering (ie, injection, snorting, smoking), in a sentinel sample of individuals assessed for substance use problems for treatment planning (Butler et al 2013). While currently available data suggest that ER opioid formulations (ie, OXYCONTIN®[1]) have deterred abuse to some extent (Butler et al 2013, Havens et al 2014) abusers can still successfully defeat the ADF properties via manipulation and extraction in many cases (Cicero and Ellis 2015), leaving a significant continued need for new ADF products.

1.2. Abuse Deterrent Evaluation

The abuse-deterrent evaluation of VANTRELA ER was conducted according to FDA guidance and with specific advice from the Agency throughout the development program. The evaluation included Category 1 (in vitro manipulation and extraction), Category 2 (human pharmacokinetic studies), and Category 3 (human abuse potential studies as well as evaluation of loss and diversion data) studies.

Because opioid products are often manipulated for purposes of abuse by different ROAs or to defeat ER properties, some abuse-deterrent technologies are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. The fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must, in the end, be able to deliver the opioid to the intended patient population, there may always be some risk for abuse of these products.

The goal of any ADF is to make the manipulated product less suitable for administration and thus less attractive to abusers. VANTRELA ER is designed to retain significant ER properties following the most likely methods of chemical and physical manipulation, maintaining limited early exposure by lowering the C_{max} and extending the time of peak concentration (t_{max}) compared to IR formulations. This should in turn reduce abusers' drug liking and thereby potential to attain the desired euphoria. As described below, in both in vitro and clinical studies, VANTRELA ER was tested against hydrocodone bitartrate active pharmaceutical ingredient (API) powder, against hydrocodone drug IR VICOPROFEN[2], and against ZOHYDRO®[3] ER, once it became commercially available.

1.2.1. Category 1 Studies: In Vitro Manipulation and Extraction

Category 1 studies ranged from simple physical manipulations to the complex tampering techniques of a sophisticated abuser. Studies included tests to defeat the ER formulation by cutting, crushing, milling, and grinding tablets. Drug release was measured in a wide variety of solvents with varying temperatures and mixing conditions, including simulated oral ingestion, simulated intranasal and IV extraction, chemical extraction, and more complex multi-step chemical extractions.

[1] OXYCONTIN® is a registered trademark of Purdue Pharma, LP.
[2] VICOPROFEN® is a registered trademark of AbbVie, Inc.
[3] ZOHYDRO® ER is a registered trademark of Pernix Ireland Pain Limited

For physical manipulation, screening studies were conducted using 15 tools representing different mechanisms. Six tools that represent the range of destructive (effective) mechanisms were selected for use in the Category 1 in-vitro studies. These tools were selected to represent the various comminution mechanisms, and thereby represent the unlimited variety of tools of similar mechanism that might be available to abusers.

These studies demonstrated that VANTRELA ER tablets present a barrier to the effect of manipulation for drug abuse. Extended-release properties were retained to a significant degree when the tablets were physically manipulated with a variety of tools and subjected to simulated oral ingestion and simulated intranasal extractions. The formulation also resisted extraction of the opioid into small volumes that simulate IV abuse conditions, and physically impeded injectability and syringeability.

In the extraction studies, VANTRELA ER exhibited a barrier to hydrocodone extraction with ingestible household solvents. Simple and multiple-step chemical extractions with advanced solvents may be used to improve the extraction of hydrocodone for methodical abusers willing to invest time to defeat the controlled-release mechanism prior to each use. However, doing so would require significant time and effort, and these techniques would not result in the extraction of a pure opioid drug substance. Even sophisticated multiple-step manipulation methods intended to separate pure hydrocodone base from excipients and solvents yielded opioid of lower purity. Manipulated ZOHYDRO ER was employed as a comparator and exhibited much greater drug release than VANTRELA ER when subjected to the simulated oral ingestion, simulated intranasal, simulated IV, and simple aqueous extractions.

Overall, the Category 1 in vitro studies demonstrated that VANTRELA ER retains ER properties following chemical and physical manipulation compared to a non-abuse deterrent opioid formulation; these properties are expected to deter abuse via the most common routes.

1.2.2. Category 2 Studies: Pharmacokinetics

Category 2 studies were designed to evaluate the pharmacokinetic profile of VANTRELA ER when administered intact or manipulated for abuse in 2 oral route studies and 1 intranasal route study. Amongst other parameters, the rate of rise of drug concentration (abuse quotient, $AQ=C_{max}/t_{max}$) was assessed because it is thought to contribute to differential abuse potential among drugs, formulations, and ROAs (Abreu et al 2001, de Wit et al 1992, de Wit et al 1993). The first oral pharmacokinetic study compared manipulated VANTRELA ER with intact VANTRELA ER and with manipulated and intact VICOPROFEN. Even when manipulated to fine powder, C_{max} was approximately 39% lower for VANTRELA ER, and t_{max} was longer compared to intact and manipulated VICOPROFEN.

The AQ for manipulated VANTRELA ER was approximately 54% lower than for intact VICOPROFEN.

In the second oral pharmacokinetic study, manipulated VANTRELA ER was compared with intact VANTRELA ER and hydrocodone bitartrate API as an IR comparator. While hydrocodone levels rose rapidly following administration of hydrocodone bitartrate API, manipulated VANTRELA ER retained part of its ER properties. The C_{max} and AQ of manipulated VANTRELA ER were approximately 54% and 86% lower than hydrocodone bitartrate API, respectively.

In the intranasal study, manipulated VANTRELA ER was compared to hydrocodone bitartrate API, manipulated ZOHYDRO ER, and intact VANTRELA ER (oral). Compared to the other intranasal treatments, manipulated VANTRELA ER showed a slower rise to a lower C_{max} and maintained some of its ER properties. Consistent with this, the AQ for manipulated VANTRELA ER administered intranasally was 16% and 42% lower than for hydrocodone bitartrate API and manipulated ZOHYDRO ER, respectively.

In addition, the pharmacokinetic profile of intact VANTRELA ER was not affected by alcohol. Oral administration of VANTRELA ER with alcohol had no effect on hydrocodone systemic exposure as measured by either C_{max} or area under the plasma concentration curve (AUC), which were bioequivalent when VANTRELA ER was taken with water or 4%, 20%, and 40% alcohol solutions. These results suggested that co-ingestion of VANTRELA ER with alcoholic beverages in an attempt by abusers to produce immediate release of opioid will not be successful. Similar protection may be provided against unintentional misuse if a patient inadvertently uses alcohol in proximity to their VANTRELA ER dose. However, like for all opioids, the co-administration of alcohol with VANTRELA ER is contraindicated.

Overall, the results of the Category 2 studies demonstrated that barriers to rapid release of hydrocodone in VANTRELA ER are retained when taken intact with alcohol and when manipulated for oral or intranasal administration. The pharmacokinetic data therefore demonstrate that the ADF properties of VANTRELA ER limit the rate and extent of rise of drug concentration following both oral ingestion and nasal insufflation of the manipulated product.

1.2.3. Category 3 Studies: Human Abuse Potential

Human abuse potential was evaluated in recreational opioid abusers in 2 studies using oral (Study 1085) and intranasal (Study 10032) ROAs. In Study 1085, subjects received, in a crossover fashion, hydrocodone bitartrate API, manipulated and intact VANTRELA ER, and placebo. In Study 10032, subjects received manipulated intranasal VANTRELA ER, oral intact VANTRELA ER, intranasal hydrocodone bitartrate API, manipulated intranasal ZOHYDRO ER, and placebo. In both studies, the abuse potential of each treatment was assessed using several subjective scales, including the Drug Liking visual analog scale (VAS; Appendix 1), which was the primary endpoint. A 45-mg dose of VANTRELA ER or comparators was used in both studies.

In Study 1085, statistically significant reductions in peak “at the moment” drug liking and overall drug liking were observed following oral administration of manipulated VANTRELA ER compared with hydrocodone bitartrate API. In Study 10032, peak “at the moment” drug liking and overall drug liking for manipulated VANTRELA ER administered via the intranasal route were significantly lower compared to intranasally administered hydrocodone bitartrate API and ZOHYDRO ER. In both studies, the intact oral VANTRELA ER product showed a similar profile to placebo. Therefore, the results of the human abuse potential studies suggest that VANTRELA ER may have lower abuse potential via 2 common routes of abuse reported for opioid analgesics (ie, oral and intranasal) compared with non-abuse deterrent opioid products. Therefore, data from the clinical abuse potential studies, along with support from the in vitro data, also indicate that VANTRELA ER has physicochemical properties that are expected to reduce abuse via the oral route when manipulated and via the intranasal route.

1.3. Efficacy Findings in Phase 3 Studies

While the purpose of this Advisory Committee is to evaluate data from abuse deterrence studies, the following information on Phase 3 efficacy studies with VANTRELA ER is provided to evaluate the potential impact of abuse deterrent technology on efficacy.

Four Phase 3 studies were conducted in the VANTRELA ER clinical development program, including two 12-week, placebo-controlled, efficacy studies (Study 3079 and 3103) and 2 open-label extension studies, 1 lasting 12 months (Study 3080) and the other lasting 6 months (Study 3104). Study 3079 was a multicenter, randomized, 12-week double-blind, placebo-controlled study to assess the efficacy of VANTRELA ER in patients with moderate to severe pain associated with osteoarthritis (OA) or low back pain who required opioid treatment for an extended period of time. Study 3103 was a multicenter, randomized, 12-week double-blind, placebo-controlled, randomized-withdrawal study to assess the efficacy and safety of VANTRELA ER in patients with moderate to severe chronic low back pain who required continuous opioid treatment for an extended period of time. Both studies had an enriched enrollment, randomized-withdrawal study design that consisted of an open-label titration period, followed by a randomized, double-blind treatment period. During the open-label titration period, patients received increasing doses of VANTRELA ER in protocol-specified increments to determine an optimal treatment dose, which was defined as the dose that produced stable pain relief without unacceptable adverse events. Patients who achieved an optimal dose of VANTRELA ER were randomly assigned to receive VANTRELA ER at the optimal dose determined during the open-label titration period or matching placebo.

The first Phase 3 clinical efficacy study, Study 3079, failed to demonstrate a statistically significant treatment effect of VANTRELA ER tablets using average pain intensity as the primary efficacy variable for reasons thought to be related to study design and assay sensitivity issues. In Study 3079, VANTRELA ER was titrated to a sub-therapeutic dose of 15 mg, which is unlikely to be an optimal dose for most patients. Overall, Study 3079 sustained a relatively high rate of discontinuation from the study which made it difficult to demonstrate a statistically significant treatment difference (see Section 4.1).

Due to the limitations of Study 3079, a second pivotal Phase 3 study, Study 3103, was agreed through discussion with the Agency. Several different study design elements were incorporated in Study 3103 to demonstrate the efficacy of VANTRELA ER for the treatment of moderate-to-severe chronic pain. Critical differences in the design elements of Studies 3079 and 3103 that were agreed to with the FDA at the end of the Phase 2 meeting included the following:

- selection of the study population
- minimum optimal dose
- choice of primary efficacy variable
- allowed rescue medication
- criteria for discontinuation from the study

Study 3103 was a multi-center, double-blind, placebo-controlled, randomized withdrawal design, aligned with precedent for other opioid products used to treat chronic pain. Patients enrolled had moderate-to-severe chronic low back pain for at least 3 months prior to screening and were

opioid-experienced or opioid-naïve. Rescue medication was allowed during the study, but was limited to hydrocodone bitartrate API. Such an approach is commonplace for the assessment of opioid efficacy in clinical studies (Section 4).

Once patients were screened, enrolled, and washed out of existing analgesic therapy, they began an open-label titration period for up to 6 weeks during which each patient's optimal dose of VANTRELA ER was determined. The optimal dose was required to be 30 mg every 12 hours (q12h) or higher. Mean decrease in weekly average worst pain intensity (WPI) score by numerical rating scale (NRS) during this open label titration period was 2.95. After the titration period, patients were randomized 1:1 to receive either their optimal dose of VANTRELA ER (30, 45, 60, or 90 mg q12h) or matched placebo. A stepwise, double-blind tapering schedule was used during the first 2 weeks to reduce withdrawal symptoms in placebo patients, and the dose was then maintained from weeks 3 through 12.

The primary endpoint for Study 3103 was defined as a change from pre-randomization baseline to week 12 in the weekly average WPI score. The primary analysis was conducted on the full analysis set with multiple imputation (MI) of missing data. Patients in the VANTRELA ER treatment group had a statistically significant lower increase from baseline in the weekly average of daily WPI scores compared to the placebo treatment group (p-value<0.001) (Section 4.2.5). Additional sensitivity analyses (which assessed missing value patterns, use of excessive rescue medication, inclusion of WPI scores after discontinuation of study drug, and use of WPI scores recorded before using rescue medication) showed that the results of the primary efficacy analysis were not sensitive to imputation method and potential confounding factors. Secondary efficacy measures included the average pain intensity over the last 24 hours. Patients in the VANTRELA ER treatment group had a statistically significant lower change from baseline in the weekly average of daily average pain intensity scores at week 12 compared to placebo-treated patients (p-value<0.001). Baseline average pain intensity scores were similar for the VANTRELA ER and placebo treatment groups (3.31 and 3.41, respectively), and mean scores at week 12 were 3.33 for the VANTRELA ER treatment group and 3.98 for the placebo treatment group.

Of the 2 long-term, open-label, extension studies, Study 3080 was a 12 month, long term safety, open-label extension study in eligible patients who completed Study 3079 (these patients were referred to as rollover patients) and newly enrolled patients who did not participate in Study 3079 (these patients were referred to as either new opioid naïve or new opioid experienced patients). Efficacy was a secondary objective in Study 3080, and included assessment of Brief Pain Inventory–Short Form (BPI-SF) at each scheduled visit throughout the open label titration period and the open-label treatment period. Overall, improvements were observed for the individual BPI-SF questions, were sustained throughout the study to endpoint, and were observed across opioid status groups, but were generally lower in new opioid-experienced, compared with new opioid-naïve and rollover patients.

Study 3104, the second long-term study, was an optional 6 month, long term safety, open-label extension study in eligible patients who completed Study 3103. As in the first long-term study, efficacy in Study 3104 was a secondary objective, quantified as the change from baseline in WPI and average pain intensity scores during the previous 24 hours at each visit throughout the study, and by the percentage of patients who withdraw from the study for lack of efficacy. After the initial decrease in WPI and average pain intensity from screening to the end of Study 3103, WPI

and average pain intensity scores remained steady throughout the 22-week open-label treatment period in Study 3104.

1.3.1. Drug Diversion

There was low risk of study drug diversion identified for VANTRELA ER based upon data collected from Phase 3 Studies 3079 and 3103, and their open-label extensions, Studies 3080 and 3104, respectively. Overall, the compliance with study drug was 96%. The incidence of study drug or rescue medication loss during the studies was 4% or less among all patients (safety analysis set) and 5% or less in the subset of patients who participated in the double-blind period (post-titration analysis set [Studies 3079 and 3103]). Across all 4 studies combined, the overall rate of diversion was less than 2%. Study drug diversion was more frequent with rescue medication than with VANTRELA ER while study drug loss was more frequent with VANTRELA ER. In addition, there was low risk of abuse and addiction associated with VANTRELA ER as measured by the Screener and Opioid Assessment for Patients with Pain - Revised (SOAPP-R), Current Opioid Misuse Measure (COMM), and Addiction Behavior Checklist (ABC) in Studies 3079 and 3080. In Study 3103, the majority of patients had no evidence of opioid withdrawal symptoms, as rated by the patient (Subjective Opiate Withdrawal Scale [SOWS]) or clinician (Clinical Opiate Measure Withdrawal Scale [COWS]), during the randomized withdrawal phase of the study after they had established a successful dose of VANTRELA ER tablets during the open-label titration phase.

1.4. Safety Findings

The observed safety profile following administration of VANTRELA ER in 3 Phase 1 studies enrolling subjects who were not concurrently receiving the opioid antagonist naltrexone (24 healthy subjects, 8 hepatically impaired subjects, and 87 nondependent, recreational opioid users) was consistent with the known safety profile of other opioids. Data collected from an additional 17 clinical pharmacology studies which included populations of subjects who were concurrently receiving naltrexone (650 healthy subjects and 35 renally impaired subjects) demonstrated no significant safety findings.

Of the 1176 patients who were enrolled in the Phase 3 studies and received at least 1 dose of VANTRELA ER (safety analysis set), 864 (73%) patients reported at least 1 adverse event. Adverse events reported by ≥5% of patients were constipation (276 [23%] patients), nausea (272 [23%] patients), headache (144 [12%] patients), somnolence (122 [10%] patients), vomiting (122 [10%] patients), dizziness (79 [7%] patients), pruritus (70 [6%] patients), fatigue (61 [5%] patients), and diarrhea (59 [5%] patients. In the double-blind studies (Studies 3079 and 3103), the incidence of reported adverse events during the post-titration period was comparable between the placebo and VANTRELA ER group (59% versus 55%, respectively). The incidence of reported adverse events during the post-titration period was highest in patients receiving 15 mg VANTRELA ER (28 [78%] patients). Similar rates of adverse events were reported in patients receiving the 30- (54 [52%] patients), 45- (64 [62%] patients), 60- (29 [55%] patients), and 90-mg (24 [59%] patients) VANTRELA ER doses.

Three deaths were reported during the Phase 3 studies; none were considered related to study drug. In Study 3080, the long-term extension of Study 3079, 2 deaths were reported, both during the post-titration period; neither was considered related to study drug. One cause of death in

Study 3080 was unknown, and the other was due to cardiac arrest secondary to hyperkalemia. The hyperkalemia was suspected to have occurred as a result of the patient's overmedication with potassium tablets to treat cramps. In the case of the unknown death, the patient had multiple medical problems and was ultimately admitted to hospice due to cancer. No further information could be obtained. Neither death was considered by the investigator as related to VANTRELA ER. The third death in the Phase 3 program occurred during the screening period in Study 3103 due to an unknown cause. In the Phase 1 program, 1 death, due to a self-inflicted gunshot wound, was reported approximately 2.5 months after completion of Study 1085.

A total of 57 (5%) patients reported at least 1 serious adverse event, with a total of 5 (0.4%) patients in the safety analysis set reported at least 1 treatment-related serious adverse event. The most common serious adverse events were renal failure acute (4 [<1%] patients), deep vein thrombosis (3 [<1%] patients), and pneumonia (3 [<1%] patients) (see Section 5.3.2).

1.5. Benefit/Risk Assessment

The diversion and abuse of prescription opioid analgesic products pose serious public health and safety risks. FDA, other US government agencies/legislators, academia, and industry have identified the need for development of abuse-deterrent opioid formulations that can hinder the ability to extract extremely high concentrations of medication and deter abuse and diversion.

VANTRELA ER is an effective ER hydrocodone product with a unique 3-layer formulation designed to deter abuse as demonstrated by in vitro, pharmacokinetic, human abuse potential and Phase 3 clinical studies. It is a single-entity product without the inclusion of acetaminophen, thereby giving the advantage of reduced risk of hepatic complications at higher doses relative to acetaminophen-containing formulations. The planned BID dosing regimen is different from HYSINGLA®[1] ER and other ER/LA abuse-deterrent opioid formulations, thereby offering the benefit of another dosing regimen.

The VANTRELA ER formulation characteristics provide significant barriers against oral, intranasal, and IV abuse. In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation of VANTRELA ER. In laboratory studies, ER properties were retained to a significant degree when the tablets were physically manipulated.

Category 2 oral and intranasal pharmacokinetic studies demonstrated that multiple physical manipulations do not defeat the ER properties or revert VANTRELA ER to an IR product, as desired by abusers. VANTRELA ER was shown to maintain a more favorable pharmacokinetic profile than the IR comparator, VICOPROFEN, as VANTRELA ER retained lower C_{max} and delayed t_{max}. These pharmacokinetic characteristics enhance the abuse deterrent properties of VANTRELA ER. The pharmacokinetic data also demonstrate that the extended-release properties of VANTRELA ER limit the rate and extent of rise of drug concentration, which is thought to contribute to differential abuse potential among drugs, formulations, and ROAs, following both oral ingestion and nasal insufflation of the manipulated product.

VANTRELA ER tablets retain their extended-release properties to a significant degree when the tablets are taken with alcohol. These results suggest that combining the VANTRELA ER tablet

1HYSINGLA® ER is a registered trademark of Purdue Pharma, LP.

with alcohol in an attempt by abusers to produce immediate release of opioid will not be successful. Likewise, there is added safety for non-abusers who ingest alcohol in proximity to a prescribed dose of ER hydrocodone for the treatment of pain, although, as with any opioid, VANTRELA ER should not be combined with alcohol.

These differences in pharmacokinetics are associated with significantly different pharmacodynamic subjective effects for VANTRELA ER when it is manipulated and administered orally or intranasally. When the VANTRELA ER tablet is manipulated and ingested orally, subjects reported statistically lower peak and "at the moment" liking as compared to hydrocodone bitartrate API. Likewise, statistically lower peak and "at the moment" liking were observed when the VANTRELA ER tablet was manipulated and insufflated intranasally as compared to hydrocodone bitartrate API and manipulated ZOHYDRO ER. Secondary measures of balance, positive effects, sedative effects, any effects, and pupillometry were supportive of these findings. Oral intact VANTRELA ER behaved similarly to a placebo. Therefore, data from the clinical abuse potential studies, along with support from the in vitro data, also indicate that VANTRELA ER has physicochemical properties that are expected to reduce abuse via the oral route when crushed and via the intranasal route. However, abuse of VANTRELA ER by these routes may still be possible.

VANTRELA ER tablets, administered at stable pain relief dosages of 30, 45, 60, or 90 mg q12h for 12 weeks, were more effective than placebo treatment in alleviating chronic low back pain in Study 3103, the pivotal Phase 3 efficacy study in opioid experienced or naïve patients. At week 12, the change from baseline in weekly average of daily WPI scores, the primary efficacy endpoint, was significantly lower in the VANTRELA ER group than in the placebo group. There was a low occurrence of diversion of VANTRELA ER in the Phase 3 studies in patients with moderate to severe pain. In addition, scales noting abuse and addiction potential evaluated in patients with chronic pain in Studies 3079 and 3080 indicated a low risk of abuse and addiction.

The safety profile of VANTRELA ER, administered at dosages ranging from 30 to 90 mg q12h to patients with chronic pain and healthy adult subjects, was similar to that of currently marketed hydrocodone bitartrate products and other opioid analgesics, and was also consistent with the underlying illnesses seen among the patients in the studies. No increase in any safety signal was observed with increasing dosages. No new safety signals were raised.

Overall, these data support labeling that Vantrela ER has properties that are expected to deter abuse.

Teva is committed to monitor for safety issues including abuse, diversion, and overdose related to VANTRELA ER. The company will be working within the framework of the FDA's Opioid Action plan and will be participants in executing some of action items specified within, including conducting the expanded Post-Marketing Requirement (PMR) studies for long-acting opioids. Teva will become an active member of the ER/LA Risk Evaluation and Mitigation Strategy (REMS) industry group with the goal to reduce serious adverse outcomes resulting from inappropriate prescribing and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications.

2. UNMET MEDICAL NEED IN TREATMENT OF PAIN REQUIRING AROUND-THE-CLOCK OPIOID TREATMENT

2.1. Background on Chronic Pain

According to the FDA, over the course of a given year, approximately 100 million people in the US suffer from pain (Califf et al 2016). Some 9 to 12 million of them have chronic or persistent pain. All of them should benefit from skillful and appropriate pain management, which includes the judicious use of opioid medicines (Califf et al 2016). Chronic pain impacts more Americans than diabetes, heart disease and cancer combined (The American Academy of Pain Medicine), and conditions include lower back pain, OA, and cancer (Argoff and Kopecky 2014).

While there are many available analgesic therapies, unmet need for effective chronic pain treatment remains high due to poor efficacy and low tolerability of existing therapies. Both IR and ER opioid therapies are an important part of a treating-physician's options to provide pain relief to people with pain. Opioid medications can provide short- or long-acting analgesia. Extended release/LA opioids are typically used for around-the-clock, maintenance treatment.

2.2. Medical Use and Abuse of Extended-Release Opioid Products

Opioid analgesics are an important component of pain management, and patients in pain require appropriate access to opioid analgesics (Trescot et al 2008). Hydrocodone bitartrate combined with a non-opioid analgesic (eg, acetaminophen or a nonsteroidal anti-inflammatory drug [NSAID]) is commonly used for the relief of acute pain. The currently marketed hydrocodone IR products are the most commonly prescribed pain medications, making hydrocodone bitartrate the most-prescribed drug in the US (DeNoon 2011). In 2011, 136.7 million prescriptions were written for hydrocodone products (Manchikanti et al 2012).

The risks of abuse and the potential sequelae of overdose and death associated with prescription opioids pose a serious and growing public health risk and constitute a serious unmet medical need. There has been a 542% increase in the non-medical use of prescription opioids since 1992 (Lourenço et al 2013). Abuse of prescription opioids lead to serious medical complications including but not limited to physical dependence, overdose, withdrawal symptoms, drug-related suicide, drug-related car crashes, spreading of serious diseases via shared drug paraphernalia, and death. In 2008, prescription opioids were involved in more overdose deaths than heroin and cocaine combined (CDC Policy Impact 2011). As sales of prescription opioids in the US increased by over 300% from 1999 to 2008 (CDC Policy Impact 2011), overdose deaths involving these products increased proportionally over the same period to 19,000 in 2014 (Califf et al 2016).

In general, when abused, IR formulations are more often administered as intact forms because they are already in a form for immediate absorption (for example, by taking multiple tablets) whereas ER formulations are more prone to be manipulated (for example, by insufflation or injection) (Katz et al 2011). Abusers looking for rapid action of the drug in a shorter amount of time try to manipulate ER products to display IR characteristics.

Until recently, all marketed analgesic formulations of hydrocodone bitartrate in the US were IR combination formulations of hydrocodone bitartrate with a non-opioid analgesic such as

acetaminophen, ibuprofen, or aspirin. Extended-release formulations of hydrocodone bitartrate do not require combination with other analgesics for maximum analgesic effect. A single-entity, bead-filled capsule formulation of hydrocodone bitartrate (ZOHYDRO ER) was approved by FDA on 25 October 2013 with marketing started in March 2014. However, the ER mechanism can easily be circumvented by crushing the beads after removing them from the capsule, which allows abusers access to rapid drug release and consequent euphoria (Turk et al 2012). Dose dumping can also occur if an ER tablet is consumed with alcohol or when a patient inadvertently bites or splits the tablet.

The first single-entity, ADF of hydrocodone bitartrate (HYSINGLA ER) was approved by FDA in November 2014 with marketing started in early 2015. This formulation has physical and chemical properties that render it difficult to crush, break or dissolve. However, even with current ADF advancements, people continue to abuse ER opioids by crushing and chewing, injecting, and insufflating (also known as snorting).

A growing body of evidence suggests that introduction of ADFs has been associated with decreased rates of abuse and diversion in the US (Sellers et al 2013, Butler et al 2013, Coplan et al 2013). However, no ADF is undefeatable. Therefore, we need different technologies that target different pathways of abuse.

2.3. Need for Alternative ADT Technologies

There has been a 542% increase in the non-medical use of prescription opioids since 1992 (Lourenço et al 2013). According to The Drug Abuse Warning Network (DAWN) Report (SAMHSA 2013), the number of emergency department visits for abuse of prescription narcotic pain relievers was 366,181 in 2011, representing a 153% increase from 2004. Of these, there were 82,480 emergency department visits in 2011 for hydrocodone products, representing a 107% increase from 2004 to 2011. FDA continues to be deeply concerned about the growing epidemic of opioid abuse and overdose, which they consider directly related to the increasingly widespread diversion of powerful opioid pain medications (Califf et al 2016).

The need to increase development of ADFs has been identified by US government agencies, academia, and industry as just one of the methods to address opioid abuse. While ADFs cannot prevent all abuse or prevent abusers or patients from ingesting large quantities of tablets, the use of these novel formulations may hinder the ability to extract extremely high concentrations of medication for immediate release, thereby reducing the incidence of adverse events, dose dumping resulting in euphoria, or overdose.

Due to the increased risk of abuse and diversion associated with opioids, clinical studies include measures of these outcomes as well as scales that assess the potential for abuse. Development of ER opioids must include mitigation of these risks while focusing on patients with severe pain who might benefit from sustained drug exposure that better controls their pain over a long period of time.

3. OVERVIEW OF VANTRELA ER FORMULATION AND DEVELOPMENT PROGRAM

3.1. Product Characteristics

Teva has developed VANTRELA ER, an abuse-deterrent, extended release, single-entity hydrocodone bitartrate tablet formulated to maintain ER properties despite intentional manipulation for the purpose of abuse. The ER and abuse deterrent properties of VANTRELA ER are achieved through rational selection of excipients and manufacturing process steps. Well characterized compendial excipients are used in a novel manner to provide a robust extended release profile for VANTRELA ER when the tablet is administered as prescribed; this formulation also limits rapid release of drug when the tablets are physically or chemically manipulated.

Unlike current abuse-deterrent products with physical barriers, the VANTRELA ER tablet itself is not exceptionally hard and is not intended to be physically difficult to manipulate. Rather, VANTRELA ER is designed to maintain some degree of ER profile even when comminuted to a fine particle size.

Five dose strengths of VANTRELA ER tablets are being registered for marketing: 15, 30, 45, 60, and 90 mg, to be administered q12h, thereby allowing a preferred BID dosing regimen in patients.

3.2. Key FDA Milestones and Guidance During Development

In 2009, TEVA submitted an Investigational New Drug (IND) application to the FDA for the development of the VANTRELA ER tablet.

In a Type B meeting held on 14 July 2010, the FDA Division of Anesthesia, Analgesia, and Addiction Products agreed that the application for registration of VANTRELA ER would be submitted via an NDA with a single pivotal efficacy study and that the application would also rely on FDA's previous finding of safety and efficacy for the IR hydrocodone component of VICOPROFEN (NDA 020716). At that meeting, there were also preliminary discussions surrounding the execution of the abuse deterrent in vitro manipulation studies as well as an oral human abuse potential study. Following revision, the Agency reviewed the in vitro manipulation protocols without further comment in September 2011.

