DSUVIA™ (sufentanil) sublingual tablet 30 mcg for management of moderate-to-severe acute pain in a medically supervised setting

October 12, 2018

AcelRx Pharmaceuticals, Inc.

Meeting of the Anesthetic & Analgesic Drug Products Advisory Committee

DSUVIA™ (sufentanil) sublingual tablet 30 mcg for management of moderate-to-severe acute pain in a medically supervised setting

Introduction

Pamela Palmer, MD PhD

Co-Founder and Chief Medical Officer

AcelRx Pharmaceuticals, Inc.

Opioid Medication Errors

- Rank of drugs with medication errors in medically supervised settings in 2005[1]

1. Insulin
2. **Morphine**
3. Potassium chloride
4. Albuterol
5. Heparin
6. Vancomycin
7. Cefazolin
8. Acetaminophen
9. Warfarin
10. Furosemide

- 2017 Institute for Safe Medication Practices list shows top drugs with medication errors are opioids[2]

1. Hahn 2007; 2. Barrett 2017

Errors with Injectable Opioids

- Many concentrations
  - IV morphine available in 10 concentrations
- Injectable opioids[1]
  - Clear solutions that look identical
  - Easily substituted with water or saline
  - Often requires wastage of unused solution

1. Parshuram 2008

DSUVIA: Single-Strength Sublingual Tablet

- Single 30 mcg dosage-strength tablet to limit errors
- Sublingual route
  - Well-tolerated
  - Rapid onset
  - Transmucosal opioids have limited analgesic indications
- Non-invasive
  - Postoperative guidelines recommend oral over IV opioids[1]
  - Advantage for patients with difficult IV access

1. Chou 2016

Sufentanil Physicochemical Properties Support Rapid Sublingual Absorption

- Highly lipophilic
  - 1500-fold more than morphine
- Fast onset of analgesia
  - Faster than IV morphine[1]
- High potency allows for small and well-tolerated dosage form
- Minimum effective dose (30 mcg) = 5 mg of IV morphine
- Immediate-release, highly bioavailable
- No active metabolites

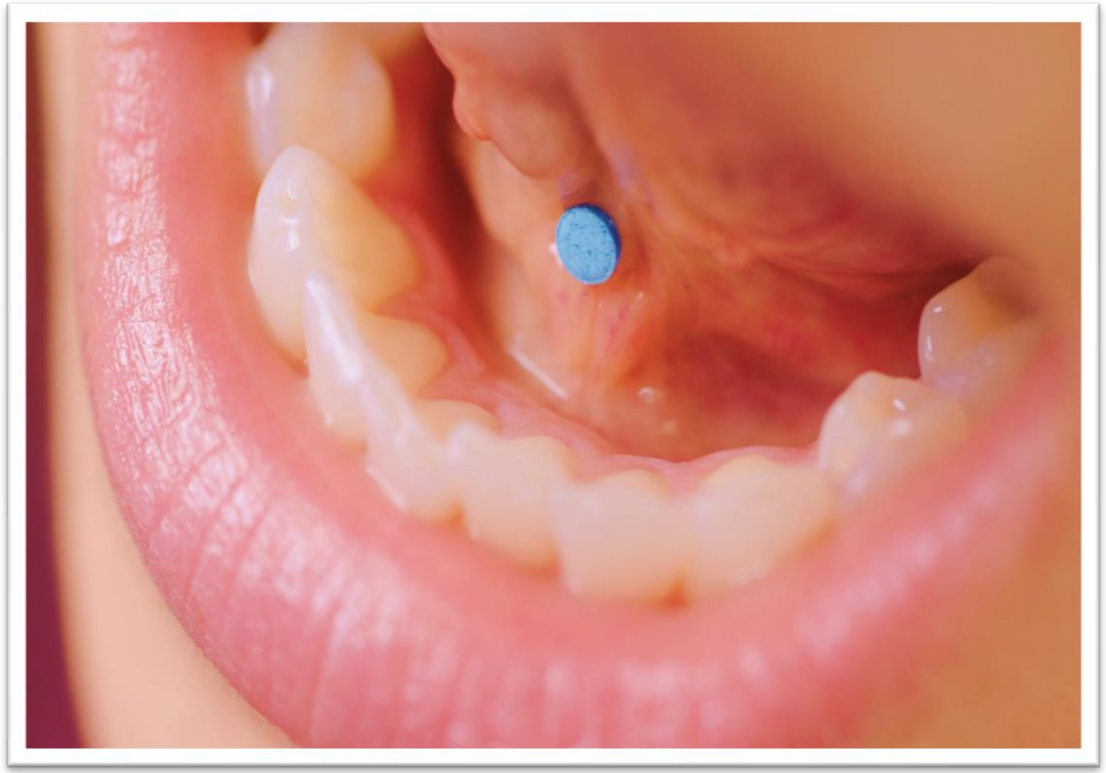
1. Melson 2014

DSUVIA Developed to Provide Non-Invasive Opioid Option for Rapid Pain Relief

- In collaboration with US Department of Defense
- Benefits for many patient types
  - Difficult-to-access veins
    e.g., obese, elderly, burns, needle-phobic
  - Oral pain medication not optimal
    e.g., dysphagic patients or NPO status

DSUVIA 30 mcg is Small, Fast-Dissolving Tablet

- Dissolves in 6 minutes
  - Bioadhesive tablet
  - Fentanyl lozenges take up to 30 min to dissolve
- 3 mm diameter does not trigger salivary response
  - Sufentanil < 10% GI bioavailability
- > 80% report taste after dosing



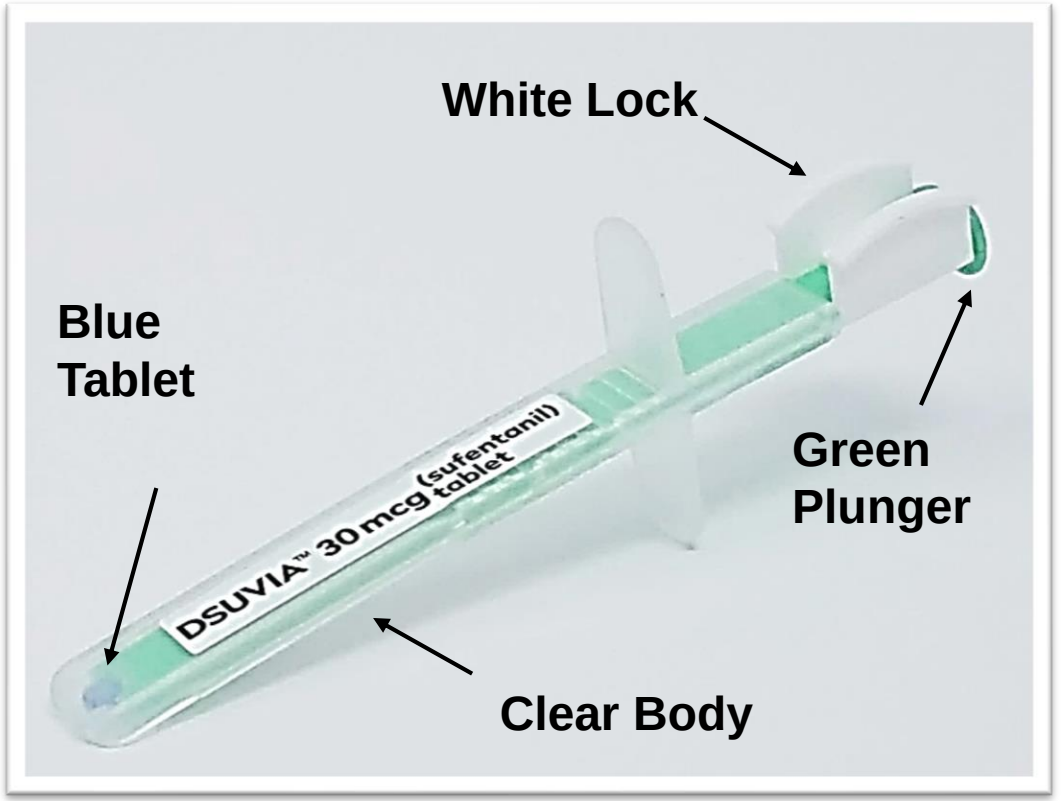
HCP Dosing Aided by Single-Dose Applicator

- Other tablets have similarly small diameters, dosed by hand, and available for home use
  - Sublingual nitroglycerine (4 mm)
  - Oral hydromorphone 2 mg (5 mm)
- Only DSUVIA offers aid of single-dose applicator
- Limited to use by HCPs in medically supervised settings
  - Not for home use

HCPs: Healthcare professionals

Safety Features of Single-Dose Applicator

- Tablet pre-filled in clear applicator body
  - Can confirm when dispensed
- Simple, removable white lock
  - Prevents accidental dispensing
- Non-retractable green plunger
  - Mitigates against refilling with substitute tablet



DSUVIA 30 mcg Single-Dose Packaging

- Single dose administered by HCP
- Sealed, tamper-evident pouch
  - Tear-open access
- Barcoded for trackability
- Fold-out Directions for Use attached

Proposed DSUVIA Indication and Dosing

Management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in ***a medically supervised setting***

- Dosed by HCP hourly as needed
  - Minimum of 1 hour between doses
  - Maximum of 12 tablets in 24 hours

DSUVIA Designed to Not Add to Opioid Crisis

- "Medically supervised setting" definition
  - REMS-certified licensed pharmacy or healthcare provider with DEA registration for C-II drugs
  - Access to equipment and personnel trained to manage opioid overdose
    - Facility must have recent experience administering IV opioids
- No retail pharmacies will carry or dispense DSUVIA

DSUVIA Regulatory Overview

- 2016: 505(b)2 New Drug Application (NDA) submitted
  - References extensive experience with Sufenta® (IV / epidural)
  - 10 Phase 2 and 3 trials of sufentanil sublingual tablets
    - Total of 686 patients exposed to ≥ 30 mcg

- June 2018: DSUVIA approved throughout EU (as DZUVEO)

DSUVIA Efficacy and Safety Supported by 2 RCTs, 2 Open-Label Studies and Selected Zalviso Patients

	Sufentanil	Placebo	Population
DSUVIA (30 mcg) Studies	**363**	**74**	
Study 202 – RCT	40	20	Bunionectomy (12 hr)
Study 301 – RCT	107	54	Abdominal surgery (48 hr)
Study 302 – Open label	76	0	Trauma/injury in emergency dept. setting (5 hr)
Study 303 – Open label	140	0	Postoperative, ≥ 40 years (12 hr)
Safety supported by Zalviso, sufentanil tablet patient-controlled system approved in EU			
Zalviso* Studies	**323**	**104**	
Studies 001, 005, 310, 311	211	104	Abdominal, knee- or hip-replacement surgery
Studies 004, 309	112	0	Abdominal, knee- or hip-replacement surgery

*Patients from Zalviso studies are included in DSUVIA safety database based on utilization of two doses of 15 mcg of sublingual sufentanil in first 20-25 minutes of treatment; approved in EU in 2015

Actions to Address FDA Complete Response Letter

- 2017: FDA issued CRL
  - Limited exposure at proposed maximal dose (24 tablets/day)
  - Requested modifications / re-validation of Directions for Use to mitigate risk due to a dropped tablet
    - Phase 3 trials occurrence of a dropped tablet (3 / 1,782 tablets)
- 2018: AcelRx responded to CRL
  - Lowered maximal dose from 24 to 12 tablets/day
  - New safety analyses supporting proposed maximal dose
  - Revised and validated Directions for Use with Human Factors study
  - Performed analysis demonstrating low risk of accidental exposure due to dropped tablet

Risk Management Includes Product-Specific REMS

- DSUVIA distributed only to REMS-certified facilities where authorized representative must attest:
  1. Facility is able to manage opioid overdose
  2. HCPs have read Directions for Use
  3. Administered only in medically supervised setting
- Verify sites are currently using IV opioids
- Monitor distribution supply chain and audit wholesalers' data
- Audit certified healthcare facilities

Agenda

Unmet Need	**James Miner, MD** **Chief of Emergency Medicine, Hennepin County Medical Center**
Clinical Pharmacology	**Dennis Fisher, MD** **Founder, *P Less Than* Pharmacometric Consulting**
Efficacy	**Pamela Palmer, MD PhD** **Chief Medical Officer, AcelRx Pharmaceuticals, Inc.**
Safety	**Neil Singla, MD** **Chief Scientific Officer, Lotus Clinical Research, LLC.**
Educational Materials, REMS Program, and Conclusion	**Pamela Palmer, MD PhD** **Chief Medical Officer, AcelRx Pharmaceuticals, Inc.**

Additional Subject Matter Experts

- **Richard Dart, MD PhD**
  Executive Director
  Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System

- **Yu-Kun Chiang, PhD**
  Statistical Consultant
  Essence Sciences, Inc.

- **Anil Dasu, MS**
  Chief Engineering Officer
  AcelRx Pharmaceuticals, Inc.

- **Karen DiDonato, MSN RN**
  Executive Director, Medical Affairs
  AcelRx Pharmaceuticals, Inc.

- **Larry Hamel**
  Chief Development Officer
  AcelRx Pharmaceuticals, Inc.

