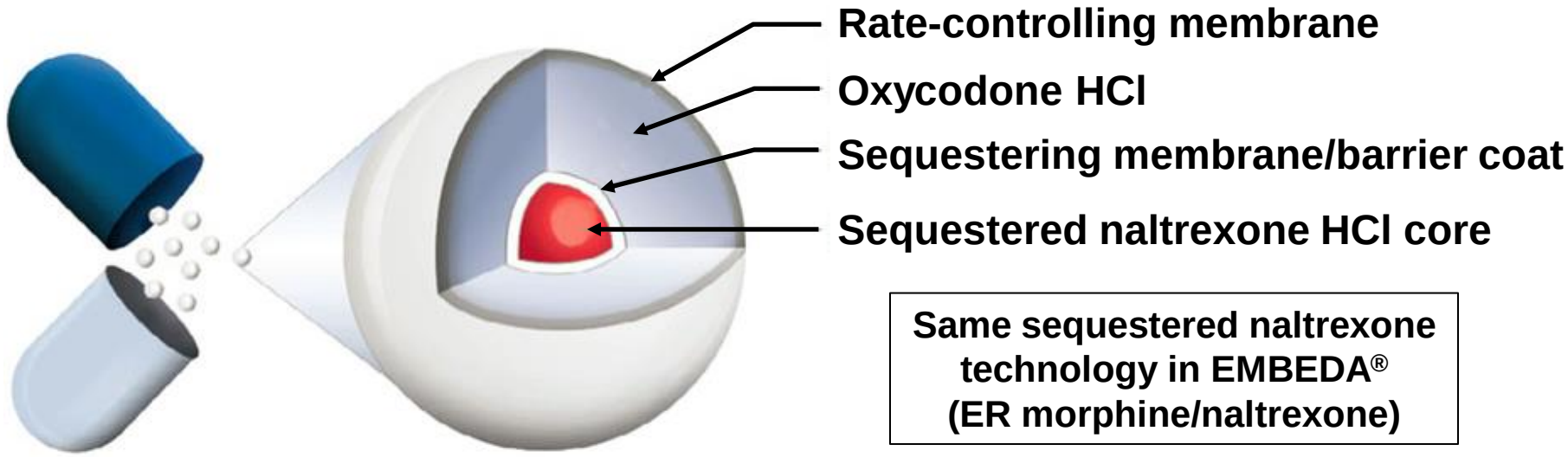
ALO-02
(Oxycodone HCl and Naltrexone HCl)

June 8, 2016

Pfizer Inc.

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

Unique Features of ALO-02: ER Oxycodone and Sequestered Naltrexone



Same sequestered naltrexone technology in EMBEDA® (ER morphine/naltrexone)

- Ratio of naltrexone HCl to oxycodone HCl is 12%
- ALO-02 capsules of six different dosage strengths (10-80 mg oxycodone) contain different amounts of the same small pellets
- When capsules/pellets are taken as directed – naltrexone is intended to remain sequestered, while oxycodone behaves as an extended-release opioid
- When capsules/pellets are crushed or chewed – naltrexone is intended to be released and to antagonize the effects of oxycodone
- No visual clues to indicate if abuser has defeated formulation

ER=Extended-Release; HCl=Hydrochloride; mg=milligram; mm=millimeter

Agenda

Topic		Speaker
Introduction		Sean Donevan, PhD
Clinical Pharmacology		Bimal Malhotra, PhD
Efficacy and Safety		Gernot Wolfram, MD, PhD
Abuse-Deterrent Program	In Vitro	Sean Donevan, PhD
	Human PK/PD	Carl L. Roland, Pharm D, MS
Conclusions		Sean Donevan, PhD

PK/PD=Pharmacokinetic/Pharmacodynamic

ALO-02 Expert Consultants

- Dr. Edward Cone, PhD
  - **Pinney**Associates
  - Abuse Liability and In Vitro Laboratory Study Design, Execution and Interpretation
- Dr. Richard Dart, MD, PhD
  - Denver Heath and Hospital Authority
  - REMS and Post Marketing Surveillance of Abuser Behavior

FACP=Fellow of the American College of Physicians; FRCPC=Fellow of the Royal College of Physicians of Canada; REMS=Risk Evaluation Mitigation Strategies

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- Dr. Richard Rauck, MD
  - Wake Forest University School of Medicine
  - President, Carolinas Pain Institute
- Dr. Edward Sellers, MD, PhD, FRCPC, FACP
  - Faculty of Medicine University of Toronto
  - DL Global Partners Inc.
  - Abuse Liability Assessment and Clinical Pharmacology

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Key Elements of the ALO-02 Development Program

- 505(b)(2) NDA submitted in December 2014 references Roxicodone® and Revia®
- Abuse-deterrent program supports abuse-deterrent labeling
  - Comprehensive battery of in vitro studies
  - Three abuse potential studies in recreational drug abusers by oral, intranasal and intravenous routes
- Safety and efficacy confirmed in two Phase 3 studies

Potential Abuse-Deterrent Opioid Product Categories (FDA Defined[1])

Technology	Description
Physical/chemical barriers	• **Physical barriers can prevent/deter manipulation** • **Chemical barriers can resist extraction of the opioid** • **Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of drug, rendering it less amenable to abuse**
Agonist/antagonist combinations	• **Antagonist added to interfere with, reduce, or defeat euphoria associated with abuse**
Aversion	• Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed
Delivery system	• Drug-release design or method of drug delivery (e.g., depot injectable) offers resistance to abuse
New molecular entities and prodrugs	• Properties could include the need for enzymatic activation, different receptor-binding profiles, slower penetration into the CNS, or other novel effects • Prodrugs with abuse-deterrent properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter abuse of the parent opioid
Combination	• Two or more of the above methods
Novel approaches	• Novel approaches or technologies not captured in the previous categories

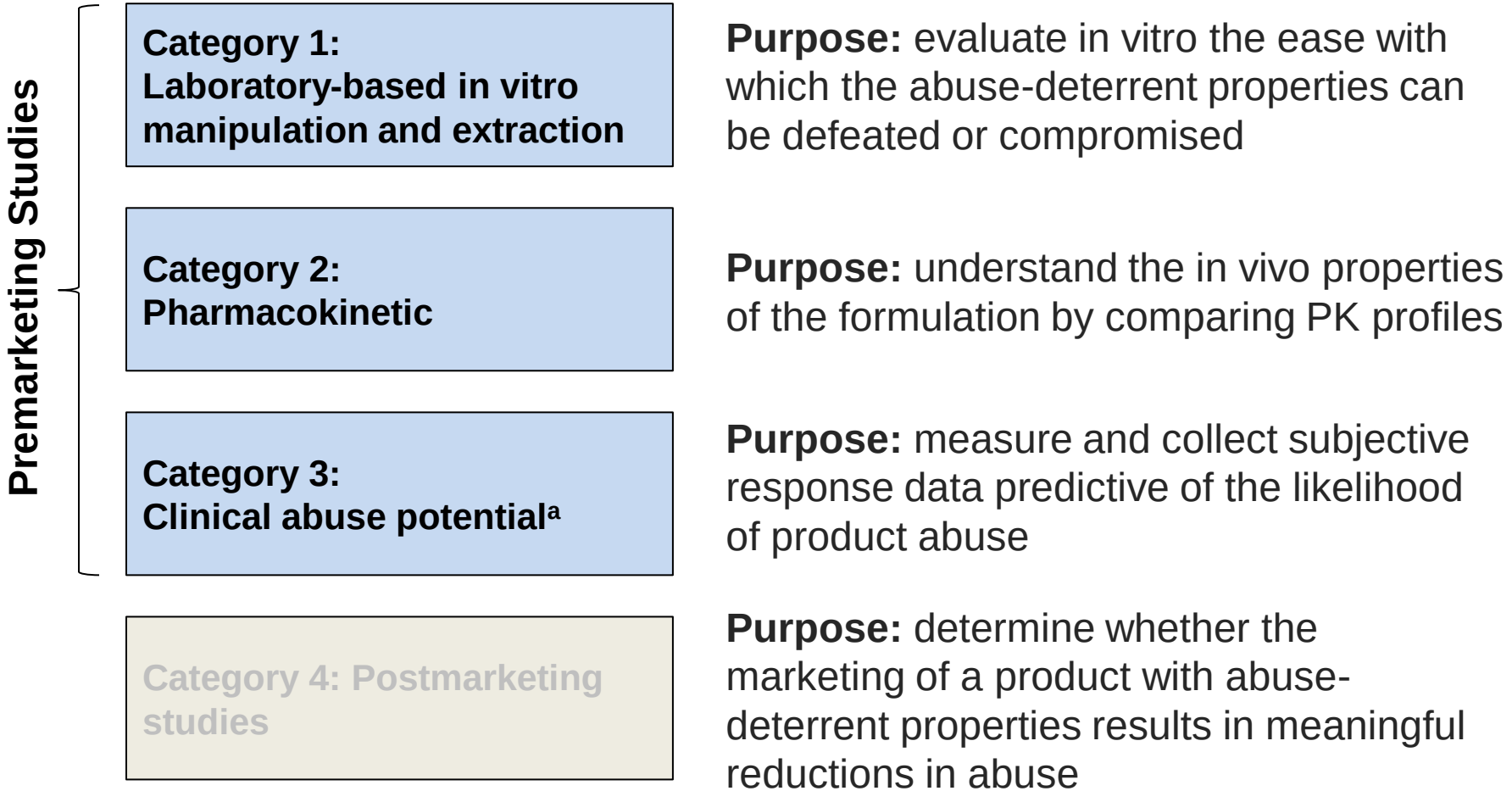
CNS=Central Nervous System

1. *Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling*. Rockville, MD: FDA; 2015.

Methods Abusers Use to Enable Use by Different Routes of Administration

Route of Abuse	Manipulation Method	Mode of Administration	
Oral	None (Intact)	Swallow	
		Dissolve in solvent and swallow	
	Chew or Crush	Swallow	
	Crush	Dissolve in solvent and swallow	
Intranasal	Crush	Snort crushed powder	
Intravenous	None (Intact)	Dissolve in small volumes, heat and inject	
	Crush	Dissolve in small volumes, heat and inject	
Smoking	None (Intact)	Heat and vaporize, then inhale	
	Crush	Heat and vaporize, then inhale	

2015 FDA Guidance: Premarketing and Postmarketing Studies of Abuse Deterrence



a. Also known as human abuse liability (HAL) studies

FDA. *Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling*. Rockville, MD: FDA; 2015.

ALO-02 Development Program

Clinical Pharmacology Studies	
B4531007	Pivotal Relative Bioavailability
B4531006	Single- and Multiple-Dose Pharmacokinetics
B4531003	Food Effect
B4531004	Ethanol Interaction
Efficacy and Safety Studies in Subjects with Chronic Pain	
B4531002	12-Week Efficacy Study
B4531001	12-Month Safety Study
Abuse-Deterrent Studies: Category 1, 2 and 3	
In Vitro Category 1 Studies	
B4531008	Oral ALO-02 vs. Oxycodone IR
B4531009	Intranasal ALO-02 vs. Oxycodone IR
B4981002	Intravenous Simulated Crushed ALO-02 vs. Oxycodone IV

IR=Immediate Release

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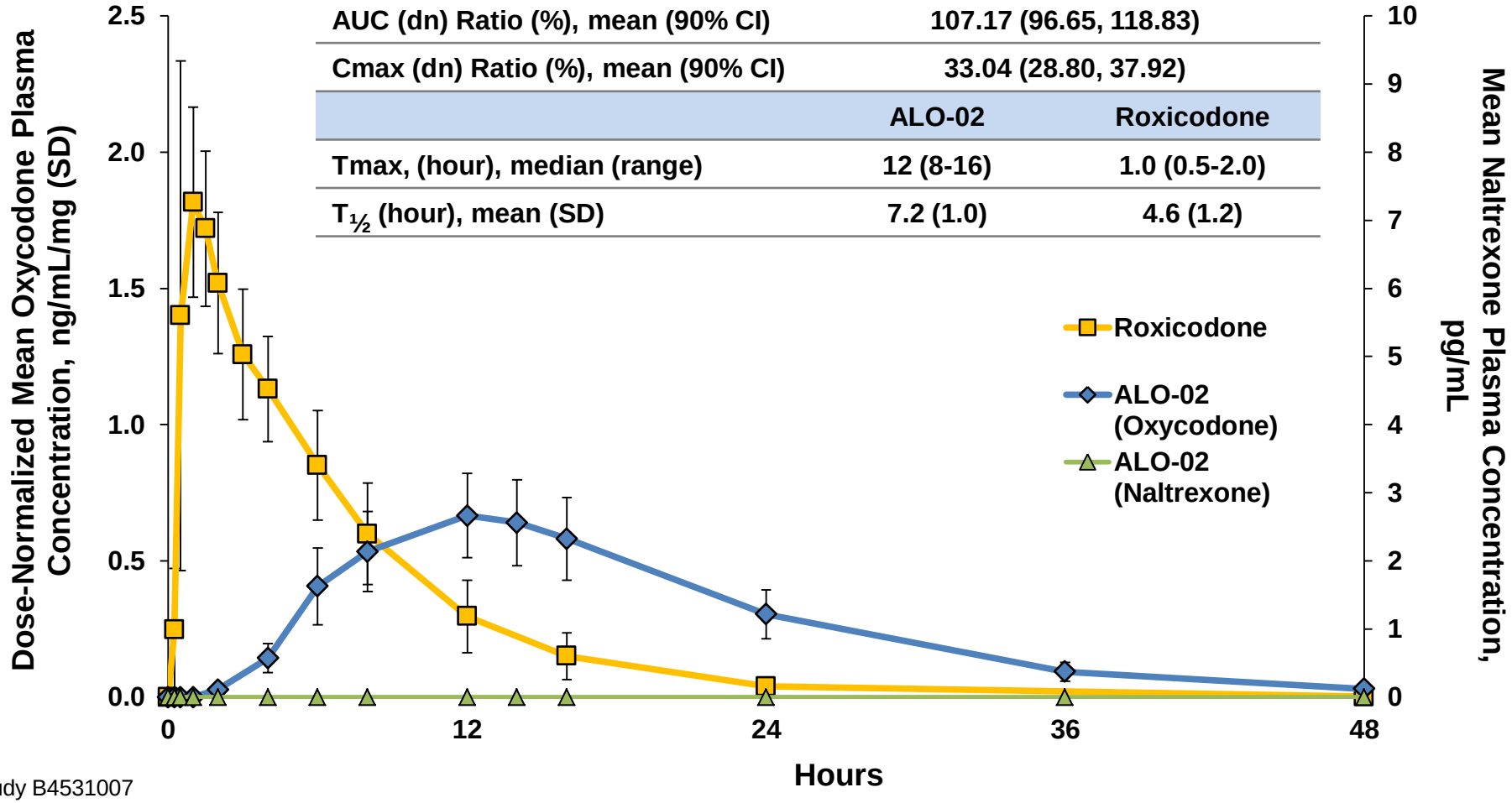
Conclusions		Sean Donevan, PhD

Extended-Release of Oxycodone with BA Equivalent to Roxicodone (N=13)

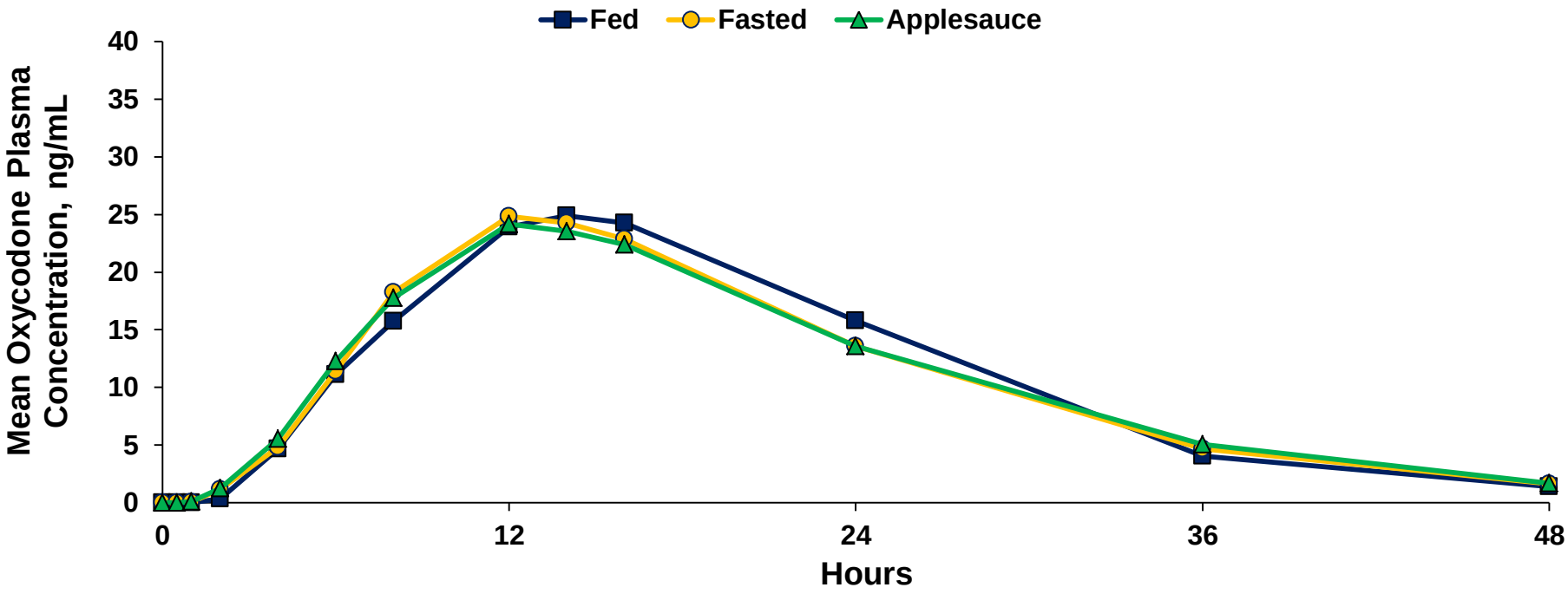
	ALO-02 vs. Roxicodone	
AUC (dn) Ratio (%), mean (90% CI)	107.17 (96.65, 118.83)	
Cmax (dn) Ratio (%), mean (90% CI)	33.04 (28.80, 37.92)	
	ALO-02	Roxicodone
Tmax, (hour), median (range)	12 (8-16)	1.0 (0.5-2.0)
$T_{½}$ (hour), mean (SD)	7.2 (1.0)	4.6 (1.2)



Study B4531007

Doses are ALO-02 40/4.8 mg and Roxicodone 20 mg; Levels below lower limit of quantitation (<4 pg/mL for naltrexone) treated as 0 in calculation of mean
AUC=Area Under Curve; BA=Bioavailability; CI=Confidence Interval; Cmax=maximum Concentration; dn=dose-normalized; mL=milliliter; ng=nanogram; pg=picogram; SD=Standard Deviation; $T_{1/2}$=Terminal elimination half life; Tmax=Time at which Cmax is observed

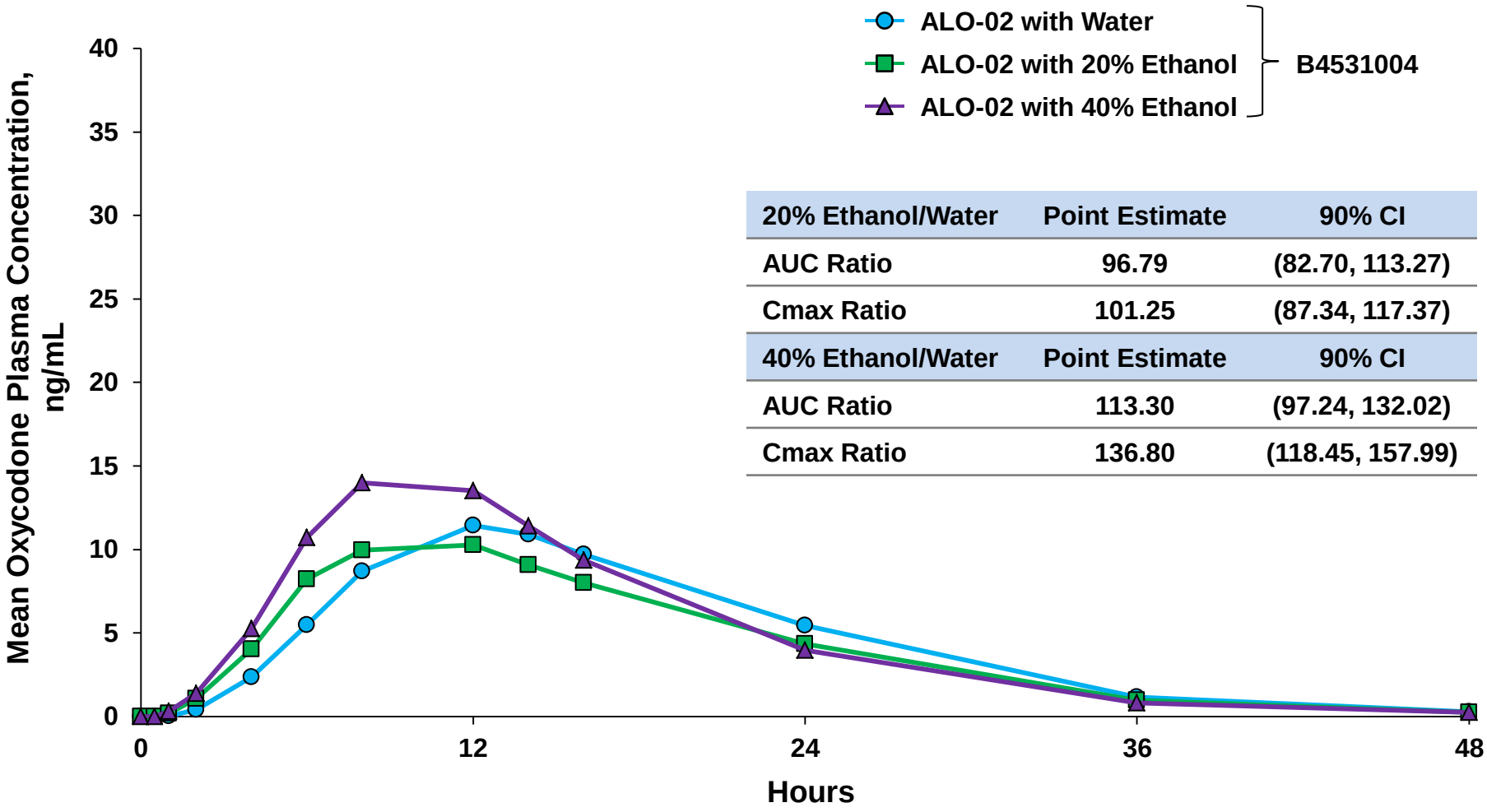
No Effect of Taking Meals with ALO-02 Capsules or Sprinkling Pellets on Applesauce (N=24)



- 90% Confidence Intervals for Cmax and AUC ratios were within 80-125%
- ALO-02 capsules may be taken orally without regards to meals
- Pellets may be sprinkled on applesauce and taken without chewing
- Naltrexone was not detected

