HYDEXOR™ (CL-108) For the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting (OINV)

US Food & Drug Administration

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

February 14, 2018

Charleston LABORATORIES

HYDEXOR (7.5 mg hydrocodone/325 mg acetaminophen/12.5 mg promethazine).

Introduction: Today's Purpose

Thomas Smith, MD

Chief Medical Officer

Charleston Laboratories, Inc.

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Why We're Here Today

- Need for better short-term management of acute pain while preventing and reducing opioid-induced nausea and vomiting (OINV)
  - HYDEXOR™ provides a favorable benefit-risk profile in this setting
- National movement to address the opioid abuse crisis
  - Charleston's commitment to abuse mitigation for HYDEXOR
  - Efforts to reduce the number of excess tablets available for abuse, misuse, and diversion

OINV: Common, Burdensome, and Costly

- OINV is common[1-5]
  - ~40% report nausea
  - ~20% report vomiting
- OINV associated with significant burden
  - Inadequate pain management and substantial effects on QoL[6]
  - Nonadherence or discontinuation[7-9]
  - Post-surgical complications[6]
  - Economic burden: higher healthcare resource use and reduced productivity[10]
- Patients and physicians are willing give up pain relief to avoid OINV[11-14]
- OINV is difficult to control, and there are no approved therapies

QoL=quality of life.

1. Kalso E, et al. *Pain*. 2004;112(3):372-380; 2. Chang DJ, et al. *Anesth Analg*. 2004;99(3):807-815; 3. Daniels S, et al. *Curr Med Res Opin*. 2009;25(6):1561; 4. Park YB, et al *Curr Med Res Opin*. 2015; 31(1):75-84; 5. Musclow SL, et al. *Pain Res Manage*. 2012;17(2):83-88; 6. Mallick-Searle T & Fillman M. *J Am Assoc Nurse Pract*. 2017;29:704-710; 7. Láinez MJ, et al. *Patient Relat Outcome Meas*. 2013;4:61-73; 8. Porreca F, et al. *Pain Med*. 2009;10(4):654-662; 9. Navari RM. *Drugs*. 2009;69(5):515-533; 10. Gajria K, et al. *J Pain Res*. 2017;10:689-698; 11. Gregorian RS Jr, et al. *J Pain*. 2010;11(11):1095-1108; 12. Farrar JT, et al. *Pain*. 2001;94(2):149-158; 13. Childs JD, et al. *Spine*. 2005;30(11):1331-1334; 14. Ostelo RW, et al. *Spine*. 2008;33(1):90-94.

HYDEXOR™: Novel Treatment of an Opioid and Antiemetic

- Provides pain relief to patients with moderate-to-severe acute pain
  - Immediate-release opioid (hydrocodone [HC] 7.5 mg)
  - Non-opioid pain reliever (acetaminophen [APAP] 325 mg)
- Prevents opioid-induced nausea and vomiting
  - Low-dose antiemetic (promethazine [PMZ] 12.5 mg)

HYDEXOR™ Met All NDA Requirements

Clinical Pharmacology

- HYDEXOR demonstrated bioequivalence to RLDs and Norco® (fasted and fed)

Clinical Efficacy

- 2 pivotal, multicenter, randomized, double-blind, placebo- and active-controlled multiple-dose trials in acute pain models (oral surgery and bunionectomy)
  - Met primary and secondary endpoints
  - First reported studies of combination treatment for acute pain and prevention of OINV

Clinical Safety

- >770 patients and subjects were exposed to HYDEXOR
  - Safety profile consistent with its individual components and their established safety profiles
  - Increased incidence of drowsiness

Abuse Liability

- No increased risk of abuse was observed at supratherapeutic doses compared to HC/APAP

RLDs=reference listed drugs.

HYDEXOR™: Treatment of Acute Pain While Preventing and Reducing OINV

Proposed indication

- Short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting (OINV)
  - Treatment generally less than 14 days
  - Indicated when alternative treatments for pain are inadequate

Dosage

- One tablet every 4 to 6 hours as needed for pain; the total daily dosage should not exceed 6 tablets

HYDEXOR™ Target Population

- Adults requiring an immediate-release opioid for acute pain
- Risk factors for OINV - based on clinical judgement
  - Gender, non-smokers, history of motion sickness, prior OINV
- Use with caution in elderly, cachectic, and debilitated patients
- Not intended for children or compromised populations
  - Respiratory depression, acute or severe bronchial asthma
  - Known or suspected gastrointestinal obstruction
  - Known hypersensitivity to any components

Charleston's Commitment to Responsible Use

- Interim REMS/Classwide IR Opioid REMS
  - Labeling for short-term use (generally less than 14 days)
  - 3-, 5-, and 7-day packs (maximum of 6 tablets per day)
- Developing HYDEXORETURN™ Program for unused tablets
- Education, Distribution, and Pharmacovigilance
- Monitoring and Active/Passive Surveillance
- Commercial audience: Selected surgeons and acute pain specialists

Draft HYDEXOR™ 3-, 5-, and 7-day packaging (F1/Child-resistant container closure system)

IR=immediate release; REMS=Risk Evaluation and Mitigation Strategy.

Agenda

Unmet Need	**Tong Joo (TJ) Gan, MD, MBA, MHS, FRCA** Stony Brook School of Medicine
Abuse Potential and Human Abuse Liability	**Sandra D. Comer, PhD** Columbia University
Clinical Development and Efficacy	**Bernard P. Schachtel, MD** Charleston Laboratories, Inc.
Clinical Safety, Responsible Use, and Benefit-Risk Assessment	**Thomas Smith, MD** Charleston Laboratories, Inc.

Additional Experts

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

- **Scott P. Novak, PhD**
  Director of Research
  Pharmacoepidemiology
  & Drug Safety
  Abt Associates

- **Robert Makuch, PhD**
  Professor, Biostatistics and
  Director, Regulatory Affairs
  Program
  Yale School of Medicine

- **Hilda Maibach, MSc**
  Statistician
  Indigo RDD, LLC

Need for New Approach to Treat Acute Pain While Preventing and Reducing OINV

Tong Joo (TJ) Gan, MD, MBA, MHS, FRCA

Professor and Chairman

Department of Anesthesiology

Stony Brook School of Medicine

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Acute Pain

- Acute Pain: Normal, predictable physiological response to a noxious chemical, thermal or mechanical stimulus[1]
  - Typically is associated with invasive procedures, trauma and disease
  - Generally lasting 6 weeks or less
- Opioid analgesics can be essential in the treatment of acute pain[1]
- Duration of pain requiring treatment with an opioid analgesic[2]
  - 4 to 9 days for general surgery procedures
  - 4 to 13 days for women's health procedures
  - 6 to 15 days for musculoskeletal procedures

1. 2013 Federation of State Medical Boards Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain. Accessed February 29, 2017.
2. Scully RE, et al. *JAMA Surg*. 2018:153(1):37-43.

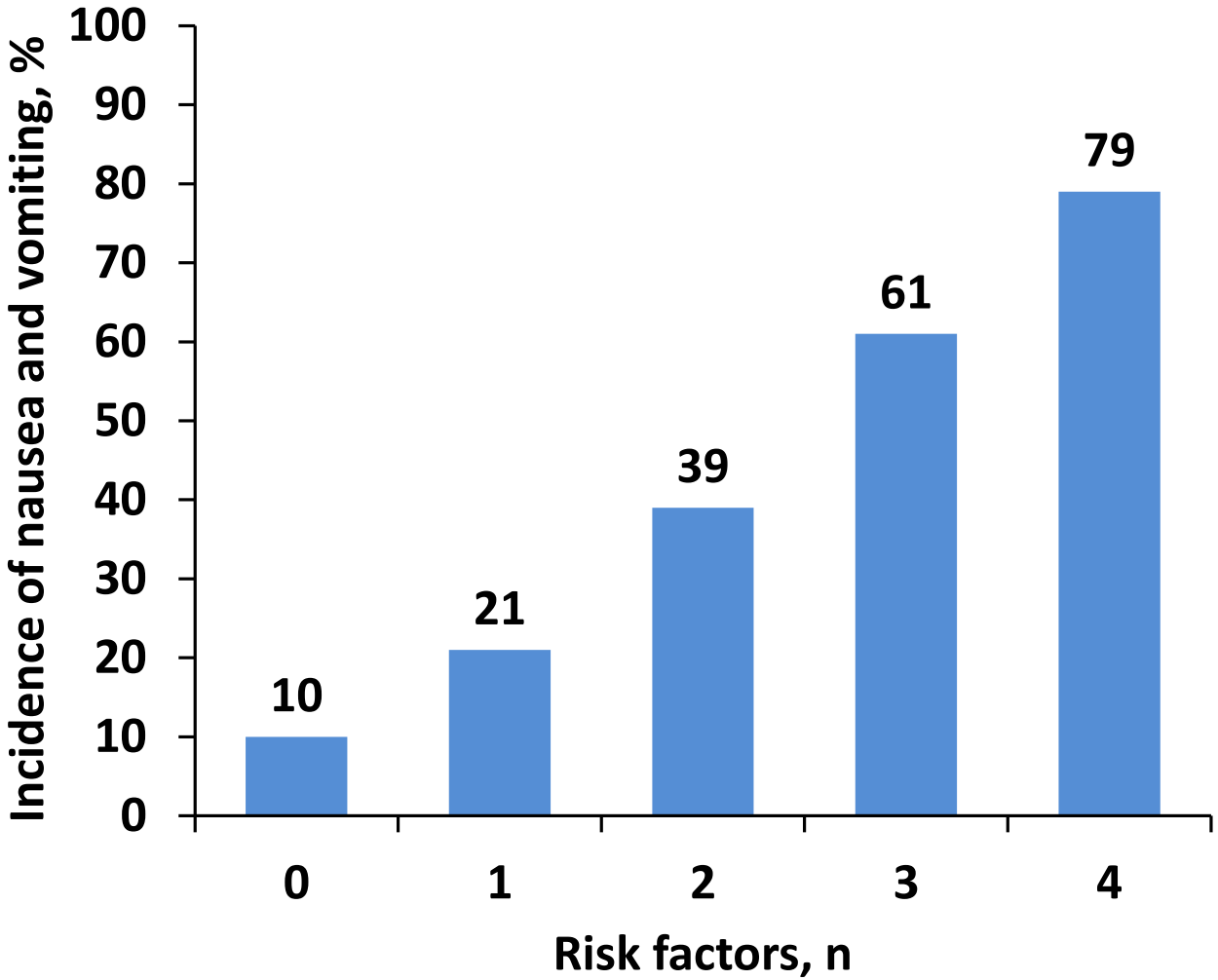
Many Patients Requiring Opioids Suffer Nausea and Vomiting

- Opioid-induced nausea and vomiting (OINV) common
  - ~40% report nausea[1-5]
  - ~20% report vomiting[1-5]
- Opioid-related side effects including OINV are associated with treatment discontinuation or inadequate analgesia[6-8]
  - Patients and physicians are willing to give up degrees of pain relief to avoid OINV[9-12]
- OINV is difficult to control and there are no approved therapies for acute pain and OINV

1. Kalso E, et al. *Pain*. 2004;112(3):372-380; 2. Chang DJ, et al. *Anesth Analg*. 2004;99(3):807-815; 3. Daniels S, et al. *Curr Med Res Opin*. 2009;25(6):1561; 4. Park YB, et al. *Curr Med Res Opin*. 2015;31(1):75-84; 5. Musclow SL, et al. *Pain Res Manage*. 2012;17(2):83-88; 6. Duensing L, et al. *Curr Med Res Opin.* 2010;26(7):1579-1585; 7. McCarberg BH, et al. *J Opioid Manag.* 2013;9(6):401-406; 8. Moskovitz BL, et al. *J Opioid Manag.* 2011;7(4):277-286; 9. Gregorian RS Jr, et al. *J Pain*. 2010;11(11):1095-1108; 10. Farrar JT, et al. *Pain*. 2001;94(2):149-158; 11. Childs JD, et al. *Spine*. 2005;30(11):1331-1334; 12. Ostelo RW, et al. *Spine*. 2008;33(1):90-94.

Risk of Nausea and Vomiting Rises as the Number of Risk Factors Increases

- Risk factors may include
  - Age
  - Female gender
  - Motion sickness
  - PONV
  - Nonsmoking
  - Postoperative opioid use

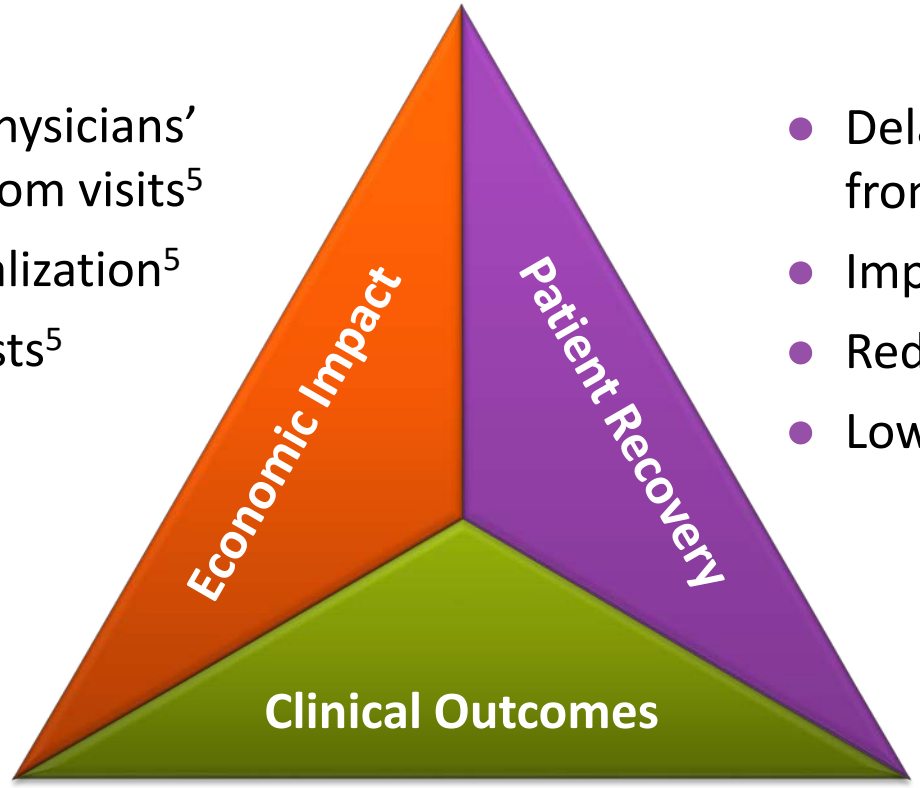


PONV=postoperative nausea and vomiting.

Apfel CC, et al. *Anesthesiology*. 1999;91(3):693-700.

Burden of OINV

- More hospitalizations, physicians' office and emergency room visits[5]
- Higher rates of rehospitalization[5]
- Increased healthcare costs[5]



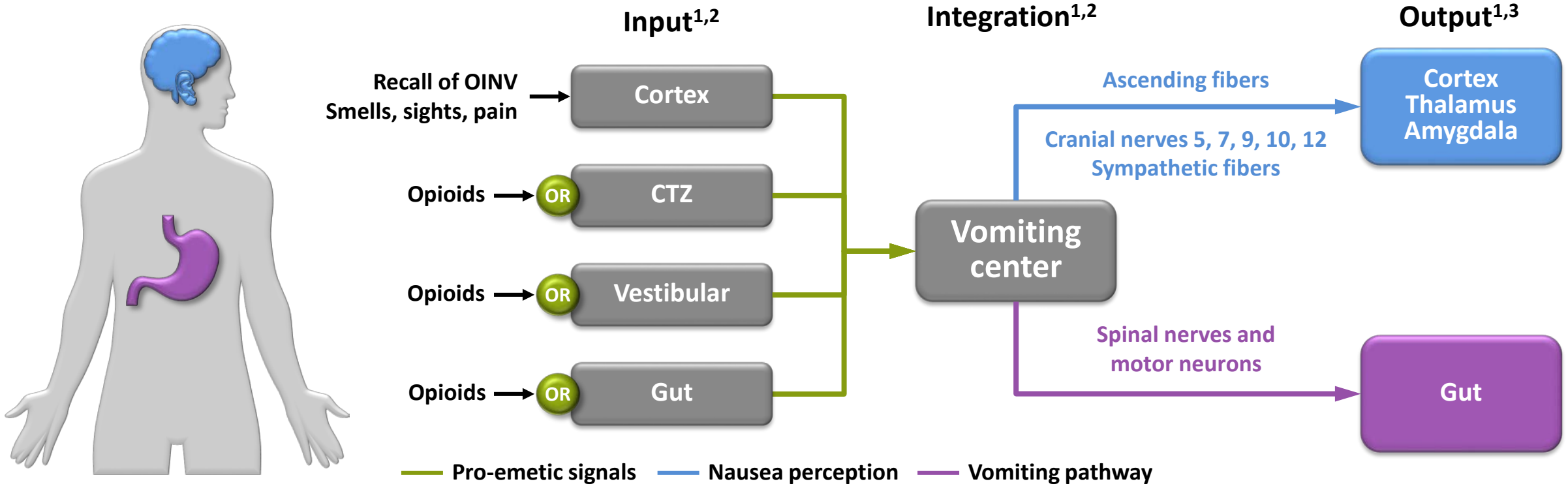
- Delay functional recovery from surgery[1]
- Impact appetite and ability to eat[2]
- Reduce patient mobility[2]
- Lower quality of life[2]

- May lead to less effective pain management
- Increase postoperative length of hospital stay by up to 25%[3]
- Lead to surgical complications[4]

1. White MC, et al. *Pediatr Anesth*. 2005;15: 683-688; 2. Mallick-Searle T & Fillman M. *J Am Assoc Nurse Pract*. 2017;29(11):704-710; 3. Pizzi LT, et al. *Pharmacotherapy*. 2012;32(6):502-514;
4. Boswell K, et al. *J Opioid Mang*. 2010;6(4):269-289; 5. Marrett E, et al. *Pain Ther*. 2016;5(2):215-226.

