IV Oliceridine for the Management of Moderate-to-Severe Acute Pain in Hospital or Controlled Clinical Settings

October 11, 2018

Trevena, Inc.

Meeting of the Anesthetic and Analgesic Drugs Products Advisory Committee

Introduction

Maxine Gowen, PhD

Founding President and CEO

Trevena, Inc.

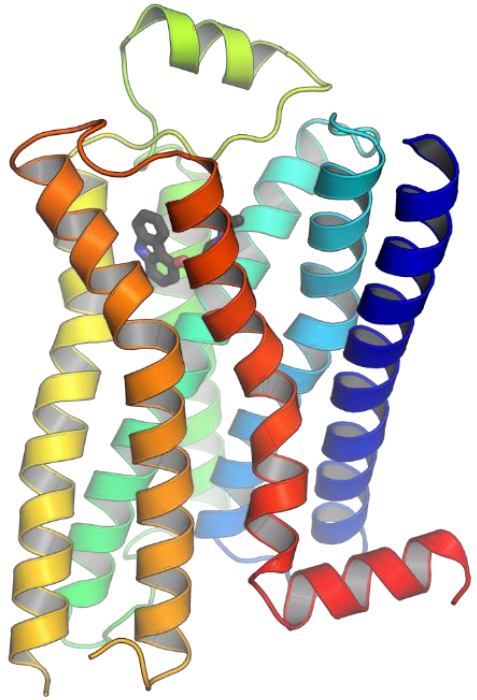
Overview of IV Oliceridine for Management of Moderate-to-Severe Acute Pain

- New chemical entity with novel mechanism of action
- Designed to deliver pain relief of conventional IV opioid with fewer opioid-related adverse events (ORAEs)
  - Improving benefit-risk profile for patients
- First new opioid molecule in decades

Oliceridine Scientific History

- Trevena founded in 2008 to translate GPCR discoveries into better medicines
- Lab of Robert Lefkowitz, Duke University
  - 2012 Nobel Prize in Chemistry for work on GPCRs

G Protein-Coupled Receptor (GPCR)

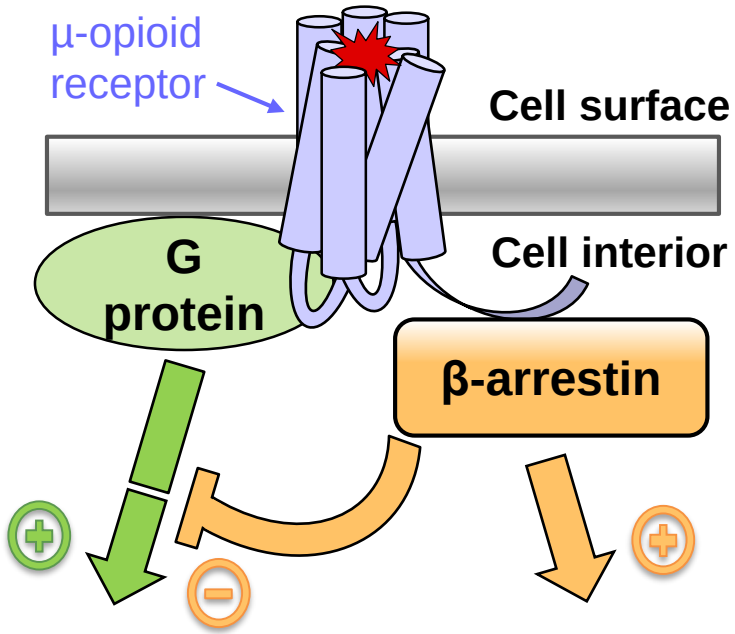


Prior Theory on GPCRs, Including μ-Opioid Receptor

- Operated like light switch
  - ON by agonist like morphine
  - OFF by antagonists like naloxone
- Beneficial and adverse effects inseparable
- Opioid analgesia only obtained with associated ORAEs

New Hypothesis: GPCRs Have Distinct Signaling Pathways

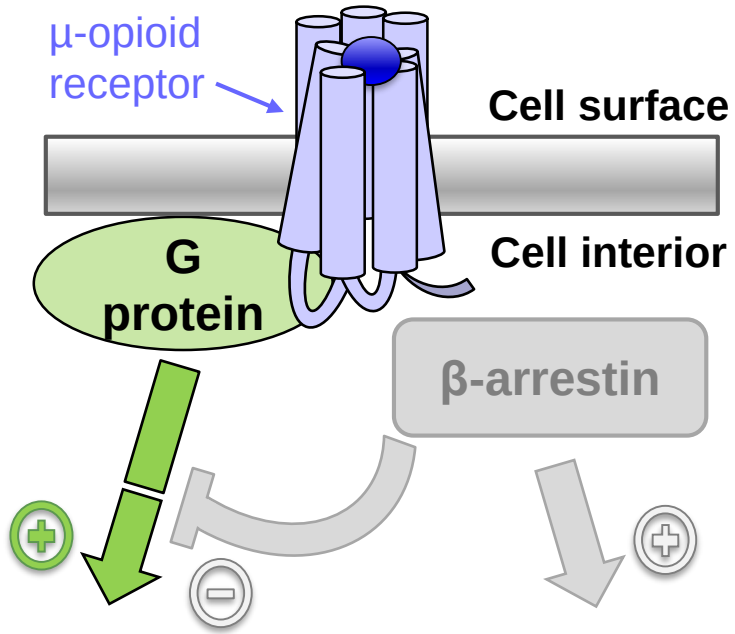
Conventional Opioids



Analgesia
Respiratory Depression
Nausea / Vomiting
Liking / Dependence

Respiratory Depression
Nausea / Vomiting

Oliceridine



Hypothesis (vs Conventional Opioids):

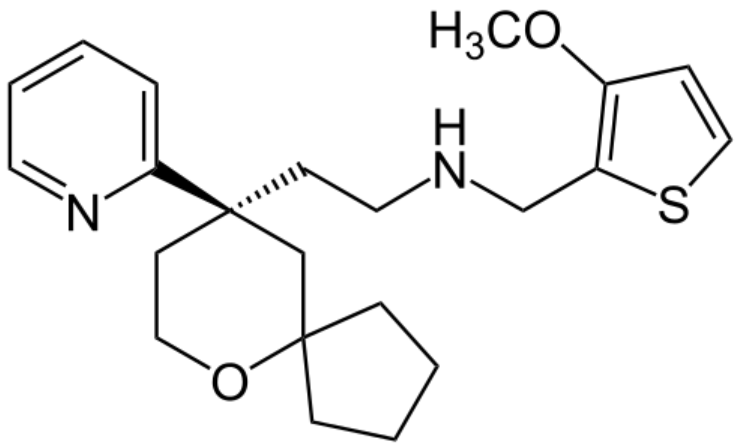
- Similar Analgesia
- Similar Liking / Dependence
- Less Respiratory Depression
- Less Nausea / Vomiting

Violin & Lefkowitz. *Trends Pharmacol Sci* 2007.
Siuda et al. *Curr Opin Pharmacol* 2017.

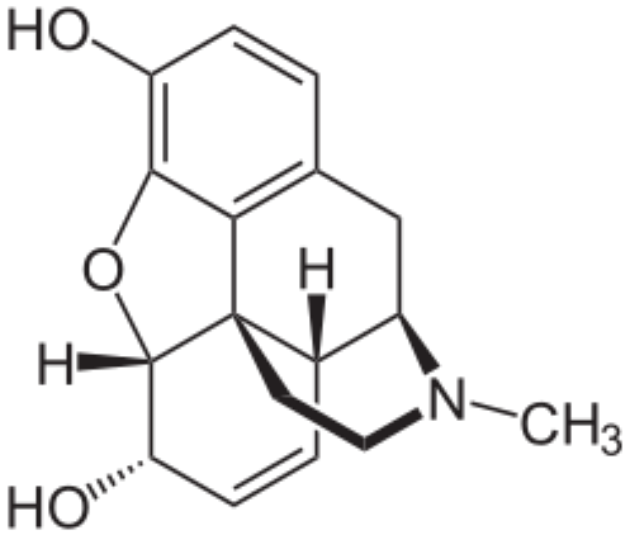
IV Oliceridine: G-Protein Biased Ligand at μ-Opioid Receptor (MOR)

- Novel MoA designed to optimize MOR pharmacology
- New chemical entity; not derivative of opium

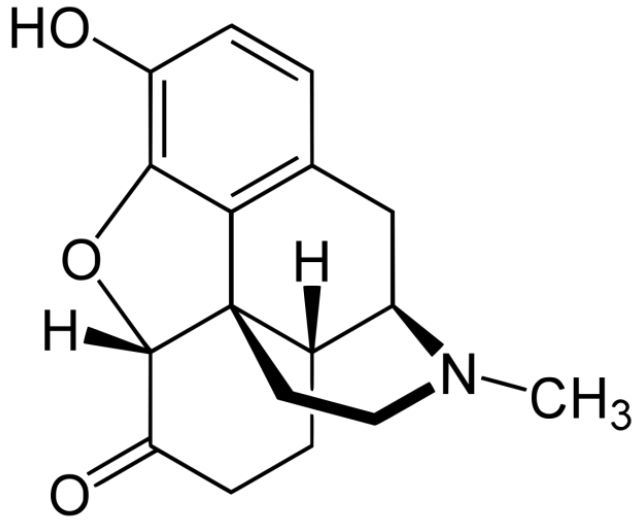
Oliceridine



Morphine



Hydromorphone



IV Opioids Essential Treatment Option for Moderate-to-Severe Acute Pain in Hospital or Controlled Setting

- Optimizing multimodal therapy and ERAS protocols
  - Reduced need for IV opioids for many procedures
- IV opioids still often necessary
  - Pain more severe, deep/visceral, longer duration
- 45 million patients received IV opioids in US hospitals[1]

ERAS: enhanced recovery after surgery

1. IQVIA Hospital Charge Detail Master Database, 2017.

Limitations of Conventional IV Opioids

- ORAEs
  - Nausea, vomiting, and respiratory depression
- Narrow therapeutic windows
  - Small dose range effective without leading to ORAEs
- Active metabolites
  - Complicates analgesic and side effect profile

IV Oliceridine in Context of Ongoing Opioid Crisis

- Schedule II product with same mandatory restrictions as other IV opioids
- Reversible by naloxone
- Not expected to affect opioid abuse crisis
  - Short-term IV use only
  - Used only in hospital or other controlled clinical setting
  - Substitute for current IV opioids

Unique Features of Oliceridine Development Program

- IV oliceridine studied in > 1,800 individuals in 17 clinical trials
- Included IV morphine as active comparator
- Used as needed (PRN) dosing
- Studied respiratory safety
  - Experimental gold standard VRH test
  - No accepted clinical endpoint for respiratory depression
    - Variety of different measures

VRH: ventilatory response to hypercapnia

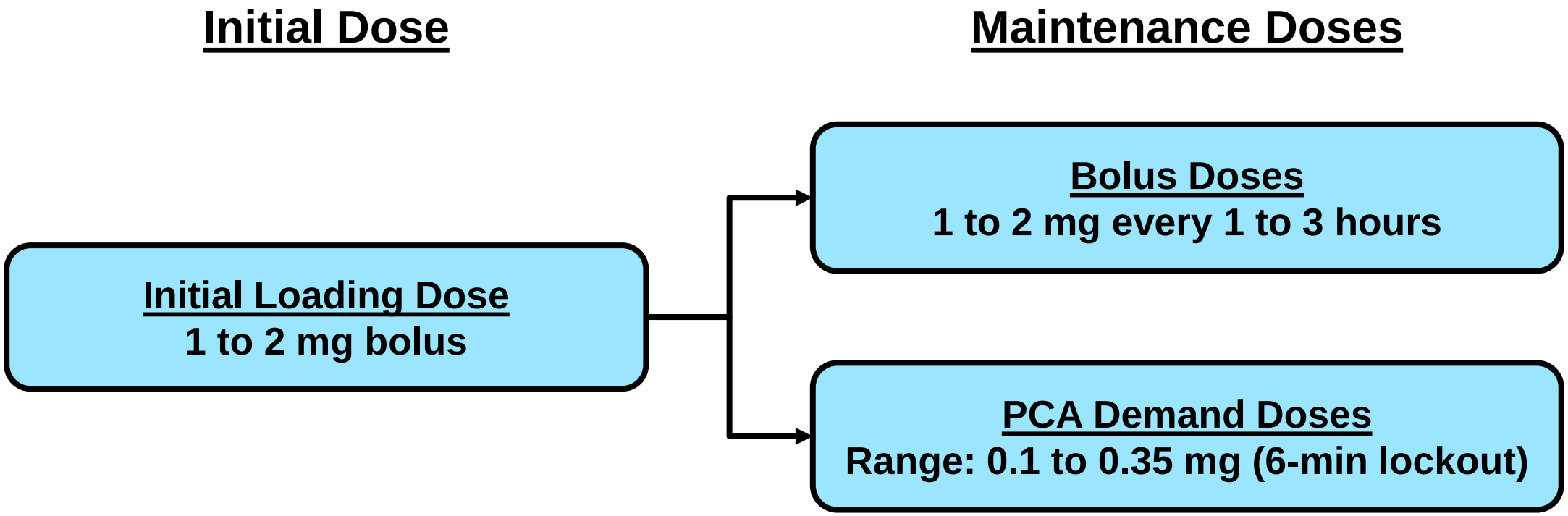
IV Oliceridine Key Efficacy and Safety Findings

- Met efficacy requirements for approval
  - Superior to placebo in both Phase 3 studies
- Safe for intended use
  - Evaluated full safe and efficacious dose range
  - Expert review found no clinically significant hepatic or cardiac safety issues
- Delivered sufficient analgesia similar to morphine
- Supportive evidence of safety benefit vs morphine across multiple safety measures, studies, and interventions
  - Not seeking label claim

Oliceridine Proposed Indication

- Oliceridine is a G protein-biased ligand at the mu-opioid receptor indicated for the management of moderate-to-severe acute pain in adult patients for whom an intravenous opioid is warranted.
- Administration supervised by trained medical personnel
  - Acute use only
  - Hospital or other controlled setting

Oliceridine Proposed Dosing



- Maximum single bolus dose of 3 mg
- Maximum daily dose of 40 mg

Agenda

Efficacy and Safety	**Mark A Demitrack, MD** Chief Medical Officer Trevena, Inc.
Special Safety Topics	**Paul Watkins, MD** Professor of Medicine, Toxicology, and Experimental Therapeutics University of North Carolina at Chapel Hill **Robert B Kleiman, MD** Chief Medical Officer, Vice President Global Cardiology eResearch Technology
Opioid-Related Adverse Events	**Jonathan Violin, PhD** Co-founder and Senior Vice President of Scientific Affairs Trevena, Inc.
Clinical Perspective	**Gregory Hammer, MD** Professor of Anesthesiology, Perioperative and Pain Medicine and of Pediatrics (Critical Care) Stanford University Medical Center

Additional Experts

Statistics	**David Burt, PhD** Senior Director, Biostatistics Trevena, Inc.
Clinical Pharmacology	**Michael Fossler, PharmD, PhD** Vice President, Clinical Operations & Quantitative Sciences Trevena, Inc.
Human Abuse Liability **Opioid-induced Respiratory Depression**	**Lynn Webster, MD** Vice President, Scientific Affairs PRA Health Sciences

Efficacy and Safety

Mark A Demitrack, MD

Chief Medical Officer

Trevena, Inc.

Efficacy and Safety Supported by Phase 2 and Phase 3 Studies

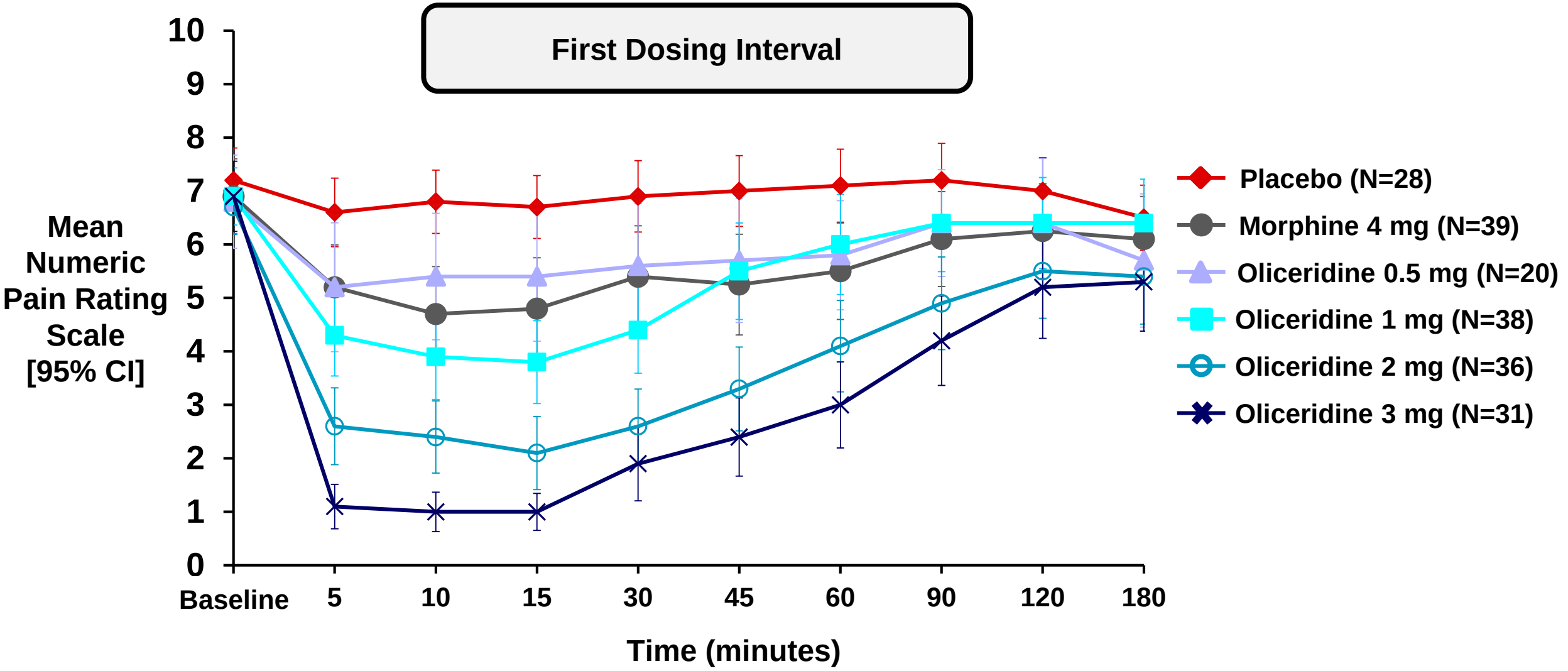
Study (Phase)	Pain Model (Design)	N Treated	Dosing
Study 2001 (Phase 2a)	Bunionectomy (RCT)	333	Fixed
Study 2002 (Phase 2b)	Abdominoplasty (RCT)	200	As Needed (PRN)
APOLLO 1 (Phase 3)	Bunionectomy (RCT)	389	
APOLLO 2 (Phase 3)	Abdominoplasty (RCT)	401	
ATHENA (Phase 3)	Diverse settings (Open-label)	768	PRN

