# BRIEFING DOCUMENT

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE (PDAC)
AND
DRUG SAFETY AND RISK MANAGEMENT (DSaRM) ADVISORY COMMITTEE

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SPONSOR BRIEFING DOCUMENT

Buprenorphine/ Samidorphan

Adjunctive Treatment for Major Depressive Disorder

Alkermes, Inc.
852 Winter Street
Waltham, MA 02451

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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| Abbreviation or Term | Explanation or Definition |
|---|---|
| ADT | Antidepressant therapy |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| CI | Confidence interval |
| CNS | Central nervous system |
| COWS | Clinical Opiate Withdrawal Scale |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| ECG | Electrocardiogram |
| EOT | End of treatment |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| HAM-D17 | Hamilton Rating Scale for Depression-17 Item |
| HAP | Human abuse potential |
| IND | Investigational New Drug |
| LSM | Least squares mean |
| LSMD | Least squares mean difference |
| MADRS | Montgomery-Åsberg Depression Rating Scale |
| MDD | Major depressive disorder |
| MDE | Major depressive episode |
| MMRM | Mixed models repeated measures |
| NDA | New Drug Application |
| PD | Pharmacodynamics |
| PTs | Preferred terms |
| RADARS | Researched Abuse, Diversion and Addiction-Related Surveillance |
| REMS | Risk Evaluation and Mitigation Strategy |
| SAE | Serious adverse event |
| SL | Sublingual |
| SNRI | Serotonin-norepinephrine reuptake inhibitor |
| SOC | System organ class |

| Abbreviation or Term | Explanation or Definition |
|---|---|
| SPCD | Sequential parallel comparison design |
| SSRI | Selective serotonin reuptake inhibitor |
| TEAE | Treatment-emergent adverse event |
| VAS | Visual analogue scale |

# 1. EXECUTIVE SUMMARY

Major depressive disorder (MDD) is a major source of morbidity and disability. In current clinical practice, two out of every three patients will have an inadequate response to standard antidepressants and will continue to experience significant symptoms. Patients with inadequate response to antidepressants have greater disease severity and morbidity, are at higher risk for suicide, are more likely to be hospitalized, have greater impairment in social function, and have an increased risk of relapse compared to treatment-responsive patients.

Standard clinical practice for patients with inadequate response to standard antidepressants is augmentation. The only US Food and Drug Administration (FDA)-approved adjunctive therapies for MDD are atypical antipsychotics which are associated with serious and sometimes treatment-limiting toxicities, including significant metabolic derangements and movement disorders. All approved antidepressants, including those approved for adjunctive therapy, work via monoaminergic mechanisms. New agents with novel and complementary mechanisms of action are urgently needed.

The fixed-dose combination of buprenorphine (BUP) and samidorphan (SAM) is a proposed new adjunctive treatment for patients suffering from MDD who have had an inadequate response to commonly prescribed medications for depression. BUP is a partial agonist at the μ-opioid receptor and an antagonist at the κ-opioid receptor. SAM, a new molecular entity, is a potent μ-opioid receptor antagonist intended to mitigate the abuse liability of BUP. The proposed therapeutic dose of BUP/SAM is one sublingual (SL) tablet daily containing BUP 2 mg and SAM 2 mg (referred to hereinafter as BUP/SAM 2/2).

The clinical development program, designed to evaluate the safety and efficacy of BUP/SAM, was comprised of 34 clinical studies, including 19 conducted with BUP/SAM and 15 with SAM alone. In the 19 studies conducted with BUP/SAM, 2165 subjects were exposed to BUP/SAM: 1860 subjects received the therapeutic dose of 2/2, including 1531 patients with MDD. Of these, 947 patients received BUP/SAM for at least 6 months and 743 patients for at least 1 year. The total MDD patient exposure was >1100 years.

The randomized, double-blind, placebo-controlled efficacy studies described herein focused on the specific subset of patients who had failed 1 or 2 lines of prior therapy within the same MDD episode. This treatment paradigm was designed to replicate the anticipated real-world use of BUP/SAM by testing it in the adjunctive setting, in combination with front-line antidepressant medications. This approach allowed patients to maintain any clinical benefit being realized by their front-line medicines while evaluating the incremental effect of a new agent with a distinct mechanism of action.

