Clinical Overview

NDA 209588

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

- Introduction/Clinical Development Program
- Support for Efficacy
  - Study 062
    - Design, primary and certain secondary endpoints
    - Time to onset of analgesia and use of rescue analgesia
  - Study 026
    - Study discontinued early due to adverse events
- Safety
  - Nausea, vomiting, dizziness, and hypoxia
    - Studies 062 and 026 (placebo-controlled)
    - Study 111 (open-label, active controlled)
    - Use of anti-emetic drugs

Acute Pain Armamentarium

- Inpatient setting
  - Parenteral opioids, NSAIDS, APAP
  - Oral analgesics (opioids, NSAIDs, APAP, gabapentinoids)
  - Local anesthetics/blocks
- Outpatient setting
  - Oral analgesics (opioids, NSAIDs, APAP, gabapentinoids)
  - Rectal

Available Clinical Data

- 7 Phase 1 studies in naltrexone-blocked healthy volunteers
- Studies in patients

Identification	Control	Active doses	Blinding	N	Efficacy data collected?
026	Placebo	0.5 TID, 1.0 BID, 1.0 TID	Yes	40	Yes
062	Placebo	0.125 TID, 0.25 TID, 0.5 TID	Yes	322	Yes
111	Opioid	0.5 TID	No	100	No

EFFICACY

Study 062

Design: Randomized, double-blind, multiple-dose, parallel-group, placebo-controlled study

Buvaya Doses: 0.125, 0.25, 0.5 mg every 8 hours

Primary Endpoint: SPID-48

Secondary Endpoints:

- SPID-4, SPID-8, and SPID-24
- Time to Meaningful Pain Relief
- Rescue analgesic use
- Subject's global evaluation of study drug

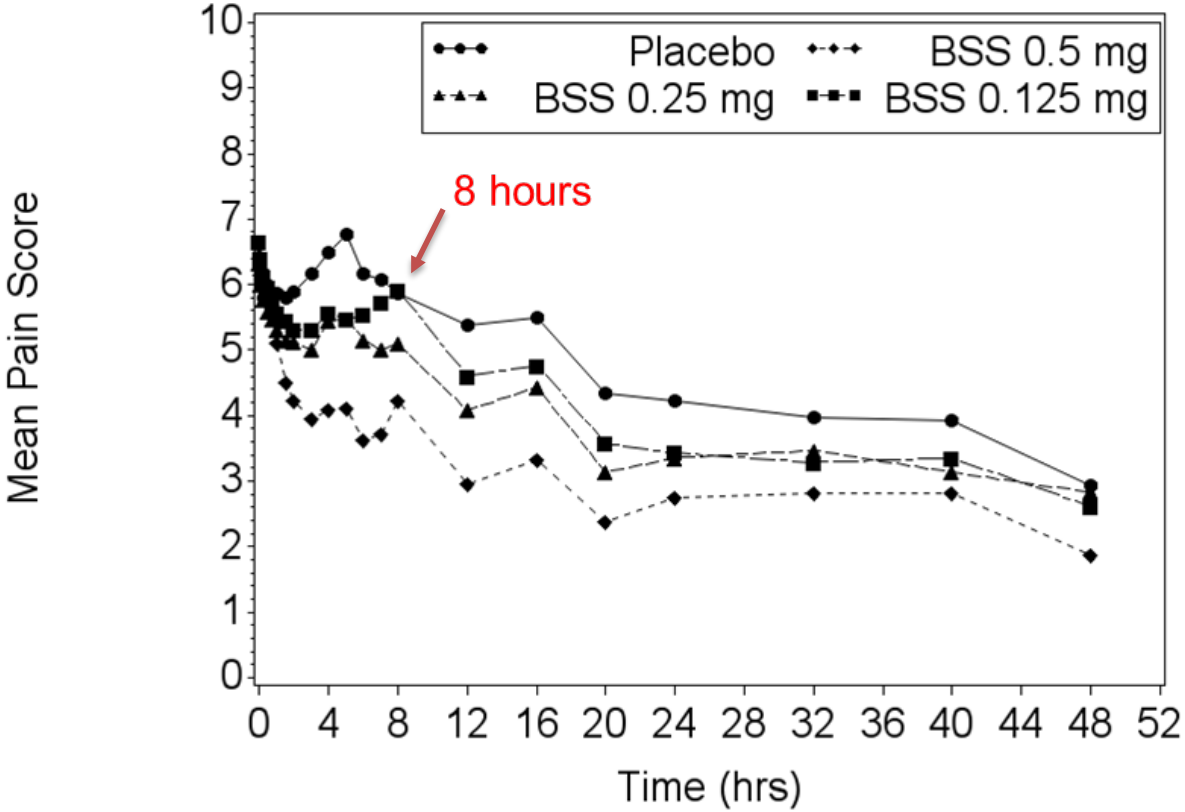
Primary Efficacy Endpoint (Study 062)