- IV morphine comparator in controlled studies

Phase 2a Bunionectomy Study (Study 2001)

- 333 randomized and treated patients
- Explored range of oliceridine dose strengths and intervals
  - Placebo and morphine 4 mg comparators
- Clearest assessment of onset, magnitude, and duration

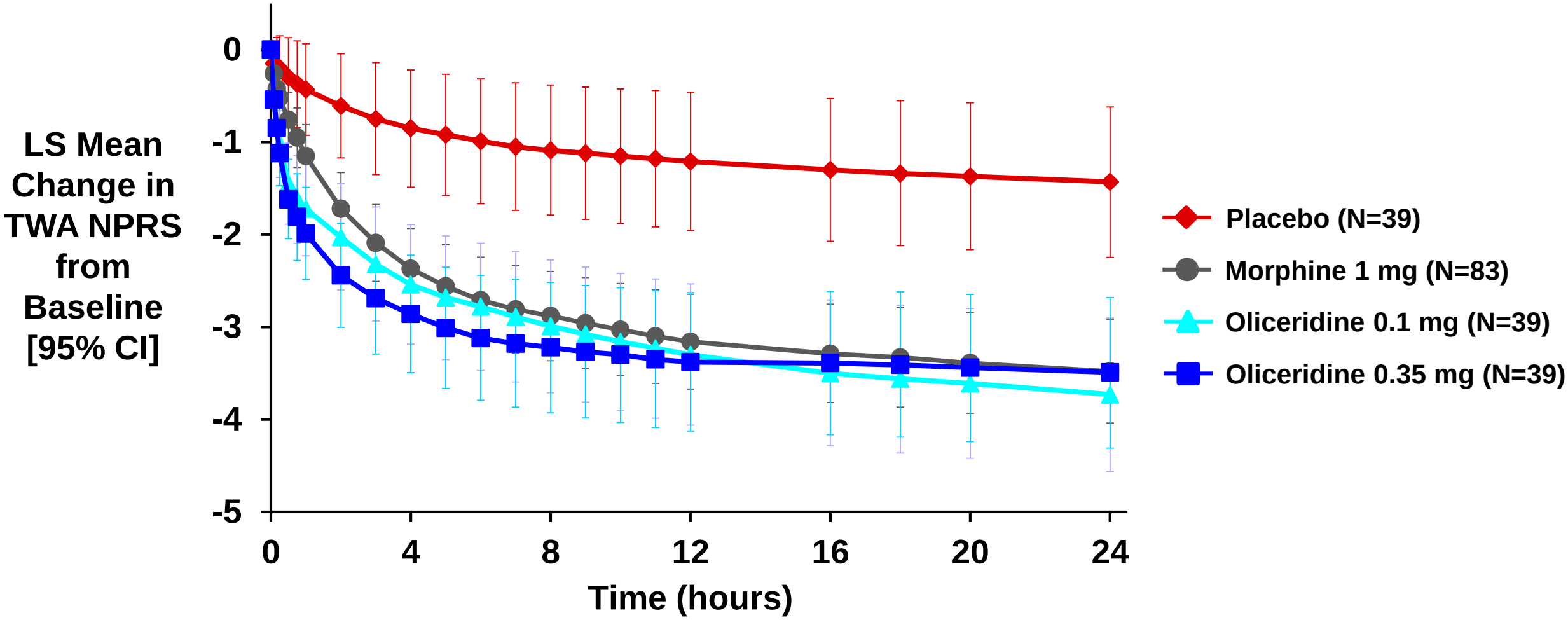
Phase 2a (Bunionectomy): Fixed Doses of Oliceridine Provided Efficacy for Moderate-to-Severe Acute Pain



Phase 2b Abdominoplasty Study (Study 2002)

- 200 patients randomized and treated
- PRN dosing to reflect clinical practice
  - Oliceridine: 1.5 mg loading with 0.1 or 0.35 mg demand doses
  - Morphine: 4 mg loading with 1 mg demand dose
  - Placebo
- 6-minute lockout intervals

Phase 2b (Abdominoplasty): Oliceridine Statistically Significant Pain Reductions vs Placebo, Similar to Morphine



Last observation carried forward (LOCF) imputation for rescue medication
TWA NPRS: time-weighted average in numeric pain rating scale

Phase 3 Bunionectomy (APOLLO 1) and Abdominoplasty (APOLLO 2) Studies

Studies 3001 and 3002

APOLLO 1 and APOLLO 2 Study Designs

Design Element	APOLLO 1	APOLLO 2
Acute pain model	Bunionectomy (hard tissue)	Abdominoplasty (soft tissue)
N randomized and treated	389	401
Treatment period	48 hours	24 hours
Anesthesia	Regional (popliteal sciatic nerve block)	General
Pain entry criteria	NRS ≥ 4 within 9 hours after discontinuation of regional anesthesia	NRS ≥ 5 within 4 hours from end of surgery

APOLLO 1 and APOLLO 2: Treatment Regimens

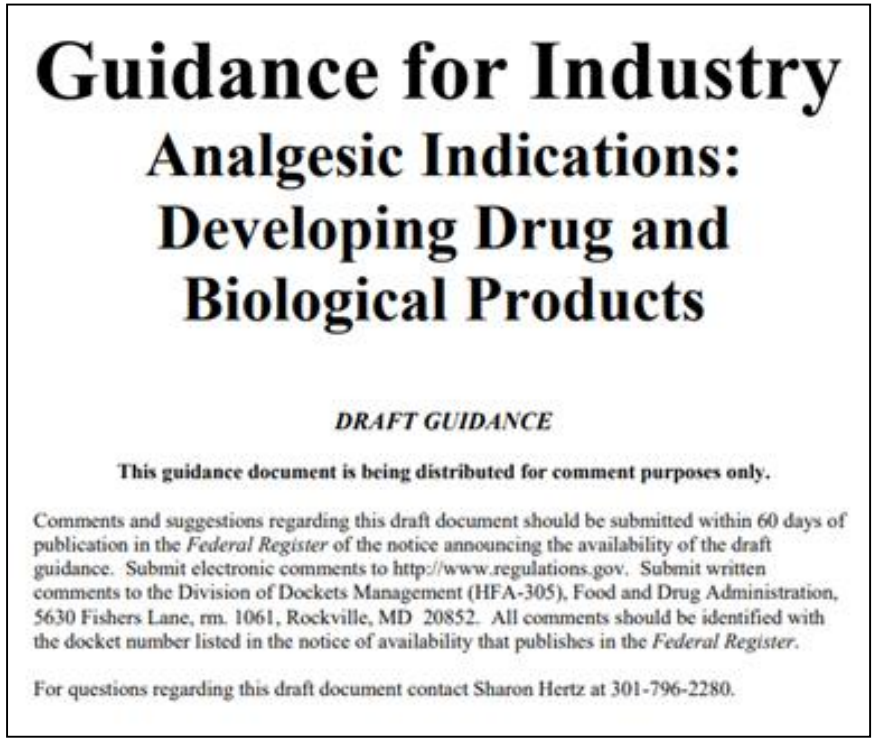
Nominal Dose	Clinician-administered Loading Dose	Patient-administered Demand Dose	Clinician-administered Supplemental Dose
Oliceridine 0.1 mg	1.5 mg	0.1 mg	0.75 mg q1h PRN
Oliceridine 0.35 mg		0.35 mg	
Oliceridine 0.5 mg		0.5 mg	
Morphine	4 mg	1 mg	2 mg q1h PRN
Placebo	Volume-matched solution	Volume-matched solution	Volume-matched solution

- Monotherapy protocol: multimodal therapy not allowed
- Rescue pain medication: etodolac 200 mg q6h PRN

Considerations for Analysis of IV Opioid Efficacy with PRN Dosing

- Treatment paradigm with opioid analgesics
  - Patients should receive what they need and no more
- Sufficiency, not magnitude, of efficacy most clinically relevant
- Efficacy greater than adequate should not be considered benefit
  - Reflects unnecessary opioid exposure and added risk
- Analyses focused on magnitude alone may bias towards treating patients with more opioid than needed
- Pre-specified treatment responder primary endpoint that measures both efficacy and tolerability

FDA Guidance Document Acknowledges Responder Analyses as Appropriate Primary Efficacy Endpoints



Guidance for Industry

Analgesic Indications: Developing Drug and Biological Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Sharon Hertz at 301-796-2280.

Section 11a – Demonstrating efficacy

"A responder analysis, in which the outcome for each subject is summarized as a success or a failure based on a single cut-off point (e.g., 30 percent reduction in pain (with early discontinuation counted as a failure)), can be used… such analyses are easy for clinicians to interpret, and they can greatly mitigate the problems of missing data."

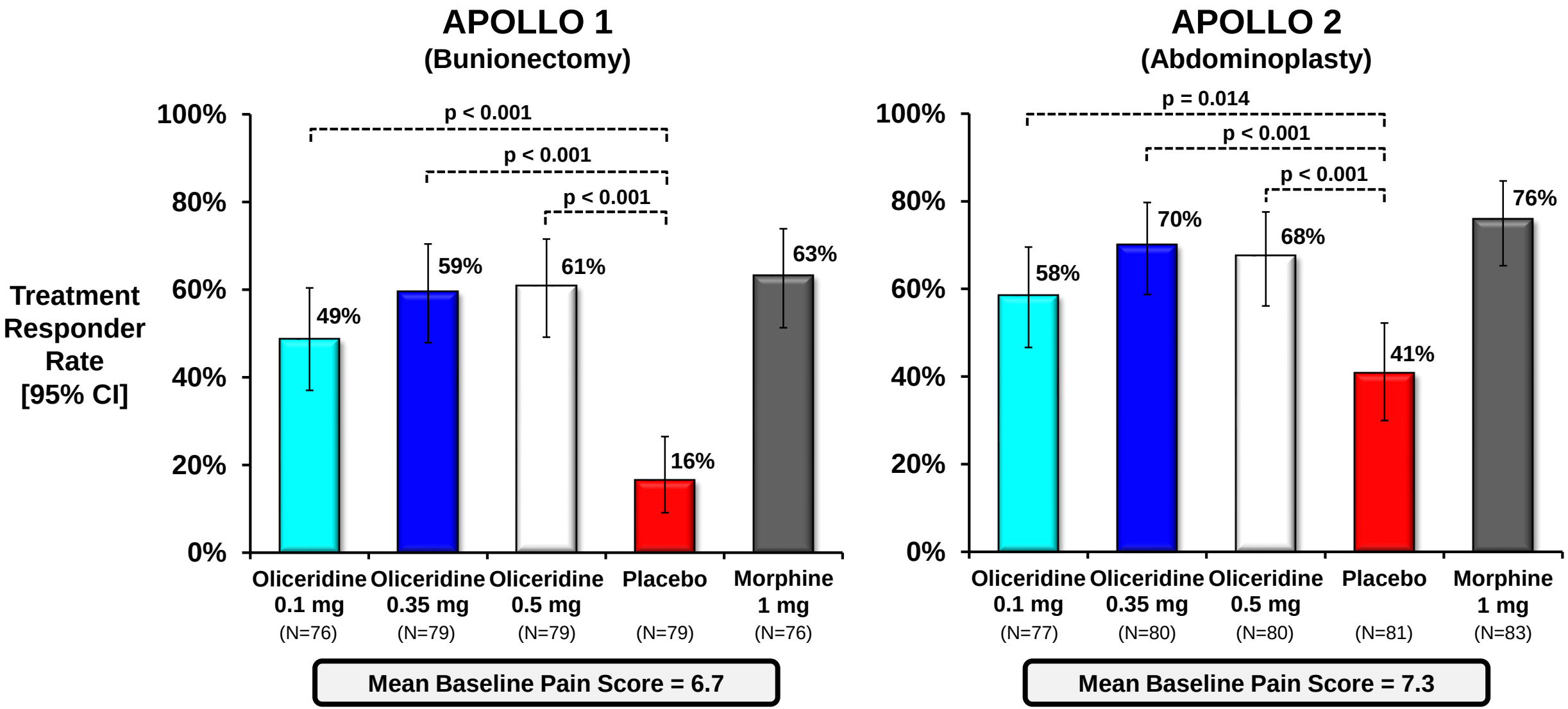
FDA. Draft Guidance for Industry: Analgesic Indications: Developing Drug and Biological Products. Feb 2014.

APOLLO 1 and APOLLO 2 Primary Endpoint

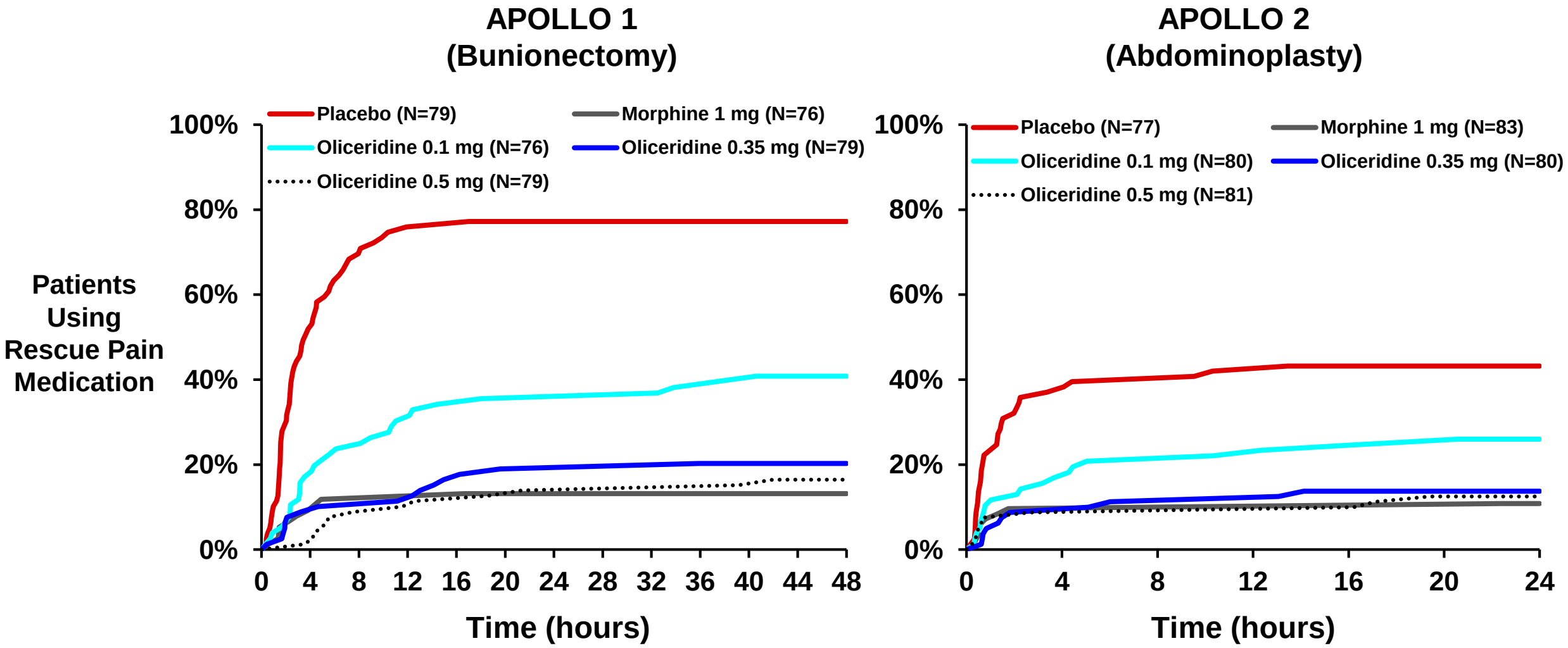
- Treatment responder if all 4 criteria met
  - ≥ 30% improvement in SPID
  - Without rescue pain medication
  - Without early discontinuation
  - Without reaching study medication dosing limit
- No imputation required for rescue medication or discontinuation
- Primary efficacy analysis vs placebo
- Analysis considerations incorporated at FDA request
  - Account for use of analgesics outside of rescue pain medication
  - Multiple imputation for missing data

SPID: sum of pain intensity differences

All Oliceridine Regimens Met Primary Endpoint



Time to First Use of Rescue Medication Consistent with Results of Primary Endpoint



Efficacy Analyses
Evaluating Sufficiency vs Magnitude

Clinical Meaningfulness of Efficacy Analyses

Efficacy Consideration	Treatment Responder	SPID with Imputations
Change in Pain Score	> 30% is adequate	Greater is better
Rescue Pain Medication	Non-responder (inadequate analgesia or lack of tolerability)	LOCF for duration of labeled dosing interval
Discontinue Study Medication for Lack of Efficacy		Not accounted for
Discontinue Study Medication for AE		Not accounted for
Discontinue Study for Lack of Efficacy		LOCF to end of treatment period
Discontinue Study for AE		BOCF to end of treatment period
What does it measure?	**Sufficiency, Comfort**	**Magnitude, Intensity**

BOCF: baseline observation carried forward

Focus on Magnitude of Efficacy Alone Favors Higher Opioid Doses

APOLLO 1 Efficacy Measure	Placebo	Oliceridine 0.35 mg	Oliceridine 0.5 mg
SPID48-LOCF-6hr (placebo-corrected)	0	27	51
Primary endpoint (treatment responder)	16%	59%	61%
Did not use rescue medication	23%	80%	84%
Discontinuation for lack of efficacy	34%	4%	5%
Patient dissatisfied (mostly/completely)	47%	10%	11%
Clinician dissatisfied (mostly/completely)	46%	8%	11%

