Buprenorphine/Samidorphan

Director’s Introduction

Mitchell V. Mathis, MD
Director
Division of Psychiatry Products
Office of Drug Evaluation-I, CDER, FDA

Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting
November 1, 2018
Introduction

• Product
• Disease
• Current available treatments
• Substantial evidence
• Management of placebo response
• Agenda
• Questions to the Committee
The Product

• Combination product
  – Buprenorphine (BUP)
    • Approved drug
    • Partial agonist opioid
  – Samidorphan (SAM)
    • New Molecular Entity (NME)
    • Antagonist at opioid receptor

• Indication
  – Adjunctive treatment of major depressive disorder (MDD)
The Disease

• Major depressive disorder
  – Debilitating and chronic illness
  – Leading cause of disability worldwide
  – Partial response to approved drugs is common
    • Sequenced Treatment Alternatives to Relive Depression (STAR*D) Study
      – Only 28% of patients remit with first line monotherapy treatment
      – Public health need for effective add-on treatments
Approved Medications for MDD

• Several drugs of different classes approved for monotherapy

• Three drugs approved for adjunctive treatment of partially responsive depression
  – Quetiapine Extended Release
  – Aripiprazole
  – Brexpiprazole

• BUP/SAM would be a new class
Substantial Evidence

• 1962 Amendment to the Food Drug and Cosmetic Act
  – Required drug manufacturers to establish a drug’s effectiveness by “substantial evidence”
    • 505(d): evidence consisting of adequate and well-controlled investigations
      – Long been FDA’s position that Congress intended at least two adequate and well-controlled trials, each convincing on its own, to establish drug’s effectiveness.
      – Independent substantiation of results with at least two trials.
Single Study Approvals

• Section 115(a) of the 1997 FDA Modernization Act (FDAMA) amended section 505(d) of the Act to make it clear that FDA may rely on “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness.
  – Usually reserved for situations where an important clinical benefit (e.g., effect on survival), is clearly (statistically and clinically) seen and a confirmatory study would be hard to repeat on ethical grounds.
  – Usually reserved for cases when the single study is obviously and significantly positive.
  – Not the case with MDD or this development program.
Evidence of Effectiveness

• Applicant has argued that they have two positive studies.
  – Study 202
  – Study 207

• FDA will disagree.
Safety

• Applicant will argue that the opiate effects of BUP are largely, but not completely, blocked by SAM.

• FDA will agree.
## Submitted Efficacy Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Primary Efficacy</th>
<th>BUP/SAM Doses</th>
<th>Trial Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>202</td>
<td>SPCD</td>
<td>HAM-D17</td>
<td>2/2, 8/8</td>
<td>Applicant: positive FDA: disagree</td>
</tr>
<tr>
<td>205</td>
<td>SPCD</td>
<td>MADRS-10</td>
<td>0.5/0.5, 2/2</td>
<td>Applicant: negative FDA: agree</td>
</tr>
<tr>
<td>206</td>
<td>Placebo run-in</td>
<td>MADRS-10</td>
<td>2/2</td>
<td>Applicant: negative FDA: agree</td>
</tr>
<tr>
<td>207</td>
<td>SPCD</td>
<td>MADRS-6&lt;sub&gt;AVG&lt;/sub&gt; MADRS-10&lt;sub&gt;AVG&lt;/sub&gt; MADRS-10&lt;sub&gt;EOT&lt;/sub&gt;</td>
<td>1/1, 2/2</td>
<td>Applicant: positive FDA: disagree</td>
</tr>
</tbody>
</table>

- SPCD: Sequential Parallel Comparison Design
- MADRS-<sub>6</sub><sup>AVG</sup> & MADRS-10<sub>AVG</sub>: refer to improvement averaged over visits.
- MADRS-10<sub>EOT</sub>: refer to improvement at end of treatment (week 5 for Stage 1, week 6 for stage 2).
Management of Placebo Response

• Placebo response: nonspecific response to treatment not related to active drug
  – Long a problem in psychiatric drug trials
  – Sequential Parallel Comparison Design (SPCD)
    • Studies 202 and 207
    • Not yet accepted by Division of Psychiatry Products
Agenda for Today

• Applicant will discuss the need for new treatments, efficacy/safety/risk-benefit of their drug product.
• FDA and our guest speaker will then present our views of efficacy, safety, abuse potential, epidemiology of misuse/abuse, the relationship of opioid use disorders and MDD, and how a Risk Evaluation and Mitigation Strategy could help to manage the risks of BUP/SAM in treating MDD.
• The Committee will then discuss and vote on several questions related to this application.
Core Questions to the Committee

• Has substantial evidence of efficacy of BUP/SAM been presented by the Applicant?
• Has the Applicant adequately characterized the safety of BUP/SAM in treating MDD?
• Do the available data support a favorable benefit-risk profile of BUP/SAM to support approval?
Buprenorphine/Samidorphan

Regulatory History

Tiffany R. Farchione, MD
Deputy Director, Division of Psychiatry Products
Office of Drug Evaluation-I
Office of New Drugs, CDER, FDA

Joint Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting
November 1, 2018
Key Interactions with the Agency

- Pre-IND Meeting: February, 2011
- End-of-Phase 2 Meeting Request: October, 2013
- Written guidance on statistical analysis plan (SAP): July, 2015
- Guidance on completed Studies 205 and 206: September, 2016
- Guidance on revised SAP and endpoints: February, 2017
- Pre-NDA meeting and feedback on MADRS-6: July, 2017
Key Interactions with the Agency

- Amended protocol and statistical analysis plan for Study 207: September, 2016
- Breakthrough Therapy Designation Advice: March, 2017
- MADRS-6 dossier submitted: April, 2017
Pre-IND Meeting

• Design to support indication for adjunctive treatment of major depressive disorder (MDD)
• Evaluation of combination drug
• Defined Study 202 as “proof of concept”
• No objection to sequential parallel comparison design (SPCD) in proof of concept trial
  – Encouraged the Applicant to provide a detailed statistical analysis plan (SAP) and seek feedback prior to initiating the trial if they intended to use the study to support an efficacy claim
End-of-Phase 2 Comments

• Expressed concerns related to sequential parallel comparison design (SPCD) analyses:

From a statistical perspective, although the proposed SPCD appears to be reasonable, there has been no analytical proof for the validity of associated statistical analyses when there are missing data.
Guidance Meeting: Statistical Analysis Plan

• Reiterated concerns related to SPCD analyses:

We would like to reiterate that we haven’t endorsed any analytical method for SPCD in a confirmatory trial setting. We are continuing making efforts in further understanding its pros and cons from a regulatory perspective. You are encouraged to collect efficacy data from both stages. However, we may determine the efficacy based on data from only Stage 1 if analysis associated with this novel design is still unsettled by the time of your NDA filing.
Guidance Meeting: Completed Studies

