Vantrela™ ER (hydrocodone bitartrate) Abuse Deterrent Extended Release Tablets

June 7, 2016
Teva Pharmaceuticals
Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee
Introduction

Douglas C. Harnish, PhD
Senior Director, Pain and Migraine
Regulatory Affairs
Teva Pharmaceuticals
Vantrela™ ER: Proposed Indication

- Hydrocodone bitartrate extended-release (ER) tablets are intended for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Vantrela ER (hydrocodone bitartrate)

- Single-entity hydrocodone product
- Taken every 12 hours (q12h)
- 15, 30, 45, 60 and 90 mg strengths
- Extended-release formulation with novel abuse-deterrent technology with 3 layers to deter abuse
Goal of Vantrela ER Program

- Provide ER formulation that produces effective analgesia when dosed twice daily
- Provide abuse deterrent properties to resist drug extraction via most common routes
- Abuse-deterrent properties are to meaningfully *deter* abuse, cannot fully *prevent* abuse
Vantrela ER Abuse-Deterrent (AD) Program Timeline

- Aug 2010
- Sep 2011
- Jan 2014
- Jul 2014
- Dec 2014
- Jul 2015
- Oct 2015

- NDA Filed
- Data Review
- PDUFA Date

FDA touch points to discuss and review AD studies
Phase 3 Study Demonstrated Efficacy, Safety and Tolerability

- Primary endpoint of Worst Pain Intensity (WPI) achieved, demonstrating significant pain reduction compared with placebo
- No unexpected safety concerns identified
- Safety profile consistent with hydrocodone and other ER opioids
Abuse-Deterrent Studies

- Test formulation to failure
  - Physical / chemical manipulations
  - Route specific manipulations (oral, IN, IV)
- Intent for Vantrela ER is to resist conversion from ER formulation to IR formulation
- As with any ER formulation, drug will continue to release over time
Vantrela ER Provides Significant Barriers to Deter Abuse

- **Category 1**
  - Physical and chemical properties expected to deter abuse via most common routes

- **Category 2**
  - Abuse-deterrent properties limit extent and rate of rise of drug concentration following manipulation

- **Category 3**
  - Reduced drug liking, expected to reduce oral and intranasal abuse
## Vantrela ER Post-Approval Alignment with FDA Opioid Action Plan

<table>
<thead>
<tr>
<th>FDA Action Plan</th>
<th>Vantrela ER Commitment</th>
</tr>
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<tbody>
<tr>
<td>Strengthen post-market requirements</td>
<td>✓</td>
</tr>
<tr>
<td>Update REMS program</td>
<td>✓</td>
</tr>
<tr>
<td>Expand access to ADFs to discourage abuse</td>
<td>✓</td>
</tr>
<tr>
<td>Support better treatment</td>
<td>✓</td>
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# Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>Chronic Pain and Opioid Abuse</td>
<td>Charles Argo, MD</td>
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<tr>
<td></td>
<td>Professor of Neurology</td>
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<td></td>
<td>Director, Comprehensive Pain Center</td>
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<td>Albany Medical Center, NY</td>
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<td>Richard Malamut, MD</td>
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<td>SVP, Global Clinical Development</td>
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<td>Teva Pharmaceuticals</td>
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<tr>
<td>Clinical Efficacy and Safety</td>
<td>Derek Moe, PhD</td>
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<td>VP, Drug Delivery Technology</td>
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<td>Teva Pharmaceuticals</td>
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<tr>
<td>Abuse Deterrence Studies (Category 1)</td>
<td>Lynn Webster, MD</td>
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<td>VP, Scientific Affairs</td>
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<td>PRA Health Sciences</td>
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<td>Salt Lake City, UT</td>
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<td>Abuse Deterrence Studies (Category 2 and 3)</td>
<td>Richard Malamut, MD</td>
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<td>Summary and Benefit-Risk</td>
<td>Richard Malamut, MD</td>
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<td>Teva Pharmaceuticals</td>
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## Additional Experts