Pathophysiology of OINV: The Brain-GI Connection

- After receiving input from the brain and gut, the vomiting center[1,2]
  - Sends signals to higher brain regions, causing the perception of nausea[3]
  - Initiates a series of coordinated motor pathways to induce vomiting[1]

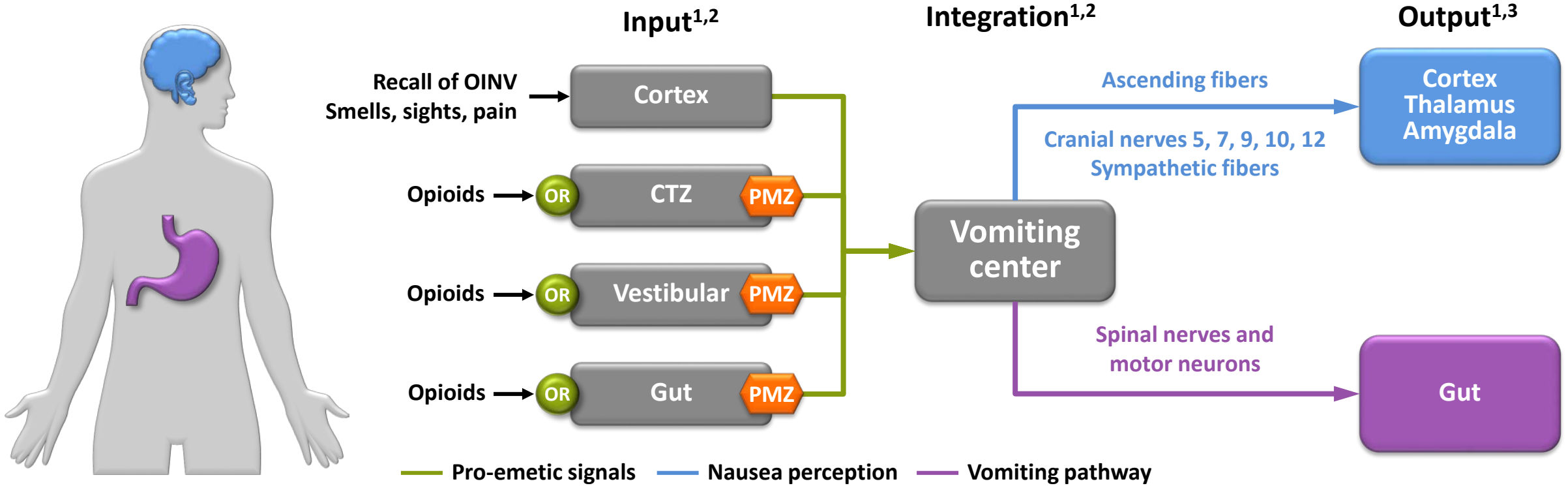


CTZ=chemoreceptor trigger zone; GI=gastrointestinal; OR=opioid receptor.

1. Coluzzi F, et al. *Curr Pharm Des.* 2012;18(37):6043-6052; 2. Porreca F, et al. *Pain Med.* 2009;10(4):654-662; 3. Horn CC, et al. *Eur J Pharmacol.* 2014;722:55-66.

Promethazine Addresses the Pathophysiology of OINV

- High CNS activity, histamine H1 receptor inverse agonist
- Safe, well-understood, highly utilized antiemetic agent effective at addressing nausea
- 12.5 mg lowest approved oral dose, dosed at 4 to 6 hours



CNS=central nervous system; CTZ=chemoreceptor trigger zone; OR=opioid receptor; PMZ=promethazine.

1. Coluzzi F, et al. *Curr Pharm Des.* 2012;18(37):6043-6052; 2. Porreca F, et al. *Pain Med.* 2009;10(4):654-662; 3. Horn CC, et al. *Eur J Pharmacol.* 2014;722:55-66.

Need New Approach for Managing Opioid-Induced Nausea and Vomiting

- Short-term use of immediate-release opioids is necessary for some acute pain patients
- OINV creates significant patient, clinical, and economic burdens
- There are no approved therapies for acute pain and OINV
- Promethazine blocks the underlying mechanisms of OINV
- Need for a single, proven therapy for the short-term management of acute pain while preventing OINV

Abuse Potential and Human Abuse Liability

Sandra D. Comer, PhD

Professor of Neurobiology (in Psychiatry)
Division on Substance Use Disorders
Columbia University

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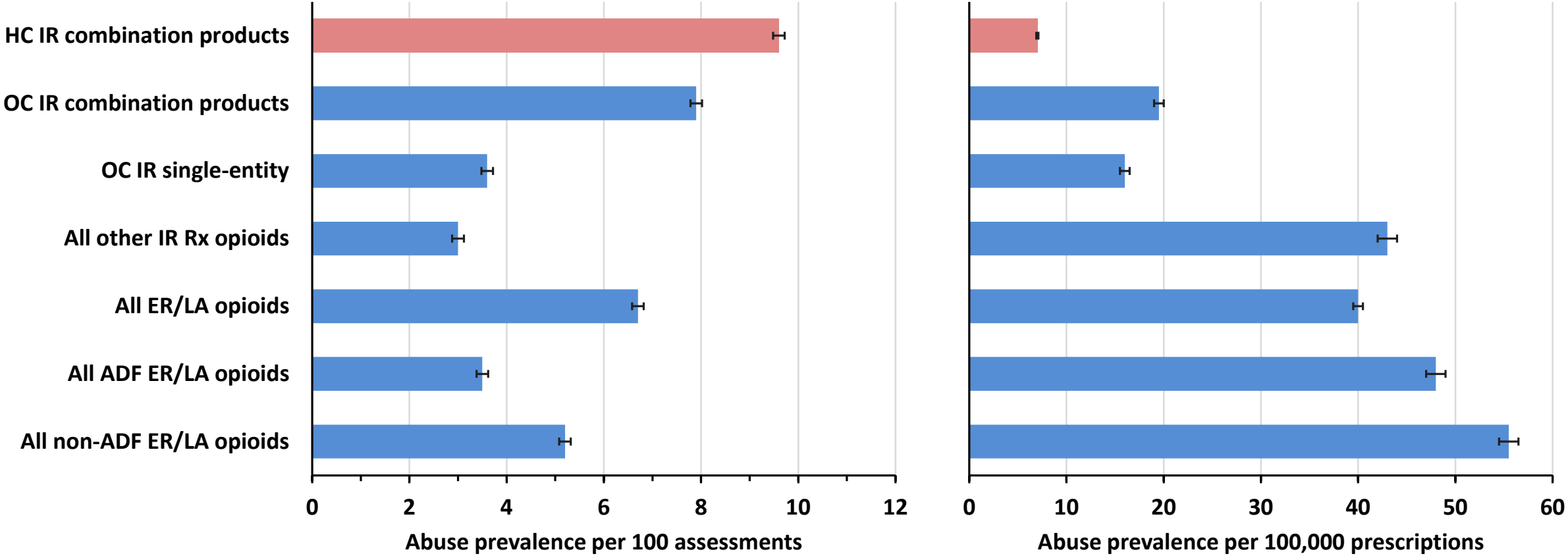
Incidence of Hydrocodone/Acetaminophen Abuse Related to Prevalence of Prescriptions

- Prevalence of past 30-day abuse and 95% CIs among adults assessed for substance abuse treatment in the NAVIPPRO® ASI-MV® system, 01/01/12 - 06/30/15

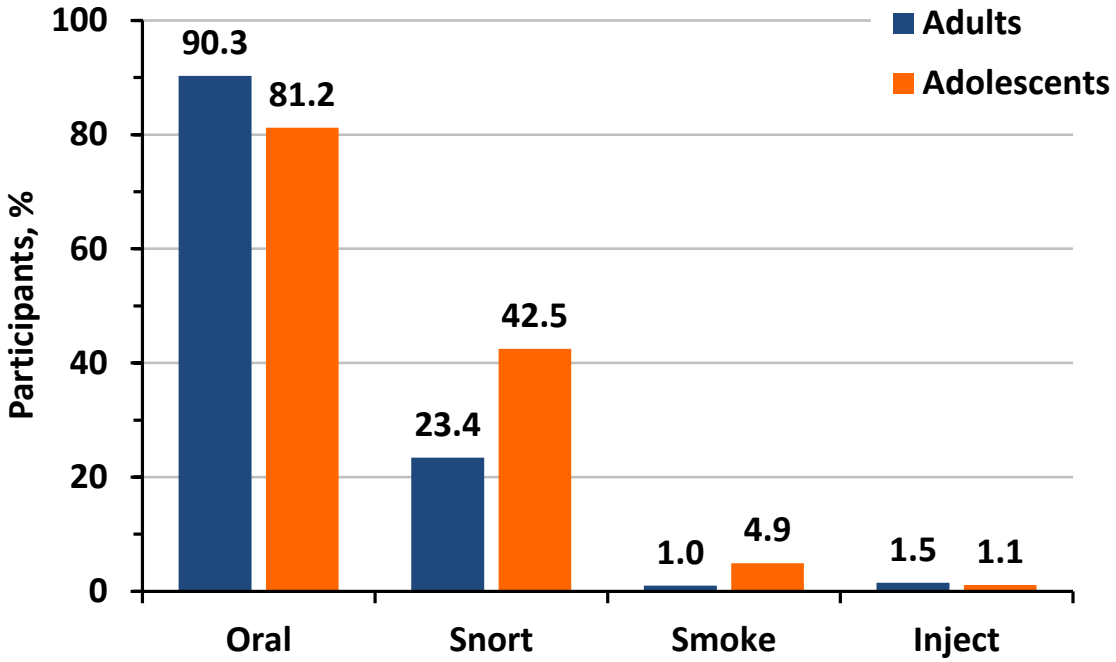


ADF=abuse deterrent formulation; CI=confidence interval; ER/LA=extended release long acting; HC=hydrocodone; IR=immediate release; OC=oxycodone; Rx=prescription.

Reprinted from Cassidy TA, et al. *Pharmacoepidemiol Drug Saf*. 2017;26:1071-1082 with permission of John Wiley & Sons, Inc.

Majority of Reported Abuse Occurs Orally

- Route of administration among past 30-day abusers of hydrocodone immediate-release combination products among adults and adolescents entering or being assessed for substance abuse treatment in the NAVIPPRO® ASI-MV® system, 01/01/12 - 06/30/15



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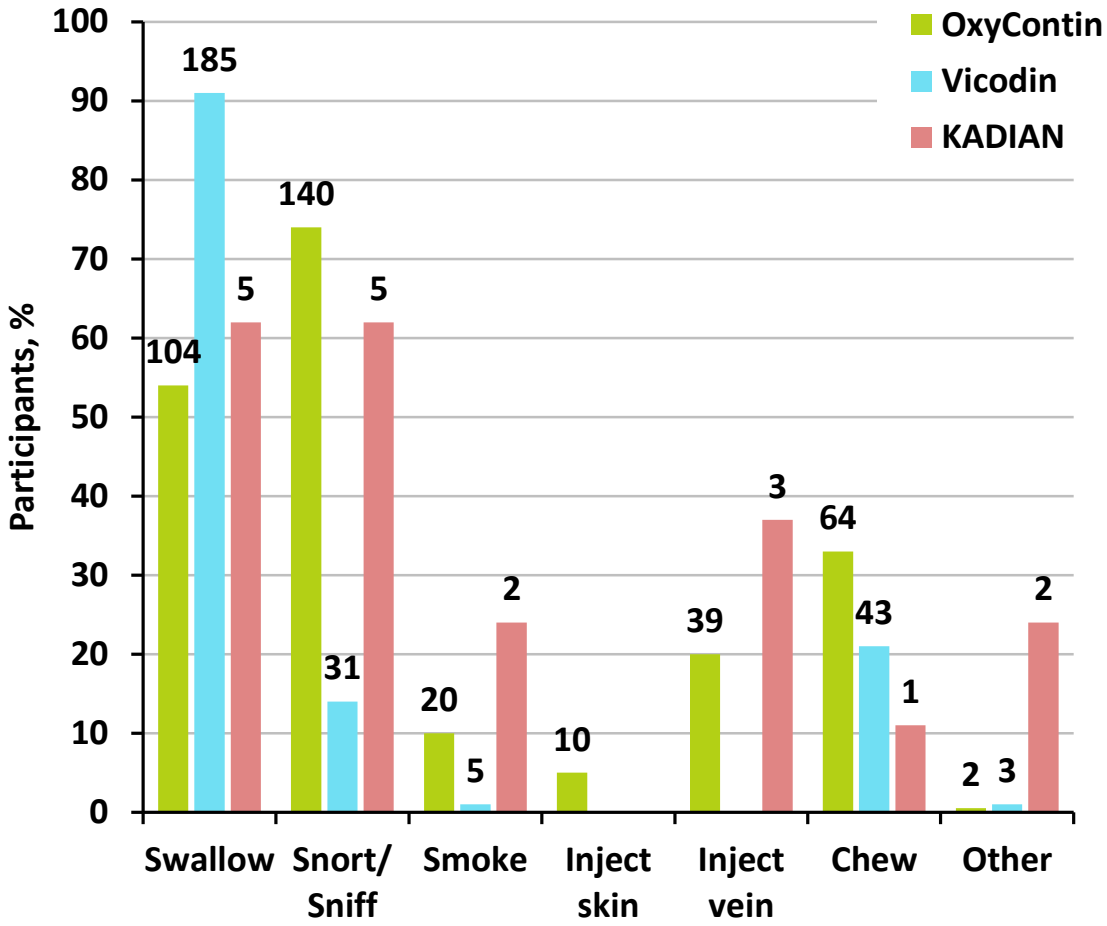
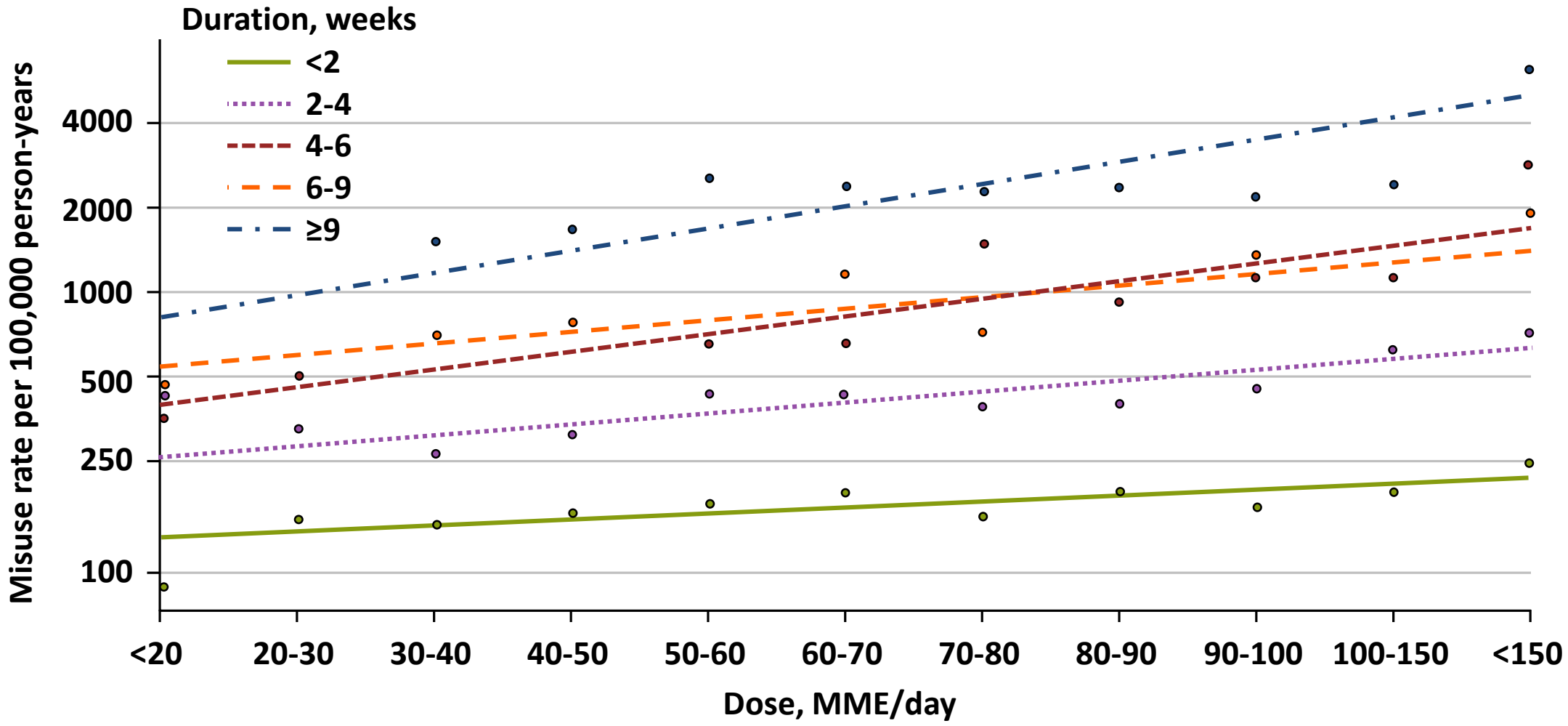


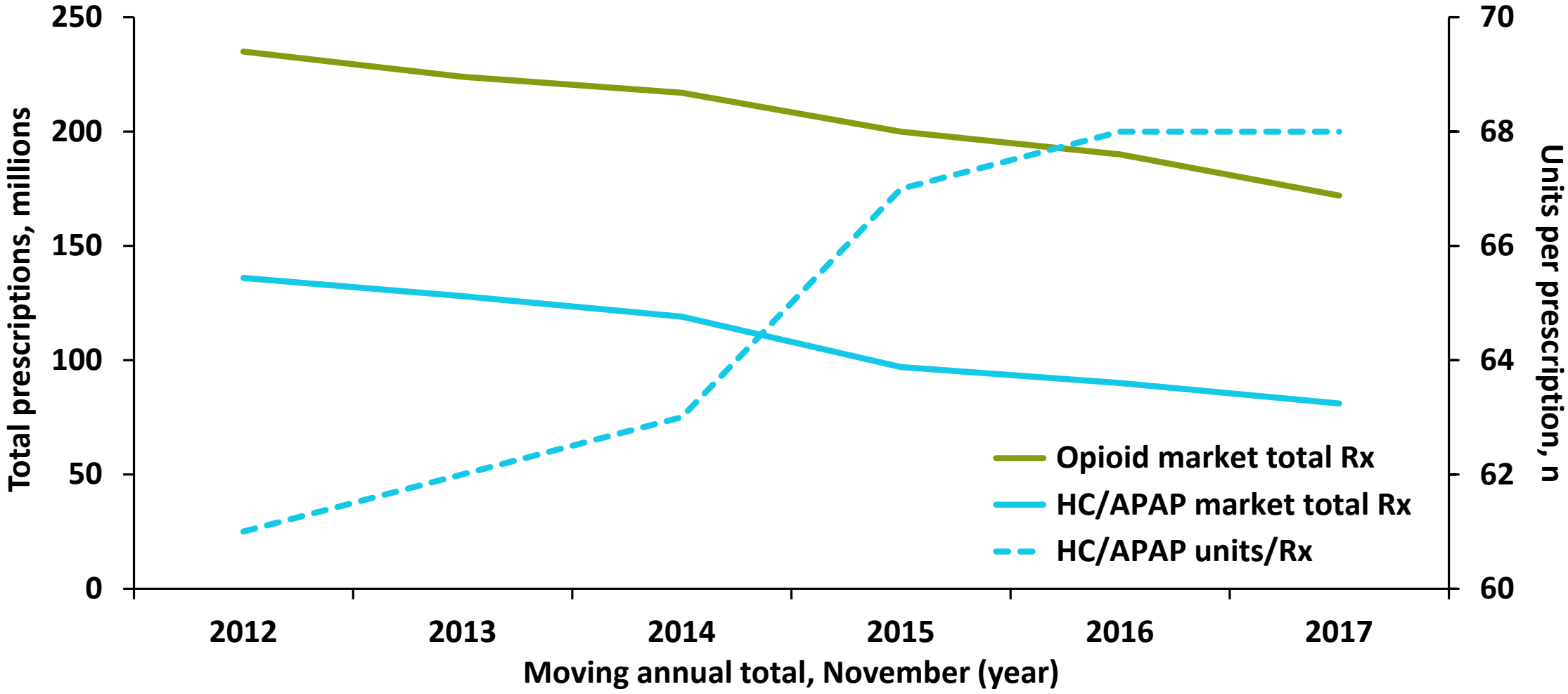
Note: Numbers above bars represent number of participants.
Reprinted from Katz N, et al. Internet-based survey on nonmedical prescription opioid use in the United States. *Clin J Pain*. 2008;24(6):528-535. https://jpournals.iww.com/clinicalpain/Abstract/2008/07001/Internet_based_Survey_of_Nonmedical_Prescription.7.aspx

Duration of Opioid Use Is Strongest Predictor of Misuse



MME=morphine milligram equivalent.