Efficacy was evaluated in four randomized, double-blind, placebo-controlled studies; one Phase 2 (202) and three Phase 3 (205, 206, and 207) studies. All four studies employed designs intended to address placebo response that is typical of antidepressant studies and may contribute to the high failure rate (~50%) seen in MDD studies with approved ADTs (Ionescu and Papakostas 2017). Three of the four studies (202, 205, and 207) employed sequential parallel comparison designs (SPCD). The fourth study (206) was a placebo run-in design. In all studies, patients with MDD with an inadequate response to antidepressant therapy (ADT) were

evaluated. Patients remained on background ADT and those randomized to BUP/SAM received adjunctive treatment at doses ranging from 0.5/0.5 to 8/8. Data presented in this document are for the BUP/SAM 2/2 dose, the proposed therapeutic dose.

Several assessment tools and scores were used to evaluate BUP/SAM efficacy across the four studies. The Hamilton Rating Scale for Depression (HAM-D17) was used as the primary assessment in Study 202. The Montgomery-Åsberg Depression Rating Scale (MADRS) was used as the primary assessment in Studies 205, 206, and 207, and as a secondary assessment in Study 202. The MADRS assessment includes 10-items. Two scores were derived using this scale: MADRS-10 and MADRS-6. The MADRS-10 score includes all 10-items while the MADRS-6 subscale includes 6-items which have been described as the core symptoms of depression (Bech et al, 2002; Bech et al, 2004). The primary endpoints specified for each study were derived using these scales at a single time point (eg, MADRS-10 End of Treatment [EOT]) or an average of several timepoints to address week-to-week variability (eg, MADRS-$10_{AVG}$ or MADRS-$6_{AVG}$).

Three of four studies (202, 205, and 207) provided evidence of efficacy. Two studies (202 and 207) were statistically significant for the pre-specified primary endpoints (HAMD-$17_{EOT}$ and MADRS-$6_{AVG}$, respectively). Studies 205 and 206 did not meet their primary endpoints (MADRS-$10_{Week\ 5}$ and MADRS-$10_{EOT}$, respectively). However, Study 205 did provide support of efficacy, while Study 206 did not demonstrate efficacy of BUP/SAM due to a high placebo response.

Efficacy was assessed using the same two endpoints, MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$, to compare results across studies. MADRS-$10_{EOT}$ for two studies (202 and 205) and MADRS-$10_{AVG}$ for three studies (202, 205, and 207) had significant *P*-values. A meta-analysis combining data from all four studies (202, 205, 206, and 207) demonstrated statistically significant improvement from placebo for both common endpoints (MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$). Efficacy was demonstrated to have a durable effect over a 1-year treatment period in a long-term, open-label, safety study (208).

BUP/SAM was generally well-tolerated. The most common adverse events (AEs) were gastrointestinal or sedation-related, were typically mild/moderate in severity, tended to occur with treatment initiation, and did not lead to treatment discontinuation. BUP/SAM treatment was not associated with metabolic disturbances or motor disorders, which are key safety concerns of atypical antipsychotics currently used as adjunctive treatments for MDD. There was no evidence of AEs commonly associated with opioids such as respiratory depression, hypotension/orthostatic hypotension, or hepatic injury, observed with BUP/SAM relative to placebo. In addition there was no evidence of hypomania/mania, sexual dysfunction, or suicidal ideation or behavior which have been associated with other antidepressants. Given the abuse liability of BUP, abuse potential was examined for BUP/SAM through a dedicated human abuse potential (HAP) study, comprehensive assessments across the clinical development program, including examination of AEs of special interest (AESIs), and the use of an objective tool to evaluate withdrawal, the Clinical Opiate Withdrawal Scale (COWS). COWS provided consistent evidence of a low abuse potential and little evidence of withdrawal with abrupt discontinuation. The above BUP/SAM clinical data support the assessment that combining SAM with BUP mitigates the abuse potential associated with BUP alone.

BUP/SAM 2/2 provides clinically meaningful efficacy in the adjunctive treatment of patients with MDD with a history of inadequate response to standard ADTs and has a favorable safety profile, including a low potential for abuse. Efficacy has been demonstrated across multiple studies and across multiple randomizations. BUP/SAM 2/2 showed durable effect over a 1-year treatment period in the long-term study in those patients continuing treatment. This totality of data, considered along with the results of individual studies, provides substantial evidence of efficacy for BUP/SAM 2/2 in the adjunctive treatment of MDD. BUP/SAM has the potential to serve as an important adjunctive therapeutic option for patients with MDD who are not achieving adequate response to existing approved ADTs.

