REMOXY™ ER (oxycodone)
Abuse Deterrent, Extended-Release Capsules

FDA Advisory Committee Meeting

June 26, 2018

Introduction

Remi Barbier
Founder and CEO
Pain Therapeutics, Inc.

Agenda

Remi Barbier	**Introduction**
Michael Crowley, PhD	**In vitro Abuse Deterrence**
Lynn Webster, MD	**In vivo Abuse Deterrence**
Nadav Friedmann, PhD, MD	**Clinical Development**
Stephen Montgomery, PhD	**Excipient Risk Assessment**
Michael Marsman, PharmD	**Risk Mitigation and Summary**

About Us

- **Pain Therapeutics, Inc. is the sponsor of REMOXY ER**
- **We are a clinical-stage company based in Austin, TX**
- **Our research programs are focused primarily on CNS drug discovery and development**

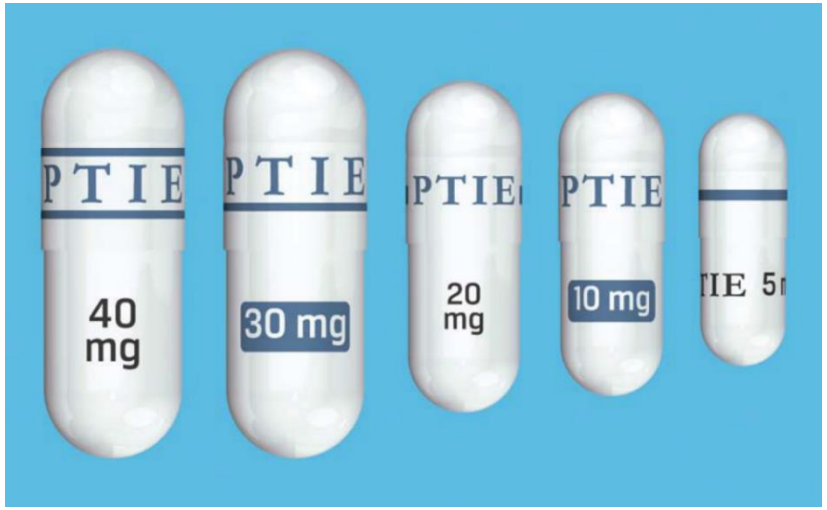
Disclosures

- **The term “abuse-deterrent” as used in these materials is not intended to designate a medical claim but rather a general description of properties to address the misuse, abuse and diversion of opioids.**

- **Consultants who are presenting for the Sponsor have a financial relationship, such as payment of professional fees, expenses, honoraria or an equity interest, that may be perceived as a conflict of interest:**

  - Michael Crowley, PhD
  - Lynn Webster, MD
  - Stephen B. Montgomery, PhD

REMOXY ER



- **REMOXY ER is in registration with the FDA as an extended-release capsule formulation of oxycodone.**
- **REMOXY ER has properties which are expected to deter formulation abuse.**
- **The Sponsor seeks label claims against abuse by the injection, snorting and smoking routes of abuse.**

Abuse Deterrence

- **FDA Guidance Document defines abuse deterrent properties as "*those properties shown to meaningfully deter abuse, even if they do not fully prevent abuse*."**

- **The design goal of an Abuse Deterrent Formulation (ADF) is a robust extended-release mechanism that resists "dose-dumping" under common conditions of abuse.**

Abuse deterrence is never abuse-proof.

Positive Impact of ADFs

- **Novice abuser:** ADFs can eliminate quick, easy, common methods of formulation abuse, such as crushing.

- **Recreational abusers:** ADFs can discourage abusers from transitioning to non-approved routes of administration, such as snorting, smoking or injection.

- **Advanced abusers:** ADFs can render manipulations more difficult, expensive and time-consuming to abuse, making manipulated drug product less rewarding.

Limitations

- **ADFs alone will not prevent prescription drug abuse.**
  - ADFs represent just one tool within a larger policy framework to improve the safe use of prescription drugs.
- **ADFs do not address longstanding issues with opioids, such as euphoric effects, tolerance, dependence or potential for addiction.**

Abuse Deterrence Needs to Evolve

- **Persistent abuse of prescription opioid drugs indicates a need for more robust ADFs.**

- **Reformulated, ADF OxyContin was approved in 2013.**
  - According to Cicero, "*Although the reformulation produced an immediate drop in abuse rates, a definite ceiling effect appeared over time, beyond which no further decrease was seen.*"[1]

[1] Cicero & Ellis, JAMA 2015 May;72(5):424-30.

Overall Message

- **ADFs can play a critical role in the fight against opioid abuse, while ensuring appropriate access to patients, but additional ADF solutions are needed.**
- **REMOXY ER may:**
  - Advance the science of abuse deterrence
  - Provide additional treatment options for physicians/patients
  - Address vulnerabilities of existing ER oxycodone products
  - Encourage uptake of effective solutions
  - Incentivize technology innovation

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Category 1
In vitro Abuse Deterrence

Michael Crowley, PhD
Acting Vice President, Drug Delivery Technologies
Pain Therapeutics, Inc.

Overview

- **Eleven Category 1 lab studies were conducted, consistent with the FDA Guidance Document.**
- **These studies characterized the abuse-deterrent properties of REMOXY ER, including the degree of effort required to bypass or defeat those properties.**
  - All studies were conducted by 3rd party laboratories.
  - FDA reviewed the protocols and provided input.

Methods

- **Category 1 methods were based on:**
  - The physical and chemical properties of REMOXY ER;
  - Methods and routes of abuse for ER opioids;
  - The FDA Guidance, specific input from FDA experts, clinical and scientific consultants, and recreational opioid abusers.

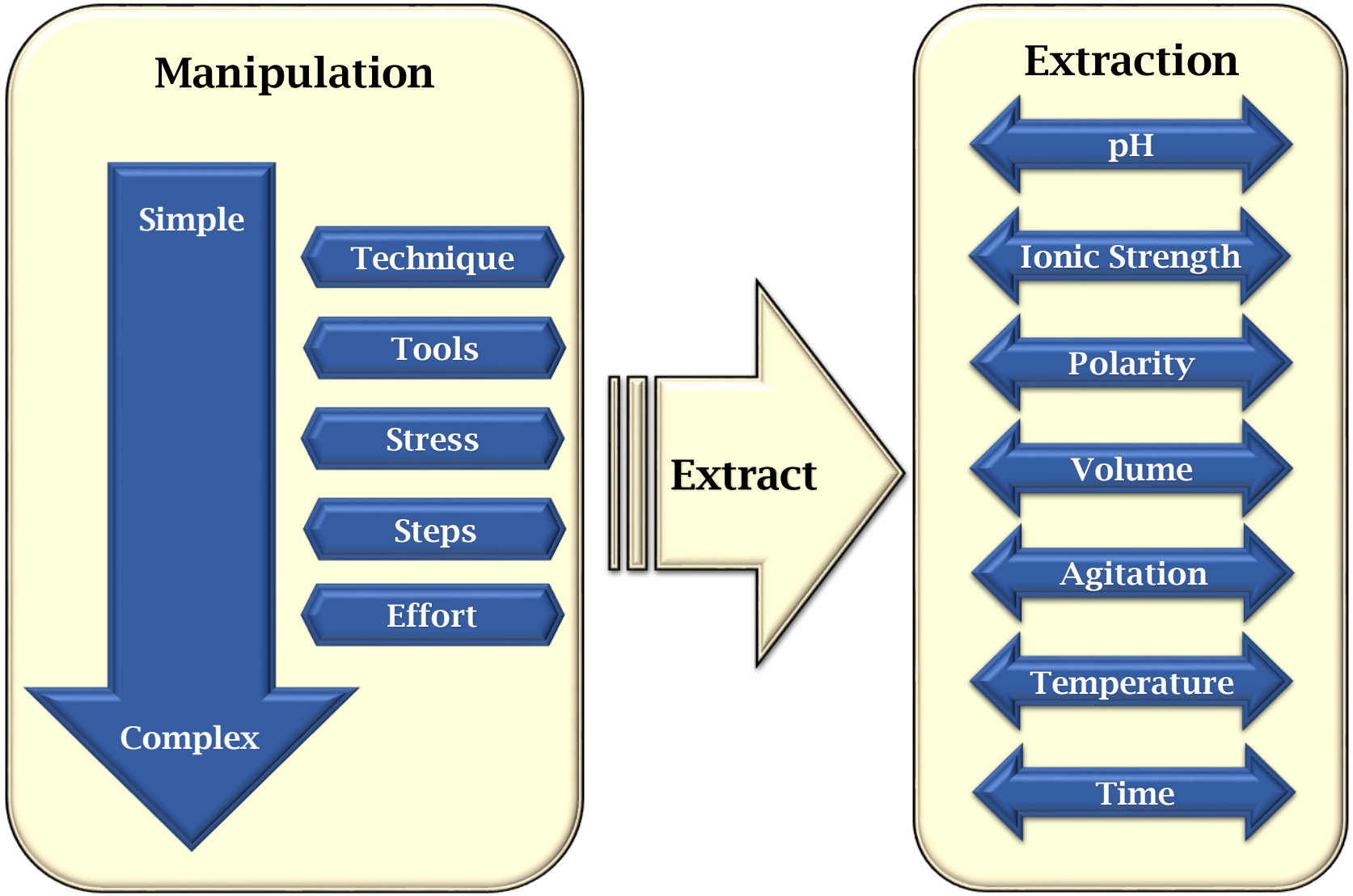
Data Generated

- **> 9,000 unique data points generated.**
- **All results from Category 1 studies are in the REMOXY ER New Drug Application.**
- **Due to time constraints, representative results that include worst case are presented.**
  - Codes for experimental conditions are included in the closed session briefing document.

Comparators

- **The FDA Guidance states, "*Abuse-deterrent properties can generally be established only through comparison to another product.*"**
- **Comparators were OxyContin ER, Xtampza ER or Roxicodone IR.**
  - Intact and manipulated

Comprehensive Category 1 Studies



Routes of Abuse Studied

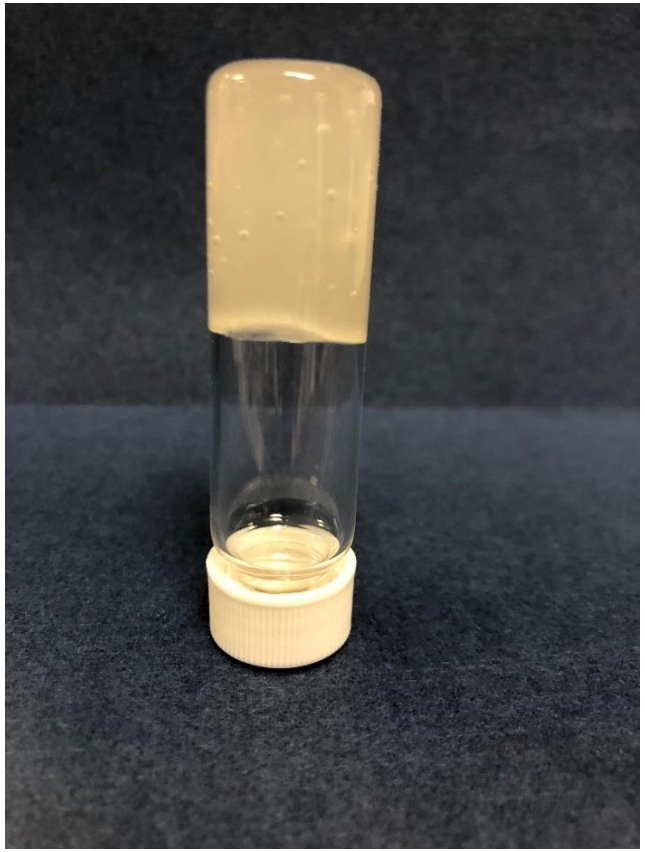
Route of Abuse	Abuse Practice	Study Objective
Oral	Manipulated, Volume D Extractions	Impact of tools Evaluate drug extraction
Injection	Syringe & Injection	Assess syringeability and injectability
	Manipulated, Volume A, B & C Extractions	Impact of tools Evaluate drug extraction
Nasal	Manipulated	Solidify Reduce particle size
Smoking	Simulated Inhalation	Quantify drug vaporized

Conditions Evaluated

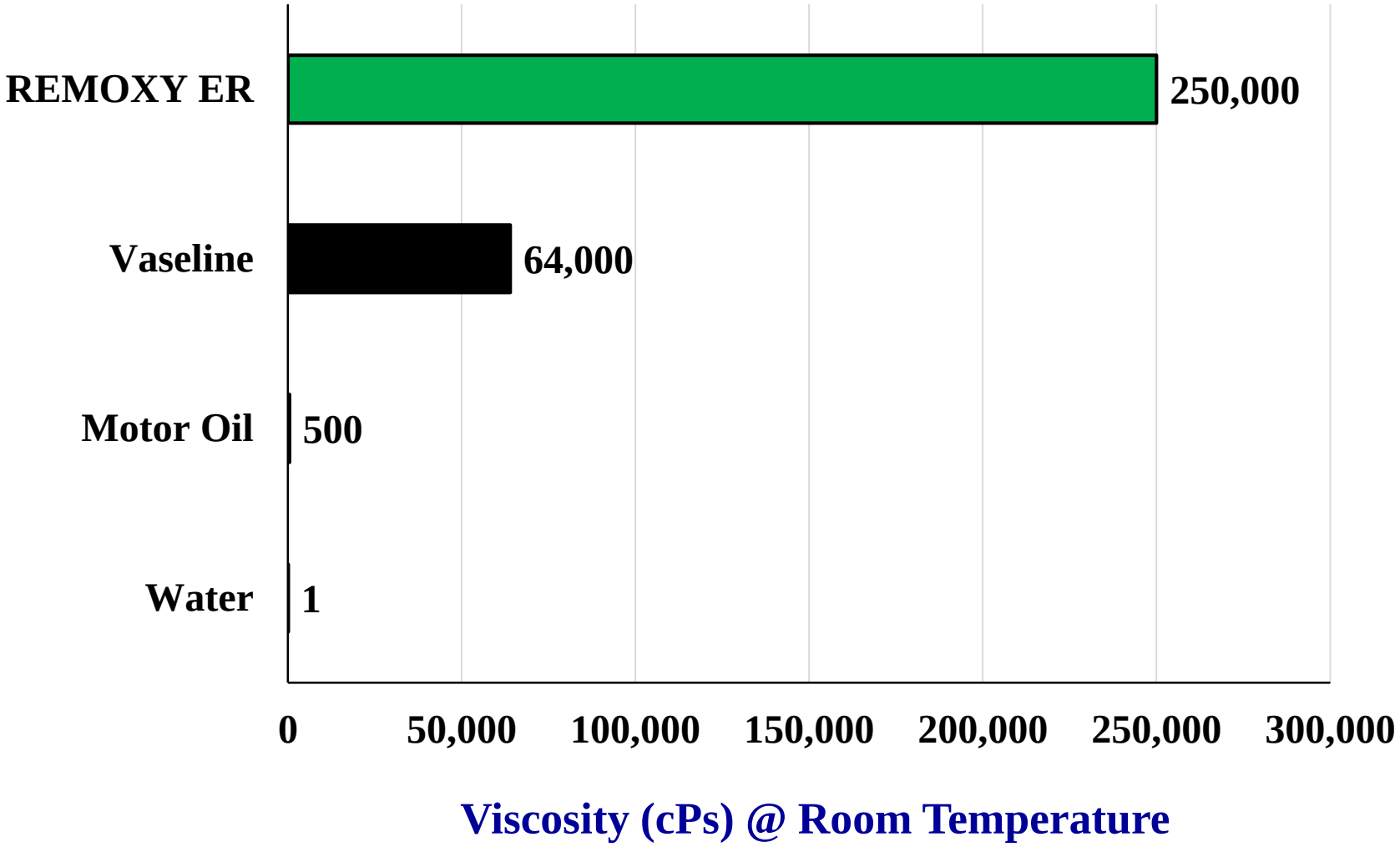
- **Abuse deterrent properties were evaluated by:**
  - 12 Manipulation Methods
  - 24 Tools
  - 3 Stress Conditions
  - 24 Solvents
  - 4 Solvent Volumes
  - 4 Agitation Methods
  - 4 Extraction Temperatures
- **Per Guidance, REMOXY ER was tested to failure**

