Buprenorphine/Samidorphan (BUP/SAM) NDA 210,417

Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Alkermes, Inc.
Introduction

Lisa von Moltke, MD
Senior Vice President, Clinical Development
Alkermes, Inc.
# Agenda

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Additional Participants

External:
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Senior Vice President, Regulatory Affairs
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Vice President, Clinical Development Psychiatry

Bhaskar Rege, PhD
Vice President, Clinical Pharmacology & Translational Medicine
Asli Memisoglu, ScD
Senior Director, Biostatistics
Arielle Stanford, MD
Medical Director, Clinical Development
Key Topics

• Significant unmet need and treatment challenges for patients with MDD
  – Need for new differentiated mechanisms

• Significant development challenges of studying MDD
  – Utilization of Sequential Parallel Comparison Design (SPCD) methodology

• Positive Benefit-Risk for Buprenorphine/Samidorphan (BUP/SAM or ALKS 5461)
  – Substantial evidence of efficacy
  – Well characterized and manageable safety profile
  – Low potential for abuse

• Approving a new opioid modulator in the midst of an opioid crisis
  – Committed to responsible risk mitigation and commercial distribution
Buprenorphine/Samidorphan (BUP/SAM)

- Opioids and BUP in particular may have antidepressant effects
  - SAM mitigates the abuse and dependence potential
- Proposed for adjunctive treatment of major depressive disorder (MDD)
  - Patients not responding to available antidepressant therapies
- Proposed therapeutic dose
  - 2 mg BUP/ 2 mg SAM (BUP/SAM 2/2) sublingual tablet
    - Following a 1-week titration (0.5/0.5 for 3 days, 1/1 for 4 days)
  - 1 mg BUP/ 1 mg SAM (BUP/SAM 1/1) for special populations
BUP/SAM Regulatory History Through Development

- Pre-IND Meeting - February 2011
  - Initial discussions regarding study designs (SPCD)
- End-of-Phase 2 Meeting - October 2014
  - Clinical study designs
- Fast Track Designation - October 2014
  - BUP/SAM has the potential to address an unmet need for a serious condition based on results of the Phase 2 study
- Two Scientific Exchange Meetings - September 2016 & February 2017
  - Share results of Phase 3 studies
- Pre-NDA Meeting – July 2017
  - NDA submission content
Major Depressive Disorder (MDD)

- Major source of morbidity and disability
  - Carries a risk of suicide
- Significant percentage of patients do not achieve adequate symptom relief with standard antidepressants
- All approved antidepressants work via monoaminergic mechanisms
  - Serotonin, norepinephrine, dopamine
- Only antipsychotics are approved as adjunctive therapies
  - Can have significant side effects
- New approaches to treat depression are urgently needed
**BUP/SAM Program Founded on Evidence of Antidepressant Effect of Opioids**

- Opioid receptors highly expressed in brain regions associated with emotional regulation
- Clinical history of efficacy with opioids, particularly BUP, in patients with MDD
  - Broader use limited by abuse and dependence potential

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**BUP/SAM for Adjunctive Treatment of MDD**

Buprenorphine (BUP)
- Partial μ-opioid agonist and κ-opioid antagonist
- Bioavailable sublingually

Samidorphan (SAM)
- New molecular entity
- Potent μ-opioid antagonist
- Optimized for:
  - High potency
  - High bioavailability with oral and sublingual administration

Co-formulation in a single sublingual tablet
Extensive Safety and Efficacy Evaluation of BUP/SAM

- 34 clinical studies
  - 19 conducted with BUP/SAM and 15 with SAM
  - Four placebo-controlled studies in MDD patients
    - Studies 202, 205, 206, & 207
    - Long-term study (Study 208)

- 2165 subjects received BUP/SAM
  - 1531 MDD patients treated with 2/2 dose
    - 947 patients treated ≥6 months
    - 743 patients treated ≥12 months
Study Population for the Development Program

• Diagnosed with MDD
  – Mean lifetime number of major depressive episodes (MDEs): 4-7
  – Cycled through multiple therapies
  – Median duration of current MDE: 9 – 10 months

• 1-2 inadequate responses to an antidepressant therapy (ADT) in current MDE

• Continued background ADT
  – SSRI, SNRI, or bupropion
Concluding Remarks

• Efficacy
  – Two studies (202 and 207) met the pre-specified primary endpoint
  – Supportive evidence of efficacy from a third study (205)
  – Clinically meaningful efficacy

• Safety
  – Generally well-tolerated and common adverse events were gastrointestinal or sedation related
  – Low abuse potential

• Favorable benefit-risk profile for adjunctive treatment of MDD
• Robust risk mitigation plan due to presence of BUP
The Unmet Need in MDD

George Papakostas, MD
Associate Professor, Harvard Medical School
Director, Treatment-Resistant Depression Studies
Depression and Clinical Research Program
Massachusetts General Hospital

DISCLOSURE:
Consultant to Alkermes. Compensated for time and travel.
MDD Is a Serious, Life-threatening Disease

- Lifetime prevalence of MDD in adults in the US is 16.6%\(^1\)
- Significantly impacts home & work life, relationships, social life\(^2\)
  - 59.3% of people with 12-month MDD reported either severe or very severe role impairment\(^3\)
  - ~35 days a year unable to work or participate in normal activities\(^3\)
- MDD is the #1 contributor to disability worldwide\(^4\)
- Burden of MDD includes increases in the relative risk of various diseases\(^5,6\)
  - Such as heart disease, diabetes mellitus, and cancer
- Patients with MDD are at increased risk for suicide\(^7\)