In preparation for the NDA submission, a Type C meeting was held on 23 January 2014 to ensure that the development program for VANTRELA ER continued to align with FDA's current expectations for abuse deterrent opioids. The outcomes from the discussion included the FDA requesting additional in vitro manipulation experiments as well as the need to conduct an intranasal human abuse potential study.

At the pre-NDA meeting held on 23 July 2014, the FDA requested additional in vitro manipulation experiments. The in vitro manipulation package and the requested intranasal human abuse potential study were submitted with the original NDA application, completed on 23 December 2014 with a Prescription Drug User Fee Act (PDUFA) date of 23 October 2015. Prior to the PDUFA date, Teva received clarifying questions from the Division about the

application and provided responses. Once there were no outstanding issues, Teva began label negotiations with the FDA on 26 September 2015.

3.3. Overview of Abuse-Deterrence Evaluation

VANTRELA ER was developed and evaluated in a manner consistent with recommendations described in FDA's draft and then final guidance on the evaluation and labeling of abuse-deterrent opioids (FDA 2013, FDA 2105) and with specific feedback from FDA throughout the development program.

Teva conducted a comprehensive evaluation of the abuse–deterrent properties of VANTRELA ER, which is consistent with FDA's Final Guidance, "Abuse Deterrent Opioids – Evaluation and Labelling" (FDA 2015). This included Category 1 in vitro manipulation studies of intact and manipulated drug product, Category 2 human pharmacokinetic studies, and Category 3 human abuse potential studies as well as evaluation of loss and diversion data from Phase 3 clinical studies. Per FDA request, the program included the assessment of relative bioavailability of VANTRELA ER to the hydrocodone component of VICOPROFEN, the only comparator available during development. Similarly, Category 2 and 3 studies included hydrocodone bitartrate powder (referred as hydrocodone API) as the surrogate for a single-entity IR hydrocodone product. Manipulated ZOHYDRO ER, a marketed ER hydrocodone bitartrate product, was employed as a comparator in Category 1 in vitro studies and in the Category 3 intranasal human abuse potential study. Teva's comprehensive development program consisted of in vitro and clinical studies, the results of which indicate that VANTRELA ER may be more resistant to abuse by manipulation followed by oral ingestion, snorting, or attempted IV injection than the comparator(s). Table 1 provides a list of the core studies conducted to assess the abuse-deterrent properties of VANTRELA ER.

Table 1: Core Abuse Deterrent Studies for VANTRELA ER

Study Title (Number, as applicable)	FDA Guidance Category[a]
In Vitro Characterization of Hydrocodone Bitartrate Extraction from VANTRELA ER Extended Release Tablets by Common Means of Tampering	Category 1
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 (Study 1076)	Category 2
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 (Study 1079)	Category 2
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 (Study 1085) (oral study)	Category 2/3
A Single-Dose, Double-Blind, Randomized Crossover Study to Assess the Intranasal Pharmacokinetics, Abuse Potential and Safety of VANTRELA ER in Healthy, Nondependent, Recreational Opioid Users (Study 10032) (intranasal study)	Category 2/3

[a] FDA Guidance for Industry, "Abuse-Deterrent Opioids—Evaluation and Labeling", April 2015
ER=extended-release

3.4. Category 1: In Vitro Manipulation and Extraction

Category 1 experiments consisted of physical manipulation of the tablets, particle size distribution (PSD) measurements for selected tools, and measurements of released drug. Drug release was assessed using robust methods that simulate various routes of abuse; simulated oral ingestion, simulated intranasal insufflation, and extractions for IV administration. In addition, simple or complex drug extraction techniques utilizing readily available [redacted] and [redacted] were assessed.

3.4.1. Physical Manipulation Studies

Prior to in vitro characterization, physical manipulation experiments were conducted on VANTRELA ER tablets to simulate commonly reported forms of manipulating opioid medications. As the variety of household and pharmacy tools that could potentially be employed for tablet manipulation is extensive, potential manipulation tools were categorized by different types of manipulation mechanisms. Tools selected for further evaluation represented the different types of manipulation mechanisms, tool availability/accessibility in the home, and included tools reported to be found useful in internet chat rooms. A panel of tools was ultimately selected to represent the various mechanisms of physical manipulation, ease of use ranging from simple to inconvenient, and was used to manipulate the tablets for the simulated abuse and extraction

studies. For each selected tool, the PSD and the drug release from manipulated tablets was characterized.

3.4.2. Overview of In Vitro Manipulation and Extraction Studies

The physically manipulated tablets were characterized in a variety of media that simulated common routes of abuse (oral, intranasal, IV) or chemical extractions designed to liberate or isolate the active drug substance.

Simulated abuse studies included:

- Simulated Ingestion (oral): in vitro dissolution in [redacted]
- Simulated Insufflation (intranasal): extraction into [redacted]
- Simulated IV: extraction for simulated IV injection, with physical assessment of the feasibility of IV abuse by syringeability and injectability tests. Initial studies were performed on manipulated tablets in Liquid a. Additional studies were performed in Liquid b and Liquid c, on intact and manipulated tablets.

Chemical extraction studies included:

- Common Aqueous Fluids: simple chemical extractions into solutions representing common, [redacted]
- Advanced Solvents: simple chemical extractions into [redacted]. After removal of the solvent, the isolated solid residues were characterized for hydrocodone content and purity.
- Complex Extractions: multiple-step, [redacted] extractions to simulate manipulation that may be performed by the most sophisticated abusers to isolate the opioid free base from the excipients. The residual solids obtained were characterized for hydrocodone content and purity.

For the simple- and multiple-step chemical extractions, solvent selection and extraction conditions were experimentally evaluated. [redacted] to reflect a range of different conditions potentially explored by a dedicated abuser.

For all of the simulated abuse and extraction experiments, quantitation of the released drug from the manipulated VANTRELA ER dosage form was performed using high performance liquid chromatography (HPLC) methodology that was validated for determination of hydrocodone bitartrate. The results were primarily expressed as percent of drug released or percent of drug recovered, that is, the percent of the entire dose extracted from 1 dose unit. The purity of isolated opioid was also determined for extraction experiments, when applicable.

Controls were executed for each type of experiment. For all extraction experiments, hydrocodone bitartrate drug substance was subjected to the same extraction conditions as manipulated VANTRELA ER to confirm the performance of each discrete extraction procedure with respect to recovery of hydrocodone bitartrate. Immediate-release VICOPROFEN tablets (containing 7.5 mg hydrocodone bitartrate and 200 mg ibuprofen) were subjected to the [redacted] (Liquid d and Liquid e) tests

after manipulation. Two VICOPROFEN tablets were used simultaneously to represent a 15 mg hydrocodone dose. The results were compared with VANTRELA ER tablets treated correspondingly.

No ER hydrocodone products were commercially available for inclusion as comparators when the initial comprehensive protocol (submitted to FDA 15 September 2011) was executed. However, ZOHYDRO ER became available March 2014 and was incorporated into the additional studies requested by the FDA as a single-agent ER comparator. Note: ZOHYDRO ER was reformulated in January 2015; studies reported in this Briefing Document were conducted using the initially-marketed formulation rather than the later-marketed product.

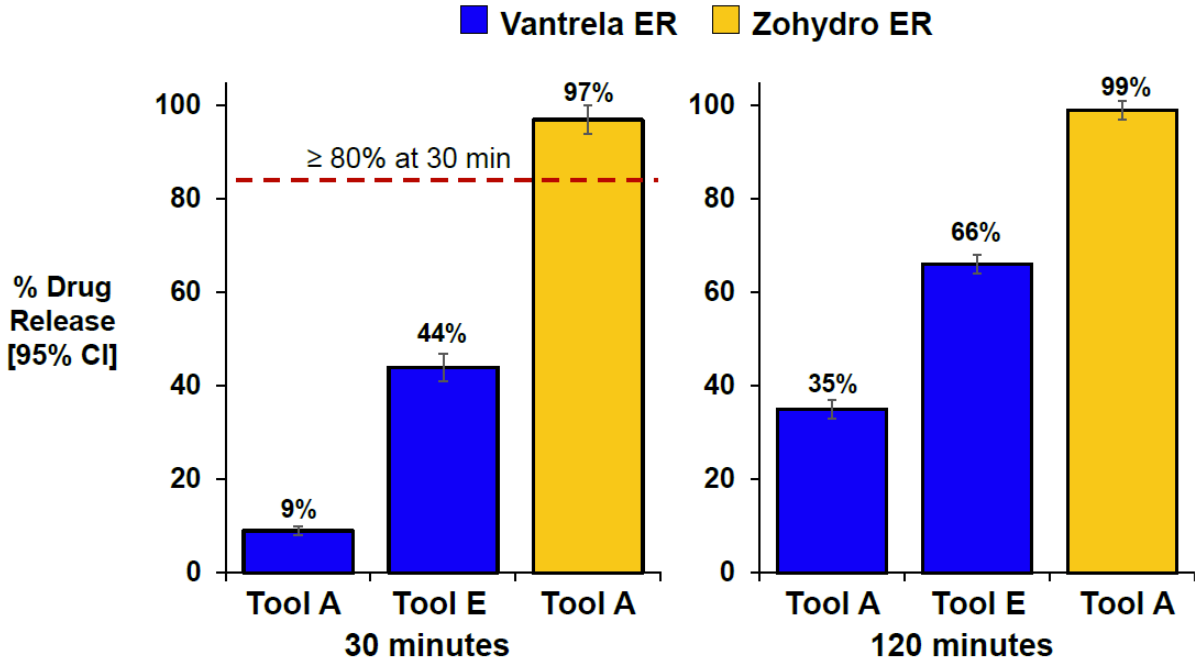
All results presented in the following sections are mean values from multiple replicates. For VANTRELA ER tablets, at least 6 replicates were performed for each experimental condition (except for Liquid b and c simulated IV studies in which a minimum of 3 replicates was employed). For drug substance controls and VICOPROFEN and ZOHYDRO ER comparators, at least 3 replicates were performed for each experimental condition. The precision of each set of replicates was assessed to determine whether it was necessary to execute additional replicates.

3.4.2.1. Simulated Oral Ingestion

VANTRELA ER tablets and the comparators IR VICOPROFEN and ZOHYDRO ER were subjected to representative mechanical manipulation techniques. The resulting powders were subjected to simulated oral ingestion using an in vitro dissolution test in [redacted] with sampling from 15 minutes to 6 hours. Drug release from the manipulated formulations was determined using HPLC.

Representative simulated oral ingestion data from VANTRELA ER manipulated with 2 tools is shown in Figure 1: the most effective tool (Tool E) and a tool representative of common and easily applied tools (Tool A) are presented. Data from the 30-minute and 120-minute time points are shown. The former is important in light of FDA's recent draft guidance "Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products", which suggests that ≥80% drug release at 30 minutes is a criterion for no abuse deterrence (the definition we are using for this briefing package) when simulating oral abuse after manipulation.

Figure 1: Simulated Oral Ingestion: Percent Drug Released at 30 and 120 Minutes for Manipulated VANTRELA ER Tablets and Manipulated ZOHYDRO ER



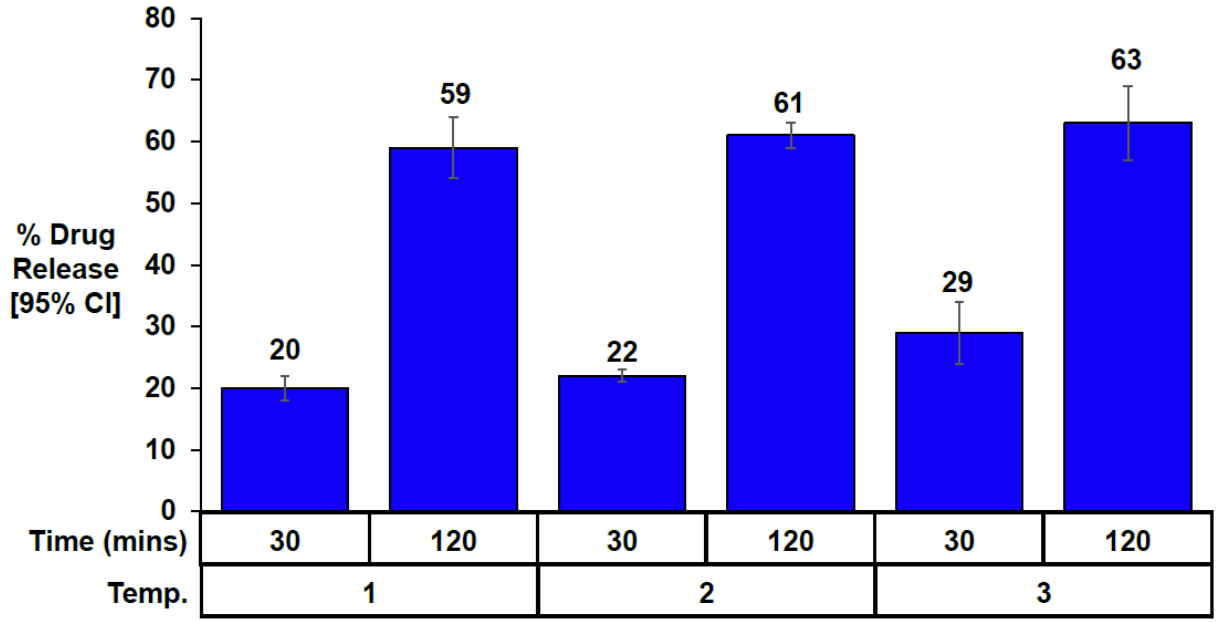
CI=confidence interval; ER=extended-release.

When VANTRELA ER was manipulated with tools intended for abuse, it was not rendered into an IR dosage form. The most effective tool resulted in a mean percent of drug released at 30 minutes higher than Tool A (and all other tools). The percent drug release from VANTRELA ER using the most effective tool (Tool E) was 44% at 30 minutes and 66% at 120 minutes, indicating a significant degree of abuse deterrence potential remained. When Tool A was employed, the mean percent of drug released at 30 and 120 minutes was 9% and 35%, respectively. The majority of product manipulation attempts by recreational abusers that crush, grind, or mill tablets are expected to result in drug release rates similar to Tool A.

Figure 1 also shows the percent of drug released for ZOHYDRO ER manipulated with Tool A. ZOHYDRO ER lost its extended release character completely: manipulated ZOHYDRO ER dumped 97% of its hydrocodone dose within 30 minutes. By contrast, manipulated VANTRELA ER retained significant extended release characteristics.

The effect of temperature extremes on VANTRELA ER tablets was investigated by pretreatment of tablets at Temperatures 1, 2, and 3 before manipulation with Tool A. The simulated oral ingestion percent of drug released results at 30 and 120 minutes are presented in Figure 2. The percent of drug released at 30 minutes for Temperature 1 and 2 was nearly identical, 20% and 22%, respectively. Pretreatment of VANTRELA ER tablets at Temperature 3 before manipulation with Tool A, resulted in a slight change in release rate of hydrocodone early in the profile. The mean percent of drug released at 30 minutes increased to 29% after manipulation. Thus, neither of the temperature extremes was an effective means of defeating the ER nature of the VANTRELA ER formulation.

Figure 2: Simulated Oral Ingestion: Effect of Pre-Manipulation Temperature (1, 2, and 3) on Percent of Drug Released from VANTRELA ER Tablets Manipulated with Tool A



CI=confidence interval; ER=extended-release; mins=minutes; Temp.=temperature.

Simulated Oral Ingestion Conclusion

The experimental dataset for simulated oral ingestion confirmed that manipulation of VANTRELA ER tablets using any of the tools did not result in an immediate release of hydrocodone. The most effective tool (Tool E) resulted in mean percent of drug release at 30 minutes of 44%. Manipulated VANTRELA ER tablets released drug much more slowly than manipulated ZOHYDRO ER comparator. Drug release from ZOHYDRO ER after manipulation with Tool A reached >95% in 15 minutes; whereas, VANTRELA ER tablets manipulated with the same tool released 35% of the dose after 2 hours. Pretreatment of tablets at extreme temperatures before manipulation of VANTRELA ER had a small effect on simulated oral ingestion drug release; however, ER properties were maintained.

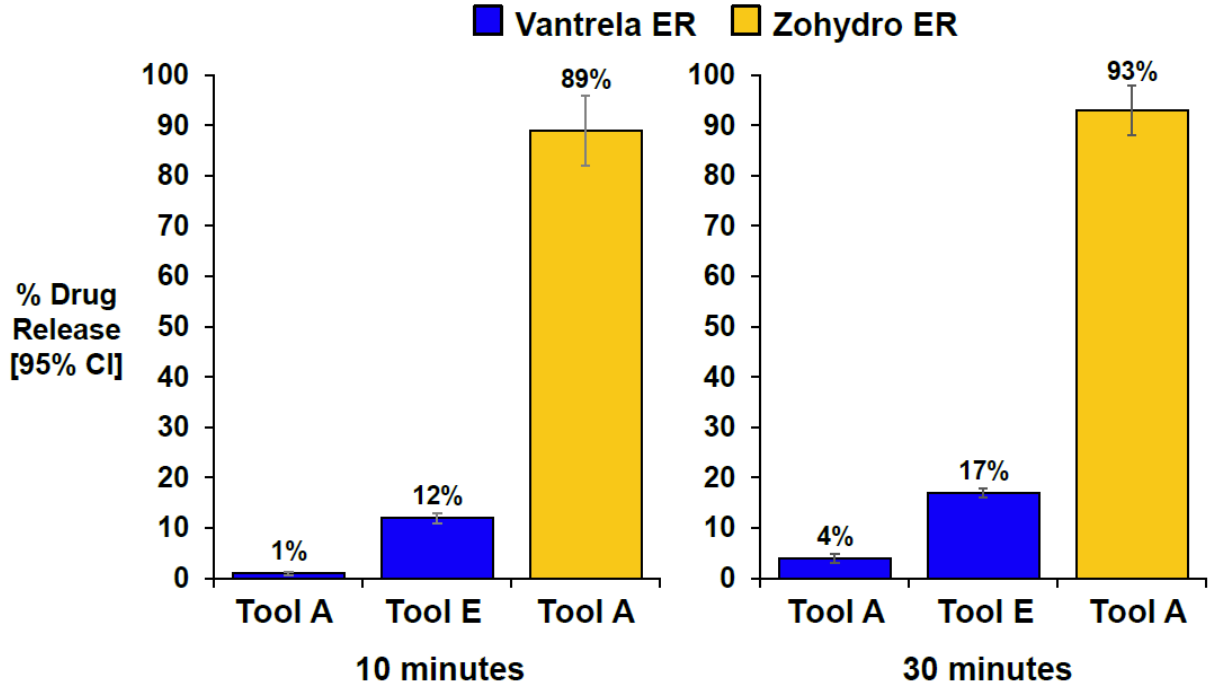
3.4.2.2. Simulated Intranasal Insufflation

Intranasal insufflation experiments included VICOPROFEN and ZOHYDRO ER comparators, and drug substance controls. Manipulation of each dosage form resulted in fine powder masses with particle size amenable for insufflation.

The percent of drug released results from simulated nasal extraction experiments on VANTRELA ER are shown in Figure 3. As with simulated oral ingestion, Tool E resulted in greater percent of drug released than Tool A (representative of other common tools evaluated). However, none of the manipulation tools resulted in immediate release of the drug from manipulated VANTRELA ER. The use of Tool E resulted in only 12% and 17% drug released after 10 and 30 minutes, respectively. The corresponding percent of drug released values when

Tool A was used for manipulation were 1% and 4%. In contrast, manipulated ZOHYDRO ER resulted in 89% of drug released in the first 10 minutes of extraction, with no extended drug release observed.

Figure 3: Simulated Intranasal Insufflation: Percent of Drug Released at 10 and 30 Minutes for Manipulated VANTRELA ER Tablets and Manipulated ZOHYDRO ER Comparator



CI=confidence interval; ER=extended-release.

The effect of temperature extremes on VANTRELA ER was investigated by pretreatment of tablets at Temperatures 1, 2, and 3 before manipulation. Temperatures 1 and 2 prior to manipulation with Tool A and [redacted] extraction resulted in similar percent drug released. Temperature 3 before manipulation with Tool A had a minor effect. The percent drug released for Temperature 3 was slightly higher than that of tablets pre-treated at the other temperatures. These findings were consistent with trends observed in the simulated oral ingestion experiments.

Simulated Intranasal Insufflation Conclusion

While the subjective effects of the gel-forming polymers in the nose after insufflation and the practicality of insufflating up to 1150 mg of material cannot be assessed with in vitro studies, VANTRELA ER clearly resisted extraction of hydrocodone in biologically-relevant volumes of [redacted] when compared to ZOHYDRO ER. Because extraction of hydrocodone from the dosage form into nasal fluid is necessary for mucosal absorption, the resistance of the formulation to releasing hydrocodone bitartrate under these conditions suggested the intranasal route may not be a preferred route of abuse for VANTRELA ER because the proportion of the drug dissolved and available for intranasal absorption is expected to be minimal.

3.4.2.3. Simulated Intravenous Injection

Simulated Intravenous Manipulation: Physical Feasibility

When the VANTRELA ER tablets were manipulated with various tools and mixed with small volumes of extraction medium, the resulting visually heterogeneous mixtures contained flocculent undissolved particulates, gelled polymer, and colorants. Extracts were often difficult to filter and syringe.

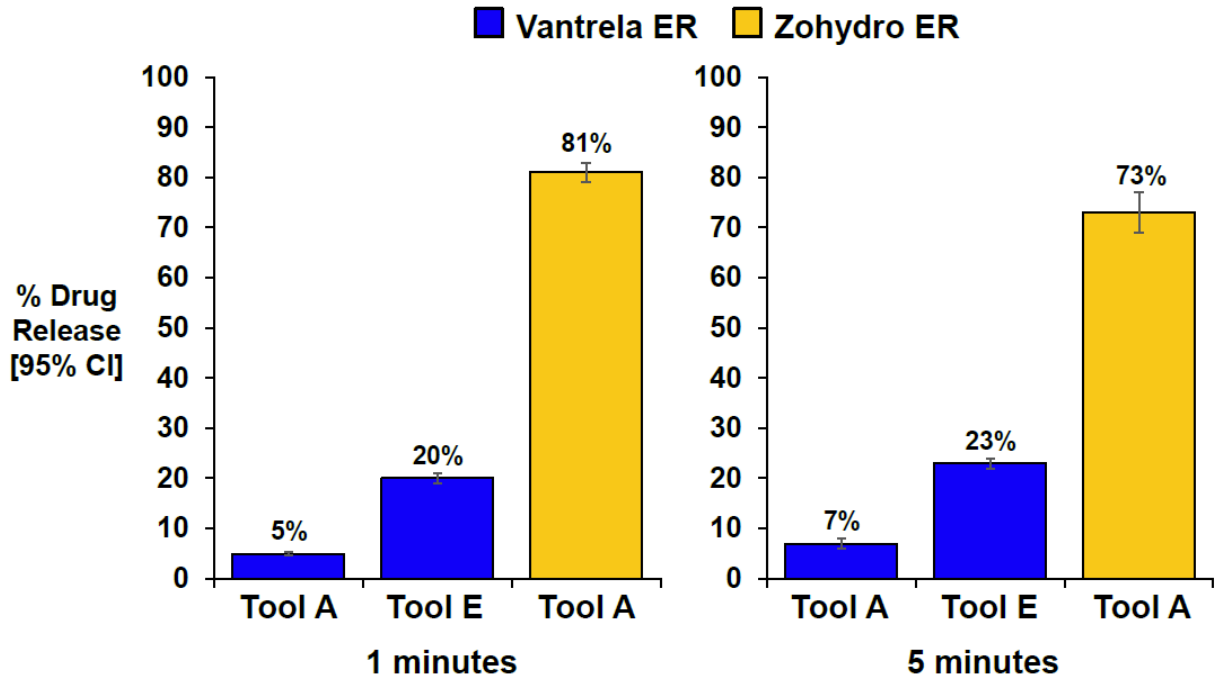
The ease of manipulation varied. In Liquid a, Agitation Method X and longer extraction time led more frequently to the need for larger extraction volumes, indicating that the viscosity of the samples had increased.

Simulated Intravenous Manipulation: Percent of Drug Recovered

The percent of drug recovered represents the maximum quantity of hydrocodone that could be obtained for injection from each tablet manipulated and extracted under the experimental conditions, relative to the tablet dose.

The parameter that exhibited the greatest impact on percent of drug recovered from VANTRELA ER samples was the manipulation tool. Tool E resulted in the highest percent of drug extracted. Representative simulated IV extraction data is presented in Figure 4, which shows the percent of drug recovered from manipulated VANTRELA ER and manipulated ZOHYDRO ER. Only 23% and 7% of drug was recovered from VANTRELA ER after manipulation with Tool E and Tool A, respectively. In contrast, Figure 4 shows that 81% of drug was recovered from manipulated ZOHYDRO ER within 1 minute of extraction in a similar medium. The percent of drug recovered for ZOHYDRO ER decreased slightly with time; however, this was due to a decrease in the volume of syringeable solution obtained. The concentration of drug remained constant from 1 minute through 30 minutes, indicating complete extraction. Thus, VANTRELA ER tablets represent a much more difficult dosage form to manipulate and extract for IV abuse than ZOHYDRO ER.

Figure 4: Simulated Intravenous Extraction of Manipulated VANTRELA ER and Manipulated ZOHYDRO ER: Percent of Drug Recovered after Extraction Agitation Method X



CI=confidence interval; ER=extended-release.

Other experimental parameters were not as strongly correlated to simulated IV extraction efficiencies. Simulated IV extraction with Agitation Method Z yielded similar percent of drug recovered results as those in Figure 4. Pretreatment of tablets at Temperatures 1, 2, and 3 prior to manipulation and simulated IV extraction also showed little difference in percent of drug recovered.

Additional experiments were performed to evaluate other aspects of extraction for IV abuse. Extraction of intact VANTRELA ER tablets in simulated IV media resulted in lower percent of drug recovered than from manipulated tablets. Extraction experiments of manipulated VANTRELA ER tablets extended to 30 minutes showed that the percent of drug recovered steadily increased over time; however, the majority of the dose remained unavailable. When the broadly representative tool (Tool A) was used for manipulation, the percent of drug recovered was ≤33% after 30 minutes; when the most effective tool (Tool E) was used the percent of drug recovered was ≤41%. The pH of the extraction medium did not adversely affect the percent of drug recovered.

Simulated Intravenous Manipulation Conclusion

The gel-forming excipients rendered small volume extraction mixtures visually unappealing and increased the difficulty of filtering and syringing samples from manipulated VANTRELA ER tablets for IV injection. These features may deter IV drug abuse. The aliquots obtained using short (≤5 minutes) extraction times contained relatively little hydrocodone, demonstrating that VANTRELA ER resisted release of hydrocodone into the small volumes required for injection. Somewhat higher hydrocodone content was obtained from extended (30 minutes) extraction

times, but the formulation still did not release the majority of the drug. In contrast, complete extraction of hydrocodone from manipulated ZOHYDRO ER was achieved within 1 minute. Small volume extracts from intact VANTRELA ER tablets were not as difficult to filter and syringe as manipulated tablets, but the amount of drug recovered was lower. For drug abusers that are not deterred by the difficult manipulation and physical properties of VANTRELA ER tablets, the limited hydrocodone in an extract may be insufficient to reinforce repeat IV abuse.

3.4.3. In Vitro Manipulations: Chemical Extractions

Chemical extractions fall into 2 categories, extractions in [redacted] and extractions using [redacted] Extractions in [redacted] aim to liberate the opioid from the ER mechanism of the formulation for oral ingestion; while extractions using [redacted] aim to separate the opioid to some extent from the tablet excipients resulting in a solid residue suitable for abuse. Both types of studies were conducted. Extraction conditions ranged from simple to complex, exploring effects of manipulation tool, agitation, solvent type, temperature, and complexity of procedures.

3.4.3.1. Simple Aqueous Extractions for Direct Ingestion

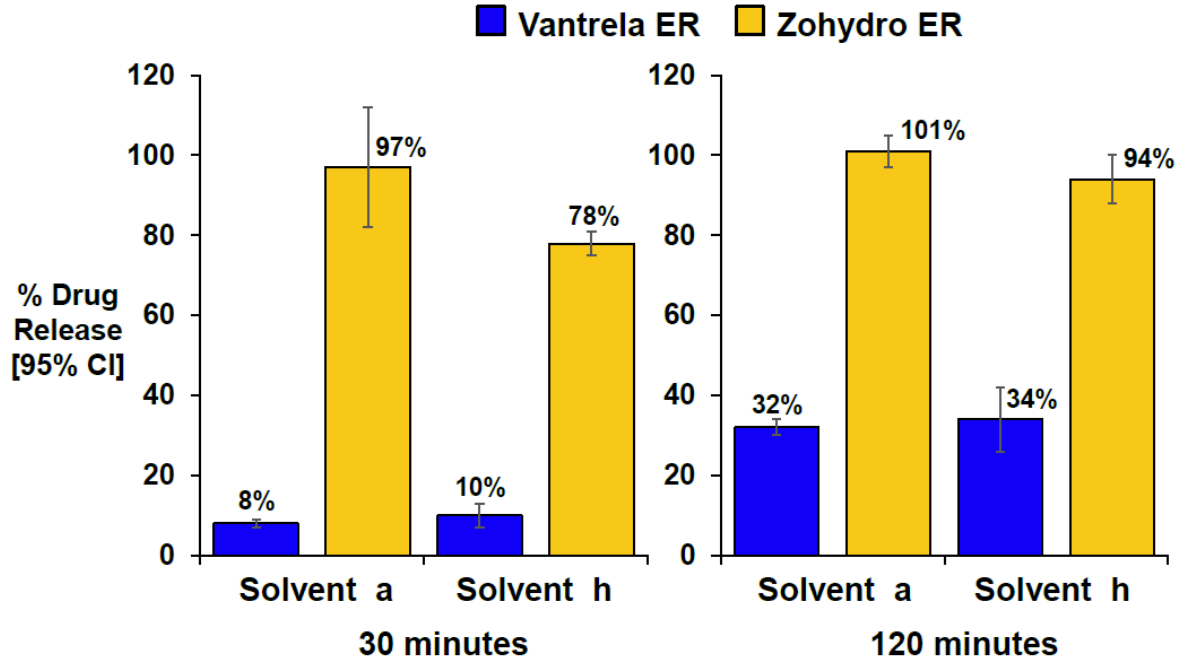
These extraction studies were conducted to evaluate rate of drug release in solvents representing readily available ingestible fluids. The solvents selected represented a range of pH and alcohol content. Dosage forms were manipulated with Tool A and Tool E. Intact dosage forms were extracted in 3 of the solvents. A range of extraction times, temperatures, and agitation conditions were characterized. Manipulated and intact ZOHYDRO ER were included as comparators.

