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

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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.

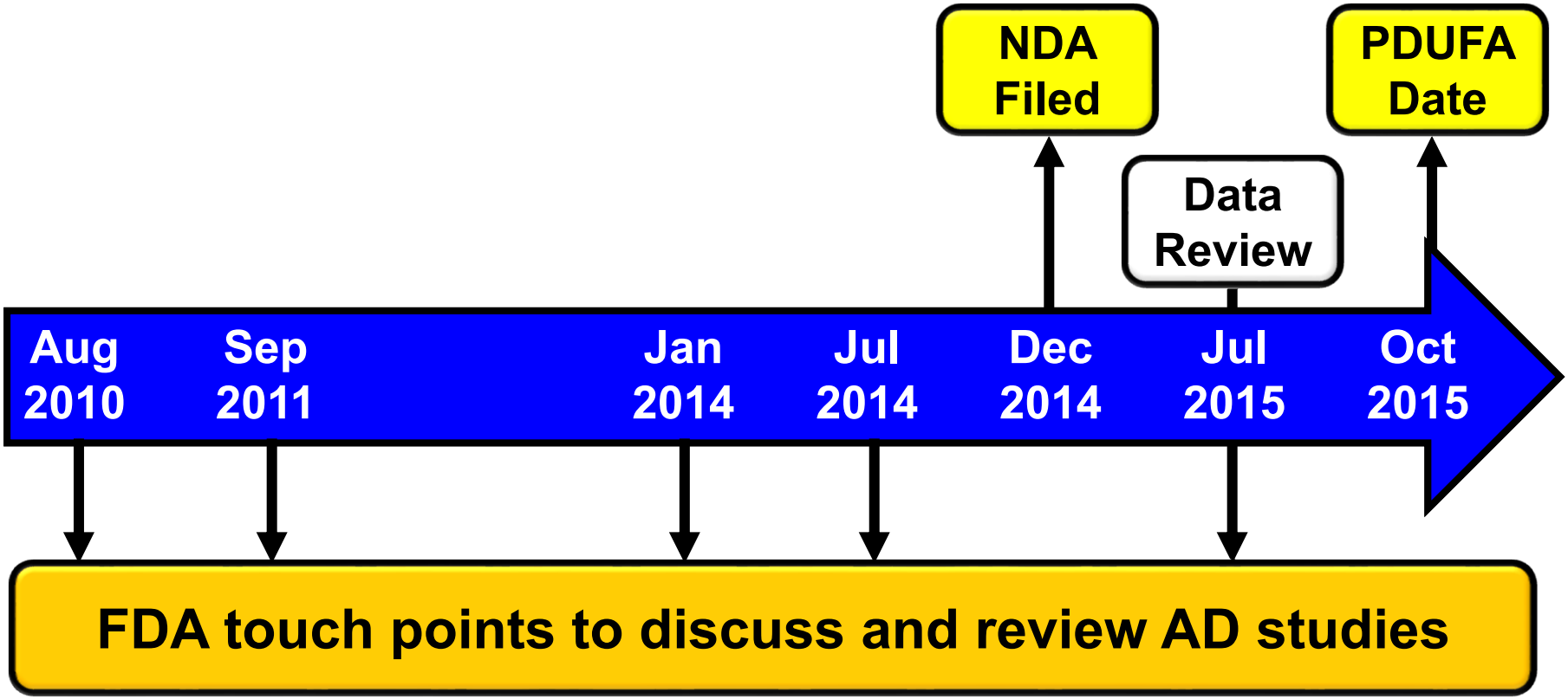
Vantrela ER (hydrocodone bitartrate)

- 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



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

FDA Action Plan	Vantrela ER Commitment
Strengthen post-market requirements	✓
Update REMS program	✓
Expand access to ADFs to discourage abuse	✓
Support better treatment	✓

Agenda

Chronic Pain and Opioid Abuse	**Charles Argoff, MD** Professor of Neurology Director, Comprehensive Pain Center Albany Medical Center, NY
Clinical Efficacy and Safety	**Richard Malamut, MD** SVP, Global Clinical Development Teva Pharmaceuticals
Abuse Deterrence Studies (Category 1)	**Derek Moe, PhD** VP, Drug Delivery Technology Teva Pharmaceuticals
Abuse Deterrence Studies (Category 2 and 3)	**Lynn Webster, MD** VP, Scientific Affairs PRA Health Sciences Salt Lake City, UT
Summary and Benefit-Risk	**Richard Malamut, MD** SVP, Global Clinical Development Teva Pharmaceuticals

Additional Experts

Mary Bond, MS, MBA	Director, Clinical Pharmacology Teva Pharmaceuticals
Ronghua Yang, PhD	Senior Director, Biostatistics Teva Pharmaceuticals
Randal Seburg, PhD	Director, Formulations Development Teva Pharmaceuticals

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

1. **Institute of Medicine.** ***Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*****. 2011.**

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

1. CDC/HCHS, National Vital Statistics System, Mortality File.
2. CDC National Center for Health Statistics 2016.
3. SAMSHA: Highlights of the 2011 Drug Abuse Warning Network (DAWN) findings on drug-related emergency department visits. 2013.
4. Am J Managed Care 2013.

Opioid Abusers Seek to Convert ER/LA Opioid to IR Opioid

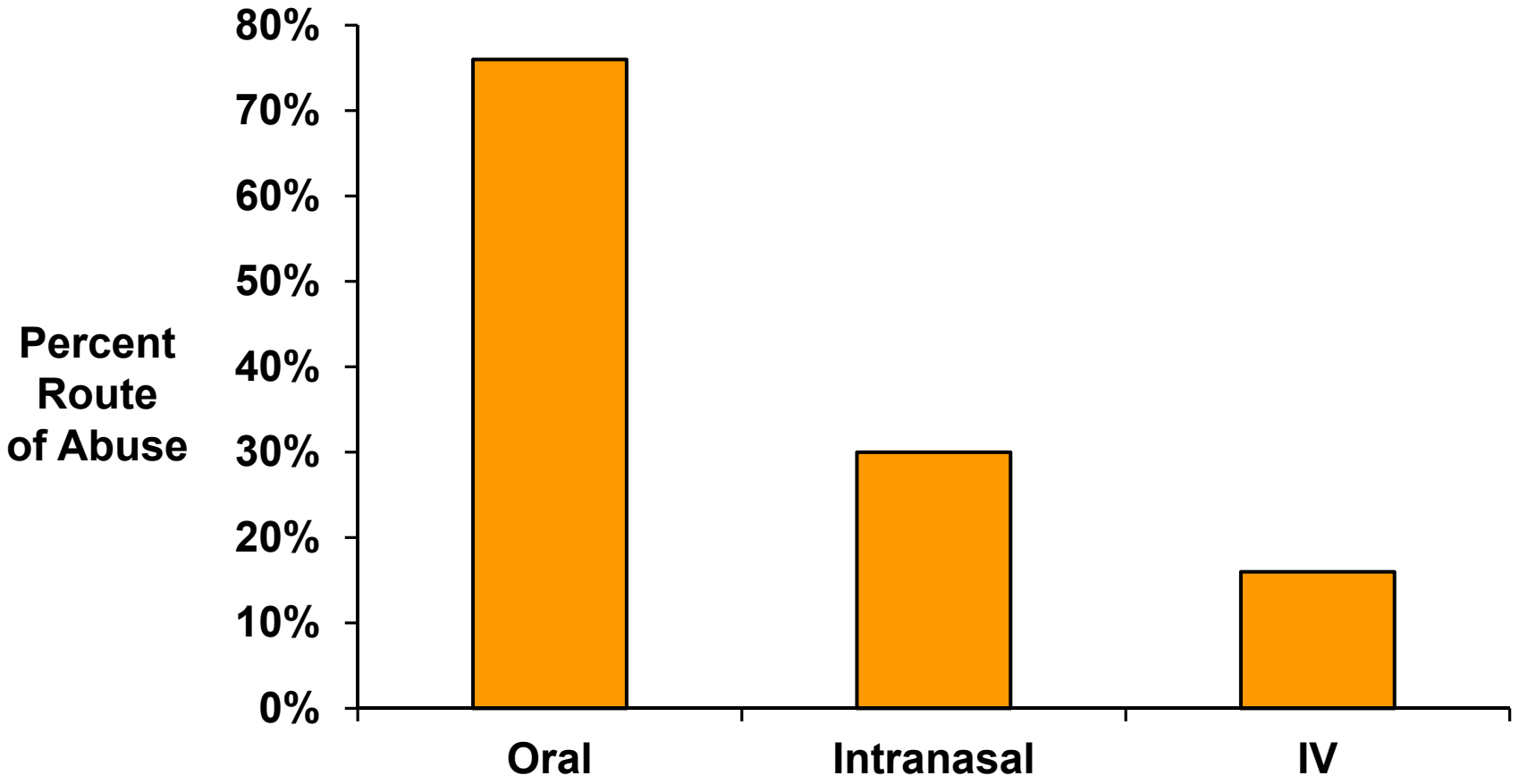
- Physical manipulation of ER opioid is typical
  - Abusers crush and grind
  - Some seek chemical extraction with solvents
- High C_{max} and short T_{max}
- Many AD products rely on hardness as a physical barrier to deter abuse

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

Sellers EM, et al. *J Psychopharmacol.* 2013.
Perrino PJ, *Pain Week.* 2013.

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

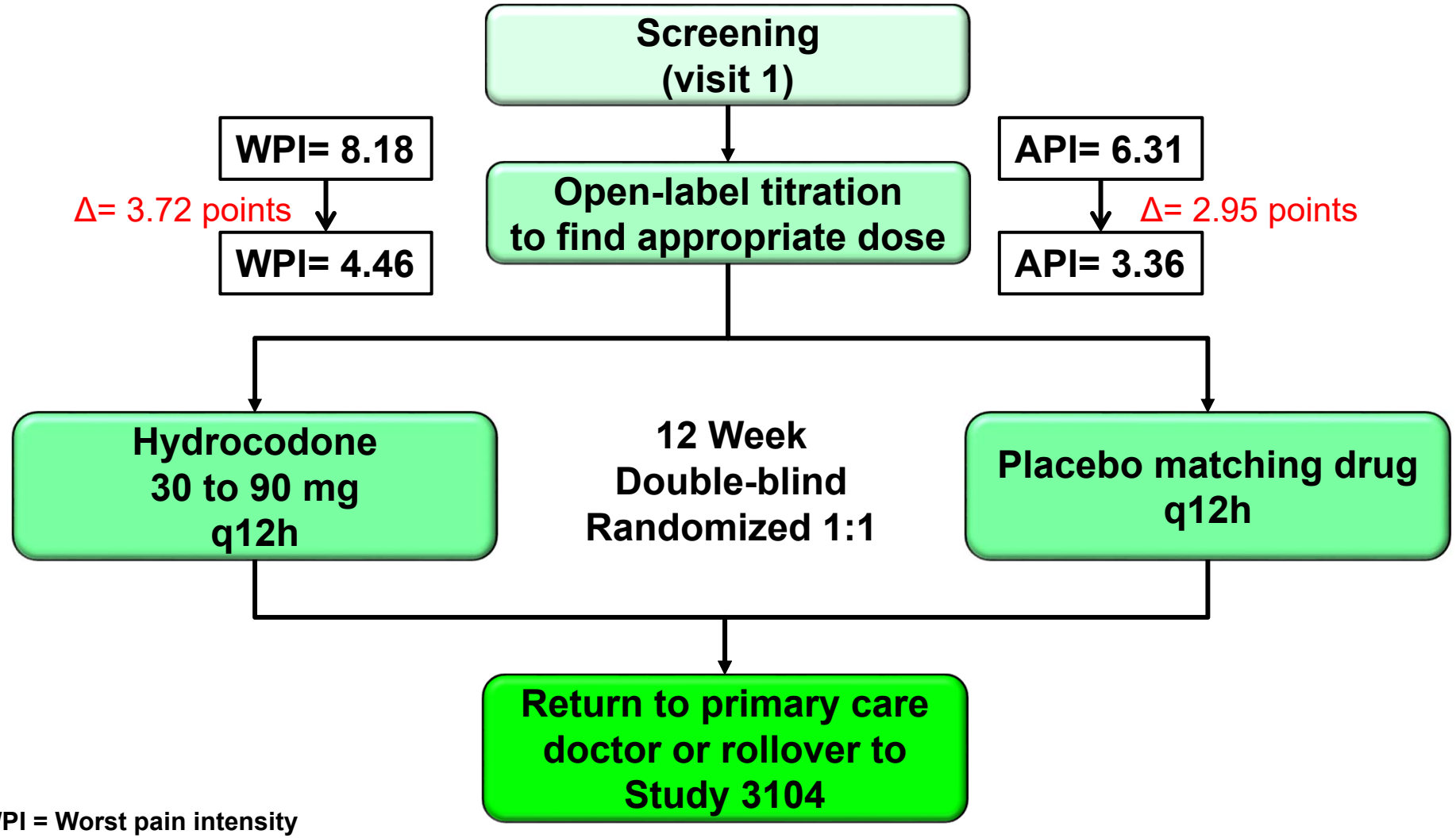
Pivotal Study 3103: Phase 3 Safety and Efficacy

- 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

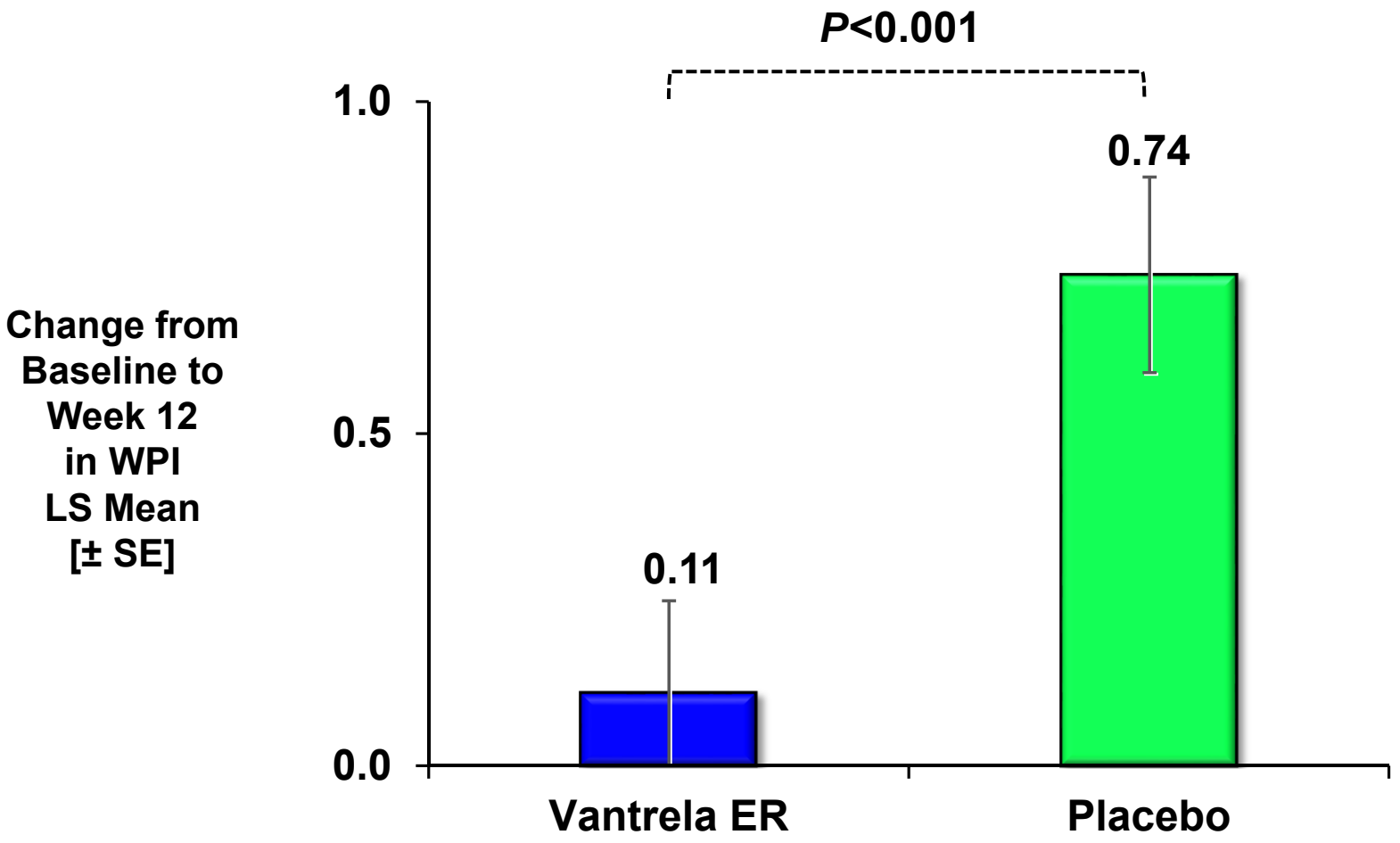
- Rescue and concomitant analgesic medication limited to immediate release hydrocodone / APAP (maximum 60 mg / 3900 mg per day)
- Study design reviewed with the FDA

