Avridi™ (Immediate-Release Oxycodone Hydrochloride) Tablets with Abuse-Deterrent Properties

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

September 10, 2015

Introduction

Richard Fanelli, PhD

Regulatory Affairs

Avridi Product Rationale

- **An estimated 90 million adults in the US report acute and chronic pain**
- **Opioid analgesics are an important option for the treatment of serious pain**
- **Use of immediate-release (IR) single-entity (SE) oxycodone products for analgesia is widespread, with approximately 16 million prescriptions annually**
- **IR oxycodone can be abused, resulting in a substantial public health burden**

Avridi Product Description

- **IR single-entity oxycodone product with abuse-deterrent properties**
- **Gelling agents and an aversive agent to reduce potential intravenous (IV) and intranasal (IN) abuse**
  - **These routes are associated with greater morbidity and mortality**
- **Proposed indication: Management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate**

Clinical Development Program

- **NDA submitted as Section 505(b)(2) application**
- **Demonstration of bioequivalence to Roxicodone®**
  - **Proven efficacy and safety of Roxicodone**
  - **Efficacy and safety studies were not required**
- **Reduced abuse potential demonstrated in in vitro (Category 1) and clinical (Category 3) studies**
- **Bioequivalence to Roxicodone**
  - **Fasted state: Avridi is bioequivalent to Roxicodone**
  - **Fed state: Avridi is not bioequivalent due to a lower Cmax and delayed Tmax**

Balance of Avridi Risks and Benefits

- **Clinically significant risk not expected based on PK modeling in the fed state**
- **Full prescribing information will include instructions to take in the fasted state**
- **Risk management and epidemiology activities to assess and manage potential risks**
  - **Appropriate patient selection**
- **Anticipated meaningful impact by reducing abuse by the high-risk IV and IN routes**

Agenda

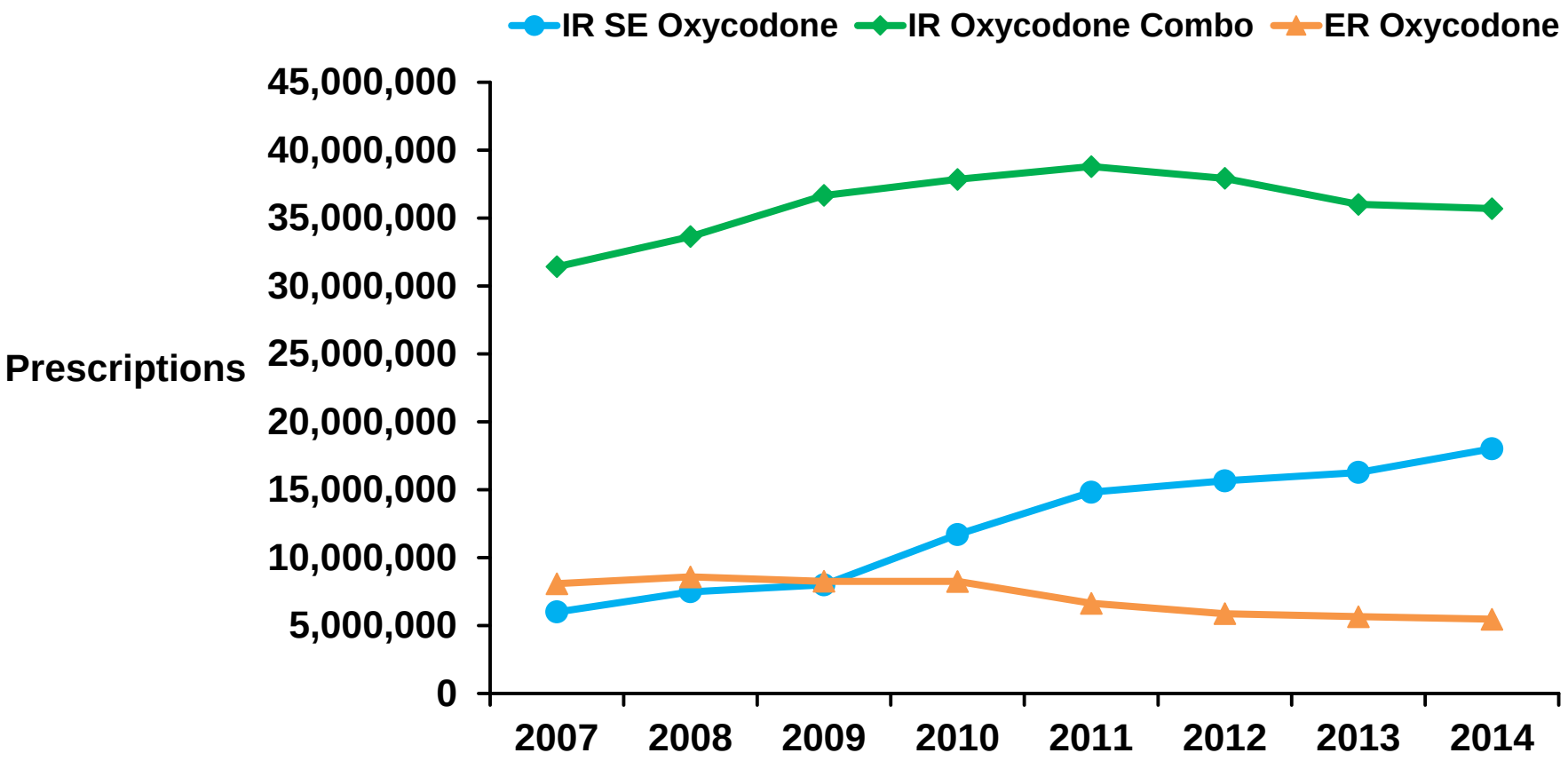
Introduction	**Richard Fanelli, PhD** Regulatory Affairs
Need for Abuse-Deterrent Immediate-Release Oxycodone Formulation	**Laura Wallace, MPH** Risk Management & Epidemiology
In Vitro Abuse Deterrence Assessment of Avridi Tablets	**Jennifer Giordano** Analytical Sciences
Avridi Intranasal Abuse Potential	**Alessandra Cipriano, MSHS** Clinical Pharmacology
Avridi Bioequivalence Evaluation	**Alessandra Cipriano, MSHS** Clinical Pharmacology
Avridi Pharmacokinetic Modeling	**Stephen Harris, MD** Clinical Pharmacology
Risk Management and Summary	**Laura Wallace, MPH** Risk Management & Epidemiology
Question & Answers	**Stephen Harris, MD** Clinical Pharmacology

Need for Abuse-Deterrent Formulation

Laura Wallace, MPH

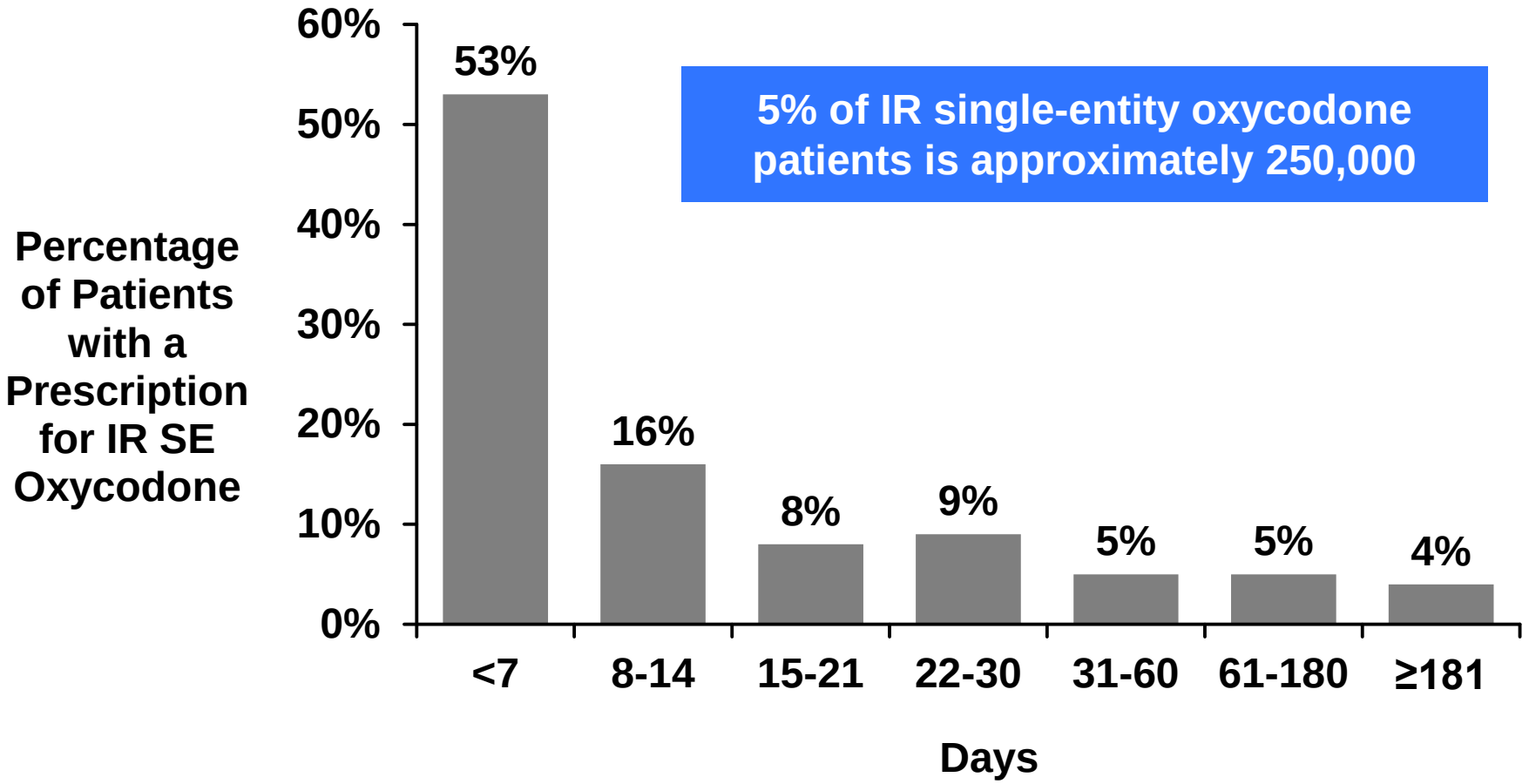
Risk Management and Epidemiology

Utilization of IR SE Oxycodone



SE=Single Entity; IR=Immediate Release; ER=Extended release.
Source: IMS Health

Duration of Prescribed IR SE Oxycodone



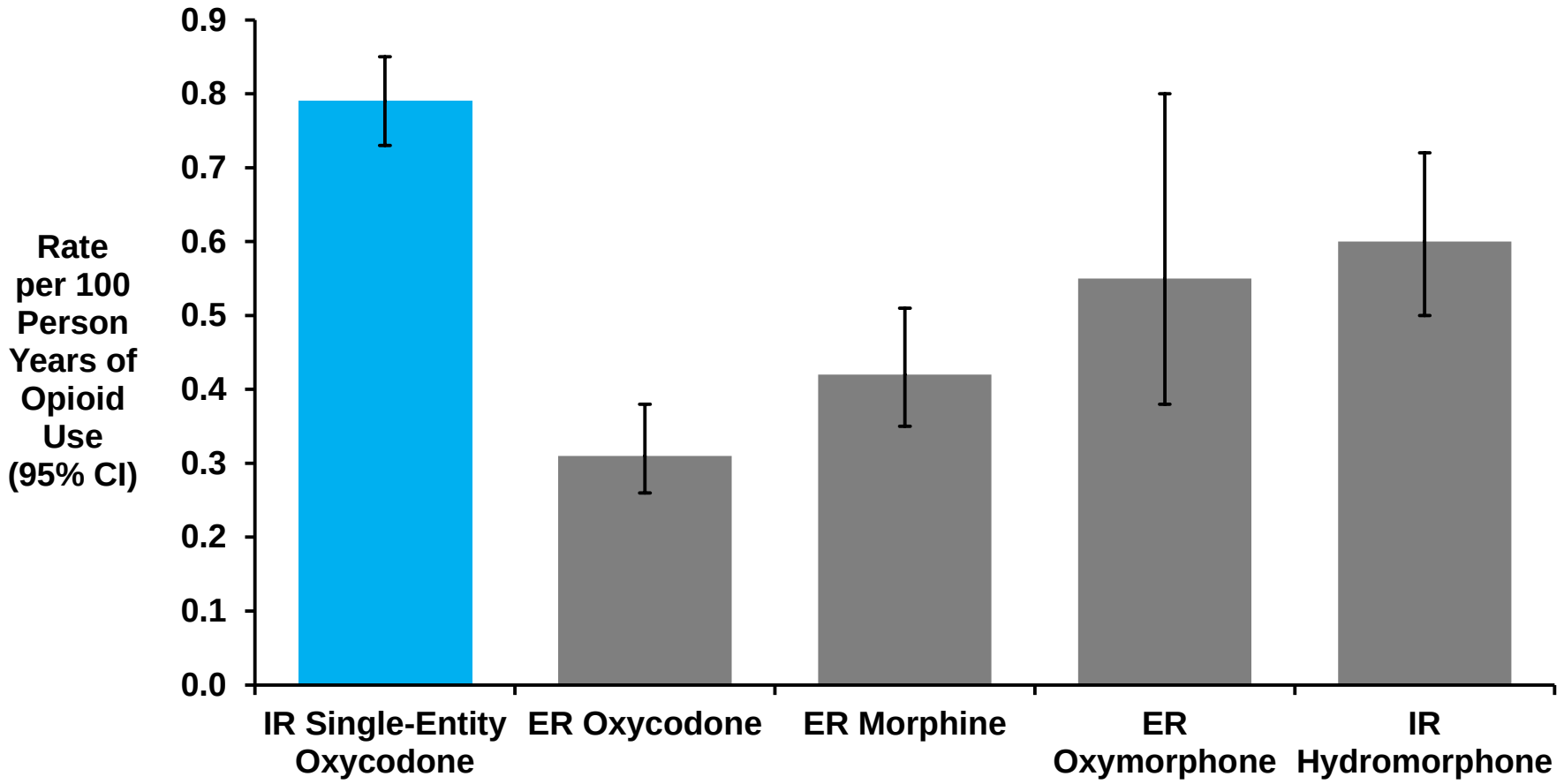
Source: Truven MarketScan Database
(Medicaid: 2008-2013; Commercial: 2008-3Q2014).

Opioid Abuse in the United States

- **1.9 million (0.7%) with opioid dependence or abuse**
  - **746,000 received treatment**
- **1.5 million new non-medical users in 2013 (down from previous years)**

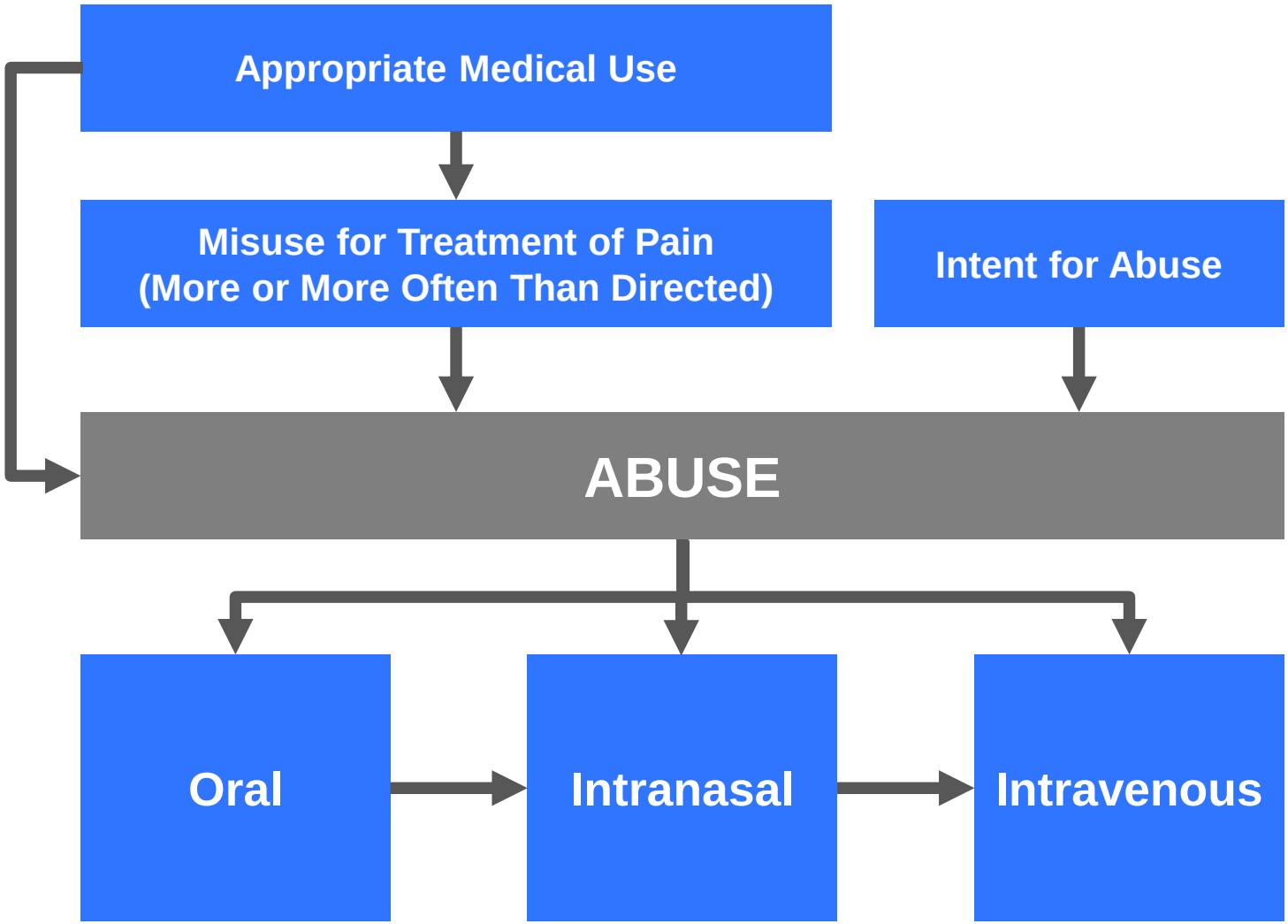
Data from NSDUH, 2013

Diagnosed Opioid Abuse Among Those with Prescriptions

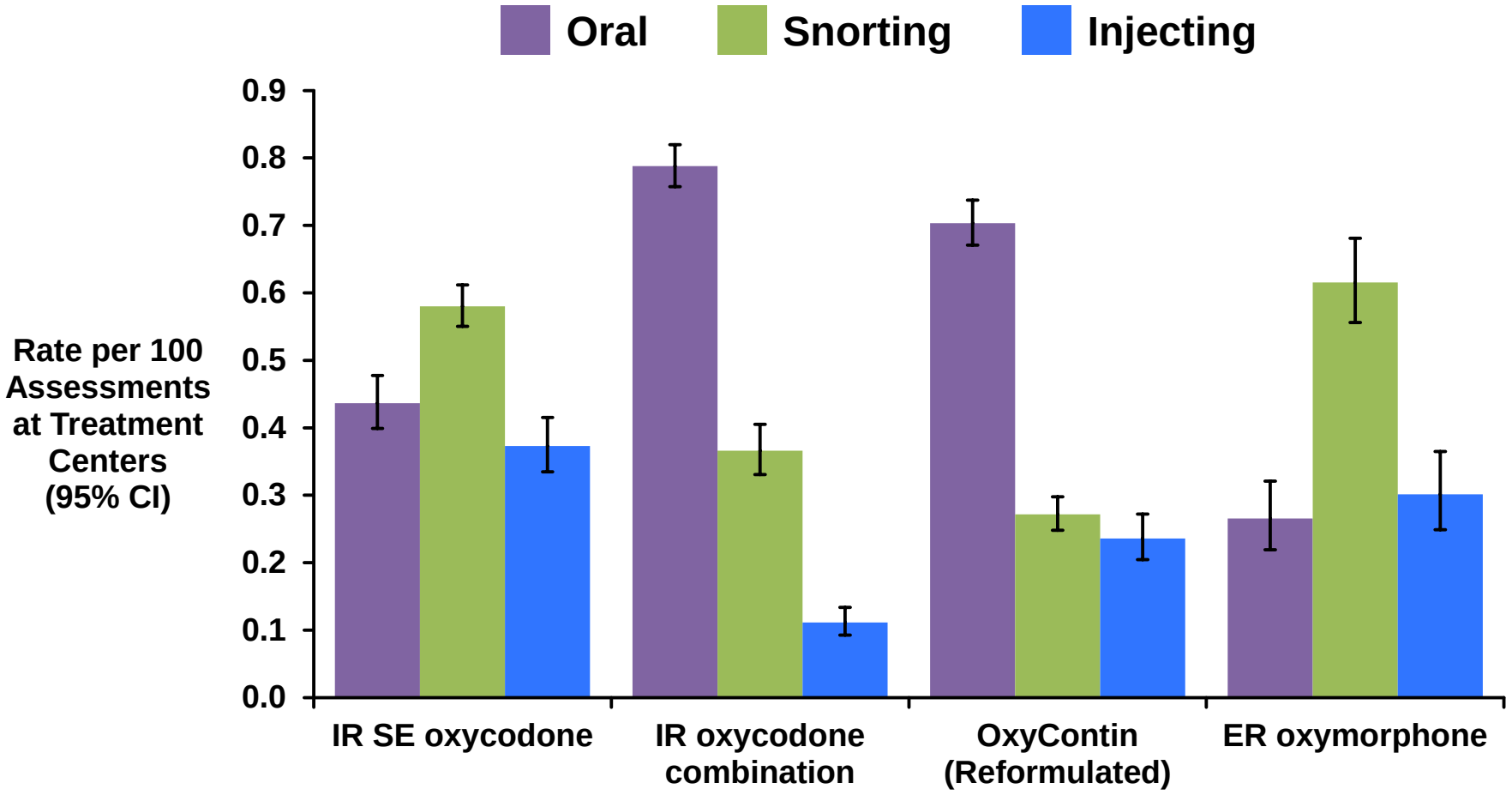


Each drug used alone, without other opioids.
Source: MarketScan Commercial Database (November 2010-October 2013).