Extraction of Manipulated Dosage Forms

The percent of drug recovered from manipulated VANTRELA ER tablets extracted into 5 solvents intended for ingestion generally increased as temperature, agitation, and extraction time increased. The percent of drug recovered was generally higher with use of Tool E relative to Tool A.

Representative percent of drug recovered for dosage forms manipulated with Tool A are presented in Figure 5. At Temperature 7 and Agitation Method Z, only 8%-10% of the drug was extracted from manipulated VANTRELA ER after 30 minutes. In contrast, ≥78% of drug was extracted from manipulated ZOHYDRO ER at 30 minutes. Over an extended extraction time of 120 minutes, 32%-34% of drug was extracted from VANTRELA ER, indicating retention of ER characteristics.

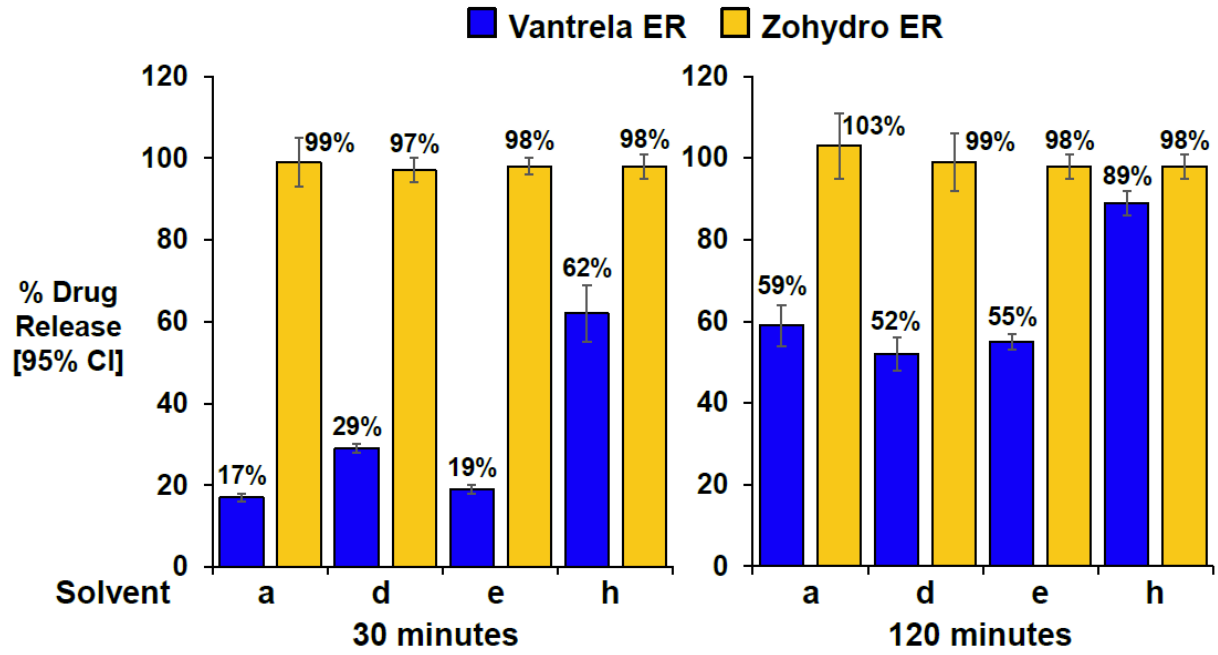
Figure 5: Percent Drug Recovered from VANTRELA ER and ZOHYDRO ER Manipulated with Tool A, Extracted at Temperature 7 with Agitation Method Z.



CI=confidence interval; ER=extended-release.

When Agitation Method W was applied to manipulated dosage forms at Temperature 7 in 4 different solvents, the percent of drug recovered increased, as shown in Figure 6. However, manipulated VANTRELA ER retained its ER properties, with the percent of drug recovered remaining below 30% at 30 minutes in 3 of the 4 solvents. Higher drug recovery was seen for Solvent h under these conditions: 62% at 30 minutes. In contrast, manipulated ZOHYDRO ER showed an immediate drug release profile in each solvent with >95% of drug recovered within 30 minutes. Extractions generally increased with time.

Figure 6: Percent Drug Recovered from VANTRELA ER and ZOHYDRO ER Manipulated with Tool A at Temperature 7 with Agitation Method W



CI=confidence interval; ER=extended-release.

The manipulation tool affected the percent of drug recovered from VANTRELA ER. The most effective tool (Tool E) resulted in somewhat higher drug extraction. The percent of drug recovered at 30 minutes (corresponding to the data in Figure 5 and Figure 6) ranged from 24%-31% and 39%−67%, respectively, for Tool A. The pH of ingestible solvents did not affect the percent of drug recovered from manipulated VANTRELA ER.

3.4.3.2. Advanced Solvent Extractions with Residues Isolated

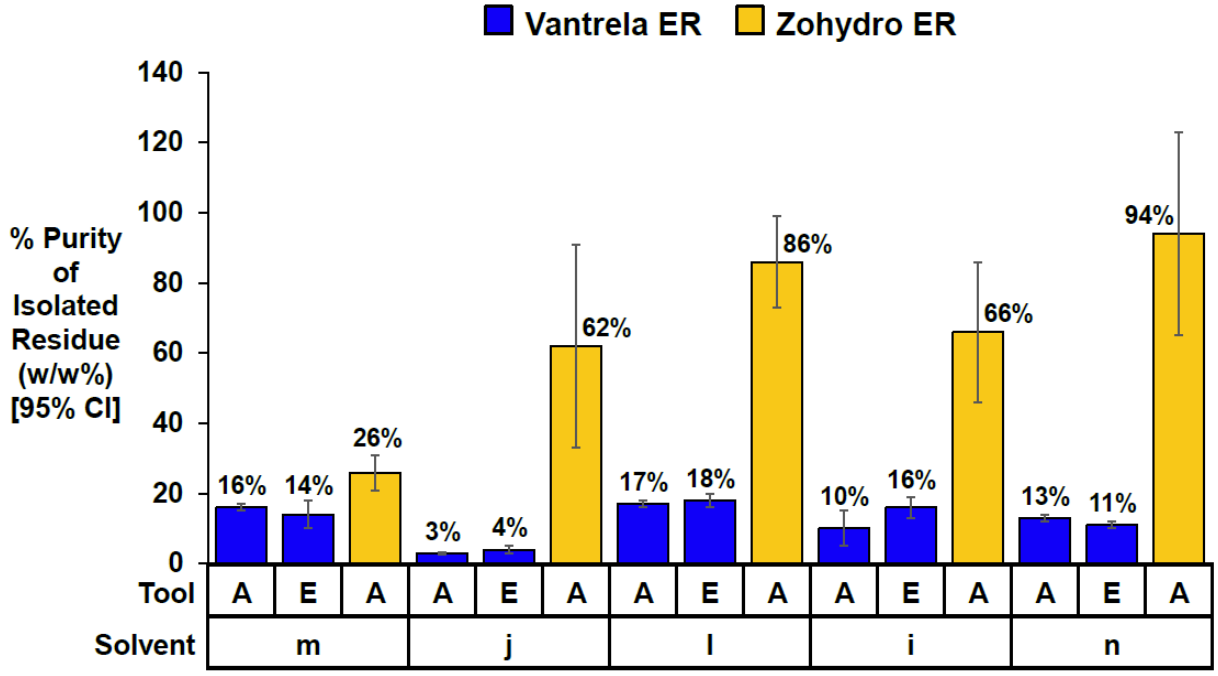
Five advanced solvents were identified with hydrocodone bitartrate solubility sufficient to be used for extraction experiments with isolation of drug residue: Solvents m, l, i, j, and n. Prior to extraction, tablets were manipulated using either Tool A or Tool E. The extractions were performed at Temperature 7, with Agitation Method W or Z, from 30 minutes to 180 minutes. Samples were filtered and the solvent removed to isolate solid material. The percent of drug recovered and the purity of the isolated residues were determined. ZOHYDRO ER manipulated with Tool A was included as a comparator.

Recovery of >80% of the drug was generally achieved within 30 minutes for VANTRELA ER, relative to the solubility limit of hydrocodone in the respective solvent. However, the purity of drug substance extracted from manipulated VANTRELA ER tablets was very low. The percent of drug recovered from manipulated ZOHYDRO ER was generally >90% within 30 minutes. The residues isolated from manipulated ZOHYDRO ER extracts, however, exhibited higher purity than those from manipulated VANTRELA ER tablets.

Purity data from 30-minute extractions in the 5 solvents with Agitation Method W are summarized in Figure 7, along with corresponding data from manipulated ZOHYDRO ER. Mean

purities ranged from 3% to 18% weight/weight (w/w) for VANTRELA ER tablets. The very low purities for the residues extracted from VANTRELA ER tablets were likely due to significant amounts of the release-controlling polymer, which is relatively soluble in the advanced solvents. The presence of the polymer also likely prevents complete removal of the solvent during the drying process.

Figure 7: Advanced Solvent Extraction: Purity of Hydrocodone in Isolated Residues from 30-Minute Extractions of Manipulated VANTRELA ER Tablets and Manipulated ZOHYDRO ER Comparator, with Agitation Method W at Temperature 7



CI=confidence interval; ER=extended-release; w/w=weight/weight.

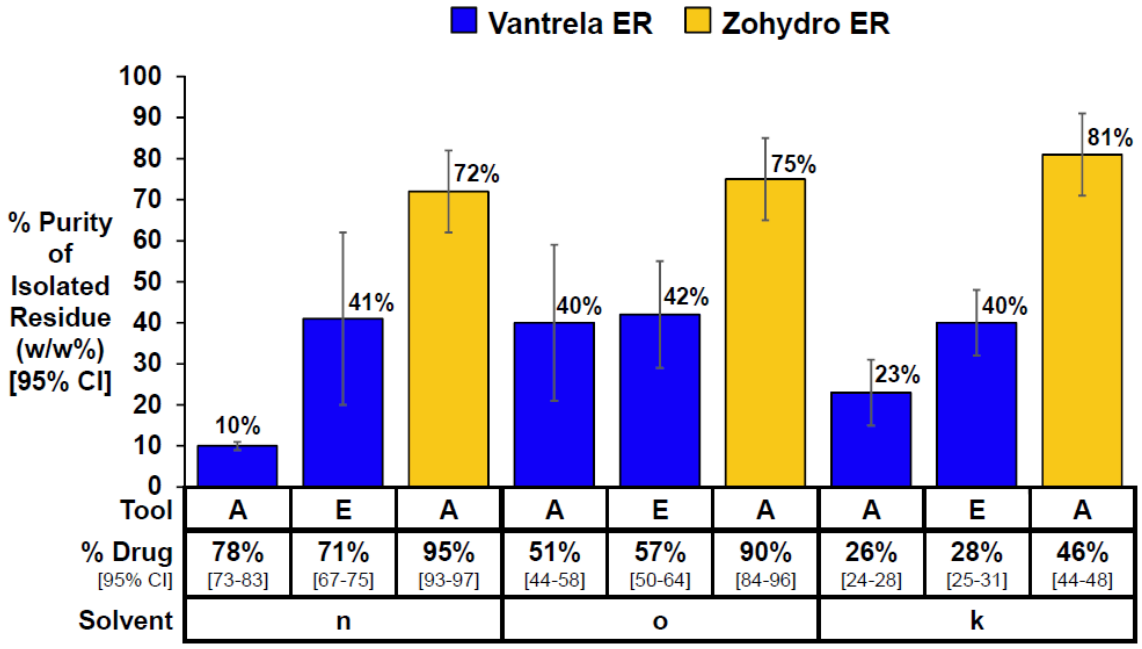
Residues isolated from manipulated ZOHYDRO ER extractions in Liquid i, n, l, and j possessed purities ranging from 62% to 94%; whereas, purities were ≤18% for drug isolated from VANTRELA ER in these solvents. Thus, even though extraction efficiencies were high for both drug products, VANTRELA ER should be less favorable for advanced solvent extractions due to the lower purity of the isolated hydrocodone bitartrate.

3.4.3.3. Multiple-step Chemical Extractions with Residues Isolated

To investigate procedures that sophisticated abusers with some knowledge of chemistry and laboratory equipment might employ, a set of multiple-step extraction studies was performed using both [redacted] The objective was to separate the drug from the excipients using liquid/liquid extractions and to isolate relatively pure drug suitable for abuse by any route. Three advanced [redacted] were evaluated and manipulation was accomplished using Tool A and Tool E. At the end of the multiple-step procedure, the drug was isolated by evaporation of the advanced solvent and its mass and purity were determined.

The percent of drug recovered and the purity of drug recovered are shown in Figure 8.

Figure 8: Multi-Step Chemical Extractions: Purity and Percent Recovered of Hydrocodone Residues from Manipulated VANTRELA ER and Manipulated ZOHYDRO ER



CI=confidence interval; ER=extended-release; w/w=weight/weight.

The purities of the isolated materials from manipulated VANTRELA ER tablets were generally higher than those obtained from the single-step advanced extractions (section 3.4.3.2); however, they did not approach 100%. Thus, some of the tablet excipients were carried through the entire liquid/liquid extraction procedure. The purities obtained from manipulated VANTRELA ER tablets were lower than those from manipulated ZOHYDRO ER.

Some experimental variability was noted in this battery of experiments. Despite considerable effort, separation of the layers was difficult due to the polymeric tablet excipients, which may have led to variable loss of drug from replicate to replicate and variation in the purities obtained. The degree of effort required to optimize the liquid/liquid extraction process could deter all but the most sophisticated abusers.

3.5. Category 2: Pharmacokinetics

The pharmacokinetic profile of VANTRELA ER drug product is important in determining its abuse potential. By manipulating an ER formulation, many abusers seek to accelerate the release of the drug product resulting in a more rapid “high”. The effect results in a much higher peak serum concentration over a shorter duration of time. This change in the pharmacokinetic profile typically results in an increased subjective response (ie, euphoria). An opioid’s AQ is a numerical measurement of the rate of rise (C_{max}/t_{max}) achieved by the drug in the blood and brain when the formulation is manipulated by an abuser (Moorman-Li et al 2012). The AQ is thought to contribute to differential abuse potential among drugs, formulations, and ROAs (Abreu et al

2001, de Wit et al 1992, de Wit et al 1993). A lower AQ indicates a slower rate of rise, and is 1 parameter that may indicate lower abuse potential compared to the reference.

When taken as intended, VANTRELA ER is expected to have a lower potential for abuse compared to IR formulations due to a slower onset with a lower C_{max} and later t_{max}. Category 2 pharmacokinetic data were meant to characterize the pharmacokinetics of manipulated VANTRELA ER following oral and intranasal administration, and the impact of alcohol ingestion on hydrocodone exposure following oral administration of intact VANTRELA ER. Some of the Category 2 data presented herein were collected within the human abuse potential studies described in Section 3.6.

Table 2: VANTRELA ER Category 2 Studies

	Study 1076	**Study 1079**	**Study 1085**	**Study 10032**
Route of Abuse	Oral	Oral	Oral	Intranasal
Test	Intact VANTRELA ER with 4%, 20% or 40% alcohol	Manipulated VANTRELA ER	Manipulated VANTRELA ER	Manipulated VANTRELA ER
Comparators	Intact VANTRELA ER with water	Intact VANTRELA ER Intact VICOPROFEN Manipulated VICOPROFEN	Intact VANTRELA ER Hydrocodone bitartrate API	Hydrocodone bitartrate API Manipulated ZOHYDRO ER Intact VANTRELA ER (oral)

API=active pharmaceutical ingredient; ER=extended-release.

The relative bioavailability of VANTRELA ER to VICOPROFEN was assessed in Studies 1079 and 1090, and to NORCO in Study 1071. Results are presented in Appendix 2.

3.5.1. VANTRELA ER Pharmacokinetics Following Manipulation for Oral Ingestion

3.5.1.1. Study 1079

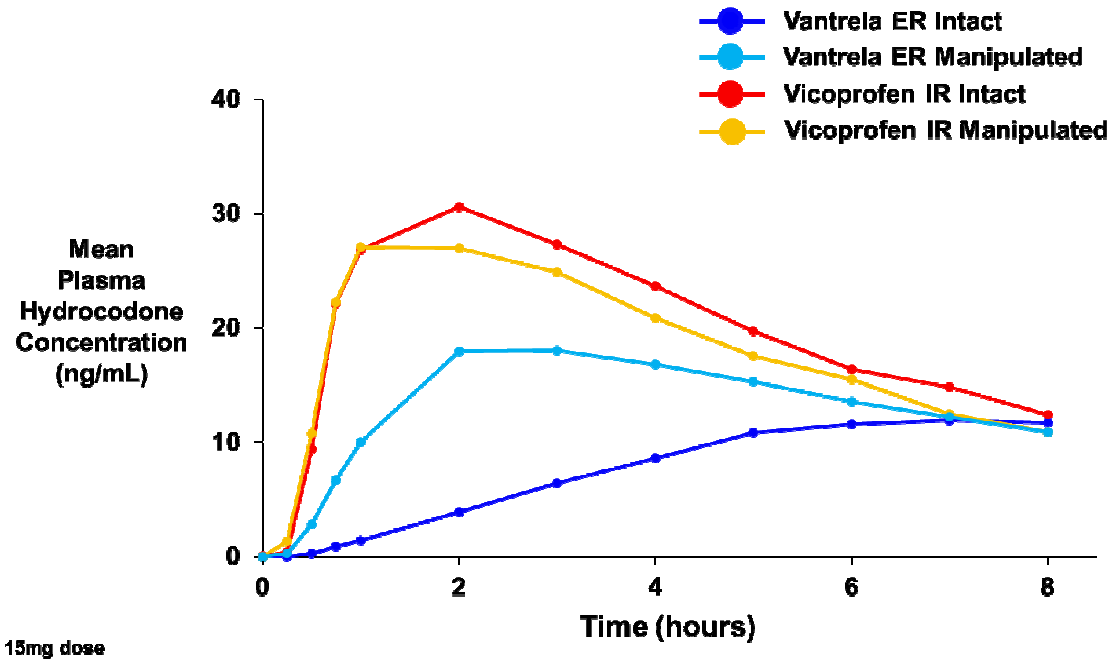
Study 1079 was designed to evaluate the pharmacokinetic profile of manipulated VANTRELA ER following oral ingestion as well as relative bioavailability to VICOPROFEN. The pharmacokinetics of hydrocodone following oral administration of a single 15-mg VANTRELA ER tablet (intact and manipulated) were compared to the pharmacokinetics of hydrocodone following oral administration of a 15-mg dose of an IR hydrocodone combination product VICOPROFEN, administered as two 7.5-mg hydrocodone/200-mg ibuprofen tablets (intact and manipulated), in an open-label, 4-period crossover study in healthy naltrexone-blocked subjects in the fasted state.

Manipulating VANTRELA ER resulted in an increase in C_{max} compared to the intact tablet; however, mean C_{max} was still approximately 40% lower than the IR comparator (Figure 9 and Table 3). Mean C_{max} for the intact VANTRELA ER tablet was approximately 65% lower than for the intact IR comparator.

Following administration of manipulated VANTRELA ER, t_{max} occurred earlier than following administration of VANTRELA ER intact (2.5 vs. 7.0 hours, respectively) but was later than with the IR product (1.8 hours). The differences in peak and time to peak resulted in notably different AQ for the intact VANTRELA ER tablet (AQ=1.8), the manipulated VANTRELA ER tablet

(AQ=9.4), and the intact IR product (AQ=24.8). Overall systemic exposure (as assessed by AUC) was comparable between the manipulated and intact treatments.

Figure 9: Mean Hydrocodone Concentration in Healthy Subjects Administered a Single 15-mg Dose of the VANTRELA ER Tablet (Manipulated and Intact) and a Single 15-mg Dose of VICOPROFEN (IR Hydrocodone Manipulated and Intact)



ER=extended-release; IR=immediate-release.
Note: Truncated profiles presented to elucidate early differences.

Table 3: Mean (SD) Selected Pharmacokinetic Parameters Following Administration of a 15-mg Hydrocodone Dose of VANTRELA ER (Intact and Manipulated) and VICOPROFEN (Intact)

Variable	Intact VANTRELA ER tablet (N=27)	Manipulated VANTRELA ER tablet (N=29)	Intact VICOPROFEN tablet (N=28)
C_{max} (ng/mL)	12.44 (2.54)	21.4 (4.41)	36.08 (8.16)
t_{max} (h)	7.0 (5.0, 9.0)	2.5 (1.5, 6.0)	1.8 (0.8, 4.0)
$AUC_{0-\infty}$ (ng·h/mL)	204 (51)	221 (51)	254 (51)
$AUC_{0-tmax'}$ (ng·h/mL)	2 (1)	15 (4)	34 (12)
AQ (ng/mL/h)	1.8 (0.61)	9.4 (3.12)	24.8 (14.53)

Variable	Change of Intact VANTRELA ER Tablet from Manipulated VANTRELA ER Tablet[a] (%) (N=26)	Change of Manipulated VANTRELA ER from Intact VICOPROFEN Tablet[a] (%) (N=26)
C_{max} (ng/mL)	–42.0	–39.8
$AUC_{0-tmax'}$ (ng·h/mL)	–85.0	–51.2
AQ (ng/mL/h)	–79.0	–54.4

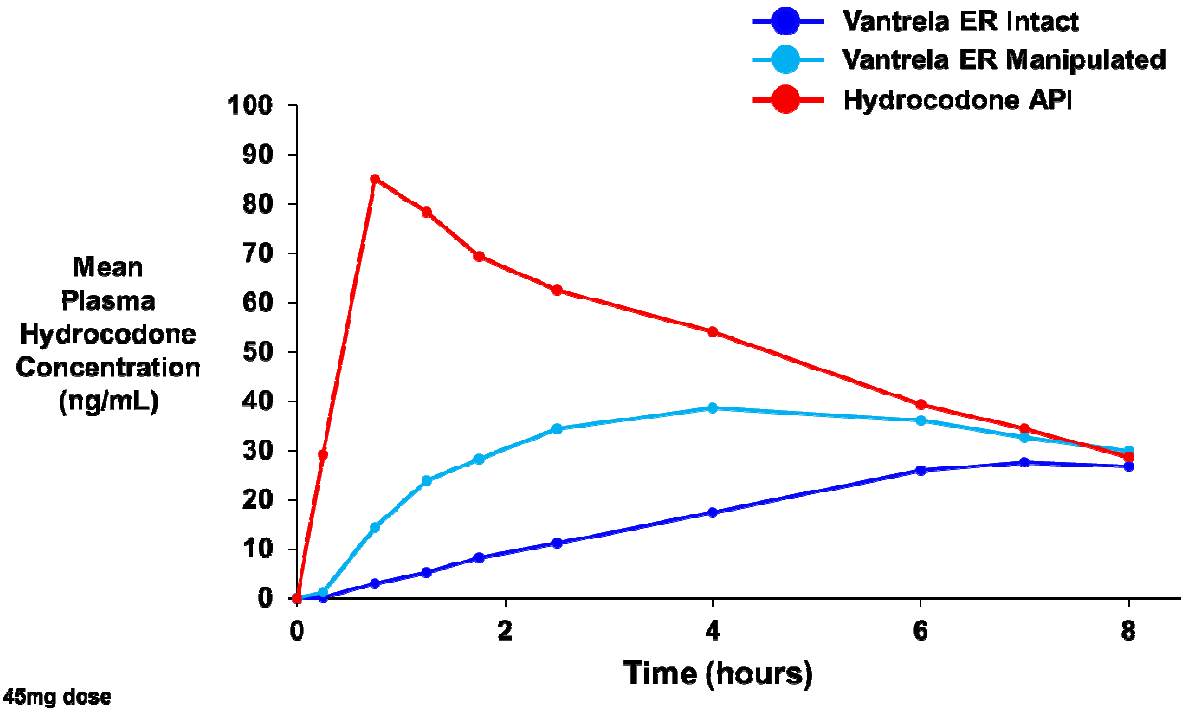
[a] Values represent the mean of individual subject differences, the percent difference for each subject was derived as (treatment ratio-1)*100.
AQ=abuse quotient (C_{max}/t_{max}); $AUC_{0-\infty}$=area under the plasma concentration curve from time 0 to infinity; AUC_{0-tmax}=AUC from time 0 to tmax′, where tmax′ is the median tmax of VICOPROFEN intact (1.8 hours); C_{max}=maximum observed plasma drug concentration; ER=extended-release; N=number of subjects; SD=standard deviation; t_{max}=time to maximum observed plasma drug concentration.
Note: Values for t_{max} are median (range). Results for Manipulated Vantrela ER tablet are dose normalized.

3.5.1.2. Study 1085

Study 1085 was designed to evaluate the pharmacokinetic profile of manipulated VANTRELA ER following oral ingestion. The pharmacokinetics of hydrocodone following oral administration of a 45-mg manipulated VANTRELA ER tablet were compared to the pharmacokinetics of hydrocodone following oral administration of a 45-mg dose of hydrocodone bitartrate API and of a 45-mg intact VANTRELA ER tablet, in a randomized, double-blind, crossover study in fasted healthy non-dependent recreational opioid users.

Overall systemic exposure (as assessed by AUC from time 0 to infinity [$AUC_{0-\infty}$]) was comparable for hydrocodone bitartrate API and VANTRELA ER (intact and manipulated). Mean C_{max} was highest following administration of hydrocodone API (Table 4). Manipulated VANTRELA ER was associated with an approximately 55% lower C_{max} compared to hydrocodone bitartrate API, and was lowest following administration of intact VANTRELA ER. Although shorter than that for oral intact VANTRELA ER, the median t_{max} for manipulated VANTRELA ER was delayed compared with that observed following administration of hydrocodone bitartrate API, indicating that VANTRELA ER retains some of its ER properties following manipulation.

Figure 10: Mean Hydrocodone Concentration Over 8 Hours Following Administration of Single 45-mg Doses of VANTRELA ER (Intact and Manipulated), and Hydrocodone API in Nondependent, Recreational Opioid Users



API=active pharmaceutical ingredient; ER=extended-release
Note: Truncated profiles presented to elucidate early differences.

Table 4: Mean (SD) Pharmacokinetic Parameters for Hydrocodone after Administration of Single Oral Doses of VANTRELA ER (Manipulated or Intact) or Hydrocodone API

Variable	45-mg Hydrocodone API (N=39)	45-mg VANTRELA ER manipulated (N=41)	45-mg VANTRELA ER intact (N=40)
C_{max} (ng/mL)	91.46 (16.817)	40.78 (10.204)	28.77 (6.088)
t_{max} (h)	0.8 (0.3, 4.1)	4.0 (1.8, 7.0)	7.1 (6.1, 12.0)
$AUC_{0-\infty}$ (ng·h/mL)	625 (137.3)	586 (138.5)	584 (124.8)
$AUC_{0-0\ 75}$ (ng·h/mL)	29 (13.5)	3 (1.7)	1 (0.3)
AQ (ng/mL/h)	108.59 (58.789)	10.97 (3.997)	3.88 (1.056)

Variable	Change of manipulated VANTRELA ER Tablet from Hydrocodone API[a] (%) (N=37)
C_{max} (ng/mL)	–53.74
$AUC_{0-0\ 75}$ (ng·h/mL)	–86.10
AQ (ng/mL/h)	–85.87

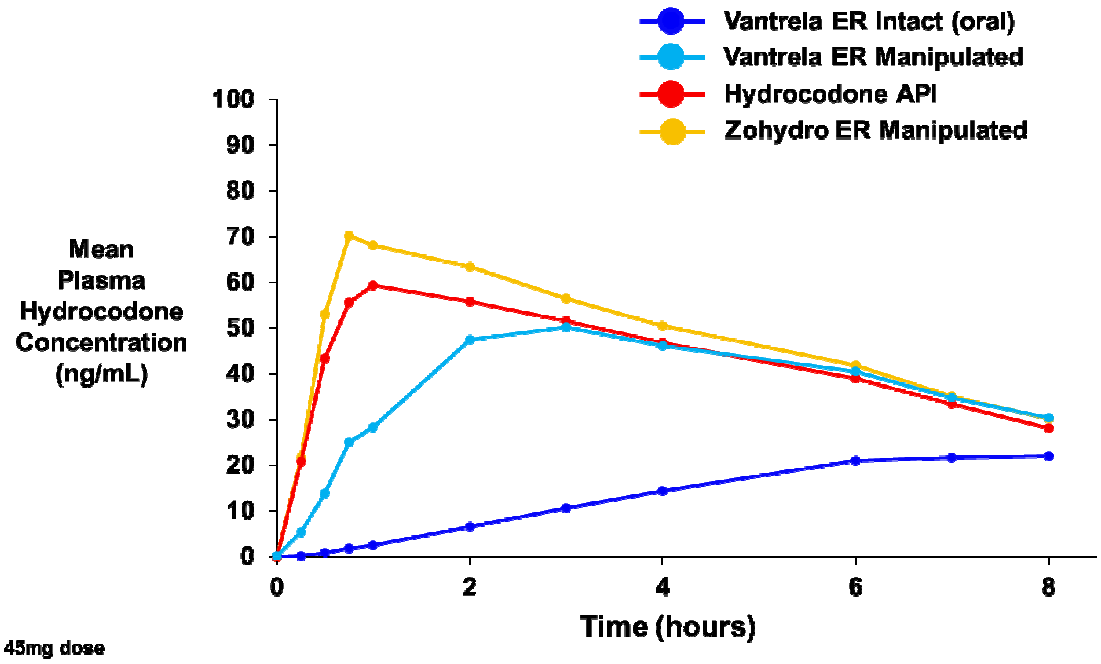
[a] Values represent the mean of individual subject differences, the percent difference for each subject was derived as (treatment ratio-1)*100.
API=active pharmaceutical ingredient; AQ=abuse quotient (C_{max}/t_{max}); $AUC_{0-\infty}$=area under the plasma drug concentration curve (AUC) from time 0 to infinity; $AUC_{0-0\ 75}$=AUC from time 0 to 0.75 hours (Hydrocodone API t_{max}) after study drug administration; C_{max}=maximum observed plasma drug concentration; ER=extended-release; SD=standard deviation; t_{max}=time to maximum observed plasma drug concentration; N=number of subjects.
Note: Values for t_{max} are median (range).