Pivotal Study 3103: Design of Phase 3



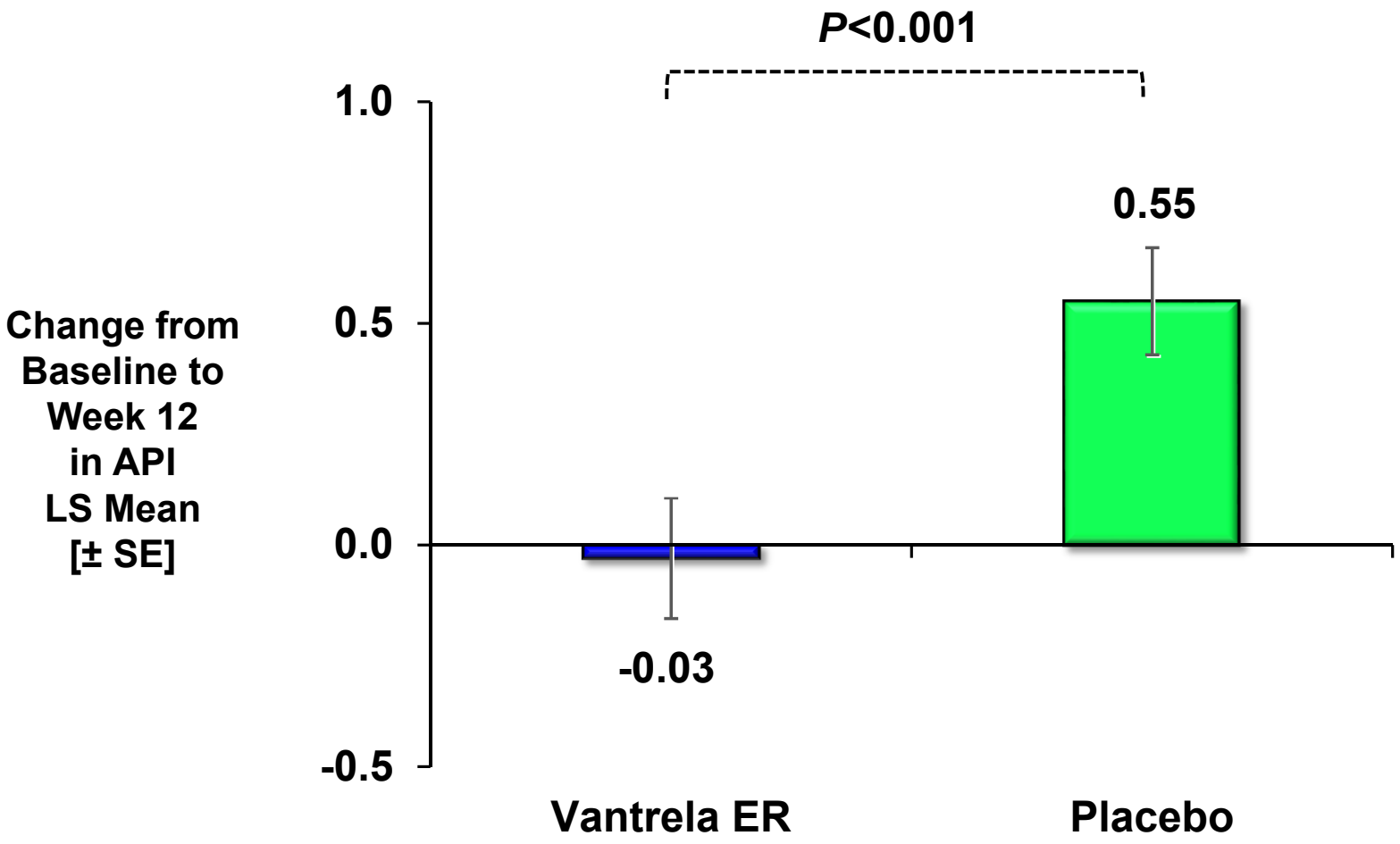
WPI = Worst pain intensity
API = Average pain intensity

Primary Endpoint (WPI) Met: Significantly Greater Pain Reduction With Vantrela ER



Pivotal Study 3103

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



Pivotal Study 3103

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

Preferred Term	Placebo (N=179)	Vantrela ER (N=191)
Patients ≥ 1 AE	49%	55%
Constipation	4%	14%
Nausea	8%	10%
Headache	4%	6%
Upper respiratory tract infection	5%	4%

AEs ≥ 5% in all Phase 3 Studies Up to 12 Months Duration

Preferred Term	Vantrela ER (N=1176)
Patients ≥ 1 AE	73%
Constipation	23%
Nausea	23%
Headache	12%
Vomiting	10%
Somnolence	10%
Dizziness	7%
Pruritus	6%
Fatigue	5%

Exposure to Vantrela ER in Phase 3 Studies

Received ≥ 1 dose of Vantrela ER	N=1176
Overall exposure (patient-years)	412.12
Maximum exposure (months)	15.8
Treated for ≥ 6 months (n)	363
Treated for ≥ 12 months (n)	197

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	Category 2	Category 3
• **Physical & chemical manipulation studies[1-3]** • **Route specific studies[1-3] (oral, intranasal, IV)**	• Study 1079 (manipulated oral)[1] • Study 1085 (manipulated oral)[2] • Study 10032 (manipulated intranasal)[3]	• 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

CDER. *Abuse-Deterrent Opioids — Evaluation and Labeling: Guidance for Industry.* April 2015.

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

	Route	Assessment
General Manipulations	**Physical**	Impact of tools using cutting, crushing, milling, grinding
	Chemical	Extraction in range of solvents, temperatures, agitation
Route-Specific Manipulations	**Oral**	Drug release
	Intranasal	Drug release
	Injection	Syringeability, injectability, and drug release

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

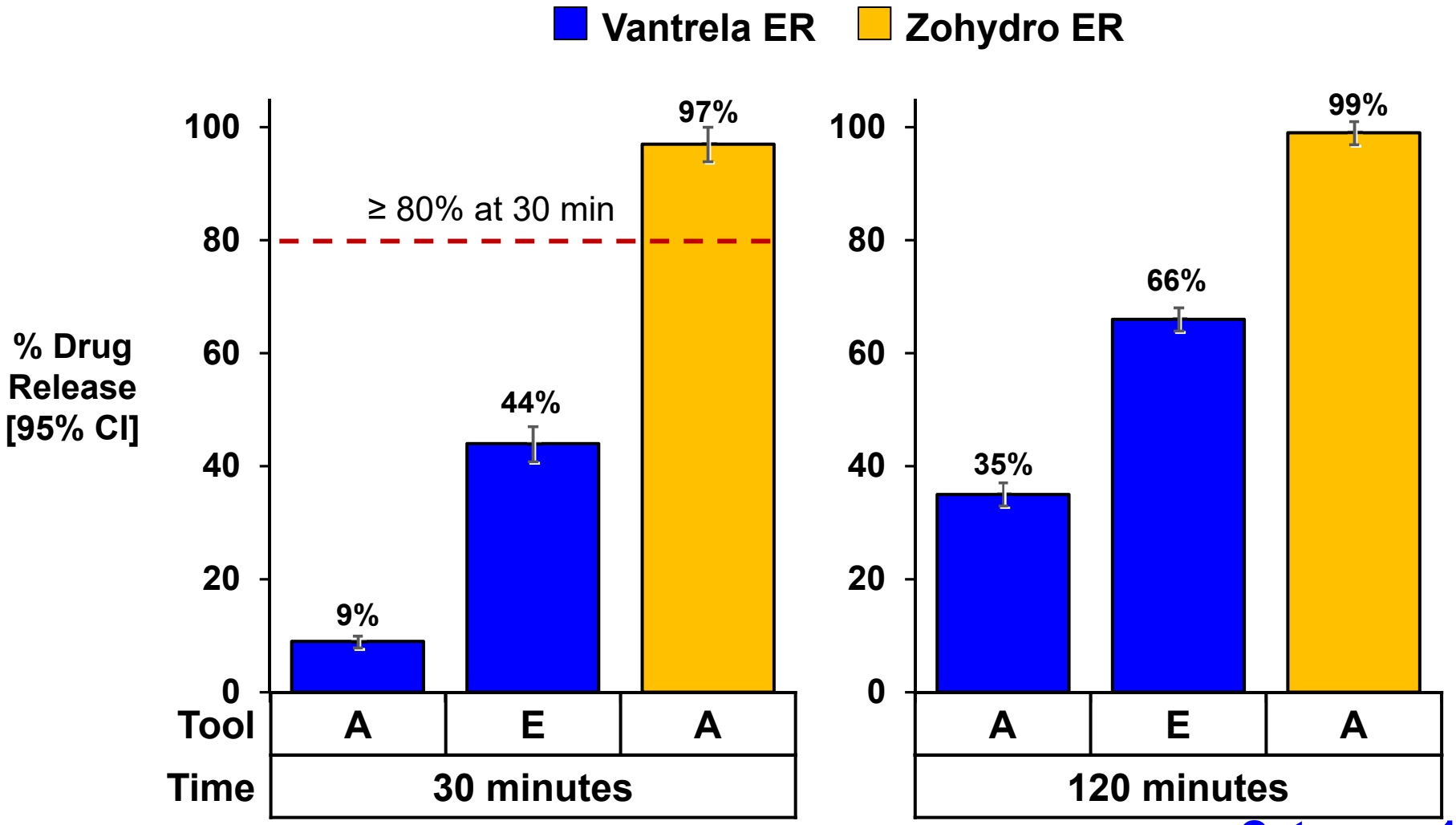
- Data presented on 2 manipulation tools
  - Tool E - worst case tool only used by dedicated abusers
  - Tool A - representative release for Vantrela as other tools and feasible for Zohydro® ER

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[1]
  - From draft FDA guidance
  - Extended-release lost if ≥ 80% drug released[1]

