Buprenorphine Sublingual Spray (Buvaya™)

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

Insys Development Co.
May 22, 2018
Introduction

Stephen Sherman, JD, MBA
Senior Vice President, Regulatory Affairs and Clinical Development
Insys Development Co.
Buprenorphine

• **Attributes**
  – Partial mu agonist with slower onset of effect
  – Reported ceiling effect for respiratory depression but not analgesia
  – Schedule III

• **Evidence of lower abuse potential**
  – Buprenorphine is low on the RADARS reporting structure
  – Diversion not for euphoria but to prevent opioid withdrawal

• **Currently only available as an injectable for acute pain**
Issues and Concerns

• Time to meaningful pain relief
  – Within the range of approved products for acute use

• Vomiting
  – Incidence expected based on patient population study
  – Prophylactic antiemetics help mitigate the risk

• Reduced oxygen saturation
  – Prescribing information and Medication Guide will address this risk

• Initiate therapy in a medically supervised setting
  – Manage adverse events and mitigate potential risk of redosing
Buprenorphine Sublingual Spray

• Non-invasive yet bypasses first pass hepatic metabolism that limits oral bioavailability\(^a\)

• Developed for around-the-clock treatment of acute pain
  – Proposed treatment duration: Up to 7 days

• Convenient device that delivers the correct dose

\(^a\) Johnson et al. 2005
Delivery Device

- Easy to use: requires little expertise, preparation, or supervision\(^a\)
- Requires no or minimal training prior to use

\(^a\) Stevens and Ghazi, 2000
Buprenorphine Sublingual Spray New Drug Application

• 505(b)(2) regulatory pathway
  – Buprenex IV and Subutex SL tablets are listed drugs
  – Data available in the public domain for other buprenorphine products

• Clinical development comprises 10 studies
  – Seven pharmacokinetic studies
  – One open label safety study
  – Two efficacy and tolerability studies
Proposed Indication

...for the treatment of moderate to severe acute pain when an opioid is needed and alternative treatments are inadequate.
# Agenda

<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Stephen Sherman, JD, MBA</td>
</tr>
<tr>
<td>Medical Landscape and Unmet Need</td>
<td>Joseph Pergolizzi, MD</td>
</tr>
<tr>
<td>Development Rationale, Pharmacokinetics, Efficacy, and Safety</td>
<td>Dean Mariano, DO</td>
</tr>
<tr>
<td>Risk Management</td>
<td>Stephen Sherman, JD, MBA</td>
</tr>
<tr>
<td>Benefit/Risk Assessment</td>
<td>Joseph Pergolizzi, MD</td>
</tr>
<tr>
<td>Q&amp;A (Sponsor Moderator)</td>
<td>Stephen Sherman, JD, MBA</td>
</tr>
</tbody>
</table>
Medical Landscape and Unmet Need

Joseph V. Pergolizzi, MD
Senior Partner and Director of Research
Naples Anesthesia and Pain Associates, Naples, Florida
Acute Pain

- Number one reason people seek medical care globally
- Different ways to classify pain
- Duration varies
- Intensity varies
- Differs from patient to patient
Moderate-to-Severe Acute Pain Examples

Duration of healing after tissue trauma (often <30 days)

• Post-surgical pain
• Traumatic pain
• Orthopedic pain
• Gastrointestinal pain
• Genitourinary pain
• Otolaryngologic pain
• Gynecological pain
• Cancer incident pain
Safety Issues with Non-opioids

GI Side Effects
- NSAIDs\(^1\)

Cardiovascular Side Effects
- COX-2 inhibitors\(^2,3\)

Hepatic/Renal Toxicity
- Acetaminophen/NSAIDs\(^1\)

Opioid Analgesics

• Act on central nervous system
• Decrease pain awareness in the brain
• Schedule II/III controlled substance
• Side effects: nausea and vomiting, constipation, androgen deficiency, sedation, respiratory depression, physical dependence, tolerance, abuse, addiction
• Withdrawal symptoms occur when stopping or reducing dose
Opioids for Acute Pain

- **Schedule III, PRN**
  - Buprenex IM or IV (bolus injection)
  - Codeine/APAP (oral)

- **Schedule II**
  - Around-the-clock
    - Xartemis XR (oral)
  - PRN
    - Morphine, hydromorphone, fentanyl, hydrocodone, oxycodone, tapentadol
    - Opioid/APAP fixed dose combination
Challenges to Current Opioids for Acute Pain

• Most Schedule II: high risk of addiction, overdose, and death
  – Respiratory depression

• Many formulations contain APAP
  – Limit use in elderly and intolerant

• Hepatic and renal diseases are prevalent
  – Limit use of many products

• PO formulations require the ability to swallow
  – Limit use in patients with difficulty swallowing (eg, dysphagia)

• Vomiting could cause the patient to lose an oral dose

• Risks in patients with history of substance use disorder or at-risk
National Estimates of Drug-related Emergency Department Visits for Misuse and Abuse in 2011

Drug Abuse Warning Network, 2011
# Top 10 Drugs Involved in Overdose Deaths in the United States, 2014¹

<table>
<thead>
<tr>
<th>Rank*</th>
<th>Referent Drug</th>
<th>Number of Deaths (n=47,055)</th>
<th>Percent</th>
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<tbody>
<tr>
<td>1</td>
<td>Heroin</td>
<td>10,863</td>
<td>23.1</td>
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<tr>
<td>2</td>
<td>Cocaine</td>
<td>5,856</td>
<td>12.4</td>
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<tr>
<td>3</td>
<td>Oxycodone</td>
<td>5,417</td>
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<tr>
<td>4</td>
<td>Alprazolam</td>
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<td>5</td>
<td>Fentanyl</td>
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<td>6</td>
<td>Morphine</td>
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<td>8.5</td>
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<tr>
<td>7</td>
<td>Methamphetamine</td>
<td>3,728</td>
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<tr>
<td>8</td>
<td>Methadone</td>
<td>3,495</td>
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<tr>
<td>9</td>
<td>Hydrocodone</td>
<td>3,274</td>
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</tr>
<tr>
<td>10</td>
<td>Diazepam</td>
<td>1,729</td>
<td>3.7</td>
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</table>

Buprenorphine (transdermal patch, buccal film, sublingual film, tablets): 11.5 million (8.8 million for opioid use disorder)

*Ranks were not tested for statistical significance
Deaths may involve other drugs in addition to the referent drug (i.e., the one listed) Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both totals.
Life-threatening Opioid-induced Respiratory Depression

- Opioids can reduce respiratory drive
- Respiratory depression: decreased rate and depth of breathing
  - Low oxygen levels, high carbon dioxide levels
- Serious complications of respiratory depression
  - Respiratory acidosis
  - Apnea (interruption of breathing)
  - Bradycardia (decreased heart rate)
  - Respiratory arrest
  - Cardiac arrest
  - Coma
  - Brain damage
  - Death
Representative Opioid Class Labeling for Life-threatening Respiratory Depression

• Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death…

• …Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of hydrocodone bitartrate and acetaminophen tablets.
Defining Life-threatening Opioid-induced Respiratory Depression

- \( \text{SpO}_2 < 80-85\% \)
- Respiratory rate <8-10 respirations per minute (bradypnea)

Interventions for Life-threatening Opioid-induced Respiratory Depression

- Oxygen therapy
- Detoxification (naloxone)
- Fluid therapy for acidosis
- Positive airway pressure (CPAP or BIPAP)
- Mechanical ventilation
- CPR
Public Health Need: Schedule III Opioid Analgesics for Acute Pain

- Reduce rates of addiction, overdose, and death
- Reduce rates of abuse, misuse, and diversion
- Balance the need for pain control against public health risks
- Evidence base supports lower risk of Schedule III opioids
- Approved Schedule III opioids for acute pain are limited
- Need new Schedule III opioid analgesics for acute pain
Buprenorphine: Schedule III Opioid Analgesic

- Partial mu agonist
  - Partial and prolonged receptor occupancy
  - Potent opioid for relief of moderate to severe pain
  - Therapeutic index is 12,000
  - Ceiling effect on PCO₂
  - Lower constipation

- Lower abuse potential (Schedule III)
  - Lower reported rates of abuse
  - Slower onset of action, time to peak effect (lower abuse quotient, AQ)
  - Used for medication assisted treatment of opioid use disorder
  - May be an option for patients with substance use disorder