REMOXY ER Properties

- **REMOXY ER's high viscosity formulation does not flow.**
  - Difficult to snort, syringe or inject
- **REMOXY ER is sticky.**
  - 20 to 30% loss of mass
- **Smoking REMOXY ER liberates irritating vapors and oxycodone degrades.**

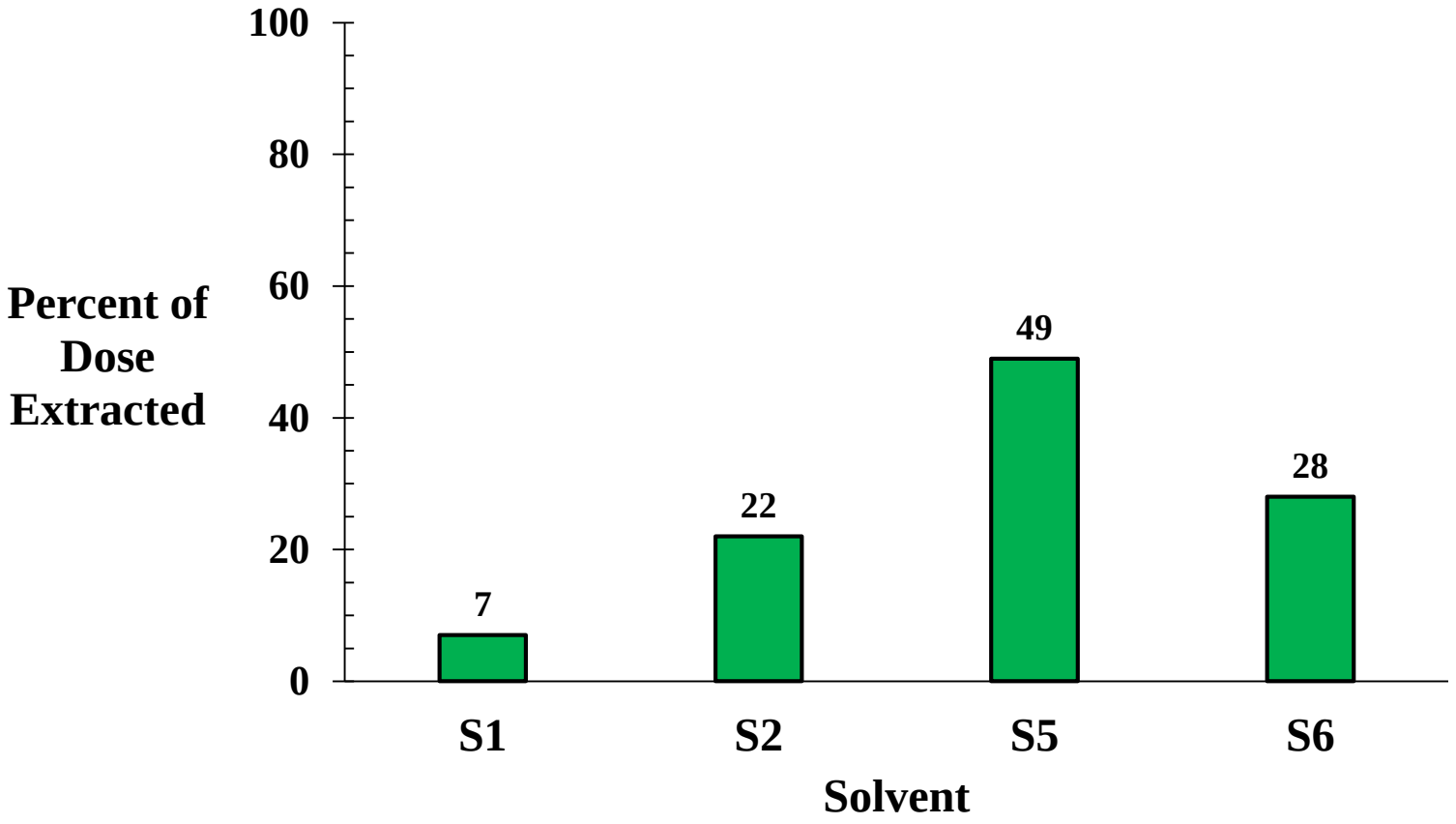


4X Thicker than Vaseline™



Oral Abuse Simulation

Oxycodone extraction from *Intact* REMOXY ER after soaking for Time O using Mixing A

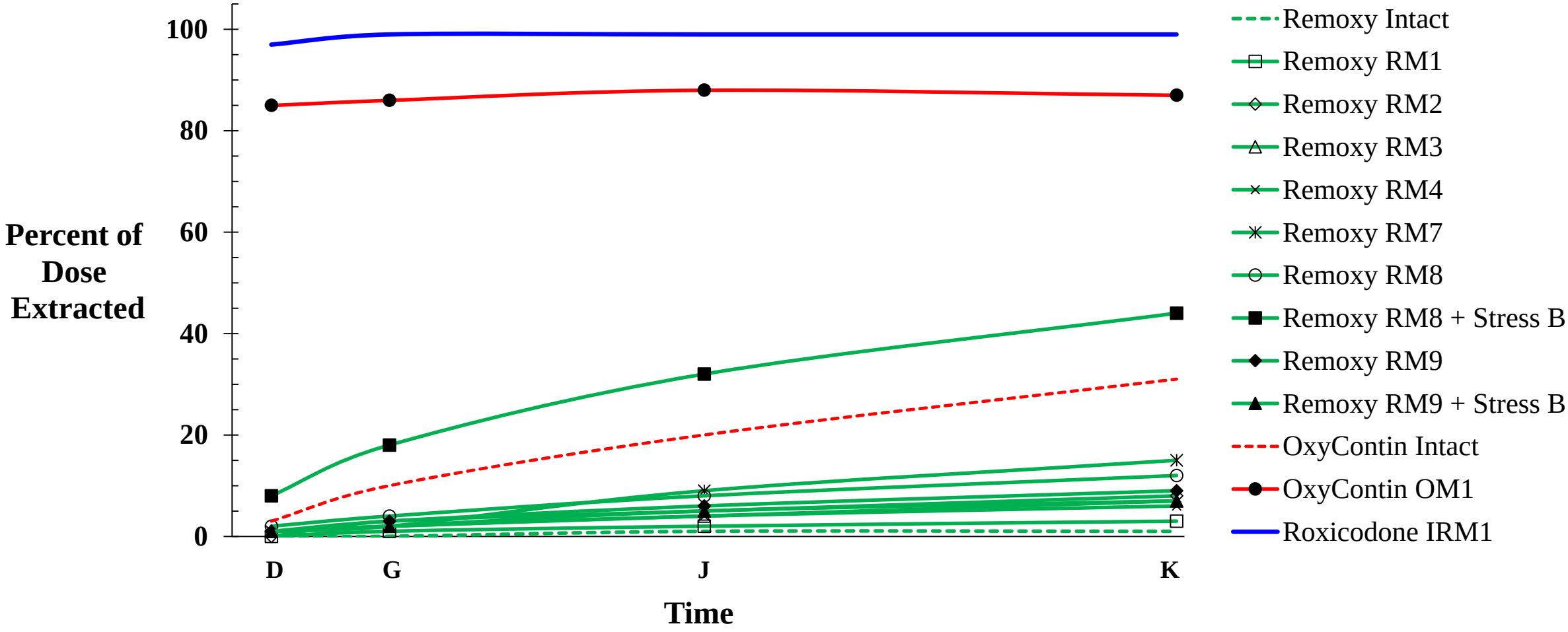


Intact REMOXY ER after soaking in Solvent S6 for Time O

Study Conditions: Volume D, Temperature B, Mixing A

Oral Abuse Simulation

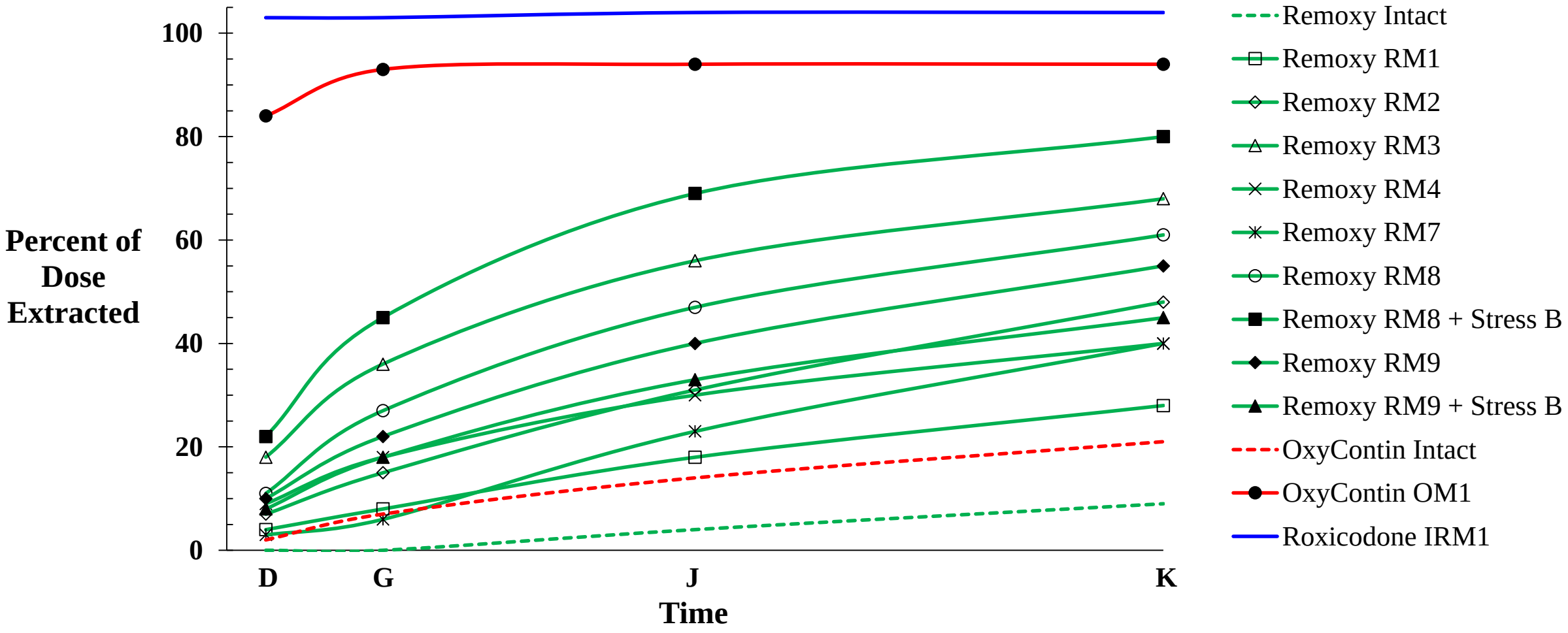
Extraction of Manipulated REMOXY ER and Comparators



Study Conditions: Solvent S1, Volume D, Temperature B

Oral Abuse Simulation: Most Effective Solvent

Extraction of Manipulated REMOXY ER and Comparators



Study Conditions: Solvent S5, Volume D, Temperature B

REMOXY ER Was Tested To Failure

- **RM10 was worst-case manipulation method.**
  - Per guidance, REMOXY ER tested to failure
  - Sophisticated manipulation, required 6 tools, 6 steps
  - Process must be done in a certain order
- **Under RM10, REMOXY ER retained rate control in 3 of 5 solvents through Time J.**
- **Under similar conditions, OxyContin ER retained rate control in 1 of 5 solvents through Time J.**

Oral Abuse Simulation: Most Effective Method

Study Conditions: Solvent S1, Volume D, **Temperature B**

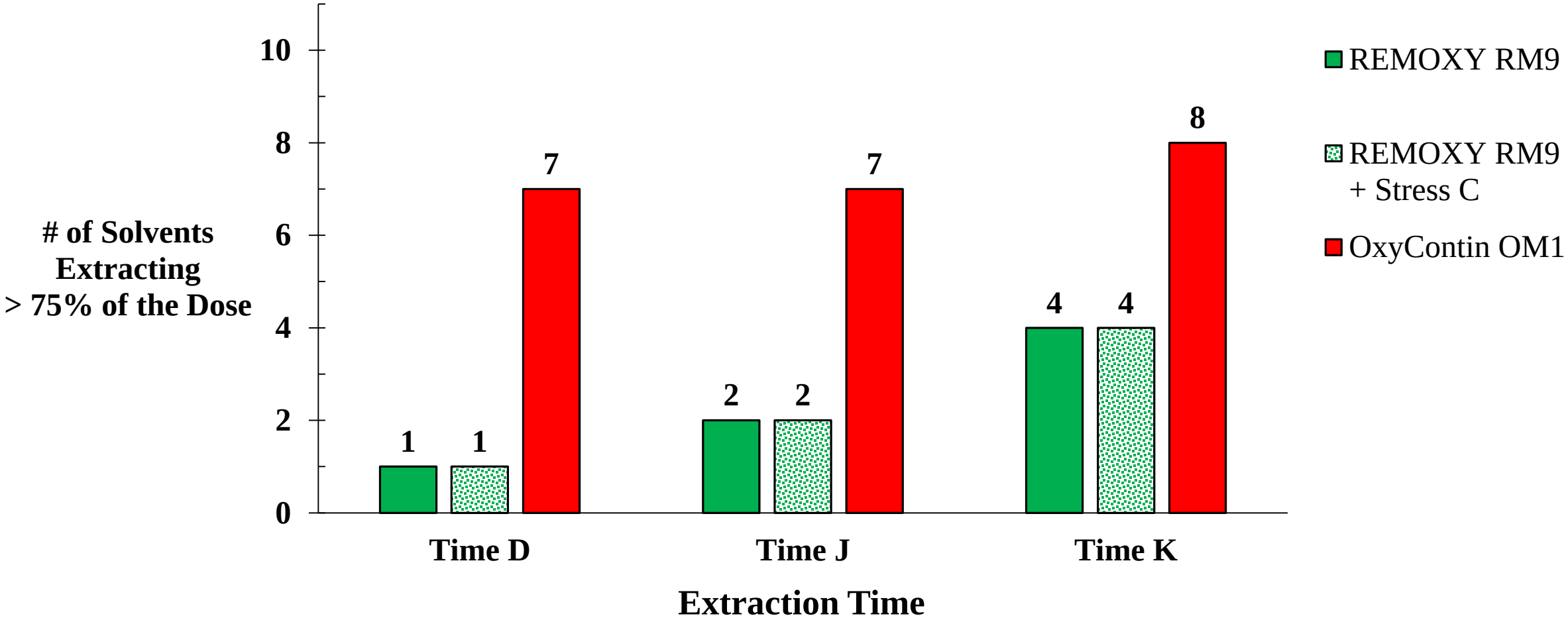
Manipulation Method	Time							
	A	D	G	J	K	L	M	O
RM9	0	1	3	6	9	11	15	26
RM9 + Tool 12	0	2	3	7	9	11	16	26
RM9 + Stress C + Tool 12	0	1	3	6	8	11	15	27
RM10 (Tool 16 + 6x Tool 12)	54	78	91	94	94	97	97	97
OxyContin ER OM1 (Tool 16 + Tool 12)	-	85	86	88	87	87	86	86