# 2. INTRODUCTION AND BACKGROUND

## 2.1. Medical Need for New Adjunctive Anti-Depressant Treatments

In 2017, the World Health Organization classified depression as the single largest contributor to global disability worldwide (7.5% of all years lived with disability), with over 300 million affected (World Health Organization 2017). In the US, lifetime prevalence for MDD is estimated to be 20.6% of the adult population (Hasin et al, 2018).

While US FDA-approved medicines for MDD have had important therapeutic utility, in clinical practice, the majority of patients have an inadequate response to treatment (Mcintyre et al, 2014). Two out of every three patients will have an inadequate response to standard ADTs and will continue to experience clinically significant symptoms (Rush et al, 2009; Trivedi et al, 2006). All approved MDD pharmacotherapies act primarily through monoaminergic mechanisms (Machado-Vieira et al, 2017). The similarity between approved agents may contribute to the significant inadequate response reported in the treatment of this heterogeneous disorder.

The consequences of inadequate treatment of MDD are significant. Patients with inadequate response to ADTs have greater disease severity and morbidity, are at higher risk for suicide, are more likely to be hospitalized, have 12 times more outpatient visits, use up to three times more psychotropic medications, have greater impairment in social function, and have an increased risk of relapse compared to treatment-responsive patients (Crown et al, 2002; Souery et al, 2007).

Patients with an inadequate response to ADTs are less likely to improve without a change or addition to their therapy (Van Beljouw et al, 2010). The only FDA-approved adjunctive therapies for MDD are atypical antipsychotics, which are associated with serious and sometimes treatment-limiting toxicities, including significant metabolic derangements and motor disorders, such as tardive dyskinesia (Carbon et al, 2017). New agents with novel mechanisms of action are urgently needed to treat patients who do not respond adequately to the monoaminergic ADTs.

## 2.2. Buprenorphine and Major Depressive Disorder

The endogenous opioid system is a fundamental regulator of mood in humans. It also plays a critical role in motivation, social functioning/attachment, and resiliency (Hsu et al, 2013; Nummenmaa and Tuominen 2017; Pecina et al, 2018). A number of independent studies have shown evidence of the antidepressant effect of BUP at doses lower than what is used to treat opioid use disorder (Serafini et al, 2018; Yovell et al, 2016).

## 2.3. Buprenorphine/Samidorphan for the Adjunctive Treatment of Major Depressive Disorder

BUP/SAM contains BUP, a μ-opioid receptor partial agonist and a κ-opioid receptor antagonist (Subutex USPI, 2018), and SAM, a μ-opioid receptor antagonist. The purpose of SAM is to reduce the risks of abuse and dependence with BUP. SAM has high potency and high bioavailability with oral and SL administration. This attribute ensures that SAM is immediately available when dosed with BUP unlike other BUP/ μ-opioid receptor antagonist combinations (eg, Suboxone®).

## 2.4. Regulatory History and Development of Buprenorphine/ Samidorphan

An Investigational New Drug (IND) application for BUP/SAM was submitted on 09 Apr 2011, and clinical development of BUP/SAM as adjunctive therapy in MDD began shortly thereafter. To date, 19 clinical studies have been completed, including four placebo-controlled efficacy studies (202, 205, 206, and 207) and an open-label study (208) assessing long-term safety, as well as durability of efficacy. Fast Track designation was granted on 09 Oct 2013 for adjunctive BUP/SAM treatment of patients with MDD who have not experienced an adequate response to standard ADT treatment.

Throughout the clinical development program, Alkermes consulted with the FDA. These interactions included Pre-IND and End of Phase 2 meetings to ensure alignment on the key study design elements and endpoints; several scientific exchange meetings to share and discuss results of Studies 205, 206, and 207 prior to the New Drug Application (NDA) filing; and a Pre-NDA meeting to align on overall submission requirements.

The NDA for BUP/SAM was submitted under the 505(b)(2) regulatory pathway. This pathway allows a Sponsor to rely in part on the FDA findings of safety and efficacy for one or more FDA-approved products for studies not conducted by the Sponsor. The BUP/SAM NDA relies primarily upon FDA's findings of nonclinical safety of BUP using BUP (Subutex®) and BUP combined with naloxone (Suboxone) SL tablets as reference products. The studies conducted by Alkermes established the effectiveness of BUP/SAM in the adjunctive treatment of MDD and provided an adequate safety database to demonstrate the safety and tolerability of BUP/SAM.