Study B4531003
Dose is ALO-02 40/4.8 mg

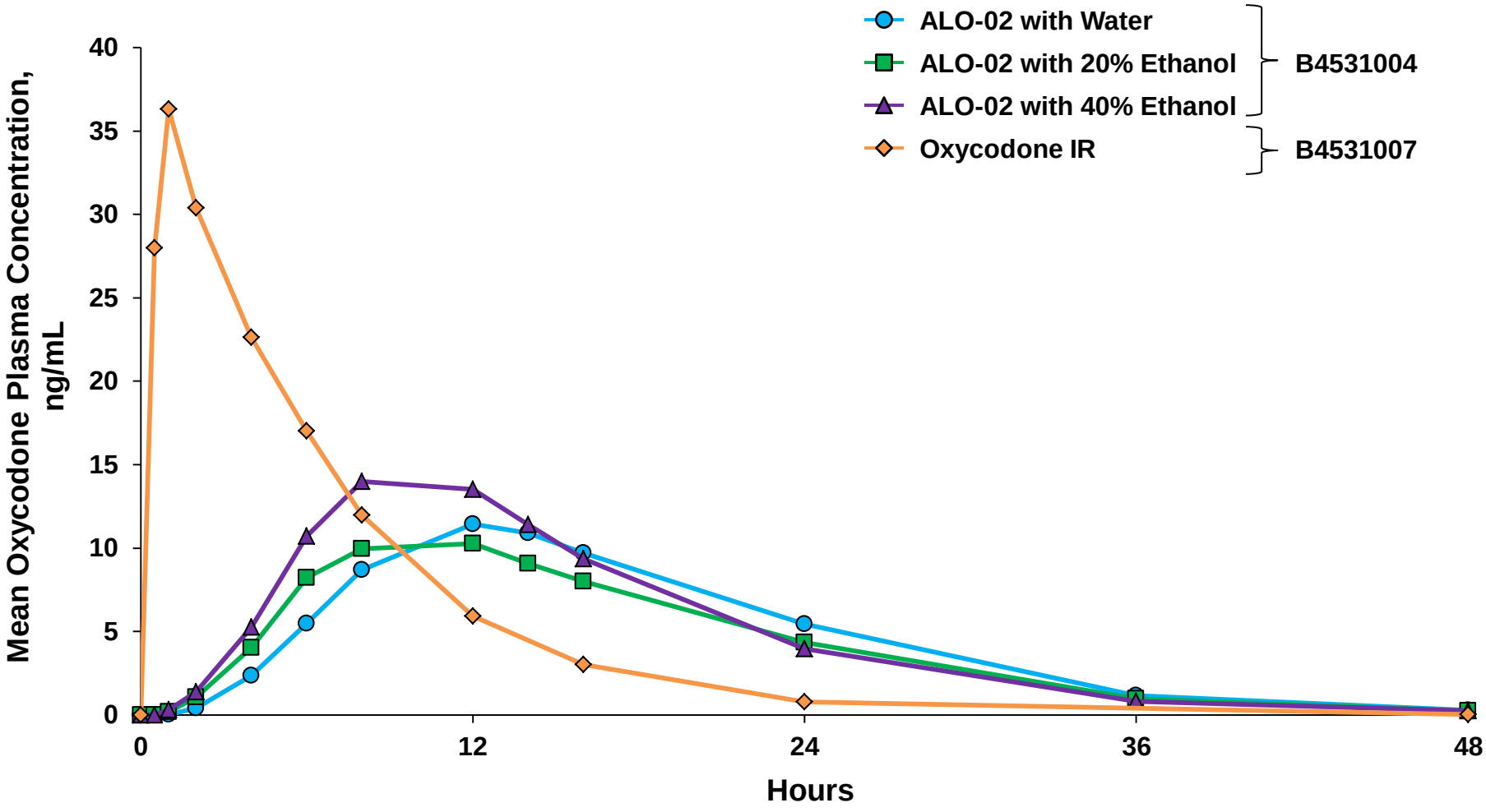
Effect of Dosing ALO-02 Capsules with 20% or 40% Ethanol on Oxycodone Exposure (N=17)



20% Ethanol/Water	Point Estimate	90% CI
AUC Ratio	96.79	(82.70, 113.27)
Cmax Ratio	101.25	(87.34, 117.37)
40% Ethanol/Water	**Point Estimate**	**90% CI**
AUC Ratio	113.30	(97.24, 132.02)
Cmax Ratio	136.80	(118.45, 157.99)

Study B4531004
Dose is ALO-02 20/2.4 mg with naltrexone block

Effect of Dosing ALO-02 Capsules with 20% or 40% Ethanol on Oxycodone Exposure (N=17)



Studies B4531004 and B4531007
Dose is ALO-02 20/2.4 mg with naltrexone block; Oxycodone IR 20 mg

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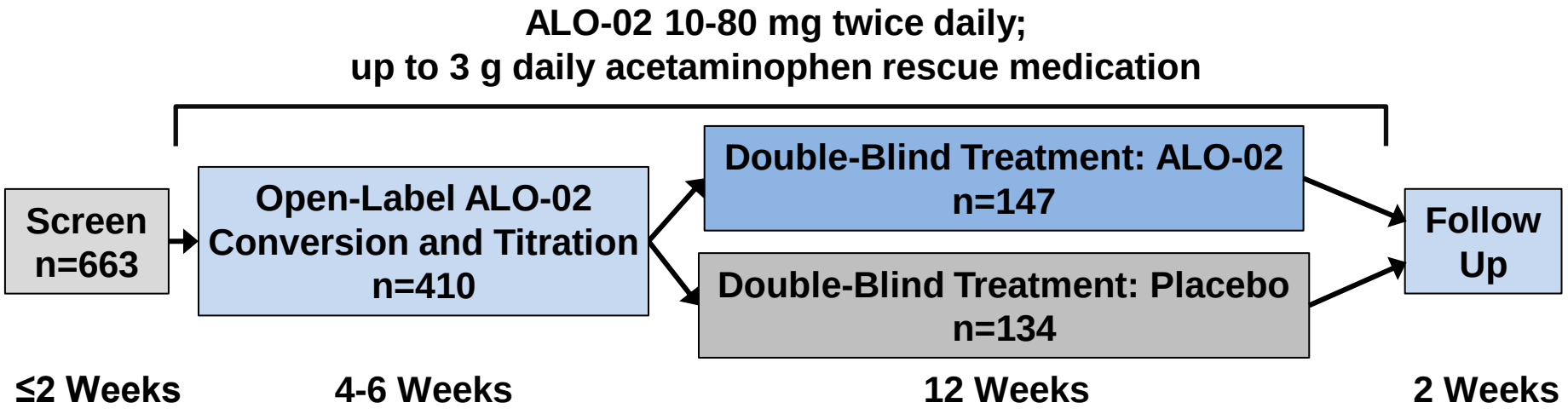
12-Week, Double-Blind, Placebo-Controlled, Randomized Withdrawal CLBP Study (B4531002)

- Population: CLBP for ≥3 months; pain score of ≥5 and ≤9; subjects, in the opinion of the investigator, were in need of a continuous around-the-clock opioid analgesic for an extended period of time



- Response Criteria: no intolerable opioid effects; pain score of ≤4; stable dose for 7 days prior to randomization
- Average starting dose during double-blind period: 65 mg/day of ALO-02

CLBP=Chronic Low Back Pain; g=grams

Superiority of ALO-02 Over Placebo in 12-Week CLBP Study (B4531002)

Primary endpoint: Mean change in weekly average NRS pain scores from randomization baseline to end-of-study

	Placebo n=134 Mean (SD)	ALO-02 n=146 Mean (SD)
Baseline at screening	**7.1 (1.20)**	
Baseline at randomization	**3.1 (1.04)**	**3.0 (1.25)**
End-of-study	**4.3 (2.24)**	**3.6 (2.04)**
Change from randomization baseline to end-of-study	**1.2 (1.93)**	**0.6 (1.81)**
Difference, LS mean (95% CI)	**-0.62 (-1.11, -0.14) p<0.05**	

LS=Least Squares; NRS=Numeric Rating Scale

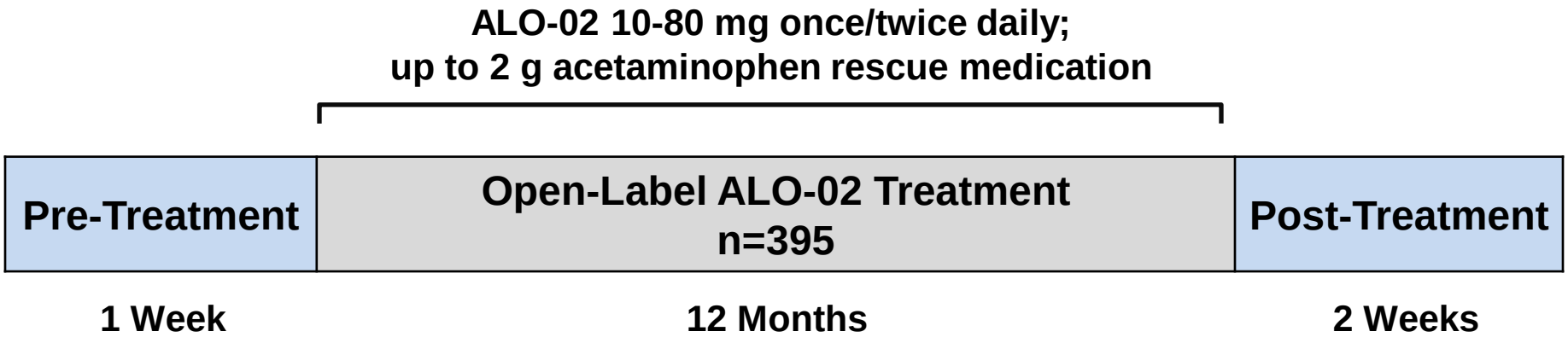
Adverse Events Consistent with Known Opioid Side Effects in 12-Week CLBP Study (B4531002)

	Open-Label	Double-Blind	
	ALO-02 N=410 n (%)	Placebo N=134 n (%)	ALO-02 N=146 n (%)
Any adverse event	258 (62.9)	75 (56.0)	83 (56.8)
Most common ADRs (>5%)			
Nausea	84 (20.5)	5 (3.7)	21 (14.4)
Constipation	61 (14.9)	3 (2.2)	5 (3.4)
Vomiting	37 (9.0)	4 (3.0)	9 (6.2)
Somnolence[a]	37 (9.0)	1 (0.7)	1 (0.7)
Headache	30 (7.3)	7 (5.2)	2 (1.4)
Pruritus[b]	27 (6.6)	0	3 (2.1)
Dizziness	24 (5.9)	1 (0.7)	6 (4.1)
Diarrhea	9 (2.2)	6 (4.5)	8 (5.5)

a. Also includes Sedation
b. Also includes Pruritus generalized
ADR=Adverse Drug Reaction

12-Month Multicenter, Open-Label, Single-Arm Safety CNCP Study (B4531001)

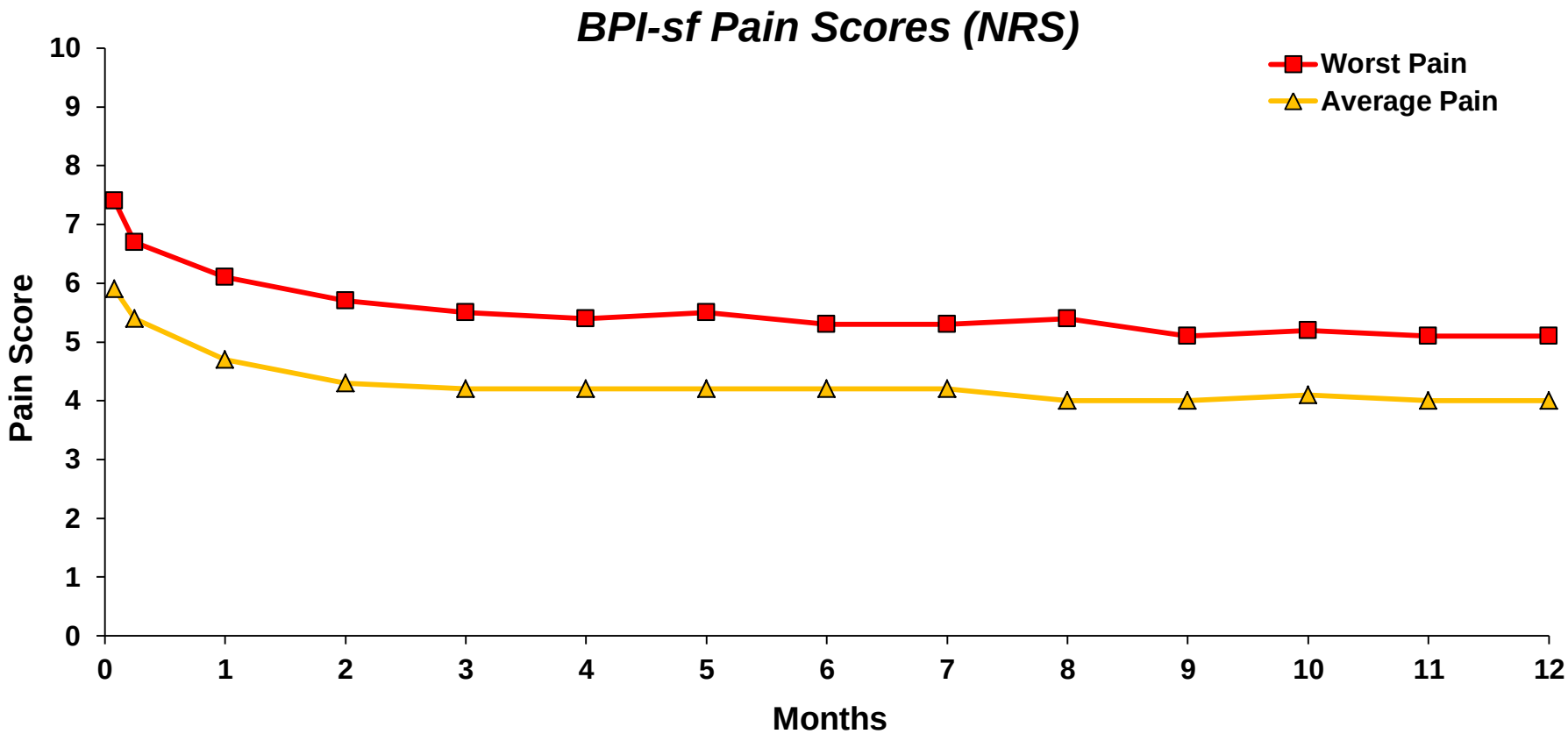
- Population: CNCP for ≥3 months; pain score of >4; subjects required, in the opinion of the investigator, a continuous around-the-clock opioid analgesic for an extended period of time



- Titration criteria for inadequate analgesia: worst pain score of >4; no intolerable opioid effects
- Average daily dose: 62.5 mg/day of ALO-02

CNCP=Chronic Non-Cancer Pain

Significant Reduction of Pain Over 12 Months in CNCP Study (B4531001)



Change in pain scores from baseline were statistically significant ($p<0.0001$) at all visits

BPI-sf=Brief Pain Inventory-short form

Adverse Events Consistent with Known Opioid Side Effects Over 12 Months in CNCP Study (B4531001)

Subjects	ALO-02 N=395 n (%)
Any adverse event	263 (66.6)
Most common ADRs (>5%)	
Nausea	100 (25.3)
Constipation	84 (21.3)
Vomiting	55 (13.9)
Headache	46 (11.6)
Somnolence[a]	38 (9.6)
Diarrhea	36 (9.1)
Fatigue	36 (9.1)
Dizziness	34 (8.6)
Abdominal pain[b]	33 (8.4)
Hyperhidrosis[c]	27 (6.8)
Back pain	25 (6.3)
Pruritus[d]	22 (5.6)
Insomnia	20 (5.1)

a. Also includes Sedation
b. Also includes Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort, and Gastrointestinal pain
c. Also includes Cold sweat
d. Also includes Pruritus generalized

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Category 1: Laboratory-Based In Vitro Manipulation and Extraction Studies

Sean Donevan, PhD

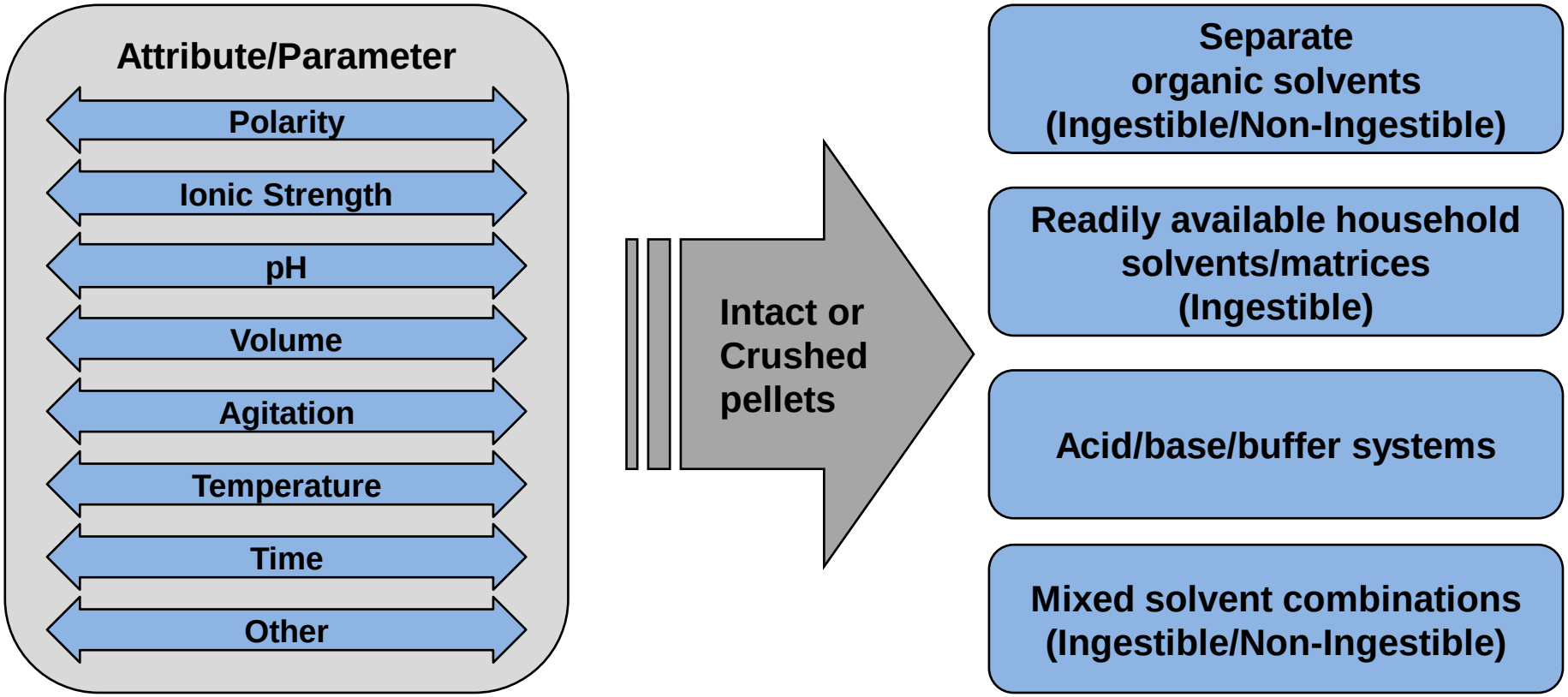
Design of ALO-02 In Vitro Program Differs from a Physical Chemical Barrier ADO

- Crushing releases naltrexone by design
- Does not form viscous gel when mixed with solvent
- Key objective is to explore ability to defeat formulation and isolate oxycodone in the absence of naltrexone
  - Evaluated crushing methods only to determine most consistent method for studies with crushed pellets
- No visual cues to confirm successful manipulation

ADO=Abuse-Deterrent Opioid

In Vitro Testing Strategy
A Diverse Battery of Challenge

- Studies conducted by independent laboratory
- 34 different solvents assessed
- Replicates typically n=6, over 5000 individual data points across all studies



In Vitro Program Addressed the Major Routes of Abuse

Route of Abuse	Manipulation Method	Mode of Administration	In Vitro Studies
Oral	None (Intact)	Swallow	Formulation not designed to reduce overconsumption
		Add to solvent and swallow	Large volume solvent extraction studies
	Chew or Crush	Swallow	See Human Abuse Potential studies with crushing
	Crush	Add to solvent and swallow	Large volume solvent extraction studies
Intranasal	Crush	Snort crushed powder	See Human Abuse Potential studies
Intravenous	None (Intact)	Add to small volumes, heat and inject	Small volume solvent extraction studies
	Crush	Add to small volumes, heat and inject	Refer to large volume solvent extraction studies with crushed pellets
Smoking	None (Intact)	Heat and vaporize, then inhale	Volatilization studies
	Crush	Heat and vaporize, then inhale	Volatilization studies

Abuse-Deterrent Mechanism of ALO-02

Extended-release of oxycodone taken intact (naltrexone sequestration)

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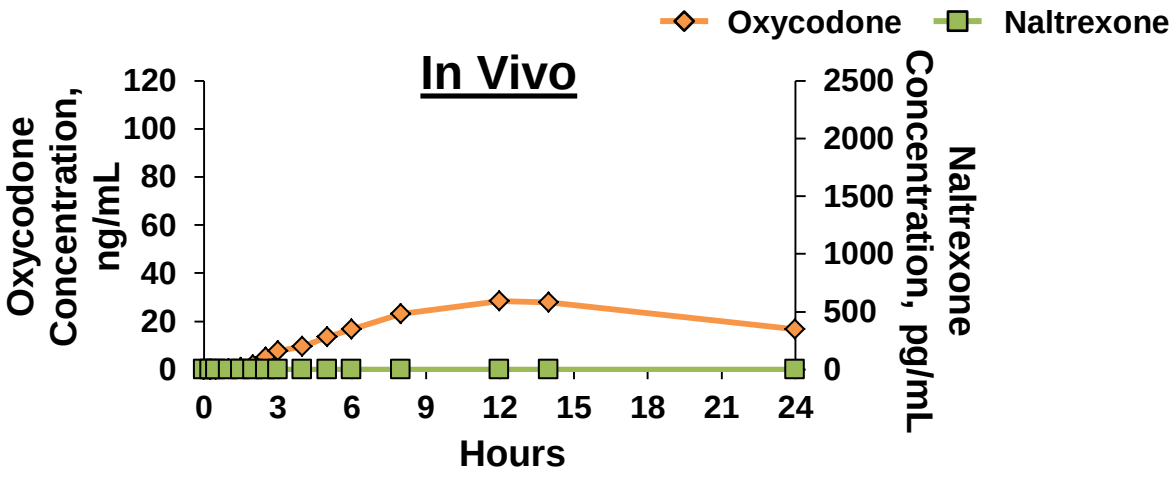

Study B4531008

Abuse-Deterrent Mechanism of ALO-02

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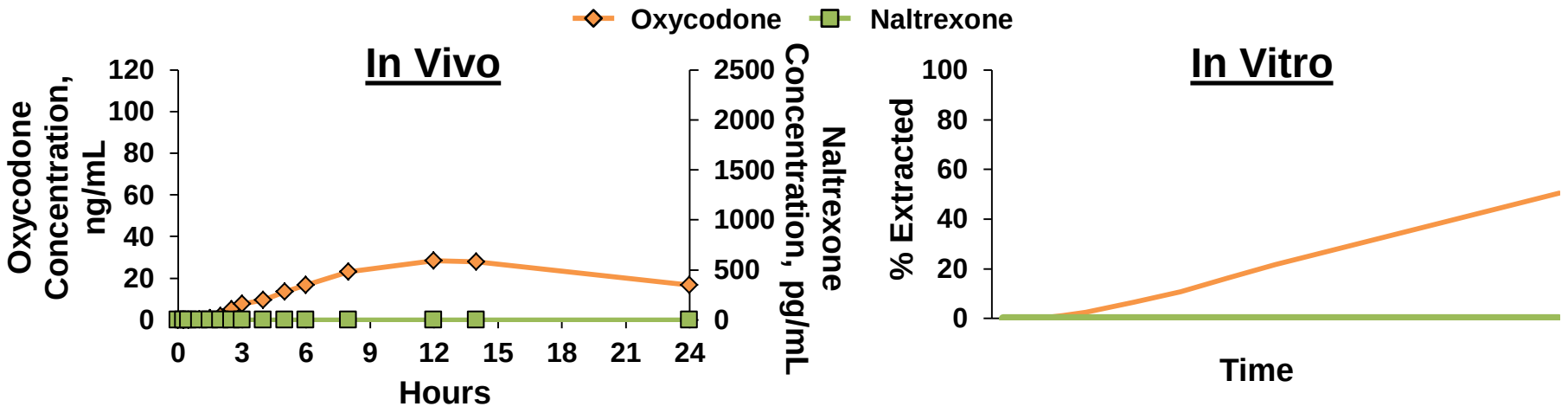

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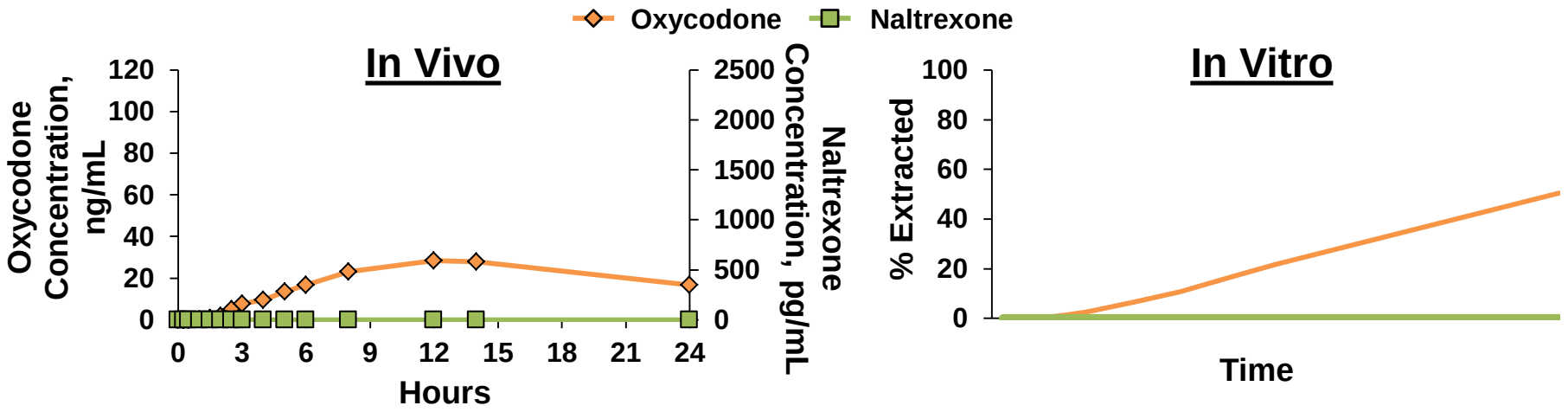