Hydrocodone Prescriptions Declining But Pills Per Prescription Increasing

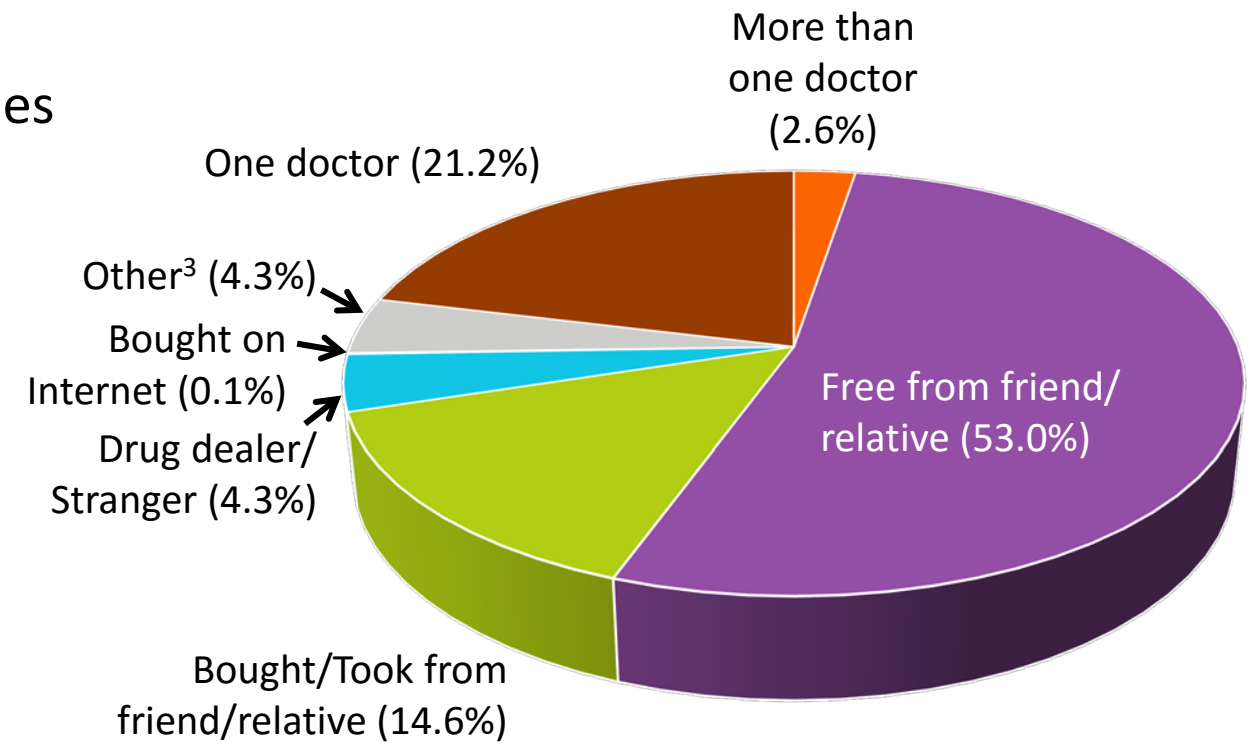


APAP=acetaminophen; HC=hydrocodone; Rx=prescription.
IQVIA NPA 2017.

Unused Opioids Contribute to Abuse and Diversion

- 67% to 92% of patients had unused opioids after completing treatment[1]
  - Based on 6 studies in 7 surgery types
    1. Orthopedic
    2. Urologic
    3. Dermatologic
    4. Thoracic
    5. Cesarean
    6. Dental
    7. General

Source where user obtained[2]



1. Bicket MC, et al. *JAMA Surg*. 2017;152(11):1066-1071.
2. Reprinted from Substance Abuse and Mental Health Services Administration, *Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings*, NSDUH Series H-48, HHS Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2014.
3. Other includes "Wrote Fake Prescription," "Stole from Doctor's Office/Clinic/Hospital/Pharmacy," and "Some Other Way."

Epidemiology of Promethazine Abuse Potential

- Prevalence is unknown, but abuse and misuse of promethazine occurs, often in combination with an opioid
  - Codeine/Promethazine cough syrup abuse reported since the 1990s[1]
  - Heroin/Promethazine abuse reported in southeast Asia in the mid 2000s[2]
  - NIH Study: ~9% of chronic pain patients tested positive for promethazine[1]
    - Half had active promethazine prescription
    - More common among patients taking long-acting opioids than those taking short-acting opioids
- Literature and surveillance systems note some associated morbidity and mortality
- Stated reasons for abuse of promethazine are varied
  - It is not clear whether desirability differs from opioids without promethazine

NIH=National Institutes of Health.

1. Lynch KL, et al. *Drug Alcohol Depend*. 2015;150:92-97; 2. Clatts M et al. *Susbst Use Misuse*. 2010;45(4):515-527.

Epidemiology of Hydrocodone and Promethazine Abuse and Misuse

- Hydrocodone and promethazine are commonly used in ways not directed by a healthcare provider, which contributes to morbidity and mortality
  - Hydrocodone is primarily abused orally
  - Reducing the duration of use and the number of tablets dispensed may help reduce opportunities for diversion and abuse
- Misuse and abuse of promethazine and opioids occur together
  - Anecdotal evidence suggests varying reasons for combined abuse
- Available epidemiologic data are not informative as to whether HYDEXOR™ is more likely to be abused, or if the addition of promethazine adds to the risk profile

Study of Abuse Potential at Supratherapeutic Doses

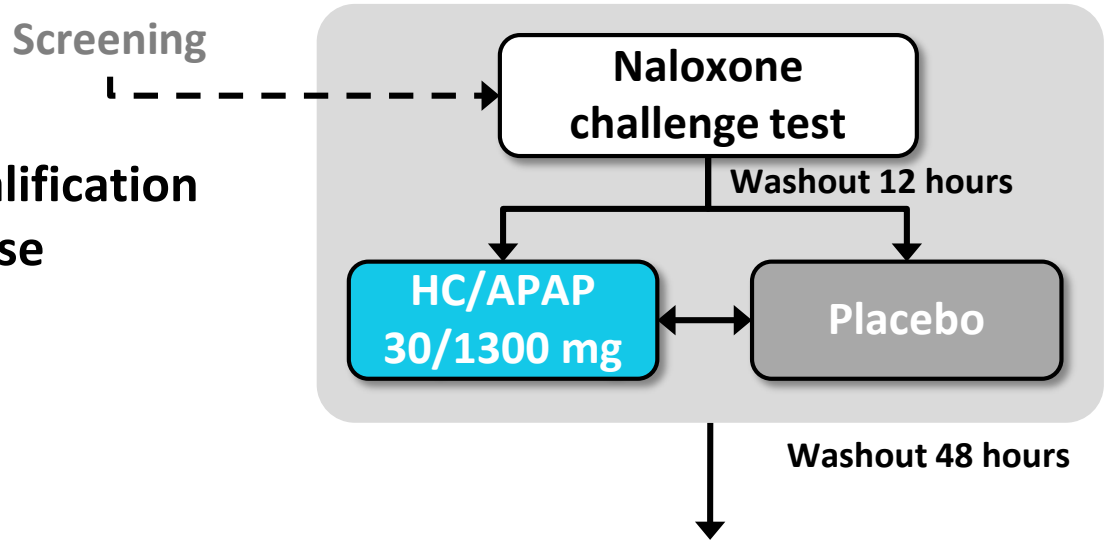
Study 007

- Single supratherapeutic doses
  - HYDEXOR™
  - Placebo
  - Hydrocodone (HC)/acetaminophen (APAP)
- Doses of HC/APAP/promethazine
  - **3x:** 22.5 mg/975 mg/37.5 mg
  - **5x:** 37.5 mg/1625 mg/62.5 mg
- Active control had no promethazine
- Primary endpoint
  - Maximum effect (E_{max}) of Drug Liking; visual analog scale 0 to 100

Therapeutic dose of HYDEXOR: 7.5 mg hydrocodone, 325 mg acetaminophen, and 12.5 mg promethazine.

Study Design

Study 007



Qualification Phase

Treatment Phase

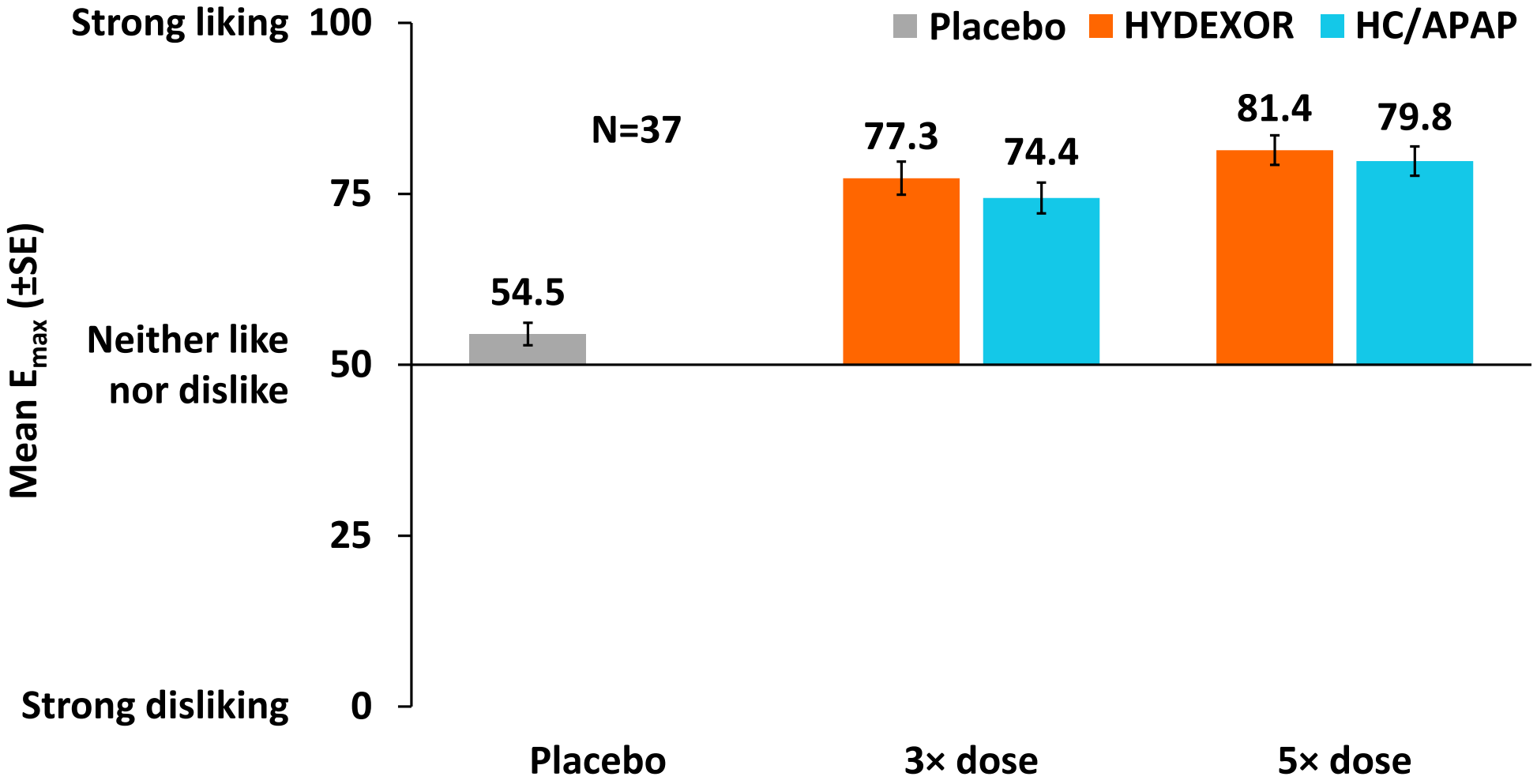
Treatment	HC/APAP/PMZ, mg
A. HYDEXOR™ 3×	22.5/975/37.5
B. HYDEXOR 5×	37.5/1625/62.5
C. HC/APAP 3×	22.5/975/—
D. HC/APAP 5×	37.5/1625/—
E. Placebo	

- ≥15 point difference on E_{max} for active to placebo
- 40 subjects randomized to a treatment sequence
- Assessments for up to 24 hr after each administration
- Washout minimum of 72 hr between treatments

APAP=acetaminophen; E_{max}=maximum effect; HC=hydrocodone; PMZ=promethazine.

No Significant Increase in Drug Liking with HYDEXOR™ vs HC/APAP

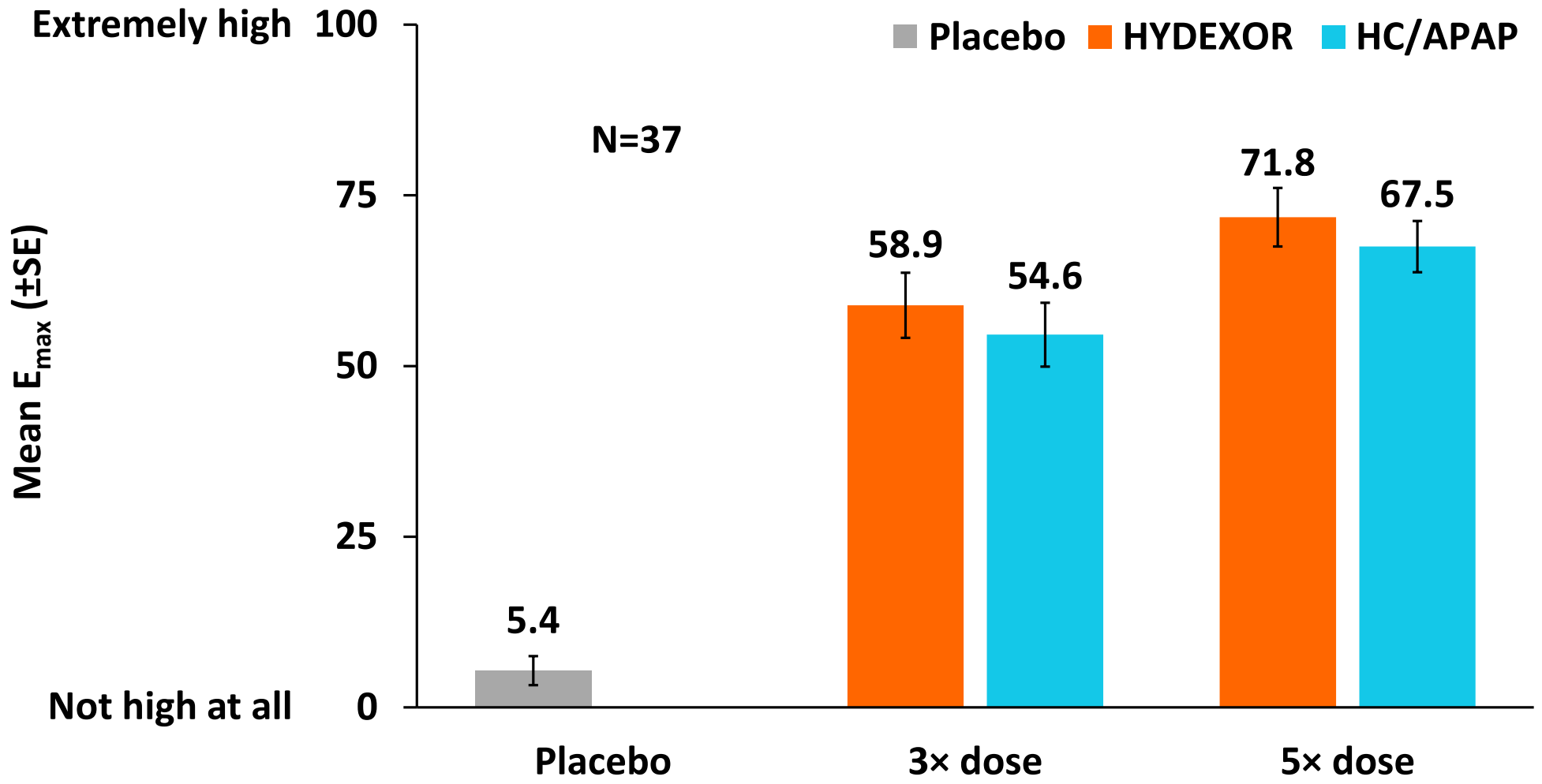
Study 007



APAP=acetaminophen; HC=hydrocodone; SE=standard error.