SPID*-48

All Randomized (ITT)		**BSS 0.50 mg N=81**	**BSS 0.25 mg N=80**	**BSS 0.125 mg N=82**	**Placebo N=79**
Primary: SPID48	N	72	75	77	75
	Mean (SD)	183 (107.3)	126 (102.2)	136 (114.0)	93 (85.1)
	Range	-18 – 415	-56 – 319	-91 – 399	-78 – 378
	LS (adjusted) Mean (SE)	171 (10.3)	126 (10.1)	125 (9.9)	89 (10.1)
	LSM Diff. v. PBO	82	36	35	
	95% CI of Diff.	(54, 110)	(8, 64)	(8, 63)	
	2-sided p-value	<0.001	0.01	0.01	

*SPID = Summed Pain Intensity Difference

Pain Intensity Scores by Time Point



Most Secondary Endpoints Support the Primary

Onset of Analgesia

- Time to meaningful pain relief was measured by the double-stopwatch method
- Each subject was instructed to stop the first stopwatch when he or she experienced any perceptible pain relief
- The second stopwatch was stopped when he or she experienced pain relief that was meaningful to them.

Time to Meaningful Pain Relief (062)

	Placebo N=79	Buprenorphine Sublingual Spray		
		0.5 mg N=81	0.25 mg N=80	0.125 mg N=82
Subjects with meaningful pain relief Number (%)	27 (34%)	53 (65%)	37 (46%)	36 (44%)
Subjects censored Number (%)	52 (66%)	28 (35%)	43 (54%)	46 (56%)
Time from first dose to onset of meaningful pain relief (minutes)				
25th quartile (95% CI)	64 (12, 121)	60 (40, 66)	71 (44, 90)	60 (29, 87)
Median (95% CI)	238 (121, NE)	92 (79, 120)	122 (90, 227)	166 (87, 240)
75th quartile (95% CI)	NE (238, NE)	55 (120, NE)	NE (189, NE)	NE (240, NE)

CI = confidence interval; NE= not estimable

Historical Controls: Time to Meaningful Analgesia

Drug	Dose	Median time (m)
Oxymorphone IR	10 and 20 mg	61 and 53
Oxycodone IR	15 mg	63
Oxycodone IR	15 mg	77
Buprenorphine SL	**0.5 mg**	**92**
Tapentadol IR	100 mg	94
Tapentadol IR	75 mg	104
Buprenorphine SL	**0.25 mg**	**122**
Tapentadol IR	50 mg	123
Buprenorphine SL	**0.125 mg**	**166**

Use of Rescue (062)

	Placebo N=79	Buprenorphine Sublingual Spray 0.5 mg N=81	0.25 mg N=80	0.125 mg N=82
Number (%) of subjects using rescue medication	77 (98%)	45 (56%)	70 (88%)	72 (88%)
Total Use of rescue medication (0-24 hours)				
n	77	41	68	71
Mean (SD)	3.8 (1.98)	2.2 (1.69)	2.6 (1.62)	2.9 (1.670
Median	3	1	2	3
Total Use of rescue medication (0-48 hours)				
n	77	45	70	72
Mean (SD)	5.6 (3.60)	2.9 (2.81)	3.7 (2.68)	3.9 (2.69)
Median	5	2	3	3
Time (minutes) from first dose to use of rescue analgesic				
25^{th} percentile (95% CI)	68 (63, 71)	141 (72, 293)	71 (65, 95)	72 (65, 81)
Median (95% CI)	107 (77, 125)	937 (349, NE)	220 (105, 260)	193 (92, 280)
75^{th} percentile (95% CI)	230 (161, 311)	NE	545 (292, 1061)	428 (305, 759)

SD = standard deviation; CI = confidence interval; NE = not estimable

SAFETY

Study 111 is a Critical Study to Understand the Safety of Buvaya

- This presentation contains historical control data
- Study 111 was an open-label, head-to-head study that compared Buvaya 0.5 mg TID to “standard opioid therapy”
- Standard opioid therapy was defined as morphine sulfate, 4 mg IV TID followed by immediate-release oxycodone, 10 mg PO TID
- No efficacy data were collected
- Prophyalctic antiemetics were administered perioperatively (ondansetron and dexamethasone)

Exposure

- 490 subjects exposed to at least one dose of Buvaya
- In Phase 2 and 3 inpatient studies 323 subjects were exposed to Buvaya for a maximum of 48 hours
- During the outpatient phase of Study 17-111, 31 patients were treated for up to 96 hours.