Co-release of naltrexone with oxycodone when crushed

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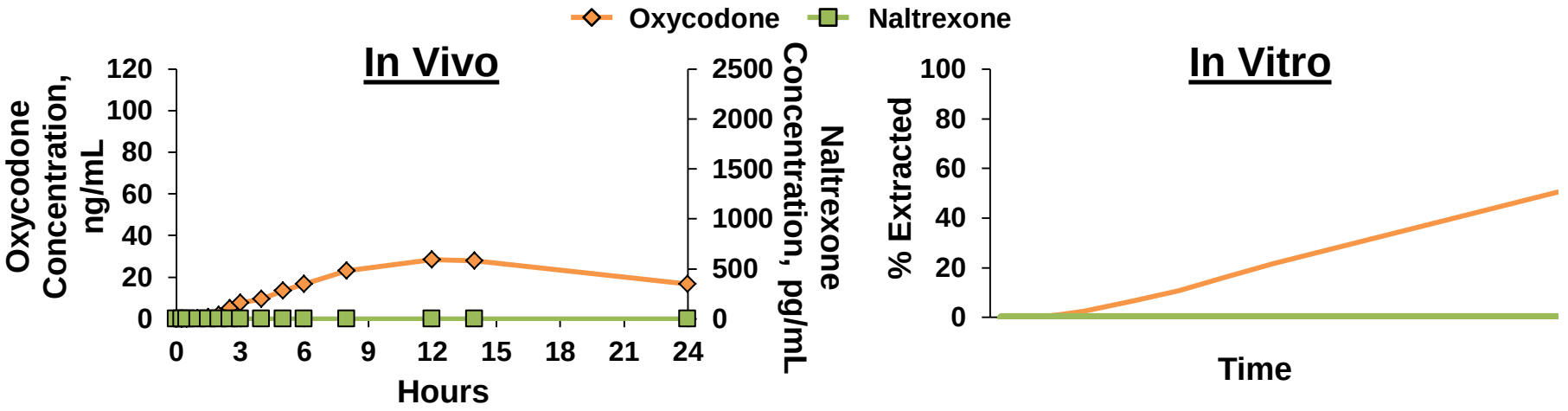

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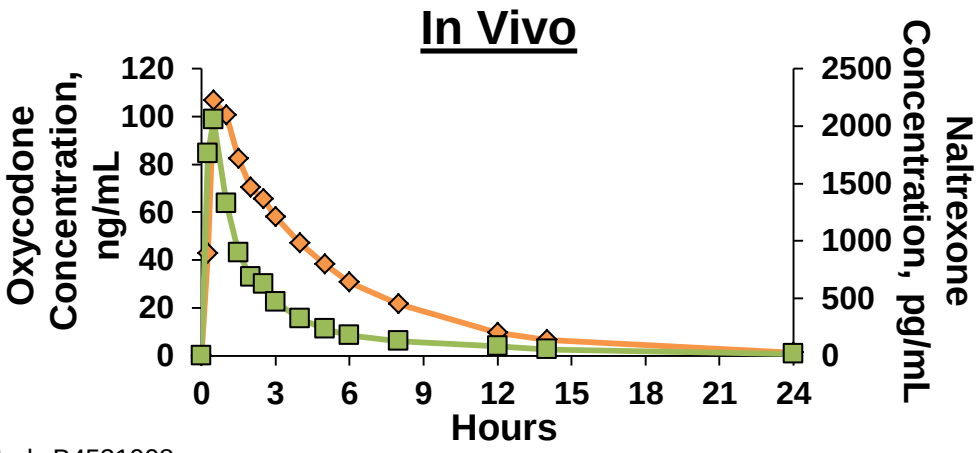

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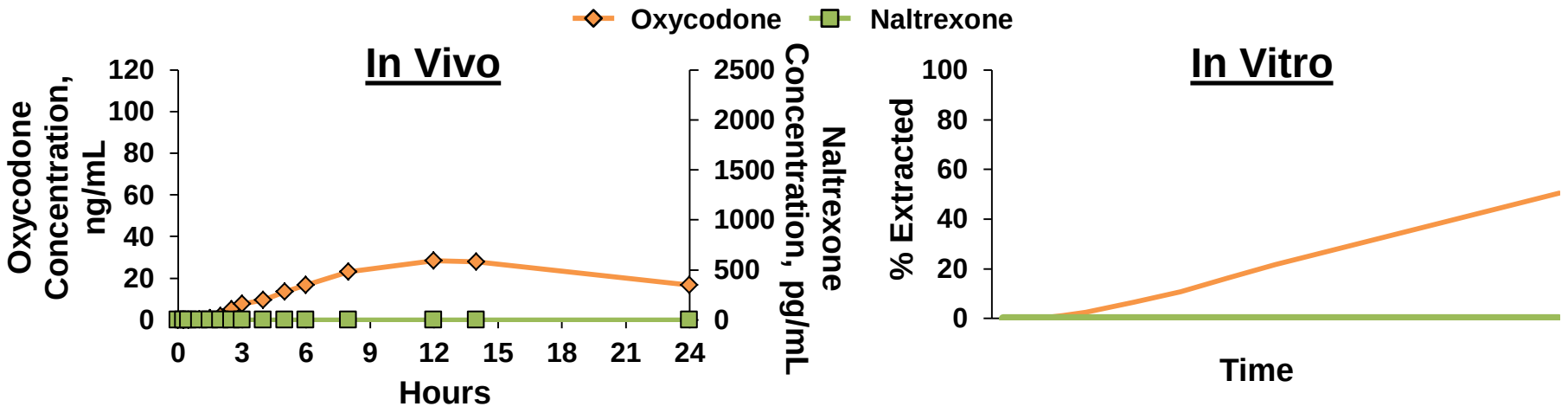

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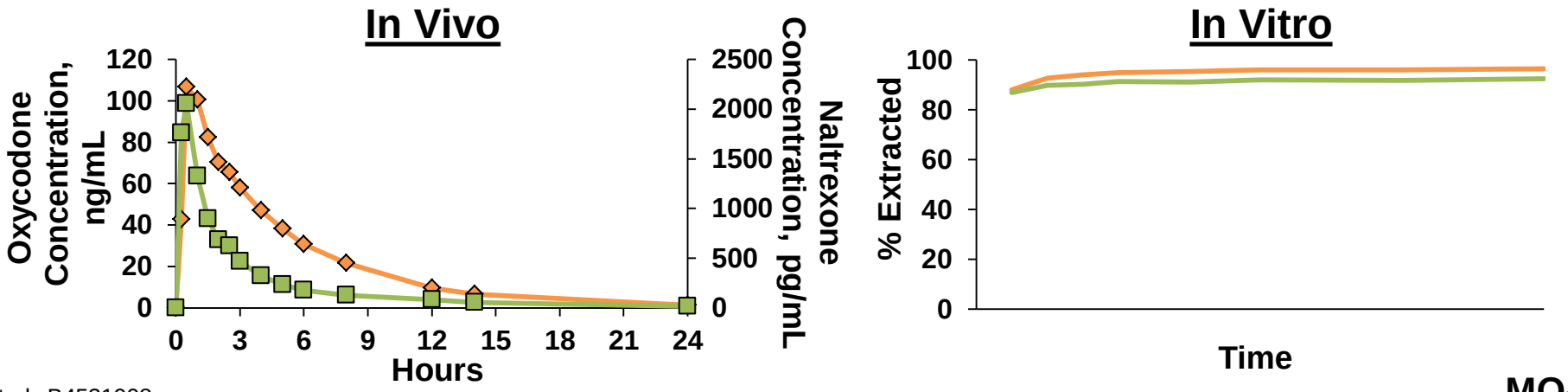
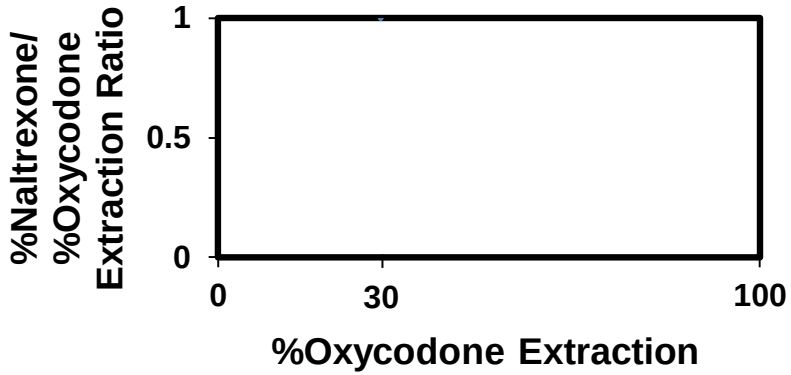


Study B4531008

Characterizing the Behavior of the Formulation and Display on a Heat Map



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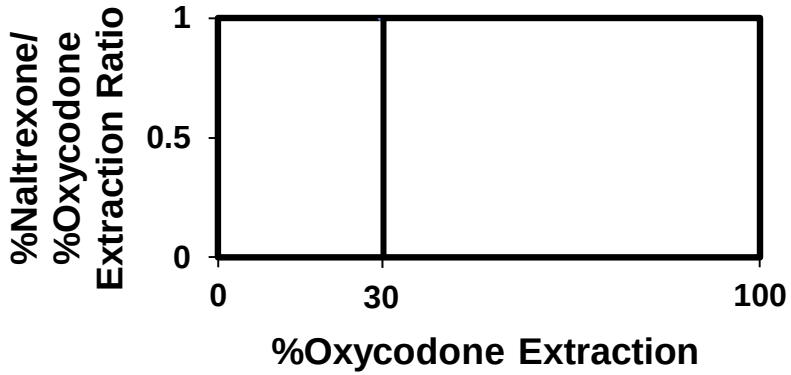

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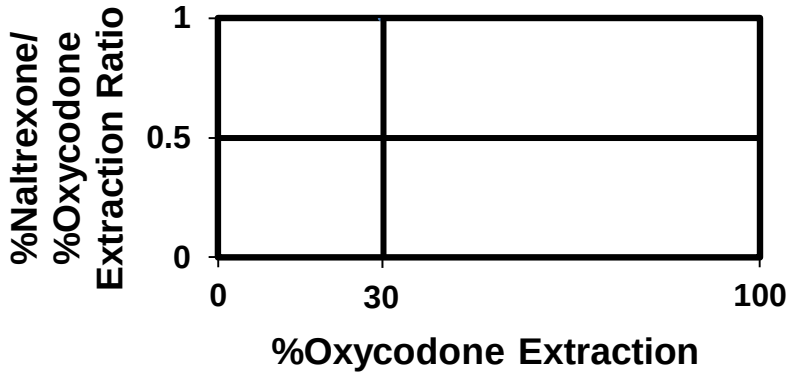

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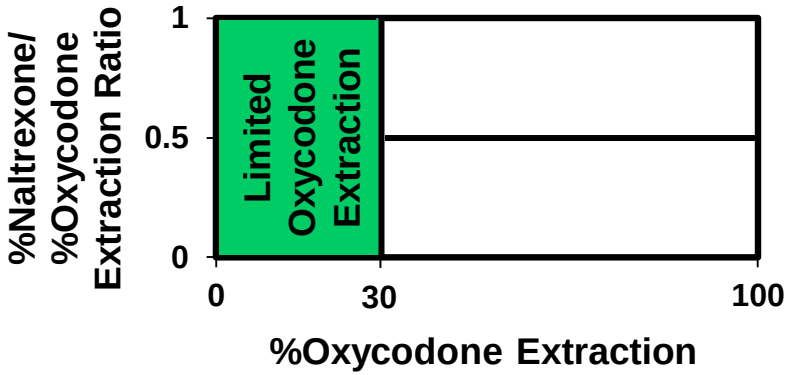

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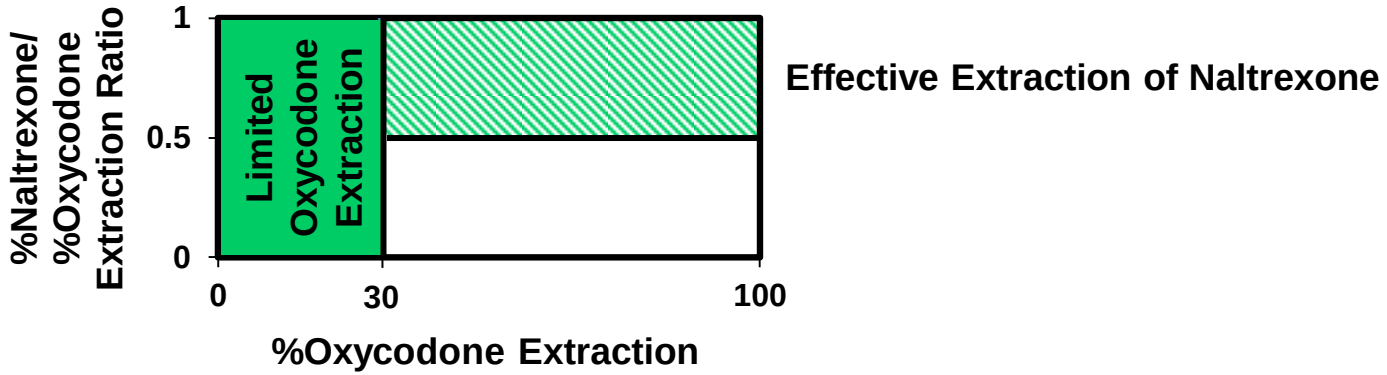

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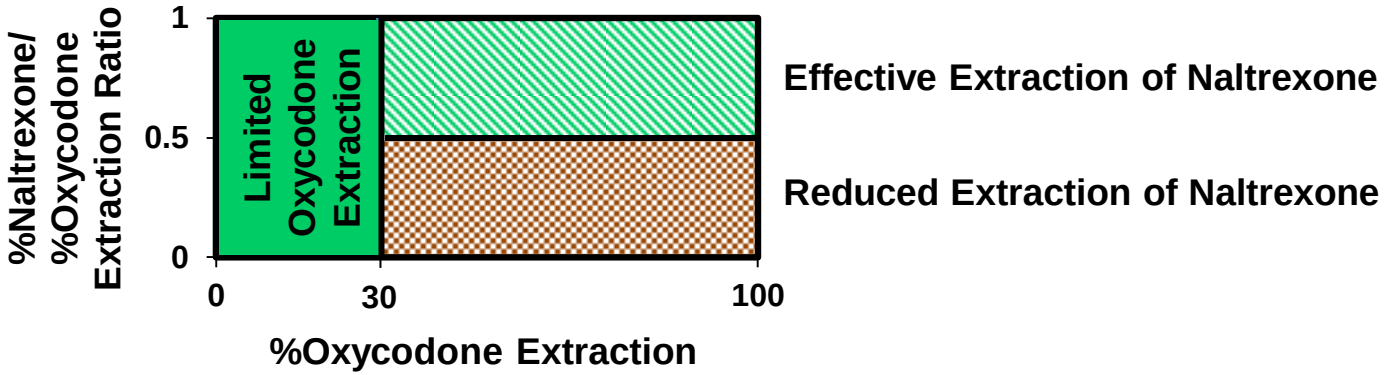

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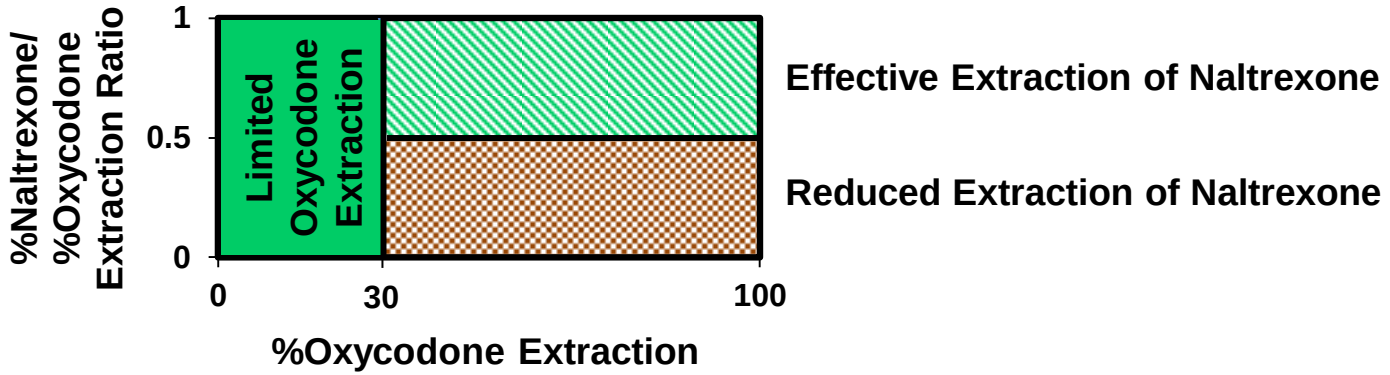
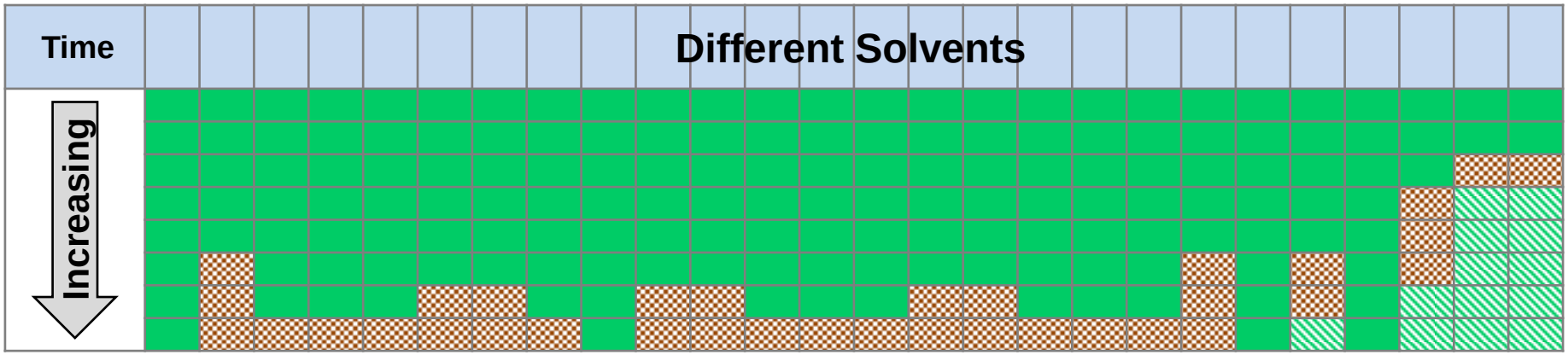
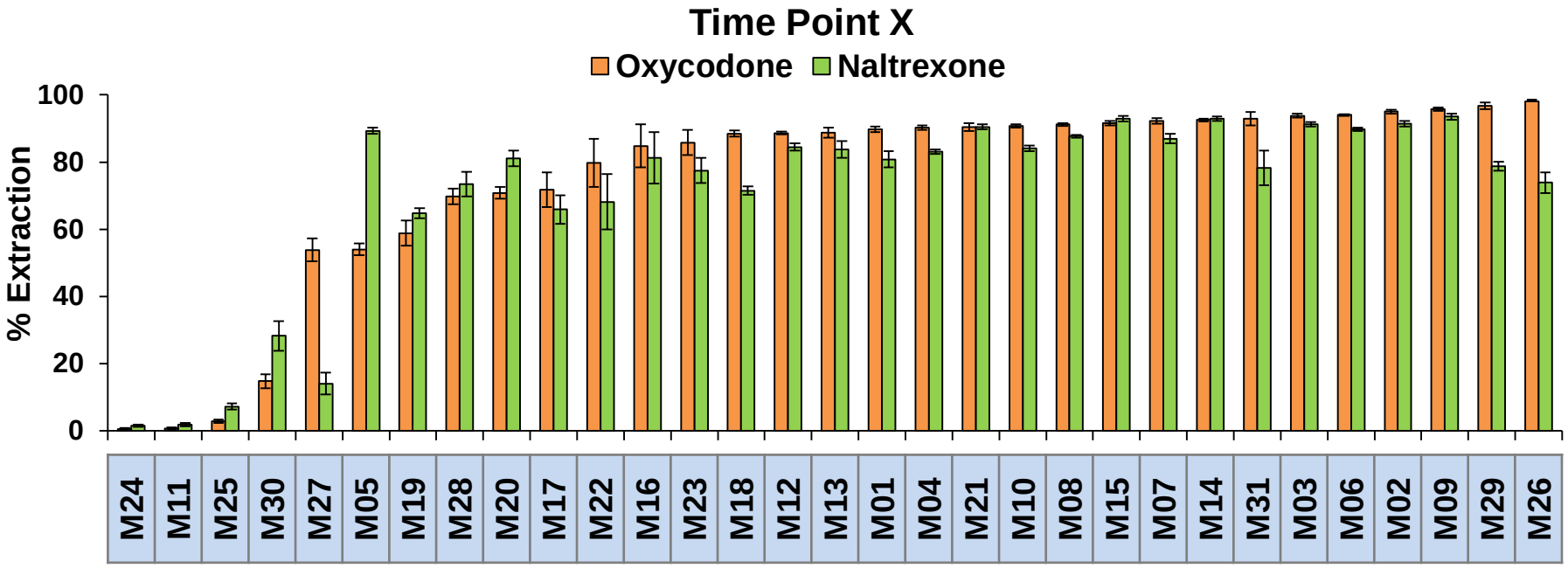


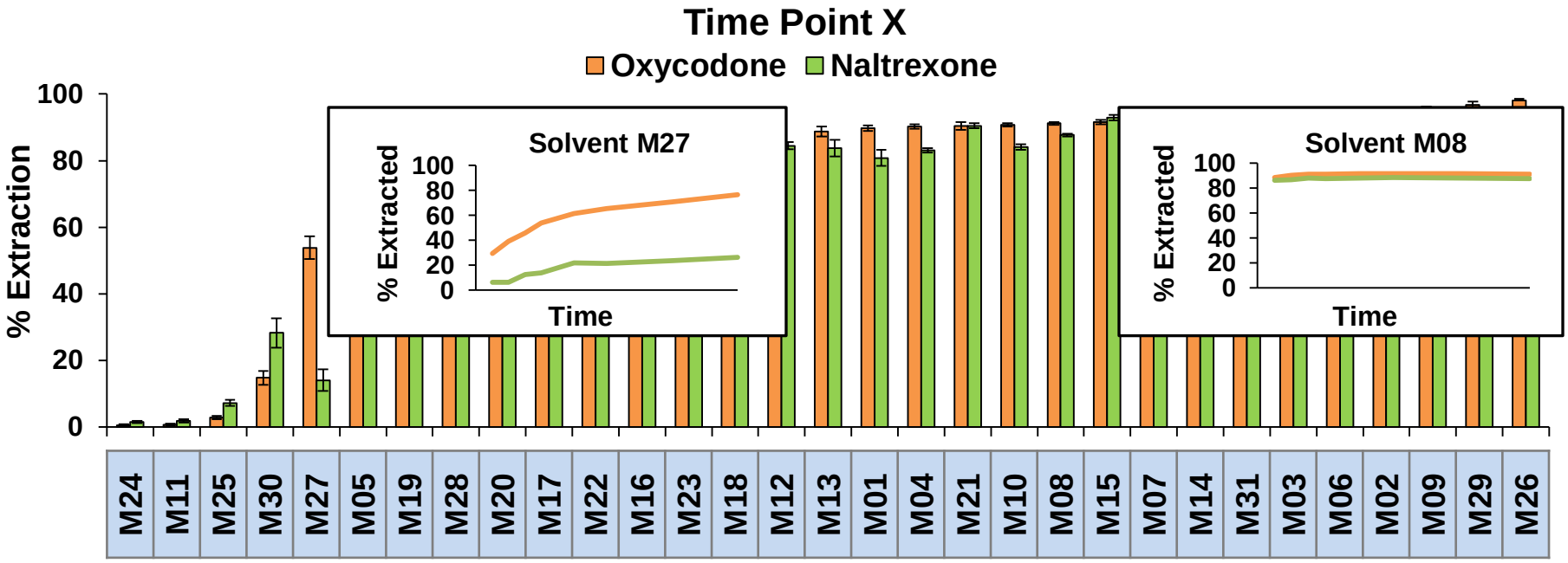


Large Volume Extraction Studies with Crushed and Intact Pellets in Different Conditions