Switching Antidepressant Treatments Is Increasingly Futile in Addressing Symptoms

Proportion of Patients Remaining Symptomatic By Line of Therapy

Persistent Symptoms Can Increase Risk of Relapse, Among Other Serious Consequences

Patients with persistent symptoms are at greater risk for early relapse

- Are ~2X more likely to be hospitalized
- Have ~2X higher odds of suicide attempt
- Use up to 3X more psychotropic medications, including antidepressants

… compared to the overall MDD patient population

Reasons for Incomplete Symptom Control Unknown

- MDD is a heterogeneous disease likely encompassing multiple pathologies\(^1\)
- Currently approved pharmacotherapies for MDD all target monoamine neurochemical pathways\(^2\)

<table>
<thead>
<tr>
<th>Year Introduced</th>
<th>SSRI (eg, fluoxetine, escitalopram)</th>
<th>SNRI (eg, venlafaxine, duloxetine)</th>
<th>TCA / MAOI (eg, nortriptyline, selegiline)</th>
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Pharmacologic Augmentation Is Often the Next Approach

• Approved adjunctive options are atypical antipsychotics
  – Also work through the monoamine pathway
  – Demonstrated efficacy in MDD

• Atypical antipsychotics are associated with potentially significant side effects that seriously discourage their use
  – Risk of weight gain and new-onset diabetes
  – Often associated with significant sedation
  – Frequently accompanied by movement disorders
    • Akathisia
    • Parkinsonism
  – Tardive dyskinesia
  – Potentially life-threatening neuroleptic malignant syndrome

Summary of Unmet Need

- Treatment of MDD is challenging\(^1\)
- Despite available therapies, many patients experience persistent symptoms\(^1,2\)
- Patients with persistent symptoms have a higher burden of illness than other patients with MDD\(^3\)
- Current therapies for MDD all target monoamine signaling,\(^4\) underscoring the need for alternative mechanisms of action
- Desired characteristics of such a therapy include
  - Clinically meaningful symptom improvement
  - Safety profile with good tolerability and manageable adverse effects

Challenges in MDD Clinical Trials

George Papakostas, MD
Associate Professor, Harvard Medical School
Director, Treatment-Resistant Depression Studies
Depression and Clinical Research Program
Massachusetts General Hospital
High Historical Failure Rate of MDD Trials

FDA Analysis

Nearly half of MDD trials of approved drugs have been unsuccessful

1983 - 2008

Successful trials

Failed trials

Evolution of Trial Design to Improve Efficiency of Signal Detection in Adjunctive MDD Clinical Trials

Simple randomization (eg, quetiapine XR)

Placebo run-in (eg, aripiprazole, brexpiprazole)

Sequential Parallel Comparison Design (SPCD) (eg, BUP/SAM)

SPCD combines elements of both simple randomization and placebo run-in designs
Placebo Run-in Design
(eg, aripiprazole, brexpiprazole)

ADT: Antidepressant therapy.
Sequential Parallel Comparison Design (SPCD)

Stage 1

Randomize

Active + Background ADT

(All-comers population)

Randomize

Placebo + Background ADT

Stage 2

Response

Active + Background ADT

Placebo + Background ADT

No Response

Active + Background ADT

Randomize

Placebo + Background ADT

ADT: Antidepressant therapy.
Fava M et al; *Psychother Psychosom* 2003:72:115-27
SPCD Is Becoming Increasingly Utilized in Studies of CNS Disease, Particularly MDD

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Indication</th>
<th>Context</th>
<th>N</th>
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Summary of Clinical Trial Challenges

- Demonstrating antidepressant efficacy in a clinical trial setting is difficult
- Evolution in clinical trial design is needed to better enable signal detection in MDD
- SPCD, which combines simple randomization and placebo run-in designs, is increasingly becoming a valuable methodology in psychiatric disease trials
Clinical Efficacy

Jerald Schindler, DrPH
Vice President, Biostatistics
Alkermes, Inc.
BUP/SAM 2/2 is Effective for the Adjunctive Treatment of MDD

• Substantial evidence of efficacy demonstrated across the clinical development program

• Four randomized, double-blind, placebo-controlled studies of BUP/SAM + antidepressant therapy (ADT) vs. placebo + ADT

• Two of the four studies (202 and 207) met the primary endpoint

• One study provided supportive evidence of efficacy (205)

• One study did not support efficacy (206)
BUP/SAM Clinical Efficacy

• Study Designs and Analysis Methods
• Primary Efficacy Results
• Comparison Across Studies with Common Endpoints
• Conclusions
**BUP/SAM 2/2 Evaluated in Four Double-blind Placebo-controlled Studies**

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<tr>
<th>Phase</th>
<th>Study</th>
<th>Design</th>
<th>Doses</th>
<th>Primary Assessment</th>
<th>Number Randomized</th>
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<tr>
<td>2</td>
<td>202</td>
<td>SPCD</td>
<td>2/2 8/8</td>
<td>HAM-D17</td>
<td>142</td>
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<td>3</td>
<td>205</td>
<td>SPCD</td>
<td>0.5/0.5 2/2</td>
<td>MADRS-10</td>
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<td>Placebo Run-In</td>
<td>2/2</td>
<td>MADRS-10</td>
<td>297</td>
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<td>3</td>
<td>207</td>
<td>SPCD</td>
<td>1/1 2/2</td>
<td>MADRS-6* MADRS-10</td>
<td>407</td>
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</table>