1. CDER. Draft General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products, March 2016.

Simulated Oral Ingestion: Vantrela ER Maintained Extended Release Properties



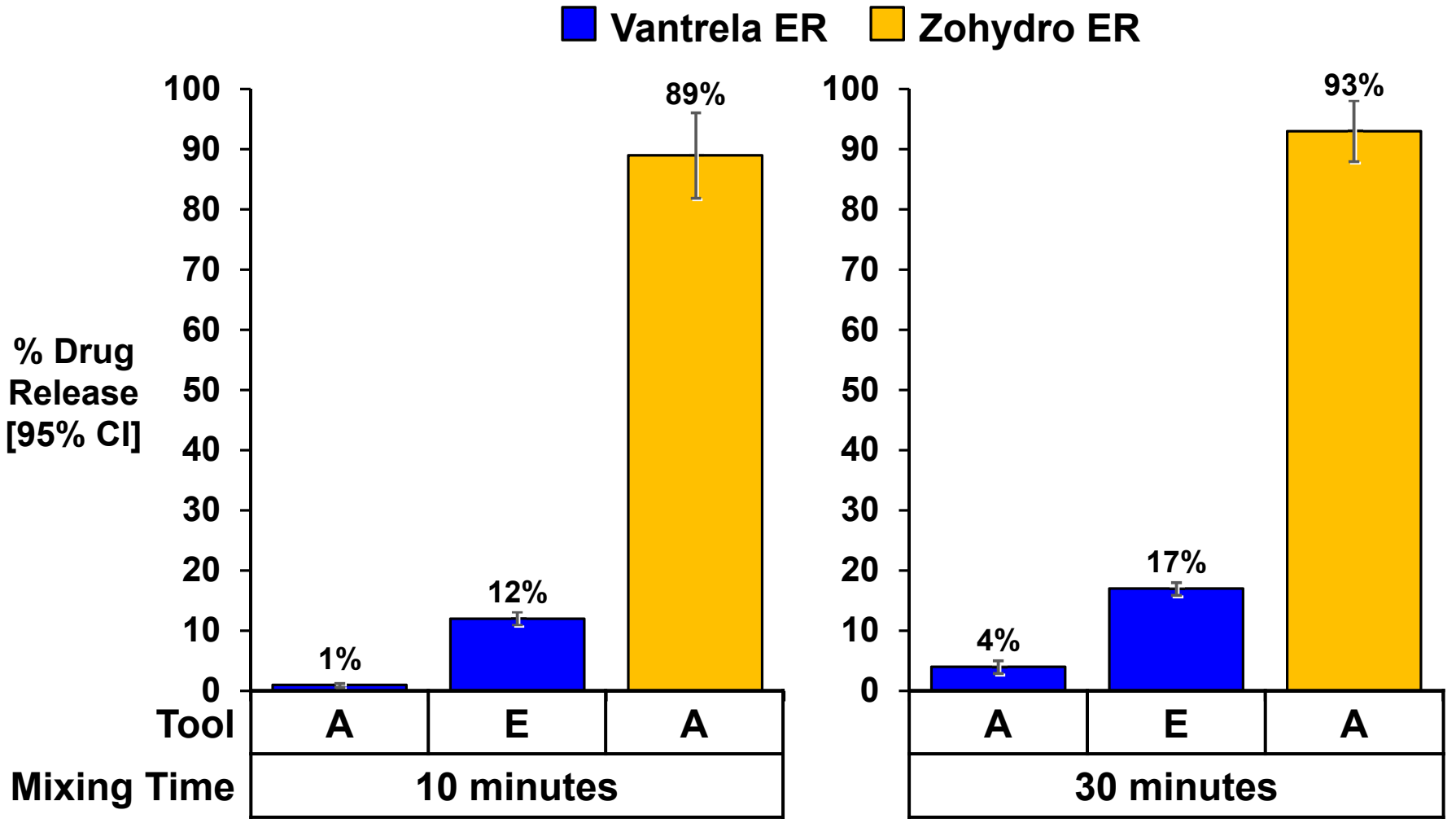
Category 1

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

Inverted vial of manipulated Vantrela ER

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

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

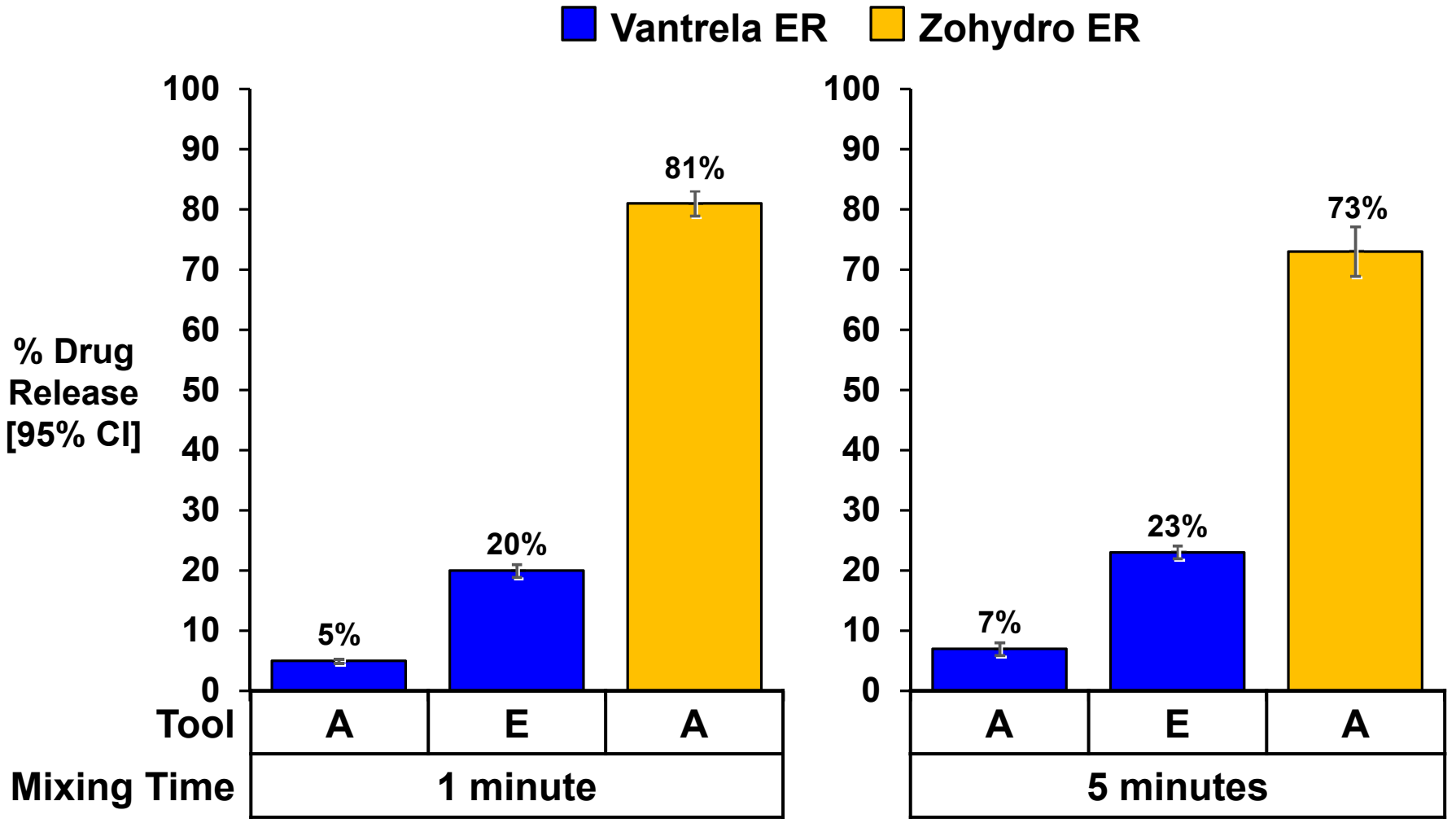


Category 1

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



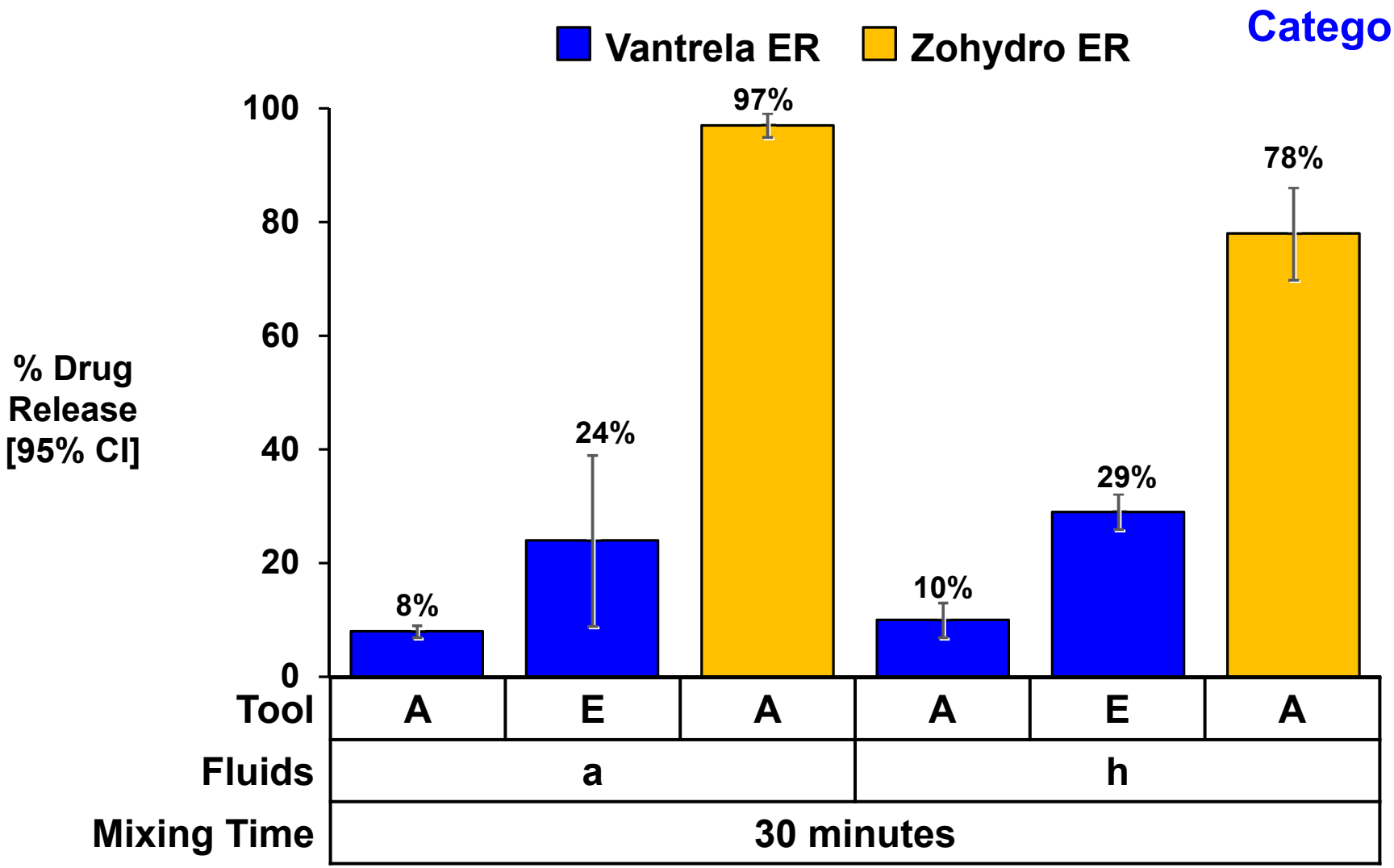
Category 1

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

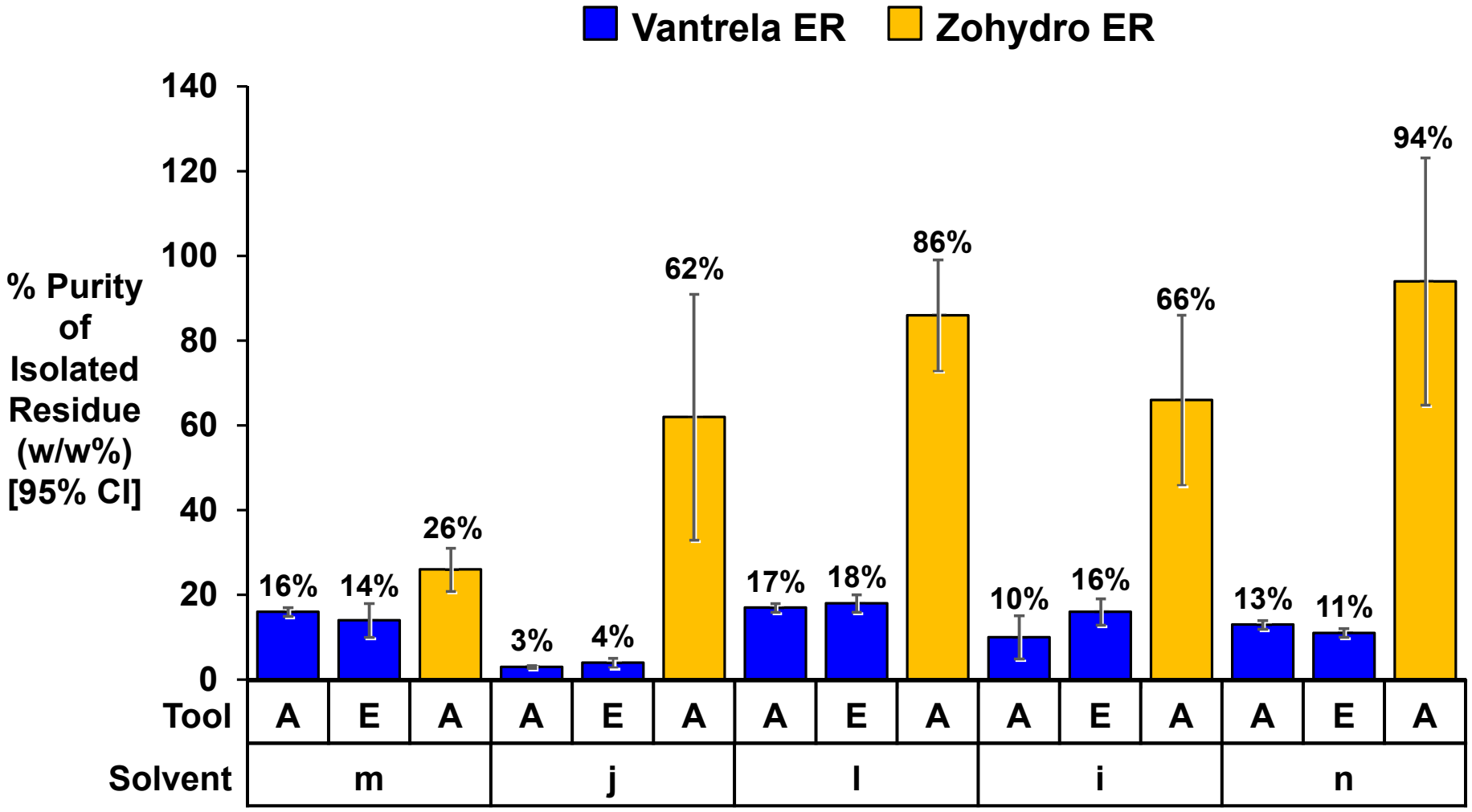
Category 1



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 ≥ 80% drug release in 30 minutes
- Abuse-deterrent, not abuse-proof

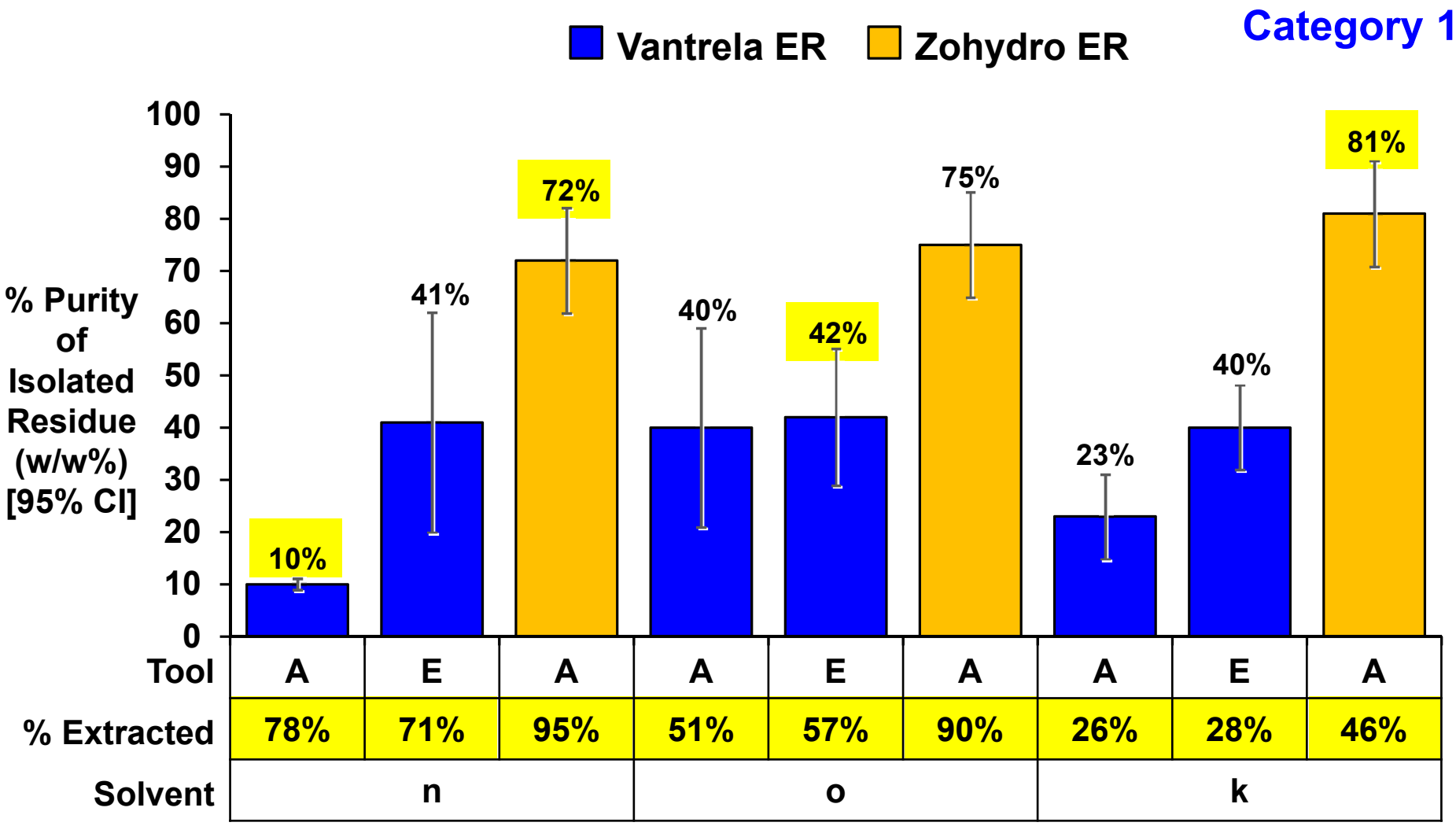
Vantrela ER Exhibits Low Purity When Extracted With Advanced Solvents



Category 1

Multi-Step Chemical Tests: Purity of Isolated Drug Substance Low

Category 1



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

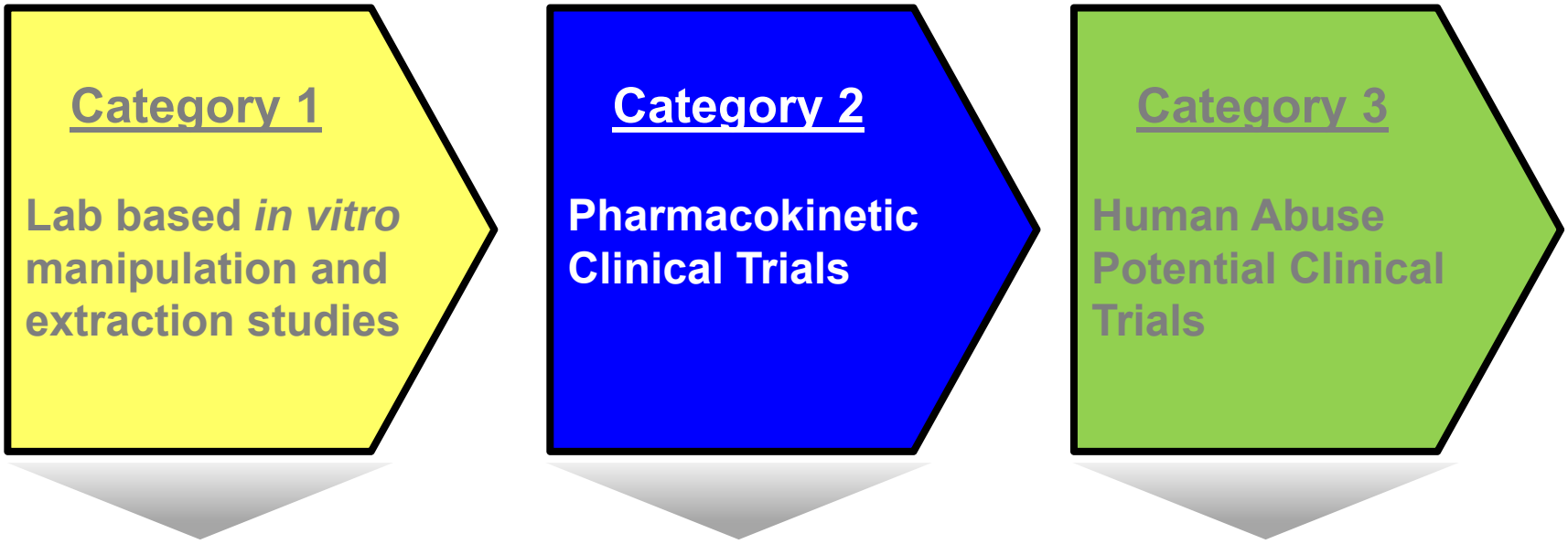
Lynn Webster, MD

VP, Scientific Affairs

PRA Health Sciences

Salt Lake City, UT

Category 2: Effect of Manipulation on Pharmacokinetics (Oral & Intranasal)

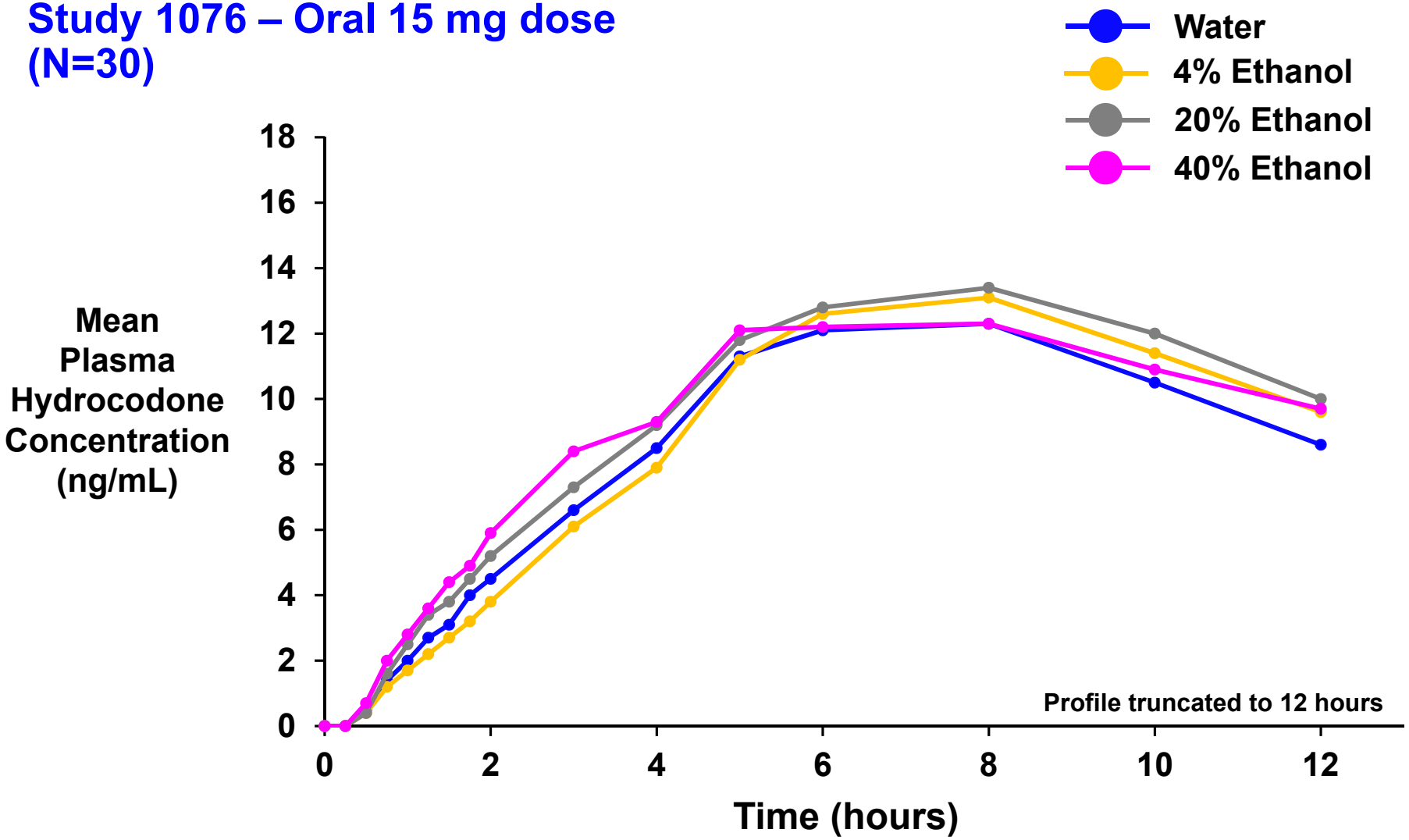


• Physical & chemical manipulation studies[1-3] • Route specific studies[1-3] (oral, intranasal, IV)	• **Study 1079 (manipulated oral)[1]** • **Study 1085 (manipulated oral)[2]** • **Study 10032 (manipulated intranasal)[3]**	• Study 1085 (manipulated oral)[2] • Study 10032 (manipulated intranasal)[3]