- Nausea and vomiting common and manageable

- Current CDC guidelines have no established MME (risk analysis associated with opioid prescribing) conversion factor
Buprenorphine: Ceiling Effect on Respiratory Depression

Dahan et al. BJA 2006
Fentanyl and Buprenorphine Effects on Ventilation

Dahan et al. BJA 2005
# Buprenorphine Treatment Landscape

## Dosing

**Medication Assisted Treatment**

- **2-24 mg/day**
  - (sublingual, implanted, injectable)

**Chronic Pain**

- **120 mcg/day to 1.8 mg/day**
  - (transdermal or buccal)

**Acute Pain**

- **300-600 mcg/day**
  - (injectable)

## Prescriptions

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<th></th>
<th>12.5 million</th>
<th>1 million</th>
<th>1.4 million</th>
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<td><strong>12 months</strong></td>
<td>for 12 months ending March 2017</td>
<td>for 12 months ending March 2017</td>
<td>for 12 months ending March 2017</td>
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</table>

Symphony data on file
Unmet Need Summary

• Few options for moderate-to-severe acute pain
• Schedule II options have higher potential for abuse
  – May lead to severe psychological or physical dependence
• Need more Schedule III treatment options for acute pain
• Buprenorphine has unique properties for pain management
  – Need a non-parenteral formulation for acute pain
  – Schedule III potent partial mu opioid agonist
  – Can effectively manage moderate to severe pain
Development Rationale, Pharmacokinetics, Efficacy, Safety, and Risk Management

Dean Mariano, DO
Senior Director, Clinical Development and Medical Affairs
Insys Development Co.
Development Rationale

• Develop a nonparenteral formulation of buprenorphine for moderate to severe acute pain
  – Schedule III has lower risks of addiction, overdose, and death

• Developed under 505(b)(2) pathway
  – Demonstrated bioavailability
  – Efficacy and safety similar to reference compounds

• Lower abuse potential than Schedule II opioids
Buprenorphine – Not Drug of Choice for Abusers

• Misused primarily to prevent withdrawal from other opioids

• Low rate of misuse and abuse reported in the literature

• In heroin-dependent individuals, buprenorphine was the only drug that had increases in “bad drug effect” and was not taken more than placebo\(^1\)

• New route of administration retains low abuse potential
  – Eight-factor analysis demonstrated that Buprenorphine Sublingual Spray has a low abuse potential, similar to Buprenex and other Schedule III buprenorphine products

1. Comer et al., NLM 2008
Around-the-Clock PRN Dosing

**Around-the-Clock**

- Should be used when pain is continuous or present for ≥12 hours each day
- Patients more adherent to regimens
- Improves pain relief
- Increases mood level
- Preferable for elderly patients
- Higher compliance

**PRN**

- Appropriate for breakthrough and intermittent pain
- In an inpatient setting, patients could be reluctant to request pain medication resulting in loss of pain control
- Must remind patients to “stay on top of pain” and request analgesia before pain is severe and out of control
- Time lag
- Higher pain intensity scores

Optimizing Dosing Schedule

- As Needed Dosing (PRN)
- Every 8 Hours Dosing
- Maximum Desired Level
- Minimum Effective Level

Drug Concentration vs. Pain Level over Time (hours)
Suboptimal PRN Dosing

Post-Operative Pain Level

Drug Concentration

Pain Level

PRN Dosing

Required 2 Doses Because of PRN Dosing
# Clinical Development Program

<table>
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<tr>
<th>Phase</th>
<th>Study No.</th>
<th>Purpose</th>
<th>Randomized</th>
<th>Completed</th>
<th>Patient/Study Model</th>
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<tbody>
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<td>INS-13-016</td>
<td>Relative bioavailability (fasted)</td>
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<td>11</td>
<td>Healthy volunteers</td>
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<td>INS-13-020</td>
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<td>INS-005-16-069</td>
<td>Temperature and pH effects</td>
<td>15</td>
<td>14</td>
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<td>INS-005-17-104</td>
<td>Comparative bioavailability (multiple dose, multiple day)</td>
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<td>56</td>
<td>Healthy volunteers</td>
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<tr>
<td></td>
<td>INS-005-17-105</td>
<td>Comparative bioavailability (multiple dose, single day)</td>
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<td>59</td>
<td>Healthy volunteers</td>
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<td>Phase 2</td>
<td>INS-005-17-111</td>
<td>Safety and tolerability</td>
<td>100</td>
<td>67</td>
<td>Abdominoplasty Bunionectomy Breast augmentation</td>
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<tr>
<td>Phase 3</td>
<td>INS-14-026</td>
<td>Efficacy and safety</td>
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<td>33</td>
<td>Bunionectomy pain</td>
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<tr>
<td></td>
<td>INS-005-15-062</td>
<td>Efficacy and safety (pivotal)</td>
<td>322</td>
<td>298</td>
<td>Bunionectomy pain</td>
</tr>
</tbody>
</table>

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*<sup>a</sup> Naltrexone 50 mg tablet was administered prior to study dose<br/><sup>b</sup> 312 projected*
Key Findings from Biopharmaceutic and Pharmacokinetic Studies

• Biopharmaceutics
  – Buprenorphine exposure
    • Buprenorphine Sublingual Spray 0.5 mg TID < Buprenex IV 0.3 mg Q6h and buprenorphine SL tablet 8 mg QD
  – Norbuprenorphine exposure
    • Buprenorphine Sublingual Spray 0.5 mg TID < Buprenorphine SL tablet 8 mg QD
  – Dose proportionality established for doses 0.125 mg, 0.25 mg, and 0.5 mg

• Pharmacokinetics
  – Buprenorphine steady state was achieved approximately Day 3
  – $t_{\text{max}}$ (median): ~2 hours for parent and active metabolite
  – $t_{\frac{1}{2}}$: 33 to 48 hours for buprenorphine and 45 to 51 hours for norbuprenorphine
Buprenorphine SL Single Dose Mean Plasma Concentrations 0-8 hours

Mean Buprenorphine Plasma Concentrations (+SD) (ng/mL)

- 0.125 mg (N=12)
- 0.25 mg (N=12)
- 0.5 mg (N=12)
Drug-drug Interactions

- Buprenorphine is metabolized to norbuprenorphine by hepatic cytochrome P-450 (CYP) 3A4 isozyme in humans\(^1\)
- Buprenorphine at therapeutic levels does not inhibit or induce isoenzyme\(^2\)
- Co-administration with other CYP 3A4 agents should be done with caution\(^1\)

1. Buprenex prescribing information
Efficacy

INS-14-026
INS005-15-062
Bunionectomy Pain Studies 026 and 062

- Double-blind, matching placebo
- Baseline pain intensity ≥4 after discontinuation of sciatic block
- Primary Outcome Measure: SPID-48
Key Inclusion Criteria

- Male or female, between 18 to 65 years
- Classified using the American Society of Anesthesiologists Physical Status Classification System as P1 to P2
- Body weight $\geq 45$ kg, BMI $\leq 40$ kg/m$^2$
Key Exclusion Criteria

- Clinically significant unstable cardiac, respiratory, renal, and/or hepatic conditions
- Long QT Syndrome, a family history of long QT Syndrome, or is taking Class IA or Class III antiarrhythmic medications
- History of nausea and vomiting with buprenorphine products
- History of alcoholism, drug abuse, or misuse, or evidence of opioid tolerance or physical dependence
- History of allergic reaction or intolerance to buprenorphine and rescue medications
Study 026: Phase 3, Randomized, Double-blind, Placebo-controlled Study (2015)

Subjects screened: N=134

R 40

Screening

Treatment Period

Follow-Up Visit (Day 5-9)

Buprenorphine Sublingual Spray 0.5 mg TID

Buprenorphine Sublingual Spray 1.0 mg BID

Buprenorphine Sublingual Spray 1.0 mg TID

Matching Placebo Spray

Treatment Day 1

Treatment Day 2

Rescue medication per protocol allowed
## Study 026: Baseline Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo N=10</th>
<th>0.5 mg TID N=9</th>
<th>1 mg BID N=11</th>
<th>1 mg TID N=10</th>
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<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>40.5 (13.5)</td>
<td>48.0 (12.1)</td>
<td>43.5 (14.3)</td>
<td>40.8 (11.2)</td>
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<tr>
<td>Male, %</td>
<td>10.0</td>
<td>22.2</td>
<td>18.2</td>
<td>30.0</td>
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<tr>
<td>Race, %</td>
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<td>American Indian or Alaska Native</td>
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<tr>
<td>Asian</td>
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<td>0</td>
<td>18.2</td>
<td>0</td>
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<td>33.3</td>
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<td>Hispanic or Latino ethnicity, %</td>
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<td>Surgery duration (hours), mean (SD)</td>
<td>0.50 (0.18)</td>
<td>0.54 (0.15)</td>
<td>0.59 (0.39)</td>
<td>0.48 (0.19)</td>
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<td>Baseline pain intensity, mean (SD)</td>
<td>6.7 (2.06)</td>
<td>6.9 (1.36)</td>
<td>6.3 (2.10)</td>
<td>7.8 (1.14)</td>
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</table>
Study 026: Disposition of Screened Subjects