• Discussed Studies 205 and 206
• Neither study met prespecified primary endpoint
• Although revised SAP was submitted a week prior to this guidance meeting, this was not sufficient time for review
Guidance Meeting: Revised SAP and Endpoints

• Change of primary efficacy endpoint from change from baseline to end-of-treatment on the MADRS-10 to three primary endpoints to be evaluated in a hierarchical fashion:
  – Change in MADRS-6 using average of changes from Baseline to Week 3 through the end of efficacy period (Week 5 for Stage 1; Week 6 for Stage 2)
  – Change in MADRS-10 score using average of changes from Baseline to Week 3 through the end of efficacy period (Week 5 for Stage 1; Week 6 for Stage 2)
  – Change in MADRS-10 score from Baseline to End-of-Treatment (Week 5 for Stage 1; Week 6 for Stage 2)
Guidance Meeting: Revised SAP and Endpoints

- We have not previously accepted the MADRS-6
  - Recommended they submit a dossier for evaluation
- We did not agree to the averaging strategy
- Noted that the protocol amendment introduced additional complexity in the SPCD analysis
  - Stage 1 and Stage 2 durations different
- Applicant also proposed pooling Studies 205 and 207
  - Agency stated that pooled analyses could only be considered exploratory
Preliminary Breakthrough Advice

• Advised Applicant that it would be difficult to grant a Breakthrough Therapy Designation
  – Had not yet determined acceptability of MADRS-6
  – Any statistical significance in phase 3 relied on *post hoc* analyses
Pre-NDA Meeting

- Discussed Clinical Outcome Assessments Staff review of MADRS-6
- MADRS-6 could not replace the MADRS-10 for use as a primary endpoint because it excludes concepts that are relevant and important in MDD
- Informed Applicant that any analyses of MADRS-6 would be considered exploratory
NDA Submission

• Initially refused to file the application
• Applicant clarified analyses intended to support application
• Agency agreed to file
Buprenorphine/Samidorphan

FDA Review of Efficacy Data

Semhar Ogbagaber, PhD

Division of Biometrics I
Office of Biostatistics
Office of Translational Sciences, CDER, FDA

Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting
November 1, 2018
## Submitted Efficacy Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Primary Efficacy</th>
<th>BUP/SAM Doses (mg/mg)</th>
<th>Trial Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>202</td>
<td>SPCD</td>
<td>HAM-D$_{17}$</td>
<td>2/2, 8/8</td>
<td><strong>Applicant:</strong> positive <strong>FDA:</strong> disagree</td>
</tr>
<tr>
<td>205</td>
<td>SPCD</td>
<td>MADRS-10</td>
<td>0.5/0.5, 2/2</td>
<td><strong>Applicant:</strong> negative <strong>FDA:</strong> agree</td>
</tr>
<tr>
<td>206</td>
<td>placebo run-in</td>
<td>MADRS-10</td>
<td>2/2</td>
<td><strong>Applicant:</strong> negative <strong>FDA:</strong> agree</td>
</tr>
<tr>
<td>207</td>
<td>SPCD</td>
<td>MADRS-6$<em>{AVG}$ MADRS-10$</em>{AVG}$ MADRS-10$_{EOT}$</td>
<td>1/1, 2/2</td>
<td><strong>Applicant:</strong> positive <strong>FDA:</strong> disagree</td>
</tr>
</tbody>
</table>

- SPCD: Sequential Parallel Comparison Design
- MADRS-6$_{AVG}$ & MADRS-10$_{AVG}$: refer to improvement averaged over visits.
- MADRS-10$_{EOT}$: refer to improvement at End-of-Treatment (Week 5 for Stage 1; Week 6 for Stage 2).
Outline

- Introduction to SPCD (Sequential Parallel Comparison Design)
- Studies 202 and 207
- General SPCD questions/concerns
- Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>BUP/SAM Doses Investigated</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>202 (proof-of-concept)</td>
<td>2/2, 8/8</td>
<td>SPCD</td>
</tr>
<tr>
<td>207 (phase 3)</td>
<td>1/1, 2/2</td>
<td></td>
</tr>
</tbody>
</table>
SPCD

**Stage 1**
- Randomize
  - Placebo
  - Drug

**Stage 2**
- Randomize
  - Placebo
  - Drug

- Removes placebo responders from Stage 1 to reduce placebo response in Stage 2; hope to get a larger treatment effect

- **SPCD estimated treatment effect (drug-placebo):** weighted average of treatment effects from both stages.
  - **Within each stage,** compare drug to placebo as in a conventional design
  - **Population:**  
    - **Stage 1:** all subjects;  
    - **Stage 2:** placebo non-responders from Stage 1
### SPCD Estimated Treatment Effect - Hypothetical Illustration

#### Stage Prespecified Weight Allocation

<table>
<thead>
<tr>
<th>Stage</th>
<th>Prespecified Weight Allocation</th>
<th>Sample Size</th>
<th>Estimated Treatment Effect</th>
<th>SPCD Estimated Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>60%</td>
<td>150</td>
<td>2</td>
<td>$60% \times 2 + 40% \times 3$</td>
</tr>
<tr>
<td>Stage 2</td>
<td>40%</td>
<td>70</td>
<td>3</td>
<td>$= 2.4$</td>
</tr>
</tbody>
</table>

**Contribution from each patient in deriving the estimate of 2.4:** Each patient’s outcome in Stage 1 is used, **but** each placebo non-responder contributes more weight because their Stage 2 outcomes are also used.
Study 202 - Design

• Phase 2, **proof of concept**, multicenter, randomized, double-blind, placebo controlled study, utilizing SPCD

• **BUP/SAM doses investigated:**
  – 2 mg/2 mg
  – 8 mg/8 mg

• **Primary Endpoint:** Change from Baseline to Week 4 in HAMD\textsubscript{17} total score

• **Goal:** Exploratory study – generated a hypothesis for the 2/2 BUP/SAM dose – to be tested in Study 207

HAMD\textsubscript{17}: higher score indicates severe depression.
Study 202 - Results

<table>
<thead>
<tr>
<th>SPCD Primary Results</th>
<th>BUP/SAM 2/2</th>
<th>BUP/SAM 8/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated treatment effect (SE*)</td>
<td>-2.8 (1.2)</td>
<td>-0.5 (1.2)</td>
</tr>
<tr>
<td>( p )-value without adjusting for multiplicity</td>
<td>0.014</td>
<td>0.699</td>
</tr>
</tbody>
</table>

