ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

INSYS DEVELOPMENT COMPANY, INC.

BUPRENORPHINE SUBLINGUAL SPRAY

NDA 209,588

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

Meeting Date: 22 May 2018

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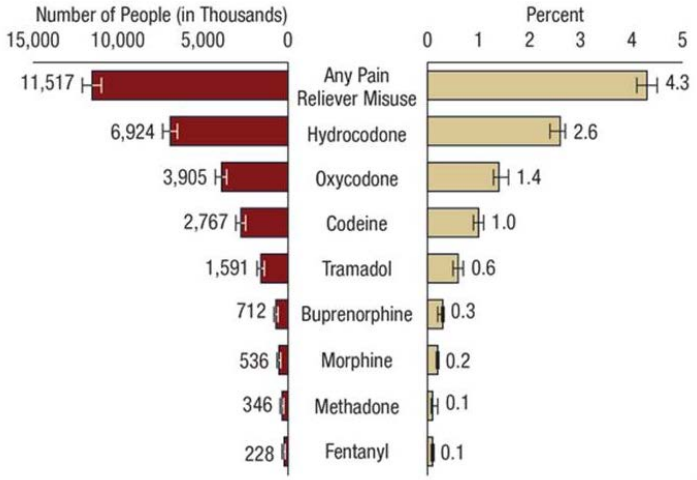
1. EXECUTIVE OVERVIEW

1.1. Introduction

The death toll is growing in the opioid crisis. From 2002 to 2015 there was a 2.8-fold increase in the number of deaths related to opioids. In 2016, more than 17,000 or 46 people per day died from overdoses involving prescription opioids. Until non-opioid pain medications are sufficient to manage moderate to severe pain, there will still be a role for opioids. Thus, there is a need for opioids that have a lower potential for abuse than the current Schedule II opioid pain medications. Buprenorphine is a Schedule III opioid that has a lower abuse potential than Schedule II opioids. This is reflected in the lower rates of abuse, misuse, overdose, and death for buprenorphine even though it is widely prescribed to millions of patients in medication assisted treatment programs for opioid abuse disorder. For example, the National Survey on Drug Use and Health by SAMHSA in 2016 an estimated 0.3 percent of people aged 12 or older misused buprenorphine products in the prior year (Figure E1). Further, much of the misuse of buprenorphine is for self-medication for the symptoms of opioid withdrawal. These characteristics suggest that buprenorphine could be useful in treating moderate-to-severe acute pain in today's current environment.

Figure E1. Prescription Pain Reliever Misuse Among People 12 or Older



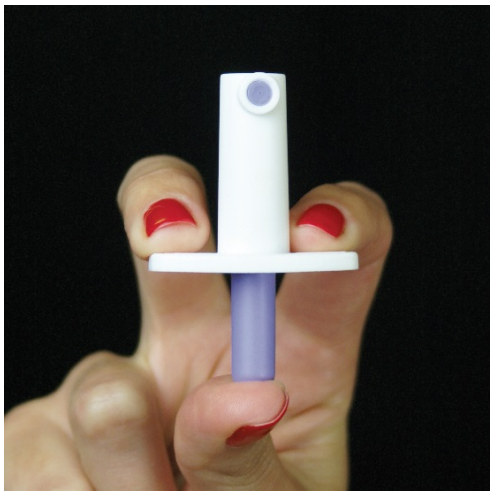
The lower abuse potential would be an advantage for anyone who requires an opioid for pain management as well as their families. Some reports in the literature suggest that the first exposure to an opioid is critical for those patients who ultimately end up abusing opioids. There may also be a broader public health advantage resulting from a lower rate of Schedule II opioid prescriptions if more people receive Schedule III alternatives.

Buprenorphine possesses unique pharmacological properties as a partial mu-opioid receptor agonist that make it a less abusable alternative to other opioids. For example, buprenorphine is thought to have a ceiling effect on respiratory depression.

INSYS Development Company, Inc. (INSYS) is developing Buprenorphine Sublingual Spray via the 505(b)(2) regulatory pathway for the treatment of moderate to severe acute pain. The application references the established safety and efficacy of Buprenex® and Subutex®. The proposed indication is for the treatment of moderate to severe acute pain. The sublingual spray

formulation of buprenorphine is supplied in a single-spray, unit-dose device shown below that contains either a 0.125 mg, 0.25 mg, or 0.5 mg dose administered three times per day (TID). Through the use of this innovative delivery system, the sublingual buprenorphine product may provide additional advantages to the existing treatment options because it is simple and easy to use and requires little expertise, preparation, or supervision (Stevens and Ghazi, 2000).

Figure E2: Buprenorphine Sublingual Spray Device



The established safety profile of currently available buprenorphine products in both the outpatient setting and inpatient setting; the low abuse potential relative to other opioids; the ceiling effect on severe respiratory compromise; and the current absence of a non-parenteral form of buprenorphine indicated for moderate to severe acute pain led to the development of the easy-to-use Buprenorphine Sublingual Spray.

Company Statement

It is understandable in consideration of media coverage about the company's legacy legal issues related to allegations of inappropriate sales and marketing practices to have some concerns about approving a new opioid for the company. To allay those concerns, we are a markedly different company today than the one portrayed in many media reports. The company is led by a new management team that has significantly strengthened compliance protocols to foster an organizational culture of high ethical standards and strives to puts the best interests of patients at the center of the process for making business decisions. In fact, more than 90% of the management team and commercial organization, including the sales force, is new to the company since 2015. Our new CEO, Saeed Motahari, joined the company in April 2017. Further, there have been four new members who have joined our Board of Directors.

We are committed to bringing effective therapies for unmet medical needs and underserved patient population to market. Over the past five years, we have invested $250 million in R&D to advance our deep and diverse product pipeline through the clinical and regulatory pathway as expeditiously as possible. Looking ahead, we intend to invest at least another $120 million in R&D, which promises to yield new treatment options for medically refractory pediatric epilepsies (including childhood *absence* seizures and infantile spasms); Prader-Willi syndrome, a

rare genetic disease that causes insatiable appetite in children and often leads to obesity, type 2 diabetes and premature death; agitation in Alzheimer's disease; and anorexia-related weight loss in cancer. In addition, we are developing intranasal and sublingual sprays of therapeutic molecules for other conditions—for example, anaphylaxis and opioid overdose.

We hope this information goes some way toward addressing your understandable concerns.

1.2. Medical Landscape and Unmet Need

1.2.1. General Landscape

Currently only two Schedule III opioids (buprenorphine and codeine when mixed with aspirin or acetaminophen) are available for the treatment of acute pain, therefore Schedule II opioids with established efficacy are utilized most often. Codeine is highly constipating, not all patients can metabolize it to active morphine, and therefore the clinical utility is low. Buprenorphine, is an effective analgesic, but has been limited in acute pain management due to the limitation of the parenteral formulation as the only approved option. The side effects of opioids that are most concerning include respiratory depression, nausea and vomiting, constipation, dependence, and abuse.

Challenges to the current treatment of acute pain include:

- Majority of opioids are Schedule II with high risk of physical and psychological dependence.
- Many formulations of opioids contain acetaminophen (APAP).
- Hepatic and renal diseases are prevalent and should limit the use of certain products in these patients including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin (ASA), and acetaminophen containing products.
- Oral formulations require the ability to swallow (dysphagia is an issue in some patients).
- Pill burden is an issue for some products.
- Vomiting could cause the patient to lose the dose if administered via a tablet or capsule route.
- Providing pain relief for patients with a prior history of opioid use disorder or at-risk for opioid use disorder is concerning.

Thus, there is a lack of treatment options for moderate to severe acute pain management between Schedule II and non-opioid alternatives.

1.2.2. Buprenorphine Landscape

Buprenorphine is a mixed agonist-antagonist opioid with an analgesic potency approximately 30 times that of morphine sulfate and a long duration of action (Buprenex® prescribing information [PI]). It is classified as a partial agonist at the mu-opioid receptor, an antagonist at the kappa-opioid receptor, an agonist at the delta-opioid receptor, and a partial agonist at the ORL-1 (nociceptin/orphanin FQ) receptor (Butrans® PI).

Buprenorphine has a long and well-established safety profile that is unique from other more commonly used opioids due, in part, to its partial agonist properties. The primary side effects of buprenorphine are similar to other full mu-opioid agonists including nausea, vomiting, and constipation, but typically of less severity. Buprenorphine exhibits a much lower incidence (1%–5%) of constipation than that observed with full mu-agonists (Kress HG, 2009; Griessinger N et al., 2005; Shipton EA, 2005). Unlike other opioids, buprenorphine does not cause spasm of the sphincter of Oddi, and may be used in acute pancreatitis.

Respiratory depression is of particular importance with the use of all opioids since it may be fatal. However, respiratory depression from buprenorphine is dose-related when given in therapeutic doses, and the peak respiratory depressant effects are slower in onset and longer in duration than morphine (Heel et al.,1979). Also, buprenorphine does have a ceiling effect for respiratory depression (Heel at al., 1979; Dahan et al., 2005). In a randomized, double-blind, placebo controlled study in healthy human volunteers, buprenorphine was administered intravenously up to 8.6 mg/kg over 90 seconds. The depression of minute ventilation caused by buprenorphine leveled off at doses of 3.0 mg/kg and above, and none of the subjects receiving buprenorphine developed apnea (Dahan et al., 2005). Further, one of the assessments of buprenorphine when given parenterally for postoperative pain found that it generally provides good or adequate pain relief with an incidence of less than 1% of drug-associated respiratory depression (Harcus et al., 1980).

Traditionally it has been believed that, as a partial agonist, buprenorphine would have a ceiling effect on both respiratory depression and analgesia. However, recent research has demonstrated that buprenorphine behaves like a full mu-opioid agonist for analgesia in clinical practice, with no ceiling effect, while also displaying a ceiling effect for respiratory depression as described above. Taken together, this constellation of properties suggests a greater safety margin and therapeutic index for buprenorphine (Dahan et al., 2006; Buprenex® PI; Pergolizzi, et al. 2010; Yassen et al., 2008).

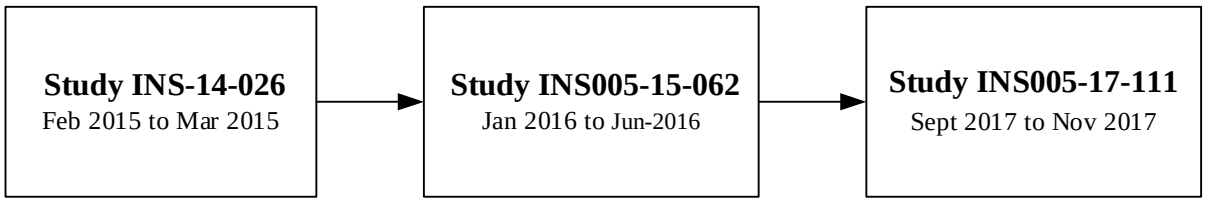
1.3. Buprenorphine Sublingual Spray Clinical Development Program

The Buprenorphine Sublingual Spray clinical development program consisted of ten studies including seven Phase 1 pharmacokinetic studies, one Phase 2 open-label 7-day safety study, and two Phase 3 efficacy studies.

Clinical studies with Buprenorphine Sublingual Spray have included males, females, and a range of heights and weights. All subjects have been adults in these studies with an age range of 18 to 65 years. A total of 490 subjects have been exposed to Buprenorphine Sublingual Spray (various doses), of whom 217 have been exposed to the highest proposed dose of 0.5 mg without significant unusual or unexpected adverse reactions or safety concerns.

The chronological sequence of the postoperative studies is outlined in Figure E3.

Figure E3. Chronological Sequence of Postoperative Studies



1.4. Efficacy

The clinical program builds on the established efficacy of buprenorphine in the treatment of pain by providing evidence of efficacy for Buprenorphine Sublingual Spray in acute pain. Buprenorphine is used for the treatment of both chronic (transdermal and buccal formulations) and acute (injection) pain. In an agreement reached with the Agency at the End-Of-Phase 2 meeting held on October 23, 2014, the 505(b)(2) New Drug Application for Buprenorphine Sublingual Spray is based on efficacy results of a single adequate, well-controlled trial, Study INS005-15-062, and is supported by the efficacy of the Listed Drug, Buprenex®, as described in its label and the other efficacy data available in the public domain for other buprenorphine products.

The efficacy of Buprenorphine Sublingual Spray was assessed in two Phase 3 double-blind, randomized, placebo-controlled studies, an initial bunionectomy study (Study INS005-14-026) that established the maximum dose to be used in Study 062 and the pivotal study (Study INS005-15-062). Both Phase 3 studies were similar in design.

The primary efficacy and related endpoints for the two studies were:

- 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.

Additional secondary endpoints for the two studies were:

- Pain Relief Score (5 point categorical).
- Peak pain relief (ΔVAS).
- 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.

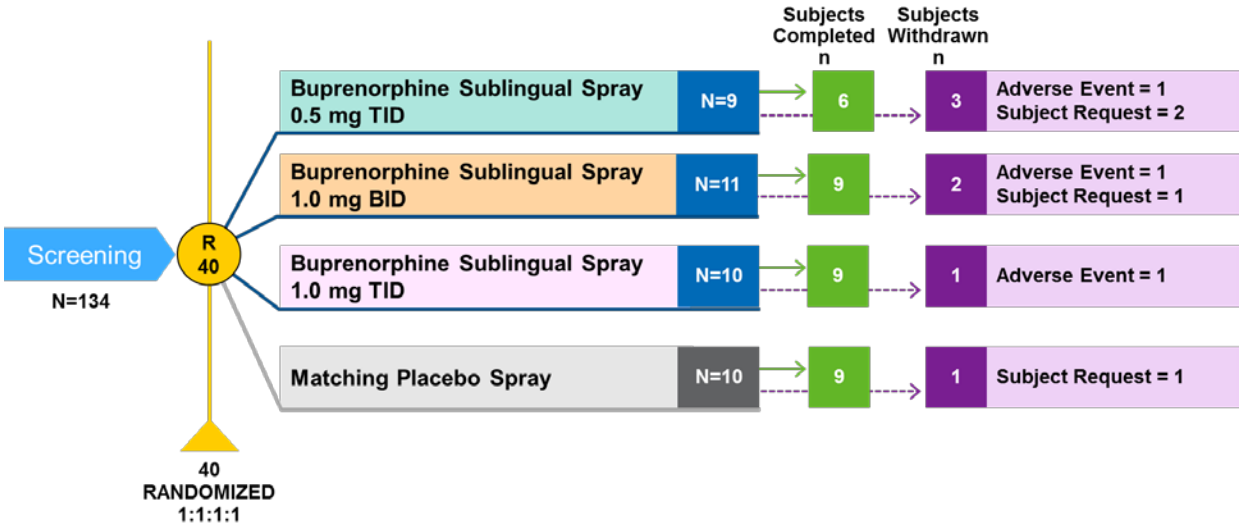
In summary, the pivotal study (Study 062) demonstrated the efficacy of all three doses (0.125 mg, 0.25 mg and 0.5 mg TID) of the sublingual spray in moderate-to-severe acute pain, demonstrating superiority over placebo on the primary endpoint SPID-48. A dose response was observed, with the greatest reductions in pain being observed with the 0.5 mg TID dose. The 0.25 mg and 0.125 mg groups demonstrated similar efficacy. The results of the secondary endpoints were also positive and further support the efficacy demonstrated for the primary endpoint. SPID and TOTPAR were nominally better than placebo in all dose groups across the time points.

1.4.1. Study 026

Study INS005-14-026 was a Phase 3, multicenter, randomized, double-blind, multiple-dose, parallel-group, placebo-controlled study to evaluate the efficacy and safety of three dosing regimens of Buprenorphine Sublingual Spray (0.5 mg TID, 1.0 mg BID, or 1.0 mg TID) and/or matching placebo in subjects with moderate to severe acute pain following bunionectomy (Figure E4). Bunionectomy is an accepted acute pain model.

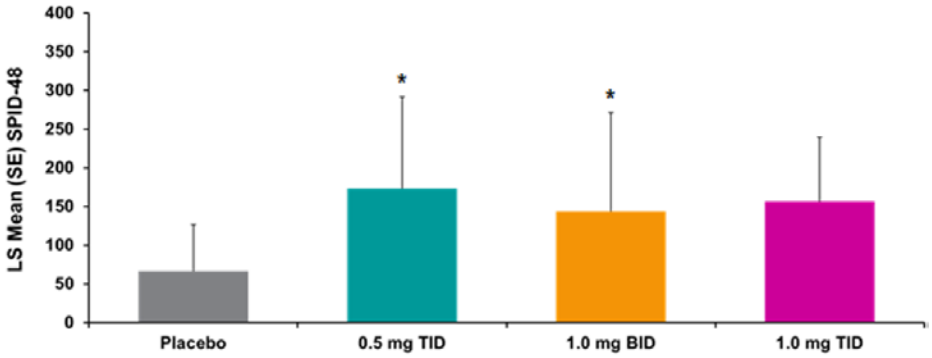
Planned enrollment was approximately 312 randomized subjects (78 subjects in each treatment group). However, the study was discontinued when 40 subjects had been randomized due to due to sedation events at higher doses. Thirty subjects received single sublingual doses of Buprenorphine Sublingual Spray and 10 subjects received single sublingual doses of placebo during the 48-hour treatment period. The results of this study indicated that while Buprenorphine Sublingual Spray was effective in reducing the postoperative pain associated with the bunionectomy procedure, doses greater than 0.5 mg TID did not result in greater efficacy (Figure E5). These results were used to guide the dose selection for the pivotal Study 062.

Figure E4: Study 026 Disposition of Screened Subjects



Source: CSR INS-14-026, Table 14.1.1

Figure E5: Study 026: Primary Endpoint: LS Mean (SE) NRS SPID-48 Scores



* $p < 0.05$
Source: CSR INS-14-026, Table 14.2.1

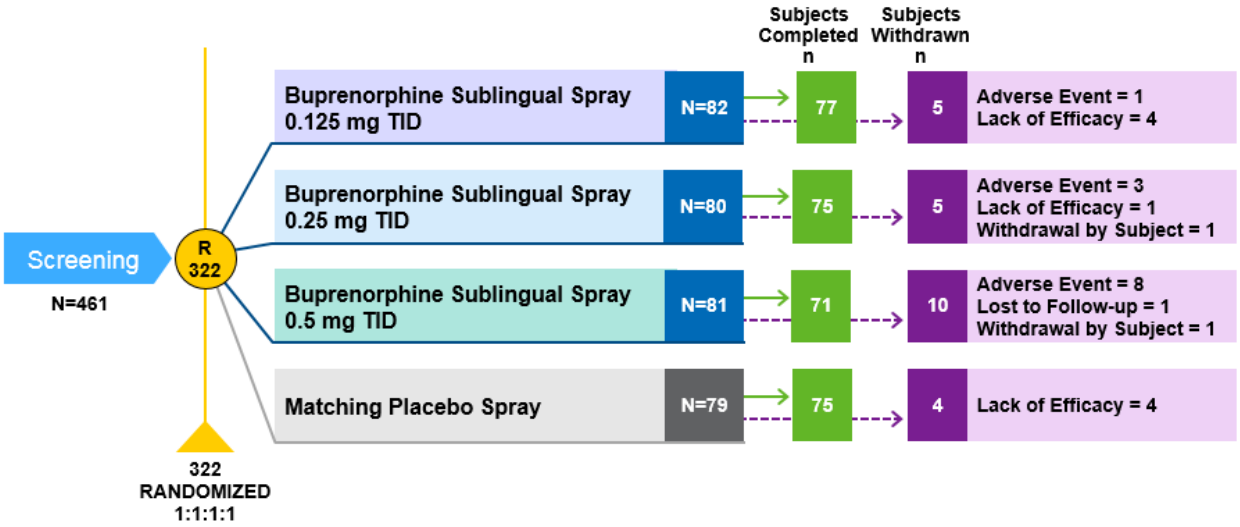
1.4.2. Study 062

Study INS005-15-062 was a pivotal Phase 3, randomized, double blind, multiple dose, parallel group, placebo-controlled study of Buprenorphine Sublingual Spray (0.5 mg TID, 0.25 mg TID, and 0.125 mg TID) for the treatment of moderate to severe acute pain. The study design was the same as for Study 026, except for the differences in doses.

A total of 322 patients signed informed consent and were randomized in the study of which 298 (92.5%) patients completed the study. Of the 24 (7.5%) subjects not completing the study, the most common reason for discontinuation in a total of 12 subjects was an adverse event (AE) (8 in 0.5 mg, 3 in 0.25 mg, 1 in 0.125 mg, 0 in placebo); other reasons for discontinuation included lack of efficacy (a total of 9 subjects; 4 in placebo, 4 in 0.125 mg and 1 in 0.25 mg, 0 in 0.5 mg), withdrawal by subject not associated with AEs (a total of 2 subjects; 1 in 0.25 mg, 1 in 0.5 mg), and loss to follow up (1 subject in 0.5 mg) (Figure E6).

The mean (standard deviation [SD]) age of subjects in the safety population overall was 45.7 (13.2) years, and ranged from 18 to 65 years. A higher proportion of patients overall were women (78.9%), and nearly all subjects were White or African American (68.9% and 24.2%, respectively). There were no substantial differences between the treatment groups with regard to age, sex, or race. There were no substantial differences between the treatment groups with regard to medical and surgical history, prior or concomitant medications, or other baseline characteristics.

Figure E6: Study 062: Disposition of Screened Subjects



Source: CSR INS005-15-062, Table 14.1.1

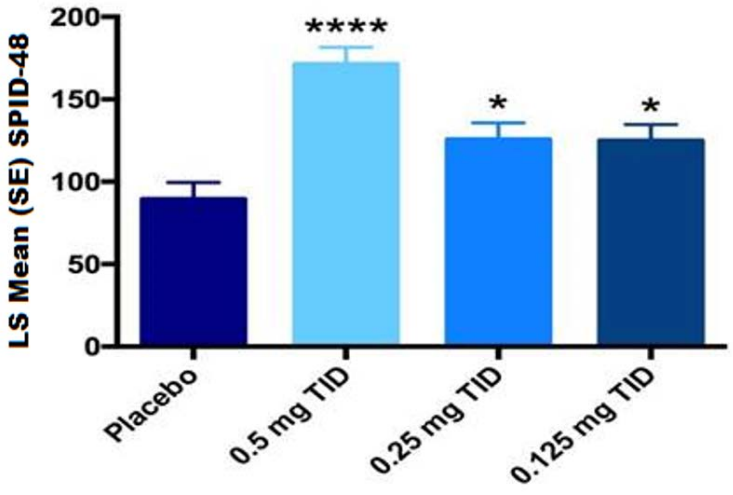
1.4.2.1. Primary Efficacy Endpoint

Testing of the primary efficacy variable SPID-48 was performed in a sequential fashion for each dose to preserve the overall alpha=0.05. The primary comparison was Buprenorphine Sublingual Spray at 0.5 mg TID vs. placebo. If the primary comparison was statistically significant at alpha=0.05, then the SPID-48 of the other doses against placebo was tested in the following order: 0.25 mg TID and 0.125 mg TID. Non-significance at any stage implied the end of formal testing and automatic non-significance for all subsequent comparisons.

This pivotal study of Buprenorphine Sublingual Spray met the primary endpoint of the SPID-48 score for all doses studied. The mean SPID-48 scores for subjects who received Buprenorphine Sublingual Spray of any dose were statistically significantly higher than for those who received placebo (Figure E7). Subjects receiving placebo had a mean (SD) SPID-48 score of 93.40 (85.06) compared with 135.84 (114.04), 125.75 (102.25), and 182.81 (107.35) for the 0.125 mg, 0.25 mg, and 0.5 mg Buprenorphine Sublingual Spray groups, respectively. The least-squares mean (SE) differences in SPID-48 scores from placebo were 35.46 (14.02; p=0.012), 36.18 (14.10; p=0.011), and 81.93 (14.28; p<0.0001) for the 0.125 mg, 0.25 mg, and 0.5 mg

Buprenorphine Sublingual Spray groups, respectively (Figure E7). The 0.5 mg group had the highest SPID-48 score, and both 0.25 mg and 0.125 mg groups demonstrated similar efficacy.

Figure E7: Study 062 Primary Efficacy Endpoint LS Mean (SE) SPID-48 Scores



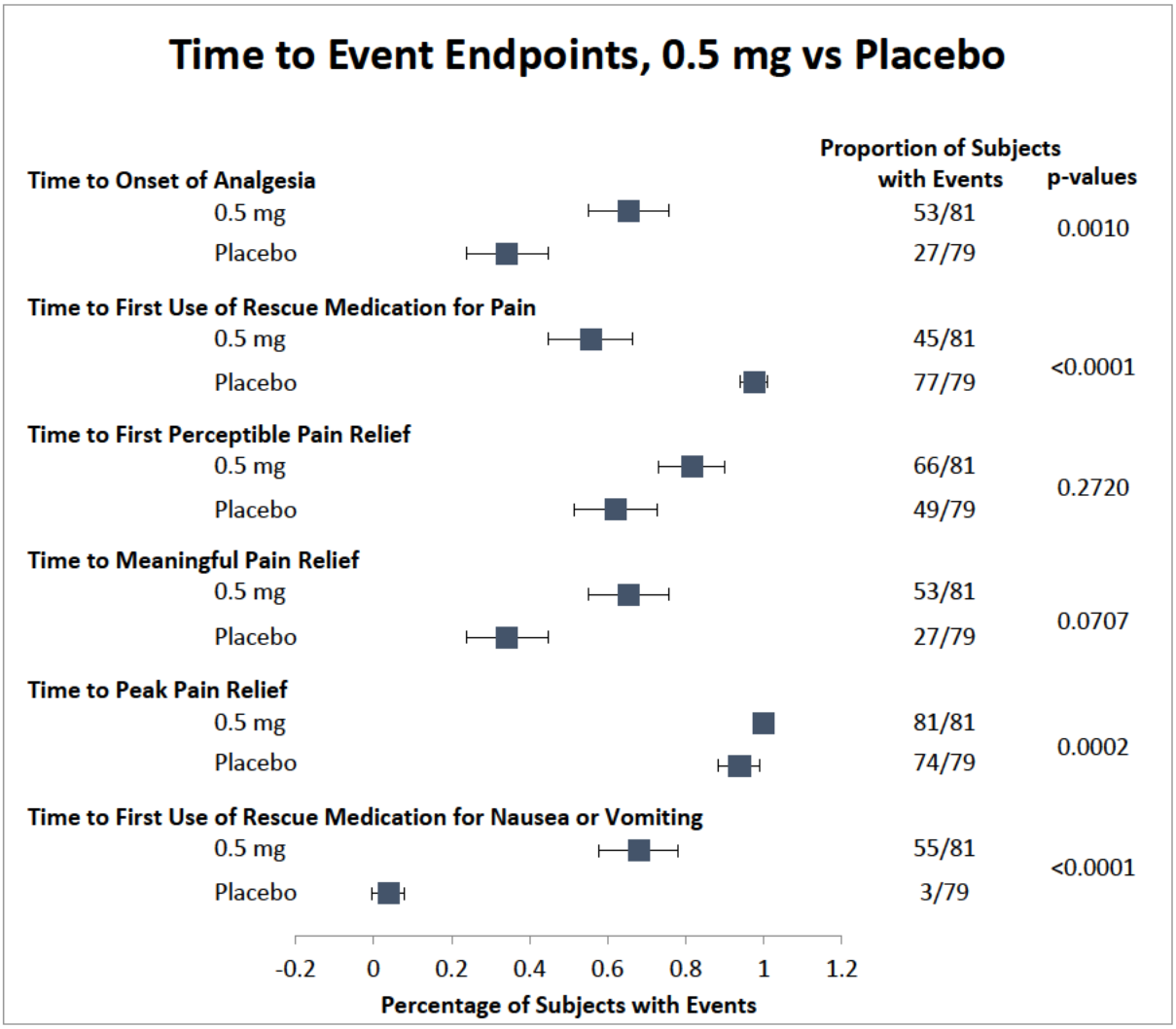
* $p < 0.05$, **** $p < 0.0001$
Source: CSR INS005-15-062, Table 14.2.1

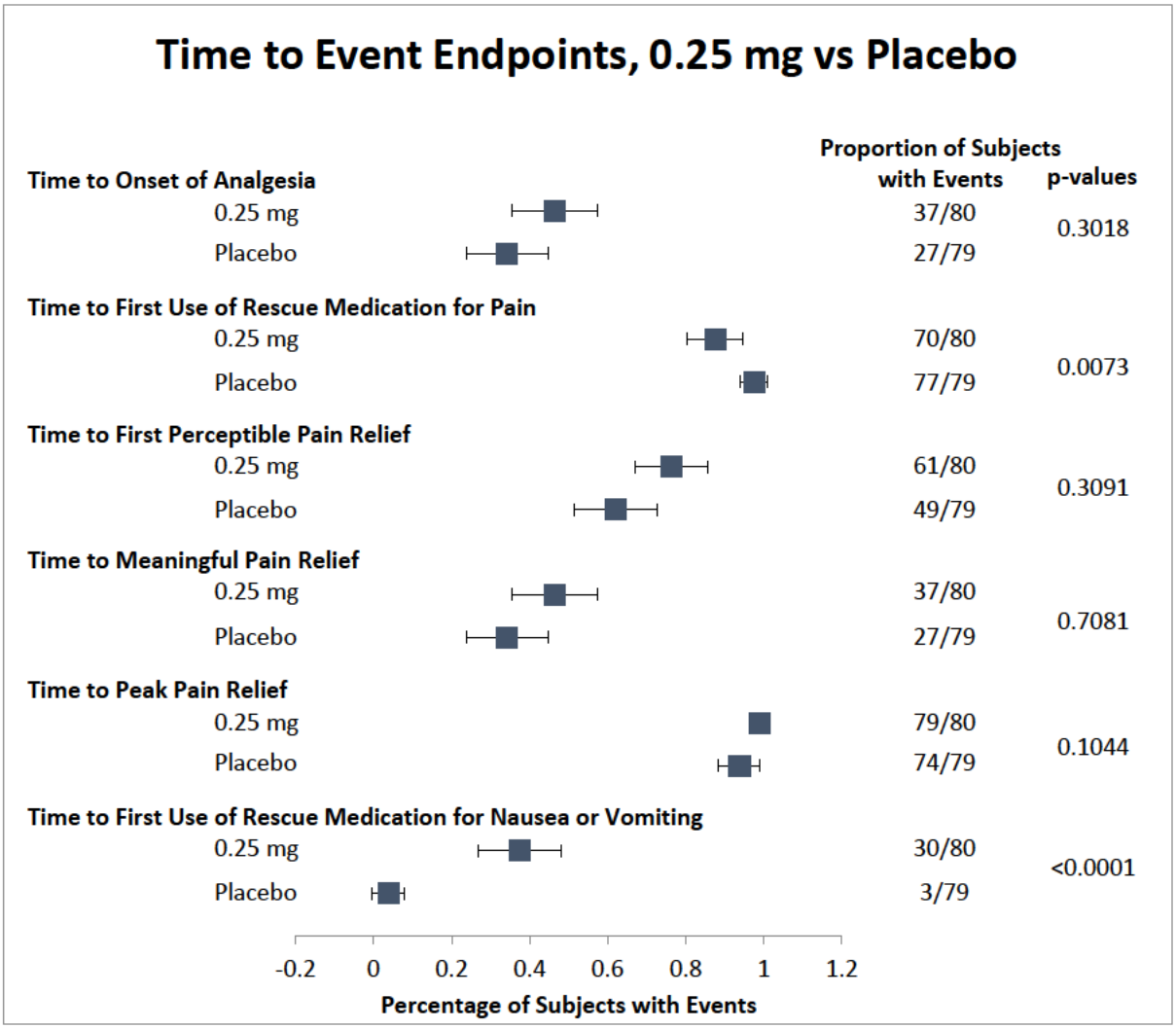
1.4.2.2. Secondary Efficacy Endpoints

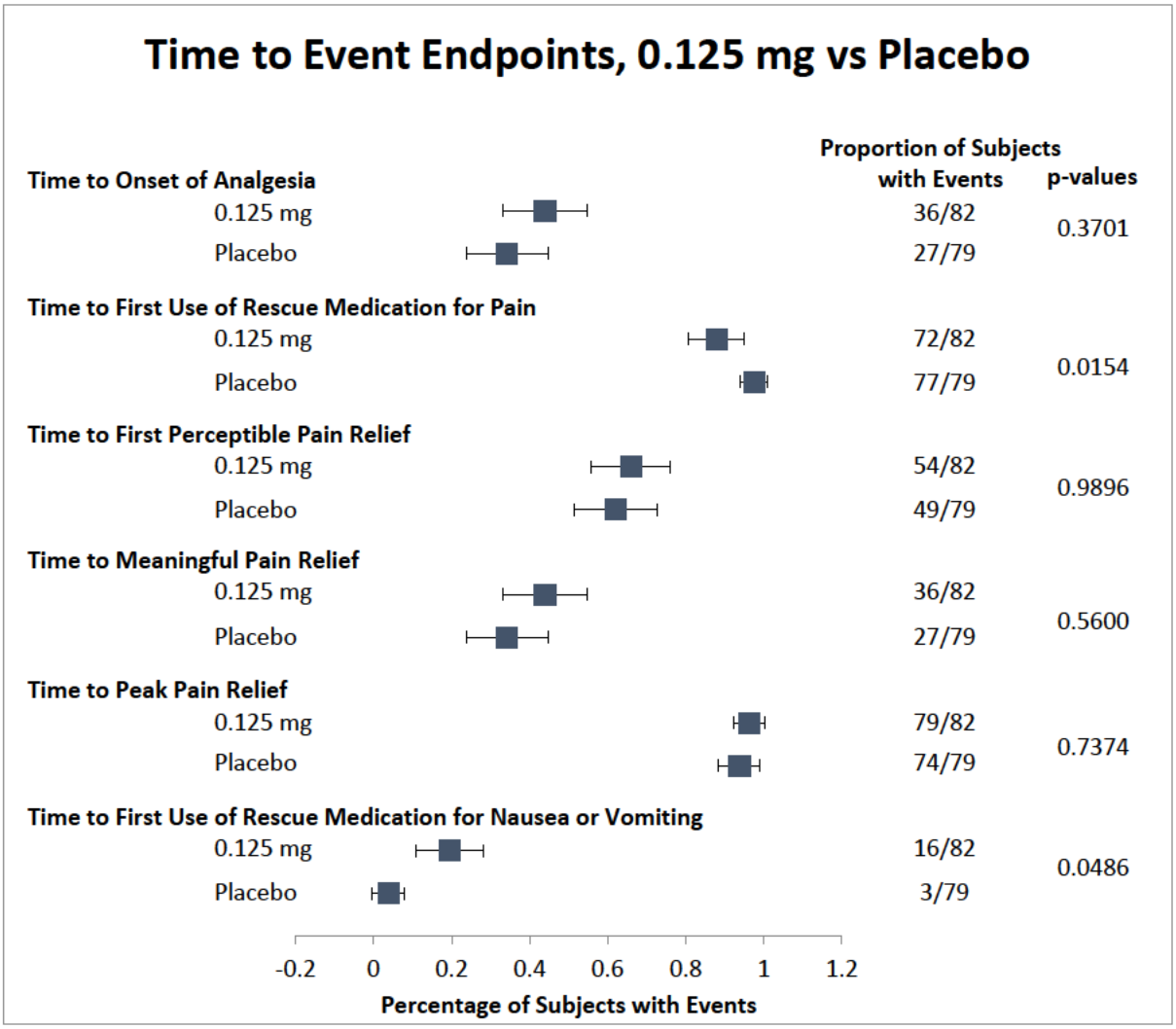
In addition to the statistically significant difference of the primary efficacy endpoint of SPID-48, the secondary endpoints consistently support both the efficacy and clinical relevance of the primary efficacy results.

SPID and TOTPAR were nominally better than placebo in all dose groups across all the time points. Ascending dose groups have increasing time to first use of rescue medication and decreasing use of rescue medication. So, while there were no perceptible differences between the SPID-48 scores for the 0.125 and 0.25 mg doses, there are differences in some secondary endpoints, and the higher use of ketorolac rescue medication in the 0.125 dose may explain the lack of separation on pain endpoints. Less rescue medication was used in 0.125 vs. placebo prior to 8 hours.

The figures below illustrate that the secondary endpoints support the efficacy of all three doses studied.


Time to Event Endpoints, 0.5 mg vs Placebo
Proportion of Subjects with Events
p-values
Time to Onset of Analgesia
0.5 mg
53/81
0.0010
Placebo
27/79
Time to First Use of Rescue Medication for Pain
0.5 mg
45/81
<0.0001
Placebo
77/79
Time to First Perceptible Pain Relief
0.5 mg
66/81
0.2720
Placebo
49/79
Time to Meaningful Pain Relief
0.5 mg
53/81
0.0707
Placebo
27/79
Time to Peak Pain Relief
0.5 mg
81/81
0.0002
Placebo
74/79
Time to First Use of Rescue Medication for Nausea or Vomiting
0.5 mg
55/81
<0.0001
Placebo
3/79
-0.2
0
0.2
0.4
0.6
0.8
1
1.2
Percentage of Subjects with Events


Time to Event Endpoints, 0.25 mg vs Placebo
Proportion of Subjects with Events
p-values
Time to Onset of Analgesia
0.25 mg
37/80
0.3018
Placebo
27/79
Time to First Use of Rescue Medication for Pain
0.25 mg
70/80
0.0073
Placebo
77/79
Time to First Perceptible Pain Relief
0.25 mg
61/80
0.3091
Placebo
49/79
Time to Meaningful Pain Relief
0.25 mg
37/80
0.7081
Placebo
27/79
Time to Peak Pain Relief
0.25 mg
79/80
0.1044
Placebo
74/79
Time to First Use of Rescue Medication for Nausea or Vomiting
0.25 mg
30/80
<0.0001
Placebo
3/79
-0.2
0
0.2
0.4
0.6
0.8
1
1.2
Percentage of Subjects with Events



1.4.3. Efficacy Summary

The results of the pivotal Phase 3 clinical trial demonstrate consistent evidence for the analgesic efficacy of Buprenorphine Sublingual Spray in a moderate to severe acute pain model with doses ranging from 0.125 mg to 0.5 mg given three times daily. This study demonstrated the efficacy of all three doses (0.125 mg, 0.25 mg and 0.5 mg TID) of the sublingual spray in acute pain, demonstrating superiority over placebo. There was a dose response, with the greatest reductions in pain being observed in the 0.5 mg TID dose. The secondary endpoints support the efficacy of the three proposed doses and also showed a dose-response favoring the 0.5 mg TID dose. In addition to the statistically significant difference of the primary efficacy endpoint of SPID-48, the secondary endpoints consistently support both the efficacy and clinical relevance of the primary efficacy results. Global evaluation assessments for Buprenorphine Sublingual Spray were better than that for placebo for all three doses studied. The global evaluation showed that the majority of patients on all three doses rated the spray Good or higher, reflecting both the efficacy and tolerability of the treatment. This is also reflected in the 92.5% completion rate.