* Basis for concluding efficacy

SPCD: Sequential Parallel Comparison Design  
HAM-D17: 17-item Hamilton Depression Rating Scale  
MADRS: Montgomery-Asberg Depression Rating Scale
202, 205, and 207 Study Design (SPCD)

STAGE 1 (2:2:9)
- BUP/SAM 2/2 + ADT
- BUP/SAM Other + ADT
- Placebo + ADT

STAGE 2 (1:1:1)
- BUP/SAM 2/2 + ADT
- BUP/SAM Other + ADT
- Placebo + ADT

Note: For Study 202, patients who received BUP/SAM in Stage 1 were switched to placebo in Stage 2.
* 202 End of Treatment
Methods for Statistical Analysis

- Longitudinal studies
  - Weekly efficacy assessments

- Mixed Models Repeated Measures (MMRM)
  - Uses all available longitudinal data without imputation
  - At each time point, model estimates:
    - Mean change from baseline by treatment group
    - Mean difference in change from baseline between BUP/SAM vs. Placebo
  - Statistical test to determine if difference between BUP/SAM vs. Placebo = 0

- SPCD studies
  - Difference estimates combined across stages
  - Weights pre-specified for Stage 1/Stage 2
  - Uses data from all subjects
**202, 205, and 207 Study Design (SPCD)**

**STAGE 1 (2:2:9)**
- BUP/SAM 2/2 + ADT
- BUP/SAM Other + ADT
- Placebo + ADT

**STAGE 2 (1:1:1)**
- BUP/SAM 2/2 + ADT
- BUP/SAM Other + ADT
- Placebo + ADT

**Week 0**

**Note:** For Study 202, patients who received BUP/SAM in Stage 1 were switched to placebo in Stage 2.

* 202 End of Treatment
202, 205, and 207 Study Design (SPCD)

**STAGE 1 (2:2:9)**
- BUP/SAM 2/2 + ADT
- BUP/SAM Other + ADT
- Placebo + ADT

**STAGE 2 (1:1:1)**
- BUP/SAM 2/2 + ADT
- BUP/SAM Other + ADT
- Placebo + ADT

**Note:** For Study 202, patients who received BUP/SAM in Stage 1 were switched to placebo in Stage 2.

* 202 End of Treatment
BUP/SAM Clinical Efficacy

- Study Designs and Analysis Methods
- Primary Efficacy Results
- Comparison Across Studies with Common Endpoints
- Conclusions
Primary Endpoint BUP/SAM vs. Placebo Difference
Consistent Improvement Across Studies

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<th>Pre-specified Primary Endpoint</th>
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<td>MADRS-10_{Week 5}</td>
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<td>MADRS-6_{AVG}</td>
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<td>MADRS-10_{EOT}</td>
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BUP/SAM 2/2 vs. Placebo
Least Squares Mean Difference (95% CI)
Study 202 (Phase 2)

- Randomized, double-blind, placebo-controlled SPCD study
- Two BUP/SAM doses (2/2 and 8/8)
- Two 4-week treatment periods
- 142 patients randomized
- Primary endpoint: HAM-D17 (Week 4)
- MADRS-10 included as secondary endpoint
Study 202: Primary Efficacy Results – HAM-D17\textsubscript{EOT}

HAM-D17
Change from Baseline by Treatment

Least Squares Mean Difference vs. Placebo (95% CI)

<table>
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<tr>
<th>Treatment</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
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<tbody>
<tr>
<td>Placebo, n</td>
<td>95</td>
<td>94</td>
<td>92</td>
<td>93</td>
<td>90</td>
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<tr>
<td>BUP/SAM, n</td>
<td>20</td>
<td>20</td>
<td>17</td>
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</table>

P-value

- BUP/SAM 2/2: 0.014
- BUP/SAM 8/8: 0.699
**Study 202: Multiplicity Adjustment**

- No pre-specified multiplicity adjustment
- Comparison of each dose of BUP/SAM vs. placebo
  - 2/2: $P = 0.014$
  - 8/8: $P = 0.699$
- Post-hoc Bonferroni multiplicity adjustment splits the alpha in half
  - 2/2 dose still significantly different from placebo
- Bonferroni adjustment very conservative and requires no prior assumption
- No prior suggestion that either BUP/SAM dose was more likely to be successful, an ordered hierarchical adjustment not appropriate
  - Complex pharmacology of BUP/SAM (agonist/antagonist)
  - Uncertain dose response
Study 202: Single Responder Does Not Drive Efficacy Results

- FDA briefing book presents analysis excluding a single responder
  - No legitimate reason to remove this patient
  - Contrary to intent-to-treat principle

- Analyses show consistent results without this patient’s data

**HAM-D17 Change from Baseline to Week 4**

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<th>Analysis Method</th>
<th>Least Squares Mean Difference (95% CI)</th>
<th>P-value</th>
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<td>Primary</td>
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<td>No replacement (FDA)</td>
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<td>Multiple Imputation (Within Treatment)</td>
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BUP/SAM 2/2 vs. Placebo
Least Squares Mean Difference (95% CI)

Favors BUP/SAM +ADT
Favors Placebo +ADT
Study 205 (Phase 3)

- Randomized, double-blind, placebo-controlled SPCD study

- Two BUP/SAM doses (2/2 and 0.5/0.5)