No Significant Difference in High with HYDEXOR™ vs HC/APAP

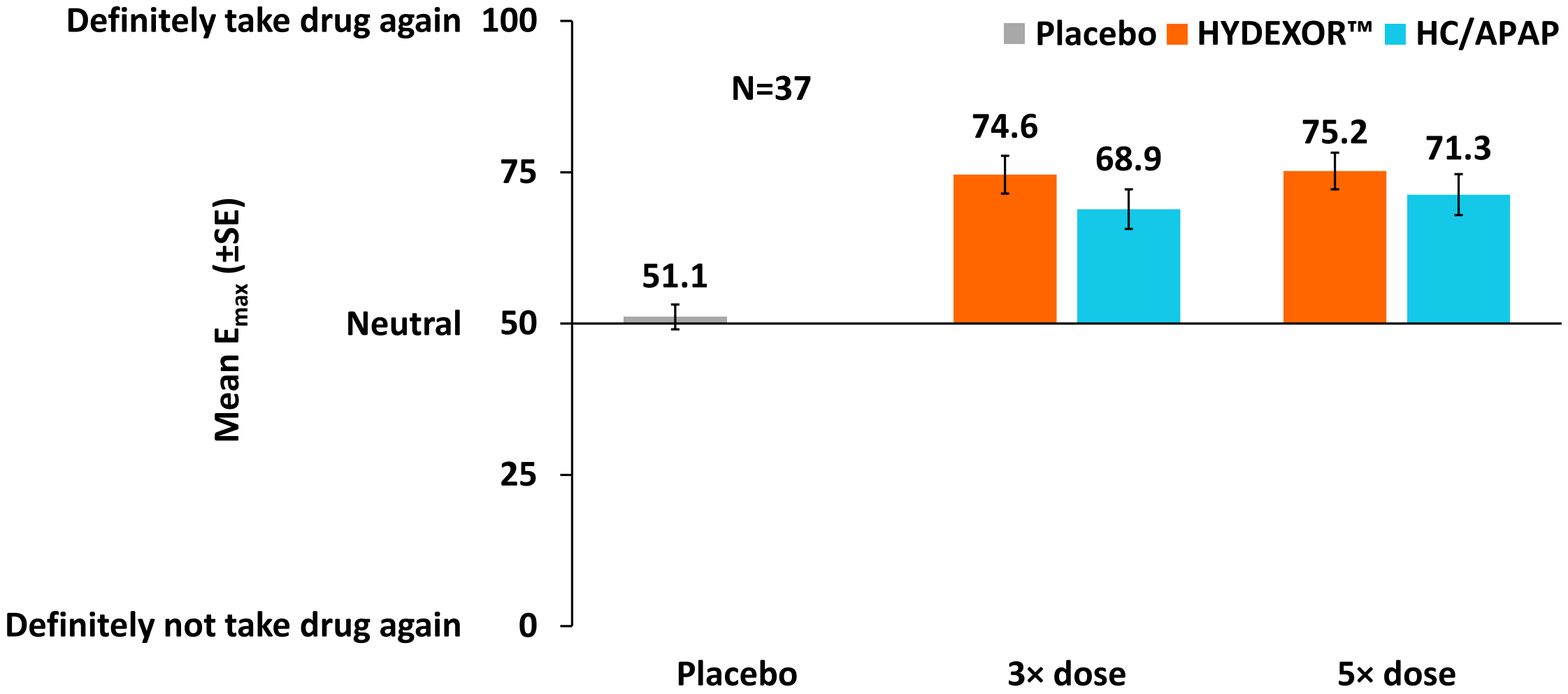
Study 007



APAP=acetaminophen; HC=hydrocodone; SE=standard error.

No Significant Difference in Take Drug Again with HYDEXOR™ vs HC/APAP

Study 007



APAP=acetaminophen; HC=hydrocodone; SE=standard error.

HYDEXOR™ Clinical Trial Product Dispensed and Returned

Studies 002, 003, and 006

Study	Patients randomized	Tablets dispensed	Tablets unaccounted, n (%)
002	211	6,002	24 (0.40)
003	252	7,560	26 (0.34)
006	179	16,110	173 (1.07)

Summary

- Study 007 showed no difference in abuse potential between HYDEXOR™ and active control, despite the addition of promethazine
  - Increased sedation with supratherapeutic doses of HYDEXOR compared to HC/APAP was observed and expected
- HYDEXOR clinical data show no evidence of abuse, misuse, or diversion
- HYDEXOR did not show an increase in abuse potential
  - HYDEXOR label contains class-wide black box warning for potential abuse, misuse, and diversion
- Charleston approach to risk mitigation targets challenges of oral abuse

Clinical Development and Efficacy

Bernard P. Schachtel, MD

Chief Scientific Officer

Charleston Laboratories, Inc.

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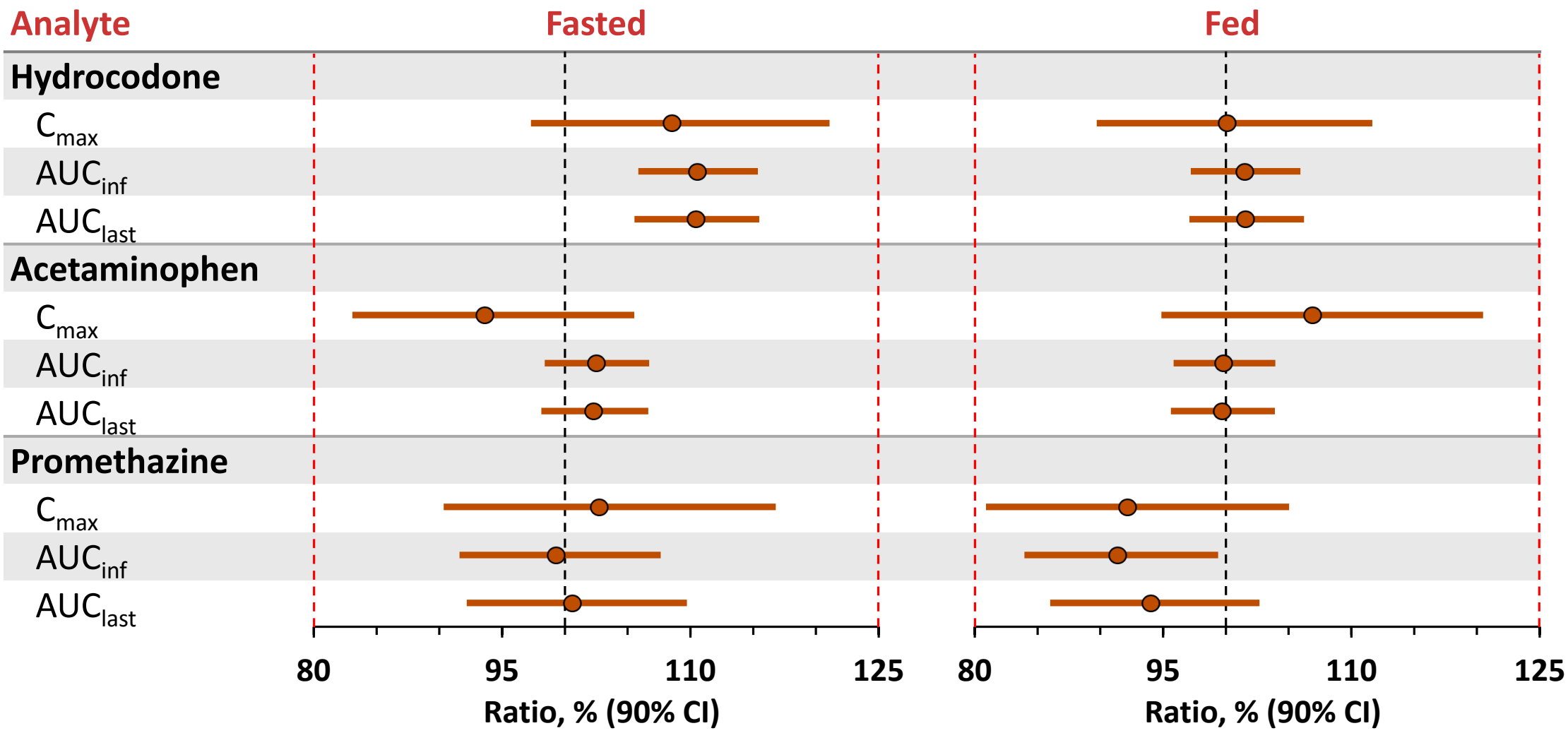
Clinical Development Program

Study	Purpose	n[1]	Patient/Study type
004	Relative bioavailability of HYDEXOR™ to RLDs (fasted, fed)	20	Healthy volunteers
012	Relative bioavailability of HYDEXOR to Norco® (fasted)	32	Healthy volunteers
013	Relative bioavailability of HYDEXOR to Norco (fed)	32	Healthy volunteers
002	Evaluate safety and efficacy	466	Oral surgery pain model
003	Evaluate safety and efficacy	552	Bunionectomy pain model
006	Evaluate safety in actual use	179	Acute osteoarthritis (flare) pain model
007	Evaluate abuse potential	40	Non-dependent, recreational opioid users

RLD=reference listed drug.
1. Randomized population.

Bioequivalence of HYDEXOR™ to Reference Listed Drugs

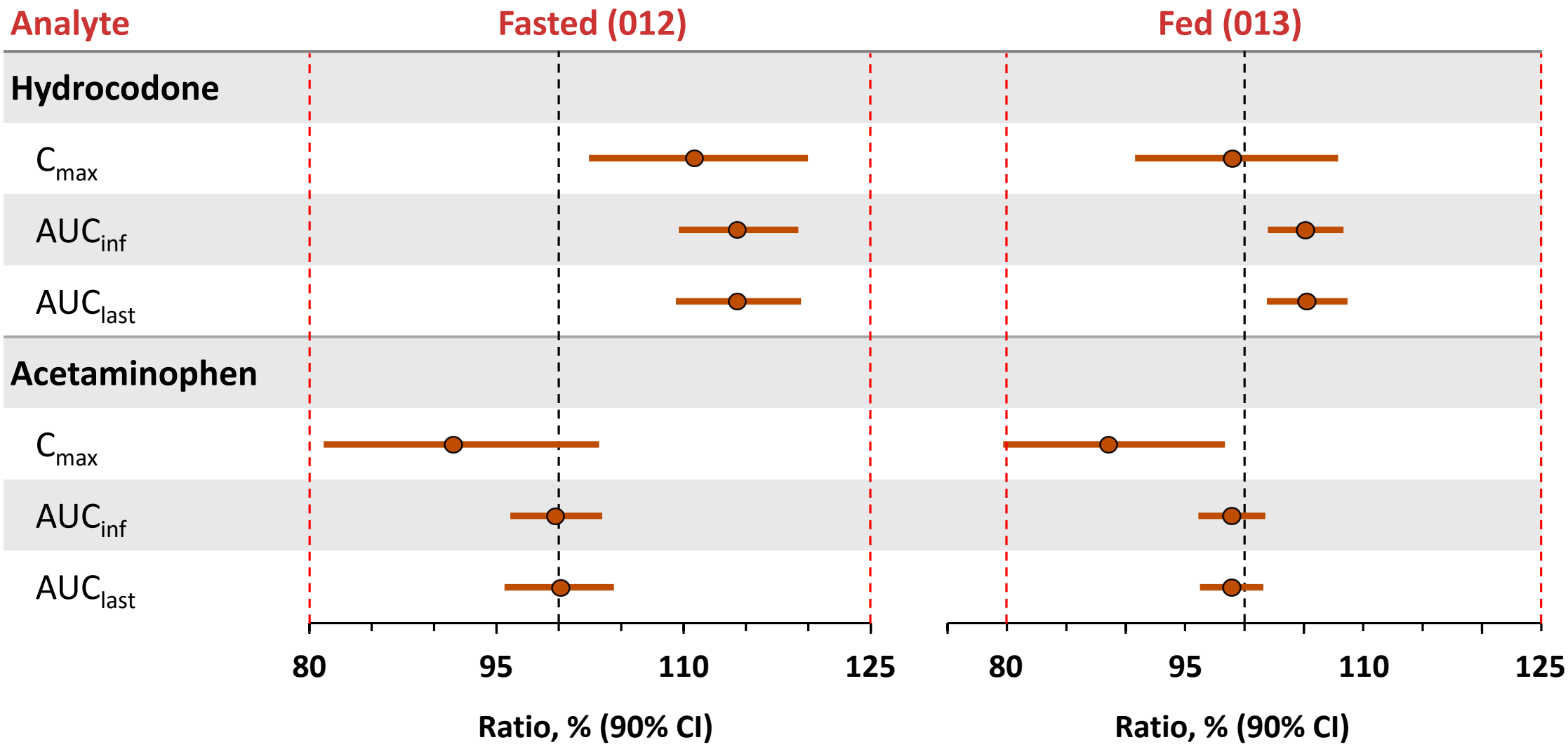
Study 004



Ratio, %=Test/Ref × 100.

Bioequivalence of Hydrocodone in HYDEXOR™ Compared With Norco®

Studies 012 and 013



Ratio, %=Test/Ref × 100.

Pivotal Efficacy Studies

Study 002 (Oral Surgery Pain Model)
Study 003 (Bunionectomy Pain Model)

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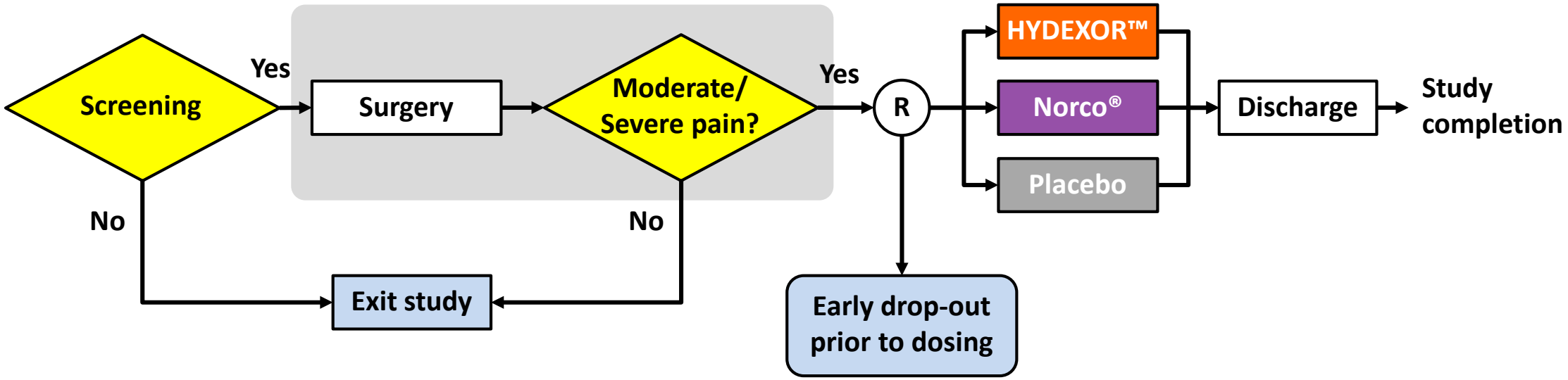
Study Design

Studies 002 and 003

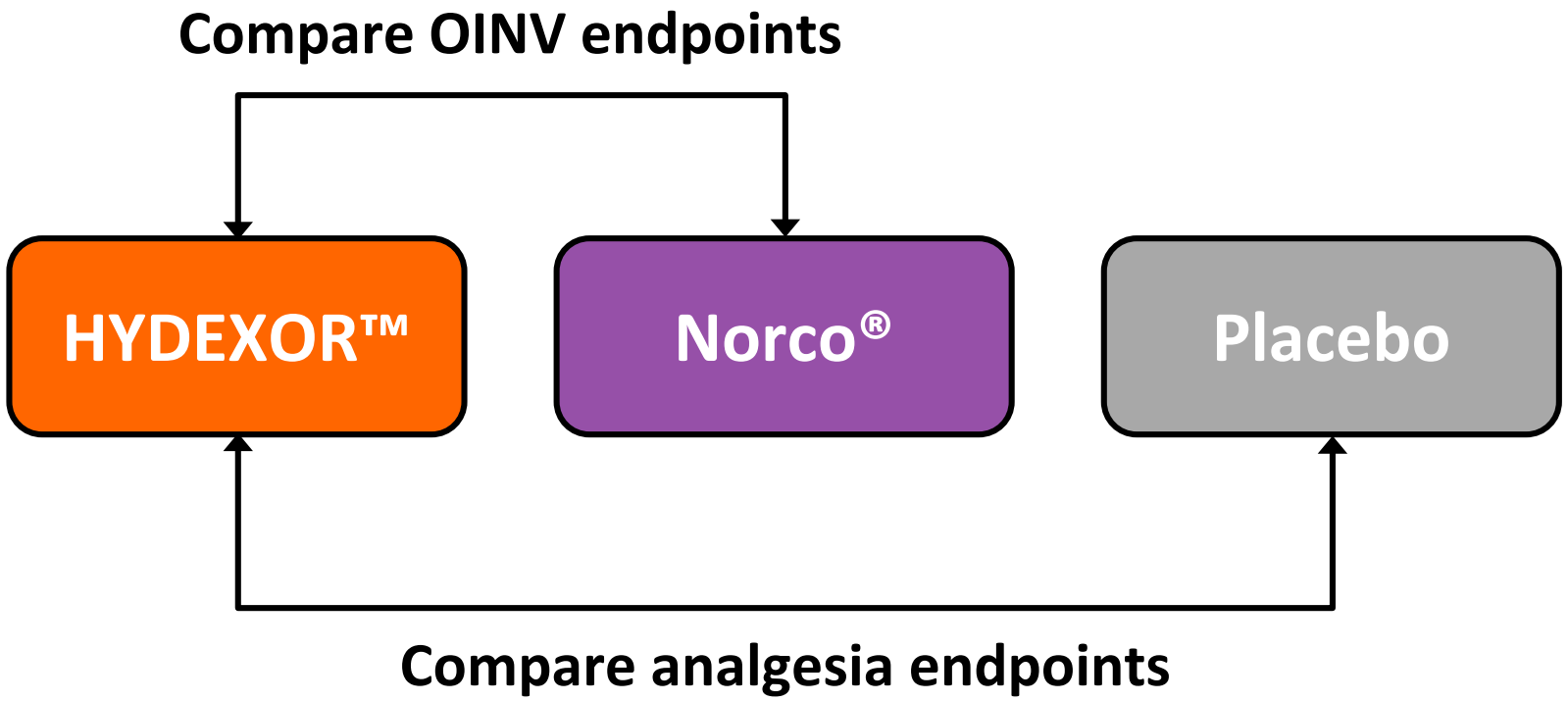
Multicenter, randomized, double-blind, placebo- and active-controlled, multiple-dose trials