Screening: N=134

- **R 40**
  - **Buprenorphine Sublingual Spray 0.5 mg TID**
    - N=9
    - Completed: 6
    - Withdrawn: 3
    - Adverse Event = 1
    - Subject Request = 2
  - **Buprenorphine Sublingual Spray 1.0 mg BID**
    - N=11
    - Completed: 9
    - Withdrawn: 2
    - Adverse Event = 1
    - Subject Request = 1
  - **Buprenorphine Sublingual Spray 1.0 mg TID**
    - N=10
    - Completed: 9
    - Withdrawn: 1
    - Adverse Event = 1
  - **Matching Placebo Spray**
    - N=10
    - Completed: 9
    - Withdrawn: 1
    - Subject Request = 1

Randomized 1:1:1:1
Study 026: Primary Endpoint – Mean NRS SPID-48 Scores

- Placebo
- 0.5 mg TID
- 1.0 mg BID
- 1.0 mg TID

* *p<0.05
Study 026: Summary

• Study discontinued due to somnolence and decreased respiratory rate at higher doses

• 0.5 mg TID demonstrated efficacy

• Subsequent pivotal trial 062 included 0.5 TID and lower doses
  – Otherwise, Study 062 had a similar design
Study 062: Phase 3, Randomized, Double-blind, Placebo-Controlled, Multiple-dose Study (2016)

Screening

Subjects Screened
N=461

Treatment Period

1:1:1:1

Follow-Up Visit (Day 5-9)

-28 -1

R 322

Subjects Randomized
322

Treatment Day 1

Treatment Day 2

Rescue medication per protocol allowed

Buprenorphine Sublingual Spray 0.125 mg TID

Buprenorphine Sublingual Spray 0.25 mg TID

Buprenorphine Sublingual Spray 0.5 mg TID

Matching Placebo
Study 026 and 062: Rescue Medication
Uses and Rules

• For breakthrough pain during anesthetic block on Day 0 and after its discontinuation but before study drug is given
  – Ibuprofen 400 mg PO every 4 to 6 hours as needed (max: 2400 mg/d)
  – Ketorolac 30 mg IV or IM every 6 to 8 hours as needed (max: 90 mg/d)
    – If insufficient pain relief or subject is unable to tolerate ibuprofen

• Patients were encouraged to wait for at least 1 hour after the first dose of study drug before receiving first rescue medication

• If regional anesthetic infusion and supplemental analgesia did not control the pain effectively, subject was to be discontinued
Study 026 and 062: Primary Efficacy and Related Endpoints

- Numerical rating scale summed pain intensity difference (NRS SPID-48) 0 to 48 hours
- Secondary endpoints that support NRS SPID-48
  - NRS SPID 0 to 4 hours, 0 to 8 hours, and 0 to 24 hours
  - NRS pain intensity difference (NRS PID) and score at each scheduled time point
  - Total Pain Relief (TOTPAR) 0 to 4 hours, 0 to 8 hours, 0 to 24 hours, and 0 to 48 hours
Study 026 and 062: Additional Secondary Efficacy Endpoints

- Pain Relief Score (5 point categorical)
- Peak pain relief ($\Delta$VAS)
- Time to peak pain relief
- Time to first perceptible pain relief
- Time to meaningful pain relief
- Time to onset of analgesia
- Proportion of patients using rescue medications
- Time to first use of rescue medication (duration of analgesia)
- Total use of rescue medication 0 to 24 hours and 0 to 48 hours
- Subject’s global evaluation of study drug
# Study 062: Baseline Characteristics

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<tr>
<th></th>
<th>Placebo</th>
<th>0.125 mg TID</th>
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<tr>
<td><strong>Age, mean (SD)</strong></td>
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<td><strong>Male, %</strong></td>
<td>20.3</td>
<td>23.2</td>
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<td><strong>Race, %</strong></td>
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<td><strong>Hispanic or Latino Ethnicity, %</strong></td>
<td>16.5</td>
<td>20.7</td>
<td>12.5</td>
<td>18.5</td>
</tr>
<tr>
<td><strong>Surgery duration (hours), mean (SD)</strong></td>
<td>0.50 (0.21)</td>
<td>0.53 (0.22)</td>
<td>0.50 (0.20)</td>
<td>0.53 (0.34)</td>
</tr>
<tr>
<td><strong>Baseline pain intensity, mean (SD)</strong></td>
<td>6.4 (1.85)</td>
<td>6.7 (1.87)</td>
<td>6.3 (1.82)</td>
<td>6.6 (1.79)</td>
</tr>
</tbody>
</table>
Study 062: Disposition of Screened Subjects

- **Screening**: N=461
- **R 322 RANDOMIZED 1:1:1:1**

### Buprenorphine Sublingual Spray

- **0.125 mg TID**
  - N=82
  - Subjects Completed: 77
  - Subjects Withdrawn: 5
  - Adverse Event = 1
  - Lack of Efficacy = 4

- **0.25 mg TID**
  - N=80
  - Subjects Completed: 75
  - Subjects Withdrawn: 5
  - Adverse Event = 3
  - Lack of Efficacy = 1
  - Withdrawal by Subject = 1

- **0.5 mg TID**
  - N=81
  - Subjects Completed: 71
  - Subjects Withdrawn: 10
  - Adverse Event = 8
  - Lost to Follow-up = 1
  - Withdrawal by Subject = 1

- **Matching Placebo Spray**
  - N=79
  - Subjects Completed: 75
  - Subjects Withdrawn: 4
  - Lack of Efficacy = 4
Per the Statistical Analysis Plan, Missing SPID48 data were not imputed for the primary efficacy analysis.
Per the Statistical Analysis Plan, missing SPID48 data were not imputed for the primary efficacy analysis.

### Study 062: SPID Results

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>LS Mean Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPID-48</td>
<td>35.46 (7.86, 63.05)</td>
<td>0.0120*</td>
</tr>
<tr>
<td></td>
<td>36.18 (8.43, 63.93)</td>
<td>0.0108*</td>
</tr>
<tr>
<td></td>
<td>81.93 (53.82, 110.04)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>SPID-24</td>
<td>20.02 (6.37, 33.67)</td>
<td>0.0042</td>
</tr>
<tr>
<td></td>
<td>24.69 (11.01, 38.38)</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>51.51 (37.66, 65.37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPID-8</td>
<td>5.76 (0.68, 10.84)</td>
<td>0.0265</td>
</tr>
<tr>
<td></td>
<td>6.93 (1.86, 12.01)</td>
<td>0.0076</td>
</tr>
<tr>
<td></td>
<td>16.24 (11.16, 21.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SPID-4</td>
<td>3.07 (0.24, 5.91)</td>
<td>0.0337</td>
</tr>
<tr>
<td></td>
<td>3.00 (0.17, 5.84)</td>
<td>0.0377</td>
</tr>
<tr>
<td></td>
<td>7.03 (4.21, 9.86)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
# Study 062: TOTPAR Results

<table>
<thead>
<tr>
<th>TOTPAR</th>
<th>0.125 mg</th>
<th>0.25 mg</th>
<th>0.5 mg</th>
<th>LS Mean Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTPAR-48</td>
<td>26.27 (13.48, 39.05)</td>
<td>21.85 (8.99, 34.70)</td>
<td>44.24 (31.21, 57.26)</td>
<td>&lt;0.0001</td>
<td>0.0009</td>
</tr>
<tr>
<td>TOTPAR-24</td>
<td>13.12 (6.83, 19.41)</td>
<td>13.17 (6.86, 19.47)</td>
<td>25.97 (19.59, 32.36)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TOTPAR-8</td>
<td>3.48 (1.15, 5.80)</td>
<td>3.75 (1.42, 6.07)</td>
<td>8.37 (6.04, 10.7)</td>
<td>0.0036</td>
<td>0.0017</td>
</tr>
<tr>
<td>TOTPAR-4</td>
<td>1.88 (0.60, 3.16)</td>
<td>1.57 (0.29, 2.85)</td>
<td>3.73 (2.45, 5.00)</td>
<td>0.0041</td>
<td>0.0162</td>
</tr>
</tbody>
</table>