- Two treatment periods
  - Stage 1: 5 weeks
  - Stage 2: 6 weeks

- 385 patients randomized

- Primary endpoint: MADRS-10 (Week 5)
Study 205: Primary Efficacy Results – MADRS-10 Week 5

MADRS-10 Change from Baseline by Treatment

Least Squares Mean Difference vs. Placebo (95% CI)

BUP/SAM 2/2 vs. Placebo +ADT

BUP/SAM 0.5/0.5 vs. Placebo +ADT

Placebo, n   256   256   255   253   250   247
BUP/SAM, n   59    59    57    54    53    52

Week 5

Stage 1

Stage 2

Change from Baseline (LS Mean)

Week

Placebo +ADT
BUP/SAM 2/2 +ADT

P-value
0.109
0.975
Insights from Study 205

- Supportive evidence of BUP/SAM 2/2 efficacy

- Average (multiple time points) vs. end of treatment (EOT, single time point)
  - Reduces influence of week-to-week variability
  - Reflects patient’s experience over time

- MADRS-6 vs. MADRS-10
  - MADRS-6 is a sensitive measure of depression symptom severity
Study 207 (Phase 3)

- Randomized, double-blind, placebo-controlled SPCD study
- Two BUP/SAM doses (2/2 and 1/1)
- Two treatment periods
  - Stage 1: 5 weeks
  - Stage 2: 6 weeks
- 407 patients randomized

Primary Endpoints
- MADRS-6_{AVG} (Week 3 to EOT) – basis for concluding efficacy
- MADRS-10_{AVG} (Week 3 to EOT)
- MADRS-10_{EOT}
- Hypothesis testing BUP/SAM 2/2 then 1/1
Study 207: Primary Efficacy Results

MADRS-6
Change from Baseline by Treatment

Least Squares Mean Difference vs. Placebo (95% CI)
Study 207: Durability of Effect

MADRS-10 Change From Baseline by Visit

<table>
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<tr>
<th>Week</th>
<th>Placebo, n</th>
<th>BUP/SAM 2/2, n</th>
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<tr>
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<td>270</td>
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<td>3</td>
<td>265</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>263</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>257</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>257</td>
<td>49</td>
</tr>
</tbody>
</table>

Stage 1

Stage 2

(Mean)
Study 206 (Phase 3)

- Randomized, double-blind, placebo-controlled, placebo run-in study

- One BUP/SAM dose (2/2)

- Two treatment periods
  - Stage 1: 4-week placebo run-in
  - Stage 2: 6-week treatment period

- 297 patients randomized

- Primary endpoint: MADRS-10 (EOT)
Study 206: Primary Efficacy Results – MADRS-10$_{EOT}$

MADRS-10
Change from Baseline by Treatment

Least Square Mean Difference
BUP/SAM 2/2 vs. Placebo

![Graph showing change from baseline (LS Mean) by week for Placebo and BUP/SAM 2/2 treatments. The graph indicates a comparison at EOT with Placebo + ADT, BUP/SAM 2/2 + ADT, and details of sample sizes at each week point.]

Placebo, n 146 146 144 140 140 138
BUP/SAM, n 142 142 141 138 136 134 131

P-value 0.782
**BUP/SAM Clinical Efficacy**

- Study Designs and Analysis Methods
- Primary Efficacy Results
- Comparison Across Studies with Common Endpoints
- Conclusions
Common Endpoints Used for Comparison Across Studies

• All four studies included weekly MADRS-10 assessments

• MADRS-10$_{AVG}$
  – Based on multiple time points
  – Average of differences from MMRM model
  – Reduces influence of week-to-week variability
  – Reflects patient’s experience over time

• MADRS-10$_{EOT}$
  – Based on single time point
  – Differences from MMRM model
  – Conventional endpoint
Consistent Improvement for BUP/SAM Across All SPCD Studies and Stages - MADRS-10

Note: Only Stage 1 placebo non-responders are included in Stage 2
BUP/SAM vs. Placebo Difference Consistent Improvement Across Studies Common Endpoint and Analysis - MADRS-10_{AVG}

BUP/SAM 2/2 vs. Placebo
Least Squares Mean Difference (95% CI)
BUP/SAM vs. Placebo Difference Consistent Improvement Across Studies Common Endpoint and Analysis - MADRS-10$_{EOT}$
BUP/SAM Clinical Efficacy

• Study Designs and Analysis Methods
• Primary Efficacy Results
• Comparison Across Studies with Common Endpoints
• Conclusions
Conclusion: Consistent Efficacy for BUP/SAM 2/2

Pre-specified Primary endpoint

- 2 of the 4 trials met their primary endpoint

MADRS-10_{AVG}

- 3 of the 4 trials demonstrate evidence of efficacy

MADRS-10_{EOT}

- 2 of the 4 trials demonstrate evidence of efficacy

Overall, these show that BUP/SAM 2/2 is effective for the treatment of MDD
Clinical Safety

Gary Bloomgren, MD
Vice President,
Drug Safety and Pharmacovigilance
Alkermes, Inc.
BUP/SAM Safety Overview

- Exposure and Pooling Strategy
- Adverse Event (AE) Profile
- Laboratory/Vital Signs/ECGs
- Topics of Special Interest
- Abuse Potential Assessment
- Summary
<table>
<thead>
<tr>
<th>Population</th>
<th>Any Dose</th>
<th>≥1 Dose</th>
<th>≥6 Months</th>
<th>≥12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Populations</td>
<td></td>
<td>2165</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/2 Dose</td>
<td></td>
<td>1860</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/2 Dose</td>
<td></td>
<td>1531</td>
<td>947</td>
<td>743</td>
</tr>
</tbody>
</table>