		Co-primary endpoints	
	Pain model	Pain	OINV
Study 002	Oral surgery	$SPID_{24}$	3-component
Study 003	Bunionectomy	$SPID_{48}$	2 component

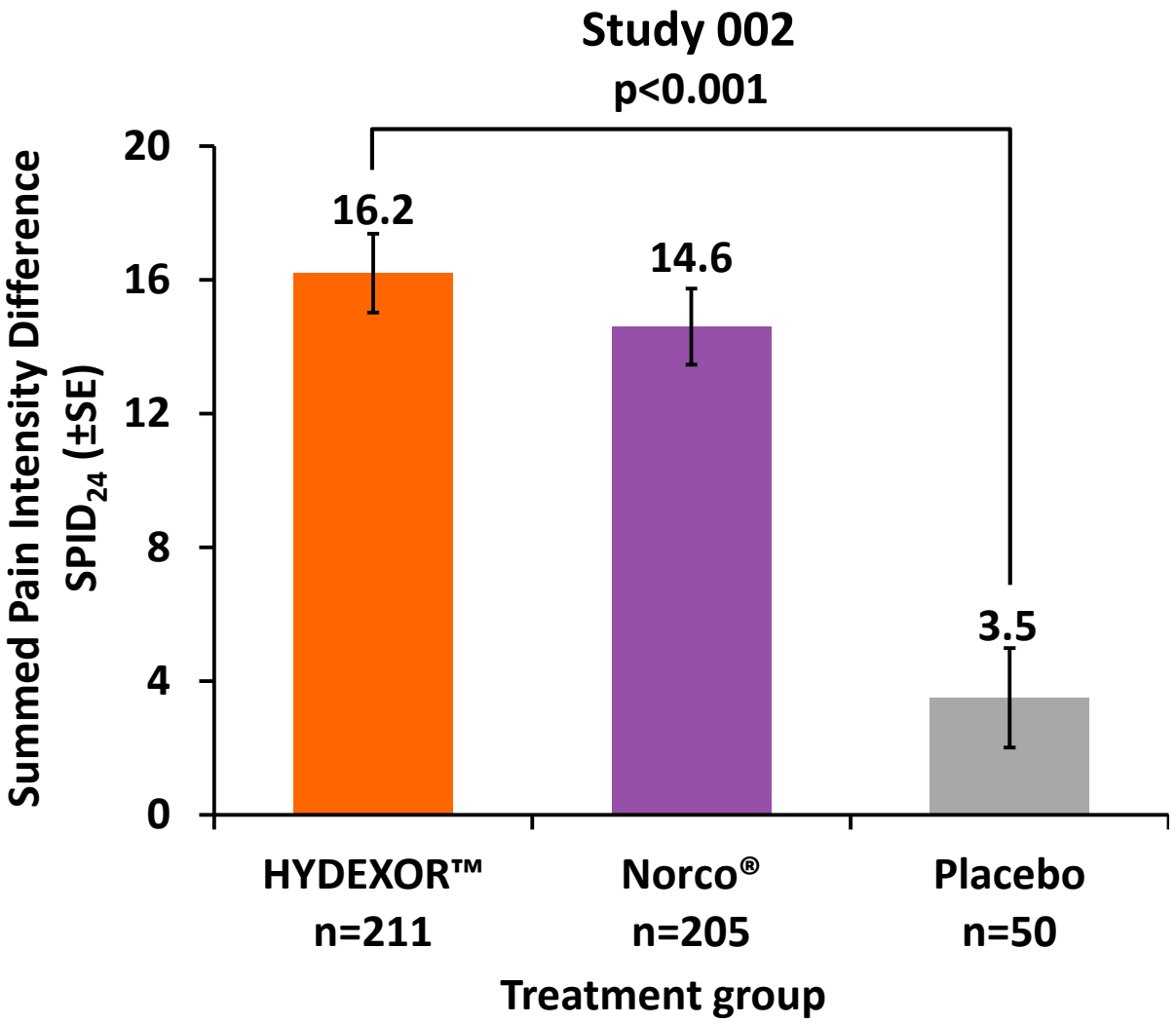
OINV=opioid-induced nausea and vomiting; R=randomized; $SPID_{24}$=summed pain intensity difference over 24 hours; $SPID_{48}$=summed pain intensity difference over 48 hours.

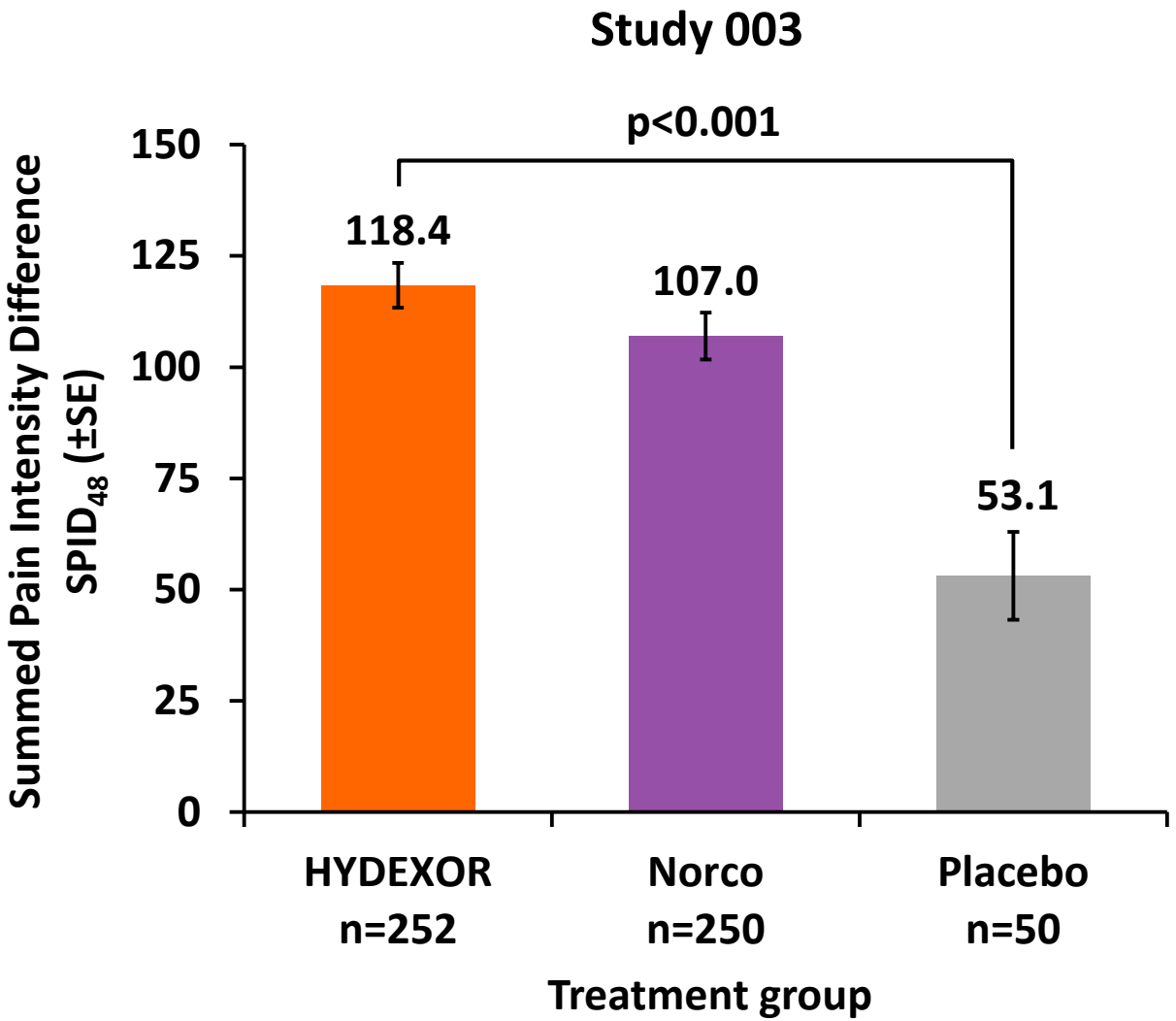
Study Designs Assess Acute Pain Reduction and Prevention and Reduction of OINV



Met Analgesic Co-Primary Endpoint

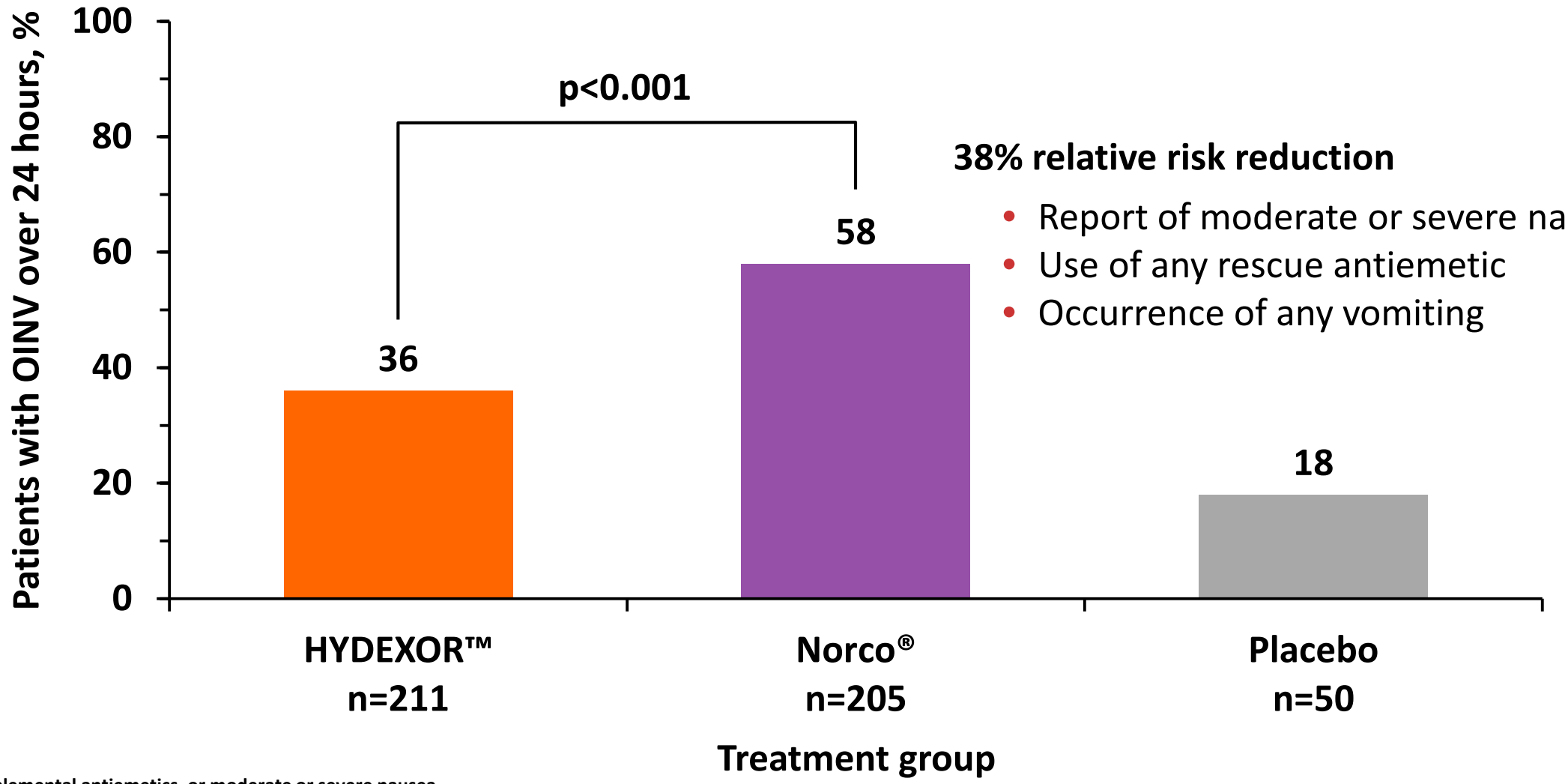
Studies 002 and 003, ITT Population





Met OINV Co-Primary Endpoint (3 Components[1])

Study 002, ITT Population



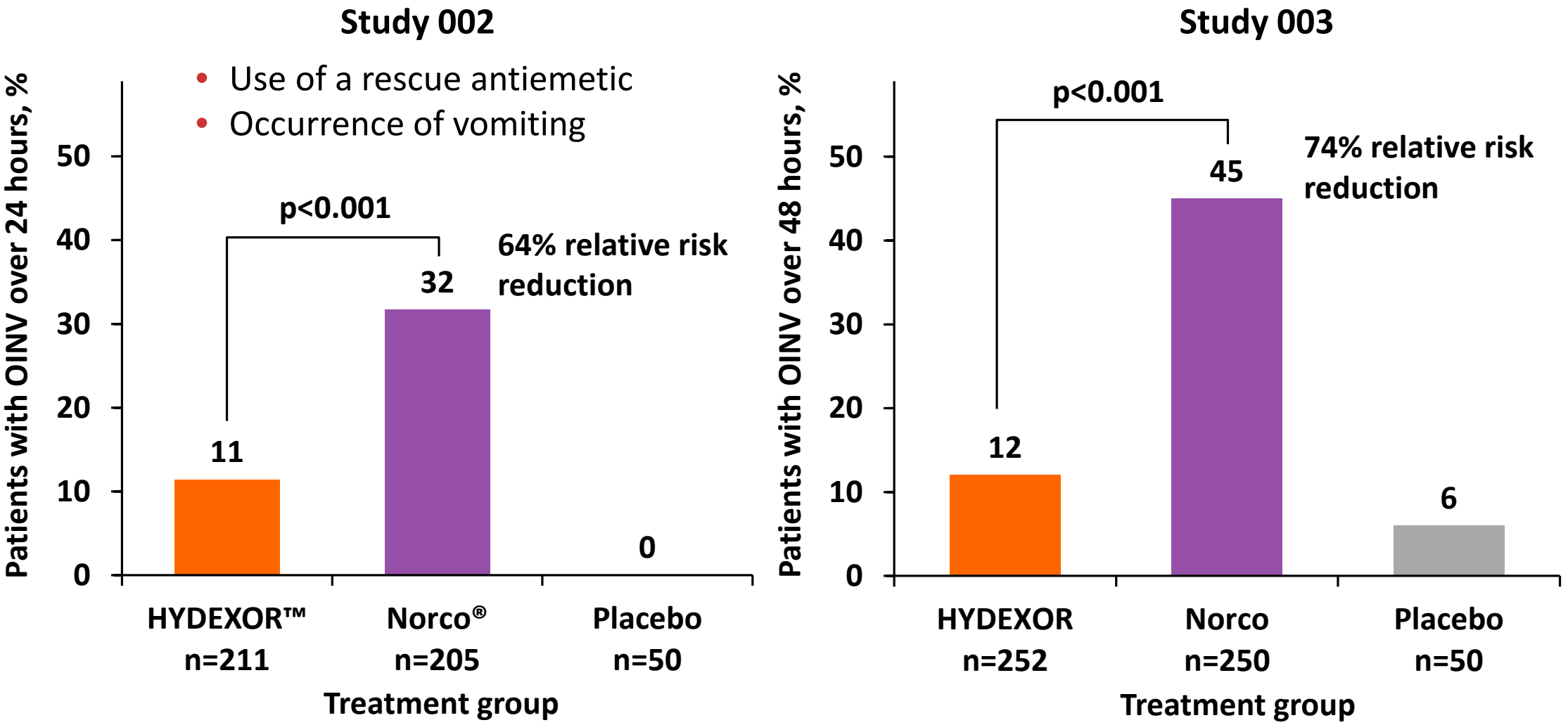
38% relative risk reduction

- Report of moderate or severe nausea
- Use of any rescue antiemetic
- Occurrence of any vomiting

1. Vomiting, use of supplemental antiemetics, or moderate or severe nausea.

Met OINV Endpoint (2 Components)