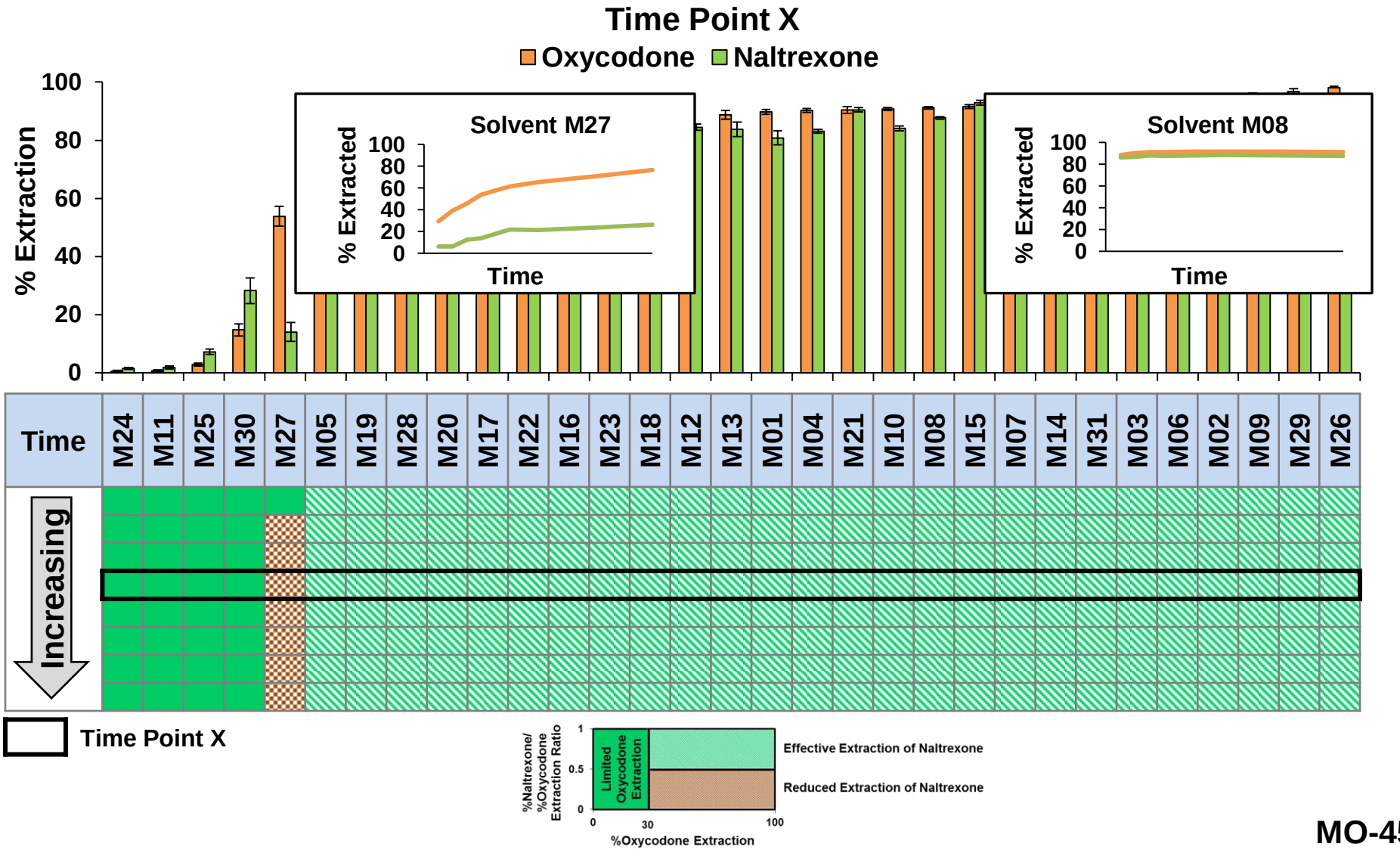
Large Volume Study – Crushed Pellets (Condition C): Similar Extraction of Oxycodone and Naltrexone in 30/31 Solvents



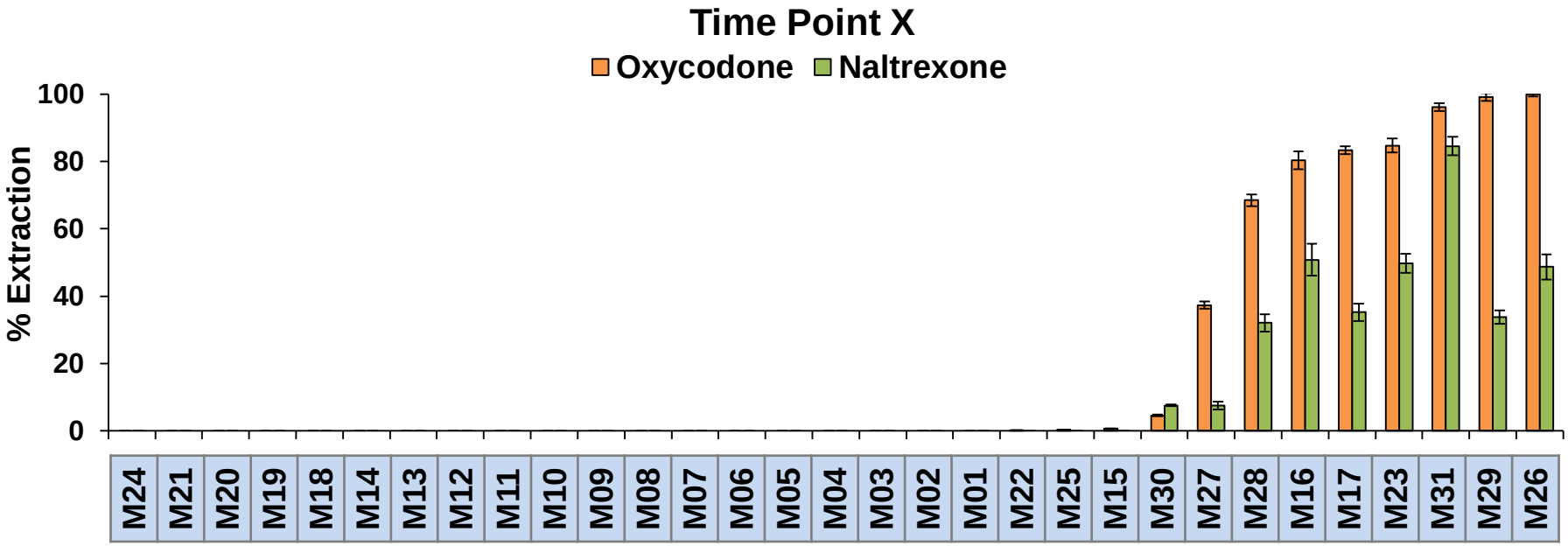
Large Volume Study – Crushed Pellets (Condition C): Similar Extraction of Oxycodone and Naltrexone in 30/31 Solvents



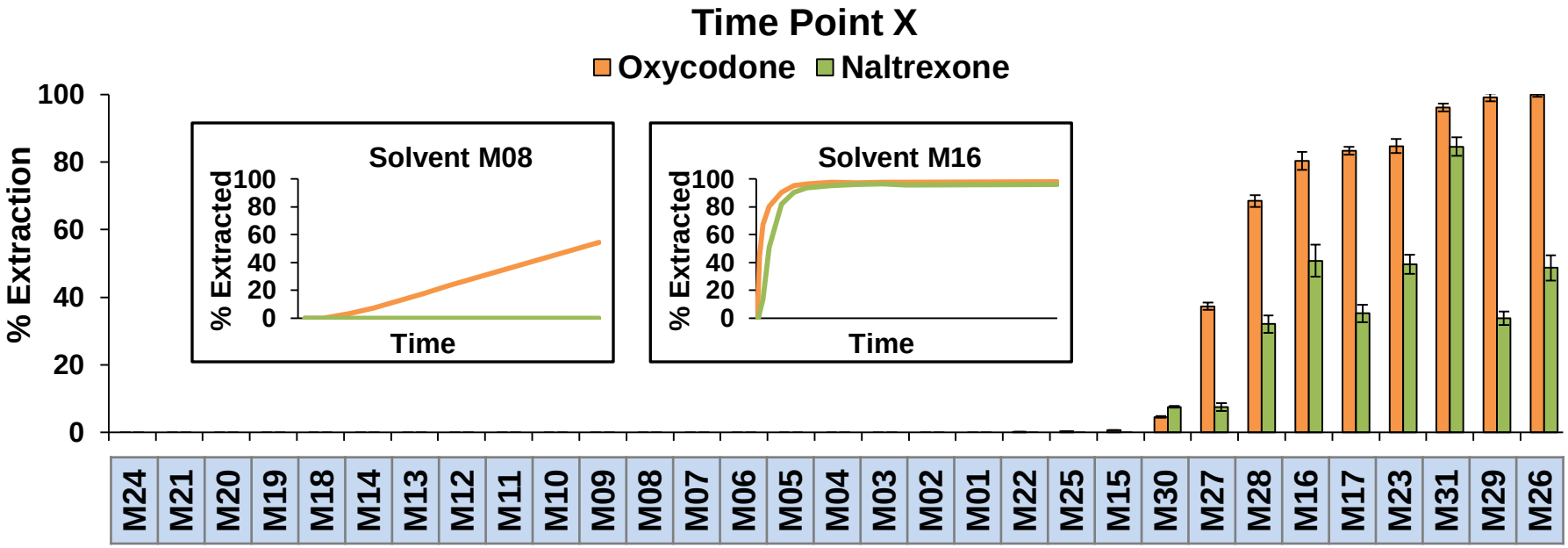
Large Volume Study – Crushed Pellets (Condition C): Similar Extraction of Oxycodone and Naltrexone in 30/31 Solvents



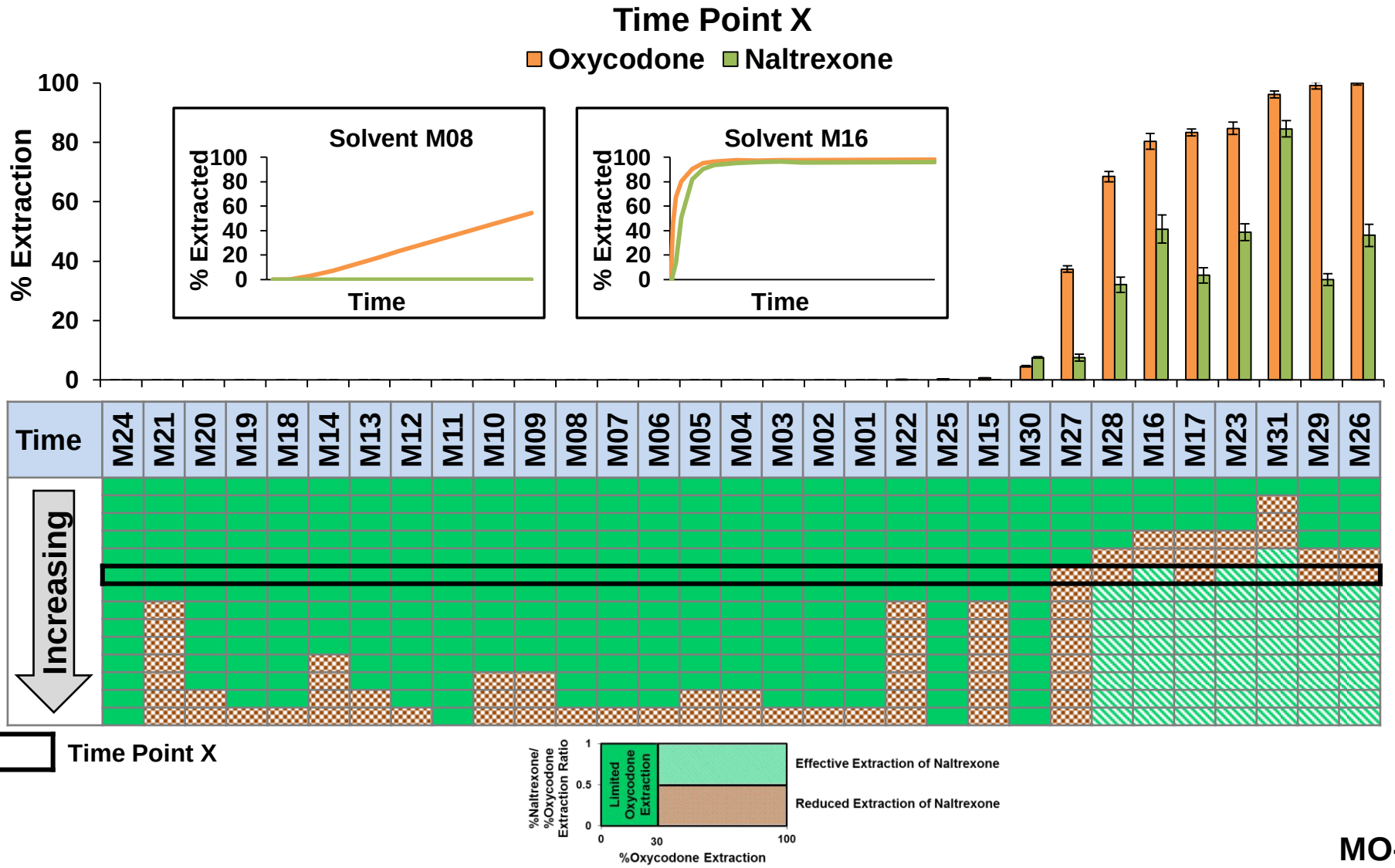
Large Volume Study – Intact Pellets (Condition B): Extraction of Oxycodone and Naltrexone



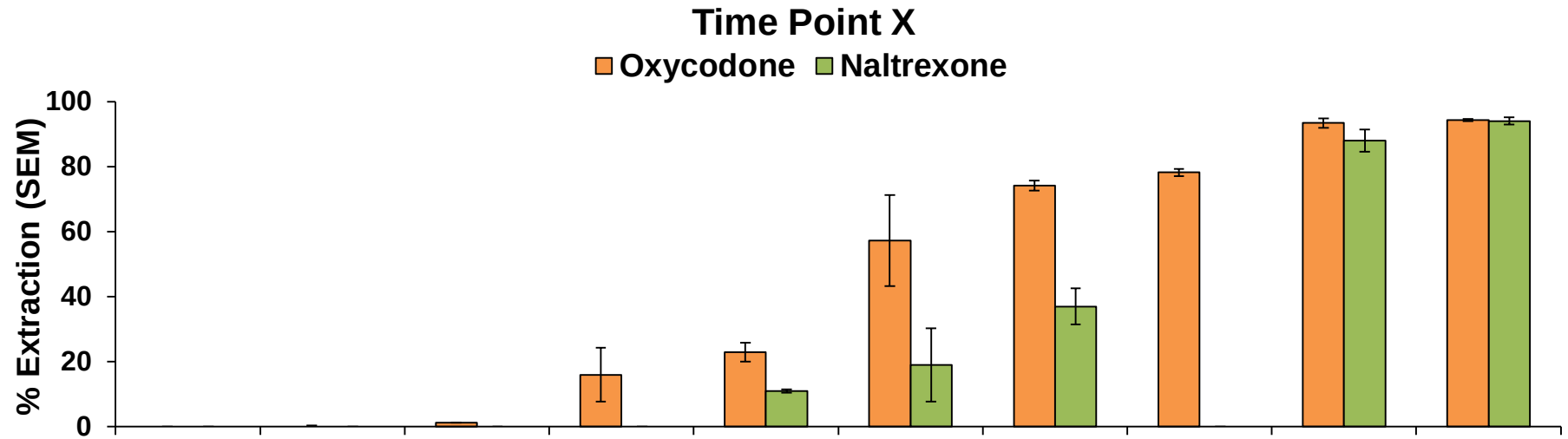
Large Volume Study – Intact Pellets (Condition B): Extraction of Oxycodone and Naltrexone

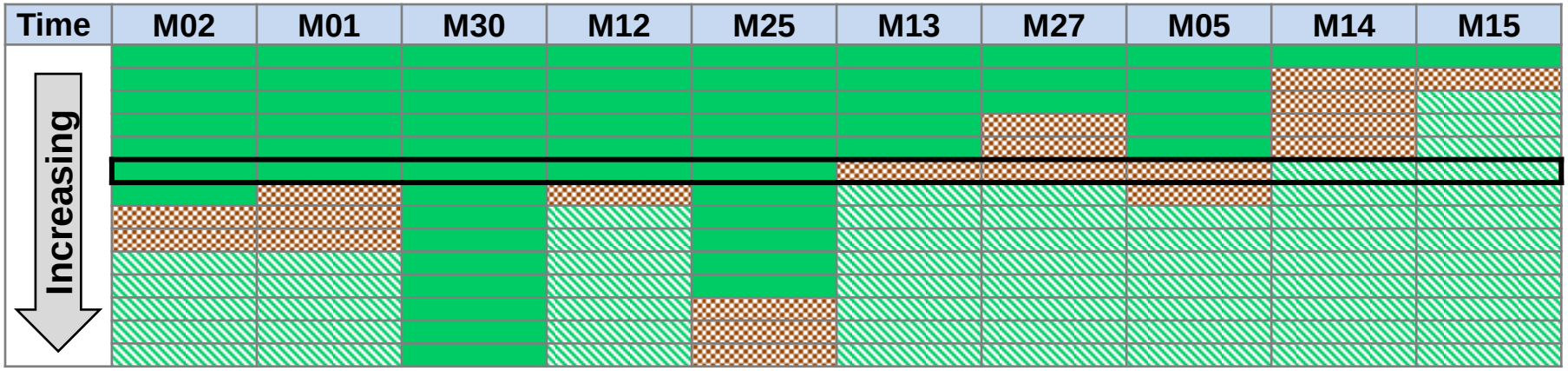


Large Volume Study – Intact Pellets (Condition B): Extraction of Oxycodone and Naltrexone

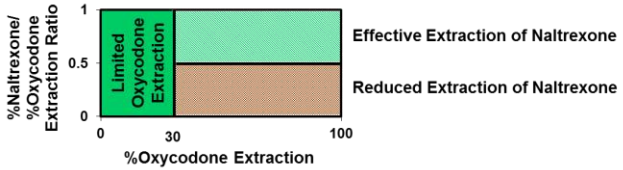


Large Volume Study – Intact ALO-02 Pellets (Condition D): Extraction of Oxycodone and Naltrexone





Time Point X



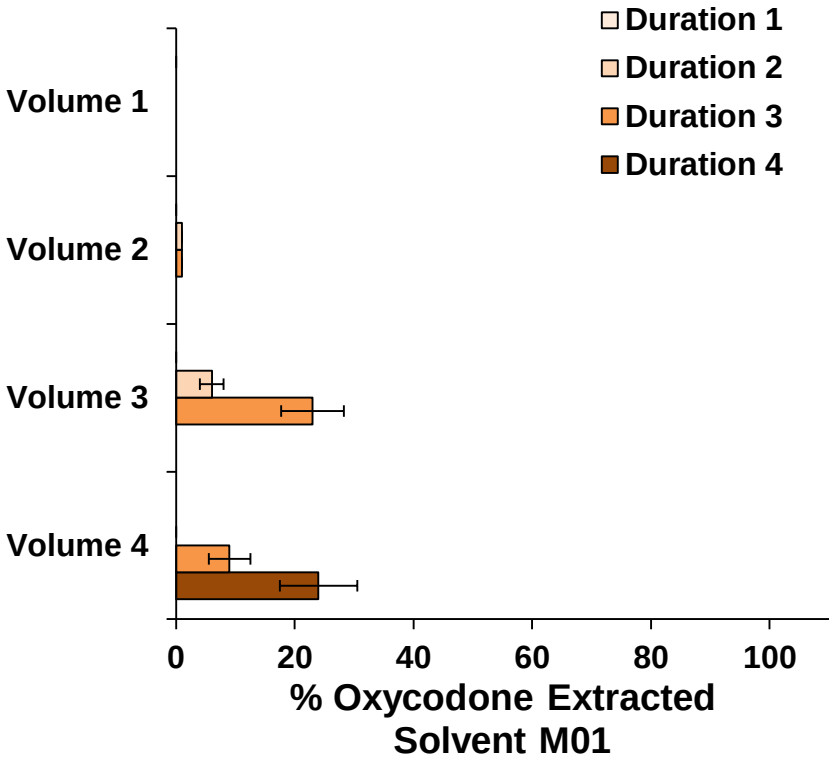
SEM=Standard Error of Mean

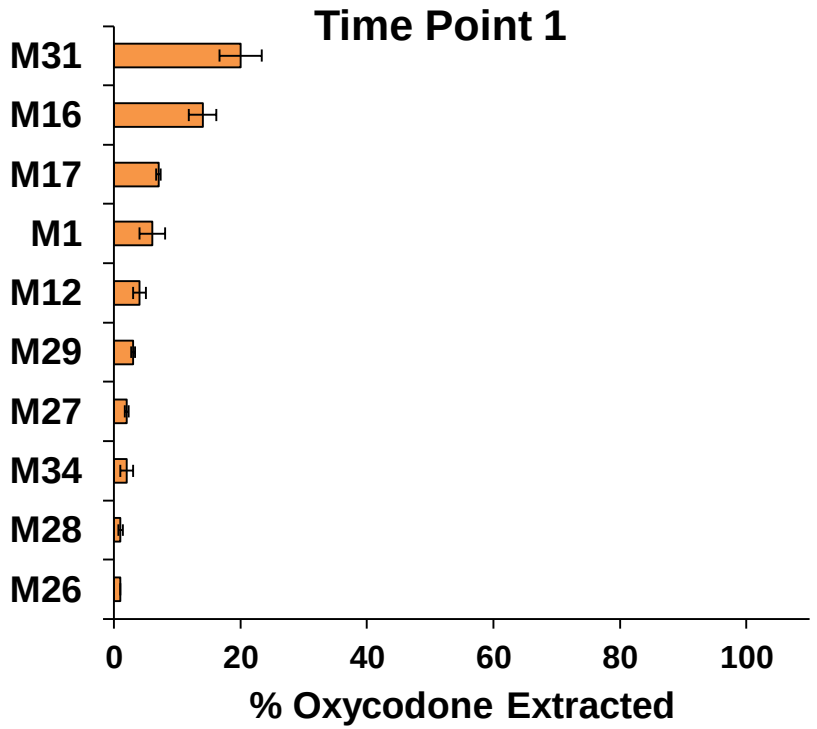
Additional Large Volume Extraction Studies with Intact ALO-02 Pellets: Conditions A, E and F

- In multi-solvent extraction studies in **Condition A** with intact pellets and different solvent combinations, there were some combinations in which oxycodone could be extracted preferentially, but most were in non-ingestible solvents. Additional steps would be required to separate oxycodone from these hazardous solvents
- In stressed **Conditions E** and **F**, there was significant oxycodone extraction with minimal naltrexone extraction

Small Volume Extraction Studies with Intact Pellets (Condition G)

Small Volume Studies – Intact ALO-02 Pellets (Condition G)





- Limited extraction of oxycodone from intact ALO-02 pellets in small volumes of all solvents tested
- Low yield would deter IV administration

IV=Intravenous

Summary

- Simultaneous release of oxycodone and naltrexone from crushed ALO-02 pellets in a variety of solvents
- Preferential release of oxycodone from intact ALO-02 pellets dependent upon time and condition
  - In most conditions only brief window of potential vulnerability which differed from solvent to solvent and from condition to condition
- In small volume studies with intact ALO-02, limited extraction of oxycodone from all solvents tested would deter IV abuse
- In volatilization studies, negligible extraction of oxycodone from crushed or intact pellets would deter smoking
- *ALO-02 formulation shows abuse-deterrent properties in vitro*
- *Lack of visual cues and fear of naltrexone are likely to limit extensive experimentation to identify potential vulnerabilities*

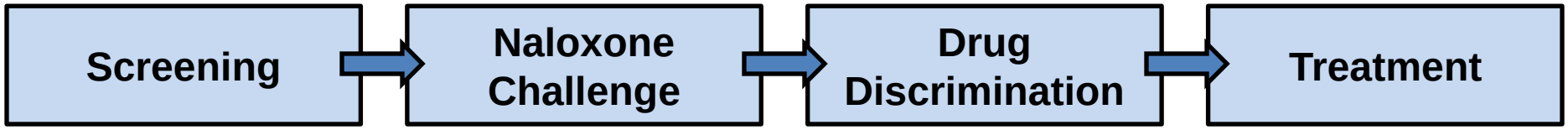
Category 2 and 3: Clinical Abuse Potential Studies