Exposure by Dose in Phase 2 and Phase 3 Pain Studies

	Buprenorphine Sublingual Spray							
Dose	**0.125 mg TID**	**0.25 mg TID**	**0.5 mg TID**	**1 mg BID**	**1 mg TID**	**Total BSS**	**Placebo**	**Standard Narcotic Therapy**
No. of Subjects	82	80	140	11	10	323	89	50

Major Safety Findings

- There were no deaths.
- There were 3 serious adverse events that did not appear to be related to Buvaya.
- There were discontinuations due to nausea, vomiting and hypoxia.
- The observed major safety findings were qualitatively consistent with the opioid class.

Selected Adverse Events Resulting in Drug Discontinuation

Parameter	Buprenorphine Sublingual Spray					Placebo N=89 n (%)	Standard Narcotic Therapy N=50 n (%)
	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 (%)		
Subjects with ≥ 1 AE	1 (1)	4 (5)	26 (19)	1 (9)	1 (10)	0	7 (14)
Nausea and/or Vomiting	1 (1)	3 (4)	17 (12)	0	0	0	1 (2)
Nausea	0	3 (4)	11 (8)	0	0	0	1 (2)
Vomiting	1 (1)	3 (4)	12 (9)	0	0	0	0
Dizziness	0	0	2 (1)	0	0	0	1 (2)
Somnolence	0	0	2 (1)	1 (9)	1 (10)	0	0
Hypoxia	0	0	6 (4)	0	0	0	2 (4)

Adverse Events of Special Interest

- Nausea
- Vomiting
- Dizziness
- Hypoxia

Nausea and Vomiting

Nausea and Vomiting Study 026 and 062

Preferred Term	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 (%)
Nausea	36 (44%)	47 (59%)	75 (83%)	10 (91%)	7 (70%)	16 (18%)
Vomiting	24 (29%)	33 (41%)	65 (72%)	8 (73%)	8 (80%)	4 (5%)

Nausea and Vomiting Study 111

System Organ Class Preferred Term	Standard Narcotic Therapy (N=50)		Buprenorphine Sublingual Spray (N=50)	
	n (%)	No. of AEs	n (%)	No. of AEs
Nausea	17 (34%)	22	39 (78%)	43
Vomiting	6 (12%)	6	26 (52%)	44

Rescue Anti-Emetic Drug (AED) Use

Study	Dose	% receiving AED	Max doses of AED
026	Placebo	10	1
026	0.5 mg TID	67	8
026	1.0 mg BID	91	4
026	1.0 mg TID	70	10
062	Placebo	5	3
062	0.125 mg TID	21	4
062	0.25 mg TID	40	4
062	0.5 mg TID	68	8
111	0.5 mg TID	74	16
111	Standard narcotic	24	10

Historical/Concurrent Controls: Nausea

AE Term	Drug	Dose	Incidence (%)
Nausea	Oxymorphone IR	10 mg Q4-6	17
Nausea	Oxymorphone IR	20 mg Q4-6	25
Nausea	Oxycodone IR	15 mg Q4-6	28
Nausea	Morphine/oxycodone	4 mg/10 mg TID	34
Nausea	Tapentadol IR	50 mg Q4-6	35
Nausea	Tapentadol IR	75 mg Q4-6	38
Nausea	**Buprenorphine SL**	**0.125 mg TID**	**44**
Nausea	Tapentadol IR	100 mg Q4-6	49
Nausea	**Buprenorphine SL**	**0.25 mg TID**	**59**
Nausea	Oxycodone IR	15 mg Q4-6	67
Nausea	**Buprenorphine SL**	**1.0 mg TID**	**70**
Nausea	**Buprenorphine SL**	**0.5 mg TID**	**78**
Nausea	**Buprenorphine SL**	**0.5 mg TID**	**78-84**
Nausea	**Buprenorphine SL**	**1.0 mg BID**	**91**