Total MDD patient exposure >1100 years
Safety Pooling Strategy

• Four placebo-controlled studies

• Each study had two randomizations
  – 1st at treatment start (Stage 1)
  – 2nd mid study (Stage 2, Stage 1 Placebo non-responders)

• Patients pooled by randomization time point
BUP/SAM Safety Overview

• Exposure and Pooling Strategy
• Adverse Event (AE) Profile
• Laboratory/Vital Signs/ECG
• Topics of Special Interest
• Abuse Potential Assessment
• Summary
Treatment Emergent Adverse Events (TEAE) Were Generally Tolerability-Related

<table>
<thead>
<tr>
<th>Placebo-Controlled Studies Incidence ≥5% and &gt;Placebo</th>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BUP/SAM 2/2 (N=162) n (%)</td>
<td>Placebo (N=658) n (%)</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>111 (68.5)</td>
<td>358 (54.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>43 (26.5)</td>
<td>46 (7.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (13.0)</td>
<td>27 (4.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>20 (12.3)</td>
<td>18 (2.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>17 (10.5)</td>
<td>59 (9.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (9.9)</td>
<td>11 (1.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (7.4)</td>
<td>10 (1.5)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>11 (6.8)</td>
<td>22 (3.3)</td>
</tr>
<tr>
<td>Sedation</td>
<td>11 (6.8)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10 (6.2)</td>
<td>29 (4.4)</td>
</tr>
</tbody>
</table>

- Majority were mild or moderate in severity and tended to occur with treatment initiation
- No meaningful differences by gender, age, race, concomitant antidepressant or benzodiazepine use
- No new findings for long-term study
### Few Adverse Events (AEs) Leading to Discontinuation

<table>
<thead>
<tr>
<th>Placebo-Controlled Studies Incidence ≥2%</th>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE Leading to Study Discontinuation</td>
<td>BUP/SAM 2/2 (N=162) n (%)</td>
<td>Placebo (N=658) n (%)</td>
</tr>
<tr>
<td></td>
<td>22 (13.6)</td>
<td>13 (2.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (4.9)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (3.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Similar findings for long-term study
Few Serious Adverse Events (SAEs)

- Placebo-controlled studies – 1.9% with BUP/SAM 2/2 vs. 0.5% in placebo
  - No deaths

- Long-term study – 3.2% of patients
  - Most common events: depression and suicidal ideation (each 0.2%)
  - Two deaths (not related)
    - Patient with COPD who died of respiratory arrest 47 days after last dose
    - Patient with hypertension and CHF who died of a cerebral hemorrhage (Day 87 of study). Family history of cerebrovascular hemorrhage
BUP/SAM Safety Overview

• Exposure and Pooling Strategy
• Adverse Event (AE) Profile
• Laboratory/Vital Signs/ECG
• Topics of Special Interest
• Abuse Potential Assessment
• Summary
No Clinically Relevant Laboratory, Vital Sign, Weight, or ECG Changes

Placebo-controlled and long-term studies:

- No meaningful post-baseline changes or outliers
- No evidence of risk of QT prolongation associated with BUP/SAM
**BUP/SAM Safety Overview**

- Exposure and Pooling Strategy
- Adverse Event (AE) Profile
- Laboratory/Vital Signs/ECG
- Topics of Special Interest
- Abuse Potential Assessment
- Summary
**Topics of Special Interest**

- CNS Depression
  - Mild to moderate sedation/somnolence with treatment initiation, resolved with continued use

- Precipitated opioid withdrawal
  - One case occurred with first dose of BUP/SAM in patient with undisclosed pre-existing opioid dependence, event was serious and related
Additional Topics of Special Interest

No Evidence of:

- Respiratory Depression
- Hypotension/Orthostatic Hypotension
- Hepatic Injury
- Hypomania/Mania
- Sexual Dysfunction
- Suicidal Ideation or Behavior

Associated with BUP

Associated with Antidepressants
## Less Suicidal Ideation or Behavior with BUP/SAM Treatment vs. Placebo

<table>
<thead>
<tr>
<th>Post-Baseline C-SSRS Categories</th>
<th>Placebo-Controlled Studies</th>
<th>Long-term Study (N=1454)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage 1</td>
<td>Stage 2</td>
</tr>
<tr>
<td></td>
<td>BUP/SAM 2/2 (N=162)</td>
<td>Placebo (N=658)</td>
</tr>
<tr>
<td>Suicidal Behavior</td>
<td>0</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>16 (9.9)</td>
<td>107 (16.3)</td>
</tr>
<tr>
<td>Self-injurious Behavior without Suicidal Intent</td>
<td>0</td>
<td>2 (0.3)</td>
</tr>
</tbody>
</table>

Columbia-Suicide Severity Rating Scale (C-SSRS)
**BUP/SAM Safety Overview**

- Exposure and Pooling Strategy
- Adverse Event (AE) Profile
- Laboratory/Vital Signs/ECG
- Topics of Special Interest
- Abuse Potential Assessment
- Summary
Evaluation of Abuse Potential

- Dedicated Human Abuse Potential Study
- In MDD Studies
  - Evaluation of Adverse Events of Special Interest (AESI) related to abuse potential, dependence and withdrawal
  - Clinical Opioid Withdrawal Scale following BUP/SAM Discontinuation
**Human Abuse Potential of BUP/SAM is Low**