## 2.5. Challenges in Antidepressant Development

Controlling placebo response, especially in longitudinal outpatient studies, is particularly problematic in MDD compared to other therapeutic indications. Among approved ADTs, approximately 50% of clinical studies failed to demonstrate efficacy (Khin et al, 2011). A high placebo response has been identified as an important contributor to the challenge of assessing efficacy in MDD clinical studies (Food and Drug Administration 2018; Khin et al, 2011).

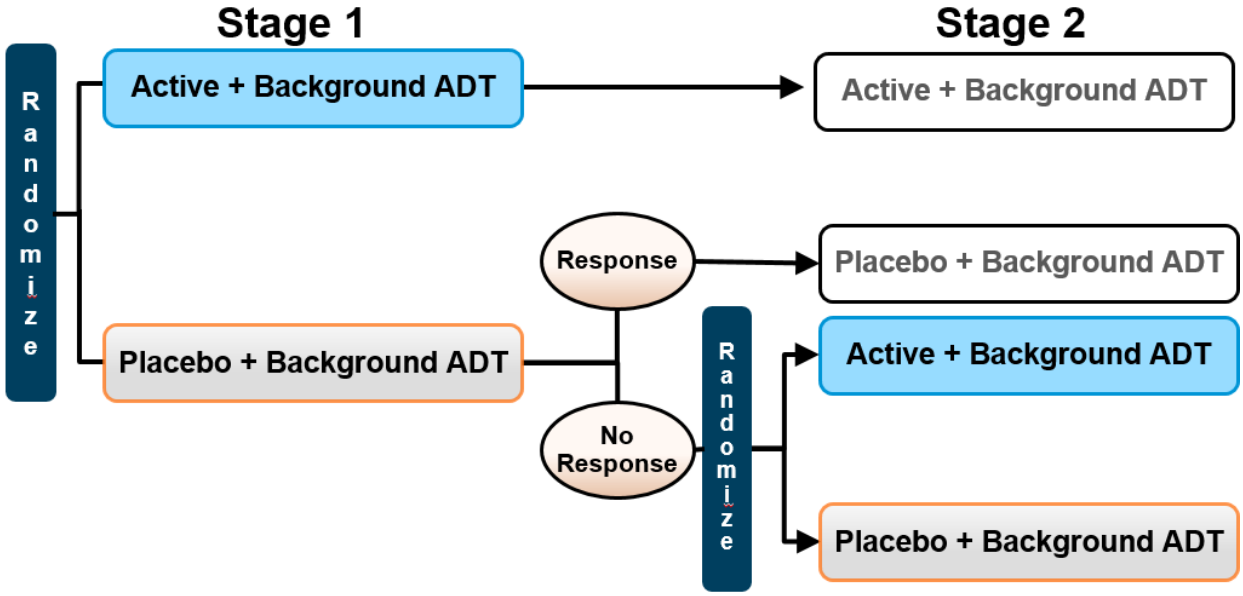
In recent decades, there has been an increase in placebo response rate and a decrease in measureable antidepressant-placebo differences in MDD studies (Undurraga and Baldessarini 2012), and this is driving a need to consider new study designs. Many earlier designs utilized to address placebo response employed single- or double-blind placebo run-ins. In placebo run-in designs, all patients in the study receive placebo for an initial period of several weeks. Patients whose depression scores indicate a substantial clinical response to placebo treatment are removed from the study. Only placebo non-responders are subsequently randomized to treatment with the test agent or placebo. ADTs, including adjunctive agents, have been approved using these designs; however, these study designs have not been reliable in reducing placebo response (Khin et al, 2011; Undurraga and Baldessarini 2012).

To address the continued and growing challenge of placebo response in randomized studies, Fava and colleagues introduced the SPCD in 2003 (Figure 1) (Fava et al, 2003). SPCD builds on the placebo run-in design, adding a randomly assigned active arm during the run-in phase. This enables the placebo run-in to occur in a double-blind manner. The intent of a double-blind run-in

stage is to address treatment-related expectations and improve ascertainment of placebo non-response.

With SPCD, the study is conducted in two treatment stages and with two randomizations within a single study. In Stage 1, patients are randomly assigned to either placebo or active treatment. Patients randomized to placebo in Stage 1 who do not demonstrate a response are then re-randomized to active treatment or placebo in a second stage (Stage 2). Stage 2 therefore is analogous to the randomization stage following a traditional placebo run-in design. The efficacy analysis includes (a) Stage 1 data from all patients randomized in Stage 1 and (b) Stage 2 data from placebo non-responders in Stage 1 who were re-randomized in Stage 2 (Baer and Ivanova 2013; Chen et al, 2011).