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<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Company</th>
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<tbody>
<tr>
<td>Mary Bond, MS, MBA</td>
<td>Director, Clinical Pharmacology</td>
<td>Teva Pharmaceuticals</td>
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<tr>
<td>Ronghua Yang, PhD</td>
<td>Senior Director, Biostatistics</td>
<td>Teva Pharmaceuticals</td>
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<tr>
<td>Randal Seburg, PhD</td>
<td>Director, Formulations Development</td>
<td>Teva Pharmaceuticals</td>
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</table>
Need for ER/LA Opioids With ADF Technologies

Charles Argoff, MD
Professor of Neurology
Director, Comprehensive Pain Center
Albany Medical Center, NY
Balancing Access to Chronic Pain Therapy While Lessening Abuse

- Proven benefit for patients with pain disorders
- Patients need access to opioids to optimally treat chronic pain conditions
- Prescribers need to work jointly to manage risk while maintaining availability
Chronic Pain is a Serious Public Health Issue

- Chronic pain affects millions of U.S. adults on a daily basis\(^1\)
  - Includes conditions such as low back pain, osteoarthritis, cancer pain
- Patient centered multimodal treatment approach
  - Medical, interventional and non-interventional approaches
- Opioids may offer substantial long-term benefit and improved QoL

Abuse and Diversion of Opioids a Public Health Issue

- Four-fold increase in deaths associated with opioids since 1999\(^1,2\)
  - In 2014, 14,000 opioid overdose associated deaths in US\(^2\)
- 420,000 ED visits in 2011 related to misuse or abuse of Rx opioids\(^3\)
- Abuse costs payers >$72 billion per year in direct healthcare costs\(^4\)
- Need appropriate access for patients without stimulating abuse

2. CDC National Center for Health Statistics 2016.
Opioid Abusers Seek to Convert ER/LA Opioid to IR Opioid

- Physical manipulation of ER opioid is typical
  - Abusers crush and grind
  - Some seek chemical extraction with solvents
- High $C_{\text{max}}$ and short $T_{\text{max}}$
- Many AD products rely on hardness as a physical barrier to deter abuse
Majority of Abusers Spend < 10 Minutes Manipulating ER Opioids

- Goal of ADF is to curb abuse for majority of abusers
- All ADFs can be defeated with time and effort
- Knowing most common abuse methods allows appropriate evaluation of AD potential

Common Routes of Abuse for ER Formulations

Butler et al., 2013. (based on observation between 08-09-2010* and 03-31-2012 [*release day of AD ER oxycodone])
Abuse-Deterrent Opioids Needed to Protect Public Health

- Abusers seek methods to defeat abuse-deterrent properties
- Urgent need for improved abuse-deterrent opioids
- Value in ER abuse-deterrent opioids
- Importance of expanding access while protecting public health
Efficacy and Safety

Richard Malamut, MD
SVP, Global Clinical Development
Teva Pharmaceuticals
Pivotal Study 3103: Phase 3 Safety and Efficacy

- Double-blind, placebo-controlled, randomized-withdrawal in patients with ≥ 3-month history of moderate-to-severe chronic lower back pain
- Randomized to Vantrela doses 30-90 mg q12h
  - 15 mg q12h utilized as a titration dose
Pivotal Study 3103: Phase 3 Safety and Efficacy

- Rescue and concomitant analgesic medication limited to immediate release hydrocodone / APAP (maximum 60 mg / 3900 mg per day)
- Study design reviewed with the FDA
Pivotal Study 3103: Design of Phase 3

Screening (visit 1)

Open-label titration to find appropriate dose

Hydrocodone 30 to 90 mg q12h

WPI = 8.18
Δ = 3.72 points
WPI = 4.46

12 Week Double-blind Randomized 1:1

API = 6.31
Δ = 2.95 points
API = 3.36

Placebo matching drug q12h

Return to primary care doctor or rollover to Study 3104

WPI = Worst pain intensity
API = Average pain intensity
Primary Endpoint (WPI) Met: Significantly Greater Pain Reduction With Vantrela ER

Change from Baseline to Week 12 in WPI LS Mean [± SE]