Unmet Need

James Miner, MD

Chief of Emergency Medicine, Hennepin County Medical Center

Vice Chair / Research Director, Emergency Medicine

University of Minnesota

Recent Guidelines on Opioids Use in Acute Pain[1,2]

- Support for use of opioids as part of multi-modal approach
  - American Pain Association
  - American Society of Regional Anesthesia and Pain Medicine
  - American Society of Anesthesiologists
- Emergency medicine physicians support appropriate use of opioids for treatment of new-onset moderate-to-severe acute pain in adult patients presenting to emergency department

1. Chou, 2016; 2. American College of Emergency Physicians (ACEP) Policy on Opioid Prescribing

Benefits of Opioid Acute Pain Management in Medically Supervised Settings

- Emergency department patients can be discharged earlier when analgesics administered earlier[1]
- Postoperative multimodal analgesia improves immediate functionality[2]
  - Less development of chronic pain[3]
- Soldiers who received opioids developed less PTSD than soldiers who didn't receive opioids[4]

1. Sokoloff 2014; 2. Tan 2015; 3. Perkins 2000; 4. Holbrook 2010

Challenges with IV Opioids

- IV route not always optimal to treat acute pain
- Current IV opioids have pharmacodynamic limitations
  - IV morphine: slow, unpredictable onset
  - IV fentanyl: small analgesic doses have rapid onset but short duration of action
- IV medication errors
- Initiating IV access

Challenges with IV Initiation

- Invasive route
  - Painful
  - Dosing gaps from catheter infiltration or IV tubing obstructions
  - Risk of infection for patient and HCP
- Time-consuming
  - Starting IV more resource-intensive
  - First IV attempt fails in 12–26% of adults[1]

1. Sabri 2013

Many Patients Suffer from Moderate-to-Severe Acute Pain Where IV Access is Limited

- Venous access may be difficult in certain patients
  - Obesity is number one reason for difficult IV access in ED[1]
  - Needle-phobia prevalence rates range from 14–38%[2-5]
  - Elderly
  - Burn patients
  - Venous access interrupted / dislodged

1. Emergency Nurses Association Clinical Practice Guidelines, 2015; 2. McMurtry et al., 2015;
3. Taddio et al., 2012; 4. Deacon and Abramowitz, 2006; 5. Armfield and Milgrom, 2011

Challenges with IM / Oral Opioids

- Intramuscular administration is painful
- Oral pills not always optimal
  - Slow onset
  - Patients who are NPO
  - Patients unable to swallow pills
    - ~15% of elderly population affected by dysphagia[1]
- Transmucosal fentanyl products available for opioid-tolerant patients suffering from cancer pain
  - High doses unsuitable for opioid-naïve patients

1. US Department of Health and Human Services, 1999

Opioids with Active Metabolites Can Be Undesirable in Certain Patients

- Commonly used opioids with active metabolites
  - Morphine
  - Hydromorphone
  - Codeine
  - Tramadol
- Active metabolites mainly cleared via kidney
- Active metabolites complicate opioid PK / PD profile

Need for Non-Invasive, Rapid, and Safe Opioid Product

- Scenario 1
  - Severe pain before IV initiation
  - e.g., first dose(s) for trauma and burn patients
- Scenario 2
  - IV catheter infiltrated
  - e.g., during transport from operating room to recovery
- Scenario 3
  - Moderate-to-severe pain and no need for IV access
  - e.g., non-displaced fractures, joint injuries, local burns

Clinical Pharmacology of Sublingual Sufentanil

Dennis M. Fisher, MD

Founder, *P Less Than* Pharmacometric Consulting

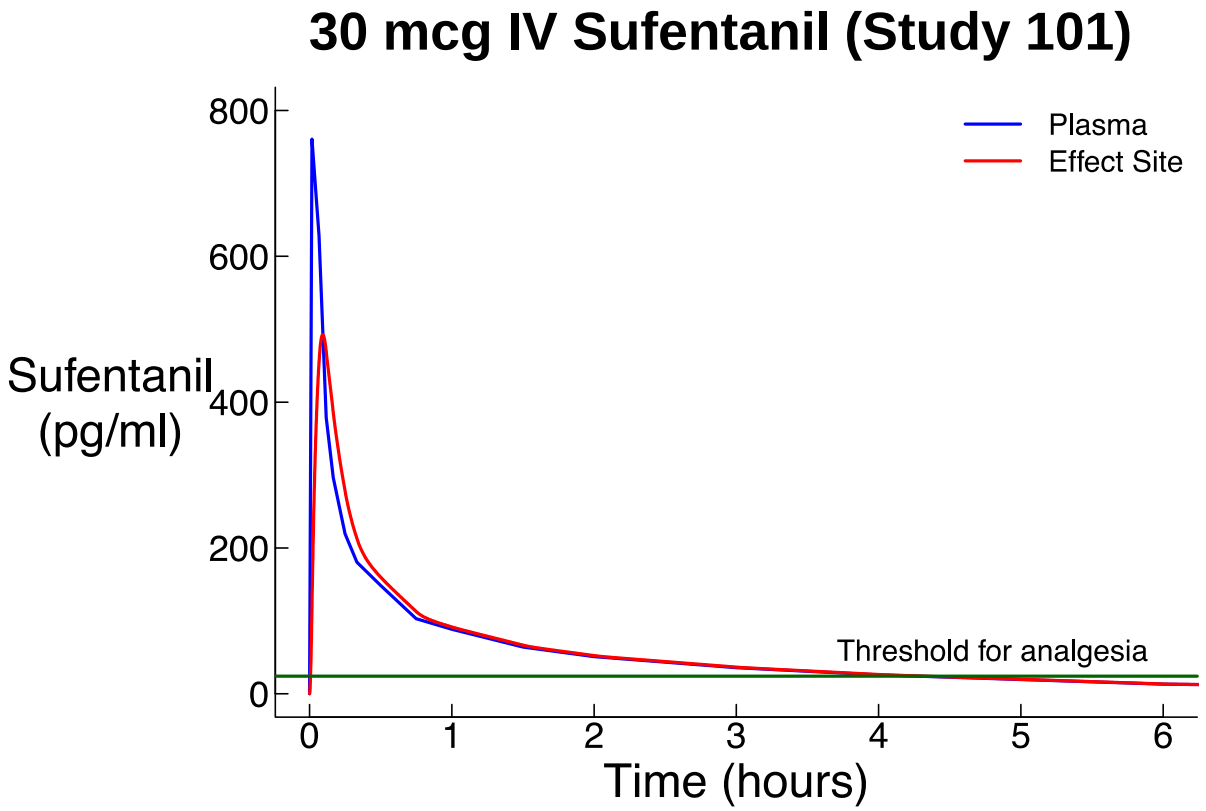
Professor (Emeritus), Department of Anesthesia

University of California, San Francisco

Agenda: Sublingual Sufentanil PK / PD

- DSUVIA PK / PD profiles suggest
  - Rapid onset with mucosal administration
  - Clinically relevant duration
  - May require repeat administration
- Characteristics allowed AcelRx to develop a product with rapid onset that can be titrated to analgesic effect
- 30-mcg dose selected to maintain analgesia but minimize risk of side effects

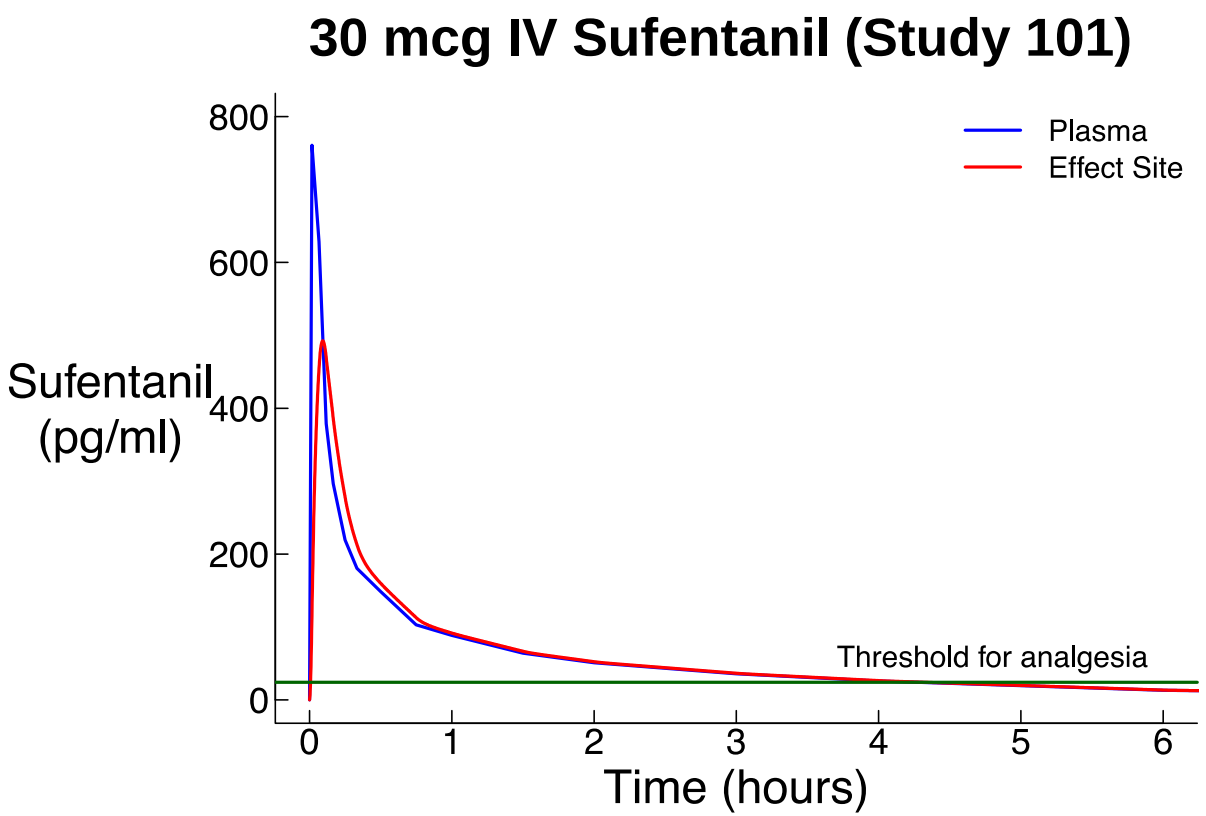
30 mcg IV Sufentanil: C_{max} vs. Duration of Analgesia

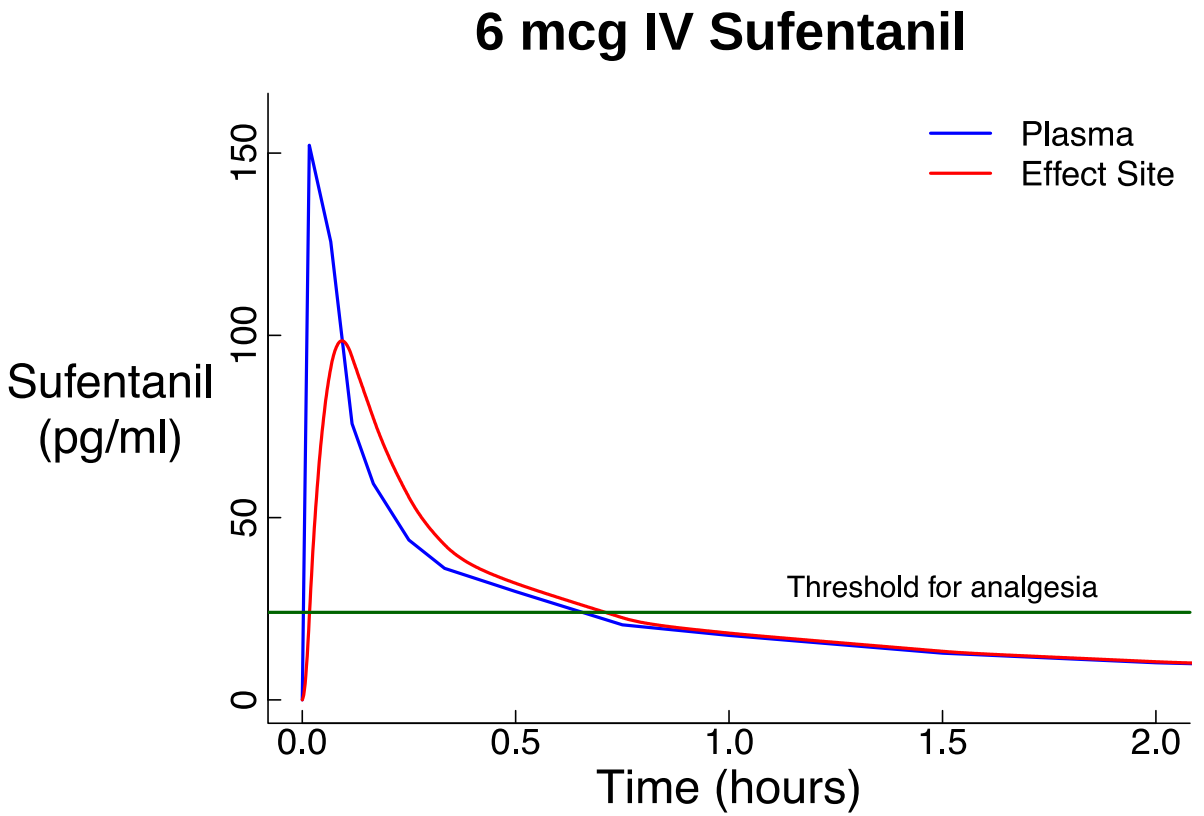


- High C_{max} creates potential for ventilatory depression
- Rapid blood-brain equilibration due to lipophilicity
- Duration of analgesia > 3 hours at expense of high C_{max}

Effect site equilibration: Scott *et al.* Anesthesiology 1991
Threshold for post-operative analgesia: Lehmann *et al.* Acta Anaesthesiol Scand 1991

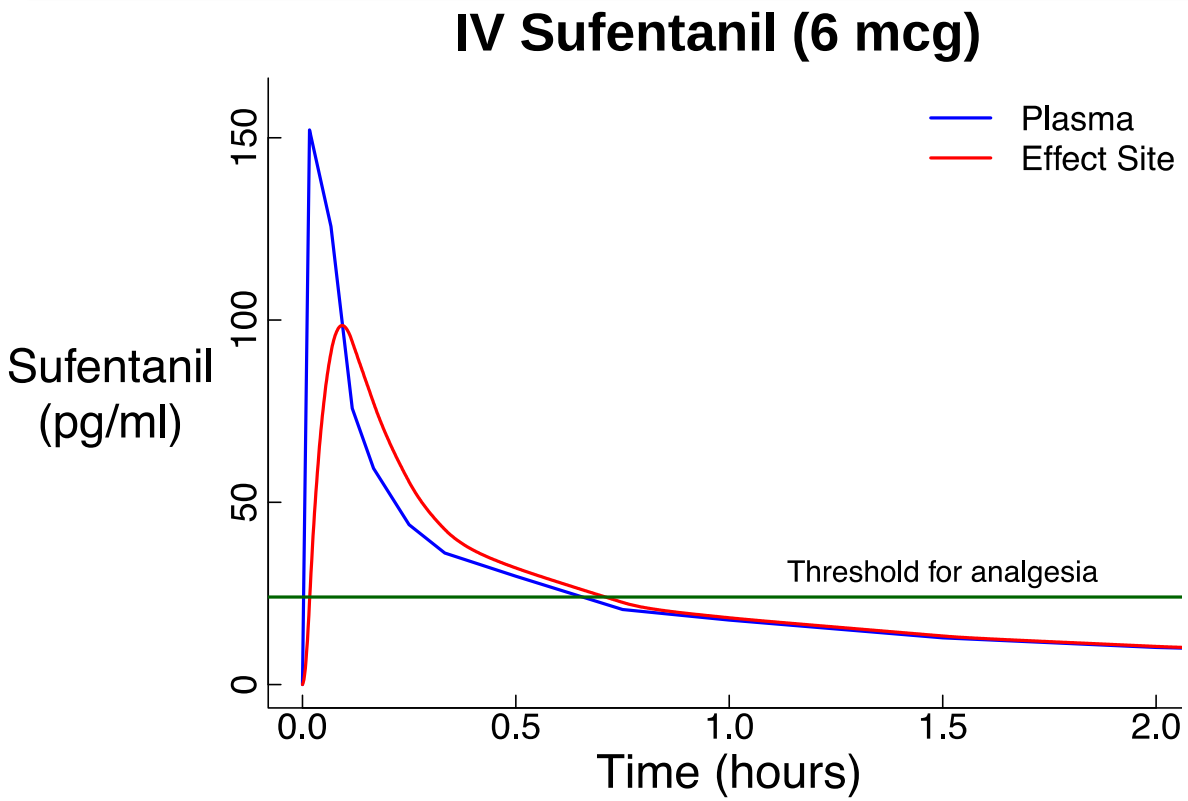
IV Sufentanil: C_{max} and Analgesia Vary with Dose