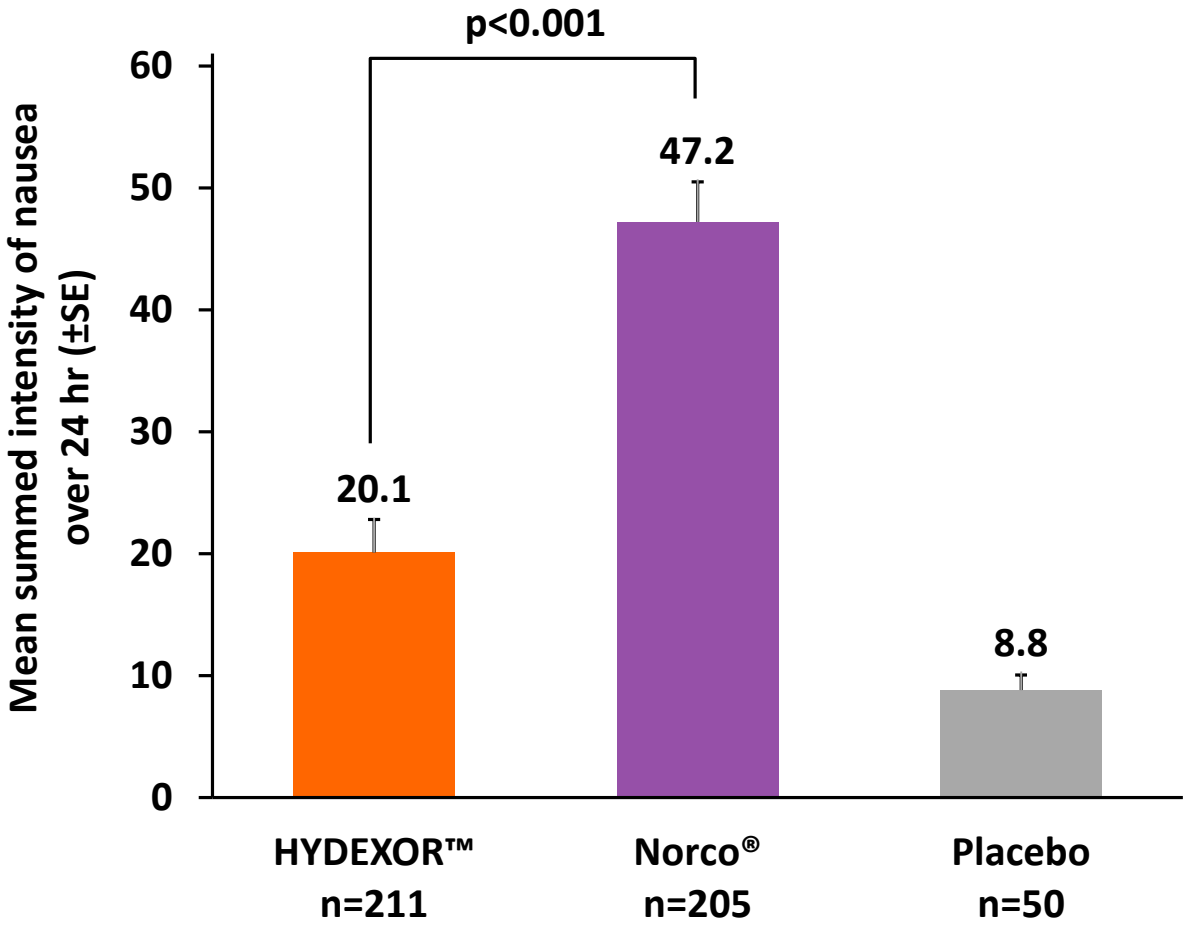
Studies 002 and 003, ITT Population



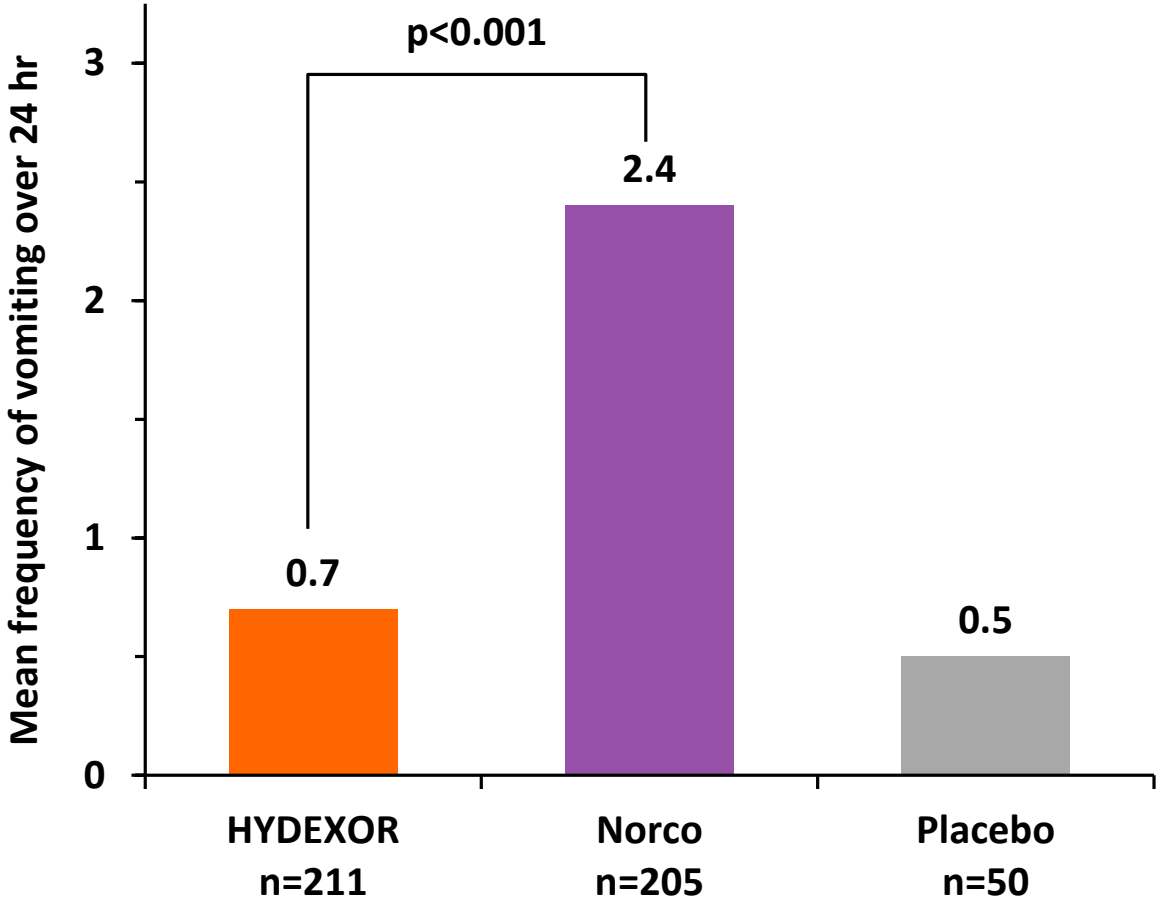
Intensity of Nausea and Frequency of Vomiting Over 24 Hours

Study 002

Intensity of nausea over 24 hours

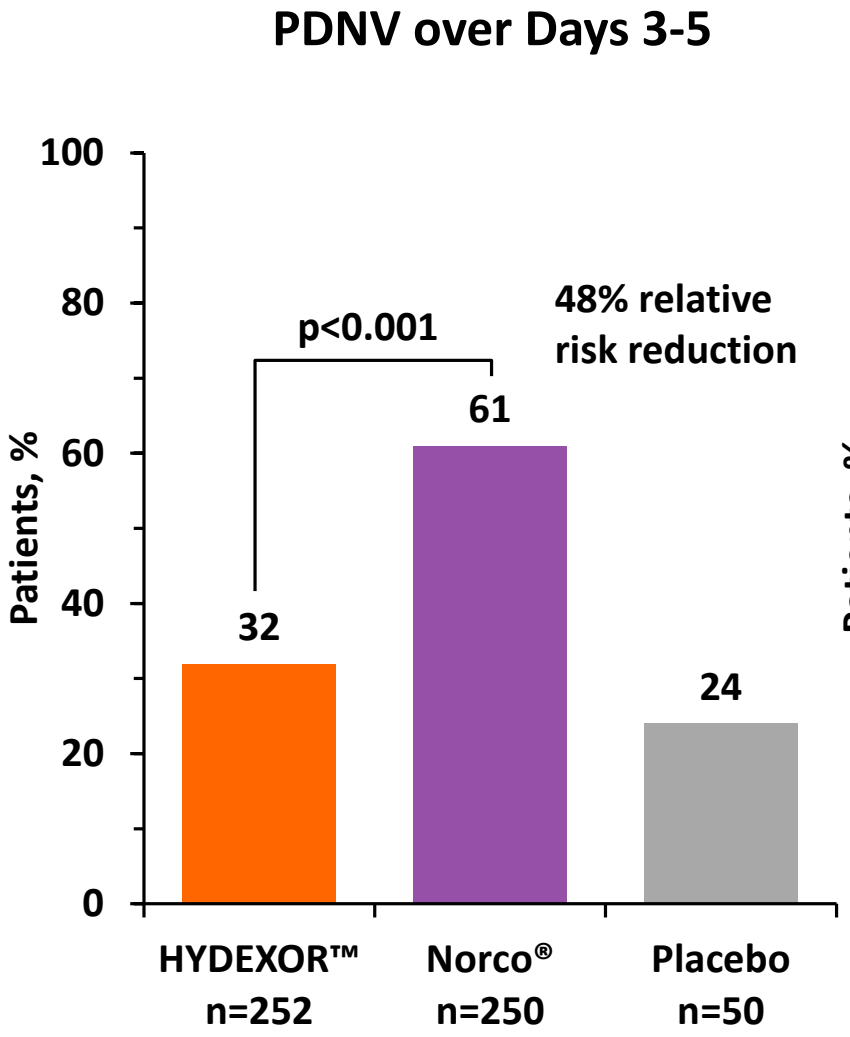


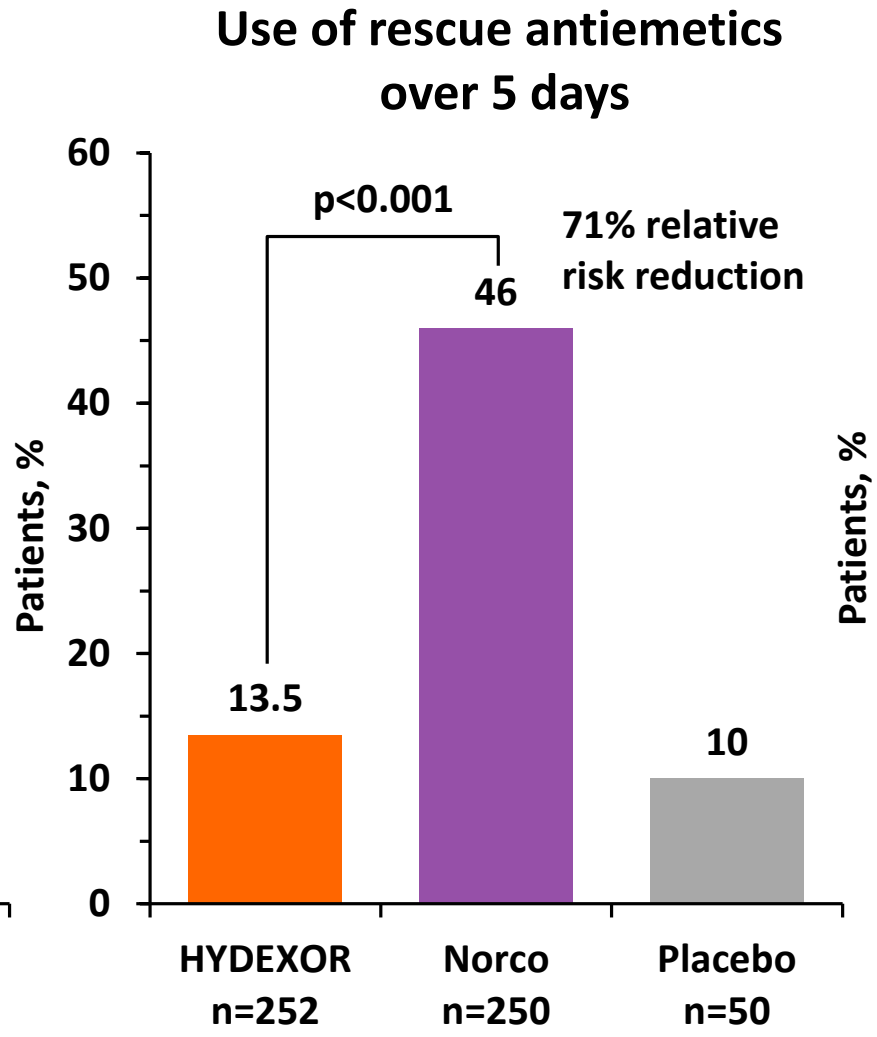
Frequency of vomiting over 24 hours

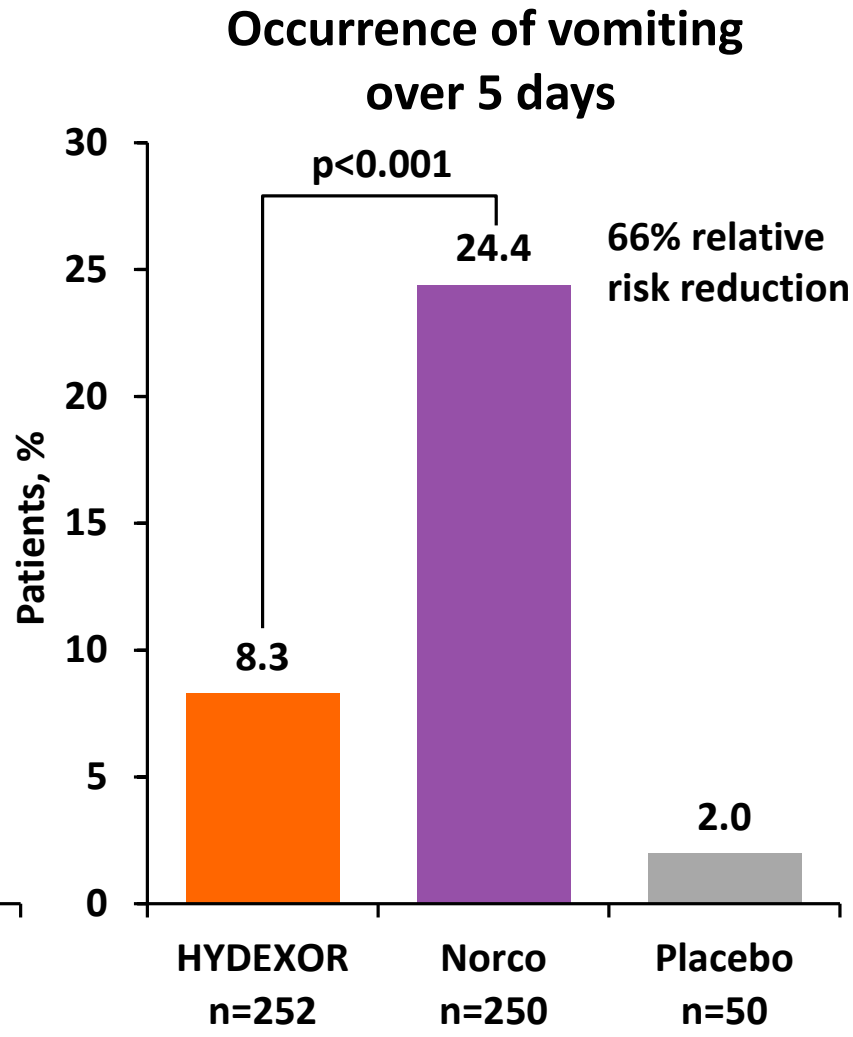


PDNV Over Days 3-5 and Use of Rescue Antiemetics and Occurrence of Vomiting Over 5 Days