Historical Controls/Concurrent: Vomiting

AE Term	Drug	Dose	Incidence (%)
Vomiting	Oxymorphone IR	10 mg Q4-6	4
Vomiting	Oxycodone IR	15 mg Q4-6	10
Vomiting	Oxymorphone IR	15 mg Q4-6	16
Vomiting	Morphine/oxycodone	4mg/10 mg TID	12
Vomiting	Tapentadol IR	50 mg Q4-6	18
Vomiting	Tapentadol IR	75 mg Q4-6	21
Vomiting	**Buprenorphine SL**	**0.125 mg TID**	**29**
Vomiting	Tapentadol IR	100 mg Q4-6	32
Vomiting	**Buprenorphine SL**	**0.25 mg TID**	**41**
Vomiting	Oxycodone IR	15 mg Q4-6	42
Vomiting	**Buprenorphine SL**	**0.5 mg TID**	**52**
Vomiting	**Buprenorphine SL**	**0.5 mg TID**	**67-73**
Vomiting	**Buprenorphine SL**	**1.0 mg BID**	**73**
Vomiting	**Buprenorphine SL**	**1.0 mg TID**	**80**

Nausea and Vomiting with Other Buprenorphine Products

Tradename	Indication	Dose	Route	Tmax (hr)	Cmax (ng/mL)	AUC (ng*hr/mL)	Nausea rate (%)	Vomiting Rate (%)	Dizziness rate (%)
Buvaya	Acute pain	0.5 mg	SL	2	1.1	21.4	78-84	52-73	22-78
Buprenex	Acute pain	0.3 mg	IV	0.05	5.6	28.2	5-10	2-10	5-10
Subutex	MAT	8 mg	SL	2	4.4	76.7	14	8	4-6
Belbuca	Chronic pain	0.3 mg	Buccal				17	7	5
Belbuca	Chronic pain	0.3 mg	Buccal	2.5	0.5	2	50	8	6
Sublocade	MAT	300 mg	SC depot		10.1		8-9	6-9	2-3
Butrans	Chronic pain	10 mcg/hr	Transdermal system				14	<5	5
Butrans	Chronic pain	11 mcg/hr	Transdermal system		0.2	**27**	23	7	10
Probuphine	MAT	320 mg	Subdermal implant	12		19.6	6	6	4

Dizziness

Dizziness Studies 14-026 and 15-062

Preferred Term	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 (%)
Dizziness	18 (22%)	26 (33%)	51 (57%)	5 (46%)	5 (50%)	7 (8%)

Dizziness Study 17-111

System Organ Class Preferred Term	Standard Narcotic Therapy (N=50)	Buprenorphine Sublingual Spray (N=50)
	n (%)	n (%)
Dizziness	5 (10%)	11 (22%)

Historical Controls/Concurrent: Dizziness

Drug	Dose	Incidence (%)
Oxymorphone IR	20 mg Q4-6	3
Oxycodone IR	15 mg	10
Morphine/oxycodone	4 mg/10 mg TID	10
Tapentadol IR	50 mg Q4-6	16
Tapentadol IR	75 mg Q4-6	22
Buprenorphine SL	**0.125 mg TID**	**22**
Buprenorphine SL	**0.5 mg TID**	**22**
Oxycodone IR	15 mg Q4-6	30
Tapentadol IR	100 mg Q4-6	31
Buprenorphine SL	**0.25 mg TID**	**33**
Buprenorphine SL	**1.0 mg BID**	**46**
Buprenorphine SL	**1.0 mg TID**	**50**
Buprenorphine SL	**0.5 mg TID**	**54-78**

Hypoxia

Hypoxia by Surgical Procedure Study 111

System Organ Class Preferred Term	Standard Narcotic Therapy (N=50)	Buprenorphine Sublingual Spray (N=50)
	n (%)	n (%)
Hypoxia	3 (6%)	14 (28%)
By Surgical Procedure		
Bunionectomy	3/17 (18%)	3/16 (19%)
Breast Augmentation	0/14 (0)	4/16 (25%)
Abdominoplasty	0/19 (0)	7/18 (39%)

Hypoxia

- In the Phase 2 and 3 studies no serious adverse events of hypoxia occurred
- Two subjects required naloxone but both patients were on doses higher than 0.5 mg TID (1mg BID and 1mg TID)
- In Study 062, 3 patients (3.7%) had hypoxia defined as oxygen saturation ≤ 92%
- In study 026 no subjects on doses of 0.5 mg or less were reported as having hypoxia defined as oxygen saturation ≤ 90%
- In study 111, 28% of subjects were reported as having hypoxia

Summary: 0.5mg TID Dose

- **Efficacy**
  - Shows significant difference vs. placebo on SPID48 (LSM difference of 82 vs placebo) and secondaries
  - Median time to meaningful pain relief 92 minutes vs. 238 for placebo (Study 062)
  - Use of rescue 56% vs 98% for placebo
- **Safety**