Study Conditions: Solvent S1, Volume D, **Temperature F**

Manipulation Method	Time							
	A	D	G	J	K	L	M	O
RM9	2	17	40	63	84	95	103	105
RM9 + Tool 12	3	22	46	73	90	98	104	104
RM9 + Stress C + Tool 12	1	15	33	61	83	93	103	104
RM10 (Tool 16 + 6x Tool 12)	83	92	94	95	95	96	94	95
OxyContin ER OM1 (Tool 16 + Tool 12)	-	85	83	85	85	85	85	84

Extraction in Solvents S6 – S16

REMOXY ER resisted extraction in S6 – S16 compared to OxyContin ER



Study Conditions: Volume D, Temperature B

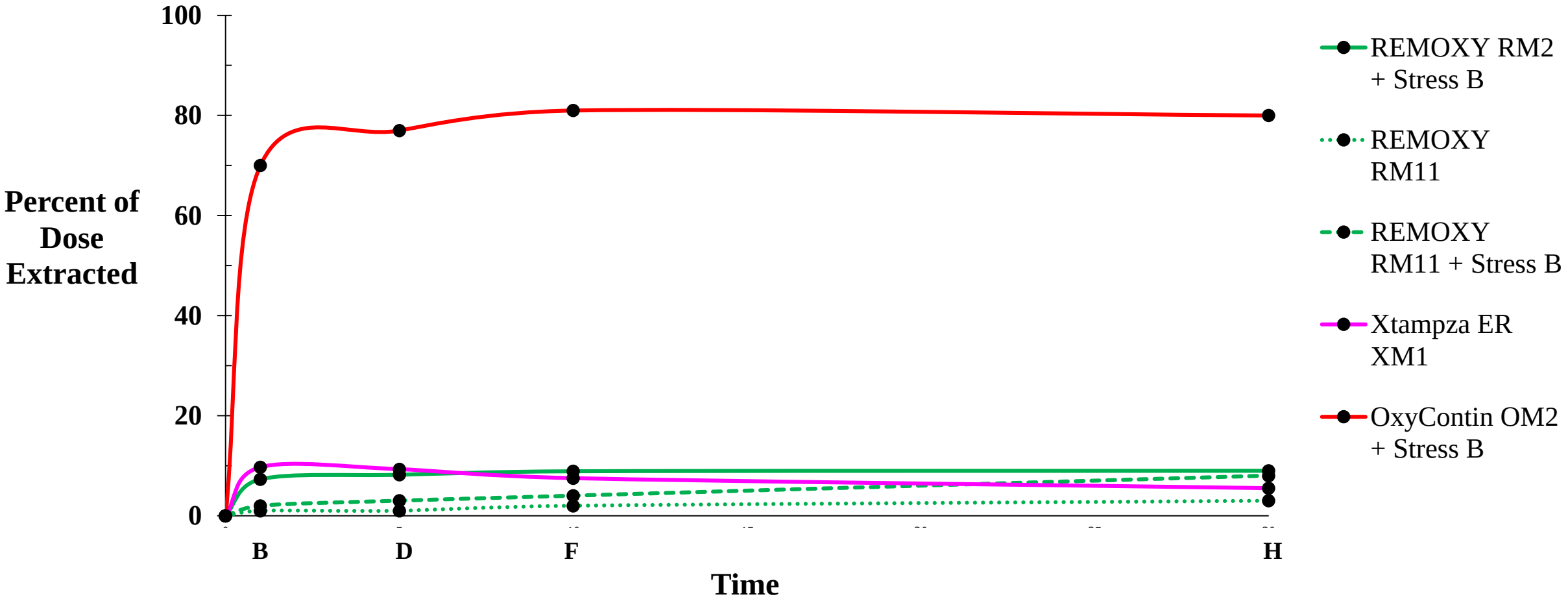
REMOXY ER Resists Snorting

- **REMOXY ER could not be converted to a form suitable for snorting.**

- **Stress A with methods RM4, RM5 and RM6 failed to convert REMOXY ER into a form suitable for snorting.**

IV Abuse Simulation

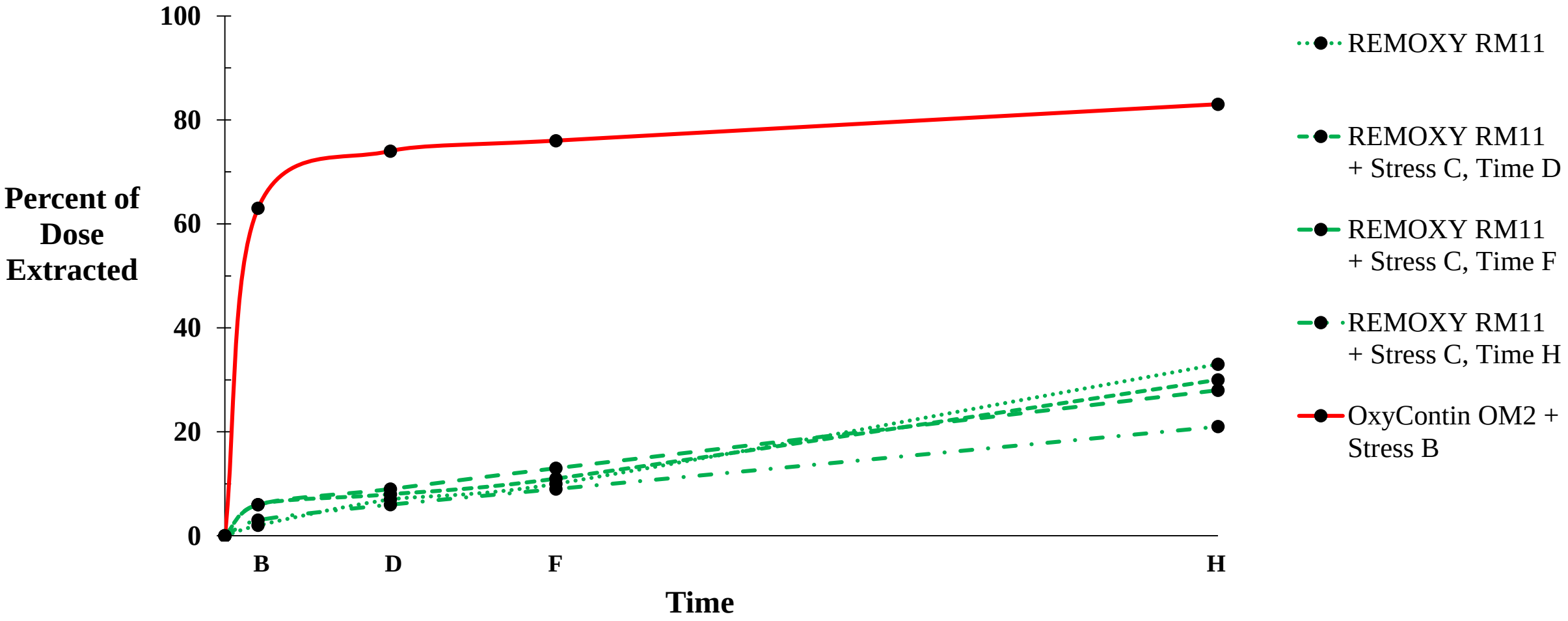
REMOXY ER Resists Extraction Compared to OxyContin ER



Study Conditions: Solvent S19, Temperature B, Volume C

IV Abuse Simulation

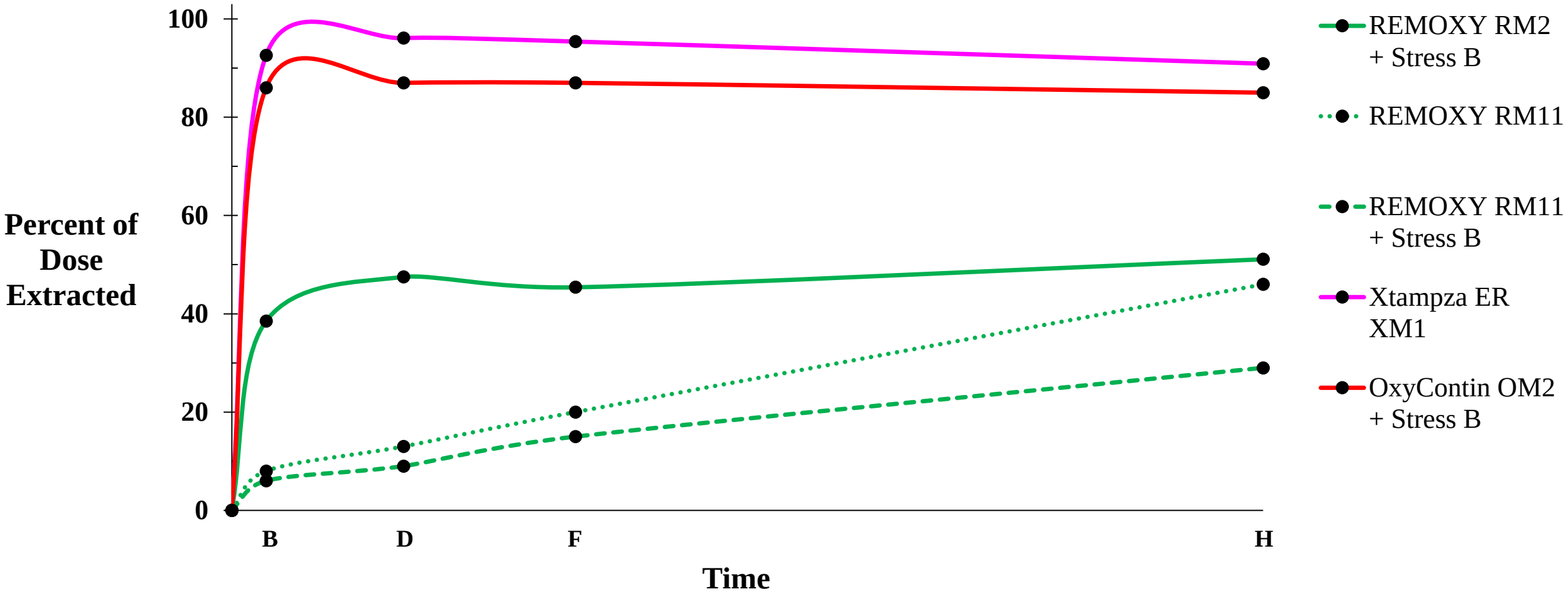
REMOXY ER Resists Extraction Compared to OxyContin ER



Study Conditions: Solvent S24, Temperature D, Volume B

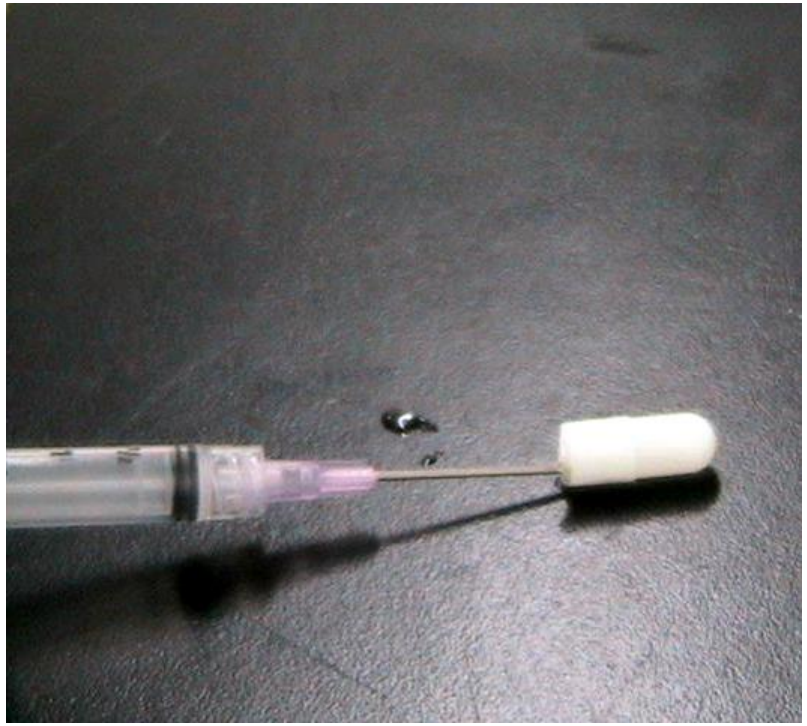
IV Abuse Simulation: Worst Case

REMOXY ER Resists Extraction Compared to OxyContin ER and Xtampza ER



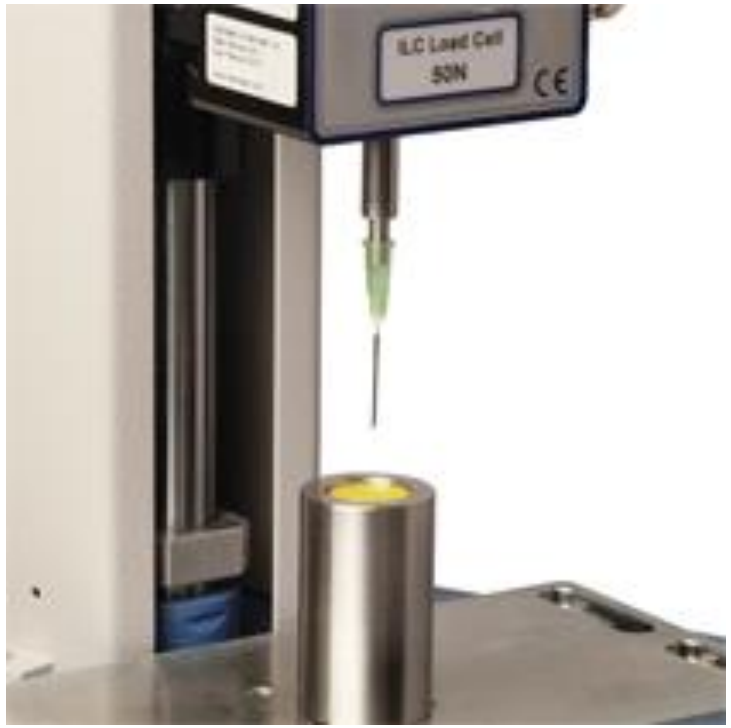
Study Conditions: Solvent S20, Temperature F, Volume C