P<0.001

Pivotal Study 3103
Secondary Endpoint: Average Pain Intensity (API) Confirms Primary Result

Change from Baseline to Week 12 in API LS Mean [± SE]

Vantrela ER: -0.03
Placebo: 0.55

P < 0.001

Pivotal Study 3103
Study 3103: AEs ≥ 5% in Double-Blind Maintenance Phase Similar to Other ER Opioids

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (N=179)</th>
<th>Vantrela ER (N=191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients ≥ 1 AE</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
<td>14%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Headache</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5%</td>
<td>4%</td>
</tr>
</tbody>
</table>
### AEs ≥ 5% in all Phase 3 Studies Up to 12 Months Duration

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Vantrela ER (N=1176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients ≥ 1 AE</td>
<td>73%</td>
</tr>
<tr>
<td>Constipation</td>
<td>23%</td>
</tr>
<tr>
<td>Nausea</td>
<td>23%</td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>10%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5%</td>
</tr>
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</table>
## Exposure to Vantrela ER in Phase 3 Studies

<table>
<thead>
<tr>
<th>Received ≥ 1 dose of Vantrela ER</th>
<th>N=1176</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall exposure (patient-years)</td>
<td>412.12</td>
</tr>
<tr>
<td>Maximum exposure (months)</td>
<td>15.8</td>
</tr>
<tr>
<td>Treated for ≥ 6 months (n)</td>
<td>363</td>
</tr>
<tr>
<td>Treated for ≥ 12 months (n)</td>
<td>197</td>
</tr>
</tbody>
</table>
Summary of Efficacy and Safety Findings

- Study 3103 met primary efficacy endpoint \( (p<0.001) \)
  - Consistent across sensitivity analyses
- Safety profile consistent with other ER opioids
Abuse Deterrence Studies

Derek Moe, PhD
Vice President, Drug Delivery Technologies
Teva Pharmaceuticals
Vantrela ER Developed in Close Collaboration with FDA

- Minimize impact of abuse by retaining ER properties following manipulation
- Target known or expected routes of abuse by majority of abusers
- Compared to immediate-release Vicoprofen®, hydrocodone API, and Zohydro® ER
- Goal is to deter intentional abuse, make less attractive to abusers
Category 1: Manipulation and Extraction Studies

Category 1
Lab based in vitro manipulation and extraction studies

- Physical & chemical manipulation studies\textsuperscript{1-3}
- Route specific studies\textsuperscript{1-3} (oral, intranasal, IV)

Category 2
Pharmacokinetic Clinical Trials

- Study 1079 (manipulated oral)\textsuperscript{1}
- Study 1085 (manipulated oral)\textsuperscript{2}
- Study 10032 (manipulated intranasal)\textsuperscript{3}

Category 3
Human Abuse Potential Clinical Trials

- Study 1085 (manipulated oral)\textsuperscript{2}
- Study 10032 (manipulated intranasal)\textsuperscript{3}

1. Compared to Vicoprofen\textsuperscript{®}; 2. Compared to hydrocodone API; 3. Compared to hydrocodone API and Zohydro\textsuperscript{®} ER
Vantrela ER is Expected to Provide Abuse Deterrence

- Vantrela ER retains extended release properties following manipulations
- Lower abuse potential for most common routes of abuse: oral and intranasal ingestion
- Studies demonstrate barrier against IV abuse
- Isolation methods with greatest extraction result in low drug purity
Studies Ranged From Simple Physical Manipulations to Complex Techniques

- Evaluated Vantrela ER against real-world methods from internet, experts, FDA
  - 844 experiments, 3798 individual results

<table>
<thead>
<tr>
<th>Route</th>
<th>Assessment</th>
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<tbody>
<tr>
<td>General Manipulations</td>
<td>Physical: Impact of tools using cutting, crushing, milling, grinding</td>
</tr>
<tr>
<td></td>
<td>Chemical: Extraction in range of solvents, temperatures, agitation</td>
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<tr>
<td>Route-Specific Manipulations</td>
<td>Oral: Drug release</td>
</tr>
<tr>
<td></td>
<td>Intranasal: Drug release</td>
</tr>
<tr>
<td></td>
<td>Injection: Syringeability, injectability, and drug release</td>
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</tbody>
</table>