1. Compared to Vicoprofen®; 2. Compared to hydrocodone API; 3. Compared to hydrocodone API and Zohydro® ER

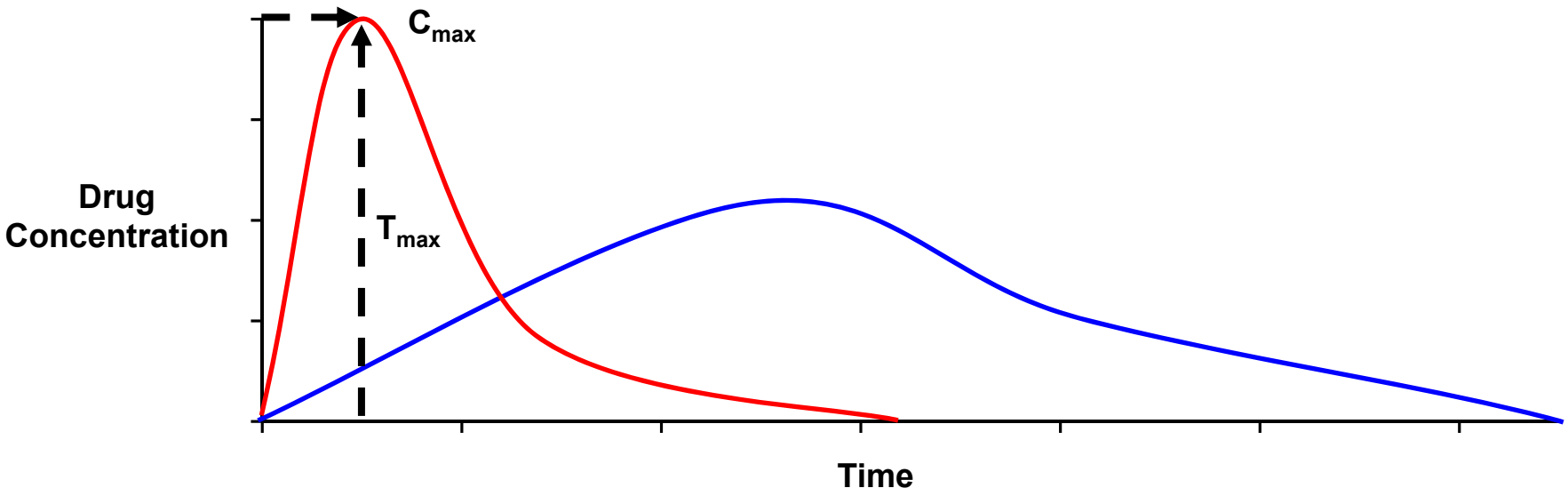
No Dose Dumping of Intact Oral Vantrela ER Tablet with Alcohol

Study 1076 – Oral 15 mg dose (N=30)



Rate of Rise May Contribute to Differential Abuse Potential

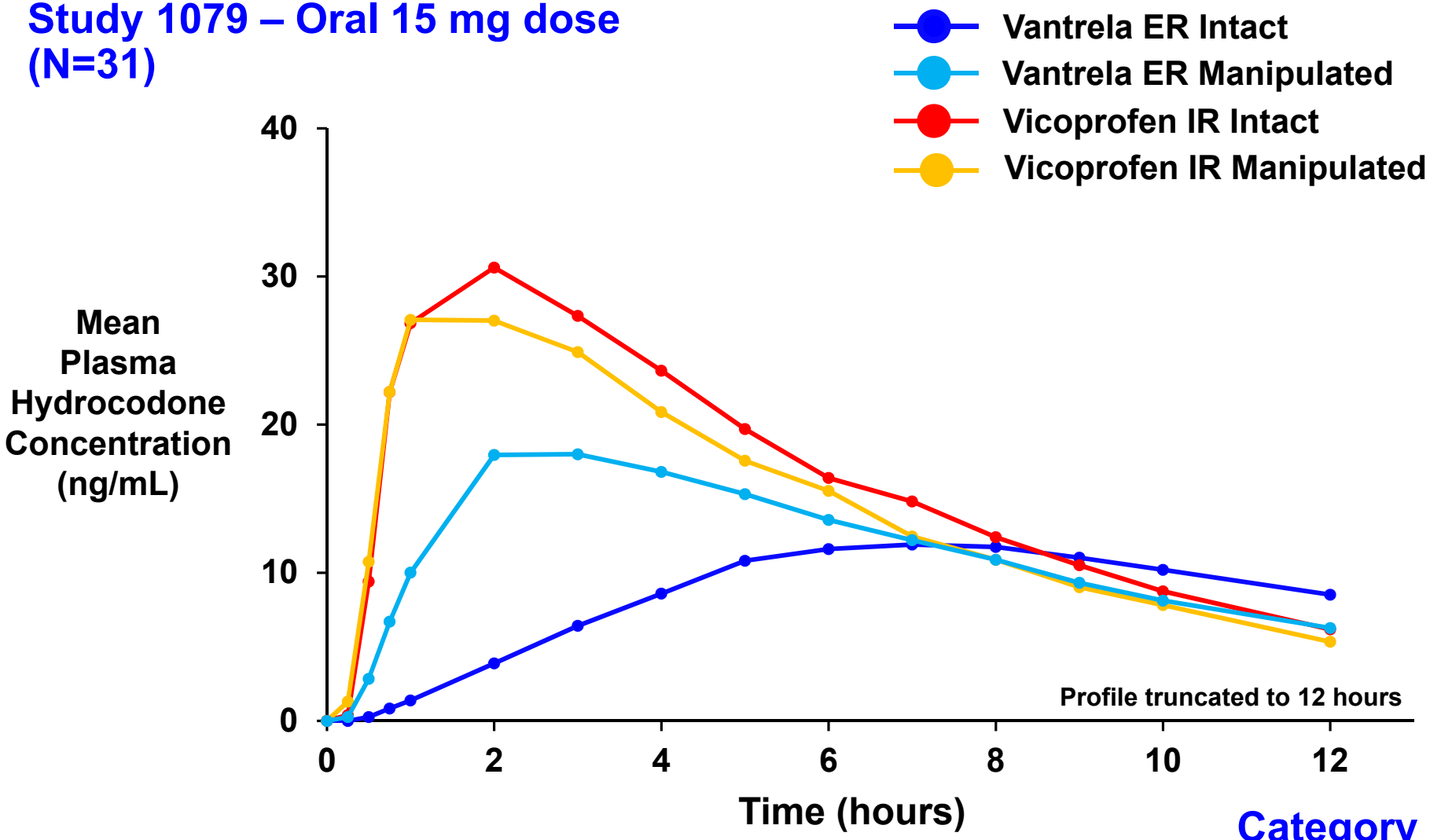
- Category 2 PK data intended to measure ‘rate of rise’, peak and early concentrations, as measured by
  - Early concentrations and partial AUCs
  - C_{max} and T_{max}



Webster, 2015.

Manipulated Oral Vantrela ER Showed Lower Peak Concentration Than IR Vicoprofen®

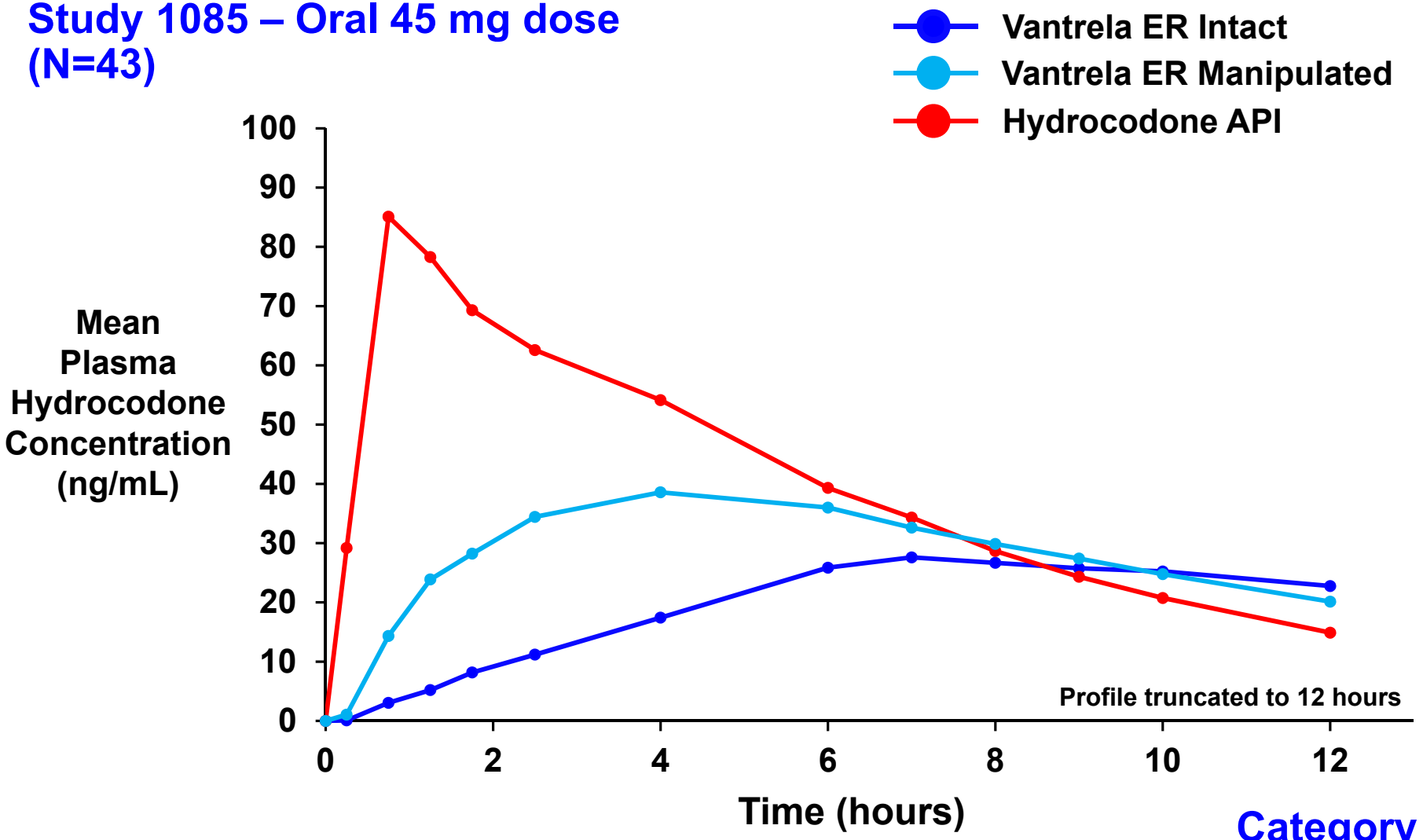
Study 1079 – Oral 15 mg dose (N=31)



Category 2

Manipulated Oral Vantrela ER Showed Lower Peak Concentration Than Hydrocodone API

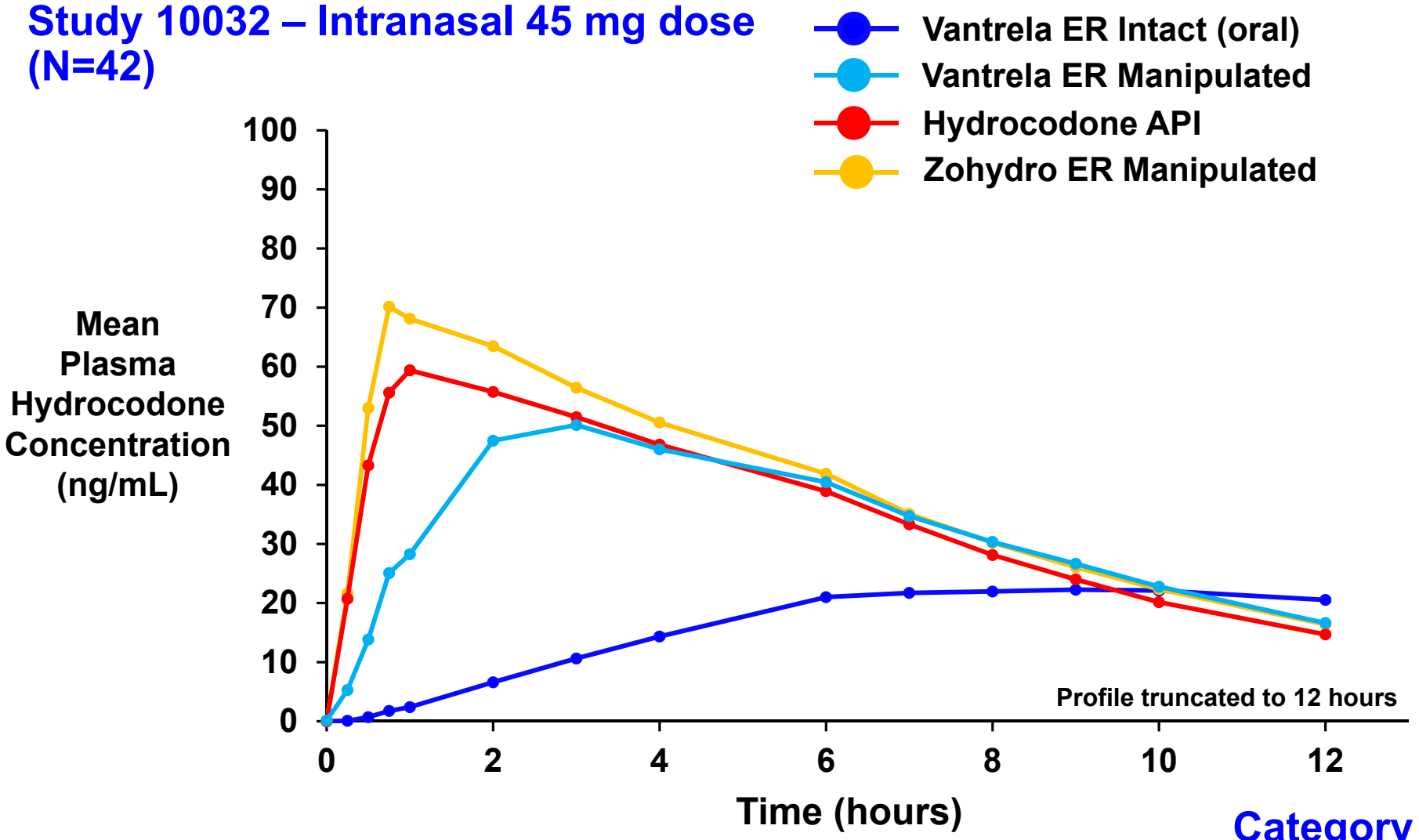
Study 1085 – Oral 45 mg dose (N=43)