3.5.2. VANTRELA ER Pharmacokinetics Following Manipulation for Intranasal Insufflation

Study 10032 evaluated the pharmacokinetics of manipulated VANTRELA ER following intranasal insufflation. The pharmacokinetics of hydrocodone were compared following intranasal insufflation of a manipulated 45-mg VANTRELA ER tablet, hydrocodone bitartrate API, and a manipulated single-entity ER hydrocodone product (ZOHYDRO ER) in a double-blind, randomized crossover study in recreational drug abusers with a history of opioid insufflation, in the fasted state. The study included also an intact oral VANTRELA ER arm.

Mean plasma hydrocodone concentrations over time for each treatment are shown in Figure 11 and pharmacokinetic parameters presented in Table 5.

Figure 11: Mean Concentration of Hydrocodone in Nondependent, Recreational Opioid Users Administered Single Intranasal Doses of VANTRELA ER (Manipulated), Hydrocodone API, or ZOHYDRO ER (Manipulated), or a Single Oral Dose of Intact VANTRELA ER



API=active pharmaceutical ingredient (hydrocodone); ER=extended-release.
Note: Truncated profiles presented to elucidate early differences.

Table 5: Mean (SD) Hydrocodone Pharmacokinetic Parameters after Intranasal Administration of VANTRELA ER (Manipulated), Hydrocodone API, or ZOHYDRO ER (Manipulated), or Oral Administration of Intact VANTRELA ER

Variable	45 mg IN Hydrocodone API (N=38)	45 mg IN ZOHYDRO ER (N=39)	45 mg IN VANTRELA ER (N=41)	45 mg OR VANTRELA ER (N=38)
C_{max} (ng/mL)	71.28 (30.48)	80.27 (29.29)	56.84 (15.07)	25.05 (7.18)
t_{max} (h)	1.38 (0.60, 7.07)	1.12 (0.55, 6.17)	2.62 (1.33, 7.02)	9.11 (4.10, 12.12)
$AUC_{0-\infty}$ (ng·h/mL)	579 (163)	639 (179)	572 (150)	568 (172)
$AUC_{0-tmax,\ API}$ (ng·h/mL)	57.5 (28.3)	66.5 (28.3)	24.9 (13.4)	1.9 (0.8)
$AUC_{0-tmax,\ ZOHYDRO\ ER}$ (ng·h/mL)	39.3 (20.9)	46.4 (21.2)	15.1 (8.7)	1.0 (0.5)
AQ (ng/mL/h)	59.6 (55.2)	75.4 (54.0)	22.6 (12.2)	3.1 (1.2)

Variable	Change of IN VANTRELA ER from IN Hydrocodone API[a] (%) (N=37)	Change of IN VANTRELA ER from IN ZOHYDRO ER[a] (%) (N=39)
C_{max} (ng/mL)	-12.21	-22.01
$AUC_{0-tmax,\ API}$ (ng·h/mL)	-51.29	-
$AUC_{0-tmax,\ ZOHYDRO\ ER}$ (ng·h/mL)	-	-62.75
AQ (ng/mL/h)	-16.59	-42.39

[a] Values represent the mean of individual subject differences, the percent difference for each subject was derived as (treatment ratio-1)*100.
API=active pharmaceutical ingredient (hydrocodone bitartrate); AQ=abuse quotient (C_{max}/t_{max}); $AUC_{0-tmax,\ API}$= area under the plasma drug concentration curve (AUC) from time 0 to the median t_{max} for intranasal hydrocodone API; $AUC_{0-\infty}$=AUC from time 0 to infinity;$AUC_{0-tmax,\ ZOHYDRO\ ER\ (IN)}$=AUC from time 0 to the median t_{max} for ZOHYDRO ER when manipulated and administered intranasally; C_{max}=maximum observed plasma drug concentration; ER=extended-release; IN=intranasal; N=number of subjects; OR=oral; SD=standard deviation; t_{max}=time to maximum observed plasma drug concentration.
Note: Values for t_{max} are median (range).

Mean C_{max} was highest following administration of intranasal ZOHYDRO ER followed by intranasal hydrocodone bitartrate API. Intranasal VANTRELA ER was associated with an approximately 12% lower C_{max} compared to intranasal hydrocodone API and a 22% lower C_{max} compared to intranasal ZOHYDRO ER. The C_{max} was lowest following administration of oral intact VANTRELA ER. Although shorter than that for oral intact VANTRELA ER, the median t_{max} for intranasal VANTRELA ER was delayed compared with that observed following administration of both hydrocodone bitartrate API and intranasal ZOHYDRO ER, indicating that VANTRELA ER retains some of its ER properties after being manipulated and insufflated.

Comparison of early exposure, as measured by AUC_{0-tmax} for the different treatments, showed findings consistent with peak exposure. Early exposure was highest with intranasal ZOHYDRO ER. Intranasal VANTRELA ER was associated with approximately 51% lower early exposure compared to intranasal hydrocodone API, as assessed by $AUC_{0-tmax,\ API\ (IN)}$. Early exposure was

even lower for intranasal VANTRELA ER compared to ZOHYDRO ER, ie, approximately 63% lower, as measured by $AUC_{0\text{-}tmax,\ ZOHYDRO\ ER\ (IN)}$. These findings translated in differences in the AQ, which was greatest for ZOHYDRO ER (AQ=75.4), followed by intranasal hydrocodone bitartrate API (AQ=59.6), intranasal VANTRELA ER (AQ=22.6), and oral intact VANTRELA ER (AQ=3.1).

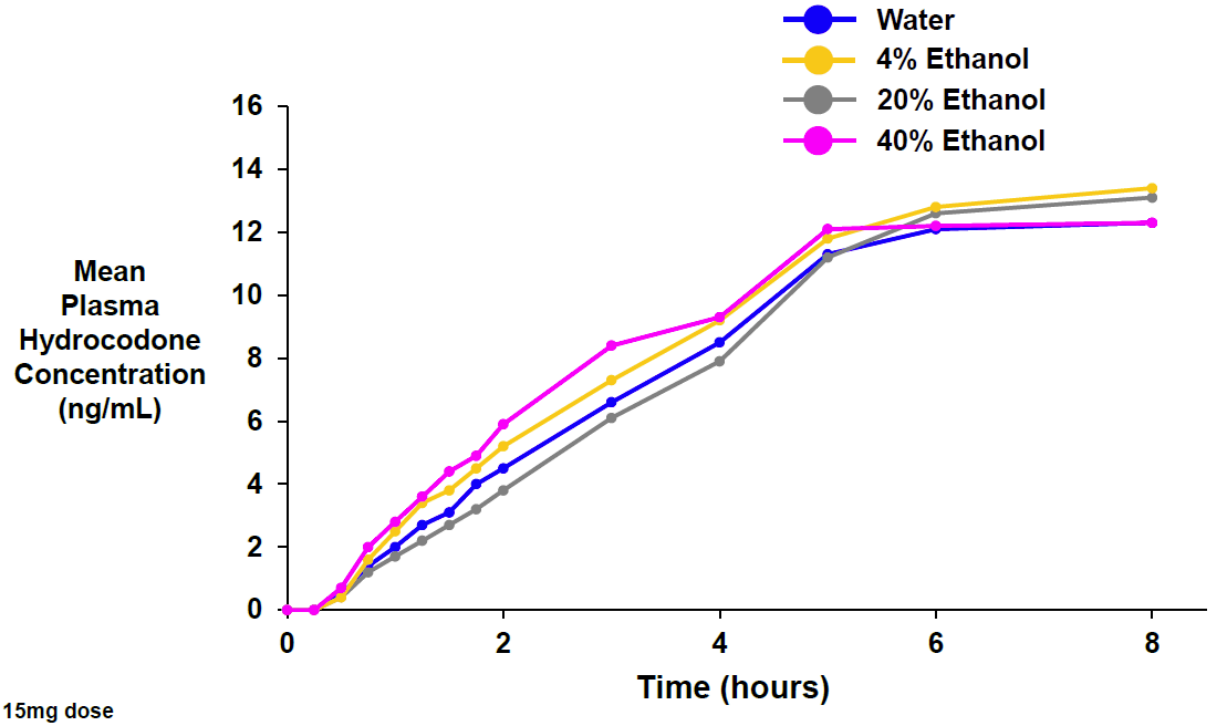
3.5.3. Effect of Alcohol on the Pharmacokinetics of the Oral Intact VANTRELA ER Tablet

The effect of alcohol on the pharmacokinetics of hydrocodone following oral administration of the intact VANTRELA ER tablet was assessed in a randomized, open-label crossover study (Study 1076) in healthy naltrexone-blocked subjects. Treatments included 15 mg VANTRELA ER dosed in the fasted state with each of the following: 240 mL of water, 240 mL of 4% volume/volume (v/v) ethanol, 240 mL of 20% v/v ethanol, and 240 mL of 40% (v/v) ethanol.

Hydrocodone mean peak and overall systemic exposure (C_{max} and $AUC_{0\text{-}\infty}$) was comparable when VANTRELA ER tablets were administered with alcohol compared with water, meeting criteria for bioequivalence (Figure 12 and Table 6). No dose-dumping was observed in the presence of alcohol, with a similar median t_{max} of approximately 6 to 8 hours for all treatments.

Results of this study suggest that patients who ingest alcohol in proximity to a prescribed dose of VANTRELA ER for the treatment of pain will not be in danger of overdose. It should be noted, however, that taking VANTRELA ER with alcohol should be avoided because combining any amount of hydrocodone with alcohol may result in or exacerbate the adverse effects of hydrocodone, particularly those involving the central nervous system (CNS).

Figure 12: Mean Hydrocodone Concentration in Healthy Subjects Administered a Single 15-mg Dose of VANTRELA ER With Water or With 4%, 20%, or 40% Volume/Volume Ethanol



ER=extended-release.

Table 6: Mean (SD) Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single 15 mg Dose of VANTRELA ER Fasting with Water and with Varying Strengths of Alcohol in Healthy Subjects

Variable	Water (N=30)	4% Alcohol (N=30)	20% Alcohol (N=27)	40% Alcohol (N=24)
C_{max} (ng/mL)	12.8 (3.21)	13.6 (3.58)	14.0 (3.85)	13.6 (2.89)
t_{max} (h)	8.0 (5.0, 10.0)	8.00 (5.00, 12.00)	8.00 (4.00, 10.00)	6.00 (3.50, 12.00)
$AUC_{0-\infty}$ (ng·hr/mL)	198 (54)	214 (53)	228 (64)	220 (59)

Variable	Ratio (95% CI) 4% Alcohol/Water (N=30)	Ratio (95% CI) 20% Alcohol/Water (N=27)	Ratio (95% CI) 40% Alcohol/Water (N=24)
C_{max} (ng/mL)	1.050 (0.992, 1.112)	1.085 (1.025, 1.147)	1.144 (1.077, 1.216)
$AUC_{0-\infty}$ (ng·hr/mL)	1.068 (1.013, 1.125)	1.129 (1.060, 1.203)	1.170 (1.110, 1.234)

$AUC_{0-\infty}$=area under the plasma concentration curve (AUC) from time zero to infinity; CI=confidence interval; C_{max}=maximum observed plasma drug concentration; ER=extended-release; N=number of subjects; SD=standard deviation; t_{max}=time to maximum observed plasma drug concentration.
Note: Values are geometric means. Results for administration with water are in fasted state.
Estimates for ratios and 95% confidence interval based on an analysis of variance model (ANOVA) with treatment, treatment sequence, and period as fixed effects and subject as a random effect. Parameter values were log-transformed prior to analysis. The resulting estimate and confidence limits were back-transformed to display the above ratio and 95% CI.

3.6. Category 3: Human Abuse Potential

Two studies have been conducted to evaluate the relative abuse potential of VANTRELA ER in nondependent recreational opioid abusers. Study 1085 assessed abuse potential following oral administration of a manipulated VANTRELA ER tablet as compared to hydrocodone bitartrate API, intact VANTRELA ER, and placebo. Study 10032 assessed abuse potential following intranasal administration of a manipulated VANTRELA ER tablet as compared to hydrocodone bitartrate API, a manipulated commercially available single-entity ER hydrocodone bitartrate product (ZOHYDRO ER), and placebo. Pharmacokinetic data collected in those studies were presented in Section 3.5.

Both studies were randomized, double-blind, placebo-controlled, single-dose, crossover studies. The study population consisted of subjects aged 18 to 52 years who were non-dependent recreational drug abusers.

The studies began with a Qualification Phase in which subjects demonstrated the ability to both tolerate the planned dose of opioid to be tested and to differentiate between the opioid and placebo through the intended ROA. Subjects who successfully passed the Qualification Phase entered the Treatment Phase where the relative abuse potential of the different treatments were assessed.

3.6.1. Abuse Potential of Manipulated VANTRELA ER Administered Orally

3.6.1.1. General Methodology

Study 1085 was designed to assess the abuse potential of orally administered manipulated and intact 45-mg VANTRELA ER compared to 45 mg hydrocodone bitartrate API, and placebo.

The overall study design was generally consistent with regulatory and other guidelines for human abuse potential studies available at the time of the study (Chen and Tsong 2007, FDA 2010, Griffiths et al 2003).

Comparator Selection

At the time this study was conducted, there were no marketed single-entity ER hydrocodone products available. Therefore, it was not possible to include an ER reference product as was included in the intranasal study (Study 10032). In addition, available hydrocodone IR products in the US contain other active ingredients (eg, acetaminophen) which would have presented additional safety concerns with the high hydrocodone dose administered. As per the FDA draft guidance available at the time, the positive comparator in an abuse potential study of an ER opioid formulation with potential abuse-deterrent properties could be an IR formulation of the same opioid (FDA 2013). Therefore, hydrocodone bitartrate API powder was selected as an IR comparator.

The VANTRELA ER tablet and matching placebo were manipulated using Tool F. Specific considerations in selection of this method were the simulated oral ingestion dissolution profile and feasibility of the manipulation method in a clinical trial setting (including material loss and staff exposure).

Pharmacodynamic Measures and Analyses

The primary pharmacodynamic endpoint in this study was the maximum effect (score) (E_{max}) of the bipolar Drug Liking VAS (question 1 of the Drug Liking and Effects Questionnaire[1] [DLEQ_1]) which evaluates "at the moment" drug liking. Secondary measures included Overall Drug Liking VAS score at 24 hours; E_{max} for Good Effects, Bad Effects, and Any Effects, Alertness/Drowsiness VAS, and Nausea VAS (DLEQ questions 2 through 6); area under the effect curve (AUEC) for all VAS (DLEQ) questions; Take Drug Again VAS; Price Value Assessment Questionnaire (PVAQ) scores at 24 hours; and E_{max} and AUEC for the Morphine Benzedrine Group (MBG), Lysergic Acid Diethylamide (LSD), and Pentobarbital Chlorpromazine Alcohol Group (PCAG) subscales of the Addiction Research Center Inventory (ARCI). Pupillometry was also assessed as an objective measure of drug effect.

The key contrasts included:

- Hydrocodone bitartrate API vs placebo (to determine study validity)

[1] Note that in the CSR for Study 1085, this question is referred to as DLEQ question 1; however, this is the same measure as administered in Study 10032, namely a bipolar "drug liking" VAS. For clarity, it will be referred to as Drug Liking VAS throughout this submission. Likewise, DLEQ questions 2-6 are the same as those used in Study 10032 and will be referred to as Good Effects, Bad Effects, Any Effects, Alertness/Drowsiness VAS, and Nausea VAS throughout.

- Hydrocodone bitartrate API vs. oral intact VANTRELA ER
- Hydrocodone bitartrate API vs. oral manipulated VANTRELA ER

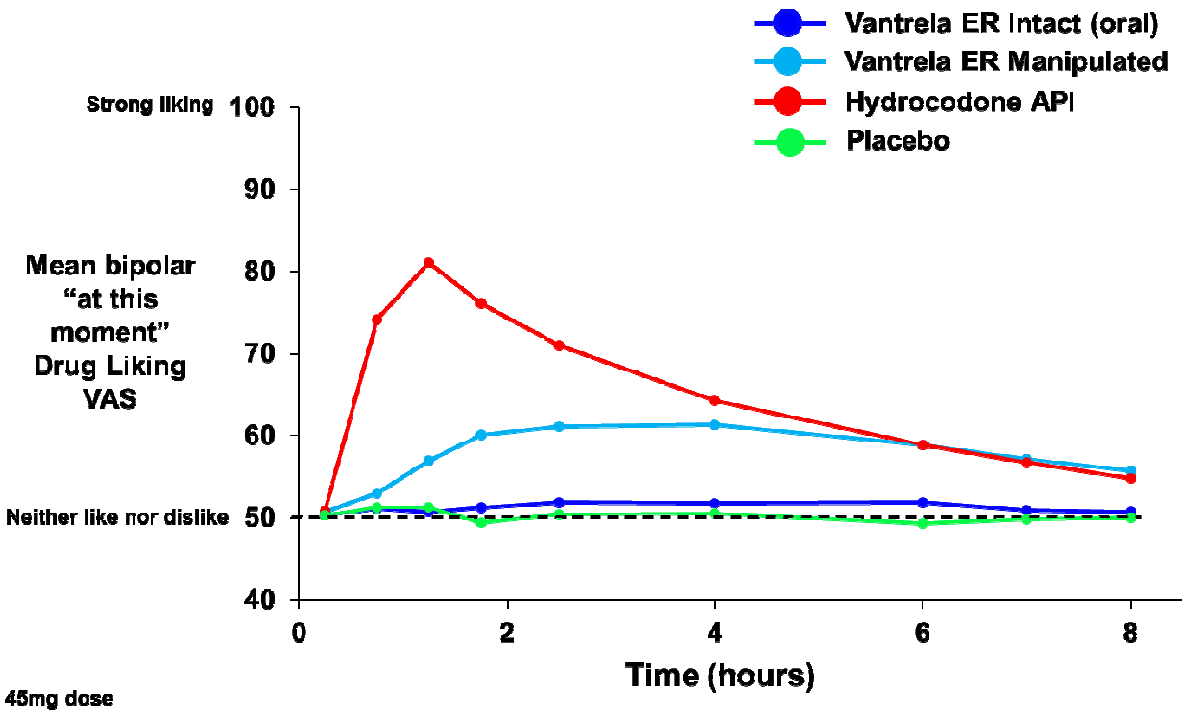
Continuous and ordinal categorical pharmacodynamic parameters were analyzed using a mixed effects analysis of variance (ANOVA) model that included study drug, treatment sequence, and period as fixed effects, and subject as a random effect. Comparisons between pairs of treatments were made using the least square means that were estimated from the ANOVA. Post-hoc analysis was also conducted using non-parametric analysis.

A responder analysis was performed post-hoc using percent reduction using the Drug Liking VAS E_{max}. In this analysis, various deciles (eg, 30%, 40%, 50%, etc.) were used and a binomial proportion test was used to test the null hypothesis that 50% or fewer subjects were responders at each decile.

3.6.1.2. Summary of Results

Mean scores over time on the primary Drug Liking VAS measure (DLEQ question 1) following administration of placebo, VANTRELA ER (manipulated and intact), and IR hydrocodone bitartrate API are presented in Figure 13.

Figure 13: Mean Drug Liking VAS Score (DLEQ Question 1) Over Time (0-8 Hours) Following Oral Administration of VANTRELA ER (Intact and Manipulated), IR Hydrocodone API, and Placebo



API=active pharmaceutical ingredient (hydrocodone); DLEQ=Drug Liking and Effects Questionnaire; ER=extended-release; IR=immediate-release (hydrocodone); VAS=visual analog scale.

Following oral administration of hydrocodone bitartrate API, scores were in the "liking" range (>50) of the scale between 0.75 and 8 hours post-dose. Following oral administration of

manipulated VANTRELA ER, a slower rise to a lower peak drug liking was observed. Liking scores were generally higher than baseline between 1.25 and 8 hours post-dose; however, only a small increase in mean scores was observed relative to placebo at peak (approximately 10 points). Drug Liking VAS scores following administration of placebo and intact VANTRELA ER had very similar profiles, showing little change over time and hovering around the neutral mark (50).

The E_{max} of Drug Liking VAS and Overall Drug Liking VAS for each treatment and treatment comparisons are presented in Table 7.

Table 7: Summary of Analysis Results on the Primary Endpoints in Healthy, Non-dependent, Recreational Opioid Users Administered Single Oral Doses of VANTRELA ER (Intact and Manipulated), Hydrocodone Bitartrate API, and Placebo

	Drug Liking VAS E_{max} (DLEQ – Q1)		Overall Drug Liking VAS E_{max}	
	N	**LS Mean (SEM)**	**N**	**LS Mean (SEM)**
Placebo	42	53.0 (1.75)	43	50.9 (2.18)
45 mg hydrocodone bitartrate API	39	85.0 (1.81)	41	74.9 (2.23)
45-mg manipulated VANTRELA ER	42	66.6 (1.75)	43	58.7 (2.18)
45-mg intact VANTRELA ER	41	54.1 (1.77)	42	49.6 (2.21)
Pairwise Comparisons	**LS Mean Difference**	**P-value**	**LS Mean Difference**	**P-value**
Comparisons of oral treatments				
Placebo– 45 mg hydrocodone bitartrate API	-31.95	**<0.001**	-23.98	**<0.001**
45-mg manipulated VANTRELA ER – 45 mg API	–18.34	**<0.001**	-16.23	**<0.001**
45-mg intact VANTRELA ER– 45 mg API	-30.89	**<0.001**	-25.30	**<0.001**
Comparisons to placebo				
45 mg hydrocodone bitartrate API – placebo	31.95	**<0.001**	23.98	**<0.001**
45-mg manipulated VANTRELA ER – placebo	13.61	**<0.001**	7.75	**0.013**
45-mg intact VANTRELA ER– placebo	1.07	0.640	-1.32	0.672
Comparison of intact and manipulated VANTRELA ER				
45-mg intact VANTRELA ER - 45-mg manipulated VANTRELA ER	-12.55	**<0.001**	-9.07	**0.004**

API=active pharmaceutical ingredient; DLEQ=Drug Liking and Effect Questionnaire; E_{max}=maximum effect; ER=extended-release; LS=least squares; N=number of subjects; Qx=question number x; SEM=Standard error of LS Mean; VAS=visual analog scale.
P-values were based on mixed model with treatment, study period, and sequence as fixed effects, and subject as a random effect. P-values are based on a mixed model that includes study drug, treatment sequence, and period as fixed effects, and subject as a random effect.

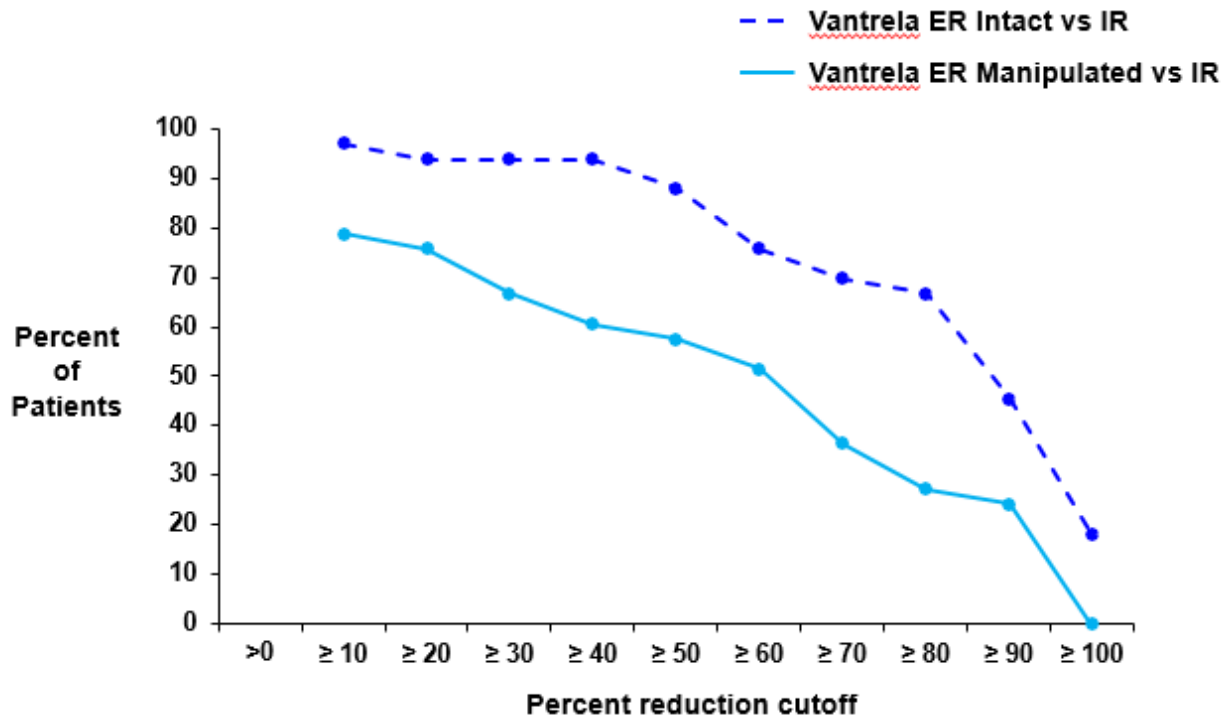
There were statistically significant differences between placebo and hydrocodone bitartrate API for Drug Liking VAS E_{max} (DLEQ Question 1), thereby confirming study validity. Consistent with the results of the primary endpoint, hydrocodone bitartrate API showed statistically significant differences from placebo on the secondary measures of balance, positive effects, negative effects, other effects, and pupillometry.

Oral intact and oral manipulated VANTRELA ER treatments were associated with significantly lower effects compared to hydrocodone bitartrate API on the primary endpoint, Drug Liking VAS, and most secondary subjective and pupillometry endpoints. In addition, VANTRELA ER

(both intact and manipulated) showed a delayed onset relative to hydrocodone bitartrate API. The differences were most pronounced with the intact tablet.

The results of a post hoc responder analysis demonstrated that for the maximum effect of "at the moment" drug liking, 94% of subjects showed ≥30% reductions with intact VANTRELA ER compared with hydrocodone bitartrate API, while 88% of subjects showed ≥50% reduction. When manipulated VANTRELA ER was compared to hydrocodone bitartrate API, approximately 67% of subjects showed greater than a 30% reduction in E_{max} and 58% of subjects showed greater than 50% reduction in E_{max} (Figure 14).

Figure 14: Proportion of Responders Decreasing "At the Moment" Drug Liking VAS E_{max} (Pharmacodynamic Analysis Set)



E_{max}=maximum effect; ER=extended-release; IR=immediate-release (hydrocodone); VAS=visual analog scale.

Oral intact VANTRELA ER showed minimal differences relative to placebo, with no statistically significant differences on the primary endpoint of Drug Liking VAS E_{max} or on the Overall Drug Liking VAS. Manipulated VANTRELA ER was associated with significantly greater liking at this moment and overall liking compared to placebo (Drug Liking VAS E_{max} and Overall Drug Liking 24-hour score).

Post-hoc analysis of the primary endpoints using a non-parametric model (Wilcoxon Signed Rank Test) revealed a similar pattern of results.

3.6.2. Abuse Potential of Manipulated VANTRELA ER Administered Intranasally

3.6.2.1. General Methodology

Study 10032 was a randomized, double-blind, quadruple-dummy, active- and placebo-controlled crossover study designed to assess the abuse potential of manipulated intranasal VANTRELA ER in healthy, nondependent recreational opioid users.

The overall design was consistent with draft FDA guidelines for abuse potential assessment of abuse-deterrent opioid formulations in humans available at the time the study was conducted (FDA 2013) and conducted based upon FDA feedback. The intranasal route was assessed in this study as epidemiological data show that this is a prevalent ROA for opioid abusers (Hays et al 2003 and Osgood et al 2012).

Subjects

This study was performed in self-reported nondependent recreational opioid users with recent (within 3 months) intranasal insufflation experience. These subjects provided the most relevant and sensitive population for an abuse potential study and were considered better able to tolerate the intranasal ROA. In addition to being history-qualified, the pre-study qualification ensured that the subjects were able to tolerate the intranasal ROA, the dose of hydrocodone, and differentiate between hydrocodone and placebo, as well as report positive subjective effects of the drug in a controlled laboratory setting.

Comparator Selection

In a study of an ADF, the comparator is typically an IR or controlled-release formulation of the same active substance. Because IR hydrocodone is primarily available as low-dose combination products with acetaminophen or other active ingredients, hydrocodone bitartrate API was used as the primary active control. Another ER hydrocodone bitartrate product (ZOHYDRO ER), which became commercially available just prior to the start of the study, was also used as a comparator. An oral intact VANTRELA ER arm was included to provide a reference relative to the intended therapeutic oral route.