**Secondary**
Study 062: Global Evaluations of Good, Very Good, or Excellent at 48 Hours

- Placebo: 48.1%
- 0.125 mg TID: 67.0%
- 0.25 mg TID: 75.1%
- 0.5 mg TID: 86.4%
Study 062: Kaplan-Meier Plot of Time to Onset of Analgesia

No. at Risk
Placebo 79 48 13 8 3 3 2
0.125 mg 82 40 10 9 7 3 1
0.25 mg 80 38 15 11 8 4 3 2 1
0.5 mg 81 29 15 12 11 10 8 7 6
Study 062: Kaplan-Meier Plot of Time to Meaningful Pain Relief

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>0.125 mg TID</th>
<th>0.25 mg TID</th>
<th>0.5 mg TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>79</td>
<td>56</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>0.125 mg</td>
<td>82</td>
<td>55</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>0.25 mg</td>
<td>80</td>
<td>55</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>0.5 mg</td>
<td>81</td>
<td>58</td>
<td>23</td>
<td>16</td>
</tr>
</tbody>
</table>
Study 062: Median Time to Meaningful Pain Relief (ITT Population)

- Placebo
- 0.125 mg TID
- 0.25 mg TID
- 0.5 mg TID

Median Time (min)
## Time to Meaningful Pain Relief

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>% of Subjects That Achieved Meaningful Pain Relief</th>
<th>Median Time to Meaningful Pain Relief (min)</th>
<th>Tmax (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine Sublingual Spray</td>
<td>0.125 mg</td>
<td>43.9</td>
<td>166</td>
<td>1.50</td>
</tr>
<tr>
<td></td>
<td>0.25 mg</td>
<td>46.3</td>
<td>122</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>0.5 mg</td>
<td>65.4</td>
<td>92</td>
<td>1.75</td>
</tr>
<tr>
<td>Tapentadol IR (Nucynta)</td>
<td>50 mg</td>
<td>79.0</td>
<td>123</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>75 mg</td>
<td>84.2</td>
<td>104</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
<td>87.3</td>
<td>94</td>
<td>1.25</td>
</tr>
<tr>
<td>AC: Oxycodone IR 15 mg</td>
<td></td>
<td>85.6</td>
<td>77</td>
<td>1.4</td>
</tr>
<tr>
<td>Oxycodone IR</td>
<td>10 mg (Stegmann 2008)</td>
<td>--</td>
<td>97</td>
<td>--</td>
</tr>
<tr>
<td>Oxycodone/Acetaminophen ER (Xartemis XR)</td>
<td>7.5 mg/325 mg</td>
<td>57.3</td>
<td>92</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Acute moderate to severe pain; Bunionectomy Model for BSS, Nucynta, and Xartemis
NE=not estimatable, AC=active control
Study 062: Mean SPID 0-2 Hours

Mean SPID vs Timepoint (Hours)

- Placebo
- 0.125 mg TID
- 0.25 mg TID
- 0.5 mg TID
Study 062: Mean SPID 0-4 Hours

- Placebo
- 0.125 mg TID
- 0.25 mg TID
- 0.5 mg TID

Timepoint (Hours)

Mean SPID
Study 062: Mean SPID 0-12 Hours

Timepoint (Hours)

Mean SPID

- Placebo
- 0.125 mg TID
- 0.25 mg TID
- 0.5 mg TID
Study 062: Ketorolac Rescue Medication 0-8 Hours

Number of Subjects

- Placebo: 35
- 0.125 mg TID: 25
- 0.25 mg TID: 20
- 0.5 mg TID: 10
Study 062: Subjects with ≥30% and ≥50% Improvement in Pain Intensity at the 8 Hour Timepoint

Pain intensity is measured on an 11 point numerical scale (0-10) where 0 represents no pain and 10 represents worst pain.
Efficacy Summary

- Demonstrated efficacy versus placebo
  - Primary and secondary endpoints
  - Dose relationship for efficacy
- Global evaluation assessments show patients rated all three doses higher than placebo, majority rated Good or higher
- 92.5% of patients completed the study
Safety
Exposure to Buprenorphine Sublingual Spray

- Total (N=490)
  - Phase 2/3 (N=323)
  - Phase 1 (N=167)
    - Phase 2 Study 111 (N=50)
  - Phase 3 (N=273)
    - Study 026 (N=30)
  - Pivotal – 062 (N=243)
Buprenorphine Sublingual Spray Exposure – Phase 1, 2, and 3

Visits

- 0.0625 mg: 6 visits
- 0.125 mg: 112 visits
- 0.25 mg: 110 visits
- 0.5 mg: 217 visits
- 1.0 mg BID: 35 visits
- 1.0 mg TID: 10 visits
Studies Contributing Safety Data for Presentation

• Phase 3, treatment period: 2 days versus placebo
  – Study 026: 0.5 mg TID, 1.0 mg BID, 1.0 mg TID
  – Study 062: 0.125 mg TID, 0.25 mg TID, 0.5 mg TID

• Phase 2, treatment period: up to 7 days versus standard opioid
  – Study 111: 0.5 mg TID
Safety Populations

- Phase 3 pooled (common AEs, dizziness)
- Study 111 (vomiting and decreased oxygen saturation)
- Study 062 and 111 (nausea, vomiting, and decreased oxygen saturation)
- All Phase 2/3 studies pooled (decreased oxygen saturation)
## Most Common AEs (≥10% in Proposed Doses)

<table>
<thead>
<tr>
<th>Subject with ≥1 adverse event</th>
<th>0.125 mg TID N=82 %</th>
<th>0.25 mg TID N=80 %</th>
<th>0.5 mg TID N=90 %</th>
<th>1 mg BID N=11 %</th>
<th>1 mg TID N=10 %</th>
<th>Placebo N=89 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with ≥1 adverse event</td>
<td>69.5</td>
<td>83.8</td>
<td>94.4</td>
<td>100.0</td>
<td>90.0</td>
<td>50.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>11.0</td>
<td>7.5</td>
<td>8.9</td>
<td>18.2</td>
<td>20.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
<td>3.8</td>
<td>5.6</td>
<td>18.2</td>
<td>10.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>43.9</td>
<td>58.8</td>
<td>83.3</td>
<td>90.9</td>
<td>70.0</td>
<td>18.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29.3</td>
<td>41.3</td>
<td>72.2</td>
<td>72.7</td>
<td>80.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22.0</td>
<td>32.5</td>
<td>56.7</td>
<td>45.5</td>
<td>50.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Headache</td>
<td>18.3</td>
<td>28.8</td>
<td>15.6</td>
<td>36.4</td>
<td>10.0</td>
<td>14.6</td>
</tr>
<tr>
<td>Somnolence</td>
<td>7.3</td>
<td>7.5</td>
<td>16.7</td>
<td>27.3</td>
<td>40.0</td>
<td>0</td>
</tr>
<tr>
<td>Tremor</td>
<td>1.2</td>
<td>3.8</td>
<td>1.1</td>
<td>9.1</td>
<td>10.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Erythema</td>
<td>0</td>
<td>0</td>
<td>1.1</td>
<td>0</td>
<td>20.0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>2.4</td>
<td>1.3</td>
<td>11.1</td>
<td>18.2</td>
<td>10.0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2.4</td>
<td>2.5</td>
<td>14.4</td>
<td>27.3</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1.3</td>
<td>2.2</td>
<td>0</td>
<td>10.0</td>
<td>3.4</td>
</tr>
</tbody>
</table>
# Serious Adverse Events (SAE), All Studies