Adverse Event	0.5 mg TID (Studies 062 and 026)	0.5 mg TID (Study 111)	Standard Opioid Therapy (Study 111)	Placebo (Studies 062 and 026)
Nausea	83	78	34	18
Vomiting	72	52	12	5
Dizziness	57	22	10	8
Hypoxia	3	28	6	0

Summary: 0.25mg TID Dose

- Efficacy
  - Shows significant difference vs. placebo on SPID48 (LSM difference of 36 vs placebo) and secondaries. Treatment effect size for SPID 48 vs. high dose is 43%.
  - Median time to meaningful pain relief 122 minutes vs. 238 for placebo (Study 062)
  - Use of rescue 88% vs 98% for placebo
- Safety
  - Nausea: 59%
  - Vomiting: 41%
  - Dizziness: 33%

Summary: 0.125mg TID Dose

- Efficacy
  - Shows significant difference vs. placebo on SPID48 (LSM difference of 35 vs placebo) and secondaries. Treatment effect size for SPID 48 vs. high dose is 43%.
  - Median time to meaningful pain relief 166 minutes vs. 238 for placebo (Study 062)
  - Use of rescue 88% vs 98% for placebo
- Safety
  - Nausea: 44%
  - Vomiting: 29%
  - Dizziness: 22%

Summary

Efficacy

- Efficacy was demonstrated with primary endpoint for all doses but largest treatment effect was with the 0.5 mg dose
- Median time to meaningful pain relief was 92 minutes for 0.5 mg dose, 122 minutes for 0.25 mg dose and 166 minutes for 0.125 mg dose
- Number of subjects using rescue medication in the lower dose groups was 88% compared to 98% for placebo

Safety

- Types of adverse events were consistent with opioid class
- Rates of nausea (44% to 83%) and vomiting (29% to 73%)
- Over double the rate of nausea and four times the rate of vomiting with Buvaya compared to standard opioid therapy
- Rates of dizziness and hypoxia appeared higher than for other opioids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Drug Utilization Analysis and Assessment of Postmarket Abuse-Related Issues

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Outline

- Background/Intro
  - Public health perspective
  - Scope of drug utilization analyses
  - Scope of epidemiologic assessment
- Drug Utilization Review
  - Prescription Data
  - Survey Data
- Epidemiologic Assessment
  - Methods
  - Questions
  - Results
- Conclusions

Background

- 2017 report from the National Academies of Sciences, Engineering, and Medicine: *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*.
  - Suggests wider framework for evaluating opioids, including assessing:
    - The potential for diversion and misuse
    - The potential risk to family members and society
    - The likelihood of promoting transition to illicit drug use
- Epidemiologic data on buprenorphine reviewed within this framework with attention to the novel dosage form and lack of a mechanism intended to deter abuse