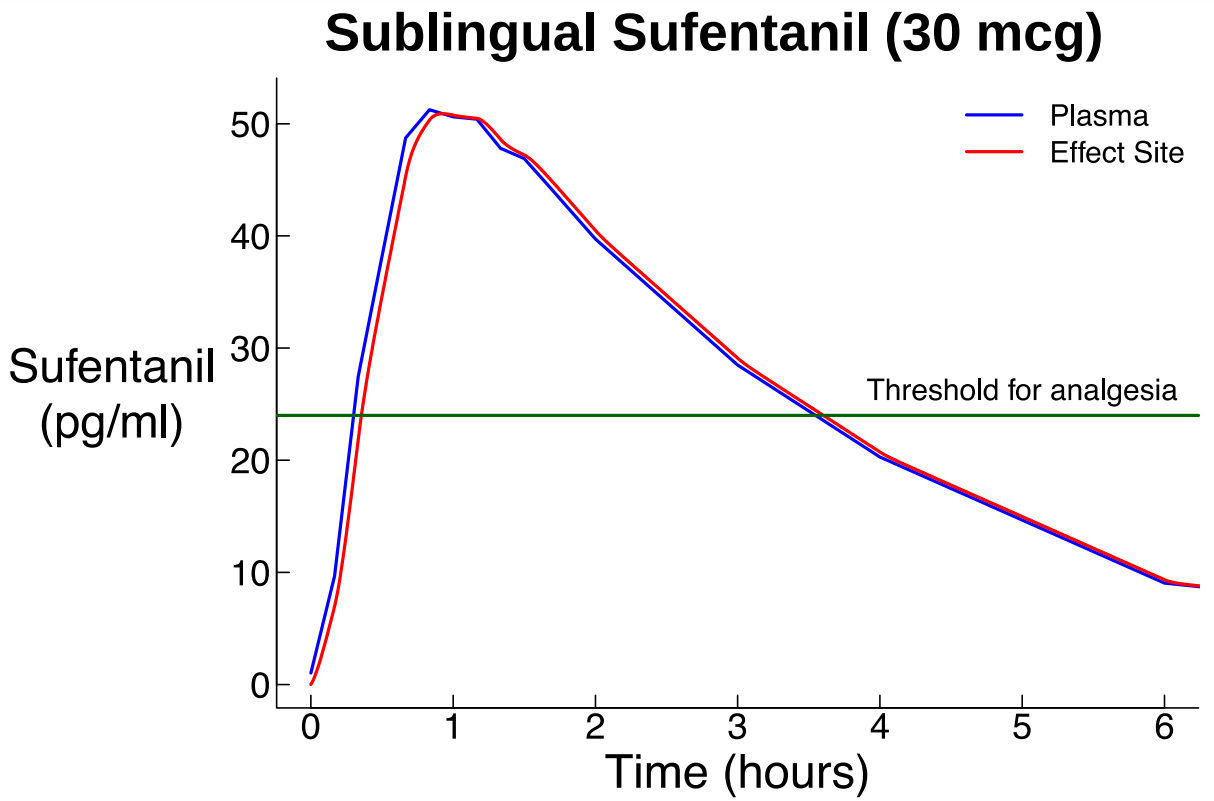




- Small dose yields lower C_{max}; decreased likelihood of ventilatory depression
- But duration of analgesia markedly shorter

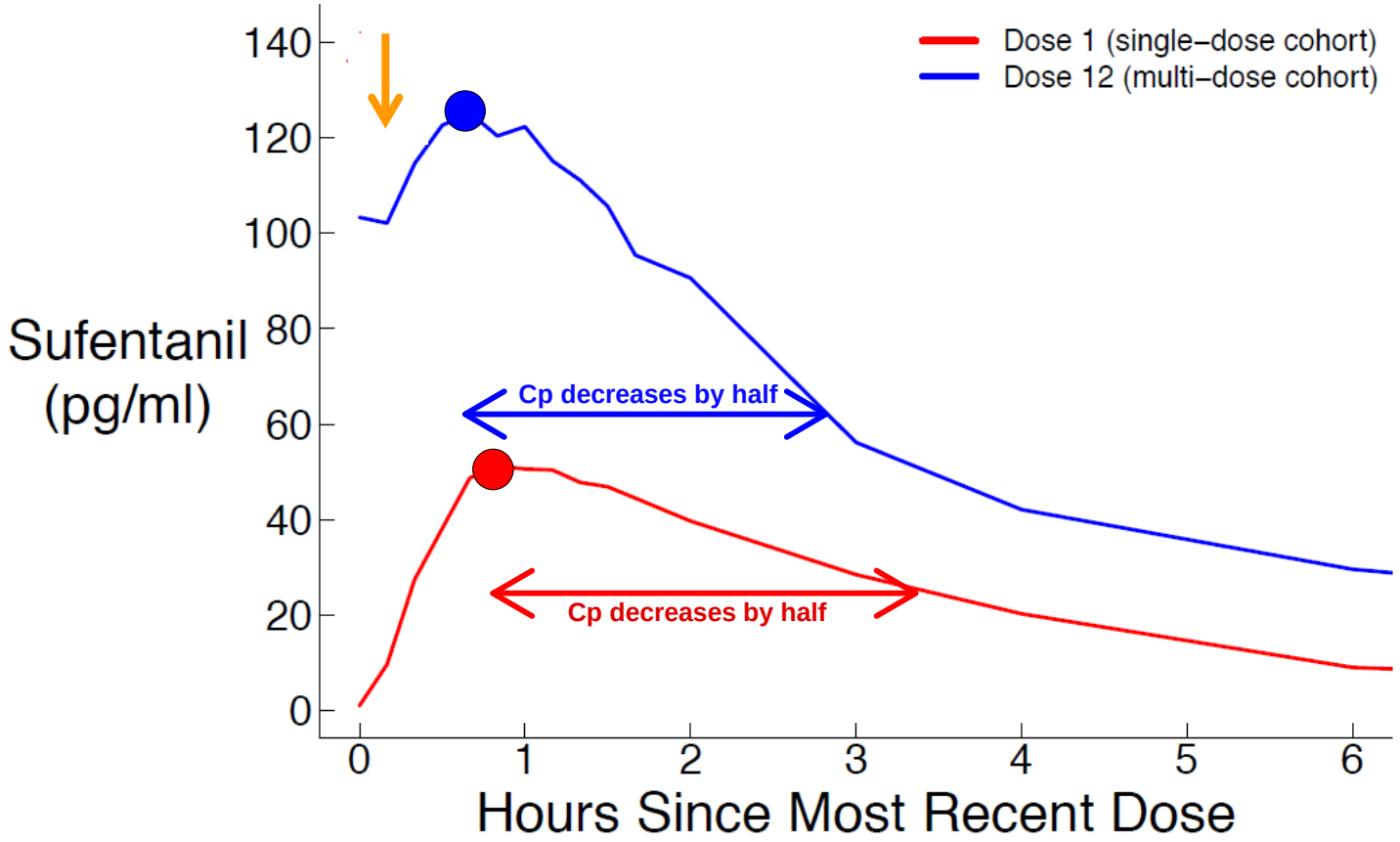
Intravenous vs. Sublingual Sufentanil: C_{max} and Analgesic Time Course





- Sublingual administration:
  - Lower C_{max} (despite larger dose)
  - Analgesic threshold reached relatively rapidly
  - Longer time above analgesic threshold

Sublingual Sufentanil: Washout Similar After 1st and 12th Doses



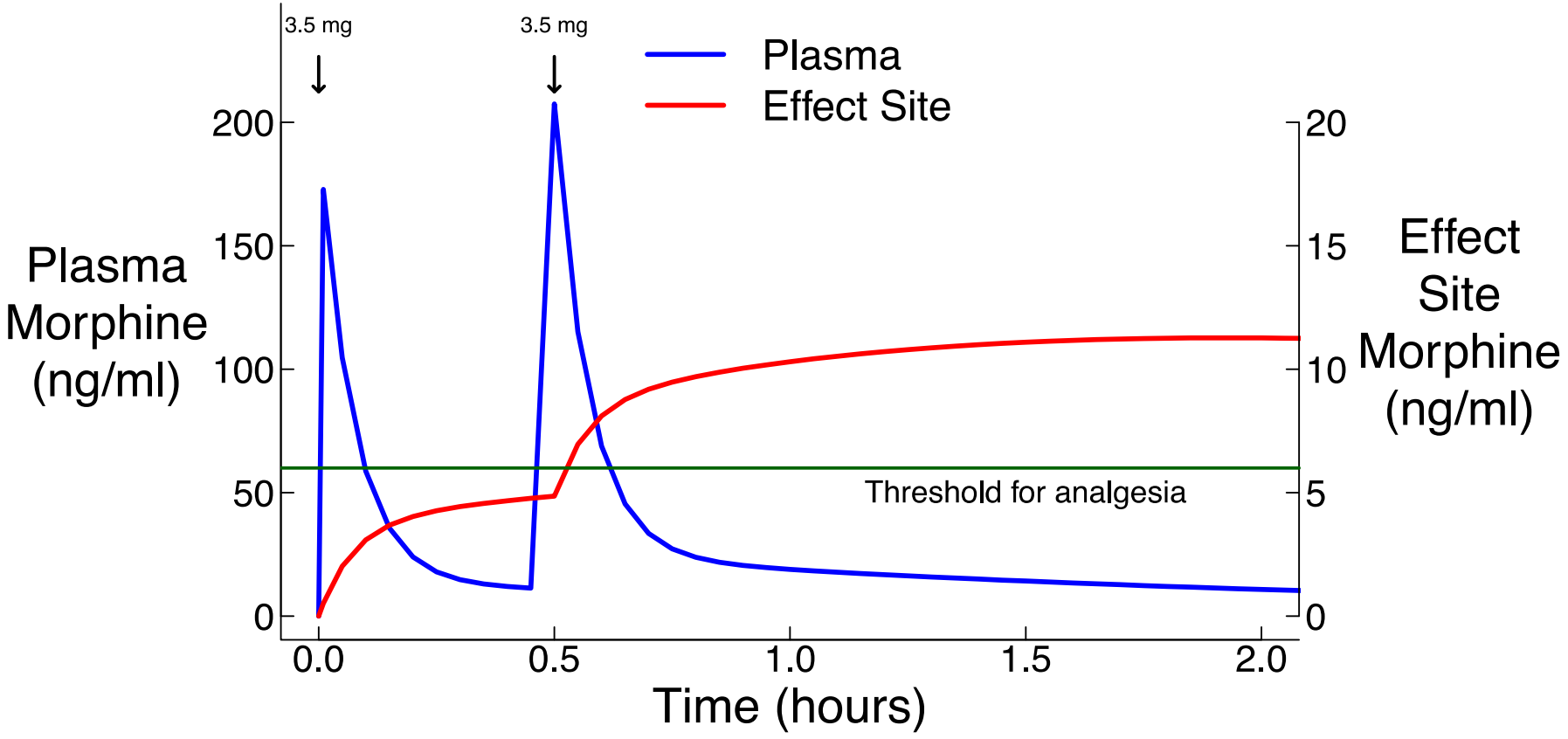
- Despite accumulation, time from C_{max} → $C_{max}/2$ (analogous to context-sensitive half-time) similar after doses 1 and 12

Sublingual Sufentanil: Factors Affecting Concentration Profile

- Clearance increases with weight (0.5% / kg)
- Clearance decreases with age (1.6% / year)
- Hepatic or renal impairment: no effect on clearance
- Inhibition of CYP3A4 by ketoconazole increases
  - C_{max} by 19%
  - AUC by 77%
- Titrating to effect on “as needed” basis will adjust for these effects

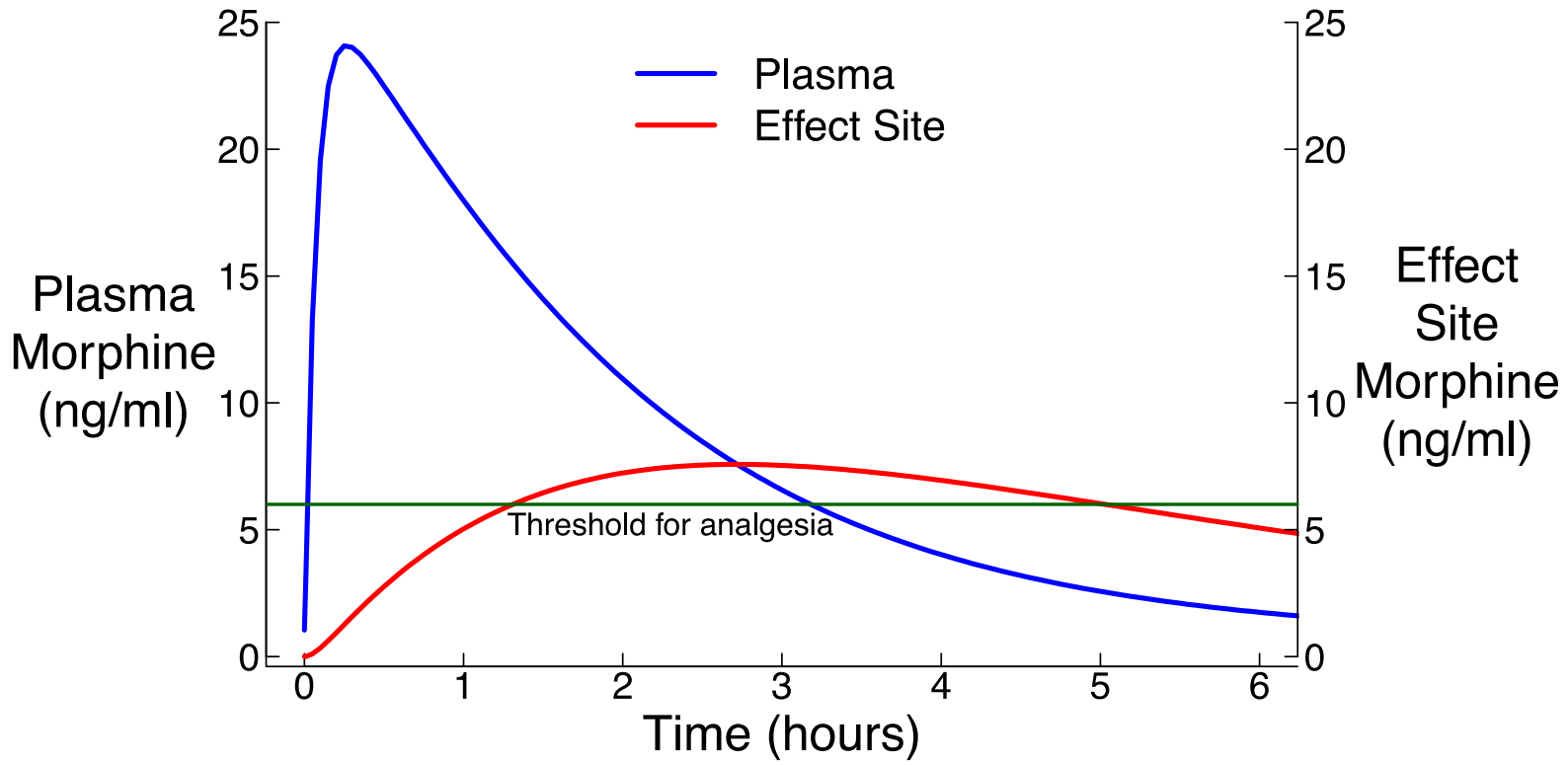
Fisher *et al*. Anesthesiology 2018.