**Figure 1: Sequential Parallel Comparison Design (SPCD)**




Note: Patients randomized to placebo and active treatment (represented by the colored boxes) are included in the efficacy analysis for each stage.
Abbreviation: ADT=antidepressant therapy.

By design, the statistical analysis of an SPCD study incorporates results from both Stage 1 and Stage 2. In essence, the SPCD study result is derived from two well-accepted study designs, capturing information from a simple parallel-group study (Stage 1) and a placebo run-in study (Stage 2). By virtue of having two randomizations in two clearly defined patient populations, the SPCD design and analysis combines the treatment effect from the intended-use population (from Stage 1) and the treatment effect in patients who are less prone to show placebo response (from Stage 2). Although SPCD studies are designed and powered to assess efficacy using both Stage 1 and Stage 2 results, descriptive analysis of individual stages also provide important information on consistency of effect.

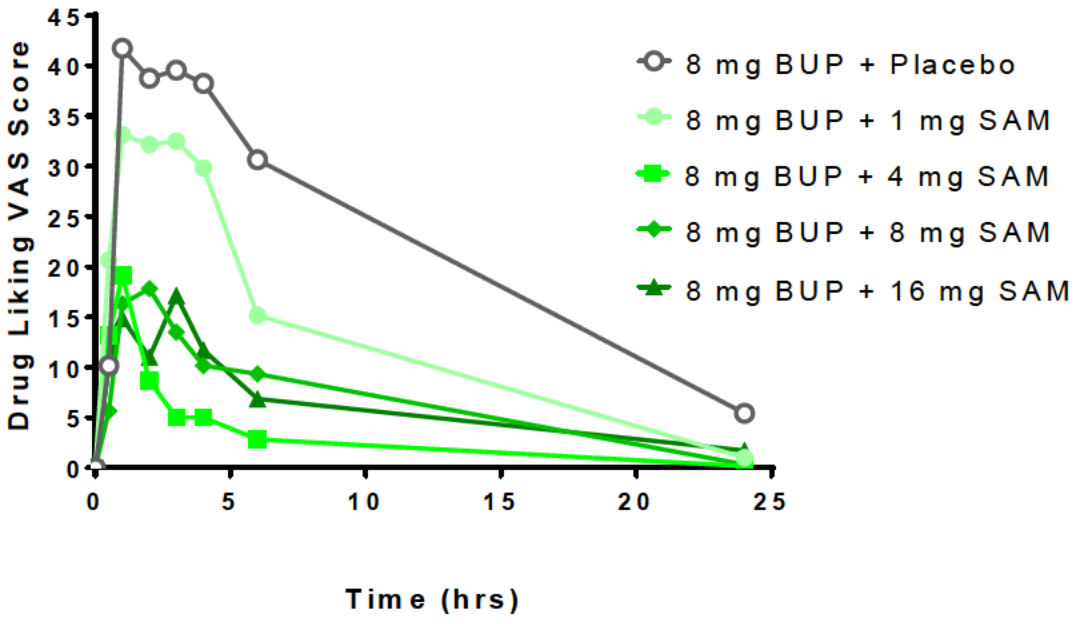
# 3. DOSE SELECTION FOR PHASE 2 AND 3 EVALUATION

Two studies were conducted to provide information regarding the optimal ratio of BUP to SAM in the combination product, as well as the dose of each component for evaluation in Phase 2 and Phase 3 clinical studies. Study 33-008 was a randomized, double-blind, placebo-controlled, three-way crossover study examining the interaction of BUP with SAM in healthy, nondependent opioid-experienced adult subjects. Study 33BUP-201 was a randomized, double-blind, 1-week placebo-controlled study examining ratios of BUP to SAM in MDD patients (see Appendix; Table 14).

Study 33-008 established maximal blockade of the μ-opioid receptor effects of BUP 8 mg by SAM 4 mg, 8 mg, and 16 mg (corresponding to BUP:SAM dose ratios of 2:1, 1:1 and 1:2, respectively) based on subjective and objective pharmacodynamics (PD) assessments (Figure 2 and Figure 3). Increasing the fraction of BUP in BUP/SAM to a higher dose ratio of 8:1 (ie, 8 mg BUP and 1 mg SAM) resulted in >60% blockade (33-008). Efficacy was initially explored in Study 33BUP-201. The results of this study indicated a 1:1 dose ratio of BUP:SAM achieved desirable antidepressant effects, and that higher doses of BUP relative to SAM were not needed to maximize the effect.

