

# **Xtampza™ ER (extended-release oxycodone) for the Treatment of Chronic Pain**

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**September 11, 2015**

Collegium Pharmaceutical, Inc.

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

## Introduction

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**Michael Heffernan, R.Ph.**  
Founder and Chief Executive Officer  
Collegium Pharmaceutical, Inc.

# Proposed Xstampza ER Indication

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**Xstampza ER** is an extended-release oxycodone product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

# Xtampza ER is a Unique Formulation of Oxycodone (DETERx Technology)



- Median microsphere size:  
~300 microns
- Contains oxycodone in the form of a lipophilic fatty acid salt
- Drug is homogeneously dispersed in fatty acid and waxes that impart ER properties
- Soft and waxy, with limited solubility in aqueous solutions

# **Chewing or Crushing ER ADF Products Carry Safety Risks**

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- All ER opioids have warnings against chewing & crushing

**[PRODUCT] TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED.**

**TAKING BROKEN, CHEWED, OR CRUSHED [PRODUCT] TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF [ACTIVE DRUG]**

- Rapid drug release is a risk for patients and the drug characteristic sought by abusers

# Xtampza ER Addresses Issues Facing Patient Care and Public Health

## **Xtampza ER**

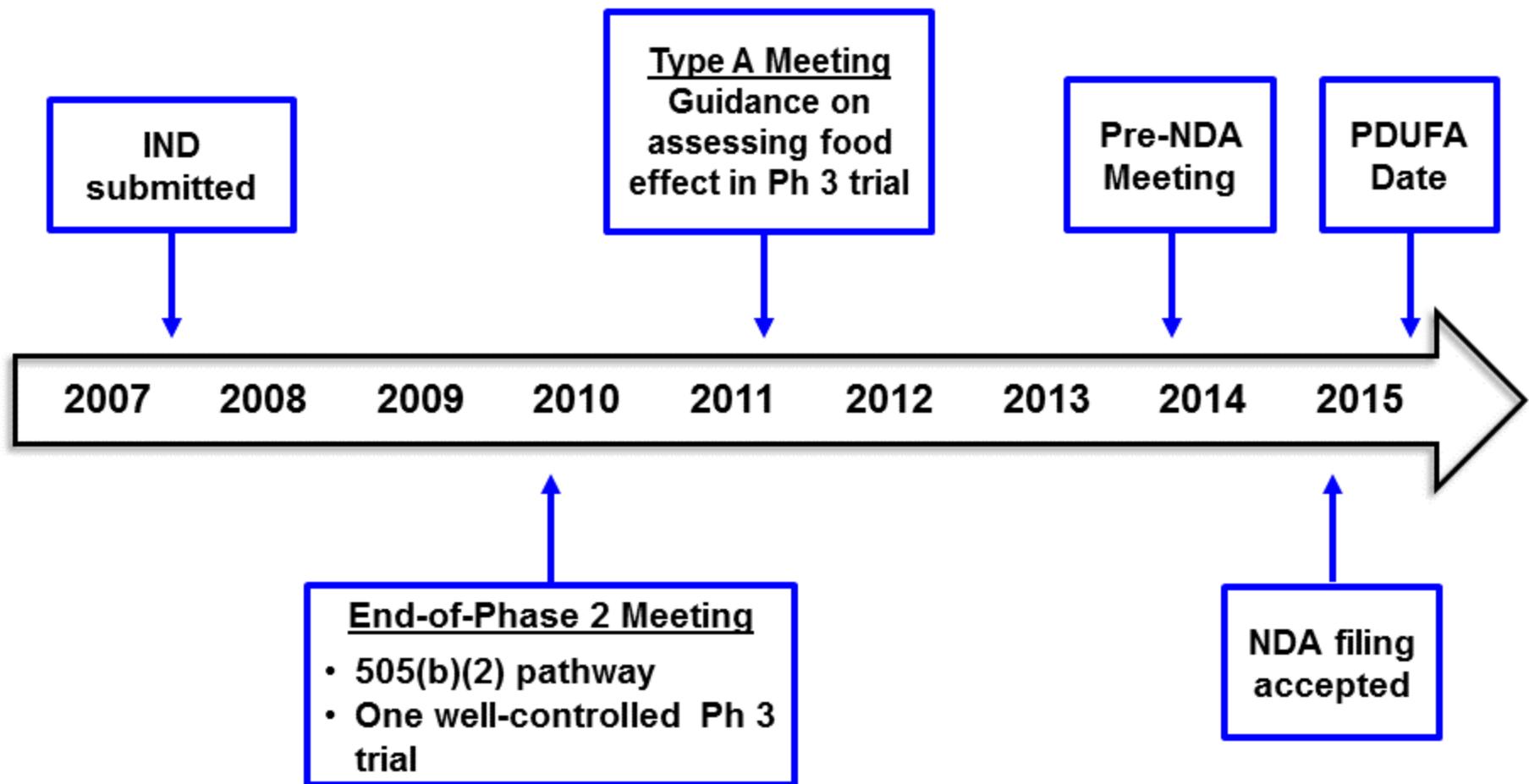
*Developed To Address 3 Key Issues*

**UNMET NEED**  
Difficulty  
Swallowing

**UNINTENTIONAL  
MISUSE**  
Crushing, Chewing,  
Dissolving

**INTENTIONAL  
ABUSE**  
Common Routes  
of Abuse

# Regulatory Milestones



# Clinical Development Program In Accordance with FDA Guidance

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- Extensive in vitro program
- 7 clinical PK studies
  - 4 oral PK, including relative bioavailability
  - 3 PK product manipulation
- 2 clinical PK/PD studies
  - Human abuse potential (oral and nasal)
- Phase 3 Clinical Trial
  - Efficacy and safety in moderate-to-severe chronic low back pain

## Phase 3 Study Demonstrated Efficacy, Safety, and Tolerability

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- Primary endpoint (superiority in pain reduction) achieved ( $P<0.0001$ )
- Safety profile consistent with similar products
- Food intake assessed with every dose in Phase 3 using electronic diary
  - Over 65,000 doses
  - No association between amount of food consumed and AEs

# Xtampza ER Provides Significant Barriers Against Abuse and Misuse

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- More difficult to manipulate/extract than OxyContin ADF
- Resistant to abuse by IV injection
- Studies show blood levels were:
  - Similar when intact, chewed, or crushed
  - Lower when crushed and snorted than intact
- More resistant to crushing than OxyContin ADF
  - Crushed Xtampza ER retains ER properties
  - Crushed OxyContin ADF bioequivalent to IR
- Met primary endpoints of nasal and oral human abuse potential studies

# Agenda

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**Public Health and Medical Need**

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**Bill McCarberg, M.D.**

Elizabeth Hospice and Neighborhood Healthcare (FQHC)

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**Abuse-Deterrence Studies**

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**Alison Fleming, Ph.D.**

Vice President of Product Development  
Collegium

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**Efficacy and Safety**

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**Ernest Kopecky, Ph.D., M.B.A.**

Vice President of Clinical Development  
Collegium

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**Clinical Pharmacology Food Effect**

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**Nicholas Fleischer, R.Ph., Ph.D**

Vice President  
The Weinberg Group Inc.

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**Risk Management**

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**Michael Heffernan, R.Ph.**

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**Benefit-Risk Profile**

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**Nathaniel Katz, M.D, M.S.**

President  
Analgesic Solutions

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# Additional Experts

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**Clinical Pharmacology  
Abuse Liability**

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**Edward Sellers, M.D., Ph.D., FRCPC, FACP**  
President  
DL Global Partners Inc.

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**Biostatistics**

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**Robert Brown, Ph.D.**  
INC Research

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**Abuse Liability**

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**Sidney Schnoll, M.D., Ph.D.**  
VP, Pharmaceutical Risk Management Services,  
Pinney Associates

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**REMS and Post-  
Marketing Surveillance**

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**Richard Dart, M.D., Ph.D.**  
Denver Health & Hospital Authority

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**Human Abuse Potential**

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**Stephanie Stanworth, M.S.**  
Independent Consultant

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## **Public Health and Medical Need**

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**Bill McCarberg, M.D.**

Hospice and Primary Care Physician

Elizabeth Hospice and Neighborhood Healthcare  
(FQHC), San Diego

President, American Academy of Pain  
Medicine

# Public Health, Patient Care Often Compromised By ER Opioid Options

## 3 Key Ways ER Opioid Treatments Can Compromise Public Health and Patient Care

Limited Options for Patients with Swallowing Difficulty

Unintentional Misuse by Crushing or Chewing

Intentional abuse to break down ER formulations

# Chronic Pain Is a Common Affliction

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- Chronic pain afflicts 25 million (11%) U.S. adults<sup>1</sup>
  - As common as heart disease, cancer, and diabetes
- Etiologies are diverse, including
  - Lower back pain
  - Osteoarthritis
  - Cancer
- Multiple treatment options
  - Surgery, injections, alternative therapies, non-opioid pharmacologics
- Opioids are appropriate choice for select patients

# Abuse and Diversion of Opioids are Public Health Challenge

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- Since 1999, four-fold increase in deaths associated with opioids<sup>1</sup>
- For every death<sup>2</sup>
  - 10 hospital admissions for misuse or abuse
  - 32 emergency room visits for abuse
  - 130 who abuse or are addicted
  - 825 non-medical users
- Challenge is appropriate access without stimulating abuse and misuse

<sup>1</sup> CDC/HCHS, National Vital Statistics System, Mortality File.

<sup>2</sup> Kochanek KD et al. *National Vital Statistics Report* 2011;60:1-117. CDC Vital Signs. 2012. Warner M et al. NCHS data brief, no 81. Hyattsville, MD: National Center for Health Statistics. 2011. National Center for Injury Prevention and Control. 2011.

# Progress in Abuse Deterrence with Current ER Opioid Formulations

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- Approaches to deter abuse include:
  - Agonist/antagonist
  - Aversive agents
  - Pro-drug
  - Physical/chemical barriers
- Most widely-used abuse-deterrent ER formulations
  - Hard, crush-resistant tablets
  - Contain polyethylene oxide, makes tablets sticky, difficult to swallow

# Hard Tablets Create Challenge for Patients with Chronic Pain and Difficulty Swallowing

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- 11 million patients in U.S. with chronic pain cannot or have difficulty swallowing pills<sup>1</sup>
- Dysphagia commonly associated with oral cancer, stroke, and Parkinson's, but affects many other patients, as well
- 2015 FDA Guidance on Tablets and Capsules<sup>2</sup>
  - Difficulty swallowing tablets and capsules may affect up to 40% of Americans
- Survey found 29% of patients taking opioids have trouble or do not like swallowing pills<sup>1</sup>

<sup>1</sup> Pergolizzi et al. *Curr Med Res Opin* 2013; 1-12.

<sup>2</sup> CDER. Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules: Guidance for Industry. June 2015.

# Dysphagia Can Lead to Patients to Misuse Their Opioid Medication

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- Manipulating ER tablets puts patients at risk for complications including respiratory depression, death
- 65% of chronic pain patients taking opioids did not know manipulating ER medicines changed the way the drug worked<sup>1</sup>

# Current Treatment Limitations for Patients with Chronic Pain, Difficulty Swallowing

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- Options for working around dysphagia
  - Transdermal patches
  - IR opioids
  - ER opioids
- FDA 2015 guidance on abuse deterrent opioids<sup>1</sup>
  - "...may need access to opioid products that are in solution or that can be crushed."

## Summary of Medical Need

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- Abuse-deterrent opioid formulations are important for public health
- Difficulty swallowing ER opioids can lead to suboptimal care
- Misusing ER formulations can lead to serious adverse reactions
- Some patients need ER opioids with flexible administration options

## **Abuse-Deterrence Studies**

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**Alison Fleming, Ph.D.**

Vice President of Product Development  
Collegium Pharmaceutical, Inc.

# Xtampza ER Abuse-Deterrent Development Program Adhered to FDA Guidance

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- Goals
  - Make manipulation more difficult to reduce unintentional misuse
  - Make abuse of manipulated product less attractive to reduce intentional abuse
- Approach
  - Targeted known or expected routes of abuse for oxycodone
  - Studies used immediate-release oxycodone and reformulated OxyContin ADF as comparators

# Studies Supporting Abuse-Deterrent Properties of Xtampza ER

## Category 1

Lab based *in vitro* manipulation and extraction studies

## Category 2

Pharmacokinetic Clinical Trials

## Category 3

Human Abuse Potential Clinical Trials

- Physical and chemical manipulation studies
- Route specific studies (IV and smoking)

**Five Clinical Trials**  
CP-17 (oral)  
CP-19 (nasal)  
CP-21 (nasal)  
CP-24 (oral)  
CP-25 (oral)

**Two Clinical Trials**  
CP-21 (nasal)  
CP-24 (oral)

# In Vitro Manipulation and Extraction Studies

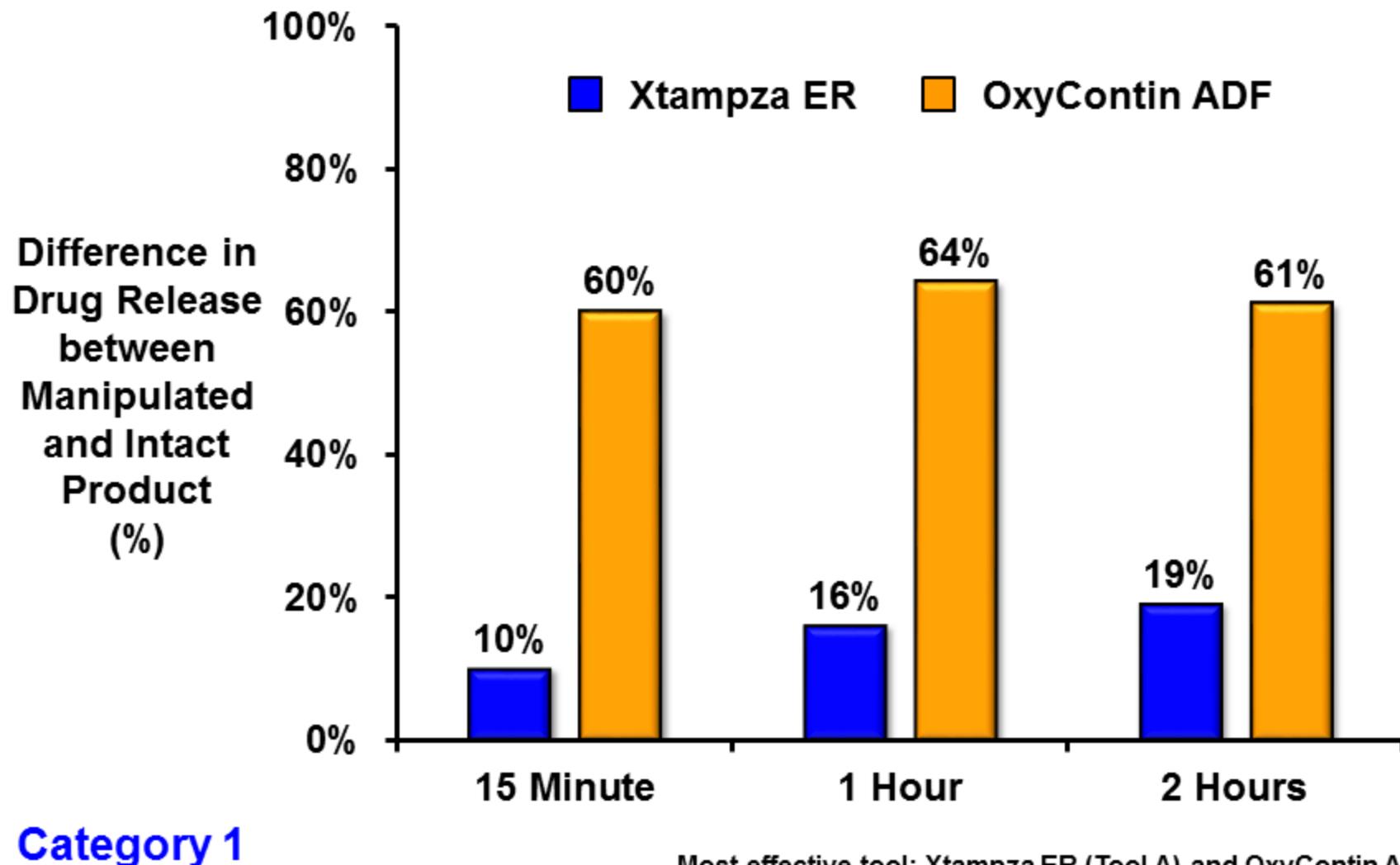
	Route	Assessment
<b>General Manipulations</b>	<b>Physical</b>	Impact of household tools on time-release mechanism
	<b>Chemical</b>	Extraction in common household solvents and more advanced solvents
	<b>Injection</b>	Extraction in small volumes of water
<b>Route-Specific Manipulations</b>	<b>Direct Injection</b>	Injectability after suspension in water or melting
	<b>Smoking</b>	Amount of drug vaporized on heating

# Physical Manipulation Studies of Xtampza ER vs OxyContin ADF

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- Literature and internet search conducted to determine common tools and methods used to crush ER formulations
  - Tools used by abusers
  - Tools used by patients/HCPs to facilitate dosing
- 11 household tools applied to Xtampza ER and OxyContin ADF
- Drug release of manipulated product compared to intact control assessed over 12 hours
  - Emphasis on first 2 hours where rapid release indicates destruction of time-release system

## Xtampza ER More Resistant to Physical Manipulation than OxyContin ADF with Most Effective Tool



Category 1

Most effective tool: Xtampza ER (Tool A) and OxyContin ADF (Tool G)

# No Tools Produced Doubling in Release of Drug with Xtampza ER

- 11 tools used to cut, grate, crush and grind

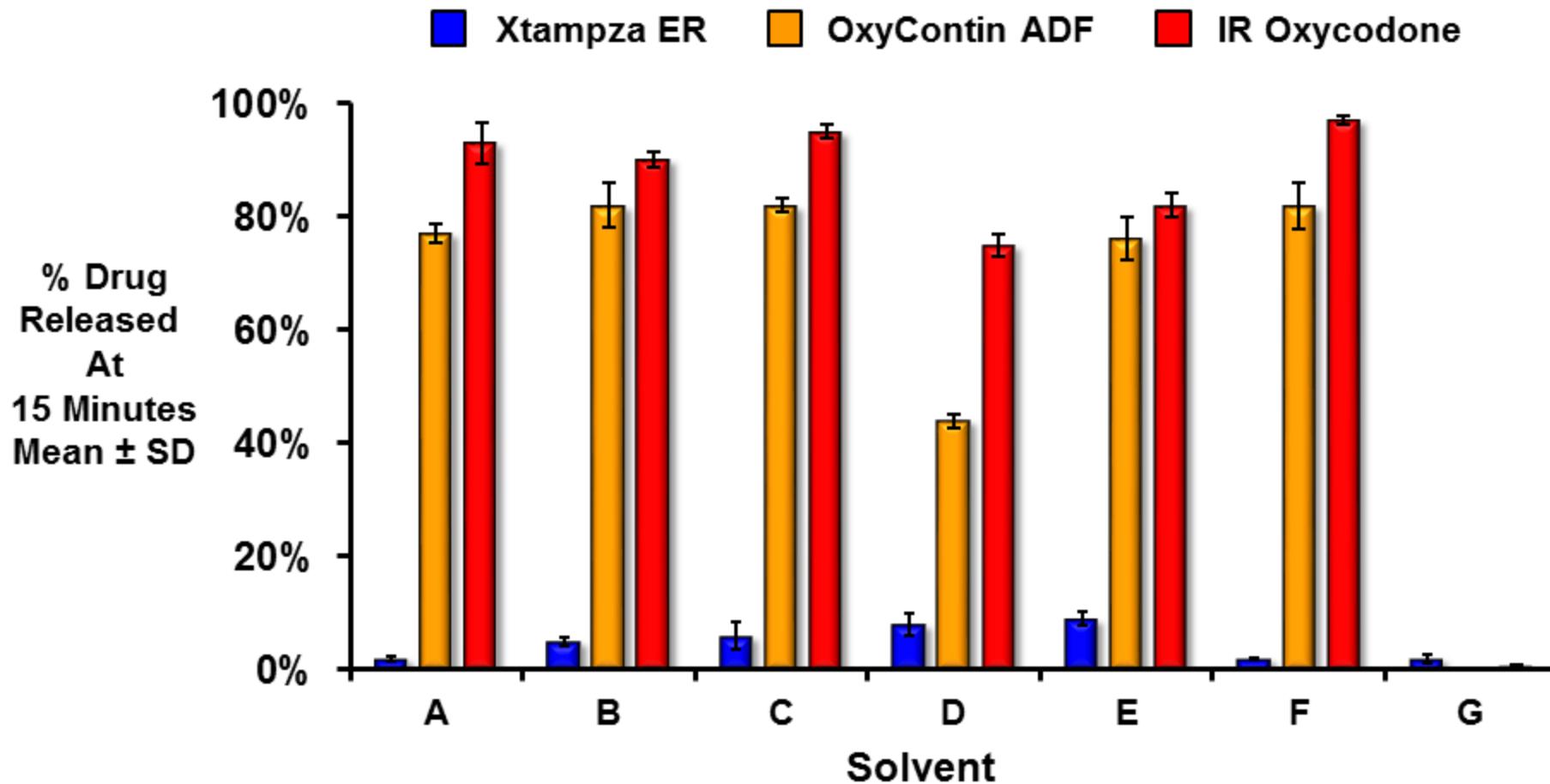
Dissolution Time Point	Number of Methods Doubling Release Compared to Intact Product	
	Xtampza ER	OxyContin ADF
15 minutes	0	7
1 hour	0	7
2 hours	0	6