SPID-LOCF suggests 0.5 mg twice as efficacious as 0.35 mg

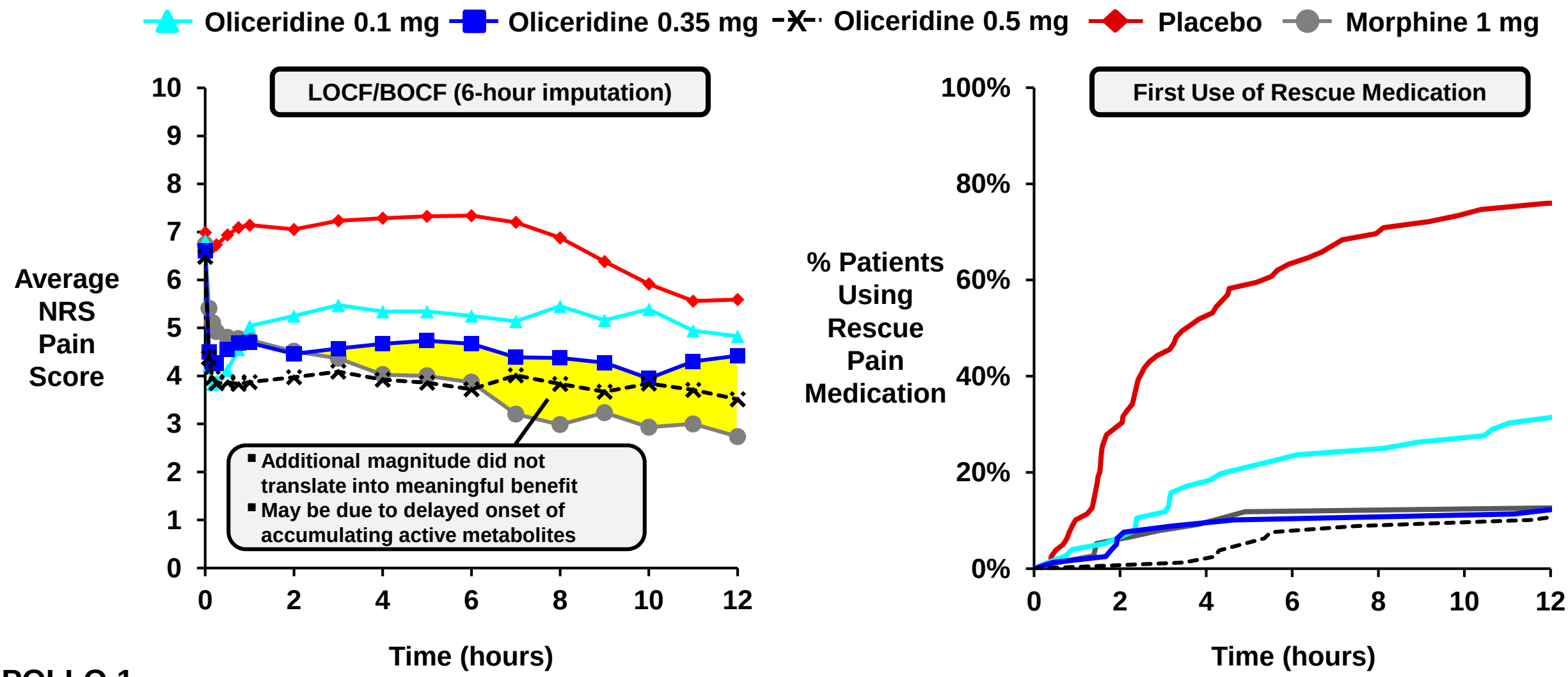
Additional efficacy measures suggest 0.35 and 0.5 mg offer comparably sufficient analgesia

SPID-LOCF

- Favors higher doses
- As primary efficacy measure, misaligned with goal of minimizing opioid exposure

APOLLO 1

Differences in Pain Scores May Not Represent Clinically Meaningful Differences in Efficacy



APOLLO 1

Summary of Efficacy Findings

- Oliceridine is efficacious IV opioid
- Evaluated broad range of doses and regimens
- Met primary endpoint vs placebo in pivotal studies
- Secondary endpoints support sufficiency of 0.1 and 0.35 mg regimens
  - No added benefit of 0.5 mg regimen
- PCA dosing regimens sought for approval
  - Initial loading dose 1 to 2 mg
  - Range of demand doses 0.1 to 0.35 mg

Safety

Incidence (%) of AEs by Treatment Regimen

Adverse Event, %	Oliceridine 0.1 mg N=153	Oliceridine 0.35 mg N=158	Oliceridine 0.5 mg N=159	Placebo N=162	Morphine N=158
Any AE	82	90	93	73	97
AE leading to discontinuation	0	3.2	5.7	0	5.1
SAE	0	0.6	2.5	0	0.6
Severe AE	5.9	6.3	6.9	3.1	8.9
Deaths	0	0	0	0	0

Pooled APOLLO Studies

Phase 3 Open-Label ATHENA Study

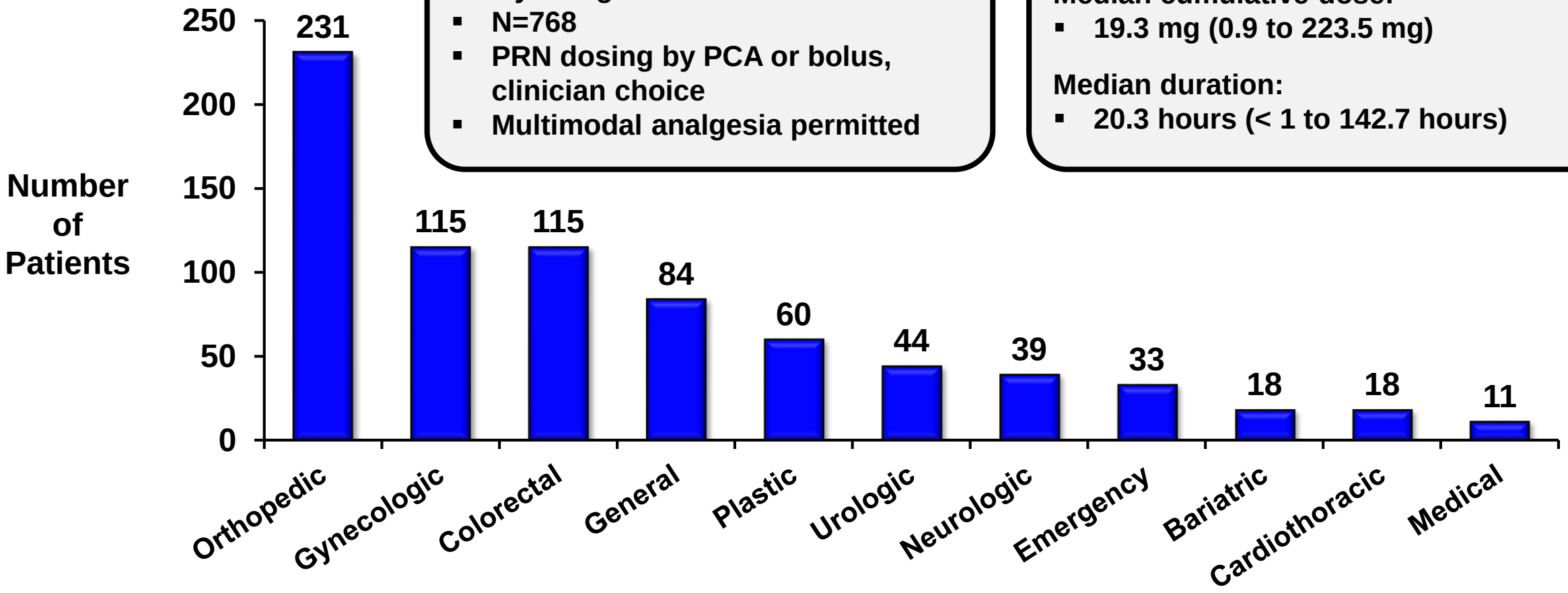
Study 3003

Broad Surgical, Medical, and Emergency Department Patient Population Treated in ATHENA

Study design features:
- N=768
- PRN dosing by PCA or bolus, clinician choice
- Multimodal analgesia permitted

Median cumulative dose:
- 19.3 mg (0.9 to 223.5 mg)

Median duration:
- 20.3 hours (< 1 to 142.7 hours)



Key Findings from ATHENA Consistent with APOLLO Studies

- ATHENA patients older with more comorbidities (32% ≥ 65 years)
- Safety and tolerability similar to APOLLO studies
  - 91% completed study using oliceridine
  - 4.3% discontinued for lack of efficacy
  - 2.2% discontinued for AE
  - 3.4% experienced an SAE
  - No deaths
- No differences in safety between bolus and PCA treatment conditions
- No new safety signal in larger, more diverse general acute pain patient population with more comorbid conditions

Special Safety Topics

Hepatic Safety

Cardiac Safety

Clinical Interpretation of Hepatic Findings

Paul Watkins, MD

Howard Q Ferguson Distinguished Professor

Schools of Medicine, Pharmacy and Public Health

Director, Institute for Drug Safety Sciences

University of North Carolina at Chapel Hill

Expert Panel of Hepatologists Convened to Assess Causality

Paul B Watkins, MD (Chair)
Howard Q Ferguson Distinguished Professor
Schools of Medicine, Pharmacy and Public Health
Director, Institute for Drug Safety Sciences
University of North Carolina

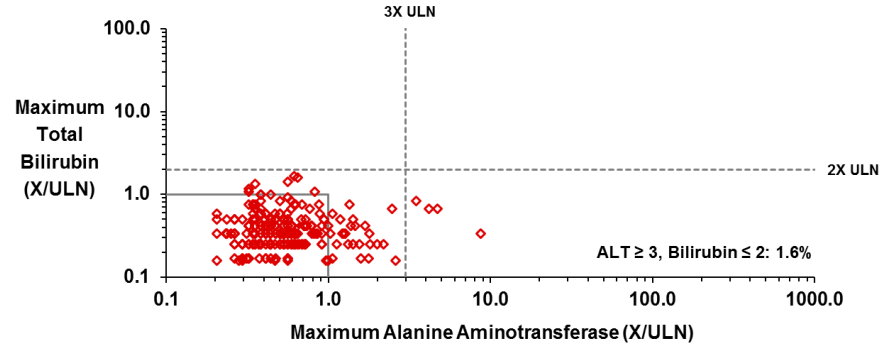
Neil Kaplowitz, MD
Thomas H Brem Professor
Chief, Division of Gastroenterology and Liver Diseases
Keck School of Medicine
University of Southern California

Hans Tillmann, MD
Clinical Associate Professor
East Carolina University
Brody School of Medicine

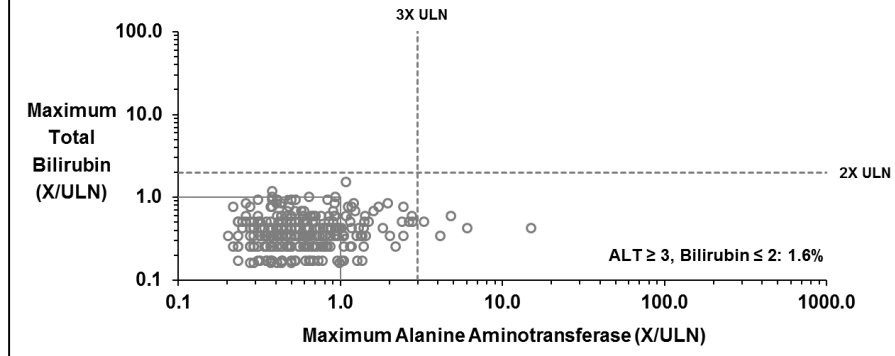
Donald C Rockey, MD
Chair, Department of Medicine
Medical University of South Carolina

eDISH Plots for Controlled Phase 2 and 3 Studies

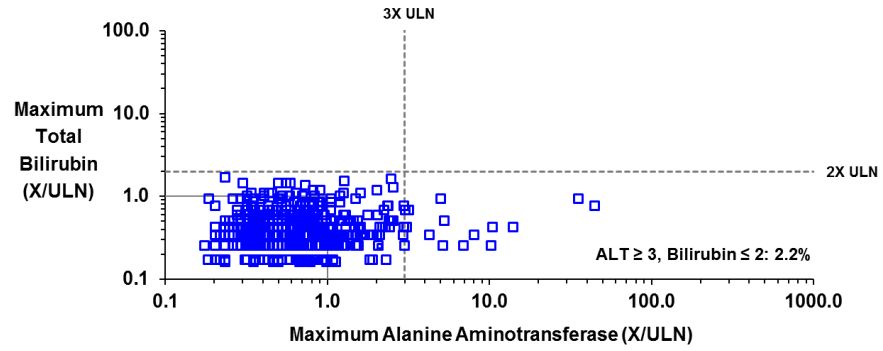
eDISH Plots for Placebo in Controlled Phase 2 and 3 Studies (N=252)



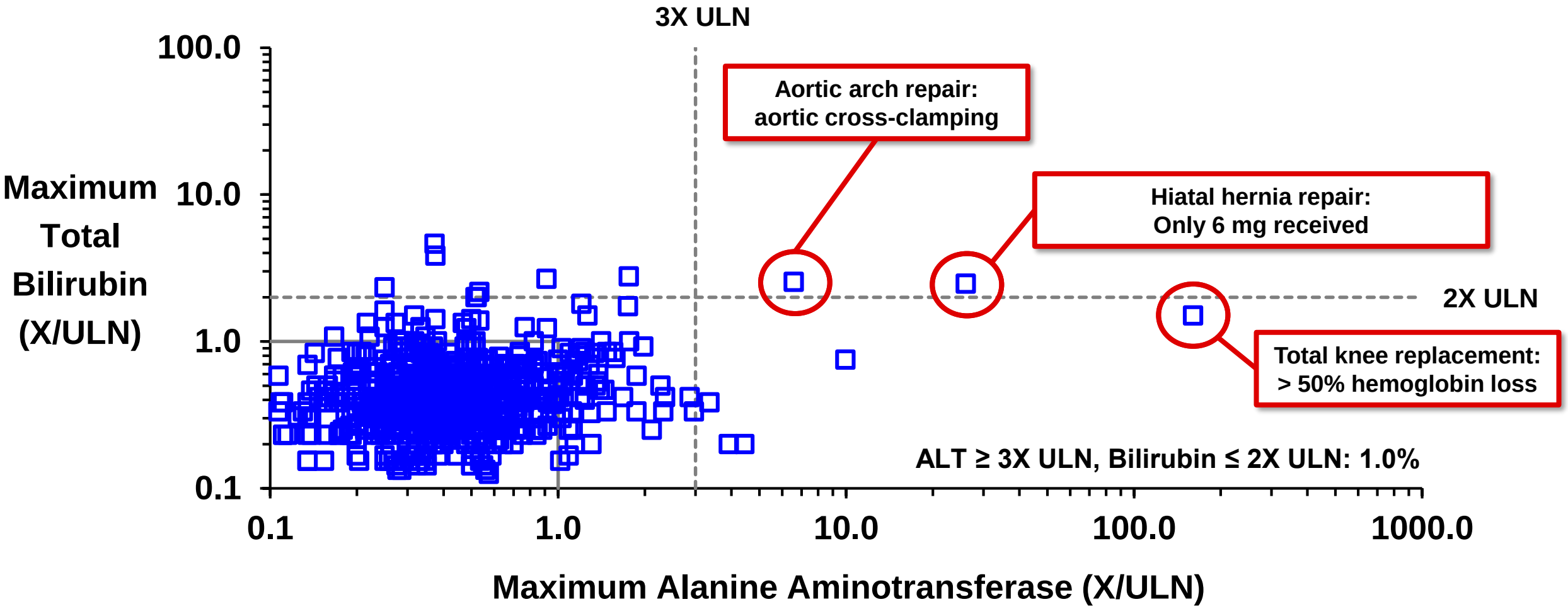
eDISH Plots for Morphine in Controlled Phase 2 and 3 Studies (N=305)



eDISH Plots for Oliceridine in Controlled Phase 2 and 3 Studies (N=767)



eDISH Plot for Oliceridine in Open-Label ATHENA Study (N=706)



Additional Considerations for Hepatic Safety

- No preclinical liver safety signal
- No relationship between dose of oliceridine received and liver events
- Total dose of oliceridine received low and duration of treatment too short to cause DILI
- Similar events were seen in placebo and morphine cases
  - Suggesting population or procedure-related risk factors

Current Data Do Not Suggest Clinically Significant Hepatic Safety Risk of Oliceridine

- Unanimous consensus of expert hepatologist panel
  - No liver events likely result of treatment with oliceridine
  - No evidence of clinically significant liver safety signal with oliceridine

Cardiac Safety

Robert B Kleiman, MD

Chief Medical Officer, Vice President Global Cardiology

eResearch Technology

Expert Cardiologists Convened to Evaluate Oliceridine's Cardiac Safety

Robert B Kleiman, MD
Chief Medical Officer,
Vice President Global Cardiology
eResearch Technology

Peter R Kowey, MD
Professor of Medicine and Clinical Pharmacology
Jefferson Medical College of Thomas Jefferson University

Emeritus Chair, Lankenau Heart Institute
William Wikoff Smith Chair for CV Research
Lankenau Institute for Medical Research

Overview of Evidence for Cardiac Safety of Oliceridine

- No preclinical signal
- Minor QT effect for supratherapeutic dose in tQT Study
- No QT prolongation in Phase 3 studies

No Clinically Relevant Effect of Oliceridine or Metabolites on Cardiac Ion Channels