<table>
<thead>
<tr>
<th>Event</th>
<th>INS14-026</th>
<th>INS005-15-062</th>
<th>INS005-17-111</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>Atrial Fibrillation (A. Fib)</td>
<td>Angioedema</td>
<td>Incision Site Hematoma</td>
</tr>
<tr>
<td>Intensity</td>
<td>Severe</td>
<td>n/a</td>
<td>Severe</td>
</tr>
<tr>
<td>Relation</td>
<td>Not Related</td>
<td>Not Related</td>
<td>Possible</td>
</tr>
<tr>
<td>Time to event (post dosing)</td>
<td>n/a</td>
<td>16.5 H</td>
<td>24 H</td>
</tr>
<tr>
<td>Time to recovery</td>
<td>2 days</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Time to resolution</td>
<td>-</td>
<td>2 days</td>
<td>24 H</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary of event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>56 yo F with history of cardiac disorder experienced a syncopal episode and developed A. Fib after the second dose of study medication. Patient was hospitalized and likely cause determined to be a combination of past cardiac rhythm abnormalities</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary of event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>65 yo F took Zofran ODT for nausea after her last dose of study medication. This was her first time using Zofran ODT and 1-hour after dosing patient noticed tongue swelling. Patient presented to the ED and was treated for Angioedema. Likely cause was determined to be Zofran ODT</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Summary of event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>32 yo F with history of one caesarean section in 2007, was given buprenorphine SL spray post abdominoplasty. She developed moderate nausea and mild vomiting the same day. Buprenorphine was stopped and the patient withdrew from the study. After 24 H, she developed a hematoma at the incision site. The event was treated and resolved the same day</strong></td>
</tr>
</tbody>
</table>
## Adverse Events Leading to Discontinuation

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Study 026</th>
<th>Study 062</th>
<th>Study 111</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 mg TID</td>
<td>1 mg TID</td>
<td>1 mg TID</td>
</tr>
<tr>
<td></td>
<td>N=9 n</td>
<td>N=10 n</td>
<td>N=10 n</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 1 1 0</td>
<td>1 3 8 0</td>
<td>20 7</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 0 0 0</td>
<td>0 3 4 0</td>
<td>7 1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 0 0 0</td>
<td>0 0 2 0</td>
<td>0 1</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>6 2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>0 1</td>
</tr>
<tr>
<td>Headache</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>0 1</td>
</tr>
<tr>
<td>Sedation</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>0 1</td>
</tr>
<tr>
<td>Rash</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Pruritis</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>0 2</td>
</tr>
<tr>
<td>Other a</td>
<td>1 1 1 0</td>
<td>0 0 0 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>0 0 0 0</td>
<td>4 1 0 4</td>
<td>0 0</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0 0 0 0</td>
<td>0 0 1 0</td>
<td>1 0</td>
</tr>
<tr>
<td>Withdrawal by subject</td>
<td>2 1 0 1</td>
<td>0 1 1 0</td>
<td>1 3</td>
</tr>
<tr>
<td>Other</td>
<td>0 0 0 0</td>
<td>0 0 0 0</td>
<td>1 0</td>
</tr>
</tbody>
</table>

*a. Atrial fibrillation, hypertension, somnolence, or decreased respiratory rate*
Nausea and Vomiting
Study 062: Percentage of Patients Experiencing Related Vomiting Events by Study Epoch

- 0-8 hours: 32%
- 8-16 hours: 28%
- 16-24 hours: 11%
- 24-32 hours: 16%
- 32-40 hours: 5%
- 40-48 hours: 2%
- 48-56 hours: 1%

Percent of Patients
Study 062 and 026: Management of Nausea and Vomiting

- Prophylactic use of antiemetics was not permitted
- Use of antiemetics was restricted to ondansetron
  - Initial dose was 4 mg IV that could be followed by an additional 4 mg IV dose in 30-60 minutes
  - After that, additional doses can be given Q4H. Max dose 8 mg
- No other antiemetics (e.g., promethazine, metoclopramide) were permitted in this study
- Patients not adequately managed by this protocol were discontinued from the study
Study 111: Bunionectomy, Breast Augmentation, and Abdominoplasty

- A Phase 2, Randomized, Open Label, Multiple-Dose, Parallel-Group, Safety and Tolerability Study of Buprenorphine Sublingual Spray versus Standard of Care Opioid Therapy for the Treatment of Post-Operative Pain
  - Buprenorphine Sublingual Spray 0.5 mg TID vs. Morphine IV 4 mg Q6h x 24 hr then Oxycodone Tablet 10 mg TID
- 100 patients randomized, 67 completed
- Primary Objective: Evaluate safety and tolerability for up to 7 days
- Secondary Objective: Evaluate impact of prophylactic antiemetic use on nausea and vomiting
Study 111: Study Design

Subjects Screened
N=162

Randomized 1:1

-28

-1

Treatment Period

Buprenorphine Sublingual Spray 0.5 mg TID (n=50)

Standard of care post-operative narcotic therapy
Morphine IV 4 mg x 24 then Oxycodone Hydrochloride tab 10 mg TID (n=50)

Treatment Days 1 to 4
Inpatient

Treatment Days 4 to 7
Outpatient

Follow-Up Visit
(Day 8-10)

Rescue medication allowed
Postoperative nausea/vomiting prophylaxis required
Study 111: Methodology

- Stratified by surgical procedure and baseline PONV risk factors
- Prophylactic antiemetics: induction with dexamethasone 10 mg then ondansetron 8 mg near the end of surgery
- Rescue analgesia: after surgery and before randomization subjects may be given morphine IV and/or fentanyl (doses per investigator discretion)
- Patients randomized and received first dose of study drug within 4 hours after surgery
Study 111: Rescue Medications Uses and Rules

• For postoperative pain
  – Inpatient period only: APAP 1000 mg every 6 hours and/or Ketorolac 30 mg IV or IM every 6 to 8 hours as needed (max: 90 mg/d)
  – Outpatient period only: APAP 1000 mg every 6 hours

• For postoperative nausea
  – Inpatient period: only ondansetron 4 mg IV
  – Outpatient period: only ondansetron 4 mg ODT
### Study 111: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Standard Opioid Therapy N=50</th>
<th>Buprenorphine Sublingual Spray N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>36.2 (10.83)</td>
<td>37.1 (11.68)</td>
</tr>
<tr>
<td>Male, %</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Female, %</td>
<td>96.0</td>
<td>96.0</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>58.0</td>
<td>62.0</td>
</tr>
<tr>
<td>Black or African America</td>
<td>30.0</td>
<td>36.0</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>6.0</td>
<td>0</td>
</tr>
<tr>
<td>Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>2.0</td>
</tr>
<tr>
<td>Asian</td>
<td>6.0</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic or Latino Ethnicity, %</td>
<td>34.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Non-Hispanic, %</td>
<td>66.0</td>
<td>72.0</td>
</tr>
<tr>
<td>PONV Low Risk, %</td>
<td>16.0</td>
<td>14.0</td>
</tr>
<tr>
<td>PONV High Risk, %</td>
<td>84.0</td>
<td>86.0</td>
</tr>
</tbody>
</table>
### Apfel Scale for the Probability of Postoperative Nausea and Vomiting (PONV)

<table>
<thead>
<tr>
<th>PONV Risk Factor Assessment</th>
<th>Points</th>
<th>PONV Risk Score</th>
<th>Probability of PONV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative opioids (if planned)</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Female gender</td>
<td>1</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>History of PONV/motion sickness</td>
<td>1</td>
<td>3</td>
<td>61</td>
</tr>
<tr>
<td>Total</td>
<td>0 to 4</td>
<td>4</td>
<td>79</td>
</tr>
</tbody>
</table>

Additional studies identify the younger age group (<50 years) as a significant risk factor for PONV compared with those who are 50 years or older.  