Category 2

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

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

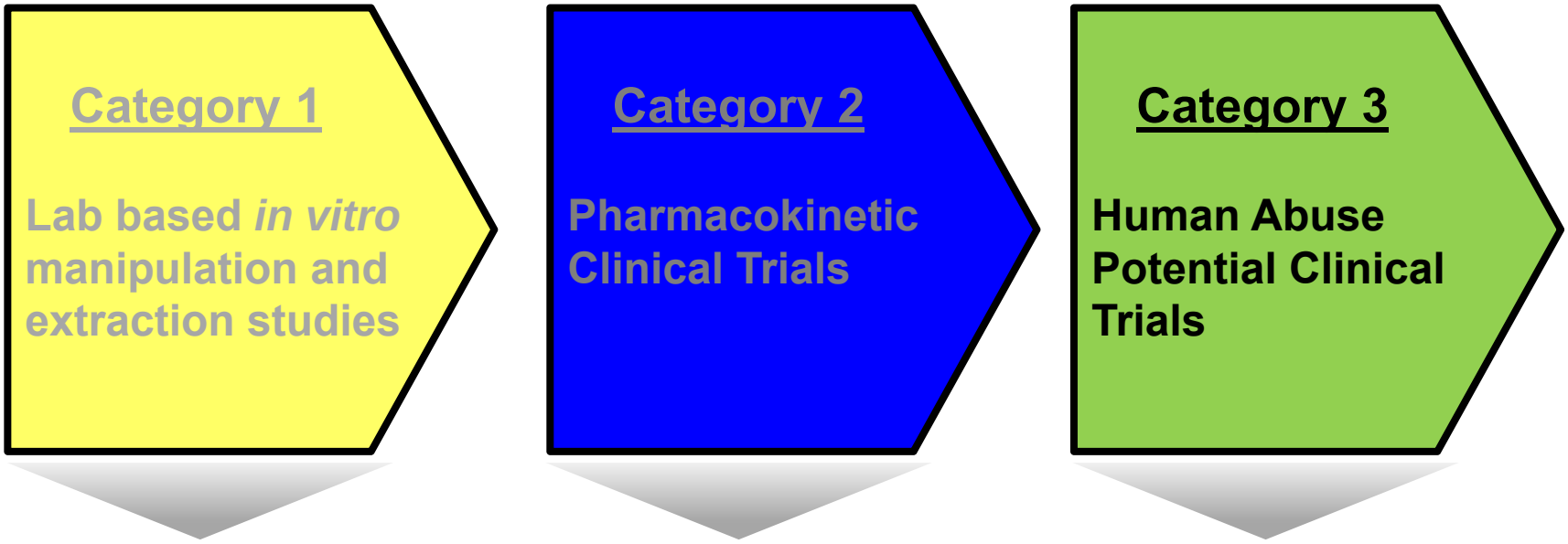


Category 2

Category 2 Conclusions

- Vantrela ER retains extended release properties following manipulation
- Lower extent and rate of rise in hydrocodone concentration following manipulation
  - Lower C_{max}
  - Later T_{max}
  - Lower early hydrocodone exposure

Category 3: Vantrela ER Human Abuse Potential (Oral and Intranasal)



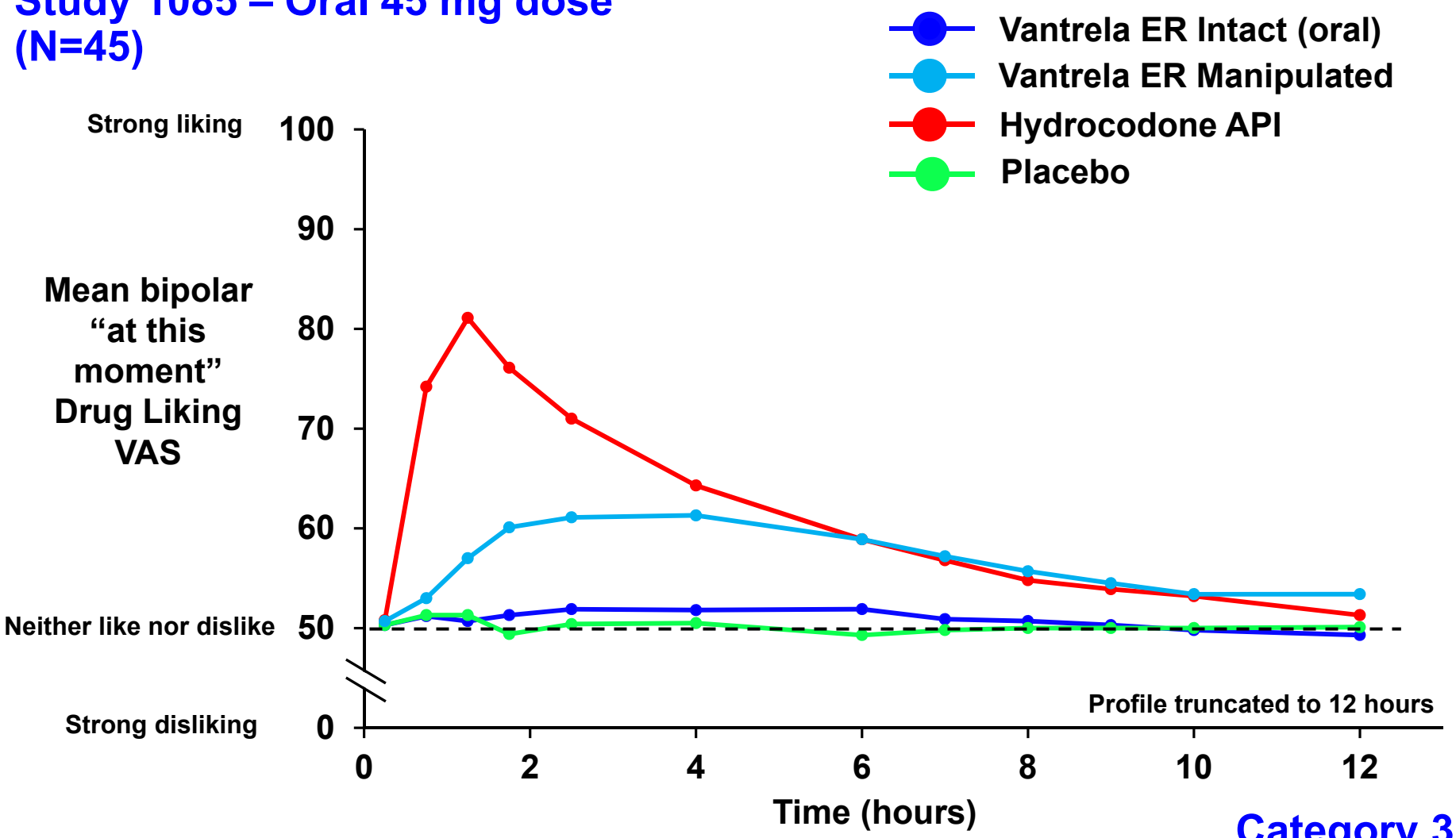
1. Compared to Vicoprofen®; 2. Compared to hydrocodone API; 3. Compared to hydrocodone API and Zohydro® ER

Drug Liking Endpoints to Measure Pharmacodynamic Effects

- Primary endpoint
  - E_{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_{max})
  - Any Effects VAS (E_{max})

Manipulated Oral Vantrela ER had Lower Drug Liking Than Hydrocodone API

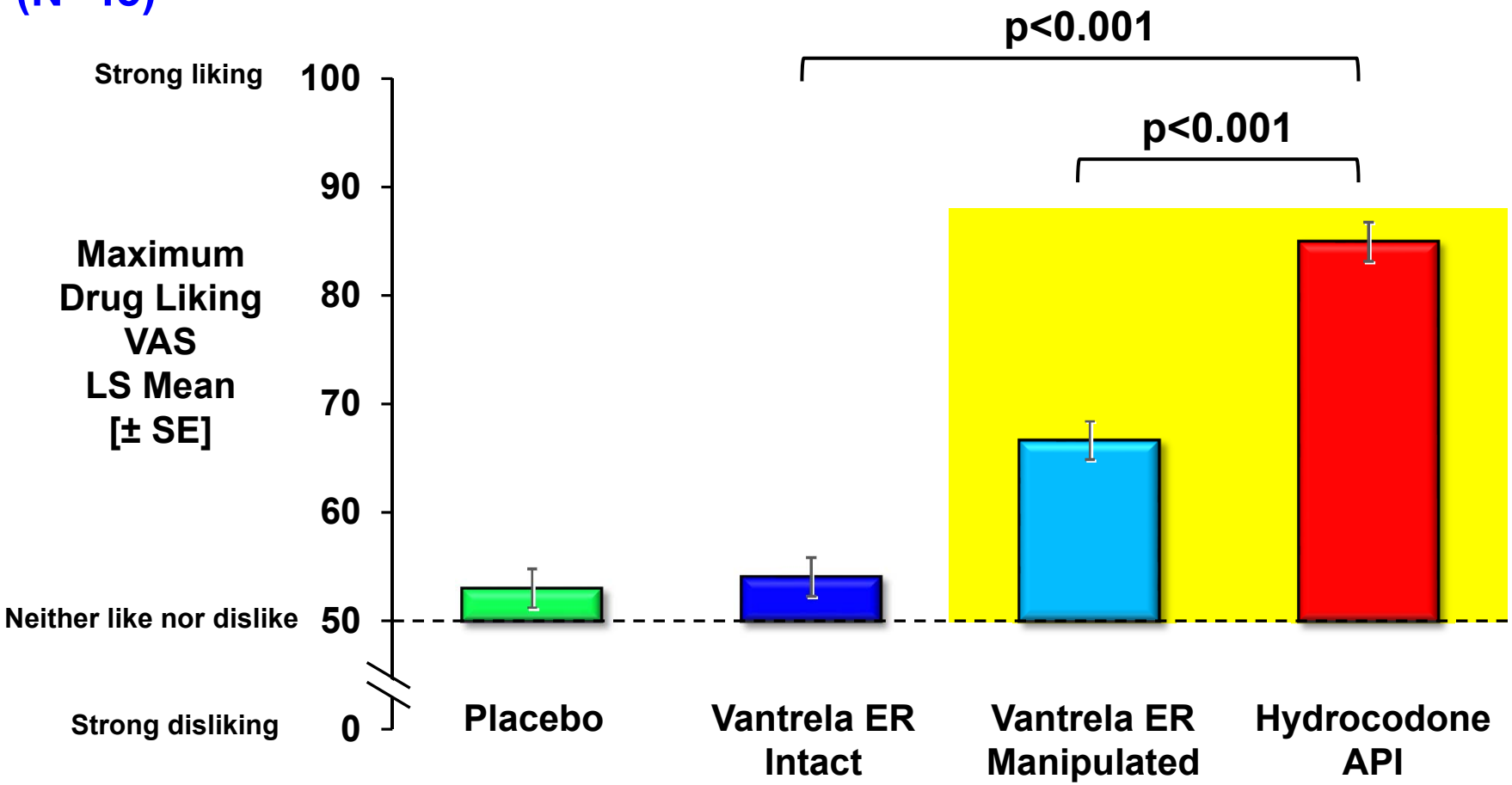
Study 1085 – Oral 45 mg dose (N=45)



Category 3

Lower Drug Liking for Manipulated Oral Vantrela ER Than Hydrocodone API

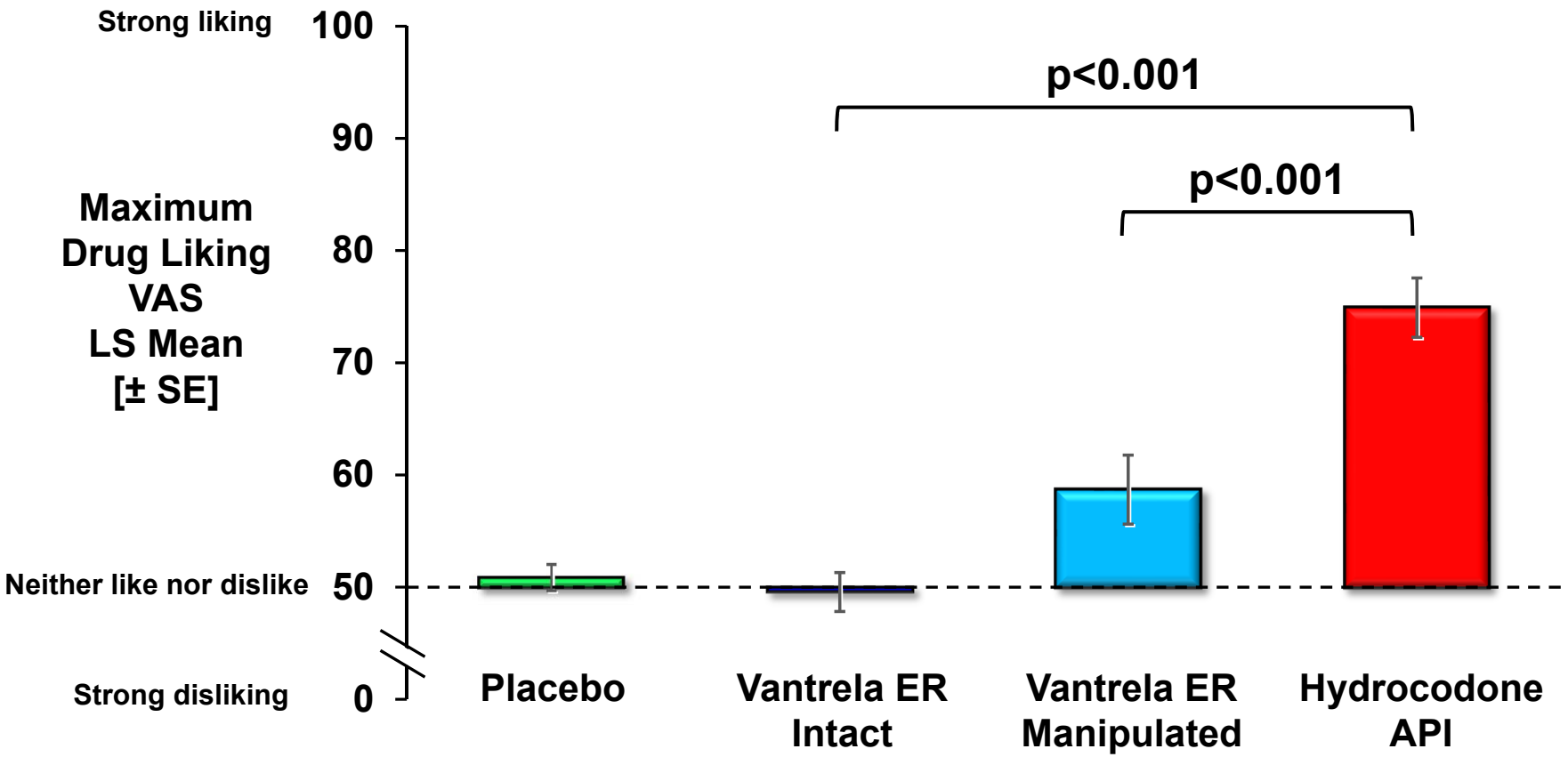
Study 1085 – Oral 45 mg dose (N=45)



Category 3

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

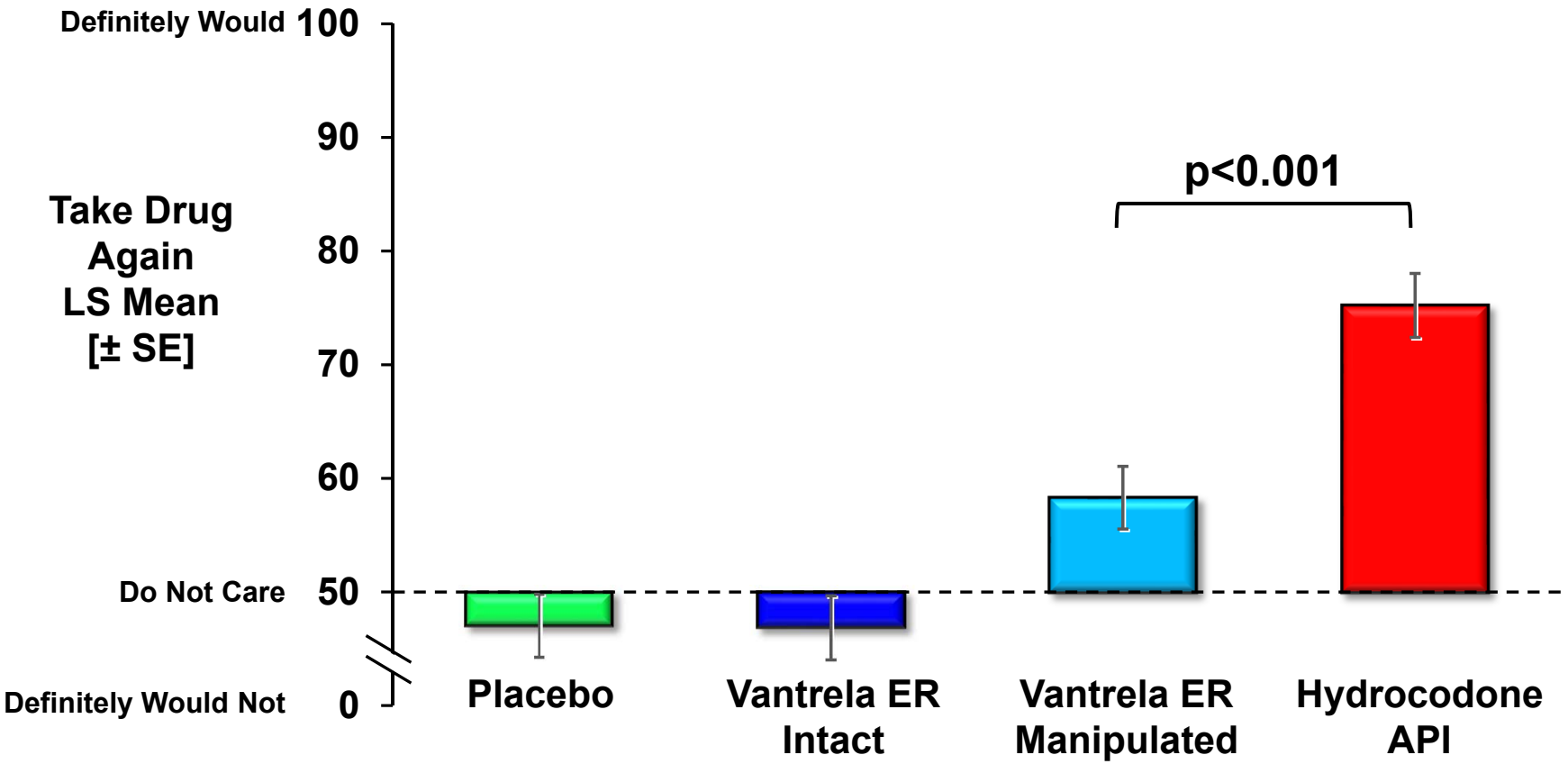
Study 1085 – Oral 45 mg dose (N=45)