# Chemical Manipulation Studies

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- Extraction studies
  - Evaluate rate of drug release in common, ingestible solvents and advanced solvents
  - Range of polarity and pH
- Studies investigated influence of exposure times and temperature
- Dosage forms crushed using most effective method of physical manipulation

# Manipulated Xtampza ER More Resistant to Extraction in Ingestible Solvents

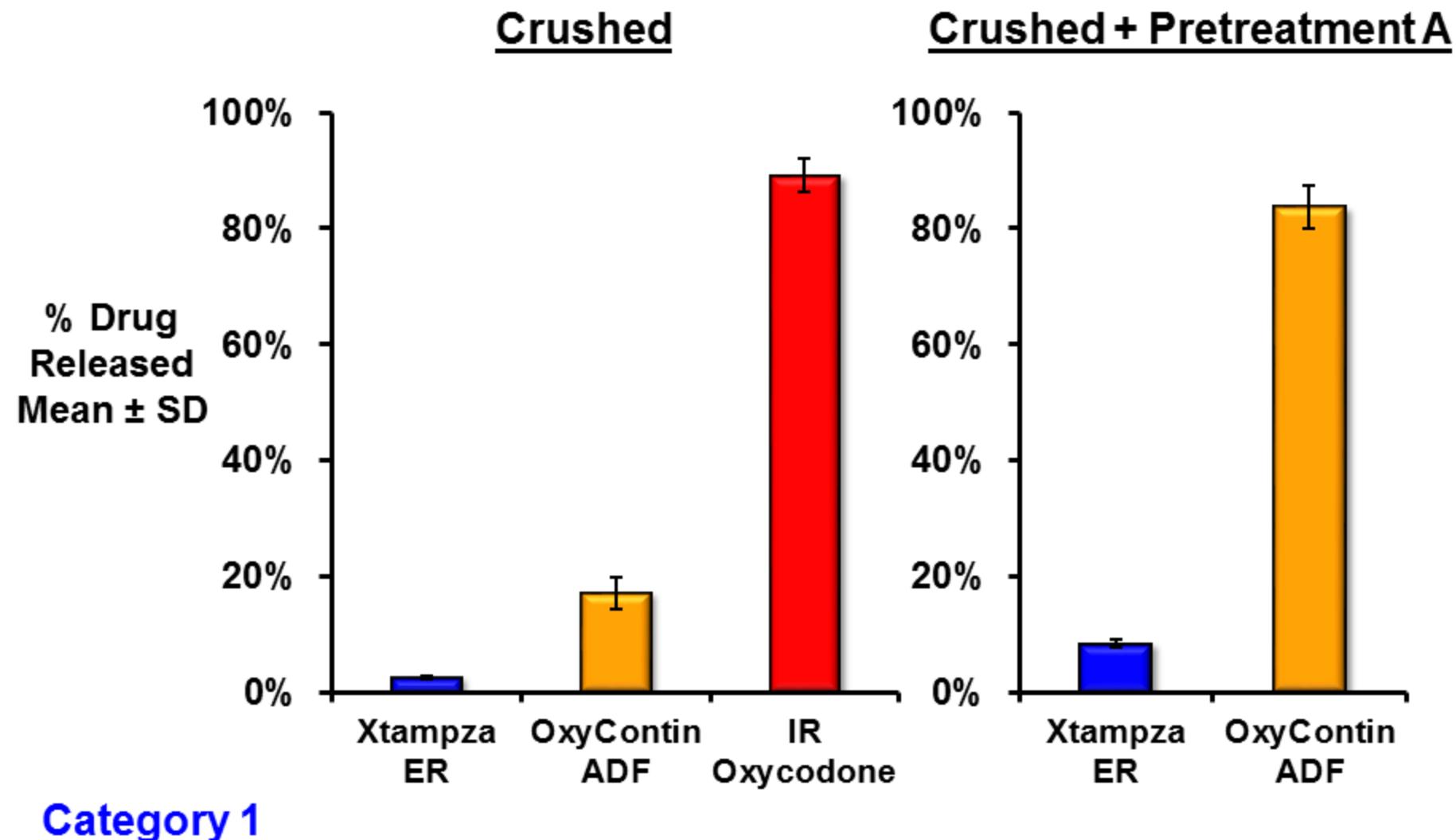


Category 1

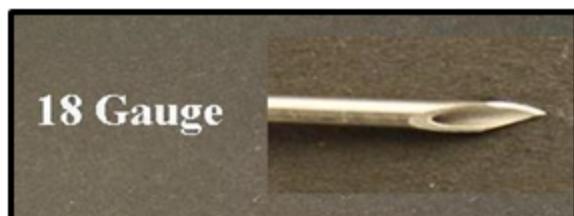
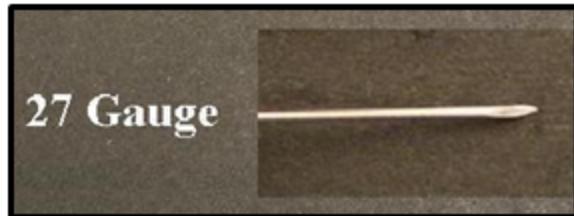
# Evaluation of IV Injection

	Route	Assessment
<b>General Manipulations</b>	<b>Physical</b>	Impact of household tools on time-release mechanism
	<b>Chemical</b>	Extraction in common household solvents and more advanced solvents
	<b>Injection</b>	Extraction in small volumes of water
<b>Route-Specific Manipulations</b>	<b>Direct Injection</b>	Injectability after suspension in water or melting
	<b>Smoking</b>	Amount of drug vaporized on heating

# Extraction for Injection Lower for Xtampza ER than Comparators



# Crushed Xtampza ER Microspheres Are Resistant to Direct Injection



Category 1

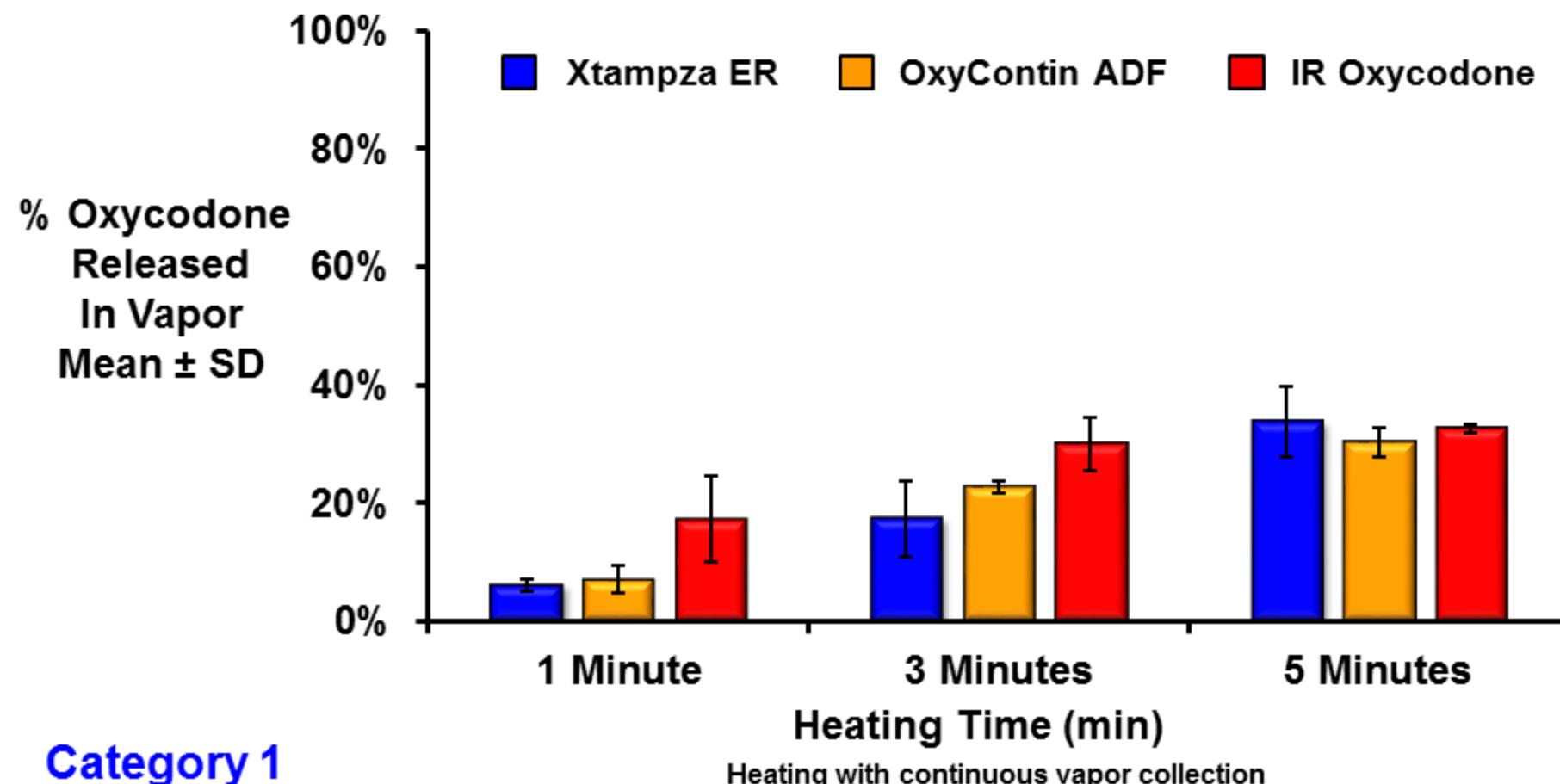
## Mean % Passage of Suspended Crushed Microspheres, 5 mL water

Needle Gauge	% of Fill Weight
27	0%
22	0%
18	13%
<b>Extreme Case:</b>	

Injecting by melting is also ineffective

# Release of Oxycodone through Smoking is Similar Across Formulations

- Only 4% of OxyContin abusers report smoking as route of abuse



Category 1

# Effect of Crushing or Chewing on PK (Oral & Nasal)

## Category 1

Lab based *in vitro* manipulation and extraction studies

- Physical and chemical manipulation studies
- Route specific studies (IV and smoking)

## Category 2

**Pharmacokinetic Clinical Trials**

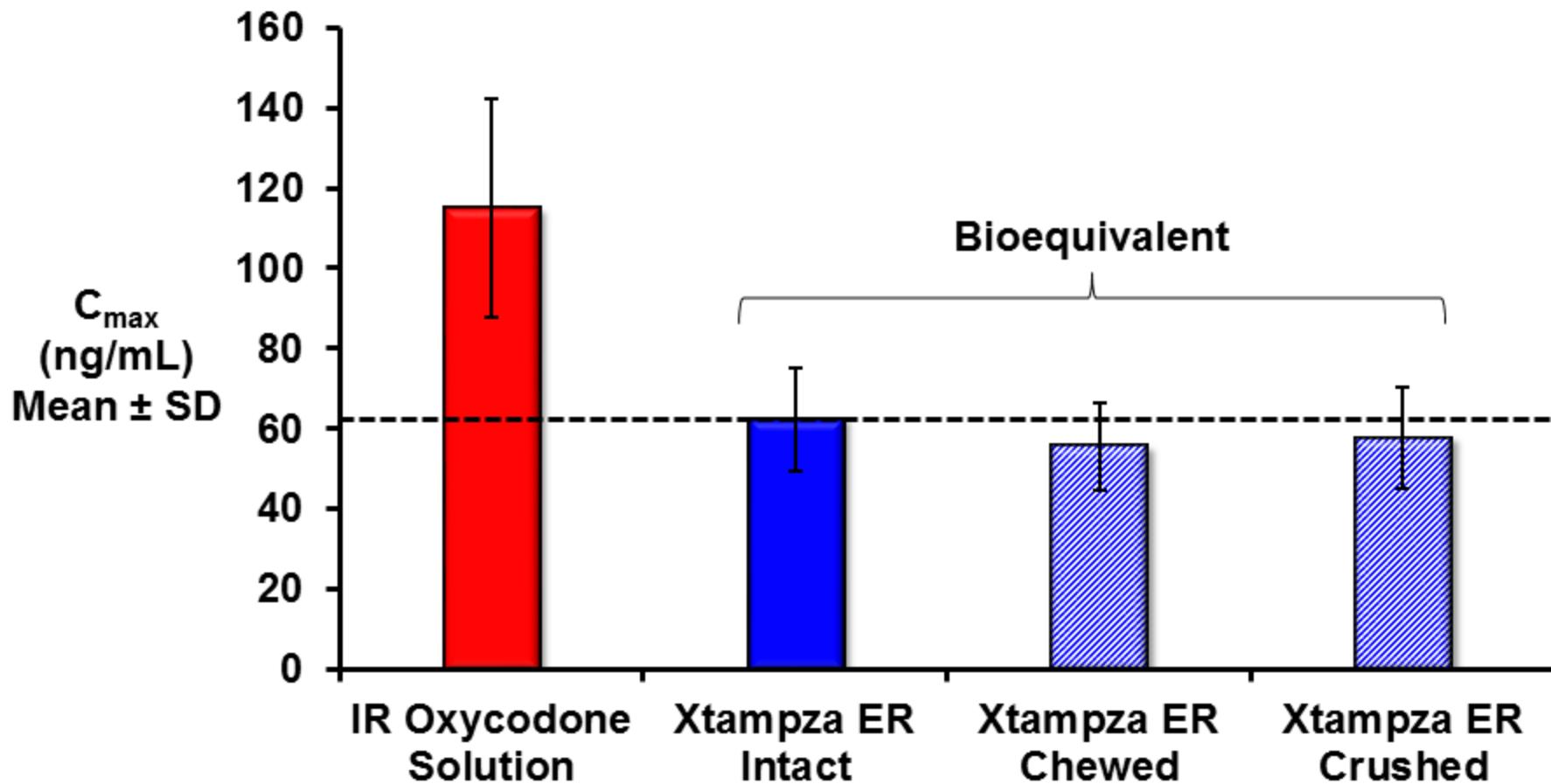
- Five Clinical Trials**
- CP-17 (oral)
  - CP-19 (nasal)
  - CP-21 (nasal)
  - CP-24 (oral)
  - CP-25 (oral)

## Category 3

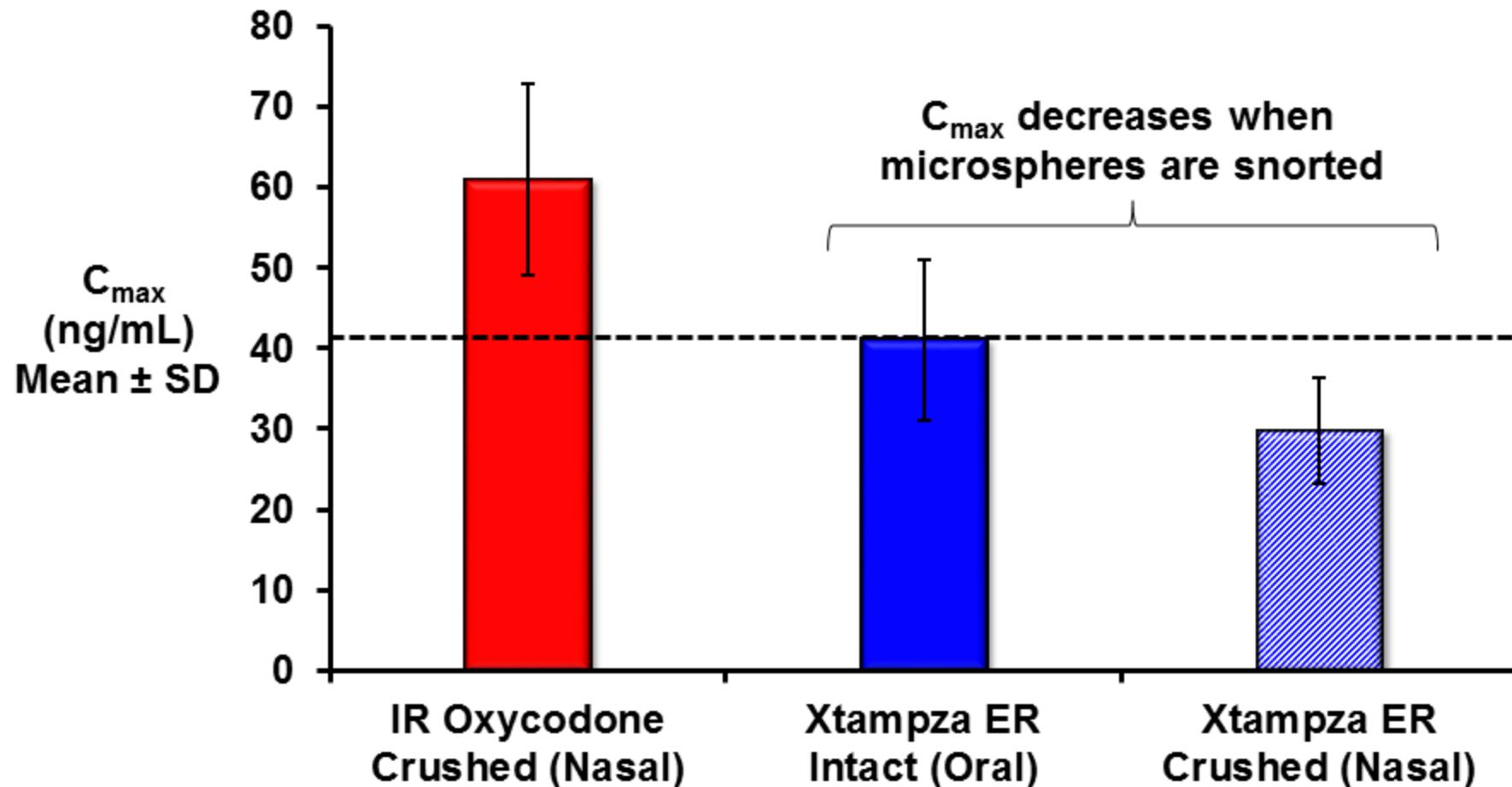
Human Abuse Potential Clinical Trials

- Two Clinical Trials**
- CP-21 (nasal)
  - CP-24 (oral)