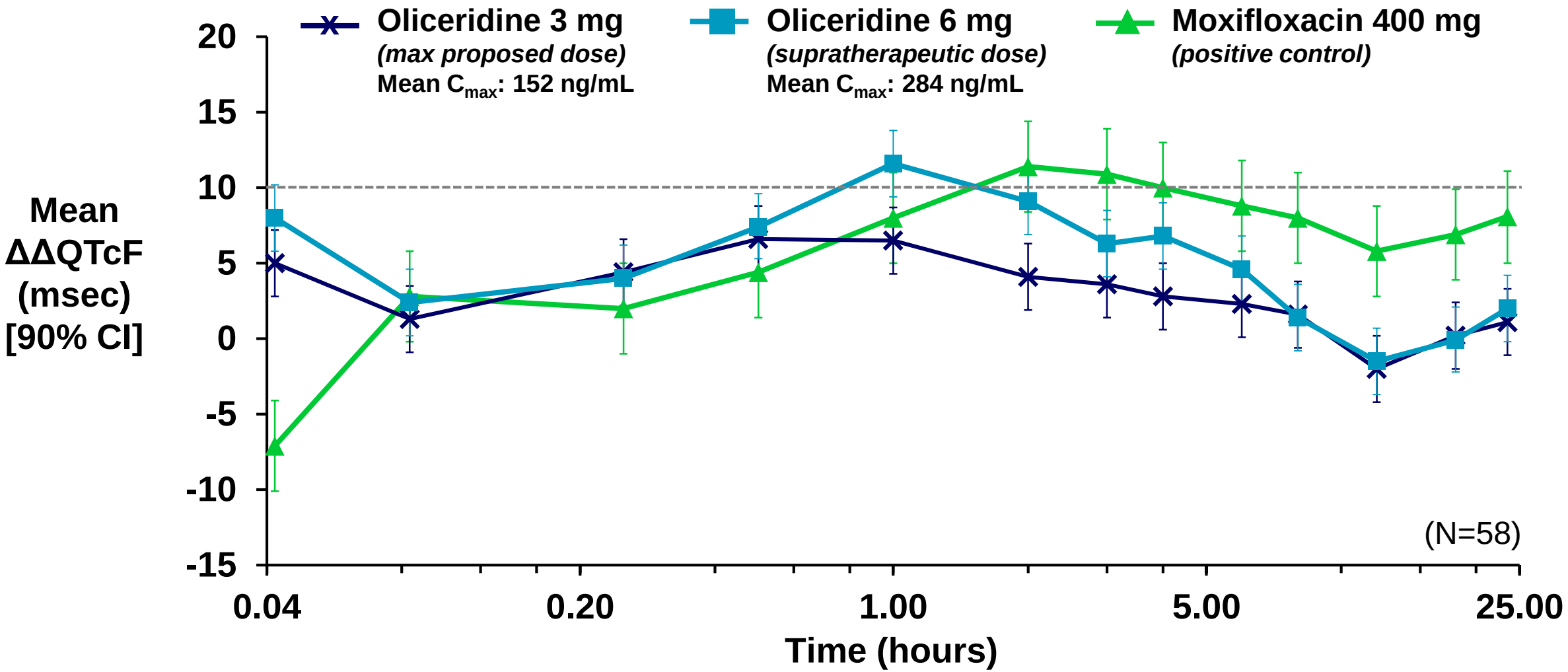
Channel	IC_{50} (Concentration blocking 50% of flow through channel)		
	Oliceridine	TRV0109662	M22
hERG	4.3 µM	> 300 µM	> 300 µM
hCav1.2	> 10 µM	> 300 µM	> 300 µM
hNav1.5 (tonic)	> 10 µM	> 300 µM	> 300 µM
hNav1.5 (phasic)	> 10 µM	> 300 µM	> 300 µM
Late hNav1.5	8.8 µM	> 300 µM	> 300 µM

- Oliceridine's major metabolites have no measurable activity at the tested channels
- IC_{50} for oliceridine at 4.3 µM (**116x** greater than maximum human exposure)
- Additional studies also showed no QT effect:
  - Isolated rabbit wedge preparation
  - Cynomolgus monkeys at 8x maximum human exposure

TQT Study Evaluated ECG Effects of Therapeutic and Supratherapeutic Oliceridine Doses

- Randomized, double-blind, placebo- and active-controlled four-period crossover study
- 58 healthy adults randomized and received at least 1 active dose
- Randomized treatment sequence
  - Placebo IV bolus over 5 min
  - Oliceridine 3 mg (max proposed dose) IV bolus over 5 min
  - Oliceridine 6 mg (supratherapeutic dose) IV bolus over 5 min
  - Moxifloxacin 400 mg PO (positive control)

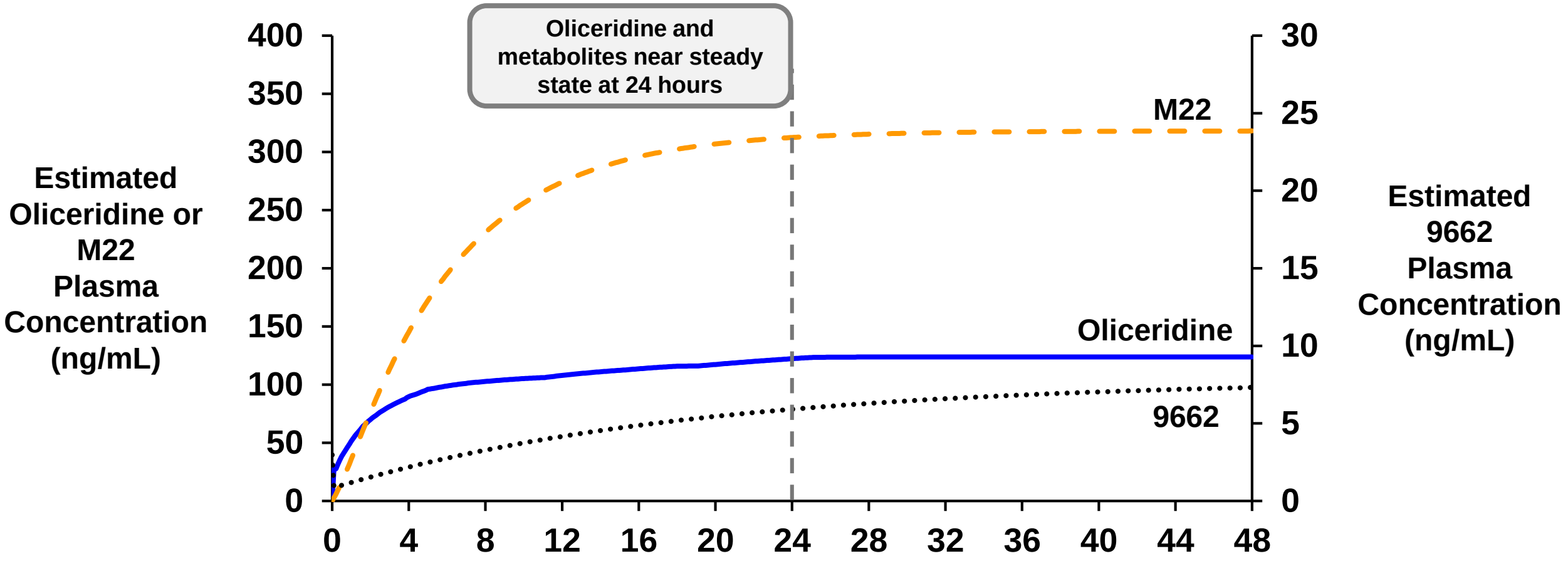
No Clinically Significant Effect of Maximum Proposed Oliceridine Dose on Cardiac Repolarization



Trevena Followed FDA Recommendations to Monitor Cardiac Safety in Phase 3

- FDA suggested ECG measurements at baseline, following first dose, and periodically at later time points
  - Sought to capture potential delayed QT effect
- Trevena incorporated ECGs for > 1,500 patients in Phase 3
  - Baseline
  - 1 hour (peak effect in tQT study)
  - 24 hours (potential delayed effects)
  - Every 24 hours thereafter (potential delayed effects)

24-Hour ECG Assessment Captures Maximum Levels of Oliceridine and Its Inactive Metabolites



Theoretical maximum dosing

- 1.5 mg loading dose
- 0.35 mg demand dose every 6 minutes

No Clinically Meaningful Differences in Incidence of QT Prolongation in Controlled Phase 3 Studies

Threshold ECG Criteria, %	Oliceridine 0.1 mg N=153	Oliceridine 0.35 mg N=158	Oliceridine 0.5 mg N=159	Placebo N=162	Morphine n=158
QTcF > 500 msec	0	0	0	0	0
QTcF change from baseline > 60 msec	0.7	0	0	0	0
QTcF change from baseline > 30 msec	9.8	7.0	8.2	7.5	8.3

ECG Assessments in ATHENA

- No control group and not designed for QT testing
- Few patients experienced QT prolongation
  - Many with QT prolongation at baseline
  - No ventricular arrhythmias
- Among patients who did not experience QT prolongation
  - 1 patient undergoing aortic valve replacement had non-sustained ventricular tachycardia

Summary of Oliceridine Cardiac Safety

- Comprehensive nonclinical program revealed no QT concerns
- tQT study: small QTc increase for supratherapeutic dose
  - Prompted enhanced ECG monitoring in Phase 3
- No differences in ECG findings in controlled Phase 3 studies
- Totality of data
  - Small QTc effect in tQT study not clinically relevant
  - Oliceridine does not pose clinically meaningful risk for drug-induced ventricular arrhythmia

Opioid-Related Adverse Events

Jonathan Violin, PhD

Co-founder and Senior Vice President of Scientific Affairs

Trevena, Inc.

Clinical Program Explored Biased Ligand Hypothesis

- Hypothesis for oliceridine
  - Provide opioid-level efficacy
  - Attenuate, but not eliminate, incidence of ORAEs
- No precedent for how to explore impact of novel MoA in clinical setting
  - Attempted to capture safety in variety of ways
  - Assessed experimental gold standard, clinically-relevant events, interventions for safety, MedDRA Preferred Terms, novel endpoints
- Goal to identify dosing regimens
  - Meaningfully reduced ORAEs
  - Provided sufficient analgesic efficacy

Respiratory Safety

- Phase 1: Gold standard VRH test for opioid-induced respiratory depression
- Phase 2 and 3: Standard and novel complementary endpoints

Phase 1 Pharmacologic Proof-of-Concept Study

- Randomized, double-blind, placebo-controlled crossover study
- 30 healthy volunteers randomized and received study drug
- 5 study periods with 2-minute IV infusions
  - Placebo, morphine 10 mg, oliceridine 1.5, 3, and 4.5 mg
- Assessed experimental models
  - Analgesic effects – cold pressor test
  - Opioid-induced respiratory depression – VRH

Cold Pressor Test Measures Analgesic Effects via Pain Tolerance

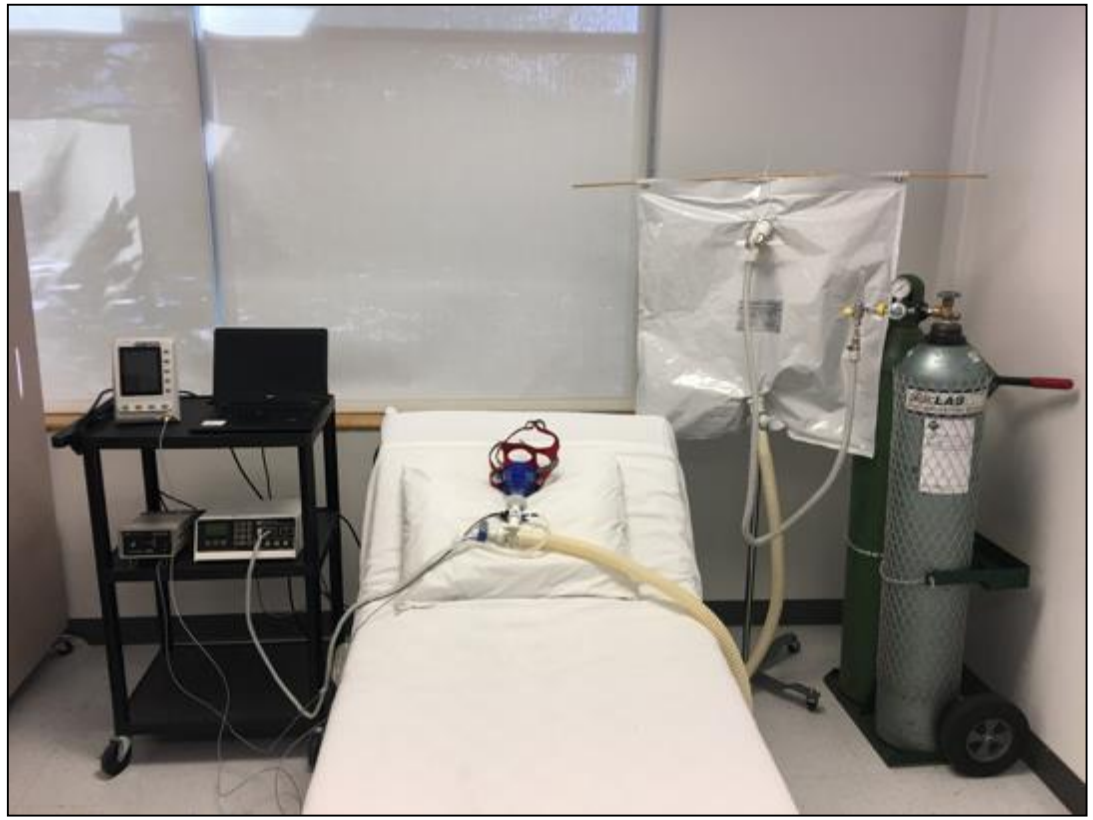
- Hand immersed in 2°C water for as long as possible (up to 180 sec)
- Analgesic effect measured as duration of hand in cold water

Cold Pressor Test

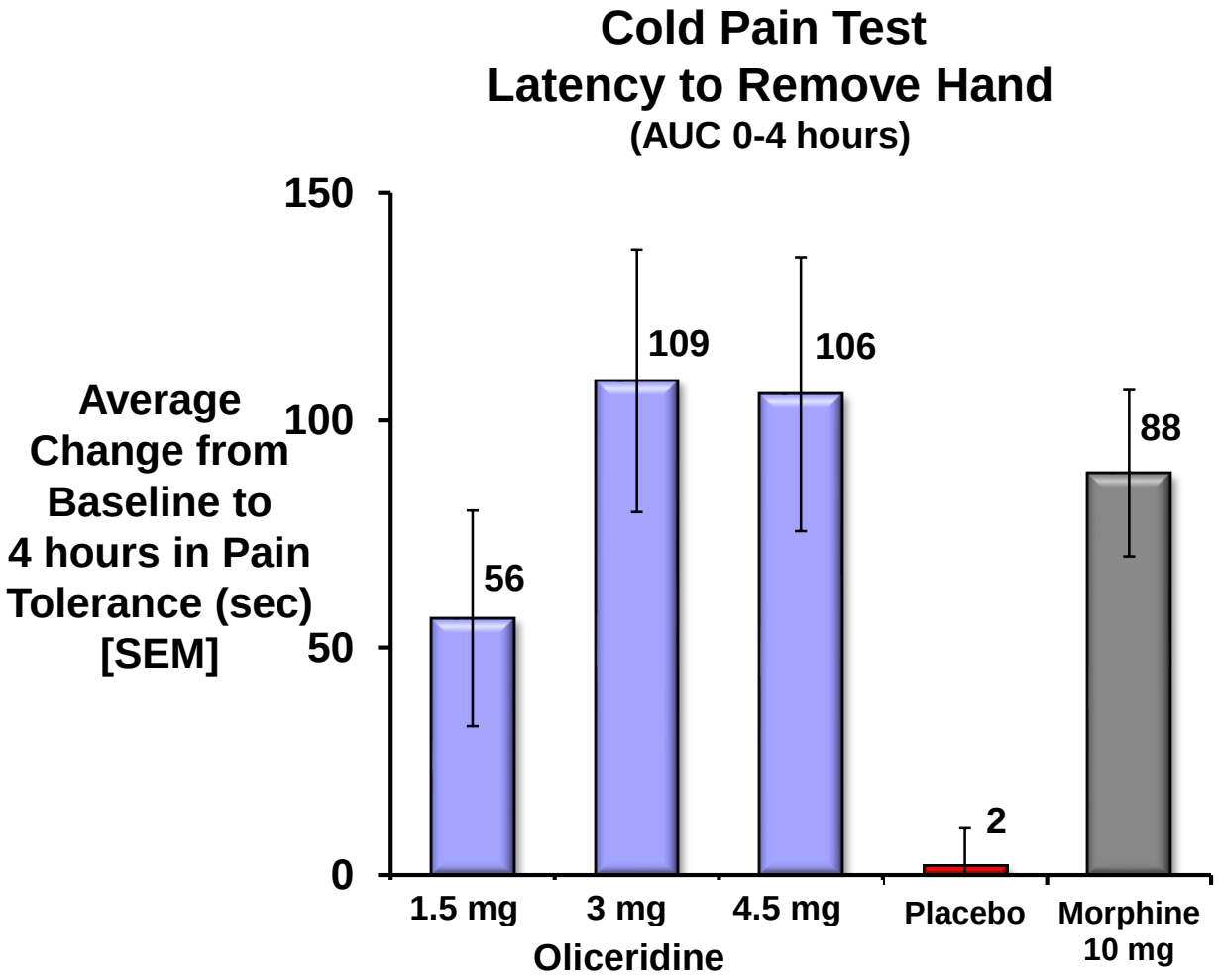
VRH Measures Respiratory Impact via Change in Ventilation