Syringe Study



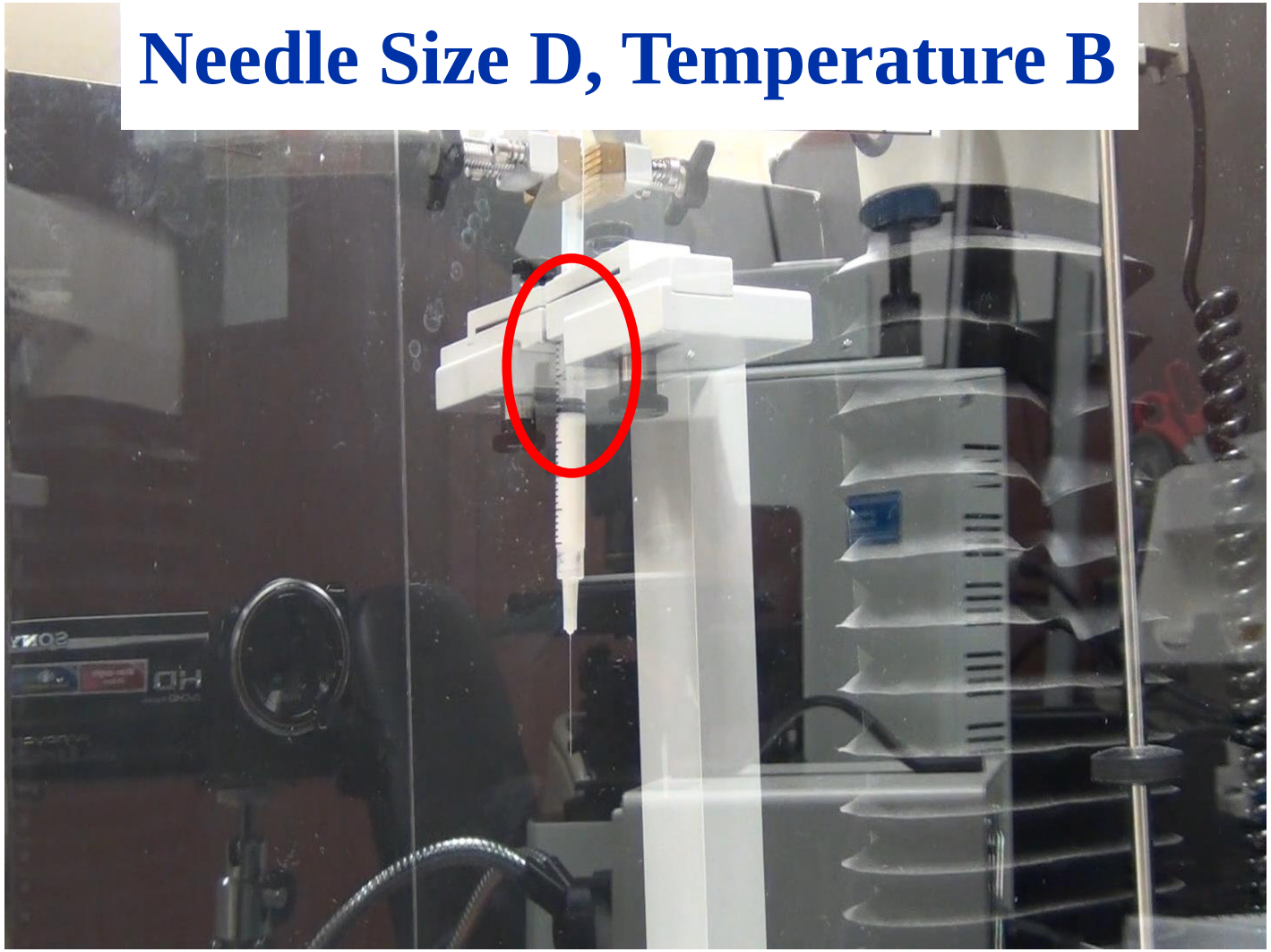
- **Attempts to draw REMOXY ER into a syringe failed.**
- **4 needle gauges were tested (Size A-D).**
- **Study was conducted by an independent lab.**

Injection Study



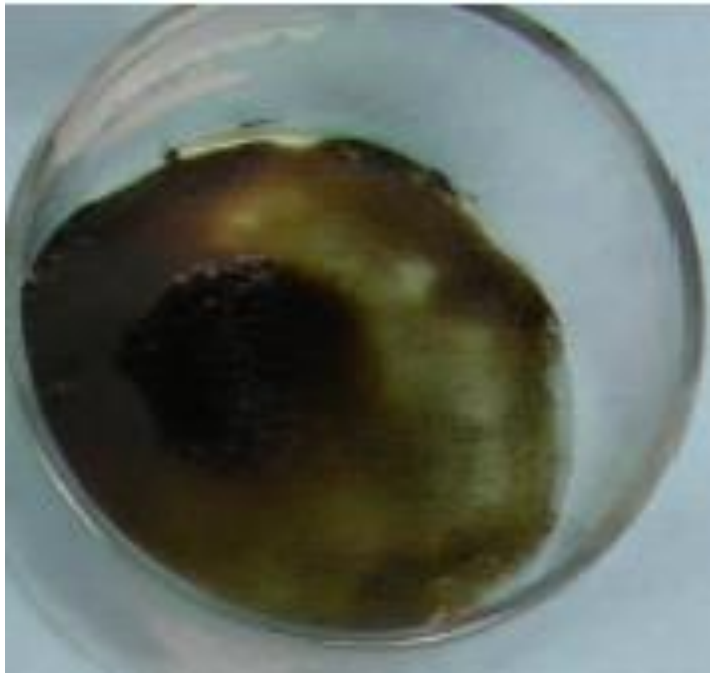
- **Attempts to inject from a syringe filled with REMOXY ER formulation failed.**
- **Different needle sizes, injection rates & temperatures were tested.**
- **Study was conducted by an independent lab.**

Injection Study: Barrel Failure



Simulated Smoking Study

- **REMOXY ER carbonizes at Temperature I.**
- **Study was conducted by an independent laboratory.**



Simulated Smoking Study

- **Minimal oxycodone was recovered from REMOXY ER.**
- **An irritating vapor was liberated.**
- **More oxycodone was recovered from the vapor of OxyContin than from REMOXY ER.**

Time	Percent of Oxycodone Recovered			
	REMOXY ER			OxyContin ER
	RM2	RM12	RM12 + Stress B	OM4
D	2.9%	Undetected	Undetected	8.8%
F	3.8%	Undetected	Undetected	10.7%

Category 1 Summary

- **The physical and chemical characteristics of REMOXY ER impart abuse deterrent properties.**
  - Provides resistance to manipulations and extractions
  - Sticks to tools
  - Difficult to syringe and inject
  - High viscosity gel could not be snorted
  - Minimal oxycodone released when vaporized

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Lynn Webster, MD	**In vivo Abuse Deterrence**
Nadav Friedmann, PhD, MD	Clinical Development
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Category 2 and 3

In vivo Abuse Deterrence

Lynn Webster, MD
Vice President, Scientific Affairs
PRA Health Sciences

HAP Overview

- **Two human abuse potential (HAP) studies were conducted with REMOXY ER.**
  - HAP oral study (B4501016) – initiated 2013
  - HAP nasal study (PTI-821-C08) – initiated 2017
- **HAP studies assessed parameters that are objective (pharmacokinetics - PK) and subjective (pharmacodynamics - PD).**

Oral HAP Study Objective

- **Primary study objective was to rigorously assess the preferences for REMOXY ER versus IR oxycodone in a population of non-dependent, recreational opioid abusers with a history of oral opioid abuse.**

Oral Study Design

- **Legacy HAP study, conducted prior to 2015 issuance of FDA Final Guidance Document.**
  - Study protocol was reviewed by FDA and comments incorporated.
- **Randomized, triple-dummy, double-blind, single-center, 4-way crossover study in recreational abusers (N=46).**
  - Screening Phase
  - Qualification Phase (naloxone challenge)
  - Drug Discrimination Phase
  - Treatment Phase

Treatments

- **Blinded treatments:**
  - REMOXY ER 40 mg, intact
  - REMOXY ER 40 mg, chewed for 5 minutes
  - IR Oxycodone 40 mg, crushed in solution
  - Matching placebos

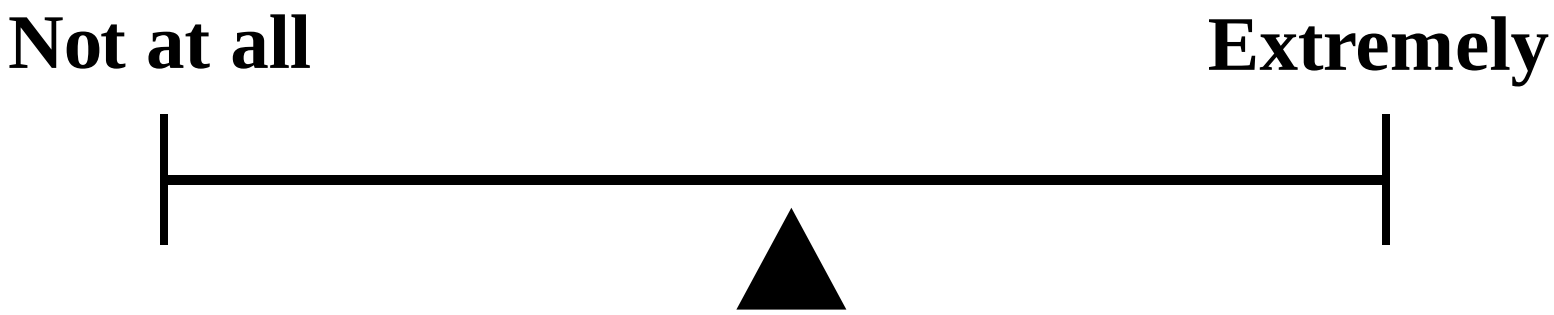
Primary Endpoints

- **4 co-primary pharmacodynamic (PD) endpoints.**
  - Drug Liking Peak Effect (Emax)
  - Drug High Peak Effect (Emax)
  - Drug Liking Area Under the Effect Curve (AUE0-2)
  - Drug High Area Under the Effect Curve (AUE0-2)
- **REMOXY ER versus IR oxycodone.**

PD Endpoint Measures

- **Unipolar VAS scale was used to measure PD endpoints**
  - For example, each subject was asked the following question regarding "Overall Drug Liking":

"Do you like the drug effect you are feeling now?"



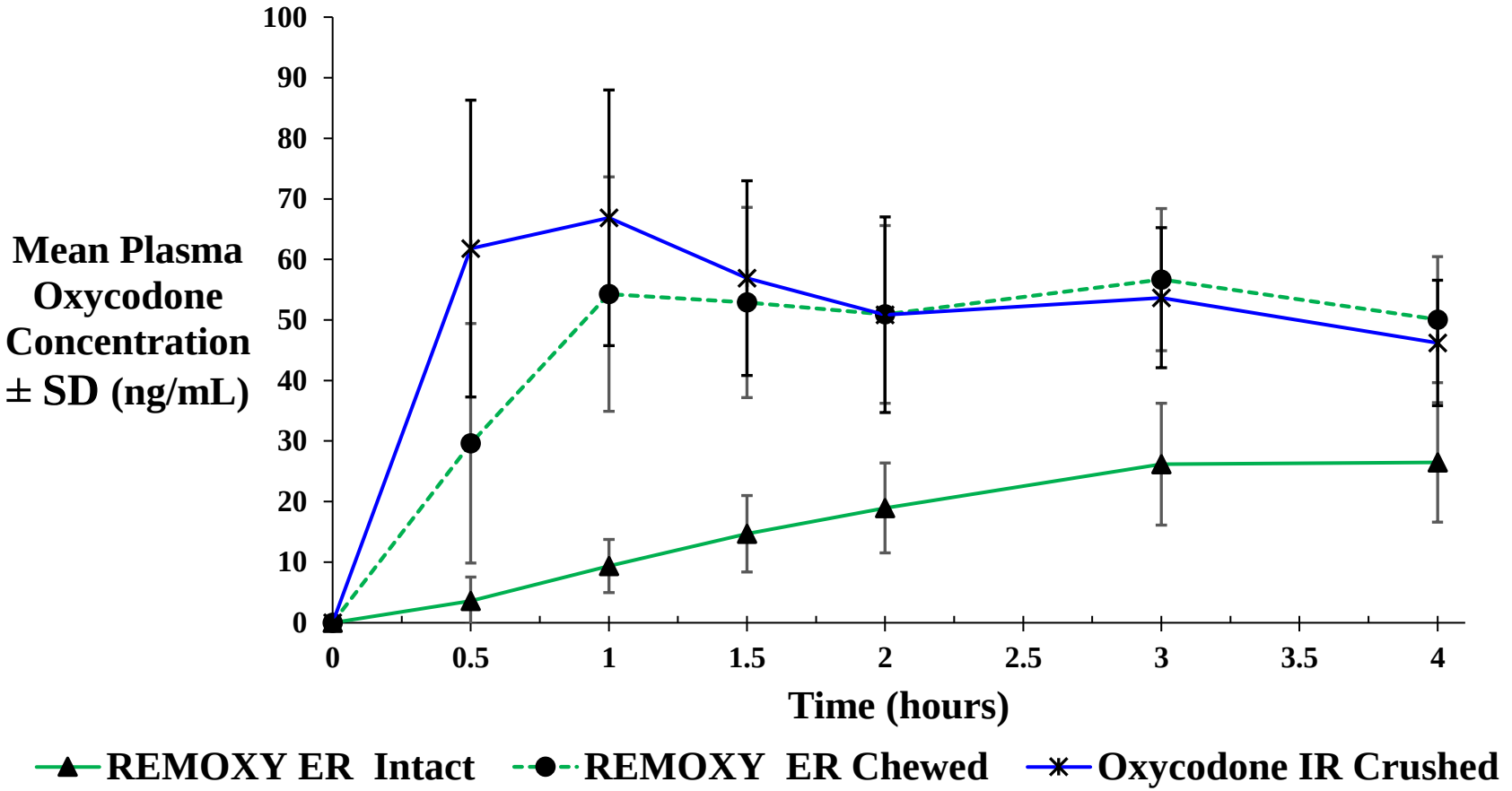
- **Data was generated from 46 completers**

Study Results

- **REMOXY ER chewed vs IR oxycodone met 2 of 4 co-primary endpoints**
  - Drug Liking (AUE_{0-2}) ($p < 0.0001$)
  - Drug High (AUE_{0-2}) ($p < 0.0001$)
- **REMOXY ER chewed vs IR oxycodone did not meet 2 of 4 co-primary endpoints**
  - Drug Liking (E_{max})
  - Drug High (E_{max})