1.5. Safety

The safety of Buprenorphine Sublingual Spray is consistent with the established safety of approved buprenorphine products. There were no unique events specific to this formulation or the delivery system observed in the clinical development program.

The rates of some events were notable for this formulation, specifically events of nausea and vomiting. In the pivotal study, the rates of these events were dose-dependent, with the highest rate of events observed for the highest dose, 0.5 mg TID. The events tended to occur with the initial doses and rates decreased with subsequent doses. INSYS believes that these events are manageable with normal antiemetic medications. In the postoperative setting, patients may benefit from prophylactic antiemetic therapy.

Two Phase 3 studies (Study 026 and Study 062) were conducted to evaluate the efficacy of Buprenorphine Sublingual Spray in a bunionectomy model for doses of 0.125 mg TID, 0.25 mg TID, 0.5 mg TID, 1.0 mg BID, and 1.0 mg TID administered for 48 hours, and one Phase 2 open label safety study (Study 111) in postoperative pain to evaluate the safety and tolerability based on the incidence of adverse experiences of Buprenorphine Sublingual Spray administered 0.5 mg TID for 7 days compared with standard postoperative narcotic therapy. In the three studies, a total of 323 subjects were exposed to Buprenorphine Sublingual Spray administered at these doses for 2 days or 7 days (up to 21 doses).

The safety endpoints in these studies were the incidence of treatment-emergent adverse events (TEAEs), physical and oral examination findings, and changes in vital signs, including pulse oximetry, and ECG measurements. In the pivotal Phase 3 study and the Phase 2 open-label 7-day safety study, all patients were continuously monitored for a decrease in oxygen saturation.

A total of 490 subjects have been exposed to Buprenorphine Sublingual Spray (various doses), of whom 217 have been exposed to the highest proposed dose of 0.5 mg without significant unusual or unexpected adverse reactions or safety concerns.

1.5.1. Most Common Adverse Events in Phase 3 Studies

The most notable AEs in the Phase 3 studies were nausea, vomiting, and reduced oxygen saturation or hypoxia. In Study 062, for the proposed doses of 0.125 mg, 0.25 mg, and 0.50 mg: nausea was reported for 43.9%, 58.8%, and 83.3%, and vomiting was reported for 29.3%, 41.3%, and 72.2% of patients, respectively (Table E1). Neither of these two studies (026 and 062) allowed prophylactic use of antiemetics, but did limit the types and dosage of antiemetic permitted. While there were some severe events of nausea and vomiting, there were no events that were considered serious. Additionally, there were seven cases of dehydration, four of which occurred in patients with severe vomiting that were concerning to the Agency.

Across all three studies (Studies 026, 062, and 111), there were a total of three SAEs. There was one serious AE in each trial all with the 0.5 mg TID dose. An SAE of atrial fibrillation in a 56 year old woman with a history of cardiac disorders and rhythm abnormalities. There was an SAE of angioedema in a 65 year old woman after her last dose of study medication. This may have been an allergic reaction to Zofran that responded to Benedryl. The third patient had an SAE of incision site hematoma. This was a 32 year old woman who developed the hematoma 24 hours

after discontinuing Buprenorphine Sublingual Spray due to nausea and vomiting. The hematoma was treated and resolved the same day.

Table E1: Most Common AEs in Phase 3 Studies (≥5% in proposed doses)

	Phase 3 Studies Pooled[1]					
	0.125 mg TID N=82 n (%)	0.25 mg TID N=80 n (%)	0.5 mg TID N=90 n (%)	1 mg BID N=11 n (%)	1 mg TID N=10 n (%)	Placebo N=89 n (%)
Subjects with ≥ 1 adverse event	57 (69.5)	67 (83.8)	85 (94.4)	11 (100.0)	9 (90.0)	45 (50.6)
Total Number of adverse events	219	296	521	67	55	109
Cardiac disorders	1 (1.2)	1 (1.3)	2 (2.2)	1 (9.1)	0 (0.0)	2 (2.2)
Eye disorders	0 (0.0)	1 (1.3)	2 (2.2)	1 (9.1)	0 (0.0)	1 (1.1)
Gastrointestinal disorders	41 (50.0)	55 (68.8)	78 (86.7)	11 (100.0)	8 (80.0)	25 (28.1)
Constipation	9 (11.0)	6 (7.5)	8 (8.9)	2 (18.2)	2 (20.0)	1 (1.1)
Dry mouth	0 (0.0)	3 (3.8)	5 (5.6)	2 (18.2)	1 (10.0)	1 (1.1)
Nausea	36 (43.9)	47 (58.8)	75 (83.3)	10 (90.9)	7 (70.0)	16 (18.0)
Vomiting	24 (29.3)	33 (41.3)	65 (72.2)	8 (72.7)	8 (80.0)	4 (4.5)
Infections and infestations	2 (2.4)	1 (1.3)	4 (4.4)	1 (9.1)	1 (10.0)	2 (2.2)
Investigations	6 (7.3)	8 (10.0)	9 (10.0)	0 (0.0)	0 (0.0)	6 (6.7)
Oxygen saturation decreased	6 (7.3)	8 (10.0)	8 (8.9)	0 (0.0)	0 (0.0)	4 (4.5)
Metabolism and nutrition disorders	3 (3.7)	1 (1.3)	9 (10.0)	1 (9.1)	0 (0.0)	2 (2.2)
Decreased appetite	3 (3.7)	1 (1.3)	5 (5.6)	0 (0.0)	0 (0.0)	2 (2.2)
Dehydration	0 (0.0)	0 (0.0)	7 (7.8)	1 (9.1)	0 (0.0)	0 (0.0)

	Phase 3 Studies Pooled[1]					
	0.125 mg TID N=82 n (%)	0.25 mg TID N=80 n (%)	0.5 mg TID N=90 n (%)	1 mg BID N=11 n (%)	1 mg TID N=10 n (%)	Placebo N=89 n (%)
Subjects with ≥ 1 adverse event	57 (69.5)	67 (83.8)	85 (94.4)	11 (100.0)	9 (90.0)	45 (50.6)
Total Number of adverse events	219	296	521	67	55	109
Nervous system disorders	33 (40.2)	44 (55.0)	62 (68.9)	9 (81.8)	7 (70.0)	22 (24.7)
Dizziness	18 (22.0)	26 (32.5)	51 (56.7)	5 (45.5)	5 (50.0)	7 (7.9)
Headache	15 (18.3)	23 (28.8)	14 (15.6)	4 (36.4)	1 (10.0)	13 (14.6)
Somnolence	6 (7.3)	6 (7.5)	15 (16.7)	3 (27.3)	4 (40.0)	0 (0.0)
Tremor	1 (1.2)	3 (3.8)	1 (1.1)	1 (9.1)	1 (10.0)	1 (1.1)
Psychiatric disorders	3 (3.7)	0 (0.0)	6 (6.7)	1 (9.1)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	8 (9.8)	4 (5.0)	11 (12.2)	1 (9.1)	1 (10.0)	5 (5.6)
Hiccups	0 (0.0)	0 (0.0)	2 (2.2)	1 (9.1)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	6 (7.3)	6 (7.5)	26 (28.9)	4 (36.4)	4 (40.0)	4 (4.5)
Erythema	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	2 (20.0)	0 (0.0)
Hyperhidrosis	2 (2.4)	1 (1.3)	10 (11.1)	2 (18.2)	1 (10.0)	0 (0.0)
Pruritus	2 (2.4)	2 (2.5)	13 (14.4)	3 (27.3)	0 (0.0)	1 (1.1)
Rash	0 (0.0)	1 (1.3)	2 (2.2)	0 (0.0)	1 (10.0)	3 (3.4)
Vascular disorders	6 (7.3)	5 (6.3)	9 (10.0)	3 (27.3)	0 (0.0)	2 (2.2)

N = number of subjects within the dose group (denominator for percentages, where applicable)
n = number of observed subjects (numerator for percentages, where applicable)
[1] INS-14-026 and INS005-15-062
Adverse event (AE) = any AE which started or worsened on or after the day of first dose (randomization).
Note: A subject is counted only once within each system organ class and preferred term category, using the event having the worst-case severity.

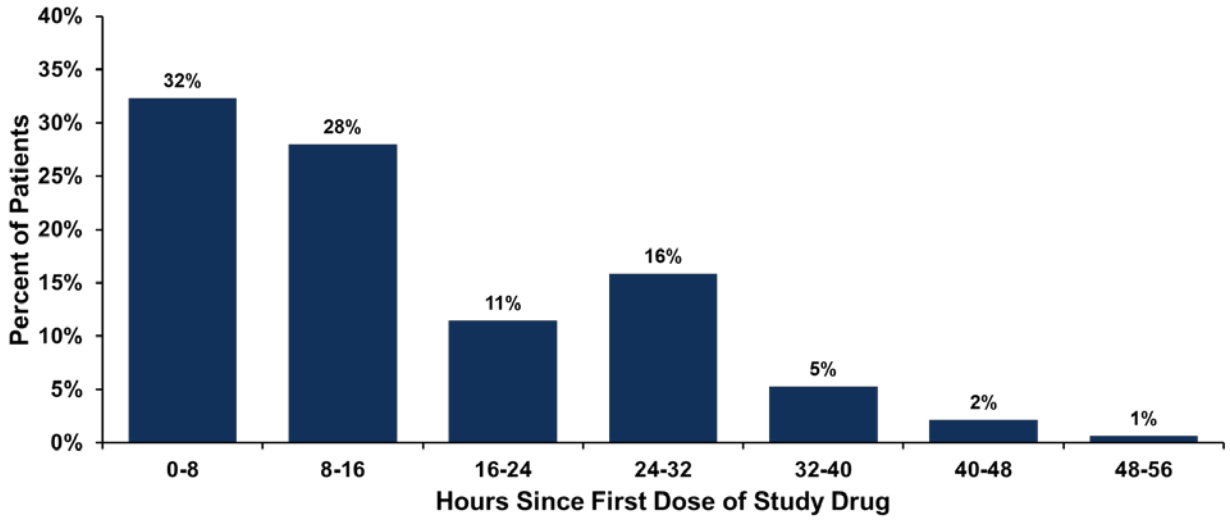
1.5.2. Nausea and Vomiting

The incidence of nausea and vomiting in this patient population is expected to high because the population was a high-risk population. Based upon the Consensus Guidelines for the Management of Postoperative Nausea and Vomiting, the general incidence of vomiting is about 30%, the incidence of nausea is about 50%, and in a subset of high-risk patients, the postoperative nausea and vomiting (PONV) rate can be as high as 80%. Risk factors such as female gender, younger age, opioid naïve, postoperative opioids, and a history of PONV or motion sickness all contribute to a higher incidence of PONV. The patient population in these two Phase 3 studies were 80% female with a mean age in the early 40s, and all patients except

those who received placebo, received an opioid postoperatively and would be considered a high-risk population.

The majority of nausea and vomiting events occurred within the first 16 hours after initiation of study drug, suggesting that the first and second doses are associated with the highest number of events (Figure E8). There were still some events at subsequent doses, but rates much lower by the third dose and down to 7 percent by the fifth dose. These rates may also be a consequence of the study design as there was no use of prophylactic antiemetic therapy.

Figure E8: Percentage of Patients Experiencing Related Vomiting Events: Study 062



1.5.3. Study 111

Study INS005-17-111 was a Phase 2, randomized (stratified according to surgery and postoperative nausea and vomiting risk factors), open label, multiple-dose, comparator controlled, parallel-group, study to evaluate the safety and tolerability of Buprenorphine Sublingual Spray (0.5 mg TID) versus standard postoperative narcotic therapy for 7 days in patients with postoperative pain. Patients had undergone bunionectomy, breast augmentation, or abdominoplasty. There were 50 patients each in the Buprenorphine Sublingual Spray (0.5 mg TID) and standard narcotic therapy groups. Standard postoperative narcotic therapy was defined as morphine intravenous (IV) injection (4 mg TID) followed by oxycodone hydrochloride tablet (10 mg TID). The primary objective of the study was to evaluate the safety and tolerability based on the incidence of adverse events of Buprenorphine Sublingual Spray (0.5 mg three times daily [TID]) compared with standard postoperative narcotic therapy in subjects with postoperative pain. A secondary objective was to evaluate impact of prophylactic antiemetic use on nausea and vomiting.

The study design and disposition of subjects is outlined in Figure E9. The treatment period consisted of a 72-hour inpatient portion, followed by a 4-day outpatient portion, for a total of 7 days. Patients had a follow-up visit between Day 8 and Day 10 inclusive.

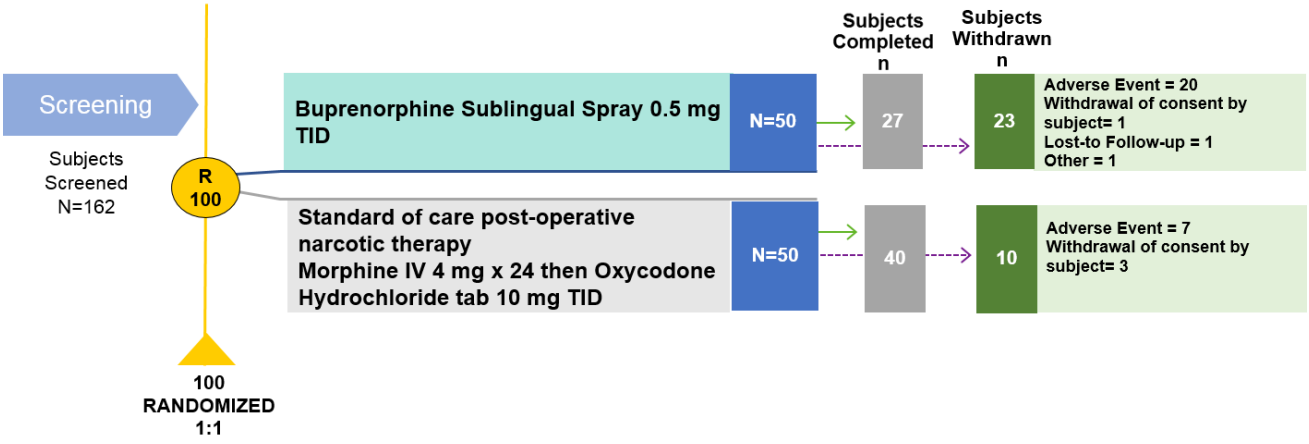
The study methodology enabled investigation of the impact of prophylactic antiemetic treatment. Patients were stratified by their baseline risk of nausea and vomiting as well as by surgical

procedure. All patients received prophylaxis antiemetic therapy starting with induction with dexamethasone 10 mg followed by ondansetron 8 mg near the end of surgery.

One hundred subjects (4 male subjects and 96 female subjects) were enrolled into the study. Almost all subjects were female (48 in each group). Overall, the mean (SD) age was 36.6 (11.22) years. Most subjects were either White (60 [60.0%]), or Black or African American (33 [33.0%]).

The majority of subjects were classified as PONV high risk: 42 (84.0%) subjects in the standard postoperative narcotic therapy group and 43 (86.0%) subjects in the Buprenorphine Sublingual Spray group.

Figure E9: Study 111: Disposition of Screened Subjects



1.5.4. Most Common Adverse Events in Study 111

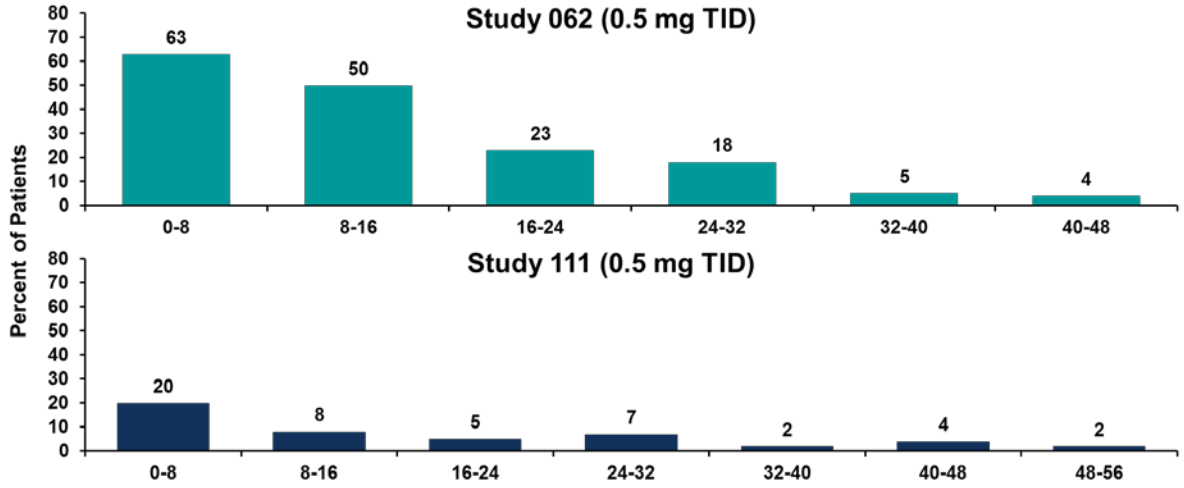
The most common AEs with severity are summarized in Table E2.

Table E2: Study 111: Most Common AEs with Severity

Preferred Term Severity	0.5 mg TID N=50 %	Standard Narcotic Therapy* N=50 %
Nausea	78	34
Mild	6	10
Moderate	72	24
Vomiting	52	12
Mild	18	8
Moderate	34	4
Hypoxia	28	6
Mild	2	0
Moderate	26	6
Headache	18	16
Mild	14	10
Moderate	4	6
Dizziness	22	10
Mild	20	10
Moderate	2	0
Pruritus	16	8
Mild	12	6
Moderate	4	2

As in prior studies, the majority of events occurred within the first 16 hours after the first dose of study drug (Figure E10). Approximately 28% of patients experienced related events of the vomiting events within 16 hours after the first dose of study drug. The frequency and timing of events compare favorably with their occurrence on the comparable 0.5 mg TID arm of Study 062, supporting the use of prophylactic antiemetics (Figure E10).

Figure E10: Percentage of Patients Experiencing Related Vomiting Events by Study Epoch for Buprenorphine SL Spray 0.5 mg TID: Study 062 and Study 111



1.5.5. Adverse Events of Special Interest

The incidence and severity of AEs of special interest are summarized in Table E3. Importantly, both the rate and severity of vomiting events observed in Study 111 were lower than those observed in Study 062. In addition, there were no severe events of nausea or vomiting and no dehydration in Study 111. In contrast, in Study 062, severe events of both nausea and vomiting, including four who had accompanying dehydration, were reported.

Table E3: Severity of Adverse Events of Special Interest

		Study 062 Patients				Study 111 Patients	
	AESI	Placebo N=79 %	0.125 mg TID N=82 %	0.25 mg TID N=80 %	0.5 mg TID N=81 %	0.5 mg TID N=50 %	Standard Narcotic Therapy N=50 %
Nausea	Mild	12.7	32.9	42.5	51.9	6	10
	Moderate	3.8	9.8	13.8	29.6	72	24
	Severe	0	1.2	2.5	2.5	0	0
Vomiting	Mild	1.3	15.9	21.3	35.8	18	8
	Moderate	2.5	12.2	12.5	28.4	34	4
	Severe	1.3	1.2	7.5	8.6	0	0

Clinical Study Report INS005-15-062, Table 14.3.6; Clinical Study Report INS005-17-111, Table 14.
Numbers represent the number of subjects that reported an event.
Standard narcotic 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

1.5.6. Study 111 Conclusions

The results of Study 111 indicate that Buprenorphine SL Spray 0.5 mg TID was generally safe and well tolerated for up to 7 days. In addition, the study showed that prophylactic antiemetic treatment resulted in a lower incidence and severity of vomiting, and severity of nausea.

1.6. Reduced Oxygen Saturation

The events related to reduced oxygen saturation in Studies 026, 062, and 111 were defined as either "hypoxia" or "oxygen saturation decreased":

- Study 026: hypoxia was defined as oxygen saturation < 90% on room air and oxygen saturation decreased was not defined or reported.
- Study 062: hypoxia was defined as oxygen saturation ≤ 92% on room air and oxygen saturation decreased was defined as any drop in oxygen saturation down to, but not exceeding 92% regardless of whether medical intervention was required.
- Study 111: hypoxia was defined as oxygen saturation < 90% on room air and oxygen saturation decreased was not defined or reported.

The rates of these events varied across studies (Table E4). The highest rates of events were observed in Study 111. In addition to bunionectomy, Study 111 included patients who had undergone breast augmentation and abdominoplasty. Both of these procedures make breathing difficult as reflected in the rates reported in these two groups. However, the rate of hypoxia in the bunionectomy population was 19%, still higher than that observed in the larger 062 study, which was 3.7% in the 0.5 mg TID dose group. No patients in the smaller 026 study had events of hypoxia on the 0.5 mg TID dose or on the higher doses.

Table E4: Severity of Reduced Oxygen Saturation

		Study 062				Study 026	Study 111	
		Placebo N=79 n (%)	0.125 mg TID N=82 n (%)	0.25 mg TID N=80 n (%)	0.5 mg TID N=81 n (%)	0.5 mg TID N=9 n (%)	0.5 mg TID N=50 n (%)	Standard Opioid Therapy N=50 n (%)
O_2 Sat Dec	Mild	4 (5.1)	6 (7.3)	8 (10)	7 (8.6)	1 (1.1)	NA	NA
	Received O_2	2 (2.5)	6 (7.3)	7 (8.8)	7 (8.6)	1 (1.1)	NA	NA
Hypoxia	Mild	0	1 (1.2)	0	3 (3.7)	0	1 (2)	0
	Moderate	0	0	0	0	0	13 (26)	3 (6)
Hypoxia	Total	0	1 (1.2)	0	3 (3.7)	0	14 (28)	3 (6)
	Received O_2	0	1 (1.2)	0	3 (3.7)	0	14 (28)	3 (6)

Clinical Study Report INS005-15-062, Table 14.3.6; Clinical Study Report INS005-17-111 Table 14; Clinical Study Report INS-14-026.
Standard narcotic 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

The greatest concern with regard to oxygen saturation on opioids is respiratory depression. Although the hypoxia for Buprenorphine Sublingual Spray observed in Study 111 were reported as moderate because of the administration of oxygen, the investigator considered these events clinically mild in severity and did not pose any type of immediate safety threat to the subject. Moreover, there are published data to suggest that there is a ceiling effect on the respiratory depression observed with buprenorphine that is unlike other opioids (Dahan et al., 2006; Pergolizzi et al., 2008). This ceiling should reduce the risk of serious respiratory events such as breathing instability and apnea.

- **Reduced Oxygen Saturation Conclusions**

The results of the Phase 2 and Phase 3 studies show that the rates of hypoxia and decreased oxygen saturation observed with Buprenorphine Sublingual Spray treatment are consistent with current opioids commonly used for outpatients. Further, the decreased oxygen saturations observed did not dip below 86%. This ceiling effect on respiratory depression should be protective.

1.7. Safety Summary

Buprenorphine Sublingual Spray was generally safe and well-tolerated for up to 7 days in the setting of moderate to severe acute pain. The data from Study 111 support the prophylactic use of antiemetics to reduce the rate of vomiting associated with the use of the drug product. The events of vomiting were reduced in number and severity by prophylactic antiemetic therapy. The events of hypoxia are consistent with commonly used opioids. Oxygen saturations did not drop below 86%.

1.8. Risk Management

The goals of the Risk Management Plan for Buprenorphine Sublingual Spray are to:

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

1.9. Benefit/Risk Conclusions

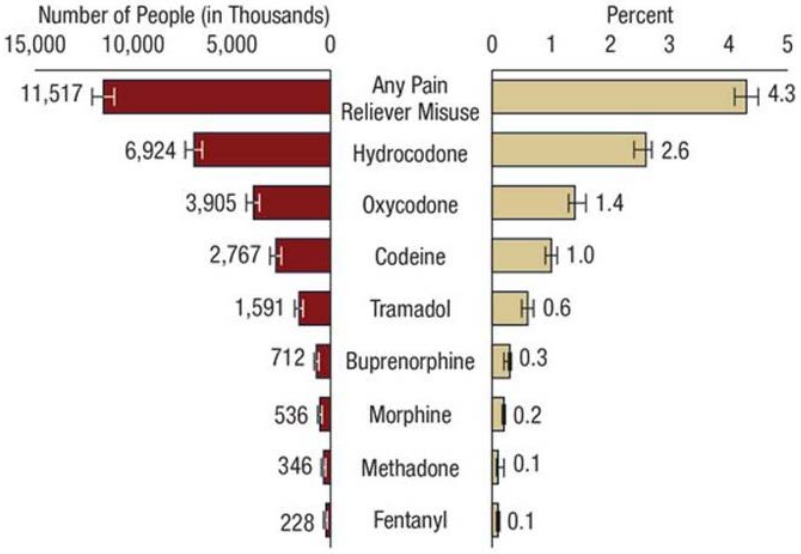
There is a medical need for a more efficacious, safe, and lower scheduled product (Schedule III versus Schedule II) with less potential for abuse for the treatment of moderate to severe acute pain. Buprenorphine is a safe and efficacious drug for the treatment of moderate to severe acute pain and possesses several characteristics that make it preferable to other opioids currently available. The only formulation currently available for the treatment of acute pain requires parenteral administration limiting its use despite two buprenorphine products available for chronic pain. Buprenorphine Sublingual Spray offers an alternative that allows physicians to take advantage of the unique pharmacology and safety profile in an easy-to-administer non-parenteral formulation for cases of moderate to severe acute pain. The Buprenorphine Sublingual Spray clinical development program demonstrated clinical efficacy in the treatment of moderate to severe acute pain at doses of 0.125 mg TID, 0.25 mg TID, and 0.5 mg TID. Further, 67%-86.4%

of the subjects reported their global evaluation to be Excellent, Very Good, or Good across the doses studied. In ten studies of a total of 490 subjects exposed to various doses of Buprenorphine Sublingual Spray, Buprenorphine Sublingual Spray was generally well tolerated with a safety profile similar to that of other buprenorphine products. Given the long and well-known safety profile and decreased abuse potential of buprenorphine, Buprenorphine Sublingual Spray would provide a valuable treatment option for the treatment of moderate to severe acute pain.

2. INTRODUCTION

The death toll is growing in the opioid crisis. From 2002 to 2015 there was a 2.8-fold increase in the number of deaths related to opioids. In 2016, more than 17,000 or 46 people per day died from overdoses involving prescription opioids. Until non-opioid pain medications are sufficient to manage moderate to severe pain, there will still be a role for opioids. Therefore, there is a need for opioids that have a lower potential for abuse than the current Schedule II opioid pain medications. Buprenorphine is a Schedule III opioid that has a lower abuse potential than Schedule II opioids. This is reflected in the lower rates of abuse, misuse, overdose, and death for buprenorphine even though it is widely prescribed to millions of patients in medication assisted treatment programs for opioid abuse disorder. For example, the National Survey on Drug Use and Health by SAMHSA in 2016 an estimated 0.3 percent of people aged 12 or older misused buprenorphine products in the prior year (Figure 1). Further, much of the misuse of buprenorphine is for self-medication for the symptoms of opioid withdrawal. These characteristics may suggest that buprenorphine could be useful in treating moderate-to-severe acute pain in today's current environment.

Figure 1: Prescription Pain Reliever Misuse Among People 12 or Older



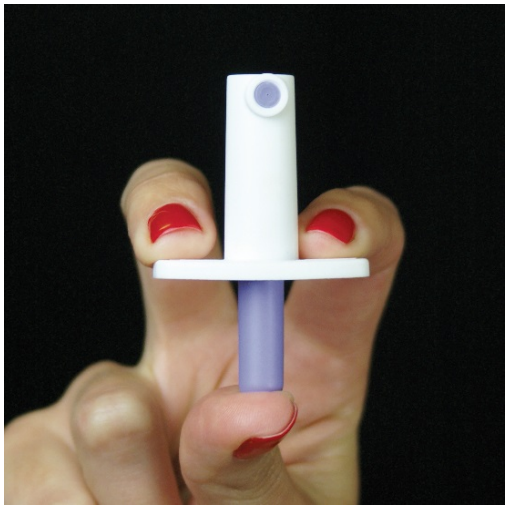
The lower abuse potential would be an advantage for anyone who requires an opioid for pain management as well as their families. Some reports in the literature suggest that the first exposure to an opioid is critical for those patients who ultimately end up abusing opioids. There may also be a broader public health advantage resulting from a lower rate of Schedule II opioid prescriptions if more people receive Schedule III alternatives.

Buprenorphine possesses unique pharmacological properties as a partial mu-opioid receptor agonist that make it a safe and efficacious alternative to other opioids. For example, buprenorphine is thought to have a ceiling effect on respiratory depression, may be associated with the development of less analgesic tolerance, and may be associated with less cognitive impairment than traditional full μ-opioid agonists, which may be useful in an acute setting of moderate to severe pain.

Despite proven clinical utility, buprenorphine has not been used widely for the treatment of acute pain in part because only Buprenex® (0.3 mg/mL), a parenteral (intravenous or intramuscular) formulation has been available for treatment in the acute setting. Development of a Buprenorphine Sublingual Spray may be a useful addition for use in the moderate to severe acute pain setting. While transdermal and buccal delivery products of buprenorphine are available for the management of long-term chronic pain, new delivery and treatment options for moderate to severe acute pain remain an unmet medical need. The oral bioavailability of buprenorphine is low because of the extensive first-pass hepatic metabolism (Johnson et al. 2005), therefore, the administration of buprenorphine sublingually allows for bypassing it.

INSYS Development Company, Inc. (INSYS) is developing Buprenorphine Sublingual Spray via the 505(b)(2) regulatory pathway for the treatment of moderate to severe acute pain. The application references the established safety and efficacy of Buprenex® and Subutex®. The sublingual spray formulation of buprenorphine is supplied in a single-spray, unit-dose device shown in the pictures below that contains either a 0.125 mg, 0.25 mg, or 0.5 mg dose administered three times per day (TID). Through the use of this innovative delivery system, the sublingual buprenorphine product may provide additional advantages to the existing treatment options because it is simple and easy to use and requires little expertise, preparation, or supervision (Stevens and Ghazi, 2000).

Figure 2: Buprenorphine Sublingual Spray Device



The established safety profile of currently available buprenorphine products in both the outpatient setting and inpatient setting; the low abuse potential relative to other opioids; the ceiling effect on severe respiratory compromise; and the current absence of a non-parenteral form of buprenorphine indicated for moderate to severe acute pain led to the development of the easy-to-use Buprenorphine Sublingual Spray.

It is understandable in consideration of media coverage about the company's legacy legal issues related to allegations of inappropriate sales and marketing practices to have some concerns about approving a new opioid for the company. To allay those concerns, we are a markedly different company today than the one portrayed in many media reports. The company is led by a new management team that has significantly strengthened compliance protocols to foster an

organizational culture of high ethical standards and strives to puts the best interests of patients at the center of the process for making business decisions. In fact, more than 90% of the management team and commercial organization, including the sales force, is new to the company since 2015. Our new CEO, Saeed Motahari, joined the company in April 2017. Further four new members have joined the Board of Directors since 2017.

We are committed to bringing effective therapies for unmet medical needs and underserved patient population to market. Over the past five years, we have invested $250 million in R&D to advance our deep and diverse product pipeline through the clinical and regulatory pathway as expeditiously as possible. Looking ahead, we intend to invest at least another $120 million in R&D, which promises to yield new treatment options for medically refractory pediatric epilepsies (including childhood *absence* seizures and infantile spasms); Prader-Willi syndrome, a rare genetic disease that causes insatiable appetite in children and often leads to obesity, type 2 diabetes and premature death; agitation in Alzheimer's disease; and anorexia-related weight loss in cancer. In addition, we are developing intranasal and sublingual sprays of therapeutic molecules for other conditions—for example, anaphylaxis and opioid overdose.

We hope this information goes some way toward addressing your understandable concerns.

3. MEDICAL LANDSCAPE AND UNMET NEED

3.1. General Landscape

Currently only two Schedule III opioids (buprenorphine and codeine when mixed with aspirin or acetaminophen) are available, therefore Schedule II opioids with established efficacy are utilized more often. Codeine is highly constipating, not all patients can metabolize it to active morphine and therefore the clinical utility is low. Buprenorphine, is an effective analgesic, but has been limited in acute pain management due to the limitation of the parenteral formulation as the only approved option. The side effects of opioids that are most concerning include respiratory depression, nausea and vomiting, constipation, dependence, and abuse.

Challenges to the current therapy for acute pain include:

- Majority of opioids are Schedule II with high risk of physical and psychological dependence.
- Many formulations of opioids contain acetaminophen (APAP).
- Hepatic and renal diseases are prevalent and should limit the use of certain products in these patients including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin (ASA), and acetaminophen containing products.
- Oral formulations require the ability to swallow (dysphagia is an issue in some patients).
- Pill burden is an issue for some products.
- Vomiting could cause the patient to lose the dose if administered via a tablet or capsule route.
- Providing pain relief for patients with a prior history of opioid use disorder or at-risk for opioid use disorder is concerning.

Thus, there is a lack of treatment options for moderate to severe acute pain management between Schedule II and non-opioid alternatives.

3.2. Buprenorphine Landscape

Buprenorphine is a mixed agonist-antagonist opioid with an analgesic potency approximately 30 times that of morphine sulfate and a long duration of action (Buprenex® prescribing information [PI]). It is classified as a partial agonist at the mu-opioid receptor, an antagonist at the kappa-opioid receptor, an agonist at the delta-opioid receptor, and a partial agonist at the ORL-1 (nociceptin/orphanin FQ) receptor (Butrans® PI).

Buprenorphine binds to mu-receptors with high affinity but with less intrinsic activity compared to full opioid agonists. Mu-receptors are considered the classic morphine-receptor type with their stimulation producing supraspinal analgesia, respiratory depression, euphoria, and physical dependence. While buprenorphine shares the CNS depressant, respiratory depressant, and hypotensive effects of opioid analgesics, these effects appear less dose-dependent than other opioids. Due to its high affinity, acute administration of buprenorphine may displace or reduce the effects of full mu-receptor agonists of lesser affinity and theoretically cause withdrawal

symptoms. However, there has been little clinical evidence supporting this concern (Pergolizzi et al., 2010). Buprenorphine binds to, and dissociates from, the mu-receptor very slowly, which likely accounts for its longer duration of action compared to morphine and for its low level of observed physical dependence. This property is also felt to be responsible for the lack of hyperalgesia associated with the use of common full mu-opioid agonists (Pergolizzi et al., 2010).

Buprenorphine has a long and well-established safety profile that is unique from other more commonly used opioids due, in part, to its partial agonist properties. The primary side effects of buprenorphine are similar to other full mu-opioid agonists including nausea, vomiting, and constipation, but typically of less severity. Buprenorphine exhibits a much lower incidence (1%–5%) of constipation than that observed with full mu-agonists (Kress HG, 2009; Griessinger N et al., 2005; Shipton EA, 2005). Unlike other opioids, buprenorphine does not cause spasm of the sphincter of Oddi, and may be used in acute pancreatitis. Buprenorphine may not lead to the same level of visual, psychomotor or cognitive dysfunction compared to morphine, methadone or fentanyl; and, in many cases, observed buprenorphine effects on cognitive and psychomotor function were comparable to those observed with placebo (Davis MP, 2012; Soyka M et al., 2005; Shmygalev S et al., 2011).

Respiratory depression is of particular importance with the use of all opioids since it may be fatal. However, respiratory depression from buprenorphine is dose-related when given in therapeutic doses, and the peak respiratory depressant effects are slower in onset and longer in duration than morphine (Heel et al.,1979). Also, buprenorphine does have a ceiling effect for respiratory depression (Heel at al., 1979; Dahan et al., 2005). In a randomized, double-blind, placebo controlled study in healthy human volunteers, buprenorphine was administered intravenously up to 8.6 mg/kg over 90 seconds. The depression of minute ventilation caused by buprenorphine leveled off at doses of 3.0 mg/kg and above, and none of the subjects receiving buprenorphine developed apnea (Dahan et al., 2005). Further, one of the assessments of buprenorphine when given parenterally for postoperative pain found that it generally provides good or adequate pain relief with an incidence of less than 1% of drug-associated respiratory depression (Harcus et al., 1980).

Traditionally it has been believed that, as a partial agonist, buprenorphine would have a ceiling effect on both respiratory depression and analgesia. However, recent research has demonstrated that buprenorphine behaves like a full mu-opioid agonist for analgesia in clinical practice, with no ceiling effect, while also displaying a ceiling effect for respiratory depression as described above. Taken together, this constellation of properties suggests a greater safety margin and therapeutic index for buprenorphine (Dahan et al., 2006; Buprenex® PI; Pergolizzi, et al. 2010; Yassen et al., 2008).

4. DESCRIPTION OF PRODUCT DEVELOPMENT

4.1. Rationale for Development of Buprenorphine Sublingual Spray

Despite proven clinical utility, buprenorphine has not been used widely for the treatment of acute pain. Development of a Buprenorphine Sublingual Spray may be a useful addition for use in the moderate to severe acute pain setting. Currently, only one buprenorphine product is available for the management of moderate to severe acute pain. Buprenex® (0.3 mg/mL), a parenteral (intravenous or intramuscular) formulation indicated for the relief of moderate to severe pain. While transdermal and buccal delivery products of buprenorphine are available for the management of long-term chronic pain, new delivery options and new treatment options for moderate to severe acute pain remain an unmet medical need. The oral bioavailability of buprenorphine is low because of the extensive first-pass hepatic metabolism (Johnson et al. 2005). Therefore, the administration of buprenorphine sublingually allows for bypassing it. Furthermore, a sublingual buprenorphine product may provide additional advantages in that it is simple and easy to use and requires little expertise, preparation, or supervision (Stevens and Ghazi, 2000). Despite proven clinical utility, buprenorphine has not been used widely for the treatment of acute pain in part because only Buprenex® (0.3 mg/mL), a parenteral (intravenous or intramuscular) formulation has been the only available option for treatment in the acute setting.