Category 1
Evaluated Range of Tools Most Attractive to Abusers

- Screened 15 tools
- Tools represented different particle size reduction methods and mechanisms
  - Milling, cutting, grinding, crushing
- 5 tools selected for Category 1 studies
Data Shown for Category 1 Results

- Data presented on 2 manipulation tools
  - Tool E - worst case tool only used by dedicated abusers
  - Tool A - representative release for Vantrela as other tools and feasible for Zohydro® ER
Physical Manipulation Studies

- Drug release of manipulated Vantrela ER compared to manipulated Zohydro® ER
  - Assessed up to 6 hours
- Emphasis on first 30 minutes for simulated oral ingestion
  - From draft FDA guidance
  - Extended-release lost if ≥ 80% drug released

Simulated Oral Ingestion: Vantrela ER Maintained Extended Release Properties

% Drug Release [95% CI]

<table>
<thead>
<tr>
<th>Tool</th>
<th>0</th>
<th>A</th>
<th>E</th>
<th>30 minutes</th>
<th>120 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>9%</td>
<td>44%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td>97%</td>
<td>99%</td>
</tr>
</tbody>
</table>

≥ 80% at 30 min

Category 1
Vantrela ER Viscosity Presents Barrier to Extraction for Intranasal and IV Abuse

- Manipulated Vantrela ER tablet in 10 mL
- Highly viscous solution does not flow
- Presents challenges to intranasal, IV abuse

Inverted vial of manipulated Vantrela ER

Category 1
Simulated Intranasal Tests: Little Drug Released Compared to Zohydro® ER

- **Category 1**

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>Tool</th>
<th>Vantrela ER</th>
<th>Zohydro ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 minutes</td>
<td>A</td>
<td>1%</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>12%</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>0%</td>
<td>93%</td>
</tr>
<tr>
<td>30 minutes</td>
<td>A</td>
<td>4%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>17%</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>0%</td>
<td>93%</td>
</tr>
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</table>
Simulated IV Tests: Demonstrated Potential Deterrence for IV Abuse

- Intact tablets in solution
  - Resulted in syringeable liquid, little drug
- Manipulated tablets in solution
  - Resulted in difficult-to-syringe viscous material, little drug
Simulated IV Tests: Little Drug Released Compared to Zohydro® ER

<table>
<thead>
<tr>
<th>Tool</th>
<th>Vantrela ER</th>
<th>Zohydro ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>81%</td>
<td>73%</td>
</tr>
<tr>
<td>E</td>
<td>5%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Mixing Time

<table>
<thead>
<tr>
<th>Mixing Time</th>
<th>Tool</th>
<th>% Drug Release [95% CI]</th>
</tr>
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<tbody>
<tr>
<td>1 minute</td>
<td>A</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>81%</td>
</tr>
<tr>
<td>5 minutes</td>
<td>A</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>73%</td>
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Category 1
Chemical Extraction Studies

- Extraction studies
  - Evaluate rate of drug release in common aqueous fluid and advanced solvents
  - Range of polarity and pH
  - Purity becomes important for advanced solvents
- Studies varied times, temperature and agitation
- Compared manipulated Vantrela ER vs Zohydro® ER
Vantrela ER Exhibited Barriers to Extraction in Common Aqueous Fluids

<table>
<thead>
<tr>
<th>Tool</th>
<th>Fluids</th>
<th>Mixing Time</th>
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<tbody>
<tr>
<td>A</td>
<td>a</td>
<td>30 minutes</td>
</tr>
<tr>
<td>E</td>
<td>h</td>
<td></td>
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- **Vantrela ER**
  - Tool A: 8% (95% CI)
  - Tool E: 24% (95% CI)
  - Tool A: 10% (95% CI)
- **Zohydro ER**
  - Tool A: 97% (95% CI)
  - Tool E: 78% (95% CI)
Most Successful Oral Extraction Conditions Require Multiple Stressors