Carl L. Roland, PharmD, MS

Abuse Potential Studies in Non-Dependent Recreational Opioid Users

	Oral Study B4531008	Intranasal Study B4531009	Intravenous Study B4981002
Study Design: Randomized, Double-Blind	**6-way crossover**	**4-way crossover**	**3-way crossover**
Treatments	• ALO-02 40/4.8 mg (crushed) • IR OXY 40 mg (crushed) • IR OXY 60 mg (crushed) • ALO-02 60/7.2 mg (crushed) • ALO-02 60/7.2 mg (intact) • Placebo	• IR OXY 30 mg (crushed) • ALO-02 30/3.6 mg (crushed) • Placebo (weight matched to IR OXY and ALO-02)	• OXY IV 20 mg • OXY 20 mg IV and NTX IV 2.4 mg • Placebo IV

- Primary Measures: Drug Liking, High
- Secondary Measures: Take Drug Again, Overall Drug Liking, Any Drug Effects, Good Drug Effects, Bad Drug Effects, Feel Sick, Nausea, Sleepy, Dizzy, and Pupillometry

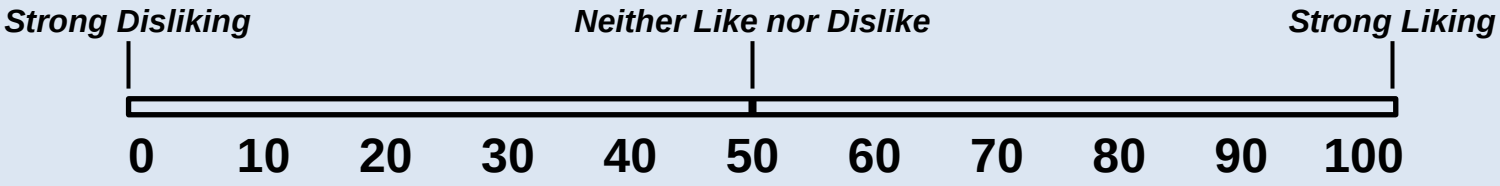


Studies were developed in cooperation with the Agency and followed the FDA Draft Guidance (January 2013)
OXY=Oxycodone; NTX=Naltrexone

Abuse Potential Study Measures

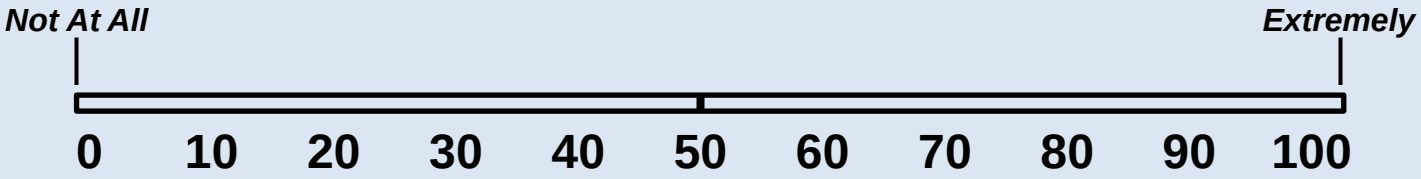
Drug Liking
(Bipolar)

At this moment, my liking for this drug is



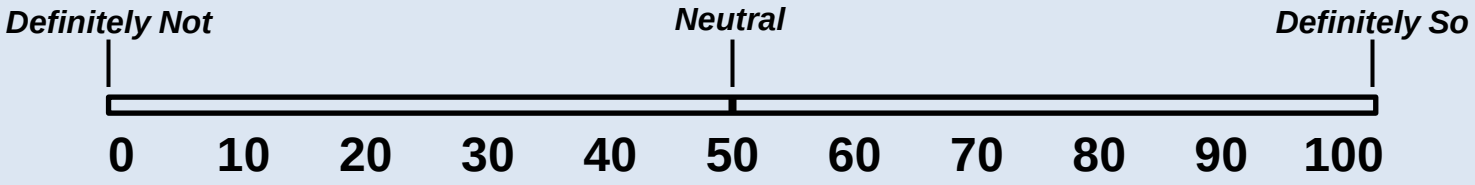
High
(Unipolar)

I am feeling high



Take Drug Again
(Bipolar)

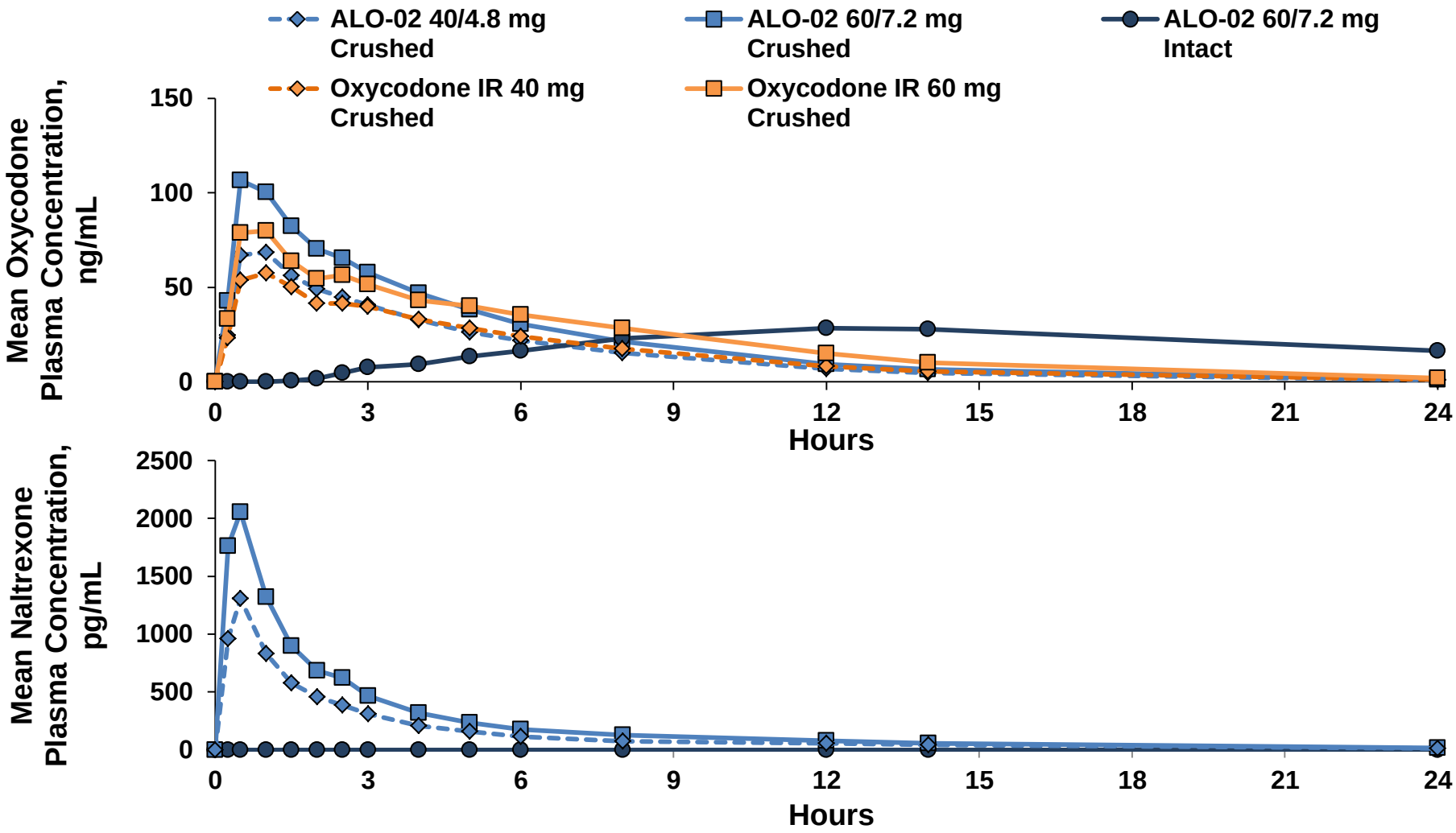
I would take this drug again



Oral Abuse Potential Study (B4531008)
N=32

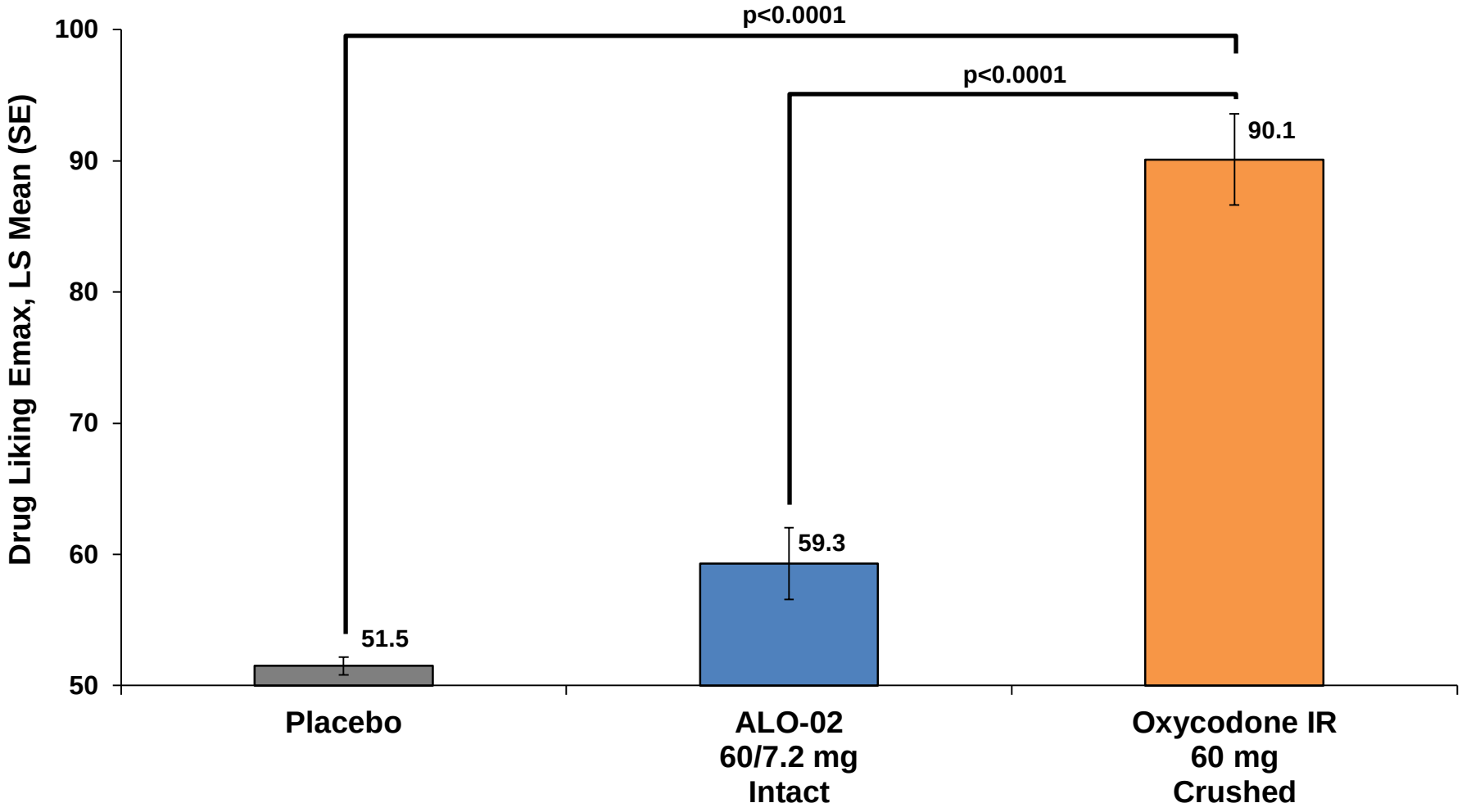
Treatment	Dose (Oxycodone/Naltrexone)	Administration
ALO-02	60/7.2 mg	Intact
ALO-02	60/7.2 mg	Crushed and administered as a suspension
Oxycodone HCl IR	60 mg	
ALO-02	40/4.8 mg	
Oxycodone HCl IR	40 mg	
Placebo		

When Crushed and Administered Orally, Oxycodone and Naltrexone are Simultaneously Released and Absorbed



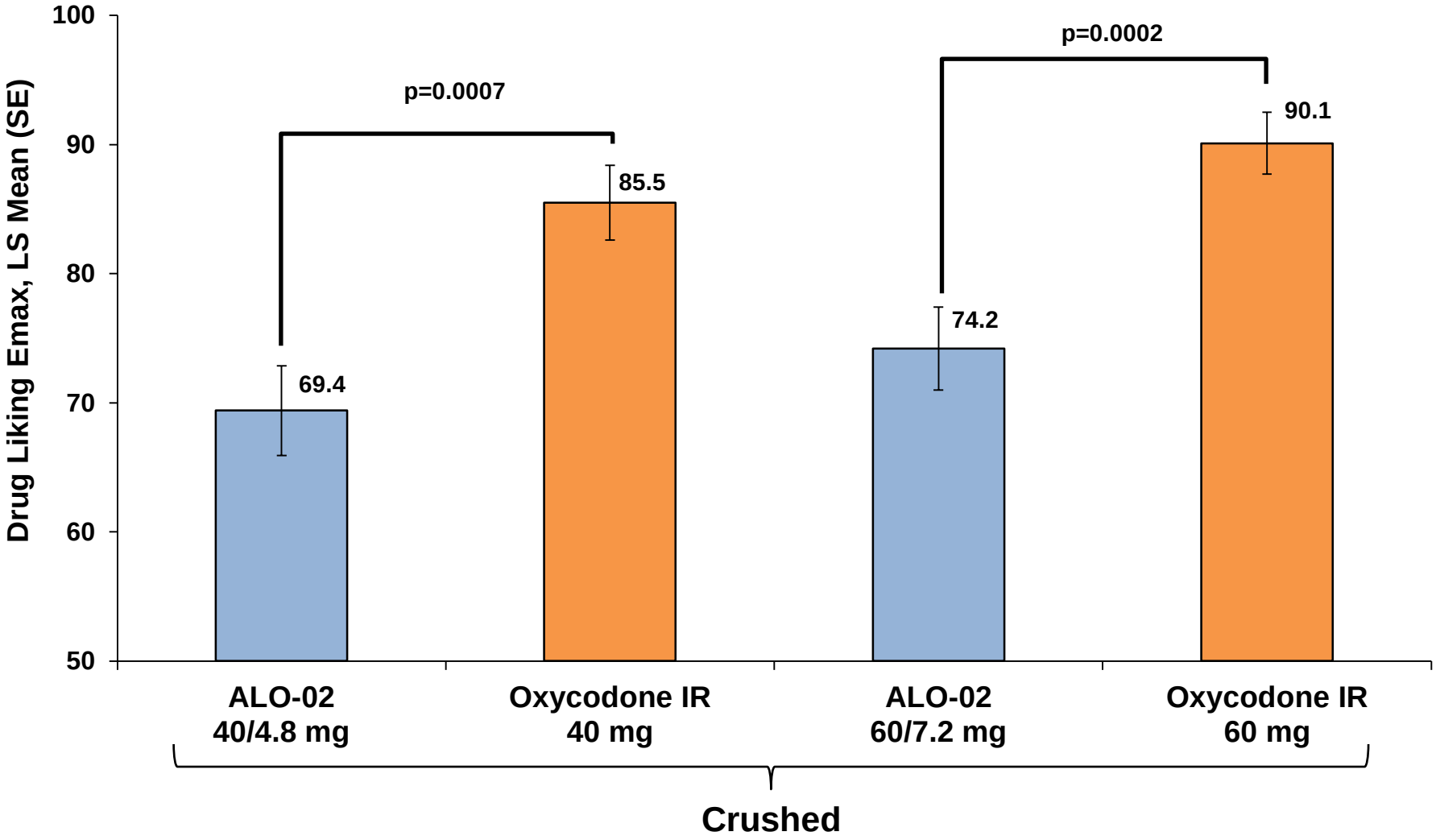
Study B4531008

Lower Drug Liking for Placebo and Intact ALO-02 Relative to Oxycodone IR: Oral Study



Study B4531008;
Emax=maximum Effect; SE=Standard Error

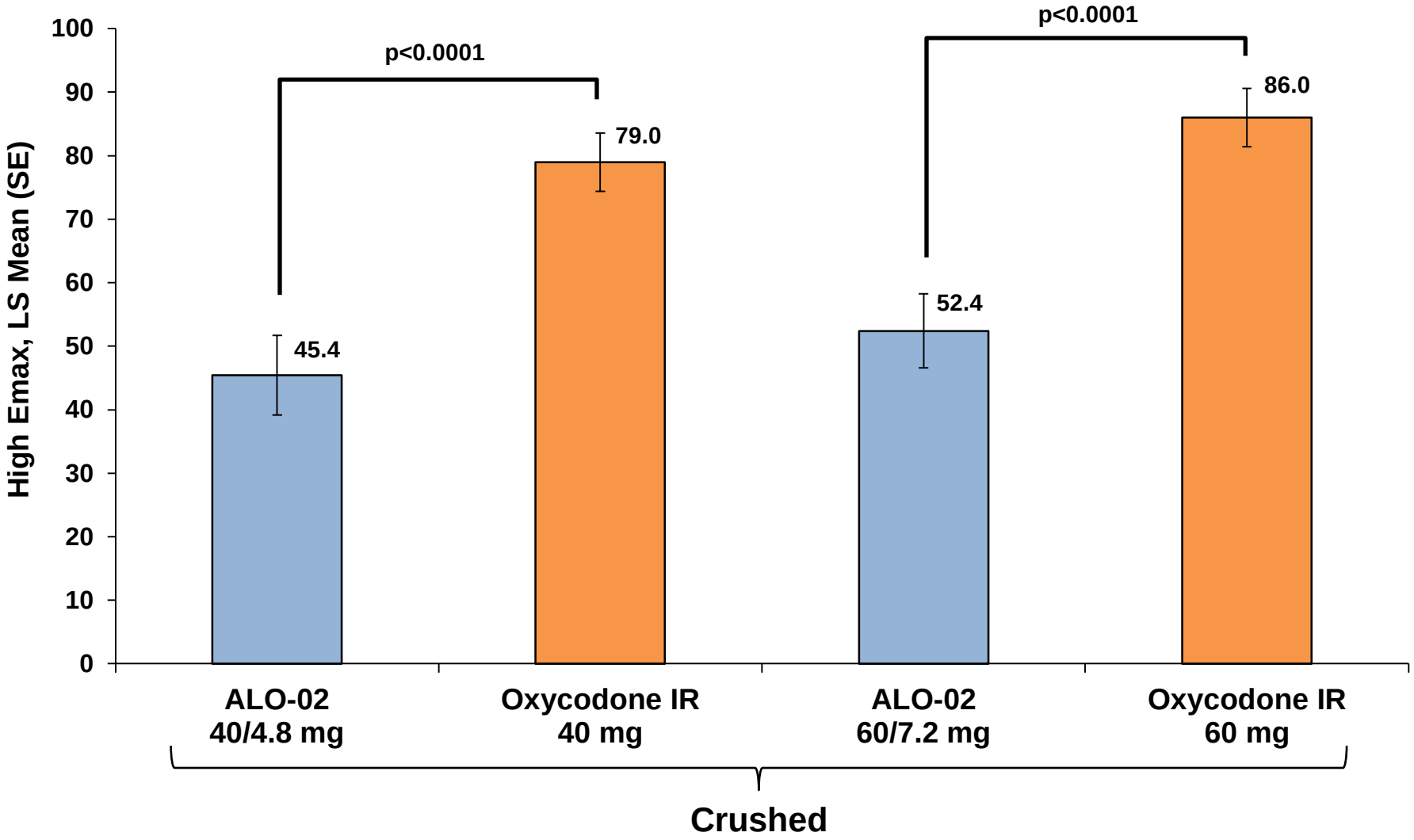
Lower Drug Liking for Oral Crushed ALO-02 than Oxycodone IR



Study B4531008

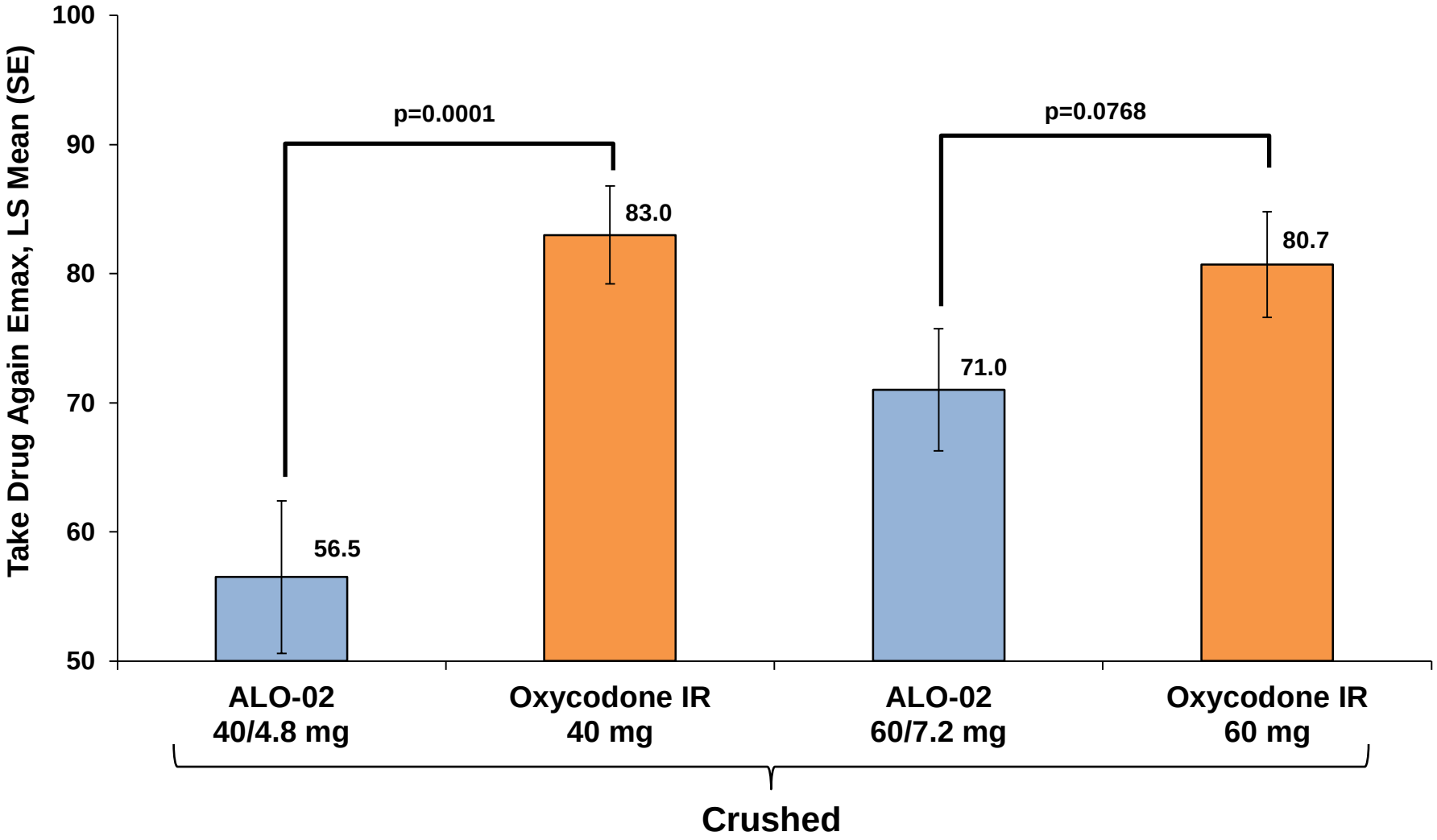
MO-60

Reduced High for Oral Crushed ALO-02 than Oxycodone IR



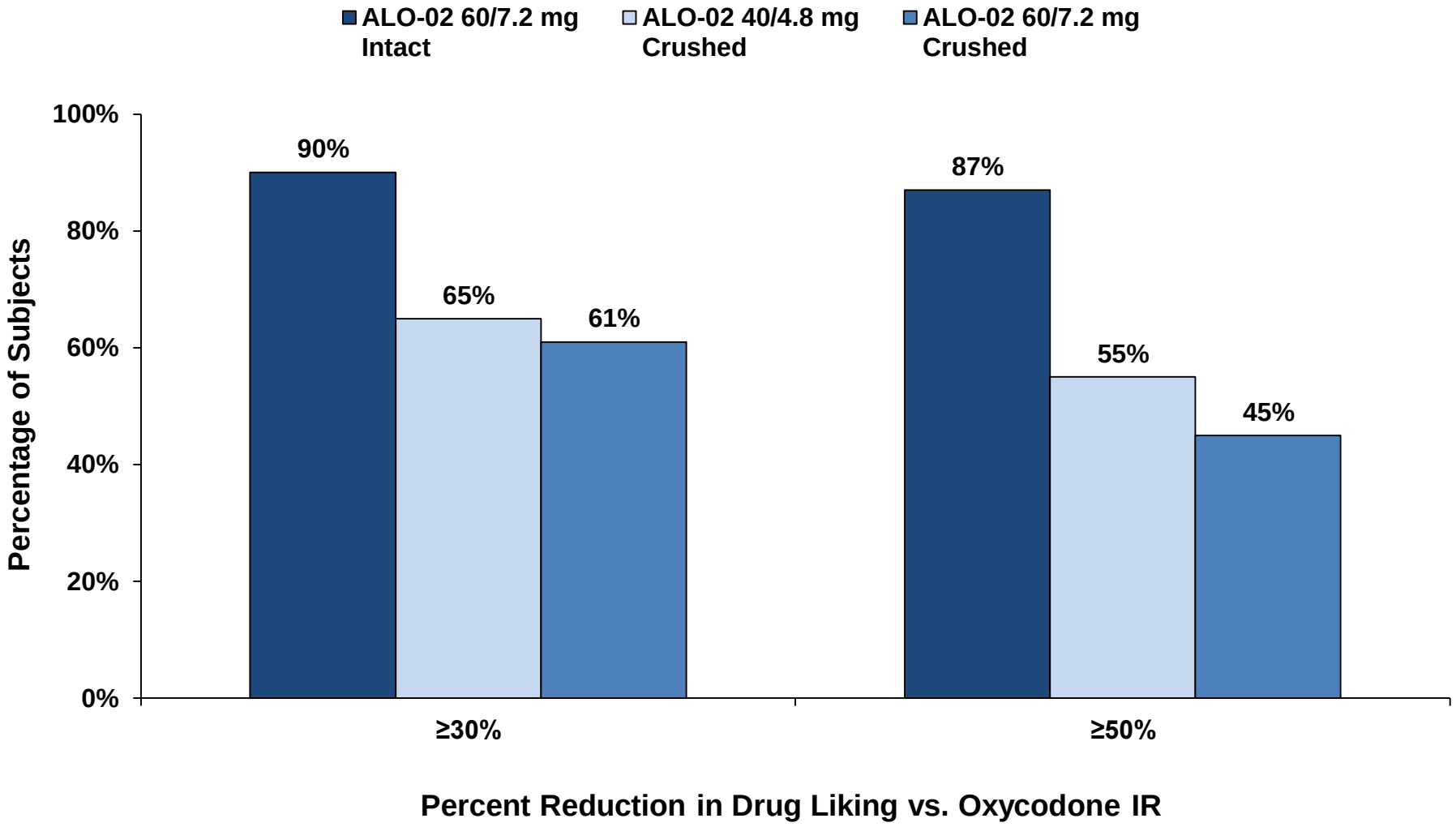
Study B4531008

Lower Take Drug Again for Oral Crushed ALO-02 than Oxycodone IR



Study B4531008

Percent Reduction in Drug Liking Emax for Crushed ALO-02 vs. Crushed Oxycodone IR: Oral