The established safety profile of currently available buprenorphine products in both the outpatient and inpatient setting; the low abuse potential relative to other opioids; the reported ceiling effect on severe respiratory compromise; and the current absence of a non-parenteral form of buprenorphine approved for moderate to severe acute pain led to the development of the easy-to-use Buprenorphine Sublingual Spray.

For delivery of the formulation, INSYS selected a unit dose sublingual spray device that is simple and easy to use option and requires little expertise, preparation, or supervision (Stevens and Ghazi, 2000). The selected unit dose device presented in Figure 3 was also selected because it guarantees only a very limited residual quantity in used units, thus limiting the risk of the secondary exposure. The device placed in a child resistant opaque blister, that requires scissors to open it (Figure 4). To mitigate the risk of the unintentional exposure to the product, the proposed packaging also includes two types of child-resistant pouches to dispose unused and used units. Various studies were conducted to demonstrate that the reclamation of the product once disposed is impossible.

Figure 3: Unit Dose Sublingual Spray Device Proposed for Buprenorphine Sublingual Spray Delivery

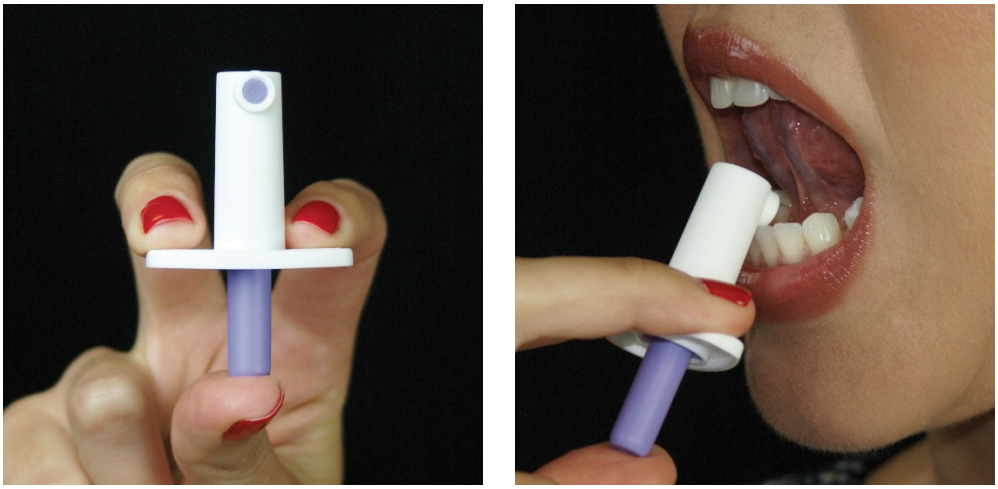


Figure 4: Blister Proposed for Buprenorphine Sublingual Spray Delivery

As discussed above, the lower abuse potential would be an advantage for anyone who requires an opioid for pain management. To assess the abuse potential of the proposed product, an eight-factor analysis was conducted. It demonstrated that Buprenorphine Sublingual Spray has a similar abuse potential to Buprenex and other Schedule III buprenorphine and buprenorphine/naloxone combination products. There is a need to advance opioid products with less misuse, abuse, and diversion to address the U.S. opioid public health crisis. INSYS is committed to addressing the concerns with the development Buprenorphine Sublingual Spray as an alternative to Schedule II opioids for the management of moderate to severe acute pain. Schedule II products are defined by the Drug Enforcement Administration (DEA) as products that have a high potential for abuse which may lead to severe psychological or physical dependence. While the proposed Buprenorphine Sublingual Spray is not an abuse-deterrent drug, buprenorphine is one of the two Schedule III opioid products and it is defined to have a lower potential for abuse than substances in Schedules I or II (DEA Schedule).

Buprenorphine is rated low on the list of most commonly abused drugs in Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System reports; usually abused to prevent massive withdrawal from other opioids. According to the Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health (2016), 0.3% of the buprenorphine products prescribed are misused. Furthermore, buprenorphine was ranked last in prevalence of abuse relative to the following drugs (from highest to lowest prevalence of abuse): oxycodone extended release, hydrocodone, other oxycodone, methadone, morphine, hydromorphone, fentanyl, and buprenorphine (Cicero et al., 2005b). Based on these considerations of the decreased ability to produce euphoria and dependence relative to other opioids, and in combination of current use trends, buprenorphine may have a lower risk of abuse potential than other opioids commonly used for the treatment of acute moderate to severe pain making it a potentially preferred analgesic where opioids are required.

The sublingual spray administration has additional benefits as it does not require administration with water, is a treatment option for patients with dysphagia or nothing by mouth (NPO) status. Most importantly, the current absence of non-invasive options for a low abuse potential relative to other opioids in an acute pain setting is the foundation that has led by INSYS Development Company, Inc. (INSYS) to the development of the easy-to-use Buprenorphine Sublingual Spray.

4.2. Buprenorphine Sublingual Spray Clinical Development Program

The development of Buprenorphine Sublingual Spray in the US was initiated by INSYS with submission of the IND on December 26, 2013. INSYS has conducted ten studies as part of the clinical development of the Buprenorphine Sublingual Spray consisting of seven Phase 1 pharmacokinetic studies, one open-label Phase 2 safety study, and two Phase 3 efficacy studies (Table 1). During the development, INSYS has met with the FDA twice and had several written communications to discuss the program and data collected. Clinical studies with Buprenorphine Sublingual Spray have included males, females, and a range of heights and weights. All subjects have been adults in these studies with an age range of 18 to 65 years. A total of 490 subjects have been exposed to Buprenorphine Sublingual Spray (various doses), of whom 217 have been exposed to the highest proposed dose of 0.5 mg without significant unusual or unexpected adverse reactions or safety concerns.

The chronological sequence of the postoperative studies is outlined in Figure 5.

Figure 5: Chronological Sequence of Phase 2 and Phase 3 Postoperative Studies

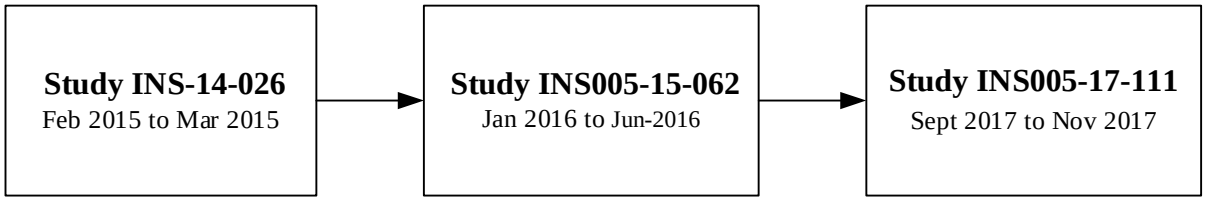


Table 1: Buprenorphine Sublingual Spray Clinical Development Program

Phase	Study No.	Purpose	Randomized	Completed	Patient/Study Model
Phase 1 [a]	INS-13-016	Relative bioavailability (fasted)	12	11	Healthy volunteers
	INS-13-020	Comparative bioavailability (fasted and fed)	18	18	Healthy volunteers
	INS005-14-032	Relative bioavailability	20	18	Healthy volunteers
	INS005-16-076	Dose proportionality	30	29	Healthy volunteers
	INS005-16-069	Temperature and pH effects	15	14	Healthy volunteers
	INS005-17-104	Comparative bioavailability (multiple dose, multiple day)	60	56	Healthy volunteers
	INS005-17-105	Comparative bioavailability (multiple dose, single day)	60	59	Healthy volunteers
Phase 2	INS005-17-111	Safety and tolerability	100	67	Abdomen Bunionectomy Breast augmentation
Phase 3	INS-14-026	Efficacy and safety	40 [b]	33	Bunionectomy pain
	INS005-15-062	Efficacy and safety (pivotal)	322	298	Bunionectomy pain

[a] Naltrexone 50 mg tablet was administered prior to study dose
[b] 312 projected
Source: Source: NDA209588, 2.5 Clinical Overview

5. BIOPHARMACEUTICS AND PHARMACOKINETICS

In summary, the seven PK studies in humans have established the pharmacokinetic characteristics of the Buprenorphine Sublingual Spray in comparison to the Listed Drugs, Buprenex® IV 0.3 mg Q6h and Buprenorphine Sublingual Tablet 8 mg QD (a generic version of Subutex® Sublingual Tablet), which are presented in Table 2. These studies demonstrated that plasma exposure of buprenorphine after single and multi-dose single-day/multiple day administration was lower than that after Buprenex IV 0.3 mg or Buprenorphine Sublingual Tablet 8 mg, and plasma exposure of norbuprenorphine, a major active metabolite of buprenorphine, was lower than that with Buprenorphine Sublingual Tablet 8 mg (Study INS-13-020, INS005-17-104, INS005-17-105). In addition, the effects of oral cavity temperature and pH on buprenorphine exposure were evaluated (Study INS005-16-069). Pretreatment with cold water, hot water, low pH or high pH beverages did not significantly buprenorphine C_{max} and AUC after administration of Buprenorphine Sublingual Spray, 0.5 mg. All subjects were blocked with naltrexone to reduce the incidence and severity of adverse events known to be associated with opioid administration. There were no serious adverse events, discontinuations due to adverse events, or deaths in these PK studies. Mean plasma buprenorphine concentrations after a single dose (Day 1) and multiple doses (Q8h up to Day 6) at 0.125, 0.25, 0.5 mg of Buprenorphine Sublingual Spray using the to-be-marketed (TBM) Formulation in heathy volunteers (HVs) are shown in Figure 6. Buprenorphine C_{max} and $AUC_{0\text{-}tau}$ values on Day 1 and Day 6 are summarized in Table 3 for comparison (Study INS005-17-104).

Table 2: Summary of Buprenorphine and Norbuprenorphine Pharmacokinetic Parameters Across Studies

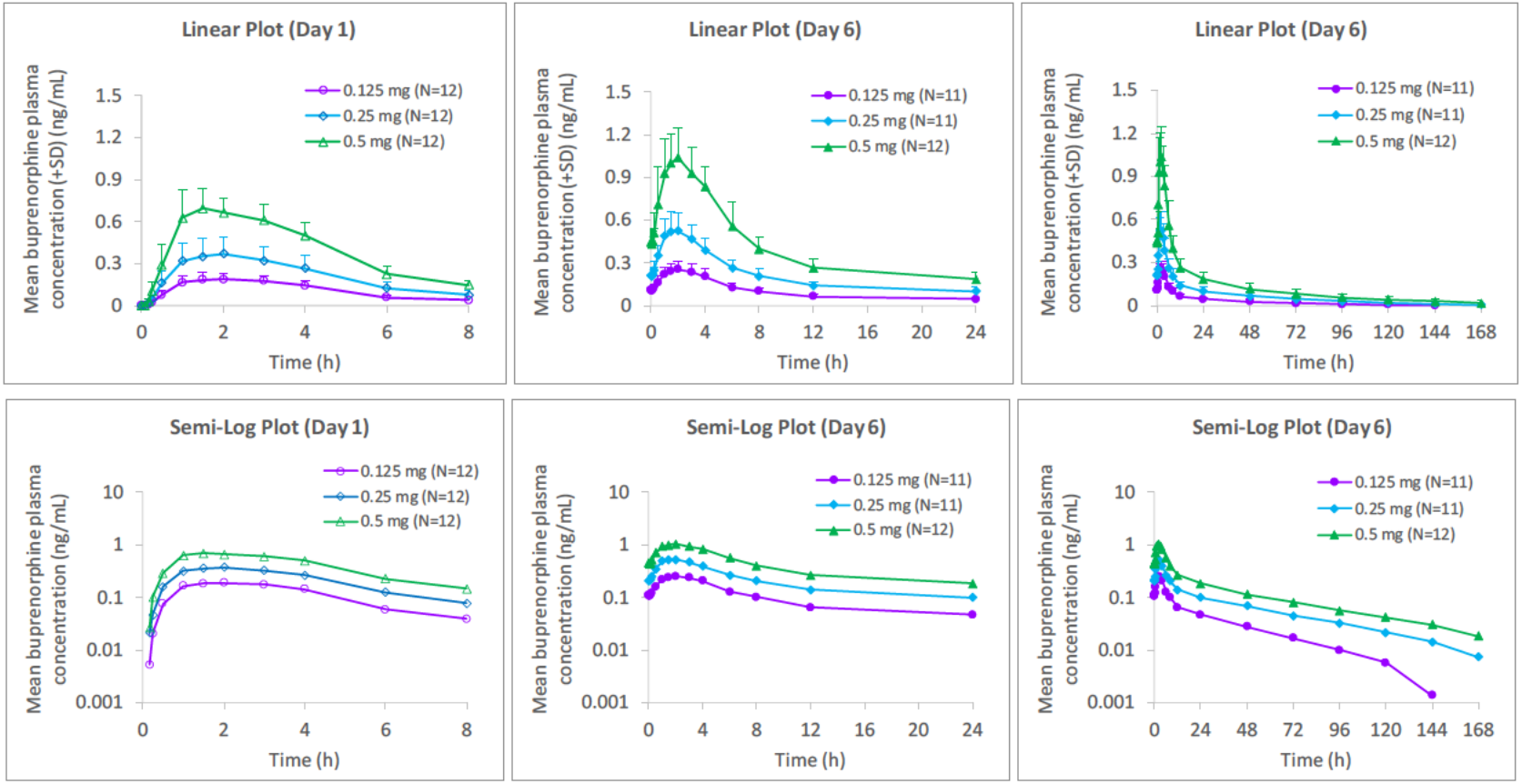
Study No.	Study	Formulation	N	Dose	Buprenorphine			Norbuprenorphine		
					C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	T_{max} (hrs)	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	T_{max} (hrs)
INS-13-016	Dose PK	Initial Formulation (multi-dose system)	12	0.5 mg (0.5 mg x 1 sprays)	0.76	4.81	1.75 [a]	0.05	2.63 [a]	6.00
				1.0 mg (0.5 mg x 2 sprays)	1.38	10.20	1.50 [a]	0.09	4.83 [a]	6.00
INS-13-020	Three-way Cross-over	Initial Formulation (multi-dose system)	18	1.0 mg single spray	1.20	8.19	1.50 [a]	0.11	6.57	3.00
				Buprenex® IM (0.3 mg/mL)	1.73	5.50	0.17	0.04	NC	1.00
				Buprenex® IV (0.3 mg/mL)	3.95[b]	5.51	0.08	0.25	2.93	0.33
INS005-14-032	Dose PK	Initial Formulation (unit-dose system)	20	0.5 mg single spray	0.66	4.52	1.43	0.06	4.37	6.48
				1.0 mg single spray	1.17	8.72	1.71	0.12	7.88	6.08
INS005-16-076	Parallel PK	To-be-marketed (TBM) Formulation	30	0.0625 mg single spray n=6	0.13	0.64	1.50 [a]	NC	NC	NC
				0.125 mg single spray n=5	0.22	1.13	1.50 [a]	NC	NC	NC
				0.25 mg single spray n=6	0.39	2.28 (n=5)	1.25 [a]	0.04 (n=3)	NC	2.00 [a] (n=3)
				0.5 mg single spray n=6	0.87	5.37 (n=4)	1.75 [a]	0.06 (n=5)	Not reported (n<2)	2.00 [a] (n=5)
				1.0 mg single spray n=6	1.57	11.36	1.50 [a]	0.10	Not reported (n<2)	3.75 [a]
INS005-16-069	Temp/ pH	TBM Formulation	15	0.5 mg single spray (cold water)	0.73	5.74	2.00 [a]	0.07	NC	4.00[a]
				0.5 mg single spray (hot water)	0.84	6.08	2.00 [a]	0.07	NC	4.00 [a]
				0.5 mg single spray (no pretreatment)	0.77	5.79	2.00 [a]	0.07	NC	4.00 [a]
				0.5 mg single spray (low pH water)	0.71	5.70	2.00 [a]	0.07	5.58	2.00 [a]
				0.5 mg single spray (high pH water)	0.76	5.87	2.00 [a]	0.06	NC	4.00 [a]

Study No.	Study	Formulation	N	Dose	Buprenorphine			Norbuprenorphine		
					C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	T_{max} (hrs)	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	T_{max} (hrs)
INS005-17-104	Multiple dose, multiple day PK (Day 6)	TBM Formulation	60	0.125 mg single spray, TID (16 sprays total), n=11	0.257	4.94	2 [a]	0.114	10.8 (n=5)	2.00 [a]
				0.25 mg single spray, TID (16 sprays total), n=11	0.543	11.6	2 [a]	0.186	10.7 (n=8)	2 [a]
				0.50 mg single spray, TID (16 sprays total), n=12	1.09	21.4	2 [a]	0.419	22.1	1.75 [a]
				Buprenex® IV (0.3mg /mL), QID (21 doses total), n=11	5.62	28.2	0.05 [a]	0.350	14.9 (n=7)	0.383 [a]
				Buprenorphine SL Tablet (8 mg), QD (6 doses total), n=11	4.43	76.7	2 [a]	3.93	188	1.00 [a]
INS005-17-105	Multiple dose, 24-hour PK (after the last dose)	TBM Formulation	60	0.125 mg single spray, TID, n=12 (3 sprays total)	0.218	4.24 (n=8)	10.0 [a]	0.0377	NC	24.0 [a] (n=7)
				0.25 mg single spray, TID, n=12 (3 sprays total)	0.501	9.94	13.5 [a]	0.0577	NC	24.0 [a]
				0.50 mg single spray, TID, n=12 (3 sprays total)	1.04	19.3	16.8 [a]	0.0941	NC	24.0 [a]
				Buprenex® IV (0.3mg /mL), Q4D, n=12 (4 doses total)	23.5	31.3	12.1 [a]	0.0789	NC	18.3 [a]
				Buprenorphine SL Tablet (8 mg), QD, n=12, (1 dose total)	3.80	37.0	2.00 [a]	0.870	48.4 (n=10)	7.92 [a]

a: median value

b: observed value at 5 minutes post dose

Figure 6: Mean Buprenorphine Plasma Concentration-Time Profiles on Day 1 (0-8h) after the First Dose and on Day 6 (0-24h, 0-168h) after the Last Dose of Buprenorphine Sublingual Spray Q8h



Source: CSR INS005-17-104

Table 3: Buprenorphine C_{max} and $AUC_{0\text{-}tau}$ Values on Day 1 and Day 6 after Q8h Doses of Buprenorphine Sublingual Spray

TID doses	Dose (mg)	C_{max} (ng/mL)	C_{max} / Dose (ng/mL/mg)	AUC0-tau (ng·h/mL)	AUC0-tau / Dose (ng·h/mL/mg)
Day 1	0.125	0.200	1.60	0.882	7.05
	0.25	0.380	1.52	1.70	6.82
	0.5	0.771	1.54	3.19	6.39
Day 6	0.125	0.257	2.06	1.42	11.3
	0.25	0.543	2.17	2.89	11.5
	0.5	1.09	2.18	5.85	11.7
Day 6 to Day 1 Ratio	0.125	**1.29**		**1.61**	
	0.25	**1.43**		**1.70**	
	0.5	**1.41**		**1.83**	

Source: CSR INS005-17-104

In summary, following Buprenorphine Sublingual Spray Q8h from 0.125 to 0.5 mg, plasma C_{max}, $AUC_{0\text{-}tau}$ of buprenorphine increased in a dose proportional manner on either Day 1 or Day 6. Steady state buprenorphine concentrations were achieved between Day 3 and Day 5. Accumulation ratio of buprenorphine C_{max} and $AUC_{0\text{-}tau}$ on Day 6 over Day 1 was within 1.5 and 2-fold, respectively.

6. EFFICACY

6.1. Overview

The clinical program builds on the established efficacy of buprenorphine in the treatment of pain by providing evidence of efficacy for Buprenorphine Sublingual Spray in acute pain. Buprenorphine is used for the treatment of both chronic (transdermal and buccal formulations) and acute (parenteral) pain. In an agreement reached with the Agency at the End-Of-Phase 2 meeting held on October 23, 2014, the 505(b)(2) New Drug Application for Buprenorphine Sublingual Spray is based on efficacy results of a single adequate, well-controlled trial, Study INS005-15-062, and is supported by the efficacy of the Listed Drug, Buprenex®, as described in its label and other efficacy data available in the public domain for other buprenorphine products.

The efficacy of Buprenorphine Sublingual Spray was assessed in two Phase 3 double-blind, randomized, placebo-controlled postsurgical bunionectomy studies, an initial study (Study INS005-14-026) and a pivotal study (Study INS005-15-062). Study 026 was initially designed as a pivotal trial but was stopped prematurely and the data established the maximum dose to be used in Study 062. Both Phase 3 studies were similar in design. Key inclusion criteria were male or female, between 18 to 65 years; baseline pain intensity rating of ≥4 on an 11-point (0-10) NRS during the 9-hour period after discontinuation of the sciatic block; classified using the American Society of Anesthesiologists Physical Status Classification System as P1 to P2; and body weight ≥45 kg, BMI ≤40 kg/m^2. Key exclusion criteria were clinically significant unstable cardiac, respiratory, renal, and/or hepatic conditions; long QT Syndrome, family history of long QT Syndrome, or was 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.

The rescue medications used and the rules for the two studies were:

- 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 I.V. or I.M. 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, the subject was to be discontinued.

The primary efficacy and related endpoints for the two studies were:

- The primary endpoint was the numerical rating scale summed pain intensity difference over 0 to 48 hours (NRS SPID-48).
- Secondary endpoints that directly support NRS SPID-48

- NRS SPID 0 to 4 hours (NRS SPID-4), 0 to 8 hours (NRS SPID-8), and 0 to 24 hours (NRS SPID-24).
- 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.

Pain intensity was measured on an 11-point numeric rating scale (NRS) at each specified time point. From these measures, pain intensity difference (PID) is calculated by subtracting the pain intensity at each time point from the pain intensity at time 0.

The summed pain intensity difference (SPID) was calculated by multiplying the PID score at each post dose time point by the duration (in hours) since the preceding time point and then summing these values over the relevant time period. The durations between nominal time points were calculated using the actual times of pain score measurement. If the actual time was missing the nominal planned time was used.

Additional secondary endpoints for the two studies were:

- Pain Relief Score (5 point categorical).
- Peak pain relief (ΔVAS).
- 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.

Statistical testing of the primary variable was done sequentially by dose to preserve overall alpha and there was no adjustment for multiplicity in the secondary endpoints. Therefore, all secondary outcomes are nominal. The secondary endpoints that directly support the SPID-48 were the SPID 4, 8, and 24, the pain intensity difference at each time point, and total pain relief, TOTPAR 4, 8, 24, and 48. Additional secondary endpoints further evaluated pain relief.

6.2. Statistical Methodology

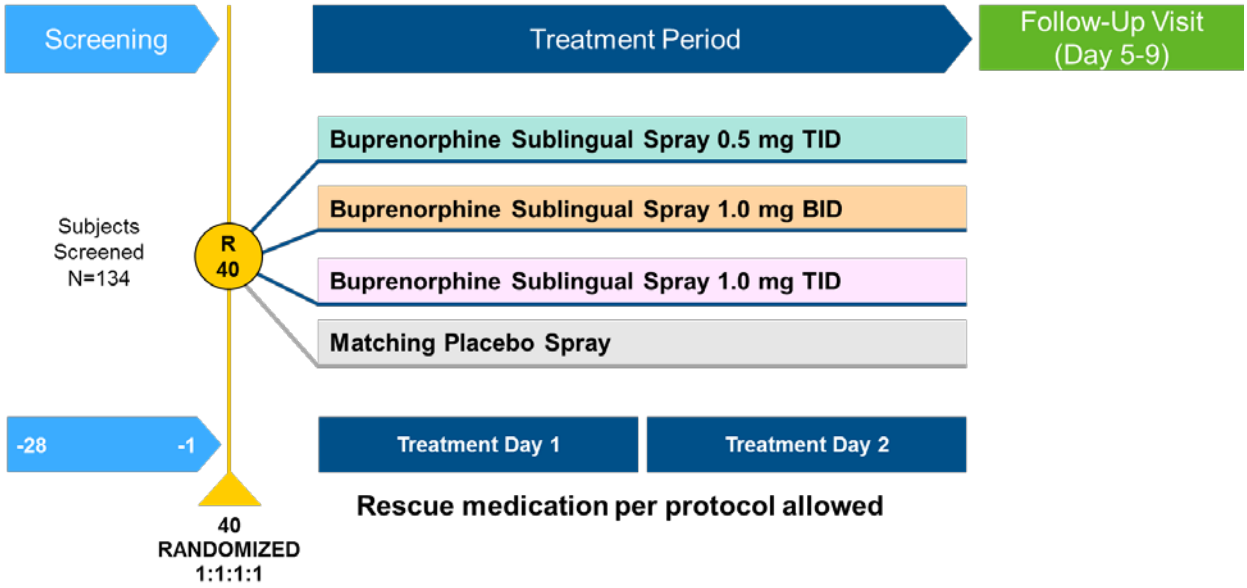
Testing of the primary efficacy variable SPID-48 was performed in a sequential fashion by dose to preserve the overall alpha=0.05. The primary comparison was Buprenorphine Sublingual Spray at 0.5 mg TID vs. placebo. If the primary comparison was statistically significant at alpha=0.05, then the SPID-48 for each of the other two doses against placebo was tested in the following order: 0.25 mg TID and 0.125 mg TID. Non-significance at any stage implied the end of formal testing and automatic non-significance for all subsequent comparisons.

In addition to a completers analysis, this document includes intent-to-treat analyses. One of them uses a repeated measures model and does not impute missing data due to dropouts. The dependent variable is pain intensity difference (PID), and statements within the model estimate SPID-48 as linear combinations of PID. This approach assumes data are missing at random (MAR). The second one is a missing not at random (MNAR) sensitivity analysis. It imputes data using a 'Jump to Reference' approach, in which missing data follow the trajectory of the placebo group, regardless of the randomized treatment. The dependent variable is again PID. Once complete datasets were created, SPID-48 was computed within subject, resulting in one SPID value per subject per imputation dataset. Each such dataset was then analyzed using the same model as the completers analysis, and the results across imputation datasets were combined using the usual Rubin's rules for multiple imputations. As an additional sensitivity analysis, we performed a non-parametric analysis in which non-completers were assigned a common SPID-48 values lower than any that was actually realized, with lower (less favorable) scores assigned to those who dropped out sooner than to those who remained on study longer. The particular numeric values imputed do not matter, because the nonparametric analysis takes into account only the relative ordering of data values.

6.3. Study INS005-14-026

Study 026 was a Phase 3, multicenter, randomized, double-blind, multiple-dose, parallel-group, placebo-controlled study to evaluate the efficacy and safety of up to four dosing regimens of Buprenorphine Sublingual Spray (0.5 mg TID, 1.0 mg BID, or 1.0 mg TID) and/or matching placebo in subjects with moderate to severe acute pain following bunionectomy (Figure 7). In this study 40 patients were randomized to one of three doses of sublingual buprenorphine or a matching placebo. The treatment period was 48 hours. Patients received blinded studied drug TID. Patients were admitted to the study site on the morning of the scheduled surgery on Day 0. They remained at the study site until post-op Day 3 for a total of 3 nights at the study site. They then returned for a follow-up visit 5-9 days after surgery.

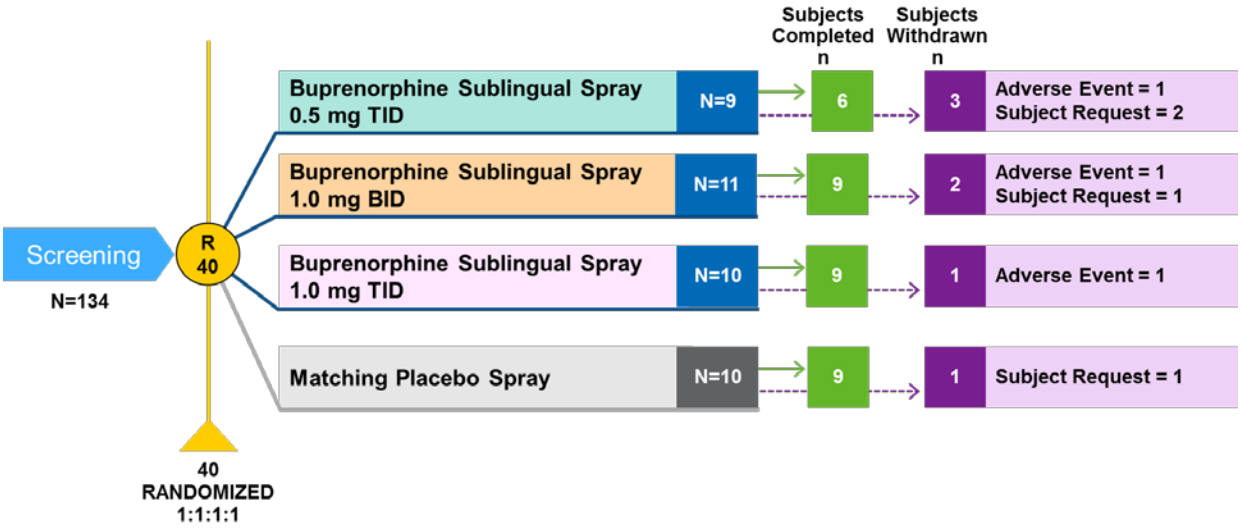
Figure 7: Study 026 Design Schematic



Planned enrollment was approximately 312 randomized subjects (78 subjects in each treatment group). However, the study was discontinued when 40 subjects had been randomized due to sedation events at higher doses. Thirty (30) subjects received sublingual doses of Buprenorphine Sublingual Spray and 10 subjects received sublingual doses of placebo during the 48-hour treatment period.

A summary of the disposition of all screened patients is provided in Figure 8. A total of 33 (82.5%) subjects completed study treatment and follow-up. Seven (17.5%) subjects discontinued treatment, of these 3 (7.5%) subjects completed follow-up and 4 (10.0%) subjects discontinued the study. There were 6 (20.0%) subjects in the Buprenorphine Sublingual Spray treatment groups, 3 subjects discontinued treatment due to AEs and 3 subjects withdrew from the study. One (10.0%) subject in the placebo group withdrew from the study.

Figure 8: Study 026 Disposition of Screened Subjects



Source: CSR INS-14-026, Table 14.1.1

The mean (standard deviation [SD]) age of subjects in the safety population ranged from 40.5 (13.5) for placebo group subjects to 48.0 (12.1) years for the 0.5 mg TID group subjects. A higher proportion of patients overall were women (80.0%), and nearly all subjects were White or African American (60.0% and 35.0%, respectively). There were no substantial differences between the treatment groups with regard to age, sex, or race (Table 4).

Table 4: Study 026: Demographics

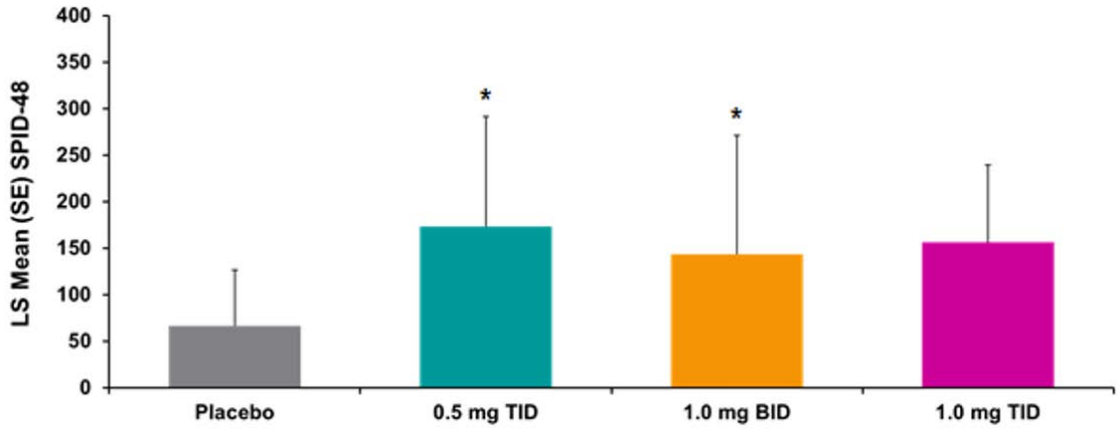
Parameter	Category	Placebo N=10	0.5 mg TID N=9	1 mg BID N=11	1 mg TID N=10
Race, n (%)	American Indian or Alaska Native	0	0	0	0
	Asian	0	0	2 (18.2)	0
	Black or African American	4 (40)	3 (33.3)	4 (36.4)	3 (30)
	Native Hawaiian or Other Pacific Islander	0	0	0	0
	White	6 (60)	6 (66.7)	5 (45.5)	7 (70)
	Other	1 (1)	0	0	0
	Unknown or Missing	0	0	0	0
Ethnicity, n (%)	Not Hispanic or Latino	8 (80)	7 (77.8)	10 (90.9)	5 (50)
	Hispanic or Latino	2 (20)	2 (22.2)	1 (9.1)	5 (50)
Gender, n (%)	Female	9 (90)	7 (77.8)	9 (81.8)	7 (70)
	Male	1 (10)	2 (22.2)	2 (18.2)	3 (30)
Age (Years)	Mean (SD)	40.5 (13.5)	48.0 (12.1)	43.5 (14.3)	40.8 (11.2)

Source: CSR INS-14-026

All doses studied demonstrated efficacy relative to placebo based on reductions in the primary endpoint NRS SPID-48. The mean SPID-48 was 260% higher, 216% higher, and 236% higher for the 0.5 mg TID, 1.0 mg BID and 1.0 mg TID doses, respectively, compared to placebo. Despite the decreased power due to the reduced sample size (40 subjects randomized versus the planned 312 subjects) and small number of subjects in each treatment group (9 to 11 subjects per group), statistically significantly larger NRS SPID-48 scores were observed relative to placebo (least squares [LS] mean difference [standard error, SE]) for the 0.5 mg TID (104.97 [39.24], p=0.012) and 1.0 mg BID (86.31 [37.53], p=0.028) groups (Figure 9). The largest NRS SPID-48 compared to placebo was observed for the 0.5 mg TID group.

The results of this study also indicated that while Buprenorphine Sublingual Spray was effective in reducing the postoperative pain associated with the bunionectomy procedure, doses greater than 0.5 mg TID did not result in greater efficacy. These results were used to guide the dose selection for the pivotal Study 062.

Figure 9: Study 026 Primary Endpoint: LS Mean (SE) NRS SPID-48 Scores

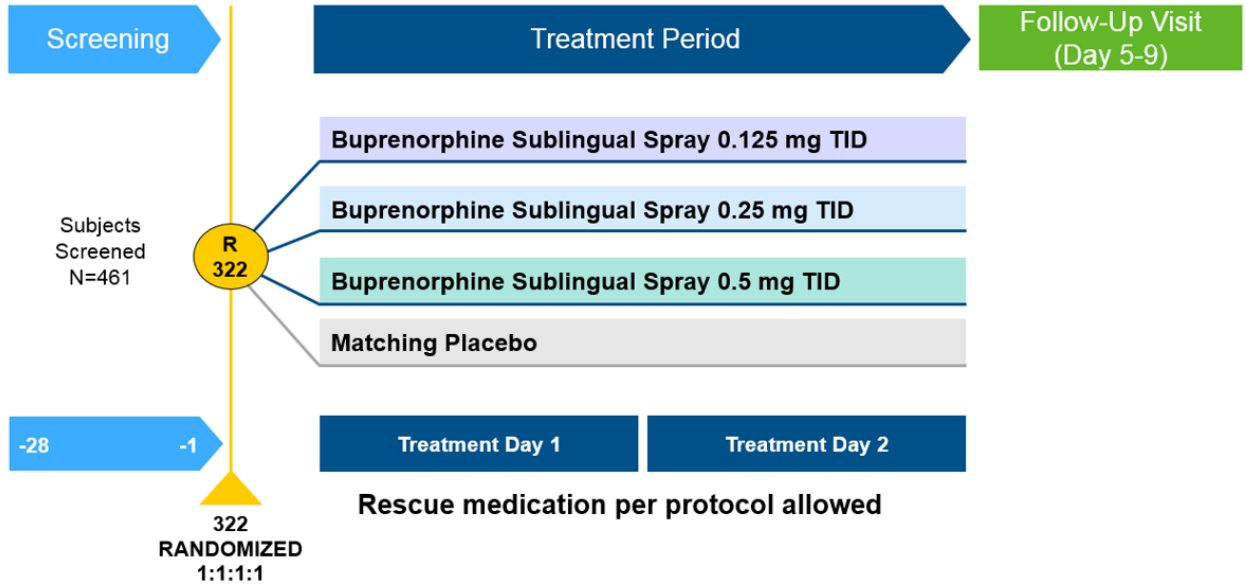


* $p < 0.05$
Source: CSR INS-14-026, Table 14.2.1

6.4. Study INS005-15-062

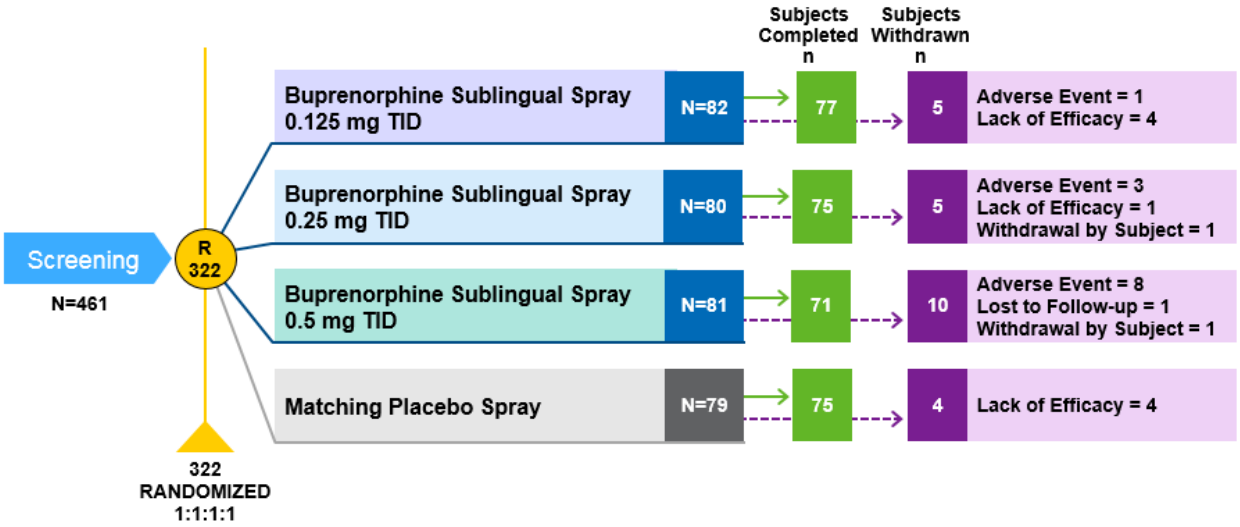
Study 062 was a Phase 3, randomized, double blind, multiple dose, parallel group, placebo controlled study of Buprenorphine Sublingual Spray (0.5 mg TID, 0.25 mg TID, and 0.125 mg TID) for the treatment of moderate to severe acute pain, in patients who had undergone a bunionectomy. The design of this study was the same as Study 026 except for the doses used (Figure 10).