Route of Abuse: Progression



Abuse by Routes Among Those Entering Substance Abuse Treatment



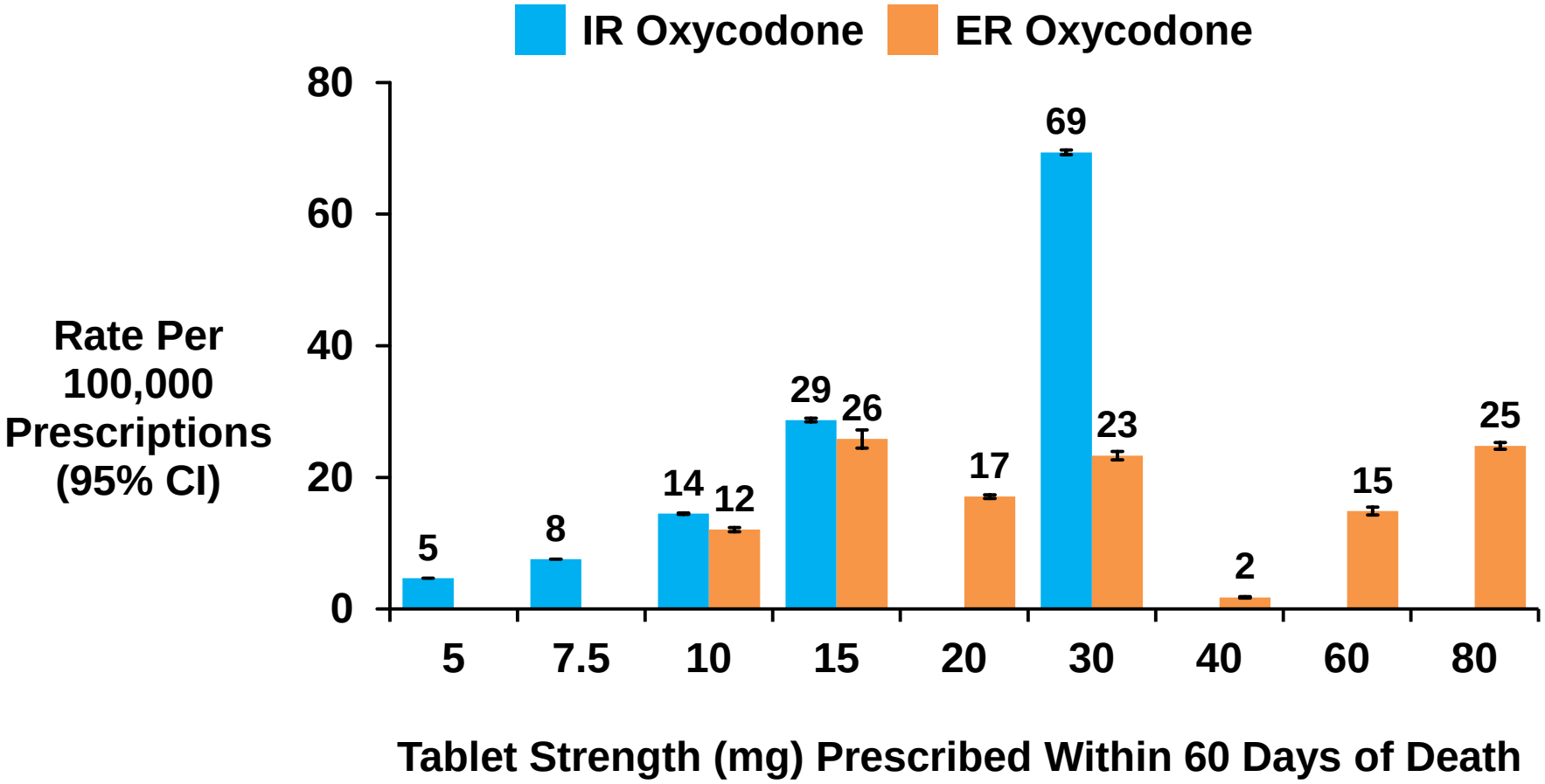
Source: NAVIPPRO Addiction Severity Index Multimedia Version® (ASI-MV); 1Q2011-4Q2013.

Risks Associated with Non-Oral Abuse

- **Morbidity**
  - **Addiction**
  - **Blood-borne bacterial and viral infection**
  - **Nasal necrosis or perforation**
  - **Overdose**

- **Mortality**

Consequences of Abuse: Overdose Deaths



Source: Hirsch, 2014.

Diversion of IR SE Oxycodone for Abuse

- **Diversion of opioids from patients to non-patients for purposes of abuse is common**
  - **Among persons who used pain relievers non-medically in the past year, 68% received them from friends or relatives**
- **Doctor and pharmacy shopping rates are highest for IR single-entity oxycodone**

Summary of Need for Abuse-Deterrent IR SE Oxycodone

- **IR SE oxycodone is commonly used**
- **Abuse of IR SE oxycodone is common**
- **Abuse, particularly by IV and IN routes, is associated with serious medical and public health consequences**
- **Need a formulation that deters IV and IN abuse**

In Vitro Abuse Deterrence Assessment of Avridi Tablets

Laboratory Based Physical and Chemical Manipulation Studies (FDA Category 1)

Jennifer Giordano

Analytical Sciences

Types of Abuse-Deterrent Formulations

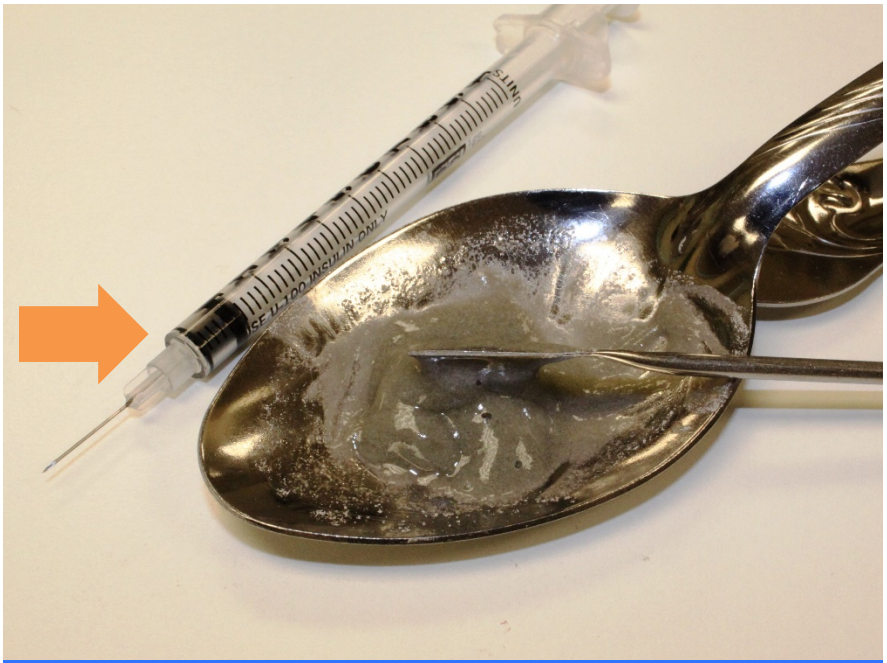
Avridi	
✓	**Physical/Chemical Barriers**
	Agonist/Antagonist Combinations
✓	**Aversion**
	Delivery System (including depot injectable formulations and implants)
	Prodrug
	Combination

Adapted from FDA Guidance for Industry Abuse-Deterrent Opioids – Evaluation and Labeling. April 2015.

AVERSIVE COMPONENT

- **Sodium lauryl sulfate (SLS)**
- **Known potent irritant**
- **Immediate strong burning sensation when snorted**
  - **Persists for hours**
- **Deters intranasal abuse**

GELLING PROPERTIES: Physical Barrier



Avridi

- **Becomes highly viscous in a small volume of water**
- **Resistant to IV preparation**
- **No liquid was drawn into the syringe**

Roxicodone

- **Easily crushed and dissolved in a small volume of water**
- **Easily drawn into a syringe**
- **Syringe is full, only tablet residue left on the spoon**

TABLET SIZE

Tablet	Weight (mg)	Length (mm)	Width (mm)	Thickness (mm)
Avridi 30 mg	397	16	7	5
Roxicodone 30 mg	101	N/A	6 (diameter)	3

Avridi 30 mg

Roxicodone 30 mg

Characterization of Abuse Deterrence

Pre-Marketing

1	*In Vitro* Manipulation & Extraction Studies	▪ Evaluate the physical and chemical properties of the formulation
2	Pharmacokinetic Studies	▪ Determine the bioavailability and pharmacokinetic profile of tablets administered intact and manipulated (orally and intranasally)
3	Clinical Abuse Potential Studies	▪ Examine various subjective measures related to liking and abuse of the formulation

Post-Marketing

4	Epidemiology Studies	▪ Assess real-world impact using post-marketing outcome data

Adapted from FDA Guidance for Industry Abuse-Deterrent Opioids – Evaluation and Labeling. April 2015.

In Vitro Abuse Deterrence Study Goals

- **The primary goals of the in vitro studies:**
  - **Separate or inactivate the aversive agent**
  - **Characterize the feasibility of preparing Avridi for IV injection**
- **To ensure robust outcomes:**
  - **Comprehensive evaluation of the strengths and weaknesses of the formulation**
  - **Studies assessed realistic abuser scenarios and extreme sophisticated laboratory manipulations**

Comprehensive Approach Ensuring Robust Study Design

- **Relevant Comparator**
  - Roxicodone 30 mg
  - Not abuse deterrent
- **Experimental Controls**
  - As needed to evaluate method performance
- **Appropriate Replicates**
  - Statistical analysis of method transfer data
- **Unbiased Results**
  - Verified methods transferred to 3rd party laboratories

Summary of In Vitro Abuse Deterrence Testing of Avridi

Study	Relevant Route of Abuse
1. Physical Manipulation (Crushing)	**IN, IV**
2. Tablet Pretreatments	**IN, IV**
3. Household Solvent Extraction	**IN**
4. Advanced Solvent Extraction	**IN**
5. Syringeability (Preparation for Injection)	**IV**
6. Simulated Smoking (Vaporization)	Smoking
7. Oxycodone Free Base Isolation	IV, Smoking

STUDY 1:
Physical Manipulation (Crushing)

Goal: Physical Manipulation Using Household Tools and Test Article Standardization

Study	Relevant Route of Abuse
1. **Physical Manipulation (Crushing)**	IN, IV
2. **Tablet Pretreatments**	IN, IV
3. **Household Solvent Extraction**	IN
4. **Advanced Solvent Extraction**	IN
5. **Syringeability (Preparation for Injection)**	IV
6. **Simulated Smoking (Vaporization)**	Smoking
7. **Oxycodone Free Base Isolation**	IV, Smoking

STUDY 1: Crushing ER vs IR Formulations

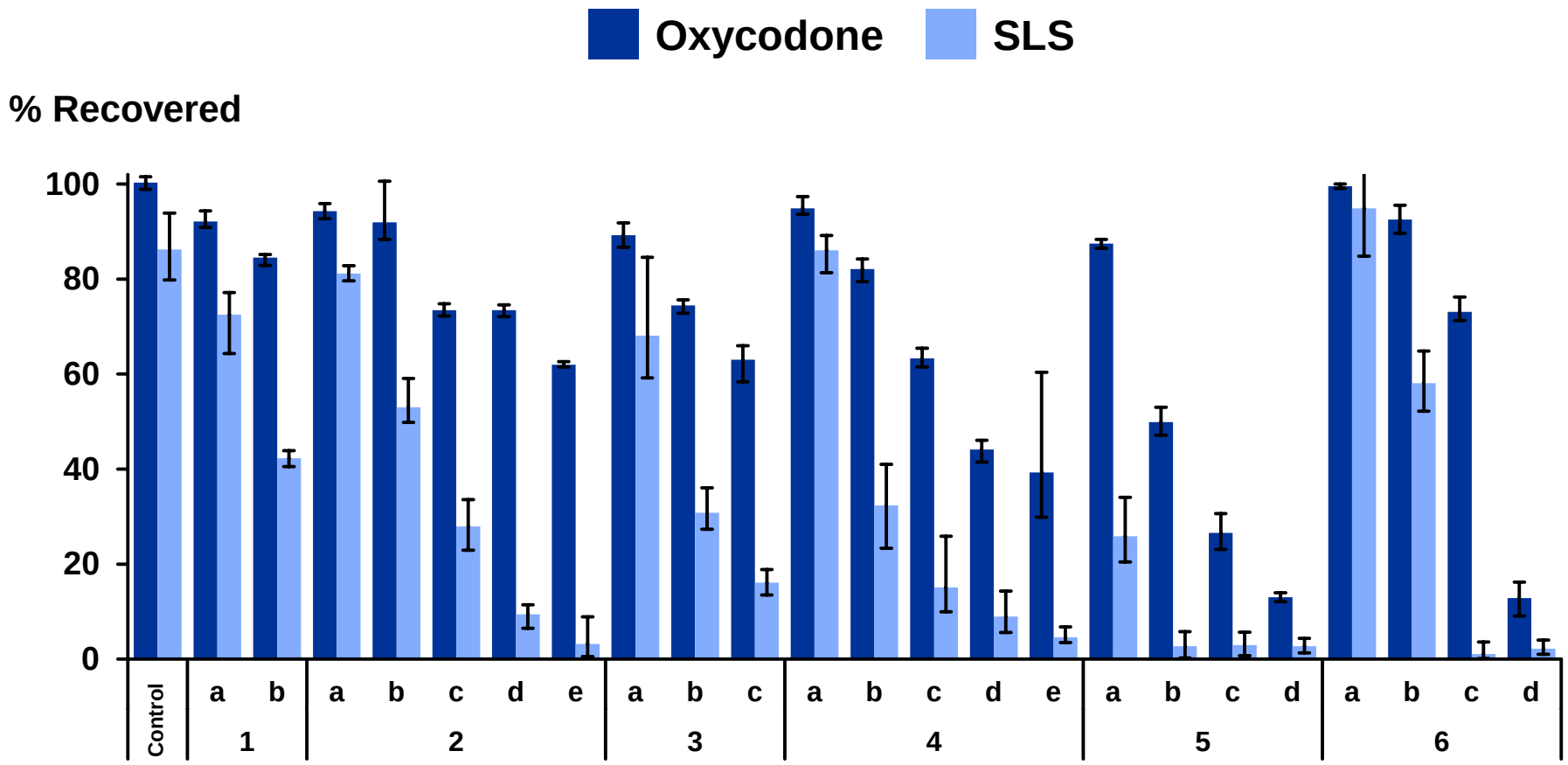
- **Extended-release formulations**
  - **Abusers attempt to crush to increase rate of release of the active ingredient**
- **Immediate-release formulations (eg, Avridi)**
  - **Rapid release of active ingredient is expected without crushing**

STUDY 2:
Tablet Pretreatment

Goal: Determine Recovery of Oxycodone HCl and SLS after Pretreatment

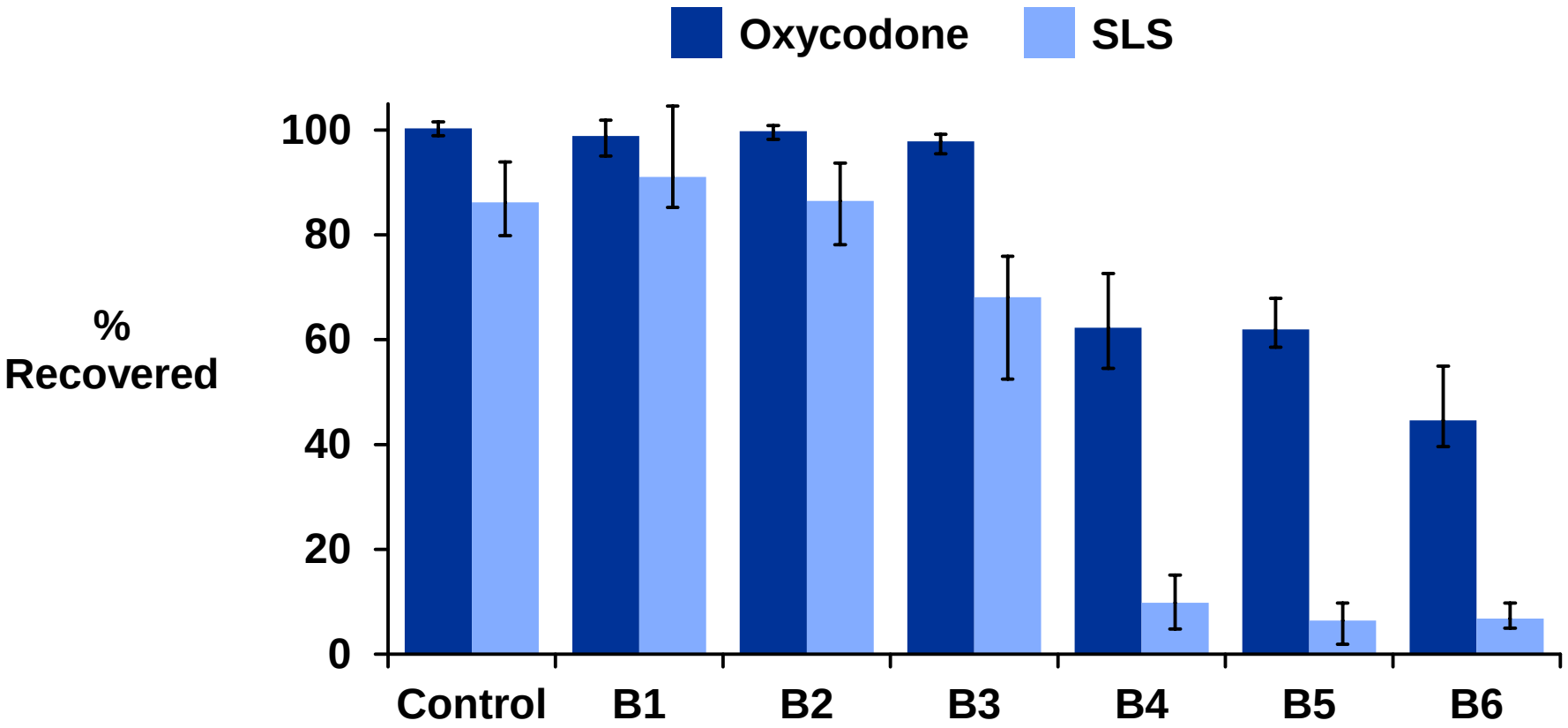
Study	Relevant Route of Abuse
1. **Physical Manipulation (Crushing)**	IN, IV
2. **Tablet Pretreatments**	IN, IV
3. **Household Solvent Extraction**	IN
4. **Advanced Solvent Extraction**	IN
5. **Syringeability (Preparation for Injection)**	IV
6. **Simulated Smoking (Vaporization)**	Smoking
7. **Oxycodone Free Base Isolation**	IV, Smoking

RESULTS: Avridi Pretreatment A Oxycodone HCl and SLS Recovery



Note: Error bars represent the range of results.