The VANTRELA ER tablet, ZOHYDRO ER, and matching placebo were manipulated using Tool C based on results of in vitro physical manipulation and extraction studies. Unlike for the method used in Studies 1079 and 1085 (where the manipulated product was orally ingested), PSD was a primary consideration for the intranasal liking study. Tool C produced materials of the smallest particle size, most appropriate for insufflation. Other considerations in selection of this method were simulated oral ingestion and simulated nasal insufflation dissolution profiles and feasibility of the manipulation method in a clinical trial setting (including material loss and staff exposure).

Pharmacodynamic Measures and Analysis

The primary pharmacodynamic endpoints for assessment of relative abuse potential in Phase C of the study were the E_{max} of the Drug Liking VAS (question 1 of the DLEQ) and E_{max} of the Overall Drug Liking VAS.

The secondary pharmacodynamic measures and endpoints for assessment of relative abuse potential in Phase C of the study included additional measures of balance of effects (Take Drug Again VAS, PVAQ), positive effects (Good Effects VAS [DLEQ question 3], ARCI MBG),

negative effects (Bad Effects VAS [DLEQ question 4], ARCI LSD, Nausea VAS [DLEQ question 5]), nasal effects (Subject-rated Assessment of Intranasal Irritation [SRAII], Ease of Snorting VAS), sedative effects (ARCI PCAG, Alertness/Drowsiness VAS [DLEQ question 2]), and other effects (Any Effects VAS [DLEQ question 6] and pupillometry).

With the exception of the intranasal scales, the measures were the same as those used in Study 1085. Pharmacodynamic endpoints for Phase C (E_{max}, minimum effect [E_{min}], and/or AUEC, as appropriate) were analyzed using a mixed effect model for a crossover study (unless non-parametric testing was required).

The key contrasts included:

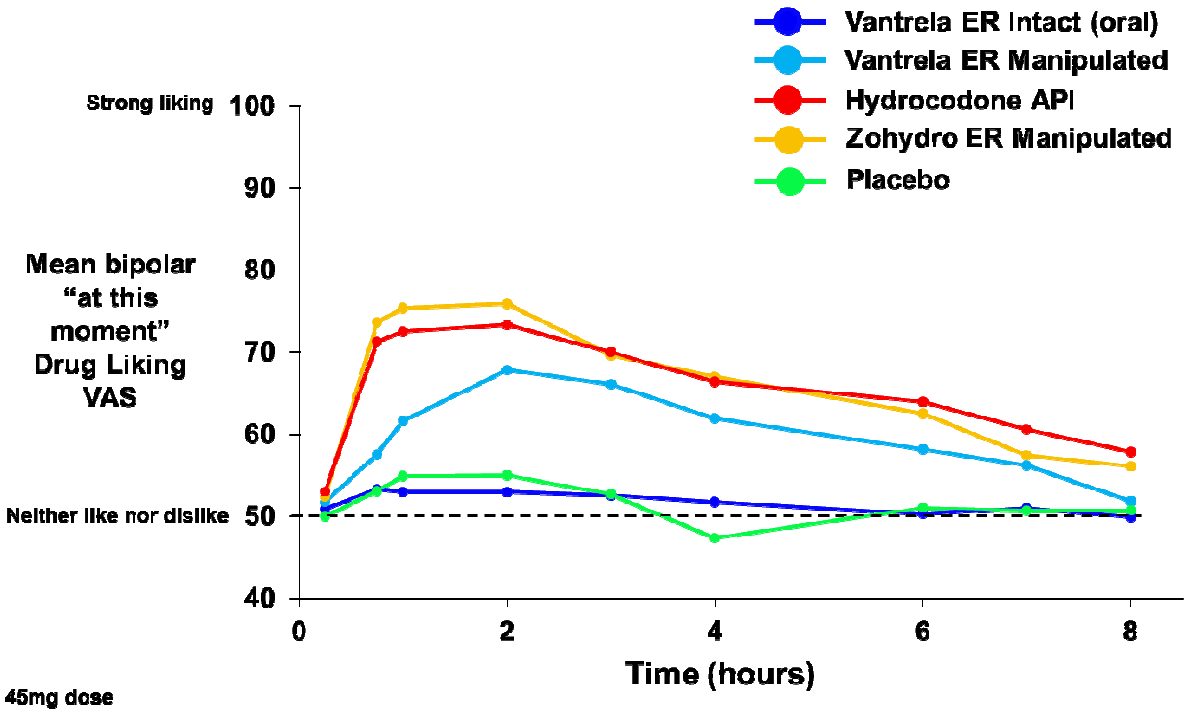
- Intranasal hydrocodone bitartrate API vs. placebo (to determine study validity)
- Intranasal manipulated VANTRELA ER vs. intranasal hydrocodone bitartrate API (primary contrast to assess the relative abuse potential of intranasal VANTRELA ER)
- Intranasal manipulated VANTRELA ER vs. oral intact VANTRELA ER (to evaluate the relative abuse potential of the intranasal route as compared to the oral route)
- Intranasal manipulated VANTRELA ER vs. placebo
- Intranasal manipulated ZOHYDRO ER vs. placebo
- Intranasal manipulated VANTRELA ER vs. intranasal manipulated ZOHYDRO ER
- Intranasal manipulated ZOHYDRO ER vs. hydrocodone bitartrate API

In addition to the primary statistical analysis, a “responder” analysis was conducted according to the draft guidance, on abuse-deterrent opioids evaluation and labeling” (FDA 2013) to determine the proportion of subjects who achieved a pre-specified level of reduction in E_{max} of the primary endpoints for VANTRELA ER relative to hydrocodone bitartrate API (and ZOHYDRO ER).

3.6.2.2. Summary of Results

Mean Drug Liking VAS (question 1 of the DLEQ) scores over time for each treatment are presented in Figure 15.

Figure 15: Mean Drug Liking VAS (DLEQ Question 1) Scores Over Time (0-8 Hours) in Healthy, Non-dependent, Recreational Opioid Users Administered Single Intranasal Doses of VANTRELA ER (Manipulated), Hydrocodone API, ZOHYDRO ER (Manipulated), or a Single Oral Dose of Intact VANTRELA ER



API=active pharmaceutical ingredient; DLEQ=Drug Liking and Effect Questionnaire; ER=extended-release; VAS=visual analog scale.
Bipolar Drug Liking VAS (DLEQ question 1): My liking for this drug is …,where 0=strong disliking, 50=neither like nor dislike, and 100=strong liking.

Mean Drug Liking VAS scores following administration of intranasal hydrocodone bitartrate API and intranasal ZOHYDRO ER increased rapidly, with a steep rate of rise and an onset of effects beginning at approximately 0.5 hours post-dose. In contrast, intranasal VANTRELA ER administration was associated with a slower rise in Drug Liking VAS scores to a lower peak effect. Mean scores were above 65 for a shorter period of time, later in the time-course profile (from 2 to 3 hours post-dose) compared with intranasal hydrocodone bitartrate API and intranasal ZOHYDRO ER. Drug Liking VAS scores over time were comparable following administration of oral intact VANTRELA ER and placebo. Both showed little increase above the neutral point of the scale (mean scores up to 55.5 with placebo and up to 53.4 with oral intact VANTRELA ER).

Table 8 presents a summary of analysis results for the 2 primary endpoints (E_{max} of Drug Liking VAS and Overall Drug Liking VAS).

Table 8: Summary of Analysis Results on the Primary Endpoints in Healthy, Non-dependent, Recreational Opioid Users Administered Single Intranasal Doses of VANTRELA ER (Manipulated), Hydrocodone API, ZOHYDRO ER (Manipulated), or a Single Oral Dose of Intact VANTRELA ER

	Drug Liking VAS E_{max} (DLEQ – Q1)		Overall Drug Liking VAS E_{max}	
	LS Mean (SEM)		LS Mean (SEM)	
Placebo (N=34)	60.8 (2.06)		59.1 (2.65)	
45 mg IN hydrocodone bitartrate API (N=34)	80.2 (2.07)		76.1 (2.65)	
45 mg IN ZOHYDRO ER (N=34)	83.3 (2.06)		79.8 (2.65)	
45 mg IN VANTRELA ER (N=34)	73.3 (2.06)		68.1 (2.65)	
45 mg OR VANTRELA ER (N=34)	57.9 (2.07)		58.6 (2.66)	
Pairwise Comparisons	**LS Mean Difference**	**P-value**	**LS Mean Difference**	**P-value**
Comparisons of intranasal treatments				
45 mg IN VANTRELA ER - 45 mg IN hydrocodone bitartrate API (primary)	-6.83	**0.004**	-8.02	**0.004**
45 mg IN VANTRELA ER - 45 mg IN ZOHYDRO ER	-9.92	**<0.001**	-11.67	**<0.001**
45 mg IN ZOHYDRO ER - 45 mg IN hydrocodone bitartrateAPI	3.09	0.189	3.65	0.189
Comparisons to placebo				
45 mg IN hydrocodone bitartrate API – placebo	19.34	**<0.001**	17.02	**<0.001**
45 mg IN ZOHYDRO ER - placebo	22.43	**<0.001**	20.67	**<0.001**
45 mg IN VANTRELA ER – placebo	12.51	**<0.001**	8.99	**0.001**
Comparison of intranasal and oral VANTRELA ER				
45 mg IN VANTRELA ER - 45 mg OR VANTRELA ER	15.39	**<0.001**	9.52	**<0.001**

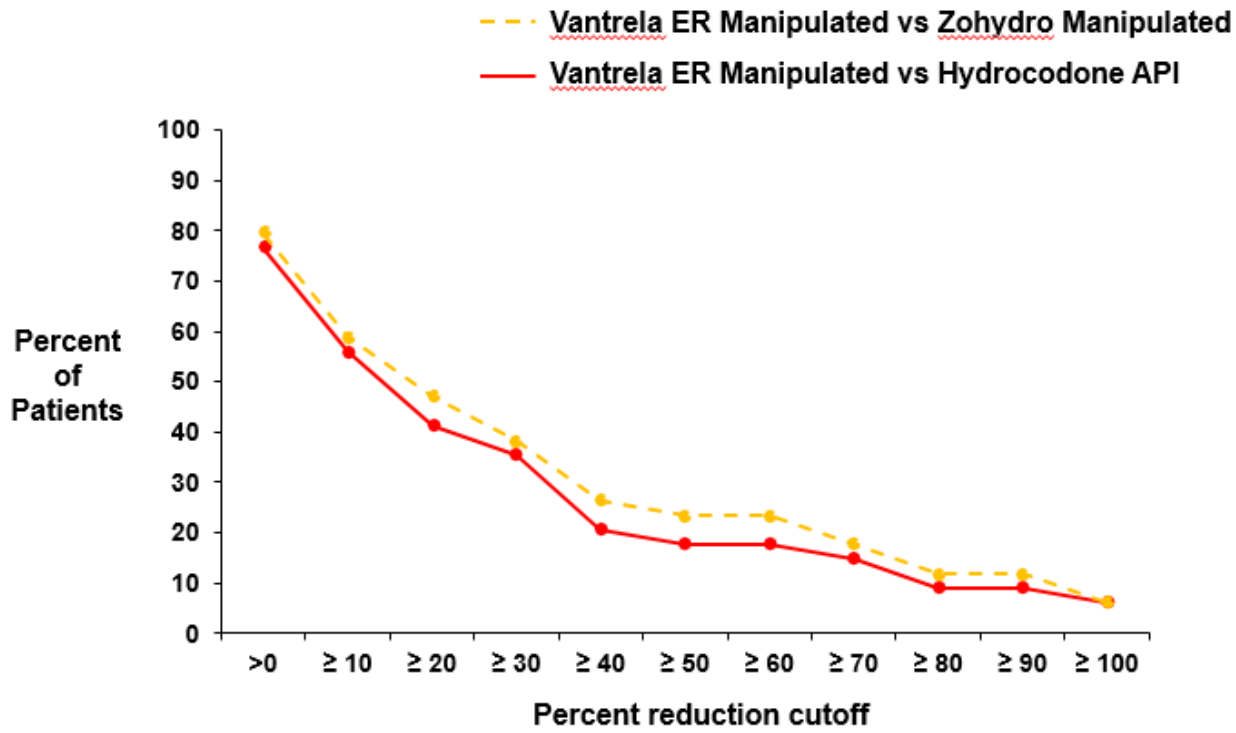
API=active pharmaceutical ingredient; DLEQ=Drug Liking and Effect Questionnaire; E_{max}=maximum effect; ER=extended-release; IN=intranasal; LS=least squares; N=number of subjects; OR=oral; Qx=question number x; SEM=Standard error of LS mean; VAS=visual analog scale.
P-values are based on a mixed model that includes study drug, treatment sequence, period, and carryover effect as fixed effects, and subject as a random effect.

Overall, there were statistically significant differences between placebo and intranasal hydrocodone bitartrate API for the primary endpoints of Drug Liking VAS E_{max} (DLEQ Question 1) and Overall Drug Liking VAS E_{max}, as well as the secondary measures of balance, positive effects, sedative effects, any effects, and pupillometry. Intranasal hydrocodone bitartrate API was also associated with statistically significant negative effects in comparison to placebo.

Intranasal manipulated VANTRELA ER was associated with significantly lower effects compared to intranasal hydrocodone bitartrate API and intranasal ZOHYDRO ER on the primary endpoints, as well as secondary balance of effects, positive, sedative and other effects endpoints. Intranasal VANTRELA ER showed greater peak "bad effects" compared to intranasal hydrocodone bitartrate API but not intranasal ZOHYDRO ER. In contrast, intranasal ZOHYDRO ER was associated with similar or greater effects on the primary and secondary pharmacodynamic endpoints compared to intranasal hydrocodone bitartrate API. Intranasal VANTRELA ER also showed a slower onset of effects compared to intranasal hydrocodone bitartrate API and intranasal ZOHYDRO ER.

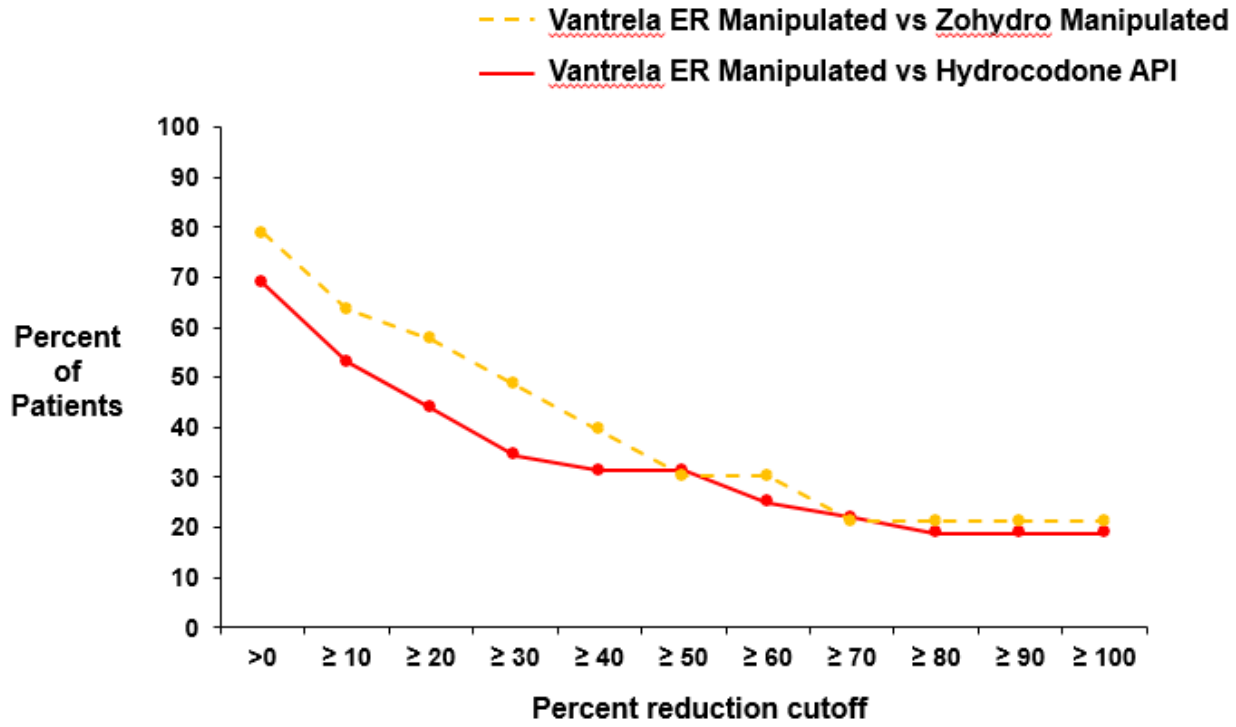
For Drug Liking VAS E_{max}, 35.3% of subjects showed ≥30% reductions with intranasal VANTRELA ER compared to intranasal hydrocodone bitartrate API, while 17.6% of subjects showed ≥50% reductions (Figure 16). For Overall Drug Liking VAS E_{max}, 34.4% and 31.3% of subjects showed reductions of ≥30% and ≥50%, respectively, with intranasal VANTRELA ER compared to intranasal hydrocodone bitartrate API (Figure 17). A larger proportion of subjects showed reductions at the ≥30% and ≥50% deciles with intranasal VANTRELA ER compared to intranasal ZOHYDRO ER (38.2% and 23.5% for Drug Liking VAS and 48.5% and 30.3% for Overall Drug Liking VAS.

Figure 16: Percent Reduction in Maximum Drug Liking for Manipulated VANTRELA ER vs. Hydrocodone API and Manipulated ZOHYDRO ER Following Intranasal Administration in Non-Dependent Opioid Users



API=active pharmaceutical ingredient (hydrocodone); ER=extended-release.

Figure 17: Percent Reduction in Maximum Overall Drug-Liking for Manipulated VANTRELA ER vs. Hydrocodone API and Manipulated ZOHYDRO ER Following Intranasal Administration in Non-Dependent Opioid Users



API=active pharmaceutical ingredient (hydrocodone); ER=extended-release.

All active intranasal treatments were associated with significantly greater effects in comparison to placebo on the primary and most secondary endpoints, while oral intact VANTRELA ER showed subjective effects similar to placebo. Consistent with the similarity between oral intact VANTRELA ER and placebo, statistical comparisons of intranasal manipulated VANTRELA ER and oral intact VANTRELA ER showed significant differences on most endpoints.

Effects on the SRAII scales (intranasal effects) were modest; most scores for all treatments were in the range of 0 (Not observed/No problem) to 2 (Mild/Slight Problem).

On the Ease of Snorting VAS, there was only 1 statistically significant difference in the pairwise comparisons: between oral intact VANTRELA ER treatment (the intranasal "dummy" treatment, essentially a 2.4:1 ratio of sugar spheres:lactose placebo) and intranasal VANTRELA ER (mean difference 12.58; p=0.017).

In general, adverse events were similar overall following administration of intranasal hydrocodone API, intranasal manipulated VANTRELA ER, intranasal manipulated ZOHYDRO ER, and oral intact VANTRELA ER, and consistent with opioid pharmacology. However, the overall incidence of adverse events was highest in subjects following administration of intranasal ZOHYDRO ER, similar between intranasal hydrocodone API and intranasal VANTRELA ER, and lowest following administration of placebo and oral intact VANTRELA ER. All adverse events were mild or moderate in severity. No deaths, other serious adverse events, or severe adverse events occurred in this study. One subject was withdrawn from the study due to adverse events (nausea and vomiting) that interfered with intranasal hydrocodone API administration;

however, this was based on the sponsor's decision due to incomplete drug administration, rather than the adverse events. Four adverse events related to the nose (all mild) were observed in 1 patient each: nasal discomfort, epistaxis, rhinalgia, and rhinorrhea after administration of intranasal placebo, intranasal hydrocodone API, intranasal ZOHYDRO ER, and intranasal VANTRELA ER, respectively.

3.7. Overall Abuse Deterrence Evaluation Conclusions

The abuse-deterrent properties of VANTRELA ER were tested in Category 1 in vitro manipulation studies of intact and manipulated drug product, Category 2 human pharmacokinetic studies, and Category 3 human abuse potential studies. Also, drug diversion, drug loss, and other measures potentially related to abuse potential were assessed in the Phase 3 clinical efficacy/safety studies (see Section 6).

VANTRELA ER tablets retained a significant degree of their ER properties when physically manipulated with a variety of tools and subjected to simulated oral ingestion and nasal extractions. The manipulated formulation resisted extraction of the opioid into small volumes at high temperature that simulate IV abuse conditions, and physically impeded injectability and syringeability. Intact tablets also resisted simulated IV extractions. The formulation exhibited a wide range of performance in simple aqueous extractions for ingestion, maintaining extended release properties under relatively passive conditions but released much of the dose under relatively aggressive conditions. Methodical abusers must be willing to invest significant time and effort to determine how to defeat the release-controlling mechanism with no guarantee of obtaining pure opioid drug substance. In contrast, ZOHYDRO ER was rendered immediate release upon manipulation for each extraction type, and the purity of opioid material obtained from manipulated ZOHYDRO ER was higher than from manipulated VANTRELA ER.

Clinical pharmacokinetic data demonstrated that the barriers to rapid release of hydrocodone when VANTRELA ER is manipulated produced a slower rise to a lower peak concentration as compared with hydrocodone API and non-abuse deterrent ER hydrocodone (ZOHYDRO ER). This lower rate and extent of rise of drug concentrations was apparent following both oral ingestion of manipulated VANTRELA ER and intranasal insufflation of manipulated VANTRELA ER as reflected by the comparative AQ data. Human abuse potential studies demonstrated that the abuse-deterrent features of the VANTRELA ER, when administered manipulated and intact, are associated with substantial reductions in drug liking compared to hydrocodone API and non-abuse deterrent ZOHYDRO ER.

Administration of VANTRELA ER with alcohol had no effect on systemic exposure as measured by either C_{max} or $AUC_{0-\infty}$, and t_{max} was similar whether taken with alcohol or water. These results suggested that combining the VANTRELA ER tablet with alcohol in an attempt by abusers to produce immediate release of opioid will not be successful. Likewise, patients who ingest alcohol in proximity to a prescribed dose of VANTRELA ER for the treatment of pain will not be in danger of overdose. It should be noted, however, that taking VANTRELA ER with alcohol should be avoided because combining any amount of hydrocodone with alcohol may result in or exacerbate the adverse effects of hydrocodone, particularly those involving the CNS.

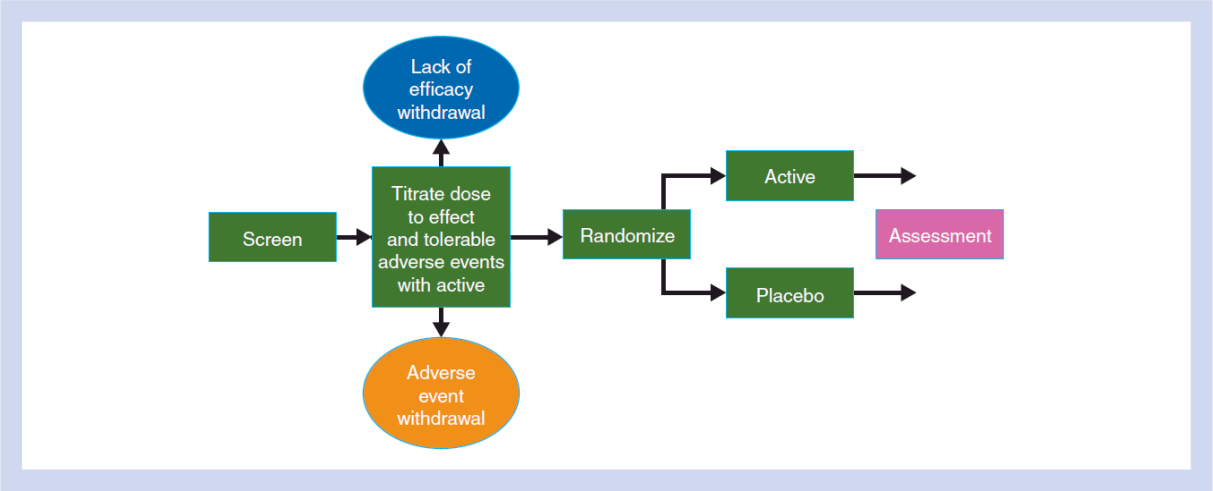
Overall, the in vitro data demonstrate that VANTRELA ER has physical and chemical properties that are expected to deter oral, intranasal and IV abuse. The pharmacokinetic data demonstrate that the abuse deterrent properties of VANTRELA ER limit the rate and extent of rise of drug

concentration following both oral ingestion and nasal insufflation of the manipulated product. The data from the human abuse potential studies also indicate that VANTRELA ER has physicochemical properties expected to reduce abuse via the oral and intranasal routes when the tablet is manipulated.

4. CLINICAL EFFICACY IN PHASE 3 STUDIES

Four Phase 3 studies were conducted in the VANTRELA ER clinical development program, including two 12-week, placebo-controlled, efficacy studies (Study 3079 and 3103) and 2 open-label extension studies, 1 lasting 12 months (Study 3080) and the other lasting 6 months (Study 3104). The enriched-enrolment-randomized withdrawal (EERW) design was used in both placebo-controlled studies (Study 3079 and 3103) to allow an increase in assay sensitivity (Moore et al 2013) (Figure 18). In brief, qualified patients after screening started the open-label titration period to find an optimally effective dose of study drug in each individual patient. At the end of titration, only patients for whom the drug was effective and with tolerable adverse events were randomized to the double-blind treatment period. After randomization and until the end of the study, patients randomized to "active" continued on the optimal dose of the study drug as identified at the end of titration; patients randomized to placebo received placebo instead of the study drug. To prevent withdrawal effects due to an abrupt cessation of opioid treatment, patients randomized to placebo started a 2-week down-titration period after randomization. A rescue medication was always available during the study.

Figure 18: The Design of an Enriched-Enrolment-Randomized Withdrawal (EERW) Chronic Pain Trial



In order to obtain satisfactory pain relief with tolerable adverse events, an initial dose titration phase gradually increased drug dose to obtain pain relief while minimizing adverse events. The titration period lasted several weeks, mimicking the clinical practice situation.

Study 3079 did not meet its primary efficacy endpoint, change from baseline to week 12 in weekly average pain intensity. Study 3103 incorporated several study design improvements and met the primary endpoint of WPI providing confirmation of the efficacy of VANTRELA ER for the treatment of chronic moderate to severe pain.

4.1. Study 3079

Study 3079 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of either opioid-naïve (ie, those taking less than 10 mg/day of oxycodone, or equivalent, for 14 days before screening) or opioid-experienced patients (ie, those taking 10 mg/day or more but not

more than a total of 135 mg/day of oxycodone or equivalent, including around-the-clock medication and rescue medications, for 14 days before screening). Of the 293 patients who participated in the double-blind treatment period, 196 (67%) patients completed 12 weeks of double-blind treatment, 94 (64%) patients in the VANTRELA ER treatment group and 102 (69%) patients in the placebo treatment group.

A total of 97 (33%) patients were withdrawn from the study during the double-blind treatment period, 52 (36%) patients in the VANTRELA ER treatment group and 45 (30%) patients in the placebo treatment group. The majority of patients in both treatment groups had low back pain (71% and 72% in the VANTRELA ER and placebo treatment groups, respectively).

Study 3079 did not demonstrate a statistically significant treatment effect of VANTRELA ER tablets using average pain intensity as the primary efficacy variable. Failure to confirm efficacy is likely explained by several study design characteristics. Most importantly, VANTRELA ER was titrated to a sub-therapeutic dose of 15 mg, which is unlikely to be an optimal dose for most patients. The results of a post hoc analysis showing change from baseline to week 12 in weekly average pain intensity excluding the 15 mg dose group in Study 3079 is shown in Appendix 3, Post-Text Table 3. There was also an allowance for concomitant use of NSAIDs in the study. Overall, Study 3079 sustained a relatively high rate of discontinuation from the study which made it difficult to demonstrate a statistically significant treatment difference. Critical differences in the design of Study 3079 and 3103 are shown in Table 9.

A post-hoc analysis confirmed that if titration to 15 mg was removed, the study results were favorable; the treatment difference was 0.59 (p-value = 0.032). This provided valuable learning during the development of design and endpoints for subsequent studies.

Table 9: Critical Differences in the Study Design Elements of Studies 3079 and 3103

Study factor	Study 3079	Study 3103	Rationale
Study population	Osteoarthritis and lower back pain	Chronic low back pain	
Primary efficacy variable	Average pain intensity	Worst pain intensity	US FDA–preferred primary variable based on End-of-Phase-2 meeting minutes
Minimum optimal dose	Allowed 15 to 90 mg every 12 hours	Allowed 30 to 90 mg every 12 hours (15 mg was only used as a titration dose)	15 mg not considered a therapeutic dose
Allowed rescue medication			
NSAIDs for period during study			
Entire study (open-label and double-blind treatment periods)	Up to 2400 mg of NSAIDs for a maximum of 10 consecutive days	NSAIDs were not permitted; other analgesics were only permitted for fever and cardiovascular prophylaxis	To obtain a reliable assessment of pain control with hydrocodone bitartrate ER tablets
Opioids for period during study			
Open-label titration period	None	Hydrocodone (5 mg)/acetaminophen (325 mg) tablets, every 4 to 6 hours, up to a total dosage of hydrocodone (10 mg)/acetaminophen (650 mg) per day	To make consistent with other study periods and to obtain a reliable assessment of pain control with hydrocodone bitartrate ER tablets throughout the study
Double-blind treatment period	*First 2 weeks, tapering:* Hydrocodone (5 mg)/acetaminophen (325 mg) every 4 to 6 hours as needed, up to a total dosage of hydrocodone (30 mg)/acetaminophen (1950 mg) per day	*First 2 weeks, tapering (down-titration):* Hydrocodone (5 mg)/acetaminophen (325 mg) tablets, every 4 to 6 hours as needed, up to a total dosage of hydrocodone (10 mg)/acetaminophen (650 mg) per day	Dose was reduced to allow for a more reliable assessment of pain control with hydrocodone bitartrate ER tablets
	After tapering: Hydrocodone (5 mg)/acetaminophen (325 mg), every 12 hours as needed, up to a total dosage of hydrocodone (10 mg)/acetaminophen (650 mg) per day[a] for a maximum of 7 consecutive days	*After tapering:*[b] Hydrocodone (5 mg)/acetaminophen (325 mg), 1 to 2 tablets, every 4 to 6 hours (as needed), up to a total dosage of hydrocodone (60 mg)/acetaminophen (3900 mg) per day[c]	To obtain a reliable assessment of pain control with hydrocodone bitartrate ER tablets
Discontinuation from the study	Patients who required 7 days of continuous rescue medication usage at the dose of 10 mg/day starting at week 3 and for the remainder of the double-blind treatment period	Patients who required excessive rescue medication (ie, 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)	To prevent a high discontinuation rate due to non-compliance

[a] During the post-tapering portion of the double-blind treatment period in Study 3079, patients who required more than 7 consecutive days of rescue medication at the dosage of hydrocodone (10 mg)/acetaminophen (650 mg) per day were to be withdrawn from the study. Patients who increased the daily dose of rescue medication above the allowed dosage of hydrocodone (10 mg)/acetaminophen (650 mg) per day on 2 occasions were also to be withdrawn from the study.
[b] The post-tapering portion of the double-blind treatment period occurred starting from week 3 and for the remainder of the double-blind treatment period until week 12 (or the last post-baseline observation).
[c] At any time during the double-blind treatment period, if the patient required rescue medication above the permitted dosage, the patient was to be withdrawn from the study for lack of efficacy. For analysis purposes, 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.
ER=extended release; FDA=Food and Drug Administration; NSAID=nonsteroidal anti-inflammatory drug; US=United States.