Figure 10: Study 062: Design Schematic



A total of 322 patients signed informed consent and were randomized in the study of which 298 (92.5%) patients completed the study. Of the 24 (7.5%) subjects not completing the study, the most common reason for discontinuation in a total of 12 subjects was an AE (8 in 0.5 mg, 3 in 0.25 mg, 1 in 0.125 mg, 0 in placebo); other reasons for discontinuation included lack of efficacy (a total of 9 subjects: 4 in placebo, 4 in 0.125 mg, 1 in 0.25 mg, and 0 in 0.5 mg), withdrawal by subject not associated with AEs (a total of 2 subjects; 1 in 0.25mg, 1 in 0.5 mg), and loss to follow up (1 subject in 0.5 mg) (Figure 11).

Figure 11: Study 062: Disposition of Screened Subjects



Source: CSR INS005-15-062, Table 14.1.1

The mean (standard deviation [SD]) age of subjects in the safety population overall was 45.7 (13.2) years, and ranged from 18 to 65 years. A higher proportion of patients overall were women (78.9%), and nearly all subjects were White or African American (68.9% and 24.2%, respectively). There were no substantial differences between the treatment groups with regard to age, sex, or race. Similarly, there were no substantial differences between the treatment groups with regard to duration of bunionectomy surgery (overall mean [SD] 0.52 [0.25] hours) or baseline pain intensity (overall mean [SD] pain intensity score 6.5 hours [1.8]). There were no substantial differences between the treatment groups with regard to medical and surgical history, prior or concomitant medications, or other baseline characteristics (Table 5).

Table 5: Study 062: Demographic and Baseline Characteristics

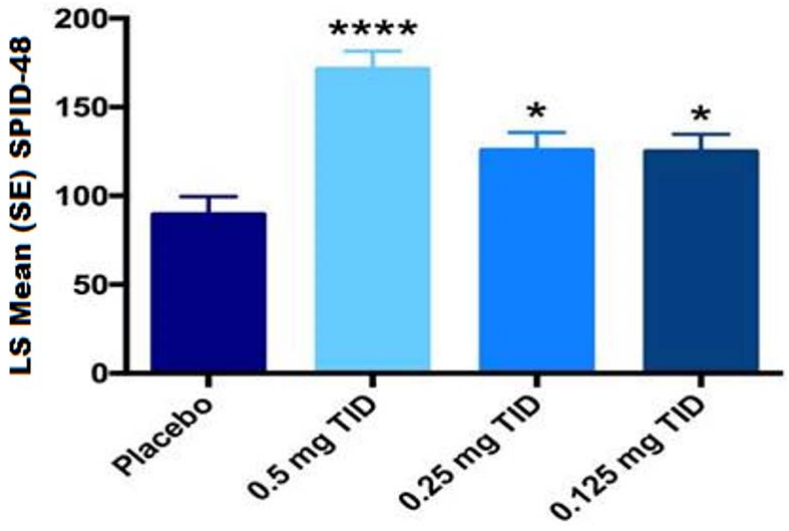
	Placebo n=79	0.125 mg TID n=82	0.25 mg TID n=80	0.5 mg TID n=81
Age, mean (SD)	45.3 (14.55)	48.4 (11.75)	45.6 (11.78)	43.7 (14.17)
Male, n (%)	16 (20.3)	19 (23.2)	16 (20.0)	17 (21.0)
Race, n (%)				
White	53 (67.1)	59 (72.0)	49 (61.3)	61 (75.3)
Black or African America	18 (22.8)	20 (24.4)	22 (27.5)	18 (22.2)
American Indian or Alaska Native	1 (1.3)	2 (2.4)	0	0
Hawaiian or other Pacific Islander	0	0	2 (2.5)	0
Asian	4 (5.1)	1 (1.2)	4 (5.0)	2 (2.5)
Other	1 (1.3)	0	2 (2.5)	0
Multiple	2 (2.5)	0	1 (1.3)	0
Hispanic or Latino Ethnicity, %	13 (16.5)	17 (20.7)	10 (12.5)	15 (18.5)
Surgery duration (hours), mean (SD)	0.50 (0.21)	0.53 (0.22)	0.50 (0.20)	0.53 (0.34)
Baseline pain intensity, mean (SD)	6.4 (1.85)	6.7 (1.87)	6.3 (1.82)	6.6 (1.79)

Source: CSR INS005-15-062, Table 14.1.2

6.4.1. Primary Efficacy Endpoint

This pivotal study of Buprenorphine Sublingual Spray met the primary endpoint of the SPID-48 score for all doses studied. All dose levels met statistical significance for superiority over placebo for the primary endpoint. The mean SPID-48 scores for subjects who received Buprenorphine Sublingual Spray of any dose were statistically significantly higher than for those who received placebo (Figure 12). Subjects receiving placebo had a mean (SD) SPID-48 score of 93.40 (85.06) compared with 135.84 (114.04), 125.75 (102.25), and 182.81 (107.35) for the 0.125 mg, 0.25 mg, and 0.5 mg Buprenorphine Sublingual Spray groups, respectively. The 0.5 mg group had the highest SPID-48 score, and both 0.25 mg and 0.125 mg groups demonstrated similar efficacy. The least-squares mean (SE) differences in SPID-48 scores from placebo were 35.46 (14.02; p=0.012), 36.18 (14.10; p=0.011), and 81.93 (14.28; p<0.0001) for the 0.125 mg, 0.25 mg, and 0.5 mg Buprenorphine Sublingual Spray groups, respectively.

Figure 12: Study 062 Primary Efficacy Endpoint: LS Mean (SE) SPID-48 Scores



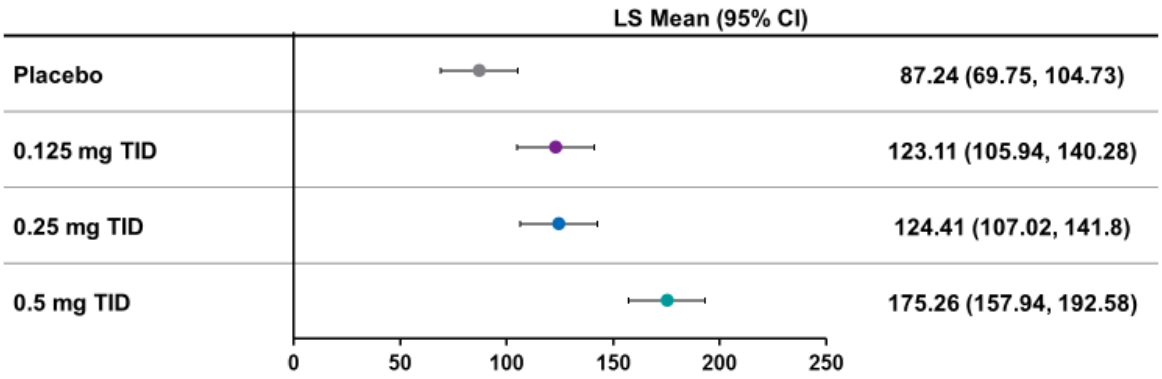
* $p < 0.05$, **** $p < 0.0001$
Source: CSR INS005-15-062, Table 14.2.1

An intent-to-treat (ITT) analysis of the primary efficacy endpoint, SPID-48, was performed without imputation of missing data. The results show the same pattern of response to the various doses as does the completers analysis (Table 6 and Figure 13). This ITT analysis was implemented using a repeated measures model with pain intensity difference (PID) as dependent variable and model factors for treatment, time, the interaction of treatment and time, study site, and the baseline pain intensity (PI) as a covariate.

Table 6: ITT Analysis of SPID-48 (Study 062)

Statistic	Placebo	Buprenorphine Sublingual Spray		
		0.5 mg	0.25 mg	0.125 mg
Least-squares mean (SE)	87.2415 (8.9228)	175.26 (8.8349)	124.41 (8.8711)	123.11 (8.7585)
95% CI	69.7496, 104.73	157.94, 192.58	107.02, 107.02	105.94, 140.28
Comparison	**Least-squares mean differences (SE)**		**95% CI**	**p-value**
0.5 mg vs. placebo	88.0179 (12.4586)		63.5945, 112.44	<0.0001
0.25 mg vs. placebo	37.1676 (12.4504)		12.7603, 61.5749	0.0028
0.125 mg vs. placebo	35.8714 (12.4031)		11.5566, 60.1861	0.0038

Figure 13: Missing at Random Analysis Without Imputation - SPID-48 (ITT Population)

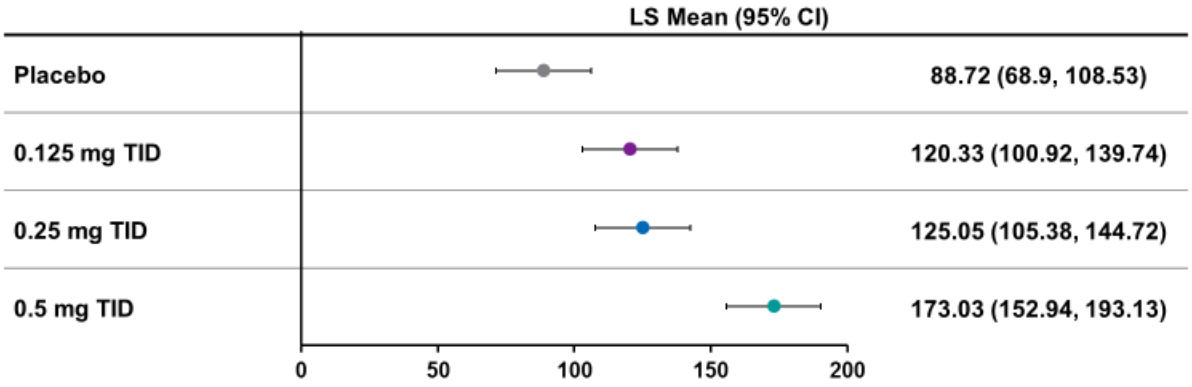


A sensitivity analysis was performed assuming pain response after dropout follows the placebo pattern, regardless of treatment assignment. This was a multiple imputation analysis using the ITT patient population. The results confirm those of the completers analysis (Table 7 and Figure 14). The imputation step of this analysis was carried out with pain intensity difference (PID) as the dependent variable. One hundred datasets were created, resulting in complete data (actual or imputed) for each subject; then SPID-48 was calculated within subject. Each such dataset was then analyzed using the same model as the completers analysis, and the 100 sets of results were combined using the usual Rubin's rules for multiple imputations.

Table 7: Sensitivity Analysis: Multiple Imputation for SPID-48

Statistic	Placebo	Buprenorphine Sublingual Spray		
		0.5 mg	0.25 mg	0.125 mg
Least-squares mean (SE)	88.72 (10.110)	173.03 (10.252)	125.05 (10.037)	120.33 (9.904)
95% CI	68.90, 108.53	152.94, 193.13	105.38, 144.72	100.92, 139.74
Comparison	**Least-squares mean differences (SE)**		**95% CI**	**p-value**
0.5 mg vs. placebo	84.32 (14.259)		56.37, 112.27	<0.0001
0.25 mg vs. placebo	36.33 (14.023)		8.85, 63.82	0.0096
0.125 mg vs. placebo	31.62 (13.964)		4.25, 58.99	0.0236

Figure 14: Sensitivity Analysis: Multiple Imputation - SPID-48 (Treatment Population)



ITT Analysis of Last SPID Carried Forward

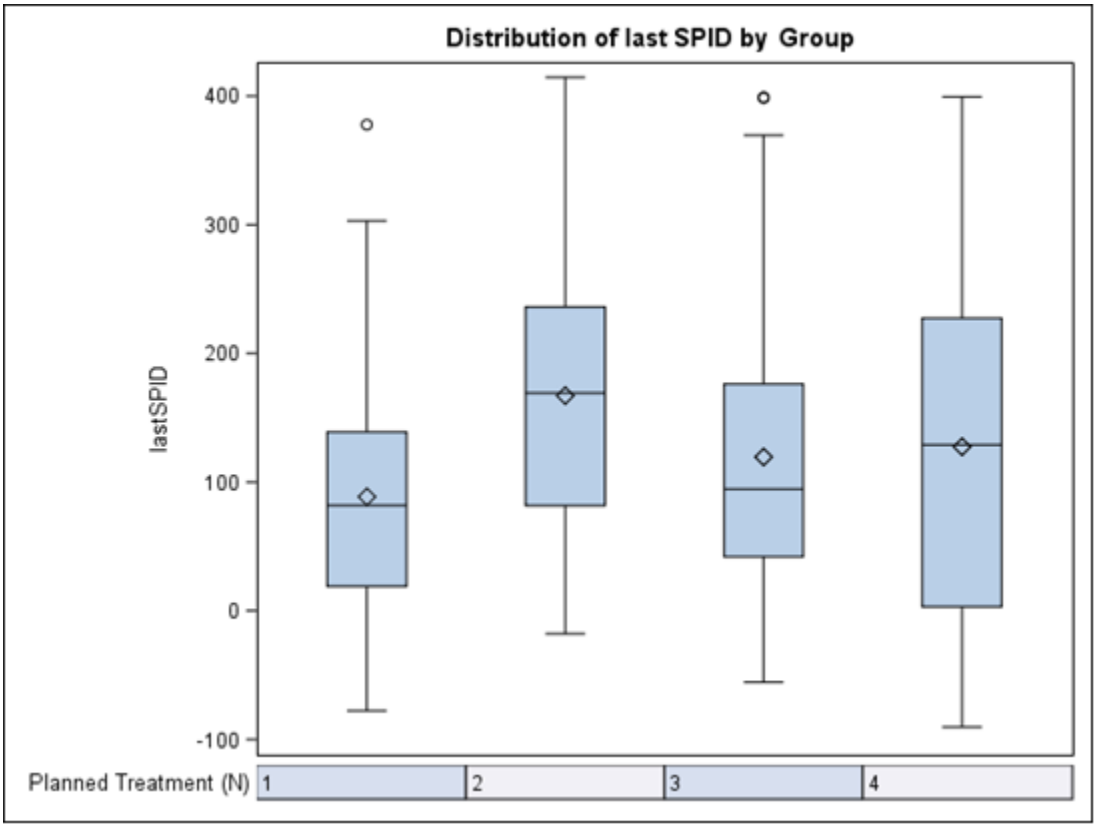
An additional ITT analysis of SPID-48 was performed by imputing, for subjects without sufficient actual data to determine SPID-48, the SPID value at the last time point at which a SPID could be calculated. In effect, this is an analysis of last SPID carried forward. Least squares means for each treatment arm and least-squares means differences are as follows (Table 8):

Table 8: Sensitivity Analysis: Last SPID Carried Forward (Study 062)

Statistic	Placebo	Buprenorphine Sublingual Spray		
		0.5 mg	0.25 mg	0.125 mg
Least-squares mean (SE)	83.74 (10.015)	157.28 (9.859)	117.10 (9.958)	117.58 (9.802)
95% CI	64.04, 103.45	137.88, 176.68	97.51, 136.70	98.30, 136.87
Comparison	**Least-squares mean differences (SE)**		**95% CI**	**p-value**
0.5 mg vs. placebo	73.54 (13.935)		46.12, 100.95	<0.0001
0.25 mg vs. placebo	33.36 (13.963)		5.89, 60.83	0.0175
0.125 mg vs. placebo	33.84 (13.894)		6.50, 61.18	0.0154

The last SPID carried forward data are shown in the following boxplot (Figure 15).

Figure 15: Distribution of Last SPID by Dose Group



Treatment 1 = Placebo, 2 = 0.5 mg, 3 = 0.25 mg, 4 = 0.125 mg

The descriptive statistics used for the plot, excluding the two outliers (circles) below are:

Table 9: Box Plot Descriptive Statistics

Planned Treatment	N Obs	Minimum	Lower Quartile	Mean	Upper Median	Quartile	Maximum
Placebo	79	-77.7	19.0	88.6	81.9	139.0	377.8
0.5 mg	81	-17.8	81.7	167.2	169.2	236.0	414.6
0.25 mg	80	-55.5	42.0	119.5	94.6	176.1	399.0
0.125 mg	82	-90.5	3.1	127.5	129.0	227.4	399.4

6.4.2. Secondary Efficacy Endpoints

In addition to the statistically significant difference of the primary efficacy endpoint of SPID-48, the secondary endpoints consistently support both the efficacy and clinical relevance of the primary efficacy results.

SPID and TOTPAR were nominally better than placebo in all dose groups across all the time points. Ascending dose groups have increasing time to first use of rescue medication and decreasing use of rescue medication. So, while there were no perceptible differences between the SPID-48 scores for the 0.125 and 0.25 mg doses, there are differences in some secondary endpoints, and the higher use of ketorolac rescue medication in the 0.125 dose may explain the lack of separation on pain endpoints. Less rescue medication was used in 0.125 vs. placebo prior to 8 hours.

The figures below illustrate that these secondary endpoints were more favorable for all Buprenorphine Sublingual Spray doses studied (Figure 16, Figure 17, and Figure 18). These data support the primary efficacy endpoint that all three doses were efficacious in the bunionectomy pain model. After the figures, each of the secondary endpoints is discussed in greater detail.

Figure 16: Time to Event Endpoints, 0.5 mg versus Placebo

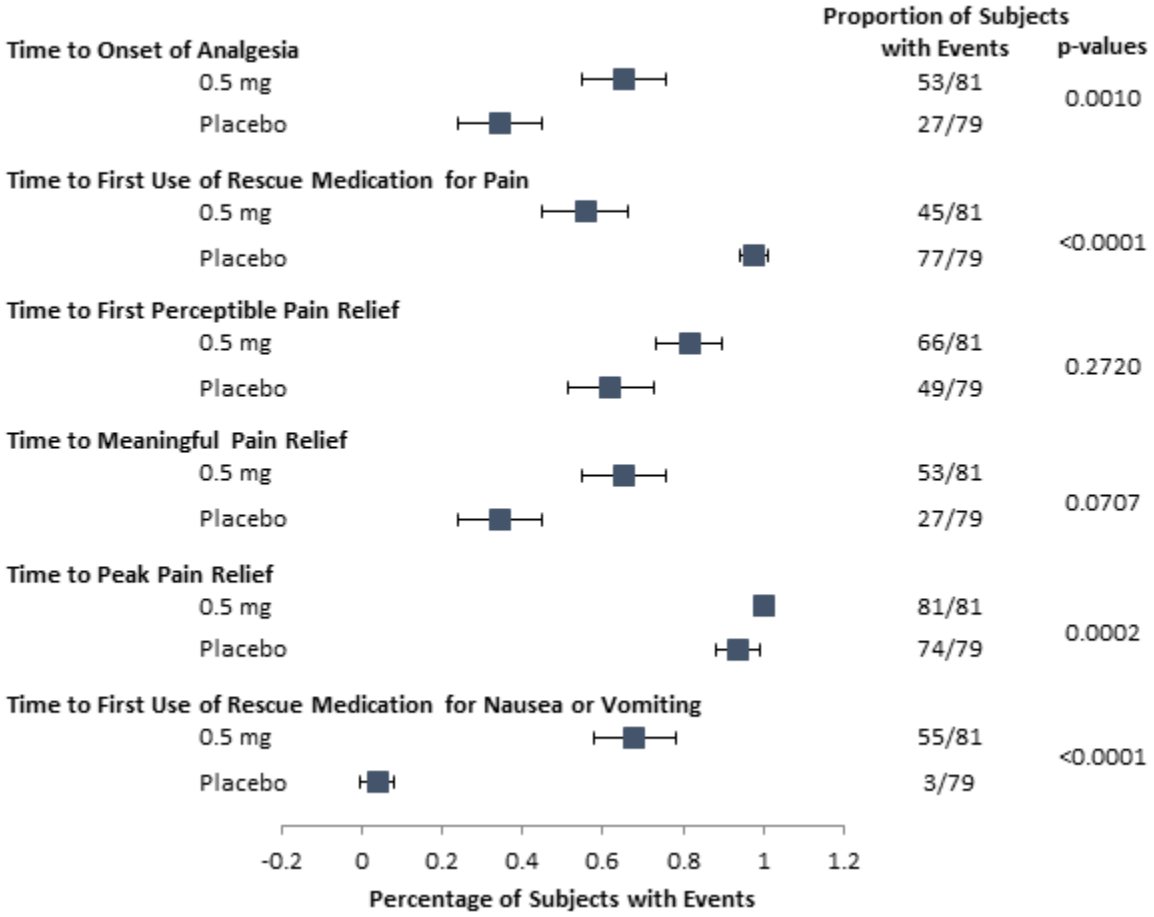


Figure 17: Time to Event Endpoints, 0.25 mg versus Placebo

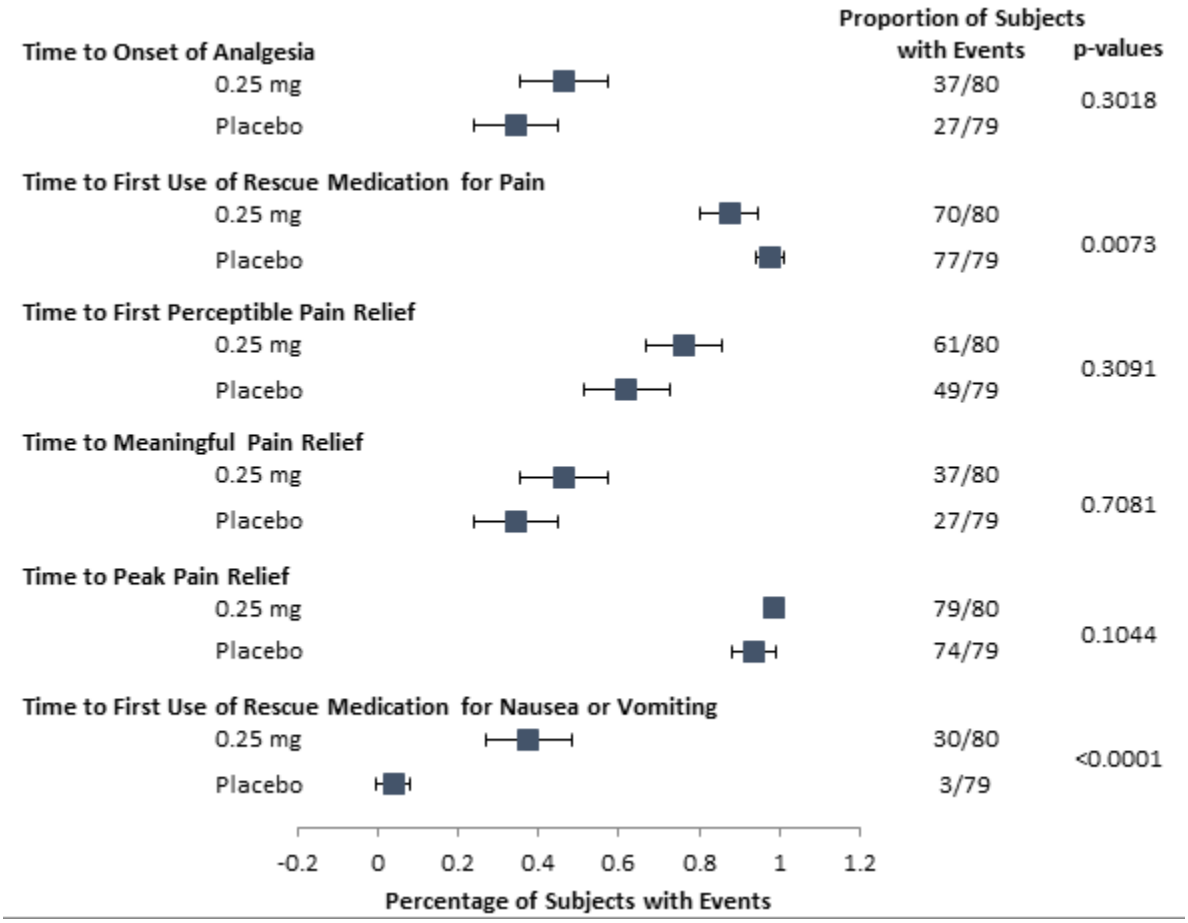
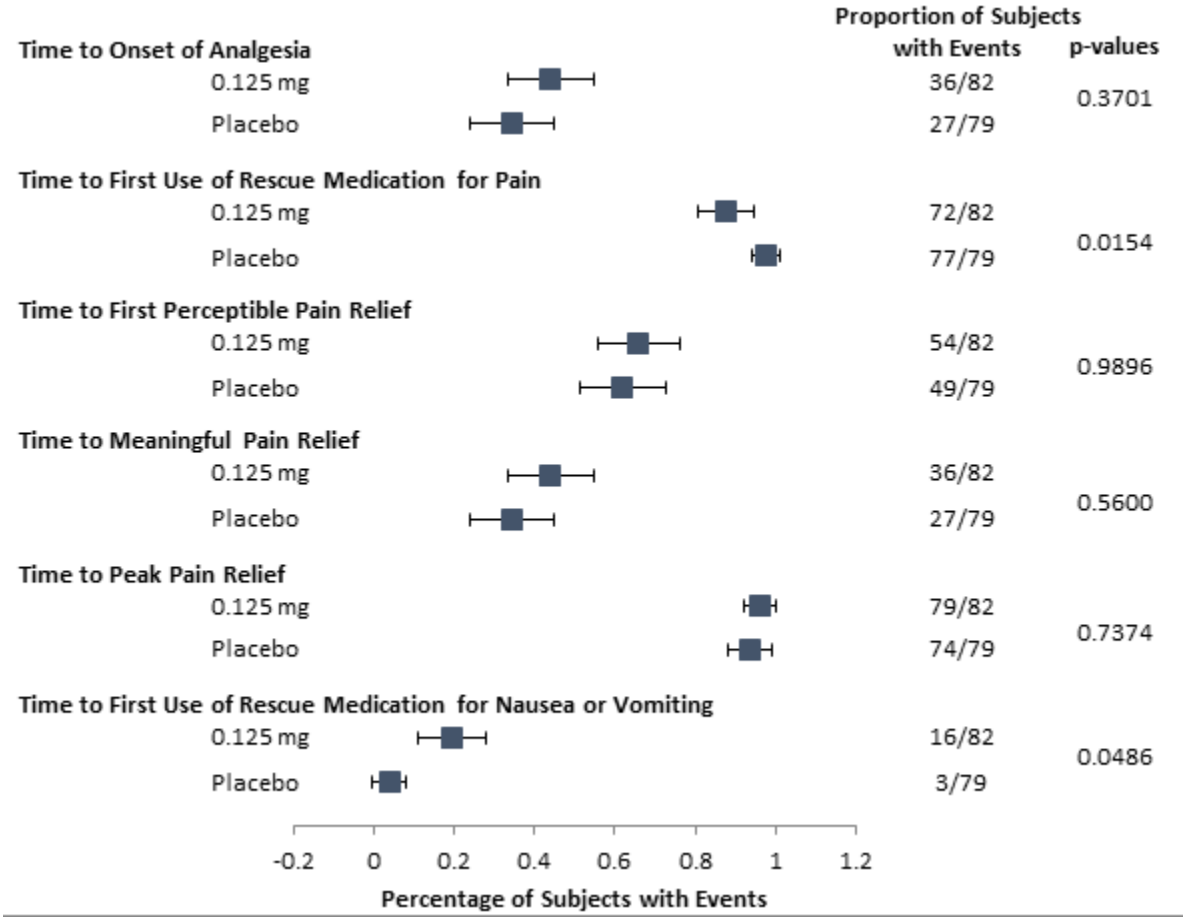


Figure 18: Time to Event Endpoints, 0.125 mg versus Placebo



Time to first perceptible pain relief and time to meaningful pain relief were based on stop watches. A failure to stop the watches before intervening events, like taking of rescue medication or receiving the second dose of study medication, was treated as censoring at the time of the intervening event. However, these intervening events are more related to the endpoint than non-informative censoring events would be. For example, the need for rescue medication is informative, in that it indicates the opposite of either perceptible or meaningful pain relief. It may therefore be more appropriate to treat these events as competing risks.

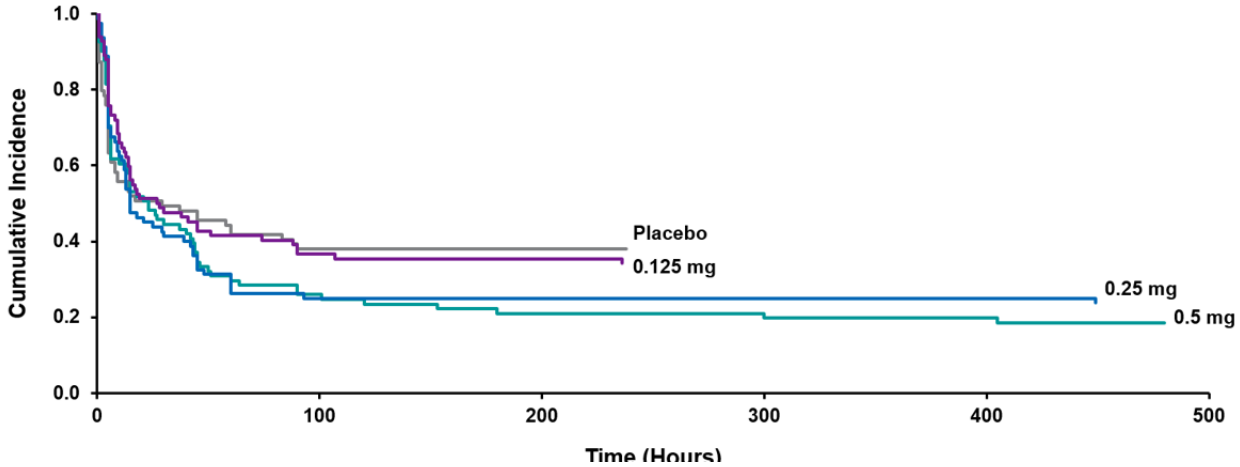
A competing risk approach for the analysis of time to first perceptible pain relief and time to meaningful pain relief is presented here. The probability of achieving pain relief was estimated by the cumulative incidence function rather than by the survival function, and BSL treatments were compared to placebo using Gray's test rather than with the log-rank test.

6.4.2.1. Time to Perceptible Pain Relief

The median time to first perceptible pain relief was 29.0 minutes in the placebo group compared with 27.0, 15.0, and 23.0 minutes in the 0.125 mg, 0.25 mg, and 0.5 mg groups, respectively. In

the placebo group 62% experienced pain relief after the first dose compared to 65.9% in the 0.125 mg group, 76.3% in the 0.25 mg, and 81.5 % in the 0.5mg Buprenorphine Sublingual Spray dose groups Figure 19.

Figure 19: Time to Perceptible Pain Relief



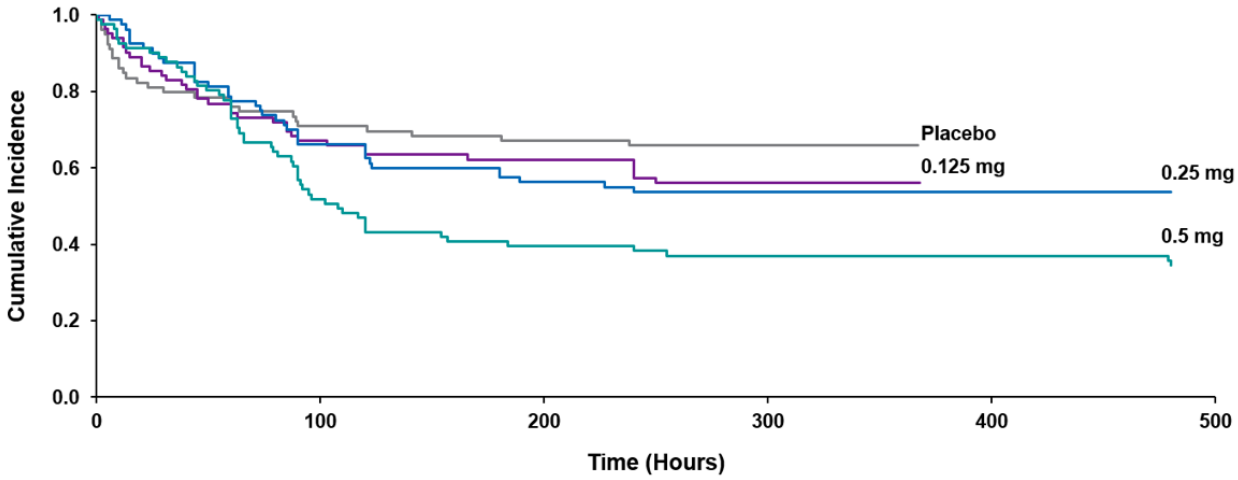
Source: CSR INS005-15-062, Table 14.2.17

6.4.2.2. Time to Meaningful Pain Relief

The median time to meaningful pain relief was 238.0 minutes in the placebo group compared with 166.0, 122.0, and 92.0 minutes in the 0.125 mg, 0.25 mg, and 0.5 mg groups, respectively, indicating that 50% of subjects in each treatment group had achieved meaningful pain relief at those times (Figure 20).

The time to meaningful pain relief shown with the study doses (0.125 mg, 0.25 mg and 0.5 mg) in the present study is generally consistent with the time to meaningful pain relief shown in other available acute pain medications in bunionectomy settings.

Figure 20: Median Time to Meaningful Pain Relief

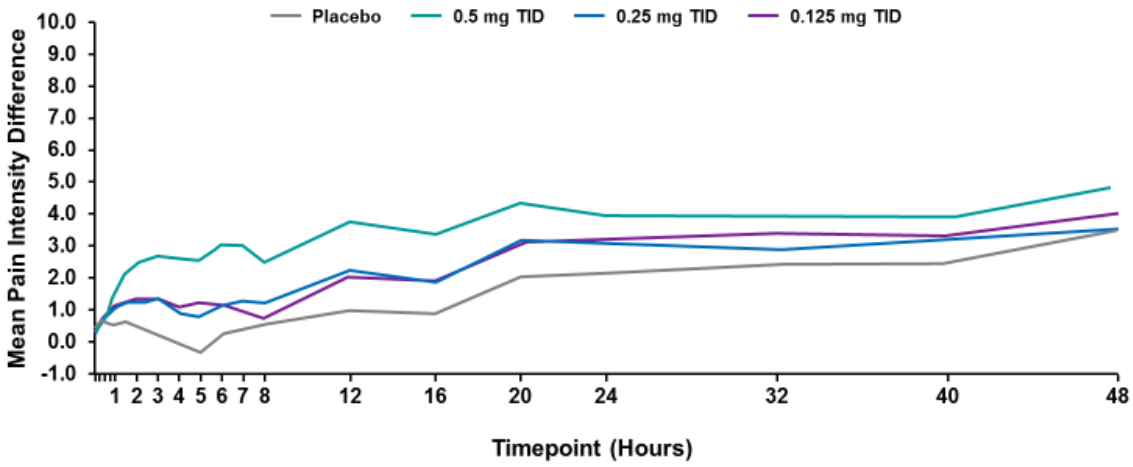


Source: CSR INS005-15-062, Table 14.2.18

6.4.2.3. Pain Intensity

Mean pain intensity scores were similar at baseline between the placebo group and the Buprenorphine Sublingual Spray groups. Scores in all three Buprenorphine Sublingual Spray groups decreased quickly after the start of dosing while placebo group scores decreased more slowly. The scores in the Buprenorphine Sublingual Spray groups remained noticeably lower than placebo until the 48-hour time point. The 0.125 mg and 0.25 mg groups showed comparable decreases in pain intensity scores. These effects are also shown in mean pain intensity differences (Figure 21).

Figure 21: Mean Pain Intensity Difference by Time Point and Treatment: Study 062



While the Pain Intensity Difference (PID) does not separate, the separation appears to decline at 8 hours between the 0.125 mg dose and placebo, this slight “dip” of mean pain intensity difference at timepoints close to dosing time is consistent with the pain intensity curves shown

with other available pain medications. This is likely due to the higher use of rescue medication in the placebo group, in particular, a high rate of ketorolac rescue.

6.4.2.4. Rescue Medication Use

During the study, ibuprofen 400 mg was allowed orally every 4 to 6 hours for up to 2400 mg/day as rescue medication. If subjects were unable to tolerate 400 mg ibuprofen or if there was insufficient pain relief, then 30 mg of ketorolac tromethamine (e.g., Toradol®) could be administered intravenously or intramuscularly every 6 to 8 hours for up to 90 mg/day as needed for pain.