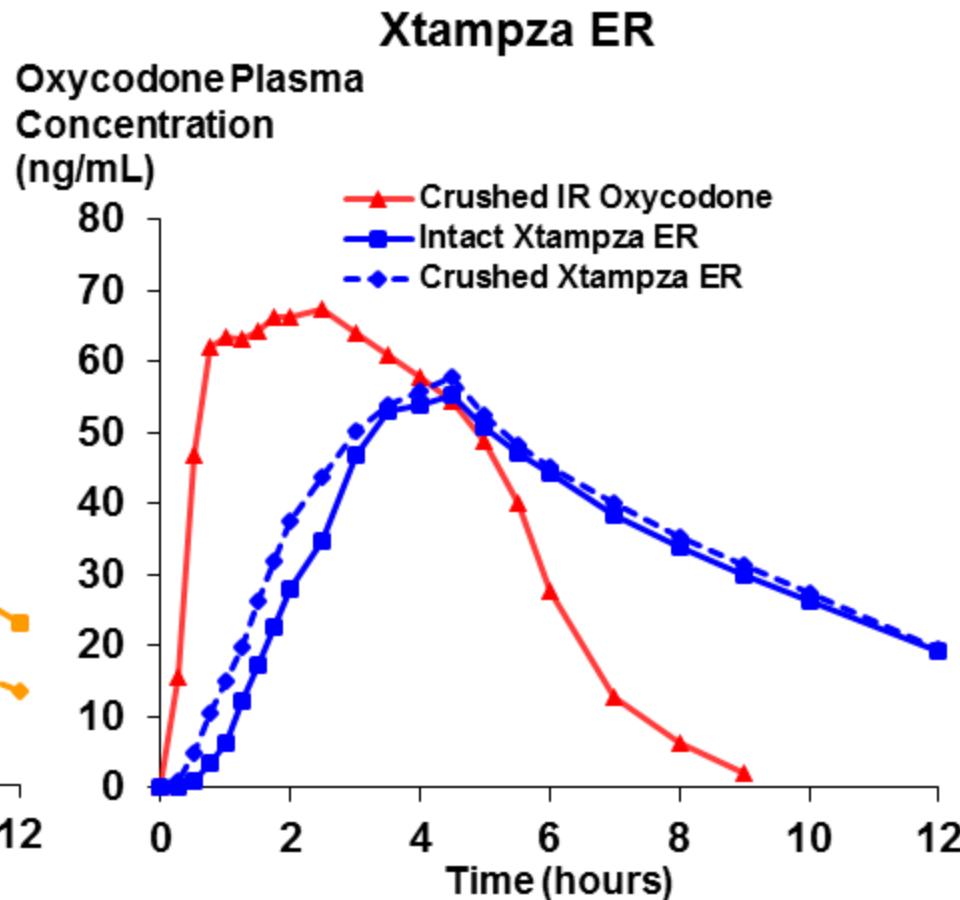
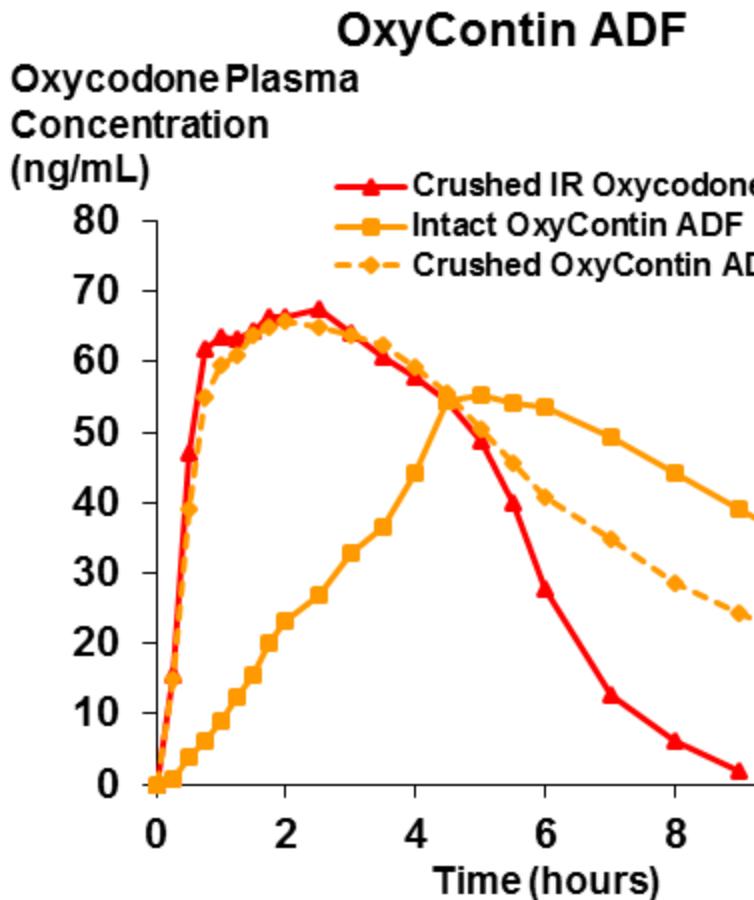
# Cewed and Crushed Xtampza ER Is Bioequivalent to Intact Dosing



# Peak Oxycodone Concentration Decreases for Snorted Xstampza ER



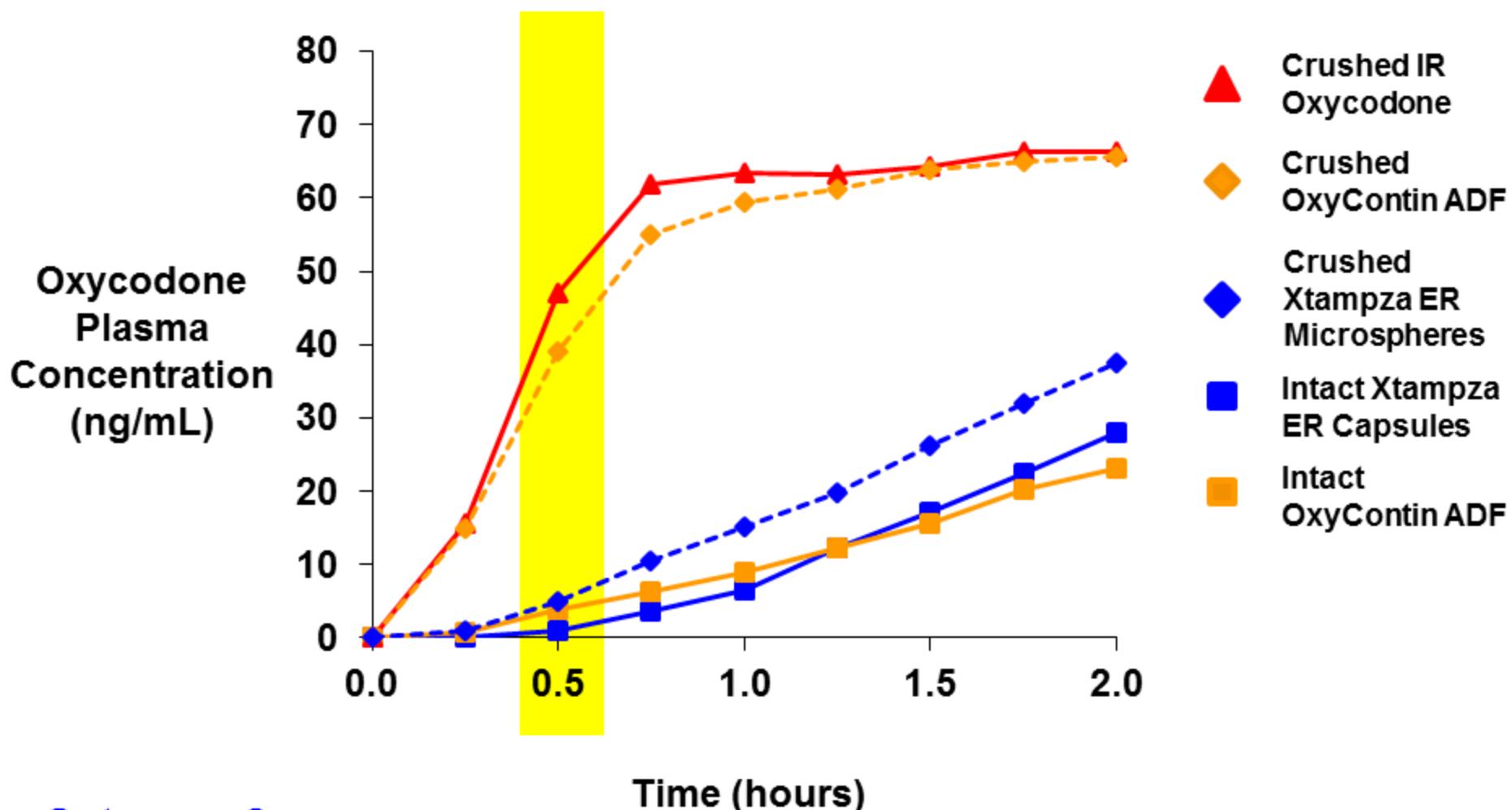
# PK of Xtampza ER Not Affected by Crushing



Crushed OxyContin ADF  
bioequivalent to IR oxycodone

Crushed Xtampza ER  
bioequivalent to intact Xtampza ER

# Minimal Elevation in Early Plasma Concentrations for Manipulated Xtampza ER



Category 2

Study 25

# Human Abuse Potential (Oral & Nasal)

## Category 1

Lab based *in vitro* manipulation and extraction studies

- Physical and chemical manipulation studies
- Route specific studies (IV and smoking)

## Category 2

Pharmacokinetic Clinical Trials

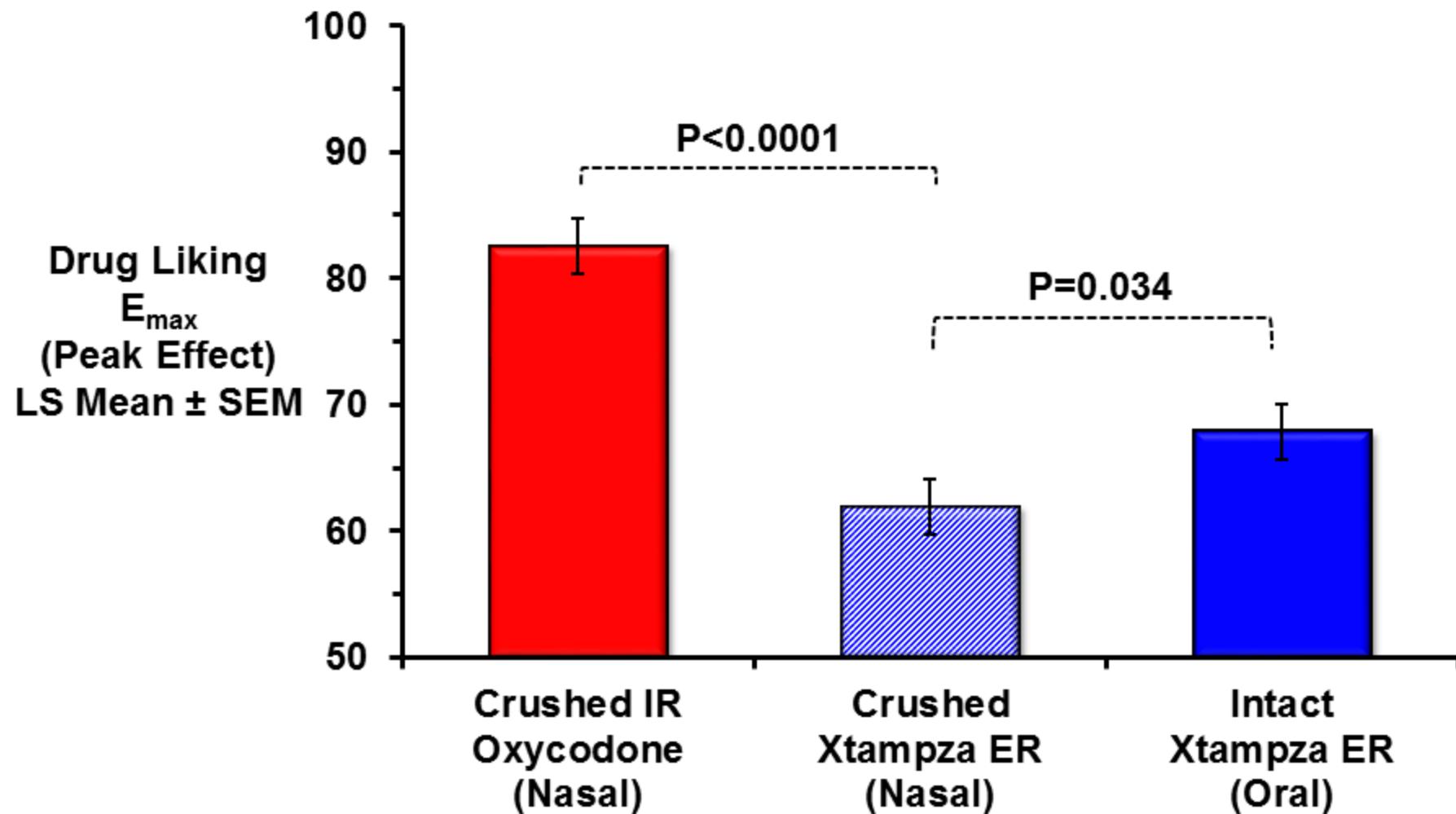
- Five Clinical Trials
- CP-17 (oral)
  - CP-19 (nasal)
  - CP-21 (nasal)
  - CP-24 (oral)
  - CP-25 (oral)

## Category 3

Human Abuse Potential Clinical Trials

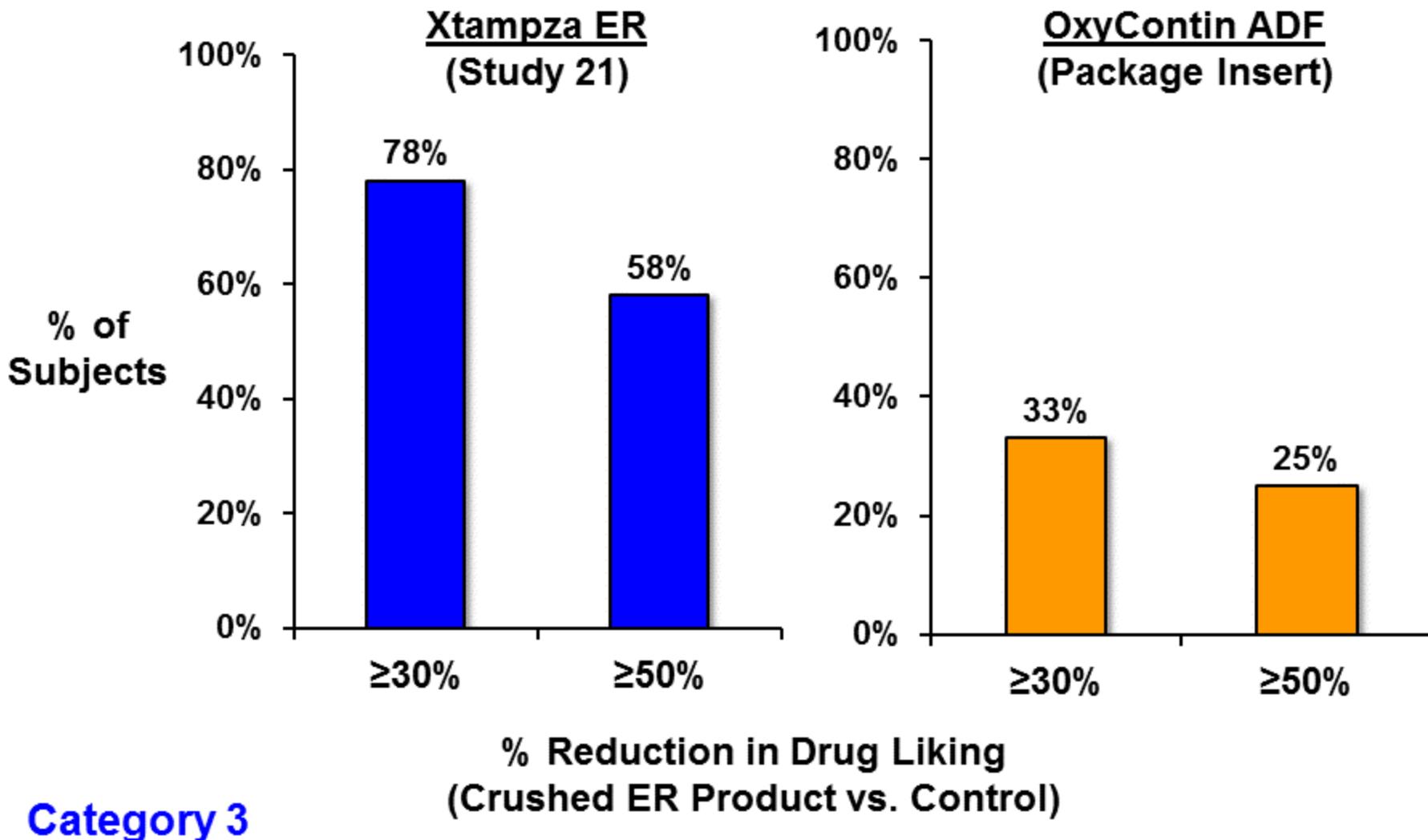
- Two Clinical Trials
- CP-21 (nasal)
  - CP-24 (oral)

## Lower Drug Liking for Snorted Xtampza ER Than Intact Dosing and Snorted IR Oxycodone

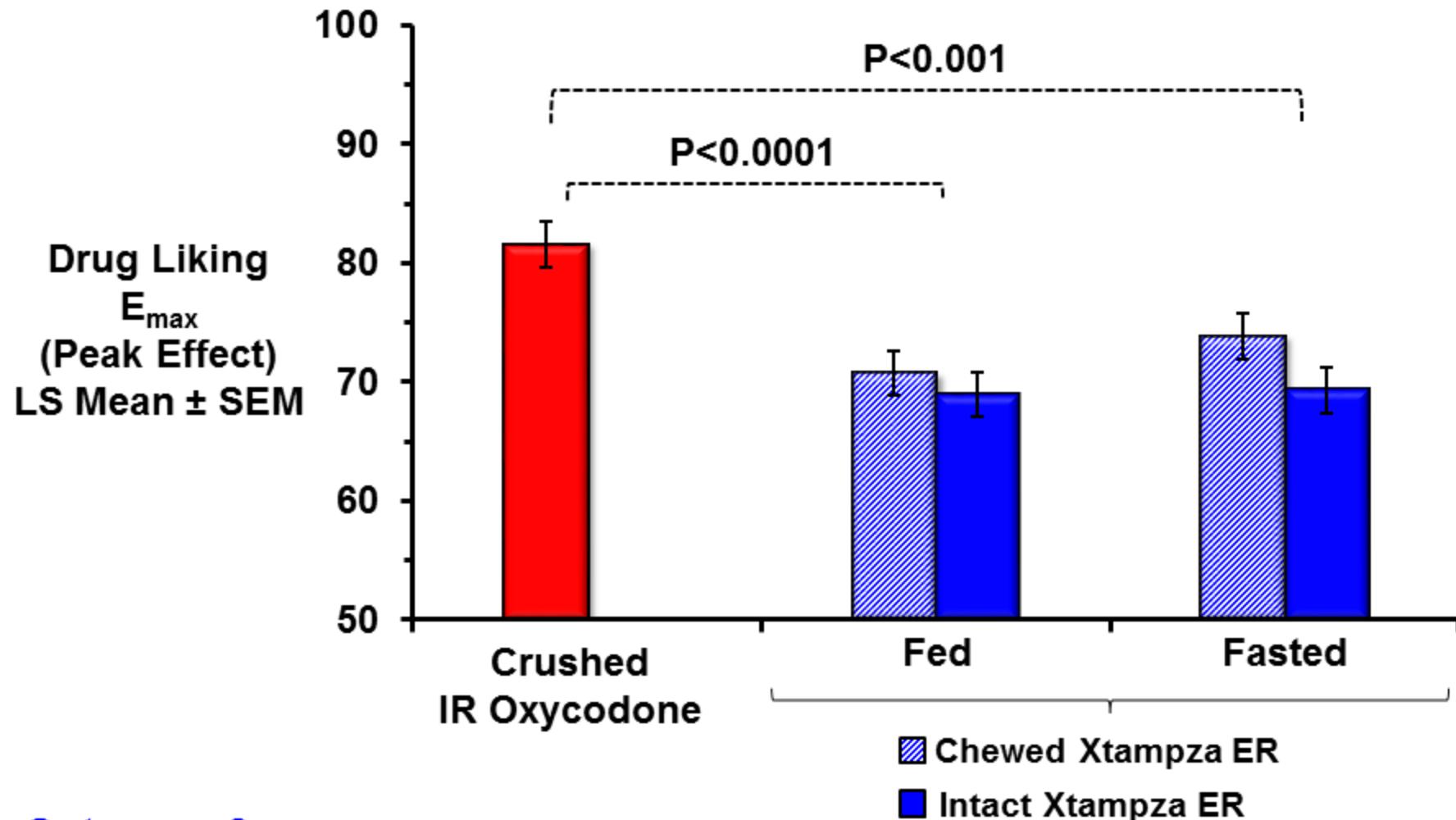


Category 3

# Significant Reduction in Drug Liking with Crushed and Snorted Xtampza ER



# Lower Drug Liking for Chewed Xtampza ER than Crushed IR Oxycodone



Category 3

# Summary of Key Endpoints for Chewed Xstampza ER in Oral HAP Study

Endpoints	P-value vs. Crushed IR Oxycodone	
	Chewed Xstampza ER HFHC	Chewed Xstampza ER Fasted
<b>Primary Endpoint</b>		
E <sub>max</sub> Drug Liking	<0.0001	0.0007
<b>Secondary Endpoints</b>		
High (E <sub>max</sub> )	<0.0001	<0.0001
Any Drug Effects (E <sub>max</sub> )	<0.0001	<0.0001
Good Drug Effects (E <sub>max</sub> )	<0.0001	<0.0001
ARCI/MBG	0.0002	0.017
Take Drug Again (E <sub>max</sub> )	0.07	0.67

# Summary of Findings from Xstampza ER Abuse-Deterrent Studies

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- Xstampza ER provides resistance to common manipulations
- Microspheres provide resistance to IV injection
- Xstampza maintained ER properties when crushed, unlike OxyContin ADF
- Snorting crushed Xstampza ER results in lower exposure than intact dosing
- Significantly lower drug liking (oral and nasal) versus IR oxycodone

## **Efficacy and Safety**

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**Ernest A. Kopecky, Ph.D, M.B.A.**  
Vice President of Clinical Development  
Head of Neuroscience  
Collegium Pharmaceutical, Inc.