At the Moment Drug Liking

- **BUP/SAM**
  - 2/2
  - 8/8
  - 16/16

- **BUP**
  - 8 mg
  - 16 mg

*Margin of clinical significance for BUP/SAM vs. Placebo

- 6-way crossover study
- Non-dependent recreational opioid users
- 38 subjects

*Assessment of Abuse Potential of Drugs Guidance for Industry 2017 (FDA)
Endpoints Predictive of Real-world Abuse Liability Show BUP/SAM Similar to Placebo

- Both measures assessed global drug effects (i.e., the entire drug experience)
- Further supports assessment of low abuse potential with BUP/SAM

Consistent Evidence of Low Abuse Potential in MDD Studies

• Abuse potential terms query
  – Majority of events non-specific to abuse potential (i.e., dizziness, somnolence, and sedation)
  – Low incidence of euphoria-related events:
    • BUP/SAM 2/2 (1.6%) vs. Placebo (0.2%) – Stage 1 and 2 combined
    • Incidence in long-term study similar (1.2%)
    • Majority associated with first dose, none recurred

• No abuse behavior
• No evidence of dependence
Little Evidence of Withdrawal: Post-discontinuation Change in COWS Scores

- Mean post-discontinuation scores were ≤1 in all treatment groups in placebo-controlled studies and the long-term study

<table>
<thead>
<tr>
<th>COWS Score Category*</th>
<th>Placebo-controlled Studies</th>
<th>Long-term Study BUP/SAM 2/2 (N=831)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BUP/SAM 2/2 (N=113)</td>
<td>Placebo (N=148)</td>
</tr>
<tr>
<td>No Withdrawal (0-4)</td>
<td>96.5%</td>
<td>97.3%</td>
</tr>
<tr>
<td>Mild Withdrawal (5-12)</td>
<td>2.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Moderate Withdrawal (13-24)</td>
<td>0.9%</td>
<td>0</td>
</tr>
<tr>
<td>Moderate-severe or Severe Withdrawal (25-48)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: COWS=Clinical Opiate Withdrawal Scale
* Patients with score of "No Withdrawal" at end of treatment period
BUP/SAM Safety Overview

• Exposure and Pooling Strategy
• Adverse Event (AE) Profile
• Laboratory/Vital Signs/ECG
• Topics of Special Interest
• Abuse Potential Assessment
• Summary
BUP/SAM General Safety Summary

• Common AEs
  – Gastrointestinal or sedation-related
  – Mild/moderate in severity
  – Typically occurred with treatment initiation

• No clinically meaningful changes in laboratory, vital signs, weight or ECGs

• No evidence of increased treatment-emergent suicidal ideation or behavior
**BUP/SAM Abuse Potential is Low**

- Human Abuse Potential Study
  - Abuse potential with BUP/SAM 2/2 is similar to placebo
  - 4-8x the therapeutic dose of BUP/SAM
    - Slightly greater than placebo
    - Significantly less than equivalent dose of BUP alone

- MDD data consistent
  - Low incidence of euphoria, typically with first dose/none recurrent
  - No evidence of dependence during treatment
  - Little evidence of withdrawal, discontinuation well-tolerated
Risk Mitigation Strategy

Gary Bloomgren, MD
Vice President,
Drug Safety and Pharmacovigilance
Alkermes, Inc.
Alkermes’ Commitment to Responsible Use

- **Product Characteristics**
  - Selection of lowest effective dose of BUP (2 mg) and addition of SAM to mitigate risk of abuse and dependence
  - Co-formulated as a homogenous mixture of BUP and SAM
  - Packaged in cards with individual tablets blistered
  - Packaged to limit unintentional pediatric exposure

- Continuous monitoring at multiple points in the distribution channel (wholesaler, third party logistics provider and manufacturer)

- Educate prescribers, pharmacists and patients

- Implement appropriate post-marketing safety initiatives and risk mitigation strategies
## Alkermes’ Proposed Education Plan

- **Objective:** Alert health care professionals and patients to important safety information and appropriate use
  - Risks and precautions associated with concomitant use of opioids
  - Instructions for safe use, storage and disposal
  - Risks of abuse, misuse and diversion
  - Risks of addiction, overdose and death

<table>
<thead>
<tr>
<th>Prescribers, Nurses &amp; Pharmacists</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Product Label</td>
<td>• Medication Guide</td>
</tr>
<tr>
<td>• Product REMS</td>
<td>• Medication ID Wallet Card</td>
</tr>
<tr>
<td>• Selection of appropriate patients</td>
<td>• Product Website</td>
</tr>
<tr>
<td>• Patient educational materials</td>
<td>• Patient Provider Discussion Guide</td>
</tr>
<tr>
<td>– Patient Counseling Tool</td>
<td>• Ongoing product information for patients who opt in</td>
</tr>
<tr>
<td>– Placebo Training Tool</td>
<td></td>
</tr>
<tr>
<td>• Trained medical staff available to respond to queries via call center or in person</td>
<td></td>
</tr>
<tr>
<td>• Healthcare professional product website</td>
<td></td>
</tr>
<tr>
<td>• Multi-media information/awareness campaigns</td>
<td></td>
</tr>
</tbody>
</table>
# Proposed BUP/SAM Risk Evaluation and Mitigation Strategy (REMS)