IV Morphine: Poor Lipophilicity Explains Slow Onset



PK: Lötsch *et al.* Clin Pharm Ther 2002; PD: Lötsch. J Pain Symptom Manage. 2005

Oral Morphine (10 mg): Slower Onset



- Absorption delays time to peak plasma concentration
- Time to analgesia later than IV administration

PK: Juul *et al.* Pharm Res 2016
PK: Lötsch *et al.* Clin Pharm Ther 2002
PD: Lötsch. J Pain Symptom Manage. 2005

Efficacy Results

Pamela Palmer, MD PhD

Co-Founder and Chief Medical Officer

AcelRx Pharmaceuticals, Inc.

DSUVIA Study 202 Supports Dose Selection and Efficacy in Musculoskeletal Pain

Study	Study Design	Dose	Patient Population	N
202	Phase 2, multi-center, randomized, placebo-controlled	Placebo 20 mcg 30 mcg	Postoperative; bunionectomy musculoskeletal pain (≤ 12 hours)	100

- Selection of 30 mcg dose based on first-hour dosing in Zalviso studies (N > 600 patients)
- Study 202 used earlier tablet formulation with 9% lower systemic exposure

DSUVIA Efficacy from Two Randomized, Controlled Trials

Study	Study Design	Dose	Patient Population	N
202	Phase 2, multi-center, randomized, placebo-controlled	Placebo 20 mcg 30 mcg	Postoperative; bunionectomy musculoskeletal pain (≤ 12 hours)	100
301	Phase 3, multi-center, randomized, placebo-controlled	Placebo 30 mcg	Postoperative; outpatient abdominal surgery soft tissue / visceral pain (≤ 48 hours)	161

Two Open-Label, Single-Arm Studies Support DSUVIA Efficacy

Study	Study Design	Dose	Patient Population	N
303	Open-label, multi-center	30 mcg	Postoperative; ≥ 40 years old (≤ 12 hours)	140
302	Open-label, multi-center	30 mcg	Trauma/injury in emergency department (≤ 5 hours)	76

Similar Study Design Among Clinical Studies

- 5- to 48-hour duration
  - Dosing by HCPs in intended-use settings
- Study drug dosing per patient request
  - Not more frequently than hourly
- Pain intensity (0–10) and pain relief (0–4) assessed at fixed timepoints throughout study period
- Opioid rescue used to minimize early termination

SPID Endpoints in Clinical Studies

SPID: Summed **P**ain **I**ntensity **D**ifference

- Cumulative measurement of pain control over time
- Allows for efficacy comparison between groups

Primary endpoint for RCTs

- SPID12: multi-dose efficacy over 12 hours
  - Commonly used endpoint for acute pain

Key secondary endpoint*

- SPID1: single-dose efficacy over first hour

*Primary endpoint in Study 302

Analgesic Onset Measured via Three Assessments

- Statistical superiority in pain intensity and pain relief scores
  - Difference from baseline
  - Difference from placebo (placebo-controlled studies)
- Double-stopwatch technique
  - Time to perceptible and meaningful pain relief

Demographics Balanced Across Arms

	Study 202 (Bunionectomy)			Study 301 (Abdominal)	
	DSUVIA 20 mcg N=40	DSUVIA 30 mcg N=40	Placebo N=20	DSUVIA 30 mcg N=107	Placebo N=54
Sex (female)	48%	50%	50%	68%	67%
Age (mean)	43 yrs	43 yrs	42 yrs	41 yrs	40 yrs
Race					
Caucasian	75%	65%	75%	71%	69%
African American	18%	30%	20%	20%	19%
Other	7%	5%	5%	9%	13%
Hispanic / Latino	20%	13%	20%	39%	35%
BMI (kg/m^2)					
< 30	63%	70%	65%	72%	65%
≥ 30	37%	30%	35%	28%	35%

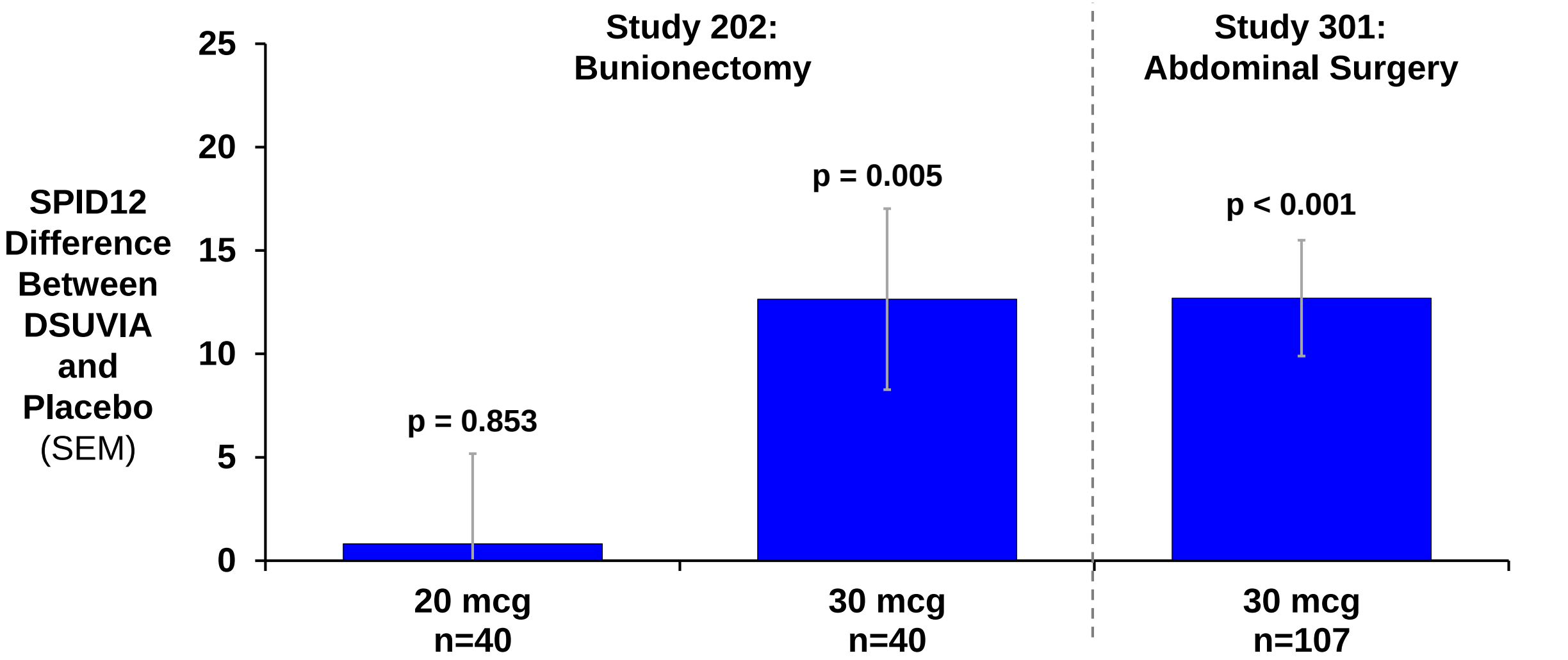
Patient Disposition in Randomized, Controlled Trials

	Study 202 (Bunionectomy) N=101			Study 301 (Abdominal) N=163	
	DSUVIA 20 mcg	DSUVIA 30 mcg	Placebo	DSUVIA 30 mcg	Placebo
Randomized	**41**	**40**	**20**	**109**	**54**
Received study drug	**40**	**40**	**20**	**107**	**54**
Terminated from study prematurely					
Lack of efficacy	2	3	1	4	10
Adverse event	0	2	0	0	2
Subject withdrawal	0	0	0	1	0
Protocol violation	0	0	0	0	1
Other	1	0	0	0	0
Analyzed for efficacy	**40**	**40**	**20**	**107**	**54**

60

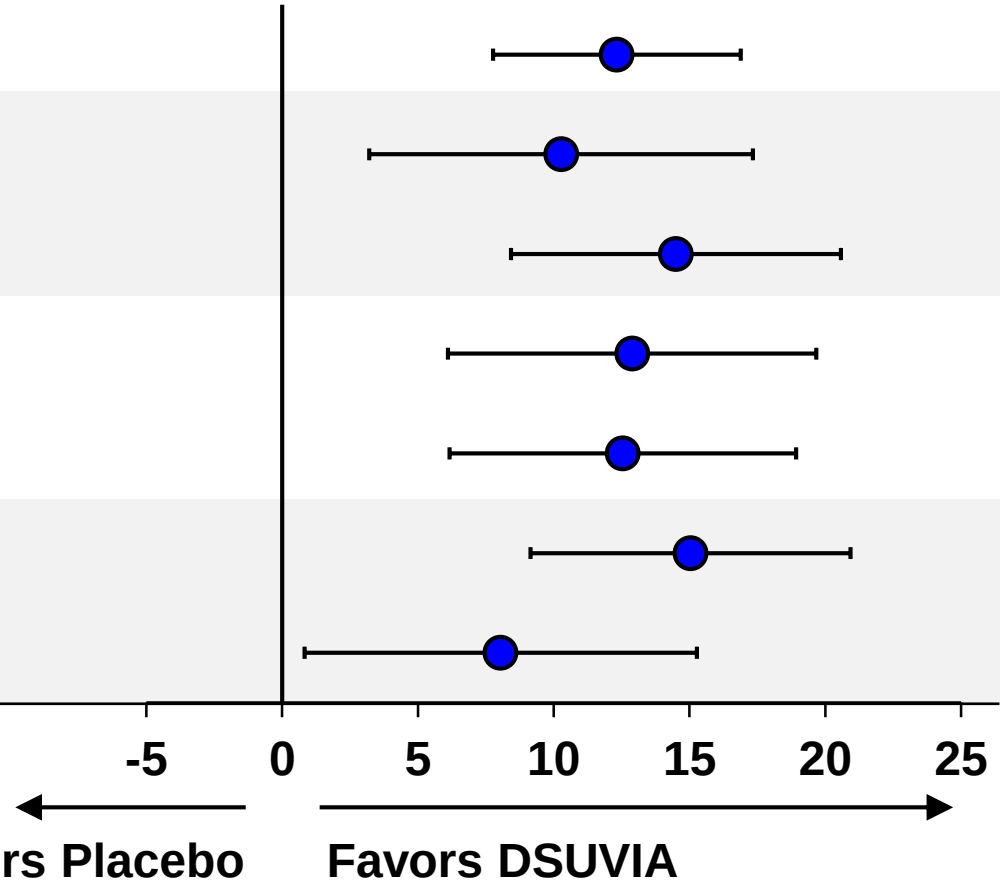
161

DSUVIA 30 mcg Selected Based on SPID12 Difference from Placebo



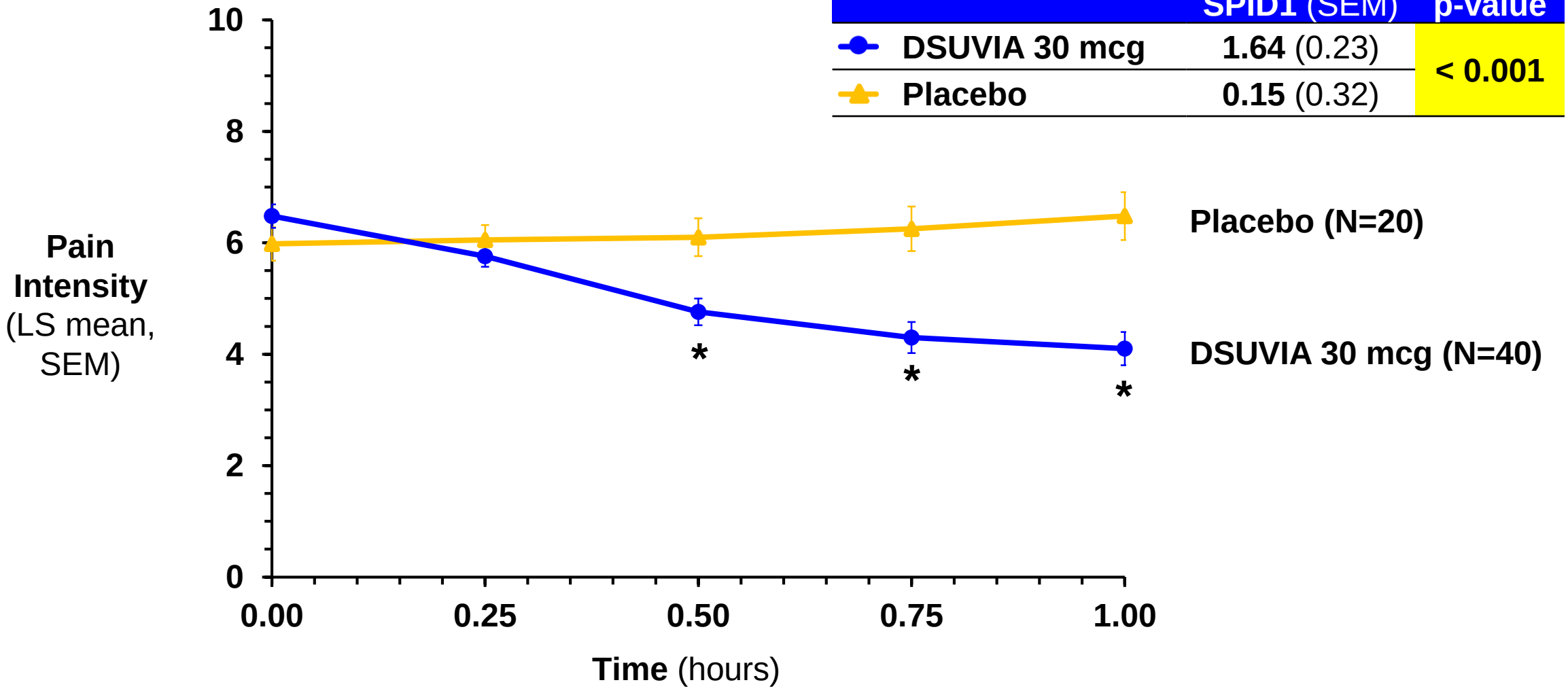
Studies 202 and 301: DSUVIA 30 mcg Efficacy Consistent Across Subgroups