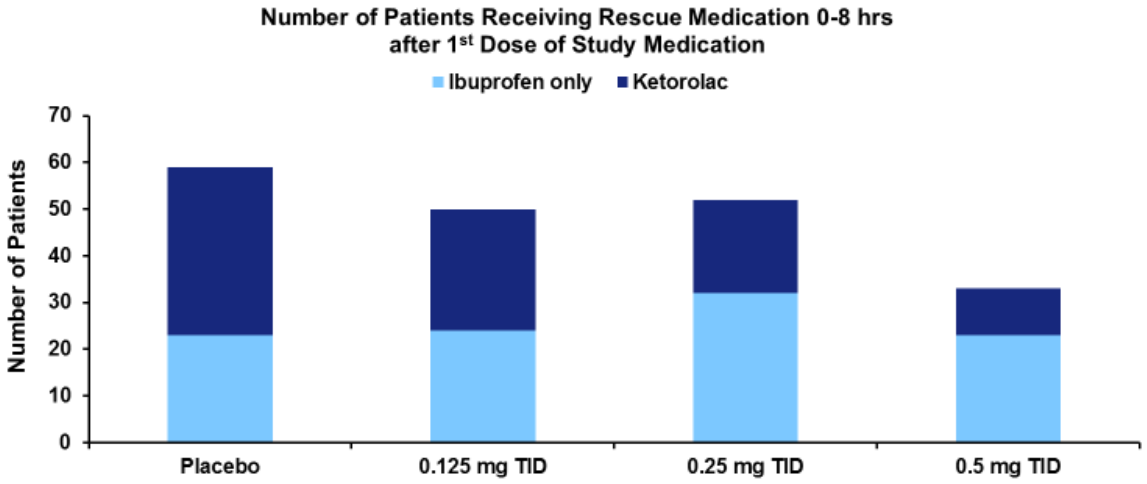
Fewer subjects needed rescue medication for pain within 8 hours for the 0.25 mg TID and 0.5 mg TID doses, and by 24 hours for all doses compared to placebo (Table 10), with nominal p-values for all comparisons below 0.05. The number of subjects receiving no rescue medication, ibuprofen, and ketorolac within 8 hours after the first dose of study medication is summarized in Figure 22. Use of any rescue medication in the first 8 hours decreased with increasing doses, and use of ketorolac in the first 8 hours decreased with increasing doses. Overall, rescue medication was utilized by a smaller percentage of subjects receiving buprenorphine compared to the placebo group with p-values below 0.05. The results were as follows: 0.5 mg TID dose (55.6% vs. 97.5 %, $p < 0.0001$), for the 0.25 mg TID dose (87.5% vs. 97.5%, $p = 0.027$), and for the 0.125 mg TID dose (87.8% vs. 97.5%, $p = 0.021$).

Table 10: Mean (SD) Doses of Rescue Medications Within 8 Hours, 24 Hours and 48 Hours from Time 0

Treatment	8 Hour	24 Hour	48 Hour
Placebo	1.97 (0.84)	3.40 (2.20)	4.55 (3.87)
0.125 mg TID	1.80 (0.74), p = 0.25	2.77 (1.80), p = 0.05	3.57 (2.82), p = 0.07
0.25 mg TID	1.67 (0.80), p = 0.05	2.44 (1.71), p = 0.004	3.42 (2.76), p = 0.04
0.5 mg TID	1.48 (0.83), p = 0.006	2.18 (1.72), p = 0.002	2.86 (2.85), p = 0.006

Source: CSR INS005-15-062, Post-hoc analysis, Tables 3.3A, 3.3B, 3.3C
Note: p-values for comparisons with placebo.

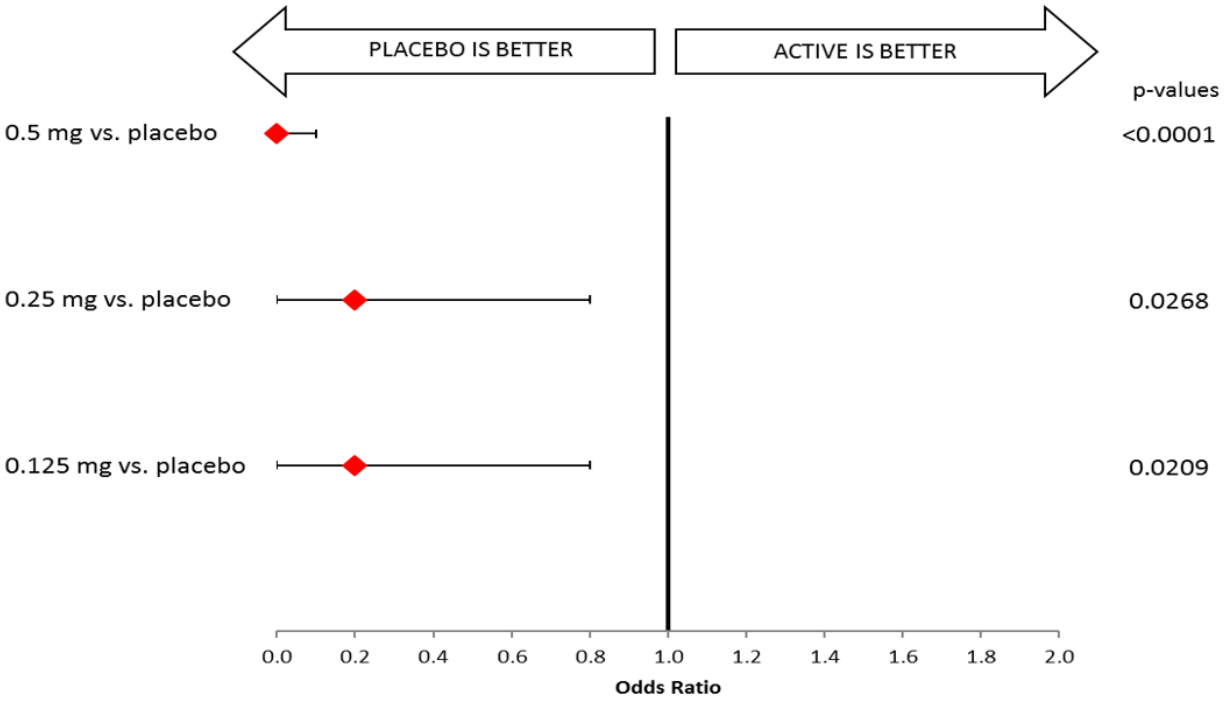
Figure 22: Study 062: Rescue Medication Within 8 Hours



Source: CSR INS005-15-062, Post hoc analysis.

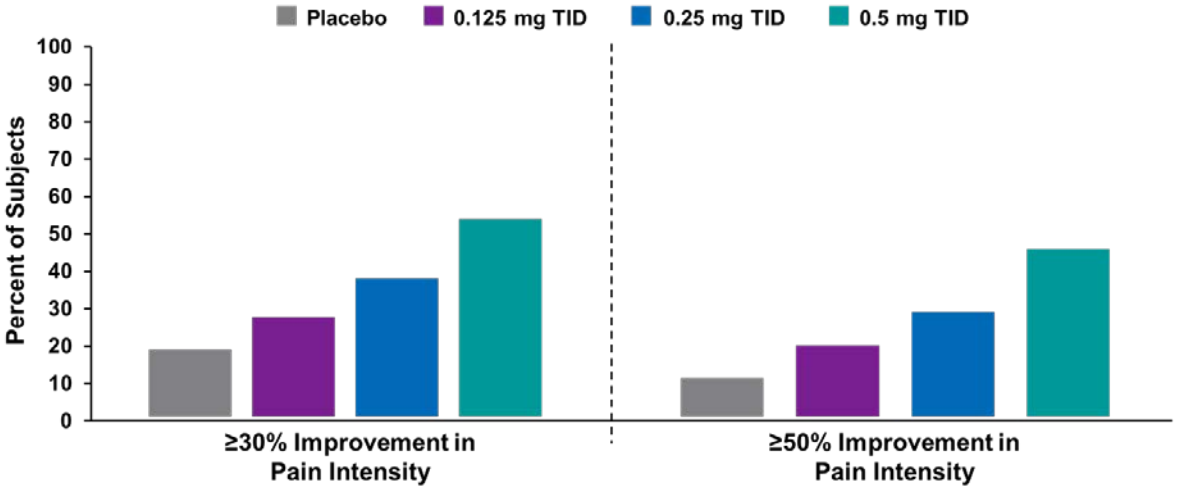
When reviewing the data concerning the use of rescue medication, INSYS also evaluated the odds ratio for receiving rescue medication by dose, which are presented below.

Figure 23: Odds Ratio for Total Use of Rescue Medication



For clinically meaningful improvements of at least 30% and at least 50% decrease in pain intensity, there was a consistent dose relationship with higher percentages of patients achieving these levels of pain relief at 8 hours for all three doses of Buprenorphine Sublingual Spray, including the 0.125 mg dose (Figure 24).

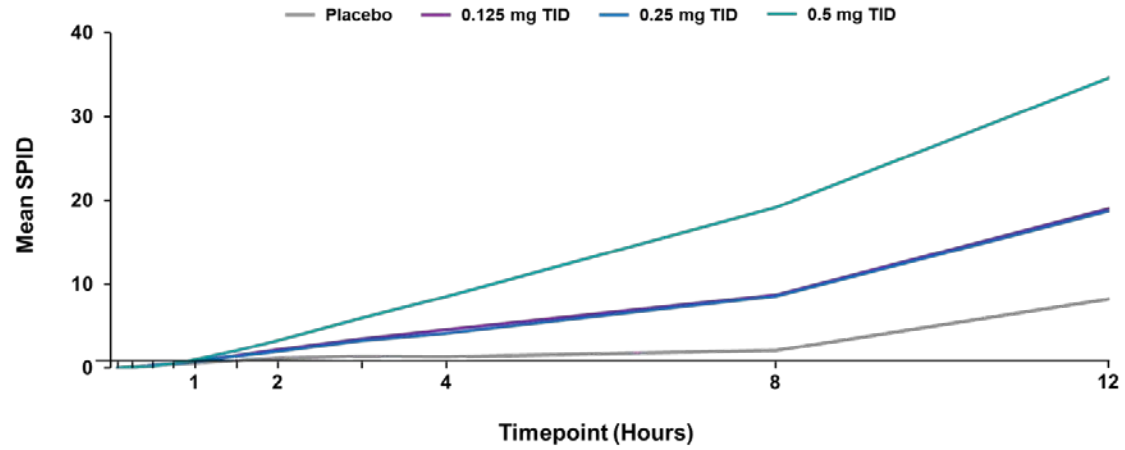
Figure 24: Subjects with ≥30% and ≥50% Improvement in Pain Intensity at the 8 Hour Timepoint



Source: CSR INS005-15-062, PostHoc Summary Tables 14.1.1.1, 14.1.1.2, 14.1.1.3, 14.1.1.4

Finally, examining the pain relief over the first 12 hours, we also see a benefit across all doses. The pain-relieving efficacy of Buprenorphine Sublingual Spray is supported by the mean SPID over the first twelve hours. The SPID-12 gives us a more granular look at the 8-hour time point, showing that all doses show changes from baseline that have a discernable separation from placebo by 4 hours which increases at hours 8 and 12 (see the figure below). This efficacy is further supported by the global evaluation of treatment at the 48-hour timepoint.

Figure 25: Study 062: Mean SPID 0-12 Hours

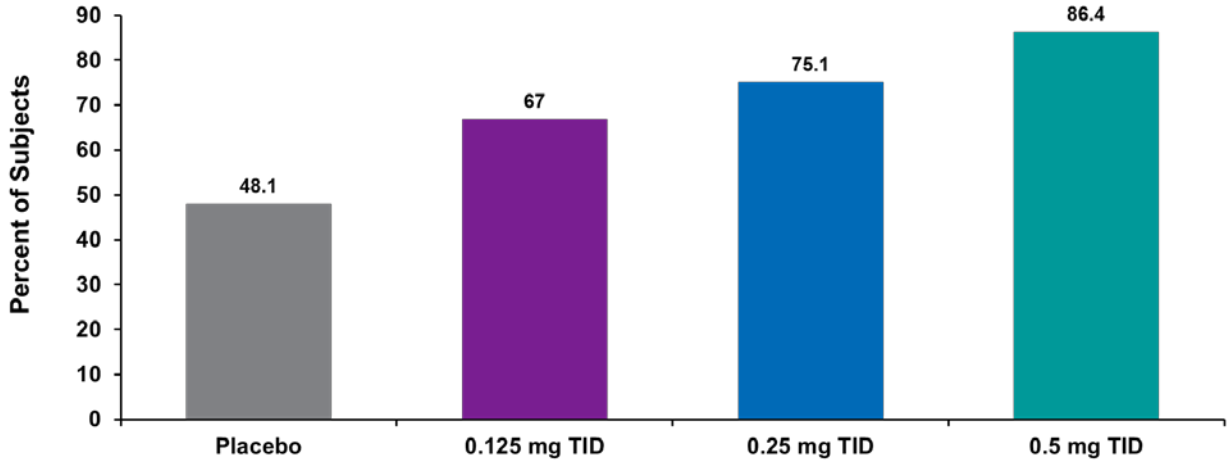


Source: CSR INS005-15-062, Tables 14.2.1-14.2.4; Tables 14.2.23-14.2.30.

6.4.2.5. Subject's Global Evaluation

Subjects rated the study's "method of pain relief" (i.e., subject's global evaluation of study drug) on a 0-to-4 scale (0 = Poor, 1 = Fair, 2 = Good, 3 = Very Good, 4 = Excellent) at the end of the treatment period before discharge from the study site or immediately before early termination if a subject discontinued prematurely. Global evaluation assessments for Buprenorphine Sublingual Spray were better than that for placebo for all doses studies. Buprenorphine Sublingual Spray was rated as Excellent, Very Good, or Good by 86.4% of the subjects receiving the 0.5 mg TID dose compared to 48.1% for the placebo group. Buprenorphine Sublingual Spray was rated as Excellent, Very Good, or Good by 75.1% and 67.0% of those receiving 0.25 mg TID and 0.125 mg TID, respectively (Figure 26). This endpoint is of clinical importance as describing patients' perspective of treatment benefit is an important component of patient-focused drug development. The majority of subjects in the Buprenorphine Sublingual Spray groups rated their medication as Excellent, Very Good, or Good, supporting the statistically significant primary efficacy endpoint as clinically significant and the relevance of Buprenorphine Sublingual Spray in controlling pain in this post-operative setting. The global evaluation results indicate that Buprenorphine Sublingual Spray may be well-received by patients.

Figure 26: Global Evaluation of Study Drug: Percent of Subjects Indicating Either Excellent, Very Good, or Good



Source: INS005-15-062 CSR Table 14.2.22

6.5. Efficacy Summary

The results of the pivotal Phase 3 study (INS005-15-062) demonstrated consistent evidence for the analgesic efficacy of Buprenorphine Sublingual Spray in a moderate to severe acute pain model with doses ranging from 0.125 mg to 0.5 mg given three times daily. By demonstrating superiority versus placebo, this study demonstrated the efficacy of all three doses (0.125 mg, 0.25 mg, and 0.5 mg TID) of the sublingual spray in acute pain. There was a dose response, with the greatest reductions in pain being observed in the 0.5 mg TID dose. The secondary endpoints support the efficacy of the three proposed doses and also showed a dose-response favoring the

0.5 mg TID dose. In addition to the statistically significant difference of the primary efficacy endpoint of SPID-48, the secondary endpoints consistently support both the efficacy and clinical relevance of the primary efficacy results. Global evaluation assessments for Buprenorphine Sublingual Spray were better than that for placebo for all three doses. The global evaluation showed that the majority of patients receiving all three doses rated the spray Good or higher, reflecting both the efficacy and tolerability of the treatment. For the 0.5 mg TID dose, 86.4% of the subjects rated Buprenorphine Sublingual Spray as Excellent, Very Good, or Good. This is further reflected in the 92.5% completion rate for subjects in the study.

7. SAFETY

7.1. Overview

The safety of Buprenorphine Sublingual Spray is consistent with the established safety of approved buprenorphine products. There were no unique events specific to this formulation or the delivery system observed in the clinical development program.

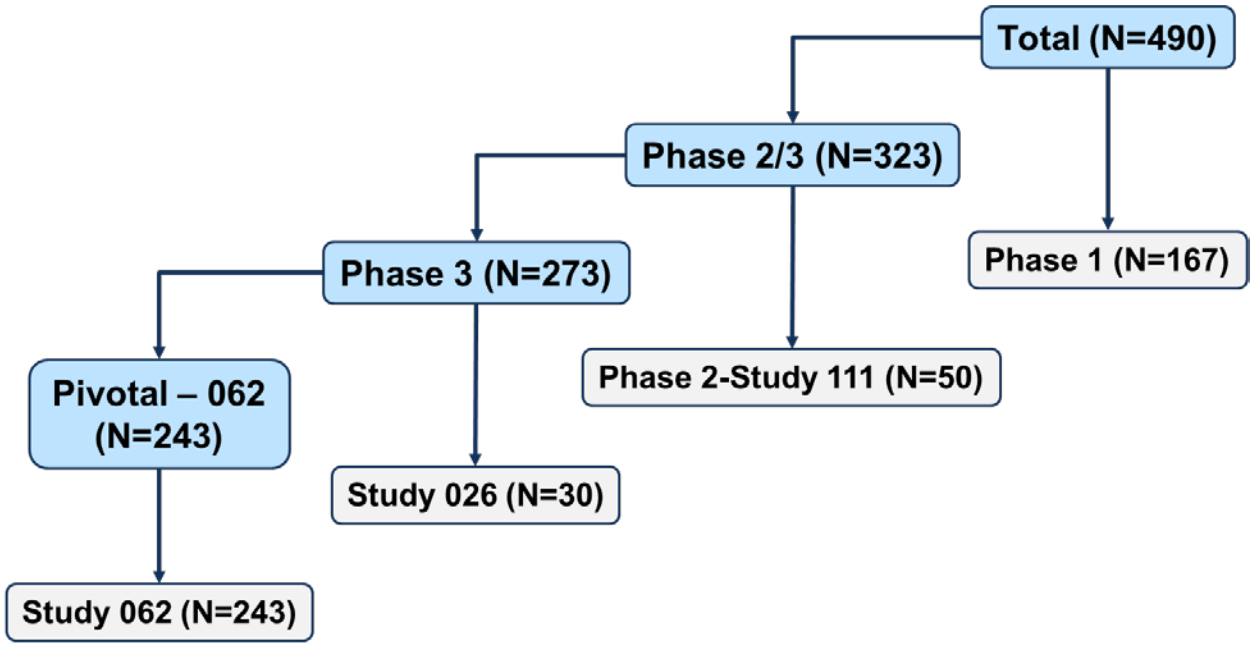
The rates of some events were notable for this formulation, specifically events of nausea, vomiting, and oxygen saturation decrease/hypoxia. In the pivotal study, the rates of nausea and vomiting were dose-dependent, with the highest rate of events observed for the highest dose, 0.5 mg TID. The events tended to occur with the initial doses and rates decreased with subsequent doses. These events appear to be manageable with normal antiemetic medications. Postsurgical patients may benefit from prophylactic antiemetic therapy.

The proposed Medication Guide will alert patients to these and the other known adverse events associated with buprenorphine use as established with approved buprenorphine therapies. Two Phase 3 studies (Study 026 and Study 062) were conducted to evaluate the efficacy of Buprenorphine Sublingual Spray in a bunionectomy model for doses of 0.125 mg TID, 0.25 mg TID, 0.5 mg TID, 1.0 mg BID, and 1.0 mg TID administered for 48 hours, and one Phase 2 open label 7-day safety study (Study 111) in postoperative pain to evaluate the safety and tolerability based on the incidence of adverse experiences of Buprenorphine Sublingual Spray administered 0.5 mg TID for 7 days compared with standard postoperative opioid therapy. In these three studies, a total of 323 subjects were exposed to Buprenorphine Sublingual Spray administered at these doses for 2 days or 7 days (up to 21 doses).

The safety endpoints in these studies were the incidence of treatment-emergent adverse events (TEAEs), physical and oral examination findings, and changes in vital signs, including pulse oximetry, and ECG measurements. In the pivotal Phase 3 study and the Phase 2 open-label safety study, all patients were continuously monitored for a decrease in oxygen saturation.

A total of 490 subjects have been exposed to Buprenorphine Sublingual Spray of various doses and timing (Figure 27). The majority of these were in the Phase 2/3 studies, 273 in the Phase 3 studies most of whom participated in the pivotal trial, Study 062. The majority of subjects (217) have been exposed to the highest proposed dose of 0.5 mg TID without significant unusual or unexpected adverse reactions or safety concerns. Summaries of subject exposure in the clinical development program by the number of exposures in subjects who completed the study by dose/study and the number of study subjects exposed to study drug by dose/dose regimen are provided in Table 11 and Table 12 respectively.

Figure 27: Buprenorphine Sublingual Spray Exposure



Three SAEs (atrial fibrillation, unrelated; angioedema, unrelated; and incisional hematoma; possibly related) were reported in the Phase 2 and Phase 3 postoperative pain studies. No deaths were reported. A total of 33 (10.2%) patients treated with Buprenorphine Sublingual Spray discontinued due to AEs. The AEs leading to discontinuation were generally those that are expected within the opioid class such as nausea, vomiting, somnolence, and dizziness. In the pivotal Phase 3 Study 062 and the open safety Phase 2 Study 111, all patients were continuously monitored for a decrease in oxygen saturation.

To examine the most common AEs, the pooled Phase 3 studies were reviewed. Study 111 provided further insight into the vomiting and decreased oxygen saturation on its own and in comparison to 062. Study 111 also showed differences in the rates and severity of nausea and vomiting with prophylactic antiemetic therapy. Finally, all three studies were used to examine the events of decreased oxygen saturation and hypoxia.

Table 11: Number of Exposures in Subjects Who Completed the Study by Dose/Study

Protocol Number	Buprenorphine Sublingual Spray Dose Received (mg)											Total Number of Exposures[a]
	0.0625	**0.125**	**0.25**	**0.375[a]**	**0.5**	**0.75[a]**	**1.0**	**1.5[a]**	**2[a]**	**4[a]**	**8[a]**	
INS-13-016	-	-	-	-	11	-	11	-	-	-	-	**22**
INS-13-020	-	-	-	-	-	-	18	-	-	-	-	**18**
INS005-14-032	-	-	-	-	18	-	18	-	-	-	-	**36**
INS005-16-076	6	5	6	-	6	-	6	-	-	-	-	**29**
INS005-16-069	-	-	-	-	70	-	-	-	-	-	-	**70**
INS005-17-104	-	-	-	-	-	-	-	-	12	12	12	**36**
INS005-17-105	-	-	-	12	-	12	-	12	-	-	-	**36**
INS-14-026	-	-	-	-	54	-	106	-	-	-	-	**160**
INS005-15-062	-	492	480	-	486	-	-	-	-	-	-	**1458**
INS005-17-111	-	-	-	-	1651	-	-	-	-	-	-	**1651**
Total	**6**	**497**	**486**	**12**	**2296**	**12**	**159**	**12**	**12**	**12**	**12**	**3506**

[a] Dose received is sum of multiple doses given during the study.
Source: Integrated Safety Summary, Table 2-1.

Table 12: Number of Study Subjects Exposed to Study Drug by Dose Regimen

Dosing Regimen	Dose Received (mg)											
	0.0625	**0.125**	**0.25**	**0.375[c]**	**0.5**	**0.75[c]**	**1.0**	**1.5[c]**	**2[c]**	**4[c]**	**8[c]**	**Total[a]**
Single dose with multi-dose unit system	-	-	-	-	12	-	29[d]	-	-	-	-	**41**
Single dose with unit dose system	6	6	6	-	26	-	24[d]	-	-	-	-	**68**
Multiple dose with unit dose system	-	-	-	12	-	12	-	12	12	12[e]	12[e]	**72**
Weekly dose[b] up to 5 weeks	-	-	-	-	15	-	-	-	-	-	-	**15**
Double blind efficacy (TID)	-	82	80	-	140	-	11	-	-	-	-	**313**
Double blind efficacy (BID)	-	-	-	-	-	-	10	-	-	-	-	**10**
Total	**6**	**88**	**86**	**12**	**193**	**12**	**74**	**12**	**12**	**12**	**12**	**519**

[a] Subjects in ascending single dose crossover studies (INS-13-016, INS005-14-032) were counted for each treatment group (dose). The total number of subjects exposed is **490**.
[b] Subjects received a single dose of 0.5 mg Buprenorphine Sublingual Spray each week in a 5-way crossover design
[c] Dose received is sum of multiple doses given during the study.
[d] 29 subjects in the 1.0 mg dose group are also counted in the 0.5 mg dose group: 11 from single dose with multi-dose unit system regimen and 18 from the single dose with unit dose system regimen
[e] Subjects received multiple doses of 0.5 mg. The total number of subjects exposed to 0.5 mg dose is 217.
Source: Integrated Safety Summary, Table 2-2.

7.2. Most Common Adverse Events in Phase 3 Studies

The most notable AEs in the Phase 3 studies were nausea, vomiting, and reduced oxygen saturation or hypoxia. For the proposed doses of 0.125 mg, 0.25 mg, and 0.50 mg: nausea was reported for 43.9%, 58.8%, and 83.3%, and vomiting was reported for 29.3%, 41.3%, and 72.2% of patients, respectively (Table 13). These two studies did not allow prophylactic use of antiemetics and also limited the types and dosage of anti-emetic permitted. While there were some severe events of nausea and vomiting, there were no events that were considered serious. Additionally, there were seven cases of dehydration, four of which occurred in patients with severe vomiting that were concerning to the Agency.

Table 13: Most Common AEs in Phase 3 Studies (≥5% in proposed doses)

	Phase 3 Studies Pooled[1]					
	0.125 mg TID N=82 n (%)	0.25 mg TID N=80 n (%)	0.5 mg TID N=90 n (%)	1 mg BID N=11 n (%)	1 mg TID N=10 n (%)	Placebo N=89 n (%)
Subjects with ≥ 1 adverse event	57 (69.5)	67 (83.8)	85 (94.4)	11 (100.0)	9 (90.0)	45 (50.6)
Total Number of adverse events	219	296	521	67	55	109
Cardiac disorders	1 (1.2)	1 (1.3)	2 (2.2)	1 (9.1)	0 (0.0)	2 (2.2)
Eye disorders	0 (0.0)	1 (1.3)	2 (2.2)	1 (9.1)	0 (0.0)	1 (1.1)
Gastrointestinal disorders	41 (50.0)	55 (68.8)	78 (86.7)	11 (100.0)	8 (80.0)	25 (28.1)
Constipation	9 (11.0)	6 (7.5)	8 (8.9)	2 (18.2)	2 (20.0)	1 (1.1)
Dry mouth	0 (0.0)	3 (3.8)	5 (5.6)	2 (18.2)	1 (10.0)	1 (1.1)
Nausea	36 (43.9)	47 (58.8)	75 (83.3)	10 (90.9)	7 (70.0)	16 (18.0)
Vomiting	24 (29.3)	33 (41.3)	65 (72.2)	8 (72.7)	8 (80.0)	4 (4.5)
Infections and infestations	2 (2.4)	1 (1.3)	4 (4.4)	1 (9.1)	1 (10.0)	2 (2.2)
Investigations	6 (7.3)	8 (10.0)	9 (10.0)	0 (0.0)	0 (0.0)	6 (6.7)
Oxygen saturation decreased	6 (7.3)	8 (10.0)	8 (8.9)	0 (0.0)	0 (0.0)	4 (4.5)
Metabolism and nutrition disorders	3 (3.7)	1 (1.3)	9 (10.0)	1 (9.1)	0 (0.0)	2 (2.2)
Decreased appetite	3 (3.7)	1 (1.3)	5 (5.6)	0 (0.0)	0 (0.0)	2 (2.2)
Dehydration	0 (0.0)	0 (0.0)	7 (7.8)	1 (9.1)	0 (0.0)	0 (0.0)

	Phase 3 Studies Pooled[1]					
	0.125 mg TID N=82 n (%)	0.25 mg TID N=80 n (%)	0.5 mg TID N=90 n (%)	1 mg BID N=11 n (%)	1 mg TID N=10 n (%)	Placebo N=89 n (%)
Subjects with ≥ 1 adverse event	57 (69.5)	67 (83.8)	85 (94.4)	11 (100.0)	9 (90.0)	45 (50.6)
Total Number of adverse events	219	296	521	67	55	109
Nervous system disorders	33 (40.2)	44 (55.0)	62 (68.9)	9 (81.8)	7 (70.0)	22 (24.7)
Dizziness	18 (22.0)	26 (32.5)	51 (56.7)	5 (45.5)	5 (50.0)	7 (7.9)
Headache	15 (18.3)	23 (28.8)	14 (15.6)	4 (36.4)	1 (10.0)	13 (14.6)
Somnolence	6 (7.3)	6 (7.5)	15 (16.7)	3 (27.3)	4 (40.0)	0 (0.0)
Tremor	1 (1.2)	3 (3.8)	1 (1.1)	1 (9.1)	1 (10.0)	1 (1.1)
Psychiatric disorders	3 (3.7)	0 (0.0)	6 (6.7)	1 (9.1)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	8 (9.8)	4 (5.0)	11 (12.2)	1 (9.1)	1 (10.0)	5 (5.6)
Hiccups	0 (0.0)	0 (0.0)	2 (2.2)	1 (9.1)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	6 (7.3)	6 (7.5)	26 (28.9)	4 (36.4)	4 (40.0)	4 (4.5)
Erythema	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	2 (20.0)	0 (0.0)
Hyperhidrosis	2 (2.4)	1 (1.3)	10 (11.1)	2 (18.2)	1 (10.0)	0 (0.0)
Pruritus	2 (2.4)	2 (2.5)	13 (14.4)	3 (27.3)	0 (0.0)	1 (1.1)
Rash	0 (0.0)	1 (1.3)	2 (2.2)	0 (0.0)	1 (10.0)	3 (3.4)
Vascular disorders	6 (7.3)	5 (6.3)	9 (10.0)	3 (27.3)	0 (0.0)	2 (2.2)

N = number of subjects within the dose group (denominator for percentages, where applicable)
n = number of observed subjects (numerator for percentages, where applicable)
[1] INS-14-026 and INS005-15-062
Adverse event (AE) = any AE which started or worsened on or after the day of first dose (randomization).
Note: A subject is counted only once within each system organ class and preferred term category, using the event having the worst-case severity.

Across all three studies (Studies 026, 062, and 111), there were a total of three SAEs (Table 14). Narratives for the three SAEs are provided in Section 7.6.2. There was one serious AE in each trial all on the 0.5 mg TID dose. An SAE of atrial fibrillation in a 56 year old woman with a history of cardiac disorders and rhythm abnormalities. There was an SAE of angioedema in a 65 year old woman after her last dose of study medication. This may have been an allergic reaction to Zofran that responded to Benedryl. The third patient had an SAE of incision site hematoma. This was a 32 year old woman who developed the hematoma 24 hours after discontinuing Buprenorphine Sublingual Spray due to nausea and vomiting. The hematoma was treated and resolved the same day.

Table 14: Serious Adverse Events, All Studies

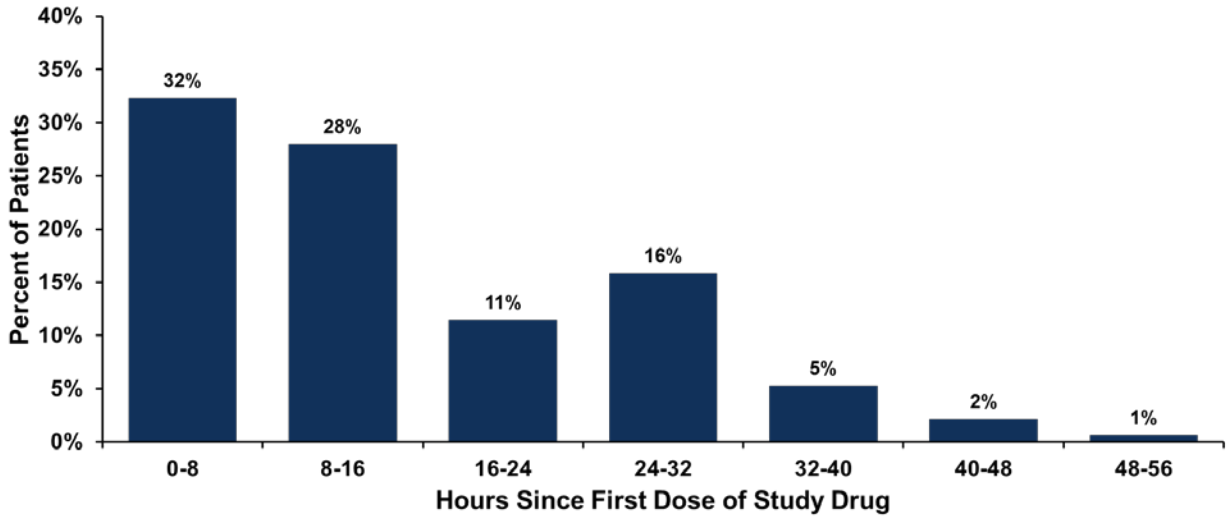
	0.5 mg TID		
	INS14-026	INS005-15-062	INS005-17-111
Event	Atrial Fibrillation (A. Fib)	Angioedema	Incision Site Hematoma
Intensity	Severe	n/a	Severe
Relation	Not Related	Not Related	Possible
Time to Event (post dosing)	n/a	16.5 H	24 H
Time to recovery	2 days	---	---
Time to resolution	---	2 days	24 H
Summary of Event	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	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 that did not subside after taking Benadryl. Patient presented to the ED and was treated for Angioedema. Likely cause was determined to be Zofran ODT	32 yo F with history of one caesarean section in (b) (6) 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

H, hours; ODT, oral disintegrating tablet; TID, three times per day; yo, year old.
Source: ISS v2.0 page 208, Patient Narrative Template_INS005-17-111.

7.3. Nausea and Vomiting

The majority of nausea and vomiting events occurred within the first 16 hours after initiation of study drug, suggesting that the first and second doses are associated with the highest number of events. There were still some events at subsequent doses, but rates were much lower by the third dose and down to 7 percent by the 5th dose (see the figure below). These rates may also be a consequence of the study design and not administering prophylactic antiemetic therapy.

Figure 28: Percentage of Patients Experiencing Related Vomiting Events: Study 062, All Doses



Source: CSR INS005-15-062, Table 14.3.7

The following guidance was provided to investigators for the management of nausea and vomiting in this study:

- Prophylactic use of antiemetics was not permitted.
- Use of antiemetics was restricted to ondansetron. Initial dose was to be 4 mg IV that could be followed by an additional 4 mg IV dose in 30-60 minutes. The total amount given was not to exceed 8 mg IV in any given 8-hour interval.
- No other antiemetics (e.g., promethazine, metoclopramide) were permitted in this study.
- Patients not adequately managed by this protocol were discontinued from the study.

7.4. Study 111

Study 111 was a Phase 2, randomized (stratified according to surgery and postoperative nausea and vomiting risk factors), open label, multiple-dose, comparator controlled, parallel-group, study to evaluate the safety and tolerability of Buprenorphine Sublingual Spray (0.5 mg TID) versus standard postoperative narcotic therapy for up to 7 days in patients with postoperative pain. Patients had undergone bunionectomy, breast augmentation, or abdominoplasty. There were 50 patients each in the Buprenorphine Sublingual Spray (0.5 mg TID) and standard narcotic therapy groups. Standard postoperative narcotic therapy was defined as morphine intravenous (IV) injection (4 mg TID) followed by oxycodone hydrochloride tablet (10 mg TID). The primary objective of the study was to evaluate the safety and tolerability based on the incidence of adverse experiences of Buprenorphine Sublingual Spray (0.5 mg three times daily [TID]) compared with standard post-operative narcotic therapy in subjects with postoperative pain. A secondary objective was to evaluate impact of prophylactic anti-emetic use on nausea and vomiting.

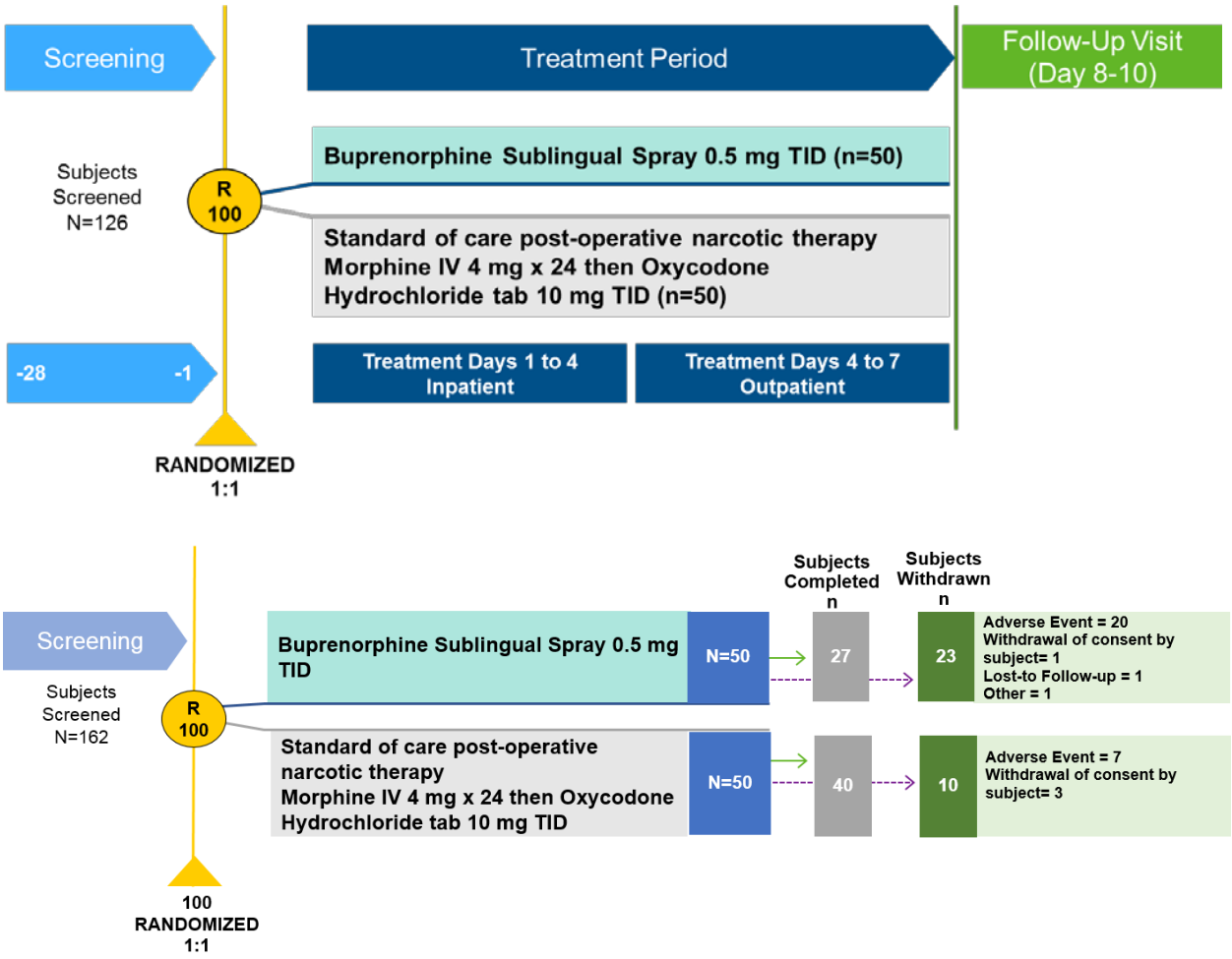
The study design and disposition of subjects is outlined in Figure 29. The treatment period consisted of a 72-hour inpatient portion, followed by a 4-day outpatient portion, for a total of 7 days. Patients had a follow-up visit between Day 8 and Day 10 inclusive.