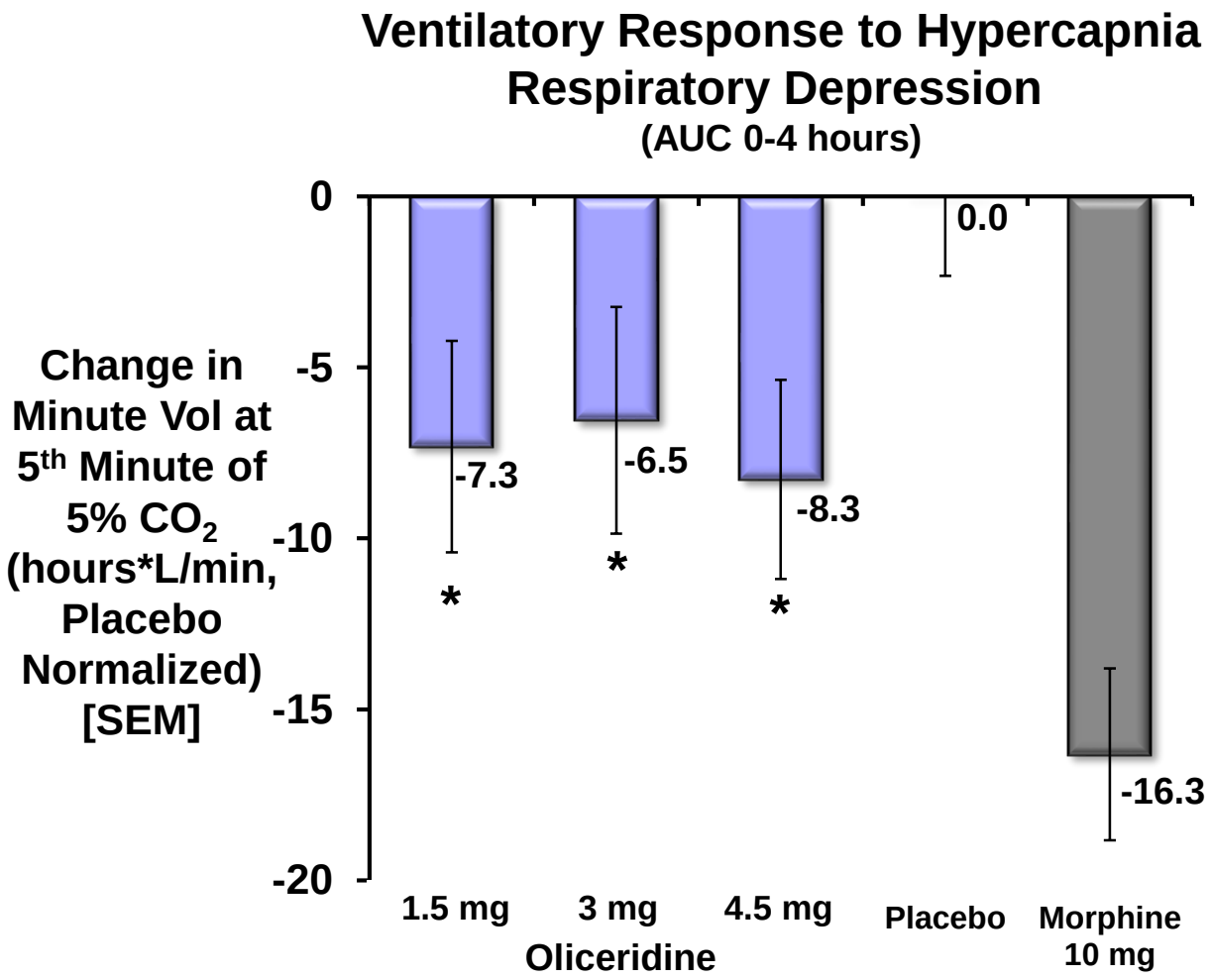
- Inhaled 5% CO_2 to experimentally induce respiratory drive
- Opioid-induced respiratory depression measured as change in minute ventilation

VRH



Oliceridine Produced Significantly Less Opioid-Induced Respiratory Depression than Morphine



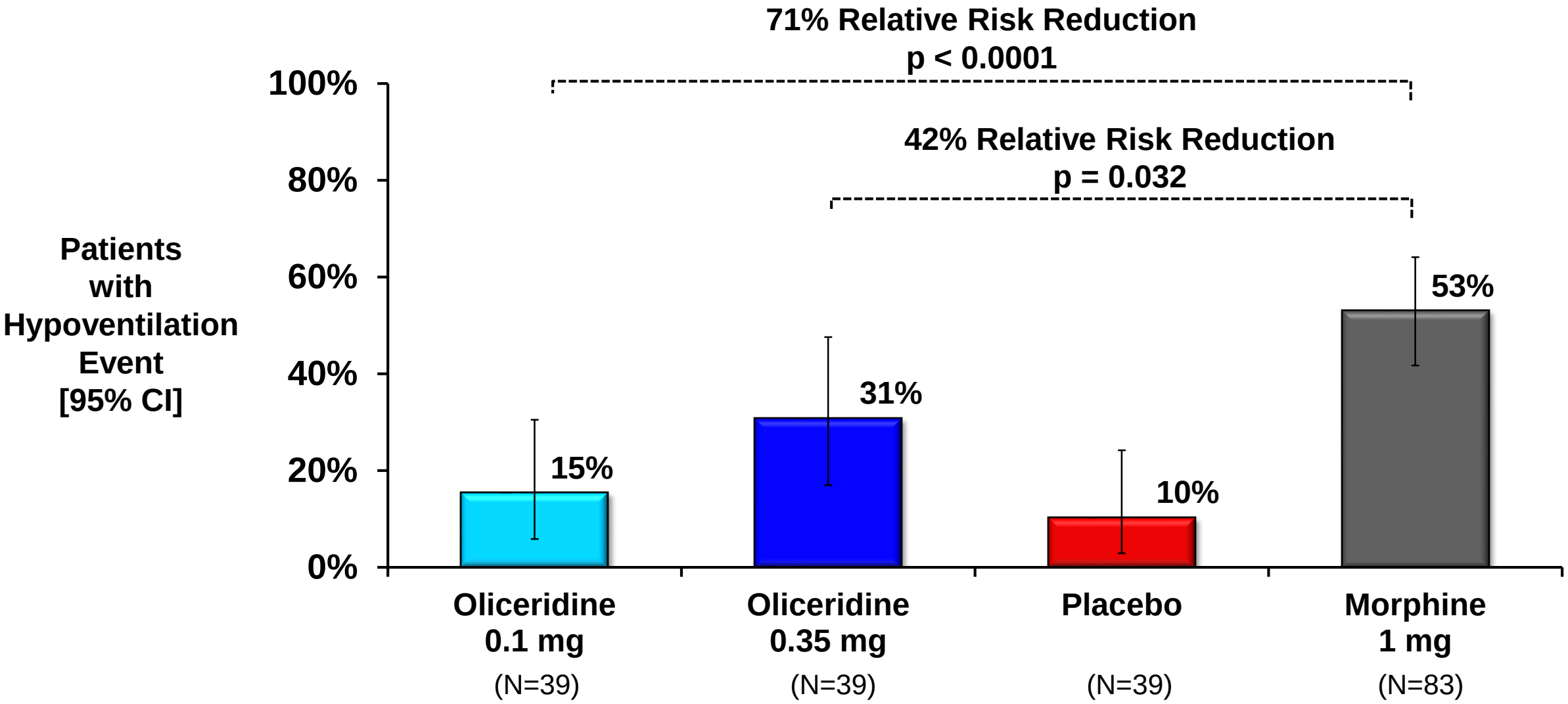


* p < 0.05 vs Morphine

Phase 2b Study: Evaluated Incidence of Clinically Significant Respiratory Events

- Hypoventilation prospectively defined as clinically apparent and persistently decreased
  - Respiratory rate
  - Respiratory effort
  - Oxygen saturation
- Respiratory events ascertained using standard clinical monitoring in blinded fashion

Phase 2b Study: Significantly Fewer Hypoventilation Events with Oliceridine than Morphine



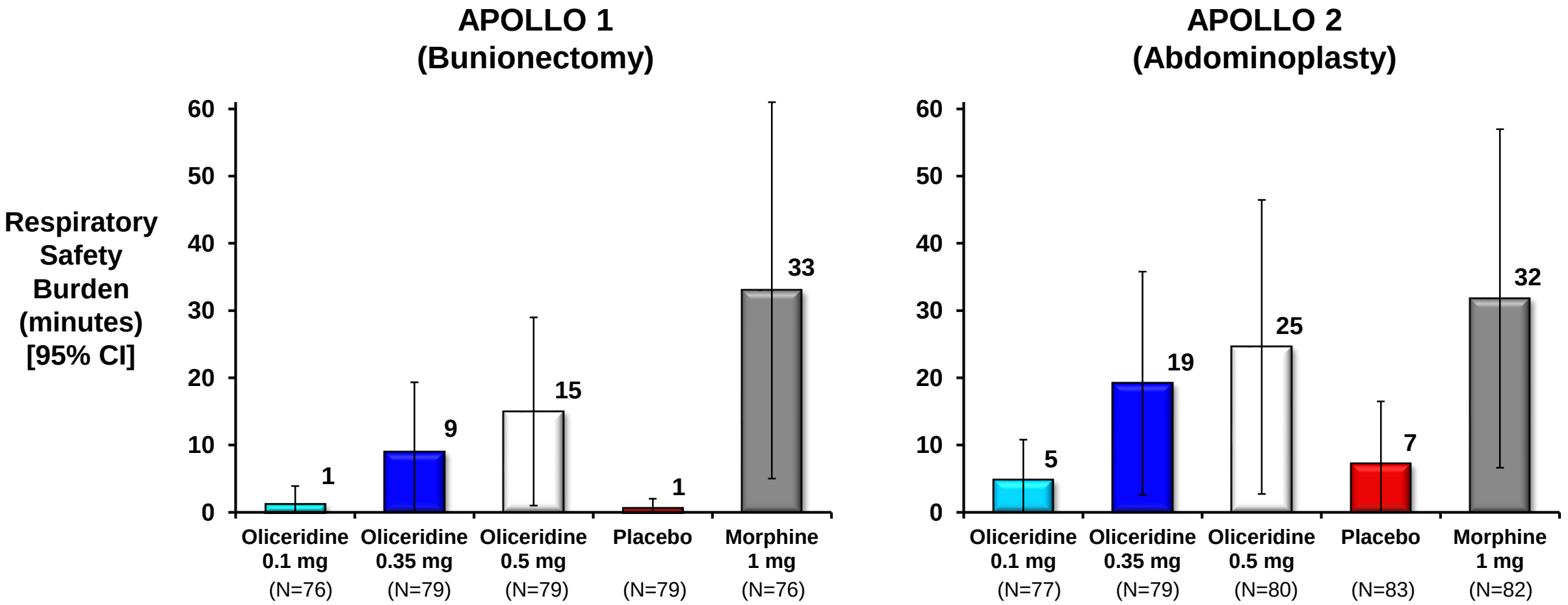
Phase 3 Studies Included Rigorous Monitoring and Assessment of Respiratory Events

- Trained anesthesiologists and certified registered nurse anesthetists (CRNA) performed all monitoring
  - Assessed signs, symptoms, and duration of respiratory effects
  - Administered clinical interventions
- Systematically captured incidence, severity, and duration
- Monitoring occurred every 2 hours or every 30 minutes during event in blinded fashion

Definitions of Respiratory Endpoints in Phase 3

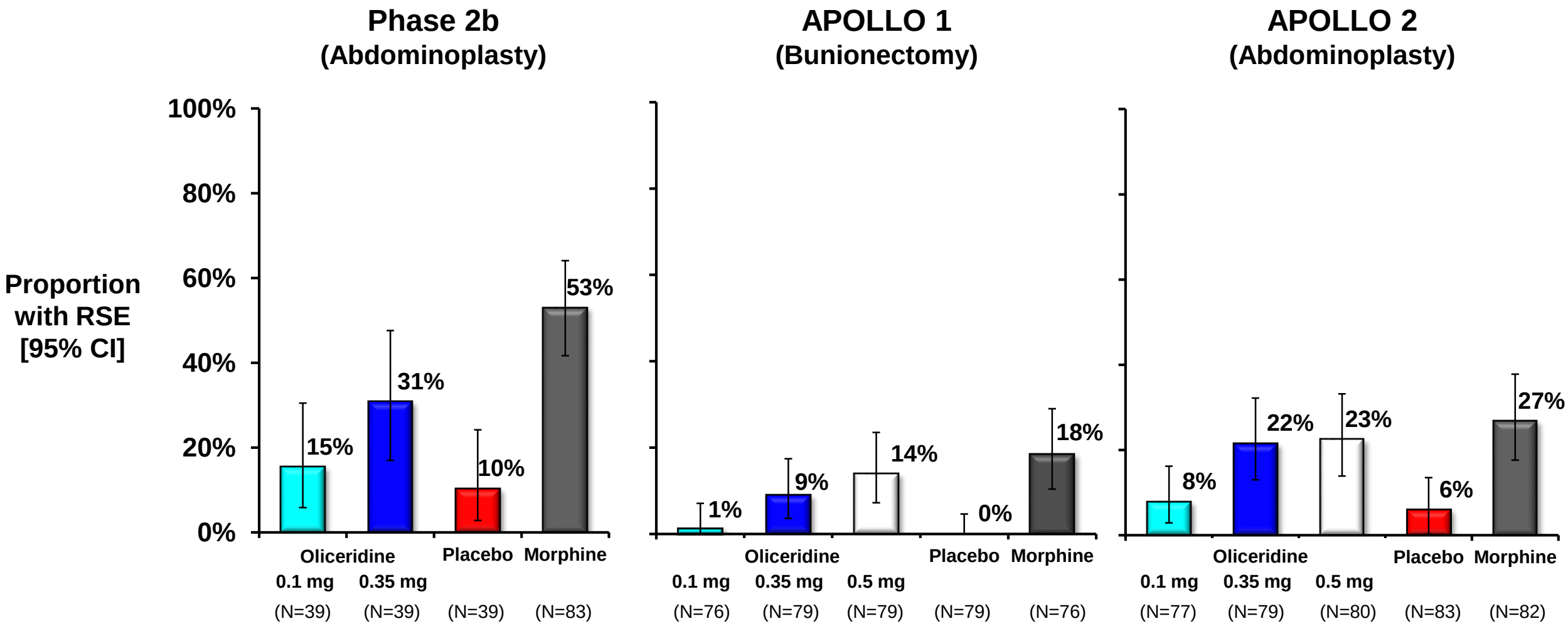
- Respiratory Safety Event (RSE)
  - Clinical expertise used to declare clinically relevant worsening in O_2 desaturation, reduced respiratory rate, or sedation
- Respiratory Safety Burden (RSB) new composite index
  - Product of RSE incidence and duration
  - Key secondary endpoint
  - Not eligible for labeling claims
- Respiratory interventions
  - Supplemental O_2 administration, dosing interruption, and study medication discontinuations

Phase 3: Reductions in RSB Dose-Regimen Dependent and Numerically Lower than Morphine



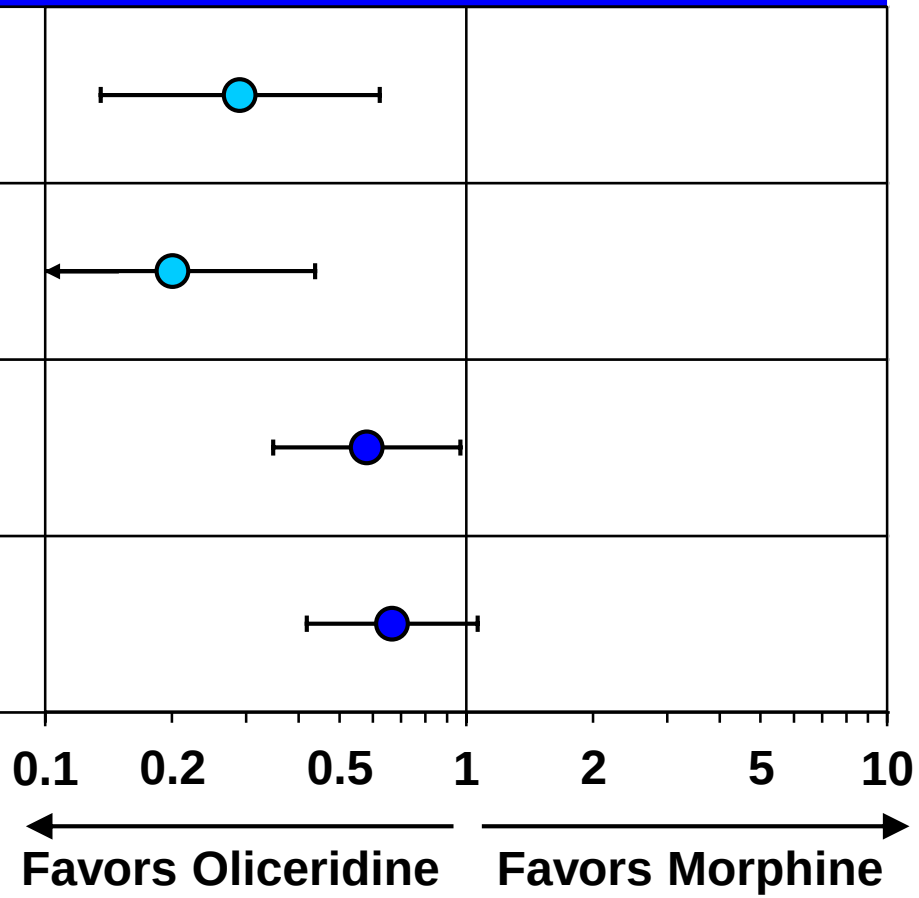
Not statistically significant

Lower Incidence of Respiratory Safety Events in All Groups in Phase 3 vs Phase 2



Similar Relative Risk Reductions in Hypoventilation and Respiratory Safety Events

Oliceridine Dosing Regimen	Phase	% of Patients Experiencing Respiratory Safety Event		Relative Risk Reduction vs Morphine
		Oliceridine	Morphine	
0.1 mg	2b	15	53	71%
	3	5	23	80%
0.35 mg	2b	31	53	42%
	3	15	23	33%