4.2. Study 3103

4.2.1. Study Design

Study 3103 was a Phase 3, multicenter, randomized, 12-week double-blind, placebo-controlled, study to assess the efficacy and safety of VANTRELA ER tablets in patients with moderate to severe chronic low back pain who required continuous opioid treatment for an extended period of time (≥3 months). The study design relied upon enriched enrollment and a randomized-withdrawal study design. An open-label titration period to identify the optimal dose was followed by a randomized, double-blind treatment period.

4.2.1.1. Procedures and Assessments

During the open-label titration period, patients received increasing doses of VANTRELA ER tablets in protocol-specified increments to determine the optimal dose that produced stable pain relief without unacceptable adverse events. Stable pain relief was defined as an average pain intensity score over the past 24 hours of 4 or less and a WPI score of 6 or less on the 11-point numerical rating scale (NRS-11) (0=no pain to 10=worst pain imaginable) for either 4 consecutive days or 4 out of 7 consecutive days without unacceptable adverse events, while the patient is maintained on the same dose of study drug for up to 7 days.

The optimal dose was required to be 30 mg q12h or higher. Patients who achieved an optimal dose of VANTRELA ER tablets were randomly assigned (1:1) to receive VANTRELA ER tablets at the optimal dose determined during the open-label titration period or matching placebo. A stepwise, double-blind tapering schedule was used during the first 2 weeks to reduce withdrawal symptoms in the placebo patients. The dose (ie, placebo) was then maintained for weeks 3 through 12. The primary efficacy measurements were taken at week 12.

4.2.1.2. Clinical Endpoints

The primary efficacy variable was the change from baseline to week 12 in the weekly average of daily WPI scores. WPI was measured using NRS-11.

Secondary variables were as follows:

- Change from baseline in the weekly average of daily average pain intensity scores at week 12, based on an 11-point NRS-11 from an electronic diary.
- Time to loss of efficacy, defined as discontinuation of study drug for lack of efficacy or the start of excessive rescue medications while taking study drug.
- Percentage of patients with both a 30% or greater increase in average pain intensity from baseline to week 12 and an average pain intensity score of 5 or higher at week 12.
- Change from baseline to end of treatment in the Roland Morris disability questionnaire (RMDQ) score.
    - 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.

4.2.1.3. Analysis Populations

The intent-to-treat (ITT) analysis set includes all randomly assigned patients. The full analysis set includes all patients in the ITT analysis set who received at least 1 dose of study drug and had at least 1 post-baseline efficacy observation. The full analysis set was used for all efficacy analyses. Overall, 191 patients in the VANTRELA ER treatment group and 179 patients in the placebo treatment group were included in the full analysis set during the double-blind treatment period.

4.2.2. Statistical Methodology

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. Change from baseline in the weekly average of daily WPI scores was analyzed using an analysis of covariance (ANCOVA) model based on a MI method to handle missing WPI scores at week 12. Consistent with the recommendations of the National Academy of Sciences report (National Research Council (US) Panel on Handling Missing Data in Clinical Trials 2010), the MI method included an assumption of missing at random (MAR) and took into account a potential bias toward the active-drug treatment group for patients who discontinued study drug because of adverse events.

Sensitivity analyses were also performed to assess the impact of the following potential confounding factors:

- Missing data assuming missing not at random (MNAR) observations
- Excessive rescue medication use (as 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)
- Inclusion of WPI scores collected after discontinuation of study drug treatment
- Use of WPI scores recorded before rescue medication use

For control of type I error rate, the hierarchical method of analysis for the primary and secondary efficacy endpoints was used to maintain the experiment-wise type I error rate of 5%. The order and method of analysis was as follows:

- Change from baseline to week 12 in weekly average of daily WPI scores was analyzed using an ANCOVA based on a similar MI method used for the primary efficacy variable.
- Time to loss of efficacy was analyzed using a Cox proportional hazards model and Kaplan-Meier method.
- The percentage of patients with both a 30% or greater increase in average pain intensity score from baseline to week 12 and an average pain intensity score of 5 or higher at week 12 was analyzed using logistic regression stratified by center with the following effects: treatment group, baseline average pain intensity, and opioid status.
- The percentage of patients with a ≥30% increase in average pain intensity and the percentage of patients with an average pain intensity score of 5 at week 12 were also summarized separately using descriptive statistics.

- Change from baseline to end of treatment in RMDQ score was analyzed using an ANCOVA model, which included the following effects: treatment group, study center, opioid status, and baseline RMDQ score.

4.2.3. Patient Disposition

Of the 625 patients who were enrolled, 623 participated in the open-label titration period. Of the enrolled patients, 371 (59%) patients achieved a successful dose and 252 (40%) patients discontinued study drug treatment during the open-label titration period. A total of 68 (11%) patients discontinued due to adverse events, 31 (5%) failed to achieve efficacy, and 31 (5%) withdrew consent during the open-label titration period. The remaining patients were discontinued due to protocol violations (18 [3%]), noncompliance with study drug or rescue drug administration, or study procedures (21 [3%]), lost to follow-up (5 [<1%]), pregnancy (5 [<1%]), or discontinued for reasons not otherwise specified (76 [12%]).

Of the 371 patients who participated in the double-blind treatment period, 277 (75%) patients completed 12 weeks of double-blind study drug treatment (147 [77%] patients in the VANTRELA ER treatment group and 130 [72%] patients in the placebo treatment group; Table 10). Overall, 93 (25%) patients discontinued study drug treatment during the double-blind treatment period (44 [23%] patients in the VANTRELA ER treatment group and 49 [27%] patients in the placebo treatment group). Most frequent reasons for discontinuation were adverse events (8% VANTRELA ER and 5% placebo) and lack of efficacy (3% VANTRELA ER and 9% placebo).

Table 10: Patient Disposition in Study 3103 (ITT Analysis Set)

Patient disposition	Number (%) of patients[a]		
	Placebo (N=180)	VANTRELA ER (N=191)	Total (N=371)
Full analysis set	179 (>99)	191 (100)	370 (>99)
Completed study drug treatment	130 (72)	147 (77)	277 (75)
Discontinued study drug treatment	50 (28)	44 (23)	94 (25)
Before double-blind treatment period	1 (<1)[b]	0	1 (<1)[b]
During double-blind treatment period	49 (27)	44 (23)	93 (25)
Adverse event	9 (5)	15 (8)	24 (6)
Lack of efficacy	17 (9)	5 (3)	22 (6)
Consent withdrawn	7 (4)	9 (5)	16 (4)
Protocol violation	9 (5)	7 (4)	16 (4)
Pregnancy	1 (<1)	0	1 (<1)
Lost to follow-up	1 (<1)	2 (1)	3 (<1)
Noncompliance to study procedures	2 (1)	1 (<1)	3 (<1)
Noncompliance to study drug administration	2 (1)	2 (1)	4 (1)
Other	1 (<1)	3 (2)	4 (1)
Completed study	141 (78)	156 (82)	297 (80)
Completed study, but not study drug treatment	11 (6)	9 (5)	20 (5)
Withdrawn from study	39 (22)	35 (18)	74 (20)
Before double-blind treatment period	1 (<1)[b]	0	1 (<1)[b]
During double-blind treatment period	38 (21)	35 (18)	73 (20)
Adverse event	5 (3)	9 (5)	14 (4)
Lack of efficacy	9 (5)	4 (2)	13 (4)
Consent withdrawn	7 (4)	9 (5)	16 (4)
Protocol violation	9 (5)	7 (4)	16 (4)
Pregnancy	1 (<1)	0	1 (<1)
Lost to follow-up	2 (1)	2 (1)	4 (1)
Noncompliance to study procedures	3 (2)	1 (<1)	4 (1)
Noncompliance to study drug administration	2 (1)	2 (1)	4 (1)
Other	0	1 (<1)	1 (<1)

Note: Study 1103 was designed to allow patients who discontinued treatment to continue in the study. Data, including pain scores, continued to be collected.
[a] Percentages are based on the number of patients in the intent-to-treat (ITT) analysis set.
[b] One patient in the placebo treatment group discontinued study drug treatment and withdrew from the study after withdrawing consent and before receiving double-blind study drug.
ER=extended-release; N=number of patients.

4.2.4. Demographics and Baseline Characteristics

Demographic characteristics were well balanced between groups for age, sex, race, ethnicity, and BMI. Across both treatment groups, more patients were categorized as opioid-naïve (58% for both treatment groups) compared with opioid-experienced (42% for both treatment groups) (Table 11).

Treatment groups were similar with regard to duration since diagnosis of chronic low back pain (mean 11.3 years and 11.5 years, VANTRELA ER and placebo respectively) and duration of opioid therapy (mean 3.5 years and 2.9 years, VANTRELA ER and placebo respectively). The majority of patients received concomitant medications during the study (Appendix 3, Post-Text Table 4). Use was similar between the VANTRELA ER and placebo treatment groups for most drug classes.

During the open label titration period, patients had a mean decrease in weekly average WPI by NRS of 3.72 and a mean decrease in weekly average pain intensity by NRS of 2.95.

Table 11: Demographic Information by Treatment Group (ITT Analysis Set)

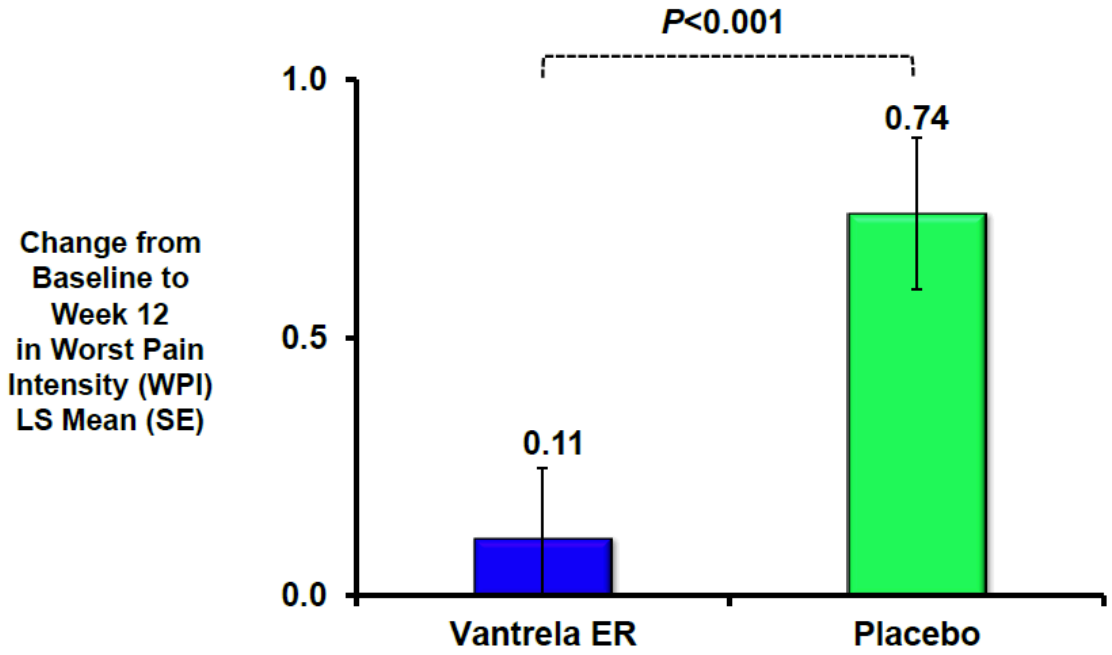
Demographic characteristic Statistic	Placebo (N=180)	VANTRELA ER (N=191)	p-value	Total (N=371)
Age, years				
Mean	51.8	51.7	0.963[a]	51.8
SD	12.51	13.48	—	13.00
Sex, n (%)				
Male	88 (49)	94 (49)	0.950[b]	182 (49)
Female	92 (51)	97 (51)	—	189 (51)
Race, n (%)				
White	129 (72)	133 (70)	0.418[b]	262 (71)
Black	41 (23)	39 (20)	—	80 (22)
Asian	8 (4)	13 (7)	—	21 (6)
American Indian or Alaska native	2 (1)	2 (1)	—	4 (1)
Native Hawaiian or other Pacific Islander	0	1 (<1)	—	1 (<1)
Other	0	3 (2)	—	3 (<1)
Ethnicity, n (%)				
Non-Hispanic and non-Latino	156 (87)	167 (87)	0.585[b]	323 (87)
Hispanic or Latino	23 (13)	24 (13)	—	47 (13)
Unknown	1 (<1)	0	—	1 (<1)
BMI, kg/m^2				
Mean	31.5	31.3	0.782[a]	31.4
SD	8.22	7.37	—	7.78
Patient opioid status, n (%)				
Opioid-naïve	105 (58)	110 (58)	0.885[b]	215 (58)
Opioid-experienced	75 (42)	81 (42)	—	156 (42)
Stable pain relief dose, n (%)				
30 mg	52 (29)	69 (36)	0.245[b]	121 (33)
45 mg	57 (32)	64 (34)	—	121 (33)
60 mg	43 (24)	32 (17)	—	75 (20)
90 mg	28 (16)	26 (14)	—	54 (15)

[a] p-value was based on ANOVA model with treatment group and study center as factors.
[b] p-value was based on Pearson's chi-square test.
ANOVA=analysis of variance; BMI=body mass index; ER=extended-release; SD=standard deviation; ITT=intent to treat; N=number of patients; n=number of patients in subgroup.

4.2.5. Primary Endpoint Results

Patients in the VANTRELA ER treatment group had a statistically significant lower increase from baseline in the weekly average of daily WPI scores at week 12 compared to placebo-treated patients (p-value<0.001; Figure 19 and Table 10). The treatment difference was 0.63 (95% confidence interval [CI]: 0.26, 1.00).

Figure 19: Mean (+SE) Change from Baseline to Week 12 in Weekly Average of Daily WPI (MI Method) in Study 3103 (Full Analysis Set)



ER=extended-release; LS=least squares; MI=multiple imputation; SE=standard error; WPI=worst pain intensity
P-values are based upon a mixed model that includes treatment, study center, opioid status, and baseline WPI score.

Table 12: Change From Baseline to Week 12 in Weekly Average of Daily Worst Pain Intensity (Full Analysis Set)

Time point Statistic	Placebo (N=179)	VANTRELA ER (N=191)
Screening		
N	179	191
Mean	8.23	8.13
SD	1.244	1.288
SE of mean	0.093	0.093
Median	8.00	8.00
Min, max	2.0, 10.0	4.0, 10.0
Baseline[a]		
N	179	191
Mean	4.47	4.45
SD	1.153	1.190
SE of mean	0.086	0.086
Median	4.57	4.57
Min, max	0.0, 6.8	0.3, 8.3
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-VANTRELA ER	0.63 (0.26, 1.00)	
p-value	<0.001	

[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.
CI=confidence interval; ER=extended-release; LS=least squares; max=maximum, min=minimum; n=number of patients in subgroup; SD=standard deviation; SE=standard error.

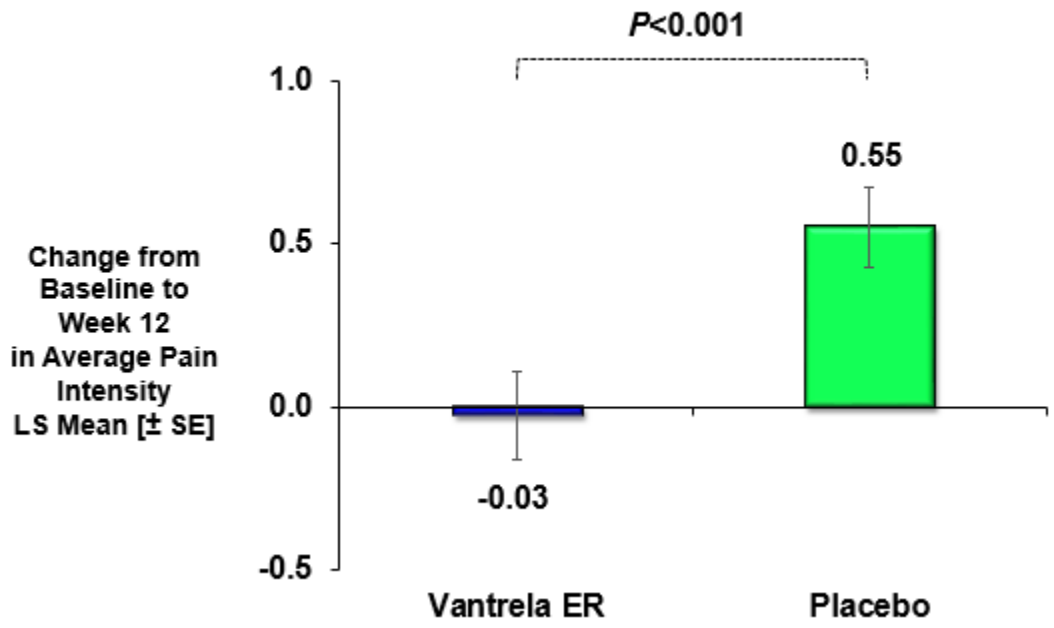
4.2.5.1. Sensitivity Analyses

The sensitivity analyses showed confirmed robust findings for multiple methods of analysis of the primary endpoint including missing value patterns (p-value range 0.008 to <0.001), use of excessive rescue medication (p-value=0.019), inclusion of WPI scores after discontinuation of study drug (p-value=0.006), and use of WPI scores recorded before using rescue medication (p-value=0.001).

4.2.6. Key Secondary Endpoints

Patients in the VANTRELA ER treatment group had a statistically significant lower change from baseline in the weekly average of daily average pain intensity scores at week 12 compared to placebo-treated patients (treatment difference of 0.58 [95% CI: 0.25, 0.91], p-value <0.001) (Figure 20).

Figure 20: Mean (+SE) Change from Baseline to Week 12 in Weekly Average Pain Intensity in Study 3103 (Full Analysis Set)



ER=extended-release; LS=least squares; SE=standard error.
P-values are based upon a mixed model that includes treatment, study center, opioid status, and baseline WPI score.

Table 13: Change from Baseline to Week 12 in Weekly Average Pain Intensity (Multiple Imputation Method) (Full Analysis Set)

Time point Statistic	Placebo (N=179)	VANTRELA ER (N=191)
Screening		
N	179	191
Mean	6.43	6.19
SD	1.418	1.476
SE of mean	0.106	0.107
Median	7.00	6.00
Min, max	2.0, 9.0	0.0, 10.0
Baseline[a]		
n	179	191
Mean	3.41	3.31
SD	0.934	1.022
SE of mean	0.070	0.074
Median	3.57	3.43
Min, max	0.0, 5.3	0.0, 6.4
Week 12		
n	179	191
Mean[b]	3.98	3.33
SE of mean[b]	0.131	0.121
Change from baseline to week 12		
n	179	191
Mean[b]	0.57	0.02
SE of mean[b]	0.126	0.116
LS mean (SE)[c]	0.55 (0.135)	–0.03 (0.121)
Difference (95% CI) placebo-VANTRELA ER	0.58 (0.25, 0.91)	
p-value	<0.001	

[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.
CI=confidence interval; ER=extended-release; LS=least squares; max=maximum; min=minimum; N=number of patients; n=number of patients in subgroup; SD=standard deviation; SE=standard error.

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, favored the VANTRELA ER treatment group (23%) compared to placebo (30%) but failed to reach statistical significance (p=0.059). Statistical testing of lowed ordered endpoints in the hierarchy ended after this result.

During the double-blind treatment period, 136 (71%) patients in the VANTRELA ER group and 145 (81%) patients in the placebo group took rescue medication. The daily mean number of tablets of rescue medication ranged from 0.8 to 1.6 tablets for the VANTRELA ER group and from 1.2 to 1.9 tablets for the placebo group, and use of rescue medication generally increased during the study for both treatment groups. Compared with patients who received placebo, patients who received VANTRELA ER used less rescue medication at all weeks. Use of rescue medication was significantly lower for the VANTRELA ER group at weeks 2 (nominal p-value=0.044) and week 4 (nominal p-value=0.019).

The proportion of patients with an increase in pain intensity, defined as a 30% or greater increase in weekly average pain intensity and an average pain intensity of 5 or greater at week 12, favored the VANTRELA ER treatment group (12.5%) compared to placebo (18.8%) (nominal p-value=0.0293). No meaningful differences in the change from baseline to end of treatment in RMDQ score were observed between the VANTRELA ER and placebo treatment groups upon review of the results (nominal p-value=0.557).

5. CLINICAL SAFETY IN PHASE 1 AND PHASE 3 STUDIES

5.1. Exposure

A total of 1964 subjects/patients were exposed to VANTRELA ER in 19 Phase 1 and 4 Phase 3 clinical studies. In the Phase 1 studies, a total of 788 unique subjects were enrolled and received at least 1 dose of VANTRELA ER. Of these, 685 subjects were in studies that required naltrexone blockade.

In the 4 Phase 3 studies (2 double-blind and 2 open-label studies), a total of 1176 patients were enrolled and received at least 1 dose of VANTRELA ER (safety analysis set), and there was 412 person-years of treatment experience with 197 subjects followed for 12 months or more.

5.2. Summary of Safety in Phase 1

The Phase 1 studies represent a different population from that of the Phase 3 program as most of these studies were conducted in healthy young subjects, and 16 studies included administration of naltrexone. The majority of adverse events in the Phase 1 studies were mild to moderate in severity. There were no deaths or other serious adverse events reported during the Phase 1 studies.

Two subjects (1 subject each in Studies 1081 and 1088) reported severe adverse events (syncope [related to study drug] and orthostatic hypotension [not related to study drug]). Overall, there were 62 (7.9%) subjects who discontinued from Phase 1 studies due to adverse events. Of these, 53 subjects were withdrawn due to emesis per prespecified criteria in the protocol.

In the 16 studies conducted in 685 healthy subjects concurrently receiving naltrexone, 60 (8.8%) subjects discontinued due to adverse events. In the 2 studies that were conducted in nondependent recreational opioid users who did not concurrently receive naltrexone (Studies 1085 and 10032), 2 (2.1%) subjects discontinued due to adverse events. None of the subjects or subjects with hepatic impairment in Study 1089 were discontinued.

5.3. Summary of Safety in Phase 3

The evaluation of the safety of VANTRELA ER treatment in patients with moderate to severe OA or chronic low back pain who require opioid treatment for an extended period of time was based primarily on data from the 2 completed Phase 3 double-blind, placebo controlled studies to assess the efficacy of VANTRELA ER (Studies 3079 and 3103) and the 2 open-label, long term safety studies (Studies 3080 and 3104).

The safety data from these studies were integrated by study design and analyzed for the safety analysis set, the post-titration analysis set, and the post-titration analysis set for the double-blind studies (Studies 3079 and 3103). The safety analysis set (N=1176) included all patients who took at least 1 dose of VANTRELA ER in the Phase 3 studies. The safety analysis set included 389 patients from Study 3079, 164 new patients from Study 3080, and 623 patients from Study 3103. Rollover patients who entered Studies 3080 and 3104 were included in the safety analysis set as part of the number of patients in Studies 3079 and 3103.

All 4 of the Phase 3 studies included a titration period (Studies 3079, 3080, 3103, and 3104) or adjustment period (Study 3104), after which patients 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 VANTRELA ER in either a double-blind (Studies 3079 and 3103) or long-term open-label period (Studies 3080 and 3104) per individual study design. The post-titration analysis set included 146 patients who received VANTRELA ER in Study 3079, a total of 213 additional patients who received VANTRELA ER in Study 3080, a total of 191 patients who received VANTRELA ER in Study 3103, and 78 additional patients who received VANTRELA ER in Study 3104 (these patients had previously received placebo in Study 3103).

The post-titration analysis set for the 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 (Studies 3079 and 3103). 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 VANTRELA ER) and 370 patients from Study 3103 (179 patients who received placebo and 191 patients who received VANTRELA ER)

The safety data from the 4 phase 3 studies are summarized in text below from the safety analysis set (presented here as “all phase 3 studies combined” and the post-titration analysis set for the double-blind studies [Studies 3079 and 3103]).

5.3.1. Adverse Events

5.3.1.1. All Phase 3 Studies Combined

Of the 1176 patients who were enrolled in the 4 Phase 3 studies and received at least 1 dose of VANTRELA ER (safety analysis set), 864 (73%) patients reported at least 1 adverse event (Appendix 5, Post-Text Table 5). Adverse events reported by ≥5% of patients were constipation (276 [23%] patients), nausea (272 [23%] patients), headache (144 [12%] patients), somnolence (122 [10%] patients), vomiting (122 [10%] patients), dizziness (79 [7%] patients), pruritus (70 [6%] patients), fatigue (61 [5%] patients), and diarrhea (59 [5%] patients.

A total of 120 (10%) patients in the 4 Phase 3 studies combined reported at least 1 adverse event that was severe. The severe adverse events reported by more than 1 patient were constipation (13 [1%] patients), nausea (9 [<1%] patients), vomiting (8 [<1%] patients), back pain (6 [<1%] patients), headache (6 [<1%] patients), diarrhea (5 [<1%] patients), muscle spasms (4 [<1%] patients), OA (3 [<1%] patients), somnolence (3 [<1%] patients), drug withdrawal syndrome (3 [<1%] patients), arthralgia (3 [<1%] patients), influenza (2 [<1%] patients), pneumonia (2 [<1%] patients), arthropod bite (2 [<1%] patients), musculoskeletal pain (2 [<1%] patients), pain in extremity (2 [<1%] patients), sedation (2 [<1%] patients), renal failure acute (3 [<1%] patients), nephrolithiasis (2 [<1%] patients), deep vein thrombosis (2 [<1%] patients), hemorrhoids (2 [<1%] patients), cellulitis (2 [<1%] patients), cholangitis (2 [<1%] patients), urinary tract infection (2 [<1%] patients), road traffic accident (2 [<1%] patients), and panic attack (2 [<1%] patients).

Of the 1176 patients who were enrolled in the Phase 3 studies and received at least 1 dose of study drug (safety analysis set), 214 (18%) patients reported at least 1 adverse event causing

discontinuation from the study. Adverse events causing discontinuation reported by more than 2% of patients were nausea (64 [5%] patients) and vomiting (32 [3%] patients).

5.3.1.2. Double-Blind Studies 3079 and 3103 Combined

5.3.1.2.1. Adverse Events During the Titration Period

During the titration period, all patients received VANTRELA ER. In the double-blind studies (Studies 3079 and 3103), 158 (47%) patients in the VANTRELA ER group and 156 (48%) patients in the placebo group reported adverse events during the titration period (based on the post-titration analysis set). In the VANTRELA ER group, adverse events reported by ≥5% of patients were constipation (55 [16%] patients), nausea (36 [11%] patients), headache (23 [7%] patients), somnolence (21 [6%] patients), and pruritus (16 [5%] patients). In the placebo group, adverse events reported by ≥5% of patients were constipation (55 [17%] patients), nausea (45 [14%] patients), headache (24 [7%] patients), somnolence (22 [7%] patients), and pruritus (16 [5%] patients).

A total of 97 (29%) patients later assigned to the VANTRELA ER group and 99 (30%) patients later assigned to the placebo group reported adverse events that were mild, and 58 (17%) patients in the VANTRELA ER group and 54 (17%) patients in the placebo group reported adverse events that were moderate. Three (<1%) patients in the VANTRELA ER group and 3 (<1%) patients in the placebo group reported adverse events during the titration period that were severe. In the VANTRELA ER group, the severe adverse events were eructation (1 [<1%] patient), muscle spasms (1 [<1%] patient), and back pain (1 [<1%] patient). In the placebo group, the severe adverse events were dental caries (1 [<1%] patient), dry mouth (1 [<1%] patient), muscular weakness (1 [<1%] patient), and OA (1 [<1%] patient).

A total of 6 (2%) patients in the VANTRELA ER group and 3 (<1%) patients in the placebo group reported adverse events causing discontinuation from the study during the titration period (based on the post-titration analysis set). In the VANTRELA ER group, nausea, somnolence, and vomiting were reported by 2 (<1%) patients each and constipation was reported by 1 (<1%) patient. In the placebo group, constipation, abdominal pain upper, anxiety, diarrhea, erectile dysfunction, and weight decreased were reported by 1 (<1%) patient each.