Subgroup	DSUVIA n	DSUVIA SPID12	Placebo n	Placebo SPID12
Age < 65 years	144	13.5	72	1.2
Male	54	8.2	28	-2.0
Female	93	19.6	46	5.1
Caucasian	62	14.2	34	1.3
Non-Caucasian	85	14.9	40	2.3
BMI < 30 kg/m^2	105	16.3	48	1.3
BMI ≥ 30 kg/m^2	42	10.9	26	2.8



Study 202: Superior Single-Dose Efficacy over First Hour (Bunionectomy)

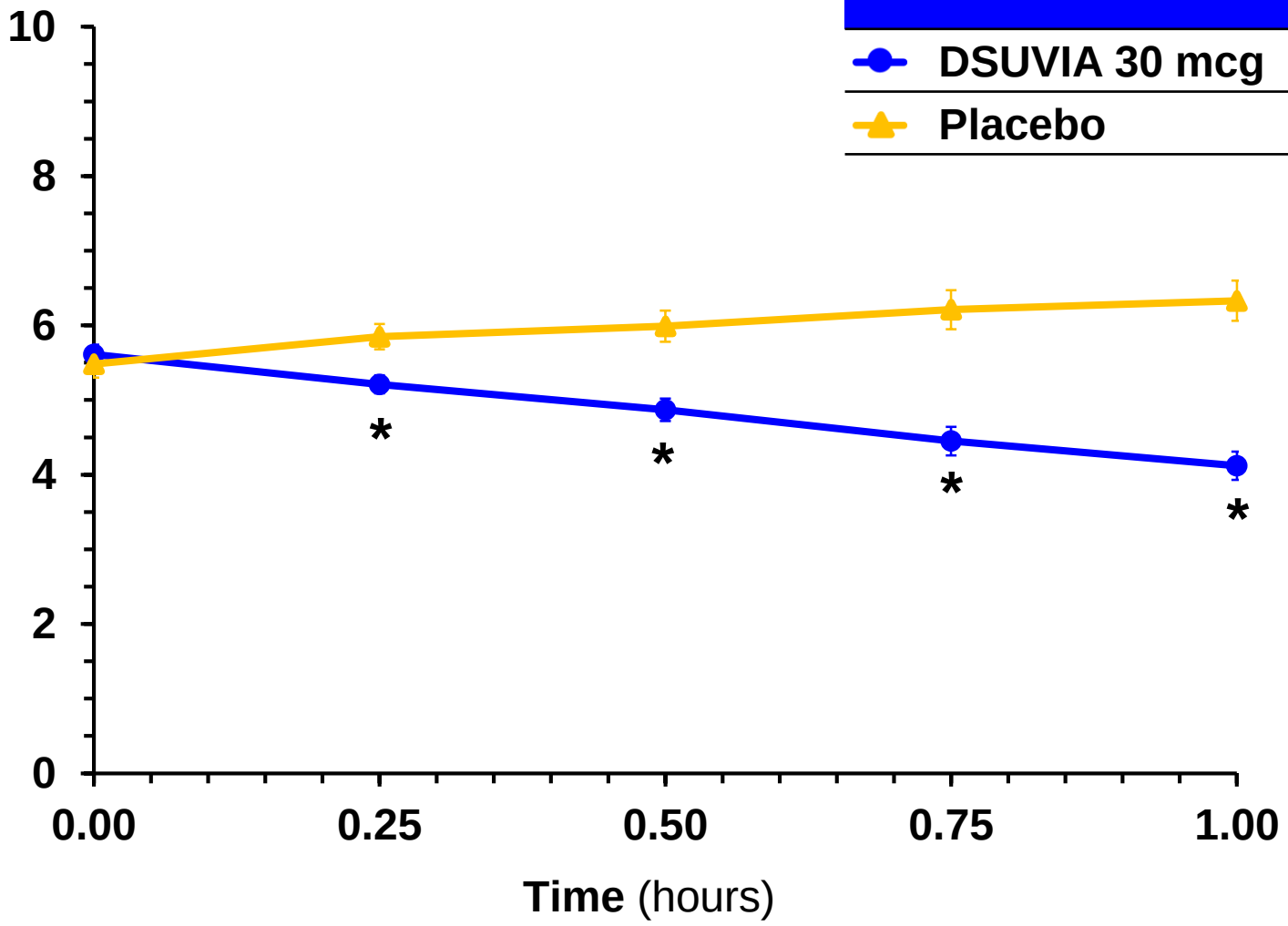
	SPID1 (SEM)	p-value
DSUVIA 30 mcg	**1.64** (0.23)	**< 0.001**
Placebo	**0.15** (0.32)	



*p < 0.01

Study 301: Superior Single-Dose Efficacy (Abdominal Surgery)

	SPID1 (SEM)	p-value
DSUVIA 30 mcg	**1.09** (0.15)	**< 0.001**
Placebo	**-0.37** (0.21)	

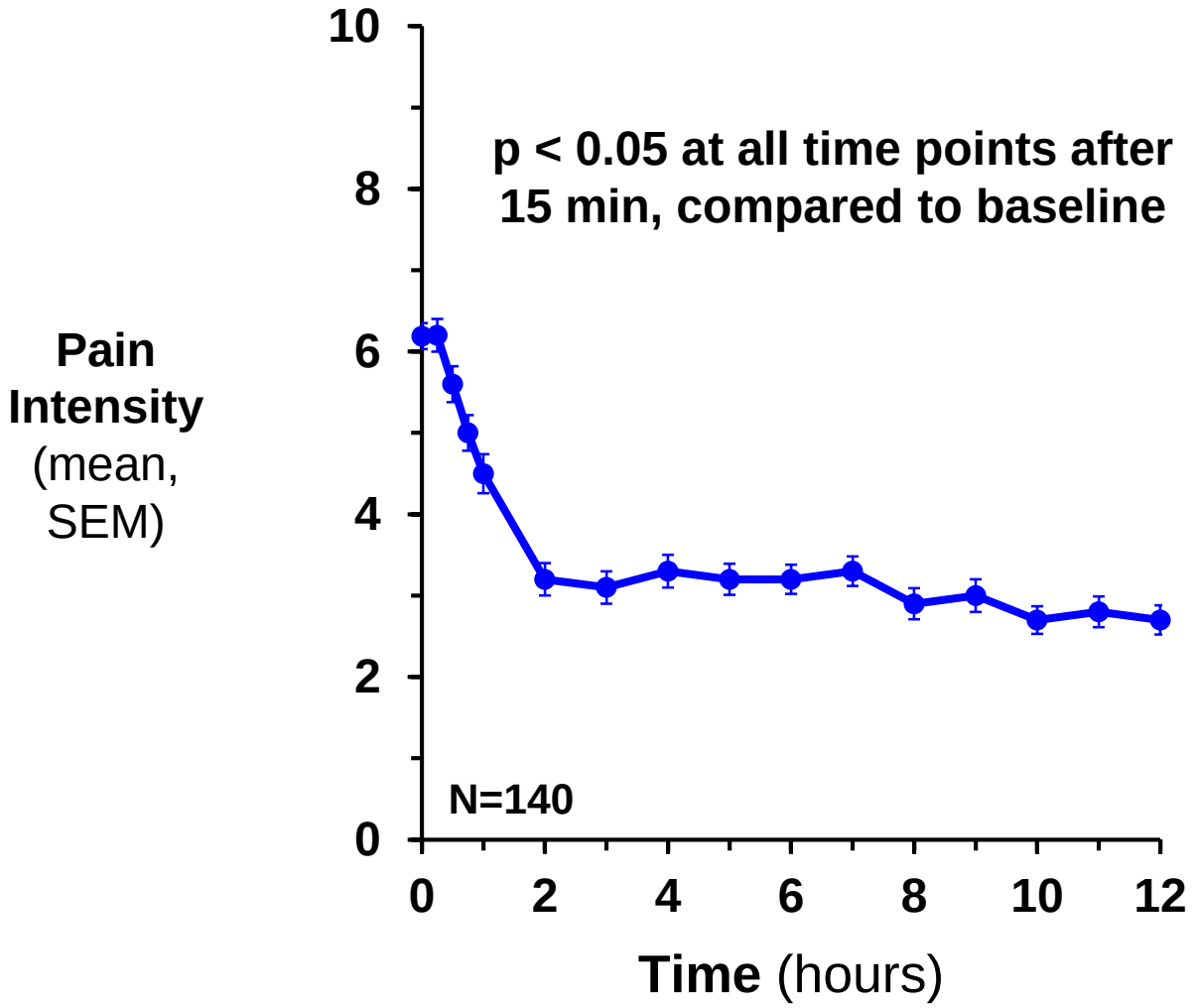


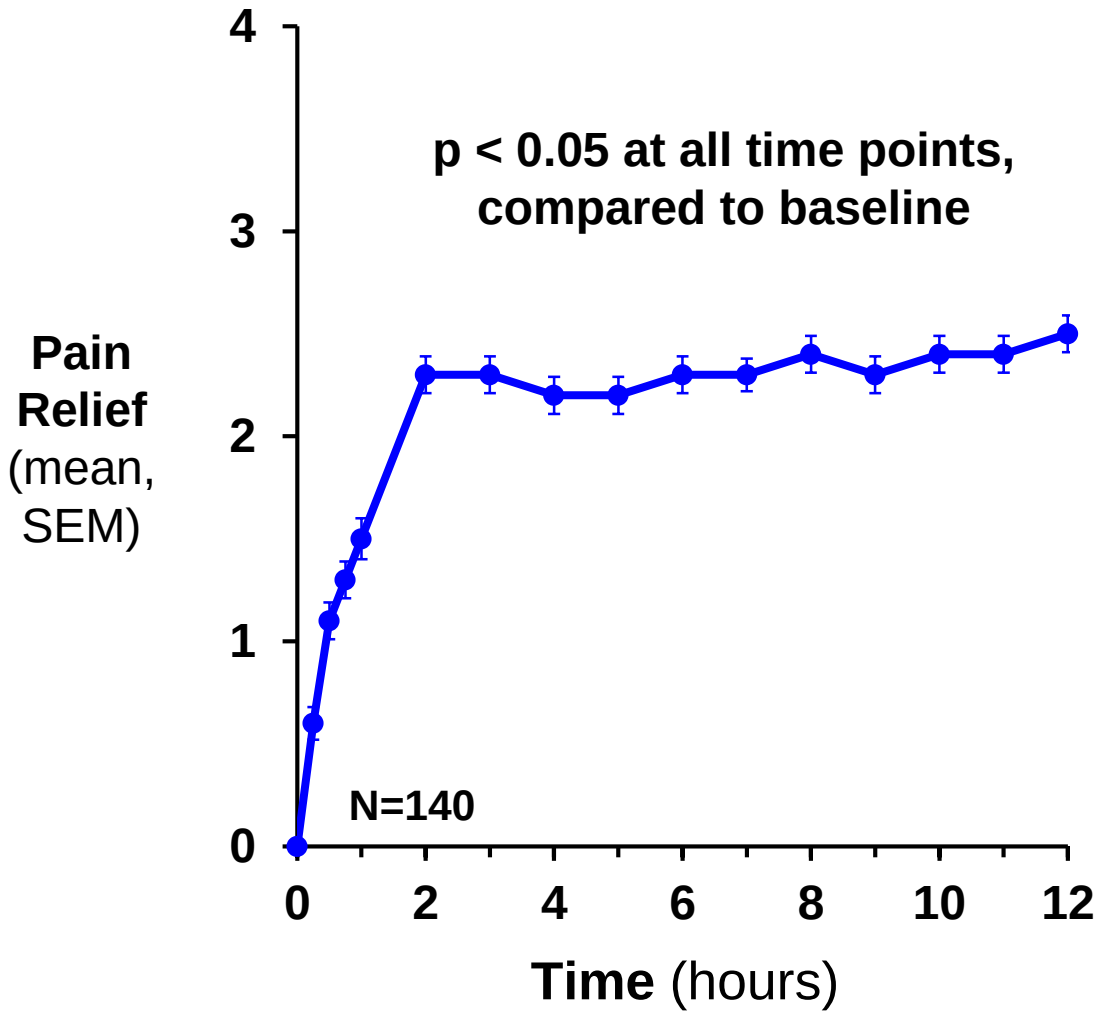
*p < 0.01

Studies 202 and 301: DSUVIA 30 mcg Analgesia Onset

Assessment Method	Study 202 (Bunionectomy) N=60	Study 301 (Abdominal Surgery) N=161
Time to Difference from baseline Pain intensity / pain relief	15 min / 15 min	15 min / 15 min
Time to Difference from placebo Pain intensity / pain relief	30 min / 30 min	15 min / 30 min
Double-stopwatch technique Time to perceptible analgesia	29 min	24 min