- Tested to failure as FDA Guidance instructs
- Vantrela not defeated in the simulated oral ingestion studies
- Most successful extraction conditions
  - Required specific combination of stressors applied simultaneously
  - Resulted in $\geq 80\%$ drug release in 30 minutes
- Abuse-deterrent, not abuse-proof
Vantrela ER Exhibits Low Purity When Extracted With Advanced Solvents

The graph shows the % purity of isolated residue (w/w%) of Vantrela ER and Zohydro ER when extracted with various solvents. The data is presented in a bar graph with error bars indicating the 95% CI. The results are categorized as follows:

- Category 1
  - Tool AEAAEA
  - Solvent: m, j, l, i, n
  - Purity values: 16%, 14%, 26%, 3%, 4%, 17%, 18%, 10%, 16%, 13%, 11%, 62%, 86%, 66%, 94%
Multi-Step Chemical Tests: Purity of Isolated Drug Substance Low

**% Purity of Isolated Residue (w/w%) [95% CI]**

<table>
<thead>
<tr>
<th>Tool</th>
<th>A</th>
<th>E</th>
<th>A</th>
<th>A</th>
<th>E</th>
<th>A</th>
<th>A</th>
<th>E</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Extracted</td>
<td>78%</td>
<td>71%</td>
<td>95%</td>
<td>51%</td>
<td>57%</td>
<td>90%</td>
<td>26%</td>
<td>28%</td>
<td>46%</td>
</tr>
<tr>
<td>Solvent</td>
<td>n</td>
<td>o</td>
<td>k</td>
<td></td>
<td></td>
<td></td>
<td></td>
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Category 1 Summary

- Studies assessed Vantrela ER against most common methods of abuse
  - Designed to push formulation to the limit
- Vantrela ER retains extended release properties compared to non-abuse deterrent opioid formulations under all but certain stressed conditions
Category 2 and 3: Clinical Pharmacokinetics and Human Abuse Potential Studies

Lynn Webster, MD
VP, Scientific Affairs
PRA Health Sciences
Salt Lake City, UT
Category 2: Effect of Manipulation on Pharmacokinetics (Oral & Intranasal)

Category 1
Lab based *in vitro* manipulation and extraction studies
- Physical & chemical manipulation studies\(^1\)-\(^3\)
- Route specific studies\(^1\)-\(^3\) (oral, intranasal, IV)

Category 2
Pharmacokinetic Clinical Trials
- Study 1079 (manipulated oral)\(^1\)
- Study 1085 (manipulated oral)\(^2\)
- Study 10032 (manipulated intranasal)\(^3\)

Category 3
Human Abuse Potential Clinical Trials
- Study 1085 (manipulated oral)\(^2\)
- Study 10032 (manipulated intranasal)\(^3\)

1. Compared to Vicoprofen\(^®\); 2. Compared to hydrocodone API; 3. Compared to hydrocodone API and Zohydro\(^®\) ER
No Dose Dumping of Intact Oral Vantrela ER Tablet with Alcohol

Study 1076 – Oral 15 mg dose (N=30)

Mean Plasma Hydrocodone Concentration (ng/mL)

Profile truncated to 12 hours
Rate of Rise May Contribute to Differential Abuse Potential

Category 2 PK data intended to measure ‘rate of rise’, peak and early concentrations, as measured by:
- Early concentrations and partial AUCs
- $C_{\text{max}}$ and $T_{\text{max}}$

Webster, 2015.
Manipulated Oral Vantrela ER Showed Lower Peak Concentration Than IR Vicoprofen®

Study 1079 – Oral 15 mg dose (N=31)

Mean Plasma Hydrocodone Concentration (ng/mL)

Profile truncated to 12 hours

Category 2
Manipulated Oral Vantrela ER Showed Lower Peak Concentration Than Hydrocodone API

Study 1085 – Oral 45 mg dose (N=43)

- Vantrela ER Intact
- Vantrela ER Manipulated
- Hydrocodone API

Mean Plasma Hydrocodone Concentration (ng/mL)