5.3.1.2.2. Adverse Events During the Post-titration Period

During the post-titration period of Studies 3079 and 3103, 199 (59%) patients in the VANTRELA ER group and 179 (55%) patients in the placebo group reported adverse events (Table 14). The most frequently occurring System Organ Classes (SOCs) (reported in ≥15% of patients) in the VANTRELA ER and placebo groups were Gastrointestinal Disorders SOC (102 [30%] and 61 [19%] patients, respectively) and Infections and Infestations SOC (57 [17%] and 62 [19%] patients, respectively).

Table 14: Adverse Events by System Organ Class and Treatment Group During the Post-titration Treatment Period, Post-titration Analysis Set for the Double-blind Studies (Studies 3079 and 3103)

MedDRA 16.0 system organ class	Placebo N=326 n (%)	VANTRELA ER N=337 n (%)
Number of patients with at least 1 AE	**179 (55)**	**199 (59)**
Gastrointestinal disorders	61 (19)	102 (30)
Infections and infestations	62 (19)	57 (17)
Nervous system disorders	34 (10)	48 (14)
General disorders and administration site conditions	26 (8)	34 (10)
Psychiatric disorders	20 (6)	31 (9)
Musculoskeletal and connective tissue disorders	33 (10)	29 (9)
Skin and subcutaneous tissue disorders	17 (5)	29 (9)
Respiratory, thoracic and mediastinal disorders	22 (7)	27 (8)
Investigations	9 (3)	15 (4)
Injury, poisoning and procedural complications	21 (6)	14 (4)
Ear and labyrinth disorders	6 (2)	7 (2)
Metabolism and nutrition disorders	6 (2)	7 (2)
Renal and urinary disorders	3 (<1)	7 (2)
Vascular disorders	11 (3)	6 (2)
Eye disorders	5 (2)	6 (2)
Immune system disorders	5 (2)	4 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (2)	3 (<1)
Blood and lymphatic system disorders	2 (<1)	3 (<1)
Reproductive system and breast disorders	2 (<1)	3 (<1)
Cardiac disorders	1 (<1)	3 (<1)
Hepatobiliary disorders	0	3 (<1)
Congenital, familial and genetic disorders	1 (<1)	0

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 system organ class category.

Patients in the VANTRELA ER group had a higher incidence of constipation and nausea compared with patients in the placebo group. In the VANTRELA ER group, adverse events reported by ≥5% of patients were constipation (46 [14%] patients), nausea (39 [12%] patients), headache (21 [6%] patients), and vomiting (17 [5%] patients) (Table 15). In the placebo group, adverse events reported by ≥5% of patients were constipation (15 [5%] patients), nausea (23 [7%] patients), headache (16 [5%] patients), and upper respiratory tract infection

(16 [5%] patients). The adverse events of upper respiratory tract infection were viral, and the incidences were similar between the placebo group (5%, 16 patients) and the VANTRELA ER group (4%, 15 patients). The incidence of pneumonia was similar between the placebo group (<1%, 1 patient) and the VANTRELA ER group (<1%, 2 patients).

Table 15: Most Frequently Occurring Adverse Events (Reported in ≥5% of Patients) by Preferred Term and Treatment Group During the Post-titration Treatment Period, Post-titration Analysis Set for the Double-blind Studies (Studies 3079 and 3103)

MedDRA 16.0 preferred term	Placebo N=326 n (%)	VANTRELA ER N=337 n (%)
Number of patients with at least 1 AE	**179 (55)**	**199 (59)**
Constipation	15 (5)	46 (14)
Nausea	23 (7)	39 (12)
Headache	16 (5)	21 (6)
Vomiting	11 (3)	17 (5)
Upper respiratory tract infection	16 (5)	15 (4)

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.

During the post-titration period of Studies 3079 and 3103, 18 (5%) patients in the VANTRELA ER group and 10 (3%) patients in the placebo group reported adverse events that were severe (Table 16). In the VANTRELA ER group, the severe adverse events reported by more than 1 patient were headache (3 [<1%] patients), constipation (2 [<1%] patients), and drug withdrawal syndrome (2 [<1%] patients). In the placebo group, the only severe adverse event reported by more than 1 patient was back pain (2 [<1%] patients). During the post-titration period, 103 (31%) patients in the VANTRELA ER group and 82 (25%) patients in the placebo group reported adverse events that were mild, and 78 (23%) patients in the VANTRELA ER group and 87 (27%) patients in the placebo group reported adverse events that were moderate.

Table 16: Adverse Events by Severity and Preferred Term During the Post-titration Treatment Period for All Adverse Events with at least One Severe Event, Post-titration Analysis Set for the Double-blind Studies (Studies 3079 and 3103)

	Placebo N=326 n (%)			VANTRELA ER N=337 n (%)		
MedDRA 16.0 preferred term	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Number of patients with at least 1 AE	**82 (25)**	**87 (27)**	**10 (3)**	**103 (31)**	**78 (23)**	**18 (5)**
Headache	8 (2)	8 (2)	0	12 (4)	6 (2)	3 (<1)
Constipation	8 (2)	7 (2)	0	30 (9)	14 (4)	2 (<1)
Upper respiratory tract infection	11 (3)	5 (2)	0	7 (2)	7 (2)	1 (<1)
Drug withdrawal syndrome	5 (2)	3 (<1)	0	0	2 (<1)	2 (<1)
Somnolence	1 (<1)	1 (<1)	1 (<1)	7 (2)	1 (<1)	1 (<1)
Panic attack	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Anxiety disorder	0	0	0	0	0	1 (<1)
Blood potassium increased	0	0	0	0	0	1 (<1)
Cholangitis	0	0	0	0	0	1 (<1)
Diabetes mellitus	0	0	0	0	0	1 (<1)
Diarrhoea	8 (2)	2 (<1)	0	8 (2)	3 (<1)	1 (<1)
Gastroenteritis viral	1 (<1)	1 (<1)	0	1 (<1)	2 (<1)	1 (<1)
Hernia obstructive	0	0	0	0	0	1 (<1)
Hyperbilirubinaemia	0	0	0	0	0	1 (<1)
Influenza	2 (<1)	2 (<1)	0	3 (<1)	1 (<1)	1 (<1)
Ocular icterus	0	0	0	0	0	1 (<1)
Pancreatitis	0	0	0	0	1 (<1)	1 (<1)

Table 16: Adverse Events by Severity and Preferred Term During the Post-titration Treatment Period for All Adverse Events with at least One Severe Event, Post-titration Analysis Set for the Double-blind Studies (Studies 3079 and 3103) (Continued)

	Placebo N=326 n (%)			VANTRELA ER N=337 n (%)		
MedDRA 16.0 preferred term	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Back pain	2 (<1)	7 (2)	2 (<1)	1 (<1)	5 (1)	0
Ankylosing spondylitis	0	0	1 (<1)	0	0	0
Arthralgia	4 (1)	4 (1)	1 (<1)	3 (<1)	2 (<1)	0
Basal cell carcinoma	0	0	1 (<1)	0	2 (<1)	0
Bipolar disorder	0	0	1 (<1)	0	1 (<1)	0
Cellulitis	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0
Hip fracture	0	0	1 (<1)	0	0	0
Hypernatraemia	0	0	1 (<1)	0	0	0
Muscle spasms	2 (<1)	0	1 (<1)	2 (<1)	1 (<1)	0
Pain in extremity	3 (<1)	0	1 (<1)	2 (<1)	3 (<1)	0
Procedural pain	0	0	1 (<1)	1 (<1)	0	0
Rhabdomyolyis	0	0	1 (<1)	0	0	0
Rib fracture	0	1 (<1)	1 (<1)	0	0	0

AE=adverse event; ER=extended-release; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in subgroup.
Note: If a patient reports an adverse event more than once, the greatest severity is presented for that adverse event. Patients are counted only once in each preferred term category.

In Studies 3079 and 3103, 20 (6%) patients in the VANTRELA ER group and 10 (3%) patients in the placebo group reported adverse events causing discontinuation from the study during the post-titration period (based on the post-titration analysis set). In the VANTRELA 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. Other adverse events causing discontinuation from the study in the VANTRELA ER group were reported in 1 (<1%) patient each. In the placebo group, nausea and abdominal pain upper were reported by 2 (<1%) patients each. Other adverse events causing discontinuation from the study in the placebo group were reported in 1 (<1%) patient each.

5.3.2. Serious Adverse Events

5.3.2.1. All Phase 3 Studies Combined

Of the 1176 patients who were enrolled in the Phase 3 studies and received at least 1 dose of VANTRELA ER (safety analysis set), 57 (5%) patients reported at least 1 serious adverse event (Appendix 5, Post-Text Table 6). Serious adverse events reported by more than 1 patient were deep vein thrombosis (3 [<1%] patients), pneumonia (3 [<1%] patients), renal failure acute (4 [<1%] patients), cellulitis (2 [<1%] patients), chest pain (2 [<1%] patients), chronic obstructive pulmonary disease (COPD) (2 [<1%] patients), dehydration (2 [<1%] patients), pancreatitis (2 [<1%] patients), and panic attack (2 [<1%] patients). Five patients (0.4%) reported at least 1 treatment-related serious adverse event. The treatment-related serious adverse events were pancreatitis (2 patients), chest pain (1 patient), dyspnea (1 patient), respiratory arrest (1 patient), and accidental overdose (1 patient).

5.3.2.2. Double-Blind Studies 3079 and 3103 Combined

5.3.2.2.1. Serious Adverse Events During the Titration Period

In the double-blind studies (Studies 3079 and 3103), there were no serious adverse events reported during the titration period in the post-titration analysis set. During the titration period, 17 (1%) patients in the safety analysis set and 2 (<1%) patients in the post-titration analysis set reported serious adverse events.

5.3.2.2.2. Serious Adverse Events During the Post-titration Period

During the post-titration period of Studies 3079 and 3103, 6 (2%) patients in the VANTRELA ER group and 6 (2%) patients in the placebo group reported serious adverse events (Table 17). In the VANTRELA ER group, pancreatitis was the only serious adverse event reported by more than 1 patient (2 [<1%] patients); both were considered related to study drug treatment by the investigator. Serious adverse events of anaphylactic reaction, cellulitis, hernia obstructive, esophagitis, and panic attack were reported by 1 patient each in the VANTRELA ER group; none of these events were considered related to study drug treatment by the investigator. In the placebo group, serious adverse events of panic attack, basal cell carcinoma, bipolar disorder, bladder cancer recurrent, hip fracture, hypernatremia, papillary thyroid cancer, and rhabdomyolysis were reported by 1 patient each.

Table 17: Serious Adverse Events by Preferred Term and Treatment Group During the Post-titration Treatment Period, Post-titration Analysis Set for the Double-blind Studies (Studies 3079 and 3103)

MedDRA 16.0 preferred term	Placebo N=326 n (%)	VANTRELA 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

[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.

5.3.3. Deaths

Three deaths were reported during the Phase 3 studies; none were considered related to study drug. In the long-term study (Study 3080), 2 deaths were reported, both during the post-titration period, and neither was considered related to study drug. One cause of death in Study 3080 was unknown, and the other was due to cardiac arrest secondary to hyperkalemia. The hyperkalemia was suspected to have occurred as a result of the patient's overmedication with potassium tablets to treat cramps. In the case of the unknown death, the patient had multiple medical problems and was ultimately admitted to hospice due to cancer. No further information could be obtained. Neither death was considered by the investigator as related to VANTRELA ER. The third death in the Phase 3 program occurred during the screening period in Study 3103 due to an unknown cause.

5.3.4. Other Safety Data

Across the 4 Phase 3 studies, there were no potentially clinically important trends in clinical laboratory results, vital signs, or electrocardiogram results. Individual patient changes in these variables were observed, but were not clinically important. In the double-blind studies (Studies

3079 and 3103), electrocardiogram values in the VANTRELA ER and placebo groups were comparable for mean heart rate, PR interval, QRS interval, QT interval, QTc interval (Bazett and Fridericia), and RR interval measurements at baseline and endpoint. Shifts from normal to abnormal occurred with comparable frequency in the VANTRELA ER and placebo treatment groups. None of the shifts was considered to be clinically meaningful. No clinically meaningful differences were seen between the treatment groups in the number of patients with potentially clinically important serum chemistry abnormalities or types of abnormalities. While 23 patients had elevated aspartate aminotransferase at endpoint (13 [4%] in the VANTRELA ER group and 10 [3%] in the placebo group), 21 patients had increased alanine aminotransferase (11 [3%] in the VANTRELA ER group and 10 [3%] in the placebo group), and 13 patients had increased alkaline phosphatase (7 [2%] in the VANTRELA ER group and 6 [2%] in the placebo group), no patients met criteria for drug-induced liver injury.

Treatment with VANTRELA ER was not associated with clinically important hearing changes (as defined by the American Speech-Language-Hearing Association), as indicated by the absence of clinically important differences in pure tone audiometry results between the VANTRELA ER and placebo groups after 12 weeks of treatment with VANTRELA ER. Of note, however, in Study 3103, 36% of patients receiving VANTRELA ER and 34% of patients receiving placebo reported having some form of hearing impairment/deficit at baseline before enrolling in the study, which may be reflective of other comorbidities or prior medication use. When considering age, the prevalence of hearing loss for subjects in the Phase 3 studies was similar to that reported previously (Agrawal et al 2008). For example, Agrawal et al reported an overall prevalence of hearing loss in the speech frequencies of 29% in adults aged 50 to 59 years. This prevalence increased to 49% for adults aged 60 to 69 years.

For patients treated with VANTRELA ER, opioid withdrawal symptoms after the open-label titration period, as assessed by patients (ie, SOWS) and clinicians (ie, COWS), were rated comparably to that of the placebo group in Studies 3079 and 3103. Results of the ABC and COMM in Studies 3079 and 3080 indicated a low risk of developing aberrant drug-use behavior.

Overall, the compliance with study drug was 96%. The incidence of study drug or rescue medication loss during the studies was 4% or less among all patients (safety analysis set) and 5% or less in the subset of patients who participated in the double-blind period (post-titration analysis set [Studies 3079 and 3103]). The incidence of study drug or rescue diversion during the studies was also 2% or less among all patients and in the subset of patients who participated in the double-blind period.

6. CLINICAL EXPERIENCE: STUDY DRUG DIVERSION AND LOSS OF STUDY DRUG

All 4 Phase 3 clinical studies examined study drug loss and diversion. A total of 1176 patients were included. Studies 3079 and its open label extension study 3080 examined patients over a 15-month period: 3 months for patients in study 3079 and 12 months for patients in study 3080. Both studies enrolled patients who were either opioid-naïve or opioid-experienced. Studies 3103 and its open label extension study 3104 examined patients over a 9-month period: 3 months in study 3103 and 6 months for patients in study 3014. Study 3103 enrolled patients who were either opioid-naïve or opioid-experienced. Study 3104 enrolled patients who had participated in study 3103 and thus, were all opioid-experienced.

The limitations of Study 3079 are presented in Section 4.1.

6.1. Study Drug Diversion

Medication was considered diverted if it was routed to someone else either intentionally or unintentionally (ie, stolen). Overall, there was low risk of study drug diversion identified for VANTRELA ER. The overall rate of diversion of study drug was 1% in Study 3079 and 2% in Study 3080, and <2% in Study 3103 and <1% in Study 3104. In Study 3079, 3 patients reported diversion of rescue medication and 1 patient with VANTRELA ER. In Study 3080, 4 patients reported diversion of rescue medication, 3 with VANTRELA ER, and 1 patient had both stolen. In study 3103, 5 patients diverted VANTRELA ER, 4 patients diverted rescue medication (hydrocodone/acetaminophen IR tablets), and 2 patients diverted both medications. In Study 3104, 1 patient diverted both VANTRELA ER and rescue medication.

Across all 4 studies combined, study drug diversion was more frequent with rescue medication than with VANTRELA ER, while study drug loss was more frequent with VANTRELA ER. Of the 1176 patients who were enrolled in the Phase 3 studies and received at least 1 dose of VANTRELA ER (safety analysis set), 28 (2%) patients reported diversion of any medication (Table 18) by the time of the 4-month safety update. Of the 28 patients, 14 (1%) patients reported diversion of VANTRELA ER tablets, 17 (1%) patients reported diversion of hydrocodone IR tablets, and 2 (<1%) patients reported diversion of placebo tablets.

Table 18: Medication Diversion, Safety Analysis Set

Category	Total N=1176 n (%)
Number of patients in whom diversion of any medication was reported	28 (2)
Diversion of VANTRELA ER	
Number of patients who diverted or reported diversion of ≥1 tablet	14 (1)
1-9 tablets	3 (<1)
≥10 tablets	10 (<1)
Unknown	1 (<1)
Diversion of rescue hydrocodone IR	
Number of patients who diverted or reported diversion of ≥1 tablet	17 (1)
1-9 tablets	1 (<1)
≥10 tablets	12 (1)
Unknown	4 (<1)
Diversion of placebo tablets	
Number of patients who diverted or reported diversion of ≥1 tablet	2 (<1)
1-9 tablets	0
≥10 tablets	2 (<1)
Unknown	0

ER=extended-release; IR=immediate-release; N=number of patients; n=number of patients in subgroup.

6.2. Study Drug Loss

The overall rate of study drug loss was <9% (35/389) for Study 3079 and 11% (36/329) for Study 3080. Most occurrences for study drug loss with either VANTRELA ER or rescue medication were for 10 or fewer tablets. The overall rate of study drug loss was approximately 3% (10/368) in study 3103 with VANTRELA ER being lost by more patients than either rescue medication or placebo (7 patients, 0 patients, and 3 patients, respectively). There was no study drug loss reported in study 3104.

7. POST-MARKETING RISK ASSESSMENT AND MANAGEMENT

Teva is committed to monitor for safety issues including abuse, diversion, and overdose related to VANTRELA ER. VANTRELA ER will be a Schedule II drug under the Controlled Substances Act, which is the most restrictive schedule for a drug that has medical use, and will have appropriate class labeling for ER and /LA opioids. In addition, Teva will join the class-wide, single, shared REMS (Appendix 6) program and conduct all PMR studies mandated by FDA. Teva is also committed to the responsible sales and marketing of VANTRELA ER.

As required by FDA, Teva will monitor adverse events and complaints for VANTRELA ER. All appropriate medical affairs, pharmacovigilance, and quality complaint personnel will be trained to assure understanding of the unique issues related to Class II opioids and to fully understand the VANTRELA ER formulation in order to be well-equipped to service clinicians, other prescribing allied healthcare professionals, and patients.

In addition, Teva will become an active member of the ER/LA REMS industry group with the goal to reduce serious adverse outcomes resulting from inappropriate prescribing and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. As part of this, a medication guide will be dispensed with each VANTRELA ER prescription. Educational materials will also be developed for patients, prescribers, and pharmacists consistent with the class-wide REMS. The patient education materials will focus on safe use and storage of their medication and the legal aspects of product diversion. The prescriber materials will address assessment of patients with chronic pain, how to monitor for possible abuse and diversion, problematic drug-drug interactions, and how to educate patients about safe use. Pharmacist education will include how to educate patients regarding appropriate use and storage, potential problematic drug interactions, and how to identify those who may be abusing or diverting their medication.

The FDA announced as part of the Opioid Action Plan in February 2016, that the ER/LA PMRs will be expanded in scope resulting in a total of 11 mandated studies (Califf et al 2016). These PMRs will address the safety concerns that have been identified and evaluate methods to assess progress in mitigating them. Teva will conduct all shared ER/LA PMRs to provide a better understanding on the serious risks of abuse associated with long-term ER/LA opioid use, predictors of opioid addiction and other important issues. Teva will also undertake epidemiologic investigations to understand the real world impact of VANTRELA ER by addressing whether the properties of VANTRELA ER intended to deter abuse actually result in a significant and meaningful decrease in abuse, and their consequences (addiction, overdose and death) in the community. Teva will conduct a clinical study assessing the group of patients receiving chronic opioid therapy for pain who are not deriving optimal benefit despite receiving high doses of opioid pain medication. Such patients are often described as having persistent significant pain associated with poor physical, psychological and/or social functioning, despite the high doses of opioid analgesia often referred to opiate-induced hyperalgesia. Finally, Teva will comply with all other post-marketing commitments post approval.

The sales and marketing of VANTRELA ER will only be focused on licensed-to-prescribe opioid experienced health care providers (pain specialists, primary care physicians, and select nurse practitioners and physician assistants) with a history of treating patients with chronic pain.

This will enable monitoring to determine the extent of prescribing outside of the network of prescribers to whom we will be marketing the drug and the prescribing patterns of those prescribers within the network to whom we will be marketing. Our sales force will be extensively trained and periodically retrained to be compliant with all pertinent regulations. This training will include knowledge of appropriate prescribing as well as tools for the sales force to identify prescribers who may be using the drug outside of acceptable practice, and therefore, require more extensive prescriber education.

Teva is aware of the epidemic associated with prescription drug abuse, and will use the programs described above to help reduce this problem and to collect data that will inform necessary changes to the programs. While no formulation can solve these issues, Teva aims to contribute to the public health goal of mitigating opioid abuse, first, by creating a product with strong abuse-deterrent properties, but also by implementing extensive educational programs for all stakeholders and collecting data that will help us understand the issues and apply strategies to reduce the problems.

8. BENEFIT/RISK ASSESSMENT

8.1. Class-wide Risks of Opioids

The diversion and abuse of prescription opioid analgesic products pose serious public health and safety risks. FDA, other US government agencies/legislators, academia, and industry have identified the need for development of abuse-deterrent opioid formulations that can hinder the ability to extract extremely high concentrations of medication and deter abuse and diversion.

Teva will be working within the framework of the FDA's Opioid Action plan and will be participants in executing some of these action items, including: joining the ongoing and expanded PMRs for long-acting opioids, participating in the updated REMS program and supporting safer prescribing and use of opioids to reduce the impact of opioid abuse while providing effective analgesics in the treatment of chronic pain.

8.2. Benefits of VANTRELA ER

Results of the pivotal Phase 3 efficacy study in opioid experienced or naïve patients with chronic low back pain (Study 3103) confirmed that VANTRELA ER tablets, administered at stable pain relief dosages of 30, 45, 60, or 90 mg q12h for 12 weeks, were more effective than placebo treatment in alleviating chronic low back pain. At week 12, the change from baseline in weekly average of daily WPI scores, the primary efficacy endpoint, was significantly lower in the VANTRELA ER group than in the placebo group. The effect of VANTRELA ER was consistent across subgroups based on demographic parameters (age, sex, and race) as well as stable pain relief dose and patient opioid status (naive and experienced).

In addition to its demonstrated effect on pain relief, results of in vitro, clinical pharmacology, and abuse liability studies also demonstrated the potential for VANTRELA ER tablets to deter abuse and decrease the risks for overdose.

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation of VANTRELA ER. In laboratory studies, ER properties were retained to a significant degree when the tablets were physically manipulated. The in vitro data demonstrate that VANTRELA ER has physical and chemical properties that are expected to deter oral, intranasal and IV abuse.

The results of the clinical pharmacokinetic studies confirm that VANTRELA ER tablets retain their extended-release properties to a significant degree when the tablets are taken with alcohol. Specifically, alcohol has no effect on systemic exposure as measured by either C_{max} or AUC. These results suggest that combining the VANTRELA ER tablet with alcohol in an attempt by abusers to produce immediate release of opioid will not be successful. Likewise, there is added safety for non-abusers who ingest alcohol in proximity to a prescribed dose of ER hydrocodone for the treatment of pain, although, as with any opioid, VANTRELA ER should not be combined with alcohol.

The rate of rise of drug concentration was also assessed because it is thought to contribute to differential abuse potential among drugs, formulations, and ROAs (Abreu et al 2001, de Wit et al 1992, de Wit et al 1993). The barriers to rapid release of hydrocodone when VANTRELA ER is

manipulated produce a slower rise to a lower peak concentration as compared to hydrocodone API and non-abuse deterrent ZOHYDRO ER. Although overall systemic exposure to hydrocodone (as assessed by $AUC_{0-\infty}$) was comparable, C_{max} was lower and occurred later following oral administration of a single manipulated VANTRELA ER tablet as compared to that of an equivalent dose of hydrocodone API. Likewise, early exposure (as assessed by $AUC_{0-0.75}$ [approximate t_{max} for hydrocodone API]) was lower for manipulated VANTRELA ER following oral administration. Following intranasal insufflation of a single manipulated VANTRELA ER tablet, C_{max} was lower and occurred later as compared to that of an equivalent dose of the IR product. The exposure to hydrocodone up to the time of peak for the IR product was also lower for the manipulated VANTRELA ER tablet. At equivalent doses, C_{max} was lower and occurred later for VANTRELA ER as compared to ZOHYDRO ER. The exposure to hydrocodone up to the time of peak for the ER product was also lower for the manipulated VANTRELA ER tablet. The pharmacokinetic data therefore demonstrate that the extended-release properties of VANTRELA ER limit the rate and extent of rise of drug concentration following both oral ingestion and nasal insufflation of the manipulated product.

These differences in pharmacokinetics are associated with significantly different pharmacodynamic subjective effects for VANTRELA ER when it is manipulated and administered orally or intranasally. When the VANTRELA ER tablet is manipulated and ingested orally, subjects reported statistically lower peak and “at the moment” liking as compared to hydrocodone API. Likewise, statistically lower peak and “at the moment” liking were observed when the VANTRELA ER tablet was manipulated and insufflated intranasally as compared to hydrocodone API and manipulated ZOHYDRO ER. Secondary measures of balance, positive effects, sedative effects, any effects, and pupillometry were supportive of these findings. Oral intact VANTRELA ER behaved similarly to a placebo. Therefore, data from the clinical abuse potential studies, along with support from the in vitro data, also indicate that VANTRELA ER has physicochemical properties that are expected to reduce abuse via the oral route when crushed and via the intranasal route. However, abuse of VANTRELA ER by these routes may still be possible.

Results of the Phase 3 studies in patients with moderate to severe pain demonstrated a low occurrence of diversion of VANTRELA ER. In addition, scales noting abuse and addiction potential evaluated in patients with chronic pain in Studies 3079 and 3080 indicated a low risk of abuse and addiction.

Overall, these data support labeling that Vantrela ER has properties that are expected to deter abuse.

8.3. Risks of VANTRELA ER

The safety profile of VANTRELA ER, administered at dosages ranging from 30 to 90 mg q12h to patients with chronic pain and healthy adult subjects, was similar to that of currently marketed hydrocodone bitartrate products and other opioid analgesics, and was also consistent with the underlying illnesses seen among the patients in the studies. No increase in any safety signal was observed with increasing dosages. No new safety signals were raised.

8.4. Overall Conclusion

Extended-release opioid formulations offer advantages over IR hydrocodone products by providing more stable pain management over a longer period of time; however, their larger opioid load presents the potential risks of abuse. VANTRELA ER was developed to provide the benefits of a single-agent hydrocodone product for effective sustained pain management while decreasing the risks of abuse or diversion associated with ER opioids.

Clinical studies have demonstrated the potential of VANTRELA ER tablets to deter abuse when manipulated and ingested or insufflated, and extensive in vitro studies have supported the potential of the VANTRELA ER tablets to deter other routes of abuse after manipulation, such as extraction for IV delivery. The tablets retain their ER properties when taken with alcohol or food.

In the Phase 3 pivotal study (Study 3103), VANTRELA ER provided significant pain relief compared to placebo and demonstrated a low occurrence of diversion. The safety profile of VANTRELA ER was similar to that of currently marketed hydrocodone products and other opioid analgesics.

Hydrocodone is listed in Schedule II of the Controlled Substances Act with a high potential for abuse, diversion, and addiction. As agreed with FDA, VANTRELA ER will follow the standard REMS for ER/LA opioids. As part of the ER/LA REMS, post-marketing studies will be conducted to monitor the safety of VANTRELA ER and assess the effectiveness of the abuse-deterrent properties of VANTRELA ER in studies evaluating real-world abuse and hyperalgesia.

Overall, the data submitted demonstrate that VANTRELA ER has the potential to:

- Decrease the risks of abuse and diversion associated with ER opioid analgesics.
- Provide effective management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Therefore, Teva believes that the benefits of VANTRELA ER treatment outweigh the risks.

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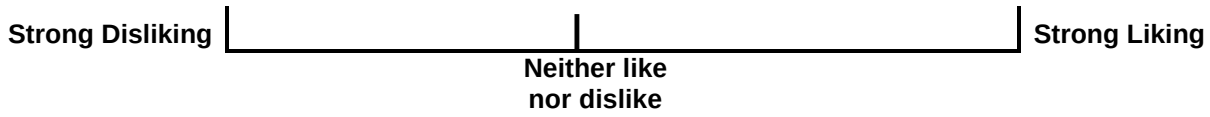
APPENDIX 1. VISUAL ANALOG SCALES (VAS)

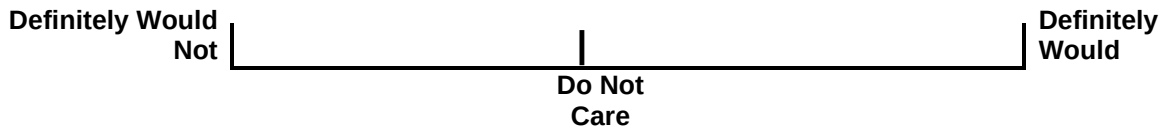
Overall Drug Liking Visual Analog Scale

Overall, my liking for this drug is:



Take Drug Again Visual Analog Scale

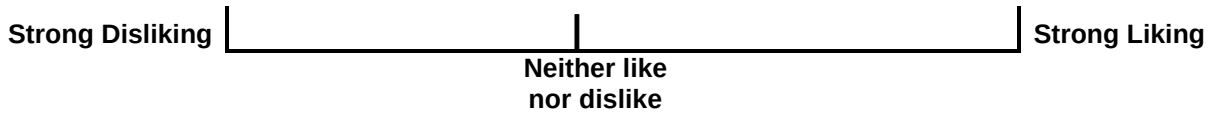
If given the opportunity, I would want to take this drug again:



Drug Liking and Effects Questionnaire

These comments relate to the drug effects you are experiencing right now. Mark a clear perpendicular line across each horizontal line depending on how you feel at this moment.