The study methodology enabled investigation of the impact of prophylactic antiemetic treatment. Patients were stratified by their baseline risk of nausea and vomiting as well as by surgical procedure. All patients received nausea prophylaxis starting with induction with dexamethasone 10 mg followed by ondansetron 8 mg near the end of surgery.

During the period between the end of surgery and prior to randomization to study drug analgesia, patients could receive rescue analgesia in the form of IV morphine and/or fentanyl dosed based on investigator discretion. Within 4 hours after the completion of surgery, patients were randomized and received their first dose of study drug. After randomization, the rules for rescue medication were different from those in the prior studies.

Rescue medication for pain during the inpatient phase was acetaminophen 1000 mg every 6 hours and/or ketorolac 30 mg IV or IM every 6 to 8 hours as needed with a maximum of 90 mg per day. Outpatients were allowed only acetaminophen 1000 mg every 6 hours. Rescue medication for nausea during the inpatient period was only ondansetron 4 mg IV and outpatient was only ondansetron 4 mg oral disintegrating tablet.

Figure 29: Study 111 Design



The randomization resulted in demographic and baseline characteristics that were very evenly balanced between arms (Table 15). One hundred (100) subjects (4 male subjects and 96 female subjects) were enrolled into the study. Almost all subjects were female (48 in each group). Overall, the mean (SD) age was 36.6 (11.22) years. Most subjects were either White (60 [60.0%]), or Black or African American (33 [33.0%]).

The majority of subjects were classified as PONV high risk: 42 (84.0%) subjects in the standard postoperative narcotic therapy group and 43 (86.0%) subjects in the Buprenorphine Sublingual Spray group. The Apfel Scale classifies patients as Low Risk if their score is 0 to 2 and High Risk if their score is 3 to 4 high risk Table 16. The scores translate to a probability of post-operative nausea and vomiting such that the highest score of 4 translates to a 79% probability of an event (Gan et al. 2014).

Table 15: Study 111: Demographics and Baseline Characteristics

	Standard Narcotic Therapy N=50	Buprenorphine Sublingual Spray N=50
Age, mean (SD)	36.2 (10.83)	37.1 (11.68)
Male, %	4.0	4.0
Female	96.0	96.0
Race, %		
White	58.0	62.0
Black or African America	30.0	36.0
American Indian or Alaska Native	6.0	0
Hawaiian or other Pacific Islander		2.0
Asian	6.0	0
Hispanic or Latino Ethnicity, %	34.0	28.0
Non-Hispanic, %	66.0	72.0
PONV Low Risk, %	16.0	14.0
PONV High Risk, %	84.0	86.0

Source: CSR INS005-17-111, Table 14.1.2

Table 16: Apfel Scale for the Probability of Postoperative Nausea and Vomiting (PONV)

PONV Risk Factor Assessment		PONV Risk Score	
Risk Factors	Points	Score	Probability of PONV
Postoperative Opioids (if planned)	1	0	10
Non-Smoker	1	1	21
Female Gender	1	2	39
History of PONV/Motion Sickness	1	3	61
Total	**0 to 4**	4	79

7.4.1. Most Common Adverse Events in Study 111

The most common AEs with severity are summarized in Table 17. The rates of nausea, vomiting, and hypoxia were numerically higher than those observed on morphine. For the Buprenorphine Sublingual Spray 0.5 mg group, nausea, vomiting, and hypoxia were reported for 78%, 52%, and 28% of subjects, respectively. For the standard narcotic therapy group, nausea, vomiting, and hypoxia were reported for 34%, 12%, and 6% of subjects, respectively. In contrast to the prior studies, in Study 111 there were no severe events of nausea, vomiting, or hypoxia. Plus, the overall rate of vomiting was less in this study than the pivotal study (062).

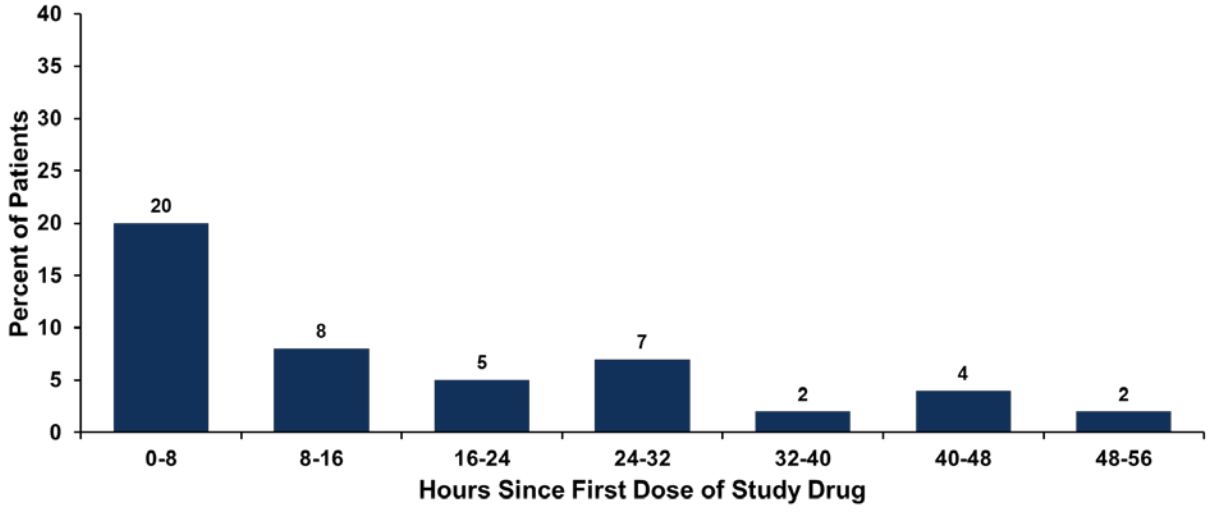
Table 17: Study 111: Most Common AEs with Severity

Preferred Term Severity	0.5 mg TID N=50 %	Standard Narcotic Therapy* N=50 %
Nausea	78	34
Mild	6	10
Moderate	72	24
Vomiting	52	12
Mild	18	8
Moderate	34	4
Hypoxia	28	6
Mild	2	0
Moderate	26	6
Headache	18	16
Mild	14	10
Moderate	4	6
Dizziness	22	10
Mild	20	10
Moderate	2	0
Pruritus	16	8
Mild	12	6
Moderate	4	2

Source: CSR INS005-17-111, Table 14.3.1.2

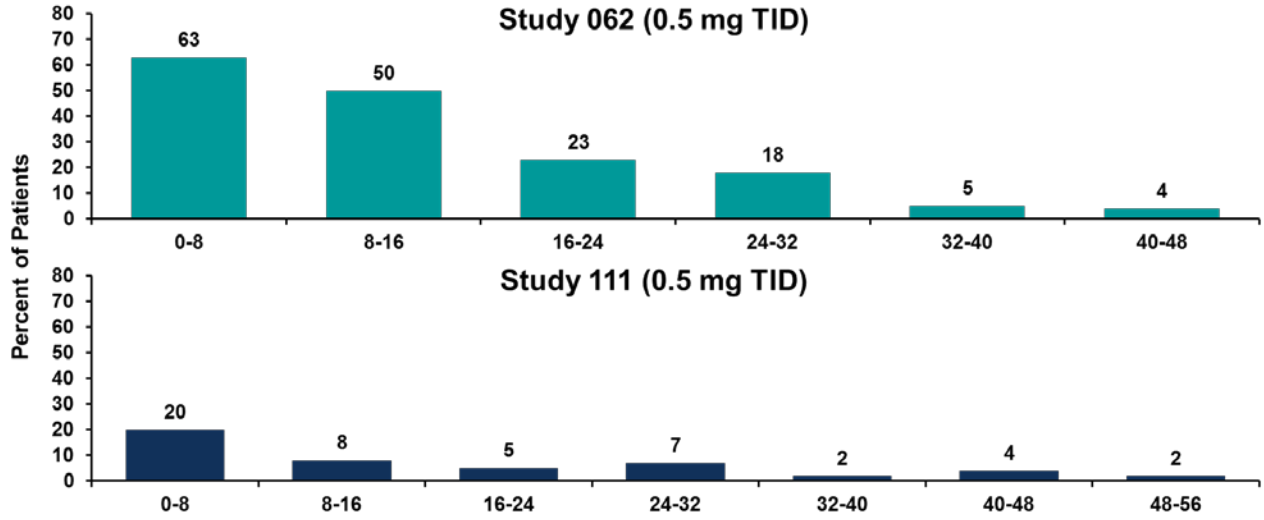
As in prior studies, the majority of events occurred within the first 16 hours after the first dose of study drug (see the figure below). Approximately 28% of patients experienced related events of vomiting within 16 hours after the first dose of study drug. The frequency and timing of events compare favorably with their occurrence on the comparable 0.5 mg TID arm of Study 062, supporting the use of prophylactic antiemetics (see Figure 31).

Figure 30: Percentage of Patients Experiencing Related Vomiting Events by Study Epoch for Buprenorphine SL Spray 0.5 mg TID: Study 111



Source: CSR INS005-17-111, Table 14.3.1.3

Figure 31: Percentage of Patients Experiencing Related Vomiting Events by Study Epoch for Buprenorphine SL Spray 0.5 mg TID: Study 062 and Study 111



Sources: CSR INS005-15-062, Table 14.3.7; CSR INS005-17-111, Table 14.3.1.3

7.4.2. Adverse Events of Special Interest

The incidence of AEs of special interest are summarized in Table 18. Importantly, both the rate and severity of vomiting events observed in Study 111 were lower than those observed in Study 062. In addition, there were no severe events of nausea or vomiting, plus no cases of dehydration were reported. In contrast, in Study 062, we saw severe events of both nausea and vomiting and a higher rate of vomiting.

Table 18: Incidence of Adverse Events of Special Interest

	Study 026 Patients				Study 062 Patients				Study 111 Patients	
AESI	Placebo N=10 n (%)	0.5 mg TID N=9 n (%)	1.0 mg BID N=11 n (%)	1.0 mg TID N=10 n (%)	Placebo N=79 n (%)	0.125 mg TID N=82 n (%)	0.25 mg TID N=80 n (%)	0.5 mg TID N=81 n (%)	0.5 mg TID N=50 n (%)	SOT N=50 n (%)
Nausea	3 (30)	7 (77.8)	10 (90.9)	7 (70)	13 (16.5)	36 (43.9)	47 (58.8)	68 (84)	39 (78)	17 (34)
Vomiting	0	6 (66.7)	8 (72.7)	8 (80)	4 (5.1)	24 (29.3)	33 (41.3)	59 (72.8)	26 (52)	6 (12)
O_2 Saturation Decrease	0	0	0	0	4 (5.1)	6 (7.3)	8 (10)	7 (8.6)	0	0
Hypoxia	0	0	0	0	0	1 (1.2)	0	3 (3.7)	14 (28)	3 (6)

Source: Clinical Study Report INS005-15-062, Table 41; Clinical Study Report INS005-17-111, Table 13; Clinical Study Report INS14-026, Table 14.
Numbers represent the number of subjects that reported an event
Standard Narcotic 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.
BID = two times per day; BSS = Buprenorphine sublingual spray; PLC = placebo; SNT = standard narcotic therapy; TID = three times per day.

7.4.3. Study 111 Conclusions

The results from Study 111 demonstrated that Buprenorphine Sublingual Spray 0.5 mg TID was generally safe and well tolerated for up to 7 days. In addition, the study showed that prophylactic antiemetic treatment reduced the incidence and severity of vomiting, and severity of nausea.

7.5. Reduced Oxygen Saturation

7.5.1. Overview of Studies Results and Discussion

The events related to reduced oxygen saturation in Studies 026, 062, and 111 were defined as either “hypoxia” or “oxygen saturation decreased”:

- Study 026: hypoxia was defined as oxygen saturation < 90% on room air and oxygen saturation decreased was not defined or reported.
- Study 062: hypoxia was defined as oxygen saturation ≤ 92% on room air and oxygen saturation decreased was defined as any drop in oxygen saturation down to, but not exceeding 92% regardless of whether medical intervention was required.
- Study 111: hypoxia was defined as oxygen saturation < 90% on room air and oxygen saturation decreased was not defined or reported.

The rates of these events varied across studies (Table 19). The highest rates of events were observed in Study 111. This may be due in part to the range of surgeries included. In addition to bunionectomy, Study 111 included patients who had undergone breast augmentation and

abdominoplasty. Both of these procedures may make breathing difficult, which is supported by the highest rates of hypoxia occurring in these two groups. However, the rate of hypoxia in the bunionectomy population of the study was 19%, still higher than that observed in the larger 062 study which was 3.7% in the 0.5 mg TID dose group. No patients in the smaller 026 study had events of hypoxia on the 0.5 mg TID dose.

Table 19: Severity of Reduced Oxygen Saturation

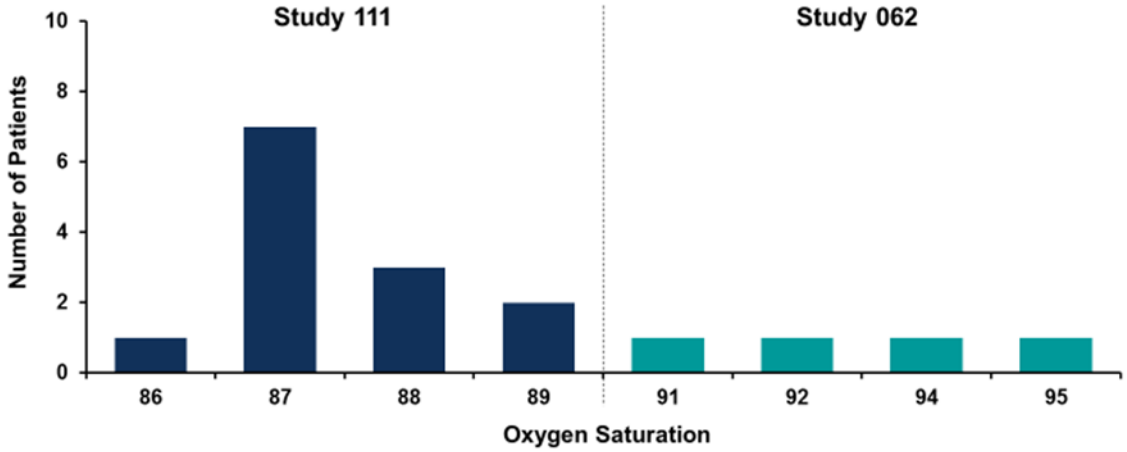
		Study 062				Study 026	Study 111	
		Placebo N=79 n (%)	0.125 mg TID N=82 n (%)	0.25 mg TID N=80 n (%)	0.5 mg TID N=81 n (%)	0.5 mg TID N=9 n (%)	0.5 mg TID N=50 n (%)	Standard Opioid Therapy N=50 n (%)
O_2 Sat Dec	Mild	4 (5.1)	6 (7.3)	8 (10)	7 (8.6)	1 (1.1)	NA	NA
	Received O_2	2 (2.5)	6 (7.3)	7 (8.8)	7 (8.6)	1 (1.1)	NA	NA
Hypoxia	Mild	0	1 (1.2)	0	3 (3.7)	0	1 (2)	0
	Moderate	0	0	0	0	0	13 (26)	3 (6)
Hypoxia	Total	0	1 (1.2)	0	3 (3.7)	0	14 (28)	3 (6)
	Received O_2	0	1 (1.2)	0	3 (3.7)	0	14 (28)	3 (6)

Clinical Study Report INS005-15-062, Table 14.3.6; Clinical Study Report INS005-17-111 Table 14; Clinical Study Report INS-14-026
Standard narcotic 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

For the patients who had reported events of hypoxia on buprenorphine, their lowest oxygen saturations reflected a wide range of pulse oximetry values (Table 19). As expected, the lowest values were observed in Study 111, which had patients who underwent abdominoplasty and breast augmentation in addition to bunionectomy. These two procedures have the potential to impair breathing. The lowest value observed in Study 111 was 86% in a patient who underwent abdominoplasty. Seven patients had values as low as 87% with one of these in the bunionectomy cohort. All of the rest having oxygen saturation levels below 90% had undergone either breast augmentation or abdominoplasty.

In Study 062, which only included bunionectomy surgery patients, the lowest value was 91% in one patient. Another had a lowest value of 92%. The other two had lowest values of 94 or 95%, which should not have qualified for the study definition of hypoxia though the investigator still reported the adverse event (see the figure below).

Figure 32: Lowest Oxygen Saturation in Buprenorphine Patients with Reported Adverse Events of Hypoxia



Sources: CSR INS005-15-062, CSR INS005-17-111

Considering all the patients with any oxygen-related event reported in Study 062, the oxygen saturations ranged from 89 to 95% for patients with events of decreased oxygen saturation and hypoxia. It's notable that the two lowest oxygen saturation levels were not included in Table 20 as they occurred in patients with reports of decreased oxygen saturation, not hypoxia. Table 21 provides a more complete representation. Table 20 also shows that there were four events in placebo subjects in the 90-92% range.

In Study 111, both arms had oxygen saturation levels less than or equal to 95%.

Table 20: Patients with AEs of Decreased Oxygen Saturation and Hypoxia in Study 062

	0.5 mg TID N=81 n	0.25 mg TID N=80 n	0.125 mg TID N=82 n	Placebo N=79 n
89	1			
90	1	1	1	1
91		3	2	2
92	6	3	4	1
93				
94	1			
95	1			

Sources: CSR INS005-15-062

To look at Study 111 more comprehensively, we assessed all patients for any oxygen saturation value at or below 95%, regardless of any reported adverse events. The lowest values were observed on the buprenorphine arm with patients at 86 and 87%. The morphine arm had a lowest value of 88%. The morphine had a total of 40 patients at or below 95% while the buprenorphine had a total of 39 patients (Table 21).

Table 21: Patients with any Oxygen Saturation Decrease ≤ 95% in Study 111

	0.5 mg TID N=50 n	Morphine 4 mg TID N=50 n
86	1	
87	7	
88	3	3
89	2	
90	3	3
91	1	2
92	1	5
93	6	3
94	6	10
95	9	14

Sources: CSR INS005-17-111

The standard definition of hypoxia is normal arterial oxygen approximately 75 to 100 millimeters of mercury (mm Hg). Values under 60 mm Hg usually indicate the need for supplemental oxygen. Normal pulse oximeter readings usually range from 95 to 100 percent. Values under 90 percent are considered low as described from the Mayo Clinic. Results show a 10% occurrence in the 0.5 mg TID and 6% in the Standard Narcotic therapy arms only. There was 1% in the placebo arm and no reports of occurrence in the 0.0125 mg TID and 0.25 mg TID arms (Table 22).

Table 22: Incidence of Oxygen saturation < 90 %

	Phase 2 and Phase 3 Postoperative Pain Studies Pooled [1]						
	0.125 mg (TID) N= 82 n(%)	0.25 mg (TID) N= 80 n(%)	0.5 mg (TID) N= 140 n(%)	1 mg (BID) N= 11 n(%)	1 mg (TID) N= 10 n(%)	Placebo N= 89 n(%)	Standard Narcotic Therapy N=50 n(%)
Incidence of oxygen saturation < 90%	0(0%)	0(0%)	14(10%)	1(9%)	1(10%)	1(1%)	3(6%)

Sources: CSR INS005-15-062; CSR INS005-17-111

The rate of hypoxia and decreased oxygen saturation for Buprenorphine Sublingual Spray observed in these studies are within the range for other opioids. Published data suggests there is a ceiling effect on respiratory depression observed with buprenorphine which is unlike other opioids (Dahan et al., 2006; Pergolizzi et, al., 2008).

7.5.2. Reduced Oxygen Saturation Conclusions

Respiratory depression is a known adverse event with opioids. It was observed in the Buprenorphine Sublingual Spray trials. The adverse events reported included the preferred terms of "oxygen saturation decreased" and "hypoxia." The studies defined hypoxia as a pulse oximetry of at less than or equal to 92% in Study 062 and less than 90% in Studies 026 and 111. The rates of these events were consistent with those observed in the most commonly prescribed opioids in the outpatient setting. The lowest oxygen saturation observed was 86% and this was in a patient who had undergone abdominoplasty.

While respiratory depression is a serious concern with all opioids, including buprenorphine, the ceiling effect on respiratory depression reported in the literature should limit the impact of this risk in patients receiving Buprenorphine Sublingual Spray.

7.6. Safety Narratives

Decreased oxygen saturation is a known risk on opioids. In order to assess the occurrence of events of decreased oxygen saturation on Buprenorphine Sublingual Spray, patients underwent continuous pulse oximetry monitoring during their entire 48-72 hours of inpatient treatment during the Phase 2 and Phase 3 trials. In addition, each trial had a definition for an AE of hypoxia and Study 062 additionally defined an event of "decreased oxygen saturation."

For any patient who was reported by the investigator as having an event of hypoxia, there is a detailed narrative available in the Appendix (Section 11).

To provide a comprehensive analysis, Table 23 shows all events of oxygen saturation decrease to a level of 95% or below as a more sensitive and comprehensive threshold. Patients with levels meeting the clinical definition of hypoxia, oxygen saturation below 90%, are highlighted in the blue box. Most of the patients in the blue box are from Study 111 while one patient is from Study 062. The majority of the patients in the blue box are patients in Study 111 who underwent abdominoplasty or breast augmentation. Study 026 was not included in the chart because the cases of hypoxia occurred in doses above the range for our highest proposed dose.

Table 23: Patients with any Oxygen Saturation ≤95% (Studies 062, 111)

	Study 062				Study 111	
	Placebo N=79 n	0.125 mg TID N=82 n	0.25 mg TID N=80 n	0.5 mg TID N=81 n	0.5 mg TID N=50 n	Morphine 4 mg TID N=50 n
86					1	
87					7	
88					3	3
89				1	2	
90	1	1	1	1	3	3
91	2	2	3		1	2
92	1	4	3	6	1	5
93					6	3
94				1	6	10
95				1	9	14

Sources: CSR INS005-15-062, CSR INS005-17-111

7.6.1. Study 026 Discontinuation Narratives

The following narratives are for two subjects who were discontinued from Study 026 due to AEs and were subsequently treated with naloxone.

Subject Number (b) (6) **MedDRA Preferred Term**: Drowsiness

Randomized Therapy: Buprenorphine Sublingual Spray 1.0 mg 2 times daily (BID)

Dose at Onset of AE: 1 mg BID, **Exposure Duration at AE Onset**: 0 days

Study Period: treatment, **AE Duration**: 1 day

Severity: severe, **Relationship**: definitely related, **Outcome**: recovered/resolved

Subjec (b) (6) is a 48-year-old Caucasian Latino female with a medical history of right foot bunion, abdominoplasty in (b) (6) constipation, premenstrual syndrome, and mild facial acne. She was receiving concomitant medications of multivitamin, magnesium, zinc, Vitamin D, flaxseed oil, Prunelax and Vitex agnus-castus at study entry. On (b) (6), the subject underwent a bunionectomy and tolerated the procedure well. She was assigned to randomized study medication Buprenorphine Sublingual Spray 1.0 mg BID. Her predose (03:18) blood pressure was 103/63 mmHg, heart rate was 58 beats per minute (bpm), and respiratory rate was 18 breaths per minute. She received her first dose of randomized study medication on (b) (6) at 03:22.

On (b) (6) at approximately 04:14, the subject experienced moderate nausea, and at 04:27 she experienced moderate emesis and was given ondansetron at 04:28. The investigator considered these adverse events to be probably and possibly related to study medication, respectively. The subject also received metoclopramide 10 mg at 07:45. She received the second dose of study medication (placebo, per protocol) at 11:22, vomited at 11:44, and received metoclopramide 10 mg at 11:58. Study medication was administered at 15:23 and

metoclopramide10 mg at 16:05. The fourth dose of study medication (placebo per protocol) was administered at 19:22.

On (b) (6) at 19:45 the subject experienced the adverse event of severe drowsiness. Protocol-directed measures of stimulation, deep breathing, and supplemental oxygen were conducted when the oxygen saturation level was <90%, and the subject's oxygen saturation level improved (no measurement available). Intravenous naloxone 2 mg was administered at 20:33, and metoclopramide 5 mg was administered at 20:38. The investigator considered the AE of drowsiness to be definitely related to study medication, and the subject was withdrawn from treatment with study medication. The AE of drowsiness resolved at 21:58.

The subject was subsequently given tramadol, oxycodone/APAP 5-325, and ibuprofen for postoperative pain on (b) (6) and (b) (6).

The emergency room physician at (b) (6) requested the blind be broken on (b) (6) at 23:00 and the medical monitor approved.

The medical monitor did not consider the event to be an SAE, because the subject was not admitted to inpatient status but only to the emergency department and since the subject was stable throughout with only occasional borderline saturations that responded to protocol-directed measures of stimulation and supplemental oxygen. The medical monitor also noted that repeated administration of metoclopramide likely contributed to the degree of sedation seen in Subject (b) (6) and recommended the site instead consider using ondansetron as first-line antiemetic.

Subject Number: (b) (6) **MedDRA Preferred Term**: Respiratory rate decreased; Drowsiness

Randomized Therapy: Buprenorphine Sublingual Spray 1 mg 3 times daily (TID)

Dose at Onset of AE: 1 mg TID, **Exposure Duration at AE Onset**: 0 days

Study Period: treatment, **AE Duration**: 1 day

Severity: severe, **Relationship**: definitely related, **Outcome**: recovered/resolved

Subject (b) (6) is a 54-year-old Caucasian male with a medical history of myopia, Lasik surgery, and allergic rhinitis. He was receiving a concomitant probiotic. On (b) (6), the subject underwent a bunionectomy on his left foot and tolerated the procedure well. He was assigned to randomized study medication Buprenorphine Sublingual Spray 1.0 mg TID. His predose (03:34) blood pressure was 143/90 mmHg, heart rate was 70 beats per minute (bpm), and respiratory rate was 16 breaths per minute. He received his first dose of randomized study medication on (b) (6) at 03:37.

At 1 hour post dose (04:37) on (b) (6), the subject's blood pressure was 127/87 mmHg, heart rate was 68 bpm, and respiratory rate was 16 breaths per minute. The subject received the second dose of study medication at 11:37, the third dose (placebo, as per protocol) at 15:39, and the fourth dose at 19:37.

On (b) (6) at 19:42, the subject experienced respiratory rate decreased (no measurement available) and drowsiness. The respiratory rate decrease was considered moderate and the drowsiness was considered severe. Protocol-directed measures of stimulation, deep breathing, and supplemental oxygen were conducted when the oxygen saturation level was <90%, and the subject's oxygen saturation level improved (no measurement available). Naloxone 2 mg was administered intravenously at 21:37.

The investigator considered both AEs to be definitely related to study medication, and the subject was withdrawn from treatment with study medication. Both the AEs resolved at 21:38.

The emergency room physician requested the blind be broken at 23:00 on (b) (6) and the medical monitor approved.

The medical monitor did not consider the event to be an SAE, because the subject was not admitted to inpatient status but only to the emergency department and since the subject's occasional borderline O2 saturations responded to protocol-directed measures of stimulation and supplemental oxygen. The medical monitor also noted that the subject was stable and responsive throughout the events. The subject's oxygen saturation level was restored and maintained.

7.6.2. Serious Adverse Event Narratives

Study INS-14-026

Subject Number: (b) (6), MedDRA Preferred Term: Atrial fibrillation

Randomized Therapy: Buprenorphine Sublingual Spray 0.5 mg TID

Dose at Onset of AE: 0.5 mg TID

Exposure Duration at AE Onset: 0 days

Study Period: treatment

AE Duration: 3 days

Severity: severe

Relationship: unlikely related

Outcome: recovered/resolved

Subjec (b) (6) is a 56-year-old Caucasian female with a medical history of right knee and wrist fractures, arrhythmia, and anxiety. She was receiving concomitant medications of multivitamin, aspirin, Vitamin D, and Omega 3. On (b) (6) the subject underwent a left foot bunionectomy and tolerated the procedure well. She was assigned to randomized study medication Buprenorphine Sublingual Spray 0.5 mg TID, and received her first dose on (b) (6) at 03:25. At 1 hour post dose (04:26), the subject's blood pressure was 111/60 mmHg, heart rate was 79 beats per minute (bpm), and respiratory rate was 18 breaths per minute.

On (b) (6) at approximately 10:30, the subject experienced AEs of lightheadedness, nausea, and emesis that were all mild and the investigator considered possibly related to study medication.

The subject's heart rate was noted to be between 110-130 beats per minute. At 11:50, an electrocardiogram (ECG) was performed and revealed atrial fibrillation. None of the subject's previous ECGs had shown atrial fibrillation. At 12:08, a second ECG was performed and also showed atrial fibrillation. At 12:35, the subject began to complain of tingling of the lips and fingertips. The subject was to be discharged to home with a cardiologist appointment for the following day, but at 13:15, the subject began to complain of lightheadedness and nausea. These symptoms continued and the investigator called Emergency Services. The subject was

transferred to the hospital and was admitted for treatment of atrial fibrillation. Study medication was permanently discontinued.

On (b) (6), laboratory results revealed an elevated white blood count (WBC) of 14.5 × 109/L (normal range 4.5 – 11.0 × 109/L). A chest X-ray was performed and revealed no acute findings. The subject received Cardizem and heparin intravenously, in the attempt to convert the subject's rhythm. On (b) (6), the subject was in normal sinus rhythm. On (b) (6) the subject was discharged home in stable condition with prescriptions for amiodarone and diltiazem HCl (Cardizem CD), and orders to follow up with her primary care physician and cardiologist.

The SAE was considered to have resolved as of (b) (6) (time unknown). The Principal Investigator determined the severity of the event of "atrial fibrillation" as severe and the relationship of the event to the study drug was assessed as unlikely related. The event outcome is recovered.

Study INS005-15-062

Subject: (b) (6)

Assigned Treatment Group: Buprenorphine Sublingual Spray 0.5 mg TID

Race/Ethnicity/Gender: White/not Hispanic or Latino/Female

Age at Screening: 65 years

Informed Consent Date: (b) (6)

Randomization Date: (b) (6)

Date/Time Study Drug First Administered: (b) (6) / 09:03

Date/Time Completion/Discontinuation: (b) (6) / 16:15

Events Meeting Narrative Writing Criteria

MedDRA PT (Verbatim)	Onset Date/ Time	End Date (Day)	Severity; Related	Outcome; Action[b]
Angioedema/ ANGIOEDEMA	(b) (6) / 17:30	(b) (6) / 14:00	Severe; Unlikely related	Recovered/resolving; None

Description of Event(s), Including Follow-up:

The subject was a 65-year-old white, non-Hispanic/non-Latino woman with a history that included allergies to codeine, latex, and food, was treated with Buprenorphine Sublingual Spray 0.5 mg 3 times daily. The subject experienced mild, transient nausea and dizziness beginning approximately 5 hours after her first dose with study treatment. She remained on treatment and experienced a number of mild to moderate AEs, including moderate vomiting and mild oxygen saturation decreased, vision blurred, dyspnea, dizziness, nausea, chills, asthenia, and nasal congestion during the Treatment Period. Most of these events were considered possibly related to

treatment, and the subject completed 6 doses of study medication as planned. Treatments during this period included ondansetron and oxygen.

Approximately 16.5 hours after the last treatment with study medication, she began experiencing severe swollen tongue within one hour of taking a dose of ondansetron oral disintegrating tablet for nausea. The subject reported to the emergency room and was diagnosed with angioedema. The subject was intubated approximately 22 hours after the last dose of study drug. The swollen tongue and angioedema resolved the following day (Day 5). All these severe events were considered unlikely related to study drug, and the angioedema was considered an SAE.

During the period of the SAE, the subject also experienced moderate mucous membrane disorder, considered possibly related to study drug, and moderate anxiety, considered not related.

Treatments included diphenhydramine hydrochloride for the swollen tongue; epinephrine, diphenhydramine hydrochloride, methylprednisone sodium succinate, and sodium chloride for angioedema; etomidate for anesthesia for intubation; propofol for anxiety, and famotidine for nausea prophylaxis.

The angioedema and all the AEs resolved, and the subject completed the study.

Sponsor's Assessment:

Angioedema is listed as an expected event for Buprenorphine, as documented in the BUPRENEX and SUBUTEX labels. In addition, a search in the FDA Adverse Event Reporting System database in 2016 lists 13 events attributed to buprenorphine products. However, the temporal relationship between Buprenorphine dosing and the onset of symptoms makes buprenorphine an unlikely causal factor. The onset of symptoms occurred approximately 17.5 hours after the last dose of Buprenorphine in the study, followed by a rapid progression thereafter. It is also noteworthy that the subject took a dose of ODT ZOFRAN® (ondansetron) for the first time, approximately 1 hour prior to onset of symptoms. Ondansetron has a known association with angioedema, shortness of breath, bronchospasm and laryngeal stridor as noted in the Zofran® label under "General Events Observed During Clinical Practice" which states that flushing, rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have been reported with ondansetron use. Importantly, the FAERS database located 13 cases of angioedema attributable to ondansetron. Therefore, the sponsor concurs with the medical monitor's assessment as unlikely related.

Study INS005-17-111

Subject (b) (6): Incision Site Hematoma; Severe; Possibly Related to Study Drug

Subject (b) (6), a 32-year old black female, began receiving Buprenorphine SL Spray on (b) (6). The subject had an abdominoplasty on (b) (6). The subject received only one dose of study drug on (b) (6), during the inpatient Treatment Period.

The subject had a past medical history of Caesarean section on (b) (6) and procedural nausea prior to dosing on (b) (6). The subject had ongoing medical history of 2 separate cases of drug intolerance starting in (b) (6) and lipodystrophy acquired starting in (b) (6)

The subject had prior medications of morphine sulfate 1 mg BID intravenously for postoperative pain; clindamycin hydrochloride 600 mg once intravenously for prophylaxis of infection; oxygen 5 L/min continuous for oxygenation; sevoflurane 4% continuous for anesthesia; propofol 200 mg once intravenously for anesthesia; dexamethasone 10 mg once intravenously for prophylaxis of nausea; ondansetron 4 mg once intravenously for prophylaxis of nausea (this was a protocol violation; subject should have received 8 mg); midazolam hydrochloride 2 mg once intravenously for anesthesia; flebobag ring lact 800 mL continuous intravenously for fluid replacement; fentanyl 50 µg twice intravenously for postoperative pain; ondansetron 4 mg twice intravenously for postoperative nausea; morphine sulfate 2 mg once intravenously for postoperative pain, all on (b) (6).

Concomitant medications included bactrim 800 mg dose, 3 separate times, from (b) (6) to (b) (6), from (b) (6) to (b) (6), and from (b) (6) to (b) (6) for prophylaxis of infection; bactrim 800 mg BID on (b) (6) for prophylaxis of infection; metoclopramide hydrochloride 10 mg once intravenously on (b) (6) for nausea; paracetamol 1000 mg once on (b) (6) for postoperative pain; morphine sulfate 2 mg TID intravenously on (b) (6) for postoperative pain; morphine sulfate 2 mg once intravenously on (b) (6) for postoperative pain; clindamycin hydrochloride 600 mg once intravenously on (b) (6) for prophylaxis of infection; oxygen 6 L/min continuous on (b) (6) for oxygenation; lidocaine hydrochloride 50 mg once intravenously on (b) (6) for anesthesia; proprofol 1160 mg intermittently intravenously on (b) (6) for anesthesia; fentanyl citrate 100 µg intermittently intravenously on (b) (6) for anesthesia; dexamethasone 4 mg once intravenously on (b) (6) for prophylaxis of nausea; metoclopramide hydrochloride 10 mg once intravenously on (b) (6) for prophylaxis of nausea; famotidine 20 mg once intravenously on (b) (6) for prophylaxis of heartburn; ondansetron 4 mg once intravenously on (b) (6) for prophylaxis of nausea; midazolam hydrochloride 2 mg once intravenously on (b) (6) for anesthesia; hyoscine butylbromide 1 patch on (b) (6) for prophylaxis of nausea; paracetamol 1 g continuous intravenously for anesthesia; proprofol 100 mg once intravenously on (b) (6) for anesthesia; flebobag ring lact 900 mL continuous intravenously on (b) (6) for fluid replacement.

On (b) (6), the subject experienced AEs of nausea and vomiting. The nausea was deemed moderate in severity and the vomiting was deemed mild in severity; both were judged to be possibly related to the study drug. The drug was withdrawn in response to both events. Concomitant medication (ondansetron 4 mg intravenously) was given in response to the nausea event; no other action was taken in response to the vomiting event. The subject withdrew from the study after receiving only one dose of study drug. The vomiting event was resolved on (b) (6) and the nausea event was resolved on (b) (6).

On (b) (6), the subject experienced an SAE of incision site hematoma, deemed severe in severity and possibly related to the study drug. This event was considered serious and medically significant. No action was taken with the study drug in response; however, treatment was given for this event, which was resolved on (b) (6).

7.7. Safety Summary

Buprenorphine Sublingual Spray was generally safe and well-tolerated for up to 7 days in the setting of moderate to severe acute pain. The data from Study 111 support the prophylactic use of antiemetics to reduce the rate of vomiting associated with the use of the drug product in a high-risk population for nausea and vomiting. The events of vomiting were reduced in number and severity by prophylactic antiemetic therapy. The events of hypoxia are consistent with commonly used opioids. Oxygen saturations did not drop below 86%.