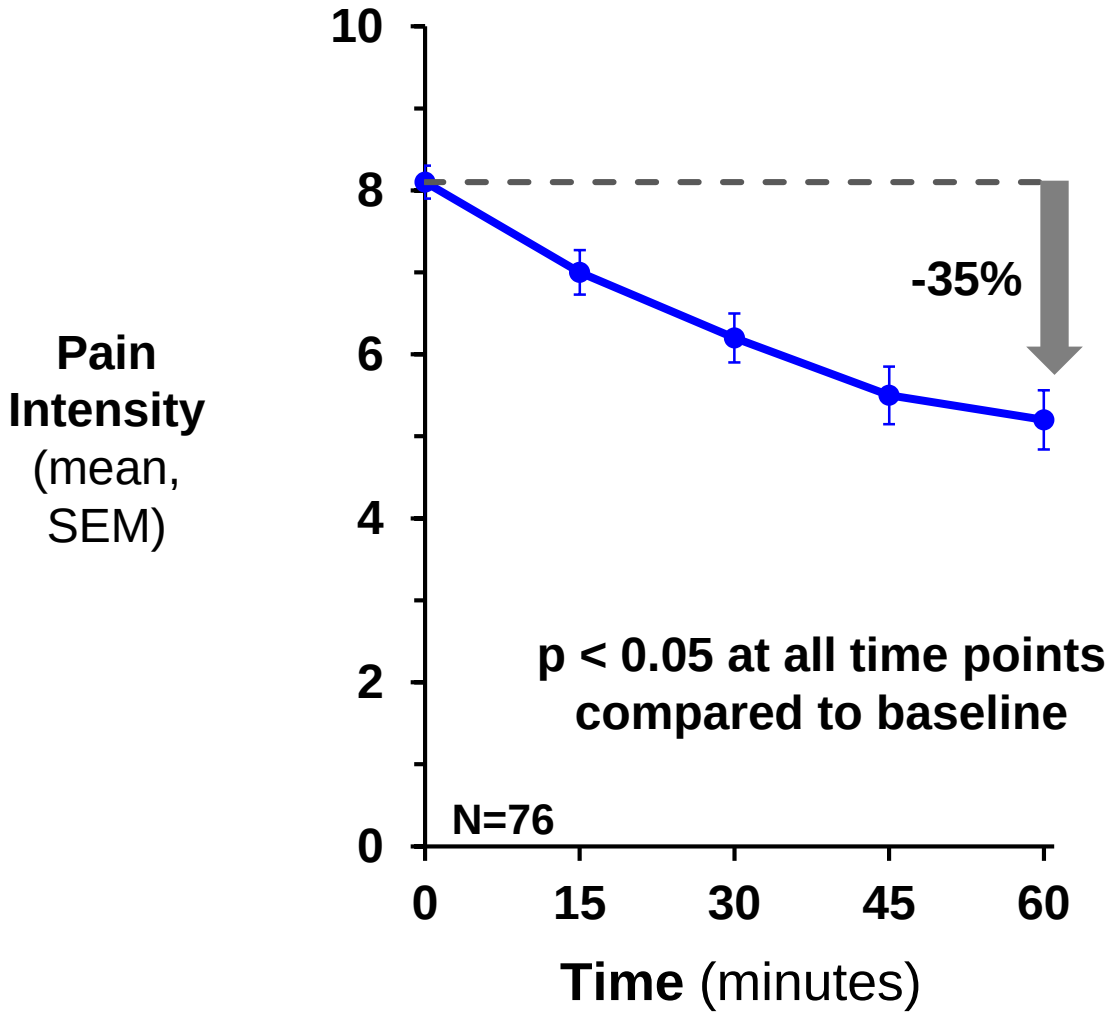
Open-Label Study 303: Pain Reduction Evident Within 15 to 30 Minutes (Postoperative ≥ 40 years)

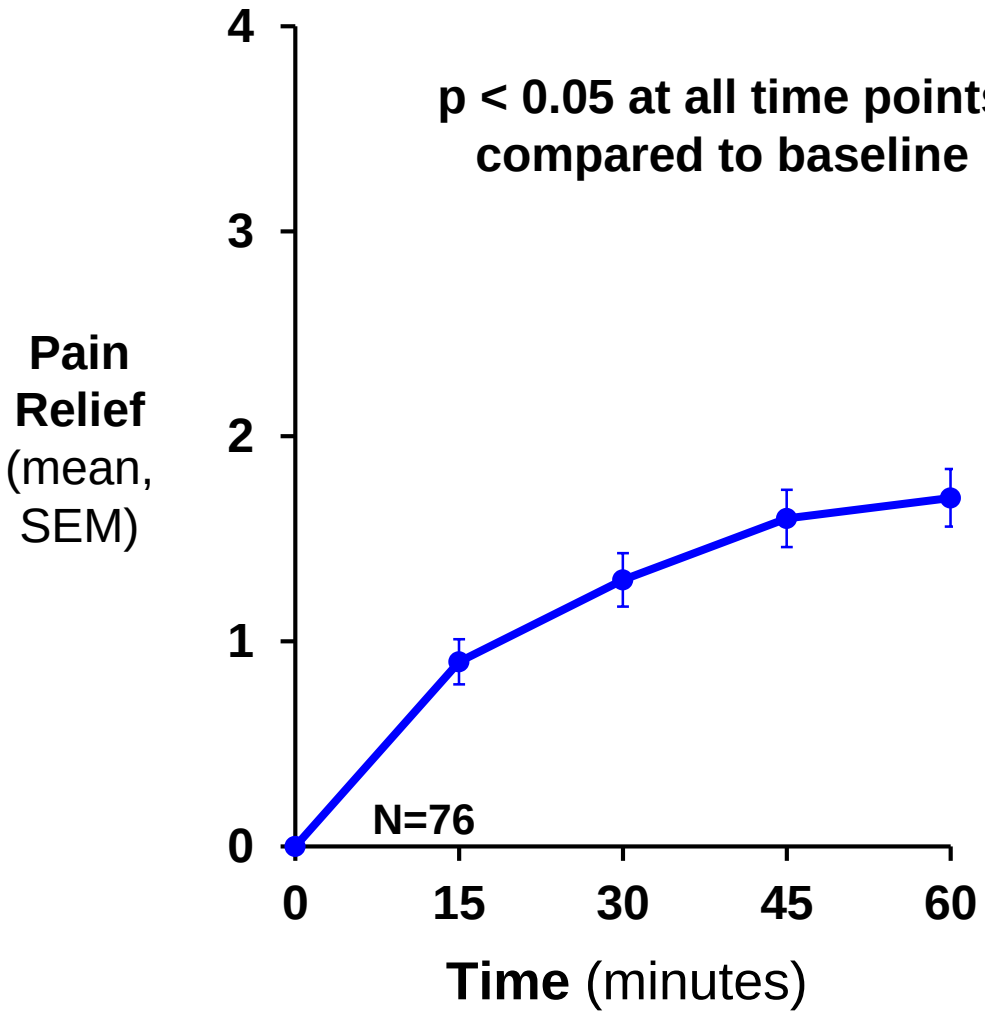




No correction for multiplicity

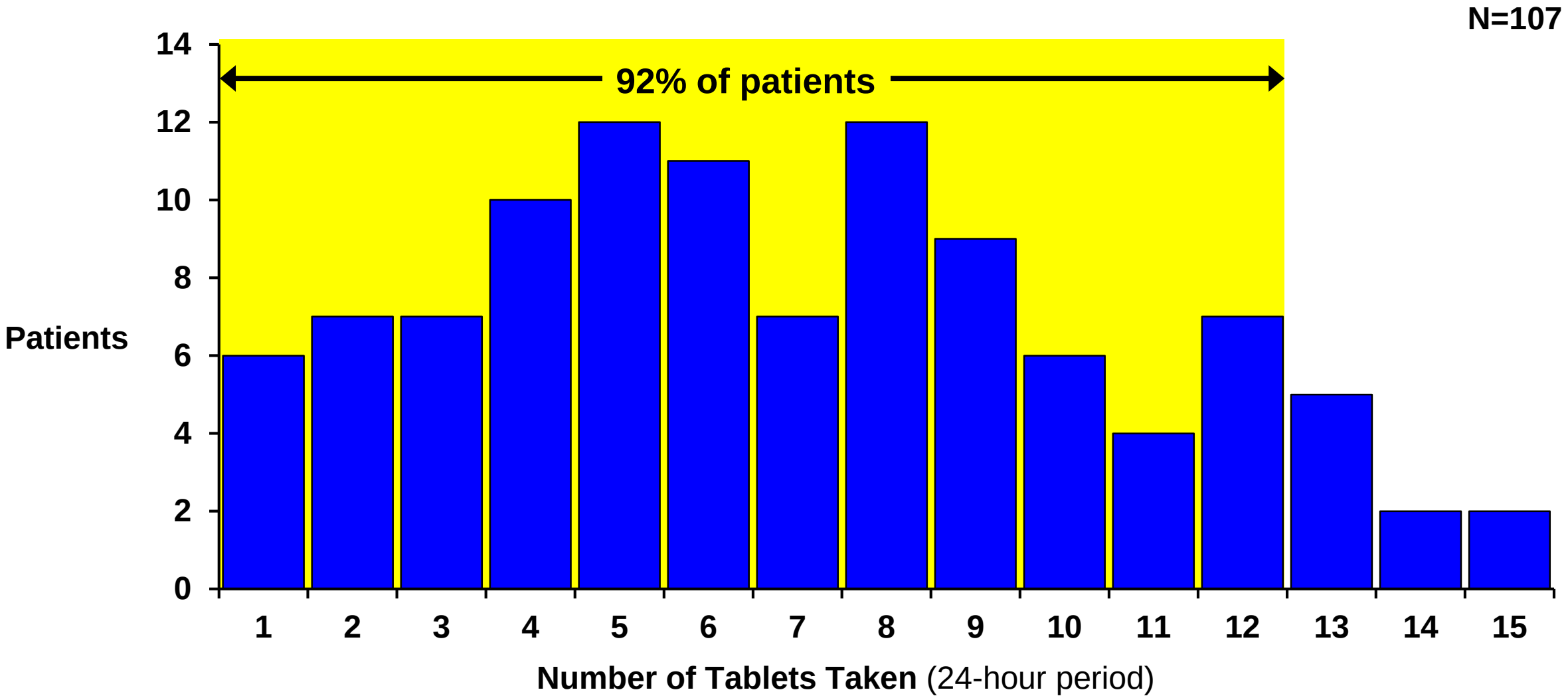
Open-Label Study 302: Pain Reduction with a Single DSUVIA 30 mcg Dose (Emergency Department)





No correction for multiplicity

Study 301: DSUVIA 30 mcg Inter-dosing Interval of 3.7 Hours; 12 Tablet Maximal Daily Dose Recommended



Study 301: abdominal surgery

DSUVIA 30 mcg Rapidly Reduced Pain Across All Studies

- Primary and secondary analyses support efficacy
- Large and consistent effect established in musculoskeletal pain and mixed soft-tissue / visceral pain
- Pain intensity reductions in ED patients mirrored postoperative patients
- Rapid onset for non-invasive analgesic and supported by Phase 1 PK data
- Single-strength product with flexible re-dosing interval

Safety Results

Neil Singla, MD

Founder and Chief Scientific Officer

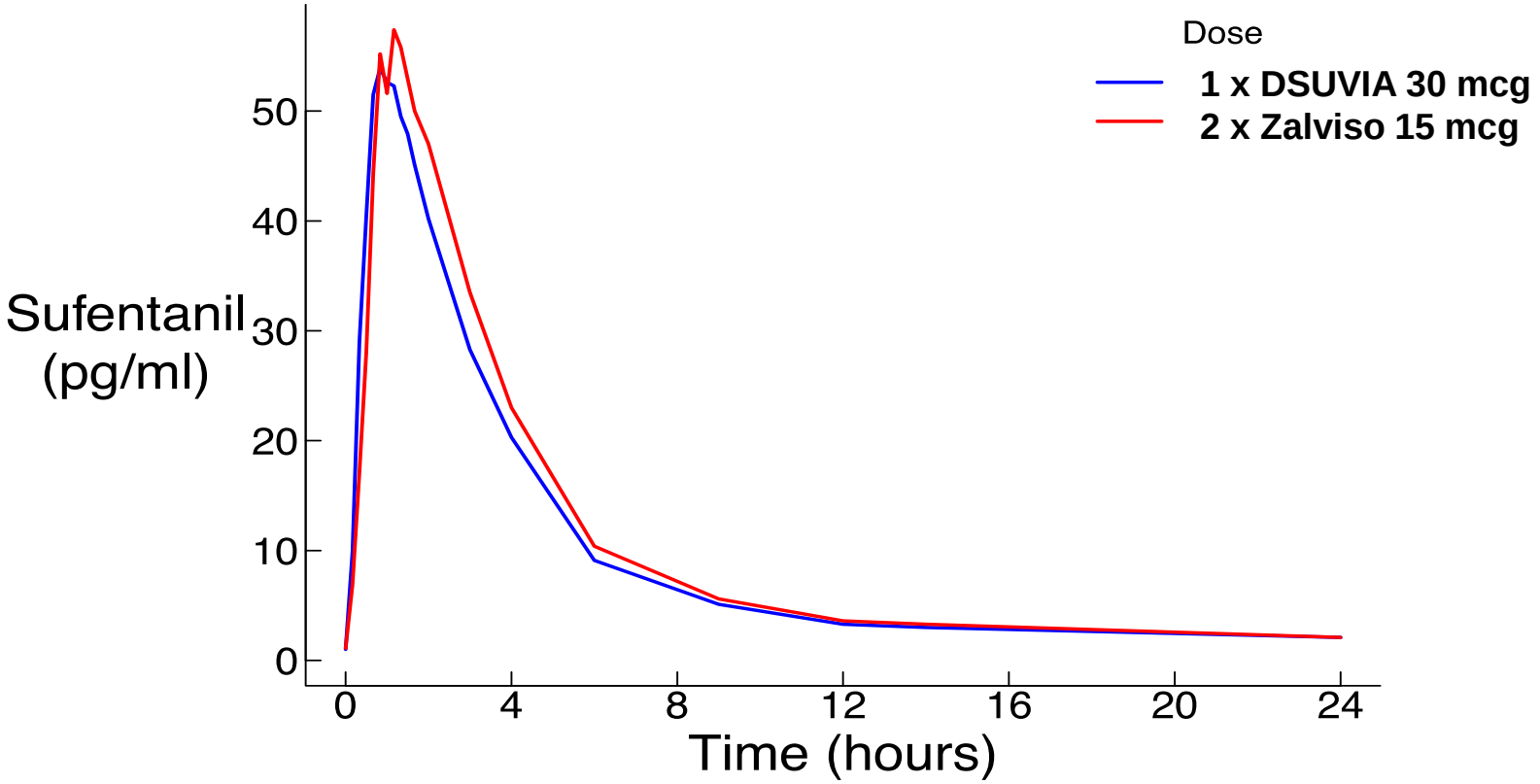
Lotus Clinical Research

DSUVIA Safety Overview: Three Patient Pools

- Overall Safety Population
  - All DSUVIA and Zalviso Phase 2/3 studies (excluding Study 202)
  - 5–72 hours in duration
- Placebo-controlled safety within first 24 hours
  - < 2% of DSUVIA AEs occurred beyond 24 hours
- Analysis of higher exposure compared to lower exposure
  - Pool 8: All studies ≥ 24 hours duration*
  - Safety data exposure ≤ 72 hours