1. Gan TJ et al., 2014
## Study 111: Most Common AEs with Severity

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>0.5 mg TID N=50</th>
<th>Standard Opioid Therapy N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severity %</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>78.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>6.0</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>72.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>52.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>18.0</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>34.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Hypoxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>28.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>26.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>18.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>14.0</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>22.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>20.0</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>16.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>12.0</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Study 111: Percentage of Patients Experiencing Related Vomiting Events by Study Epoch for Buprenorphine SL Spray 0.5 mg TID

![Bar chart showing the percentage of subjects experiencing related vomiting events by study epoch](image-url)
Study 062 and 111: Percentage of Patients Experiencing Related Vomiting Events by Study Epoch for Buprenorphine SL Spray 0.5 mg TID

**Study 062 (0.5 mg TID)**

- 0-8 hours: 63 subjects
- 8-16 hours: 50 subjects
- 16-24 hours: 23 subjects
- 24-32 hours: 18 subjects
- 32-40 hours: 5 subjects
- 40-48 hours: 4 subjects

**Study 111 (0.5 mg TID)**

- 0-8 hours: 20 subjects
- 8-16 hours: 8 subjects
- 16-24 hours: 5 subjects
- 24-32 hours: 7 subjects
- 32-40 hours: 2 subjects
- 40-48 hours: 4 subjects
- 48-56 hours: 2 subjects

Percent of Subjects

Hours Since First Dose Study Drug
## Severity of Adverse Events of Special Interest (AESI)

<table>
<thead>
<tr>
<th>AESI</th>
<th>Placebo N=79 %</th>
<th>0.125 mg TID N=82 %</th>
<th>0.25 mg TID N=80 %</th>
<th>0.5 mg TID N=81 %</th>
<th>0.5 mg TID N=50 %</th>
<th>Standard Opioid Therapy N=50 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>12.7</td>
<td>32.9</td>
<td>42.5</td>
<td>51.9</td>
<td>6.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.8</td>
<td>9.8</td>
<td>13.8</td>
<td>29.6</td>
<td>72.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>1.2</td>
<td>2.5</td>
<td>2.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1.3</td>
<td>15.9</td>
<td>21.3</td>
<td>35.8</td>
<td>18.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.5</td>
<td>12.2</td>
<td>12.5</td>
<td>28.4</td>
<td>34.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Severe</td>
<td>1.3</td>
<td>1.2</td>
<td>7.5</td>
<td>8.6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Standard opioid therapy: morphine IV 4 mg TID for 24 h, followed by oxycodone hydrochloride tablet, 10 mg TID for the remainder of the study period. Includes patients that are coded for emesis.
Nausea and Vomiting Conclusions

• Buprenorphine SL Spray 0.5 mg TID was generally safe and well tolerated for up to 7 days

• Prophylactic antiemetics resulted in a lower incidence and severity of vomiting and severity of nausea

• Initiation in a medically supervised setting
  – Assure vomiting prophylaxis
  – Manage early events
Dizziness
Time to Dizziness Across All Studies and Doses

- Study 062 Placebo
- Study 062 0.125 mg TID
- Study 062 0.25 mg TID
- Study 062 0.5 mg TID
- Study 026 Placebo
- Study 026 0.5 mg TID
- Study 111 SOT
- Study 111 0.5 mg TID

Number of Subjects

Time to Onset (hours)
Reduced Oxygen Saturation
Reduced Oxygen Saturation

**Study 026**
- Hypoxia defined as oxygen saturation <90% on room air
- “Oxygen saturation decreased” defined as >92% and ≤95%

**Study 062**
- Hypoxia defined as oxygen saturation ≤92% on room air
- “Oxygen saturation decreased” defined as ≤95% and >92%

**Study 111**
- Hypoxia defined as oxygen saturation <90% on room air
- “Oxygen saturation decreased” not defined or reported
Severity of Reduced Oxygen Saturation

<table>
<thead>
<tr>
<th>O₂ Sat Dec</th>
<th>Placebo N=79 %</th>
<th>Standard Opioid Therapy N=50 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>5.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Received O₂</td>
<td>2.5</td>
<td>0</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Study 026 N=9 %</th>
<th>Study 111 N=50 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.125 mg TID</td>
<td>0.25 mg TID</td>
<td>0.5 mg TID</td>
</tr>
<tr>
<td>N=82 %</td>
<td>N=80 %</td>
<td>N=81 %</td>
</tr>
<tr>
<td>7.3</td>
<td>10.0</td>
<td>8.6</td>
</tr>
<tr>
<td>8.6</td>
<td>8.6</td>
<td>1.1</td>
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<tr>
<td>0</td>
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</tbody>
</table>

Includes patients that are coded for emesis.

Standard opioid therapy: morphine IV 4 mg TID for 24 h, followed by oxycodone hydrochloride tablet, 10 mg TID for the remainder of the study period.

CC-94
Lowest Oxygen Saturation in Buprenorphine Patients with Reported Adverse Events of Hypoxia

Study 111

Study 062

Oxygen Saturation

Number of Subjects

0 2 4 6 8 10

86 87 88 89 91 92 94 95
### Study 062: Patients with AEs of Decreased Oxygen Saturation and Hypoxia

<table>
<thead>
<tr>
<th>Oxygen Saturation</th>
<th>0.125 mg TID N=82 n</th>
<th>0.25 mg TID N=80 n</th>
<th>0.5 mg TID N=81 n</th>
<th>Placebo N=79 n</th>
</tr>
</thead>
<tbody>
<tr>
<td>89</td>
<td></td>
<td></td>
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<td></td>
</tr>
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<td>90</td>
<td>1</td>
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<tr>
<td>91</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
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<tr>
<td>92</td>
<td>4</td>
<td>3</td>
<td>6</td>
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<td>93</td>
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<tr>
<td>95</td>
<td></td>
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</tbody>
</table>
Studies 062 and 111: Patients with any Oxygen Saturation ≤95%

<table>
<thead>
<tr>
<th>Oxygen Saturation</th>
<th>Study 062</th>
<th>Study 111</th>
<th>Morphine 4 mg TID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>0.125 mg TID</td>
<td>0.25 mg TID</td>
</tr>
<tr>
<td></td>
<td>N=79 (n)</td>
<td>N=82 (n)</td>
<td>N=80 (n)</td>
</tr>
<tr>
<td>86</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>87</td>
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<td>88</td>
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<td>2</td>
<td>3</td>
</tr>
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<td>92</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>93</td>
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<tr>
<td>94</td>
<td>1</td>
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<td></td>
</tr>
<tr>
<td>95</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Safety Summary

• Buprenorphine Sublingual Spray was generally safe and well-tolerated for up to 7 days

• Events of vomiting were lower in number and severity with prophylactic antiemetic therapy
  – No severe events or dehydration with prophylactic antiemetic use

• Oxygen saturations at or below 95% occurred
  – Lowest oxygen saturation observed on buprenorphine was 86%
  – Lowest oxygen saturation observed on morphine was 88%
  – No subjects required naloxone on the proposed doses
  – No subjects at any dose required resuscitation measures
Risk Management Program

Stephen Sherman, JD, MBA
Senior Vice President, Regulatory Affairs and Clinical Development
Insys Development Co.
Risk Management Goals

- Reduce and mitigate the risk of vomiting
- Mitigate the risk of respiratory depression
- Reduce risks of misuse, abuse, diversion, addiction, overdose, and death
- Reduce the risk of unintentional exposure
Vomiting Risk Management

• Vomiting can occur with Buprenorphine Sublingual Spray
  – Highest rates reported with first and second dose; dose related
  – Recognized class risk with opioids
  – Literature shows that opioid naïve, younger females are at higher risk
• Use of prophylactic antiemetics was associated with a lower rate and severity of vomiting (Study 111) in the postsurgical setting
• Management
  – Prophylactic antiemetics recommended
  – Seek medical attention if vomiting occurs
• Education materials for both the patient and provider to help identify those at greatest risk of vomiting
Mitigation of Risk of Hypoxia/Respiratory Depression

• Hypoxia/respiratory depression is a known risk related to use of opioids even when used as recommended managed using:
  – Patients should initiate buprenorphine therapy in a medically-supervised setting
  – Label
    • Boxed Warning: Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with the use of BUVA YA. Monitor closely, especially upon initiation of therapy. Instruct patients on the proper administration of BUVA YA to reduce the risk
    • Medication Guide: Get emergency help right away if you take too much BUVA YA (overdose). When you first start taking BUVA YA, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Taking BUVA YA with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death
  – Education of healthcare providers to communicate to patients concerning how to recognize and manage hypoxia/respiratory depression
  – Patient education using Patient Counseling Document
Mitigation of Risk of Hypoxia/Respiratory Depression

Patient Counseling Document

Call 911 or your local emergency service right away if:
- You take too much medicine
- You have trouble breathing, or shortness of breath
- A child has taken this medicine by accident

Know how to recognize signs of respiratory depression:
- Shortness of breath, or slow and shallow breathing (less than 12 breaths per minute) accompanied with other signs as tiredness, daytime sleepiness, bluish lips, body, or fingers, headache, confusion, seizures.