Scope of Drug Utilization Analysis

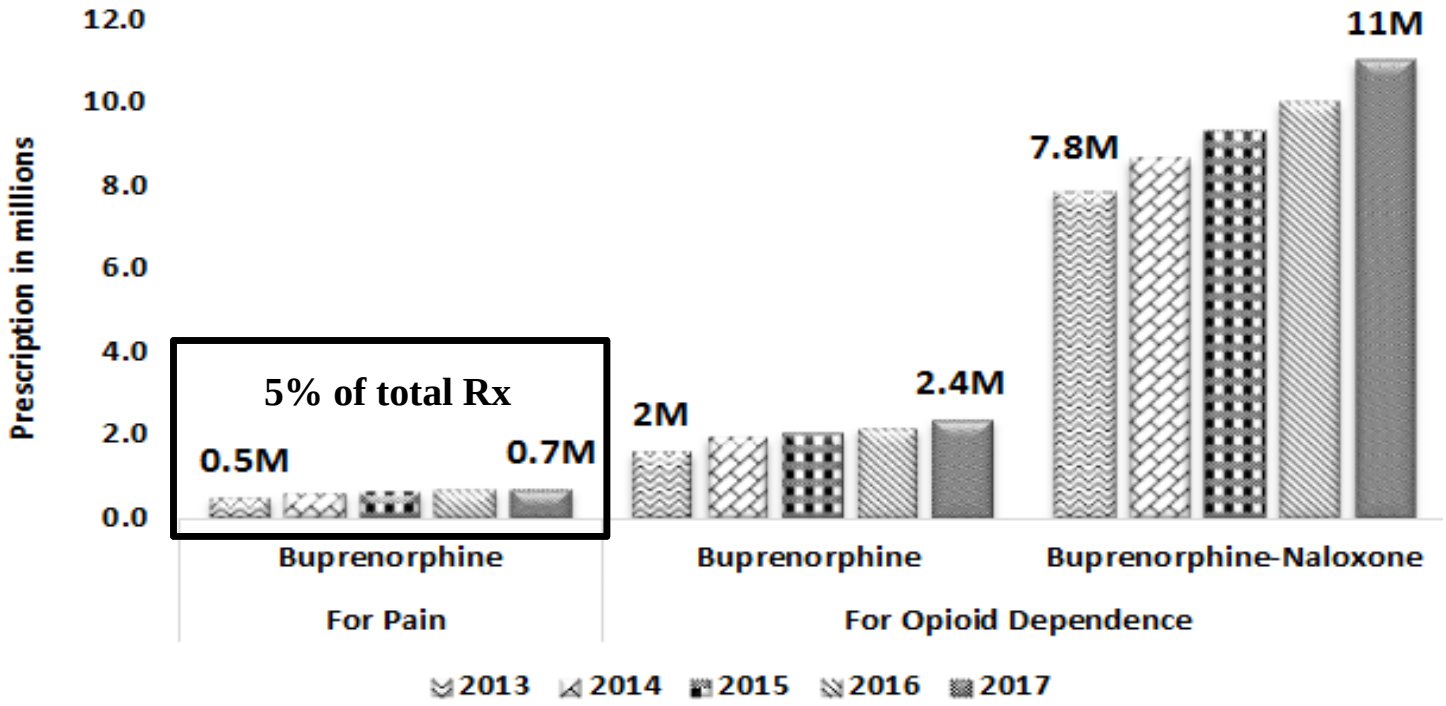
- Drug utilization data intended to provide context for issues being discussed
- There are currently three buprenorphine products indicated for treatment of pain:
  - Butrans (buprenorphine transdermal delivery system, BTDS),
  - Belbuca (buccal film), and
  - Buprenex (injectable buprenorphine)
- Buprenex is not often used in the outpatient setting, and will not be included in this analysis.

Scope of Epidemiologic Assessment

- There are many epidemiologic studies on the misuse and abuse of buprenorphine used in medication assisted treatment (MAT)
- Not the focus of this assessment
  - Buprenorphine products indicated for analgesia have a lower dosage range than those indicated for MAT
  - Abuse rates and patterns associated with buprenorphine MAT products may differ substantially from analgesic products