Profile truncated to 12 hours

Category 2
Manipulated Intranasal Vantrela ER Showed Lower Peak Concentration Than Hydrocodone API and Zohydro® ER

Study 10032 – Intranasal 45 mg dose (N=42)

Mean Plasma Hydrocodone Concentration (ng/mL)

Profile truncated to 12 hours
Category 2 Conclusions

- Vantrela ER retains extended release properties following manipulation
- Lower extent and rate of rise in hydrocodone concentration following manipulation
  - Lower $C_{\text{max}}$
  - Later $T_{\text{max}}$
  - Lower early hydrocodone exposure
Category 3: Vantrela ER Human Abuse Potential (Oral and Intranasal)

**Category 1**
Lab based *in vitro* manipulation and extraction studies
- Physical & chemical manipulation studies\(^1\)\(^-\)\(^3\)
- Route specific studies\(^1\)\(^-\)\(^3\)
  - (oral, intranasal, IV)

**Category 2**
Pharmacokinetic Clinical Trials
- Study 1079 (manipulated oral)\(^1\)
- Study 1085 (manipulated oral)\(^2\)
- Study 10032 (manipulated intranasal)\(^3\)

**Category 3**
Human Abuse Potential Clinical Trials
- Study 1085 (manipulated oral)\(^2\)
- Study 10032 (manipulated intranasal)\(^3\)

1. Compared to Vicoprofen\(^®\);
2. Compared to hydrocodone API;
3. Compared to hydrocodone API and Zohydro\(^®\) ER
Drug Liking Endpoints to Measure Pharmacodynamic Effects

- Primary endpoint
  - $E_{\text{max}}$ of Drug Liking Visual Analog Scale (VAS)
- Primary (10032) / key secondary (1085) endpoint
  - Overall Drug Liking VAS
- Key secondary endpoints
  - Take Drug Again VAS
  - Good Effects VAS ($E_{\text{max}}$)
  - Any Effects VAS ($E_{\text{max}}$)
Manipulated Oral Vantrela ER had Lower Drug Liking Than Hydrocodone API

Study 1085 – Oral 45 mg dose (N=45)

Mean bipolar “at this moment” Drug Liking VAS

- Strong liking
- Neither like nor dislike
- Strong disliking

Profile truncated to 12 hours
Lower Drug Liking for Manipulated Oral Vantrela ER Than Hydrocodone API

Study 1085 – Oral 45 mg dose (N=45)

Maximum Drug Liking VAS
LS Mean [± SE]

Strong liking

Neither like nor dislike

Strong disliking

Placebo  Vantrela ER Intact  Vantrela ER Manipulated  Hydrocodone API

p<0.001  p<0.001

Category 3
Lower Overall Drug Liking for Manipulated Oral Vantrela ER Than Hydrocodone API

Study 1085 – Oral 45 mg dose (N=45)

Maximum Drug Liking

<table>
<thead>
<tr>
<th>Condition</th>
<th>LS Mean [± SE]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>50</td>
</tr>
<tr>
<td>Vantrela ER Intact</td>
<td></td>
</tr>
<tr>
<td>Vantrela ER Manipulated</td>
<td>70</td>
</tr>
<tr>
<td>Hydrocodone API</td>
<td>90</td>
</tr>
</tbody>
</table>

*p<0.001*
Lower Take Drug Again for Manipulated Oral Vantrela ER Than Hydrocodone API

Study 1085 – Oral 45 mg dose (N=45)

Take Drug Again LS Mean [± SE]

Definitely Would

Do Not Care

Definitely Would Not

Placebo

Vantrela ER Intact

Vantrela ER Manipulated

Hydrocodone API

p<0.001

Category 3
Manipulated Intranasal Vantrela ER had Lower Drug Liking Than Hydrocodone API and Zohydro® ER

Study 10032 – Intranasal 45 mg dose (N=34)