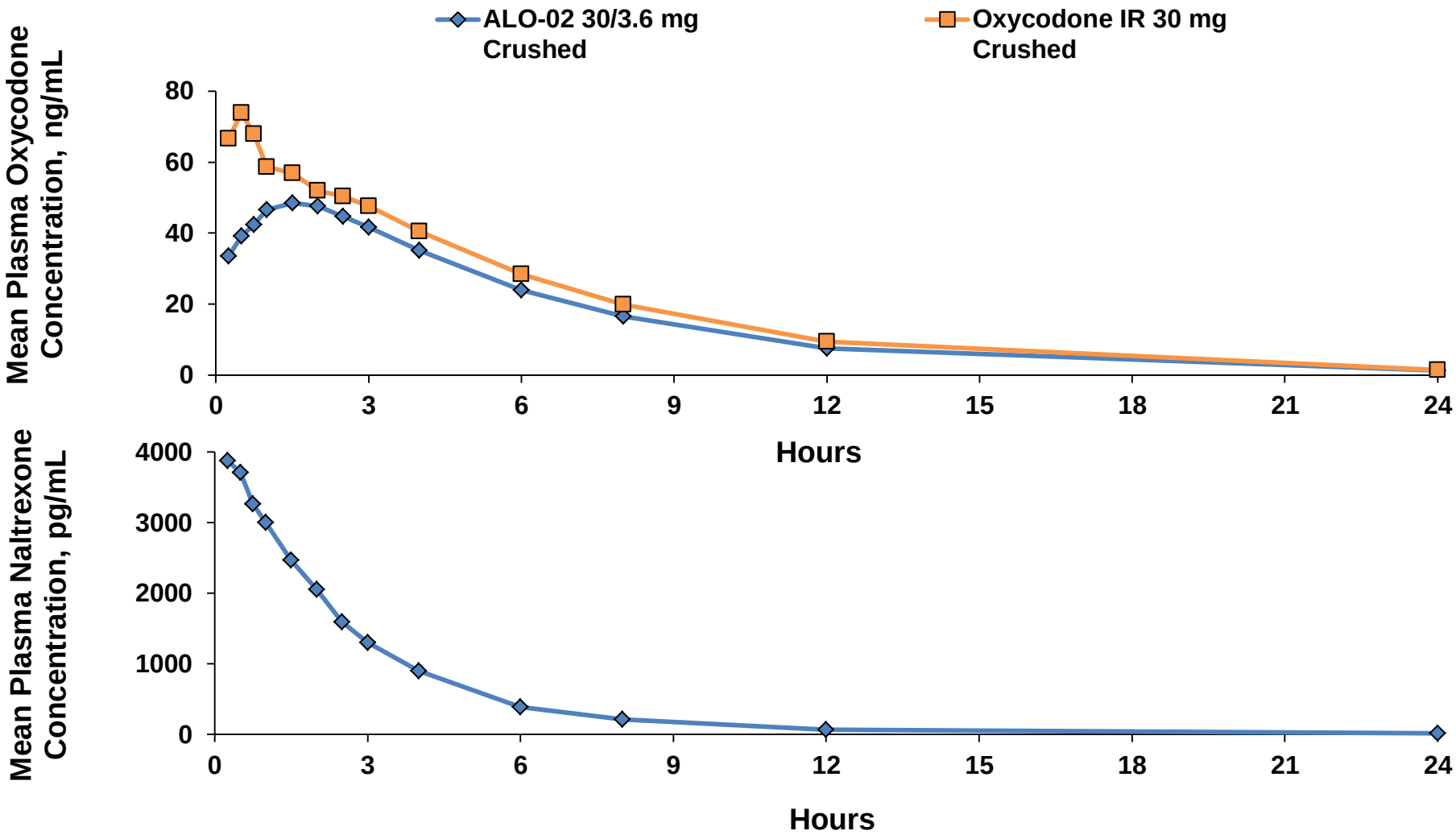


Study B4531008

Intranasal Abuse Potential Study (B4531009)
N=28

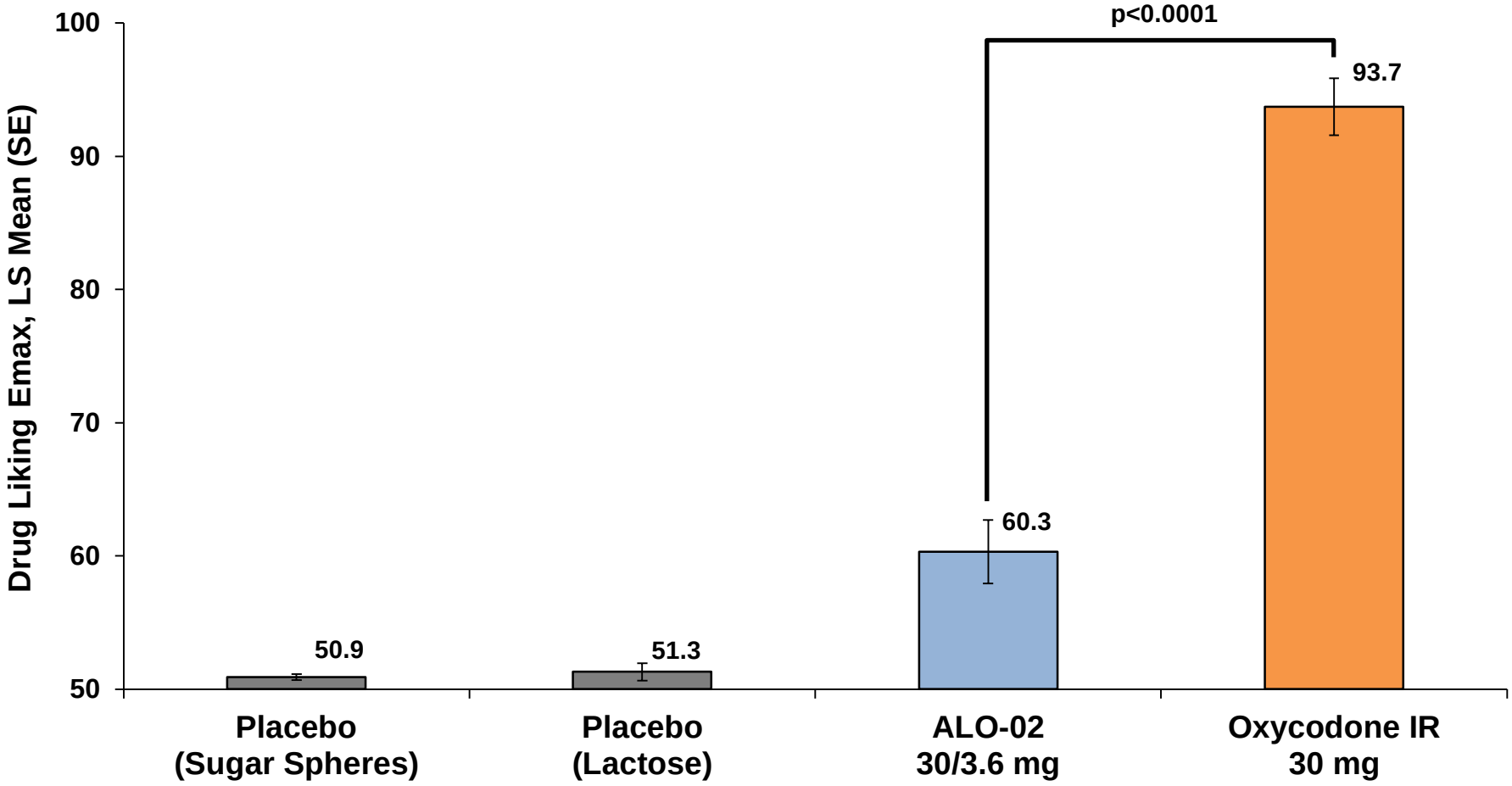
Treatments	Dose	
Placebo	Sugar Spheres	Crushed and weight matched to ALO-02
ALO-02	30 mg/3.6 mg	Crushed (1 × 30 mg/3.6 mg capsule crushed)
Placebo	Lactose Tablets	Crushed and weight matched to Oxycodone IR
Oxycodone IR	30 mg	Crushed (3 × 10 mg tablets crushed)

When Crushed and Administered Intranasally, Oxycodone and Naltrexone are Simultaneously Released and Absorbed



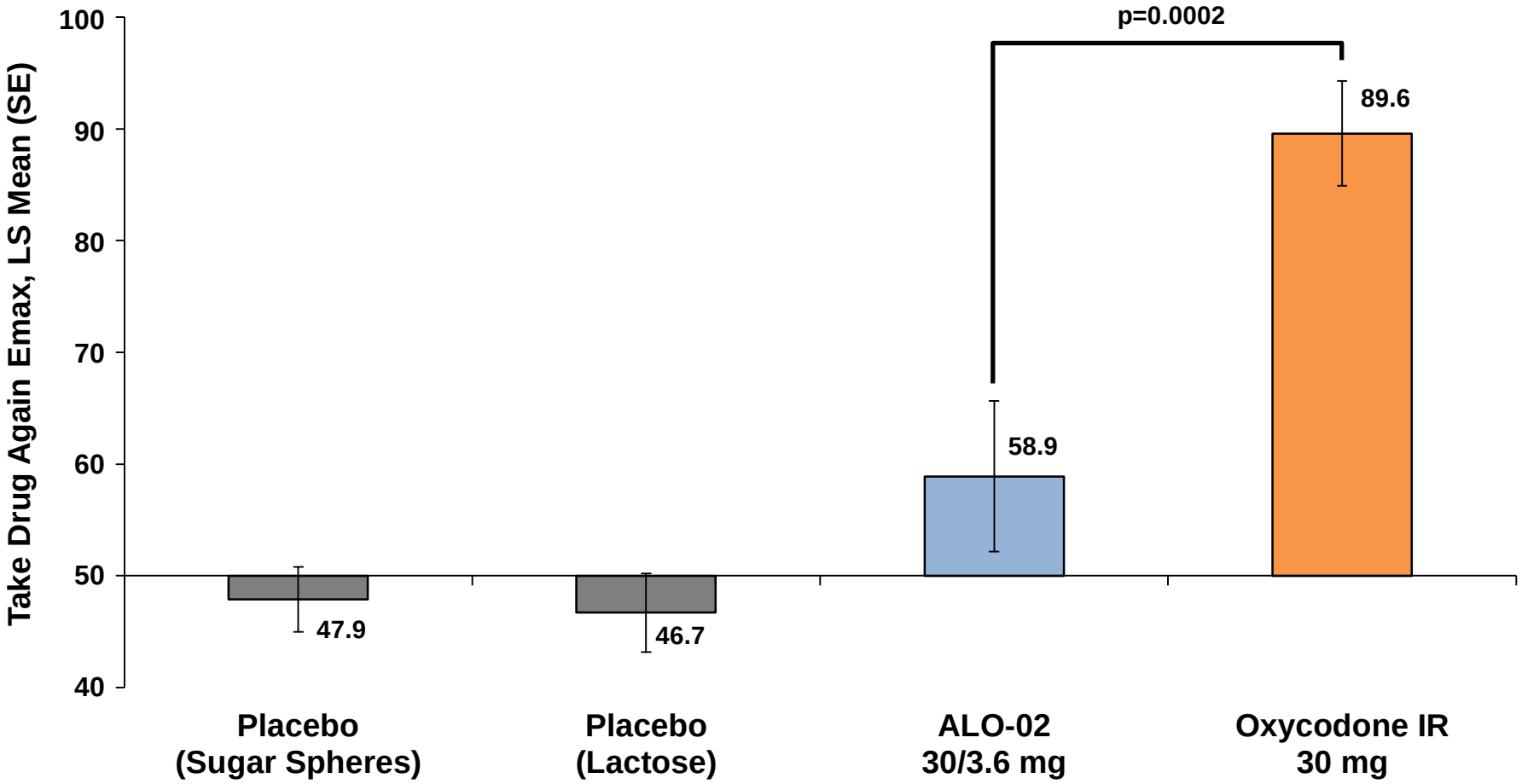
Study B4531009

Lower Drug Liking for Intranasal Crushed ALO-02 than Oxycodone IR



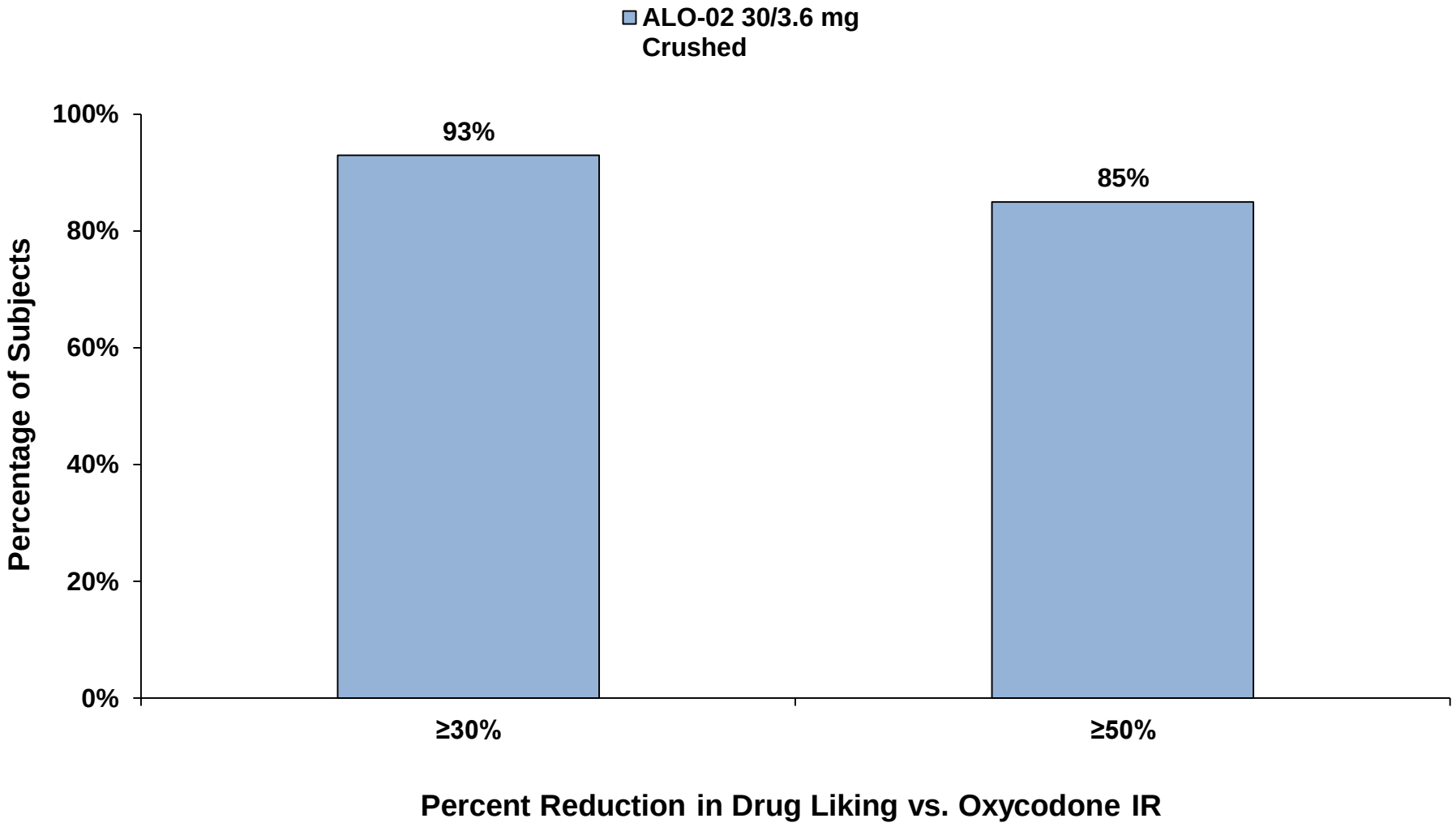
Study B4531009

Lower Take Drug Again for Intranasal Crushed ALO-02 than Oxycodone IR



Study B4531009

Percent Reduction in Drug Liking Emax for Crushed ALO-02 vs. Crushed Oxycodone IR: Intranasal

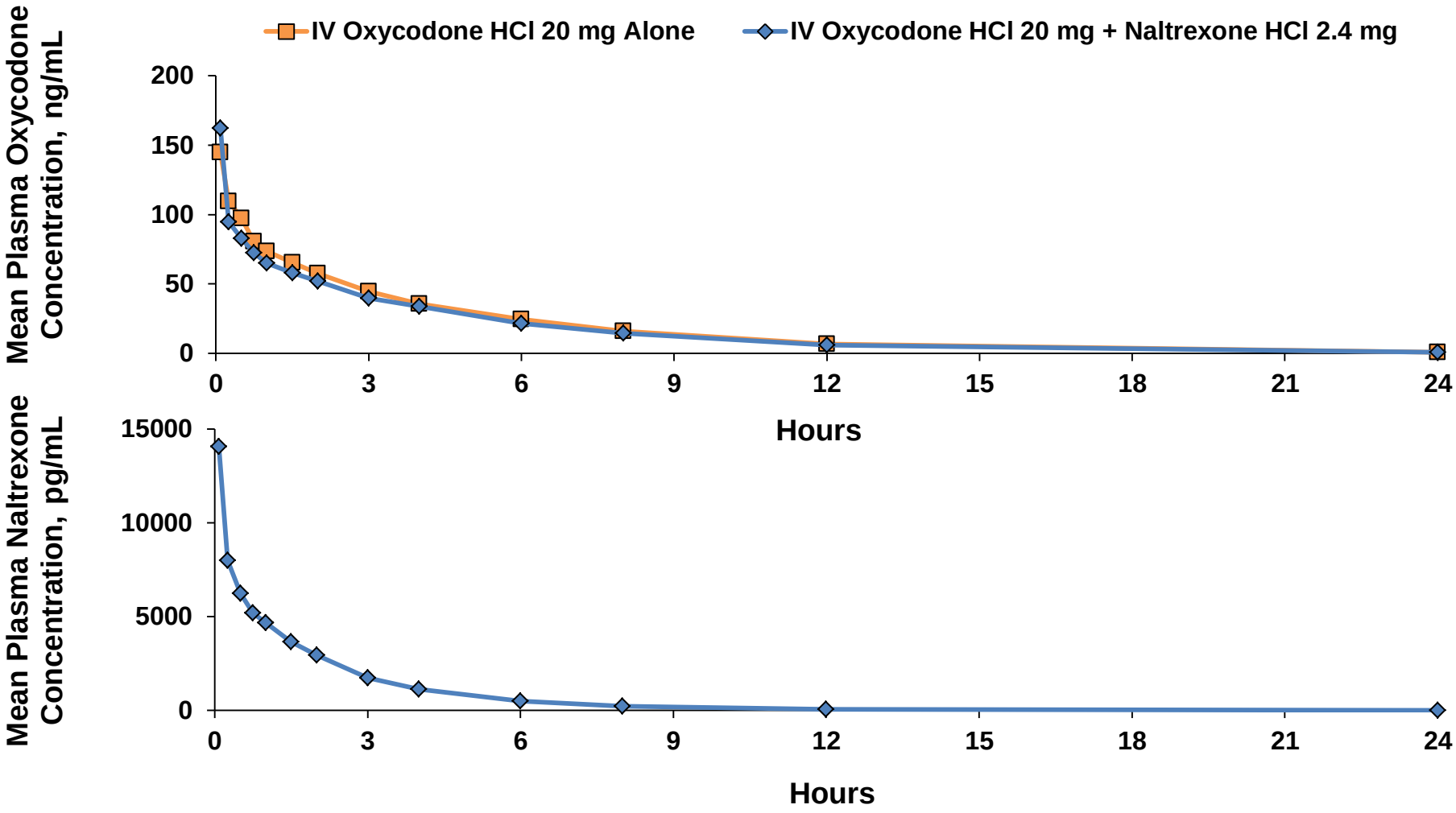


Study B4531009

IV Abuse Potential Study (B4981002)
N=29

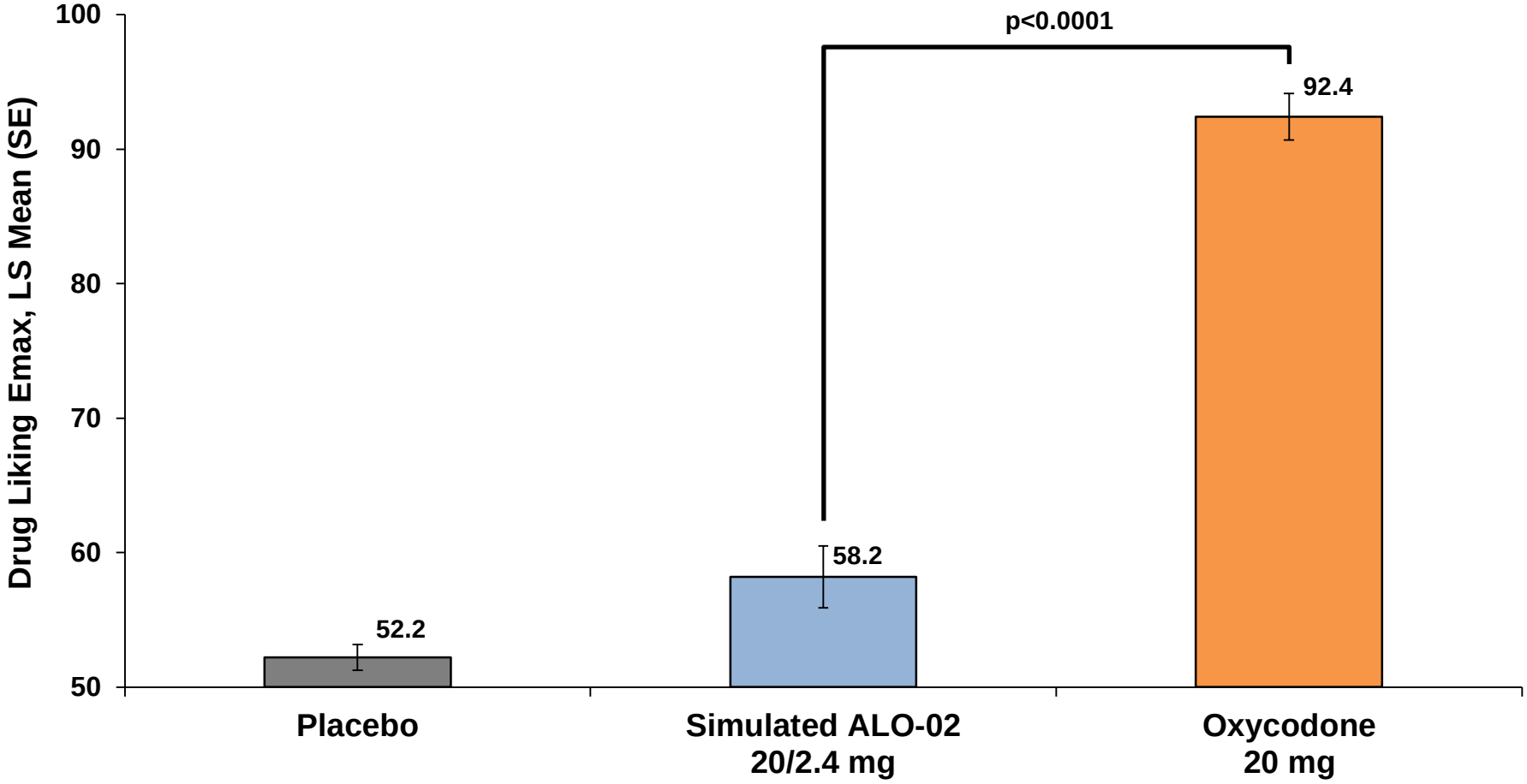
IV Treatments	Dose
Placebo	–
Simulated dose of ALO-02	20 mg/2.4 mg
Oxycodone HCl	20 mg