Study 003



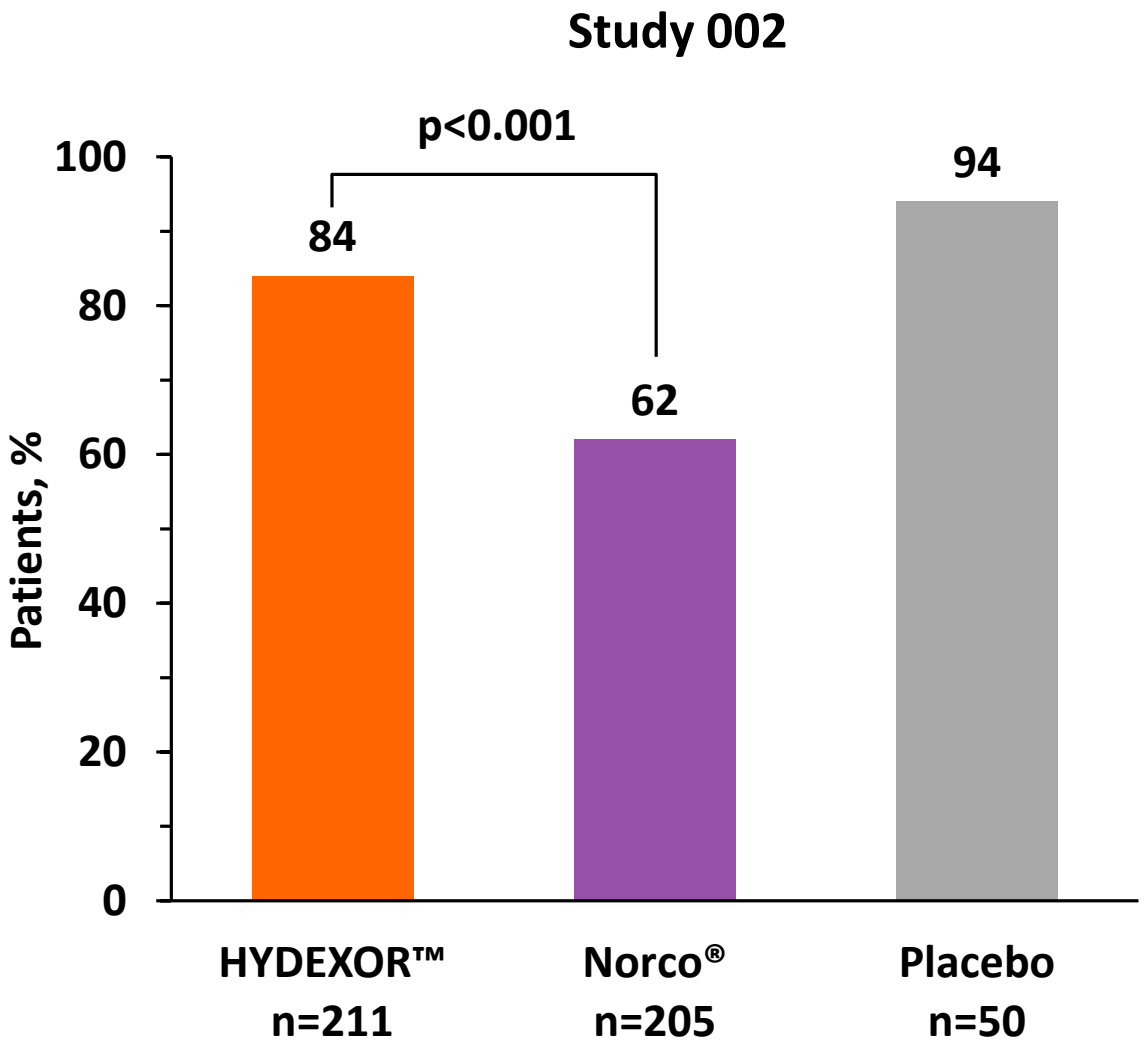


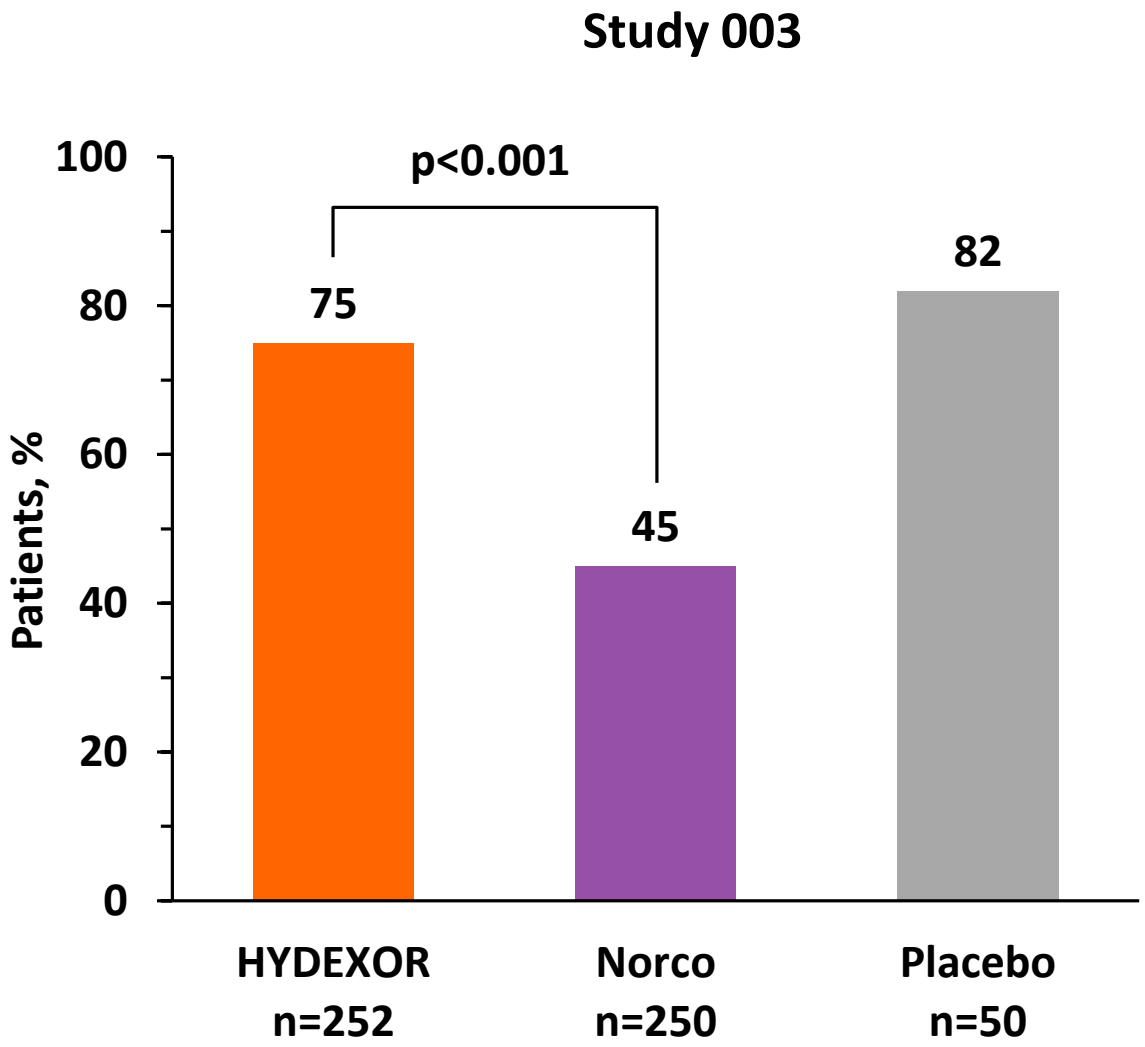


PDNV=post-discharge nausea and vomiting.

Complete Response Over 5 Days

Studies 002 and 003





No emetic episode and no use of rescue antiemetic.

Efficacy Conclusions: HYDEXOR™

- Demonstrated bioequivalence to hydrocodone, acetaminophen, and promethazine
- Two pivotal trials demonstrated
  - Significant reduction in pain compared with placebo
  - Significant reduction in the risk of OINV compared with Norco®
  - Consistent results across secondary endpoints
  - Results durable over the 5-day treatment period

HYDEXOR™ Safety

Thomas Smith, MD

Chief Medical Officer

Charleston Laboratories, Inc.

Charleston LABORATORIES

Clinical Safety

- HYDEXOR™ ingredients are well-known; no new safety concerns identified
- HYDEXOR was generally well-tolerated
  - Adverse events (AEs) were mostly mild or moderate in intensity and limited in duration
  - Increased incidence of drowsiness observed
  - Increased incidence of lowered blood pressures observed within 24 hours
  - No respiratory depression
- Warnings and precautions proposed for HYDEXOR are consistent with those of the reference listed drugs (RLDs)

Clinical Development Program

Study	Purpose	n[1]	Patient/Study type
002	Evaluate safety and efficacy	466	Oral surgery pain model
003	Evaluate safety and efficacy	552	Bunionectomy pain model
006	Evaluate safety in actual use	179	Acute osteoarthritis (flare) pain model
007	Evaluate abuse potential	40	Non-dependent, recreational opioid users

RLD=reference listed drug.
1. Randomized population.

Adverse Event Collection

Studies 002 and 003

- Pooled analysis of 2 randomized pivotal studies
  - Study 002: Pain following dental surgery – 466 patients
  - Study 003: Pain following bunionectomy – 552 patients
- Solicited surveillance by directive questionnaire
  - Nausea and vomiting (assessed as efficacy measures)
  - Nine other common opioid side effects ('Opioid Symptoms Scale' – OSS)
- All other AEs captured in conventional spontaneous reporting fashion (non-directive)
- Three SAEs noted across 3 studies[1] (1197 pts) – none study drug related

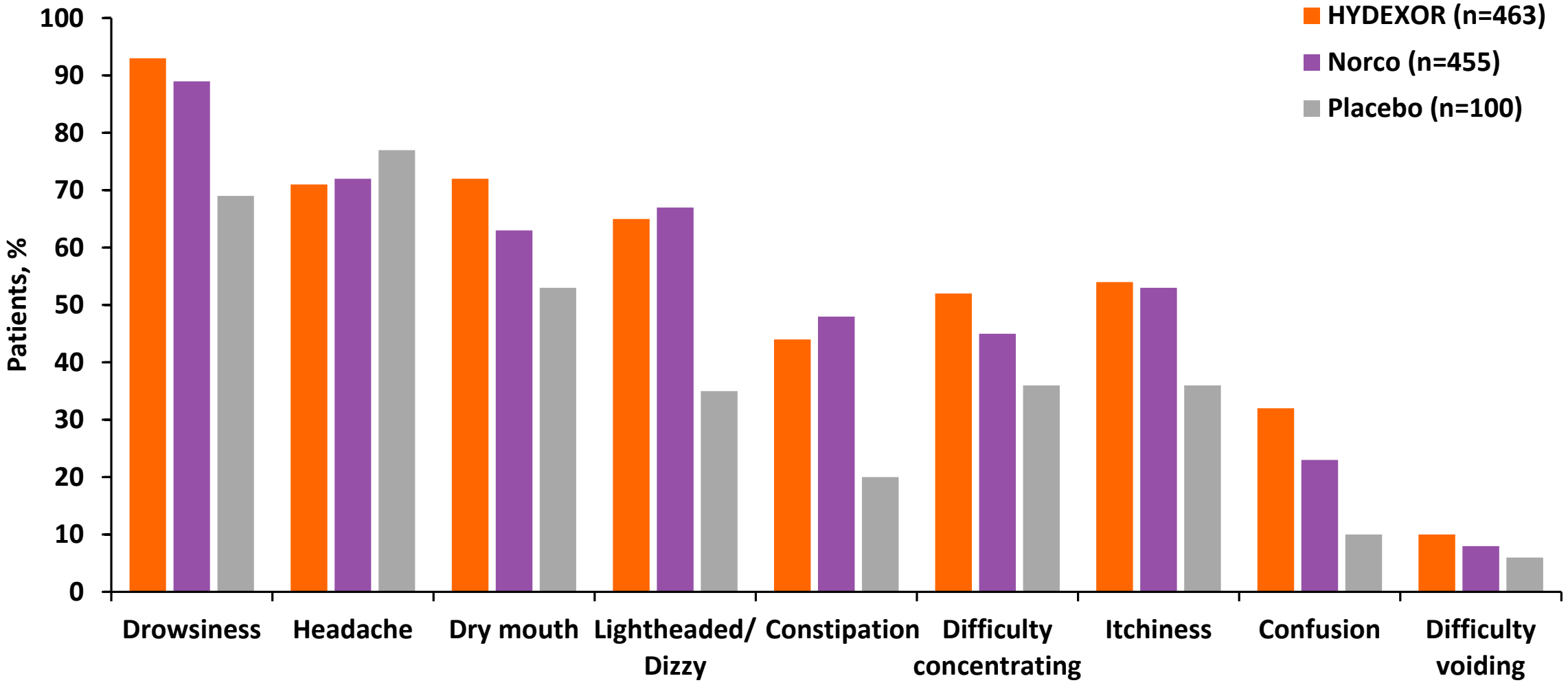
SAE=serious adverse event.
1. Studies 002, 003, and 006

Opioid Symptoms Scale (OSS) to Solicit Opioid-Related Side Effects

- Other 9 common opioid-related side effects
  - Drowsiness, headache, dry mouth, dizziness, constipation, difficulty concentrating, itchiness, confusion, and difficulty voiding
- Each symptom rated on a 0-10 Likert scale

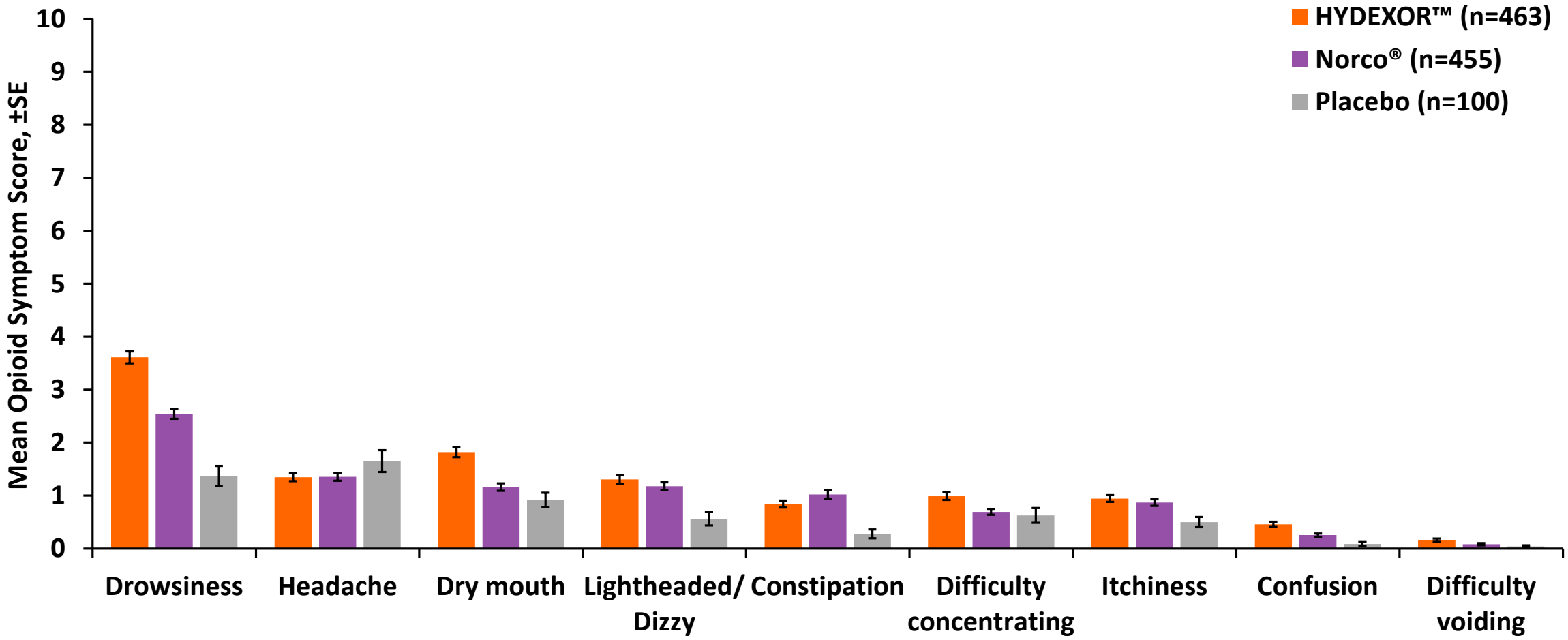
Opioid Symptoms Comparable Between HYDEXOR™ and Norco® (Solicited)

Studies 002/003



Mean Intensity of Opioid Symptoms Over a 5-Day Time Period (Solicited)

Studies 002/003



Most Adverse Events Were Mild or Moderate (Spontaneously Reported, Excluding N/V and Opioid-Related)

Studies 002/003

	HYDEXOR™ n=463	Norco® n=455	Placebo n=100
Total adverse events, n	**167**	**176**	**42**
Patients with AEs, n	122	119	28
Mild, n (%)	68 (56)	65 (55)	22 (79)
Moderate, n (%)	44 (36)	51 (43)	5 (18)
Severe, n (%)	10 (8)	3 (3)	1 (4)

N/V=nausea and vomiting.

Incidence of Adverse Events of Special Interest (AESI) (Spontaneously Reported)

Studies 002/003

AESI	Patients, n (%) HYDEXOR™ n=463	Norco® n=455	Placebo n=100
Syncope/Presyncope	8 (1.8)	0	1 (1.0)
Hypotension/Blood pressure decreased	3 (0.6)	3 (0.7)	1 (1.0)
Pyrexia/Body temperature increased	11 (2.4)	1 (0.2)	3 (3.0)
Respiratory depression	0	0	0
Dyspnea	1 (0.2)	4 (0.9)	1 (1.0)
Seizure	0	0	0
Dyskinesia	1 (0.2)	0	0

No AESIs were deemed severe or resulted in dose reduction or clinically significant consequences or sequelae.

Adverse Events of Special Interest

Studies 002/003

- No severe AESIs
- No dose reductions, study-drug interruptions, or discontinuations
- No clinically significant consequences or sequelae
- All resolved without recurrence while on treatment
- All events noted in the labels of the RLDs are included in the proposed warnings and precautions for HYDEXOR™

Study 006 (Actual-Use Safety Study)

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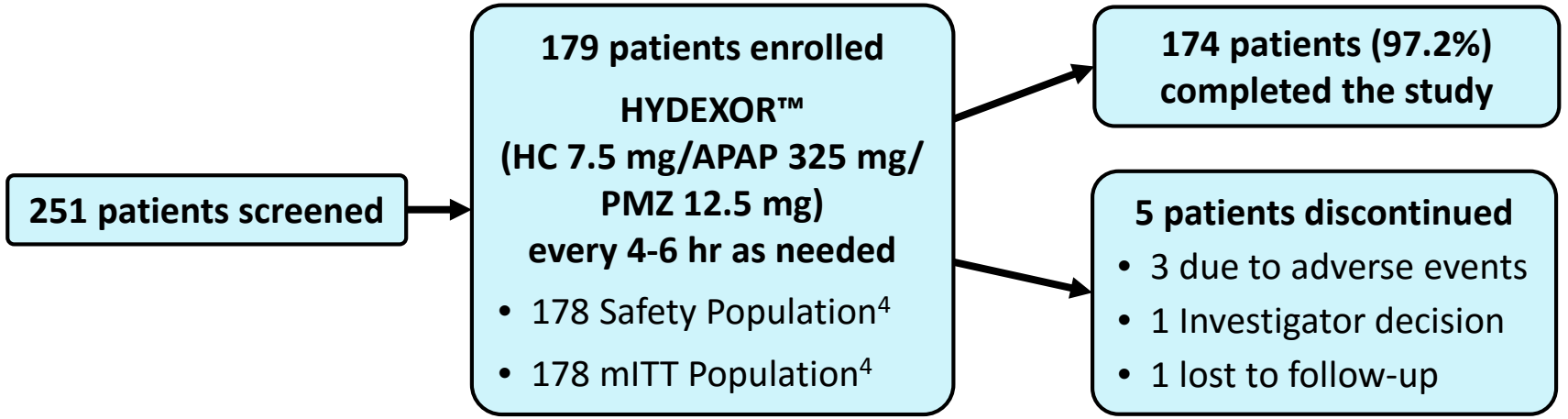
Study 006, an Open-Label, Actual-Use,[1] Single-Group Phase 3 Safety Study in Osteoarthritis (OA)[2,3]

- Adults ≥18 years old with acute flares of OA of the knee and/or hip
- Moderate to severe pain of signal joint during an acute flare
- Dissatisfied with NSAIDs
- Opioid naïve



On average, patients used 2.0 doses/day of HYDEXOR for acute flares of OA of the knee or hip

HC/APAP=hydrocodone and acetaminophen; mITT=modified Intent-to-Treat; NSAID=nonsteroidal anti-inflammatory drug; PMZ=promethazine.

1. Patients with osteoarthritis used HYDEXOR on an as-needed basis to treat an acute flare of OA of the knee or hip over a 14-day study to evaluate the safety and effectiveness of HYDEXOR.
2. Schachtel B, et al. Poster presented at: 32th Annual Meeting of the American Academy of Pain Medicine; Palm Springs, CA: February 18-21, 2016.
3. Food and Drug Administration website. http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm484345.pdf. Accessed on July 5, 2016.
4. One patient was excluded from the analysis populations; patient was enrolled and had study drug dispensed but decided not to participate and returned all study drug unused.