RESULTS: Avridi Pretreatment B Oxycodone HCl and SLS Recovery



Note: Error bars represent the range of results.

CONCLUSIONS: Tablet Pretreatment

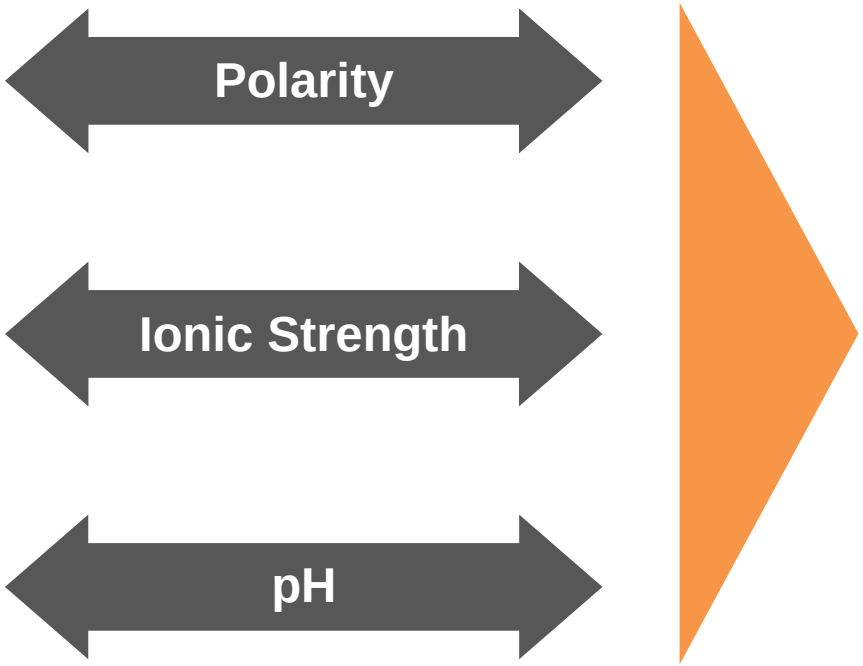
- **Most conditions degraded both oxycodone HCl and SLS**
  - **SLS degrades faster than oxycodone HCl**
- **Laboratory controlled experiments using a systematic approach**
  - **Very difficult to discover optimal conditions**
  - **Even if successful once, difficult to replicate**
- **Difficult for an abuser to degrade SLS without substantial loss of oxycodone HCl**
- **Substantial time, effort, and loss of oxycodone would discourage most abusers**

STUDY 3:
Extraction in Household Solvents

Goal: 1) Time Course for Extraction of Oxycodone HCl and SLS
2) Characterize SLS Separation Potential Due to Solubility Differences

Study	Relevant Route of Abuse
1. **Physical Manipulation (Crushing)**	IN, IV
2. **Tablet Pretreatments**	IN, IV
3. **Household Solvent Extraction**	IN
4. **Advanced Solvent Extraction**	IN
5. **Syringeability (Preparation for Injection)**	IV
6. **Simulated Smoking (Vaporization)**	Smoking
7. **Oxycodone Free Base Isolation**	IV, Smoking

Household Solvents Selected Cover a Wide Range of Chemical Properties

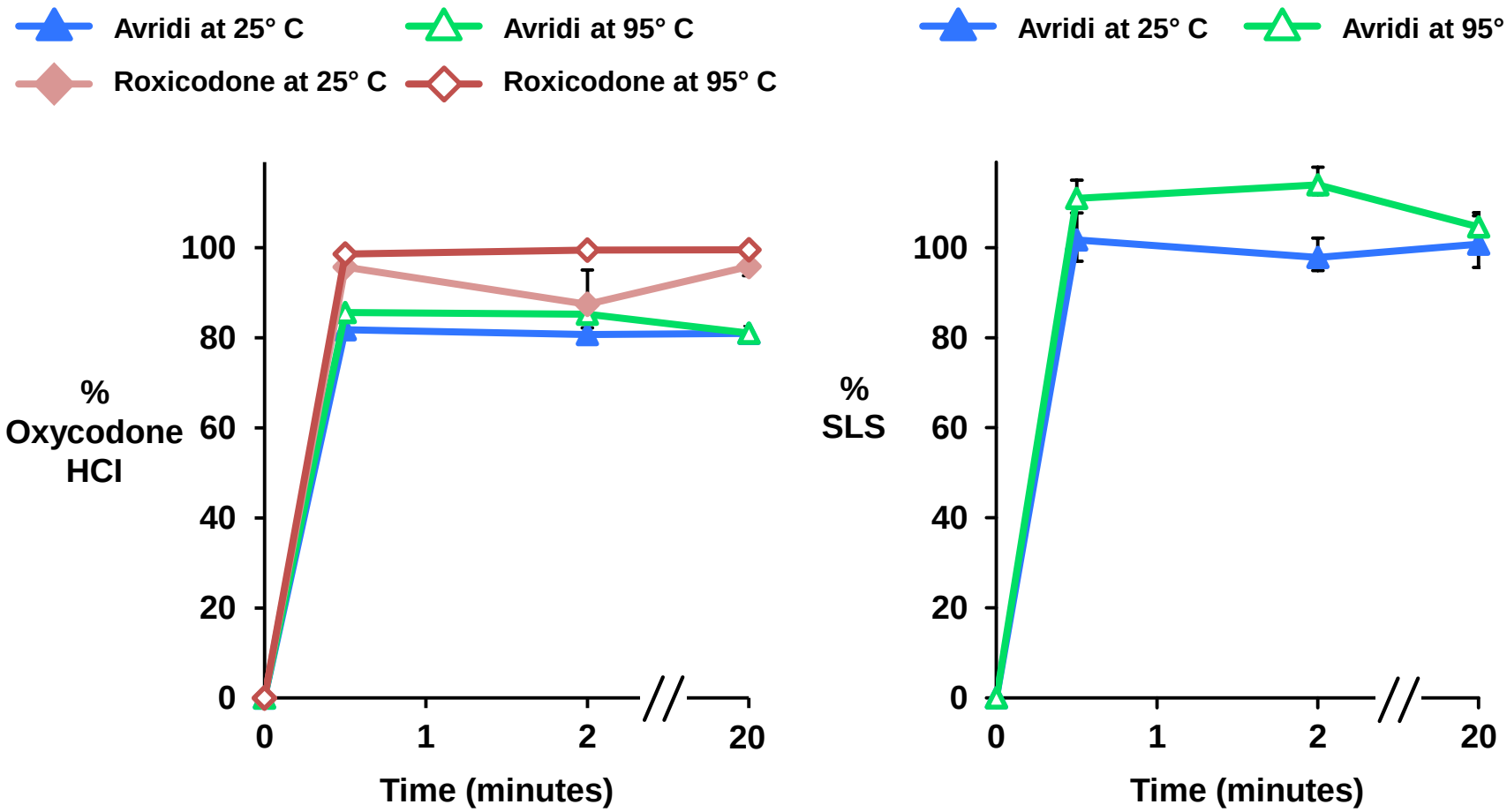


Ingestible
- Solvent A
- Solvent B
- Solvent C
- Solvent D
- Solvent E

Non-ingestible
- Solvent F

Buffers
- pH G
- pH H
- pH I
- pH J

RESULTS: Solvent A Ground Tablet Extraction



Note: Error bars represent the range of results.

CONCLUSIONS: Household Solvents

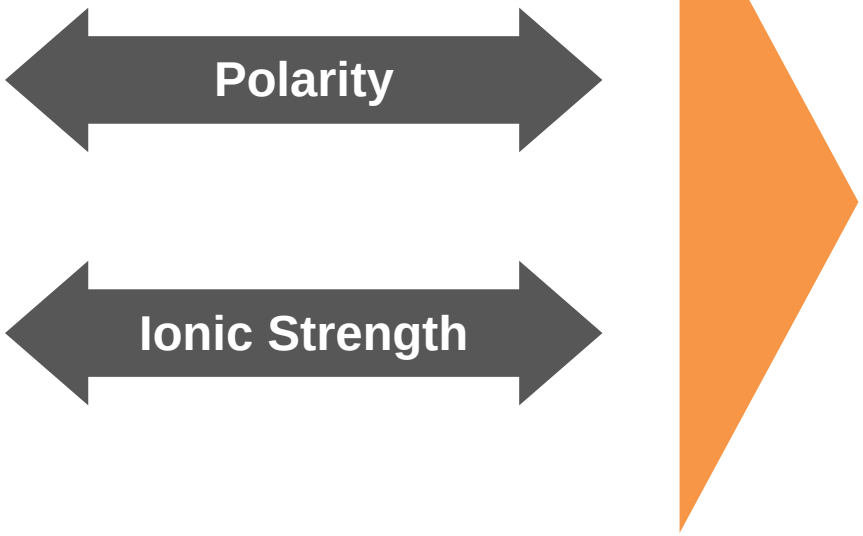
- **Solvent A results are representative**
- **Rapid extraction of oxycodone HCl and SLS**
- **Difficult to separate SLS from oxycodone HCl**

STUDY 4:
Extraction with Advanced Solvents

Goal: Characterize SLS Separation Potential due to Solubility Differences

Study	Relevant Route of Abuse
1. **Physical Manipulation (Crushing)**	IN, IV
2. **Tablet Pretreatments**	IN, IV
3. **Household Solvent Extraction**	IN
4. **Advanced Solvent Extraction**	IN
5. **Syringeability (Preparation for Injection)**	IV
6. **Simulated Smoking (Vaporization)**	Smoking
7. **Oxycodone Free Base Isolation**	IV, Smoking

Ten Advanced Solvents



Ingestible
- Solvent B

Non-ingestible
- Solvent A
- Solvent C
- Solvent D
- Solvent E
- Solvent F

Other Solutions
- Solvent G
- Solvent H
- Solvent I
- Solvent J

RESULTS: Advanced Solvent Extraction

	Avridi 30 mg	
	% Oxycodone HCl	% SLS
Solvent A	82	93
Solvent B	93	94
Solvent C	77	64
Solvent D	60	N/A
Solvent E	86	96
Solvent F	88	89
Solvent G	94	N/A
Solvent H	95	N/A
Solvent I	91	N/A
Solvent J	96	N/A

CONCLUSIONS: Advanced Solvent Extraction

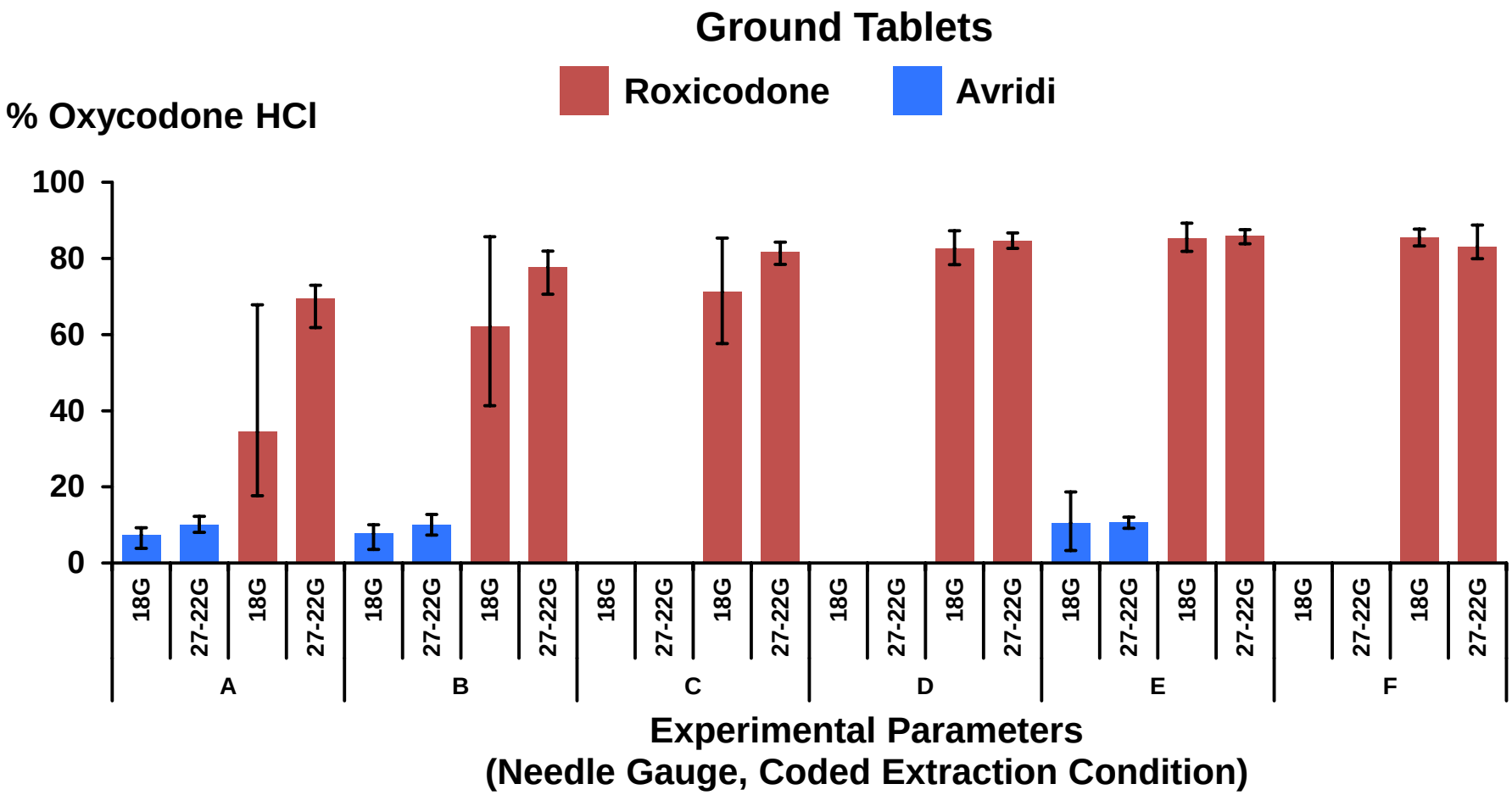
- **Solubility differences were observed between oxycodone HCl and SLS with a few specific solvent systems**
- **It is doubtful that these attempts would be routinely successful in a household setting**
  - **Additional complex steps required to isolate oxycodone HCl**
- **This requires significant motivation, time, effort, knowledge, and access to specific chemicals in some instances**

STUDY 5:
Syringeability (Preparation for Injection)

Goal: Determine How Much Oxycodone HCl Can Be Aspirated for Injection

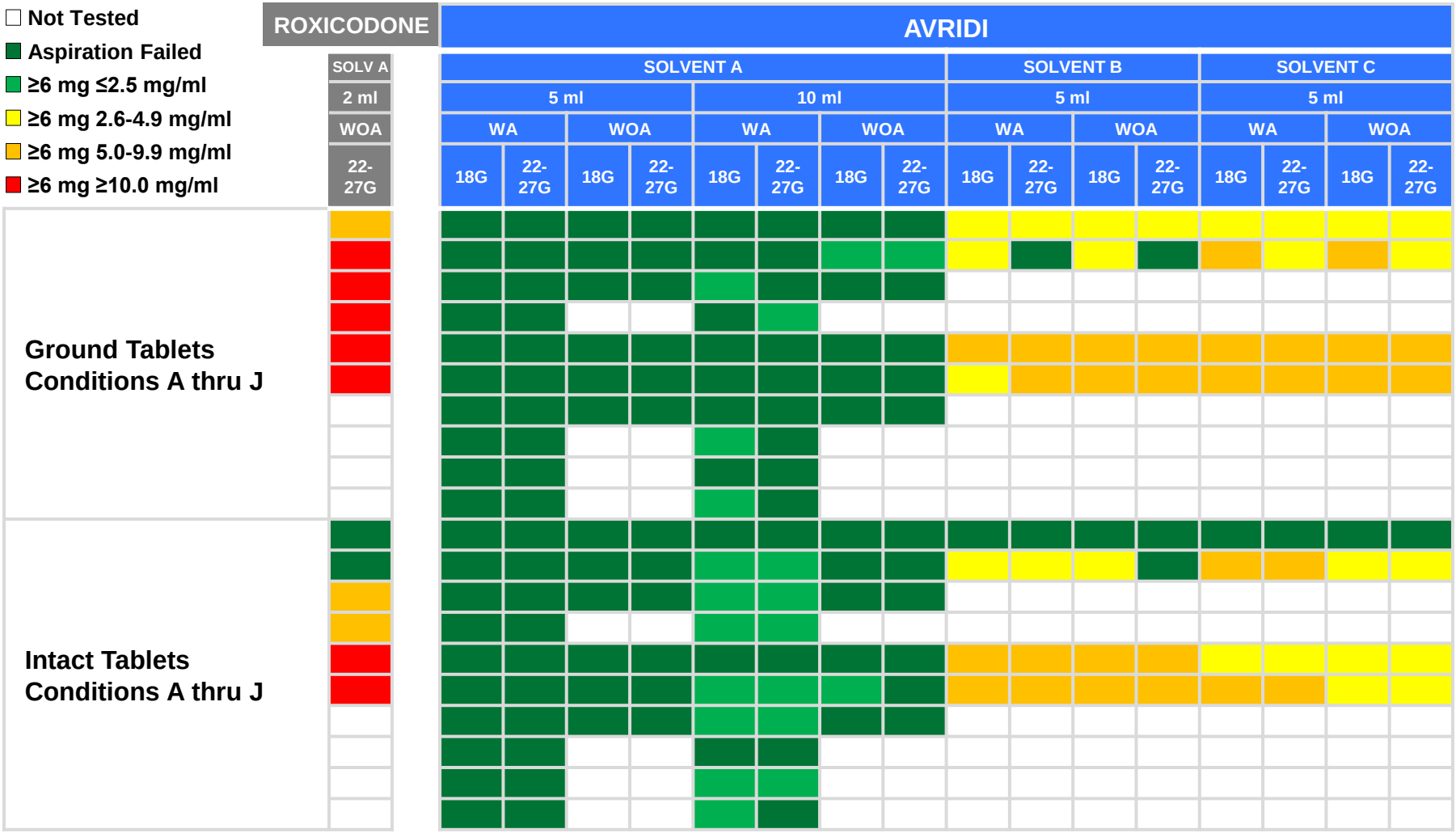
Study	Relevant Route of Abuse
1. **Physical Manipulation (Crushing)**	IN, IV
2. **Tablet Pretreatments**	IN, IV
3. **Household Solvent Extraction**	IN
4. **Advanced Solvent Extraction**	IN
5. **Syringeability (Preparation for Injection)**	IV
6. **Simulated Smoking (Vaporization)**	Smoking
7. **Oxycodone Free Base Isolation**	IV, Smoking

RESULTS: Solvent A Syringeability Starting Volume 5 mL



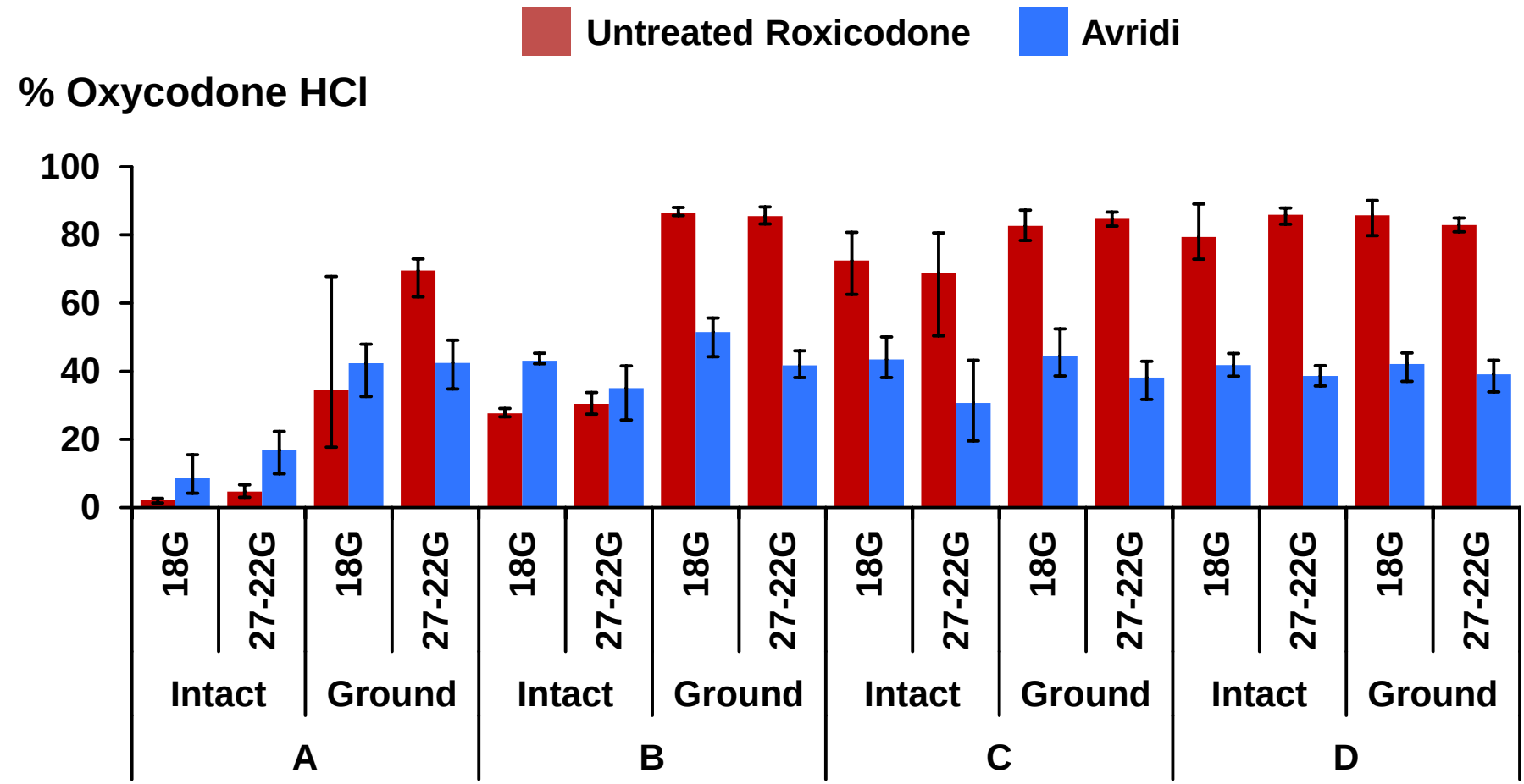
Note: Error bars represent the range of results.