Summary of Respiratory Safety Interventions

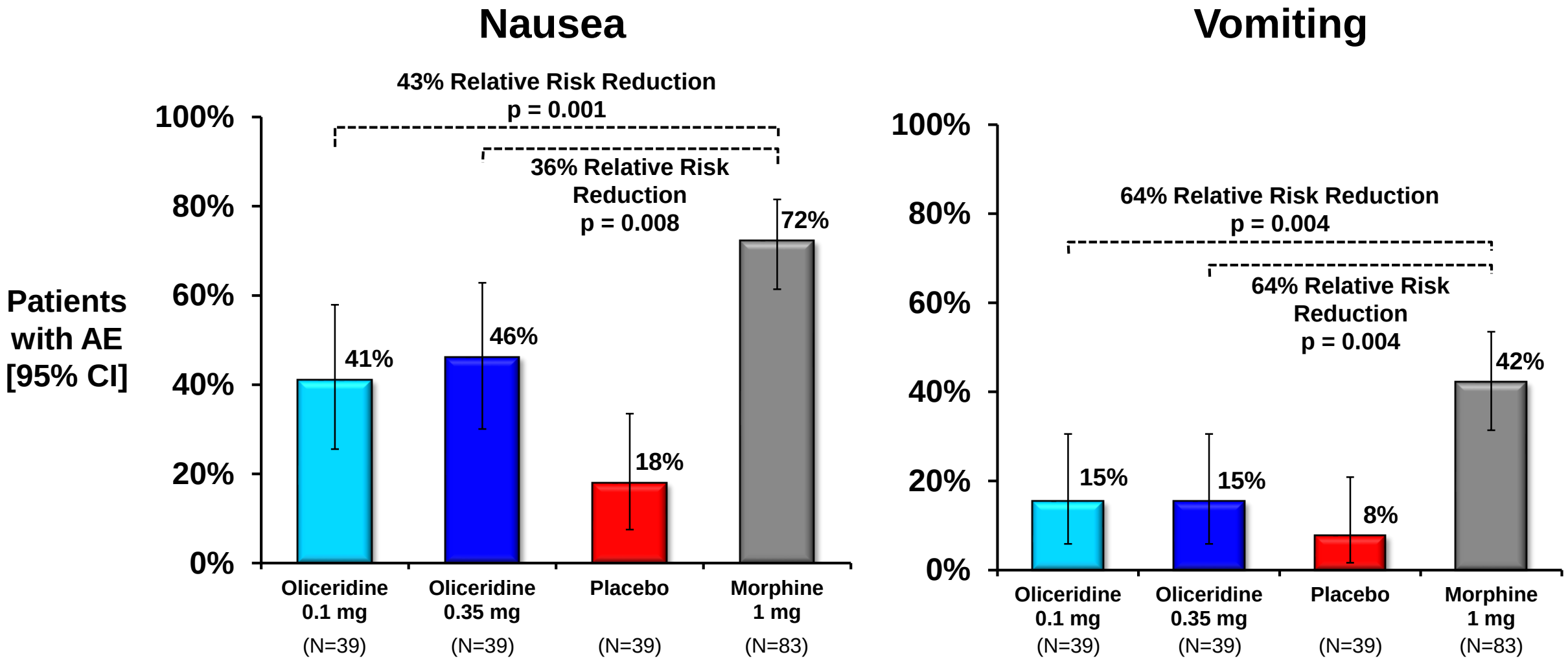
Safety Parameter, %	Oliceridine 0.1 mg N=153	Oliceridine 0.35 mg N=158	Oliceridine 0.5 mg N=159	Morphine 1 mg N=158	Relative Risk Reduction (p-value) 0.1 mg vs Morphine	Relative Risk Reduction (p-value) 0.35 mg vs Morphine
O_2 Saturation < 90%	5.9	14.6	17.0	22.2	73% (< 0.001)	34% (0.11)
Dosing Interruption	3.9	14.6	17.6	24.7	83% (< 0.001)	41% (0.033)
Supplemental O_2	4.6	14.6	17.6	22.8	80% (< 0.001)	36% (0.083)

Pooled APOLLO Studies

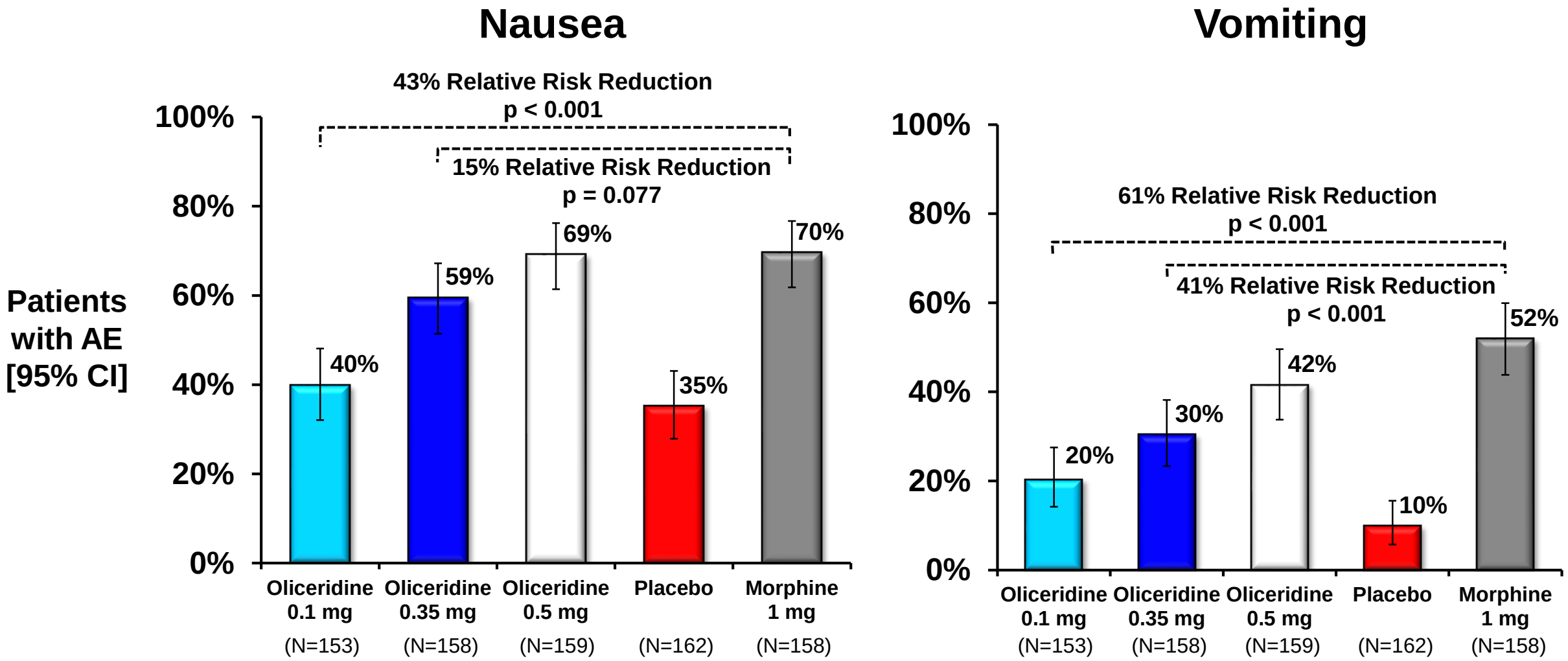
Nausea and Vomiting

- MedDRA Preferred Terms for Nausea and Vomiting

Incidence of Nausea and Vomiting in Pivotal Phase 2b Study

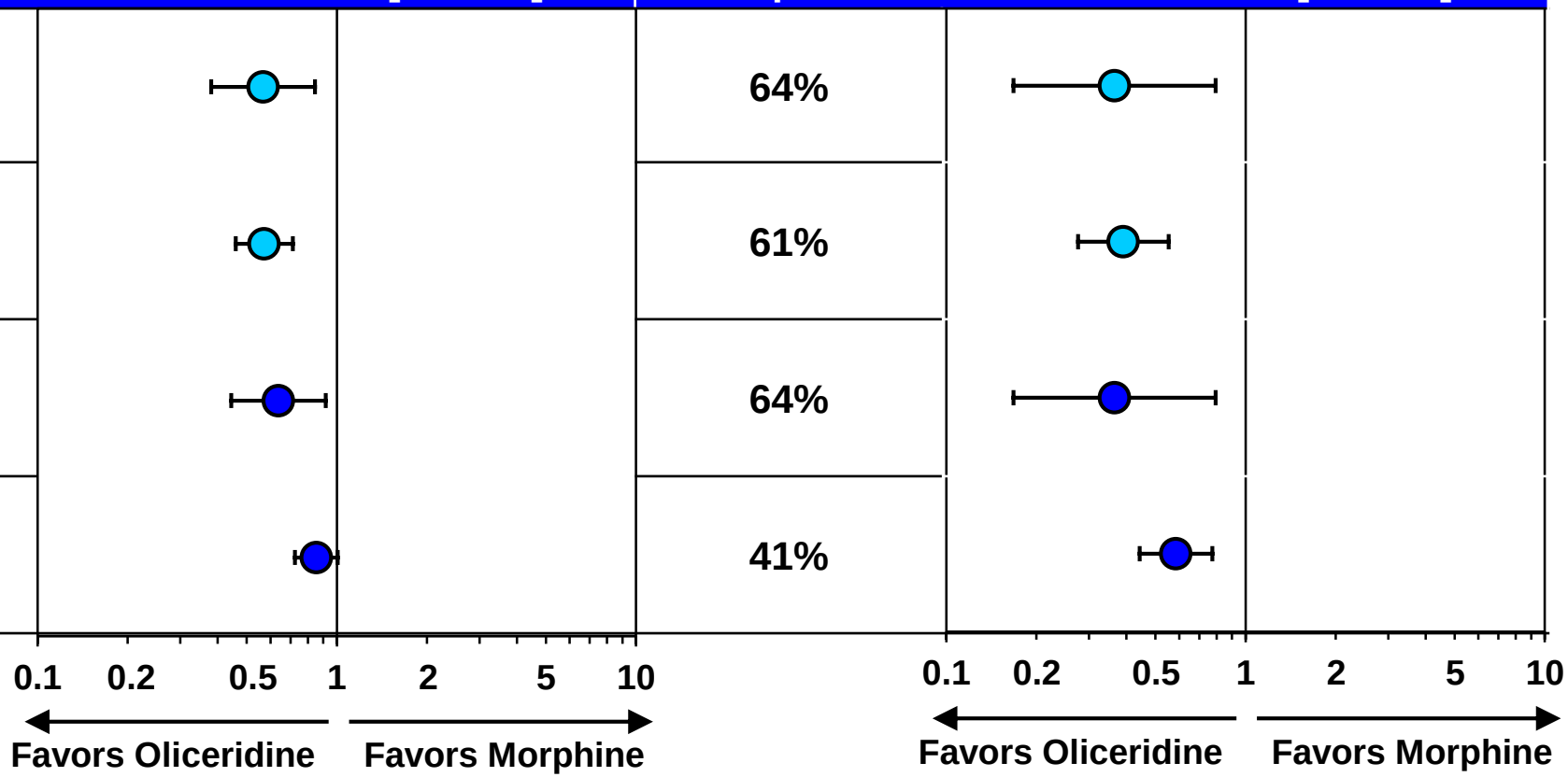


Incidence of Nausea and Vomiting in Pivotal Phase 3 Studies



Oliceridine Associated with Clinically Relevant Reductions in Nausea and Vomiting

Oliceridine Dosing Regimen	Phase	Nausea: Relative Risk Reduction vs Morphine	Vomiting: Relative Risk Reduction vs Morphine
0.1 mg	2b	43%	64%
	3	43%	61%
0.35 mg	2b	36%	64%
	3	15%	41%

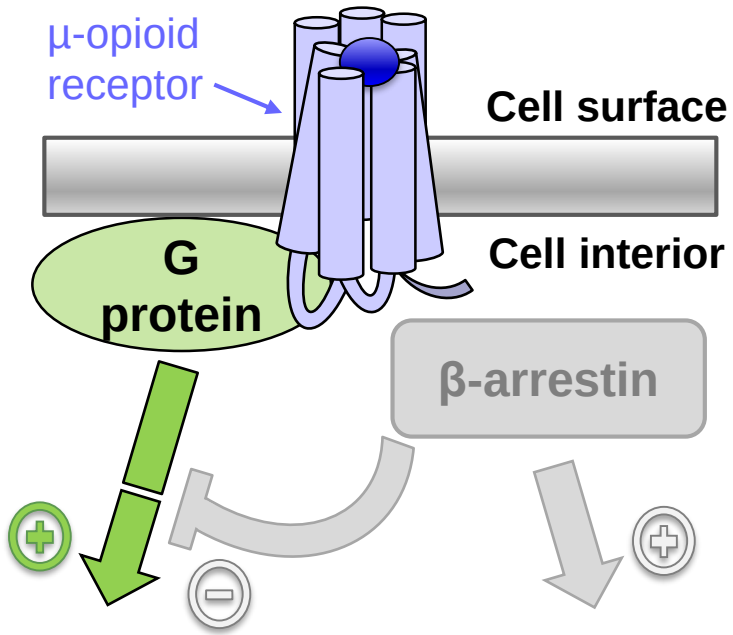


Benefit-Risk Assessment

- Summary of comparative ORAEs
- Sufficiency of analgesia vs risks

Clinical Results Provide Support for G Protein Biased Ligand Hypothesis

Oliceridine

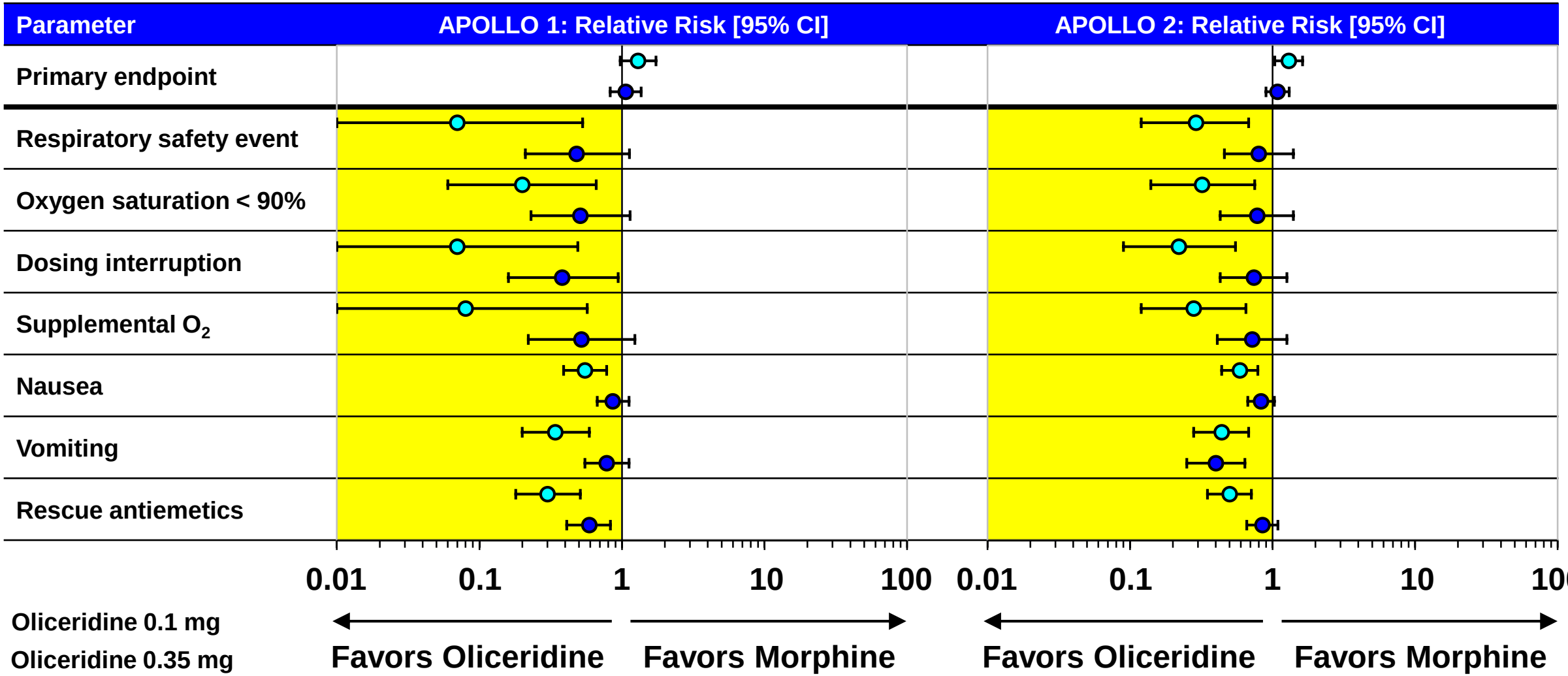


Hypothesis (vs Conventional Opioids):

- **Similar Analgesia**
- **Similar Liking / Dependence**
- **Less Respiratory Depression**
- **Less Nausea / Vomiting**

Hypothesis	Current Evidence
Similar analgesia	▪ Met primary endpoint for all doses in both Phase 3 studies
Similar liking / dependence	▪ Similar liking to equianalgesic morphine
Less respiratory depression	▪ 50% less opioid-induced respiratory depression vs morphine (gold standard) ▪ Consistent reductions in safety events and interventions
Less nausea / vomiting	▪ Consistently reduced in Phase 2 and 3 studies

Positive Benefit-Risk Profile of Oliceridine



Clinical Perspective

Gregory Hammer, MD

Professor of Anesthesiology, Perioperative and Pain Medicine and of Pediatrics (Critical Care)

Stanford University Medical Center

Need for Incremental Improvement in IV Opioid Therapy

- Most surgical inpatients require IV opioids
  - Adequate pain management may be challenging
- No significant advances in IV opioids over several decades
- Biased ligands first in new class of targeted pain therapies
  - Opioid-level efficacy with fewer adverse effects
- Need to embrace step-wise approach

Oliceridine: First Step in Biased Ligand Discovery

- Important incremental improvement in pain management
- Provides opioid-level analgesia with improved safety and tolerability profile

IV Opioid Safety: Nausea and Vomiting

- Nausea and vomiting common opioid side-effects
  - Patients would rather avoid nausea/vomiting than pain[1]
- May mitigate with antiemetics but come with other side effects

1. Macario et al. *Anesth Analg* 1999.

Oliceridine Associated with Clinically Relevant Reductions in Nausea and Vomiting

Phase 2b

- 3 in 4 morphine patients had nausea
  - Oliceridine reduced incidence by **35-40%**
- 2 in 5 morphine patients experienced vomiting
  - Oliceridine reduced incidence by **64%**