Category 3

Lower Take Drug Again for Manipulated Oral Vantrela ER Than Hydrocodone API

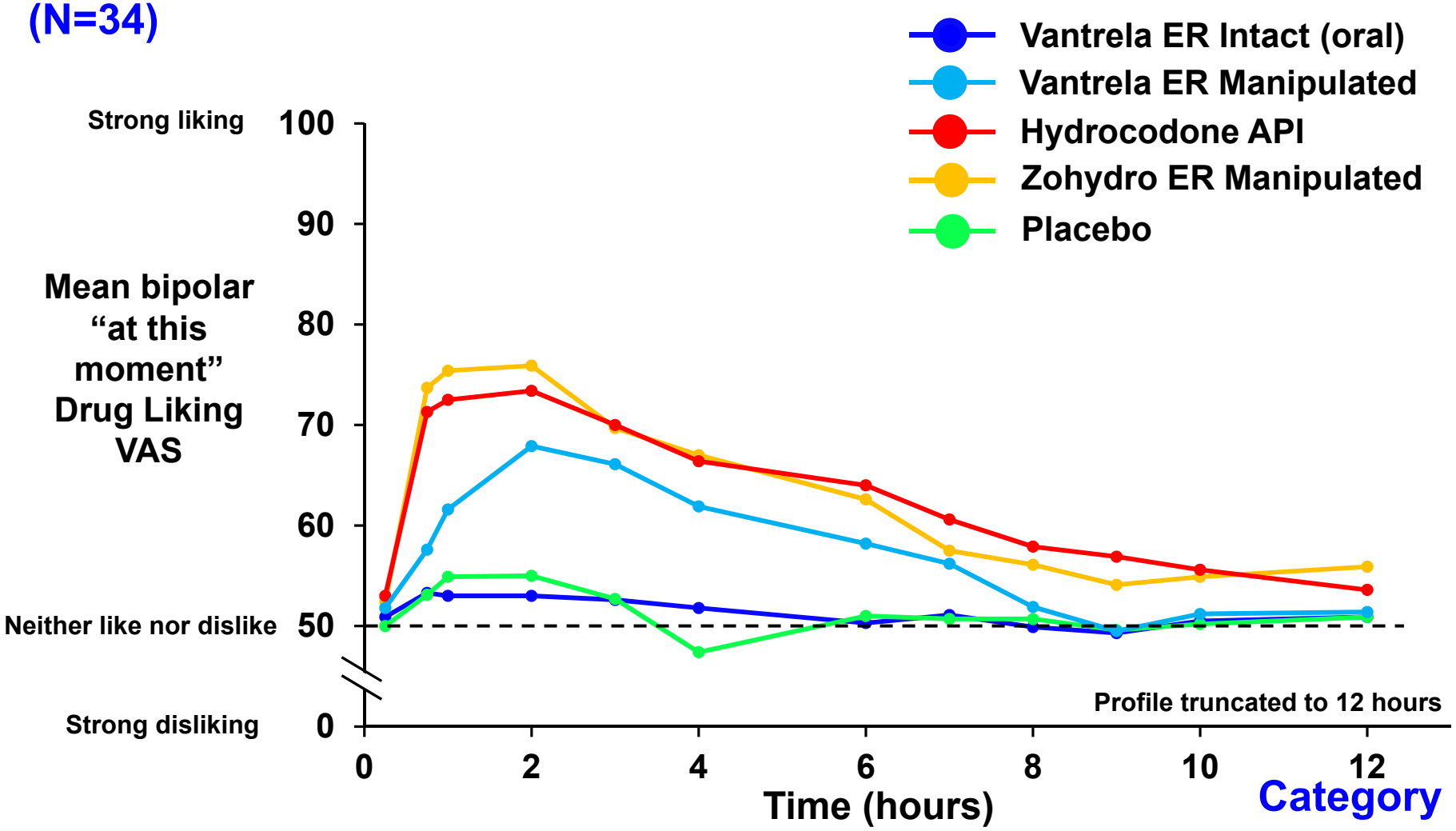
Study 1085 – Oral 45 mg dose (N=45)



Category 3

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

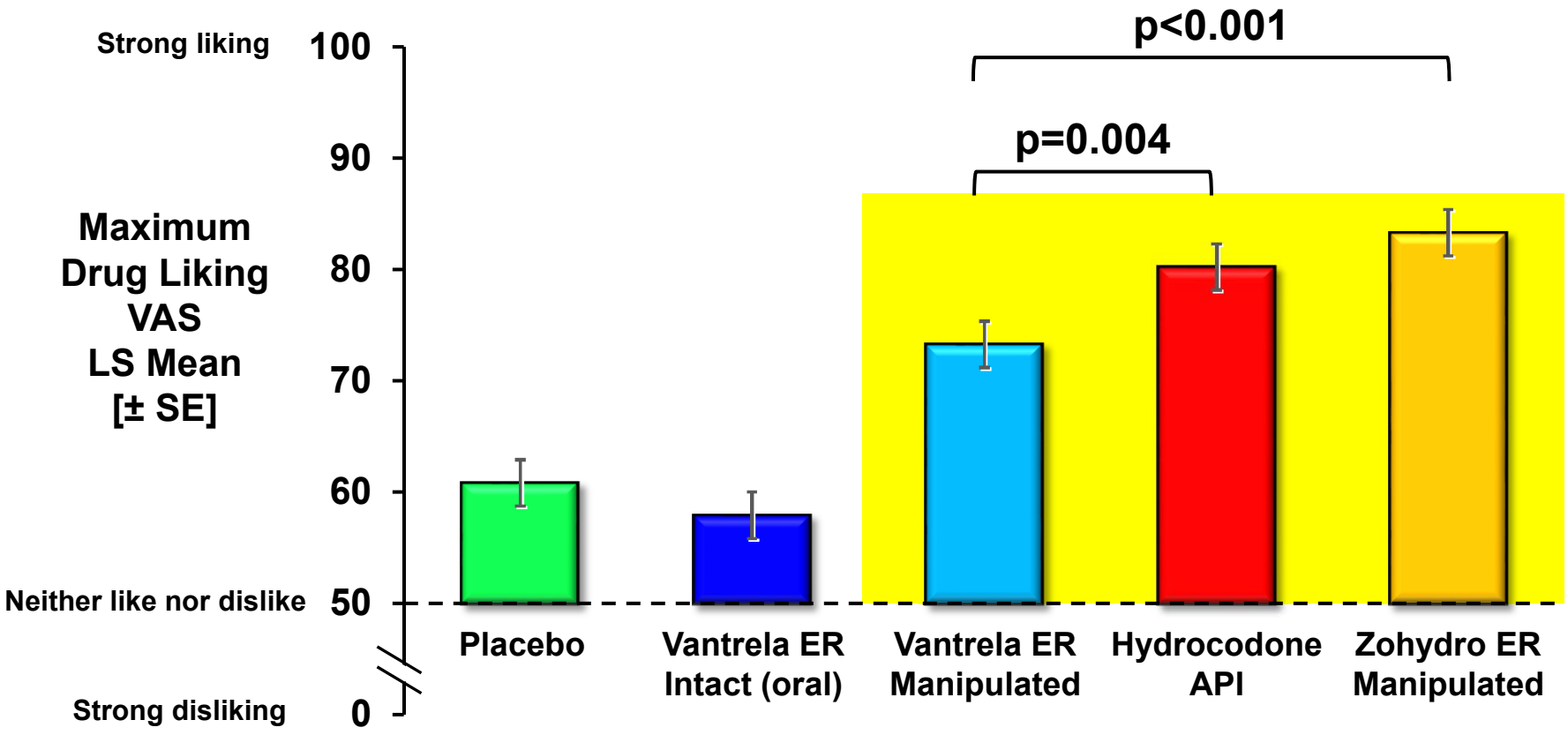
Study 10032 – Intranasal 45 mg dose (N=34)



Category 3

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

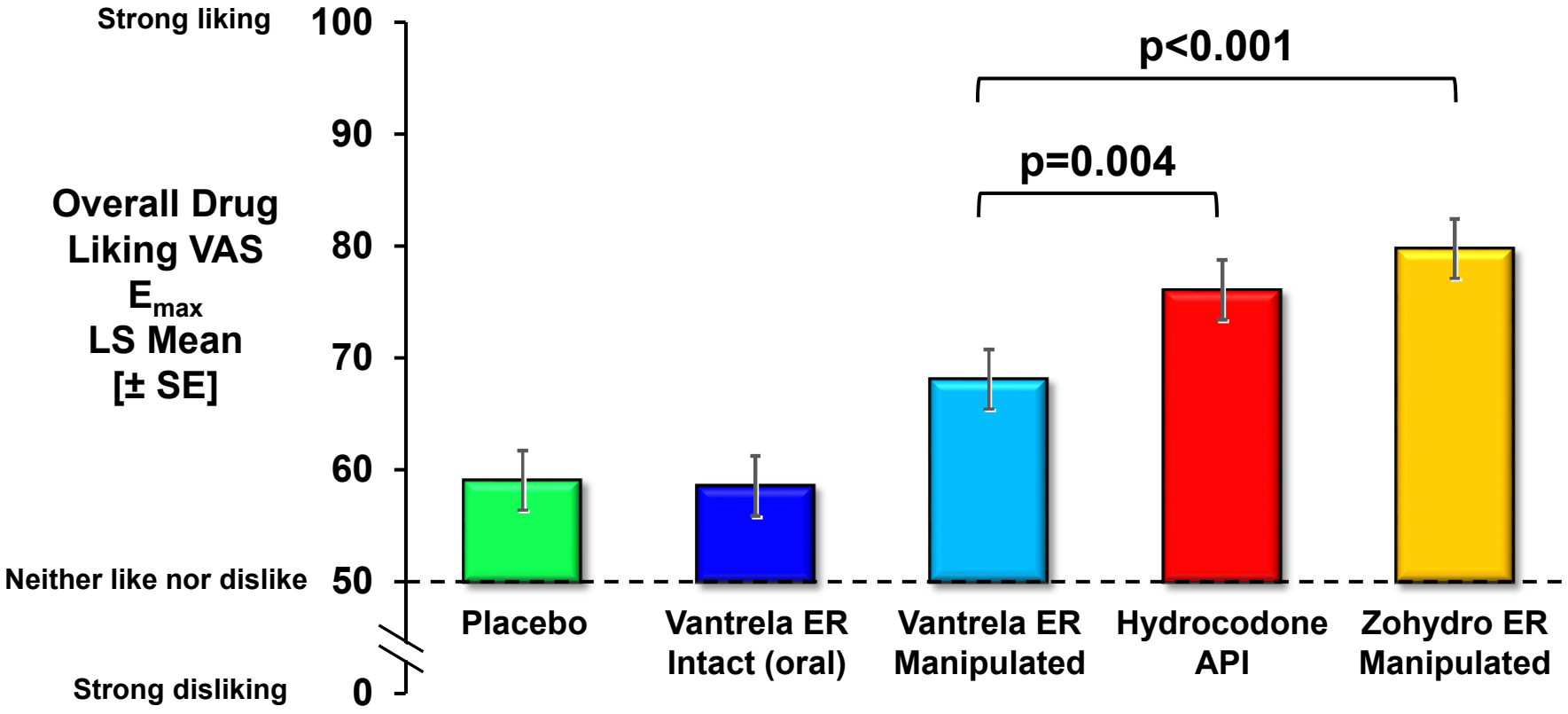
Study 10032 – Intranasal 45 mg dose (N=34)



Category 3

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

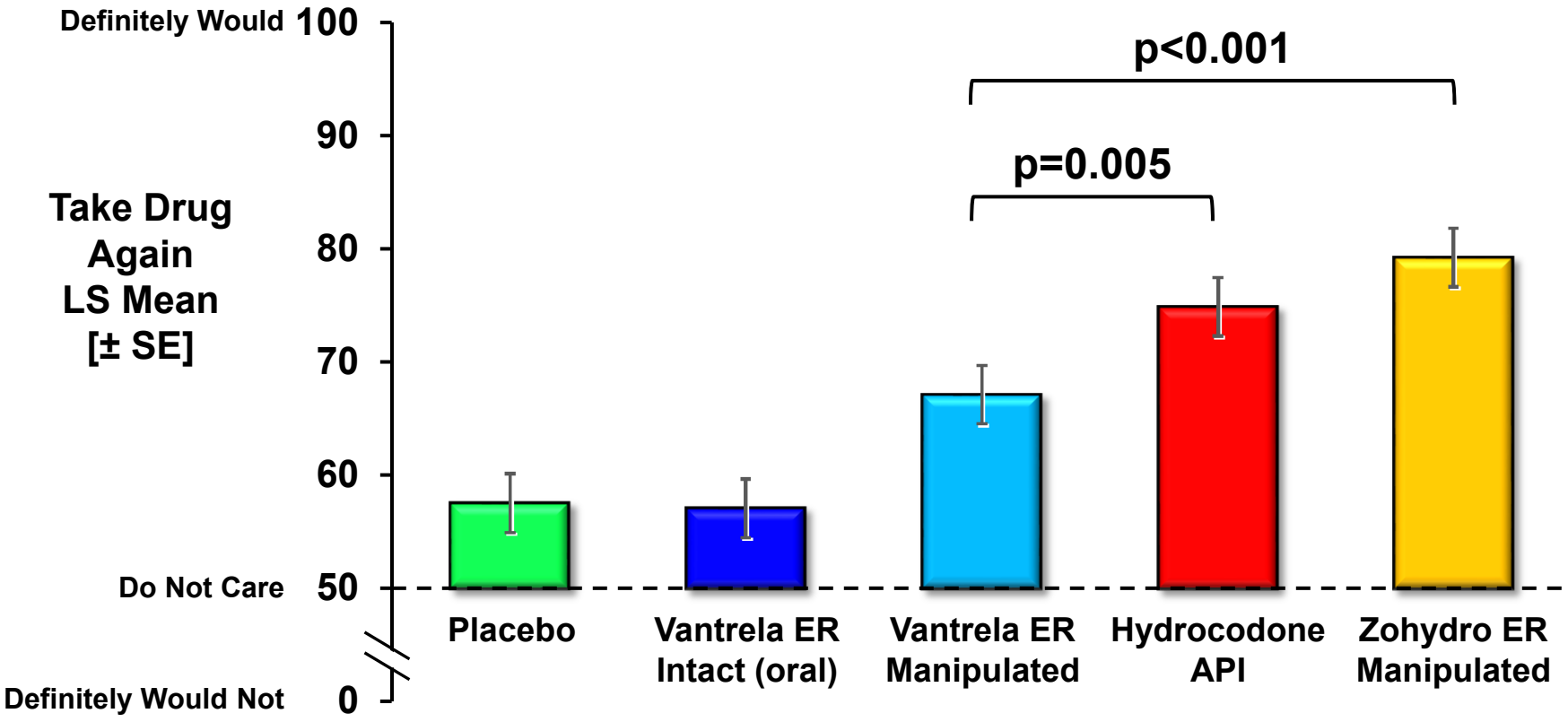
Study 10032 – Intranasal 45 mg dose (N=34)



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)



Category 3

Summary of Key Category 3 Endpoints from Human Abuse Potential Studies

Endpoints	Study 1085 (Oral)	Study 10032 (Intranasal)	
	Manipulated Vantrela ER vs Hydrocodone API	Manipulated Vantrela ER vs Hydrocodone API	Manipulated Vantrela ER vs Manipulated Zohydro® ER
Primary Endpoint			
Drug Liking VAS	-18.3 (<0.001)	-6.8 (0.004)	-9.9 (<0.001)
Primary (10032) / Key Secondary (1085)			
Overall Drug Liking VAS	-16.2 (<0.001)	-8.0 (0.004)	-11.7 (<0.001)
Key Secondary Endpoints			
Take Drug Again VAS	-16.9 (<0.001)	-7.8 (0.005)	-12.1 (<0.001)
Good Effects (E_{max})	-39.7 (<0.001)	-11.0 (<0.001)[a]	-23.5 (<0.001)[a]
Any Effects (E_{max})	-40.7 (<0.001)	-13.4 (0.006)	-22.5 (<0.001)

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_{max} and later T_{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