## Phase 3 Study Overview

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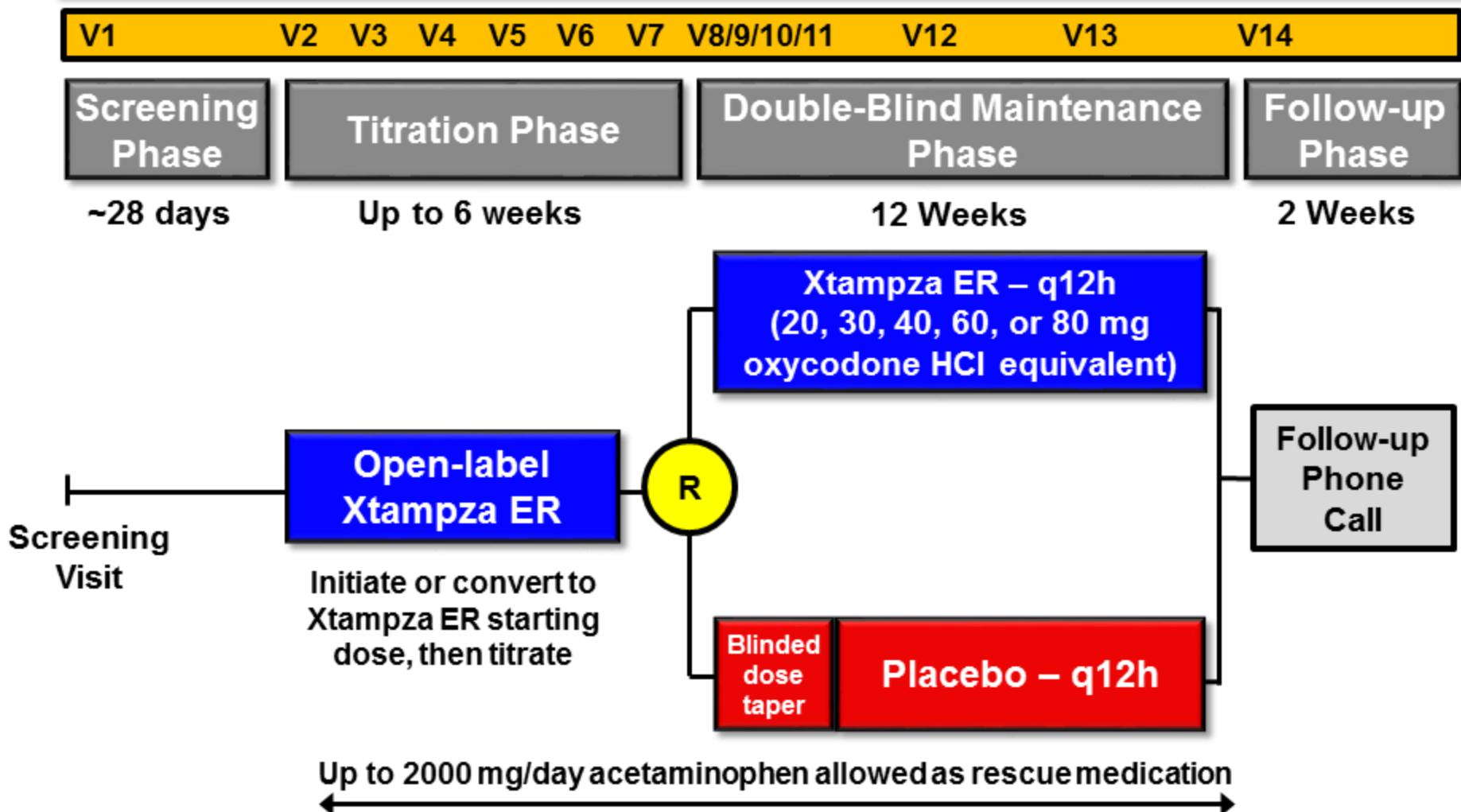
- Enriched-enrollment randomized withdrawal (EERW) double-blind, placebo-controlled study
- Enrolled subjects with  $\geq 6$ -month history of moderate-to-severe chronic lower back pain
  - Opioid-experienced and naïve subjects
  - Score of  $\geq 5$  and  $\leq 9$  on 11-point PI-NRS
- Compliant with FDA guidance and IMMPACT recommendations

# Food Instructions Emulated Real-World Use

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- Xtampza ER will be labeled “take with food”
- Study drug to be taken in morning and evening with food
  - No specific kind of meal/food required
- Food intake with study drug captured in electronic diary
  - No meal, snack, light meal, heavy meal

# Design of Phase 3 Study



R = Randomization; V = Visit; q12h = every 12 hours

# Primary Efficacy Endpoint

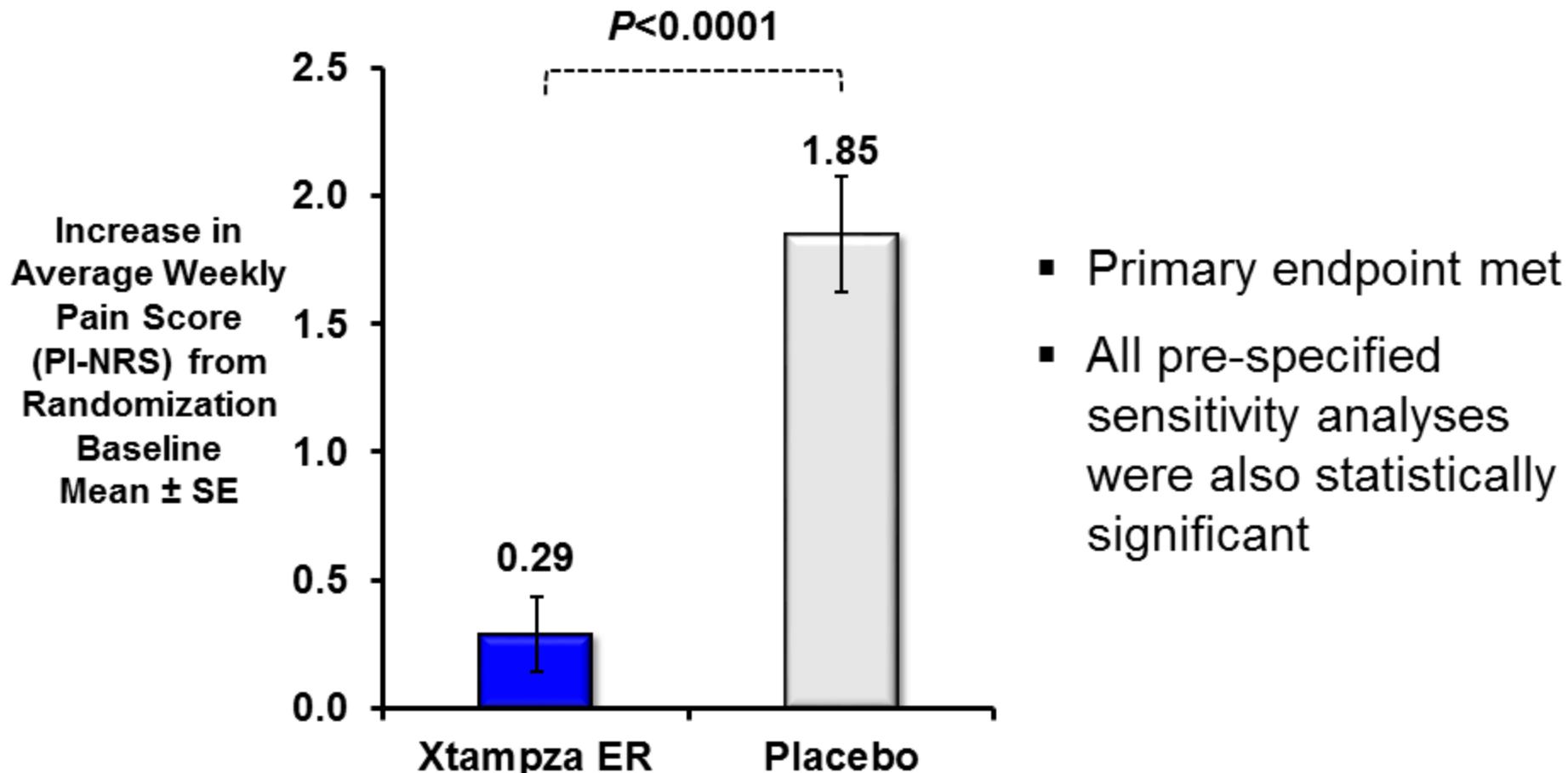
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- Change in average PI-NRS score from Randomization Baseline to Week 12
- Primary analysis on ITT population
  - All randomized subjects with a post-randomization dose
- Statistics
  - Primary analysis: 2-piece linear model
  - Multiple sensitivity analyses

# Subject Disposition – Double-blind Maintenance Phase

	Xtampza ER (N=193)	Placebo (N=196)
ITT Population	100%	100%
Completed Study	63%	51%
Discontinued Study	37%	49%
<b>Reasons for Discontinuation</b>		
Protocol violation	17%	13%
Adverse event	7%	7%
Lack of efficacy	4%	17%
Subject request	3%	7%
Lost to follow-up	2%	4%
Other <sup>1</sup>	4%	2%

# Primary Endpoint Met: Significantly Greater Reduction in Pain With Xtampza ER



# Most Common AEs in Double-Blind Maintenance Phase

Preferred Term	Xtampza ER (N=193)	Placebo (N=196)
Nausea	10.9%	4.6%
Headache	6.2%	11.7%
Constipation	5.2%	0.5%
Urinary tract infection	4.7%	1.0%
Diarrhea	4.1%	3.6%
Drug withdrawal syndrome	4.1%	1.5%
Fatigue	4.1%	1.0%
Vomiting	4.1%	1.5%
Nasopharyngitis	3.1%	2.0%
Upper respiratory tract infection	3.1%	4.1%

All AEs occurring at a ≥3% rate in the Xtampza ER treatment group are shown.

# Summary of Pivotal Phase 3 Study Findings

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- Study designed according to FDA guidance and IMMPACT recommendations
- Met primary efficacy endpoint ( $P<0.0001$ )
  - Consistent across sensitivity analyses
  - Treatment effect similar to other EERW trials of opioids
- Safety profile consistent with other ER opioids

# **Clinical Pharmacology and Food Effect**

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**Nicholas Fleischer, R.Ph., Ph.D**

Vice President,

Clinical Pharmacology and Biopharmaceutics  
The Weinberg Group Inc.

# Evaluation of the Food Effect with Xtampza ER

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- PK Evaluation of Food Effect
  - Single-dose, NTX blocked
  - Steady state, NTX blocked
  - Single-dose, non-NTX blocked
- Food Effects in Other Opioid Products
- Evaluation of Food Effect in Phase 3 Study
  - Safety
  - Efficacy

# Xtampza ER Bioavailability Similar to OxyContin ADF with Food

## Study 15: Single-dose, NTX blocked

Xtampza ER vs OxyContin ADF (**Fasted**)

$C_{max}$

$AUC_{last}$

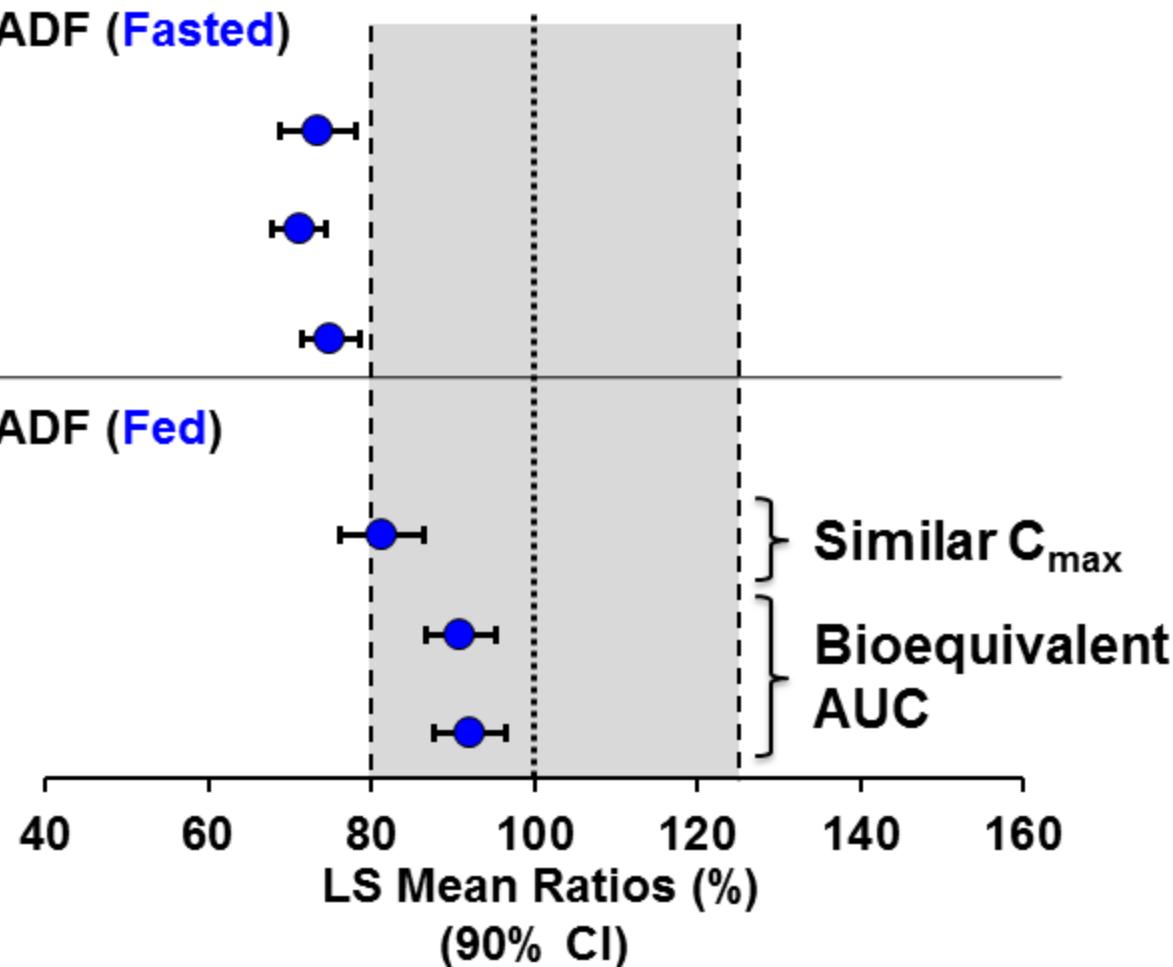
$AUC_{inf}$

Xtampza ER vs OxyContin ADF (**Fed**)

$C_{max}$

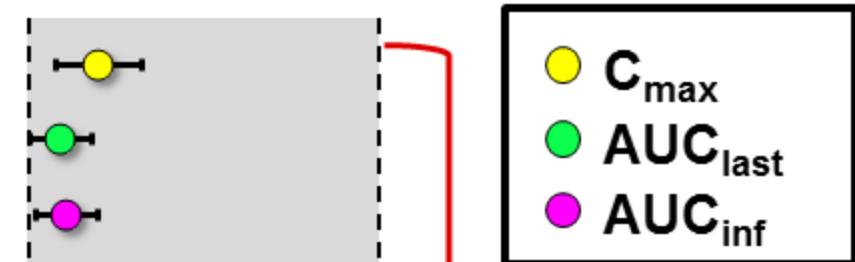
$AUC_{last}$

$AUC_{inf}$

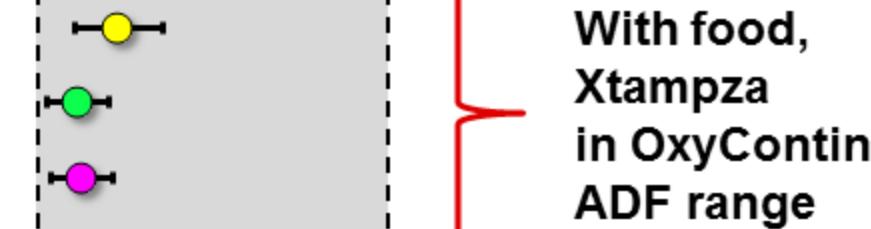


# Any Size Meal With Xtampza ER Produces PK Profile Comparable to OxyContin ADF

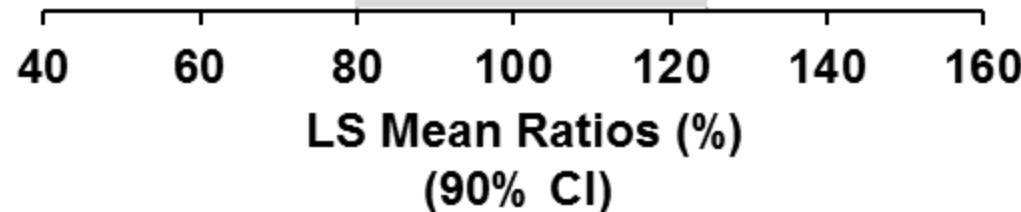
Xtampza, ~100 kcal, low-fat  
Vs OxyContin Fasted