*Standard error

**FDA Comments:** Study didn’t pre-specify multiplicity adjustment procedure to control overall Type I error rate

- Without the pre-specification, Study 202 is not an adequate and well-controlled trial and statistical interpretability is undermined
- In a *post hoc* exploration, conclusion becomes inconsistent when using Bonferroni or fixed-sequence testing procedure; if the 2/2 and 8/8 treatment groups are combined and compared to placebo, result is not statistically significant.
Study 202 – Site 124

- Site 124 enrolled a single subject (on the 2/2 dose) with an extreme result

Office of Scientific Investigations at FDA:

“The subject’s eligibility for the study cannot be determined due to incomplete and contradictory source information. Therefore, it is not recommended to use the data from this subject”
Extreme Result of Patient at Site 124

BUP/SAM 8/8 (mean)
Placebo (mean)
BUP/SAM 2/2 (mean)
Patient from Site 124

HAMD-17 Change from Baseline

Time (weeks)

Number of Patients
Placebo 95 94 92 93 90
BUP/SAM 2/2 20 20 17 17 17
BUP/SAM 8/8 20 20 16 15 14
Site 124 1 1 1 1 1
Impact: After removing the single patient from this site, the strength of evidence for BUP/SAM 2/2 diminished.

<table>
<thead>
<tr>
<th>Dose Compared with Placebo</th>
<th>SPCD Results</th>
<th>Including Site 124</th>
<th>Excluding Site 124</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUP/SAM 2/2</td>
<td>Estimated treatment effect</td>
<td>-2.8</td>
<td>-2.2</td>
</tr>
<tr>
<td></td>
<td>p-value without adjustment</td>
<td>0.014</td>
<td>0.057</td>
</tr>
<tr>
<td>BUP/SAM 8/8</td>
<td>Estimated treatment effect</td>
<td>-0.5</td>
<td>-0.4</td>
</tr>
<tr>
<td></td>
<td>p-value without adjustment</td>
<td>0.70</td>
<td>0.72</td>
</tr>
</tbody>
</table>
Study 202

• FDA Conclusions:
  – Not an adequate and well-designed study
  – No prospective plan to control the Type I error rate
  – Nominally positive results for the 2/2 dose depend on a single patient; further undermines strength of evidence
  – If Study 202 had been adequate and well controlled, and if statistical significance of results for 2/2 dose had not been sensitive to the contribution of a single patient, the neutral results with the 8/8 dose would undercut the persuasiveness of the results with the 2/2 dose (lack of internal consistency).
Study 207

• **Phase 3** multicenter, randomized, double-blind using SPCD

• **BUP/SAM dose investigated**
  – 1 mg/1 mg
  – 2 mg/2 mg

• Eligible subjects must have shown no improvement or inadequate response to anti-depressant therapy (ADT) during their current major depressive episode
Study 207 – SPCD Design

Stage 1
- Randomize
  - Placebo + ADT
  - BUP/SAM 1/1 + ADT
  - BUP/SAM 2/2 + ADT

Non-responders

Stage 2
- Randomize
  - Placebo + ADT
  - BUP/SAM 1/1 + ADT
  - BUP/SAM 2/2 + ADT

Week 0 1 2 3 4 5
Not used for efficacy

0 1 2 3 4 5 6
Study 207 –
Proposed Primary Efficacy Endpoints

• Change in MADRS-6 total score using average of changes from baseline to Week 3 through end of efficacy period (Week 5 for Stage 1, Week 6 for Stage 2)

• Change in MADRS-10 total score using average of changes from baseline to Week 3 through end of efficacy period

• Change in MADRS-10 total score from baseline to end of treatment period

Notes:
(1) Changes of primary endpoints made in late stage of the trial.
(2) MADRS-10: a 10-item instrument and the total score ranges from 0 to 60. Higher MADRS score indicates severe depression.
# MADRS-10 vs. MADRS-6

<table>
<thead>
<tr>
<th>MADRS-10</th>
<th>MADRS-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparent sadness</td>
<td>Apparent sadness</td>
</tr>
<tr>
<td>Reported sadness</td>
<td>Reported sadness</td>
</tr>
<tr>
<td>Inner tension</td>
<td>Inner tension</td>
</tr>
<tr>
<td>*Reduced sleep</td>
<td>Reduced sleep</td>
</tr>
<tr>
<td>*Reduced appetite</td>
<td>Reduced appetite</td>
</tr>
<tr>
<td>*Concentration difficulties</td>
<td>Concentration difficulties</td>
</tr>
<tr>
<td>Lassitude</td>
<td>Lassitude</td>
</tr>
<tr>
<td>Inability to feel</td>
<td>Inability to feel</td>
</tr>
<tr>
<td>Pessimistic thoughts</td>
<td>Pessimistic thoughts</td>
</tr>
<tr>
<td>*Suicidal thoughts</td>
<td>Suicidal thoughts</td>
</tr>
</tbody>
</table>

**Clinical Outcome Assessment Staff at FDA:** MADRS-6 total score not accepted due to the omission of clinically important symptoms included in MADRS-10
Study 207:
MADRS-10 Total Score at Each Week

Visit 0: baseline visit
Study 207:
Mean Change from Baseline in MADRS-10 Total Score at Each Week

Stage 1

Visit 0: baseline visit

Stage 2

Visit 0: baseline visit
### Study 207 - Applicant’s Efficacy Results

<table>
<thead>
<tr>
<th>Measures</th>
<th>Stage</th>
<th>BUP/SAM 1/1 vs Placebo</th>
<th>BUP/SAM 2/2 vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LSMD</td>
<td>95% CI</td>
</tr>
<tr>
<td>MADRS-10&lt;sub&gt;Avg&lt;/sub&gt;</td>
<td>Stage 1</td>
<td>-0.7</td>
<td>(-3.0, 1.6)</td>
</tr>
<tr>
<td></td>
<td>Stage 2</td>
<td>-1.2</td>
<td>(-3.6, 1.3)</td>
</tr>
<tr>
<td></td>
<td>Two Stages Combined</td>
<td>-0.9</td>
<td>(-2.6, 0.7)</td>
</tr>
</tbody>
</table>

\[p = 0.026\]

| MADRS-10<sub>EOT</sub> | Stage 1               | -1.1                   | (-3.7, 1.4)            | -1.6                   | (-4.3, 1.0)            |
|                        | Stage 2               | -1.5                   | (-4.2, 1.2)            | -1.7                   | (-4.4, 0.9)            |
|                        | Two Stages Combined   | -1.3                   | (-3.2, 0.5)            | -1.7                   | (-3.6, 0.2)            |

\[p = 0.076\]

Mean baseline MADRS-10 total score: ~32 for Stage 1; 27 for Stage 2

CI = confidence interval; AVG = average; EOT = End-of-Treatment (5 weeks for Stage 1; 6 weeks for Stage 2); LSMD = least squares mean difference from placebo
Study 207 - Conclusions

• **BUP/SAM 2/2**: Efficacy supported based on $\text{MADRS-10}_{\text{AVG}}$, but not $\text{MADRS-10}_{\text{EOT}}$
  – **MADRS-10$_{\text{AVG}}$ Results**: mean of -1.9 with 95% confidence interval (-3.6, -0.2) on a 60-point scale

• **FDA did not agree with MADRS-10$_{\text{AVG}}$ as a primary endpoint**
  – Averaging of the change in MADRS-6 or MADRS-10 tends to obscure a possible drop-off in drug efficacy after the first few weeks of treatment.