<table>
<thead>
<tr>
<th>Objectives: Mitigate risk of misuse and accidental exposure</th>
<th>BUP/SAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication Guide</td>
<td>✔</td>
</tr>
<tr>
<td>REMS Website &amp; Call Center</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Communication Materials</strong></td>
<td>✔ ✔ ✔</td>
</tr>
<tr>
<td>Health Care Provider (HCP) Letter</td>
<td>✔</td>
</tr>
<tr>
<td>HCP Brochure</td>
<td>✔</td>
</tr>
<tr>
<td>Appropriate Use Checklist</td>
<td>✔</td>
</tr>
<tr>
<td>Monitoring for misuse, abuse, dependence, or diversion (RADARS*)</td>
<td>✔</td>
</tr>
<tr>
<td>Identify new HCPs annually</td>
<td>For 3 years</td>
</tr>
<tr>
<td>Submission of REMS assessments to FDA</td>
<td>At 18 months, 3 years, and 7 years</td>
</tr>
</tbody>
</table>

*RADARS = Researched Abuse, Diversion and Addiction-Related Surveillance – Managed by the Rocky Mountain Poison and Drug Center
Clinical Perspective and Benefit-Risk Profile

Sanjay Mathew, MD
Professor of Psychiatry and Behavioral Sciences
Marjorie Bintliff Johnson and Raleigh White Johnson, Jr Chair for Research in Psychiatry
Menninger Dept of Psychiatry & Behavioral Sciences
Director, Mood Anxiety Disorders Program
Baylor College of Medicine

DISCLOSURE:
Consultant to Alkermes. Compensated for time and travel.
BUP/SAM Would Be for Patients With MDD Who Are Candidates for Adjunctive Treatment

**General Patient Characteristics**

- Long-standing depression
- Little or no success from several monotherapy antidepressants despite adequate dose & duration
- Current antidepressant is addressing some symptomatology
- Persistent symptoms significantly impact work or personal life
- Patient is willing to add another treatment to their regimen
BUP/SAM Would Be for a Patient Like J.D.

- Mid-40s experiencing her 2\textsuperscript{nd} major depressive episode
- Antidepressant treatment history in current episode
  - Escitalopram 10-20mg for about 3 months
    - QIDS-SR improvement from 21 to 16
  - Venlafaxine XR up to 225 to 300mg over about 3 months
    - Minimal to no improvement in QIDS-SR
    - Experienced concerning BP elevations at highest dose
Augmentation with BUP/SAM Gives J.D. an Opportunity to Address Her Persistent Symptoms

• Depressive symptoms continue to significantly impact her home and personal life
  – Anhedonia, social withdrawal
  – Affects entire family
    • Unable to meet needs of 2 school-age children
BUP/SAM Offers Efficacy Comparable to a Recently Approved Adjunctive Treatment for MDD

And does so through a different mechanism of action

BUP/SAM Would Be an Attractive Therapeutic Option for J.D.

- Considered augmentation with aripiprazole or quetiapine
- Her main concern is weight gain
  - Current BMI of 30
  - Borderline diabetic
- Also worried about somnolence
  - Caring for 2 young children
BUP/SAM Safety Summary

• Common adverse events are GI or sedation
  – Mainly associated with treatment initiation
  – Generally mild or moderate in severity

• Low potential for abuse
  – Human abuse potential study
    • BUP/SAM 2/2 similar to placebo
  – Clinical trial patients with MDD
    • Low incidence of euphoria
    • No dependence
    • Little evidence of withdrawal upon discontinuation
BUP/SAM Has a Positive Benefit-Risk Profile

<table>
<thead>
<tr>
<th>Risk Considerations</th>
<th>Benefit Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Abuse liability related to BUP addressed</td>
<td>• Consistent antidepressant effects</td>
</tr>
<tr>
<td>• Adverse effects (eg, nausea, vomiting, constipation)</td>
<td>• Clinically meaningful efficacy in difficult-to-treat patients</td>
</tr>
<tr>
<td>are manageable</td>
<td>• Efficacy consistent with available adjunctive therapies</td>
</tr>
<tr>
<td>• Lack of weight gain, metabolic impact, and movement</td>
<td>– Accomplished via a different mechanism of action</td>
</tr>
<tr>
<td>side effects</td>
<td></td>
</tr>
<tr>
<td>• No apparent precipitation of suicidality</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• BUP/SAM has a positive benefit-risk profile
• Efficacy comparable to current adjunctive medications, but through a different mechanism of action
  – Offers an alternative approach in patients who have not found adequate relief through monoaminergic therapies
• Favorable safety profile
• BUP/SAM would be an important new treatment option for patients who urgently need more options
  – Patients like J.D.
Conclusions

Lisa von Moltke, MD
Senior Vice President, Clinical Development
Alkermes, Inc.
Conclusions

• Significant unmet need and treatment challenges for patients with MDD
  – Need for new differentiated mechanisms

• BUP/SAM works through opioid system modulation
  – Maintains the efficacy of BUP while mitigating the risk for abuse and dependence

• Significant development challenges of studying MDD
  – Utilization of SPCD methodology

• Positive Benefit-Risk for BUP/SAM
  – Substantial evidence of efficacy
  – Well characterized and manageable safety profile

• Committed to responsible risk mitigation and commercialization
Backup Slides Shown
BUP/SAM Offers Efficacy Comparable to a Recently Approved Adjunctive Treatment for MDD