If this happens, what to do:
- Call 911 or your local emergency service
- While waiting, sit up or stand up
- Take several deep breaths and/or cough

Take this card with you every time you see your healthcare provider and tell him/her:
- Your complete medical and family history, including any history of substance abuse or mental illness
- If you are pregnant or are planning to become pregnant
- Your treatment goals
- All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements
- Any side effects that you may be having

Take your BUVAAYA pain medicine exactly as prescribed by your healthcare provider.

Patient Name: Patient Specific Information

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- Your treatment goals
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- Any side effects that you may be having

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- All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements
- Any side effects that you may be having

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- If you are pregnant or are planning to become pregnant
- Your treatment goals
- All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements
- Any side effects that you may be having

Take your BUVAAYA pain medicine exactly as prescribed by your healthcare provider.
Initiate in a Medically Supervised Setting

• Monitor respiratory status first 12 hours
  – Determine if patient can continue therapy in an outpatient setting

• Allows for the administration of prophylactic antiemetic therapy and any subsequent needs
  – Mitigates the risk of vomiting

• Allows the use of rescue medication when the onset of pain is not optimal
  – Mitigates risk of redosing
Reduce Risk of Misuse, Abuse, Addiction, Diversion, and Overdose

• Participate in upcoming Opioid Analgesic REMS
  – Until available, follow Insys REMS and cover all elements of the FDA Opioid Analgesic REMS Education Blueprint

• Educate prescribers, pharmacists, and patients on the potential for misuse, abuse, diversion, addiction, and overdose
  – Prescribe and dispense product only to appropriate patients
  – Patient and caregiver understanding of Medication Guide
  – Patient Counseling Document and other tools
Reduce the Risk of Unintentional Exposure

- Preventing accidental exposure to children and others for whom it was not prescribed
  - Assure safe disposal
  - Patient education on safe use, storage, and disposal
- Child-resistant packaging
- Warnings in and on packaging
- Similar packaging configuration and disposal system as currently marketed Schedule II fentanyl product
Proposed Primary Packaging

• Same packaging configuration as currently marketed Cll product
• 6 years post-marketing experience
  – Data show safe and effective for opioid products
• Unit dose spray device
  – Single dose
  – Cannot be reused; less than 0.02 ml residue
Proposed Secondary Packaging

- Individually-sealed child resistant, opaque blister packages
  - Must be cut with scissors to remove the device for use.
Proposed Safe Disposal System: Used Units

- For the disposal of USED units, place the used device in the single child resistant disposal bag.
Assessment of Efficacy of the Proposed REMS Program

• The efficacy of the proposed REMS program will be assessed and submitted to the FDA
  – At Months 6 and 12 and annually thereafter
• If persistent pattern of diversion or any additional risks are identified, Insys will implement an adjustment to the REMS
Healthcare Provider Education

- Individual product REMS program replaced by class REMS
- Product label
- Alert healthcare professionals and patients to potential adverse events, especially nausea and vomiting and hypoxia
- Patient and caregiver education materials for providers
- Selection of appropriate patients
- Monitor for possible misuse, abuse, or diversion
- Educate patients on safe use, storage, and disposal
Patient Education

- Medication Guide
- Patient Counseling Document
- Enhanced education for patients
  - Education on the risks and precautions associated with opioids
  - Instructions for safe use, storage, and disposal
  - Education on the risks of abuse, misuse, and diversion
  - Education on the risks of addiction, overdose, and death
  - Buprenorphine Sublingual Spray prescribing instructions
- Provider education of patients
- Product website
Pharmacovigilance Program

- Spontaneous adverse event reporting
- Review and reporting of serious AE case assessments
- Quarterly review of aggregated AE information for trends and signals
- Weekly review of scientific literature for patient safety issues
- Review of case assessments for possible product quality issues that could impact patient safety
- Employee training program to assure all AEs are reported and evaluated
Surveillance for Abuse, Misuse, and Diversion

• Established prescription tracking programs
  – IQVIA
• RADARS system
Insys Commitment to Responsible Sales and Marketing

• Monitor prescription patterns
  – Develop and monitor “no-call” list

• Monitor supply chain for suspicious orders

• Train external-facing employees on compliance with all applicable laws and regulations, then monitor them

• Compliance is factored into sales compensation based upon field monitoring
Risk Management Summary

- Recommend prophylactic antiemetic therapy
- Initiation of treatment in a medically-supervised setting
- Individual product REMS until Class REMS
- Patient and healthcare provider education
- Product packaging
  - Child resistant
  - Printed warnings and precautions
- Safe Disposal System
- Pharmacovigilance
- Surveillance
Benefit/Risk

Joseph V. Pergolizzi, MD
Senior Partner and Director of Research
Naples Anesthesia and Pain Associates, Naples, Florida
Public Health Perspective

• Need for new Schedule III treatment options for moderate to severe acute pain

• Buprenorphine is a Schedule III opioid
  – Low rates of addiction, overdose, and death
  – Low rates of ER visits for abuse or misuse

• Sublingual spray enables easy administration
  – Injectable formulation for acute pain has limited utility

• Around-the-clock dosing enables better pain management
  – Reduced risk of medication gaps and potential for extra dosing
### History of Buprenorphine Scheduling

<table>
<thead>
<tr>
<th>Decade</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970s</td>
<td>During development: CII</td>
</tr>
<tr>
<td>1981</td>
<td>Buprenex (IV/IM) 0.3 mg approval: CII</td>
</tr>
<tr>
<td>1985</td>
<td>Buprenex (IV/IM) 0.3 mg real-world experience: CV</td>
</tr>
<tr>
<td>2000s</td>
<td>Subutex/Suboxone 2-24 mg approvals: CIII</td>
</tr>
<tr>
<td></td>
<td>HHS reviewed numerous scientific studies and years of human experience</td>
</tr>
<tr>
<td></td>
<td>DEA: Independent 8-factor analysis in accordance with 21 U.S.C. 811(c)</td>
</tr>
<tr>
<td>2018</td>
<td>Buprenorphine Sublingual Spray up to 0.5 mg (exposure=0.24 mg)</td>
</tr>
</tbody>
</table>

Buprenorphine Sublingual Spray
Beneficial Features

• **Formulation**
  – Ease of administration
  – Does not require swallowing
  – Avoids first-pass metabolism

• **Buprenorphine**
  – Schedule CIII
  – Molecule has low rate of abuse (RADARS data)
  – Publications support ceiling effect on respiratory depression
  – Lower rate of constipation than full mu agonists (literature)
  – No adjustment needed for age or renal impairment
  – Minimal drug-drug interactions
Benefits

• Efficacious pain relief
  – Statistically significantly superior to placebo (Studies 026 and 062)

• Patient satisfaction
  – Majority of patients rated Good, Very Good, or Excellent

• Generally well tolerated
  – 3.7% discontinuation rate for AEs (Study 062)
Risks

• Class risks
  – Abuse, misuse, diversion
  – Addiction, overdose, death
  – Accidental exposure
  – Respiratory depression
  – Sedation
  – Nausea, vomiting

• Product-specific risks
  – No new risks identified

• Initiation of therapy under medical supervision
  – Mitigates several risks
Benefit/Risk Conclusions

• Risks are well characterized and manageable
  – No new risks identified for formulation
  – Buprenorphine has safety advantages over other opioids

• Benefits are demonstrated for this formulation
  – Efficacious
  – Patient satisfaction with treatment

• Benefits outweigh risks
Backup Slides Shown
Ceiling Effect on Buprenorphine Respiratory Depression (Opioid Naïve Population)

- Buprenorphine Induces Ceiling In Respiratory Depression But Not In Analgesia

Insys conducted the following medical and scientific analyses consisting of the eight factors described in CSA (21 U.S.C. 811(c)):

1. Its actual or relative potential for abuse
2. Scientific evidence of its pharmacological effect, if known
3. The state of current scientific knowledge regarding the drug or other substance
4. Its history and current pattern of abuse
5. The scope, duration, and significance of abuse
6. What, if any, risk there is to the public health
7. Its psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled
Phase 2 and Phase 3 Studies: Percentage of Patients Experiencing Hypoxia Events – All Doses

Study 062 Placebo
Study 062 0.5 mg TID
Study 111 SOT
Study 111 0.5 mg TID

Percent of Patients

Time to Onset of Hypoxia

0 to <8 8 to <16 16 to <24 24 to <32 32 to <40 40 to <48 48 to <56 56+

BU-364
Subjects with ≥30% and ≥50% Improvement in Pain Intensity at the 48 Hour Timepoint