RESULTS: Color Coded Syringeability Solvent A, B, and C



WA=With Agitation; WOA=Without Agitation. Failed=Not possible or less than 5 mg oxycodone HCl aspirated

RESULTS: Syringeability
Avridi after Pretreatment B



Note: Error bars represent the range of results.

CONCLUSIONS: Syringeability

- **Avridi is difficult to prepare for IV injection**
- **Gelling properties of Avridi excipients in combination with the large tablet size make it too viscous for injection**
- **Optimized pretreatment conditions may somewhat increase the amount of oxycodone aspirated**
  - **Very difficult to discover optimal conditions**
  - **Even if successful once, difficult to replicate**
- **In contrast, Roxicodone is easily prepared for injection**

Avridi In Vitro Abuse Deterrence Study Outcomes

Study	Relevant Route of Abuse	Outcomes
Physical Manipulation (Crushing)	IN, IV	IR product not formulated to resist crushing, facilitates exposure to the aversive agent when snorted
Tablet Pretreatments	IN, IV	SLS degrades faster than oxycodone HCl, difficult for an abuser to avoid substantial loss of oxycodone
Solvent Extractions	IN	Few solubility differences between oxycodone HCl and SLS
Syringeability (Preparation for Injection)	IV	Due to gelling properties and large tablet volume, Avridi is difficult to prepare for IV injection
Simulated Smoking	Smoking	Not amenable to smoking
Oxycodone Free Base Isolation	IV, Smoking	Requires knowledge/forethought, difficult, tedious, frequently unsuccessful

Avridi In Vitro Abuse Deterrence Study Conclusions

- **Compared with Roxicodone, Avridi requires substantially more time, cost, and effort to abuse**
- **The gelling and aversive components of Avridi tablets are expected to deter the IV and IN routes of abuse**

Avridi Intranasal Abuse Potential

Alessandra Cipriano, MSHS

Clinical Pharmacology

Characterization of Abuse Deterrence

Pre-Marketing

1	*In Vitro* Manipulation & Extraction Studies	▪ Evaluate the physical and chemical properties of the formulation
2	Pharmacokinetic Studies	▪ Determine the bioavailability and pharmacokinetic profile of tablets administered intact and manipulated (orally and intranasally)
3	Clinical Abuse Potential Studies	▪ Examine various subjective measures related to liking and abuse of the formulation

Post-Marketing

4	Epidemiology Studies	▪ Assess real-world impact using post-marketing outcome data

Adapted from FDA Guidance for Industry Abuse-Deterrent Opioids – Evaluation and Labeling. April 2015.

Intranasal Abuse Potential Study Design

- **Randomized, double-blind, placebo and positive-controlled study conducted in nondependent recreational opioid users**
- **Consistent with FDA's Final Guidance on Abuse-Deterrent Opioids – Evaluation and Labeling (April 2015)**

Intranasal Abuse Potential Study Design

Qualification Phase
2 Period Crossover

- **Intranasal crushed Roxicodone (30 mg)**
- **Intranasal Placebo (Lactose NF powder)**

Intranasal Abuse Potential Study Design

Qualification Phase
2 Period Crossover

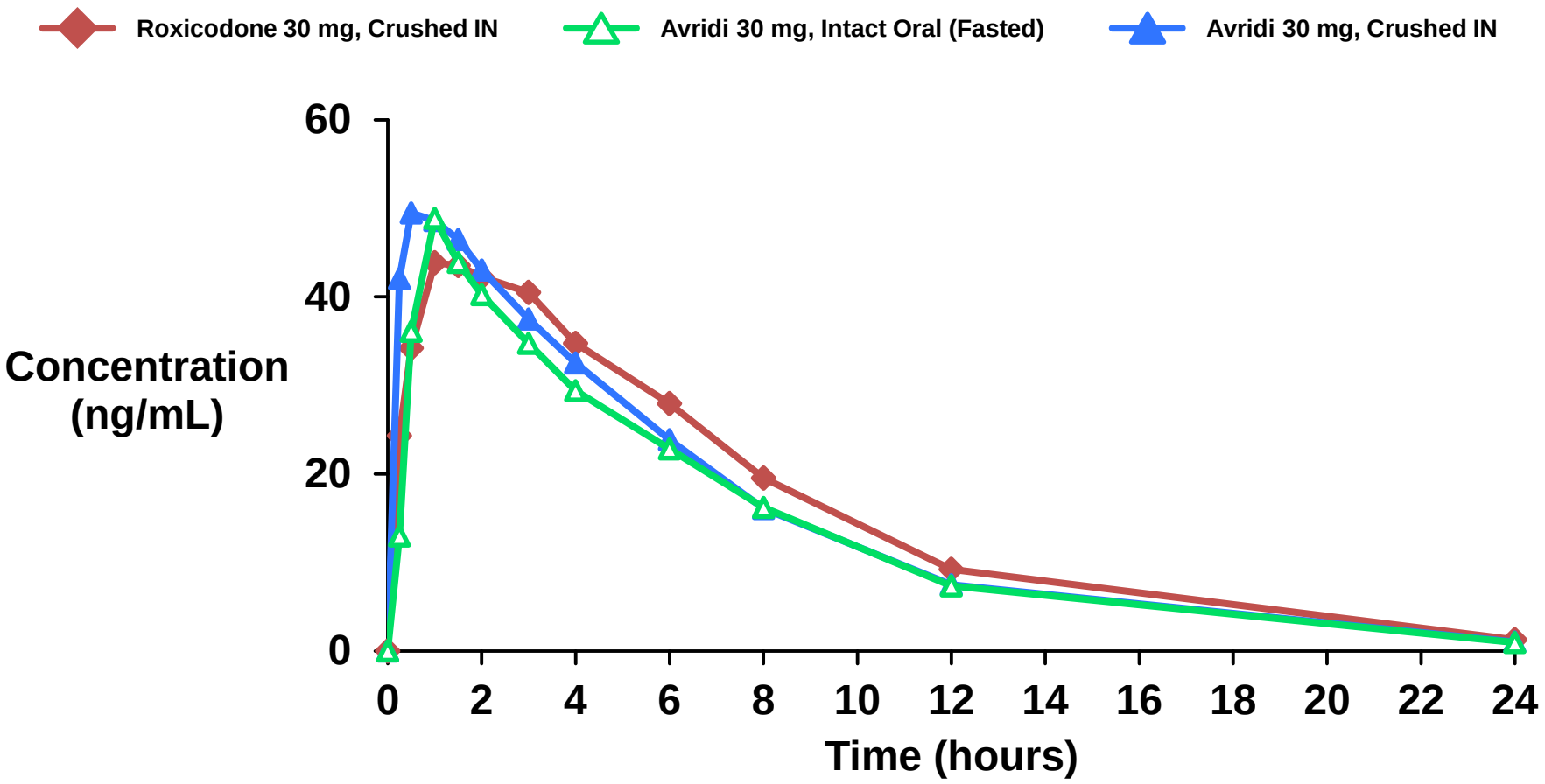
- Intranasal crushed Roxicodone (30 mg)
- Intranasal Placebo (Lactose NF powder)

Treatment Phase
4 Period Crossover
(N=36 dosed, 35 completed)

- Intranasal crushed Avridi tablets (30 mg)
- Intranasal crushed Roxicodone tablets (30 mg)
- Intranasal Placebo (Lactose NF powder)
- Oral intact Avridi tablets (30 mg)

Standardized laboratory methods were used to reproducibly prepare crushed Avridi tablets.

Oxycodone Pharmacokinetics

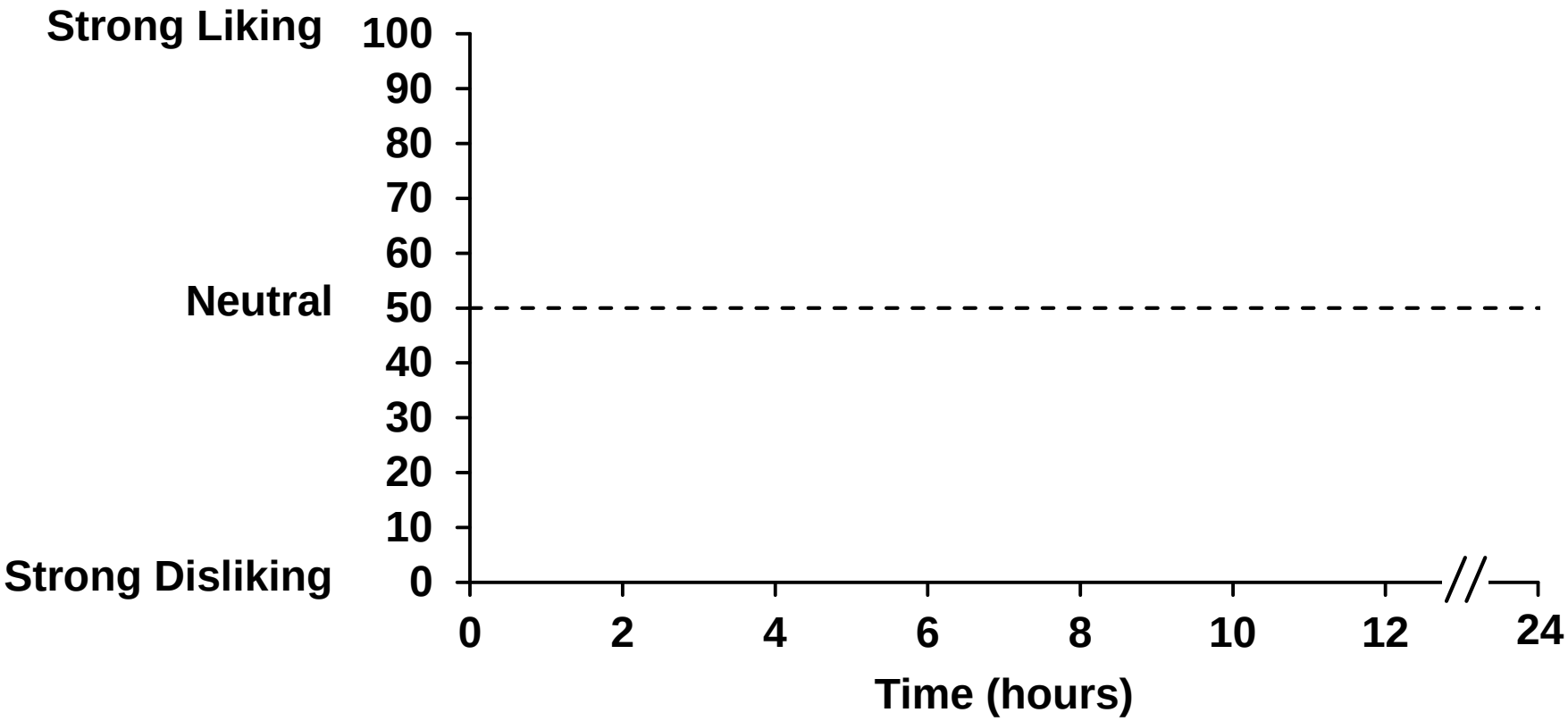


Pharmacodynamic Assessments

- **Primary pharmacodynamic measures**
  - **Bipolar VAS**
    - **'At this Moment' Drug Liking (Emax, Emin)**
    - **Overall Drug Liking (Emax)**
    - **Take Drug Again (Emax)**
- **Subject-rated assessment of nasal irritation**
  - **Unipolar VAS, Emax**
    - **Nasal burning**
    - **Need to blow nose**
    - **Nasal discharge**
    - **Facial pain or pressure**
    - **Nasal congestion**
- **Descriptive statistics, 95% CI and *P* values were computed**

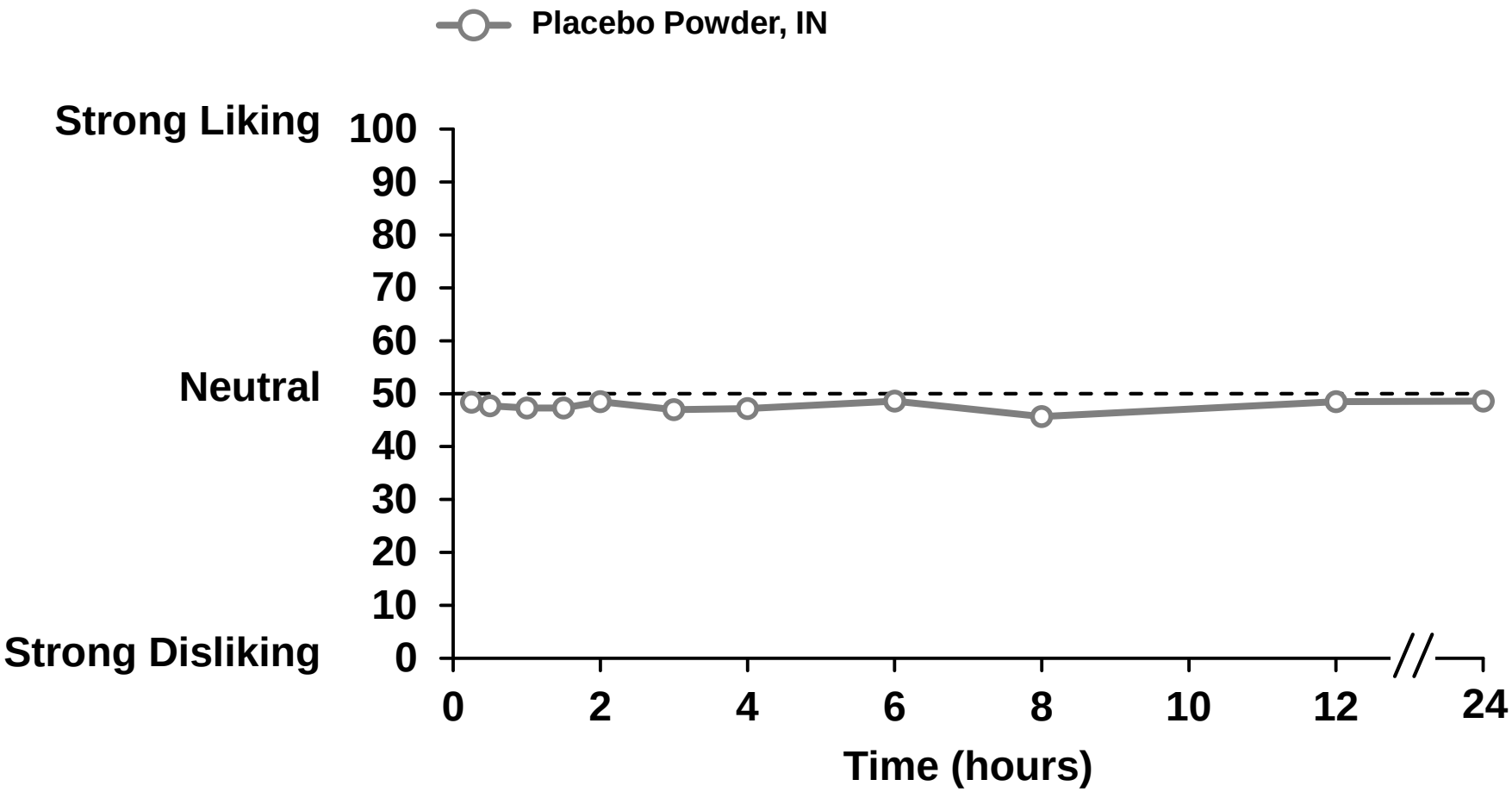
VAS=Visual Analog Scale; Emax=Maximum Effect; Emin=Minimum Effect.

‘At this Moment’ Drug Liking VAS



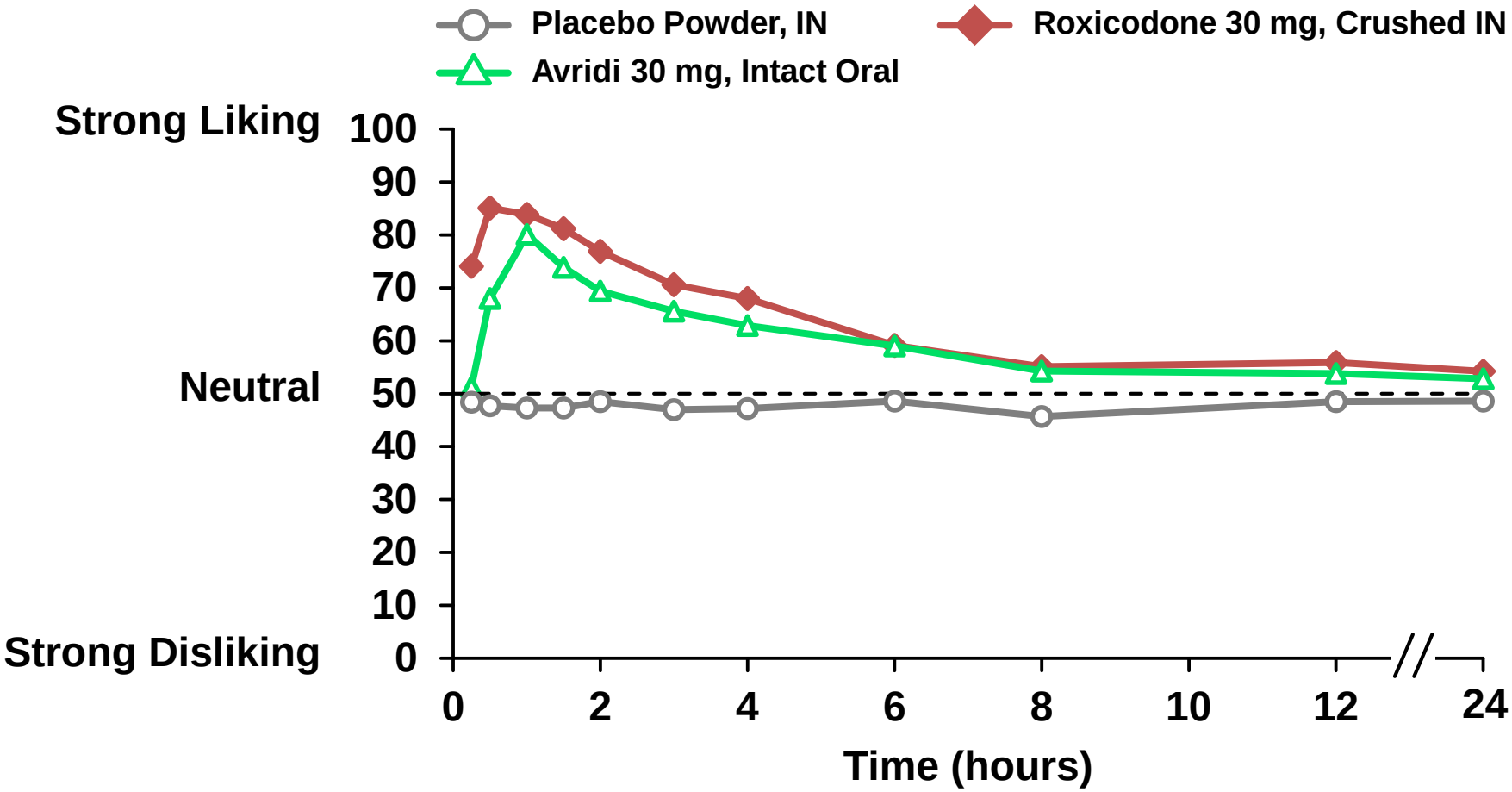
VAS=Visual Analog Scale.