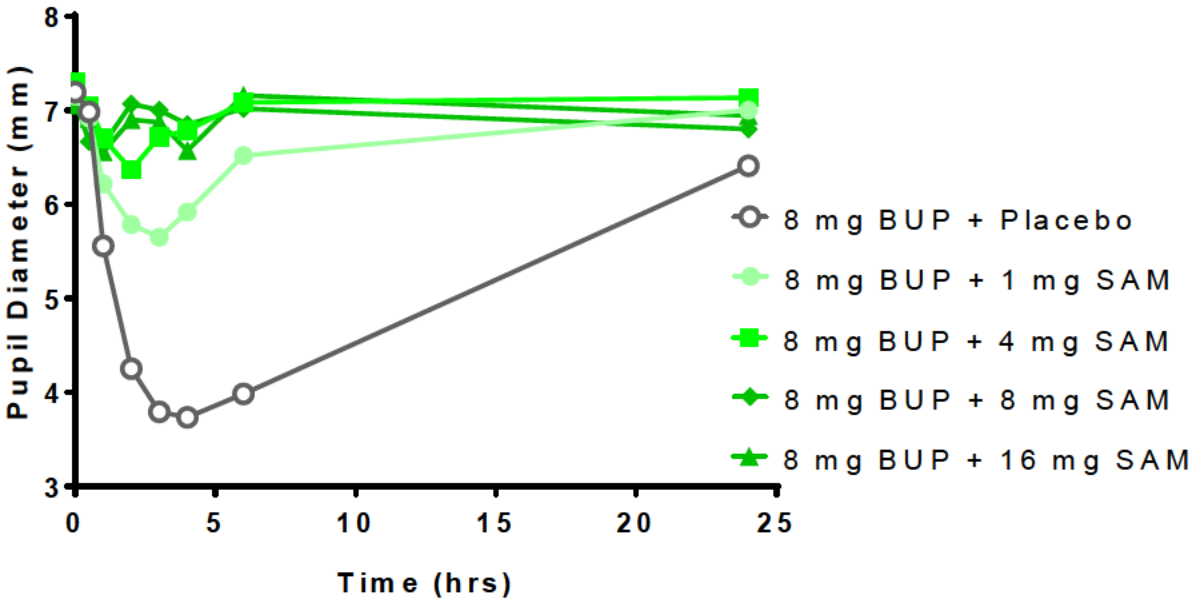
Based on the results of Studies 33-008 and 33BUP-201, a BUP:SAM dose ratio of 1:1 was chosen for evaluation in the Phase 2 and Phase 3 studies in patients with MDD, and a range of doses were investigated: 0.5/0.5 (205), 1/1 (207), 2/2 (all studies), and 8/8 (202) (see Section 5.7).

**Figure 2: Mean Drug Liking Visual Analogue Scale Scores for Buprenorphine (8 mg) Coadministered with Samidorphan (1 mg-16 mg) or Placebo**




Abbreviations: BUP=buprenorphine; SAM=samidorphan; VAS=visual analogue scale.
Note: Study 33-008.

**Figure 3: Mean Pupil Diameters for Buprenorphine (8 mg) Coadministered with Samidorphan (1 mg-16 mg) or Placebo**




Abbreviation: BUP=buprenorphine; SAM=samidorphan.
Note: Study 33-008.

# 4. DESIGN AND POPULATION OF PHASE 2 AND 3 STUDIES

Safety and efficacy was evaluated in four randomized, double-blind, placebo-controlled studies; one Phase 2 (202) and three Phase 3 (205, 206, and 207) studies. All four studies were designed and conducted with the same rigor as a pivotal trial and were randomized, double-blind, placebo-controlled. All studies employed designs intended to address high placebo response that is typical of antidepressant studies. Three of the four studies (202, 205, and 207) employed SPCD and the fourth study (206) was a placebo run-in design (see Section 4.1).

A long-term study was conducted to evaluate safety and included efficacy assessments which provided evidence of durability of effect (see Section 4.2). BUP/SAM titration schedules were evaluated in Study 210 (for study details see Table 14).

In all studies, patients with MDD and an inadequate response to ADT were evaluated. Patients remained on background ADT and received adjunctive treatment with BUP/SAM at doses ranging from 0.5/0.5 to 8/8.