Baseline Characteristics

Study 006, ITT Population

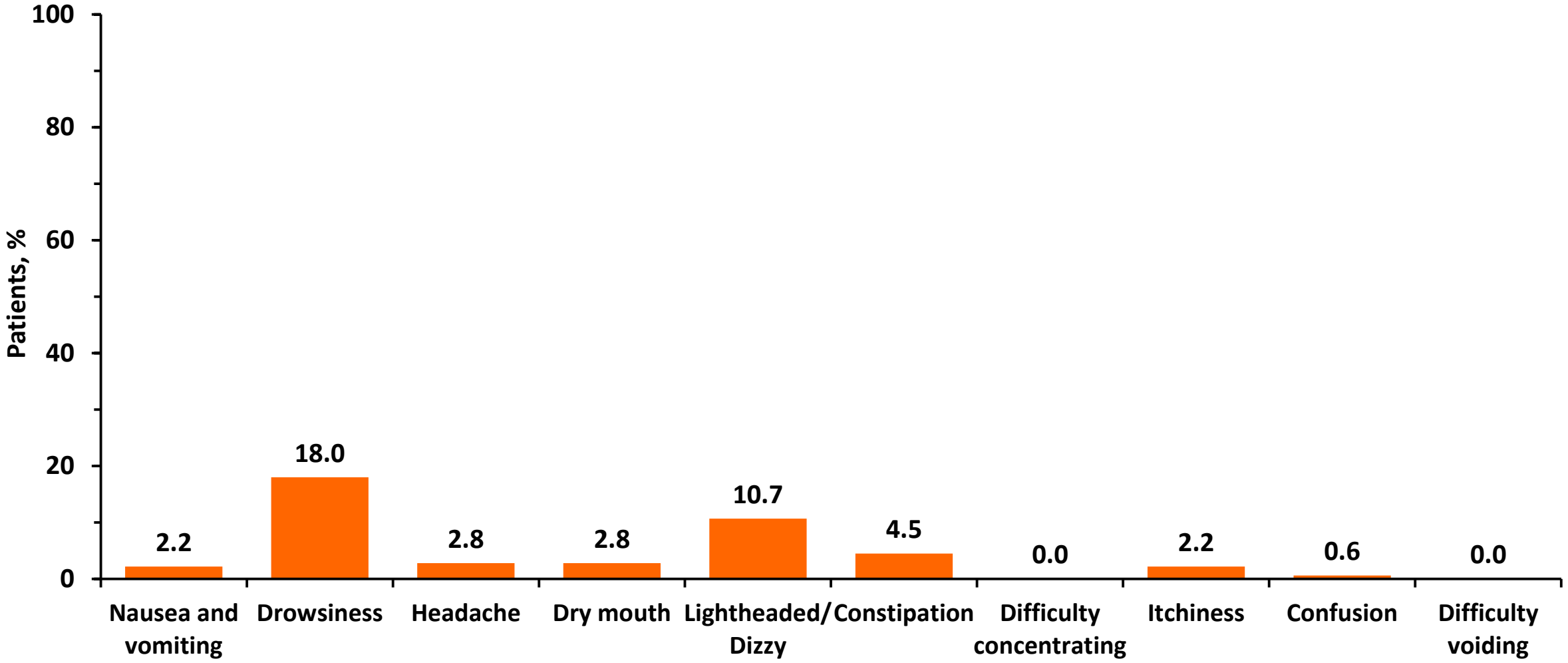
Characteristic		HYDEXOR™ N=178
Age, years	Mean	61.2
	≥65 yr, %	37
Race, %	White	85
	Black	15
	Asian	0
	Other	0

Characteristic		HYDEXOR N=178
Non-Hispanic/Non-Latino, %		84
Female, %		62
Mean BMI, kg/m^2		29.4
Non-smoker, %		65
Pain, %	Moderate	46
	Severe	53

BMI=body mass index.

Frequency of Spontaneously Captured Opioid-Related Symptoms

Study 006, ITT Population



ITT=intent to treat
Captured via diary entries at bedtime.

Summary: Clinical Safety

- HYDEXOR™ ingredients are well-known
- Manageable and predictable safety profile: no new safety concerns identified
- HYDEXOR generally well-tolerated
- AEs were mostly mild or moderate in intensity and limited in duration
  - Increased incidence of drowsiness observed
  - Increased incidence of lowered blood pressures observed within 24 hours
- Warnings and precautions proposed for HYDEXOR are consistent with those of the reference listed products

Risk Mitigation and Responsible Use

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HYDEXOR™ Proposed Interim REMS

- **Package Insert** – educates HCPs
  - Risks, responsible prescribing and dispensing, and safe use
  - Patient selection
  - Short-course packaging
- **Medication Guide** – educates patients
  - Risks and safe use and handling
  - Disposal of unused tablets
- **Communication Plan** – educates all stakeholders
  - Risks, responsible prescribing and dispensing, and safe use
  - Short-course packaging
  - Disposal of unused tablets
- **Assessment** – conducted annually
  - Program performance and effectiveness
  - Risk surveillance and monitoring

HCP=healthcare provider; REMS=Risk Evaluation and Mitigation Strategy.

HYDEXOR™ Labeling and Dosing to Limit Quantity Prescribed

Proposed indication

- Short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting (OINV)
  - Treatment generally less than 14 days
  - Indicated when alternative treatments for pain are inadequate

Dosage

- One tablet every 4 to 6 hours as needed for pain; the total daily dosage should not exceed 6 tablets

Acute Pain Packaging to Limit Dosing and Reduce Quantity of Tablets Provided

- Packaging – Aligned with evidence-based treatment recommendations[1]
  - 3-day pack (18 tablets)
  - 5-day pack (30 tablets)
  - 7-day pack (42 tablets)

Draft HYDEXOR™
3-, 5-, and 7-day packaging (F1/Child-resistant container closure system)

1. Scually RE, et al *.JAMA Surg.* 2018;153(1):37-43.

Responsible Commercialization Approach

- Distribution plan
- Developing 

Program for unused tablets
- Education and training for all customer-facing personnel
- Monitoring and reporting of commercial activities and market response
  - Patient experience and use
  - Physician prescribing patterns
  - Pharmacy ordering and dispensing
- Pharmacovigilance

Risk Mitigation Advisory Board (RMAB)

- External advisory board of practicing pain and addiction clinicians, law enforcement, and other relevant experts
  - Interface with Charleston management quarterly to review safety events and topics regarding
    - Ordering and dispensing
    - Appropriate use and handling
    - Prescribing trends
  - Provide guidance on HYDEXOR™ return program
  - Consult on risk mitigation efforts

Charleston's Commitment to Responsible Use

- Interim REMS/Classwide IR Opioid REMS
  - Labeling for short-term use (generally less than 14 days)
  - 3-, 5-, and 7-day packs (maximum of 6 tablets per day)
- Developing HYDEXORETURN™ Program for unused tablets
- Education, Distribution, and Pharmacovigilance
- Monitoring and Active/Passive Surveillance
- Commercial audience: Selected surgeons and acute pain specialists

Draft HYDEXOR™ 3-, 5-, and 7-day packaging (F1/Child-resistant container closure system)

IR=immediate release; REMS=Risk Evaluation and Mitigation Strategy.

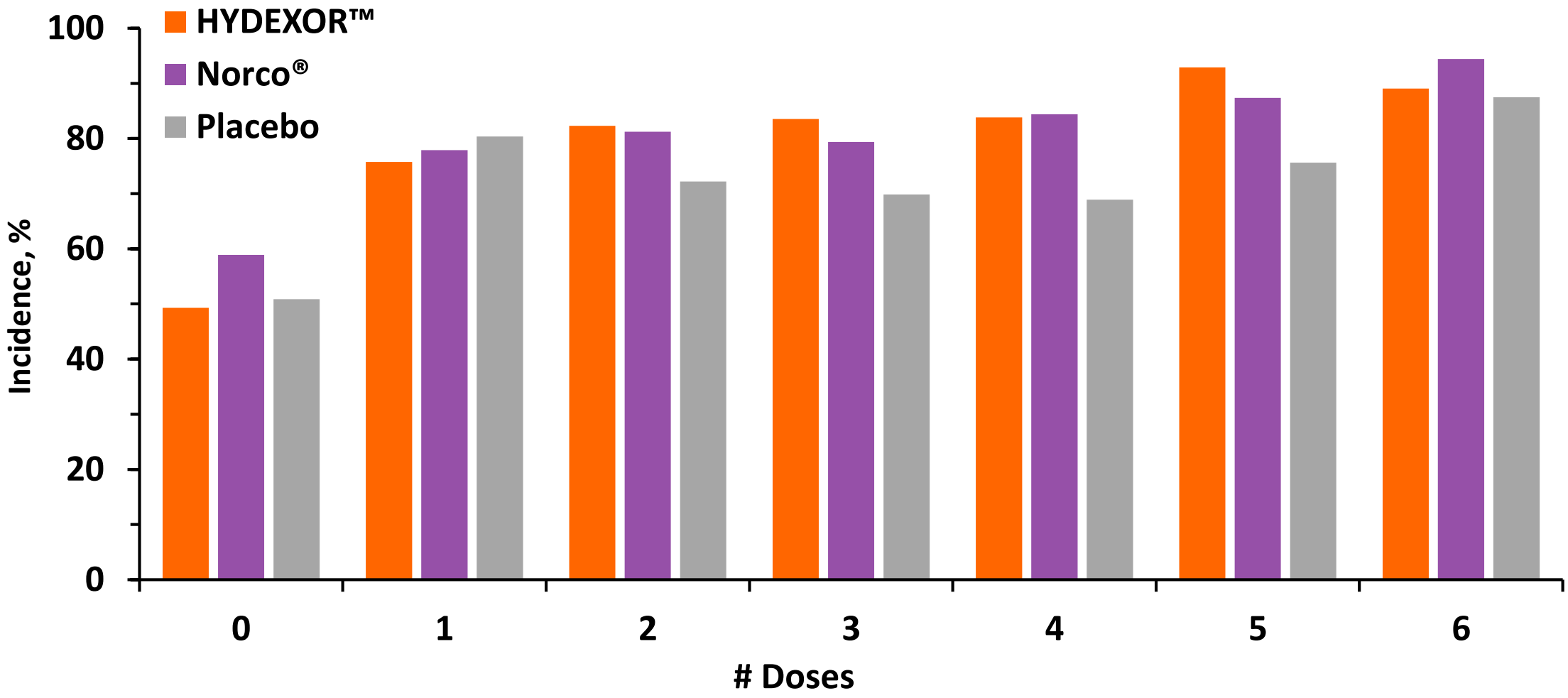
Favorable Benefit-Risk Assessment for HYDEXOR™

- **Unmet need: OINV creates significant burdens**
  - Patient recovery
  - Clinical outcomes
  - Economic impact
- **Demonstrated efficacy**
  - Significant relief of pain compared to placebo
  - 64% to 74% reduction in risk of OINV compared to Norco®
  - Consistent and durable results
- **No new safety concerns**
  - Increased risk of drowsiness observed (addressed in label)
- **No difference in abuse potential**
  - Compared to HC/APAP
- **Commitment to responsible use**
  - REMS and labeling
  - Limited dosing and packaging
  - HYDEXOR Return program
  - Abuse mitigation

APAP=acetaminophen; HC=hydrocodone; OINV=opioid-induced nausea and vomiting: REMS=Risk Evaluation and Mitigation Strategy.

Incidence of Any OSS by Dose

Study 002/003



SBP and DBP Hypotension: Potentially Clinically Significant (PCS) Low[1] Incidence

Study 003 Safety Population

	Patients, (%)					
	DBP <60 mmHg[3]			SBP <90 mmHg[2]		
Timepoint[4]	HYDEXOR n=252	Norco n=250	Placebo n=50	HYDEXOR ™ n=252	Norco® n=250	Placebo n=50
Hour 6	55 (21.9%)	36 (14.4%)	3 (6.1%)	14 (5.6%)	8 (3.2%)	1 (2.0%)
Hour 12	43 (17.6%)	20 (8.2%)	7 (14.9%)	15 (6.1%)	4 (1.6%)	2 (4.3%)
Hour 24	43 (17.4%)	43 (17.6%)	4 (8.5%)	15 (6.1%)	6 (2.4%)	0
Hour 36	29 (12.0%)	34 (14.3%)	3 (6.7%)	6 (2.5%)	2 (0.8%)	3 (6.7%)
Hour 48	37 (14.9%)	30 (12.4%)	2 (4.3%)	5 (2.0%)	5 (2.1%)	2 (4.3%)

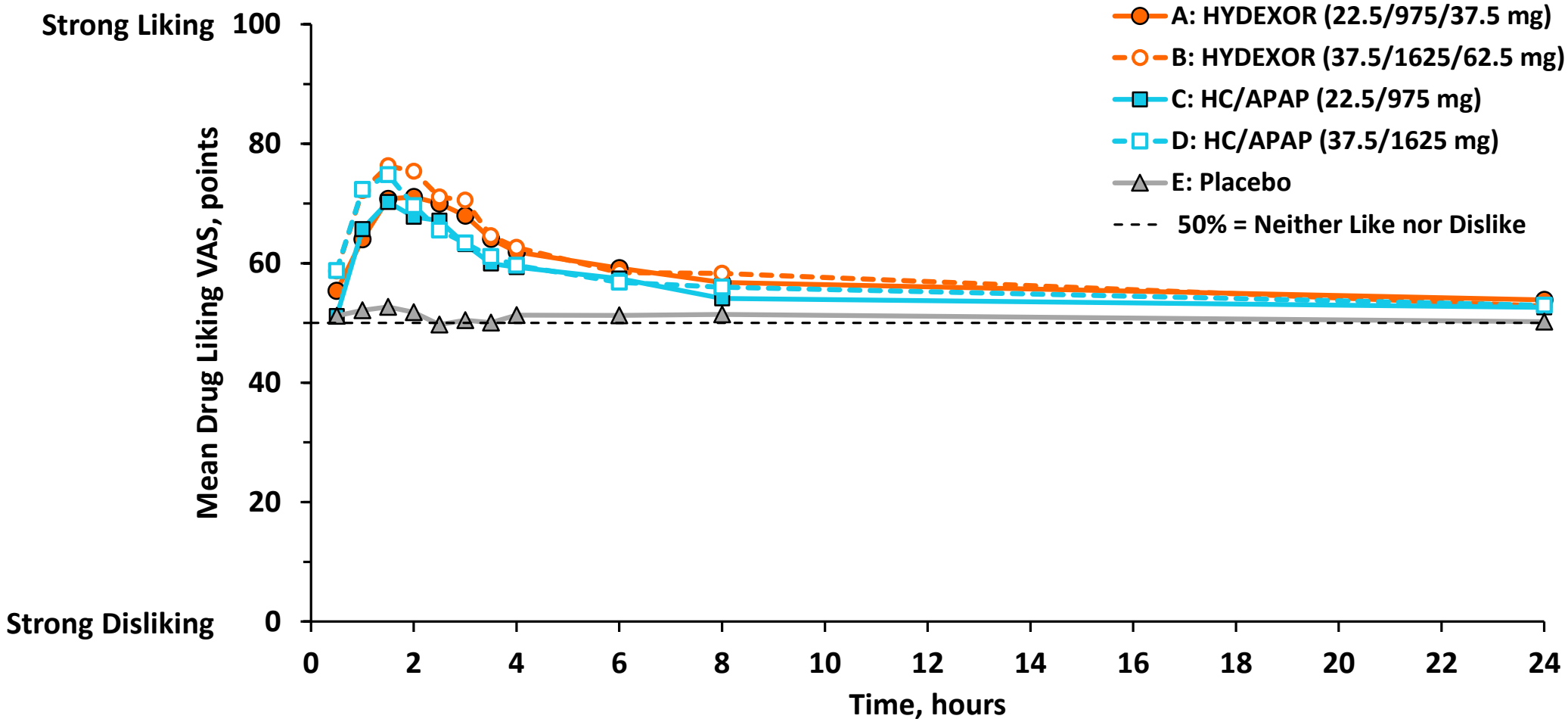
1. PCS low criteria from Study 003 SAP.
2. PCS low SBP defined as <90 mmHg.
3. PCS low DBP defined as <60 mmHg .
4. Baseline: last observation before first dose.

Hypotensive cases in HYDEXOR™ in Phase 3 Trials

- Studies 002/003: 7 events of hypotension in 7 patients; all occurring on first day of dosing
  - 3 associated with HYDEXOR
  - 3 associated with Norco (1 event rated as severe)
  - 1 associated with PBO
  - All cases resolved and did not reoccur
  - All subjects continued study med without interruption or decrease in dose
    - Including other events such as diaphoresis, falls, seizures, or injury
- Study 006: No events of hypotension reported

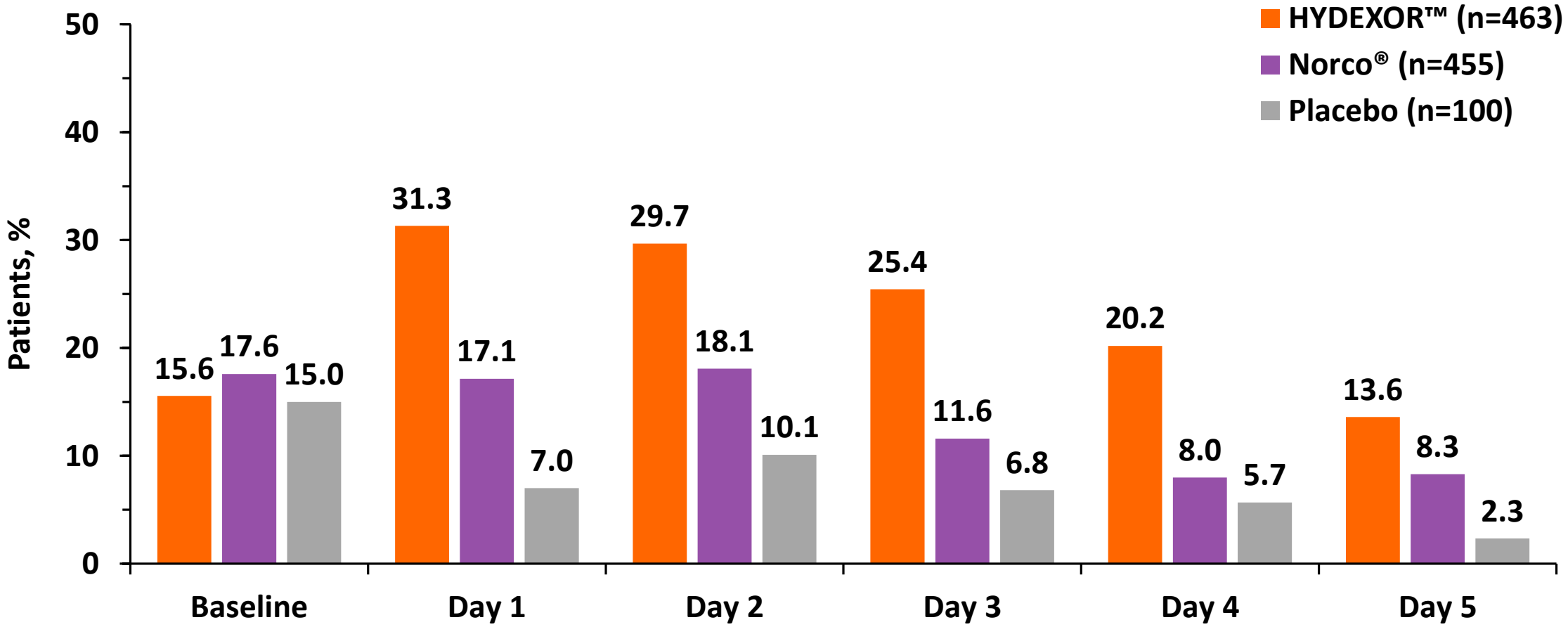
Mean Drug Liking Over Time

Study 007



Incidence of Severe Drowsiness, Lightheaded/Dizziness, Confusion, and Difficulty Concentrating Over Days 1-5

Studies 002/003



Drowsiness, Days 1-14

Study 006