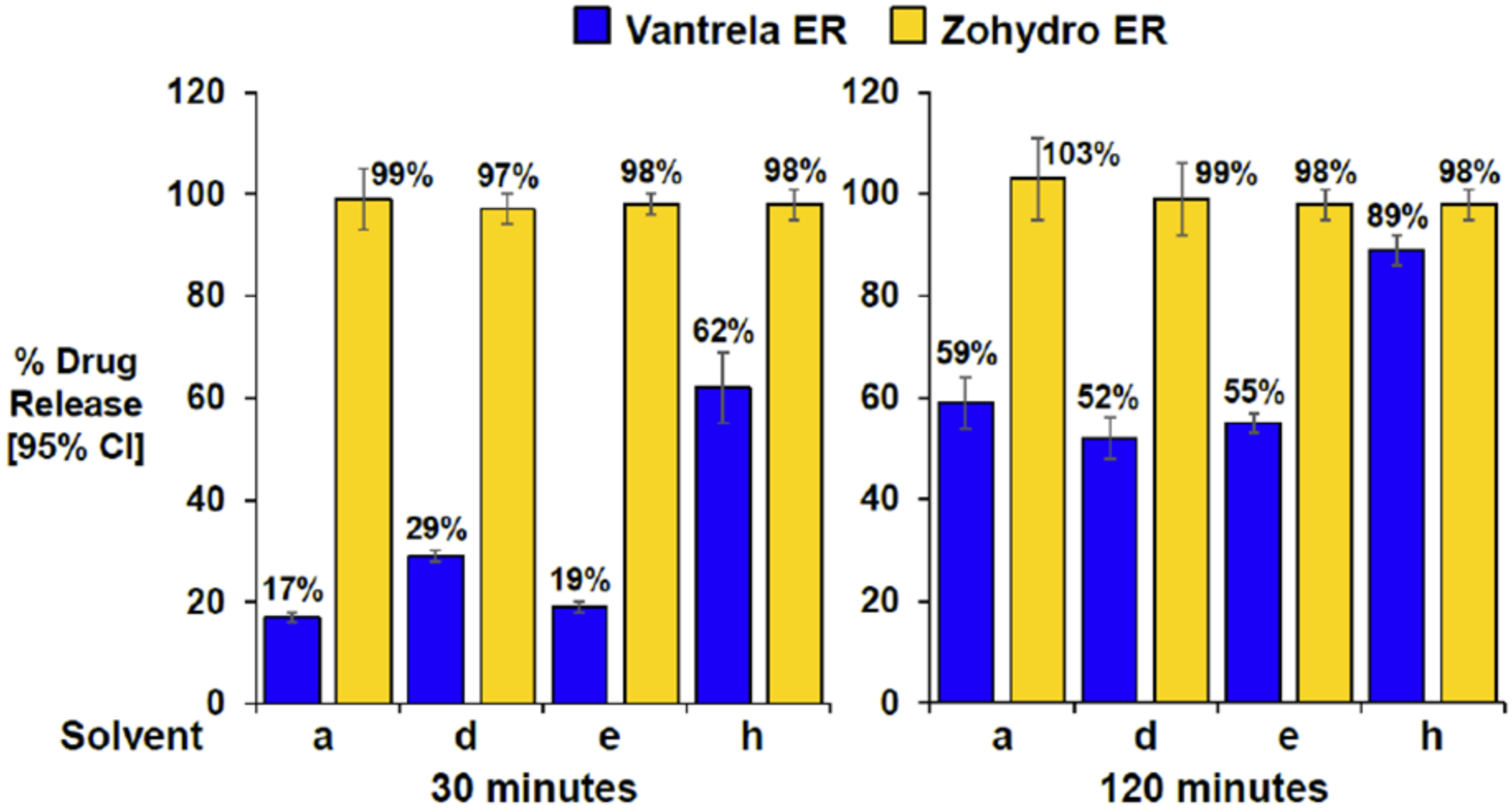
June 7, 2016

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



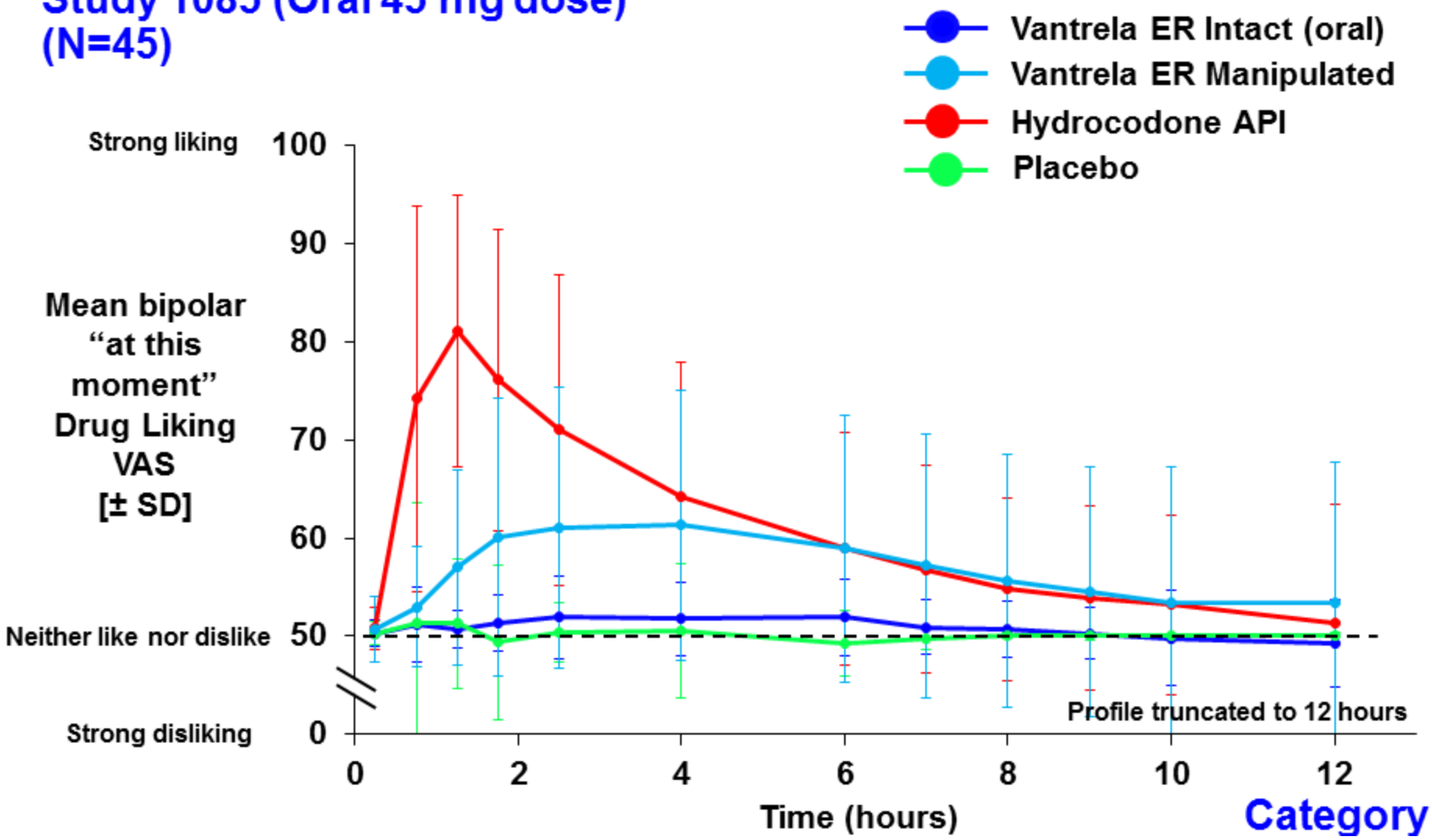
CI=confidence interval; ER=extended-release.

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

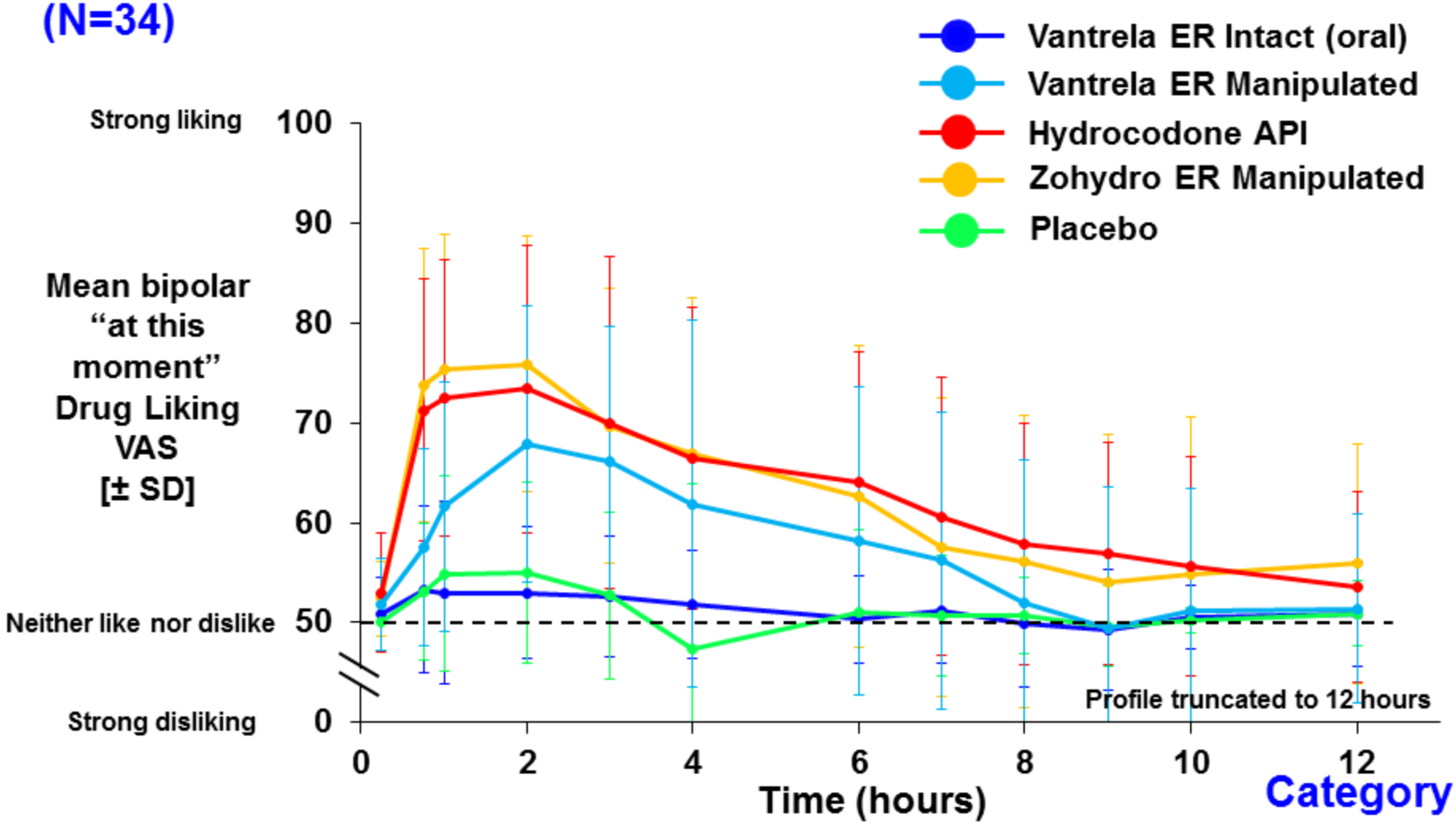
Study 1085 (Oral 45 mg dose) (N=45)



Category 3

Manipulated Intranasal Vantrela ER Had Lower Drug Liking Than Comparators

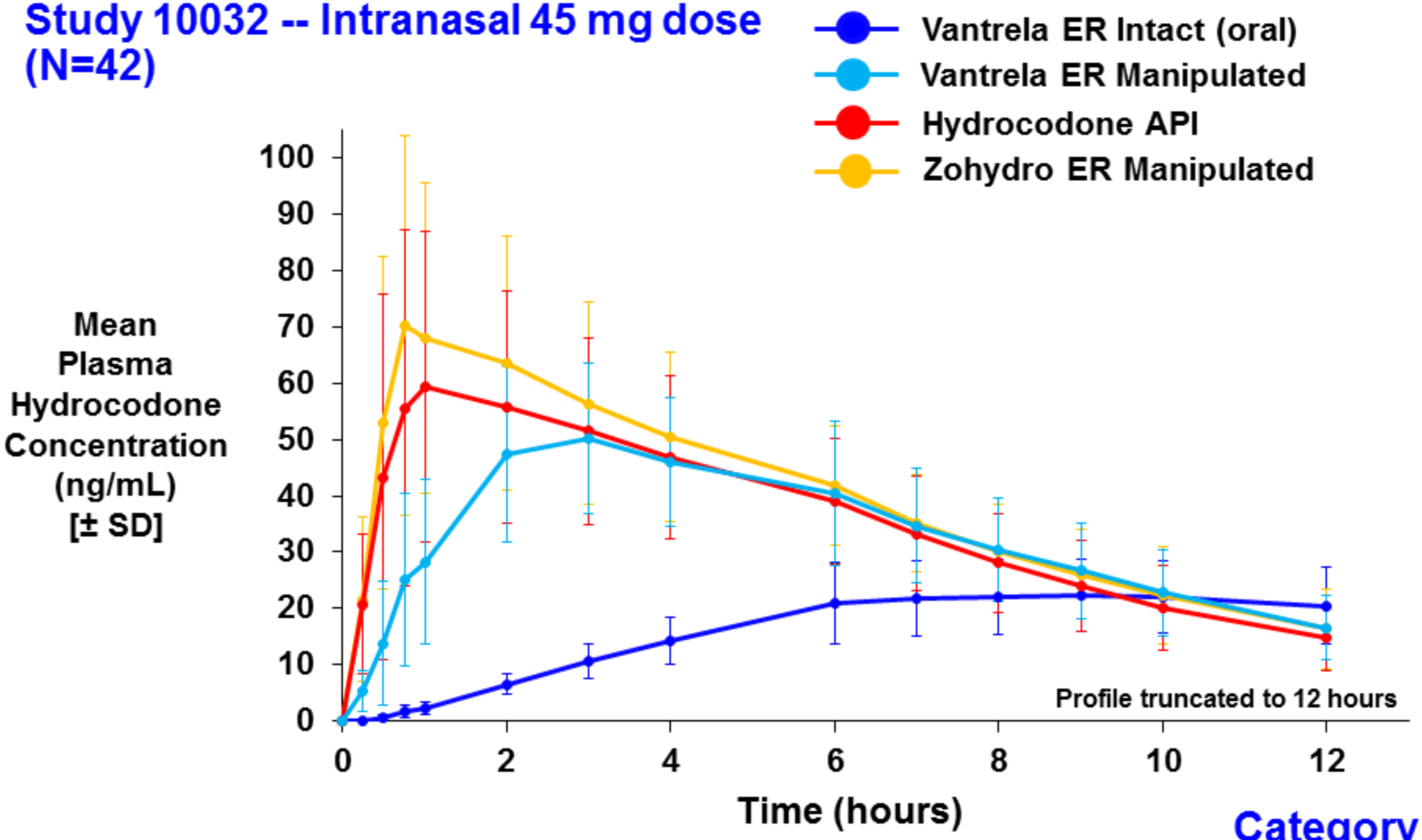
Study 10032 (Intranasal 45 mg dose) (N=34)



Category 3

Manipulated Intranasal Vantrela ER Showed Lower Peak Concentration than Hydrocodone API and Zohydro® ER

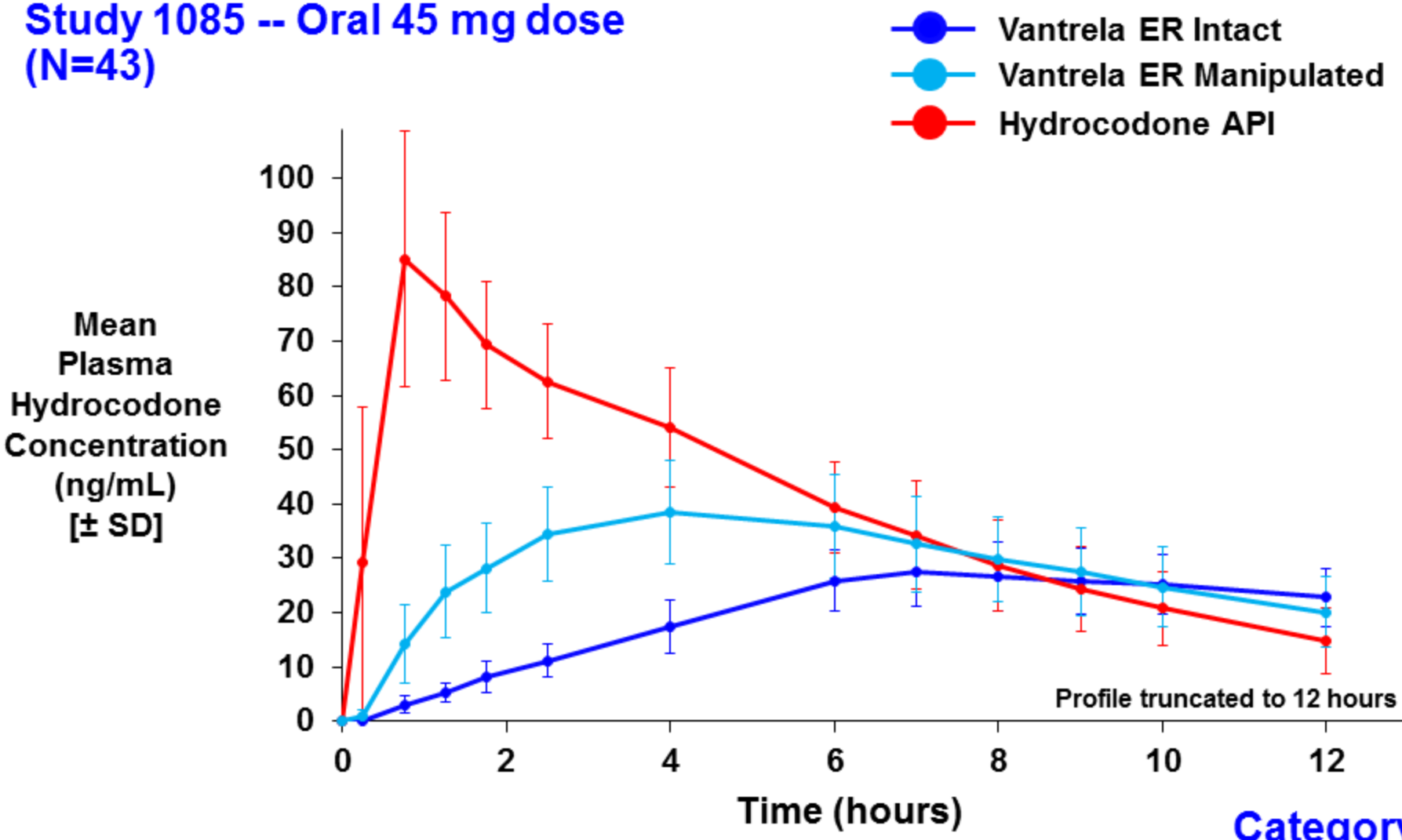
Study 10032 -- Intranasal 45 mg dose (N=42)