And does so through a different mechanism of action

Sensitivity Analysis with Multiple Imputation
202 HAM-D17_{EOT} and MADRS-10_{EOT}

HAM-D17_{EOT}

MADRS-10_{EOT}

BUP/SAM 2/2 vs. Placebo
Least Squares Mean Difference (95% CI)
Single Patient with High Response (202) Efficacy Assessments

Stage 1 (BUP/SAM 2/2)
- HAM-D17
- MADRS-10

Week
- Started taper

Stage 2 (Placebo)

Week
- Started taper

Start of taper

CGI-S Score
Consistent Efficacy Results Regardless of Number of Weeks Included in Average – 207 MADRS-10

Note: EOT was Week 5 in Stage 1 and Week 6 in Stage 2

BUP/SAM 2/2 vs. Placebo
Least Squares Mean Difference (95% CI)
Study 207: Primary Efficacy Results

MADRS-6
Change from Baseline by Treatment

Least Squares Mean Difference vs. Placebo (95% CI)
Switching Antidepressant Treatments Is Increasingly Futile in Addressing Symptoms

Proportion of Patients Remaining Symptomatic By Line of Therapy

BUP/SAM vs. Placebo Difference Consistent Improvement Across Studies Common Endpoint and Analysis - MADRS-10_{EOT}

BUP/SAM 2/2 vs. Placebo
Least Squares Mean Difference (95% CI)
Study 205: Primary Efficacy Results – MADRS-10 \( \text{Week 5} \)

MADRS-10 Change from Baseline by Treatment

Least Squares Mean Difference vs. Placebo (95% CI)

BUP/SAM 2/2

BUP/SAM 0.5/0.5

Placebo, n 256 256 255 253 250 247
BUP/SAM, n 59 59 57 54 53 52

Week
-5 -4 -3 -2 -1 0 1 2 3 4 5

Change from Baseline (LS Mean)

Stage 1

Stage 2

Favors BUP/SAM +ADT

Favors Placebo +ADT

\( P \)-value

0.109

0.975
Consistent Efficacy Equal Number of Weeks Included in Average – 207 MADRS-10

Week 3 through EOT$^a$

Week 3 through Week 5

BUP/SAM 2/2 vs. Placebo
Least Squares Mean Difference (95% CI)

$^a$ Includes Weeks 3-5 in Stage 1 and Weeks 3-6 in Stage 2
## Summary of Documents Confirming Eligibility of Subject in 202 (Provided to FDA)

<table>
<thead>
<tr>
<th>Record Type</th>
<th>Content Includes (but not limited to)</th>
<th>Signed and Dated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Note</td>
<td>Depression history, Zoloft switch to Prozac in August 2012, remaining signs and symptoms of depression</td>
<td>Signed and dated by MD 10/24/12</td>
</tr>
<tr>
<td>Psychiatric Evaluation of Depression</td>
<td>Dates of depression diagnoses and episodes, Prozac 20 mg 8/13/12 to current Zoloft 100 mg June 2011-June 2012</td>
<td>Signed and dated by coordinator 10/24/12</td>
</tr>
<tr>
<td>MGH ATRQ Site version</td>
<td>Supports treating of current episode Checks present for at least 10 wks for Prozac and Zoloft, No ECT therapy, % improved &lt;25%</td>
<td>Signed by MD Document dated 10/24/12</td>
</tr>
<tr>
<td>SAFER Interview form with 3rd party ATRQ performed by CTNI</td>
<td>Fluoxetine x 1 week and Zoloft at least 8 wks (see PDF page 14) Addendum note (see PDF page 13) indicating Fluoxetine x 10 wks, made by Chang CTNI rater following discussion and confirmation with the site</td>
<td>Signed and dated by CTNI rater 10/29/12 Addendum dated 10/31/12</td>
</tr>
<tr>
<td>Concomitant Medication Log</td>
<td>Fluoxetine listed (among others), 20 mg, start 8/13/12 with “ongoing” checked</td>
<td>No overall signature and date for the log. However some corrections were noted with AA initials and dates for 2012 and 2013.</td>
</tr>
</tbody>
</table>
Study 202 HAMD-17 Change from Baseline By Patient

Stage 1

Stage 2

BUP/SAM

Placebo

MADRS-10 Score Change from Baseline

MADRS-10 Score Change from Baseline

BUP/SAM

Placebo
BUP/SAM Offers Efficacy Comparable to a Recently Approved Adjunctive Treatment for MDD

And does so through a different mechanism of action

Study 202 HAMD-17 Percent Change from Baseline By Patient

Stage 1

Stage 2

BUP/SAM

Placebo

MADRS-10 Score Percent Change from Baseline

BUP/SAM

Placebo
### Discontinuation Rates with BUP/SAM Similar to Approved Adjunctive ADTs

<table>
<thead>
<tr>
<th></th>
<th>Discontinuation Rate</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short-Term Studies</td>
<td>Long-Term Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(6-11 weeks)</td>
<td>(52 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUP/SAM</td>
<td>8-14%</td>
<td>51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>6-12%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51%&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


BUP/SAM Treatment Effect (MADRS-10_{EOT}) is Comparable to Approved Adjunctive Treatments for MDD

**BUP/SAM 2/2**

**Brexpiprazole**

**Aripiprazole**

**Quetiapine**

* Based on post-hoc analyses

Rexulti USPI, 2018
Abilify USPI, 2016
Seroquel XR USPI, 2017

Least Squares Mean Difference (95% CI)