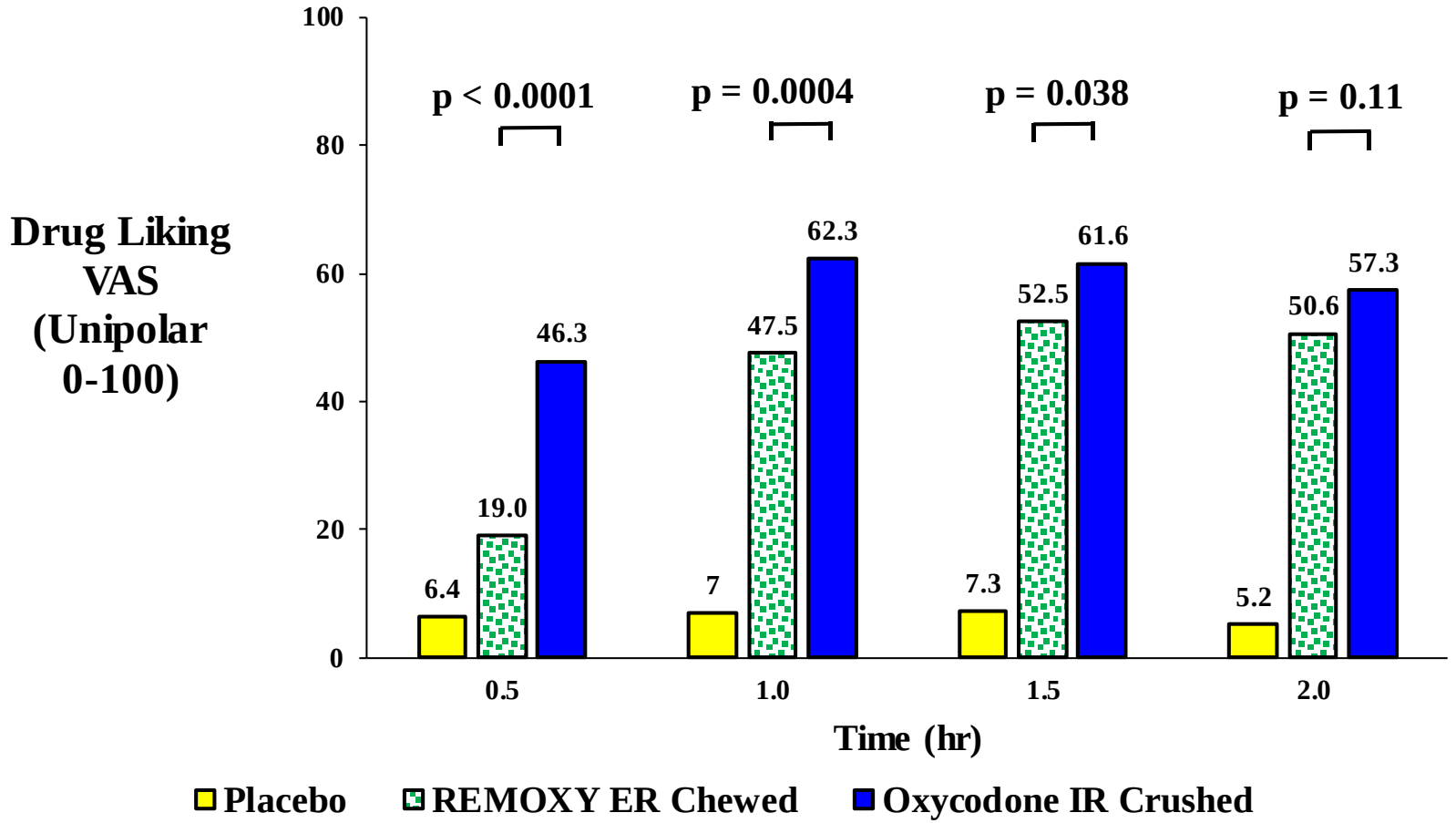
PK Results - Early Timepoints

Chewed REMOXY ER showed Lower Drug Concentrations at Early Timepoints



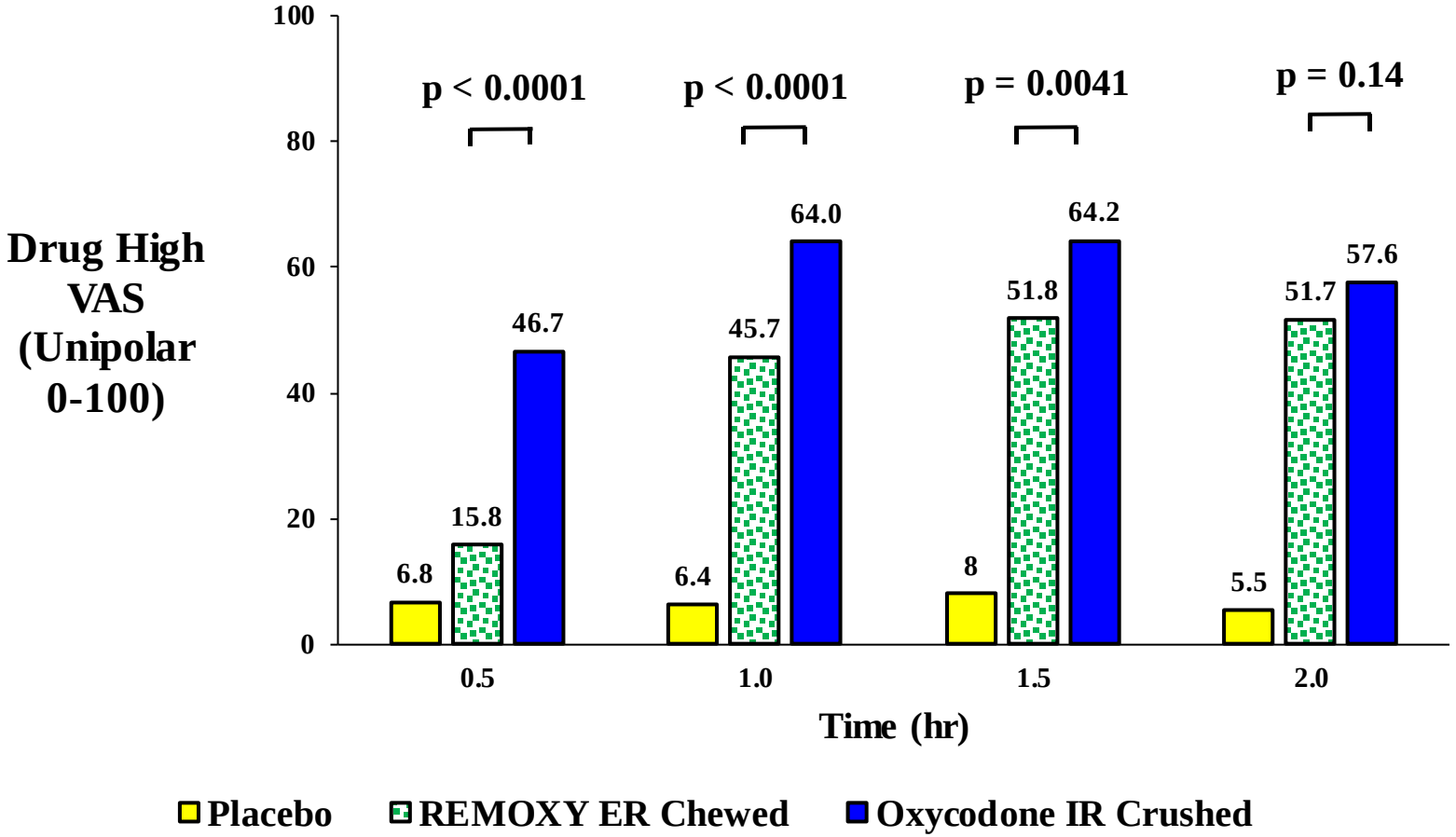
PD Results - Drug Liking

Chewed REMOXY ER Showed Less Drug Liking at Early Timepoints



PD Results - Drug High

Chewed REMOXY Showed Lower Drug High at Early Timepoints



Oral HAP Study Conclusions

- **Study met 2 of 4 Primary PD Endpoints (p< 0.0001).**
  - PD results are consistent with PK results
- **At the early time-points post-dose, abusers preferred IR oxycodone over chewed REMOXY ER.**
- **Chewing REMOXY did not defeat extended-release characteristics.**

Nasal HAP Study Objective

- **Primary objective of study PTI-821-C08 was to compare the relative abuse potential of nasal REMOXY ER (manipulated and intact) vs. nasal IR oxycodone in a population of non-dependent, recreational opioid abusers.**
- **A separate open-label arm compared PK parameters of intranasal REMOXY ER to OxyContin ER.**
- **Nasal HAP study was completed in 2017.**

Nasal Study Design

- **Randomized, double-blind, single-center, 4-way crossover study in recreational opioid abusers (N=36).**
  - Screening Phase
  - Qualification Phase (naloxone challenge)
  - Drug Discrimination Phase
  - Treatment Phase
- **Following double blind portion of the study, an Open Label comparison to OxyContin ER (N=20).**
- **Study was developed in accordance with final FDA Guidance document.**
  - Study protocol and statistical analysis plan were reviewed by FDA and comments incorporated

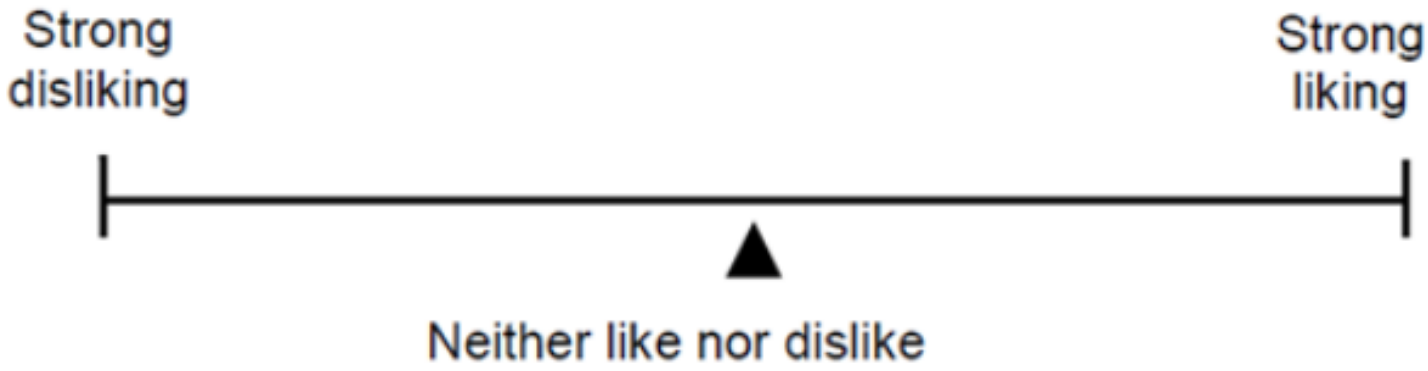
Treatments

- **Four blinded treatments (N=36)**
  - REMOXY ER 40 mg, intact
  - REMOXY ER 40 mg, manipulated
  - IR Oxycodone 40 mg, crushed
  - Placebo
- **One non-blinded treatment (N=20)**
  - OxyContin ER 40 mg, manipulated

Primary Endpoint

- **Primary endpoint was Drug Liking (Emax)**
  - REMOXY ER versus oxycodone IR
- **Bipolar VAS scale was used to measure PD endpoints**
  - For example, each subject was asked the following question regarding "Drug Liking':

Do you like the drug effect you are feeling now?

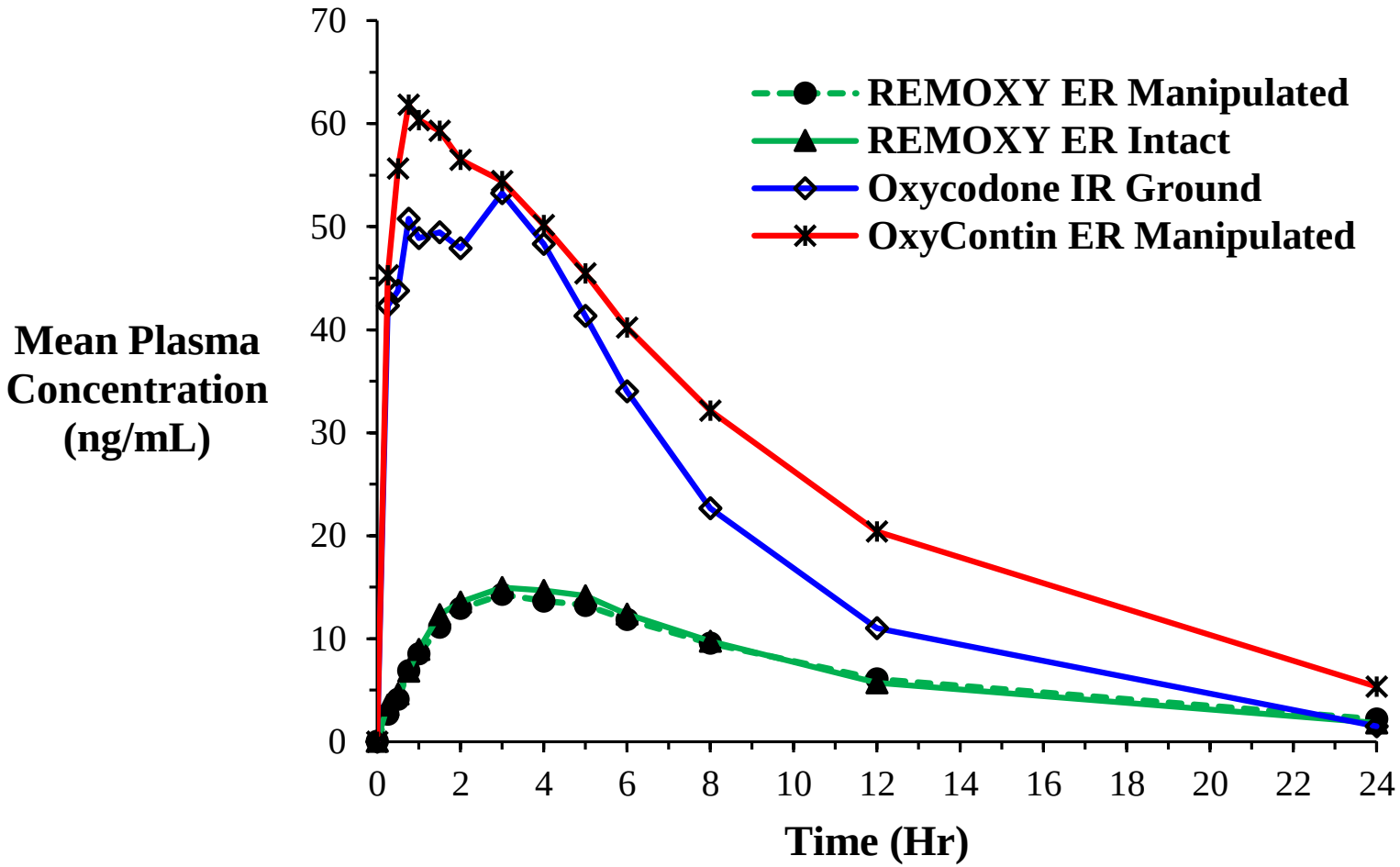


Statistical Analysis

- **Statistical analysis plan was pre-specified in the protocol, reviewed by FDA, and FDA comments were incorporated**
  - Data were generated for 36 completers from blinded portion
  - Data were generated for 20 completers from the open portion