‘At this Moment’ Drug Liking VAS



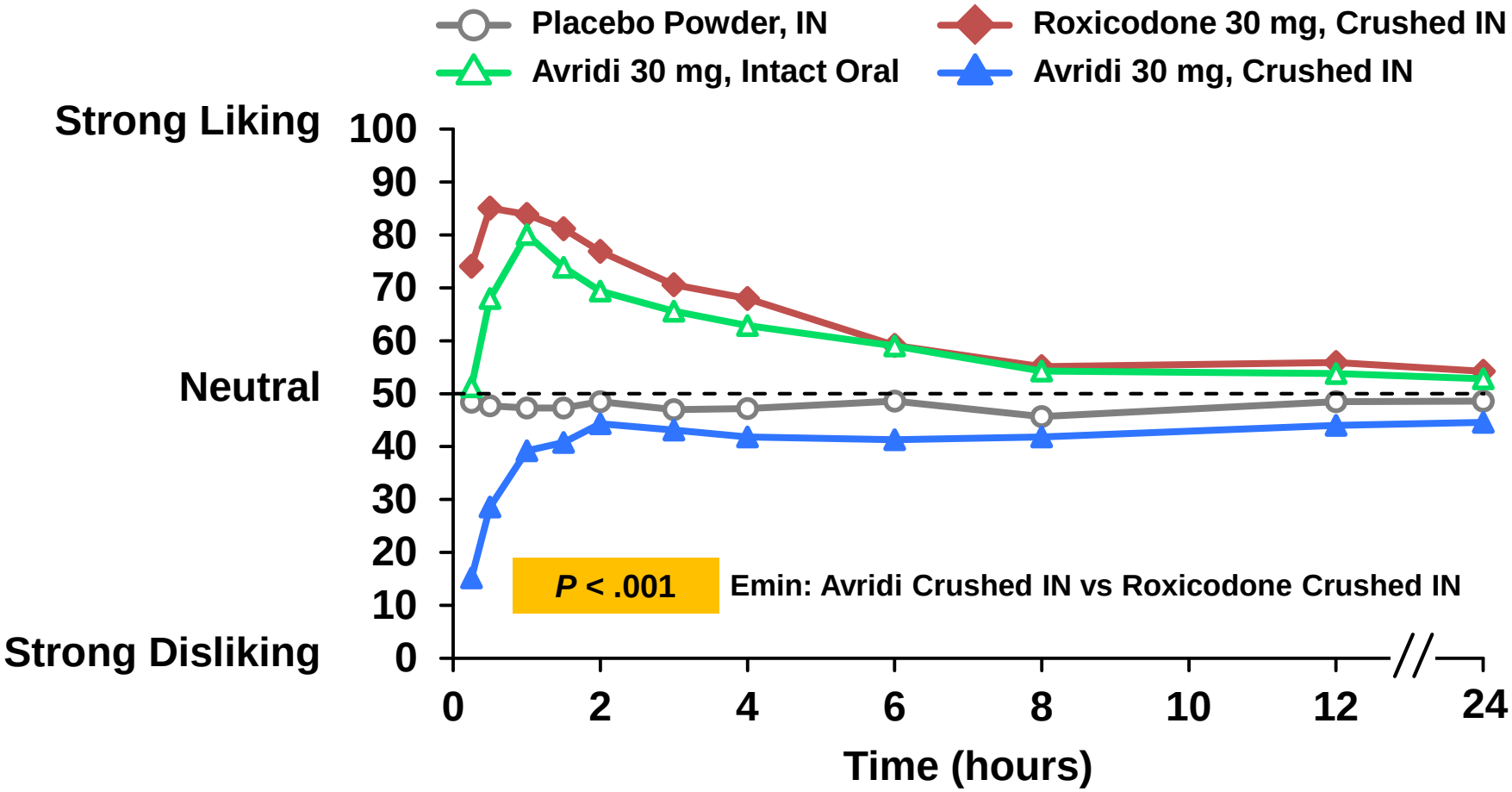
VAS=Visual Analog Scale.

‘At this Moment’ Drug Liking VAS



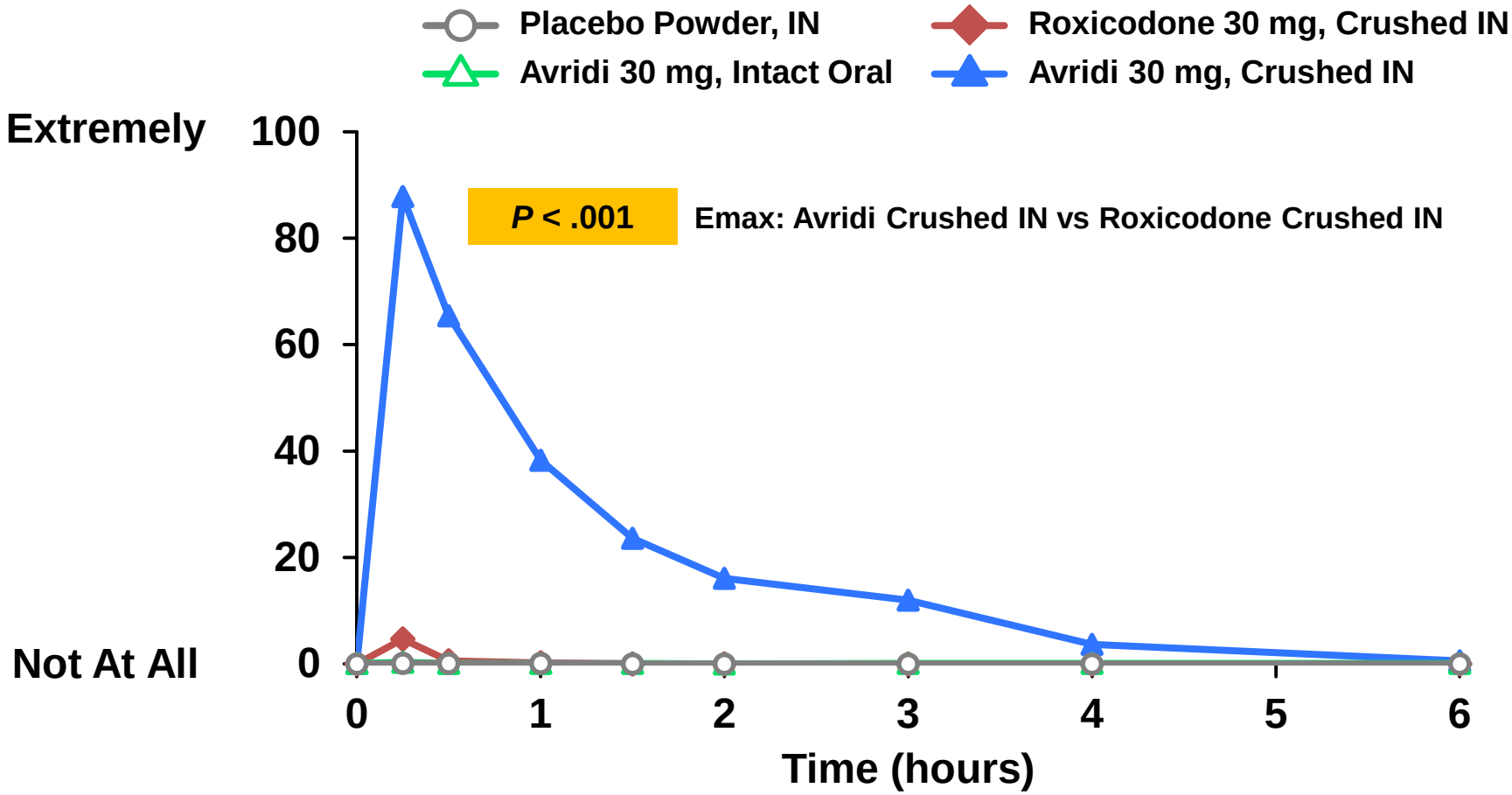
VAS=Visual Analog Scale.

‘At this Moment’ Drug Liking VAS



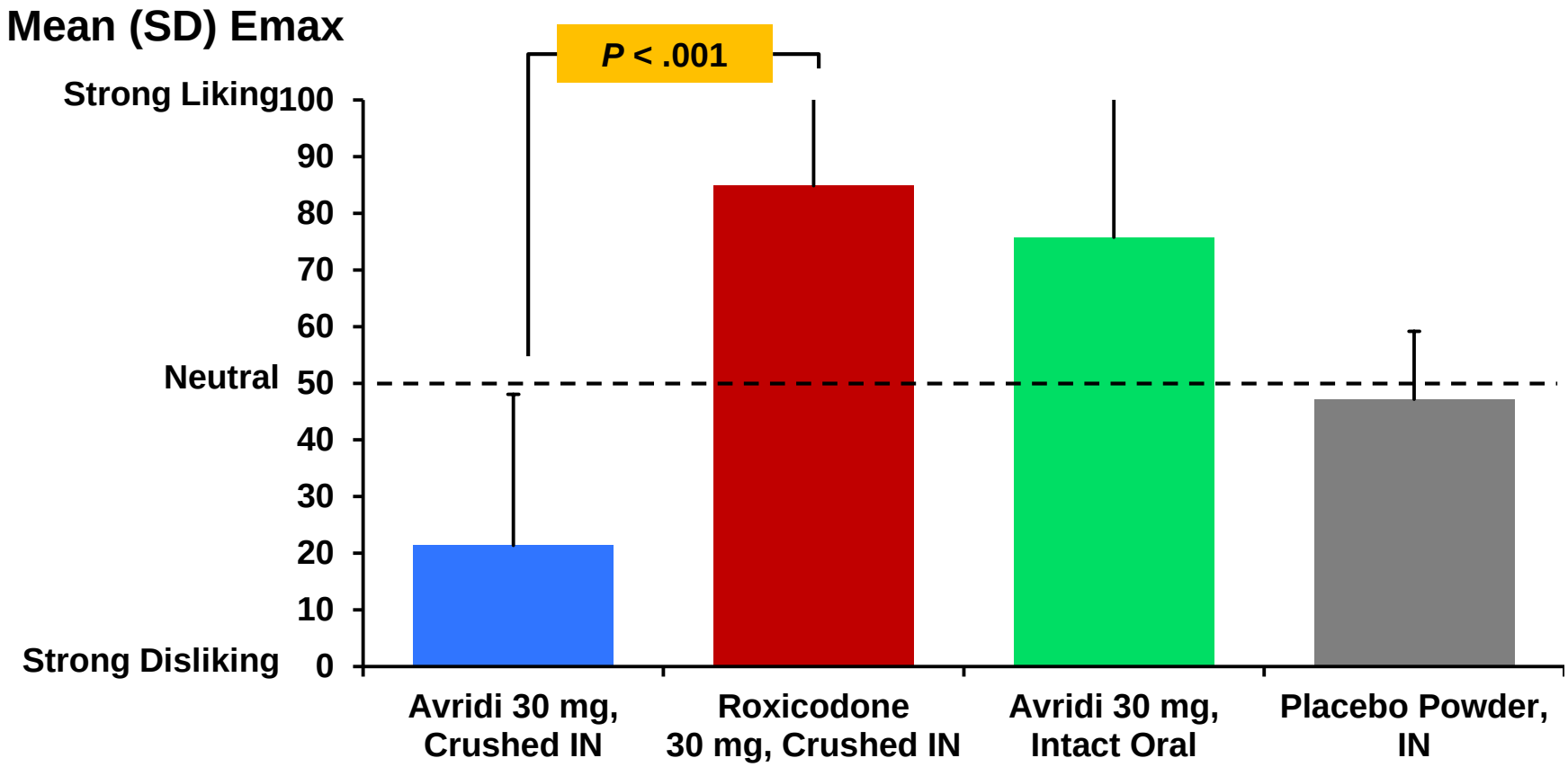
VAS=Visual Analog Scale; Emin=Minimum Effect.

Subject-Rated Intranasal Burning VAS



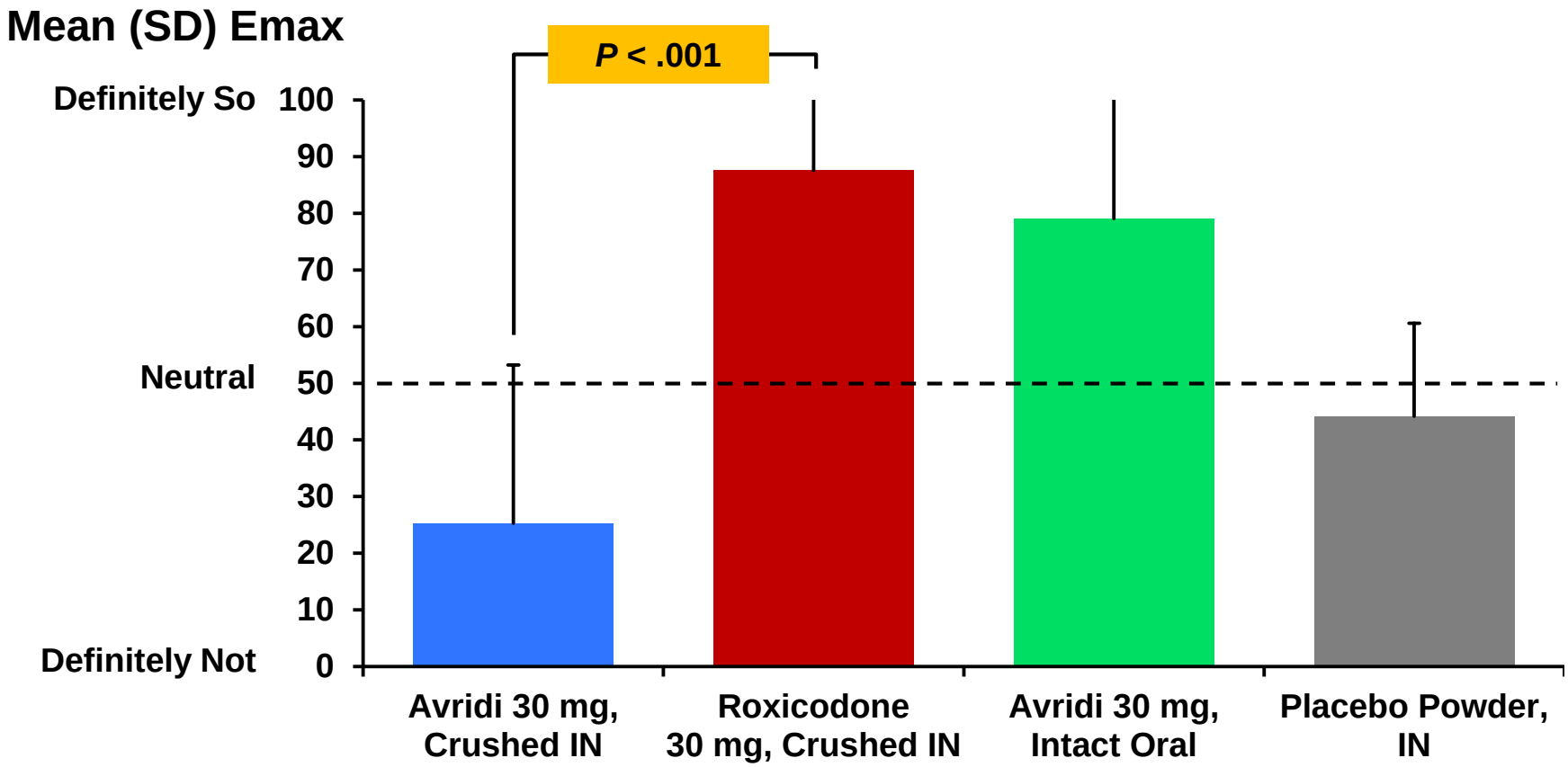
VAS= Visual Analog Scale; Emax=Maximum Concentration.

Global Balance of Effects
Overall Drug Liking at 24 Hours Postdose



Emax=Maximum Effect

Global Balance of Effects
Take Drug Again at 24 Hours Postdose



Emax=Maximum Effect

Safety Overview: Intranasal Abuse Potential

- **No serious adverse events, majority of adverse events were mild or moderate in severity**
- **Most common adverse event among all treatment groups**
  - **Nasal discomfort**
  - **Highest incidence reported for intranasal crushed Avridi**
- **Common adverse events reported for intranasal crushed Avridi included:**
  - **Nasal congestion, throat irritation, rhinorrhea, cough, dyspnea, somnolence, generalized pruritus, lacrimation increase and ocular hyperemia**

Intranasal Abuse Potential Summary

- **Avridi demonstrated significant reduction in intranasal abuse compared to Roxicodone**
  - **Significantly lower**
    - **‘At this Moment’ Drug liking**
    - **Overall liking**
    - **Willingness to take the drug again**
  - **Significantly greater local aversive effects**
    - **Burning**
    - **Nasal congestion**
    - **Facial pain or pressure**
    - **Need to blow nose/runny nose**
    - **Throat irritation**

Overall Abuse Potential Conclusions

- **Avridi has physicochemical properties that make injection more difficult**
- **The local aversive properties of Avridi are expected to result in meaningful reductions in misuse and abuse by the intranasal route**
- **Outcomes of the abuse deterrence assessment support the following proposed labeling:**
  - ***In vitro data demonstrate that Avridi has physicochemical properties expected to make abuse via injection difficult***
  - ***The data from the human abuse potential study indicate that Avridi, when crushed and insufflated, has local aversive properties that are expected to significantly reduce abuse via the intranasal route***

Avridi Bioequivalence Evaluation

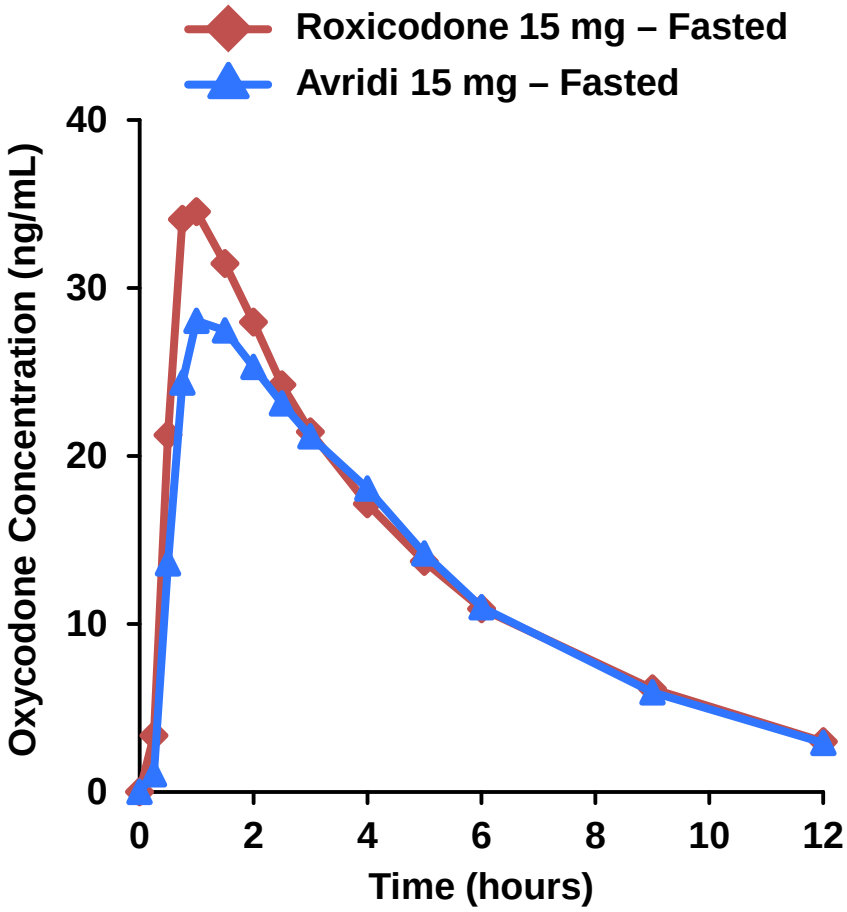
Alessandra Cipriano, MSHS

Clinical Pharmacology

Avridi Bioequivalence Studies

- **Two bioequivalence (BE) studies**
  - **Randomized single-dose, two treatment crossover design**
  - **Healthy subjects**
  - **Avridi and Roxicodone treatments: one 15 mg tablet**
  - **Naltrexone blockade used to minimize opioid adverse events**
- **Study OCI1002 – Fasted BE**
  - **53 subjects randomized**
- **Study OCI1003 – Fed BE**
  - **55 subjects randomized**
  - **Doses administered after FDA-defined high-fat, high-calorie meal**