## 4.1. Placebo-Controlled Study Designs

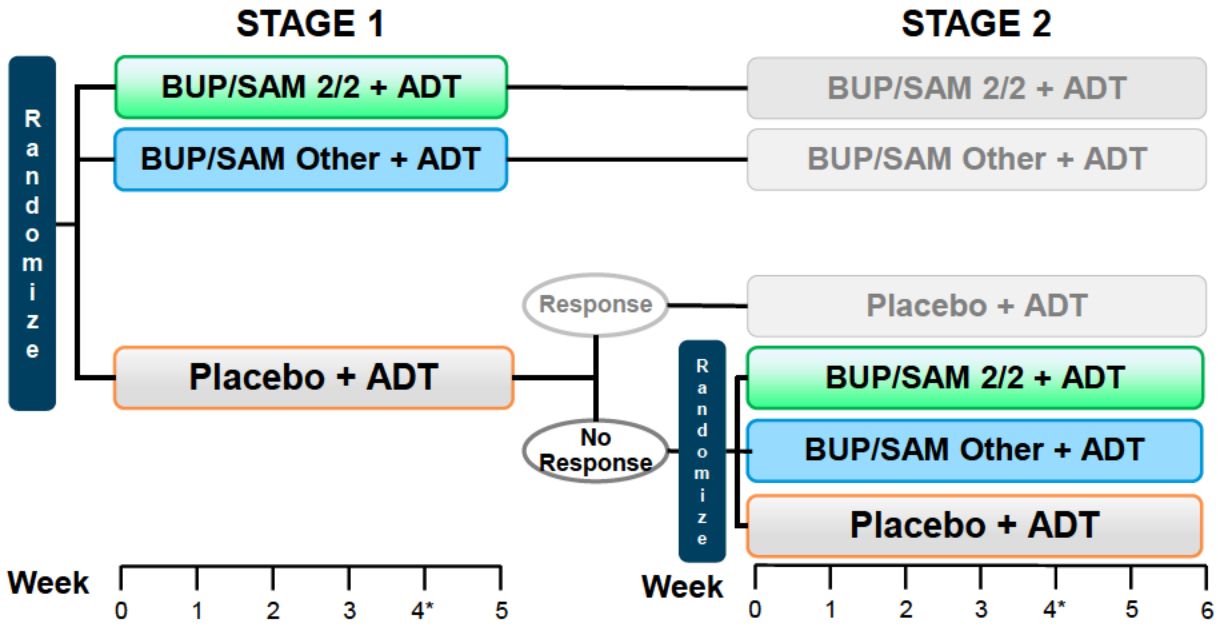
### 4.1.1. Studies 202, 205, and 207: Sequential Parallel Comparison Design Studies

Three of the four studies (202, 205, and 207) employed the SPCD study design to address placebo response, as described in Section 2.5.

Study 202, the first SPCD study in the BUP/SAM development program, evaluated BUP/SAM doses of 2/2 and 8/8. Each stage included a 4-week treatment period followed by a 1-week taper period, resulting in a treatment duration of 10 weeks overall. Efficacy evaluation was based on the 4-week treatment period for each stage (Figure 4). In contrast to Studies 205 and 207, patients in Study 202 given BUP/SAM during Stage 1 were given placebo during Stage 2. Due to the absence of withdrawal symptoms in Study 202, the remaining studies did not include a BUP/SAM taper at the end of the treatment period.

Studies 205 and 207 had similar treatment period designs to Study 202, except for the BUP/SAM doses evaluated (Figure 4). Upon treatment initiation in Studies 205 and 207, BUP/SAM was titrated from 0.5/0.5 to a maintenance dose of 1/1 or 2/2. Titration and dosing schedules of BUP/SAM in the clinical studies discussed in this briefing document are provided in Table 13. Both studies evaluated BUP/SAM 2/2 and a lower dose (0.5/0.5 in 205 and 1/1 in 207). The overall duration of treatment in 205 and 207 was 11 weeks, with Stage 1 lasting 5 weeks and Stage 2 lasting 6 weeks.

**Figure 4: 202, 205, and 207 Study Designs (SPCD)**




Abbreviations: ADT=antidepressant therapy; BUP=buprenorphine; SAM=samidorphan.
* In Study 202 the treatment period used for efficacy evaluation was 4 weeks in duration.
Note: Patients randomized to placebo and active treatment (represented by the colored boxes) were included in the efficacy analysis for each stage.
Note: For Study 202, patients who received BUP/SAM in Stage 1 were switched to placebo in Stage 2.