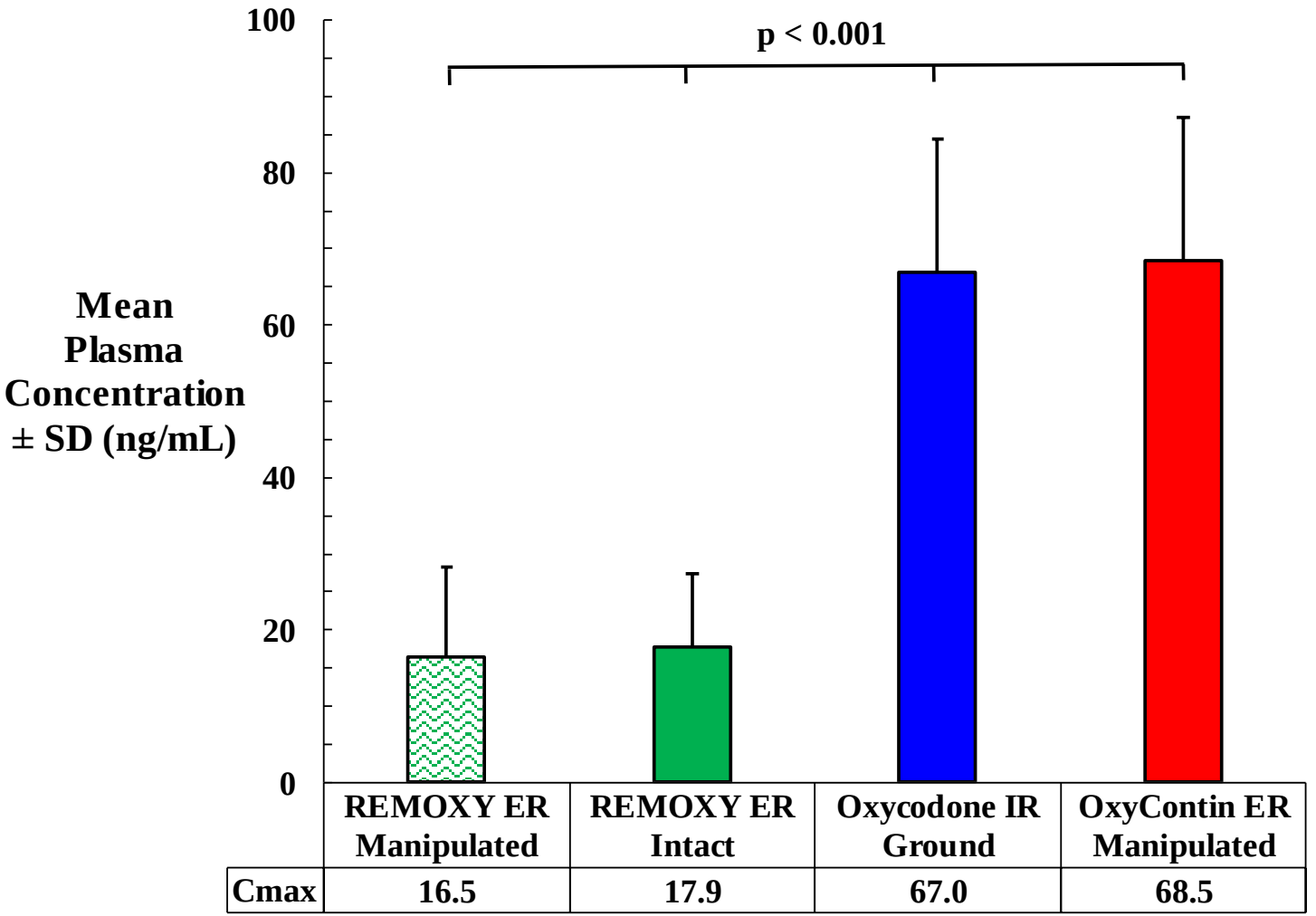
PK Results

Significantly Less Drug Absorption from REMOXY ER



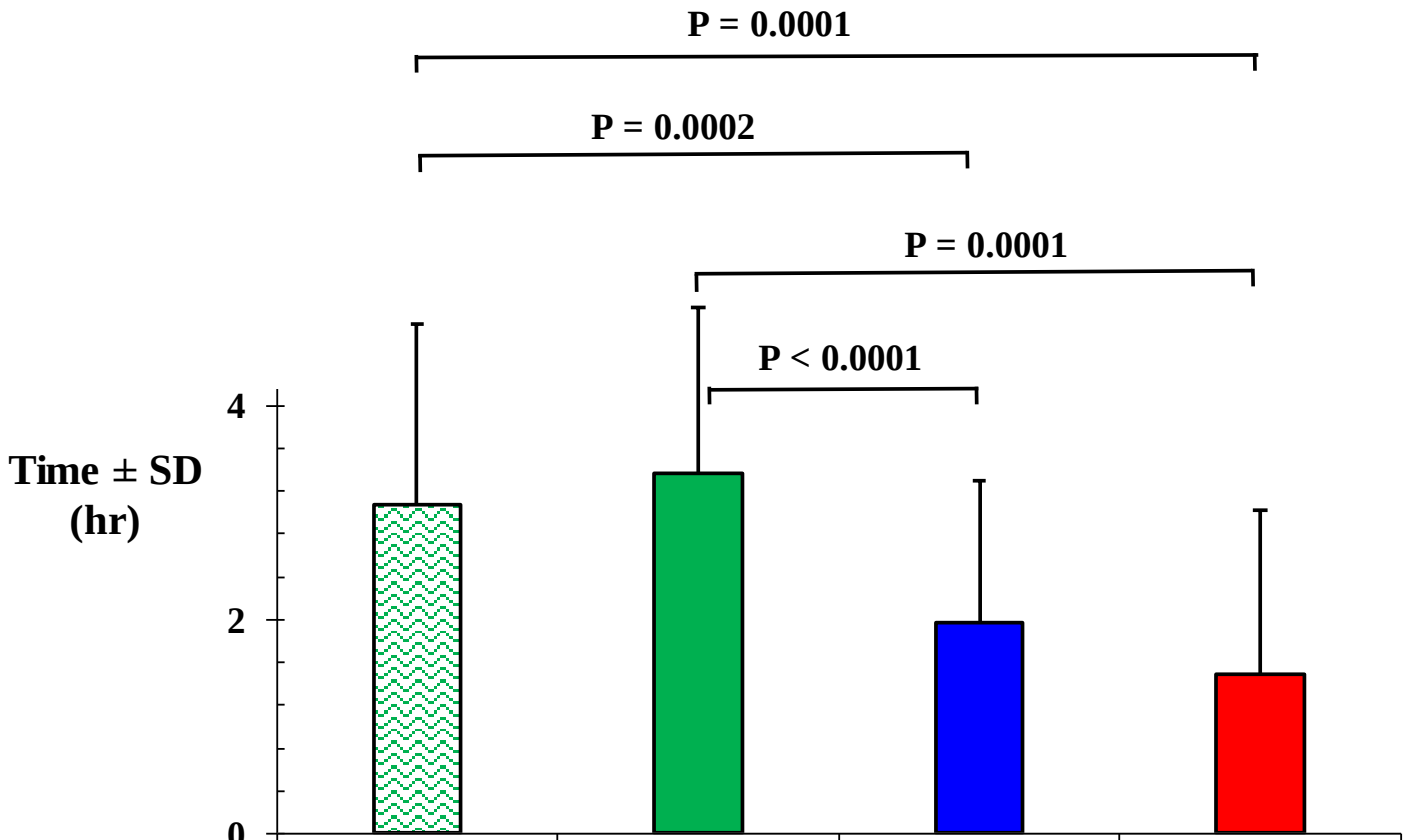
PK Results – C_{max}

Significantly Lower C_{max} for REMOXY ER



PK Results – T_{max}

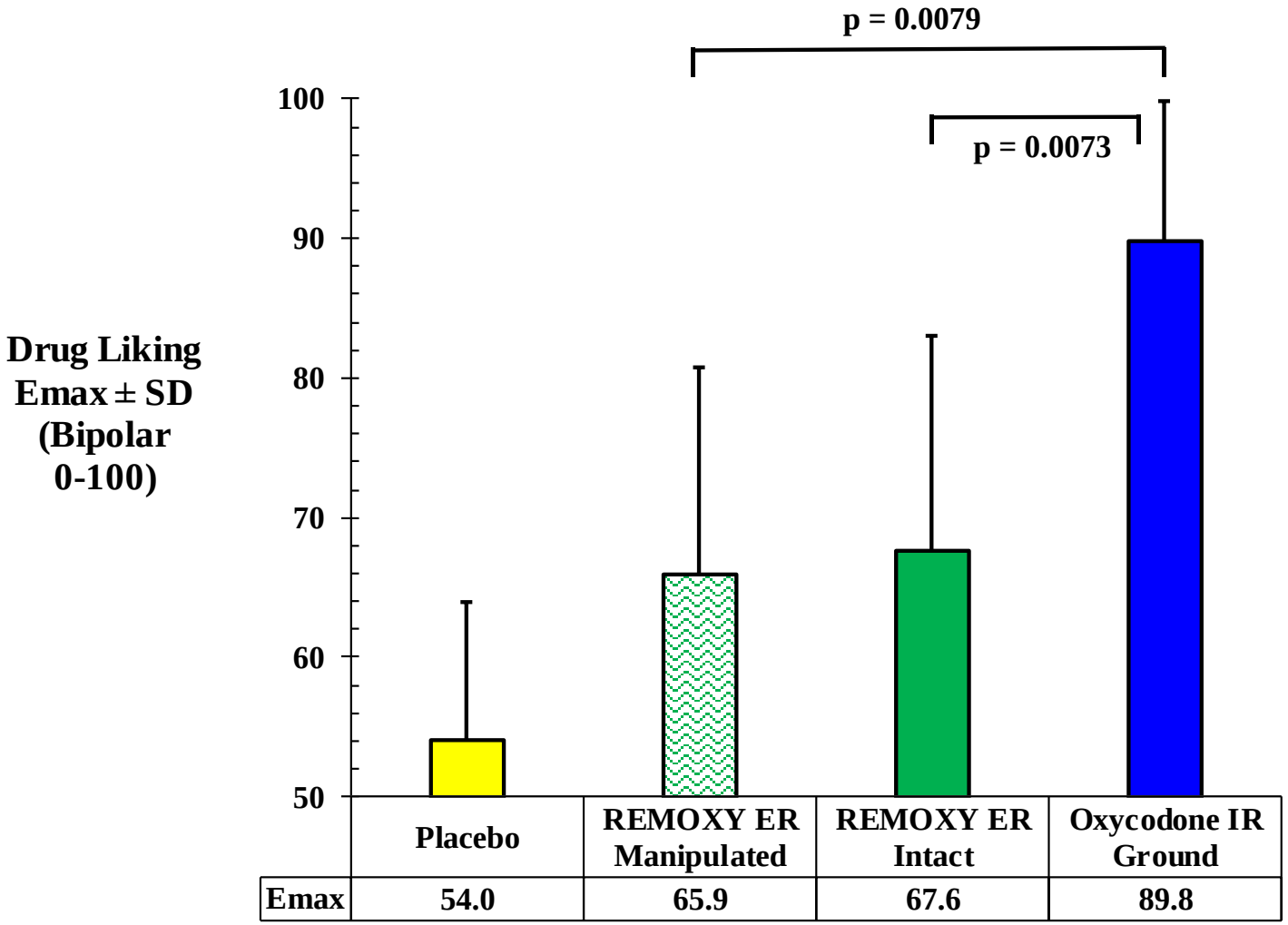
Significantly Longer T_{max} for REMOXY ER



	REMOXY ER Manipulated	REMOXY ER Intact	Oxycodone IR Ground	OxyContin ER Manipulated
Tmax	3.1	3.4	2.0	1.5

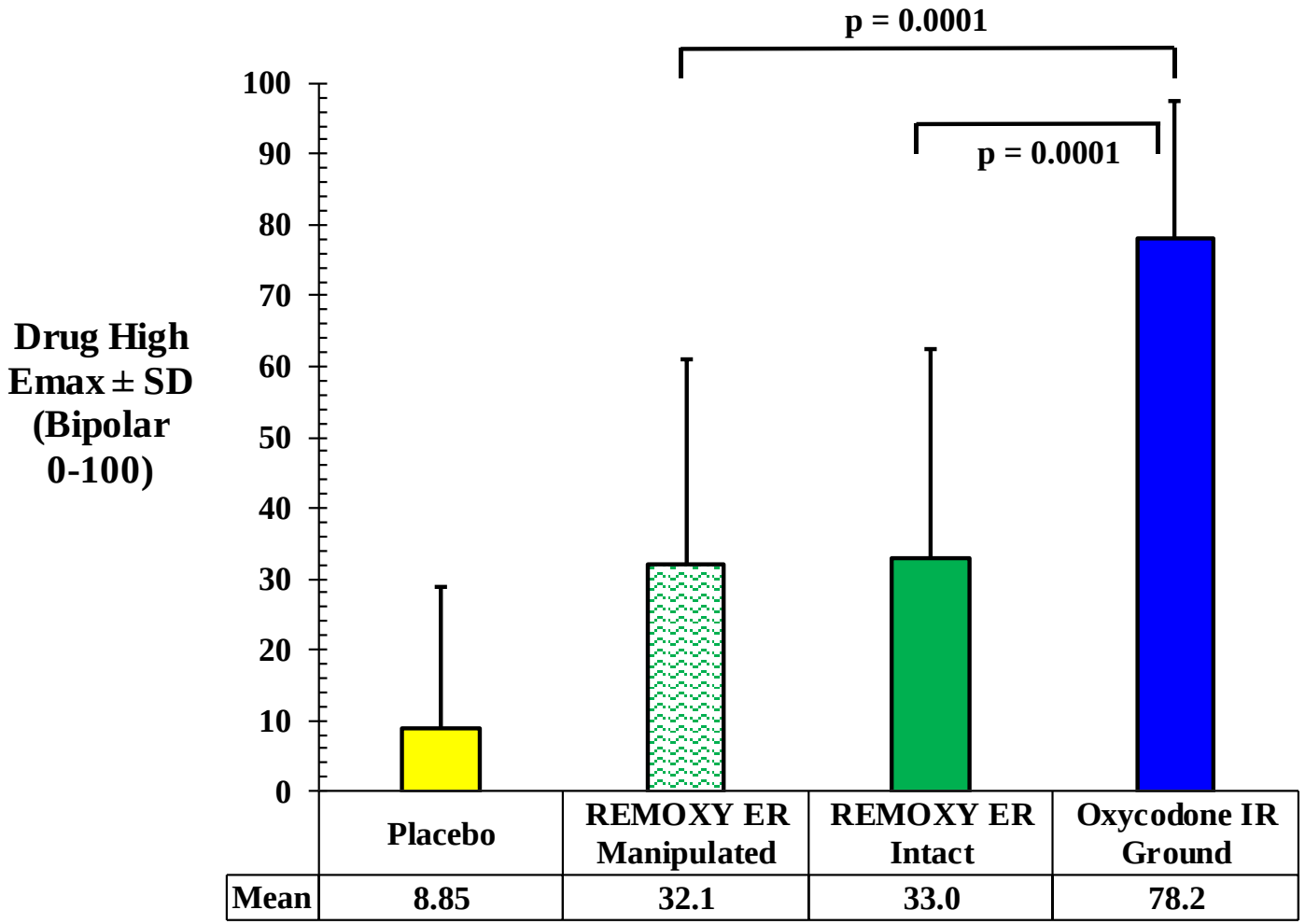
Study Results – Primary Endpoint

REMOXY ER Met Primary Endpoint



PD Results – E_{max}

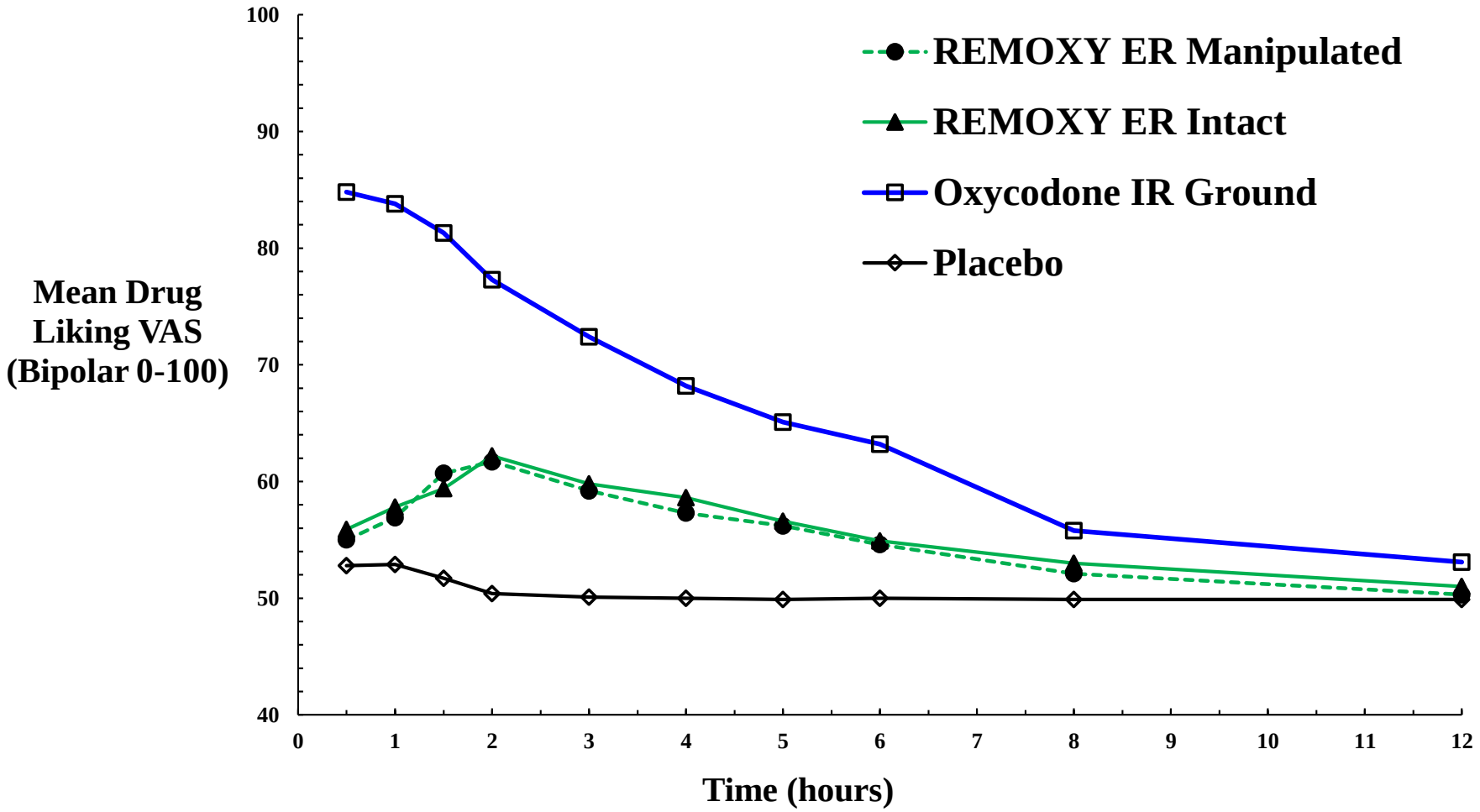
Significantly Lower Drug High E_{max} for REMOXY ER