Mean bipolar “at this moment” Drug Liking
VAS

Strong liking

Strong disliking

Neither like nor dislike

Profile truncated to 12 hours

Category 3

Time (hours)
Lower Drug Liking for Manipulated Intranasal Vantrela ER Than Hydrocodone API and Zohydro® ER

Study 10032 – Intranasal 45 mg dose (N=34)

Maximum Drug Liking VAS
LS Mean [± SE]

Strong liking

Neither like nor dislike

Strong disliking

Placebo
Vantrela ER Intact (oral)
Vantrela ER Manipulated
Hydrocodone API
Zohydro ER Manipulated

p<0.001
p=0.004

Category 3
Lower Overall Drug Liking for Manipulated Intranasal Vantrela ER Than Hydrocodone API and Zohydro® ER

Study 10032 – Intranasal 45 mg dose (N=34)

Overall Drug Liking VAS

\( E_{\text{max}} \)

LS Mean [± SE]

Strong liking 100

90

80

70

60

50

40

30

20

10

0

Neither like nor dislike

Strong disliking

Placebo

Vantrela ER Intact (oral)

Vantrela ER Manipulated

Hydrocodone API

Zohydro ER Manipulated

p<0.001

p=0.004

Category 3
Lower Take Drug Again for Manipulated Intranasal Vantrela ER Than Hydrocodone API and Zohydro® ER

Study 10032 – Intranasal 45 mg dose (N=34)

Definitely Would

Take Drug Again
LS Mean [± SE]

Do Not Care

Definitely Would Not

Placebo
Vantrela ER Intact (oral)
Vantrela ER Manipulated
Hydrocodone API
Zohydro ER Manipulated

p<0.001
p=0.005

Category 3
## Summary of Key Category 3 Endpoints from Human Abuse Potential Studies

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Study 1085 (Oral)</th>
<th>Study 10032 (Intranasal)</th>
<th>Manipulated Vantrela ER vs Hydrocodone API</th>
<th>Manipulated Vantrela ER vs Hydrocodone API</th>
<th>Manipulated Vantrela ER vs Zohydro® ER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Liking VAS</td>
<td>-18.3 (&lt;0.001)</td>
<td>-6.8 (0.004)</td>
<td>-9.9 (&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary (10032) / Key Secondary (1085)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Drug Liking VAS</td>
<td>-16.2 (&lt;0.001)</td>
<td>-8.0 (0.004)</td>
<td>-11.7 (&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Key Secondary Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Take Drug Again VAS</td>
<td>-16.9 (&lt;0.001)</td>
<td>-7.8 (0.005)</td>
<td>-12.1 (&lt;0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good Effects ($E_{max}$)</td>
<td>-39.7 (&lt;0.001)</td>
<td>-11.0 (&lt;0.001)$^a$</td>
<td>-23.5 (&lt;0.001)$^a$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Effects ($E_{max}$)</td>
<td>-40.7 (&lt;0.001)</td>
<td>-13.4 (0.006)</td>
<td>-22.5 (&lt;0.001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data shown as LS mean difference (p-value), except where noted with “a”; shown as median difference Category 3
Category 3 Data Conclusions

- PD consistent with Category 2 PK results
- Significantly lower drug liking, overall liking and willingness to take drug again vs non-ADF comparators
- Abuse-deterrent for two most common routes of abuse: oral and intranasal
Summary and Benefit-Risk

Richard Malamut, MD
Vantrela ER: Positive Clinical Data

- Significant pain relief compared to placebo
- Safety profile similar to other opioid products from our phase 3 program
Category 1: Vantrela ER has Physical and Chemical Properties Expected to Deter Abuse

- ER properties maintained after applying techniques known to be utilized by potential abusers
- Physical and chemical properties expected to deter most common routes of abuse
  - Oral, intranasal, IV injection
Category 2: PK Results Show Manipulated Vantrela ER Retains Extended Release Properties

- When manipulated for oral, intranasal abuse, Vantrela ER exhibits
  - Lower extent and rate of rise in hydrocodone concentration
  - Lower $C_{\text{max}}$ and later $T_{\text{max}}$ than non-abuse deterrent opioids
Category 3: PD Studies Show Reduced Human Abuse Potential for Vantrela ER