Category 2

Manipulated Oral Vantrela ER Showed Lower Peak Concentration Than Hydrocodone API

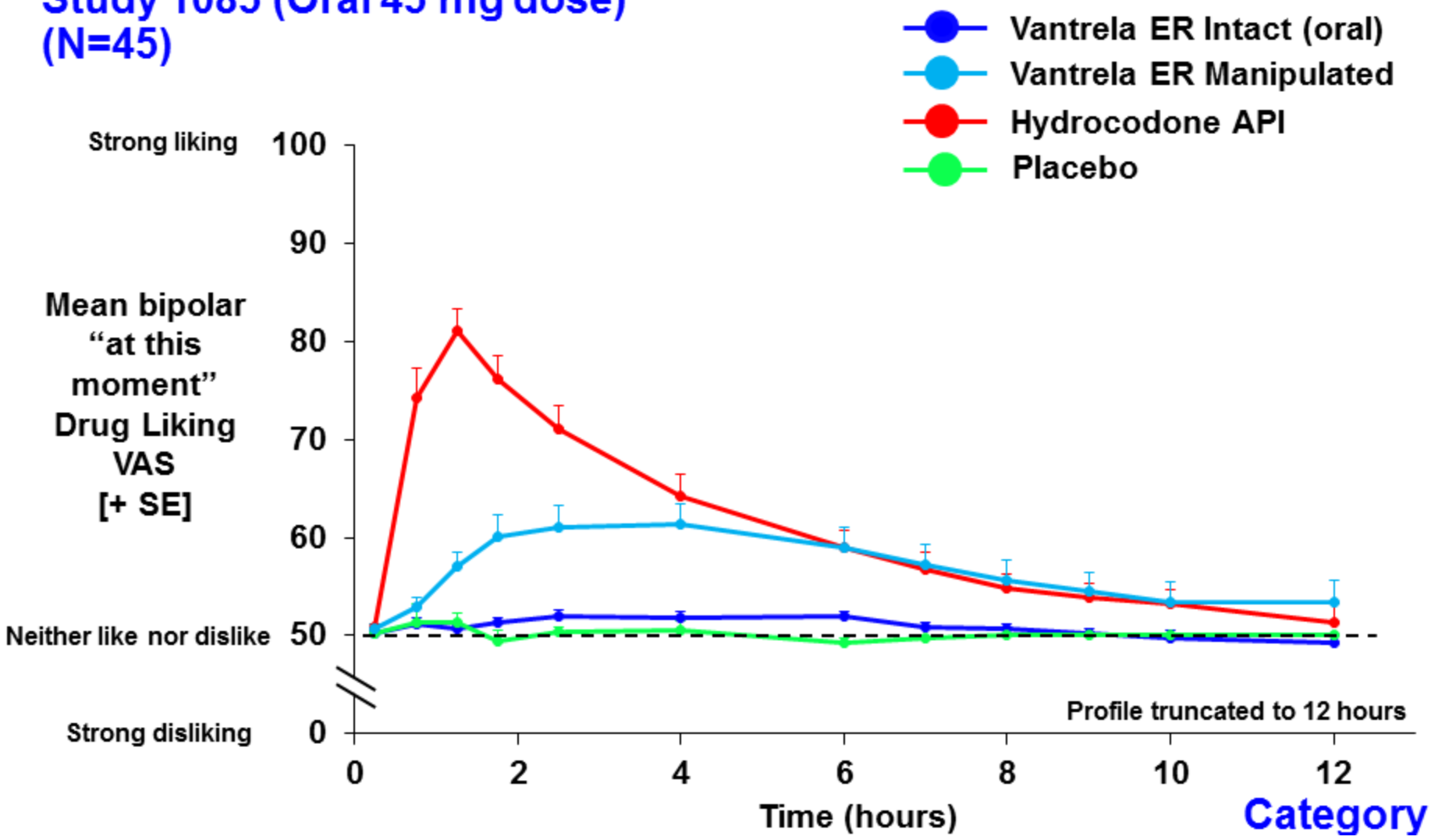
Study 1085 -- Oral 45 mg dose (N=43)



Category 2

Manipulated Oral Vantrela ER Had Lower Drug Liking Than Hydrocodone API

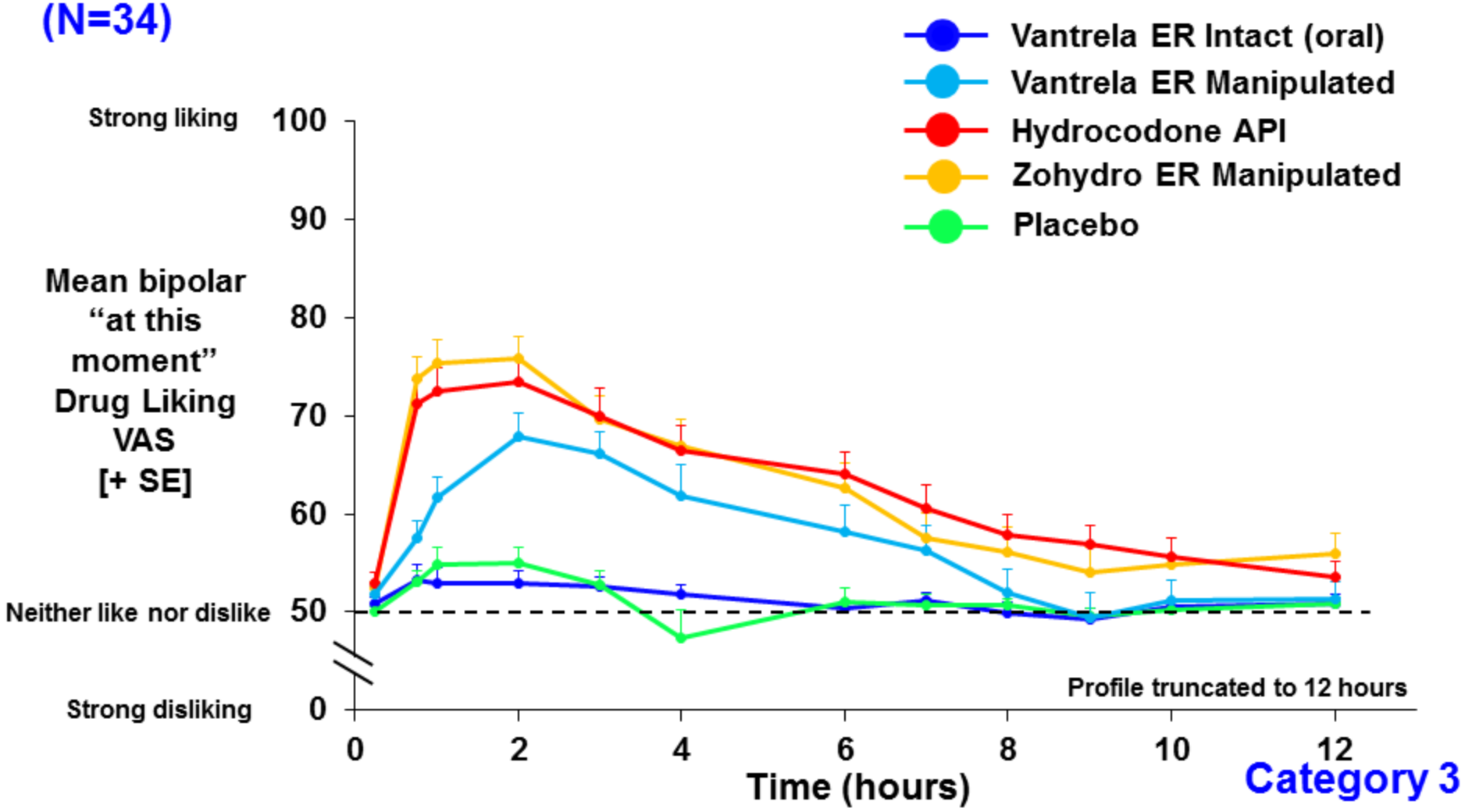
Study 1085 (Oral 45 mg dose) (N=45)



Category 3

Manipulated Intranasal Vantrela ER Had Lower Drug Liking Than Comparators

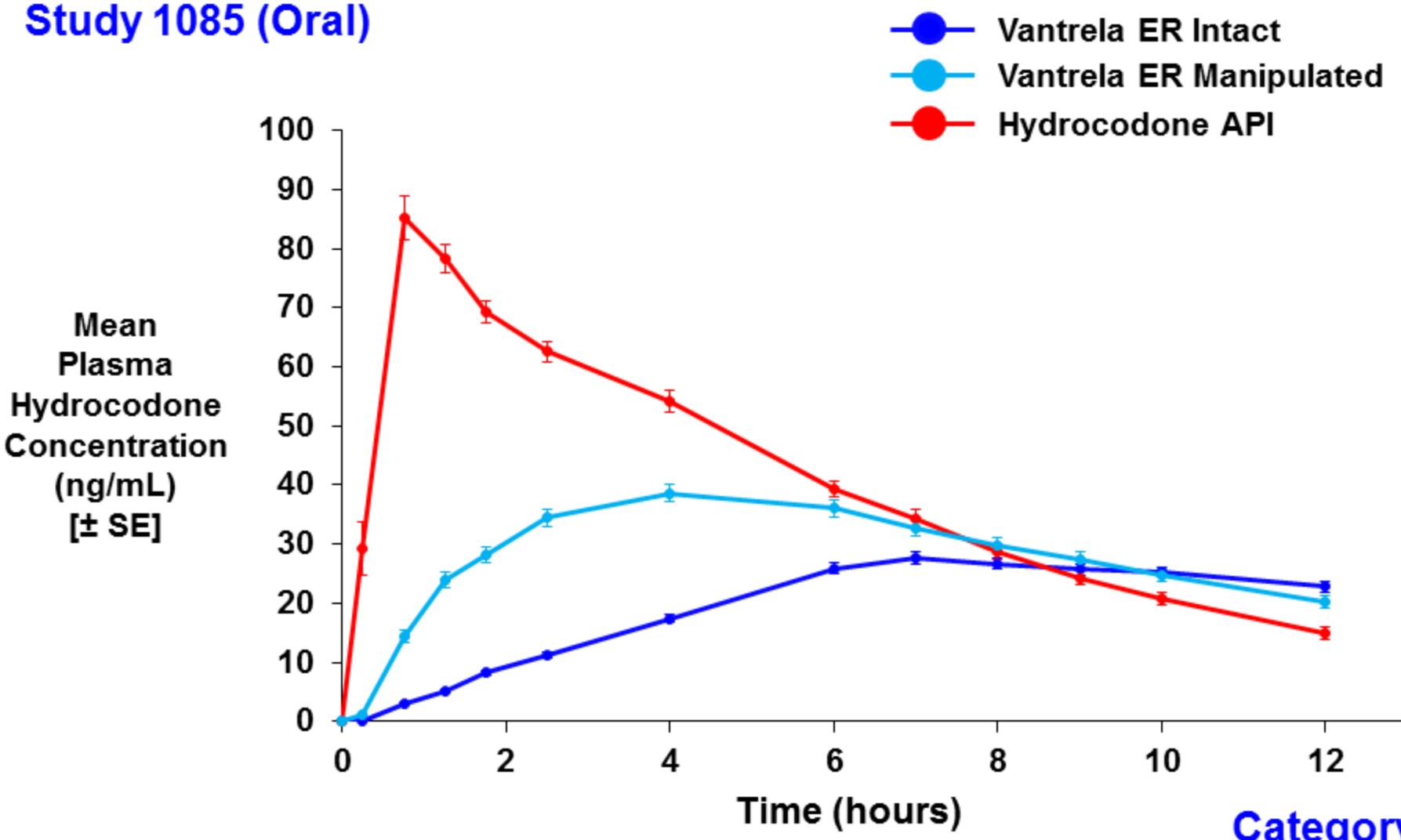
Study 10032 (Intranasal 45 mg dose) (N=34)



Category 3

Manipulated Oral Vantrela ER Showed Lower Peak Concentration than Hydrocodone API

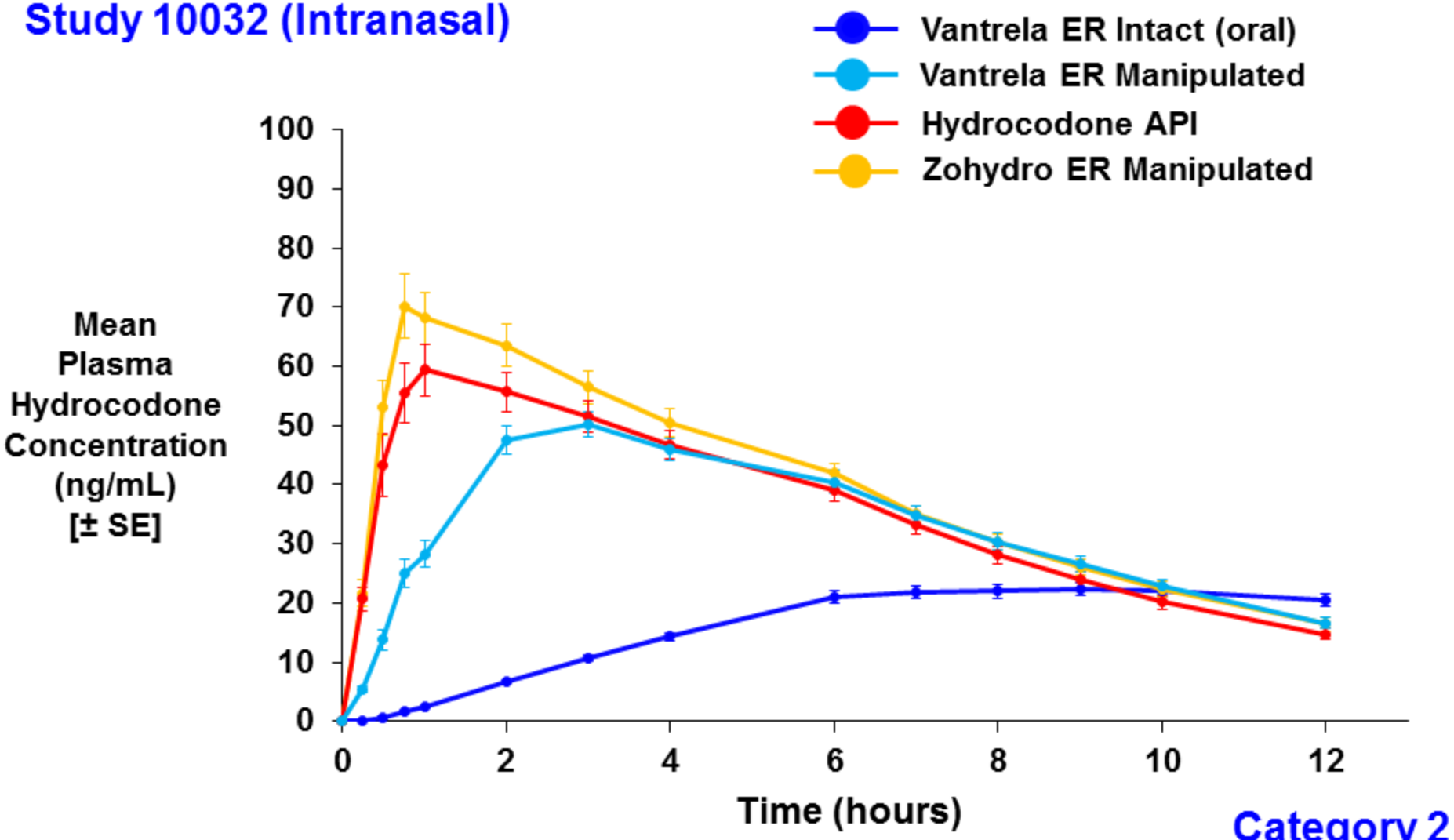
Study 1085 (Oral)



Category 2

Manipulated Intranasal Vantrela ER Showed Lower Peak Concentration than Hydrocodone API and Zohydro® ER

Study 10032 (Intranasal)



Category 2