• **Clinical call regarding acceptability and/or interpretability of**
  – MADRS-10$_{\text{AVG}}$
  – SPCD, and unequal durations between stages
SPCD: Clinical Questions

• **Question 1: Mixed Patient Populations**

  – Which stage deserves more weight?
    
    • **Stage 1:** Usual trial population. (Many trials conducted in this patient population fail because of large placebo-response.)
    
    • **Stage 2:** Placebo non-responders – an enriched population selected to increase “signal” over “noise,” but less similar to the patient population for whom drug would be prescribed. For an effective drug, one would expect to see a treatment effect in Stage 2; however, sample size is smaller.

  – **Concern if dropouts are substantial**
    
    • Placebo non-responders who stay through the end of Stage 1 may be intrinsically different from the placebo dropouts.
SPCD: Clinical Questions

• **Question 2: Pre-specified Weight Allocation** (Study 202: 60%/40%; **Study 207**: 50%/50%)
  
  – Is there a *clinically sensible weight allocation*? If so, what is sensible?
    
    • Different weight allocation leads to a different treatment effect estimate and may affect strength of statistical significance
  
  – **Placebo non-responders are re-used**: more influence on estimating treatment effect than all other patients.

• **Question 3: Unequal Durations Between Stages**
  
  – Clinical relevance of combining estimated treatment effects over unequal durations between Stage 1 (5 weeks) and Stage 2 (6 weeks)?

• **Question 4: Labeling**
  
  – If drug is to be approved based on SPCD results, even if neither stage demonstrates efficacy, how does one describe the estimated treatment effect?
SPCD: Statistical Concerns

- **Concern 1:** Applicant’s analysis method was based on assumption of zero correlation between Stage 1 and Stage 2 treatment effect estimates, but the correlation may not be zero because placebo non-responders were used in both stages
  - **Potential Impacts:**
    - Type I error inflation when drug is not effective
    - Bias in estimating treatment effect (e.g., confidence interval) when drug is effective
  - **FDA Reviewer’s Evaluation:** To assess impact of possible violation of the assumption above, performed bootstrap sampling based statistical inference without such rigorous assumption for Study 207
    - Conclusion (empirical 95% CI) consistent with Applicant’s (normal-based 95% CI)
• **Concern 2:** Substantial Dropouts
  – **Potential Impact:** Type I error rate Inflation
    • Impact still under research in statistical community
  – In this application, however, the dropout rates were not substantial
Meta-Analysis Concerns

- **Meta-Analysis**: Included in Applicant’s NDA package

- A meta-analysis does not meet the usual standard for substantial evidence. Two adequate and well-controlled trials provide substantiation and protection against a false positive finding.

- **FDA Comments:**
  - The meta-analysis was not prospectively planned or agreed to as a means to provide evidence of effectiveness.
  
  - Combinability of SPCD and non-SPCD studies using meta-analysis does not appear to be sound due to incompatibility of populations in Stage 1 and Stage 2.
  
  - Rationale behind combining effects based on endpoints that were not specified in the SAP/protocol (such as MADRS-10_{AVG} in studies 202, 205, 206) is questionable.
Summary – FDA’s View

• **Study 202:** Efficacy was not demonstrated; the study is deemed to be a negative study.
  – No prospective plan for multiple testing
  – Site 124 further undermined strength of evidence
  – Neutral results for 8/8 dose would undercut any finding of efficacy for 2/2 dose.

• **Study 207:**
  – **BUP/SAM 2/2:** Efficacy supported based on MADRS-10_{AVG}, but not MADRS-10_{EOT}
  – Acceptability and/or interpretability (1) MADRS-10_{AVG}, (2) use of SPCD, and (3) unequal durations between stages?

• **Meta-Analysis:** Does not meet the usual standard of adequate and well-controlled trials for substantial evidence
Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee Meeting

Safety Review
Buprenorphine + Samidorphan for the adjunctive treatment of major depressive disorder

Daniel Lee, MD, Division of Psychiatry Products

November 1, 2018
SAFETY REVIEW
Safety Analysis Background

• General and opiate-specific safety concerns were reviewed

• Safety analysis in Sequential Parallel Comparison Design (SPCD) is challenging
  – Within and between trial heterogeneity
  – Disparate randomization ratios within (Stage 1/Stage 2) and across trials
  – Pooling of safety data across SPCD trials can produce misleading results
High Level Safety Observations

• No deaths were reported in the four submitted efficacy trials
• Eleven serious adverse events occurred in the four submitted efficacy trials (6 drug: 5 placebo)
• One serious adverse event warrants mention:
  – A participant concealed concomitant use of methadone from investigators. BUP/SAM precipitated withdrawal [Related]
• Adverse events consistent with µ-opiate agonism in the gut and central nervous system were observed in all four trials
• Mild opiate withdrawal was observed in some participants using the Clinical Opiate Withdrawal Scale (COWS)
## Pertinent Gastrointestinal Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event (Trial #)</th>
<th>Stage 1 / Group 1</th>
<th>Stage 2 / Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5mg/0.5mg</td>
<td>1mg/1mg</td>
</tr>
<tr>
<td>Nausea (202)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nausea (205)</td>
<td>14 (24%)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea (206)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nausea (207)</td>
<td>-</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>Constipation (202)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Constipation (205)</td>
<td>4 (7%)</td>
<td>-</td>
</tr>
<tr>
<td>Constipation (206)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Constipation (207)</td>
<td>-</td>
<td>9 (14%)</td>
</tr>
<tr>
<td>Abdominal Pain/Discomfort/Distension (202)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal Pain/Discomfort/Distension (205)</td>
<td>4 (7%)</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal Pain/Discomfort/Distension (206)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal Pain/Discomfort/Distension (207)</td>
<td>-</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**Source:** FDA analysis of Applicant’ safety data. *Data from drug / placebo sequence excluded.
### Pertinent Nervous System Adverse Events