IV Administration of Oxycodone and Naltrexone in Solution to Simulate IV Administration of Crushed ALO-02 in Solution



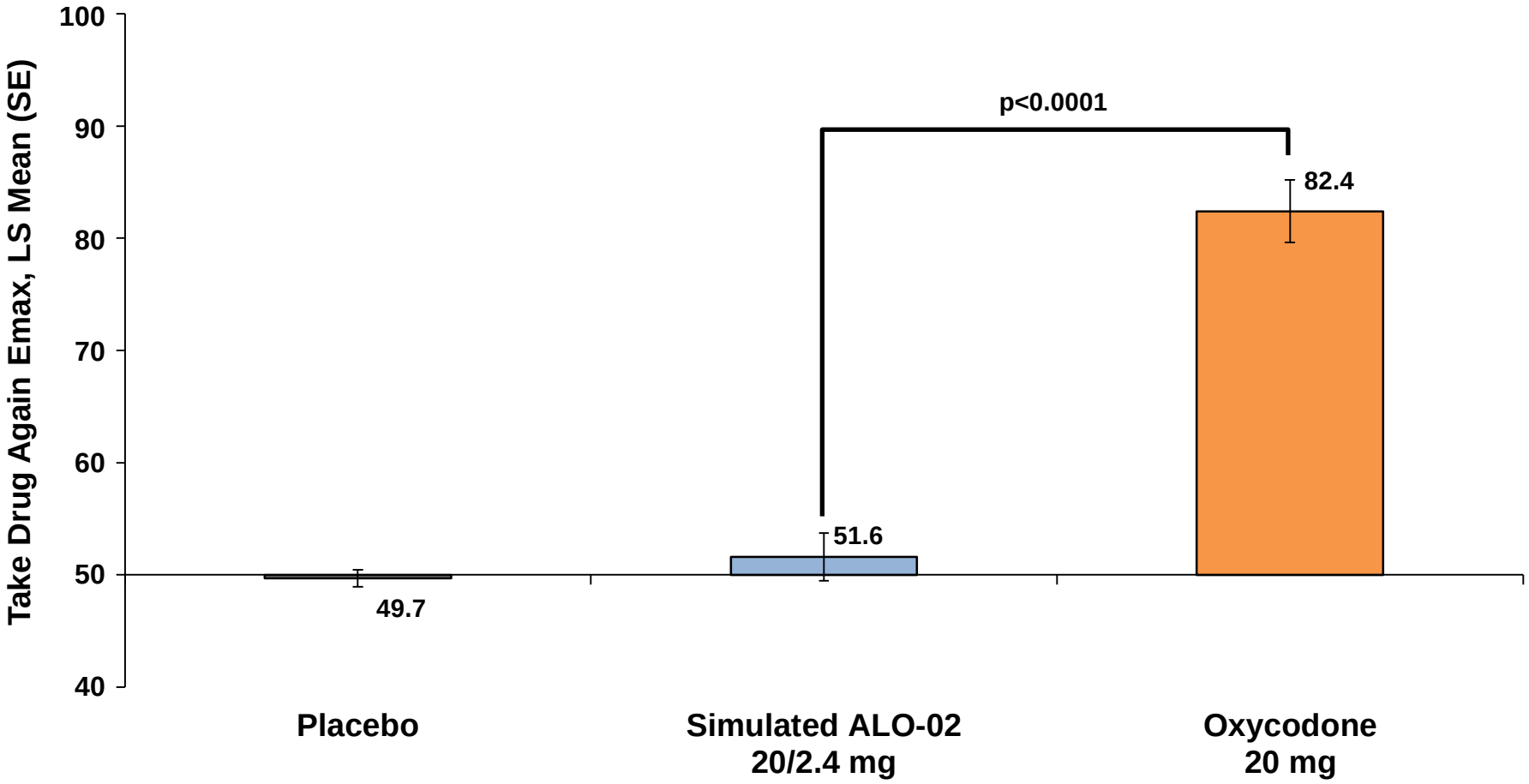
Study B4981002

Lower Drug Liking for Simulated IV ALO-02 than IV Oxycodone



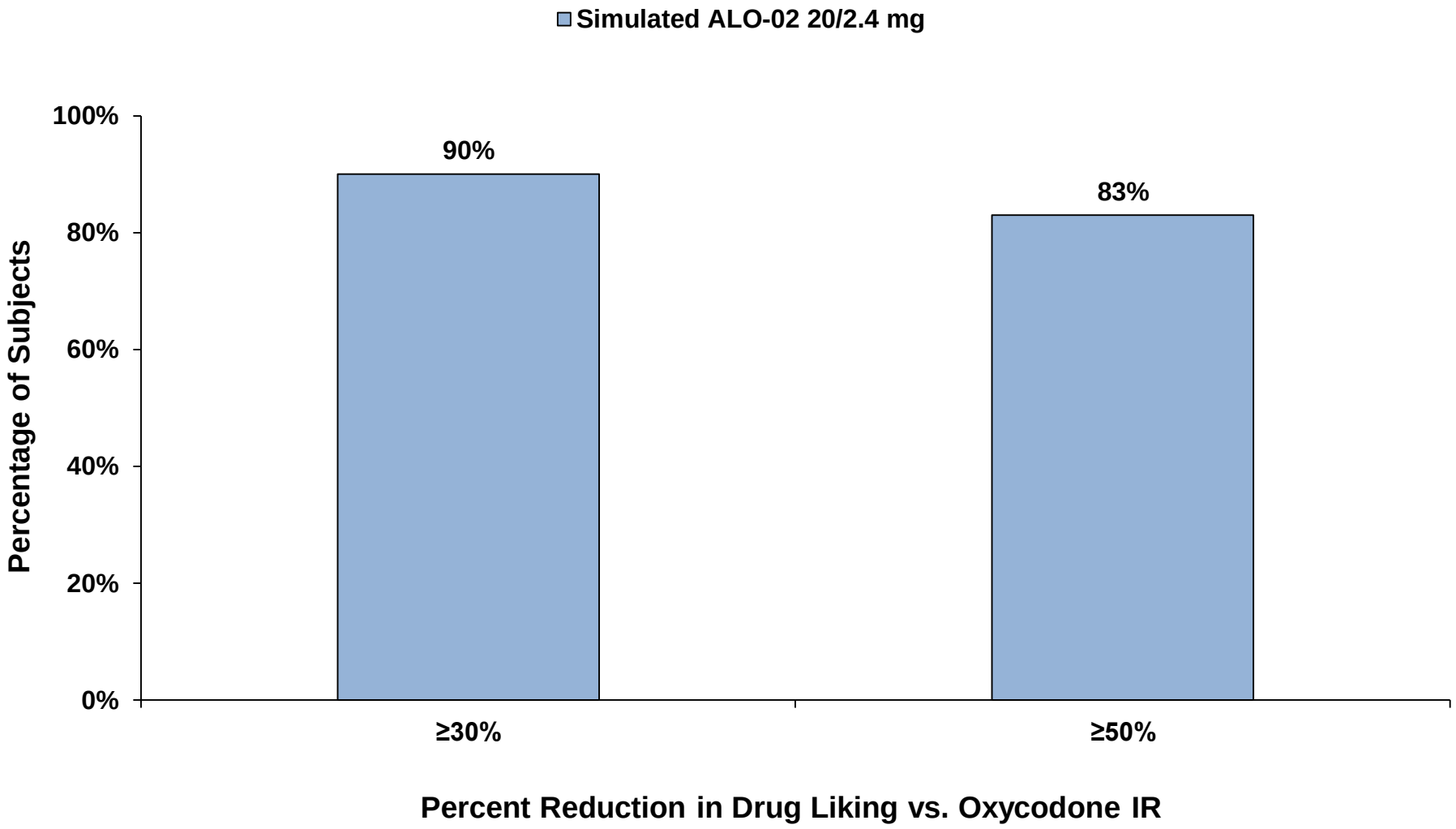
Study B4981002

Lower Take Drug Again for Simulated IV ALO-02 than IV Oxycodone



Study B4981002

Percent Reduction in Drug Liking Emax for Simulated ALO-02 vs. Oxycodone: IV



Study B4981002

Abuse Deterrence Summary

- The Category 1 (in vitro) and Category 2 (PK) data demonstrate that crushing ALO-02 pellets results in the simultaneous release and absorption of oxycodone HCl and naltrexone HCl
- These data in combination with the results from the Category 3 (HAP) studies demonstrate that ALO-02 has abuse-deterrent properties following manipulation and administration via the oral and non-oral routes
- These data support the labeling of ALO-02 as an abuse-deterrent product

ALO-02 Development Program

Clinical Pharmacology Studies		Outcome
B4531007	Pivotal Relative Bioavailability	BA equivalent to Roxicodone
B4531006	Single- and Multiple-Dose Pharmacokinetics	BID dosing
B4531003	Food Effect	No food effect
B4531004	Ethanol Interaction	No dose dumping
Efficacy and Safety Studies in Subjects with Chronic Pain		
B4531002	12-Week Efficacy Study	Superior to placebo in CLBP
B4531001	12-Month Safety Study	Established safety and maintenance of efficacy up to 12 months in CNCP
Abuse-Deterrent Studies: Category 1, 2 and 3		
In Vitro Category 1 Studies		Simultaneous extraction of oxycodone and naltrexone when crushed
B4531008	Oral ALO-02 vs. Oxycodone IR	Reduced Drug Liking and other abuse potential outcomes
B4531009	Intranasal ALO-02 vs. Oxycodone IR	
B4981002	Intravenous Simulated Crushed ALO-02 vs. Oxycodone IV	

BID=twice daily

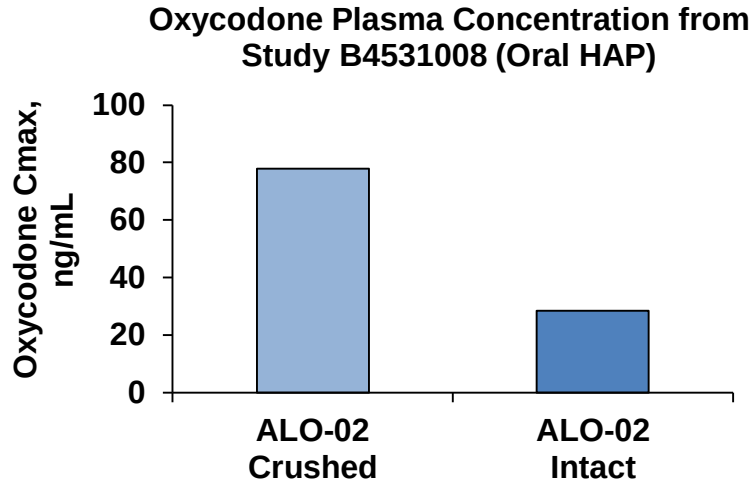
Conclusions

- Safety and efficacy established in chronic pain
- In vitro and PK data demonstrated that crushing results in the simultaneous release and absorption of oxycodone and naltrexone
- Human abuse potential studies demonstrated reduced abuse potential of ALO-02 when manipulated and when taken via the oral, intranasal, and IV routes
- The totality of evidence supports abuse-deterrent labeling for ALO-02

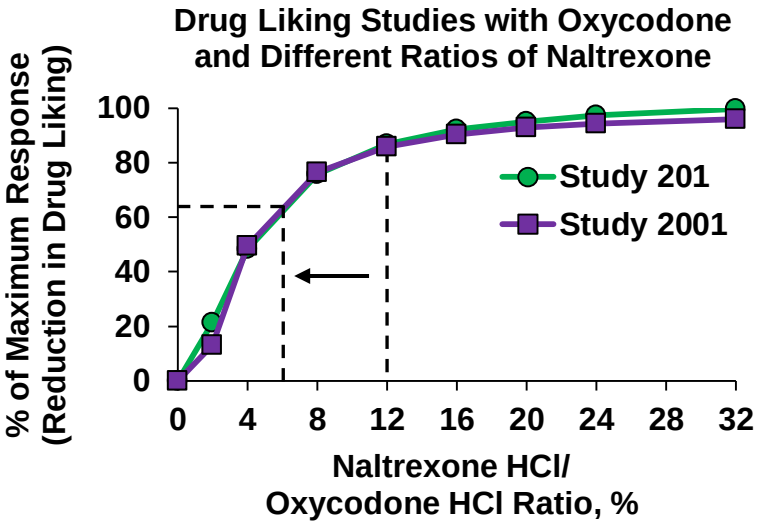
Backup Slides Called

Rationale for Cut Points

- **Oxycodone Extraction >30%**
  - Oxycodone Cmax with intact ALO-02 is approximately 30% of oxycodone Cmax of crushed ALO-02

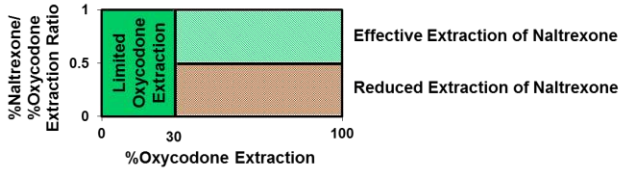


- **$\frac{\text{\% Naltrexone Extraction}}{\text{\% Oxycodone Extraction}}$ <0.5**
  - Reducing ratio of naltrexone/ oxycodone by half (from 12% to 6%) still resulted in ~60% of maximal reduction in drug liking



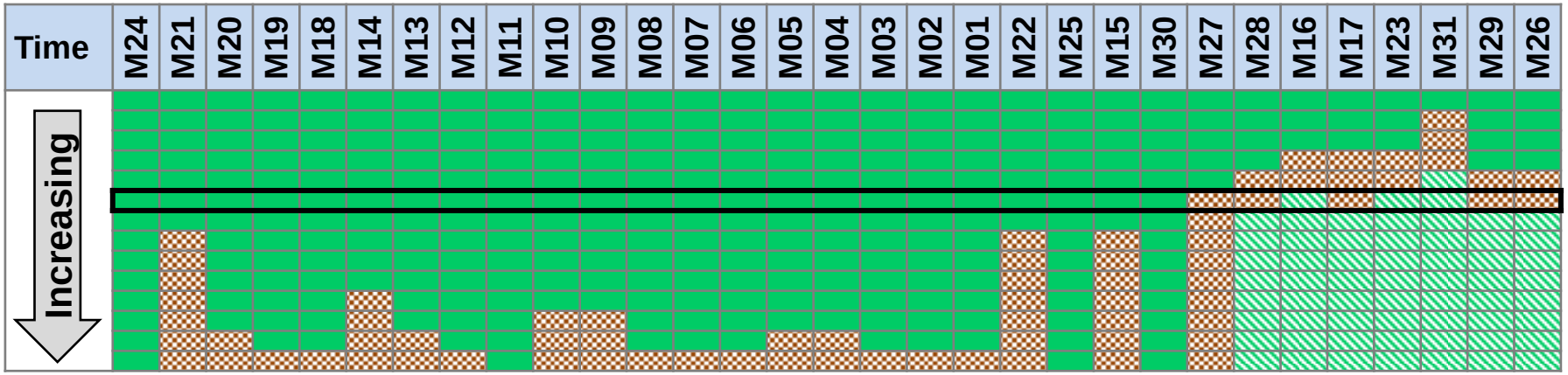
Studies ALO-02-07-201 and ALO-02-09-2001
Cmax=maximum Concentration; HAP=Human Abuse Potential study

Sensitivity Analyses: Reduction of %Oxycodone Extraction

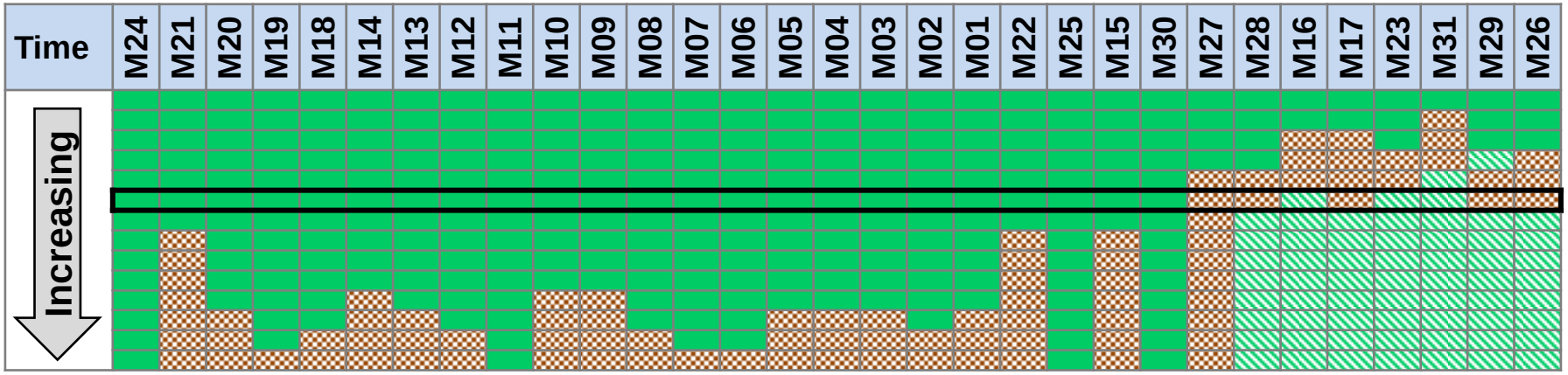


Large Volume Study – Intact Pellets (Condition C)

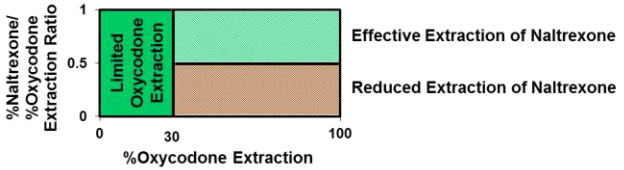
%Oxycodone <30%



%Oxycodone <20%



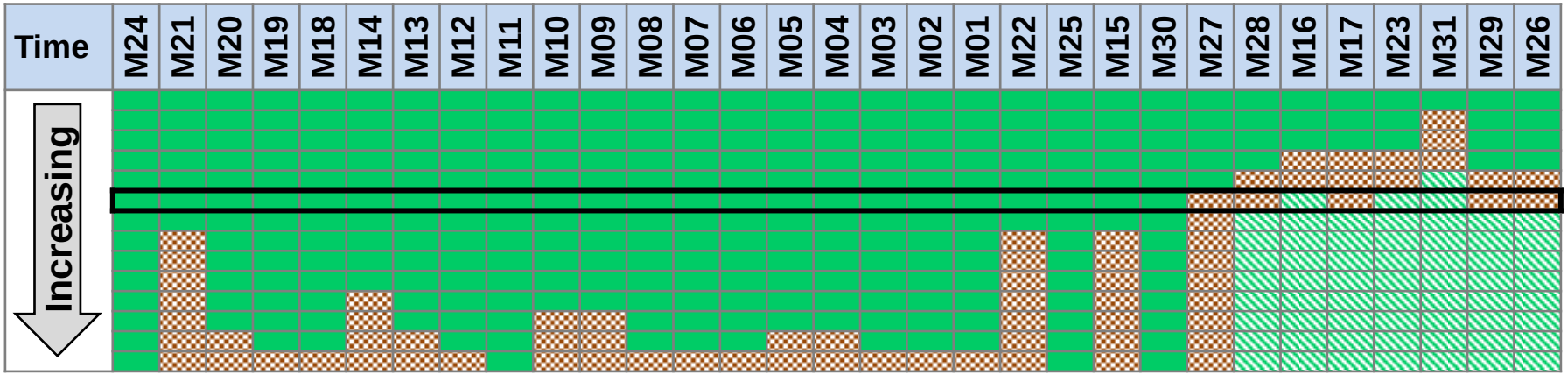
Time Point X



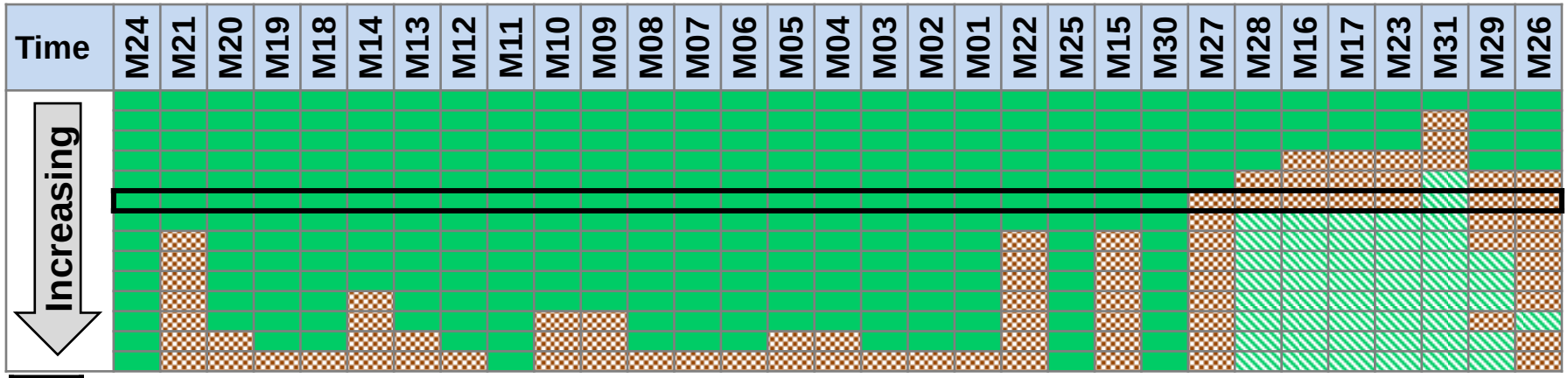
Sensitivity Analyses: Increase in Ratio of %Naltrexone/%Oxycodone

Large Volume Study – Intact Pellets (Condition C)