Phase 3

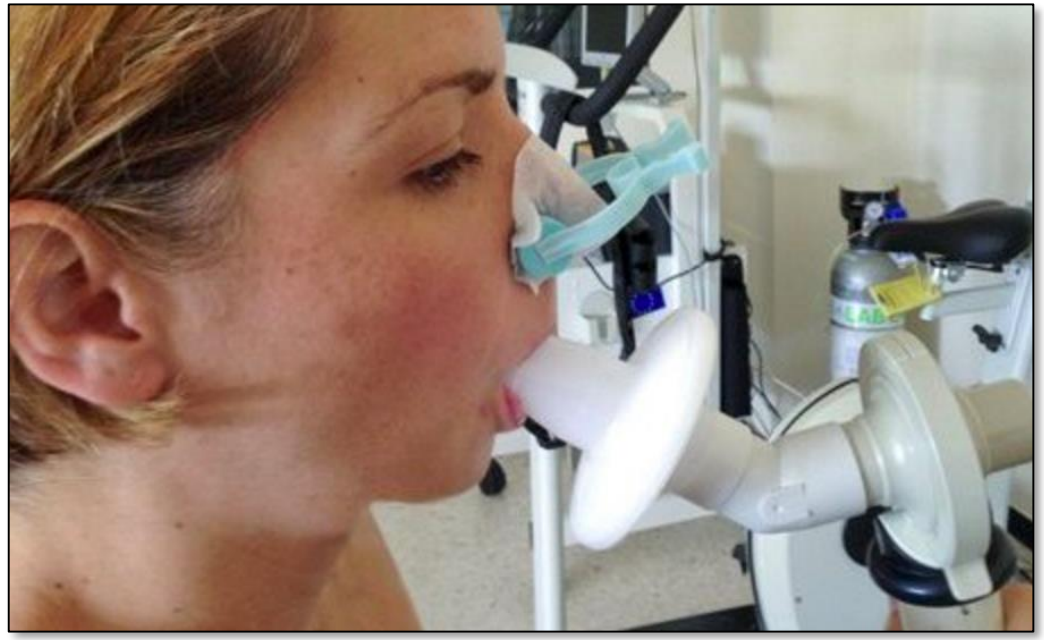
- 2 in 3 morphine patients had nausea
  - Oliceridine reduced incidence by **15-40%**
- 1 in 2 morphine patients experienced vomiting
  - Oliceridine reduced incidence by **40-60%**

Opioid-Induced Respiratory Depression

- Minimize risk by titrating medications gradually to effect
- Conventional IV opioids have narrow therapeutic window
- Overshoot opioid dose
  - Discontinue opioid
  - Administer or increase supplemental oxygen, high-flow nasal cannula therapy, or CPAP
  - Rare cases may need naloxone reversal, positive pressure ventilation

IV Oliceridine Reduces Opioid-Induced Respiratory Depression

- VRH gold standard for respiratory depression since 1960s
- 50% less respiratory depression
  vs equianalgesic morphine dose



Respiratory Safety Benefit: Consistent Safety Signal Across Clinical Studies

Phase 2b

- 1 in 2 morphine patients had hypoventilation event
  - Oliceridine reduced incidence by **40-70%**

Phase 3

- 1 in 4 morphine patients had respiratory safety event
  - Oliceridine reduced incidence by **33-80%**
- 1 in 4 morphine patients had PCA taken away for respiratory issues
  - Oliceridine reduced incidence by **40-80%**

Clinical Practice: Titrate Dose to Response

- Initial loading dose (1 to 2 mg)
- Analgesia maintained with demand doses
  - PCA dose range: 0.1 to 0.35 mg
- 0.1 mg demand dose
  - Smaller, more “fragile” patients
  - History of opioid sensitivity, PONV
  - Relatively minor procedures
  - Sufficient in many patients
- Titrate dose as needed

Summary of Clinical Perspective

- IV opioids important medications with many safety liabilities
- Need to move beyond current opioid formulations
  - Make potent analgesic molecules safer
- Oliceridine first potent analgesic pharmacology engineered to reduce ORAEs
  - Reduces respiratory events, nausea, and vomiting
  - Does not eliminate ORAEs or reduce drug liking
- **Incremental improvements should be embraced**

Trevena Perspective on FDA Questions

Jonathan Violin, PhD

Co-founder and Senior Vice President of Scientific Affairs

Trevena, Inc.

Trevena Perspective on FDA Questions

FDA Question	Key Findings
1. Substantial evidence of efficacy	▪ Superior to placebo in all pivotal Phase 3 studies ▪ Comparable analgesic efficacy to morphine
2. Adequacy of safety profile	
a. Safety database	▪ > 1,800 individuals have received oliceridine ▪ Max daily dose of 40 mg based on median of top 350 exposures
b. Hepatic safety	▪ Expert panel found no evidence for clinical safety issue
c. Respiratory safety	▪ ~50% less opioid-induced respiratory depression vs morphine ▪ Consistent relative risk reductions in clinical studies
d. QT prolongation	▪ No clinically meaningful risk for drug-induced arrhythmia
3. Impact on public health	▪ Acute use in controlled setting ▪ Similar abuse potential to morphine
4. Approvability	▪ Meets regulatory requirements for approval ▪ Incremental improvement vs conventional IV opioids

IV Oliceridine for the Management of Moderate-to-Severe Acute Pain in Hospital or Controlled Clinical Settings

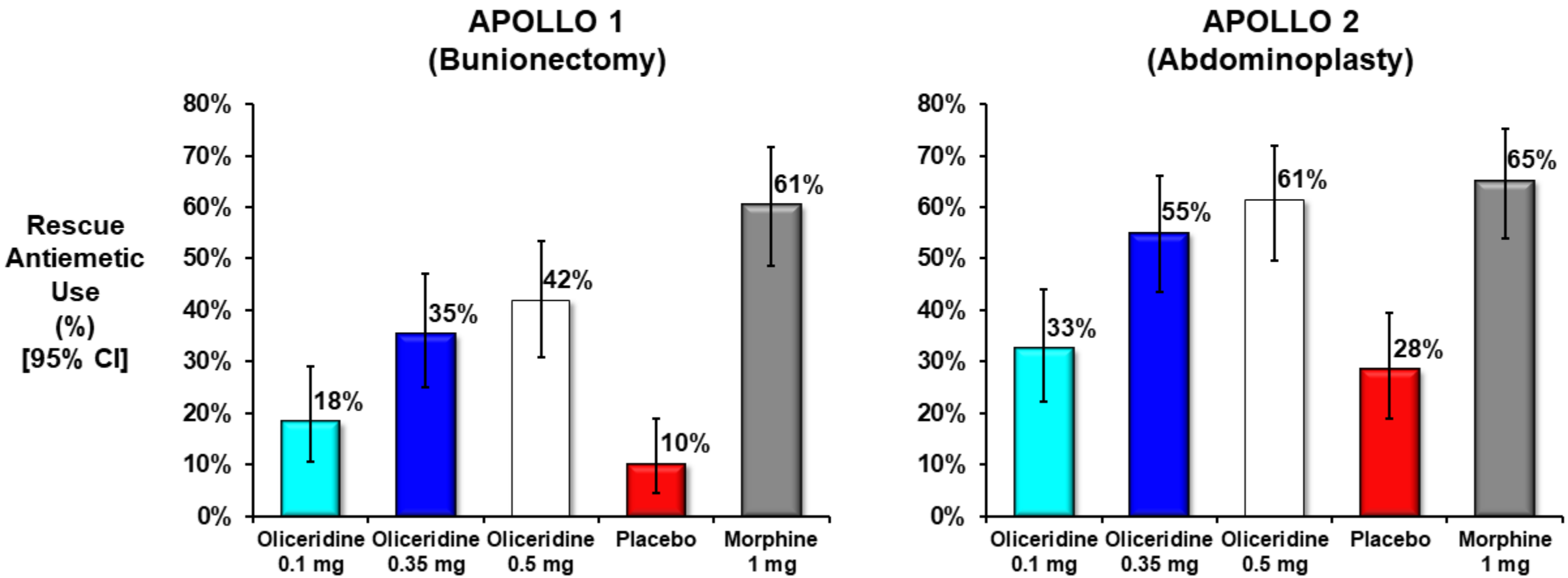
October 11, 2018

Trevena, Inc.

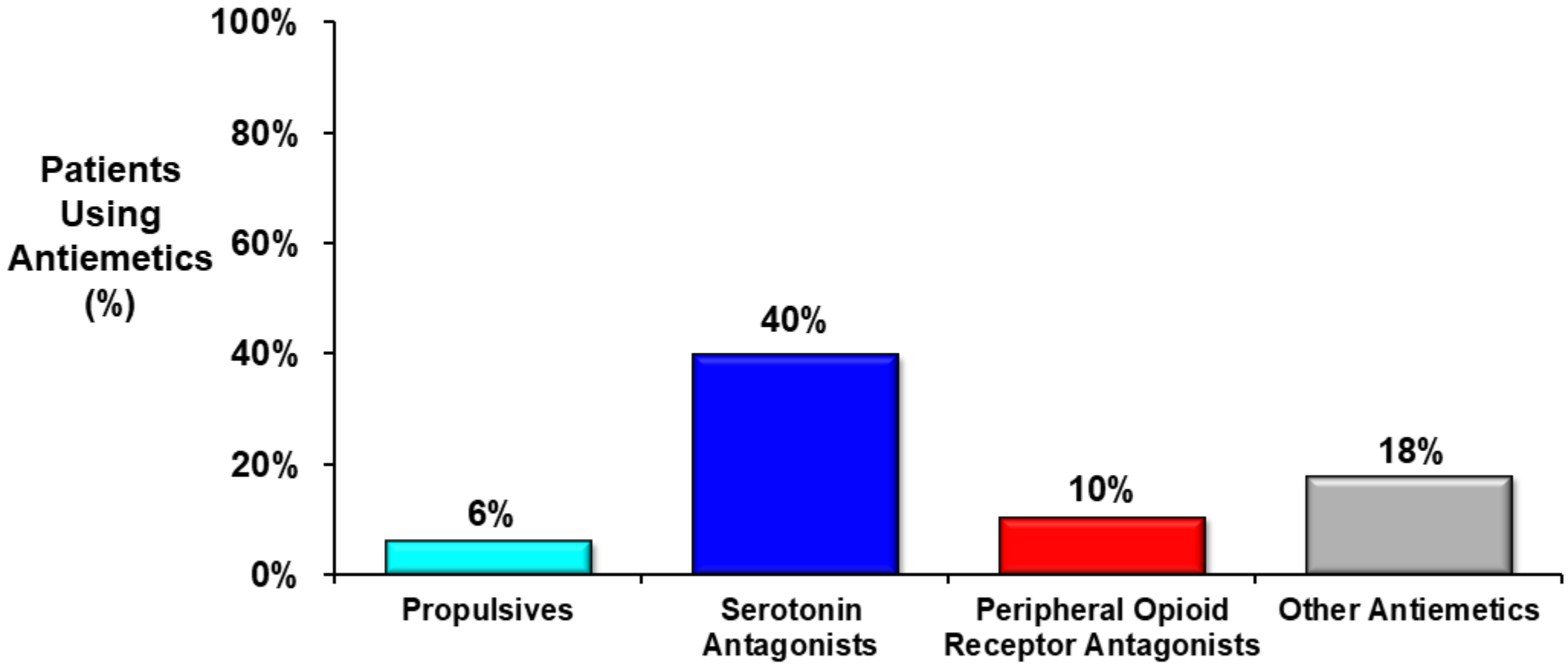
Meeting of the Anesthetic and Analgesic Drugs Products Advisory Committee

BACKUP SLIDES

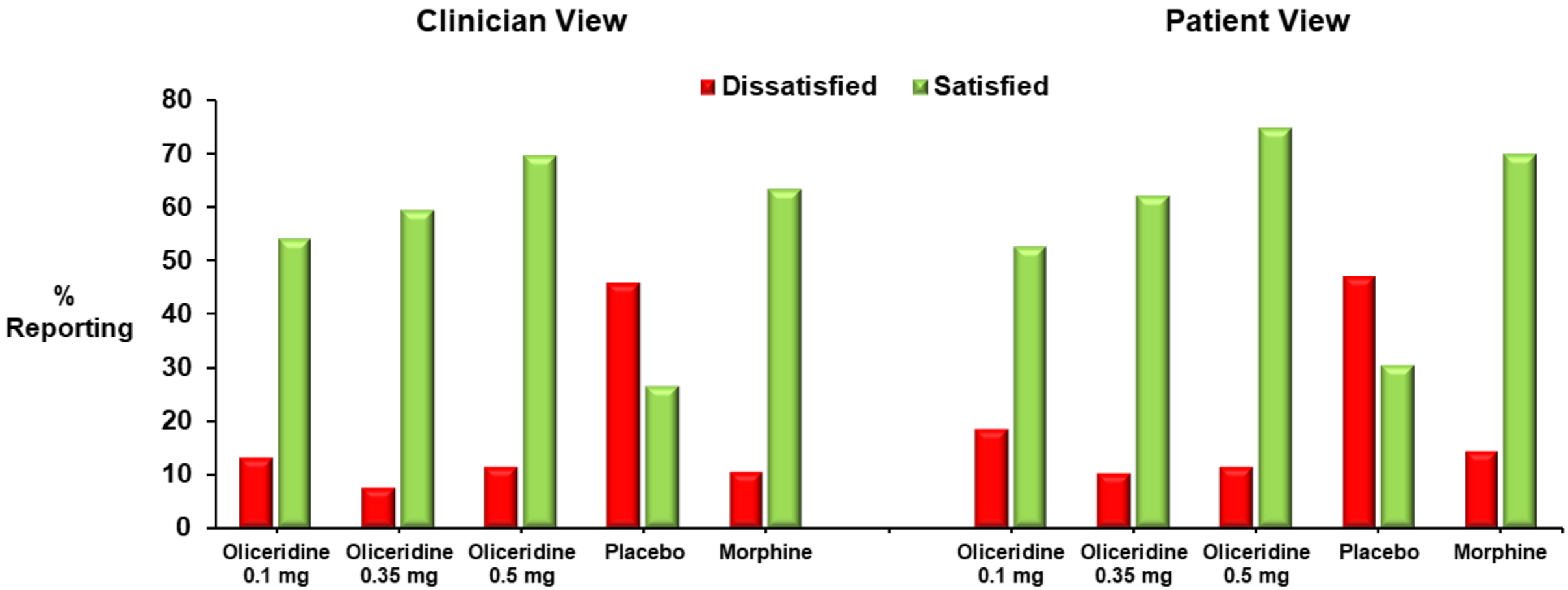
APOLLO Studies: Rescue Antiemetic Use



ATHENA: Concomitant Antiemetics



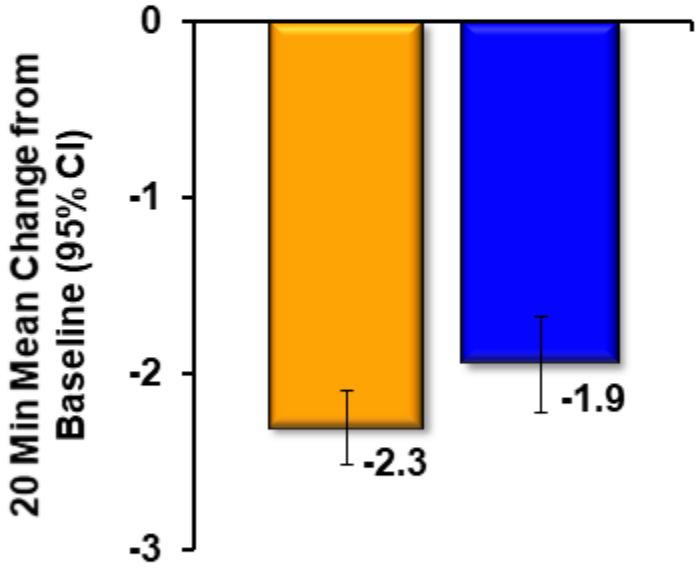
APOLLO 1: Clinician and Patient Satisfaction Self-Reported Global Outcomes



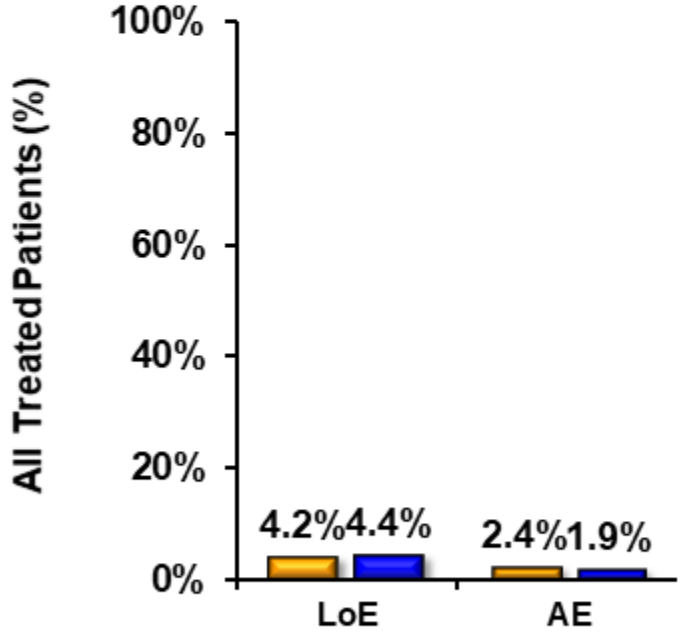
NOTE: *'Dissatisfied' = Mostly/Completely Dissatisfied*
'Satisfied' = Mostly/Completely Satisfied

ATHENA: Benefit/Risk Evaluation by Sex

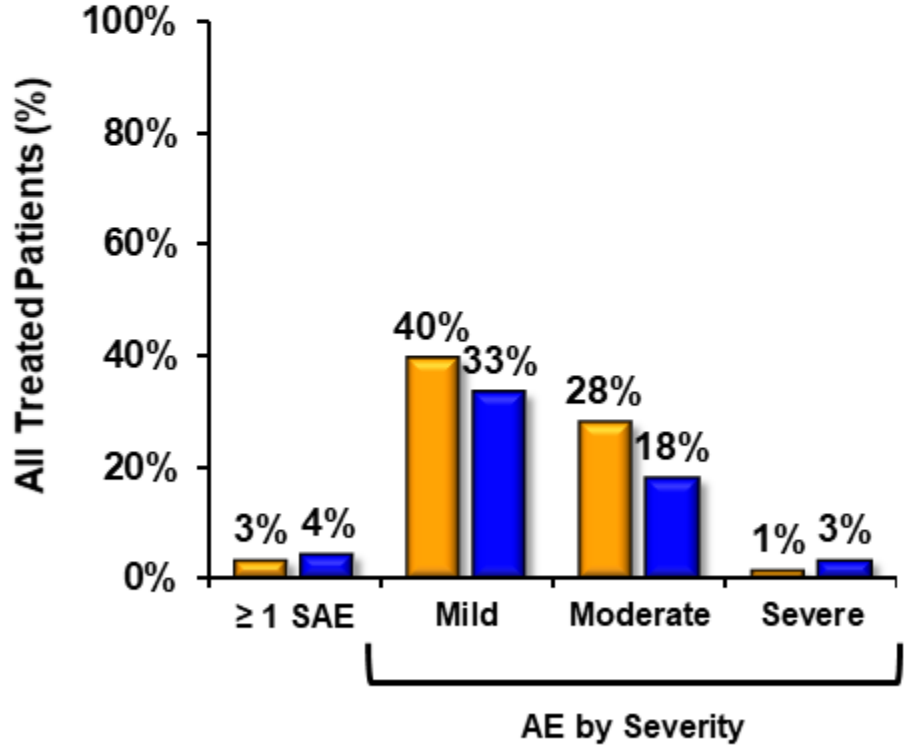
NRS: Change from Baseline



Discontinuation for AE and Lack of Efficacy (LoE)