OCI1002 Fasted BE Results

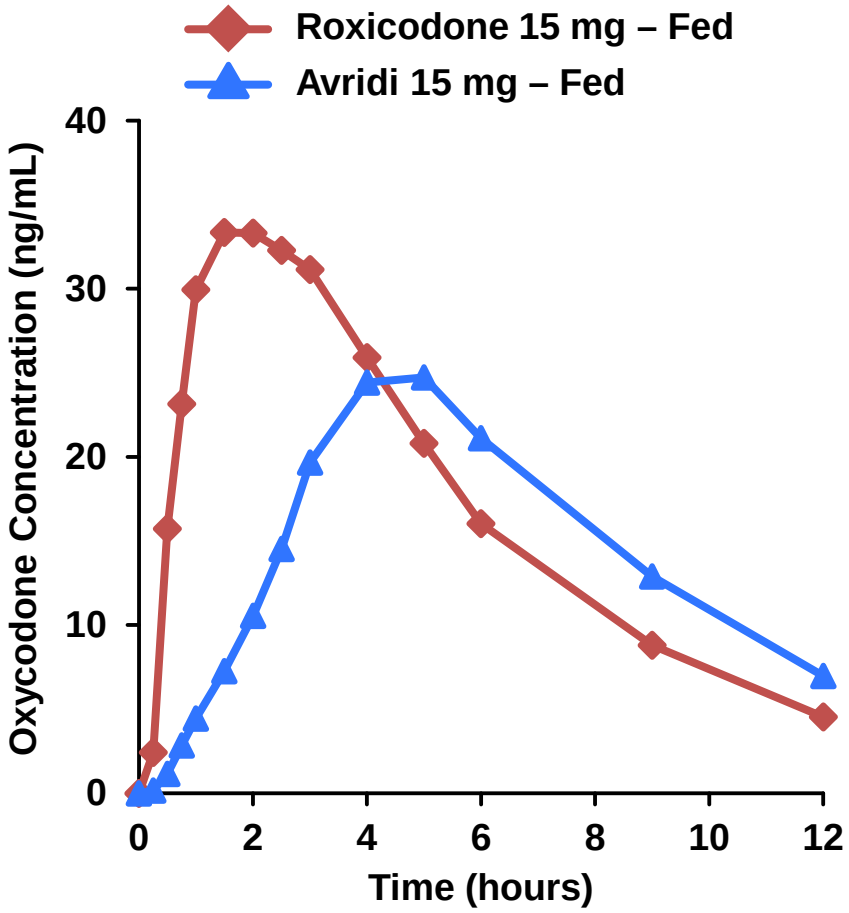


Metric (unit)	LS Mean Ratio (%) (Avridi/ Roxicodone)	90% CI of Ratio
AUCt (h*ng/mL)	93.6	90.9, 96.4
AUCinf (h*ng/mL)	93.6	91.0, 96.3
Cmax (ng/mL)	86.3	81.0, 92.1

Metric (unit)	Median (range)	
	Avridi	Roxicodone
Tmax (hour)	1.03 (0.5, 5.0)	1.0 (0.5, 6.07)

AUC=total oxycodone exposure; Cmax=maximum oxycodone concentration;
Tmax=time to maximum oxycodone concentration

OCI1003 Fed BE Results



Metric (unit)	LS Mean Ratio (%) (Avridi/ Roxicodone)	90% CI of Ratio
AUCt (h*ng/mL)	93.4	91.1, 95.9
AUCinf (h*ng/mL)	93.5	91.1, 95.9
Cmax (ng/mL)	72.6	68.4, 77.0

Metric (unit)	Median (range)	
	Avridi	Roxicodone
Tmax (hour)	4.0 (1.0, 9.05)	1.50 (0.5, 4.05)

AUC=total oxycodone exposure; Cmax=maximum oxycodone concentration;
Tmax=time to maximum oxycodone concentration

Bioequivalence Conclusions

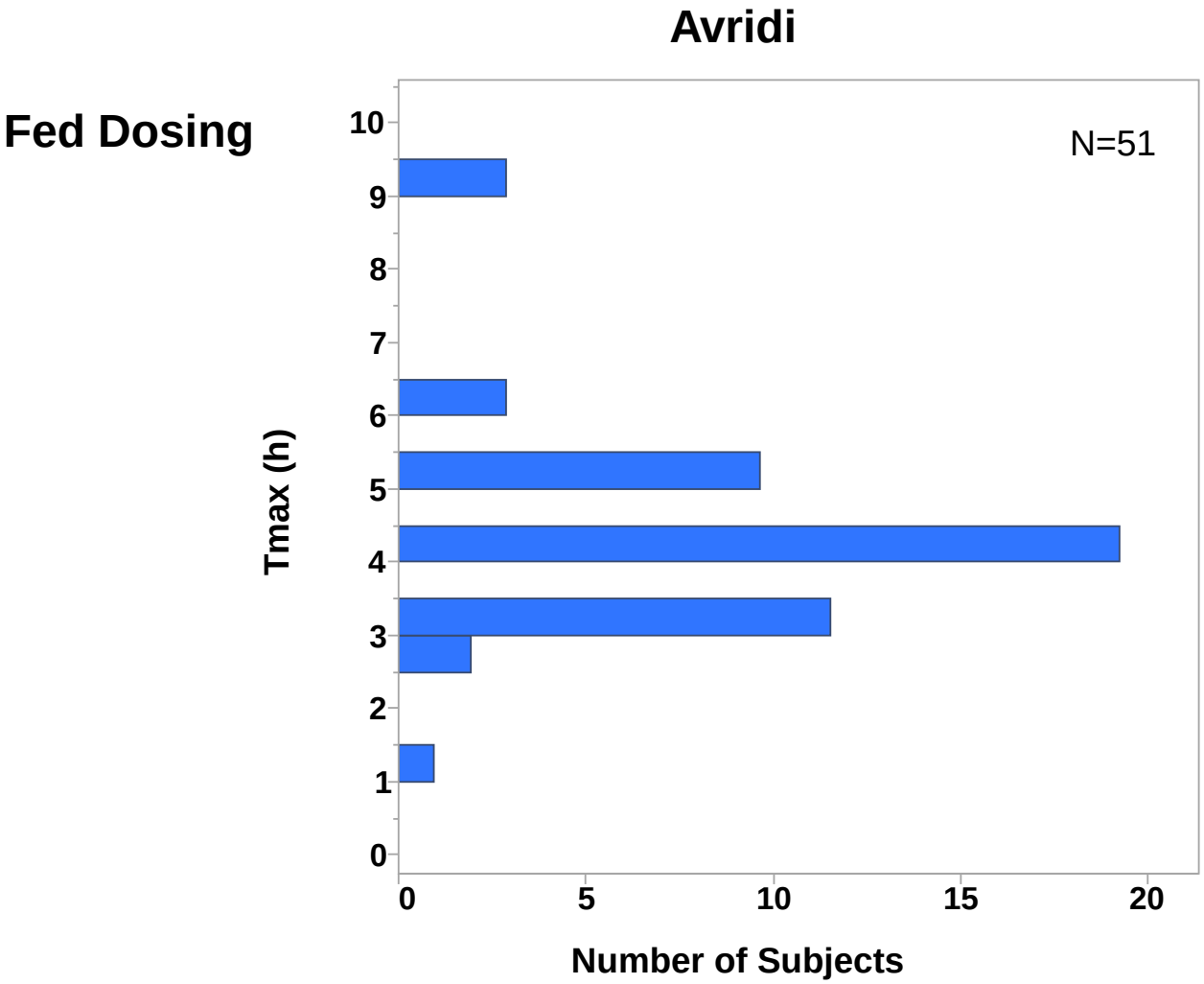
- **Avridi is bioequivalent to Roxicodone in the fasted state**
- **Avridi is not bioequivalent to Roxicodone in the fed state**
  - **Total oxycodone exposure (AUC) is bioequivalent**
  - **Maximum oxycodone concentration (Cmax) is not bioequivalent**
  - **Start of oxycodone absorption and time to peak oxycodone concentration may be delayed**

Avridi Pharmacokinetic Modeling

Stephen C. Harris, MD

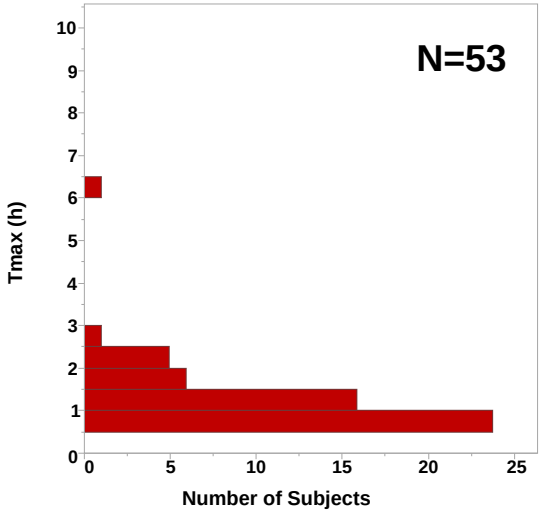
Clinical Pharmacology

Tmax Distributions from Avridi Single-Dose BE Studies

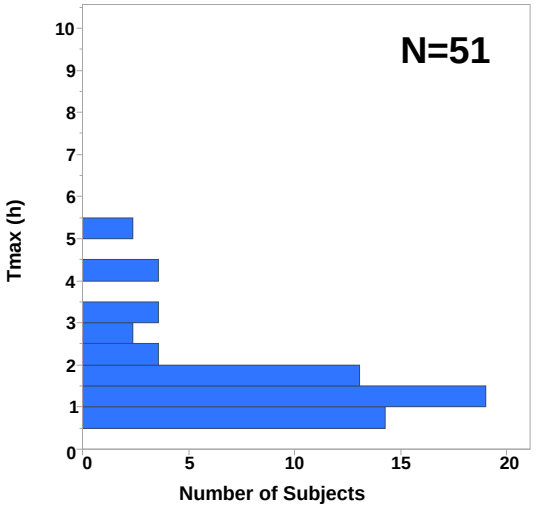


Tmax Distributions from Avridi Single-Dose BE Studies

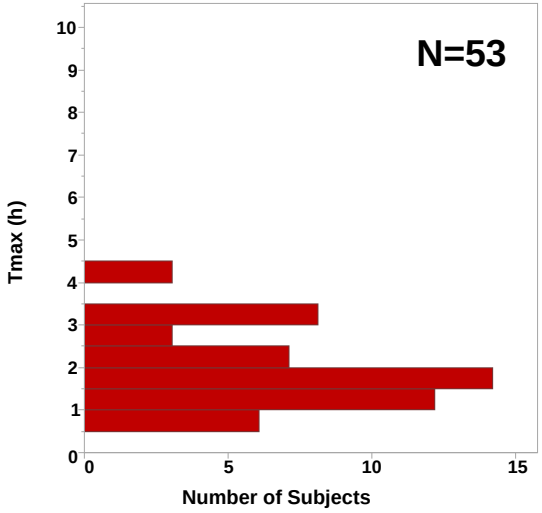
Roxicodone



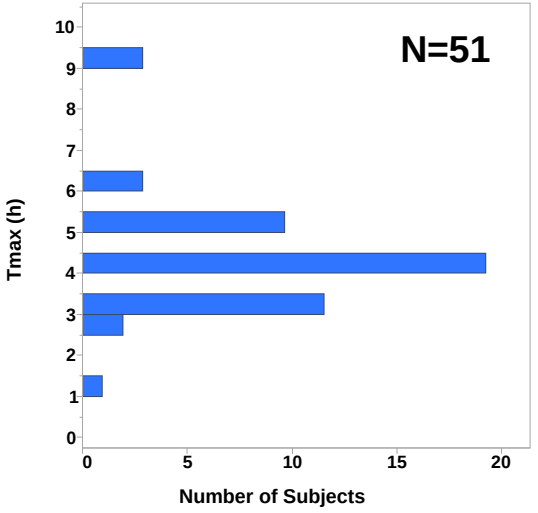
Avridi



Fasted Dosing



Fed Dosing



Avridi Dosing Instructions

- **Avridi should be administered on an empty stomach, at least one hour before or two hours after eating**
- **Immediate-release oxymorphone precedent**
  - **Full mu-agonist opioid**
  - **Same indication as Avridi, also dosed every 4 to 6 hours**
  - **Dosing instructions:**
    “Oxymorphone hydrochloride tablets should be administered on an empty stomach, at least one hour prior to or two hours after eating.”

IR Oxycodone Utilization Patterns

ATC IR

Around-the-clock IR Oxycodone Every 4 to 6 Hours

- **Patients likely to use around-the-clock IR oxycodone include those with acute pain of greater than several days duration or with chronic pain**

PRN IR

PRN IR Oxycodone at 4- to 6-Hour Intervals, as needed

- **Patients likely to use IR oxycodone on a PRN basis include those with acute pain from injury or surgery or those with intermittent pain**

PK Modeling Methodology

- **Modeling methods explored**
  - **Nonparametric superposition**
  - **Compartmental modeling**
  - **Similar assumptions required for each method**
- **Results were generally similar**
- **Nonparametric superposition selected because:**
  - **Can be applied using individual subject data**
  - **Preserves patterns of delayed onset and reduced rates of oxycodone absorption**
  - **Can be used to model regular and irregular dosing regimens**

Safety and Efficacy of Oxycodone Exposures

- **Relationship between oxycodone concentration and response varies**
  - **Demographics (Age, Sex, Race/Ethnicity)**
  - **State of health**
  - **Pain type and etiology**
  - **Extent of previous opioid treatment (dose, duration, tolerance)**
- **Oxycodone exposures associated with labeled Roxicodone regimens can be used to assess the safety and efficacy of various Avridi dosing scenarios**

IR Oxycodone Utilization Patterns

ATC IR

Around-the-Clock IR Oxycodone Every 4 to 6 Hours

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PRN IR

PRN IR Oxycodone at 4- to 6-Hour Intervals, as needed

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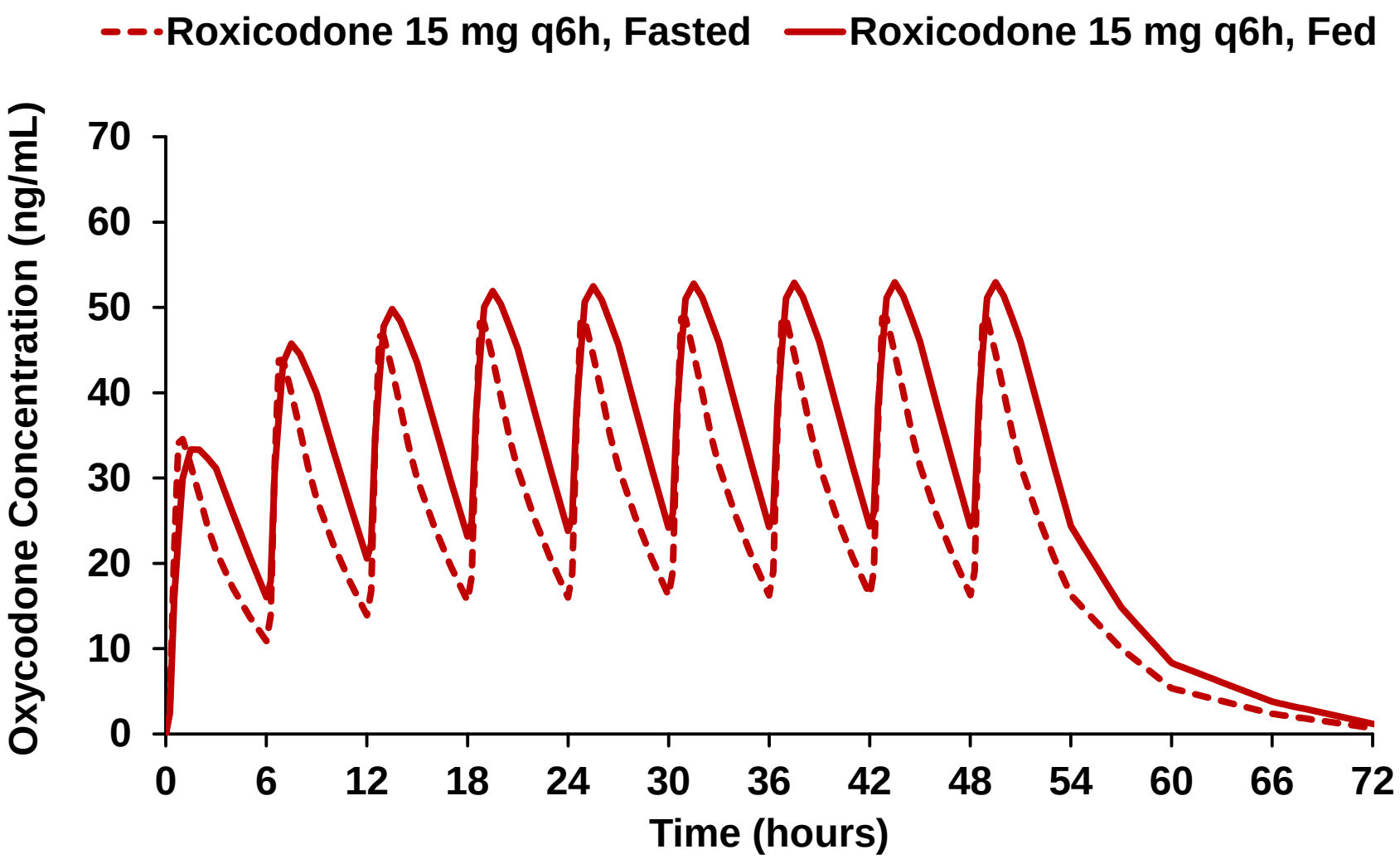
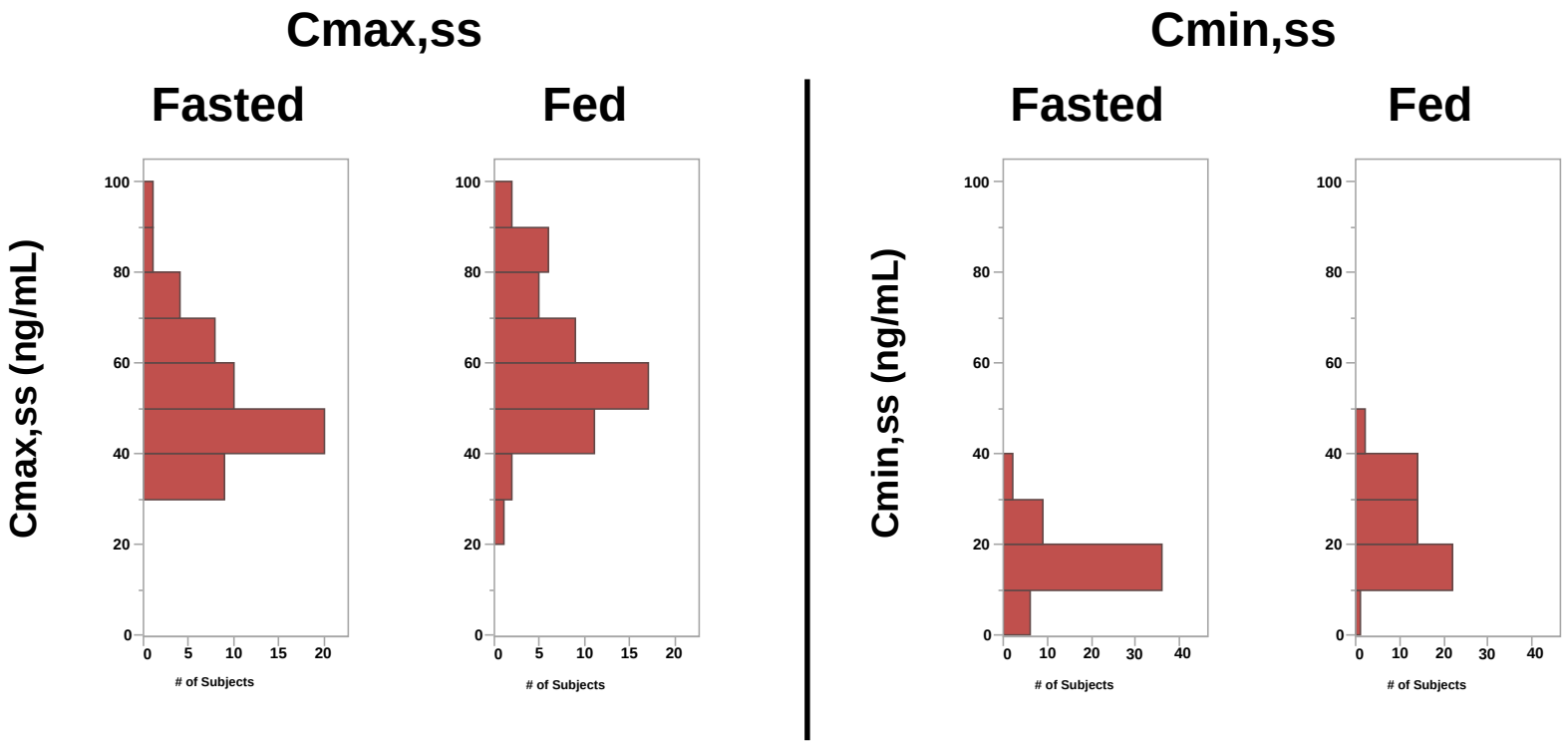
Roxicodone Around-the-Clock (ATC) Reference Dosing, q6h Fasted and Fed