#### Adverse Events Associated with Central Nervous System Depression or Alteration of Consciousness

<table>
<thead>
<tr>
<th>Adverse Event (Trial #)</th>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5mg/0.5mg</td>
<td>1mg/1mg</td>
</tr>
<tr>
<td>Dizziness/Syncope/Vertigo (202)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness/Syncope/Vertigo (205)</td>
<td>4 (7%)</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness/Syncope/Vertigo (206)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness/Syncope/Vertigo (207)</td>
<td>-</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Sedation/Somnolence/Lethargy/Hypersomnia (202)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sedation/Somnolence/Lethargy/Hypersomnia (205)</td>
<td>8 (14%)</td>
<td>-</td>
</tr>
<tr>
<td>Sedation/Somnolence/Lethargy/Hypersomnia (206)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sedation/Somnolence/Lethargy/Hypersomnia (207)</td>
<td>-</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Fatigue (202)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue (205)</td>
<td>3 (5%)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue (206)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue (207)</td>
<td>-</td>
<td>5 (8%)</td>
</tr>
</tbody>
</table>

**Source:** FDA analysis of Applicant’s safety data. *Data from drug / placebo sequence excluded.*
# Pertinent Adverse Events Associated with Trial Discontinuation

<table>
<thead>
<tr>
<th>Adverse Event (Trial #)</th>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5mg/0.5mg</td>
<td>1mg/1mg</td>
</tr>
<tr>
<td>Nausea (205)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea (207)</td>
<td>-</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Abdominal Pain/Discomfort (202)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal Pain/Discomfort (205)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal Pain/Discomfort (207)</td>
<td>-</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Constipation (207)</td>
<td>-</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dizziness/Syncope (202)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness/Syncope (205)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness/Syncope (207)</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>Sedation/Somnolence (202)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sedation/Somnolence (205)</td>
<td>1 (2%)</td>
<td>-</td>
</tr>
<tr>
<td>Sedation/Somnolence (207)</td>
<td>-</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Fatigue (205)</td>
<td>1 (2%)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue (207)</td>
<td>-</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

**Source:** FDA analysis of Applicant trial report safety data. *Data from drug / placebo sequence excluded.
CLINICAL OPIATE WITHDRAWAL SCALE (COWS) DATA
Clinical Opiate Withdrawal Scale – Study 202

Visit 11 (Day 64)

- 8/8 + Placebo
- 2/2 + Placebo
- Placebo (R) + Placebo
- Placebo (NR) + 8/8
- Placebo (NR) + 2/2
- Placebo (NR) + Placebo

Visit 12 (Day 71)

- 8/8 + Placebo
- 2/2 + Placebo
- Placebo (R) + Placebo
- Placebo (NR) + 8/8
- Placebo (NR) + 2/2
- Placebo (NR) + Placebo

% of Patients

Source: FDA analysis of Applicant trial report. R = Responders; NR = Non-Responders
Clinical Opiate Withdrawal Scale – Study 205

Visit 13 (Day 78)  Visit 14 (Follow Up)

<table>
<thead>
<tr>
<th>Group</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUP/SAM 2/2</td>
<td></td>
</tr>
<tr>
<td>BUP/SAM 0.5/0.5</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Source: FDA analysis of Applicant trial report.
Clinical Opiate Withdrawal Scale – Study 206

Visit 12 (Day 71)               Visit 13 (Follow Up)

BUP/SAM 2/2

Placebo

Placebo + BUP/SAM 2/2

Placebo + Placebo

% of Patients

Source: FDA analysis of Applicant trial report.
Clinical Opiate Withdrawal Scale – Study 207

Visit 13 (Day 78)  Visit 14 (Follow Up)

Source: FDA analysis of Applicant trial report.
CONTROLLED SUBSTANCE STAFF (CSS) REVIEW
Abuse Potential of Buprenorphine/Samidorphan (BUP/SAM)

FDA Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting

November 1, 2018

Edward Hawkins, PhD
Controlled Substance Staff (CSS)
Center for Drug Evaluation and Research
Food and Drug Administration
Assessing the Abuse Potential of Samidorphan and Buprenorphine

• The Applicant is proposing a new drug product that combines the mu partial agonist, buprenorphine, with samidorphan, a drug with mu opioid antagonist properties, formulated as sublingual tablets (BUP/SAM).

• *In vitro* studies indicate that it is possible to separate to some degree the buprenorphine from samidorphan in BUP/SAM.

• No studies were conducted to determine the safety or abuse liability of BUP/SAM after manipulation.
  • This includes studies regarding different methods of administration that are typically associated with abuse (e.g. intranasal).
Assessing the Abuse Potential of Samidorphan

• Samidorphan is a new molecular entity that is chemically synthesized from thebaine-derived naltrexone.
• Under the Controlled Substances Act, all derivatives of thebaine are Schedule II substances until such time as they are down-scheduled or decontrolled, following an abuse potential assessment.
• Thus, it was necessary to conduct an abuse assessment for both samidorphan alone, and in combination with buprenorphine.
Preclinical Abuse-Related Data with Samidorphan

• *In vitro* receptor binding and functional studies show that samidorphan acts at mu opioid receptors as an antagonist.

• Although samidorphan is derived from an opioid (thebaine), administration of samidorphan alone does not produce analgesia in animals.

• However, it can reduce the analgesic effects of the mu opioid receptor agonist, morphine, and can reverse the cardiac and respiratory depressant effects of the mu opioid agonist, fentanyl.

• These data demonstrate that in whole animals, samidorphan has activity as a mu opioid antagonist.
Animal Drug Discrimination Studies

• Drug discrimination is an experimental method of determining whether a test drug produces pharmacological effects which elicit physical and behavioral responses in the animal that are similar to their responses to a training drug (known drug of abuse).

• Test drugs that produce a response similar to a training drug with known abuse potential are also likely to be abused by humans.
Animal Drug Discrimination Study with Samidorphan

- In rats trained to discriminate morphine from vehicle:
  - Morphine produced full generalization (97.4%) to the morphine cue.
  - Samidorphan produced no generalization (5.4%) to the morphine cue.
- These data show that samidorphan did not produce sensations that are similar to those produced by morphine.
- This was expected, since samidorphan is a mu opioid antagonist.
Animal Self-Administration Studies

- Self-administration is a method that assesses whether a test drug produces rewarding effects that increase the likelihood of behavioral responses in order to obtain additional drug (positive reinforcement).
- Drugs that are self-administered by animals are likely to produce rewarding effects in humans.
- The ability of a test drug to produce self-administration is indicative that the drug has abuse potential.
Animal Self-Administration Study with Samidorphan

- Rats learned to lever-press for intravenous heroin as the training drug.
- After self-administration of heroin was stable, animals were allowed intravenous access to the following substances, which produced varying degrees of self-administration (infusions/session):
  - samidorphan (0.068 mg/kg/infusion, i.v.) = 9.2 infusions
  - heroin (0.015 mg/kg/infusion) = 18.8 infusions
  - naltrexone (0.0136 mg/kg/infusion) = 8.1 infusions
  - placebo = < 5 infusions
- These data show that samidorphan does not produce rewarding properties that sustain positive reinforcement, similar to naltrexone.
Human Abuse Potential (HAP) Studies

• HAP studies evaluate the ability of a test drug to produce positive subjective responses in subjects compared to a known drug of abuse (a “positive control”) and to placebo.