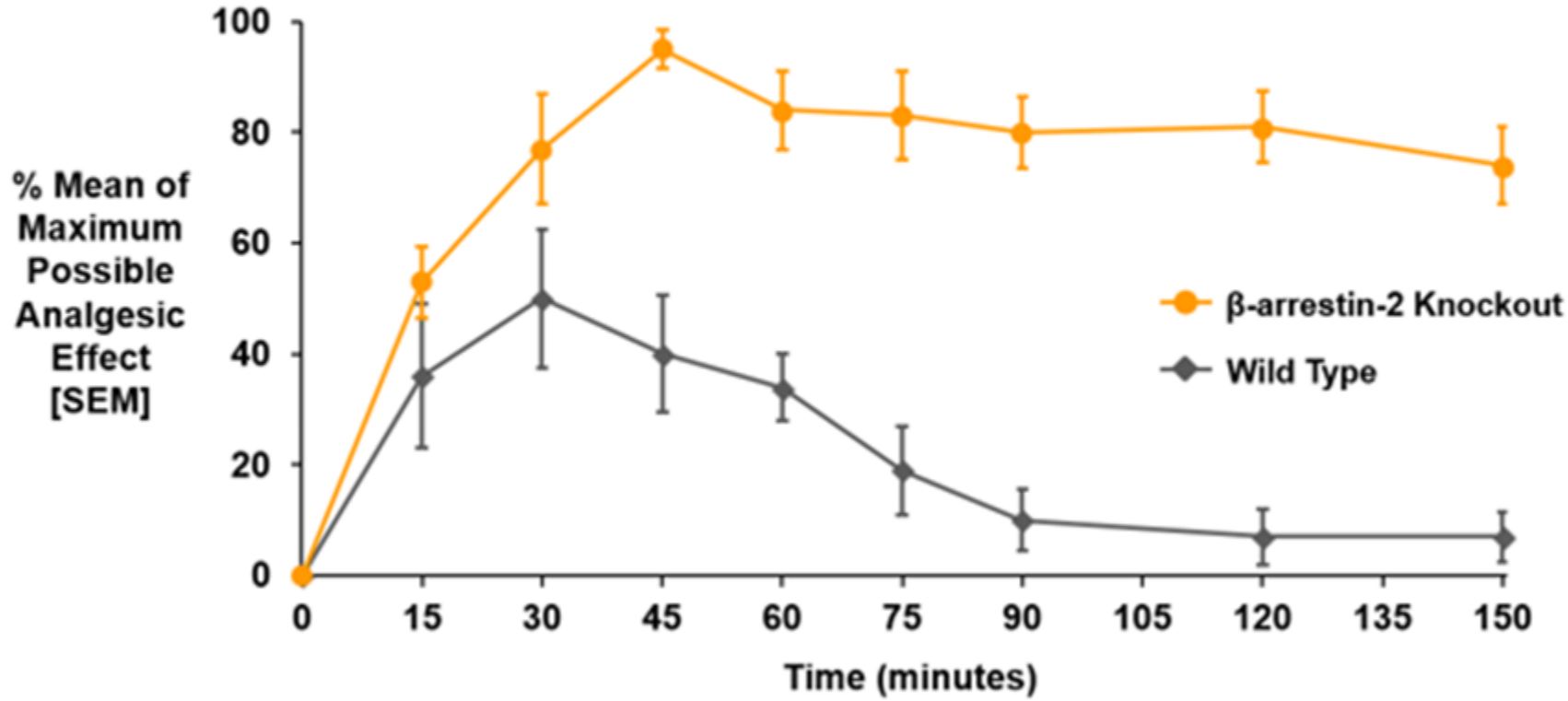


Adverse Events



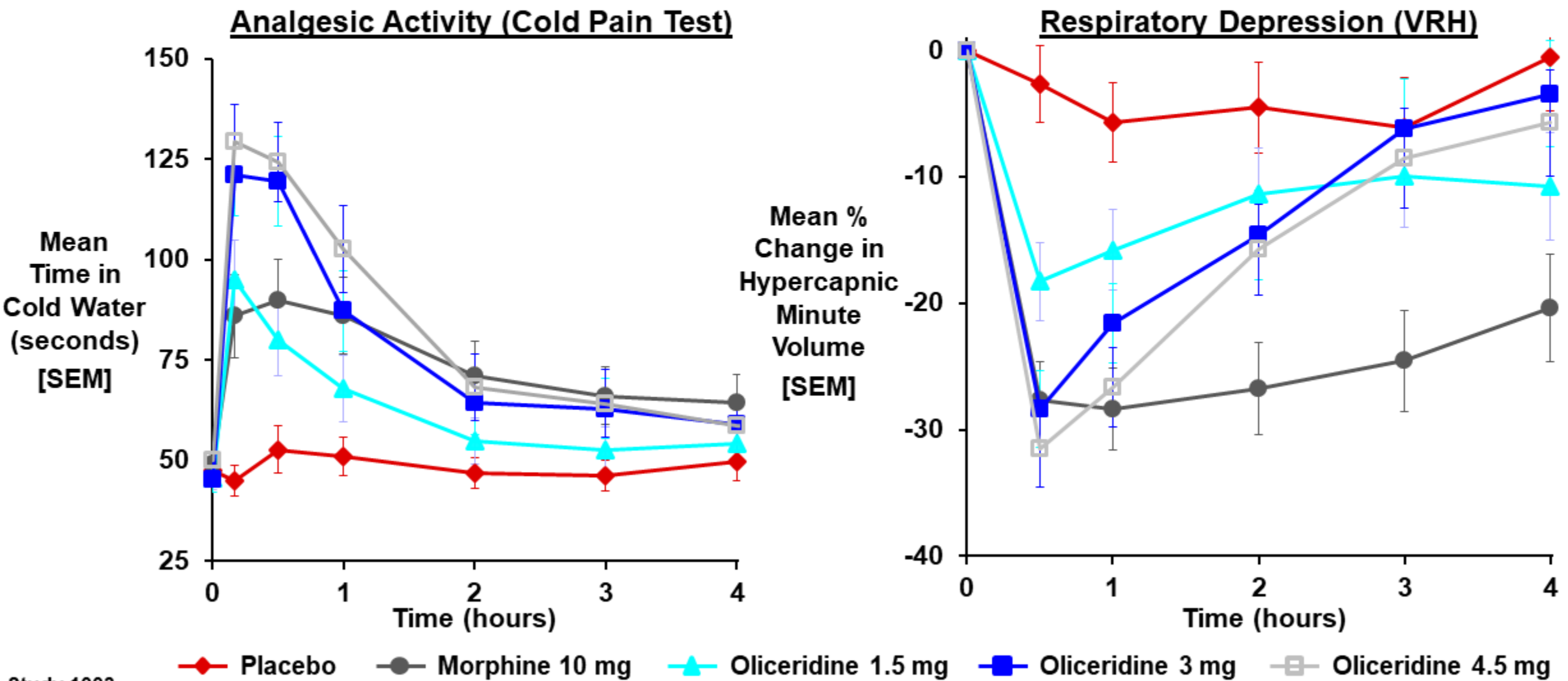
Female (N=498) Male (N=270)

Figure 15: Analgesic Effect of Morphine in β-arrestin-2 Knockout Mice in Hot Plate Assay



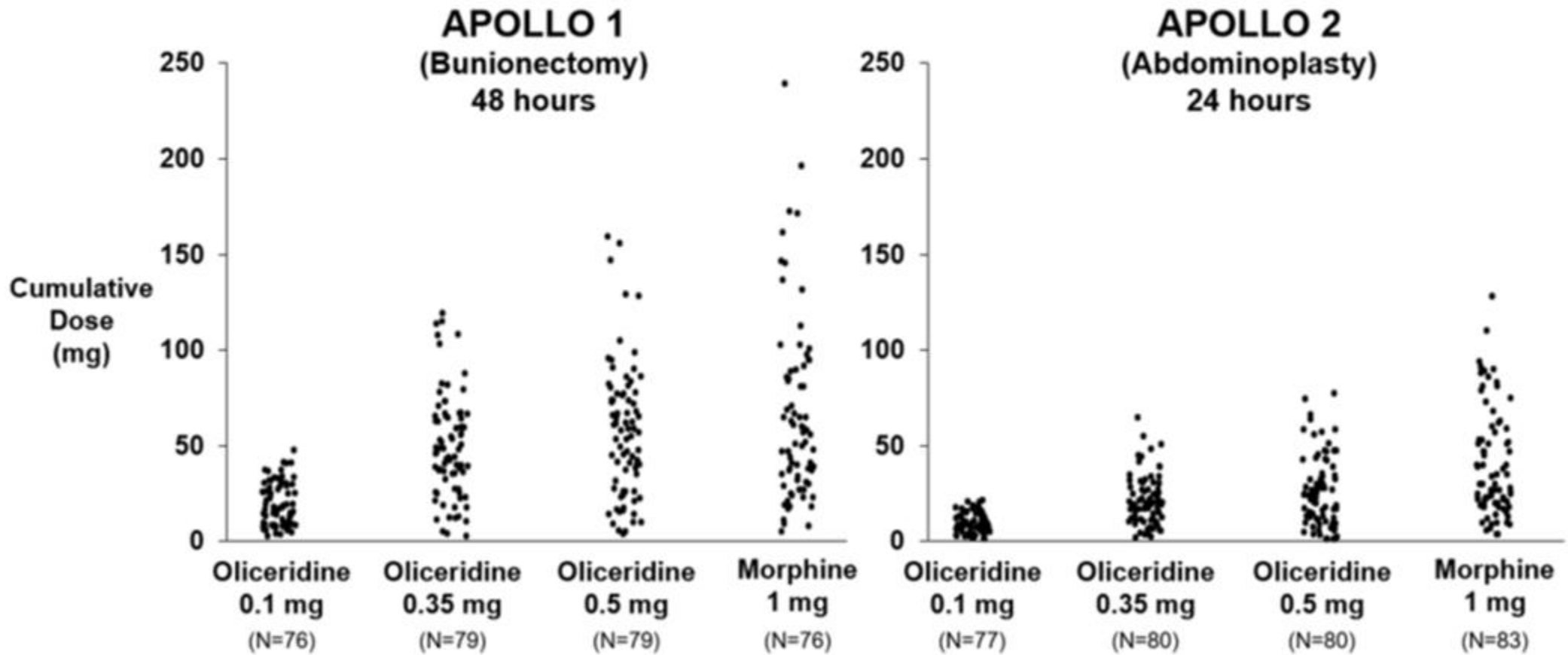
Morphine dose: 10 mg/kg s.c.
Adapted from Bohn et al. *Science*, 1999

Phase 1: Oliceridine Showed Favorable Balance Between Analgesia and Respiratory Safety

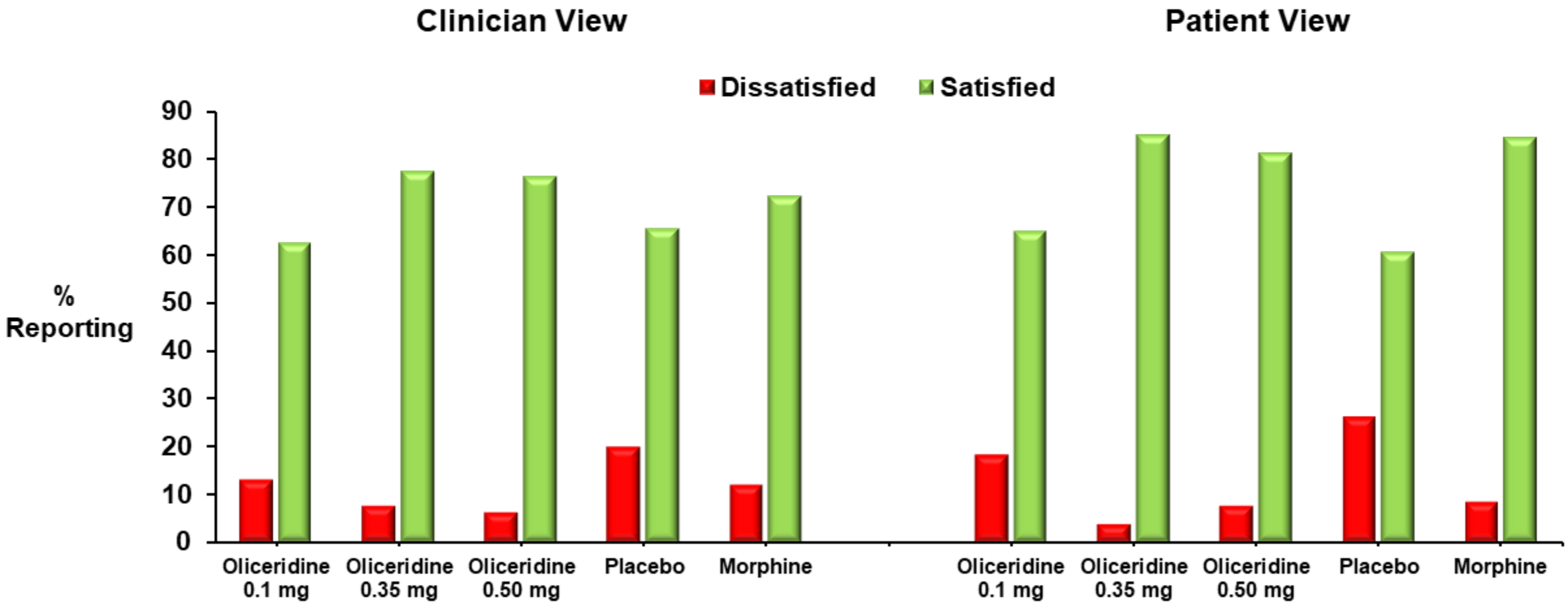


Study 1003

Figure 29: Cumulative Dose of Study Medication in APOLLO 1 and APOLLO 2

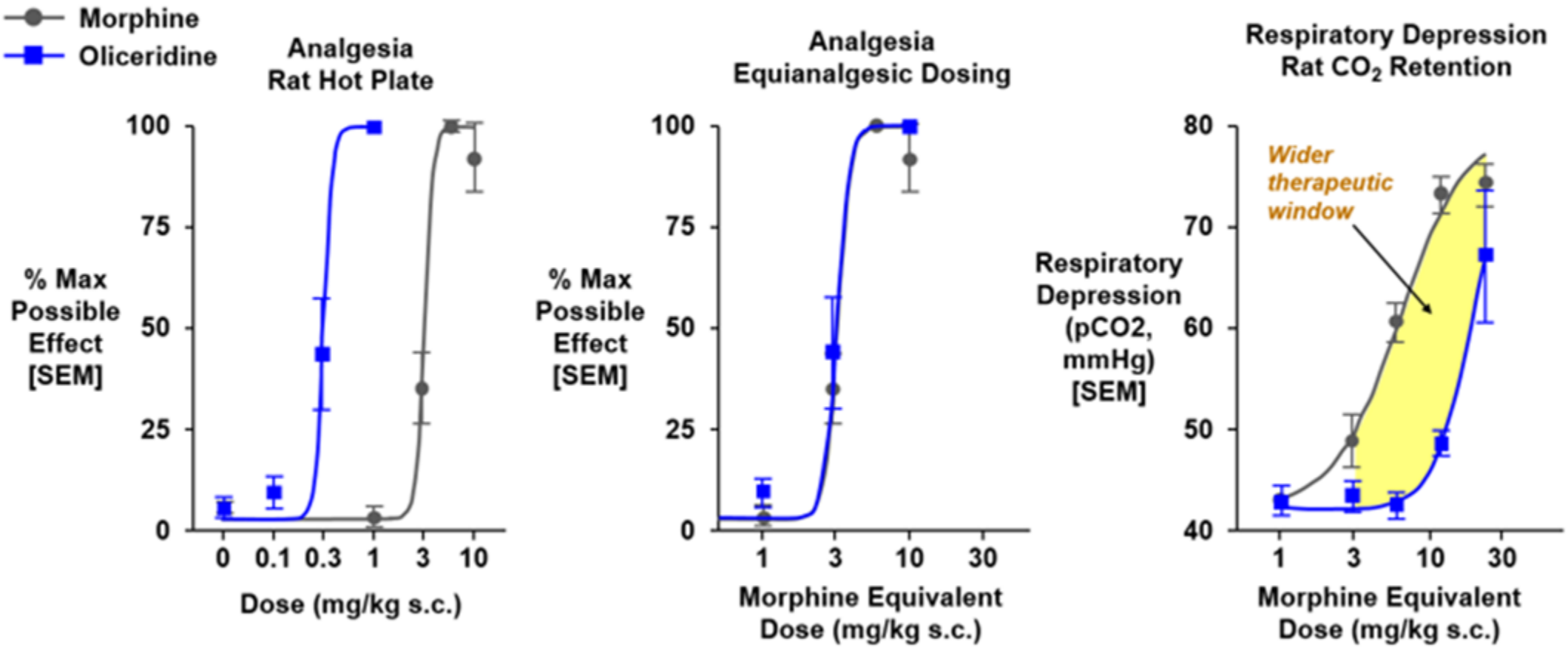


APOLLO 2: Clinician and Patient Satisfaction Self-Reported Global Outcomes



NOTE: *'Dissatisfied' = Mostly/Completely Dissatisfied*
'Satisfied' = Mostly/Completely Satisfied

Figure 20: Log-Transformed Oliceridine and Morphine Dose-Response Curves for Analgesic Activity and Respiratory Depression in Rats



Source: Adapted from Violin et al. *Trends Pharmacol Sci*, 2014