Xtampza, ~400 kcal, med-fat  
Vs OxyContin HFHC

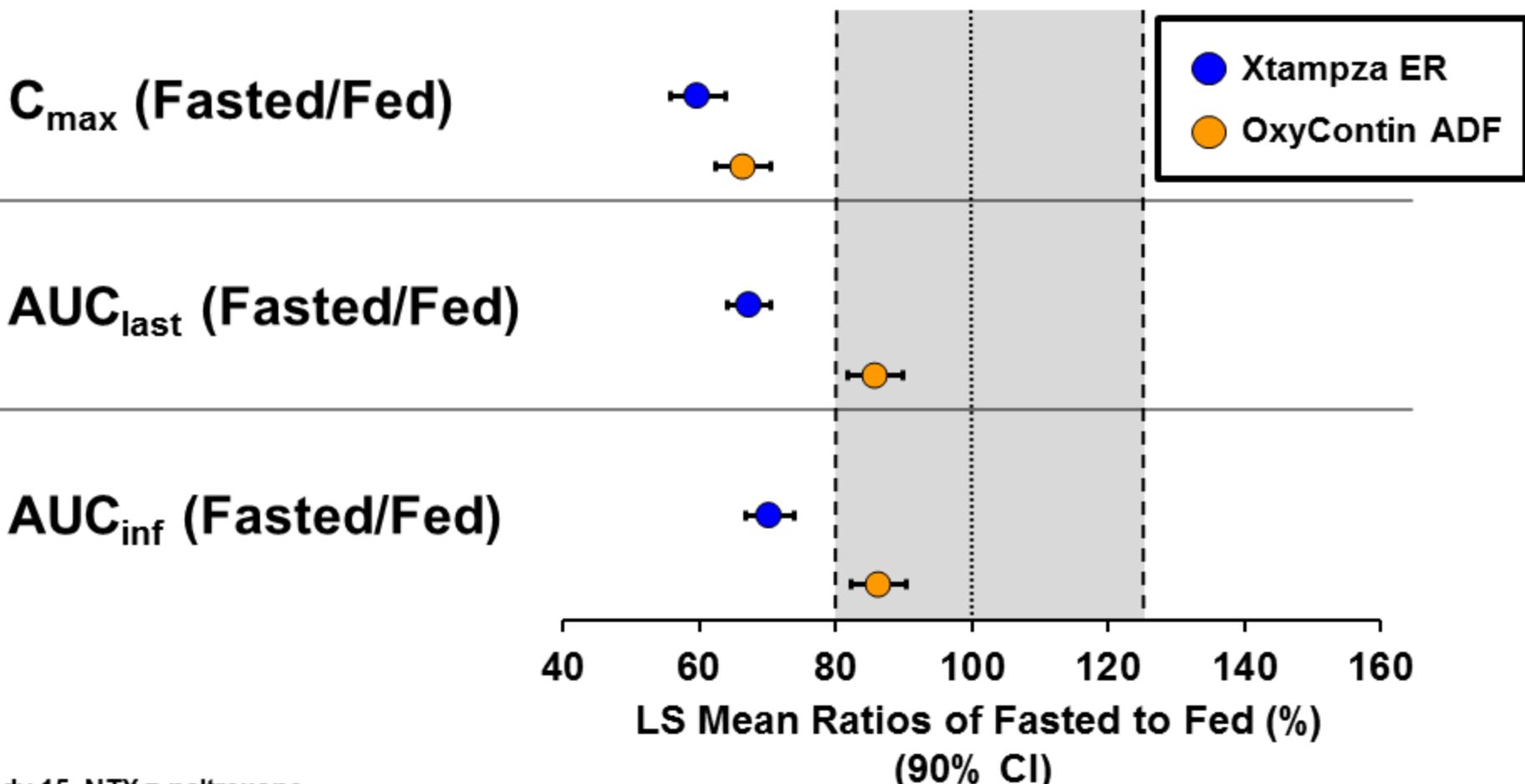


Xtampza, ~900 kcal, high-fat  
Vs OxyContin HFHC



# Xtampza ER and OxyContin ADF Both Show a Food Effect with NTX

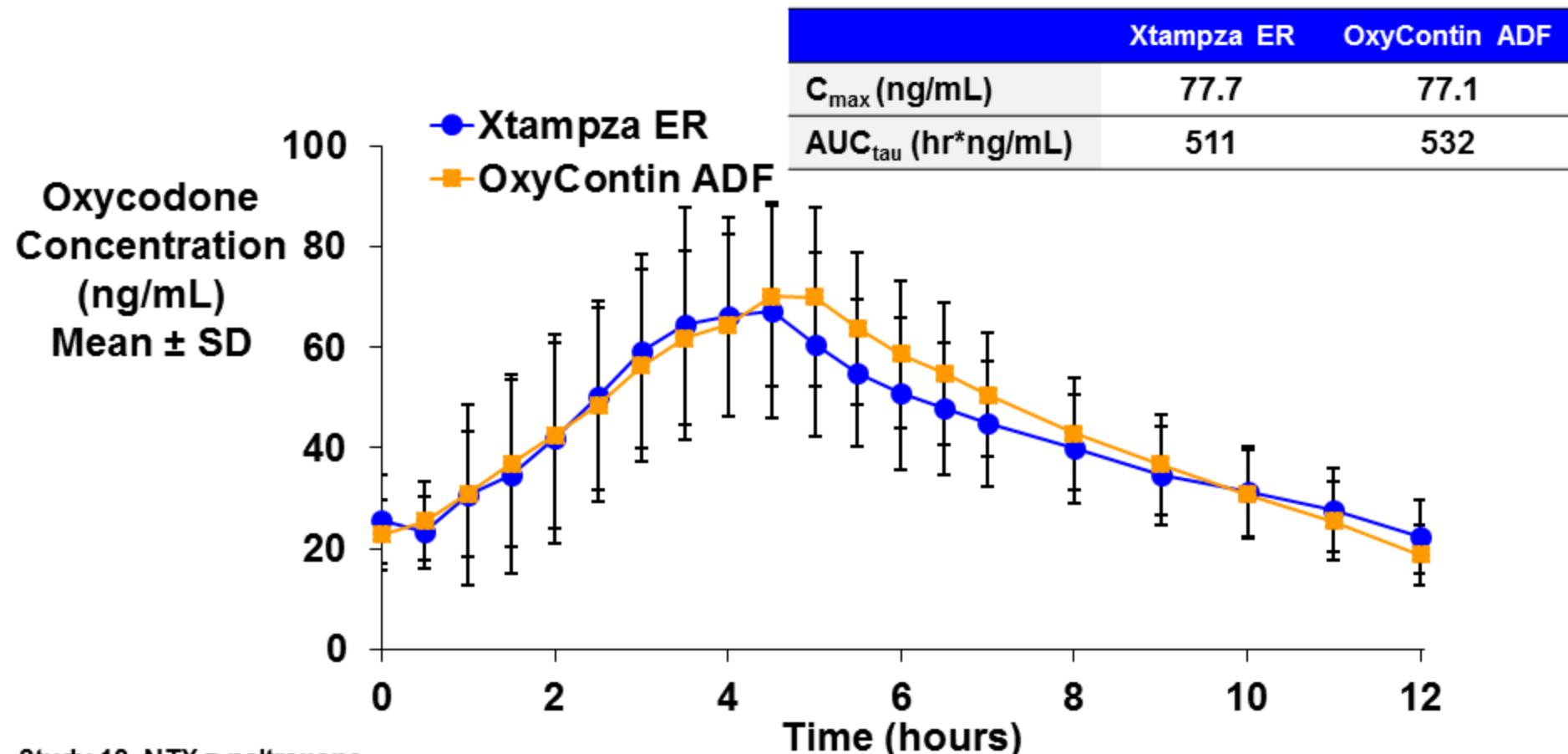
## Study 15: Single-dose, NTX blocked



# Xtampza ER and OxyContin ADF Are Bioequivalent At Steady State With Compliant Food Instruction

## Study 18: Steady-State, NTX blocked

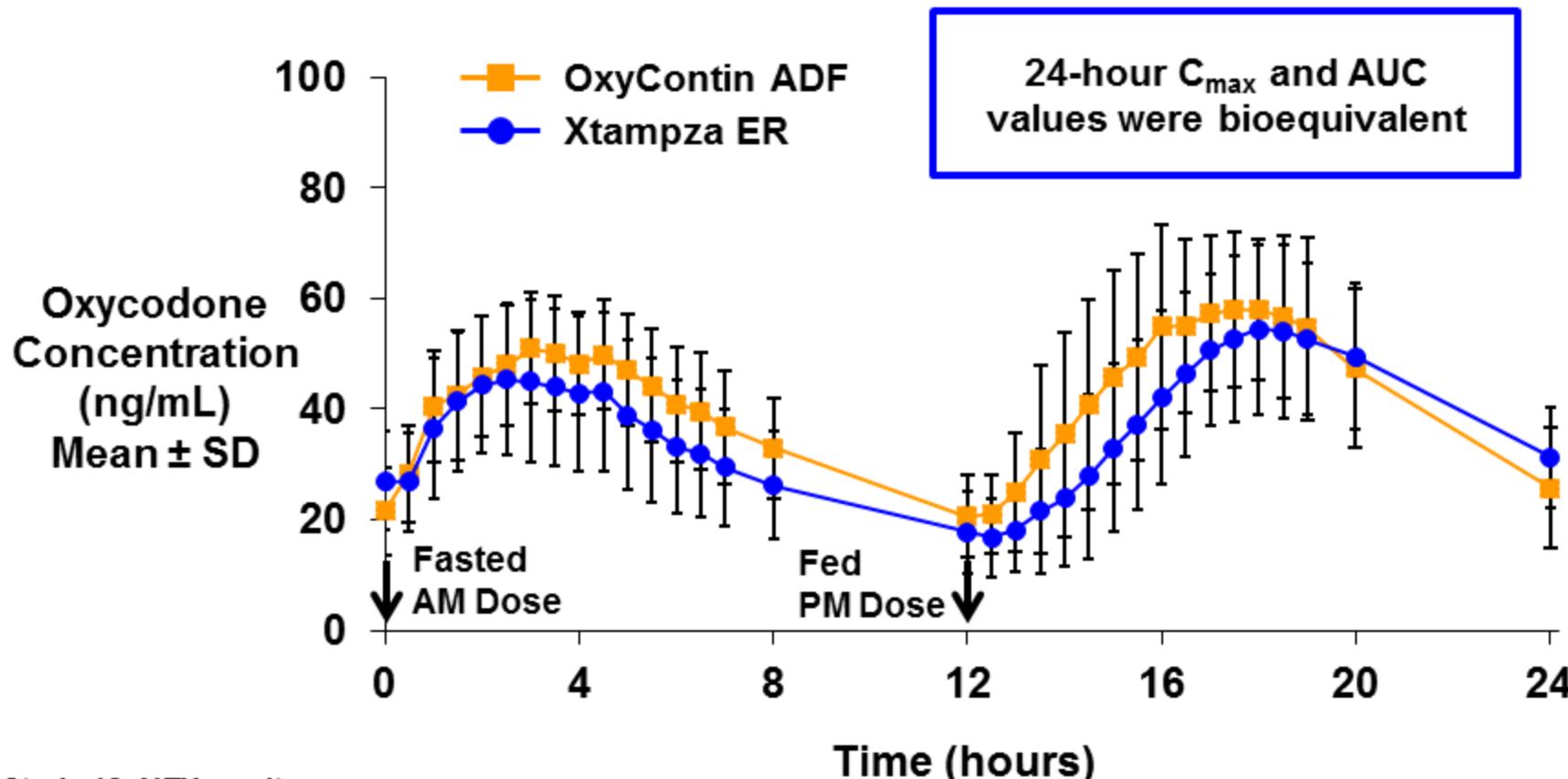
*Q12h Dosing, Fed Conditions – Day 5*



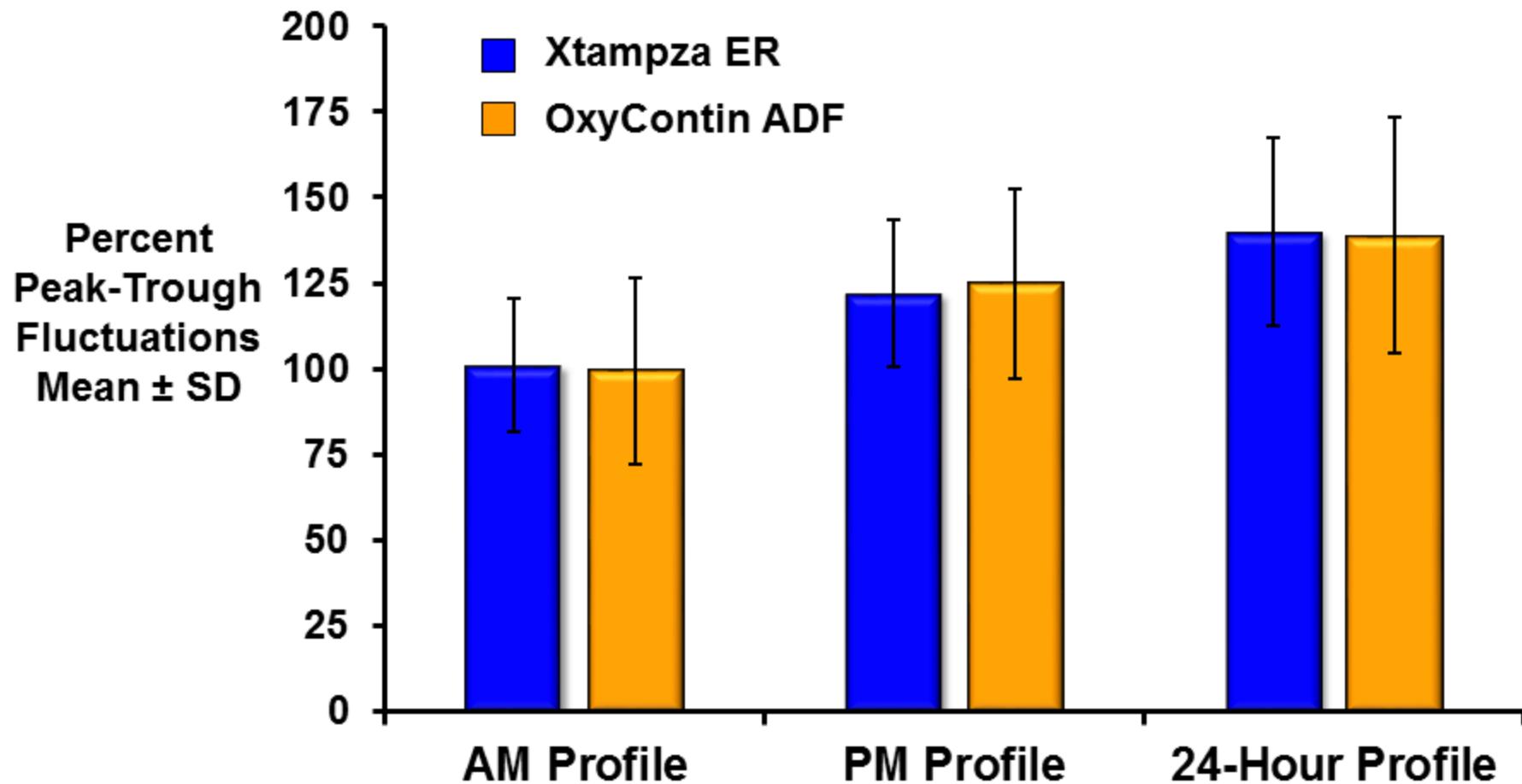
## Xtampza ER and OxyContin ADF Have Similar PK Profiles At Steady State When Non-Compliant With Food Instruction

### Study 18: Steady-State, NTX blocked

*Q12h Dosing, Fasted AM / Fed PM Conditions – Day 5*



# Similar Peak-Trough Fluctuations at Steady State Under Non-Compliant Conditions



# Naltrexone Block Can Enhance Opioid Absorption

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- Xtampza ER PK program primarily under NTX block
- Co-administration of opioids with NTX can enhance absorption<sup>1</sup>
- Food effect data for Xtampza ER collected from study without NTX (Study 24)

# Naltrexone Block Enhances Magnitude of Food Effect with Xtampza ER

**C<sub>max</sub> (Fasted/Fed)**

With NTX



**AUC<sub>last</sub> (Fasted/Fed)**

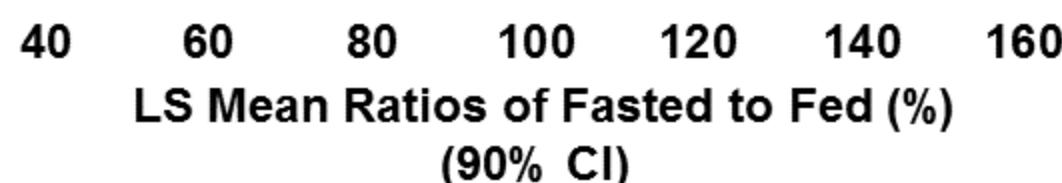
With NTX

Without NTX

**AUC<sub>inf</sub> (Fasted/Fed)**

With NTX

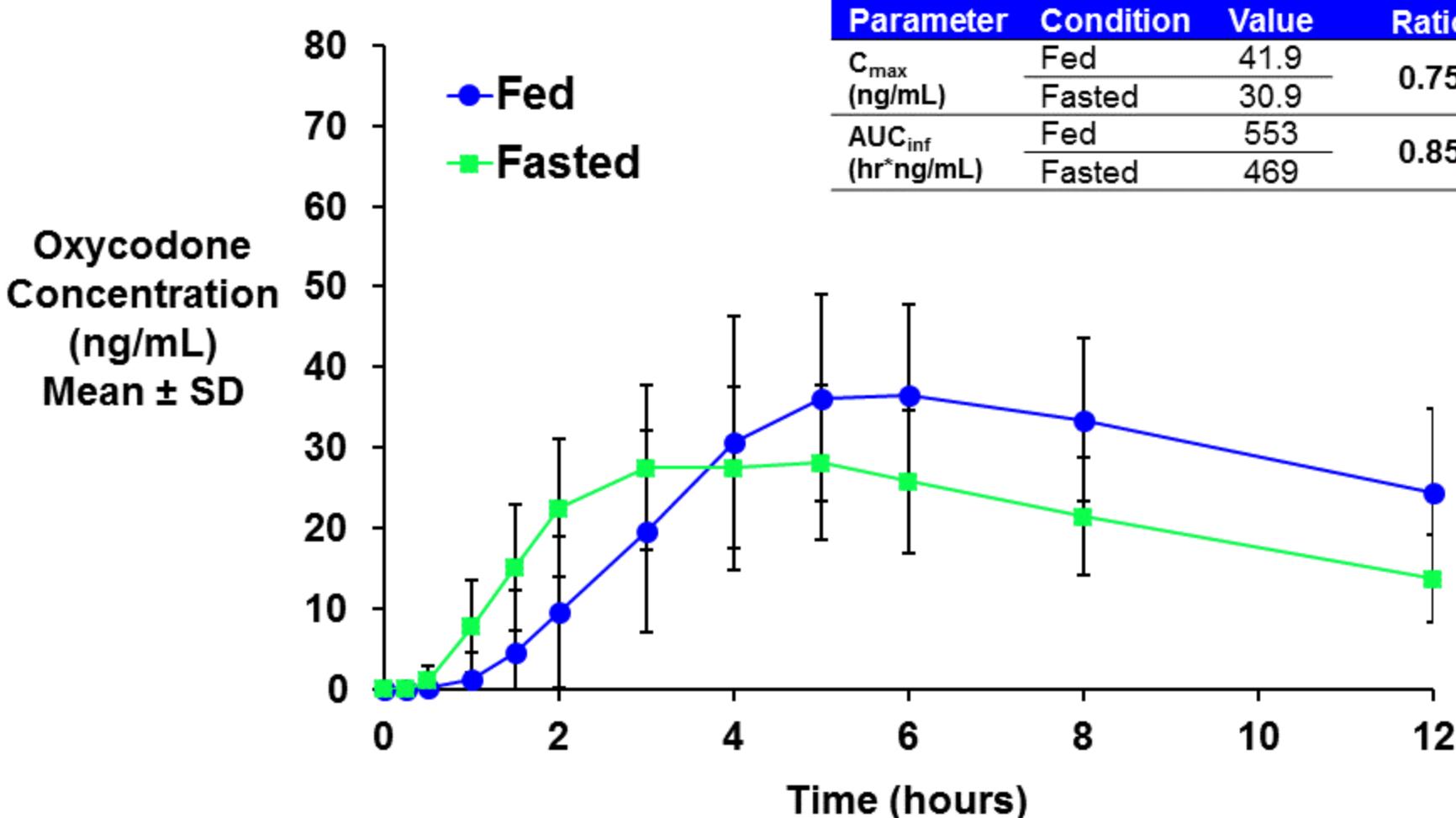
Without NTX



Study 15 (single dose with naltrexone)

Study 24 (single dose without naltrexone)

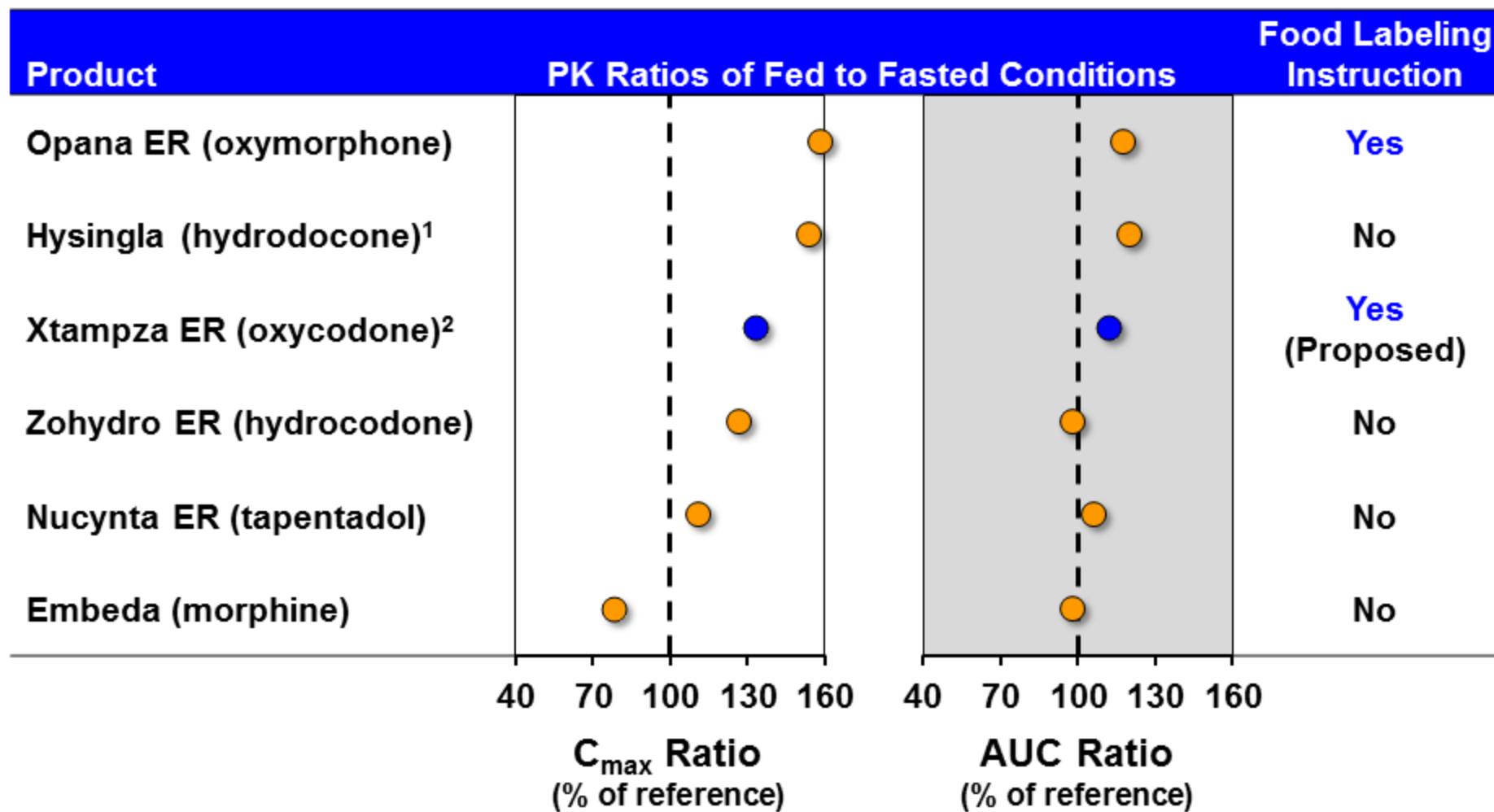
# Oxycodone Exposure Over Time for Fasted and Fed States Without Naltrexone



# High C<sub>max</sub> Ratios Influenced by Study Conditions (Naltrexone & Steady-State)

Treatment	C <sub>max</sub> Ratio (Fed/Fasted)	Fed C <sub>max</sub> (ng/ml)	Fasted C <sub>max</sub> (ng/ml)	Difference
<b>Single Dose, NTX Block (Studies 15, 17, 26, 27)</b>				
Xtampza ER	5.9	79.9	13.5	66.4
	5.0	64.8	12.9	51.9
<b>Single Dose, No NTX (Study 24)</b>				
Xtampza ER	2.1	36.9	17.2	19.7
	2.1	33.5	16.0	17.5
<b>Steady State, NTX Block (Study 18)</b>				
Xtampza ER	2.0	52.0	25.4	26.6
	2.0	58.5	29.9	28.6
OxyContin ADF	2.3	92.0	40.1	51.9
	1.8	80.5	43.9	36.6

# Food Effect with Xtampza ER Falls Within Range of Other Opioid Products



<sup>1</sup> Conducted under naltrexone block. <sup>2</sup> Data from Study 24.