• Subjects in HAP studies are individuals with a history of recreational drug use but they are not drug dependent.

• When the test drug produces consistently large responses on positive subjective scales that are far outside the acceptable placebo range, it is likely that the test drug has abuse potential.
Human Abuse Potential Studies with Samidorphan

• The first of two HAP studies evaluated the oral abuse potential of:
  • Samidorphan (2.5, 10, and 20 mg)
  • Oxycodone (15 and 30 mg)
  • Placebo

• This study used a randomized, double-blind, placebo-controlled, crossover design in healthy non-dependent recreational opioid users.
Human Abuse Potential Study: Results

Primary Measure:

Visual Analog Scale (VAS) Drug Liking, as a bipolar scale from 0 (extreme disliking) to 100 (extreme liking), with 50 as neutral

- The positive control drug, oxycodone (15 and 30 mg), produced statistically significantly higher mean Drug Liking scores (77 and 85, respectively) compared to placebo (54), which establishes assay sensitivity and validates the study.

- Samidorphan at all three doses (2.5, 10, and 20mg) produced mean Drug Liking scores (57, 58, and 60) that are within the placebo range (40-60).
Human Abuse Potential Study: Results

Secondary Measures:

**VAS Overall Drug Liking, High, Good Drug Effects, Take Drug Again**

- Oxycodone (15 and 30 mg) produced mean scores on each of these positive subjective measures that were statistically significantly greater than placebo.

- Samidorphan at all three doses (2.5, 10, and 20 mg) produced mean scores on each of these positive subjective measures that were within the placebo range.
Human Abuse Potential Studies with Samidorphan

- The second of two HAP studies evaluated the abuse potential of:
  - Samidorphan (10 and 30 mg, oral)
  - Oxycodone (40 mg, oral)
  - Pentazocine (30 mg, intravenous)
  - Naltrexone (100 mg, oral)
  - Placebo (oral and intravenous)

- This study used a randomized, double-blind, double-dummy, placebo-controlled, crossover design in healthy non-dependent recreational opioid users.
Human Abuse Potential Study: Results

Primary Measure:

**VAS Drug Liking, as a bipolar scale from 0 (extreme disliking) to 100 (extreme liking), with 50 as neutral**

- The positive control drugs, oxycodone (40 mg) and pentazocine (30 mg), produced statistically significantly higher mean Drug Liking scores (80 and 81, respectively) compared to placebo (54), which establishes assay sensitivity and validates the study.

- Samidorphan (10 and 30 mg) produced mean Drug Liking scores (59 and 61, respectively) that were, statistically, within the placebo range (40-60). This was also observed for naltrexone (100 mg), which produced a score of 58.
Secondary Measures:

**VAS Overall Drug Liking, High, Good Drug Effects, Take Drug Again**

- Oxycodone (40 mg) and pentazocine (30 mg) produced mean scores on each of these positive subjective measures that were statistically significantly greater than placebo.

- Samidorphan at both doses (10 and 30 mg) produced mean scores on each of these positive subjective measures that were within the placebo range. This was also observed for naltrexone (100 mg).
Human Abuse Potential Study with Samidorphan and Buprenorphine (BUP/SAM)

• A third HAP study evaluated the abuse potential of SL tablets of:
  • Buprenorphine + samidorphan (2 mg + 2 mg, 8 mg + 8 mg, and 16 mg + 16 mg)
  • Buprenorphine (8 and 16 mg, alone)
  • Placebo

• This study used a randomized, double-blind, placebo-controlled, crossover design in healthy non-dependent recreational opioid users.
Human Abuse Potential Study: Results

Primary Measure:

**VAS Drug Liking, as a bipolar scale from 0 (extreme disliking) to 100 (extreme liking), with 50 as neutral**

- The positive control drug, buprenorphine (8 and 16 mg) produced statistically significantly higher mean Drug Liking scores (76 and 82, respectively) compared to placebo (52), which establishes assay sensitivity and validates the study.

- Samidorphan + buprenorphine (2 + 2 mg, 8 + 8 mg, and 16 + 16 mg) produced mean Drug Liking scores (60, 61, and 64, respectively) that were barely outside of the placebo range (40-60).
Human Abuse Potential Study: Results

Secondary Measures:

VAS Overall Drug Liking, High, Good Drug Effects, Take Drug Again

- Buprenorphine (8 and 16 mg) produced mean scores on each of these positive subjective measures that were statistically significantly greater than placebo.

- Samidorphan + buprenorphine at all three doses (2 + 2 mg, 8 + 8 mg, and 16 + 16 mg) produced mean scores on each of these positive subjective measures that were either within the placebo range or barely outside of this range.
Human Abuse Potential Studies: Conclusions

• Two single-dose HAP studies conducted with samidorphan indicate that the drug does not produce positive subjective responses.

• In a third HAP study, the combination of samidorphan and buprenorphine produced positive subjective responses that were much less than those produced by buprenorphine alone; however, they were slightly outside of the placebo range.
FINAL CONCLUSIONS: Abuse Potential of Samidorphan, and BUP/SAM

• Animal and human studies consistently show that samidorphan is a mu opioid antagonist with no meaningful abuse potential (similar to the mu opioid antagonist, naltrexone).

• BUP/SAM produces subjective responses that are lower than those from administration of the same dose of BUP alone, but does retain some clinically significant abuse potential.

• Overall, the positive subjective responses reported after administration of BUP/SAM showed that the combination has a low potential for abuse.
FDA Review of the Epidemiologic and Surveillance Data

Joint Meeting of the Psychopharmacologic Drugs Advisory Committee & Drug Safety and Risk Management Advisory Committee  
November 1st, 2018

Celeste Mallama, PhD, MPH    
Epidemiologist    
Division of Epidemiology II, OPE, OSE, CDER
Call to Consider Public Health Impact at Time of Drug Approval


• Recommends that FDA evaluation of benefit-risk for opioid review, approval, and monitoring include assessing evidence of a product’s potential for misuse and diversion and predicted risks to family members and society.
Objectives of Epidemiology Review

• Inform broader consideration of benefit-risk balance for buprenorphine/samidorphan:
  – Use, misuse, and abuse of currently marketed buprenorphine and buprenorphine-naloxone products.
  – Complex relationships between depression, pain, and substance use disorders.