8. RISK MANAGEMENT

8.1. Identification of Risks Associated with Use of Buprenorphine Sublingual Spray

8.1.1. Misuse, Abuse, Addiction, and Overdose

Over the last several years, the inappropriate use of opioids has led to an epidemic of opioid misuse in the U.S. that has been responsible for thousands of deaths. Despite the fact that buprenorphine products are reported to be less abused than other CII opioid products, the risk of misuse and abuse is present and communicated and managed in the proposed Prescribing Information and Medication Guide of Buprenorphine Sublingual Spray. The proposed label for Buprenorphine Sublingual Spray contains the same warning and precautions messages as approved for the currently marketed opioids and buprenorphine containing products such as Buprenex, Subutex, Suboxone, Belbuca, and Butrans.

In addition, all buprenorphine containing products are prescribed and dispensed through different REMS programs. Therefore, INSYS also proposed a REMS program for the risk management related to the use of Buprenorphine Sublingual Spray.

8.1.2. Vomiting

It was identified during the clinical studies that the use of Buprenorphine Sublingual Spray is associated with a higher risk of vomiting for females, who are opioid naïve, younger in age (≤ 40 years of age), and have a history of postoperative nausea and vomiting or motion sickness similar to other opioids. Therefore, it is proposed to integrate the management of vomiting into this dedicated REMS for Buprenorphine Sublingual Spray.

8.1.3. Hypoxia and Other Respiratory Events

Similar to other opioids, the use of Buprenorphine Sublingual Spray can be associated with serious, life-threatening, or fatal respiratory depression, even when used as recommended. This risk will be managed using the same tools as those for other opioids, such as Prescribing Information and education of the prescribers and patients using tools described in the proposed REMS program.

8.1.4. Unintentional Exposure

To prevent unintentional exposure, the same packaging configuration and disposal system as those used for the currently marketed CII product is proposed. The proposed packaging is child resistant and the disposal configuration offers a safe and effective method to dispose of used and unused products.

8.1.5. Dose Stacking

To prevent patients taking doses outside of the recommended regimen (three times a day, every 8 hours), INSYS will include information in the proposed label concerning the risks of administering doses above the recommended maximum.

8.2. Rationale for the Proposed REMS Program

As there is not a shared REMS for the short-acting opioids, INSYS reviewed the current existing REMS programs for buprenorphine containing products. Three different REMS programs are currently implemented:

- REMS for SUBOXONE sublingual film, SUBOXONE sublingual tablets, and SUBUTEX sublingual tablets marketed for treatment of opioid dependence.
- BTOD shared system REMS implemented for the buprenorphine containing transmucosal products for treatment of opioid dependence such as Bunavail, Zubsolv, and various Buprenorphine containing generic products.
- Extended-Release and Long-Acting (ER/LA) Opioid Analgesics shared system REMS implemented for buprenorphine containing products such as Butrans and Belbuca marketed for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

All of these programs are designed to mitigate the risk of misuse, abuse, addiction, and overdose by:

1. Prescribing and dispensing buprenorphine containing products only to appropriate patients.
2. Educating prescribers and patients on the potential for misuse, abuse, addiction, and overdose of these products.

Because Buprenorphine Sublingual Spray is proposed for analgesia, and the FDA recommendation is that a REMS is necessary for IR opioid analgesics, it would be subject to the same REMS requirements as the ER/LA opioid analgesics (https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm), INSYS used the ER/LA) Opioid Analgesics shared system REMS as a base for proposing a dedicated REMS for Buprenorphine Sublingual Spray. Once a class shared REMS program becomes available, INSYS will join the program.

The use of Buprenorphine Sublingual Spray is associated with a risk of vomiting. The management of vomiting will be integrated into this dedicated REMS for Buprenorphine Sublingual Spray. The population at particular risk of vomiting will need to be identified by the prescriber and informed about the management of this adverse event. The training modules will contain the appropriate information on how to identify and counsel these patients. INSYS will work with the FDA on how to appropriately address this need.

8.3. Summary of the Proposed REMS Program

The goals of the Buprenorphine Sublingual Spray REMS Access program are to mitigate the risk of:

- misuse, abuse, addiction, overdose, and serious complications due to medication errors.
- vomiting that may be present in the high risk population.

The mitigation of these risks will be achieved by:

1. Prescribing and dispensing TRADENAME products only to appropriate patients, which includes use only in patients with acute pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.
2. Preventing accidental exposure to children and others for whom it was not prescribed.
3. Educating prescribers and patients on the potential for misuse, abuse, addiction, and overdose of TRADENAME products. This module will include training of the prescriber on how the patient would recognize the possible signs and symptoms of respiratory depression and seek for medical attention.
4. Educating prescribers on the identification of the population at particular risk of vomiting and management of this adverse event.

Under the conditions specified in this REMS program, prescribers of Buprenorphine Sublingual Spray are strongly encouraged to do all of the following:

- **Train -** Educate themselves by completing a REMS-compliant education program offered by an accredited provider of continuing education (CE) for their respective discipline.
- **Counsel** their patients by discussing the safe use, serious risks, storage, and disposal of Buprenorphine Sublingual Spray opioid analgesics with patients and/or their caregivers every time they prescribe these medicines.
- **Emphasize** Patient and Caregiver understanding of the Medication Guide by stressing to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time a Buprenorphine Sublingual Spray is dispensed to them.
- **Consider** using other tools in addition to the Patient Counseling Document provided with the drug, there are other publicly available tools to improve patient, household, and community safety, as well as compliance with conditions of treatment.

The patient education will be assured by:

- Medication Guide
- Label
- Enhanced Education for patients that includes:
  - 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
  - Education on the risks and precautions associated with opioids
  - Buprenorphine Sublingual Spray prescribing instructions
- Provider education of patients as described above.
- Product web site.

In addition to the program described above, INSYS will conduct post-marketing surveillance to assess the potential abuse, misuse, and diversion of Buprenorphine Sublingual Spray as it is already established for other opioid analgesics. This will include using the established tracking programs such as IMS prescription tracking to evaluate potential abuse, misuse and division. INSYS will also work with the RADARS reporting system to understand patterns of abuse, including data from poison control centers, government agencies that track drug transactions, patients entering opioid abuse treatment facilities, college surveys on opioid abuse, data on the street costs of drugs, and internet monitoring of user reports of abuse of opioid products and methods of abuse.

The efficacy of the proposed REMS program and postmarketing surveillance will be assessed and submitted to the FDA after the initial 6 months and 12 months from the initial approval date of the REMS, and annually thereafter. In case of identification of a persistent pattern of diversion or any additional risks, INSYS will work with the FDA on how to appropriately mitigate them.

8.4. Management of Risks of Unintentional Exposure

For the marketing of Buprenorphine Sublingual Spray, INSYS chose to package the product in the same packaging configuration and to use the identical disposal system as those used for the currently marketed CII product. INSYS believes that the proposed packaging and disposal configuration are safe and effective for opioid products, based on extensive data collected during the development of Buprenorphine Sublingual Spray and more than 6 years of post-marketing experience with a similar product. The unit dose device was also selected because it guarantees only a very limited residual quantity in used units, thus limiting the risk of the secondary exposure. The packaging and disposal system are presented in Figure 34 and described below:

- Primary Packaging: Unit dose spray device.
  The formulation is filled into a unit-dose sublingual spray device. Upon actuation, device delivers one dose of the product (Figure 3). Once actuated, the spray cannot be re-used. The vial that held the formulation before actuation contains a theoretic amount of less than 0.04 mL of the residual product once used. The studies demonstrated that residual drug product is not visually apparent and is not accessible unless the device is taken apart and respective parts are rinsed carefully and all the rinsing solution is collected with great care. The Instructions for Use direct the user to dispose of the used device by placing it in a single child resistant disposal bag provided in the carton. Once sealed, the use of scissors is necessary to open the bag.
- Secondary packaging: The unit dose spray devices are packaged in individually-sealed child resistant, opaque protective blister packages that must be cut with scissors to remove the device for use (refer to Figure 4).
- Disposal System:
  To dispose of the unused units, INSYS provides a pouch lined with an absorbent material. The Instruction for Use will indicate to spray the unused units into the pouch. Studies were conducted to demonstrate that once the product is absorbed, the reclamation is not possible. The absorbent lined pouch is disposed the same way as

the used device by placing it in a single child resistant disposal bag provided in the carton (Figure 33).

Figure 33: Disposal of Unused Units

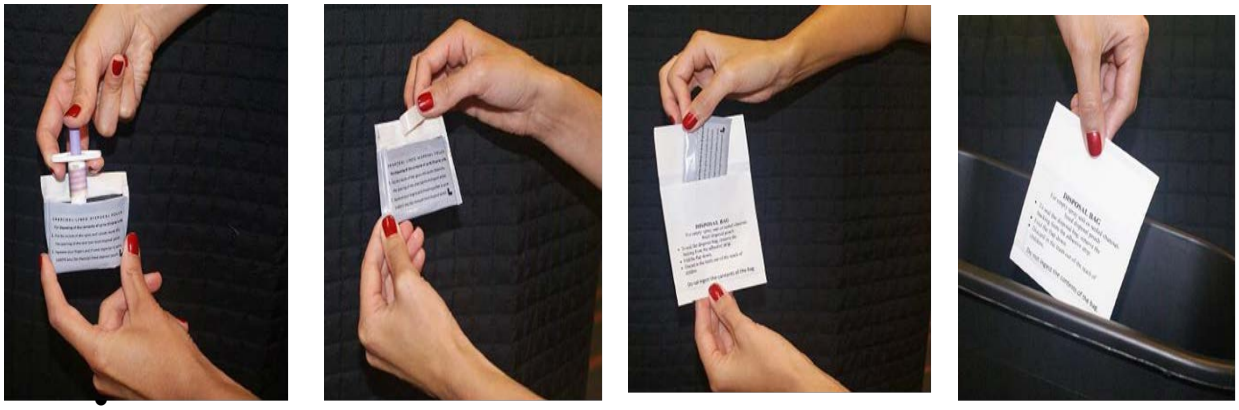
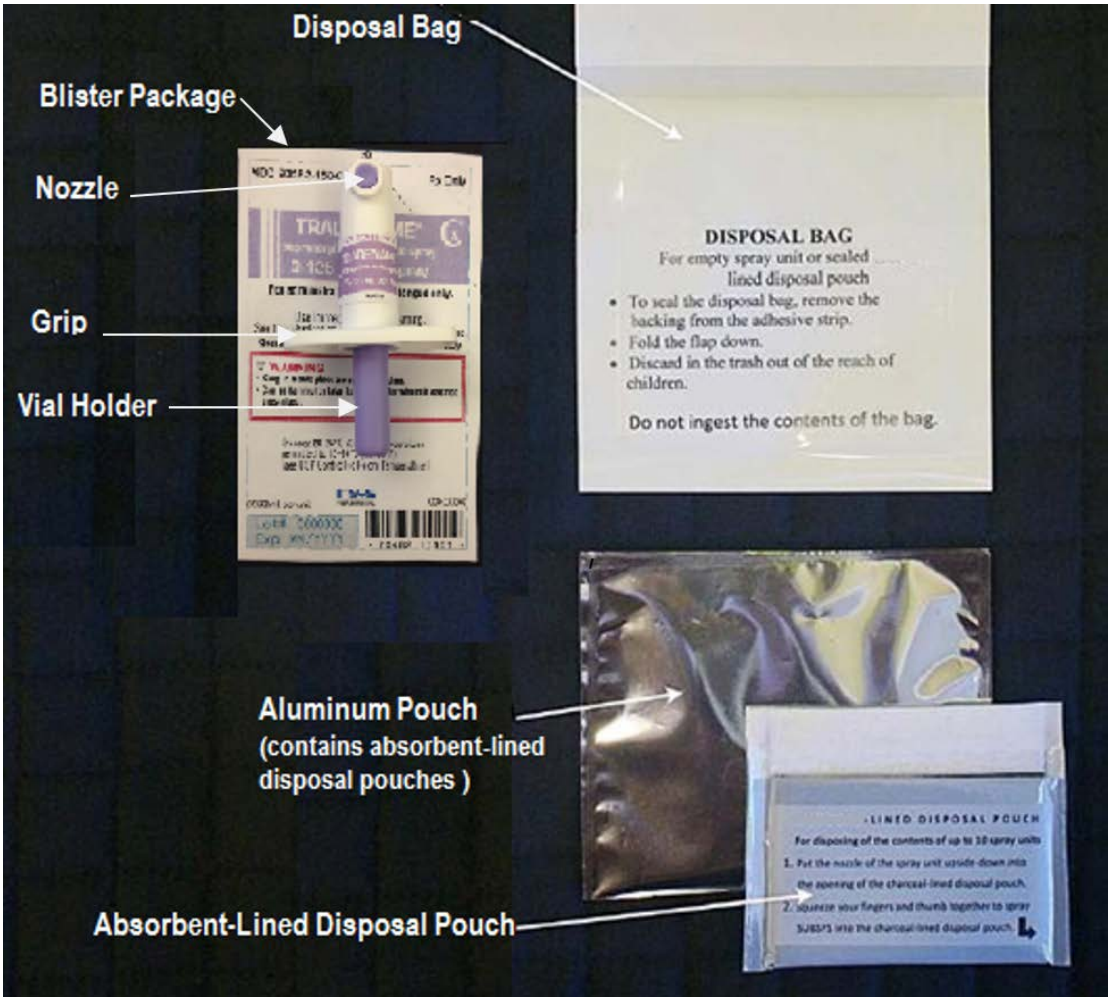


Figure 34: Packaging and Disposal System Proposed for Buprenorphine Sublingual Spray



8.5. Pharmacovigilance Program

The pharmacovigilance program will include gathering spontaneous reports of adverse events, and review and reporting of serious adverse event case assessments. As part of this program, employee training program is implemented to assure that all spontaneous adverse events are reported and evaluated.

Quarterly review of aggregated spontaneous adverse event information for trends and signals related to the branded products and/or their active moieties will be conducted along with the weekly review of scientific literature for patient safety issues related to the branded products or their active moieties. In addition, individual spontaneous adverse event case assessments for possible product quality issues that could impact patient safety are made.

Periodic Adverse Drug Experience Report Periodic Adverse Drug Experience Report (PADER) will be submitted to the FDA as required by FDA regulations 314.80(c)(2) quarterly for the first three years after the NDA approval and annually thereafter.

8.6. Conclusion

In summary, INSYS has a comprehensive Risk Management program that builds on the experience with its existing program for the transmucosal immediate release Schedule CII sublingual spray product, the currently approved Extended-Release and Long-Acting (ER/LA) Opioid Analgesics shared system REMS, and the experience collected during the development of the product.

The proposed program includes:

- creation of individual REMS program and when become available adherence to the shared class REMS program,
- patient and healthcare provider education,
- special single use unit sprays in child resistant packaging that includes warnings on the packaging and a safety disposal system,
- ongoing pharmacovigilance of adverse events, and
- surveillance for events of abuse, misuse, and diversion.

This risk management will allow to mitigate the risks related to the use of Buprenorphine Sublingual Spray and allow a safe utilization of the product in the appropriate population. The efficacy of the proposed programs and post-marketing surveillance will be assessed periodically and submitted to the FDA. In case of identification of persistent pattern of diversion or any additional risks, INSYS will work with the FDA on how to appropriately mitigate them.

9. BENEFIT/RISK CONCLUSIONS

Buprenorphine Sublingual Spray is a novel formulation of buprenorphine that has a positive benefit/risk ratio for the treatment of moderate-to-severe acute pain.

There is a medical need for additional treatment options for acute pain. Until non-opioid pain medications are adequate, there will be a role for opioids. In light of the opioid crisis, the greatest current need is for opioid pain medications with a lower potential for abuse. As most of the current medications for this category of pain are Schedule II, a Schedule III opioid pain medication that is easy to use and generally well tolerated would be an important advance.

Buprenorphine is a Schedule III opioid with established safety and efficacy. Buprenorphine has several characteristics that make it preferable to other opioids. It has a lower potential for abuse than Schedule II opioids as reflected both in its scheduling and in lower reported rates of abuse, misuse, diversion, overdose, and death (National Survey on Drug Use and Health, SAMHSA, 2016). These findings may be the result of its partial agonism at the mu opioid receptor. Literature suggests that buprenorphine may have a ceiling effect on respiratory depression that may be reflected in the lower rates of Emergency Department visits and overdose deaths compared to other opioids (Drug Abuse Warning Network, 2014). Additionally, compared to full mu opioid agonists, buprenorphine has lower rates of drug liking and euphoria, less cognitive impairment, less analgesic tolerance, and lower rates of constipation (Kress HG, 2009; Griessinger N et al., 2005; Shipton EA, 2005; Davis MP, 2012; Soyka M et al., 2005; Shmygalev S et al., 2011; Khanna IK, et al., 2015). It does not cause spasm in the sphincter of Oddi (Khanna IK, et al., 2015). Studies in elderly patients (aged ≥ 65 years) indicate that the pharmacokinetic profile, efficacy, and adverse events of buprenorphine do not alter with age. The ADME profile of buprenorphine also provides several advantages over other opioids. It's primarily metabolized by CYP 3A4. Buprenorphine does not induce or inhibit Cytochrome P450 isoenzymes at therapeutic levels. Nor is it substantially affected by drugs that inhibit the CYP 3A4 isoenzyme. As a result, it has few drug-drug interactions. It is primarily eliminated in stool and has limited renal metabolism or renal effects. Because of these characteristics, buprenorphine is reported to be a preferred opioid for patients with compromised renal or hepatic function (Khanna IK, et al, 2015).

The only buprenorphine formulation currently available for acute pain is a parenteral formulation that is administered as an IV or IM injection. Buprenorphine Sublingual Spray offers an alternative that allows physicians to take advantage of the unique pharmacology and safety profile of buprenorphine in an easy-to-administer non-parenteral formulation for moderate to severe acute pain. The spray can be administered by a patient or caregiver as well as a healthcare professional. Human Factors studies demonstrated that it is easy to use with little or no training for adults and the elderly. It does not require swallowing which is particularly important for patients with swallowing difficulties or who cannot take medications orally. The sublingual spray avoids the first-pass effect that limits the bioavailability of oral buprenorphine. The 8-factor analysis of Buprenorphine Sublingual Spray demonstrated that this formulation shares the low abuse potential of other buprenorphine products.

The clinical development program for Buprenorphine Sublingual Spray demonstrated that it has the expected efficacy for the around-the-clock management of acute pain and no new safety concerns associated with this novel formulation. All three doses demonstrated statistically significant differences from placebo that favored buprenorphine for the primary endpoint, the SPID-48. All of the secondary and exploratory efficacy endpoints also favored buprenorphine. Though the statistical testing was not alpha-protected, most of the secondary endpoints had nominal p-values below 0.05 and showed a dose effect with the greatest magnitude of benefit at the highest dose, 0.5 mg TID. Notably, the majority of subjects rated their overall satisfaction with treatment as Good, Very Good, or Excellent. There was also a 92.5% completion rate in the pivotal trial that may also reflect an overall satisfaction with treatment.

The safety findings for Buprenorphine Sublingual Spray were consistent with the established safety of buprenorphine. There were no new or unexpected adverse events associated with this formulation. Overall, Buprenorphine Sublingual Spray was generally well tolerated. The rate of discontinuation for adverse events in the pivotal Phase 3 trial was 3.7%.

There were high rates of GI events, specifically nausea and vomiting, in the pivotal trial. The rates of these events were dose-related, with the highest rates in the highest dose (for 81 patients on the 0.5 mg TID dose, nausea: 84.0% and vomiting: 72.8%). The rates of these events were lower in Study 111, which included the use of prophylactic antiemetics (for 50 patients on the 0.5 mg TID dose, nausea: 78.0% and vomiting: 52.0%) and there were no severe events in Study 111.

Nausea and vomiting are known events associated with the use of opioids and can be managed routinely in standard medical practice. The risk of these events will be addressed in the proposed label and patient and provider education.

Respiratory depression is a known risk of opioids and can occur with Buprenorphine Sublingual Spray. In the clinical program, there were reports of reduced oxygen saturation and hypoxia. While none of the cases in the trials were considered severe or serious at the proposed doses, serious life-threatening respiratory depression can occur with opioids even if used properly. The risk is known to be greatest at the initiation of therapy or at dose titration. Patient and provider education will address these risks, which are opioid class risks.

Buprenorphine shares the same risks as all approved opioids, including the boxed warnings. These include risks of addiction, abuse, and misuse, which can lead to overdose and death. Serious, life-threatening, or fatal respiratory depression may occur. Accidental exposure, especially in children, can result in fatal overdose. Prolonged use during pregnancy can result in neonatal opioid withdrawal syndrome that may be life-threatening. Concomitant use of opioids with benzodiazepines or other central nervous system depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

Until non-opioid alternatives are sufficient to manage moderate-to-severe acute pain, there will still be a role for opioid pain medications. Buprenorphine has favorable characteristics for the management of pain that are well established in the literature. The Buprenorphine Sublingual Spray clinical program demonstrated that the product has benefits that outweigh its risks. The

key benefit is efficacy in the around-the-clock management of moderate-to-severe acute pain as demonstrated across multiple trials and endpoints. The risks are well characterized and manageable. In the clinical trials, there were no new risks identified for the spray formulation.

In light of the opioid crisis and the need for Schedule III opioid pain medications to manage moderate-to-severe acute pain, buprenorphine has characteristics that make it a good choice for many patients. It has a lower abuse potential than Schedule II opioids and has a favorable profile for a wide range of patients, including the elderly and those with hepatic or renal impairment. The spray formulation is a useful advance in that it offers an easy-to-use alternative for acute pain, compared to the only approved treatment option which is an injectable.

Buprenorphine Sublingual Spray represents an important new treatment option. It has a favorable benefit/risk profile for the treatment of moderate-to-severe acute pain.

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11. APPENDIX: SAFETY NARRATIVES

11.1. Hypoxia and Decreased Oxygen Saturation Narratives

11.1.1. Study 111

Discontinuation and Hypoxia

Subject (b) (6): Oral cavity irritation Mild; Possibly related to study drug

Subject (b) (6), a 57-year-old white female received first dose of Buprenorphine SL spray (0.5 mg TID) on (b) (6). The subject had bunionectomy of right foot on (b) (6). The subject received the last dose of study drug on (b) (6) for a total of 9 doses during Inpatient Treatment Period.

The subject had past medical history of epicondylitis (tennis elbow) in (b) (6) The subject had ongoing medical history including post menopause from (b) (6) foot deformity from (b) (6) and overweight from (b) (6)

The subject had taken prior medications including phentermine 37.5 mg QD from (b) (6) to (b) (6) for weight loss, midazolam 2 mg once intravenously for anesthesia, lidocaine 10 mL once for local anesthesia, fentanyl 50 µg once intravenously for intraoperative pain, propofol 210 mg once intravenously anesthesia, ketorolac 30 mg once intravenously for intraoperative pain, dexamethasone 10 mg once for nausea prophylaxis, cefazolin 1 g once intravenously for infection prophylaxis, oxygen 2 L continuous inhalation, and lactated Ringers 600 mL continuous intravenously for hydration, all on (b) (6).

The subject did not receive ondansetron during surgery for nausea prophylaxis.

The concomitant medication included oxygen 2 L continuous inhalation for hypoxia on (b) (6). The Investigator defined hypoxia as any drop in oxygen saturation below 90%.

The subject also experienced moderate disorientation and mild to moderate hypoxia that was considered possibly related to study drug. The oxygen saturation was in the low 70% range at 11:30 on (b) (6). The subject was given oxygen via a canula and oxygen saturation was 90 at 11:35 and 92% at 13:35. The moderate hypoxia started approximately 4.5 hour after sixth dose of study drug. The event was treated with oxygen and resolved approximately 1 hour after onset. Mild hypoxia began approximately 8 hours after the last inpatient dose (Dose #9). The event did not require intervention and resolved approximately 5 days later.

On Day 2, during the 48-hour oral cavity examination, local irritation was noted as an abnormal finding. An AE was open for mild oral cavity irritation and was considered possibility related to study drug. The event resolved prior to the last inpatient dose (Dose #9). Even through the AE resolved, the subject was withdrawn from treatment and not discharged with study drug.

On (b) (6), 2 days after starting the study drug, the subject reported with an adverse event of oral cavity irritation that was considered mild in severity and possibly related to the study drug. The study drug was withdrawn in response to the event. Oral irritation as noted in the 48-hour assessment with no mucositis, blistering or redness. The event was considered resolved on (b) (6).

The subject received ondansetron 4 mg intravenously from (b) (6) to (b) (6) for an AE of nausea while at the research site.

Other AEs:

- Hypoxia of moderate severity on (b) (6) deemed possibly related to the study drug. The subject was noted to have low oxygen saturation on room air and remained sleepy for approximately 9.5 hours. Standard of care stimulation maneuvers that was part of routine post-operative nursing care for starting oxygen was not captured in progress notes or source documentation.

  The subject received oxygen 2 L continuous inhalation for hypoxia on (b) (6) after which the event was considered resolved. Even though in the Investigator's opinion the hypoxia event was clinically mild in severity and did not pose any type of immediate safety threat to the subject, per the protocol, the hypoxia event was reported as moderate in severity due to treatment of oxygen. The subject had another event of hypoxia on (b) (6) of mild severity which was deemed possibly related to the study drug. The oxygen saturation was noted at 88%, which was deemed resolved on (b) (6).

- Disorientation of moderate severity on (b) (6) deemed possibly related to the study drug which was considered resolved the same day.

- The subject experienced moderate nausea beginning approximately 3 hours on (b) (6) after first dose with study treatment. The nausea was treated with ondansetron. The event was considered possibly related to study drug and resolved prior to the second dose of study treatment. The subject remained on treatment and completed the 8 and 16 hour dose of study drug. Approximately 6 hours after the third dose (22 hours after beginning treatment) (b) (6), the subject experienced moderate nausea that was probably related to study drug. The nausea was treated with ondansetron but did not resolve until approximately 48 hours after onset. The event was considered resolved on (b) (6).

Hypoxia

Subject (b) (6): Hypoxia; Mild; Not related to study drug

Subject (b) (6), a 40-year-old white male received first dose of study drug on (b) (6). The subject had bunionectomy of left foot on (b) (6). The subject received the last dose of study

drug on (b) (6) for a total of 9 doses during Inpatient Treatment Period and 12 doses during Outpatient Treatment Period.

The subject had ongoing medical history of foot deformity from (b) (6) attention deficit hyperactivity syndrome (ADHD) and depression from (b) (6)

The subject had taken prior medications including midazolam 2 mg once intravenously for sedation, lidocaine 2% 20 mL once subcutaneously for anesthesia, propofol 400 mg intravenously once for general anesthesia, ondansetron 8 mg once intravenously for nausea prophylaxis, cefazolin 2 g once intravenously for infection prophylaxis, dexamethasone 10 mg intravenously for nausea prophylaxis, lactated Ringers 1 L continuous intravenously for hydration and oxygen 1 L continuous respiration for oxygenation all on (b) (6)

The concomitant medications included Adderall 20 mg QD for ADHD from (b) (6) and fluoxetine 20 mg QD for depression from (b) (6)

On (b) (6), 2 days after starting the study, the subject reported an adverse event of hypoxia, which was deemed mild in severity and started after the 8th dose of study drug (approximately 53 hours after beginning treatment). The event resolved approximately 7 hours after onset.

The event was deemed not related to the study drug. There was no change in the study drug in response to the event.

The Investigator defined hypoxia as any drop in oxygen saturation below 90%.

The subject was assessed and found to have oxygen saturation below 90% on room air. The subject was encouraged to sit up and take deep breaths and the oxygen saturation was found to remain above 90% with verbal commands. There was no supplemental oxygen required. Even though in the Investigator's opinion the hypoxia event was clinically mild in severity and did not pose any type of immediate safety threat to the subject, per the protocol, the hypoxia event was reported as moderate in severity due to treatment of oxygen.

The oxygen saturation level was at 89% on (b) (6) at 21:00 hours, the time of the AE. At 00:02 on (b) (6) the oxygen saturation was measured at 90% (60-hour assessment). Again at 01:57 on (b) (6) the oxygen saturation was measured at 86% (62-hour assessment). On (b) (6) at 0355 (64-hour assessment) the oxygen saturation was at 90%. The event was considered resolved on (b) (6)

Other Adverse Events:

- Euphoria of mild severity that started at the time of first outpatient dose (Dose #10; Approximately 72 hours after beginning treatment) deemed possibly related to the study drug on (b) (6), which was considered resolved on (b) (6)

- Sleepiness of moderate severity that started at time of first outpatient dose (Dose #10; Approximately 72 hours after beginning treatment) deemed possibly related to the study drug on (b) (6), which was considered resolved on (b) (6)

- Loopiness of mild severity that started at time of first outpatient dose (Dose #10; Approximately 72 hours after beginning treatment) deemed possibly related to the study drug on (b) (6), which was considered resolved on (b) (6)

Discontinuation and Hypoxia

Subject (b) (6) Hypoxia; Moderate; Possibly Related to Study Drug

Subjec (b) (6), a 48-year old white female, received first dose of Buprenorphine SL Spray (0.5 mg mg TID) on (b) (6). The subject had an abdominoplasty on (b) (6). The subject received her last dose of study drug on (b) (6) for a total of 9 doses during the Inpatient Treatment Period.

The subject had past medical history of hysterectomy from (b) (6) to (b) (6) and uterine leiomyoma from (b) (6) to (b) (6). The subject had ongoing medical history of lipodystrophy acquired from (b) (6) and gastrooesophageal reflux disease from (b) (6)

The subject had prior medications of cefazolin sodium 1 g once intravenously for prophylaxis of infection; oxygen 2 L/min continuous for oxygenation; nitrous oxide 3 L/min continuous for anesthesia; sevoflurane 6% continuous for anesthesia; propofol 120 mg once intravenously for anesthesia; fentanyl citrate 150 mg once intravenously for anesthesia; dexamethasone 10 mg once intravenously for prophylaxis of nausea; ondansetron 8 mg once intravenously for prophylaxis of nausea; midazolam hydrochloride 1 mg once intravenously for anesthesia; lactated Ringers 0.65 L once intravenously for fluid replacement, all on (b) (6).

Concomitant medications included cefalexin 500 mg TID from (b) (6) to (b) (6) for prophylaxis of infection; docusate sodium 100 mg BID from (b) (6) to (b) (6) for prophylaxis of constipation; and oxygen 2 L/min continuous inhalation from (b) (6) to (b) (6) for hypoxia.

On (b) (6), the same day as starting study drug, the subject experienced an AE of hypoxia that was deemed moderate in severity and possibly related to the study drug. The oxygen saturation at 22:30 was 86% and the subject received supplemental oxygen. The oxygen saturation at 22:32 was 96%. On (b) (6) at 20:53, the oxygen saturation dropped to 88% and oxygen was started after which it was 97% at 20:55. On (b) (6), the oxygen saturation was 89% at 20:25 and the saturation went up to 95% and was sustained at 97% at 9:07. The oxygen saturation on (b) (6) at 9:09 and 12:02 was 94%.

The Investigator defined hypoxia as any drop in oxygen saturation below 90%. Standard of care stimulation maneuvers that were part of routine post-operative nursing care for starting oxygen

was not captured in progress notes or source documentation. Even though in the Investigator's opinion the hypoxia event was clinically mild in severity and did not pose any type of immediate safety threat to the subject, per the protocol, the hypoxia event was reported as moderate in severity due to treatment of oxygen.

The moderate hypoxia started approximately 3 hours after the second dose of study drug (approximately 11 hours after beginning treatment). The subject was withdrawn treatment after completing all the required doses for inpatient treatment (9 doses). The event resolved approximately 5 hours (approximately 69 hours after beginning treatment) after the ninth dose of study drug.

The event lasted 4 days and was considered resolved on (b) (6)

Other adverse events:

- Nausea of moderate severity which started approximately 0.5 hours after the 7th dose of study drug (approximately 48.5 hours after beginning treatment) on (b) (6) Ondansetron was administered immediately and the AE resolved approximately 0.5 hours after onset.

  The event was deemed possibly related to the study drug

Discontinuation and Hypoxia

Subject (b) (6): Hypoxia; Moderate; Possibly Related to Study Drug

Subject (b) (6), a 30-year old black female, received the first dose of Buprenorphine SL Spray (0.5 mg TID) on (b) (6). The subject had a breast augmentation on (b) (6). The subject received her last dose of study drug on (b) (6) for a total of 9 doses during the Inpatient Treatment Period.

The subject had no past medical history reported. The subject had ongoing medical history of skin abrasion starting on (b) (6), and micromastia starting in (b) (6)

The subject had prior medications of midazolam hydrochloride 2 mg once intravenously for anesthesia; cefazolin sodium 1 g once intravenously for prophylaxis of infection; oxygen 6 L/min continuous from for oxygenation; sevoflurane 2% continuous for anesthesia; lidocaine 20 mg once intravenously for anesthesia; propofol 200 mg once intravenously for anesthesia; fentanyl citrate 200 µg intermittently intravenously from for anesthesia; dexamethasone 10 mg once intravenously from for prophylaxis of nausea; ondansetron 8 mg once intravenously for prophylaxis of nausea; fentanyl 50 µg intermittently intravenously for postoperative pain; lactated Ringers 0.9 L once intravenously for fluid replacement, all on (b) (6).

Concomitant medications included norlestrin FE 1 tablet QD from (b) (6) for birth control; oxygen 2 L/min continuous inhalation from (b) (6) to (b) (6) and (b) (6) to

(b) (6) for hypoxia; cephalexin 500 mg TID from (b) (6) to (b) (6) for prophylaxis of infection; docusate sodium 100 mg BID from (b) (6) to (b) (6) for prophylaxis of constipation.

On (b) (6), the subject experienced an AE of hypoxia deemed moderate in severity and possibly related to the study drug. The hypoxia started approximately 4 hours after the fifth dose of study drug (approximately 36 hours after beginning treatment). The subject was withdrawn treatment after completing all the required doses for inpatient treatment (9 doses). The event resolved approximately 1 hour (approximately 65 hours after beginning treatment) after the ninth dose of study drug. The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The site staff followed standard of care stimulation maneuvers as oxygen saturation fell from the normal range to the upper 80% range on (b) (6). The oxygen saturation at 1:27 was 88%. Standard of care stimulation maneuvers that was part of routine post-operative nursing care for starting oxygen was not captured in progress notes or source documentation. Oxygen was started via nasal cannula for hypoxia and the oxygen saturation was 97% at 5:41. Attempts were made to wean the subject off oxygen; however, there was a recurrent need for oxygen on (b) (6) at 3:04, oxygen saturation was 88%. The subject was able to wean completely off of oxygen on (b) (6) as the oxygen saturation was 97% at 3:06 and 96% at 6:31. The event of hypoxia was considered resolved the next day. Study drug was withdrawn in response to the event and concomitant medication was required.

Even though in the Investigator's opinion the hypoxia event was clinically mild in severity and did not pose any type of immediate safety threat to the subject, per the protocol, the hypoxia event was reported as moderate in severity due to treatment of oxygen.

Other adverse events:

- Nausea of moderate severity that started approximately 1 hour after first dose of study treatment on (b) (6). The event was deemed possibly related to the study drug. The event resolved approximately 3.5 hours after second dose of study drug (approximately 11.5 hours after beginning treatment) on (b) (6). Ondansetron 4 mg intravenously was administered in response to the event.

- Dizziness of mild severity that started approximately 1.5 hours after the 6th dose of study treatment (approximately 41.5 hours after beginning treatment) on (b) (6). The event was deemed possibility related to the study drug. No action was taken and the event was resolved on (b) (6), approximately 3.5 hours after last inpatient dose (Dose #9) of study drug (approximately 67.5 hours after beginning treatment).

Discontinuation and Hypoxia

Subject (b) (6): Vomiting; Moderate; Possibly related to study drug

Subject (b) (6), a 56-year-old white female received the first dose of Buprenorphine SL spray (0.5 mg TID) on (b) (6). The subject had bunionectomy of right foot on (b) (6). The

subject received the last dose of study drug on (b) (6) for total 9 doses in Inpatient Treatment Period.

The subject had past medical history including food allergy from (b) (6) to (b) (6) Caesarean section in (b) (6) (b) (6) (b) (6) and (b) (6) temporomandibular joint syndrome in (b) (6) salpingectomy in (b) (6) ectopic pregnancy in (b) (6) hemorrhoid operation in (b) (6) gastrointestinal tract adenoma from (b) (6) to (b) (6) foot deformity in (b) (6) muscular weakness in (b) (6) balance disorder in (b) (6) influenza in (b) (6) meniscus injury and arthroscopy in (b) (6) folliculitis in (b) (6) Ongoing medical conditions included drug and rubber hypersensitivity from (b) (6) hemorrhoids from (b) (6) mitral valve prolapse from (b) (6) foot deformity from (b) (6) peripheral edema from (b) (6) dysphagia from (b) (6) temporomandibular joint syndrome from (b) (6) type 2 diabetes from (b) (6) varicose veins from (b) (6) sciatica and back pain from (b) (6) postmenopause from (b) (6) diverticulitis from (b) (6) neurodermatitis from (b) (6)

The subject had taken prior medications including midazolam 2 mg once intravenously for anesthesia, lidocaine hydrochloride 10 mL once for local anesthesia; fentanyl 100 µg once intravenously for intraoperative pain, propofol 250 mg once intravenously for anesthesia, ketorolac 30 mg once intravenously for intraoperative pain (a deviation from the surgical and anesthesia protocol); ondansetron 8 mg once intravenously for nausea prophylaxis, dexamethasone 8 mg intravenously for nausea prophylaxis (a deviation from the prophylactic nausea treatment), cefazolin sodium 1 g once intravenously for infection prophylaxis, oxygen 5 L by inhalation for oxygenation, lactated ringers 1 L intravenously continuously for hydration, all on (b) (6).

The subject was taking concomitant medications including metformin 500 mg twice daily for Type 2 diabetes; multi-vitamin once daily for general health; replenex once daily for general health; nutratherm twice daily for general health, all from (b) (6) oxygen 2 L by inhalation for hypoxia on (b) (6).

On (b) (6), 2 days after starting the study drug, the subject reported with an adverse event of vomiting which was deemed moderate in severity and possibly related to the study drug.