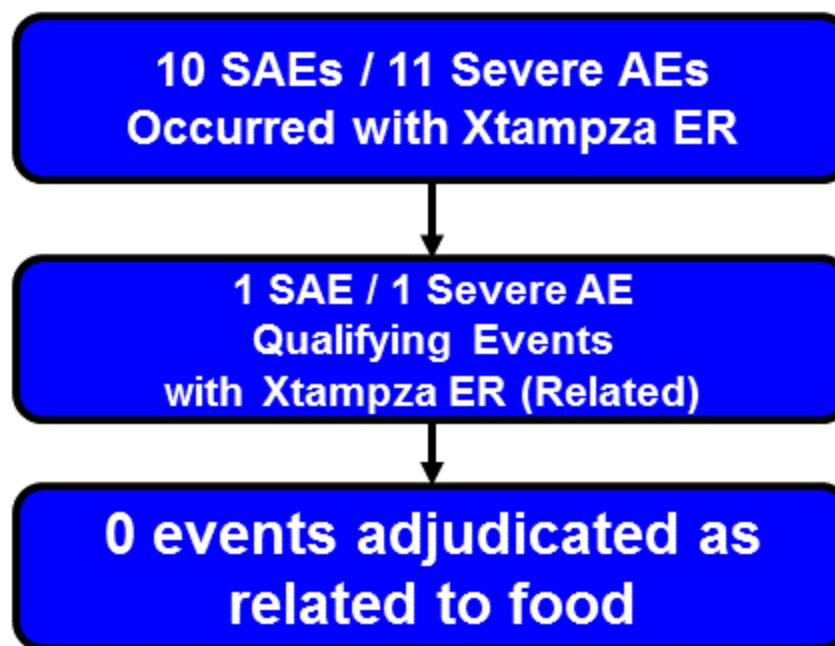
# Phase 3 Study Food Effect Safety Protocol and Adjudication

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- Pre-specified food-effect PK safety protocol developed to collect information on qualifying events
  - SAE or severe AE potentially, probably, or definitely-related to study drug per Principal Investigator
  - Association between food and qualifying events assessed by independent adjudication committee

# No Association Between Qualifying Events with Xstampza ER and Food

- ~65,000 doses of Xstampza ER in Phase 3 study
- Exposure to Xstampza ER up to 4.5 months



# Phase 3 Study Compared Specific Meal Patterns to Incidence of AEs

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- Meal pattern analysis assessed potential association between specific meal patterns and AEs (all, related, and opioid-associated)
- Categorized meals for analysis
  - High = light or heavy meal
  - Low = no meal or snack
- Meal patterns: 2 consecutive meals consumed at the times of study drug dosing at the time of the AE

# No Indication of a Food Association with AEs in Meal Pattern Analysis

Meal Pattern	AE Rate per 100 Person-Days in Double-blind Maintenance Phase	
	Xtampza ER	Placebo
Consistent	Low-Low	1.9
	High-High	1.3
Inconsistent	Low-High	1.9
	High-Low	1.4

- **Low** = “no meal” or “snack”
- **High** = “light meal” or “heavy meal”

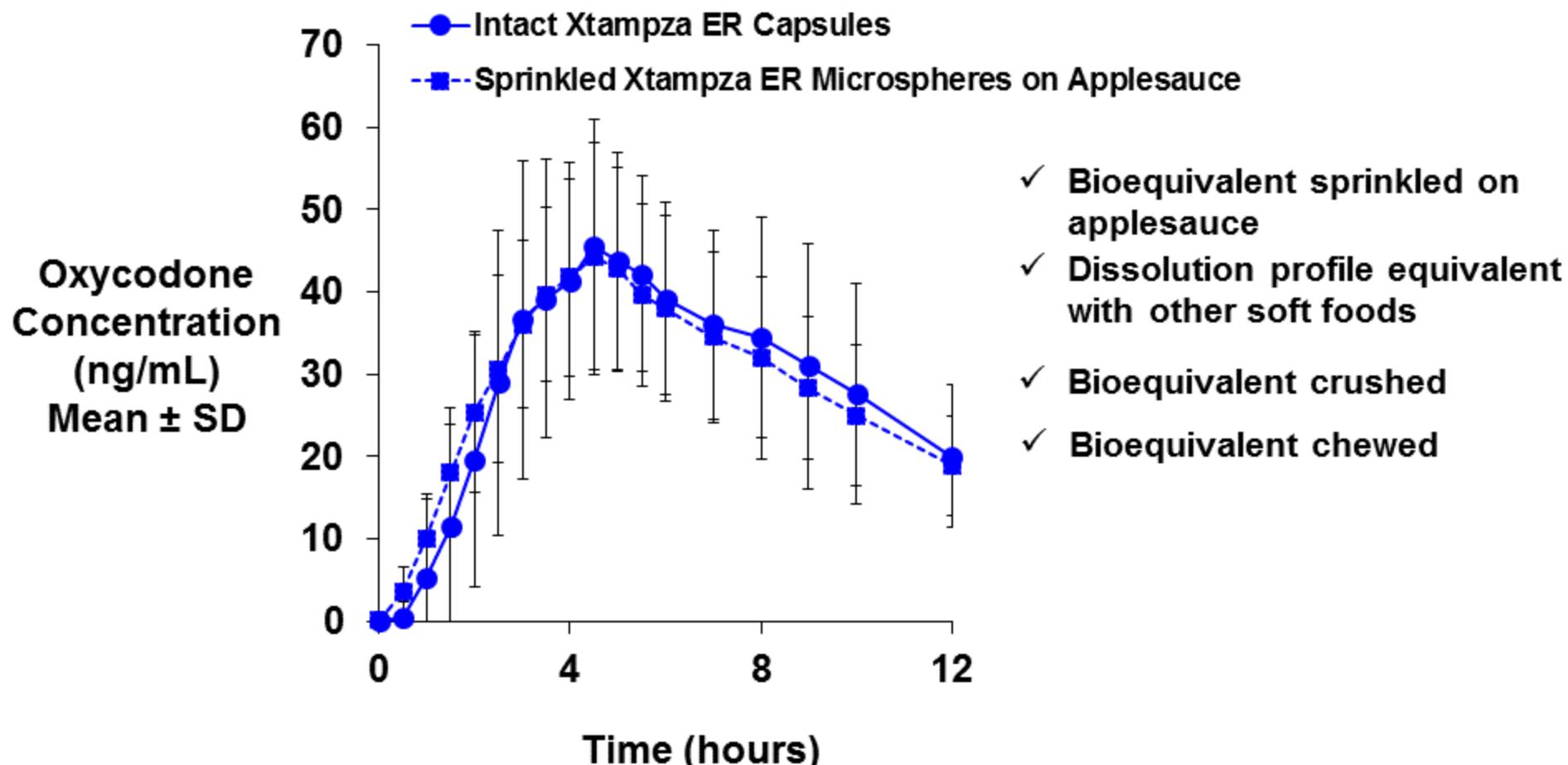
# No Association of Food Association with Efficacy in Xtampza ER Group

Meal Pattern		Number of Days with Meal Pattern	24-Hour Pain Score Xtampza ER Mean (SE)
Consistent	Low-Low	2,127	4.0 (0.1)
	High-High	11,390	4.1 (0.1)
Inconsistent	Low-High	5,410	4.1 (0.1)
	High-Low	1,738	4.1 (0.1)

- **Low** = “no meal” or “snack”
- **High** = “light meal” or “heavy meal”

# PK of Xtampza ER Not Altered by Sprinkling on Applesauce

## Study 27: Single-dose, NTX blocked



# Other Key Findings from Clinical Pharmacology Program

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- Co-ingestion with up to 40% alcohol produced comparable  $C_{max}$  as when dosed with food, and no “dose dumping”
- No change in drug release in vitro when passed through feeding tubes and flushed with different delivery vehicles

# Summary of Food Effect and Clinical Pharmacology

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- Food effect seen in single-dose, NTX-blocked studies
  - Food effect with  $C_{max}$  also observed for OxyContin ADF
- Magnitude of food effect lower for Xtampza ER under clinically relevant conditions
  - Study without naltrexone block ( $AUC_{inf}$  BE)
  - Steady state study vs. OxyContin ADF
- No clinical consequences associated with food in the Phase 3 study (>65,000 doses)
- Propose “take with food” label instruction
- No “dose dumping” in alcohol interaction study
- In vivo and in vitro studies demonstrated the utility of Xtampza ER microspheres by alternative administration methods

# **Risk Management**

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**Michael Heffernan, R.Ph.**

Chief Executive Officer

Collegium Pharmaceutical, Inc.

# Collegium Commitments To Encourage Responsible Use of Xstampza ER

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1. Participation in class-wide REMS
2. Drug safety and pharmacovigilance
3. Xstampza ER safe use program

# Xtampza ER Safe Use Program Will Provide Educational Support to Key Stakeholders

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- Patient education tools
  - Safe storage, misuse, abuse
- Physician education tools
  - Appropriate opioid prescribing
  - Risks of misuse and abuse
  - Label compliance
  - Warnings, precautions
- Pharmacist education

# Collegium Commitments To Encourage Responsible Use of Xstampza ER

---

1. Participation in class-wide REMS
2. Drug safety and pharmacovigilance
3. Xstampza ER safe use programs
4. Responsible sales and marketing

# Collegium Commitment to Responsible Sales and Marketing of Xtampza ER

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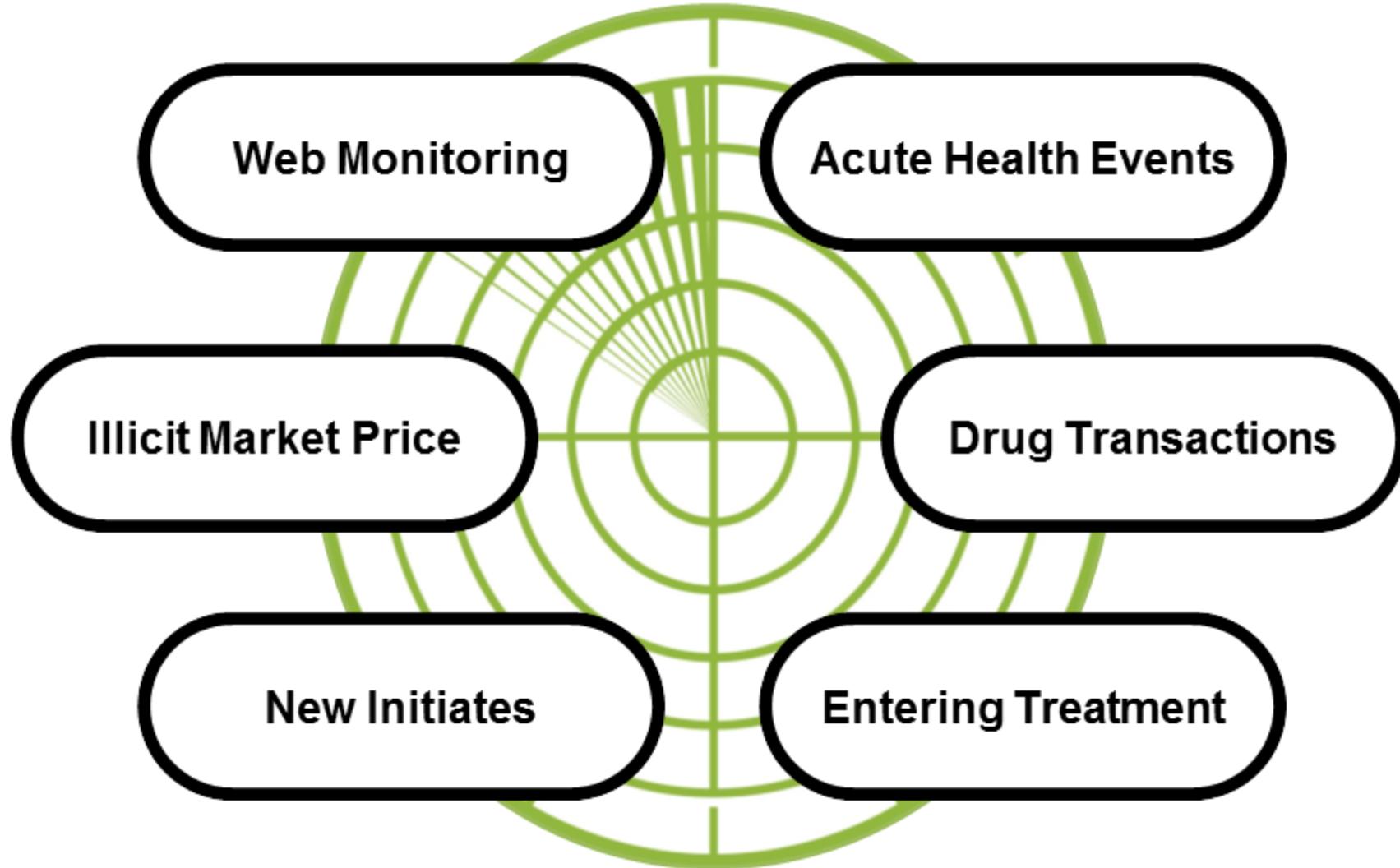
- Focus on pain specialist practitioners treating patients with chronic pain
- Prescriber-level monitoring of Xtampza ER/Opioid prescription patterns
  - Development and monitoring of “no-call” list
- Supply chain monitoring (wholesale, pharmacy)
- Reimbursement monitoring (e.g., cash pay)
- Internal training and compliance program to monitor external-facing employee communications

# Collegium Commitments To Encourage Responsible Use of Xstampza ER

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1. Participation in class-wide REMS
2. Drug safety and pharmacovigilance
3. Xstampza ER safe use programs
4. Responsible sales and marketing
5. Surveillance programs – safety and abuse
  - RADARS® to collect/analyze abuse data

# RADARS® System: Robust Surveillance of Prescription Drug Abuse



# Summary of Xtampza ER Risk Management Programs

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- Xtampza ER's strong abuse-deterrent properties paired with risk management programs are intended to play a role in reducing prescription opioid abuse

## **Benefit-Risk Profile**

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**Nathaniel Katz, M.D., M.S.**