• Contextual information - Not intended as prediction of expected abuse of buprenorphine/samidorphan.
Nationally Estimated Number of Prescriptions for Buprenorphine-Containing Oral Solid Formulations Dispensed from US Outpatient Retail Pharmacies, 2013-2017


MAT: Medication Assisted Treatment; US: United States
Buprenorphine Misuse in a National Population Survey

Past-year Misuse* of Rx Pain Relievers, Ages 12+ Years, NSDUH 2017

*NSDUH defines misuse as any use other than as directed by a healthcare provider

NSDUH: National Survey on Drug Use and Health; Rx: Prescription
Comparing Misuse and Abuse of Buprenorphine to Other Opioids is Challenging

• Majority of buprenorphine dispensed in the US is for evidence-based treatment for opioid use disorder.
• This population has an elevated risk of opioid misuse and abuse.
• Therefore, directly comparing levels of buprenorphine misuse and abuse to other opioids can be misleading.
Buprenorphine Abuse Through Non-Oral Routes is Common in Cases that Come to Medical Attention, Including Formulations with Naloxone (1)

Abuse-Related Calls to US Poison Control Centers, NPDS 2013-2017

- NPDS captures information on a near real-time basis from a national network of poison centers receiving calls from the public or health care workers.

NPDS: National Poison Data System
Buprenorphine Abuse Through Non-Oral Routes is Common in Cases that Come to Medical Attention, Including Formulations with Naloxone (2)

Abuse Cases Presenting to US Emergency Departments, NEISS-CADES 2016-2017

- Nationally representative sample of emergency department visits in the US.
Buprenorphine Injection is Also Common in Patients Entering Treatment for Opioid Use Disorder

- 34.4% of respondents entering treatment who reported past-month buprenorphine use “to get high” indicated injection route.
- Among respondents reporting injection of buprenorphine:
  - 43.6% injected buprenorphine-naloxone tablets.
- Participants reported a number of simple methods they believed separated buprenorphine from naloxone, resulting in “pure buprenorphine” injection.

Key Points from Epidemiologic Data

• Majority of buprenorphine market is buprenorphine-naloxone products indicated for treatment of opioid dependence.
• Abuse of buprenorphine, even in combination with naloxone, is common and occurs through both oral and non-oral routes, including injection.
  – Respondents entering treatment reported using separation methods they believed resulted in “pure buprenorphine”.
• Comparison of buprenorphine abuse patterns with other opioids is challenging due to the high-risk nature of the populations in which buprenorphine is used.
• Buprenorphine/samidorphan product under review has a new, orally bioavailable antagonist, and is indicated for a new population. Not known whether similar misuse/abuse patterns will be seen.

MAT: Medication Assisted Treatment
Depression Effects on Long-Term Prescription Opioid Use, Abuse and Addiction

Mark Sullivan, MD, PhD
University of Washington
Psychiatry and Behavioral Sciences
Anesthesiology and Pain Medicine
Bioethics and Humanities
Risk Management for Buprenorphine/Samidorphan

November 1, 2018

Somya Dunn, MD
Commander, United States Public Health Service
Risk Management Analyst
Center for Drug Evaluation and Research
Division of Risk Management
Presentation Overview

• Background on Risk Evaluation and Mitigation Strategies (REMS)
• Summary of the REMS for buprenorphine-containing products
• Potential safety concerns associated with the use of buprenorphine/samidorphan (BUP/SAM)
• Risk Management for BUP/SAM
Background on Risk Evaluation and Mitigation Strategies (REMS)
A REMS is a drug safety program that FDA can require for certain drugs

- REMS are designed to achieve specific goals to mitigate risks associated with the use of a drug.
- REMS include strategies beyond labeling to ensure that the benefits of a drug outweigh the risks.
- The FDA Amendments Act (FDAAA) of 2007 authorized FDA to require Applicants or Application holders to develop and comply with REMS programs if determined necessary to ensure the benefits outweigh the risks.
- The FDA has authority to require a REMS pre-approval or post-approval.
A REMS can include a number of components

1. Medication Guide or Patient Package Insert
2. Communication plan for healthcare providers (HCPs)*
3. Elements to assure safe use (ETASU)
4. Implementation System
5. Must include a timetable for submission of assessments*

* This requirement only applies to NDAs and BLAs.
A REMS can include any of the following ETASUs if determined necessary:

- Certification and/or specialized training of **HCPs** who prescribe the drugs
- Certification of pharmacies or other dispensers of the drug
- Dispensing/administration of drug in **limited settings**, e.g., hospitals
- Each patient using the drug is subject to certain **monitoring**
- Drug is dispensed/administered only with **evidence of safe-use conditions**, e.g., pregnancy test
- Enrollment of treated patients in a **registry**
Summary of the REMS for buprenorphine-containing products
Buprenorphine-containing products

For Opioid Dependence:

– Subutex® (buprenorphine) sublingual tablet and generic equivalents
– Suboxone® (buprenorphine/naloxone) sublingual tablet and generic equivalents
– Zubsolv® (buprenorphine/naloxone) sublingual tablet
– Bunavail® (buprenorphine/naloxone) buccal film
– Probuphine® (buprenorphine) subdermal implant
– Sublocade® (buprenorphine) extended-release subcutaneous injection
– Cassipa™ (buprenorphine/naloxone) sublingual film

For Pain:

– Butrans® (buprenorphine) extended-release transdermal film
– Belbuca® (buprenorphine) buccal film
– Buprenex (buprenorphine) injection
**REMS for buprenorphine-containing products**

<table>
<thead>
<tr>
<th><strong>Suboxone/Subutex and Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS</strong></th>
<th><strong>Probuphine REMS</strong></th>
<th><strong>Sublocade REMS</strong></th>
<th><strong>Opioid Analgesic REMS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks Mitigated in REMS:</td>
<td>Risks Mitigated in REMS:</td>
<td>Risk Mitigated in REMS:</td>
<td>Risks Mitigated in the REMS:</td>
</tr>
<tr>
<td>• Accidental Overdose</td>
<td>• Migration</td>
<td>• Serious harm or death that could result from intravenous self-administration</td>
<td>• Adverse Outcomes of addiction unintentional overdose, and death resulting from inappropriate prescribing abuse and misuse</td>
</tr>
<tr>
<td>• Misuse</td>
<td>• Protrusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abuse</td>
<td>• Expulsion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nerve damage associated with insertion and removal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Accidental Overdose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Misuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Abuse</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# REMS for buprenorphine-containing products