	Placebo	REMOXY ER Manipulated	REMOXY ER Intact	Oxycodone IR Ground
Mean	8.85	32.1	33.0	78.2

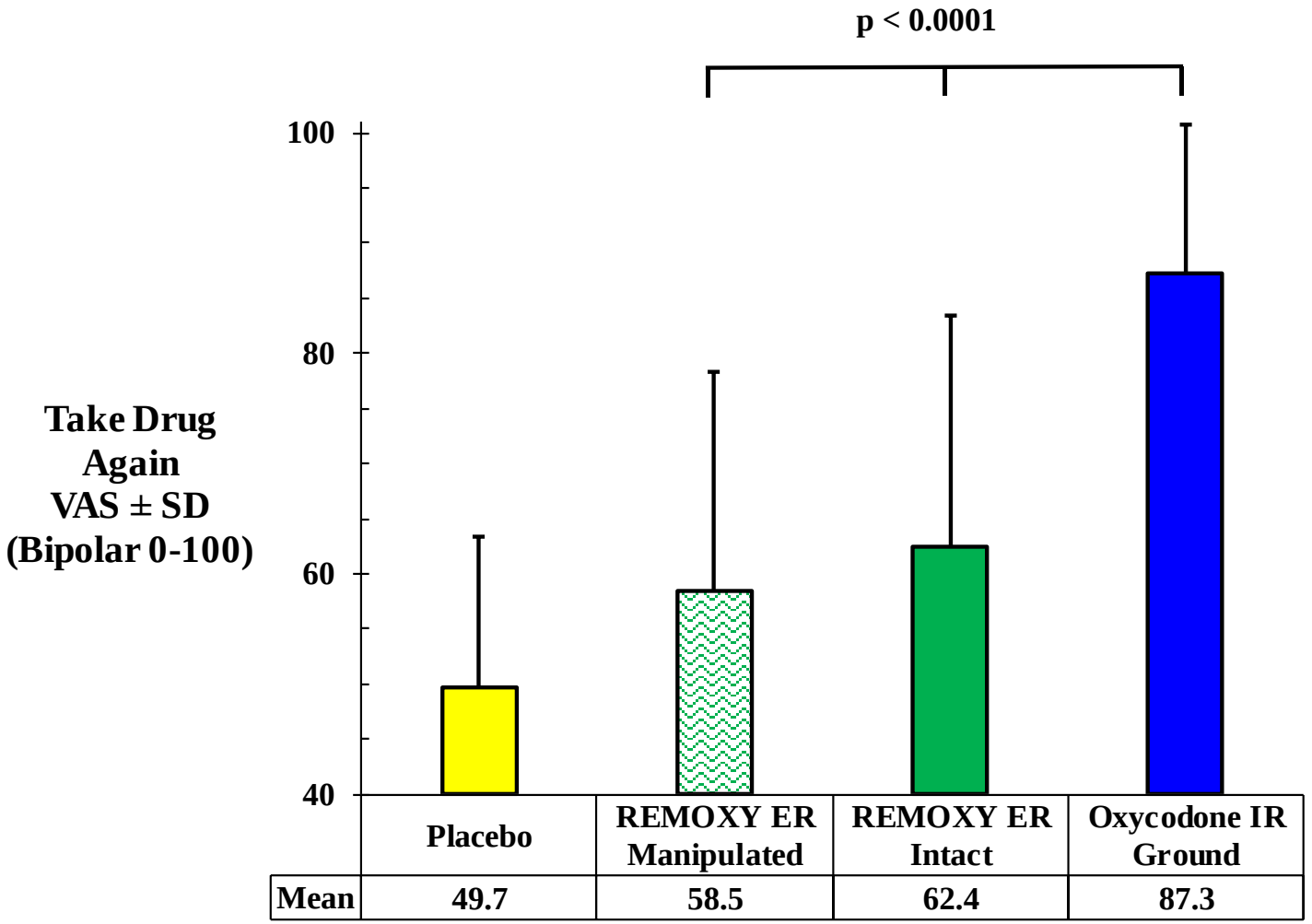
PD Results – Drug Liking

Significantly Lower Drug Liking for REMOXY ER



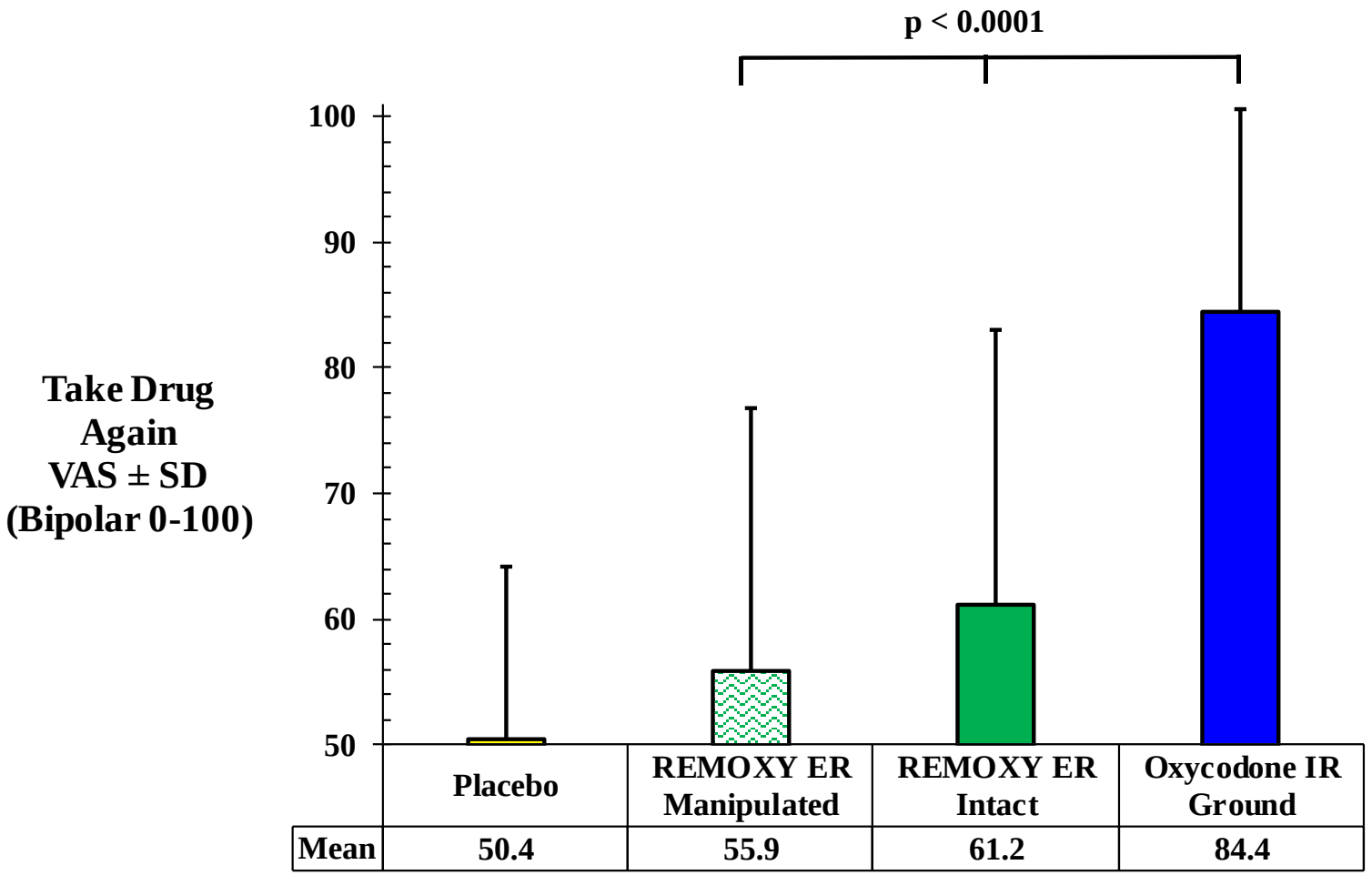
PD Results – Take Drug Again

Significantly Lower Take Drug Again (12 hrs) for REMOXY ER



Nasal Results – Take Drug Again

Significantly Lower Take Drug Again (24 hrs) for REMOXY ER



Drug Effects Questionnaire

Drug Effects Questionnaire were all statistically significant in favor of REMOXY ER.

Parameter	REMOXY ER Manipulated vs oxycodone IR		REMOXY ER Intact vs oxycodone IR	
	LS Mean Difference (Test-Reference)	Two-sided P-value	LS Mean Difference (Test-Reference)	Two-sided P-value
Dizziness	-7.21	0.0011	-8.11	0.0002
High	-46.11	<.0001	-45.23	<.0001
Nauseous	-9.71	0.0007	-9.57	0.0009
Feeling Sick	-9.25	0.0004	-10.56	<.0001
Sleepiness	-19.18	0.0002	-24.53	<.0001
Any Drug Effects	-45.32	<.0001	-44.35	<.0001
Bad Drug Effects	-7.32	0.0104	-8.32	0.0037
Good Drug Effects	-45.56	<.0001	-44.92	<.0001
Pupil Constriction	-1.57	<.0001	-1.39	<.0001

Nasal Study Conclusions

- **Study met Primary Endpoint (p< 0.001), indicating Drug Liking was significantly lower for nasal REMOXY ER vs. nasal oxycodone IR.**
  - Abusers significantly preferred IR oxycodone over nasal REMOXY ER at all measured time-points
  - Secondary endpoints follow primary results
  - PD results are consistent with PK results
- **REMOXY ER maintained its extended-release profile when manipulated and demonstrated less abuse potential than the comparators.**

Agenda

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Michael Crowley, PhD	In vitro Abuse Deterrence
Lynn Webster, MD	In vivo Abuse Deterrence
Nadav Friedmann, PhD, MD	**Clinical Development**
Stephen Montgomery, PhD	Excipient Risk Assessment
Michael Marsman, PharmD	Risk Mitigation and Summary

Clinical Development

Nadav Friedmann, PhD, MD
Chief Operating and Medical Officer
Pain Therapeutics, Inc.

Agenda

- REMOXY ER Product Profile
- Goals & Methods of Clinical Program
- Safety and Efficacy Profile

REMOXY ER - Product Profile

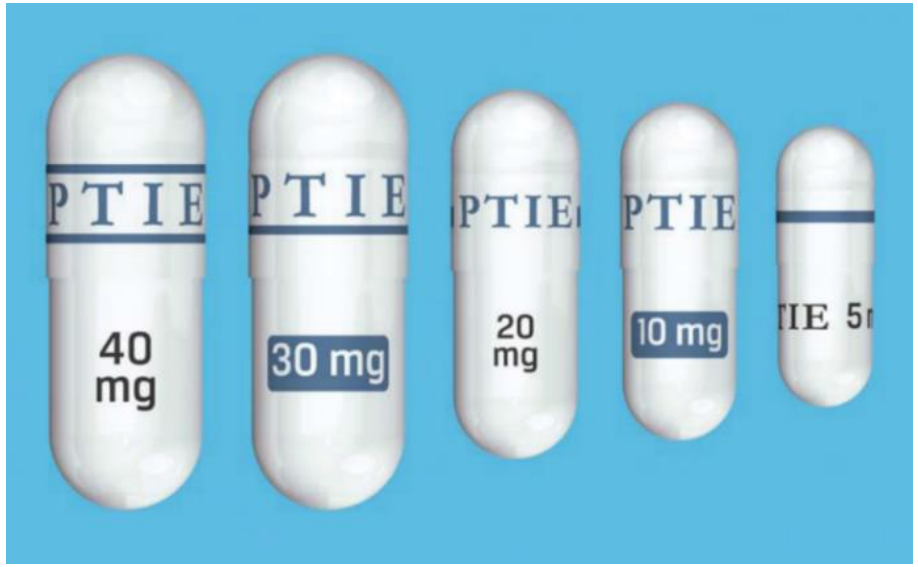
Description: oxycodone base (CII) inside a sealed capsule

Formulation: gel, extended-release, with abuse deterrent properties

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

Dosage and Administration: twice-daily, oral

Dosage Strengths: 5, 10, 20, 30 and 40 mg



Development Goals & Methods

- **Demonstrate safety and efficacy of REMOXY ER in patients with moderate-to-severe chronic pain.**

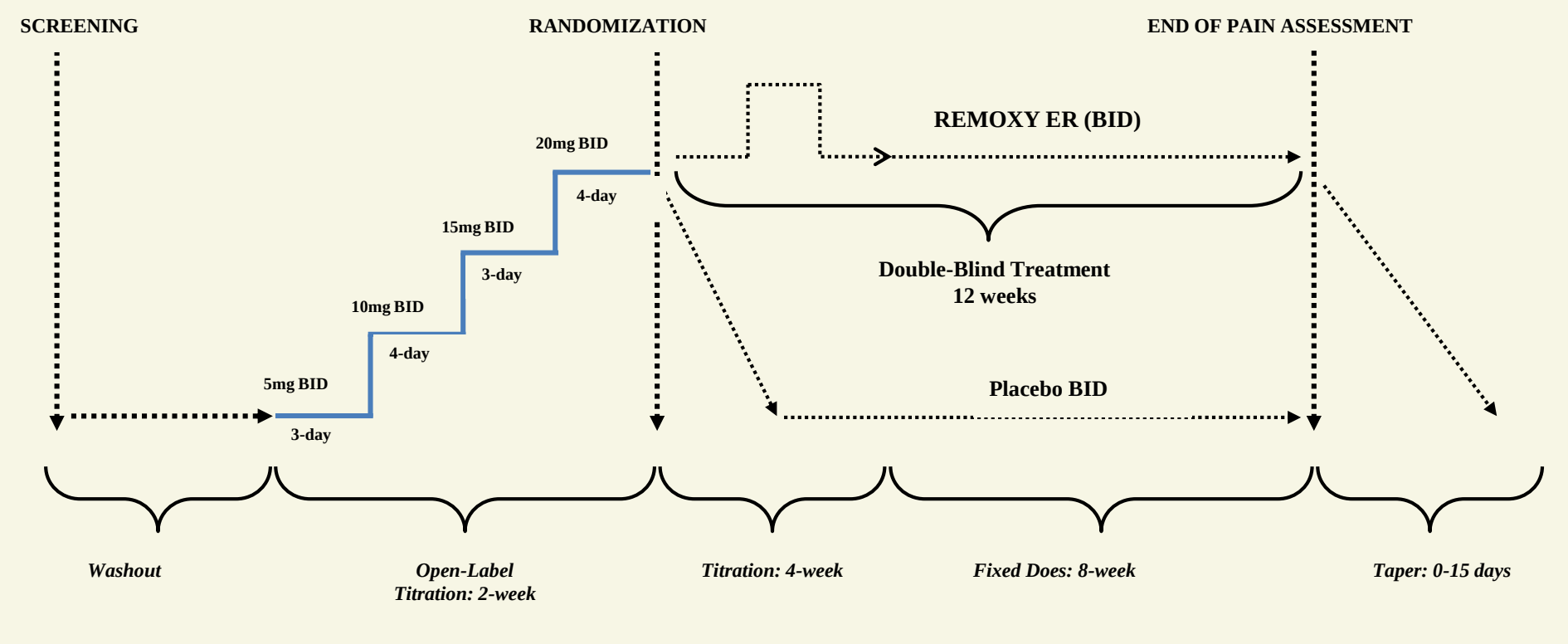
- **Clinical efficacy program for REMOXY ER was developed in close collaboration with FDA through a Special Protocol Assessment (SPA).**
  - Under an SPA, study design, clinical endpoints, and statistical analyses are all acceptable for FDA evaluation

Phase III Efficacy Study

- Study PTI-821-CO compared the analgesic effects of REMOXY ER to placebo in a chronic pain population.