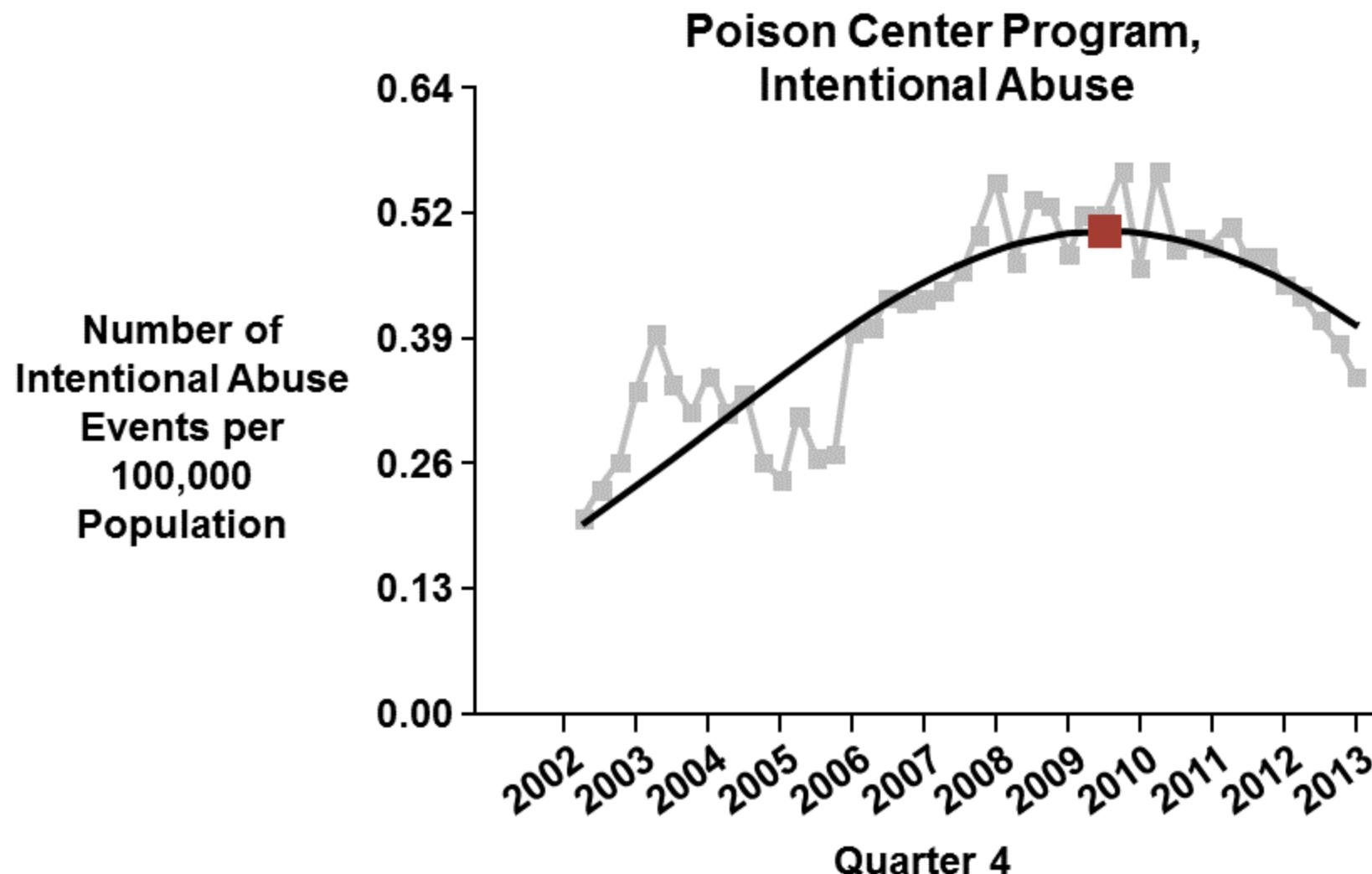
President

Analgesic Solutions

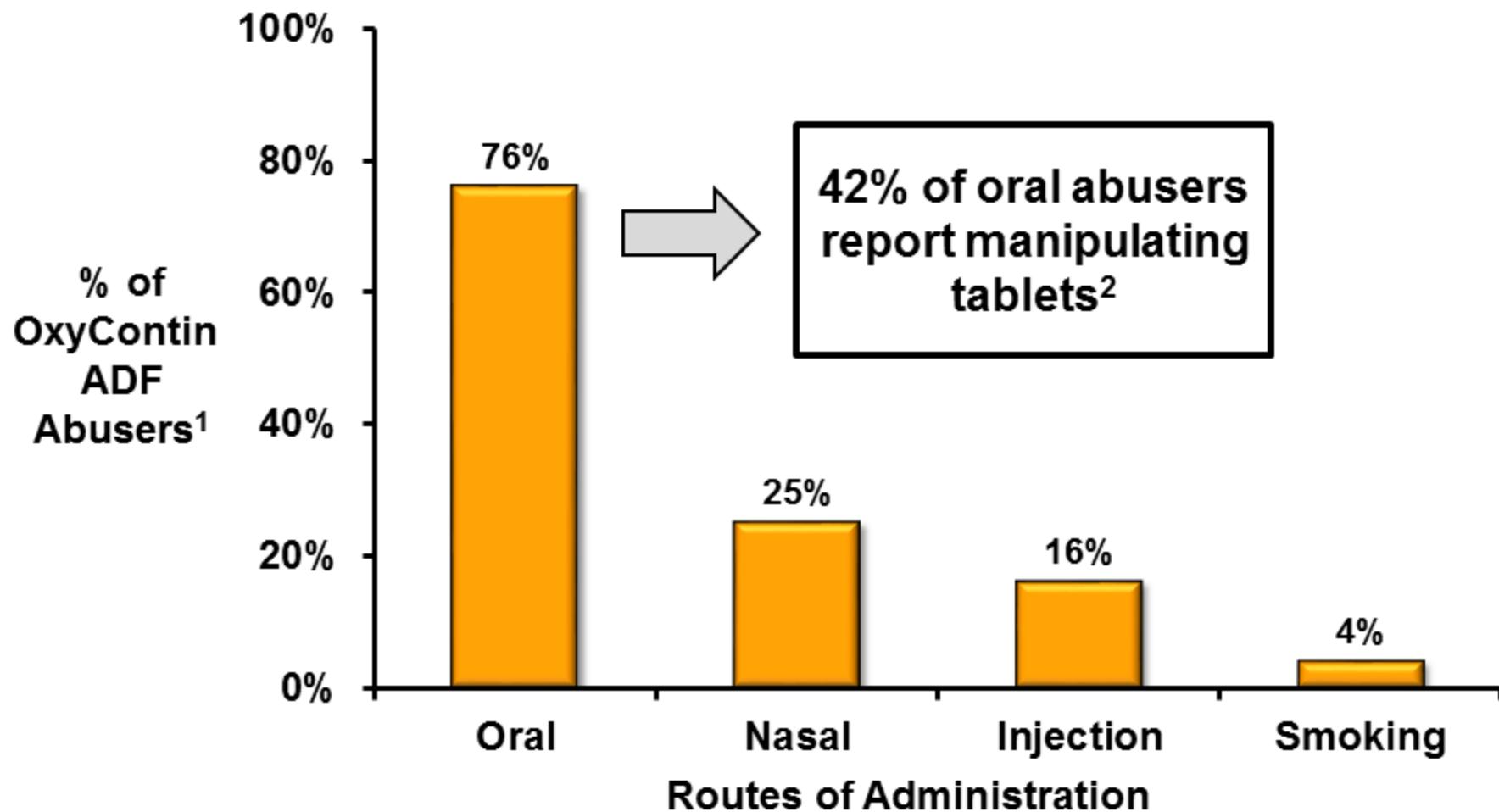
Adjunct Assistant Professor

Tufts University School of Medicine

## Intentional Rates of Abuse Declined After Introduction of Reformulated OxyContin ADF



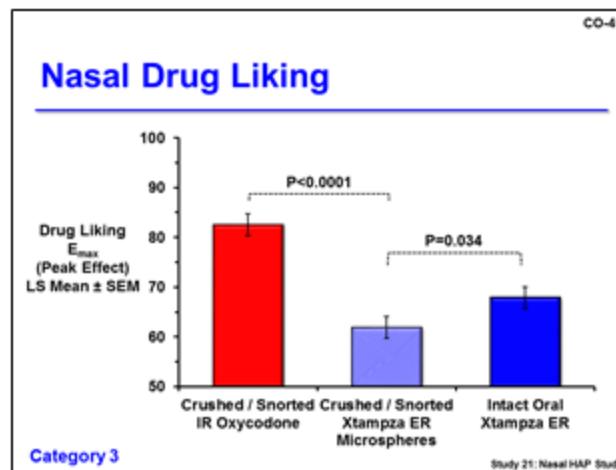
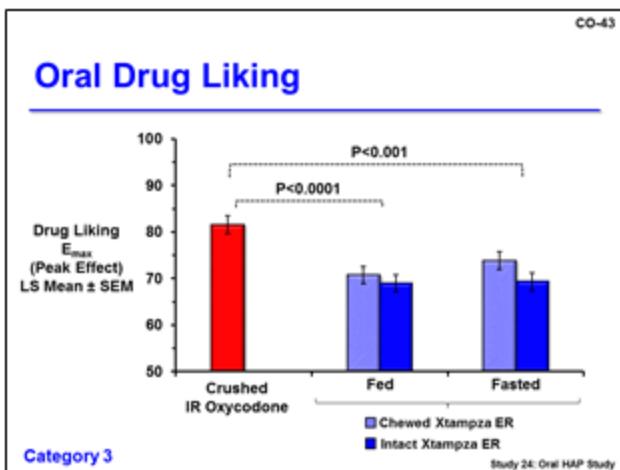
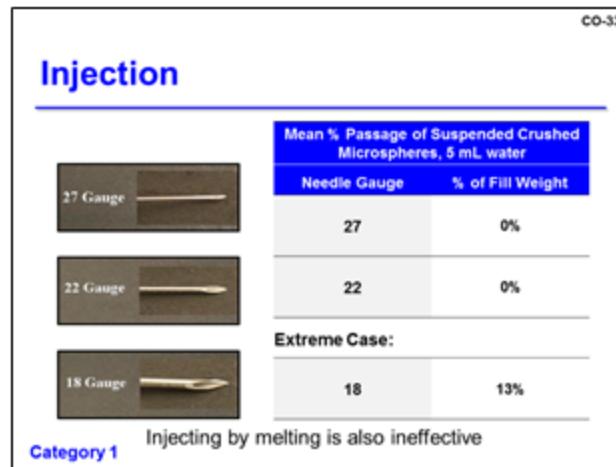
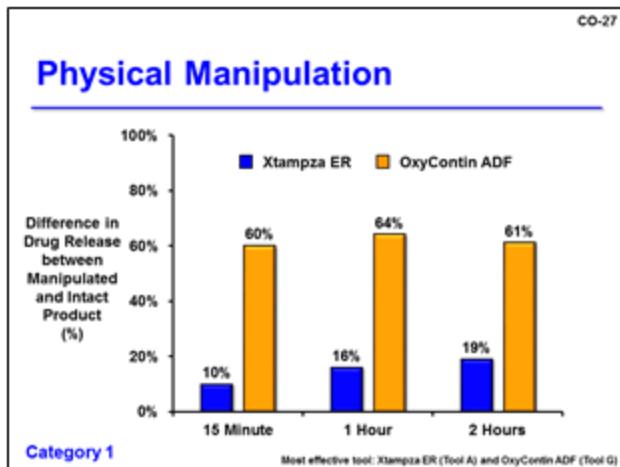
# OxyContin ADF Abuse Remains A Problem



1 Butler et al. J Pain 2013;14:351-8

2 Pooled analysis for OxyContin ADF, Nucynta ER, Opana ER Butler et al. Inflexxion, Inc.

# Xtampza ER Represents an Improvement in Abuse Deterrent Formulations



# Xtampza ER Addresses Issues Facing Patient Care and Public Health

## INTENTIONAL ABUSE

- Resistant to manipulation
- Maintains ER properties after manipulations
- Resistant to injection
- Lower drug liking

## UNINTENTIONAL MISUSE

- No effect on release profile for crushing, chewing, or dissolving
- No “dose dumping”
- Low safety risk

## DIFFICULTY SWALLOWING

- May be sprinkled on soft foods or directly in mouth
- May be used with feeding tubes
- Improvement over sprinkle formulations without abuse-deterrent features

# Totality of Food Effect Analyses: No Clinically Meaningful Impact on Safety or Efficacy

Study	Description	Food Effect Finding
<b>PK Studies 15, 26, 27</b>	Single-dose NTX blocked	Food affects absorption
<b>PK Study 18</b>	Steady-state NTX blocked	Xtampza ER similar to OxyContin, <b>even fasted-fed</b>
<b>HAP Study 24</b>	Single-dose non-NTX blocked	Total drug exposure was bioequivalent fed or fasted
<b>Food effects comparison</b>	Comparison to other products	Xtampza ER similar to other ER opioids
<b>Pivotal Trial</b>	Food-related AE adjudication	No Severe AEs or SAEs related to food
	Meal pattern analysis of ~65,000 doses	No safety consequence of inconsistent meal intake

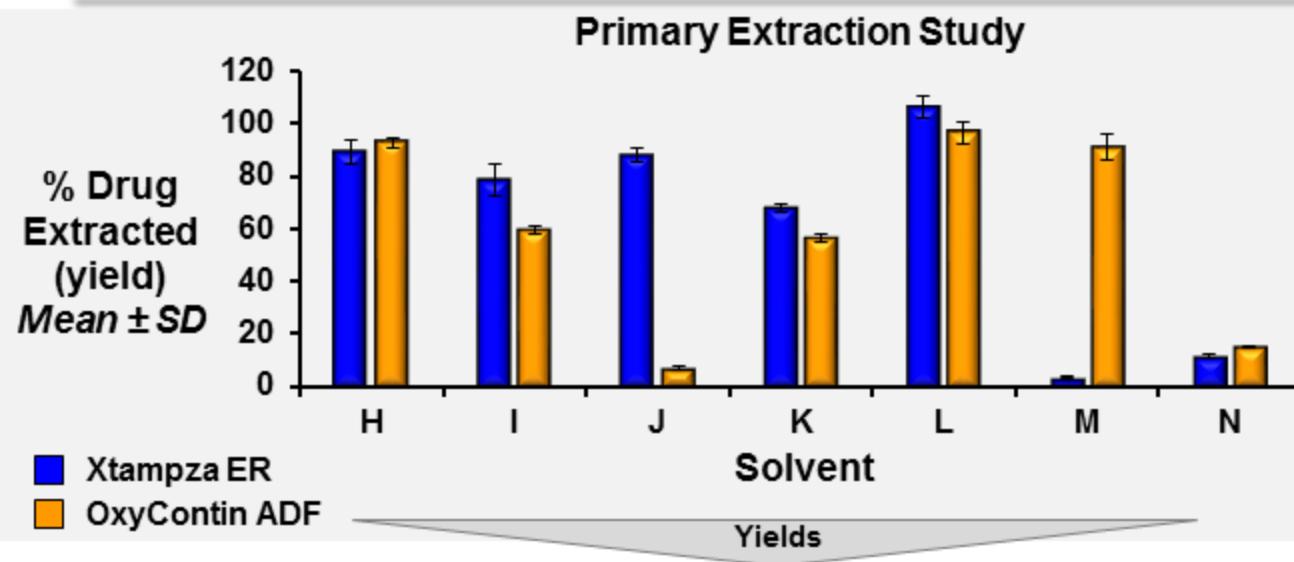
## Benefit-Risk Summary

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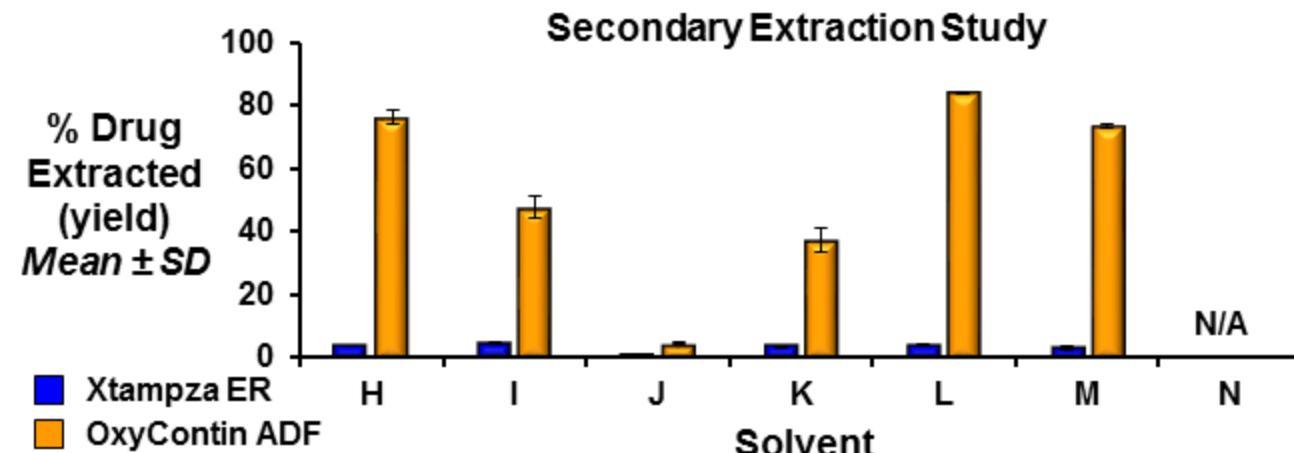
- Improved abuse deterrence profile
- Safer with inadvertent manipulation
- Ease of use for patients with swallowing difficulty
- Food effect not likely to be clinically relevant

# Backup Slides Shown

# Non-ingestible Chemical Solvents – Primary and Secondary Extraction of Crushed Products



- Extraction with organic solvents requires secondary extraction to get abusable “non-toxic” drug



- Xtampza ER exhibits significantly lower non-toxic drug yield than OxyContin ADF

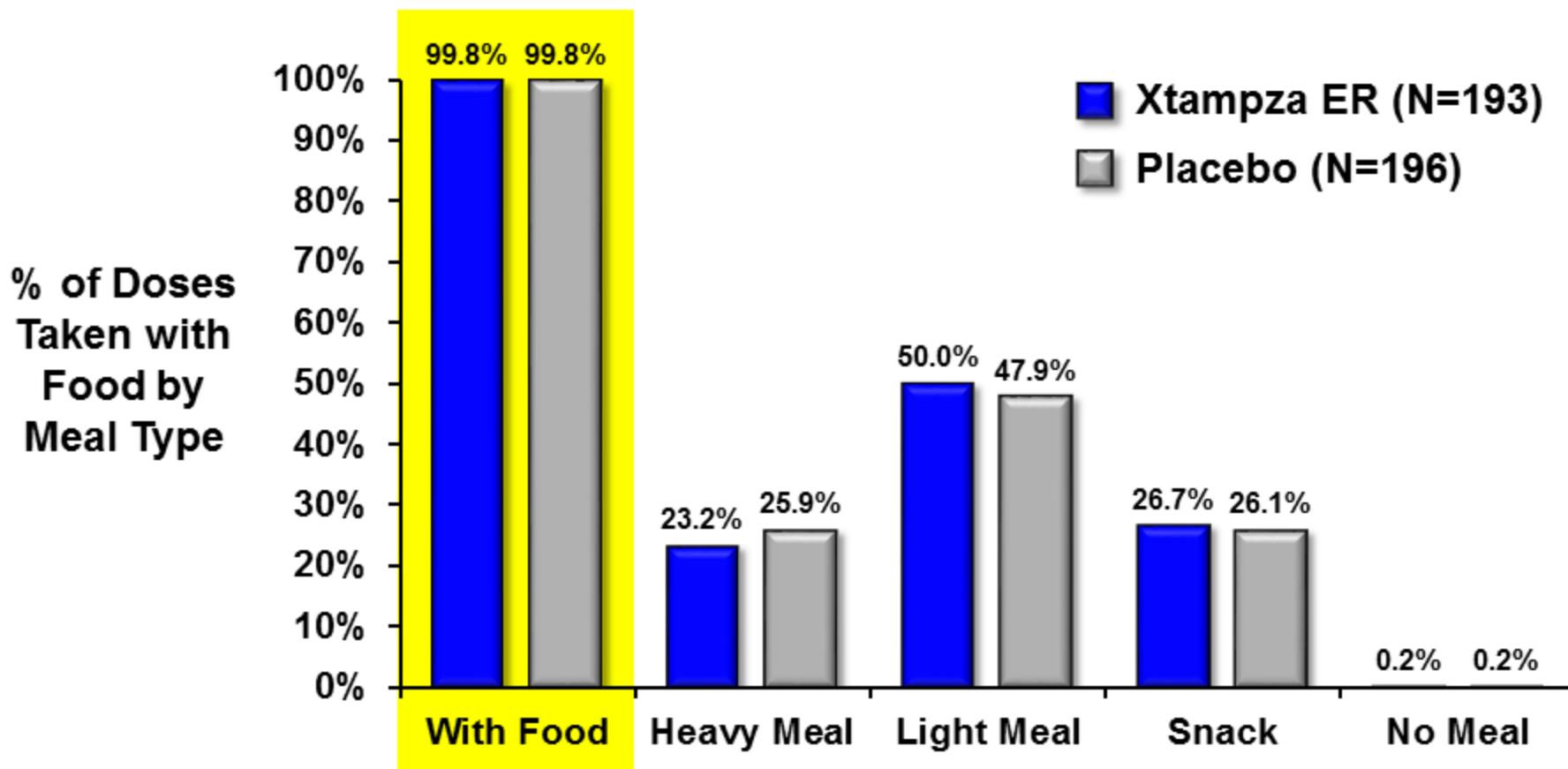
Error bars = Standard deviation

# Phase 3 Primary Efficacy Endpoint: Summary of All Analysis Methods and Results

Analysis Method	p-value
Primary Analysis (Marginal Mean: 2-piece Linear Model)	<0.0001
24-hr Pain Score – Secondary Analysis (Linear Model - Xtampza; 2-piece Linear Model – Placebo)	<0.0001
Change in Average Pain Score (Linear Model) Xtampza: 2-piece Linear Model Placebo: Worst Pain Score Imputation	<0.0001
Mixed-effect Model, Repeated Measures (MMRM)	0.0001
Last Observation Carried Forward (LOCF) / Baseline Observation Carried Forward (BOCF)	0.0002

# High Compliance with Taking Study Drug with Food: Double-Blind Maintenance Phase

- >99% Compliance in Double-Blind Maintenance Phase



# Information About Food Consumption with Dosing Collected in Phase 3 Study

## Information about food consumption via e-diary:

- Taken with food (yes/no)
- Time of food relative to dosing
- Qualitative description of food consumption (snack, light meal, heavy meal)

Did you take your Study Drug with food?

Yes  
 No

12:10 ?

What time did you eat?

12 : 10 AM PM

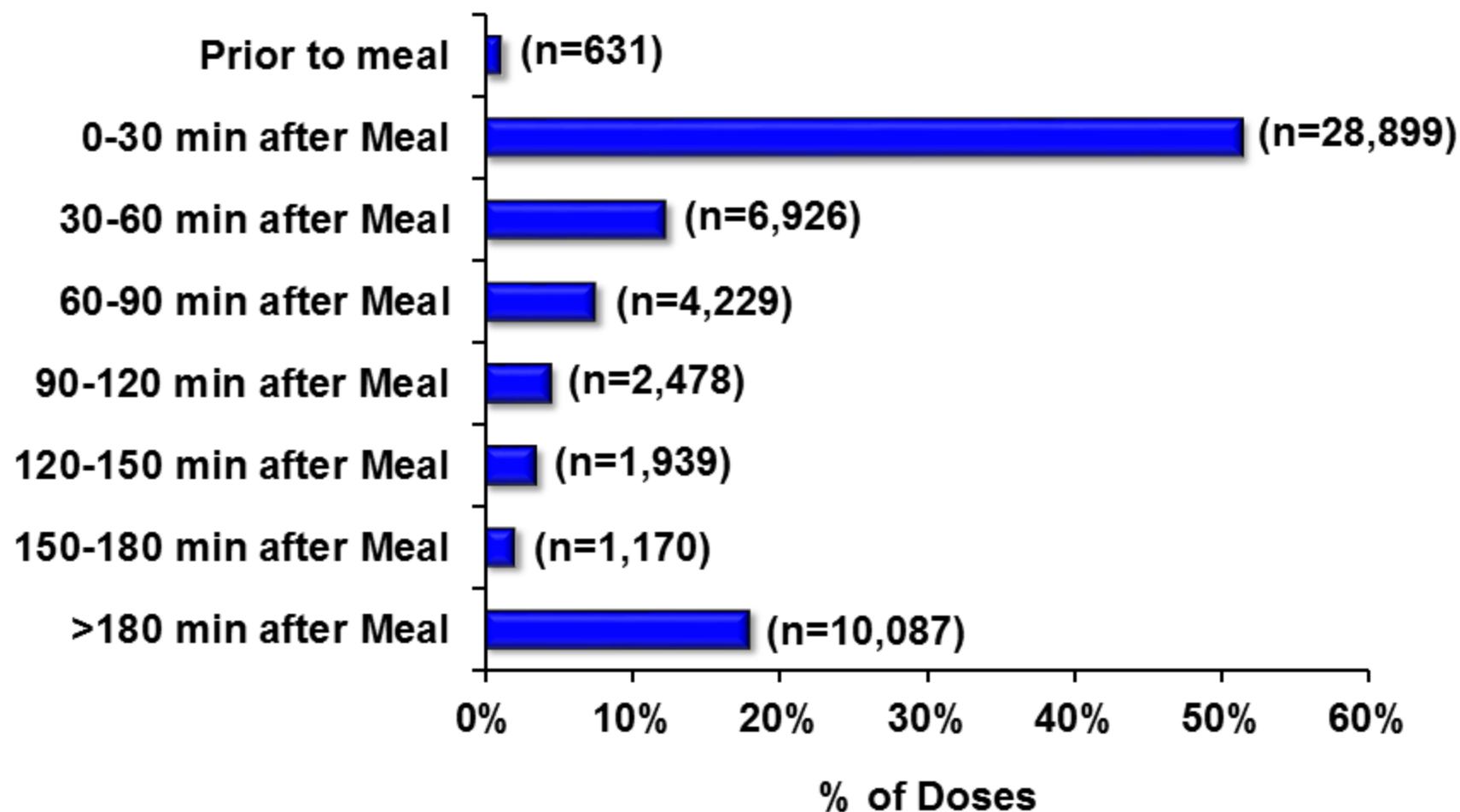
12:10 ?

What type of food did you have with your Study Drug?

Snack  
 Light Meal  
 Heavy Meal

12:10 ?