Pain intensity is measured on an 11 point numerical scale (0-10) where 0 represents no pain and 10 represents worst pain.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>≥30% Improvement</th>
<th>≥50% Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>77%</td>
<td>56%</td>
</tr>
<tr>
<td>0.125 mg TID</td>
<td>82%</td>
<td>73%</td>
</tr>
<tr>
<td>0.25 mg TID</td>
<td>84%</td>
<td>68%</td>
</tr>
<tr>
<td>0.5 mg TID</td>
<td>97%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Percent of Subjects

≥30% Improvement in Pain Intensity

≥50% Improvement in Pain Intensity
### Study 062: Global Evaluation of Study Drug

<table>
<thead>
<tr>
<th>Global Evaluation (Score)</th>
<th>Placebo N=79 n (%)</th>
<th>0.125 mg N=82 n (%)</th>
<th>0.25 mg N=80 n (%)</th>
<th>0.5 mg N=81 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (0)</td>
<td>20 (25.3)</td>
<td>12 (14.6)</td>
<td>4 (5.0)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Fair (1)</td>
<td>20 (25.3)</td>
<td>13 (15.9)</td>
<td>13 (16.3)</td>
<td>6 (7.4)</td>
</tr>
<tr>
<td>Good (2)</td>
<td>15 (19.0)</td>
<td>12 (14.6)</td>
<td>21 (26.3)</td>
<td>13 (16.0)</td>
</tr>
<tr>
<td>Very good (3)</td>
<td>15 (19.0)</td>
<td>20 (24.4)</td>
<td>24 (30.0)</td>
<td>26 (32.1)</td>
</tr>
<tr>
<td>Excellent (4)</td>
<td>8 (10.1)</td>
<td>23 (28.0)</td>
<td>15 (18.8)</td>
<td>31 (38.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p-value(^a) comparisons</th>
<th>0.125 mg vs. Placebo</th>
<th>0.25 mg vs. Placebo</th>
<th>0.5 mg vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0001</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^a\) p-value from a proportional odds model with factors for the site, treatment, and baseline pain intensity
## Study 062 Adverse Events Leading to Discontinuations

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>0.125 mg TID</th>
<th>0.25 mg TID</th>
<th>0.5 mg TID</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=79</td>
<td>N=82</td>
<td>N=80</td>
<td>N=81</td>
<td>N=322</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Completed</strong></td>
<td>75 (94.9)</td>
<td>77 (93.9)</td>
<td>75 (93.8)</td>
<td>71 (87.7)</td>
<td>298 (92.5)</td>
</tr>
<tr>
<td><strong>Adverse event</strong></td>
<td>0</td>
<td>1 (1.2)</td>
<td>3 (3.8)</td>
<td>8 (9.9)</td>
<td>12 (3.7)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>0</td>
<td>1 (1.2)</td>
<td>3 (3.8)</td>
<td>6 (7.4)</td>
<td>10 (3.1)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>0</td>
<td>0</td>
<td>3 (3.8)</td>
<td>4 (4.9)</td>
<td>7 (2.2)</td>
</tr>
<tr>
<td><strong>Dizziness</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (2.5)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td><strong>Lack of efficacy</strong></td>
<td>4 (5.1)</td>
<td>4 (4.9)</td>
<td>1 (1.3)</td>
<td>0</td>
<td>9 (2.8)</td>
</tr>
<tr>
<td><strong>Lost to follow-up</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.2)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Withdrawal by subject</strong></td>
<td>0</td>
<td>0</td>
<td>1 (1.3)</td>
<td>1 (1.2)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Observed Effect Size for 0.5 mg dose Exceeds Protocol Assumption

- Effect size of 0.45 for SPID-48 effect of 0.5 mg dose was assumed in sample size calculations for Study 062
- Effect size actually observed for 0.5 mg dose is 0.71 – 0.85, depending on statistical analysis assumptions
- Effect sizes for the 0.25 mg and 0.125 mg doses are in the range of 0.30 to 0.37

Effect size is defined as treatment difference (versus placebo), divided by the population standard deviation.
Sensitivity Analyses of SPID-48 Confirm the Primary Analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>0.125 mg</th>
<th>0.25 mg</th>
<th>0.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completers analysis of SPID-48</td>
<td>0.0120</td>
<td>0.0108</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ITT analysis of SPID-48</td>
<td>0.0038</td>
<td>0.0028</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multiple imputation (missing at random)</td>
<td>0.0131</td>
<td>0.0051</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multiple imputation (jump to reference)</td>
<td>0.0236</td>
<td>0.0096</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Last SPID carried forward</td>
<td>0.0154</td>
<td>0.0175</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
## Study 111 Patient Stratification via PONV Score and Classification

**Parameter**

<table>
<thead>
<tr>
<th>Baseline PONV Risk Factor</th>
<th>Standard Opioid Therapy N=50</th>
<th>0.5 mg TID N=50</th>
<th>Overall N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2 (4.0)</td>
<td>0</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>2</td>
<td>6 (12.0)</td>
<td>7 (14.0)</td>
<td>13 (13.0)</td>
</tr>
<tr>
<td>3</td>
<td>35 (70.0)</td>
<td>34 (68.0)</td>
<td>69 (69.0)</td>
</tr>
<tr>
<td>4</td>
<td>7 (14.0)</td>
<td>9 (18.0)</td>
<td>16 (16.0)</td>
</tr>
</tbody>
</table>

**Baseline PONV Risk Factor Classification**

| Low Risk                  | 8 (16.0)                    | 7 (14.0)       | 15 (15.0)     |
| High Risk                 | 42 (84.0)                   | 43 (86.0)      | 85 (85.0)     |

PONV=Postoperative Nausea and Vomiting
Study 062: Rescue Medication Within 8 Hours

Number of Patients Receiving Rescue Medication 0-8 hrs after 1st Dose of Study Medication

- Ibuprofen only
- Ketorolac
### Sensitivity Analyses of SPID-48 Confirm the Primary Analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Placebo</th>
<th>0.125 mg</th>
<th>0.25 mg</th>
<th>0.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completers analysis of SPID-48</td>
<td>89.4</td>
<td>124.9</td>
<td>125.6</td>
<td>171.3</td>
</tr>
<tr>
<td>ITT analysis of SPID-48</td>
<td>87.2</td>
<td>123.1</td>
<td>124.4</td>
<td>175.3</td>
</tr>
<tr>
<td>Multiple imputation (missing at random)</td>
<td>88.2</td>
<td>122.5</td>
<td>126.8</td>
<td>174.6</td>
</tr>
<tr>
<td>Multiple imputation (jump to reference)</td>
<td>88.7</td>
<td>120.3</td>
<td>125.1</td>
<td>173.0</td>
</tr>
<tr>
<td>Last SPID carried forward</td>
<td>83.7</td>
<td>117.6</td>
<td>117.1</td>
<td>157.3</td>
</tr>
</tbody>
</table>
Rescue medication during treatment period (after continuous infusion is discontinued):
1. Initiate with Ibuprofen (Advil) – 400 mg orally every 4-6 hours as needed for pain; max. 8 tablets (2400 mg)
2. Ketorolac (Toradol) – 30 mg intravenously or intramuscularly every 6-8 hours as needed for pain; max. 90 mg
# PK Parameters of Buprenex, Our Product and Belbuca

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dose (mg)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (h*ng/mL)</th>
<th>Regimen, Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>SL Spray</td>
<td>0.125</td>
<td>0.215</td>
<td>1.150</td>
<td>Single dose, Sublingual</td>
</tr>
<tr>
<td>SL Spray</td>
<td>0.25</td>
<td>0.385</td>
<td>2.476</td>
<td>Single dose, Sublingual</td>
</tr>
<tr>
<td>SL Spray</td>
<td>0.5</td>
<td>0.865</td>
<td>5.549</td>
<td>Single dose, Sublingual</td>
</tr>
<tr>
<td>SL Spray</td>
<td>1</td>
<td>1.17 to 1.38 (~1.275)</td>
<td>8.715 to 10.2 (~9.45)</td>
<td>Single dose, Sublingual</td>
</tr>
<tr>
<td>Subutex</td>
<td>8</td>
<td>2.88</td>
<td>28.39</td>
<td>Single dose, PO</td>
</tr>
<tr>
<td>Subutex</td>
<td>16</td>
<td>5.47</td>
<td>32.63</td>
<td>Single dose, PO</td>
</tr>
</tbody>
</table>