Roxicodone ATC
Reference Cmax & Cmin Distributions

Roxicodone 15 mg q6h Projected Steady-State (ss)

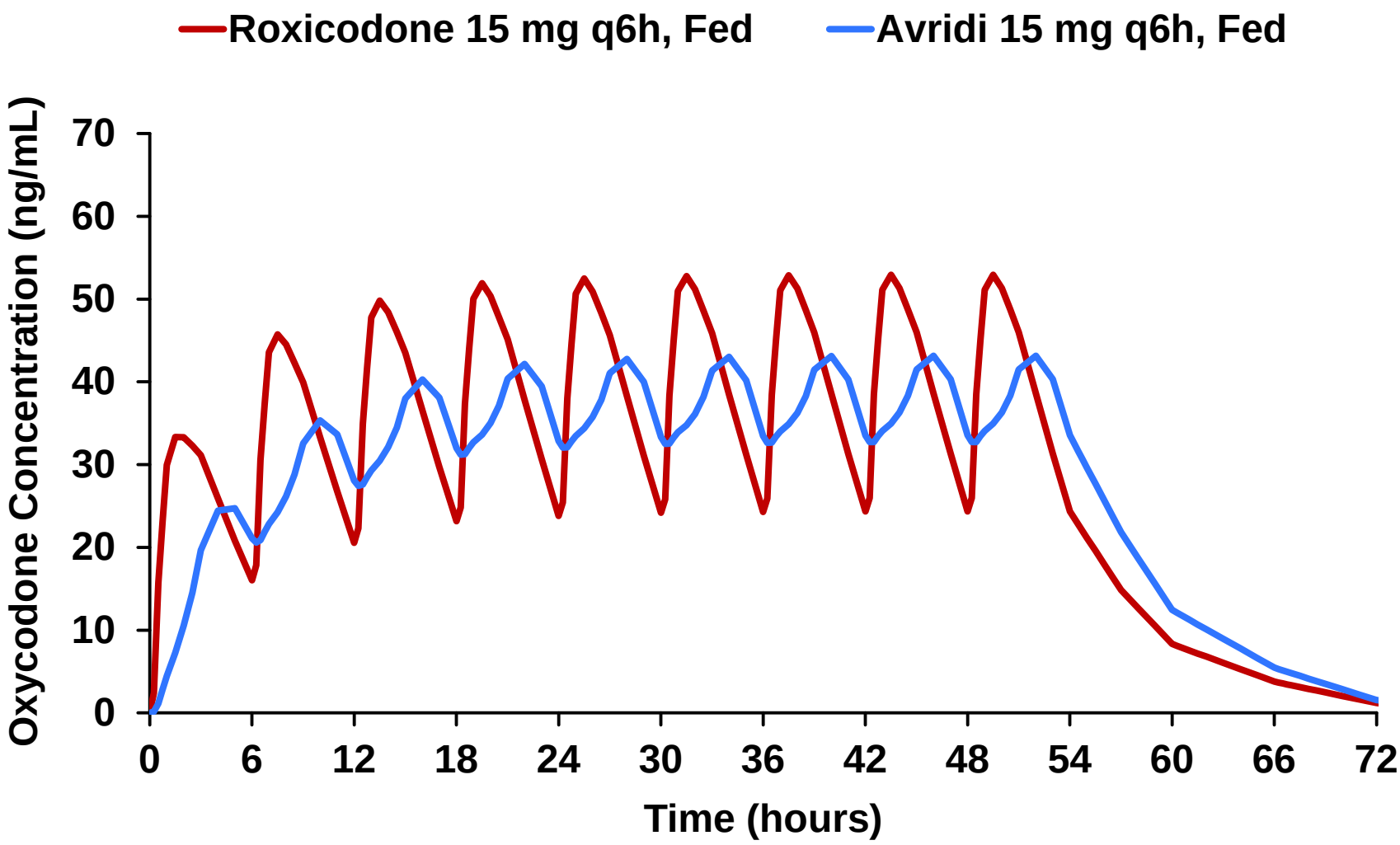


Steady-state maximum (Cmax,ss) and minimum concentrations (Cmin,ss) projected for Roxicodone define reference exposure ranges

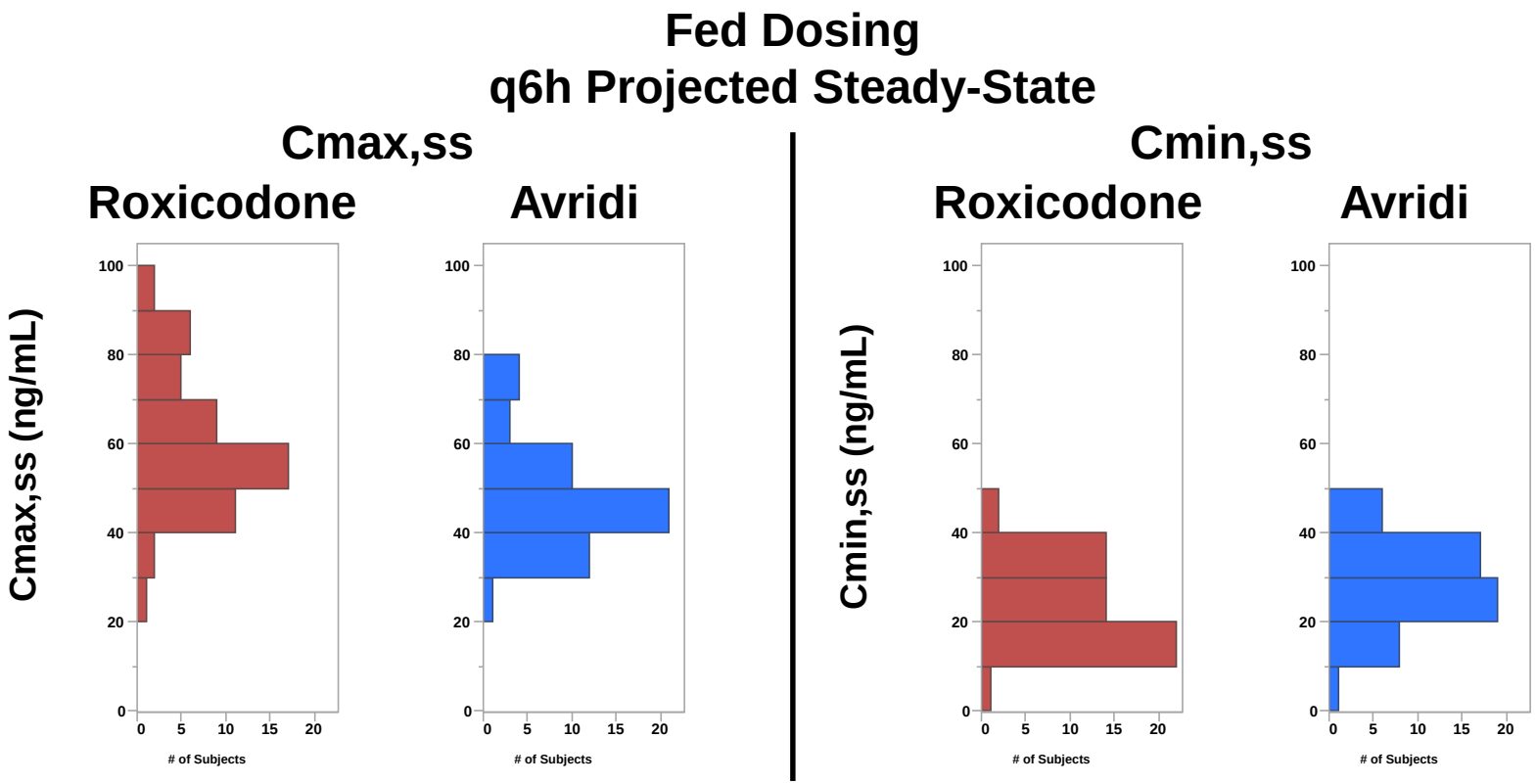
ATC Avridi Fed Dosing Scenario

- **Around-the-Clock dosing of Avridi with all doses taken in the fed state**
  - **Projections based on each subject's fed Avridi PK profile for each dose**
  - **Reference Roxicodone projections based on each subject's fed Roxicodone PK profile for each dose**
  - **Comparisons are made for both every 6-hour (q6h) and every 4-hour (q4h) around-the-clock dosing at steady state**

ATC Avridi Fed Dosing Scenario
Projected Mean Steady-State PK Profiles



ATC Avridi Fed Dosing Scenario
Projected Steady-State Cmax and Cmin Distributions

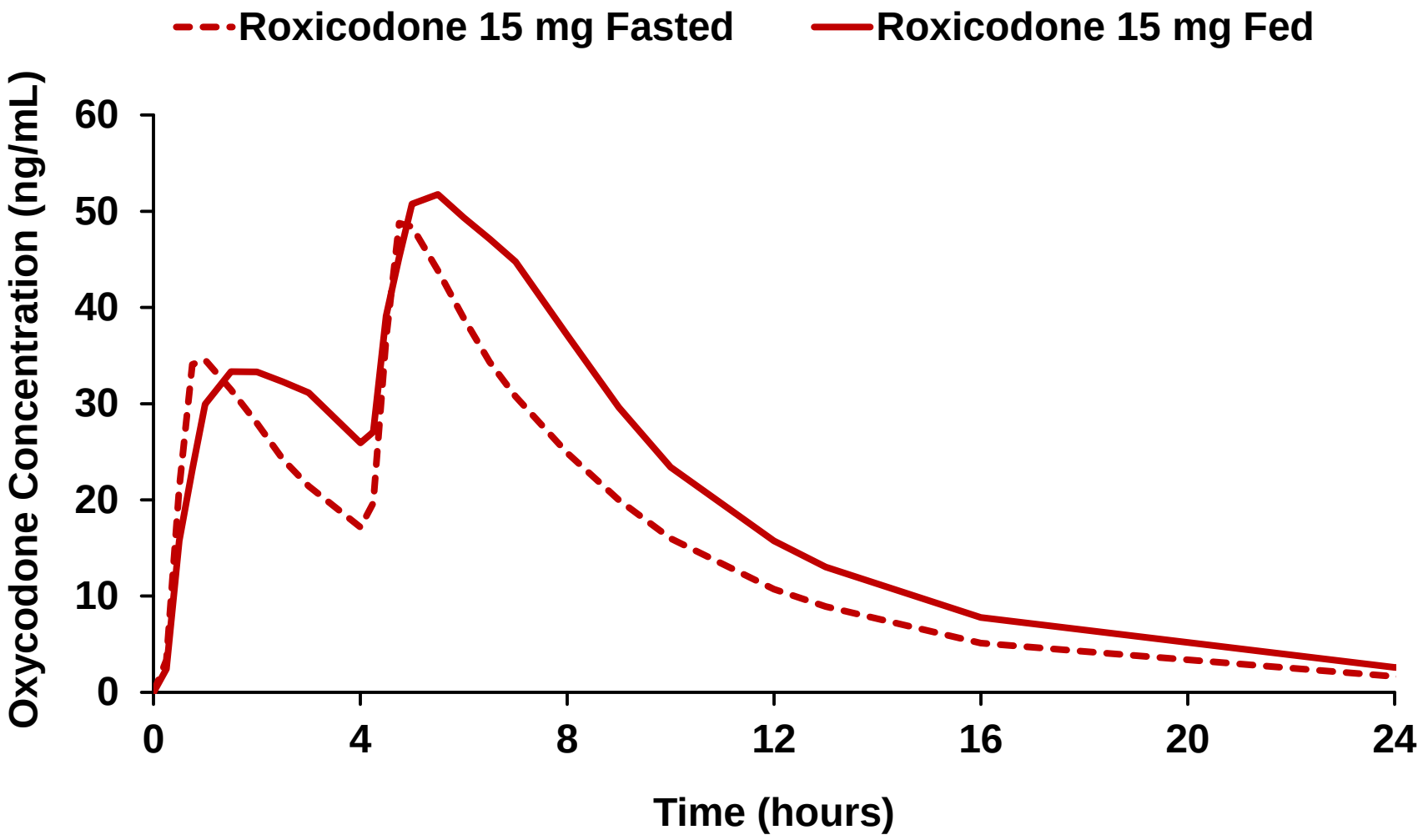


Steady-state maximum and minimum concentration ranges for Avridi lie within the ranges projected for Roxicodone

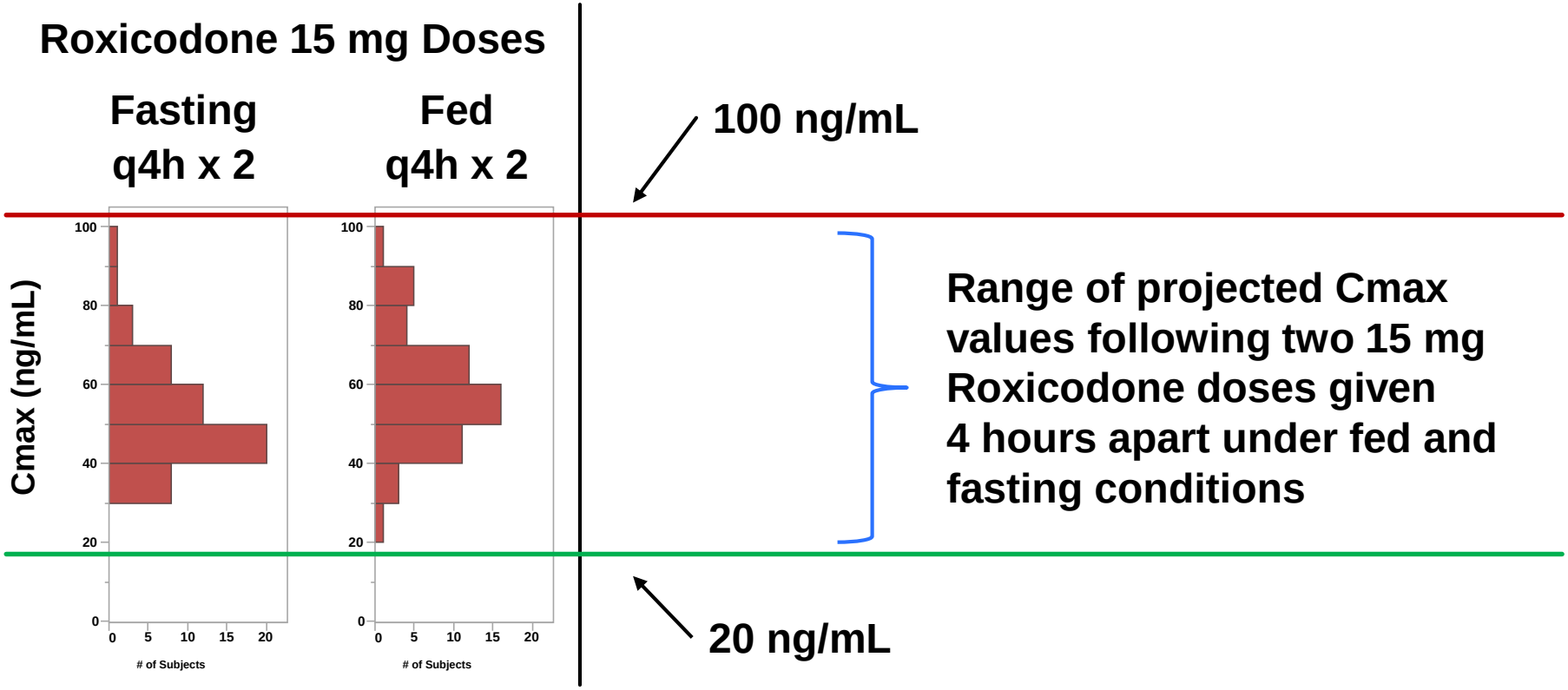
IR Oxycodone Utilization Patterns

ATC IR	PRN IR
Around-the-Clock IR Oxycodone Every 4 to 6 Hours	PRN IR Oxycodone at 4- to 6-Hour Intervals, as needed
▪ Patients likely to use around-the-clock IR oxycodone include those with acute pain of greater than several days duration or with chronic pain	▪ **Patients likely to use IR oxycodone on a PRN basis include those with acute pain from injury or surgery or those with intermittent pain**

Roxicodone PRN Reference Dosing
Two Fed Roxicodone Doses, 4 hours Apart



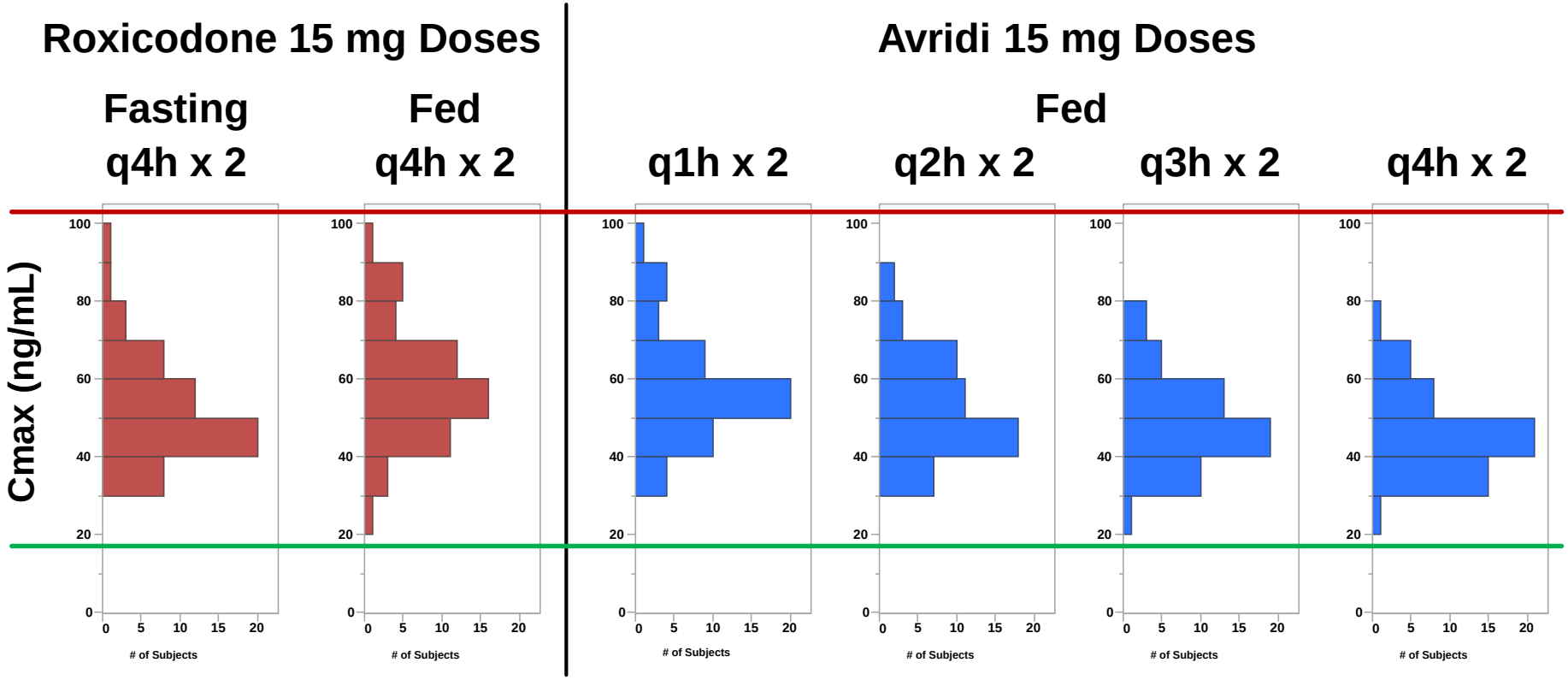
Roxicodone PRN Reference Cmax Distributions