*Pool 8: DSUVIA Study 301 and Zalviso Studies 309, 310, 311

Sublingual Sufentanil: 2 x Zalviso 15 mcg is Bioequivalent to 1 x DSUVIA 30 mcg



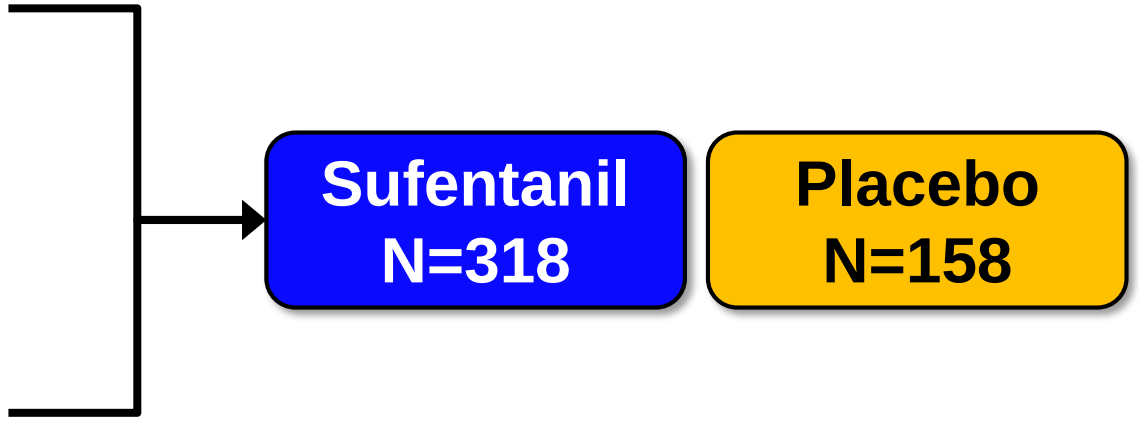
- Bioequivalence criteria met for AUC, C_{max}
- Allows inclusion of 323 Zalviso patients in DSUVIA safety database

Patient Exposure in Sufentanil Sublingual Tablet Studies

	Sufentanil N	Placebo N	Safety Population
DSUVIA (30 mcg) Studies	**363**	**74**	
Study 202	40	20	Bunionectomy
Study 301	**107**	**54**	**Abdominal surgery**
Study 302	**76**	**0**	**Trauma/injury in emergency dept. setting**
Study 303	**140**	**0**	**Postoperative, ≥ 40 years**
Zalviso Studies	**323**	**104**	
Studies 001, 005, 310, 311	**211**	**104**	**Abdominal, knee- or hip-replacement surgery**
Studies 004, 309	**112**	**0**	**Abdominal, knee- or hip-replacement surgery**

Patient Exposure in Sufentanil Sublingual Tablet Studies

	Sufentanil N	Placebo N	Safety Population
DSUVIA (30 mcg) Studies	363	74	
Study 202	40	20	
Study 301	107	54	
Study 302	76	0	
Study 303	140	0	
Zalviso Studies	323	104	
Studies 001, 005, 310, 311	211	104	
Studies 004, 309	112	0	



DSUVIA Safety Profile Consistent with Acute Opioid Treatment

Adverse Events (≥ 2%) Placebo-controlled Studies	Pooled Sufentanil N=318		Pooled Placebo N=158	
	n	%	n	%
Patients with at least 1 AE	215	67%	91	58%
Nausea	132	42%	49	31%
Headache	31	10%	15	10%
Vomiting	31	10%	5	3%
Pyrexia	16	5%	8	5%
Dizziness	16	5%	4	3%
Pruritus	15	5%	4	3%
Anemia	14	4%	2	1%
Hypotension	12	4%	4	3%
Tachycardia	10	3%	1	1%
Hypertension	8	3%	5	3%
Insomnia	8	3%	2	1%
Oxygen saturation decreased	7	2%	0	0

AEs Leading to Discontinuation

Placebo-controlled Studies	Pooled Sufentanil N=318		Pooled Placebo N=158	
	n	%	n	%
Patients with ≥ 1 AE	11	4%	6	4%
Nausea	3	0.9%	0	0
Sedation	2	0.6%	0	0
Respiratory rate decreased	1	0.3%	1	0.6%
Oxygen saturation decreased	1	0.3%	0	0
Back pain	1	0.3%	1	0.6%
Dizziness	1	0.3%	1	0.6%
Anxiety	1	0.3%	0	0
Confusional state	1	0.3%	0	0
Hypoventilation	1	0.3%	0	0
Hemiparesis	0	0	1	0.6%
Somnolence	0	0	1	0.6%
Syncope	0	0	1	0.6%
Tremor	0	0	1	0.6%
Abdominal pain	0	0	1	0.6%

Placebo-Controlled Studies: Serious Adverse Events

Treatment	AE Preferred Term	Severity	Naloxone
Zalviso	Oxygen saturation decreased	Severe	Yes
Zalviso	Pulmonary embolism	Mild	No
	Hypoxia	Moderate	No
	Confusional state	Moderate	No
DSUVIA Placebo	Syncope	Moderate	No
DSUVIA Placebo	Hemiparesis	Severe	No

- No SAEs reported for DSUVIA

Deaths in Clinical Program

- No deaths in DSUVIA studies
- One death in patient receiving Zalviso
  - 69-year old woman
  - Total knee replacement surgery
  - Died of acute renal failure 30 days after last dose
  - Event considered unrelated to treatment by investigator

Safety Topics of Special Interest

- Respiratory events
- Comparison of high and low exposure
- Human Factors study to assess safe use

Placebo-Controlled Studies: Respiratory Events Leading to Discontinuation

	Pooled Sufentanil N=318		Pooled Placebo N=158	
	n	%	n	%
Respiratory rate decreased	1	0.3%	1	0.6%
Oxygen saturation decreased	1	0.3%	0	0
Hypoventilation	1	0.3%	0	0

Comparison of High and Low Exposure

- Proposed label: ≤ 12 tablets in 24-hour period
- FDA request for safety evaluation following maximal dosing
- Comparison of high and low exposure in 24-hour period
  - ≥ 300 mcg vs. < 300 mcg
- Safety based on studies ≥ 24 hours (Pool 8)
  - DSUVIA: Study 301
  - Zalviso: Studies 310, 311, and 309

Comparison of High and Low Exposure (Pool 8)

	DSUVIA		Zalviso	
	< 300 mcg n=81	≥ 300 mcg n=26	< 300 mcg n=107	≥ 300 mcg n=180
AEs	58%	58%	77%	83%
Severe AEs	5%	4%	3%	0.6%
SAEs	0	0	3%	0.6%
AEs leading to discontinuation	0	4%	14%	3%

Pool 8: DSUVIA Study 301 and Zalviso Studies 309, 310, 311

Comparison of High and Low Exposure (Pool 8): Adverse Events

	DSUVIA		Zalviso	
	< 300 mcg N=81	≥ 300 mcg N=26	< 300 mcg N=107	≥ 300 mcg N=180
Typical Opioid AEs	58%	58%	77%	83%
Nausea	30%	42%	40%	52%
Vomiting	9%	4%	9%	11%
Pruritus	1%	4%	7%	8%
Dizziness	6%	4%	7%	4%
Oxygen saturation decreased	0	4%	8%	6%
Hypotension	5%	4%	4%	6%
Somnolence	2%	4%	2%	0
Constipation	0	0	3%	9%
Confusional state	0	0	5%	2%
Hypoxia	1%	0	3%	2%
Sedation	0	0	4%	0.6%
Respiratory rate decreased	0	0	2%	0

Pool 8: DSUVIA Study 301 and Zalviso Studies 309, 310, 311

EU Zalviso Experience

- Zalviso EU launch in April 2016
- Pharmacovigilance through June 2018
  - 26,200 patients
  - Reported AEs similar to sublingual sufentanil clinical trials and representative of opioid use in post-operative population

Safety Summary

- Sufentanil has well-characterized safety profile > 30 years
- DSUVIA 30 mcg data consistent with safety expectations for opioid treatment
- Safety profile consistent for < 300 mcg and ≥ 300 mcg in 24 hours

Human Factors Study

To address concern regarding dropped tablet

Human Factors Study Goals

- Validate revised Directions for Use
- Assess proper DSUVIA administration and confirm placement
- Mitigate risk of dropped tablet

Changes Made to Directions for Use

- Emphasis on handling of single-dose applicator to prevent accidental actuation
- Emphasis on confirmation of tablet placement
- Modifications to illustrations of mouth anatomy
- Steps if tablet is not in patient's mouth after plunger actuated
  - Locate and dispose of tablet
- Directions for Use attached to each DSUVIA package

HCPs Can Successfully Administer DSUVIA

- All HCPs (N=45) successfully administered and confirmed placement of placebo tablet to 3 mock patients
- No dropped tablets
- DMEPA determined that product-user interface supports safe and effective use

DMEPA: Division of Medication Error Prevention and Analysis

Educational Materials, REMS Program, and Conclusion

Pamela Palmer, MD PhD

Co-Founder and Chief Medical Officer

AcelRx Pharmaceuticals, Inc.

DSUVIA Educational Materials

- Proper administration and confirmation of tablet placement
  - Directions for Use attached to each pouch
  - Instructional video
  - Product safe-use guide
  - Placebo units available for in-service training
- 24-hour product support line
- REMS website

REMS Implementation: Three-prong Approach to Risk Management

- Before ordering
  - REMS certification required
- Before administration
  - Directions for Use training to emphasize proper administration and placement
- Ongoing assessment and monitoring
  - Real-time review of product complaints and pharmacovigilance
  - Supply chain audits, including healthcare facility
  - RADARS to assess any accidental exposure, abuse, misuse, or diversion

DSUVIA 30 mcg Unique Alternative for Acute Pain

- Unique analgesic alternative with rapidly-equilibrating opioid
  - Avoids IV placement and swallowing pills
  - Onset in 15–30 minutes
  - 24-hour average re-dosing interval: 3.7 hours
  - No active metabolites
- 4 DSUVIA trials demonstrated efficacy / safety in patients with moderate-to-severe acute pain
- Well-tolerated with safety profile similar to other opioids

DSUVIA™ (sufentanil) sublingual tablet 30 mcg for management of moderate-to-severe acute pain in a medically supervised setting

October 12, 2018

AcelRx Pharmaceuticals, Inc.

Meeting of the Anesthetic & Analgesic Drug Products Advisory Committee

Backup Slides Shown

Overall Safety Population: Demographics

	DSUVIA N=323	Zalviso N=323
Sex (female)	55%	65%
Age		
Mean (min, max)	47.2 (18, 84)	64.0 (19, 86)
≥ 65	11%	51%
Caucasian	53%	84%
BMI (kg/m^2)		
Mean (min, max)	29 (18, 67)	30 (18, 62)
< 30	62%	54%
≥ 30	38%	46%
ASA		
II	42%	Not recorded
III	9%	Not recorded

SAP303: SPID12 by Demographic Groups

Demographic	N	Baseline PI LS Mean (95% CI)	SPID12 LS Mean (95% CI)	p-value
Age (years)				
<65	109	6.3 (5.9, 6.6)	36.4 (32.9, 40.0)	0.569
≥ 65	18	5.7 (4.8, 6.6)	33.7 (24.9, 42.5)	
Gender				
Male	63	6.2 (5.7, 6.6)	35.6 (30.9, 40.3)	0.790
Female	64	6.2 (5.8, 6.7)	36.5 (31.9, 41.1)	
Race				
Caucasian	86	5.9 (5.5, 6.3)	34.5 (30.5, 38.5)	0.191
Non-Caucasian	41	6.7 (6.1, 7.3)	39.2 (33.4, 45.0)	
BMI (kg/m^2)				
<30	71	6.3 (5.8, 6.7)	37.4 (33.0, 41.8)	0.360
≥ 30	56	6.1 (5.6, 6.6)	34.3 (29.4, 39.3)	

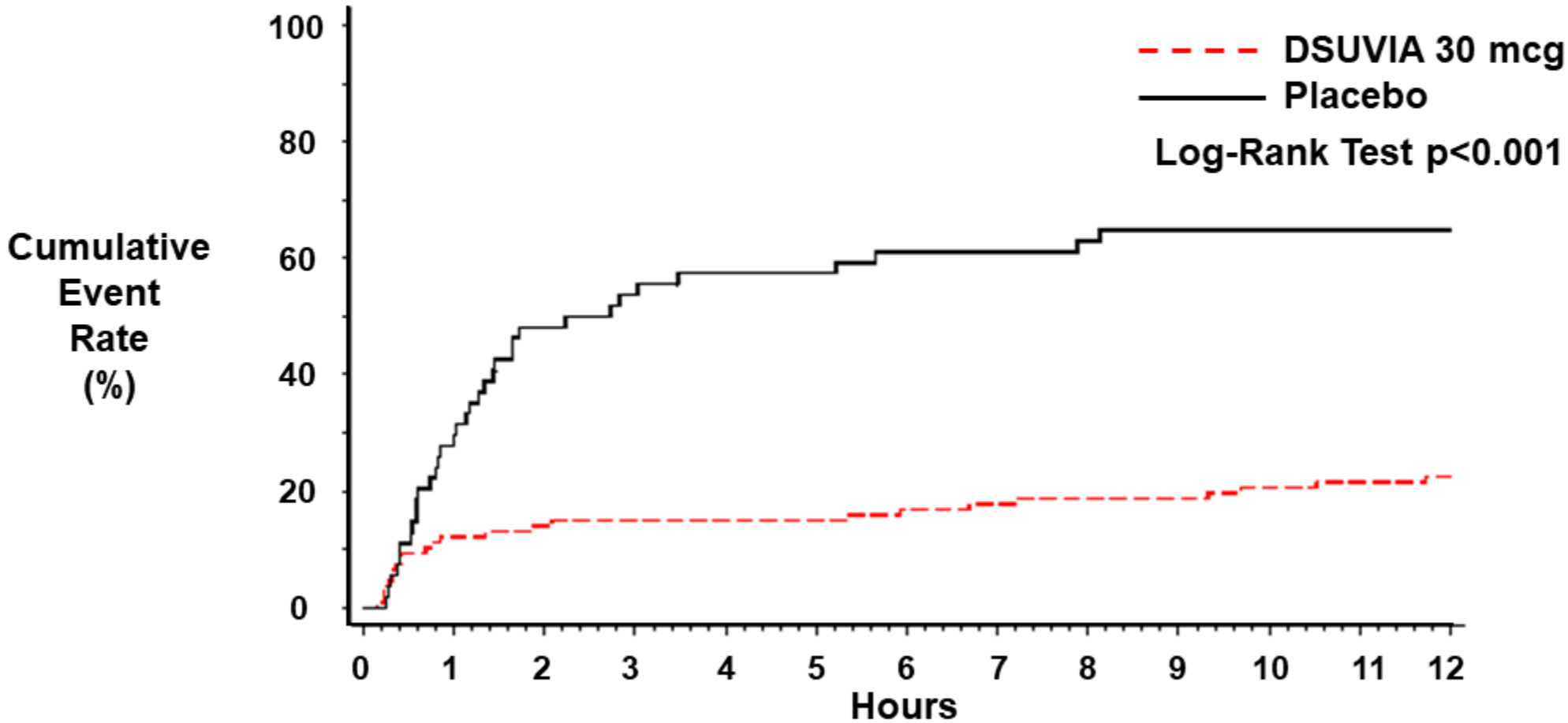
SAP302: SPID1 by Demographics

Demographic	N	Baseline LS Mean (95% CI)	SPID1 LS Mean (95% CI)	p-value
Age (yrs)				
<65	**67**	**8.0** (7.6-8.5)	**2.1** (1.6-2.6)	**0.925**
≥ 65	**9**	**8.4** (7.3-9.6)	**2.1** (0.6-3.5)	
Gender				
Male	**46**	**7.6** (7.1-8.1)	**2.4** (1.8-3.1)	**0.142**
Female	**30**	**8.8** (8.2-9.4)	**1.6** (0.8-2.4)	
Race				
Caucasian	**34**	**7.9** (7.4-8.5)	**2.3** (1.5-3.0)	**0.563**
Other	**42**	**8.2** (7.7-8.7)	**2.0** (1.3-2.6)	
BMI (km/m^2)				
<30	**44**	**8.1** (7.5-8.6)	**2.1** (1.5-2.7)	**0.728**
≥ 30	**28**	**8.2** (7.5-8.8)	**2.2** (1.5-3.0)	