1. My liking for this drug is:



2. My mental state is:

Very Drowsy |_____|_____| **Very Alert**
Neither drowsy nor alert

3. I can feel good drug effects:

Not at all |_____| **Extremely**

4. I can feel bad drug effects:

Not at all |_____| **Extremely**

5. I am feeling nausea:

Not at all |_____| **Extremely**

6. I can feel any drug effects:

Not at all |_____| **Extremely**

APPENDIX 2. PHARMACOKINETICS OF VANTRELA ER

In addition to the evaluations described above related to Category 2 studies, the clinical pharmacology program of VANTRELA ER included studies to characterize the pharmacokinetics of hydrocodone following administration of single and multiple doses of VANTRELA ER, studies aimed to characterize relative bioavailability relative to other hydrocodone products, and characterization of the food effect. Studies were also conducted to characterize the pharmacokinetics in subjects with varying degrees of renal function and in subjects with normal hepatic function versus those with moderate hepatic impairment.

Exposure following administration of single doses of VANTRELA ER increases in a dose-proportional manner over the range of 15 through 90 mg. Following administration of a single dose of VANTRELA ER, maximum plasma concentrations of hydrocodone are achieved at approximately 8 hours, and decline from peak typically occurs in an apparent biphasic manner. Steady-state concentrations are attained by day 4 of administration of the VANTRELA ER tablet every 12 hours. Systemic exposure at steady state is approximately 3-fold higher than that after a single dose, with maximum plasma concentrations being achieved approximately 5 hours after administration. Mean fluctuation (variation around the average concentration) is approximately 35%, and mean swing (difference from peak to trough concentration) is approximately 45%. These findings demonstrate that plasma hydrocodone concentrations are sustained with little change over a dosing interval following administration of VANTRELA ER, supporting that this formulation is well suited for its intended indication.

Administration of a single dose of VANTRELA ER with food increases the C_{max} by approximately 34% to 45% with no notable impact on time to maximum concentration or overall exposure. Of note, mean plasma concentrations were lower in the fed state than in the fasted state for a sustained period of time after dosing (4 hours, on average), indicating that consumption of food with VANTRELA ER does not increase early exposure to hydrocodone. In order to characterize more clinically relevant conditions, the effect of food was also studied following administration of multiple BID doses of VANTRELA ER 90 mg. The effect of food on the pharmacokinetics of hydrocodone at steady state was less pronounced than after administration of a single-dose, and under steady state conditions, C_{max} and AUC over a dosing interval met criteria to conclude bioequivalence.

The half-life of hydrocodone following administration of VANTRELA ER is approximately 11 to 12 hours. The mean apparent total plasma clearance of hydrocodone following administration of VANTRELA ER is approximately 70 to 90 L/h. Renal clearance of hydrocodone is approximately 60 mL/h/kg (Mikus and Weiss 2005). Approximately 11% of the total dose of hydrocodone is recovered in the urine, approximately 50% of which is parent (Cone et al 1978). This supports the hypothesis that biliary excretion may represent an important pathway for elimination.

There are no known effects of age, race, sex, BMI, or CYP2D6 metabolizer status on the pharmacokinetics of hydrocodone. Subgroup analyses from the pooled clinical pharmacology study database confirm the lack of effect of these covariates on systemic exposure to hydrocodone. Exposure to hydrocodone is higher in patients with moderate or severe renal impairment and in patients with moderate hepatic impairment as compared to patients with

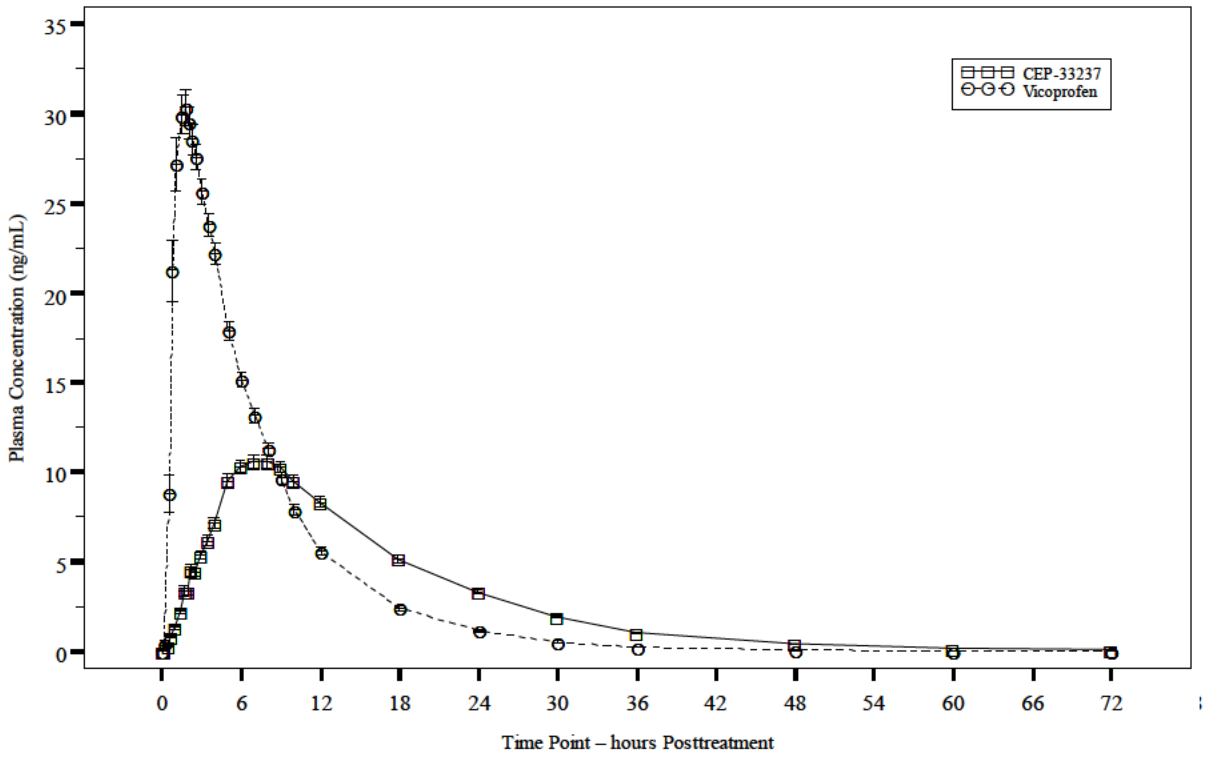
normal organ function. Although there was no consistent trend towards an increase in C_{max} with increasing severity of renal impairment, mean C_{max} was up to 50% higher in the renally impaired. Overall systemic exposure (as assessed by $AUC_{0-\infty}$) was up to approximately 70% higher in patients with moderate or severe renal impairment as compared to patients with normal renal function. Following a single dose of hydrocodone, C_{max} was approximately 30% higher and $AUC_{0-\infty}$ was approximately 70% higher in patients with moderate hepatic impairment as compared to those with normal hepatic function.

Relative Bioavailability as Compared to VICOPROFEN

The relative bioavailability of VANTRELA ER to VICOPROFEN, has been assessed in 2 studies. A 15-mg dose of VANTRELA ER (Study 1079) or a 90 mg dose of VANTRELA ER (Study 1090) were tested with a single 15 mg dose of VICOPROFEN. In addition to the analyses performed for each individual study, data from these 2 studies were integrated and used to characterize the bioavailability of VANTRELA ER as compared with VICOPROFEN. Given the demonstrated proportionality of VANTRELA ER over the dose range of 15 through 90 mg, data following administration of a 90 mg dose of VANTRELA ER were normalized to 15 mg for the purpose of this characterization.

Post-Text Figure 1 presents the mean (±SE) dose normalized plasma concentration versus time profile of hydrocodone over 72 hours following administration of VANTRELA ER and VICOPROFEN.

Post-Text Figure 1: Mean (±SE) Hydrocodone Plasma Concentration Following Administration of a Single 15 mg Dose of VANTRELA ER and a Single 15 mg Dose of Hydrocodone within VICOPROFEN in Fasted Healthy Subjects



CEP-33237=VANTRELA ER

Comparisons of mean pharmacokinetic parameter values following administration of 15 mg of VANTRELA ER or a 15 mg dose of hydrocodone within VICOPROFEN are presented in Post-Text Table 1.

Post-Text Table 1: Comparison of Mean Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single Dose of VANTRELA ER (Dose Normalized to 15 mg) and a Single 15 mg Dose of Hydrocodone within VICOPROFEN in Healthy Subjects (Pharmacokinetic Analysis Set, Bioavailability Subset)

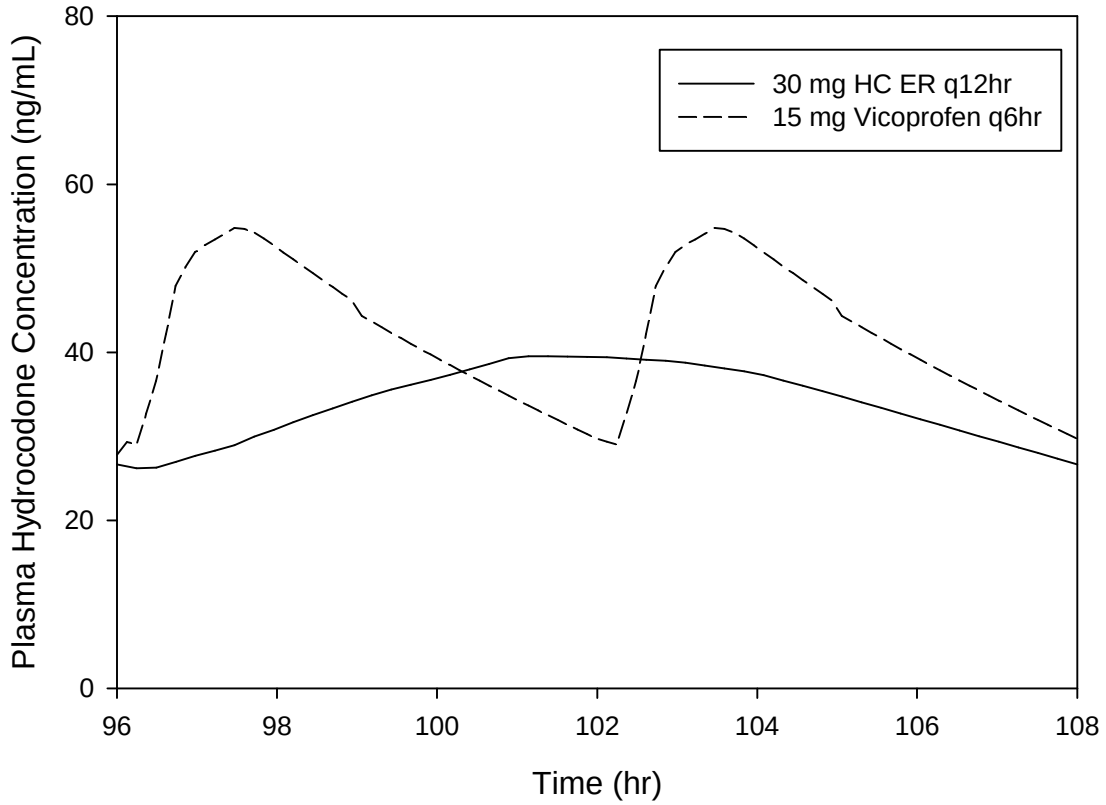
Parameter (unit)	VICOPROFEN (N=60)	VANTRELA ER (N=60)	Ratio of VANTRELA ER:VICOPROFEN	90% CI
C_{max} (ng/mL)	34.0 (8.33)	10.8 (2.72)	0.319	0.297, 0.342
$AUC_{0-\infty}$ (ng·h/mL)	227 (53.45)	190.8 (48.11)	0.840	0.783, 0.902

NOTE: Values for C_{max} and $AUC_{0-\infty}$ are geometric mean (standard error of the mean).
CI=Confidence Interval; C_{max}=maximum observed plasma drug; $AUC_{0-\infty}$=area under the plasma drug concentration versus time curve (AUC) from time zero to infinity.

As would be expected for a comparison of an ER to an IR product, overall systemic exposure (as assessed by $AUC_{0-\infty}$) was generally similar following administration of the VANTRELA ER and VICOPROFEN, whilst VANTRELA ER showed a flatter pharmacokinetic profile with a lower C_{max}.

More importantly, simulated profiles for repeated administration of an equivalent total daily dose of 60 mg (achieved either by twice daily administration of VANTRELA ER 30 mg or by 4 times daily administration of VICOPROFEN 15 mg) suggest that steady state plasma concentrations of hydrocodone following administration of VANTRELA ER are within the range of exposures following administration of therapeutic doses of VICOPROFEN (Post-Text Figure 2).

Post-Text Figure 2: Simulated Mean Plasma Concentration versus Time Profiles for Hydrocodone at Steady State Following Administration of a 30 mg Dose of VANTRELA ER Every 12 Hours and a 15 mg Dose of Hydrocodone within VICOPROFEN Every 6 Hours in Healthy Subjects



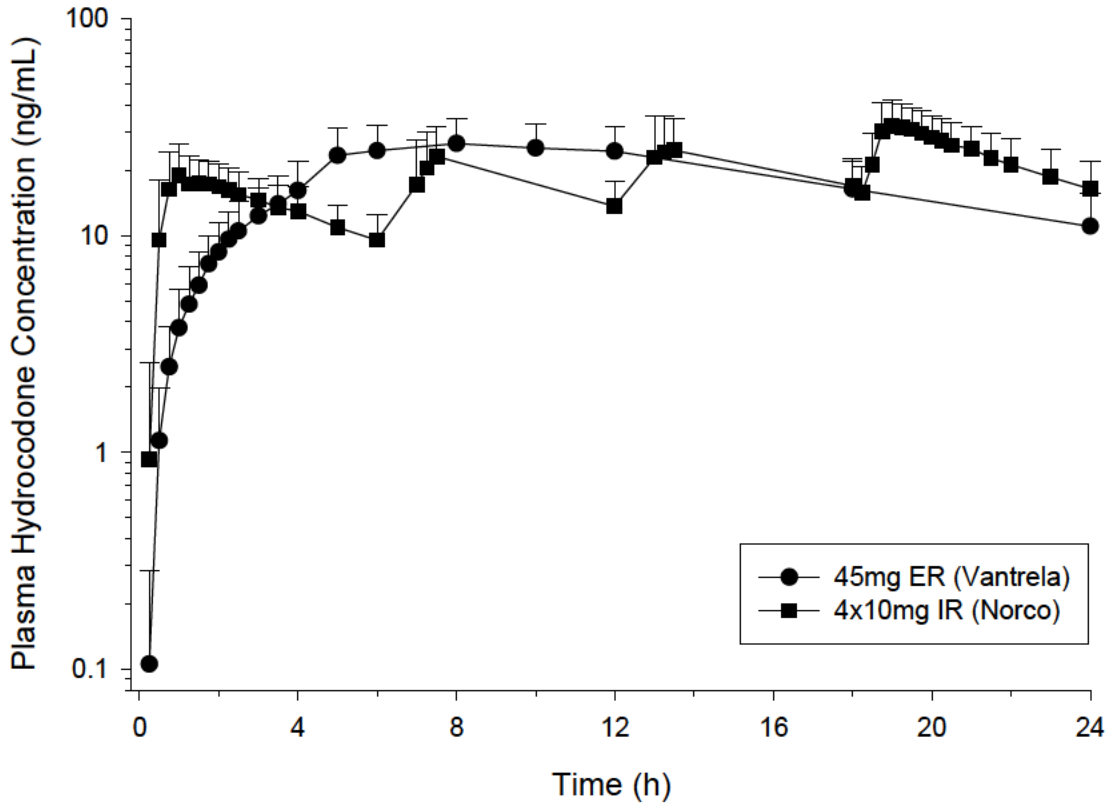
HC ER=Hydrocodone ER (ie, VANTRELA ER)

Relative Bioavailability as Compared to NORCO

Study 1071 characterized the relative bioavailability of a pilot formulation of VANTRELA ER compared to NORCO, as part of the product development.

The mean (+SD) hydrocodone plasma concentrations following administration of a single 45 mg dose of VANTRELA ER (early formulation) and following administration of a single tablet of NORCO (10 mg hydrocodone/325 mg acetaminophen) administered every 6 hours are provided in Post-Text Figure 3.

Post-Text Figure 3: Mean (+SD) Hydrocodone Plasma Concentration Following Administration of a Single 45 mg Dose of Hydrocodone ER and Following Administration of NORCO (10 mg Hydrocodone/325 mg Acetaminophen Every 6 hours for a Total of 4 Doses) in Fasted Healthy Subjects



ER=extended-release; IR=immediate release.

Post-Text Table 2 presents the mean (SD) pharmacokinetic parameter values for a 45 mg dose of the early VANTRELA ER formulation and for a 10 mg dose of hydrocodone within NORCO (given every 6 hours for a total of 4 doses).

Post-Text Table 2: Mean (SD) Pharmacokinetic Parameter Values for Hydrocodone Following Administration a Single 45 mg Dose of an Early VANTRELA ER Formulation and Following Administration of NORCO (10 mg Hydrocodone/325 mg Acetaminophen) Every 6 hours for a Total of 4 Doses in Fasted Healthy Subjects

Parameter (unit)	VANTRELA ER 45 mg (n=36)	NORCO 40 mg (10 mg q6h) (n=36)
C_{max} (ng/mL)[a]	28.4 (7.5)	22.6 (6.0)
$AUC_{0-\infty}$ (ng·hr/mL)	578 (188)	581 (167)
AUC_{0-t} (ng·h/mL)	568 (182)	577 (165)
t_{max} (h) [a]	8.0 (5.0, 11.9)	1.0 (0.5, 3.5)
$t_{1/2}$ (h)	11.3 (3.95)	9.1 (3.99)

[a] C_{max} and t_{max} for NORCO are relative to the first dose
NOTE: Median (range) is presented for t_{max}.
q6h=administered every 6 hours; 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-t}=AUC from time 0 to time of the last measurable plasma drug concentration; t_{max}=time to maximum observed plasma drug concentration; $t_{1/2}$=elimination half-life

Systemic exposure following administration of four 10 mg doses of the IR product administered every 6 hours was comparable to that observed following administration of a single 45 mg dose of VANTRELA ER. Peak exposure following the first 10 mg dose of the IR product was only slightly less than that observed following a single 45 mg dose of VANTRELA ER and dose normalized C_{max} for the IR product is approximately 3-4 fold higher than that for VANTRELA ER. In light of the known characteristics of the IR product and ER formulation, these results demonstrate that peak and overall exposure to hydrocodone following administration of VANTRELA ER are expected to be well within the range of those observed following administration of a therapeutic regimen of approved IR products. These expectations are supported by the results of steady state simulations.

APPENDIX 3. STUDY 3079: POST-HOC ANALYSIS RESULTS

Post-Text Table 3: Change From Baseline to Week 12 in Weekly Average Pain Intensity Excluding the 15-mg Dose Group (Post Hoc Analysis [Full Analysis Set]; Study 3079)

Time point	Statistic[a]	Placebo (N=147)	VANTRELA ER (N=146)
Screening[b]	n	104	110
	Mean	6.81	6.80
	SD	1.207	1.262
	SE of mean	0.118	0.120
	Median	7.00	7.00
	Min, max	4.0, 10.0	3.0, 10.0
Baseline[c]	n	104	110
	Mean	3.77	3.82
	SD	0.811	0.980
	SE of mean	0.080	0.093
	Median	4.00	4.00
	Min, max	0.9, 5.7	0.3, 6.4
Week 12	n	104	110
	Mean	4.25	3.64
	SE of mean	0.189	0.221
	Min, max	4.1, 4.3	3.5, 3.8
Change to week 12	n	104	110
	Mean	0.48	–0.18
	SE of mean	0.191	0.222
	Min, max	0.36, 0.54	–0.36, –0.02
	LSM (SE)	0.40 (0.185)	–0.20 (0.214)
Difference (95% CI) placebo-VANTRELA ER[a]		0.59 (0.05, 1.14)	
p-value		0.032	

[a] The statistics were based on 5 sets of imputed data for which the mean was the average of the means from the 5 individual data sets, and the SE of the mean was adjusted based on the within-imputation variances and the between-imputation variance. Minimum and maximum were the lowest and the highest of the 5 means.
[b] Screening values were obtained before the open label titration period.
[c] 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.
SD=standard deviation; SE=standard error; min=minimum; max=maximum, LSM=least squares mean; CI=confidence interval.

APPENDIX 4. CONCOMITANT MEDICATIONS

Post-Text Table 4: Concomitant Medications in at Least 5% of Patients in Either Treatment Group in Study 3103 (Full Analysis Set)

	Number (%) of patients	
Therapeutic classification[a]	**Placebo (N=179)**	**VANTRELA ER (N=191)**
Patients receiving concomitant medication	**169 (94)**	**174 (91)**
Agents acting on the renin-angiotensin system	52 (29)	56 (29)
Analgesics	146 (82)	140 (73)
Antianemic preparations	13 (7)	11 (6)
Antiepileptics	3 (2)	14 (7)
Antibacterials for systemic use	14 (8)	24 (13)
Antiemetics and antinauseants	6 (3)	11 (6)
Antihistamines for systemic use	18 (10)	25 (13)
Anti-inflammatory and antirheumatic products	16 (9)	10 (5)
Antithrombotic agents	41 (23)	33 (17)
Beta blocking agents	21 (12)	25 (13)
Calcium channel blockers	24 (13)	22 (12)
Cough and cold preparation	12 (7)	8 (4)
Diuretics	21 (12)	19 (10)
Drugs for acid-related disorders	35 (20)	35 (18)
Drugs for constipation	39 (22)	38 (20)
Drugs for obstructive airway diseases	19 (11)	21 (11)
Drugs used in diabetes	30 (17)	27 (14)
General nutrients	14 (8)	16 (8)
Lipid-modifying agents	52 (29)	65 (34)
Mineral supplements	18 (10)	15 (8)
Muscle relaxants	22 (12)	13 (7)
Nasal preparations	14 (8)	12 (6)
Psychoanaleptics	33 (18)	53 (28)
Psycholeptics	31 (17)	52 (27)
Sex hormones and modulators of the genital system	15 (8)	9 (5)
Thyroid therapy	15 (8)	15 (8)
Unspecified herbal and traditional medicine	11 (6)	10 (5)
Urologicals	9 (5)	10 (5)
Vitamins	45 (25)	45 (24)

[a] Patients are counted only once in each therapeutic classification category.
ER=extended-release; N=number of patients.

APPENDIX 5. ADVERSE EVENTS IN PHASE 3 STUDIES

Post-Text Table 5: Adverse Events Occurring in 5% or More of Patients in the Combined Phase 3 Studies (Safety Analysis Set)

System Organ Class MedDRA 16.0 Preferred Term, n (%)	Total (N=1176)
Number of patients with at least 1 AE	**864 (73)**
Ear and labyrinth disorders	**37 (3)**
Gastrointestinal disorders	536 (46)
Nausea	272 (23)
Vomiting	122 (10)
Constipation	276 (23)
Diarrhoea	59 (5)
General disorders and administration site conditions	**163 (14)**
Fatigue	61 (5)
Infections and infestations	**263 (22)**
Injury, poisoning and procedural complications	**113 (10)**
Investigations	**63 (5)**
Metabolism and nutrition disorders	**58 (5)**
Musculoskeletal and connective tissue disorders	**178 (15)**
Nervous system disorders	**353 (30)**
Headache	144 (12)
Somnolence	122 (10)
Dizziness	79 (7)
Psychiatric disorders	**136 (12)**
Respiratory, thoracic and mediastinal disorders	**120 (10)**
Skin and subcutaneous tissue disorders	**163 (14)**
Pruritus	70 (6)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in subgroup.
Preferred terms are sorted by descending order of incidence within high level term. Patients are counted only once in each preferred term category, only once in each high level term category, and only once in each system organ class category.

Post-Text Table 6: Serious Adverse Events in the Combined Phase 3 Studies (Safety Analysis Set)

System Organ Class MedDRA 16.0 Preferred Term, n (%)	Total (N=1176)
Number of patients with at least 1 serious AE	**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	1 (<1)
Gastrointestinal disorders	**6 (<1)**
Pancreatitis	2 (<1)
Small intestinal obstruction	1 (<1)
Gastritis	1 (<1)
Intestinal obstruction	1 (<1)
Oesophagitis	1 (<1)
Abdominal adhesions	1 (<1)
General disorders and administration site conditions	**4 (<1)**
Chest pain	2 (<1)
Death	1 (<1)
Hernia obstructive	1 (<1)
Hepatobiliary disorders	**3 (<1)**
Cholecystitis	1 (<1)
Cholecystitis acute	1 (<1)
Cholelithiasis	1 (<1)
Cholangitis	1 (<1)
Cholestasis	1 (<1)
Immune system disorders	**1 (<1)**
Anaphylactic reaction	1 (<1)
Infections and infestations	**15 (1)**
Pneumonia	3 (<1)
Lobar pneumonia	1 (<1)
Device related infection	1 (<1)

System Organ Class MedDRA 16.0 Preferred Term, n (%)	Total (N=1176)
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, poisoning and procedural complications	**3 (<1)**
Tracheal injury	1 (<1)
Road traffic accident	1 (<1)
Accidental overdose	1 (<1)
Laceration	1 (<1)
Investigations	1 (<1)
Electrocardiogram T wave inversion	1 (<1)
Metabolism and nutrition disorders	**4 (<1)**
Dehydration	2 (<1)
Diabetic ketoacidosis	1 (<1)
Hyperkalaemia	1 (<1)
Musculoskeletal and connective tissue disorders	**1 (<1)**
Osteoarthritis	1 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (<1)**
Breast cancer metastatic	1 (<1)
Colon neoplasm	1 (<1)
Prostate cancer	1 (<1)
Papillary thyroid cancer	1 (<1)
Nervous system disorders	**4 (<1)**
Sedation	1 (<1)
Syncope	1 (<1)

System Organ Class **MedDRA 16.0 Preferred Term, n (%)**	**Total** **(N=1176)**
Lumbar radiculopathy	1 (<1)
Hemiparesis	1 (<1)
Hypoaesthesia	1 (<1)
Speech disorder	1 (<1)
Tremor	1 (<1)
Pregnancy, puerperium and perinatal conditions	**1 (<1)**
Abortion spontaneous	1 (<1)
Psychiatric disorders	**4 (<1)**
Panic attack	2 (<1)
Depression	1 (<1)
Impulsive behaviour	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)
Dyspnoea	1 (<1)
Respiratory arrest	1 (<1)
Pulmonary oedema	1 (<1)
Pulmonary embolism	1 (<1)
Vascular disorders	**4 (<1)**
Deep vein thrombosis	3 (<1)
Hypotension	1 (<1)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients in subgroup.
Preferred terms are sorted by descending order of incidence within system organ class. Patients are counted only once in each preferred term category, and only once in each system organ class category.

APPENDIX 6. RISK EVALUATION AND MITIGATION STRATEGIES (REMS): OVERVIEW

In 2007, a new law that gave FDA many new authorities and responsibilities to enhance drug safety was enacted. It is called the Food and Drug Administration Amendments Act - sometimes called "FDAAA"- and one of its provisions gave FDA the authority to require a Risk Evaluation and Mitigation Strategy-(REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.

A REMS may be required by FDA as part of the approval of a new product, or for an approved product when new safety information arises. Essentially, a REMS is a safety strategy to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such medicines by managing their safe use.

Since medicines are very different from each other, each REMS for each medicine is also different.

Many factors are taken into consideration, some of which include:

- Seriousness of the disease or condition to be treated
- Size of the patient population
- Expected benefit of the drug
- Expected duration of treatment
- Seriousness of the known or potential adverse events

These evaluations are performed not only prior to the approval of a new drug, but also throughout the entire life cycle of the drug. This serves as a means to continuously assess the safety and efficacy of existing drugs based on adverse event reports and results from post-marketing clinical studies.

For every drug approved by FDA, the risks associated with its use are communicated through the product package insert. In some cases, however, the manufacturer and/or FDA may determine that a REMS is necessary to go beyond product labeling to manage risks and thereby ensure that the benefits outweigh the risks.

The provisions of the FDAAA give FDA the authority to:

- Require post-approval studies or clinical trials to assess a known or serious risk, or to learn more about a hypothetical serious risk,
- Require that new safety information be added to the product labeling, and
- Require that companies submit REMS when deemed necessary to ensure that the product’s benefits outweigh the risks

For a new drug, the manufacturer must include the proposed REMS as part of its submission. Once approved, the REMS creates enforceable obligations for the manufacturer and the FDA.

REMS Requirements

To assist manufacturers in developing REMS, FDA has issued an outline of specific elements that should be included in the proposed document. The proposed REMS should be concise and specific and include the goal(s) along with the explicit components that will be developed to ensure that the drug will be used safely and appropriately.

The manufacturer should also describe how it intends to evaluate whether the REMS is meeting its goal(s) and objective(s) at various time points from the time of launch and beyond.

REMS Elements

Proposed REMS may contain any of the following elements:

- Medication Guide – Document written for patients highlighting important safety information about the drug; this document must be distributed by the pharmacist to every patient receiving the drug.
- Communication Plan – Plan to educate healthcare professionals on the safe and appropriate use of the drug and consists of tools and materials that will be disseminated to the appropriate stakeholders.
- Elements to Assure Safe Use – These are strictly controlled systems or requirements put into place to enforce the appropriate use of a drug. Examples of EASUs include physician certification requirements in order to prescribe the drug, patient enrollment in a central registry, distribution of the drug restricted to certain specialty pharmacies, etc.
- Implementation Plan – A description of how certain Elements to Assure Safe Use will be implemented.
- Timetable for Submission of Assessments – The frequency of assessment of the REMS performance with regard to meeting the goal(s) and objective(s). FDA requires that assessments be conducted at 18 months, 3 years, and 7 years post-launch, at a minimum. Results of these evaluations must be reported to the FDA and will determine whether additional actions or modifications to the REMS program are required.