- PD results consistent with PK results
- Manipulated Vantrela ER maintains AD properties in human abuse potential studies
- Expected to reduce most common routes of abuse: oral and intranasal
- Significantly lower drug liking, willingness to take drug again
- Abuse deterrence expected to be confirmed in post-marketing, real-world abuse studies
Committed to Responsible Pain Management While Protecting Overall Public Health

- Goal is to promote appropriate opioid use
- Internal audits, training and compliance program to monitor employee communications
- Teva will join ER/LA Opioid Analgesics REMS
- Teva will participate in
  - 11 shared observational post-market requirement studies
  - Vantrela ER-specific post-market requirement studies
Vantrela ER: Positive Benefit-Risk Profile

- Significant barriers against abuse
- Effective chronic pain management
- Safety profile consistent with other ER opioids
- Vantrela ER offers needed option for patients and HCPs, while providing part of the solution to public health issue of abuse
Vantrela™ ER (hydrocodone bitartrate) Abuse Deterrent Extended Release Tablets

June 7, 2016
Teva Pharmaceuticals
Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee
Back-up Slides Shown
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.
Most Successful Extraction Conditions: Most Rapid Drug Release

- Vantrela ER was tested to failure as FDA Guidance instructs
- Extreme extraction conditions were found that resulted in ≥ 80% drug release in 30 minutes
- Specific conditions were:
  - Liquid H
  - Agitation W
  - Temperature 8
  - Tools A and E
Manipulated Oral Vantrela ER Had Lower Drug Liking Than Hydrocodone API

Study 1085 (Oral 45 mg dose) (N=45)

- Vantrela ER Intact (oral)
- Vantrela ER Manipulated
- Hydrocodone API
- Placebo

Profile truncated to 12 hours
Manipulated Intranasal Vantrela ER Had Lower Drug Liking Than Comparators

Study 10032 (Intranasal 45 mg dose) (N=34)

- Vantrela ER Intact (oral)
- Vantrela ER Manipulated
- Hydrocodone API
- Zohydro ER Manipulated
- Placebo

Graph showing the mean bipolar "at this moment" drug liking VAS [± SD] over time (hours) with error bars for each condition. The profile is truncated to 12 hours.
Manipulated Intranasal Vantrela ER Showed Lower Peak Concentration than Hydrocodone API and Zohydro® ER

Study 10032 -- Intranasal 45 mg dose (N=42)

Mean Plasma Hydrocodone Concentration (ng/mL) [± SD]

Profile truncated to 12 hours

Category 2
Manipulated Oral Vantrela ER Showed Lower Peak Concentration Than Hydrocodone API

Study 1085 -- Oral 45 mg dose (N=43)

Mean Plasma Hydrocodone Concentration (ng/mL) [± SD]

Profile truncated to 12 hours

Time (hours)
Manipulated Oral Vantrela ER Had Lower Drug Liking Than Hydrocodone API

Study 1085 (Oral 45 mg dose) (N=45)

Mean bipolar “at this moment” Drug Liking VAS [+ SE]

Strong liking

Neither like nor dislike

Strong disliking

Profile truncated to 12 hours

Category 3
Manipulated Intranasal Vantrela ER Had Lower Drug Liking Than Comparators

Study 10032 (Intranasal 45 mg dose) (N=34)

- Vantrela ER Intact (oral)
- Vantrela ER Manipulated
- Hydrocodone API
- Zohydro ER Manipulated
- Placebo

Mean bipolar “at this moment” Drug Liking VAS [+ SE]

Strong liking

Neither like nor dislike

Strong disliking

Time (hours) Profile truncated to 12 hours

Category 3
Manipulated Oral Vantrela ER Showed Lower Peak Concentration than Hydrocodone API

Study 1085 (Oral)

Mean Plasma Hydrocodone Concentration (ng/mL) [± SE]

Time (hours)
Manipulated Intranasal Vantrela ER Showed Lower Peak Concentration than Hydrocodone API and Zohydro® ER

Study 10032 (Intranasal)