For Products Indicated for Opioid Dependence

<table>
<thead>
<tr>
<th>Suboxone/Subutex and Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risks Mitigated in REMS:</strong></td>
</tr>
<tr>
<td>• Accidental Overdose</td>
</tr>
<tr>
<td>• Misuse</td>
</tr>
<tr>
<td>• Abuse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probuphine REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risks Mitigated in REMS:</strong></td>
</tr>
<tr>
<td>• Migration</td>
</tr>
<tr>
<td>• Protrusion</td>
</tr>
<tr>
<td>• Expulsion</td>
</tr>
<tr>
<td>• Nerve damage associated with insertion and removal</td>
</tr>
<tr>
<td>• Accidental Overdose</td>
</tr>
<tr>
<td>• Misuse</td>
</tr>
<tr>
<td>• Abuse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sublocade REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Mitigated in REMS:</strong></td>
</tr>
<tr>
<td>• Serious harm or death that could result from intravenous self-administration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opioid Analgesic REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risks Mitigated in the REMS:</strong></td>
</tr>
<tr>
<td>• Adverse Outcomes of addiction unintentional overdose, and death resulting from inappropriate prescribing abuse and misuse</td>
</tr>
</tbody>
</table>
## REMS for buprenorphine-containing products

<table>
<thead>
<tr>
<th>Suboxone/Subutex and Buprenorphine Transmucosal Products for Opioid Dependence (BTOD) REMS</th>
<th>Probuphine REMS</th>
<th>Sublocade REMS</th>
<th>Opioid Analgesic REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risks Mitigated in REMS:</strong></td>
<td><strong>Risk Mitigated in REMS:</strong></td>
<td><strong>Risk Mitigated in REMS:</strong></td>
<td><strong>Risks Mitigated in the REMS:</strong></td>
</tr>
<tr>
<td>• Accidental Overdose</td>
<td>• Migration</td>
<td>• Serious harm or death that could result from intravenous self-administration</td>
<td>• Adverse Outcomes of addiction unintentional overdose, and death resulting from inappropriate prescribing abuse and misuse</td>
</tr>
<tr>
<td>• Misuse</td>
<td>• Protrusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abuse</td>
<td>• Expulsion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nerve damage associated with insertion and removal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Accidental Overdose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Misuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Abuse</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Suboxone/Subutex and BTOD REMS

- Provider and pharmacy educational materials
- Appropriate use checklist
- Training is not required as part of the REMS
Buprenorphine-containing products used for opioid use disorder

Can be prescribed outside of an Opioid Treatment Program (OTP) if they obtain a DATA 2000 waiver

- The Substance Abuse and Mental Health Services Administration (SAMHSA) manages the Drug Addiction Treatment Act of 2000 (DATA 2000)
  - Sets eligibility and certification requirements for the DATA 2000 waiver which includes required training
  - Physicians that hold DATA 2000 waivers can prescribe and/or dispense buprenorphine products for opioid use disorder in settings other than OTPs

*http://www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management/qualify-for-physician-waiver
Opioid Analgesic REMS

Buprenorphine-containing products approved for the treatment of pain are covered in the Opioid Analgesic REMS*

• Requires manufacturers to make training available to healthcare providers involved in the management of patients with pain
• Training is not required to prescribe or dispense and is focused is on:
  • Pain management
  • Identifying risk factors for abuse and addiction
  • How to counsel patients and their families on the safe use of opioids
  • Fundamentals on addiction medicine

*Prescribers of buprenorphine-containing products for pain are not required to take training under DATA 2000
Potential Safety Concerns Associated with the Use of BUP/SAM
Safety concerns regarding BUP/SAM for depression

• In the U.S., the majority of patients with depression are treated by primary care clinicians*
  – It is important for prescribers to understand that BUP/SAM contains an opioid

• Use for depression will be chronic
  – Chronic use could lead to addiction, dependence, and withdrawal

*Mark TL, Levit KR. et al. Psychiatr Serv. 2009;60:1167
Safety concerns regarding BUP/SAM for depression

• There is a potential for concomitant opioid and benzodiazepine use
  – Mental illness, including depression, is associated with comorbidities including pain conditions,* opioid use disorder and anxiety – concomitant use of an opioid agonist or benzodiazepine could put patients at risk for respiratory depression
  – Mental illness, including depression, is associated with misuse and abuse of prescription opioids
  – Higher doses of opioids may be needed for analgesia

* Sullivan MD. *The Clinical journal of pain.* Sep 2018;34(9):878-884
Safety concerns in women of child-bearing potential

• The prevalence of moderate to severe major depressive disorder is 9.3% in women aged 18 to 39*

• Women who are pregnant may be putting their unborn infants at risk for development of Neonatal Opiate Withdrawal Syndrome (NOWS); this was not evaluated in the clinical program for BUP/SAM
  – Labeling for approved buprenorphine products addresses the risk of NOWS

*NHANES, https://www.cdc.gov/nchs/data/databriefs/db172.htm
Product specific safety concerns with BUP/SAM

• Lack of adherence to therapy* with BUP/SAM along with concomitant opioid use may potentiate the risks (withdrawal, respiratory depression) due to changing opiate μ-agonist and antagonist effects

• Concerns regarding the ability to separate buprenorphine from samidorphan

Risk Management for BUP/SAM
Applicant’s Proposed REMS

- The Applicant’s proposed REMS is designed to mitigate the risks of misuse and accidental exposure.
- Training is made available to healthcare providers.
- Training is not required to prescribe or dispense BUP/SAM.
Risk Management for BUP/SAM

• Risks for BUP/SAM include those associated with opioids as well as other potential safety concerns
• Prescribers of BUP/SAM for depression will not be required to take training under DATA 2000
• In conclusion, if approved, FDA will likely require a REMS for BUP/SAM and is considering:
  – How a REMS can best address the potential concerns with BUP/SAM in the indicated population
  – Whether training for potential prescribers of BUP/SAM is necessary as part of the REMS
Back-up Slides Shown
Study 202: Spaghetti Plot

Observations from the 2 mg/2 mg group (Stage 1)

Patient from site 124
If two treatment groups can have unequal variances (i.e., this will induce a nonzero correlation discussed above), then variance of the weighted estimator is not yet developed for MMRM estimators.

To account for potential differences in variances and covariances, we conducted a bootstrap inference
Dropout Patterns – Study 207 Stage 1

(Source: FDA Reviewer’s plot)
Dropdown Patterns – Study 207 Stage 2

(Source: FDA Reviewer’s plot)