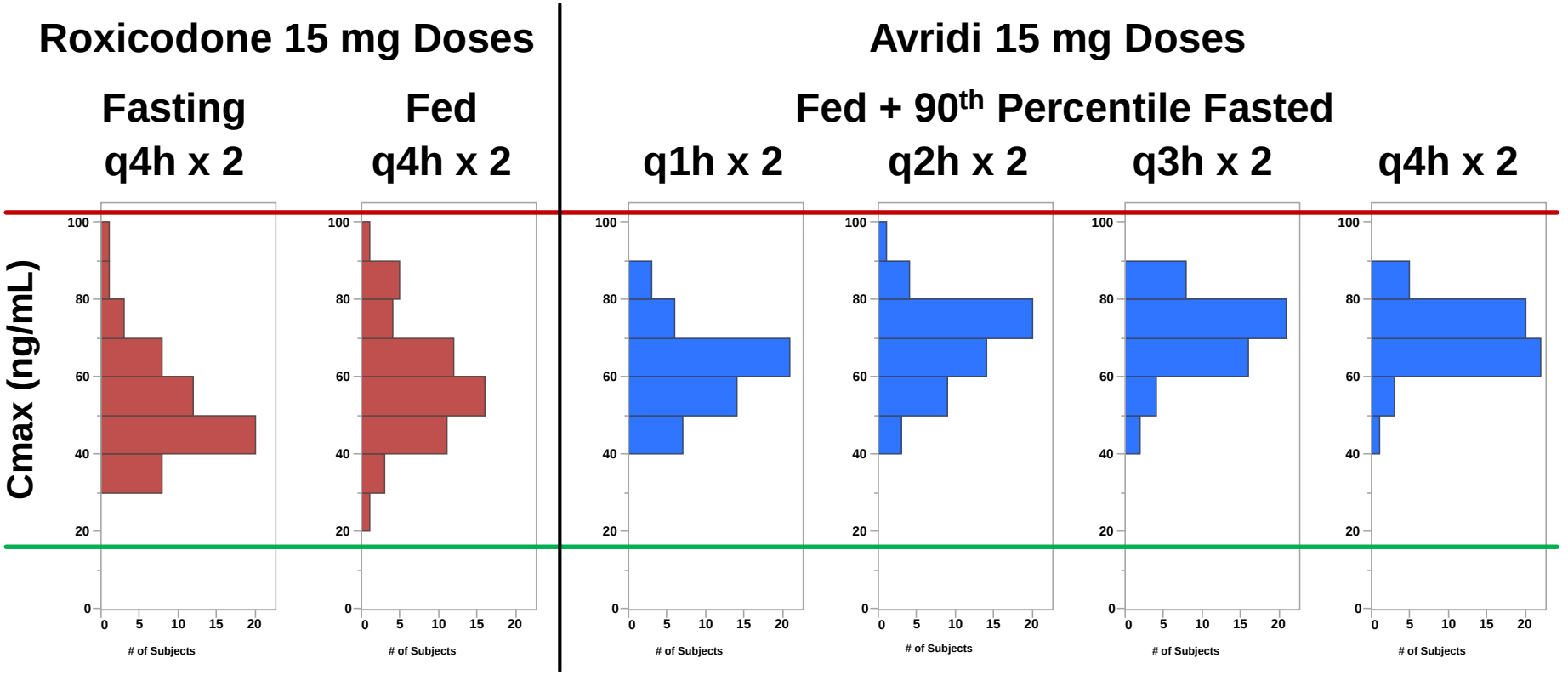
PRN Fed Avridi Use Scenarios

- **Scenario 1: Fed Avridi dose followed by early second fed Avridi dose**
  - **Dose intervals of 1, 2, 3 and 4 hours were modeled**
  - **Projections based on each subject's fed Avridi PK profile for each dose**
- **Scenario 2: Fed Avridi dose followed by early second fasting Avridi dose**
  - **Dose intervals of 1, 2, 3 and 4 hours were modeled**
  - **Projections based on each subject's fed Avridi PK profile for the first dose and the 90th percentile fasting Avridi PK profile for the second dose**

PRN Avridi Scenario 1:
Two Fed Avridi Doses, 1-4 hours Apart



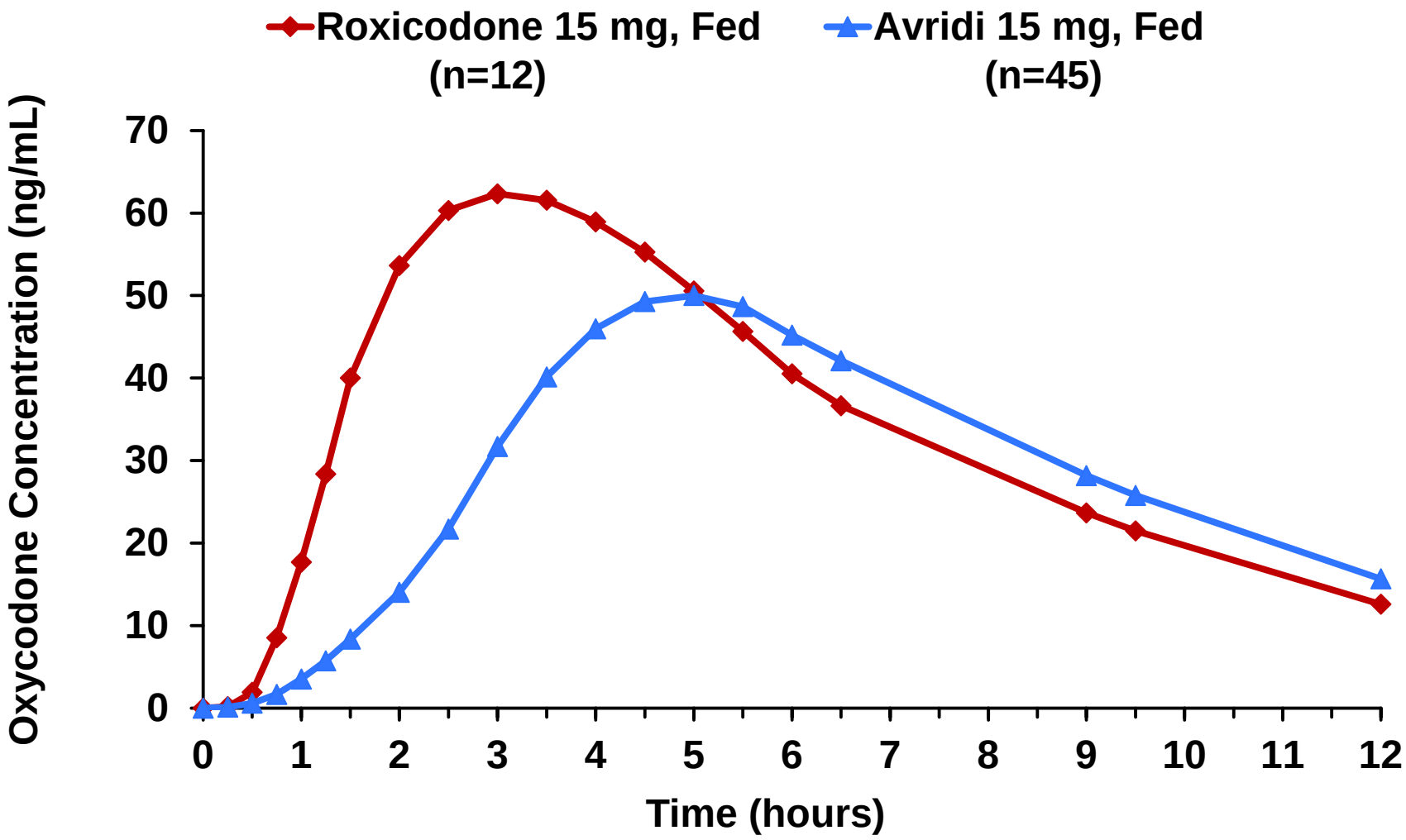
PRN Avridi Scenario 2
Fed + Fasted Avridi Doses, 1-4 hrs Apart



PRN IR Oxycodone
Two Fed Doses, 0.5 Hours Apart

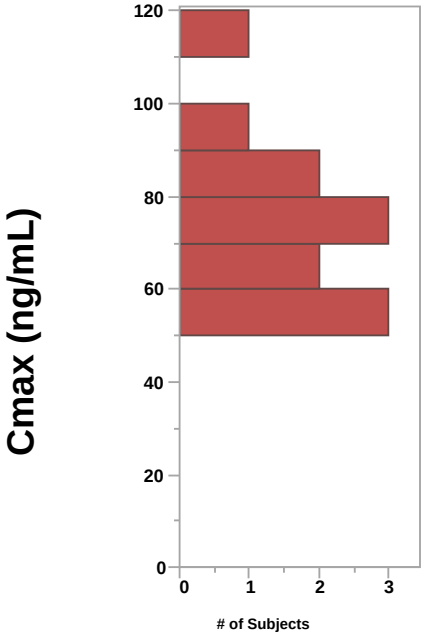
- **Fed IR oxycodone dose followed by an early second fed IR dose 30 minutes later**
- **Subtherapeutic concentrations defined as less than 10% of Cmax**
- **Identified subjects with subtherapeutic concentrations 30 minutes after fed dosing**
  - **Avridi: 45 of 51 subjects**
  - **Roxicodone: 12 of 53 subjects**

PRN IR Oxycodone
Two Fed Doses, 0.5 Hours Apart

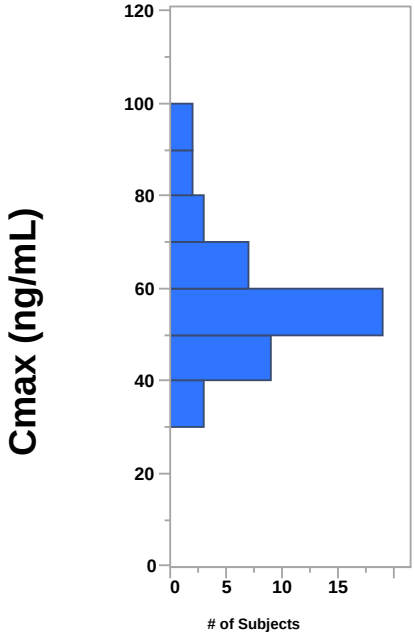


PRN IR Oxycodone
Two Fed Doses, 0.5 Hours Apart

Roxicodone 15 mg (n=12)
q0.5h x 2
Fed



Avridi 15 mg (n=45)
q0.5h x 2
Fed



The maximum projected Cmax value for Avridi was lower than the maximum projected for Roxicodone

PK Modeling Conclusions: Fed Dosing of Avridi

- **Around-the-clock dosing**
  - **No efficacy or safety concerns**
- **PRN dosing**
  - **May be associated with significant delay in absorption and delayed onset of analgesia**
  - **Projected Cmax values did not exceed the upper bound of the corresponding Cmax range for Roxicodone**

None of the modeled fed Avridi dosing scenarios indicated significant safety concerns

Risk Management and Summary

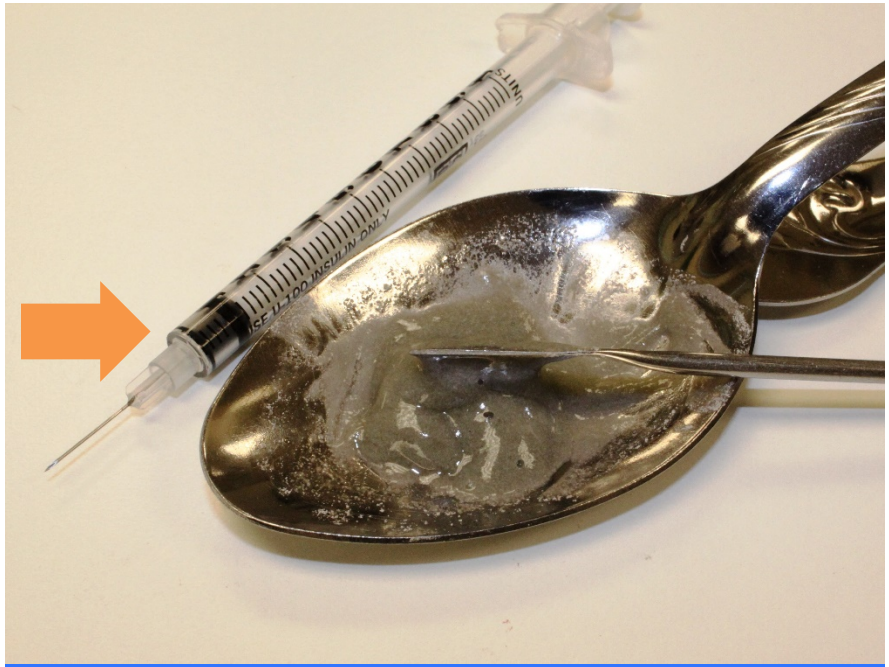
Laura Wallace, MPH

Risk Management and Epidemiology

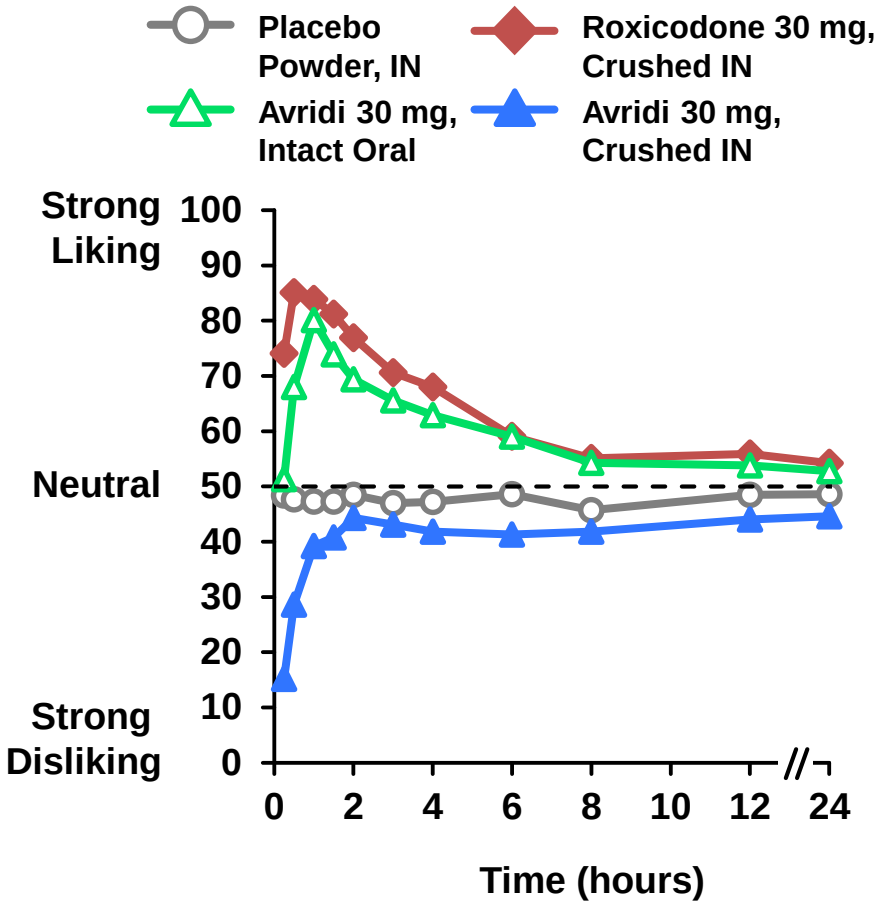
Overall Efficacy and Safety

- **Avridi tablets have similar efficacy and safety profiles to other currently approved IR single-entity oxycodone products, when taken as directed**
- **Under fasted conditions, Avridi is bioequivalent to Roxicodone, the reference drug**

Anticipated Abuse Deterrence Benefits



Avridi



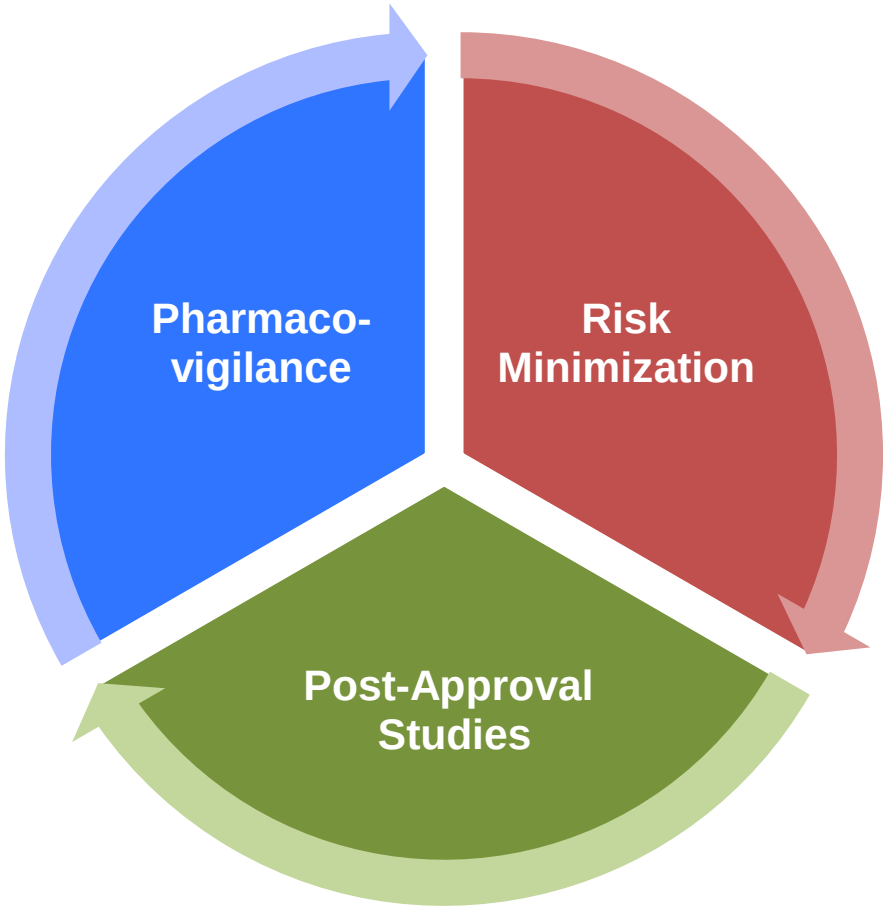
Anticipated Impact of Fed Dosing

- **If taken with food despite dosing instructions:**
  - **Potentially delayed onset of analgesia**
  - **Some patients might dose prior to recommended interval**

Clinical Considerations

- **Dosing scenario**
- **Pain patterns**
- **Lifestyle and meals**
- **Dosing needs and concomitant medications**

Risk Evaluation and Management



Pharmacovigilance

- **For known and well-characterized class risks**

Abuse Related Risks	Adverse Events	Tolerability Effects
▪ Abuse, misuse, addiction, and diversion	▪ Respiratory depression, hypotension, and overdose	▪ Constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia

- **Intended to detect differences in event type or frequency from what is expected for an IR oxycodone product**

Enhanced Pharmacovigilance

- **Targeted questionnaire for:**
  - **Overdose**
  - **Respiratory depression**
  - **Accidental injury AEs**
  - **Lack of efficacy**
- **Assess relationship to taking Avridi with meals**

Other Risk Management Activities

- **Proposed labeling to include a statement about the food effect**
- **Prescriber and pharmacist communications to ensure appropriate prescribing and dosing**
- **Patient information**
  - **Formulation-specific patient counseling information stating, “Avridi should be taken on an empty stomach, at least one hour prior to, or two hours after eating.”**

Studies of Avridi's Impact on Abuse

- **Postmarketing research program to assess levels of abuse of Avridi relative to existing formulations of IR single entity oxycodone products without abuse-deterrent properties, as well as other opioid analgesics**
- **In accordance with the FDA 2015 Guidance to Industry: *Abuse-Deterrent Opioids – Evaluation and Labeling***

Conclusions

- **Avridi is expected to provide favorable benefit-risk profile compared to other approved IR oxycodone products**
- **No notable increased risk based on anticipated effect of fed dosing**
- **Anticipated meaningful impact on reducing abuse by the high-risk IV and IN routes**

ATC Avridi Fed Dosing Scenario
Projected Mean Steady-State PK Profiles