# Subjects in Phase 3 Study Realistically Interpreted “Take With Food”



# Patient Focused Resources to Inform “Food Effect” Prescribing Information for Xtampza ER

Physician-provided resources to patients	Pharmacy-provided resources to patients	Digital resources for patients and HCPs	HCP and Pharmacist resources
<ul style="list-style-type: none"><li><b>Patient Toolkit:</b> To include key information on taking XTAMPZA ER, including a reminder on taking product with food</li><li><b>Co-pay card:</b> Will include call-out to remind patients to take product with food</li></ul>	<ul style="list-style-type: none"><li><b>Pharmacy print-out:</b> To be packaged with med guide, will include key support information and reminder to take product with food</li></ul>	<ul style="list-style-type: none"><li><b>HCP and Patient websites:</b> To include homepage callouts with important product information, including reminder to take product with food</li></ul>	<ul style="list-style-type: none"><li><b>REMS</b></li><li><b>Pharmacist education:</b> Communication tool designed to encourage pharmacists to highlight key prescribing information, with emphasis on food effect, when dispensing to patients</li></ul>

# Effect of Naltrexone on The Food Effect with OxyContin (Original Formulation)

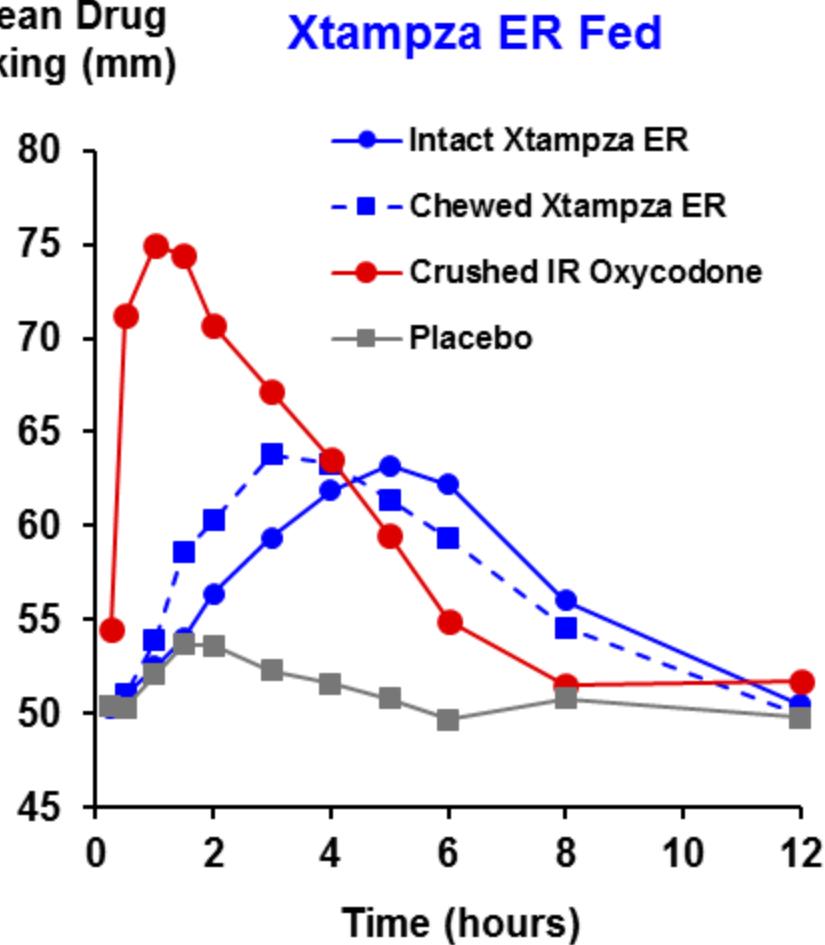
- Effect of NTX not characterized in a cross-over study for OxyContin
- Impact of NTX referenced in OxyContin ADF package insert: *“data obtained while volunteers received naltrexone which can enhance absorption”*
- Cross study comparison available for original OxyContin (40 mg) with and without NTX

Condition	Reference	Ratio (Fasted/Fed)	
		C <sub>max</sub>	AUC
With Naltrexone*	NDA 22,272 review	79%	83%
No Naltrexone	NDA 20,553 review	109%	103%

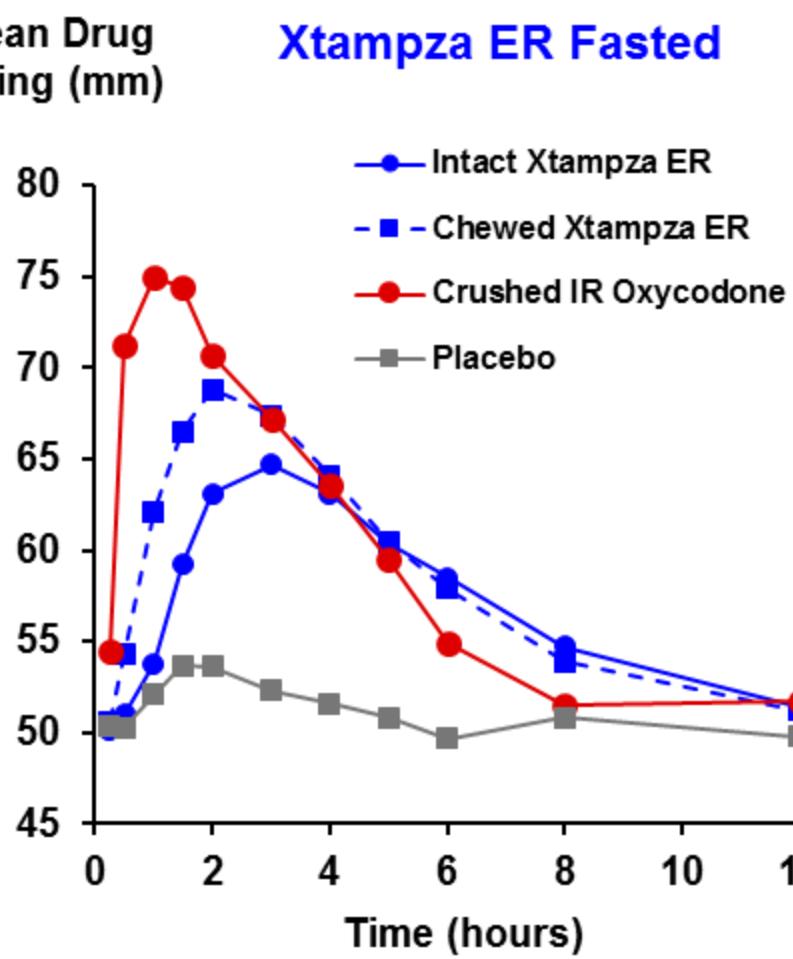
\*Fed and fasted conditions characterized in separate studies

# Drug Liking versus Time After Oral Administration (Primary Outcome)

Mean Drug Liking (mm)



Mean Drug Liking (mm)



# Opioid-Associated AEs by Meal Pattern on Days with AEs in Double-blind Maintenance Phase

		Opioid-Associated AE Rate per 100 Person-Days in Double-blind Maintenance Phase	
Meal Pattern on Days with AEs		Xtampza ER	Placebo
<b>Consistent</b>	Low-Low	0.4	0.2
	High-High	0.2	0.1
<b>Inconsistent</b>	Low-High	0.3	0.1
	High-Low	0.1	0.2

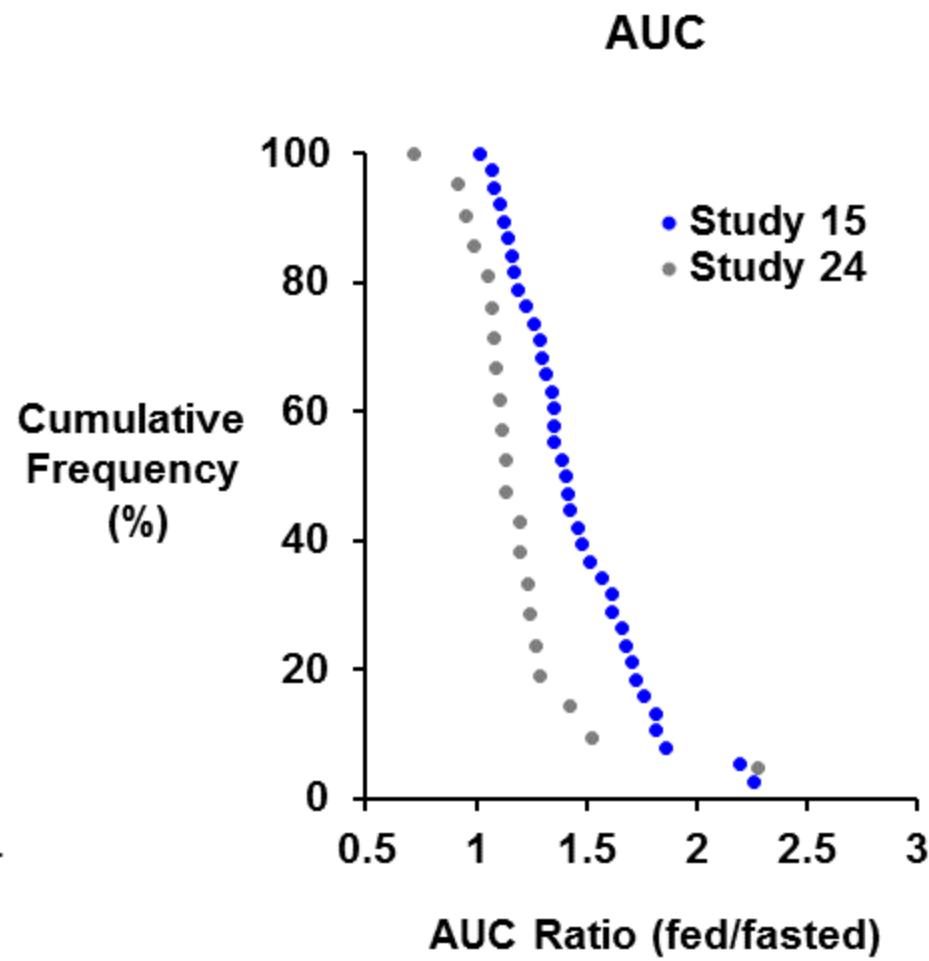
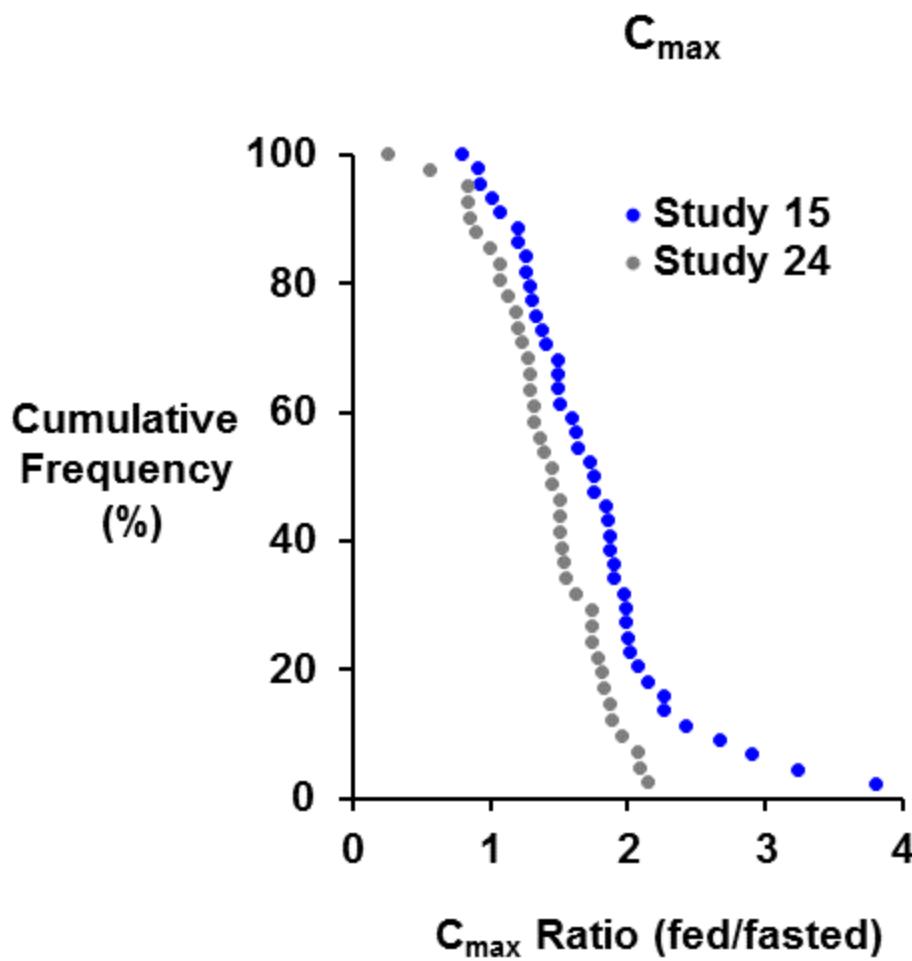
- **Low** = “no meal” or “snack”
- **High** = “light meal” or “heavy meal”

## All Withdrawal AEs by Meal Pattern on Days with AEs in Double-blind Maintenance Phase

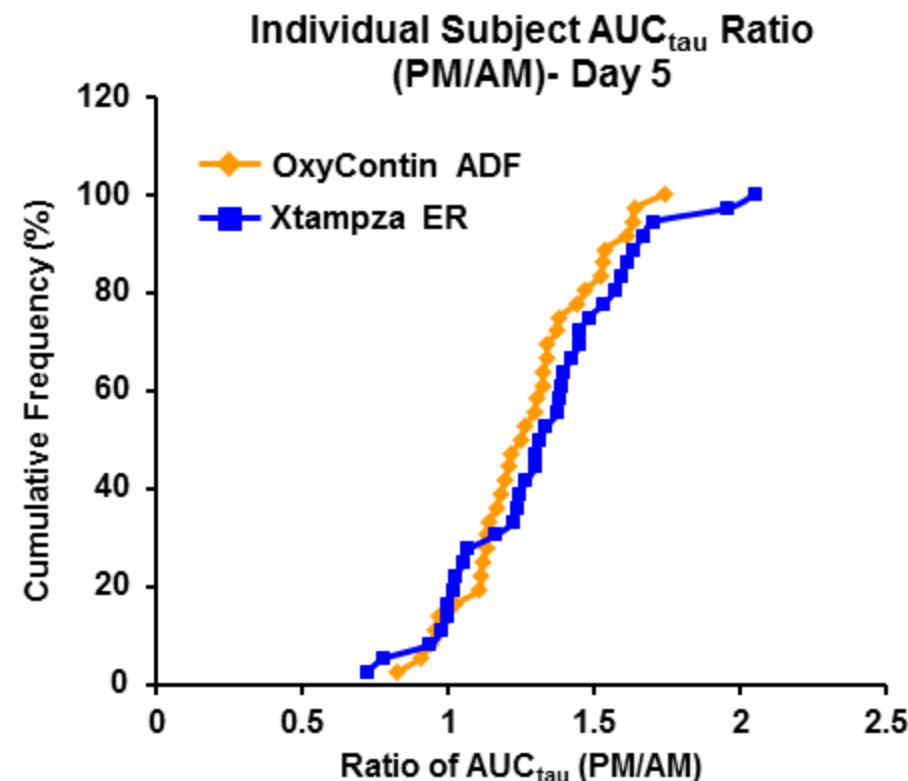
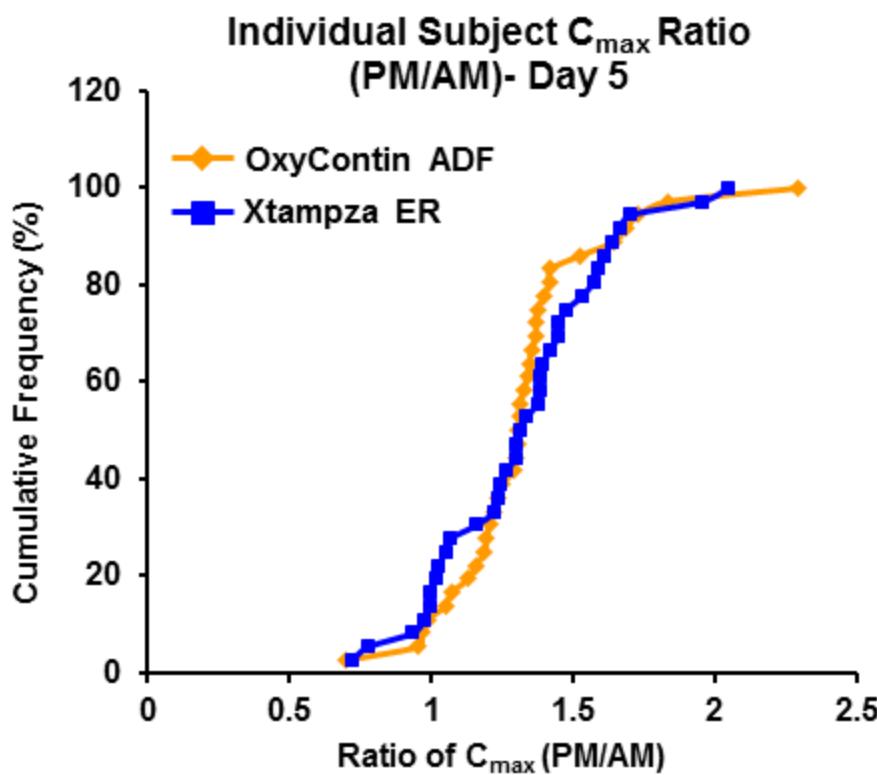
		AE Rate per 100 Person-Days in Double-blind Maintenance Phase	
Meal Pattern on Days with AEs		Xtampza ER	Placebo
<b>Consistent</b>	<b>Low-Low</b>	0.09	0.1
	<b>High-High</b>	0.03	0.02
<b>Inconsistent</b>	<b>Low-High</b>	0.07	0.0
	<b>High-Low</b>	0.0	0.0

- **Low** = “no meal” or “snack”
- **High** = “light meal” or “heavy meal”

# Cumulative Frequency Ratios (Study 15 vs. Study 24)



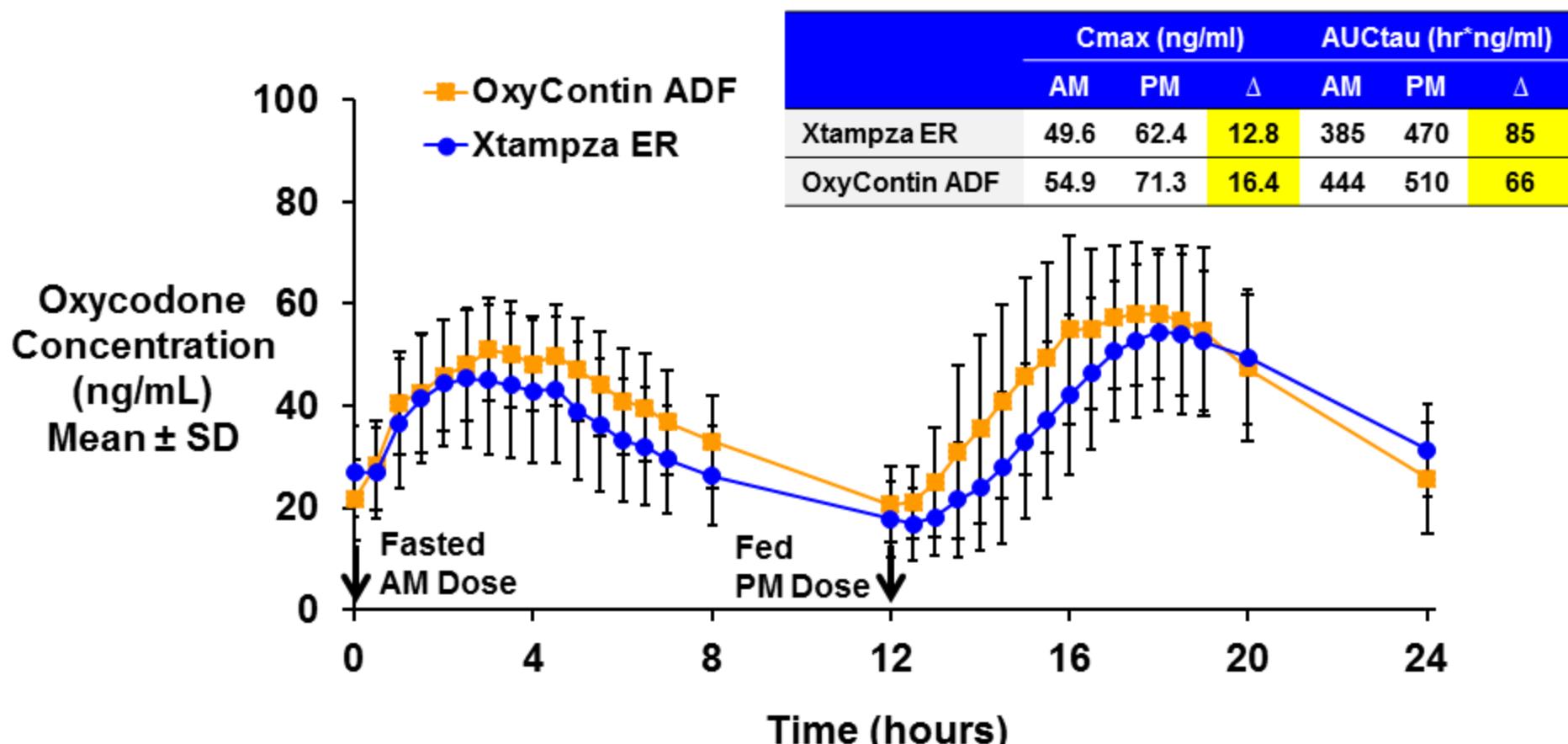
# Similar Individual Subject - Level PK Ratios at Steady State with Xtampza ER and OxyContin ADF



# Xtampza ER and OxyContin ADF Have Similar PK Profiles At Steady State When Non-Compliant With Food Instruction

## Study 18: Steady-State, NTX blocked

*Q12h Dosing, Fasted AM / Fed PM Conditions – Day 5*



# Quality of Life Research

Qual Life Res

DOI 10.1007/s11136-011-0012-7

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BRIEF COMMUNICATION

## Determining the clinically important difference in visual analog scale scores in abuse liability studies evaluating novel opioid formulations

Thomas A. Eaton · Sandra D. Comer · Dennis A. Revicki ·

Jeremiah J. Trudeau · Richard G. van Inwegen ·

Joseph W. Stauffer · Nathaniel P. Katz