Overall Safety Population: DSUVIA AEs > 5% in Patients by Age

AE	< 65 years n=289	≥ 65 to < 75 years n=26	≥ 75 years n=8
Patients with ≥ 1 AE	40.1%	50.0%	12.5%
Nausea	24.9%	30.8%	0
Headache	9.3%	7.7%	0
Dizziness	2.8%	19.2%	0
Somnolence	1.7%	3.8%	12.5%
O_2 saturation decreased	1.4%	3.8%	12.5%

Study 301 (ITT): Time to First Rescue Medication



DSUVIA	N=107	94	92	91	91	91	89	88	87	87	85	84	83
Placebo	N=54	39	28	25	23	23	21	21	20	19	19	18	18

Event is time of first use of rescue medication

Number of Rescue Medication Doses by Study Mean/Median

Study	DSUVIA 30 mcg	Placebo	p-value
202 (0 – 12 hrs)	1.1 / 1.0	2.1 / 2.0	<0.001
301 (0 – 24 hrs)	0.5 / 0.0	2.1 / 1.0	<0.001
302 * (0 – 5 hrs)	0.08 / 0.0 *	n/a	n/a
303 (0 – 12 hrs)	0.2 / 0.0	n/a	n/a

* Excludes patients in first cohort who used RM after one hour when additional study drug was not allowed per protocol

Patients (%) Using Rescue Medication by Study

Study	Patients (%) Using Rescue Medication		p-value
	DSUVIA 30 mcg	Placebo	
202	70%	100%	0.006
301	27%	65%	<0.001
302	8%*	n/a	n/a
303	14%	n/a	n/a

*Excludes patients in first cohort who used RM after one hour when additional study drug was not allowed per protocol

Studies 202 and 301: Rescue Doses for Patients Using Rescue

	Number of Doses		
	DSUVIA	Placebo	p-value
Study 202 (0–12 hours)	n=28	n=20	
Mean	1.5	2.1	0.004
Min, Max	1, 3	1, 3	
Study 301 (0–24 hours)	n=29	n=35	
Mean	2.0	3.3	0.047
Min, Max	1, 11	1, 14	

Median Time to Analgesia Onset Double-Stopwatch Study 301

	DSUVIA 30 mcg N=107	Placebo N=54	p-value
Perceptible Median (95% CI)	 24 min (18, 29)	 78 min (27, n/a)	 0.002
Meaningful Median (95% CI)	 54 min (44, 72)	 84 min (56, 250)	 0.156

Study 302: Cognitive Impairment Assessment

Six Item Screener for Cognitive Impairment:
5-6 non-impaired
< 5 cognitive impairment

Score	Baseline N=75	After 1 hour N=75
6	63	70
5	9	3
< 5	3	2

- 73 patients either had the same score or increase their score
- 2 patients had a decrease of 1 point compared to baseline

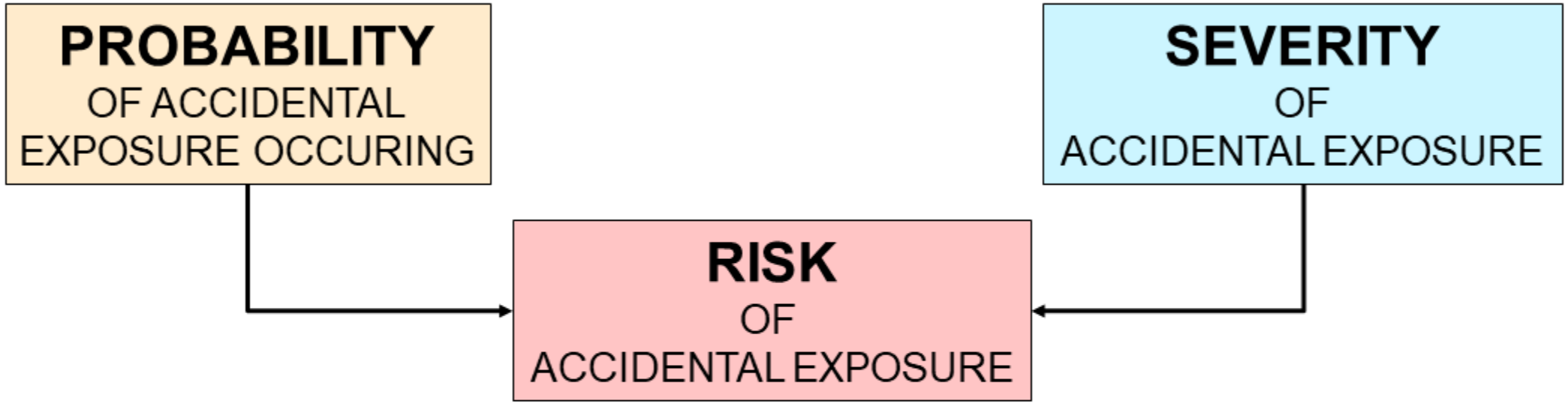
REMS Audit Plan: Certified Healthcare Facilities

- AcelRx will audit 100% of initial active user facilities to assess compliance with REMS
  - REMS training records for HCPs administering DSUVIA
  - Any reports of dropped tablets
  - Patterns of use within facility
  - Any DEA Form 106 filed (lost or stolen controlled substances)
  - Automated Dispensing Cabinet wastage records
- Based on findings, a statistically verified sampling of sites will be selected for audits moving forward

Overall Safety Population: Naloxone Use

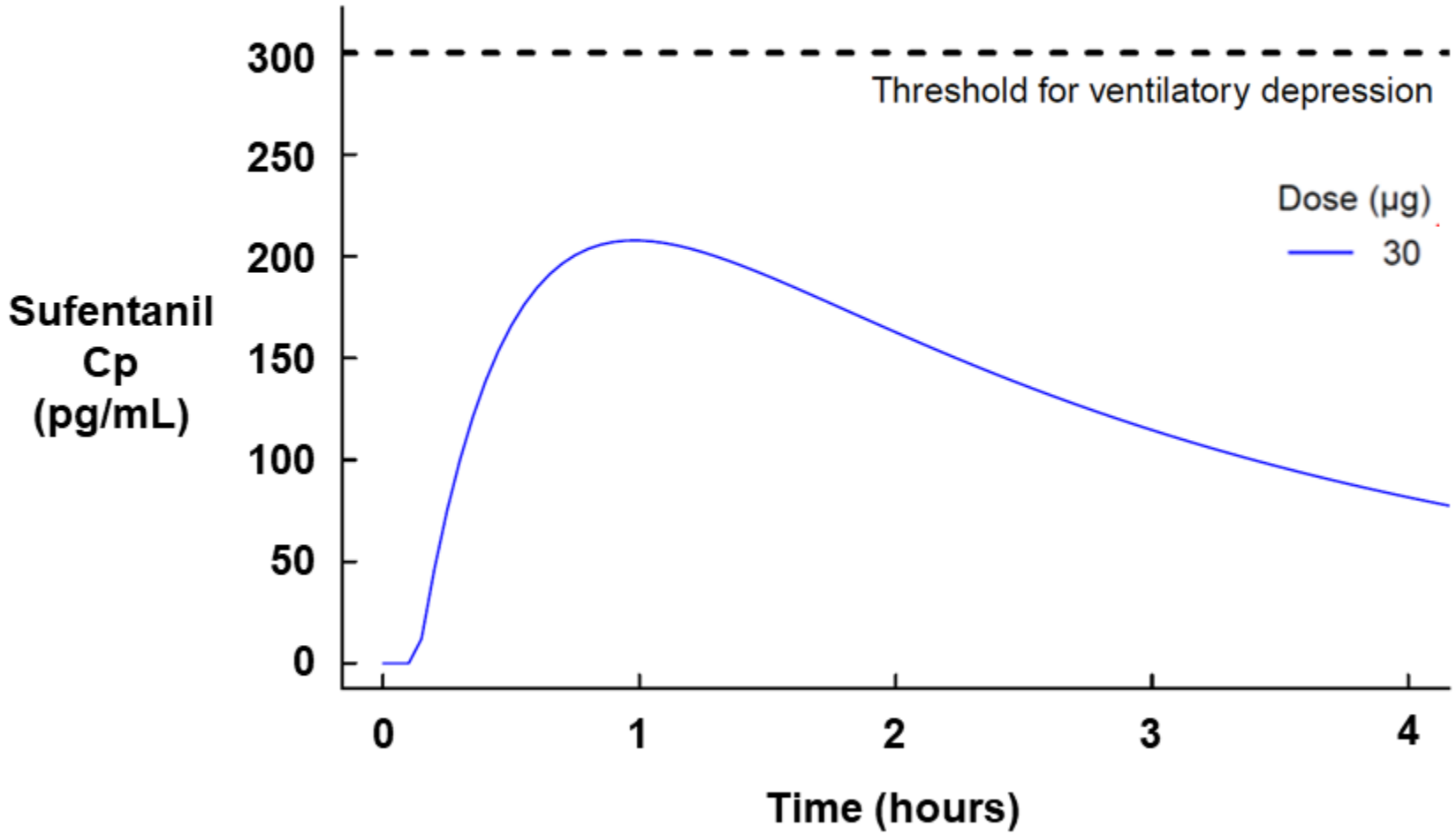
- No DSUVIA patients required naloxone
- 3 Zalviso patients
  - IAP311 Zalviso – oxygen saturation decreased (SAE)
  - IAP311 Zalviso – sedation
  - IAP309 Zalviso – narcotic reversal
- 2 placebo patients
  - IAP311 Placebo – shaking
  - SAP301 Placebo – anxiety

Risk Assessment: Accidental Exposure Due to a Dropped Tablet



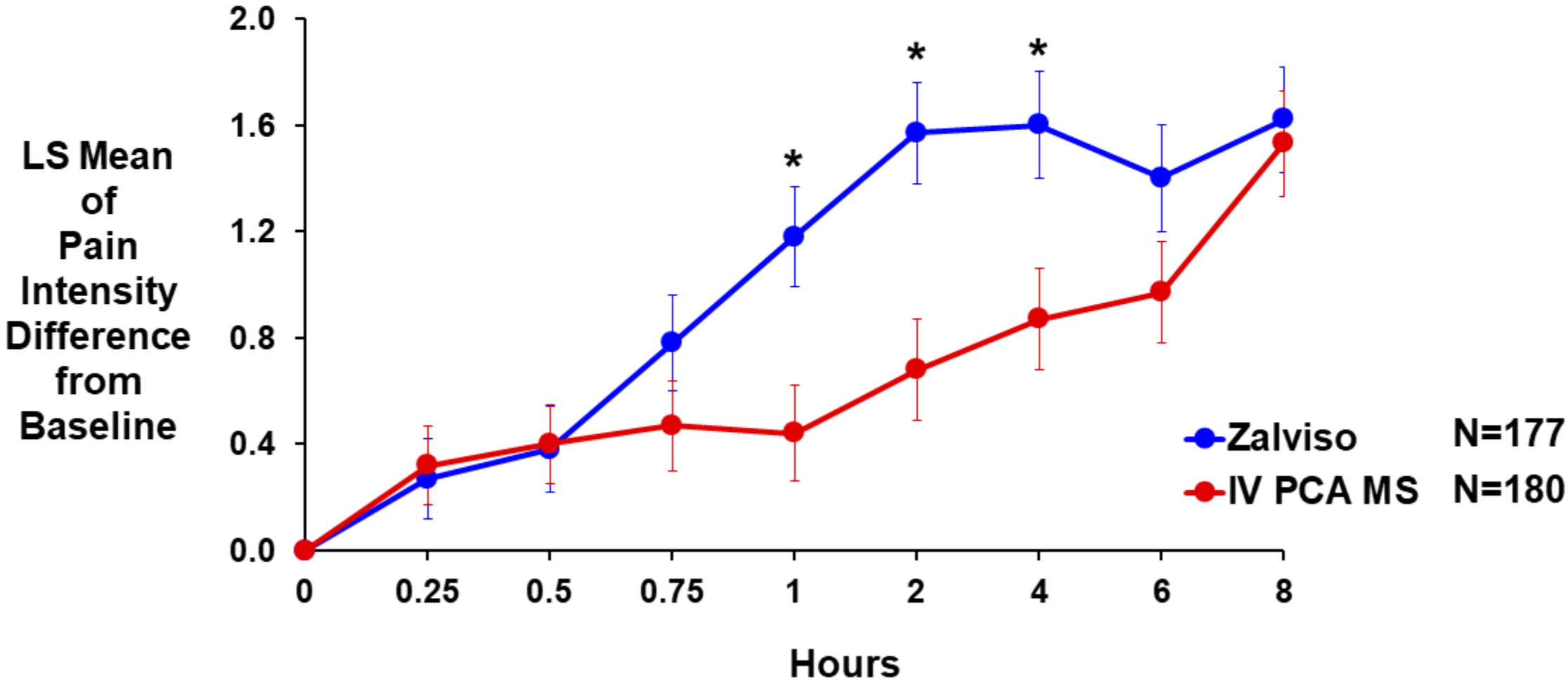
- **PROBABILITY** of a dropped tablet leading to accidental exposure to DSUVIA, administered by an HCP in a medically supervised setting is extremely low
- **SEVERITY** of accidental exposure to a dropped tablet, for the most vulnerable population, a toddler (12-kg), is unlikely to cause respiratory depression
- Resulting **RISK** of accidental exposure due to a dropped tablet is extremely low

Modeled Sufentanil Plasma Concentration for 1 DSUVIA Tablet in a Toddler (12-kg)



- Haynes, et al. 1993 - Intranasal sufentanil with peak plasma concentrations averaging 300 pg/mL resulted in no respiratory depression

Pain Intensity Difference Over Time: Zalviso vs. IV PCA Morphine (Study 309)



* p <0.01