Drug Utilization Analysis

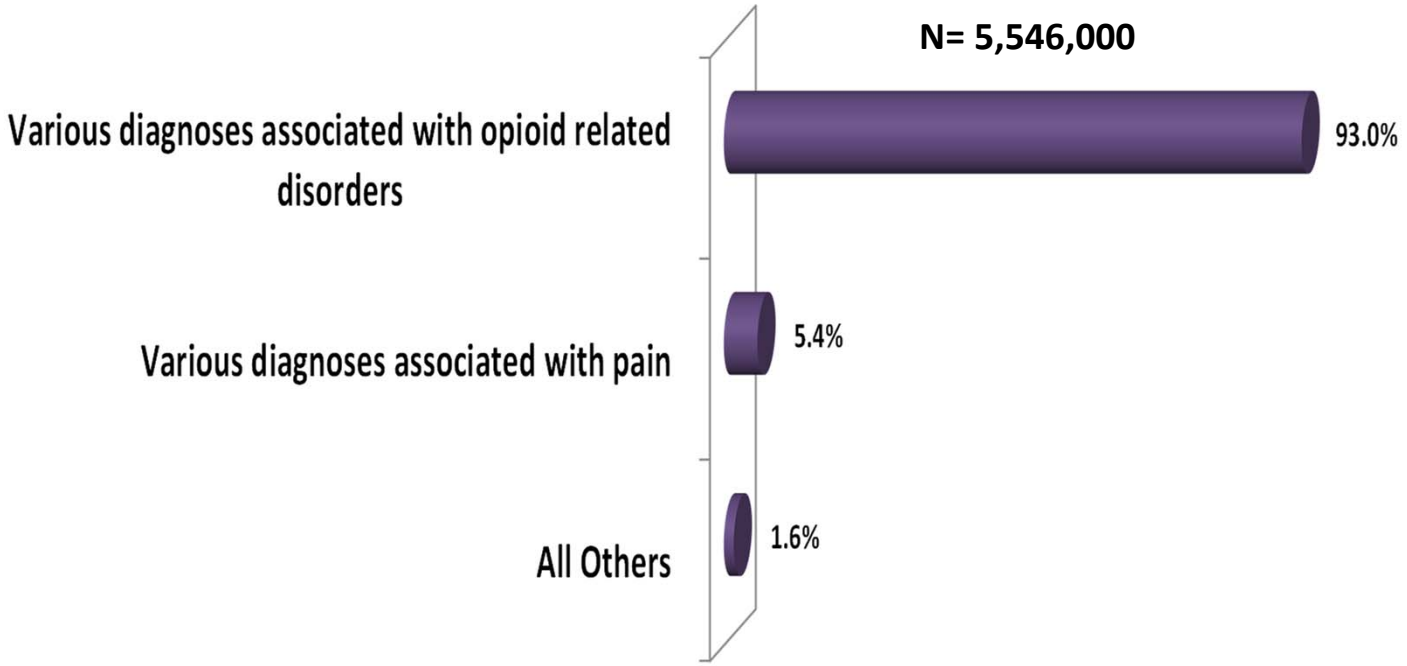
Prescription Data



Nationally estimated number of prescriptions dispensed for buprenorphine-containing products, stratified by labeled indications for pain management or treatment of opioid dependence, from U.S. outpatient retail pharmacies

Source: IQVIA, National Prescription Audit™ (NPA). January 2013- December 2017. Data extracted March 2018.

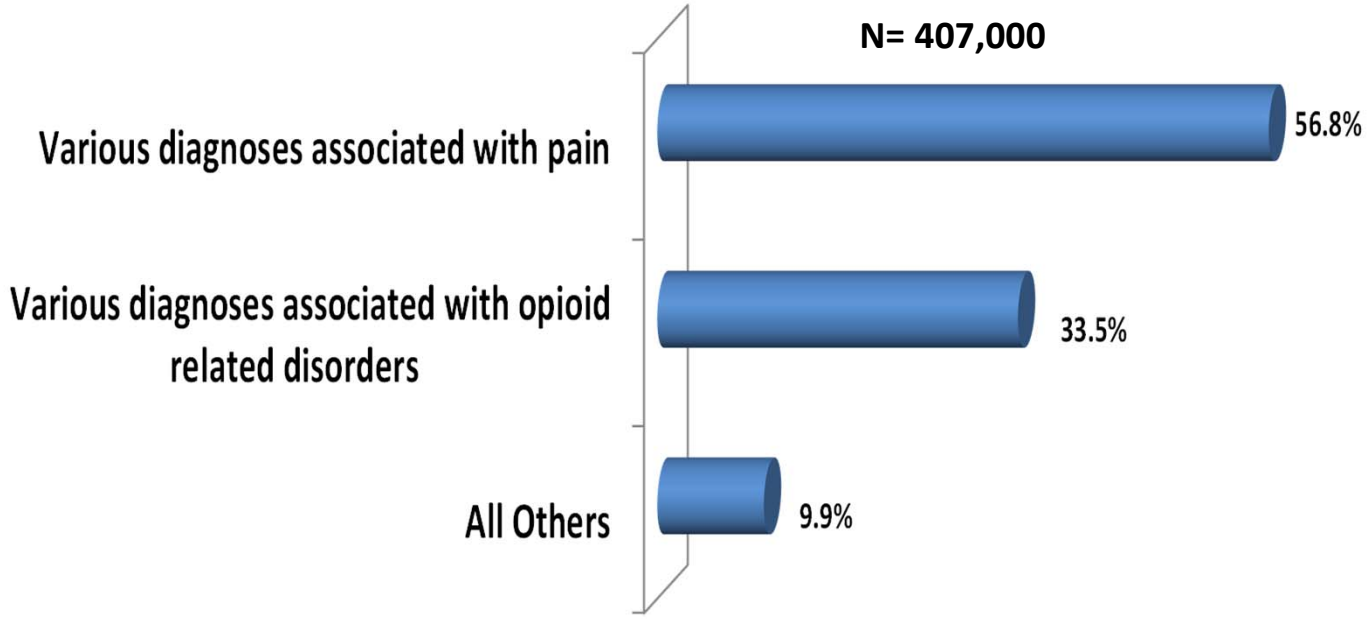
Survey Data:
Buprenorphine Products Labeled for Opioid Dependence, 2017



Diagnoses (ICD-10) in terms of drug use mentions associated with the use of buprenorphine products labeled for opioid dependence, as reported by office-based physician surveys, 2017

Source: Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel, 2017. Data extracted March 2018.