- Double-blind, randomized, placebo-controlled, multi-center study in patients (N=412) with moderate-to-severe chronic pain due to osteoarthritis of the hip or knee.

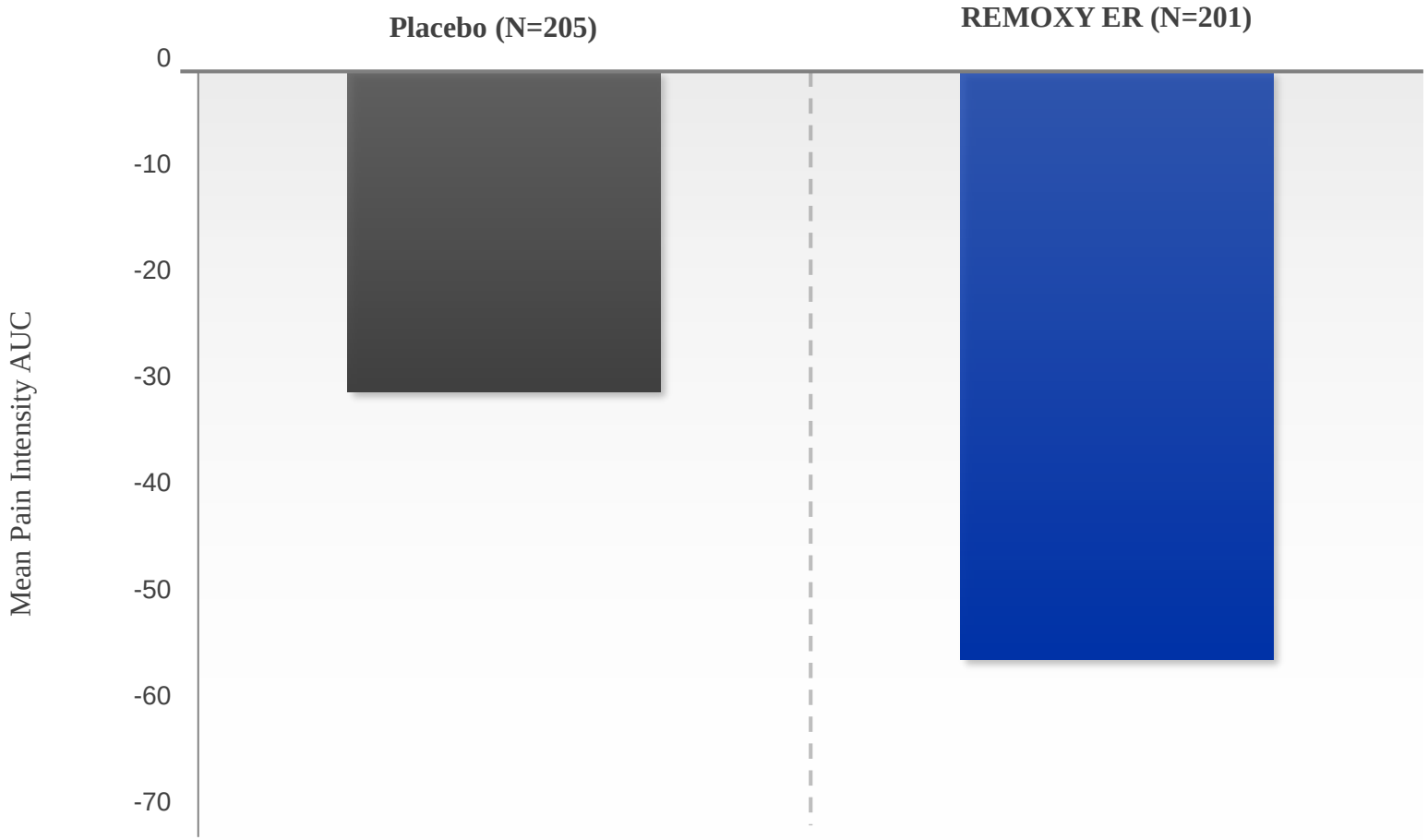
Phase III Efficacy Study Design



Met Primary Endpoints

Phase III Study for REMOXY ER met Primary Endpoint

Change in Pain Intensity Over 12 Weeks (P=0.007)



Met Secondary Endpoints

- **Phase III efficacy study for REMOXY ER met all secondary endpoints related to pain**

Quality of Analgesia	p = 0.004
Global Assessment	p = 0.007
SF-12 Health Survey: physical component	p = 0.003
WOMAC OA Index: pain subscale	p = 0.023

Phase III Study - Safety

Adverse Events ≥ 5%, similar to other ER opioids

	Placebo N (%)	REMOXY ER N (%)
Gastrointestinal Disorders	**39 (18.8)**	**84 (41.0)**
Constipation	9 (4.3)	35 (17.1)
Diarrhea	12 (5.8)	9 (4.4)
Nausea	20 (9.7)	41 (20.0)
Vomiting	6 (2.9)	29 (14.1)
Nervous System Disorders	**23 (11.1)**	**45 (22.0)**
Dizziness	9 (4.3)	17 (8.3)
Headache	11 (5.3)	10 (4.9)
Somnolence	4 (1.9)	23 (11.2)

Exposure to REMOXY ER

- **>2,400 subjects were treated with REMOXY ER.**
  - 469 patients were treated for 6 months
  - 381 patients were treated for 1 year
- **Overall, side effect profile was similar to those of other ER opioid drug products.**
- **No new or unexpected adverse events were noted.**

Summary of Safety and Efficacy

- **Phase III Study (PTI-821-CO) with REMOXY ER met the primary efficacy endpoint (p = 0.007).**
  - Pain-related secondary endpoints confirmed the primary result

- **Safety profile was consistent with other ER opioids.**

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Excipient Risk Assessment

Stephen Montgomery, PhD
Regulatory and Toxicology Consultants, LLC

In Vitro Excipient Extraction Study

- **Conducted by an independent contract laboratory.**
- **REMOXY ER (40 mg) Capsule samples manipulated and extracted according to Category 1 conditions:**
  - Manipulations: (i) RM11, (ii) RM11 + Stress B, and (iii) RM11 + Stress C at Temp H
  - Extraction: Solvent S19 (Volume B) with agitation (Mixing Type D) at Temps B and E
- **Analytical Methods developed for each excipient and decomposition products.**
  - GC-MS, UPLC-CAD, SEC-RI, or RA
  - Limit of Quantitation (LOQ) for excipients ranged from < 1 to 80 µg/mL
  - LOQ for decomposition components ranged from 50 to 600 µg/mL

In Vitro Excipient Extraction Study - Results

- **Quantifiable low levels of only two excipients were detected:**
  - Triacetin
  - Hydroxyethyl cellulose (HEC)
- **Quantifiable low levels of only two excipient decomposition products were detected:**
  - Acetic acid
  - Myristic acid

In Vitro Excipient Extraction – Data Summary

Material Identification	Limit of Quantitation (LOQ) (mg/mL)	Extraction in Solvent S19, Volume B, with Mixing Type D					
		Manipulation RM11 Extraction Temp E		Manipulation RM11 + Stress B Extraction Temp B		Manipulation RM11 + Stress C at Temp H Extraction Temp E	
		Time D	Time J	Time D	Time J	Time D	Time J
Formulation Excipients (mg/mL)							
Triacetin	0.02	8.31	18.63	3.44	10.14	3.29	7.05
HEC	0.02	0.16	1.52	< LOQ	0.16	< LOQ	< LOQ
Decomposition Products of Excipients (mg/mL)							
Acetic Acid	0.07	< LOQ	0.15	< LOQ	< LOQ	< LOQ	< LOQ
Myristic Acid	0.6	0.6	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ

Safety Assessment by Alternate Routes of Administration

- **Searched the published scientific literature.**
  - PubMed, TOXLINE, HSDB, IPSC INCHEM, WHO/FAO, FDA, EPA, and Google
- **Focused on toxicity associated with intravenous (IV) injection of the excipients and decomposition products quantified in the extracts.**
- **Attempted to identify a No Observed Adverse Effect Level (NOAEL) with IV injection.**
- **Margin of Safety**
  - Based on the IV NOAEL (mg/kg) divided by the highest level of the extracted excipient or decomposition product from 2 REMOXY ER (40 mg) capsules (mg/kg)

Safety Assessment of Triacetin with IV Injection

- It is rapidly metabolized systemically to endogenous constituents.
- It is listed in the FDA Inactive Ingredient Database (IID) for use in approved oral drug products.
- It has been experimentally evaluated as a component of total parenteral nutrition.
- The intravenous LD_{50} in animals ranges from 870 mg/kg to 2300 mg/kg.
  - Clinical observations of muscle weakness and ataxia were noted
- Animals receiving 31600 mg/kg by IV infusion daily for 7 days showed no evidence of toxicity.
- Safety Margin = 10096-fold the amount extracted in 2 REMOXY ER (40 mg) capsules.

Safety Assessment of Triacetin with Inhalation Exposure

- No toxicity occurred in animals with inhalation exposure to 8200 ppm (saturated vapor) for 6 hours per day for 5 days.
- No toxicity occurred in animals with inhalation exposure to 250 ppm for 6 hours per day, 5 days/week for 13 weeks.
- Slight ocular irritation in one animal study was reported with direct eye application.

Safety Assessment of HEC with IV Injection

- It is an approved IV drug product for hypovolemia/dehydration with a maximum recommended dose of 3000 mg/kg/day.
- It is listed in the FDA IID for use in approved oral drug products.
- It does not readily undergo metabolism systemically and is eliminated through the reticuloendothelium system and kidney.
- Acute IV injection of a 2.3% solution in animals produced hemodilution without toxicity.
- Repeated IV infusion of a 10% solution to animals produced hypervolemia without toxicity.
- Safety Margin = 12000-fold the amount extracted from 2 REMOXY ER (40 mg) capsules.

Safety Assessment of Acetic Acid with IV Injection

- It is a natural constituent readily metabolized in most tissues with endogenous plasma concentrations ranging from 13.5–22.8 µg/mL.
- It is listed in the FDA IID for use in approved IV drug products at levels up to 0.4% (Injection) and 1% (Infusion).
- It was detected at a level equivalent to 0.015% at a single temperature timepoint.
- Toxicity is a consequence of its irritant property.
- The IV LD50 (undiluted) in animals is 525 mg/kg with clinical signs of CNS toxicity.
- Margin of Safety relative to the LD50 = 21000-fold the amount extracted in 2 REMOXY ER (40 mg) capsules.

Safety Assessment of Myristic Acid with IV Injection

- It is a natural C14 fatty acid metabolized via β-oxidation pathway; endogenous human plasma concentrations range from 2.4 – 2.6 µg/mL.
- It is listed in the FDA IID for use in approved oral drug products; but it is a component of parenteral nutrition therapy at levels of 0.1% to 5.5%.
- It was detected at a level equivalent to 0.06% at a single temperature timepoint.
- IV LD50 (undiluted) in animals was reported to be 43 mg/kg.
- IV (but not IP) injection of 1 - 5 mg/kg to animals transiently lowered platelet counts, similar to stearic (C18), palmitic (C16), and lauric (C12) acids.
- Margin of Safety based on IV LD50 = 4300-fold the amount extracted in 2 REMOXY ER (40 mg) capsules.

Summary of Safety Margins

Material Identification	Maximum Amount Extracted (mg/mL)	Safety Margin*
Formulation Excipients		
Triacetin	18.63	10096
HEC	1.52	12000
Decomposition Products of Excipients		
Acetic Acid	0.15	21000
Myristic Acid	0.6	4300

* Based on the amount extracted from 2 REMOXY ER (40 mg) capsules

Conclusion

- In vitro extraction of the manipulated REMOXY ER (40 mg) capsule formulation detected two excipients and two decomposition products
- Systemic exposures to Triacetin and the two decomposition products are expected to be transient relative to their rapid metabolism to endogenous constituents
- Systemic exposure to HEC is eliminated by the reticuloendothelial system (RES) over a longer duration
- Results show a very low (negligible) risk for toxicity, and consequently, a very low potential for adverse effects with misuse

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Risk Mitigation and Summary

Michael Marsman, PharmD
Sr. Vice President, Regulatory Affairs
Pain Therapeutics, Inc.

Responsible Use

- **The Sponsor is committed to encouraging responsible and safe use of REMOXY ER.**
- **Sponsor will assure appropriate post-marketing safety initiatives and risk mitigation strategies are in place, as follows.**
  - Full participation in class-wide ER/LA Risk Evaluation and Mitigation Strategy (REMS)
  - Comprehensive drug safety and pharmacovigilance programs
  - Safe packaging, storage, disposal program for REMOXY ER
- **Sponsor currently has observer status in the REMS consortium and plans to convert to full voting membership after approval of REMOXY ER.**

REMOXY ER Risk/Benefit

- **REMOXY ER demonstrates a favorable risk/benefit profile.**
  - REMOXY ER met the clinical endpoints in a large, well-controlled Phase III efficacy study.
  - Safety profile of REMOXY ER is similar to other ER opioid products.
    No new or unexpected adverse events.
  - Based on the totality of Category 1, 2 and 3 study results, REMOXY ER can be expected to meaningfully deter injection, nasal, and smoking routes of abuse.

Conclusion

- **ADFs such as REMOXY ER can play an important role against prescription opioid abuse, while still ensuring appropriate access to patients suffering from chronic pain.**
- **REMOXY ER's unique formulation advances the science of abuse deterrence.**
  - Increases the range of available abuse-deterrent technologies
  - Provides another treatment option for chronic pain
  - Addresses vulnerabilities of existing ER oxycodone products
  - Demonstrates properties that can be expected to deter abuse by the nasal, injection, and smoking routes

THANK YOU

Open for Questions

Backup Slides Shown

REMOXY ER Steady-State PK Parameters

PK Parameter	PTI-821-CX REMOXY ER 40 mg	Collegium Study CP-OXYDET-18	
		Xtampza ER 40 mg	OxyContin ER 40 mg
C_{max} (ng/mL), mean ± SD	64.4 ± 26.3	77.7 ± 23.6	77.1 ± 17.8
T_{max} (hr), mean ± SD	4.3 ± 1.5	3.5 * (1.0 - 5.5)	4.5 * (1.0 - 6.5)
C_{min} (ng/mL), mean ± SD	25.6 ± 7.1	21.3 ± 7.1	21.2 ± 6.4
AUC_{tau} (hr*ng/mL), mean ± SD	510.2 ± 156	511 ± 116	532 ± 118
% PTF (12-hour dosing interval) **	87.9 ± 33.3	134 ± 35.8	127 ± 18.9

* T_{max} values are reported as median (range)

** % PTF = Percentage of peak-trough fluctuation within dosing interval

Remoxy Development: Preclinical Overview

- A comprehensive preclinical toxicological program was conducted to support the safety of REMOXY when taken by the intended clinical route of administration and consisted of the following studies in multiple species:
  - Acute, sub-chronic, and chronic oral toxicity
  - Genotoxicity
  - Carcinogenicity
  - Reproductive toxicity
  - Other toxicity
- The preclinical program was conducted in accordance with current FDA/ICH guidelines and discussions with FDA
- The nonclinical safety assessment of the oxycodone in the novel delivery matrix and of the inactive ingredients is complete and supports market registration of REMOXY for the intended clinical indication