%Naltrexone Extraction/%Oxycodone Ratio ≥0.5

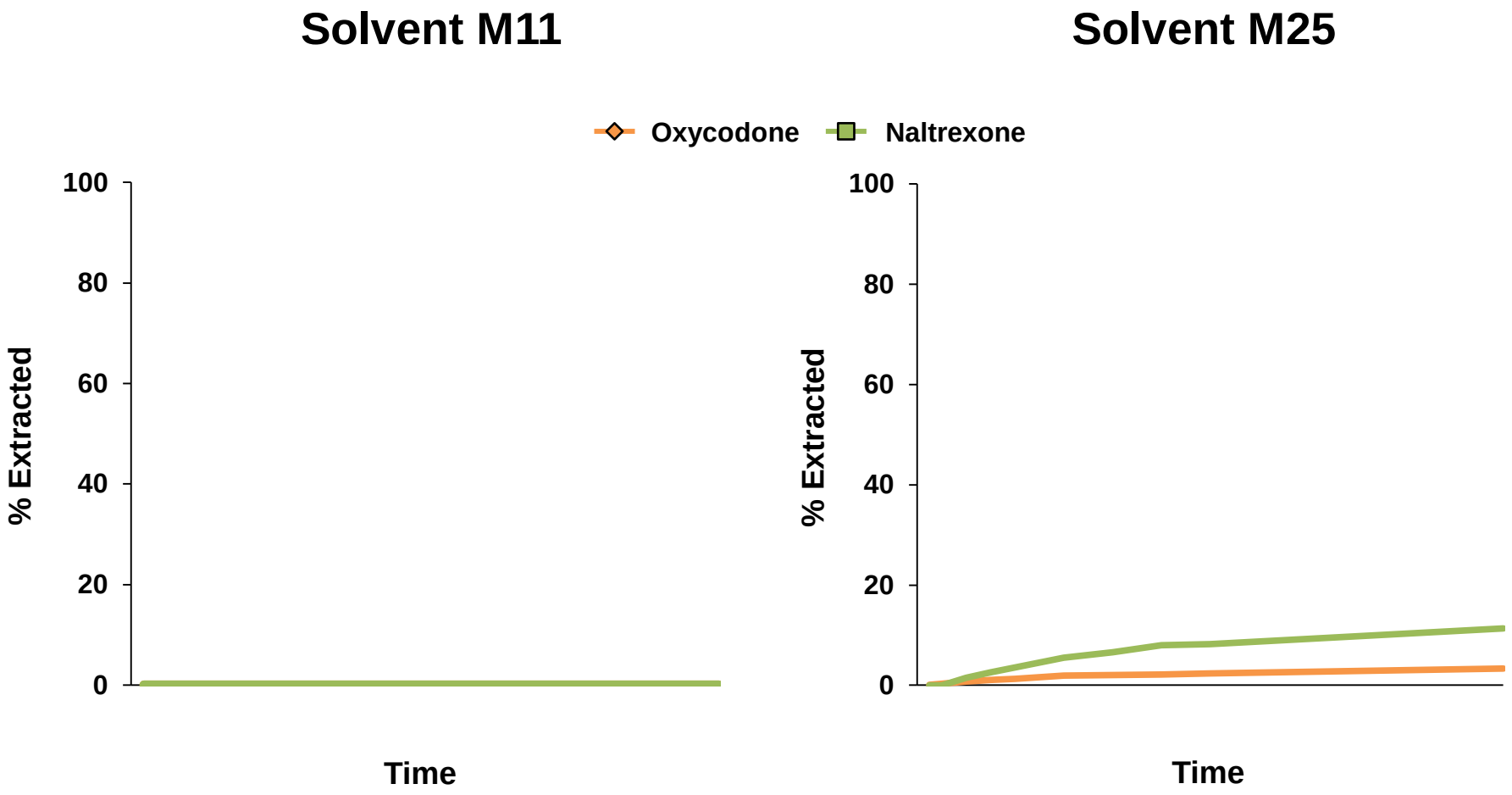


%Naltrexone Extraction/%Oxycodone Ratio ≥0.75



Time Point X

Large Volume Extraction Studies with Crushed Pellets (Condition C) Examples



NTX/OXY Ratios by Intravenous, Intranasal and Oral Routes and Reduction in Drug Liking

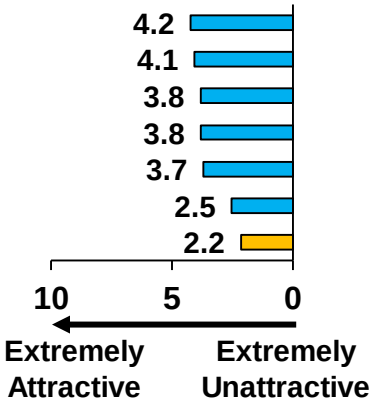
Route	OXY Dose	NTX/OXY Ratio in Crushed ALO-02	NTX/OXY Cmax Ratio	Difference in Drug Liking Emax vs. OXY
Intravenous	20 mg	12%	9.1%	34.2
Intranasal	30 mg		7.8%	33.4
Oral	40 and 60 mg*		1.5%	16.0

*mean values shown for 40 mg and 60 mg doses
Studies B4981002, B4531008, B4531009

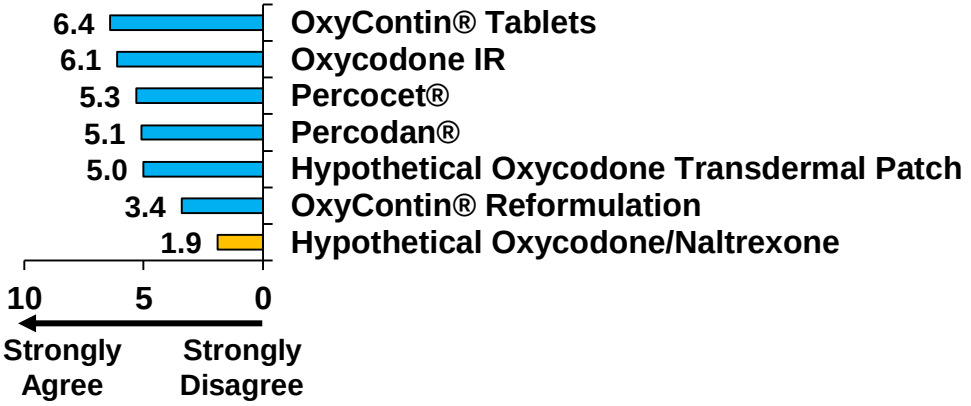
Drug Abusers Avoid Antagonist Containing Products

UNIVERSITY OF TORONTO

Opioid Attractiveness Scale

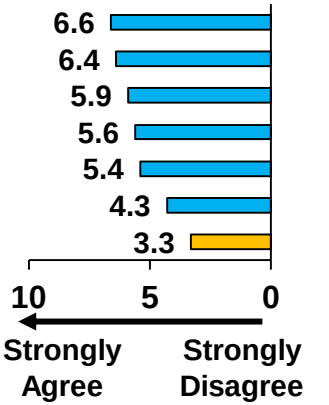


Value of Product



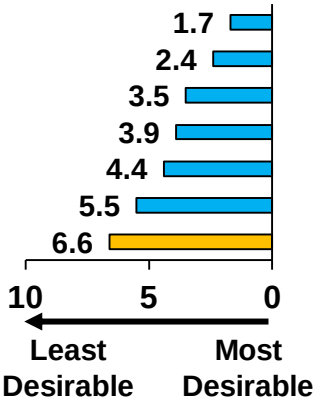
"This product would be very valuable to me."

Likelihood to Tamper

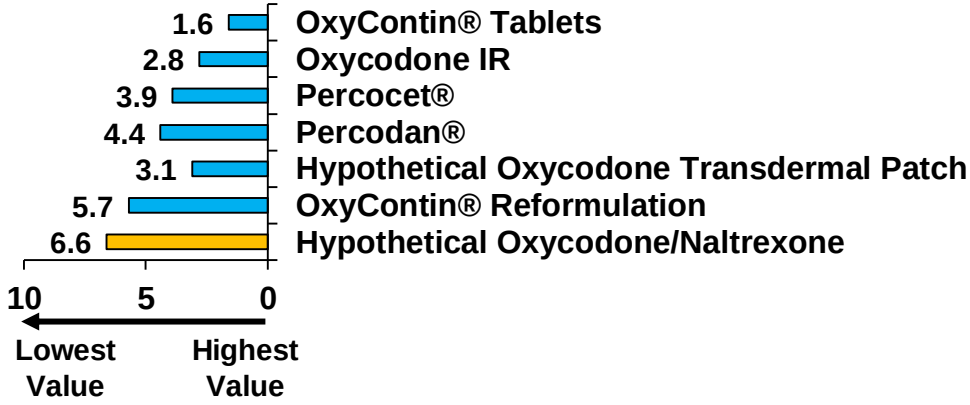


"I, or someone I know, would definitely tamper with [product]."

Overall Desirability



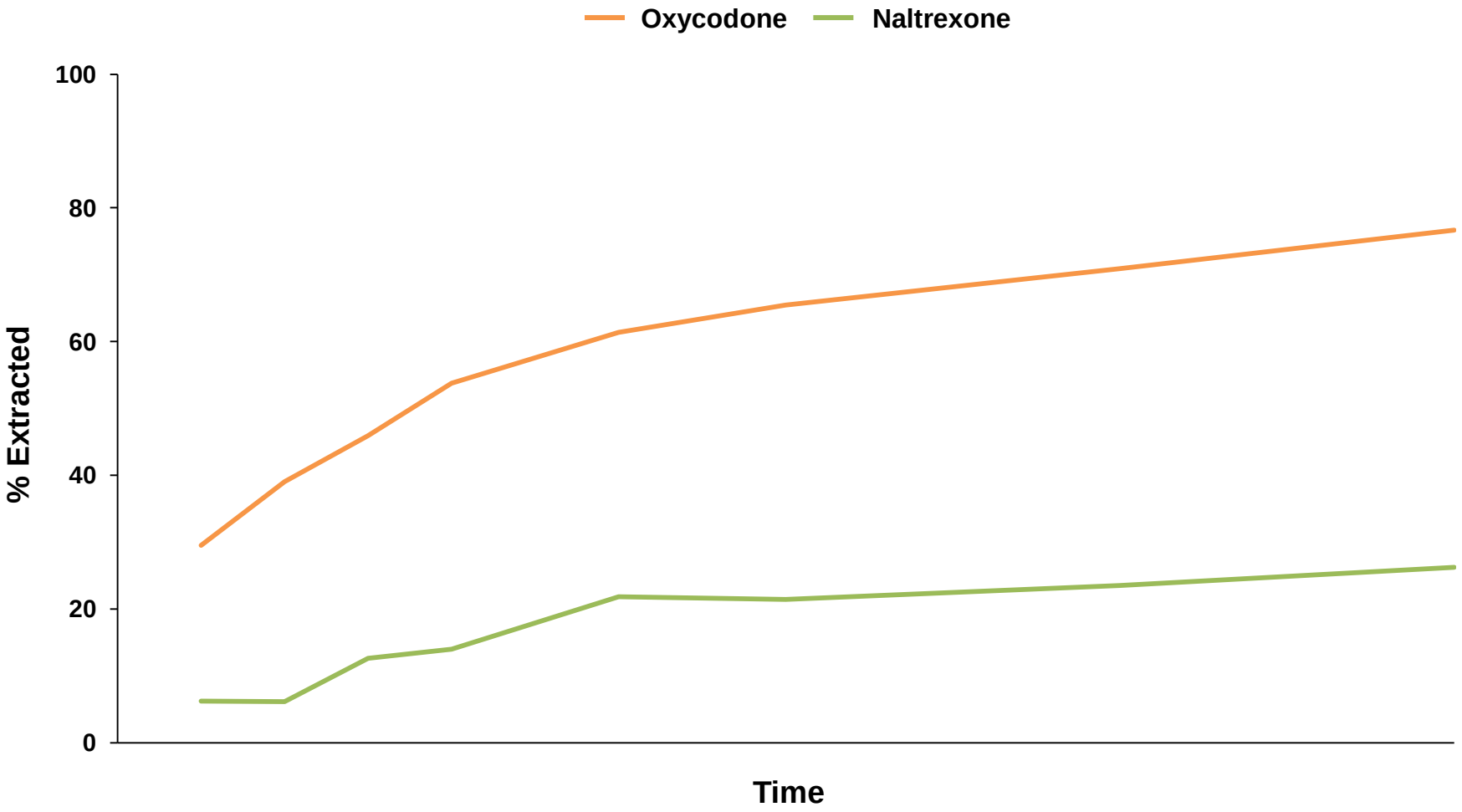
Estimated Street Value



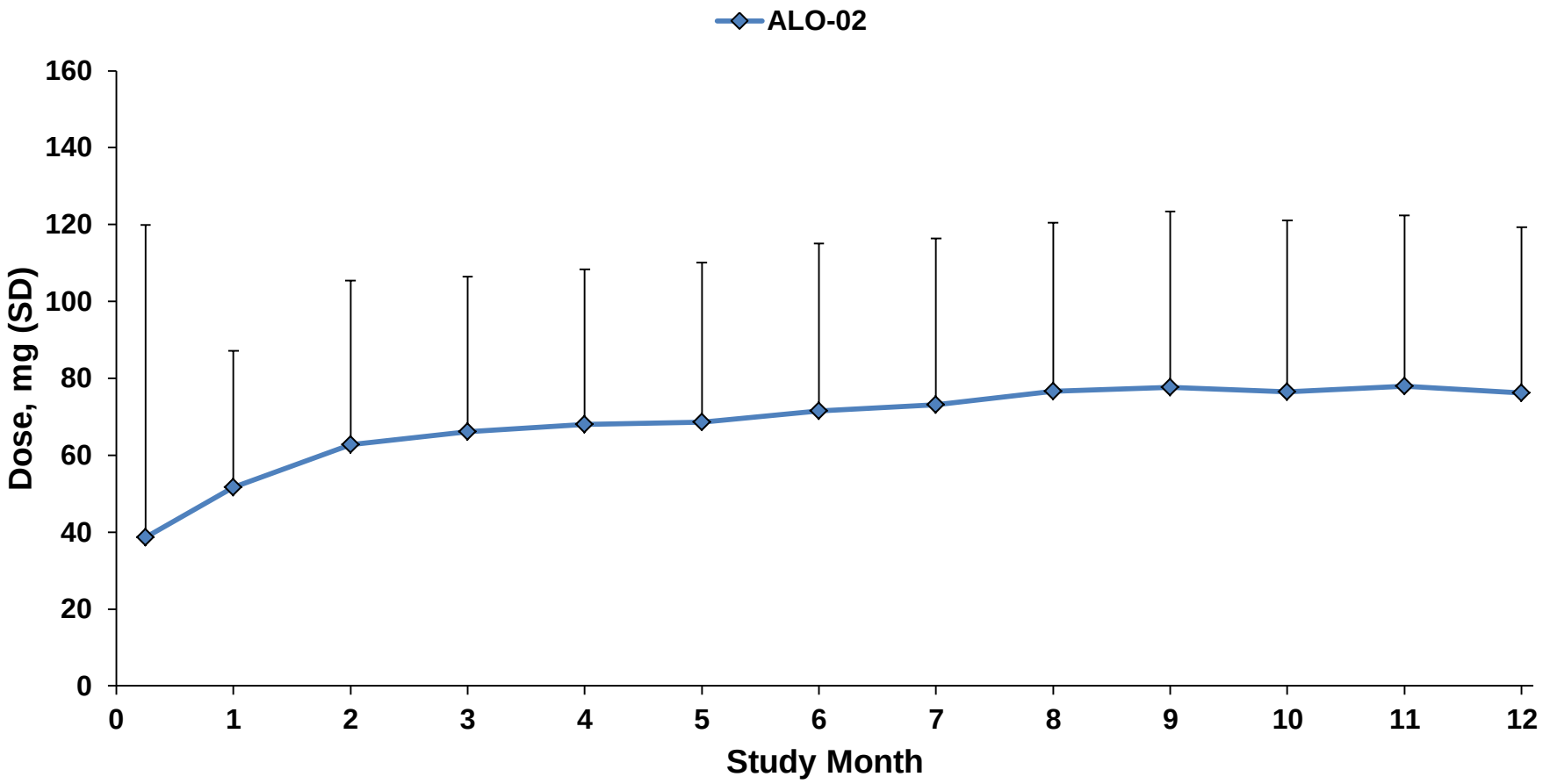
For each product, a mean score was calculated by dividing the sum of the scores by the number of features rated (i.e. 14 drug features)
Adapted from Sellers, et al. (2013) *J Psychopharmacol* 27(9) 808-816.

'Intact' corrected to 'Crushed' by Dr. Donevan when he presented this slide during the meeting

Large Volume Extraction Studies with Intact Pellets – (Condition C) Solvent M27



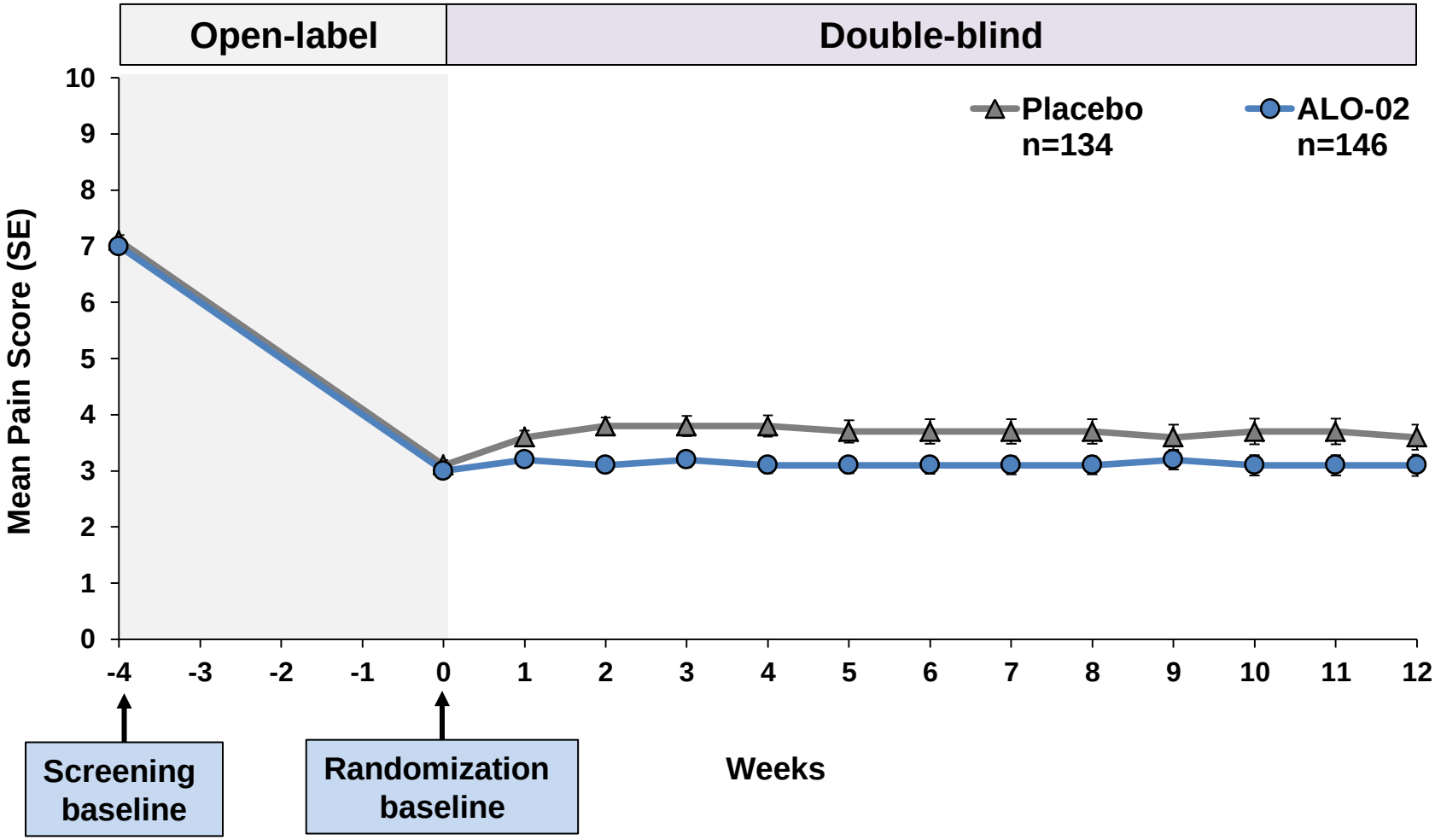
Observed Data: ALO-02 Dose Over 12 Months in CNCP Study (B4531001)



Average dose (mg)	38.6	51.7	62.8	66.1	68.0	68.6	71.5	73.1	76.7	77.7	76.5	77.9	76.2

Efficacy of ALO-02 Over 12 Weeks in CLBP Study B4531002

Mean weekly average NRS pain scores over time



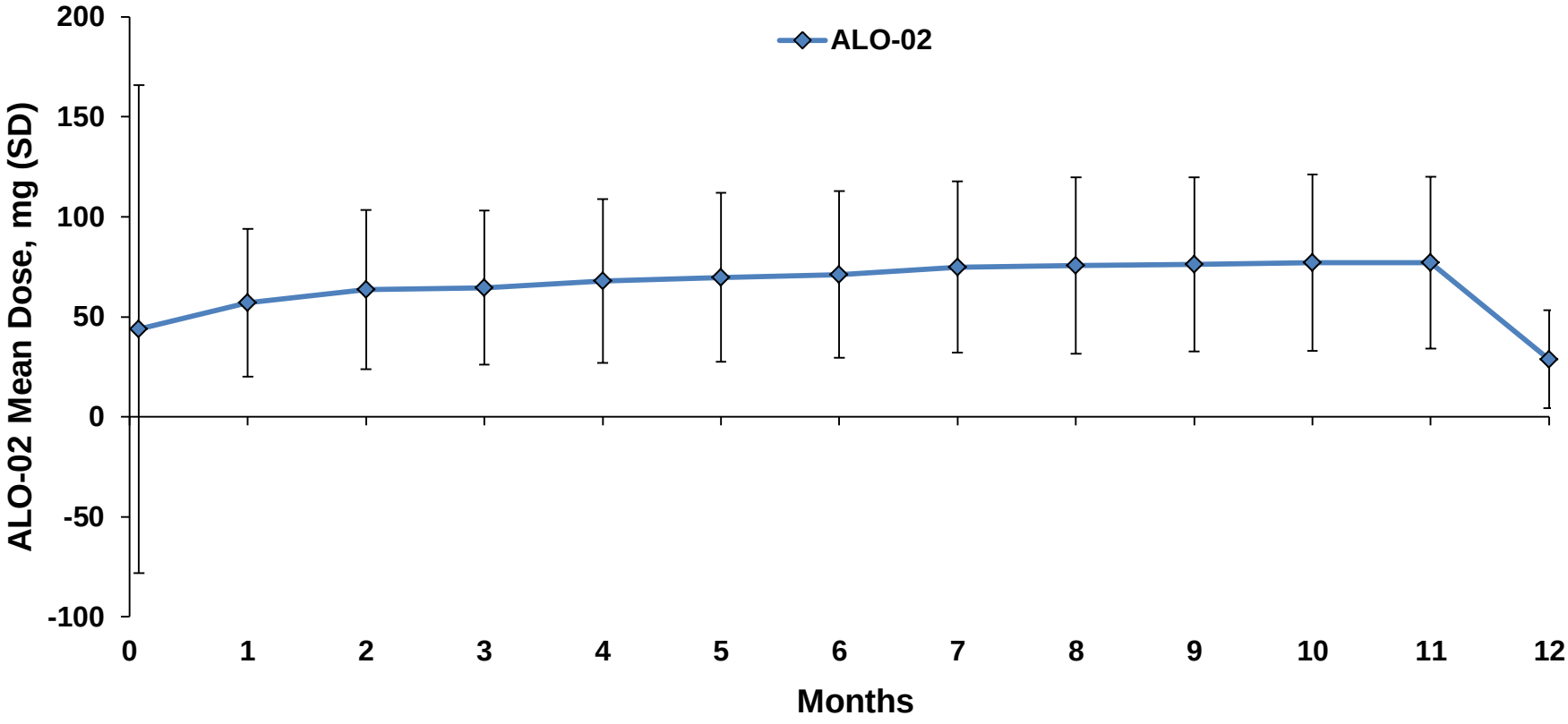
Sensitivity Analyses in CLBP Study B4531002

- The results of a sensitivity analysis were consistent with the primary analysis, i.e., statistically favoring ALO-02

Difference of LS mean pain scores from randomization to final 2 weeks of the double-blind treatment period

	Placebo	ALO-02	Difference (SE)	p-value
Primary analysis	**1.2**	**0.6**	**-0.62 (0.25)**	**<0.05**
Sensitivity analyses				
Complete-case	**0.57**	**0.26**	**-0.30 (0.24)**	**0.21**
Pattern mixture model	**1.06**	**0.61**	**-0.45 (0.25)**	**0.07**
Single imputation	**1.02**	**0.54**	**-0.48 (0.22)**	**<0.05**
Mixed-model repeated measures	**1.02**	**0.22**	**-0.80 (0.23)**	**<0.001**
Screening observation carried forward only	**1.88**	**1.27**	**-0.61 (0.27)**	**<0.05**

Completer Data: ALO-02 Average Daily Dose Over 12 Months (Study B4531001)



Average dose (mg/day)	43.9	57.1	63.7	64.6	67.9	69.7	71.2	74.9	75.6	76.3	77.1	77.1	28.7

Subject Disposition in CNCP Study B4531001