Survey Data:
Buprenorphine Products Labeled for Pain Management, 2017



Diagnoses (ICD-10) in terms of drug use mentions associated with the use of buprenorphine products labeled for pain management, as reported by office-based physician surveys, 2017

Source: Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel, 2017. Data extracted March 2018.

Drug Utilization Analysis Limitations

- Only dispensing patterns in the outpatient retail setting were assessed
- Diagnosis information and drug mentions are not linked to dispensed prescriptions
- Diagnoses data were derived from surveys of office-based physician practices

Epidemiologic Assessment

Questions

- The novel combination of product, dosage form, and indication led to a series of questions relating to the abuse of:
  - Sublingual spray formulations
  - Single-ingredient buprenorphine products compared to BNX combination products
  - BTDS and Belbuca overall
  - BTDS and Belbuca via injection

- Off-label use and patient characteristics associated with analgesic buprenorphine prescribing

Methods

- PubMed search of epidemiologic studies including buprenorphine and sublingual spray fentanyl products published between 2012 and 2018
  - Fentanyl sublingual spray included because of dosage form similarity
  - Clinical trials and studies focused on buprenorphine for MAT were excluded
- Search of the American of Poison Control Centers (AAPCC) National Poison Data System (NPDS) for BTDS and Belbuca
  - Abuse and misuse exposure calls between Jan 2015 and March 2018
  - Limited to closed cases and human exposure calls

Abuse of Sublingual Spray Opioids

- Epidemiologic literature very limited
- A single short article describing misuse of Instanyl (intranasal fentanyl spray) in France was found*
  - Small, non-U.S. study population
  - Unique definition of misuse
  - Insufficient detail on study methods
- Unable to draw conclusions about the abuse of transmucosal spray delivery systems in general

*Blin 2014

Abuse of Single-Ingredient vs. Combination Products

- Can provide information on impact of naloxone on abuse risk
  - Abuse patterns between MAT and analgesic products may differ substantially
- Two studies and a prior FDA review* found no preference for abuse of single-ingredient compared to BNX combination tablets
  - Both studies conducted in Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) databases
  - Wide geographic representation, but not nationally representative

*Lavonas 2014, Cicero 2014, McAninch 2013

Risk of Abuse Associated with BTDS and Belbuca

- Insights into how buprenorphine sublingual spray may be abused
  - Dose and dosage form may have important effects on the risk of abuse
- BTDS had a lower abuse rate compared to other buprenorphine products and selected opioids*
- Very limited information on Belbuca
- In a 3-year period, 25 exposure calls for BTDS abuse and misuse in AAPCC/NPDS; 6 calls for Belbuca

*Wiegand 2016, Coplan 2017

Risk of Injection BTDS Abuse

- Injection abuse of buprenorphine widely recognized public health issue abroad and in U.S.
- Most of the investigations focused on injection abuse of MAT products
- In three studies that included BTDS*, results were inconsistent on whether BTDS had a different rate of injection abuse compared to other buprenorphine dosage forms or other opioid analgesic products.
- AAPCC/NPDS data did not have any calls that mentioned injection abuse of either BTDS or Belbuca

*Lavonas 2014, Cicero 2014, Wiegand 2016

Off-Label Use of Buprenorphine

- Examining off-label use of buprenorphine for MAT may provide insight into the potential for off-label use of analgesic buprenorphine
- Extensive off-label drug use contributes to increased availability of a drug product for abuse in the community
- Studies document off-label use of buprenorphine* in patients with
  - Complex chronic pain
  - Depression or other psychiatric issues
  - Suspected or confirmed substance abuse

*Pade 2012, Chen 2014, Cote 2014, Kornfeld 2015, Kamajian 2016

Epidemiologic Study Limitations

- Abuse can be difficult to measure, particularly for low-volume products
- None of the U.S. data sources can provide national abuse prevalence estimates for these products
- Products may be misidentified in self-report data
- Unclear how well abuse patterns for marketed products inform potential abuse of new market entrants with different dose and delivery systems

Conclusions

- Overall outpatient utilization for buprenorphine has increased
- Of the total buprenorphine market, buprenorphine analgesics products represented only 5% of dispensed products
- Sizeable literature on abuse of buprenorphine MAT products, but less on abuse of analgesic buprenorphine
- While BTDS is abused, rates are generally lower compared to buprenorphine MAT products and other opioid analgesics
- Base study populations difficult to define and may not reflect the abuse patterns in the broader population

Bottom Line

Overall, the epidemiologic data provide very limited insight into the risks of misuse or abuse associated with buprenorphine sublingual spray compared to other buprenorphine products or other opioid analgesics.

Acknowledgement

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