The subject experienced multiple episodes of moderate vomiting beginning approximately 2.5 hours after the first dose of study medication and multiple events of moderate nausea beginning approximately 3 hours after the first dose of study medication. The events were considered possibly related to study drug. The nausea and vomiting were treated with ondansetron. The final episode of vomiting began approximately 7 hours after the sixth dose of study medication (47 hours after beginning treatment), and it ended approximately 4 hours later. The final event of nausea began approximately 5.5 hours after the second dose of study medication (13.5 hours after beginning treatment), and resolved approximately 0.5 hours later.

The event of vomiting was considered resolved the same day. The study drug was withdrawn in response to the event.

The subject also reported with hypoxia of moderate severity on (b) (6) deemed possibly related to the study drug beginning approximately 3 hours after the seventh dose of study drug (51 hours after beginning treatment). The oxygen saturation level and duration of oxygen drop was not recorded. The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The standard of care stimulation maneuvers that were part of routine post-operative nursing care for starting oxygen were not captured in progress notes or source documentation.

The subject was assessed and found to have oxygen saturations below 90%. The subject was repositioned to sitting position and encouraged to take deep breaths and cough. The oxygen saturation improved to 90% but the subject was unable to maintain oxygen saturation 90% or above. The subject was encouraged to take deep breaths. There was some improvement, however the oxygen level was not maintained above 90%. A nasal cannula was placed with 2 L of oxygen. The oxygen saturation was found to be maintained above 90%, after which the nasal cannula was removed and it was confirmed that the subject was able to maintain saturation above 90% on room air. The event of hypoxia was considered resolved on (b) (6), approximately 3 hours after onset.

Even though in the Investigator's opinion the hypoxia event was clinically mild in severity and did not pose any type of immediate safety threat to the subject, per the protocol, the hypoxia event was reported as moderate in severity due to treatment with oxygen.

The subject received rescue medications including ondansetron 4 mg intravenously for nausea rescue from (b) (6) through (b) (6).

Other Adverse Events:

- An event of nausea of moderate severity on (b) (6) and (b) (6) deemed possibly related to the study drug, which was considered resolved on the same day.
- Four events of vomiting reported on (b) (6) and three events of vomiting on (b) (6), all of moderate intensity deemed possibly related. The events were resolved on the same day.

Discontinuation and Hypoxia

Subject (b) (6): Hypoxia; Moderate; Possibly related to study drug

Subjec (b) (6), a 32-year-old white female received first dose of Buprenorphine SL spray (0.5 mg TID) on (b) (6). The subject had abdominoplasty on (b) (6). The subject

received the last dose of study drug on (b) (6) for total 9 doses in Inpatient Treatment Period.

The subject had past medical history including Caesarean section in (b) (6) and postpartum depression in (b) (6)

The ongoing medical condition included lipodystrophy from (b) (6) and nausea from (b) (6), which was ongoing during the Treatment Period.

The subject had taken prior medications including midazolam 2 mg once intravenously for anesthesia, lidocaine hydrochloride 50 mg once intravenously for local anesthesia; fentanyl 300 µg intravenously for anesthesia and 50 µg for postoperative pain, propofol 700 mg once intravenously for anesthesia, ondansetron 8 mg total intravenously for nausea prophylaxis and 4 mg for postoperative nausea , dexamethasone 10 mg intravenously for nausea prophylaxis, cefazolin sodium 1 g once intravenously for infection prophylaxis, oxygen 10 L/min by inhalation for oxygenation, sevoflurane 1.5% by inhalation for anesthesia, lactated ringers 1.1 L intravenously continuously for hydration, all on (b) (6).

The subject was taking concomitant medications including oxygen 2 L by inhalation for hypoxia on (b) (6), (b) (6) and (b) (6); levonorgestrel intrauterine birth control from (b) (6); docusate sodium 100 mg BID for constipation prophylaxis from (b) (6) to (b) (6); cephalexin 500 mg TID for infection prophylaxis from (b) (6) to (b) (6).

On (b) (6), the same day of starting the study drug, the subject reported with an adverse event of hypoxia that was deemed moderate in severity and possibly related to the study drug. The moderate hypoxia started approximately 2 hours after the first dose of study drug. The hypoxia resolved approximately 6.5 hours after the seventh dose of study drug (approximately 62.5 hours after beginning treatment). On (b) (6) at 13:21, the oxygen saturation was 88% and at 13:23 it was 98%; on (b) (6) at 9:30, the oxygen saturation was 99%; 97% at 9:33; 89% at 12:48; 95% at 12:50. The subject was administered supplemental oxygen when the oxygen level dropped below 90%. On (b) (6), at 16:20 it was 98%; at 16:22 it was 96% and at 23:51, the level dropped to 89% after which supplemental oxygen was started and the oxygen saturation increased to 96%. On (b) (6), the oxygen saturation was 97% at 7:28; 94% at 7:30 and 88% at 8:49 at which time supplemental oxygen was initiated.

The study drug was withdrawn in response to the event. The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The standard of care stimulation maneuvers that were part of routine post-operative nursing care for starting oxygen were not captured in progress notes or source documentation.

The subject was administered 2 L oxygen by inhalation from (b) (6) to (b) (6) on which date, the event was considered resolved. Even though in the Investigator's opinion the hypoxia event was clinically mild in severity and did not pose any type of immediate safety

threat to the subject, per the protocol, the hypoxia event was reported as moderate in severity due to treatment with oxygen.

Other Adverse Events:

- Nausea of moderate severity on (b) (6) deemed possibly related to the study drug that was considered resolved on (b) (6), shortly after the fourth dose of study medication. The subject received rescue medications including ondansetron 4 mg twice intravenously for nausea rescue on (b) (6). The medical history reported the nausea was an ongoing event during treatment and overlapped with AE of moderate nausea beginning approximately 2 hours after first dose of study drug.

- Vomiting of moderate severity on (b) (6) beginning approximately 2 hours after first dose of study drug deemed possibly related to the study drug. The subject received rescue medications including ondansetron 4 mg twice intravenously and the event was considered resolved on the same day approximately 4 hours after the second dose of study medication (12 hours after beginning treatment).

- Dizziness of moderate severity on (b) (6), approximately 3.5 hours after the second dose of study medication (12.5 hours after beginning treatment) deemed possibly related to the study drug. The event was considered resolved on the same day within 1 minute of onset.

- Dyspnea of mild severity on (b) (6), which started approximately 7.5 hours after the third dose of study drug (23.5 hours after beginning treatment) deemed possibly related to the study drug which was considered resolved on (b) (6), immediately after the seventh dose of study drug (56 hours after beginning treatment).

Headache of mild severity on (b) (6), which started approximately 4 hours after the sixth dose of study drug (44 hours after beginning treatment), deemed possibly related to the study drug which was considered resolved on (b) (6), approximately 12 hours after the last inpatient dose (Dose #9) of study drug (76 hours after beginning treatment).

Discontinuation and Hypoxia

Subject (b) (6): Hypoxia; Moderate; Possibly related to study drug

Subject (b) (6), a 42-year-old black or African American female received the first dose of standard narcotic therapy on (b) (6). The subject had abdominoplasty on (b) (6). The subject received the last dose of study drug on (b) (6) for a total 9 doses in Inpatient Treatment Period.

The subject had past medical history including procedural nausea on (b) (6); mammoplasty in (b) (6); Caesarean section in (b) (6).

The ongoing medical condition included lipodystrophy acquired from (b) (6)

The subject had taken prior medications including midazolam 1 mg once intravenously for anesthesia, fentanyl 125 µg total intravenously for anesthesia and 50 µg (twice) for postoperative pain, propofol 120 mg once intravenously for anesthesia, ondansetron 8 mg for prophylactic treatment of nausea and 4 mg intravenously for postoperative nausea, dexamethasone 10 mg once intravenously for nausea prophylaxis, cefazolin sodium 1 g once intravenously for infection prophylaxis, oxygen 2 L/min by inhalation for oxygenation, sevoflurane 6.0% by inhalation for anesthesia, lactated ringers 0.975 L intravenously continuously for hydration, nitrous oxide 3 L/min by inhalation, all on (b) (6); phentermine 1 tablet once daily for weight loss from (b) (6) to (b) (6).

The subject was taking concomitant medications including copper IUD from (b) (6), docusate sodium 100 mg BID for constipation prophylaxis from (b) (6) to (b) (6), cephalexin 500 mg TID for infection prophylaxis from (b) (6) to (b) (6), oxygen 2 L/min by inhalation for hypoxia from (b) (6) to (b) (6).

On (b) (6), the same day of starting the study drug approximately 1 hour after the first dose, the subject reported with an adverse event of hypoxia that was deemed moderate in severity and possibly related to the study drug. The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The standard of care stimulation maneuvers that were part of routine post-operative nursing care for starting oxygen were not captured in progress notes or source documentation.

The oxygen saturation fell from the normal range to the high 80% range on (b) (6) Oxygen was started via nasal cannula for hypoxia. Numerous attempts were made to wean, however there was a recurrent need for oxygen. Saturations would fall to high 80% range while ambulating to the restroom off of oxygen. The oxygen saturation level and duration of oxygen drop was not recorded.

The subject was able to wean completely off of oxygen on the day of discharge, (b) (6) The hypoxia episode did not resolve until approximately 6 hours after the last inpatient dose (Dose #9; 70 hours after beginning treatment). Given the hypoxia and use of supplemental oxygen over several days during the inpatient dosing period up through the day of discharge, the study drug was withdrawn in response to the event.

Even though in the Investigator's opinion the hypoxia event was clinically mild in severity and did not pose any type of immediate safety threat to the subject, per the protocol, the hypoxia event was reported as moderate in severity due to treatment with oxygen.

The subject received ondansetron 4 mg intravenously for nausea rescue from (b) (6) to (b) (6)

Other Adverse Events:

Nausea of moderate severity on (b) (6) beginning approximately 5 minutes after first dose of study drug deemed possibly related to the study drug, which was considered resolved on (b) (6). The nausea was treated with ondansetron and resolved approximately 12.5 after the last dose of inpatient treatment (76.5 hours after beginning treatment).

Discontinuation and Hypoxia

Subject (b) (6): Hypoxia; Moderate; Possibly related to study drug

Subject (b) (6) a 55-year old white female, received first dose of Buprenorphine SL Spray (0.5 mg TID) on (b) (6). The subject had abdominoplasty on (b) (6). The subject received the last dose of study drug on (b) (6) for total 9 doses in Inpatient Treatment Period.

The subject had past medical history including appendicitis and appendectomy in (b) (6)

The ongoing medical condition included postmenopausal from (b) (6), abdominal lipodystrophy acquired from (b) (6)

The subject had taken prior medications including midazolam 2 mg once intravenously for anesthesia, fentanyl 150 µg intravenously for anesthesia and fentanyl 50 µg for postoperative pain, propofol 150 mg once intravenously for anesthesia, nitrous oxide 2 L/min by inhalation for anesthesia, ondansetron 4 mg intravenously for nausea prophylaxis, dexamethasone 10 mg intravenously for nausea prophylaxis, cefazolin sodium 1 g once intravenously for infection prophylaxis, oxygen 6 L/min by inhalation for oxygenation, sevoflurane 2.0% intravenously for anesthesia, lidocaine hydrochloride 50 mg once intravenously for anesthesia, lactated Ringers 1.6 L intravenously continuously for hydration, all on (b) (6).

The subject was taking concomitant medications including oxygen 2 L/min by inhalation for hypoxia and cephalexin 500 mg TID for infection prophylaxis, both from (b) (6) to (b) (6); docusate sodium 100 mg BID for constipation prophylaxis from (b) (6) to (b) (6).

The oxygen saturation fell from the normal range to the high 80% range on (b) (6). The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The standard of care stimulation maneuvers that were part of routine postoperative nursing care for starting oxygen were not captured in progress notes or source documentation.

Oxygen was started via nasal cannula for hypoxia. Numerous attempts were made to wean, however there was the recurrent need for oxygen. The subject was able to wean completely off of oxygen on the day of discharge, (b) (6). The oxygen saturation level and duration of oxygen drop was not recorded. Given the hypoxia and use of supplemental oxygen over several days during the inpatient dosing period up through the day of discharge, the study drug was withdrawn in response to the event. Even though in the Investigator's opinion the hypoxia event was clinically mild in severity and did not pose any type of immediate safety threat to the subject, per the protocol, the hypoxia event was reported as moderate in severity due to treatment of oxygen.

The event was considered resolved on (b) (6) according to the database.

Other Adverse Events:

- Nausea of moderate severity on (b) (6) deemed possibly related to the study drug that was considered resolved on (b) (6). The subject received ondansetron 4 mg intravenously for nausea rescue on (b) (6).
- Vomiting of mild severity on (b) (6) deemed possibly related to the study drug that was considered resolved on (b) (6).
- Dizziness of mild severity on (b) (6) deemed possibly related to the study drug that was considered resolved on (b) (6).
- Headache of mild severity on (b) (6) deemed unlikely related to the study drug that was considered resolved the same day.

Hypoxia

Subject (b) (6)*: Hypoxia; Moderate; Possibly related to study drug*

Subjec (b) (6) a 33-year old white female received the first dose of Buprenorphine SL Spray (0.5 mg TID) on (b) (6). The subject had abdominoplasty on (b) (6). The subject received the last dose of study drug on (b) (6) for total 9 doses in Inpatient Treatment Period and 12 doses in Outpatient Treatment Period.

The subject had past medical history including hyperthyroidism and parathyroidectomy in (b) (6) Caesarean section in (b) (6) female sterilization, Caesarean section in (b) (6) menometrorrhagia from (b) (6) to (b) (6)

The ongoing medical condition included lipodystrophy acquired from (b) (6) drug hypersensitivity from (b) (6)

The subject had taken prior medications including midazolam 1 mg once intravenously for anesthesia, fentanyl 100 µg intravenously for anesthesia and 25 µg for post-operative pain, propofol 120 mg once intravenously for anesthesia, lidocaine 20 mg once intravenously for local anesthesia; sevoflurane 6.0% by inhalation for anesthesia, ondansetron 8 mg intravenously for nausea prophylaxis, dexamethasone 10 mg intravenously for nausea prophylaxis, cefazolin 1 g once intravenously for infection prophylaxis, oxygen 5 L/min by inhalation for oxygenation, nitrous oxide 3 L/min by inhalation for anesthesia, lactated ringers 1.0 L intravenously continuously for hydration, all on (b) (6).

The subject was taking concomitant medications including cephalexin 500 mg TID for infection prophylaxis from (b) (6) to (b) (6) and docusate sodium 100 mg BID for constipation prophylaxis from (b) (6) to (b) (6), magnesium hydroxide 45 mL once for

constipation on (b) (6), oxygen 2 L/min by inhalation for hypoxia from (b) (6) to (b) (6).

On (b) (6), 1 day after starting the study drug, the subject reported with an AE of hypoxia of moderate severity deemed possibly related to the study drug. The staff followed the usual standard of care stimulation maneuvers as oxygen saturation fell from the normal range to the high 80% range on (b) (6). The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The standard of care stimulation maneuvers that were part of routine post-operative nursing care for starting oxygen were not captured in progress notes or source documentation.

Oxygen was started via nasal cannula and the subject was able to wean off (b) (6). A second episode of hypoxia the following night was noted and the subject was again able to wean off oxygen on (b) (6). The subject had two discrete episodes of hypoxia while sleeping, with no other evidence of sedation, bradypnea, etc. and the decision was made to discharge the subject on study drug. The subject completed the study.

Even though in the Investigator's opinion the hypoxia event was clinically mild in severity and did not pose any type of immediate safety threat to the subject, per the protocol, the hypoxia event was reported as moderate in severity due to treatment with oxygen. The event of hypoxia was considered resolved on (b) (6).

The subject received 1000 mg acetaminophen on (b) (6) for pain rescue and ondansetron 4 mg orally on (b) (6) for nausea rescue.

Other Adverse Events:

- Nausea of moderate severity on (b) (6) deemed possibly related to the study drug which was considered resolved the same day.
- Pruritis of mild severity on (b) (6) deemed possibly related to the study drug which was considered resolved on (b) (6).
- Nausea of moderate severity on (b) (6) deemed unlikely related to the study drug which was considered resolved the same day.
- Constipation of moderate severity on (b) (6) deemed unlikely related to the study drug which was considered resolved on (b) (6).

Hypoxia

Subject (b) (6) Hypoxia; Moderate; Possibly related to study drug

Subject (b) (6), a 38-year old white female received first dose of standard narcotic therapy on (b) (6). The subject had abdominoplasty on (b) (6). The subject received the last dose

of study drug on (b) (6) for a total of 9 doses during Inpatient Treatment Period and 2 doses during Outpatient Treatment Period. Subject stopped taking narcotic therapy because her pain resolved.

The subject had past medical history of wisdom teeth removal on an unknown date. The subject had ongoing medical history of lipodystrophy acquired from (b) (6)

The subject had taken prior medications including lidocaine 50 mg intravenously for anesthesia, midazolam 2 mg once IV for anesthesia, fentanyl 200 µg intravenously for anesthesia and 50 µg for post-operative pain, propofol 600 mg intravenously once for general anesthesia, sevoflurane 1.0% by inhalation for anesthesia, ondansetron 8 mg once intravenously for nausea prophylaxis, cefazolin 1 g once intravenously for infection prophylaxis, dexamethasone 10 mg intravenously for nausea prophylaxis, lactated ringers 1 L continuous intravenously for hydration and oxygen 10 L/min continuous respiration for oxygenation, all on (b) (6).

The concomitant medications included cephalexin 500 mg TID for infection prophylaxis from (b) (6) to (b) (6) and docusate sodium 100 mg BID for constipation prophylaxis from (b) (6) to (b) (6), milk of magnesia 30 mL once for constipation on (b) (6) to (b) (6), oxygen 2 L/min by inhalation for hypoxia on (b) (6).

On (b) (6), 3 days after starting the study drug, the subject reported an adverse event of hypoxia that was deemed moderate in severity and possibly related to the study drug. There was no change in the study drug in response to the event.

The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The standard of care stimulation maneuvers that were part of routine post-operative nursing care for starting oxygen were not captured in progress notes or source documentation.

The oxygen saturation fell from the normal range to 88% at 1:40 on (b) (6). Oxygen was started via nasal cannula for hypoxia and oxygen saturation at 1:42 was 97%. The subject was able to wean promptly the following morning at 6:39 when oxygen saturation was 99% and at 6:41, oxygen saturation was 95% after stopping the supplemental oxygen. The subject had a single discrete episode of hypoxia with no other evidence of sedation, bradypnea etc. during the inpatient period and the decision was made to discharge the subject home on study drug.

Even though in the Investigator's opinion the hypoxia event was clinically mild in severity and did not pose any type of immediate safety threat to the subject, per the protocol, the hypoxia event was reported as moderate in severity due to treatment with oxygen.

The subject received ondansetron 4 mg intravenously on (b) (6) for nausea rescue.

The event of hypoxia was considered resolved on (b) (6).

The subject called the research site to inform that she no longer had pain and stopped study drug (b) (6). She returned to complete study procedures on (b) (6).

Other Adverse Events:

- Nausea of moderate severity deemed possibly related to the study drug on (b) (6) that was considered resolved on (b) (6).
- Dizziness of mild severity deemed possibly related to the study drug on (b) (6) that was considered resolved on (b) (6).
- Constipation of moderate severity deemed possibly related to the study drug on (b) (6) that was considered resolved on (b) (6).

Discontinuation and Hypoxia

Subject (b) (6): Hypoxia; Moderate and Possibly related to study drug

Subject (b) (6), a 34-year-old black or African American female received first dose of Buprenorphine SL Spray (0.5 mg TID) on (b) (6). The subject had breast augmentation on (b) (6). The subject received the last dose of study drug on (b) (6) for a total of 9 doses during Inpatient Treatment Period.

The subject had past medical history of abdominal hernia, abdominal hernia repair, and female sterilization in (b) (6) The subject had ongoing medical conditions including micromastia in (b) (6) drug hypersensitivity from (b) (6) and drug intolerance from (b) (6)

The subject had taken prior medications including midazolam 2 mg once intravenously for anesthesia, lidocaine 50 mg intravenously for anesthesia, fentanyl 200 µg intravenously for anesthesia and 25 µg for post-operative pain, propofol 200 mg intravenously once for general anesthesia, sevoflurane 4.0% by inhalation for anesthesia, ondansetron 8 mg once intravenously for nausea prophylaxis, cefazolin 1 g once intravenously for infection prophylaxis, dexamethasone 10 mg intravenously for nausea prophylaxis, lactated ringers 1.27 L continuous intravenously for hydration and oxygen 5 L/min continuous respiration for oxygenation, all on (b) (6).

The concomitant medications included cephalexin 500 mg TID for infection prophylaxis from (b) (6) to (b) (6), ondansetron 4 mg once intravenously for emesis on (b) (6), normal saline 1000 mL once intravenously for emesis from (b) (6) to (b) (6), clindamycin 600 mg BID for infection prophylaxis from (b) (6) to (b) (6), oxygen 2 L/min by inhalation for hypoxia from (b) (6) to (b) (6).

On (b) (6), the same day of starting the study drug, the subject reported an adverse event of hypoxia that was deemed moderate in severity and possibly related to the study drug. The oxygen saturation dropped to 87% at 20:06 and after oxygen was initiated, increased to 95% at 20:08; 98% at 6:20 on (b) (6). During a weaning attempt on the morning of (b) (6) oxygen saturation decreased to 89% at 6:55 and after oxygen of 2 L/min was initiated, increased to 99% at 06:58. There was a subsequent drop to 88% at 15:46 and oxygen was initiated, after

which the level went up to 98% at 15:49. There was a drop on (b) (6) at 8:03 to 88% and oxygen was initiated after which the oxygen saturation increased to 98%.

Although the event resolved prior to the last dose of the study drug, the study drug was withdrawn in response to the event.

The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The standard of care stimulation maneuvers that were part of routine post-operative nursing care for starting oxygen were not captured in progress notes or source documentation.

The event of hypoxia was considered resolved on (b) (6).

Even though in the Investigator's opinion the hypoxia event was clinically mild in severity and did not pose any type of immediate safety threat to the subject, per the protocol, the hypoxia event was reported as moderate in severity due to treatment with oxygen.

The subject received 30 mg ketorolac on (b) (6) for pain rescue and ondansetron 4 mg intravenously once on (b) (6), twice on (b) (6) and once on (b) (6) for nausea rescue.

Other Adverse Events:

- Nausea of moderate severity deemed possibly related to the study drug on (b) (6) approximately 3.5 h after first dose of the study drug, which was considered resolved on (b) (6), approximately 7 hours after 5th dose of study drug.
- Emesis of moderate severity deemed possibly related to the study drug on (b) (6), approximately 3.5 h after first dose of the study drug, which was considered resolved on (b) (6), approximately 7 hours after the fifth dose of the study drug.

Discontinuation and Hypoxia

Subject (b) (6): Nausea; Moderate; Possibly Related to Study Drug; Vomiting; Moderate; Possibly Related to Study Drug

Subject (b) (6), a 28-year old white female, began receiving Buprenorphine SL Spray on (b) (6). The subject had a breast augmentation on (b) (6). The subject received her last dose of study drug on (b) (6) for a total of 6 doses during the Inpatient Treatment Period.

The subject had a past medical history of herpes zoster in (b) (6) The subject had ongoing medical history of migraine starting in (b) (6) and micromastia starting in (b) (6)

The subject had prior medications of paracetamol 500 mg QD from (b) (6) to (b) (6) for migraine headache; as well as cefazolin sodium 1 g once intravenously for prophylaxis of

infection; oxygen 5 L/min continuous for oxygenation; sevoflurane 3% continuous for anesthesia; propofol 140 mg once intravenously for anesthesia; fentanyl citrate 100 µg once intravenously for anesthesia; dexamethasone 10 mg once intravenously for prophylaxis of nausea; ondansetron 4 mg once intravenously for prophylaxis of nausea; midazolam hydrochloride 2 mg once intravenously for anesthesia; and fentanyl citrate 25 µg twice intravenously for postoperative pain, all on (b) (6).

Concomitant medications included cilest 1 tablet QD from (b) (6) for contraception; cefalexin 500 mg TID from (b) (6) to (b) (6) for prophylaxis of infection; docusate sodium 100 mg BID from (b) (6) to (b) (6) for prophylaxis of constipation; metoclopramide hydrochloride 10 mg once intravenously from (b) (6) to (b) (6) for nausea; oxygen 2 L/min continuous from (b) (6) to (b) (6) for hypoxia; and sodium chloride 500 mL once intravenously from (b) (6) to (b) (6) for prophylaxis of dehydration.

On (b) (6), 1 day after starting the study drug, the subject experienced an AE of nausea and an AE of vomiting, both deemed moderate in severity and possibly related to the study drug. Both were recurrent and treated with concomitant medication, including ondansetron. After numerous episodes, neither AE improved with ondansetron treatment and the subject declined to continue dosing with study drug. It was decided to withdraw the subject during the inpatient period on (b) (6), and both AEs were resolved on the same day.

The subject also had hypoxia during the Inpatient Period deemed moderate in severity and possibly related to the trial drug. The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The site staff followed usual standard of care stimulation maneuvers as oxygen saturation fell from the normal range to 88% at 21:59 hours on (b) (6). Concomitant medication was required and oxygen was started via nasal cannula for hypoxia, with oxygen saturation rising to 98% at 22:00 hours. The subject was able to wean completely off of oxygen on (b) (6) as oxygen saturation was 98% on room air at 05:57 hours and the event was considered resolved on the same day.

Discontinuation and Hypoxia

Subject (b) (6): Nausea; Moderate; Possibly Related to Study Drug; Vomiting; Moderate; Possibly Related to Study Drug

Subject (b) (6), a 35-year old white female, began receiving Buprenorphine SL Spray on (b) (6). The subject had an abdominoplasty on (b) (6). The subject received her last dose of study drug on (b) (6) for a total of 7 doses during the Inpatient Treatment Period.

The subject had a past medical history of Caesarean section in (b) (6) (b) (6) and (b) (6) female sterilization in (b) (6) and adnexal torsion in (b) (6) The subject had ongoing medical history of lipodystrophy acquired starting in (b) (6)

The subject had prior medications of cefazolin sodium 1 g once intravenously for prophylaxis of infection; oxygen 2 L/min continuous for oxygenation; nitrous oxide 3 L/min continuous for anesthesia; sevoflurane 6% continuous for anesthesia; propofol 100 mg continuous intravenously for anesthesia; fentanyl citrate 100 µg intermittently intravenously for anesthesia; dexamethasone 10 mg once intravenously for prophylaxis of nausea; ondansetron 8 mg once intravenously from for prophylaxis of nausea; midazolam hydrochloride 1 mg once intravenously for anesthesia; fentanyl 50 µg twice intravenously for postoperative pain; flebobag ring lact 1300 mL continuous intravenously for fluid replacement, all on (b) (6).

Concomitant medications included cefalexin 500 mg TID from (b) (6) to (b) (6) for prophylaxis of infection; docusate sodium 100 mg BID from (b) (6) to (b) (6) for prophylaxis of constipation; oxygen 2 L/min continuous from (b) (6) to (b) (6) and from (b) (6) to (b) (6) for hypoxia; sodium chloride 1000 mL continuous intravenously from (b) (6) to (b) (6); and ondansetron 4 mg once intravenously from (b) (6) to (b) (6) for emesis.

On (b) (6), 1 day after starting the study drug, the subject experienced AEs of nausea and vomiting, both deemed moderate in severity and possibly related to the study drug. Both AEs were recurrent and required concomitant medication, including ondansetron. After numerous episodes that did not improve with ondansetron treatment, the subject declined to continue dosing with study drug, which was withdrawn in response to both AEs. The subject was withdrawn during the inpatient period on (b) (6) and the nausea and vomiting events were resolved on the same day.

The subject also experienced an AE of hypoxia on (b) (6) deemed moderate in severity and possibly related to the study drug. The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The site staff followed the usual standard of care stimulation maneuvers as oxygen saturation fell from the normal range to 85% on (b) (6). Concomitant medication was required as oxygen was started via nasal cannula at 21:00 for hypoxia. Attempts were made to wean; however, there was the recurrent need for oxygen. The subject remained on oxygen until 16:36 hours on (b) (6), at which point oxygen was discontinued. By 19:42 hours, oxygen saturation fell to 89% and oxygen was readministered, with the oxygen saturation level at 98% at 19:44 hours. The subject was able to wean completely off of oxygen on (b) (6) at 09:32 hours.

Other Adverse Events:

- Dizziness of mild severity deemed possibly related to the study drug on (b) (6). No action was taken and the event was resolved on (b) (6).
- Chest discomfort of moderate severity deemed not related to the study drug on (b) (6). No action was taken and the event was resolved on the same day.

- Dyspnea of moderate severity deemed not related to the study drug on (b) (6). No action was taken and the event was resolved on the same day.

Discontinuation and Hypoxia

Subject (b) (6): Hypoxia; Moderate; Possibly Related to Study Drug

Subjec (b) (6), a 46-year old white female, began receiving Buprenorphine SL Spray on (b) (6). The subject had an abdominoplasty on (b) (6). The subject received her last dose of study drug on (b) (6) for a total of 9 doses during the Inpatient Treatment Period.

The subject had a past medical history of mammoplasty in (b) (6) liposuction in (b) (6) hip fracture in (b) (6) fracture treatment in (b) (6) intervertebral disc protrusion in (b) (6) and intervertebral disc operation in (b) (6) The subject had ongoing medical history of lipodystrophy acquired starting in (b) (6) and drug hypersensitivity starting in (b) (6)

The subject had prior medications of clindamycin hydrochloride 500 mg once intravenously for prophylaxis of infection; oxygen 6 L/min, 2 L/min, and 1 L/min continuous for oxygenation; sevoflurane 2% and 1.5% continuous for anesthesia; lidocaine 50 mg once intravenously for anesthesia; propofol 200 mg once intravenously for anesthesia; fentanyl citrate 250 mg intermittently intravenously anesthesia; dexamethasone 10 mg once intravenously for prophylaxis of nausea; ondansetron 4 mg once intravenously for prophylaxis of nausea (protocol violation; subject should have received 8 mg); midazolam hydrochloride 2 mg once intravenously for anesthesia; flebobag ring lact 1000 mL continuous intravenously for fluid replacement; fentanyl citrate 50 μg and 25 μg, each given once intravenously for postoperative pain; and morphine sulfate 2 mg once intravenously for postoperative pain, all on (b) (6).

Concomitant medications included oxygen 2 L/min intermittently from (b) (6) to (b) (6) for hypoxia (defined as a drop in oxygen saturation below 90%); bactrim 1 tablet BID from (b) (6) to (b) (6) and from (b) (6) to (b) (6) for prophylaxis of infection; and docusate sodium 100 mg BID for prophylaxis of constipation.

On (b) (6), the same day the subject started study drug (approximately 2 hours after the first dose), the subject experienced an AE of hypoxia deemed moderate in intensity and possibly related to the study drug. The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The site staff followed the usual standard of care stimulation maneuvers as oxygen saturation fell from the normal range to 88% at 15:06 hours on (b) (6). Oxygen was started as concomitant medication via nasal cannula for hypoxia, with oxygen saturation rising to 98% at 15:08 hours. Attempts were made to wean; however, there was a recurrent need for oxygen over several days. At 01:27 hours on (b) (6) the subject was placed on room air, however by 01:50 hours the subject's oxygen saturation was 87% and oxygen administration was resumed until 12:13 hours on (b) (6) when oxygen saturation was 99%. By 22:46 hours on (b) (6) oxygen saturation was again 87% and oxygen administration was resumed, with oxygen saturation rising to 98% at 22:47 hours. The subject was able to wean completely off of

oxygen on the day of discharge ([(b) (6)] at 12:10 hours; oxygen saturation 96%). Given the intermittent hypoxia and use of supplemental oxygen during the inpatient dosing period up through the day of discharge, the decision was made to withdraw the subject and not discharge them on study drug at home. Study drug was considered withdrawn in response to this event and the event was considered resolved on [(b) (6)].

Other Adverse Events:

- Nausea of moderate severity deemed possibly related to the study drug on [(b) (6)]. Rescue medications 1 through 5 (ondansetron 4 mg intravenously) were given in response and the event was resolved on [(b) (6)].
- Headache of moderate severity deemed possibly related to the study drug on [(b) (6)]. Non-medication therapy was given in response and the event was resolved on [(b) (6)].

Discontinuation and Hypoxia

Subject [(b) (6)]: Hypertension; Moderate; Possibly Related to Study Drug

Subject [(b) (6)], a 49-year old black female, began receiving Buprenorphine SL Spray on [(b) (6)]. The subject had an abdominoplasty on [(b) (6)]. The subject received her last dose of study drug on [(b) (6)] for a total of 9 doses during the inpatient Treatment Period.

The subject had a past medical history of adnexal torsion in [(b) (6)] oophorectomy in [(b) (6)] macular hole in [(b) (6)] and eye operation in [(b) (6)] The subject had ongoing medical history of hypertension starting in [(b) (6)] and lipodystrophy acquired starting in [(b) (6)]

The subject had prior medications of nitrous oxide 3 L/min continuous for anesthesia; sevoflurane 5% continuous for anesthesia; propofol 150 mg once intravenously for anesthesia; fentanyl citrate 100 μg twice intravenously for anesthesia; dexamethasone 10 mg once intravenously for prophylaxis of nausea; ondansetron 8 mg once intravenously for prophylaxis of nausea; midazolam hydrochloride 1 mg once intravenously for anesthesia; and flebobag ring lact 600 mL continuous intravenously for anesthesia, all on [(b) (6)].

Concomitant medications included atenolol 12.5 mg QD starting in [(b) (6)] for hypertension; spironolactone 50 mg, 0.5 tablet QD starting in [(b) (6)] for hypertension; lisinopril 40 mg BID starting in [(b) (6)] for hypertension; cephalexin 500 mg TID from [(b) (6)] to [(b) (6)] for prophylaxis of infection; docusate sodium 100 mg BID from [(b) (6)] to [(b) (6)] for prophylaxis of constipation; and oxygen 2 L/min once from [(b) (6)] to [(b) (6)] for hypoxia.

On [(b) (6)], 2 days after starting the study drug, the subject experienced an AE of hypertension deemed moderate in severity and possibly related to the study drug. While the subject had an ongoing medical history of hypertension, this was considered a worsening of

hypertension as the subject's blood pressure was 186/101 during the inpatient dosing period, despite the subject continuing on her usual outpatient regimen. Concomitant medication was required as a result. The hypertension persisted intermittently during the inpatient dosing period. The decision was made to discontinue the study drug on (b) (6) due to this event. The subject's blood pressure returned to normal and the event was considered resolved on (b) (6).

The subject also had an AE of hypoxia during the inpatient period on (b) (6) deemed moderate in severity and possibly related to study drug. The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The site staff followed usual standard of care stimulation maneuvers as oxygen saturation fell from the normal range to 87% at 03:31 hours. Oxygen was started as concomitant medication via nasal cannula with oxygen saturation rising to 100% at 03:32 hours. The subject was able to wean completely off of oxygen the morning of (b) (6) as oxygen saturation was 95% at 10:59 hours (prior to removal of oxygen) and 95% at 16:33 hours (on room air) and the event was resolved on the same day.

Other Adverse Events:

- Nausea of moderate severity deemed possibly related to the study drug on (b) (6). Rescue medications 1, 2, and 3 (ondansetron 4 mg intravenously) were given in response and the event was resolved on (b) (6).

- Vomiting of moderate severity deemed possibly related to the study drug on (b) (6). No action was taken in response and the event was resolved on the same day.

Discontinuation and Hypoxia

Subject (b) (6) Hypoxia; Moderate; Possibly Related to Study Drug

Subject (b) (6), a 44-year old white female, began receiving Standard Narcotic Therapy on (b) (6). The subject had an abdominoplasty on (b) (6). The subject received her last dose of study drug on (b) (6) for a total of 9 doses during the Inpatient Treatment Period.

The subject had a past medical history of ovarian cyst ruptured in (b) (6) and skin abrasion from (b) (6) to (b) (6). The subject had ongoing medical history of tinnitus starting in (b) (6) migraine starting in (b) (6) palpitations starting in (b) (6) acquired lipodystrophy starting in (b) (6) and postmenopause starting on (b) (6)

The subject had prior medications of cefazolin sodium 1 g once intravenously for prophylaxis of infection; nitrous oxide 3 L/min continuous for anesthesia; oxygen 5 L/min and 2 L/min continuous for oxygenation; sevoflurane 6% continuous for anesthesia; propofol 100 mg once intravenously for anesthesia; fentanyl citrate 150 µg intermittently intravenously for anesthesia; dexamethasone 10 mg once intravenously for prophylaxis of nausea; ondansetron 8 mg once intravenously for prophylaxis of nausea; midazolam hydrochloride 1 mg once intravenously for anesthesia; fentanyl 50 µg twice intravenously for postoperative pain; sevoflurane 1.5% and 1.2% continuous for anesthesia; flebobag ring lact 400 mL continuous intravenously for fluid replacement, all on (b) (6).

Concomitant medications included cefalexin 500 mg TID from (b) (6) to (b) (6) for prophylaxis of infection; docusate 100 mg BID from (b) (6) to (b) (6) for prophylaxis of constipation; and oxygen 2 L/min intermittently from (b) (6) to (b) (6) for hypoxia.

On (b) (6), the subject experienced an AE of hypoxia, deemed moderate in severity and possibly related to study drug. The Investigator defined hypoxia as any drop in oxygen saturation below 90%. The site staff followed usual standard of care stimulation maneuvers as oxygen saturation fell from the normal range to 88% at 21:43 hours. Oxygen was started as concomitant medication via nasal cannula, with oxygen saturation rising to 96% at 21:45 hours. The subject was administered oxygen until 08:46 hours on (b) (6), when oxygen saturation was 96%. However, the subject's oxygen saturation fell to 88% at 21:22 hours on the same day when oxygen was administered again. Oxygen saturation rose to 94% at 21:24 hours, and the subject was weaned off oxygen at 08:20 hours on (b) (6). The drug was withdrawn in response to the event and concomitant medication (oxygen) was required. The event was resolved on (b) (6), and the subject withdrew from the study on (b) (6).

Other Adverse Events:

- Dizziness of mild severity deemed possibly related to the study drug on (b) (6). No action was taken in response and the event was resolved on (b) (6).