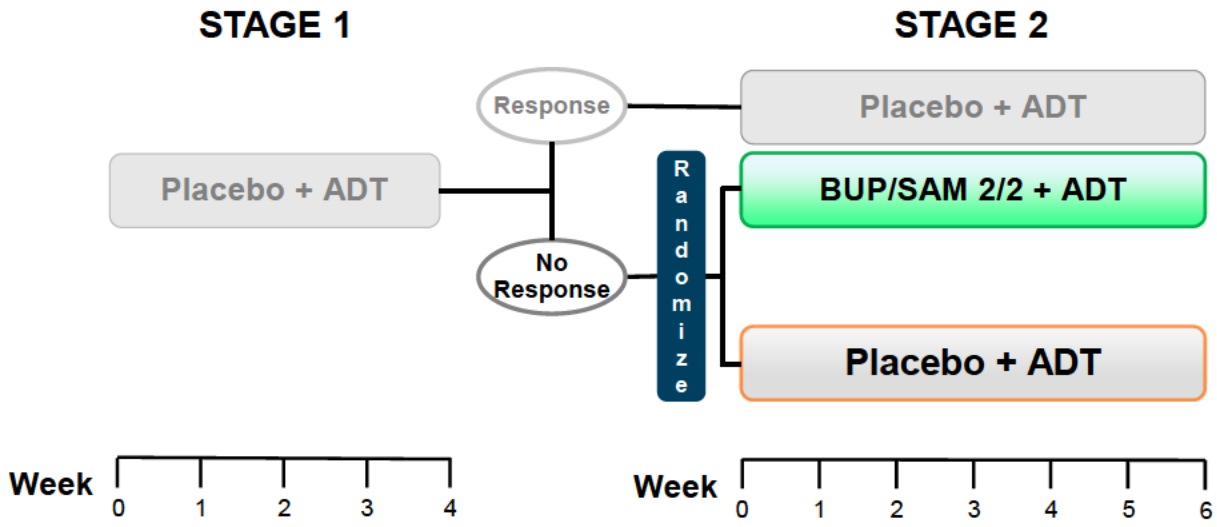
In all three SPCD studies, randomization ratios in Stage 1 were 2:2:9 for BUP/SAM 2/2, BUP/SAM other dose, and placebo; and in Stage 2 were 1:1:1 for BUP/SAM 2/2, BUP/SAM other dose, and placebo.

### 4.1.2. Study 206: Placebo Run-in Study

The fourth placebo-controlled efficacy study (206) employed a placebo run-in design to control placebo response (Figure 5). The double-blind placebo run-in period included patients in Group 1 (those with baseline HAM-D17 score ≥20). Following the placebo run-in, placebo non-responders were randomized in Stage 2 to either placebo or BUP/SAM 2/2 in a 1:1 ratio. These patients comprised the efficacy analysis population.

In addition, Study 206 included a second group of patients (Group 2 [baseline HAM-D17 score=18-19]) who were randomized to placebo or BUP/SAM in Stage 1. Inclusion of Group 2 patients was solely intended to reduce inflation of baseline depression symptom scores (by allowing patients with lower HAM-D scores to enter the study) and to provide double-blinding of the placebo run-in in Group 1. All active treatment in Study 206 began with a 1-week titration period with patients receiving BUP/SAM from 0.5/0.5 to a maintenance dose of 2/2 (see Table 13).

**Figure 5: 206 Study Design (Placebo Run-In): Group 1 Patients**




Abbreviations: ADT=antidepressant therapy; BUP=buprenorphine; SAM=samidorphan.
Note: Patients randomized to placebo and active treatment (represented by the colored boxes) were included in the efficacy analysis.

### 4.1.3. Patients and Treatment Durations for the Placebo-controlled Studies

Table 1 provides details on the number of patients and treatment durations for the placebo-controlled studies.

**Table 1: BUP/SAM Phase 2 and 3 Studies for Adjunctive Treatment of MDD**

| Study # | Study Design | N Patients Randomized[a] | Duration | Doses |
|---|---|---|---|---|
| **Phase 2** | | | | |
| 202 | SPCD | 142 (Stage 1)<br>65 (Stage 2) | Stage 1: 4 weeks+1-week taper<br>Stage 2: 4 weeks+1-week taper | BUP/SAM 2/2, 8/8[b], or Placebo |
| **Phase 3** | | | | |
| 205 | SPCD | 385 (Stage 1)<br>168 (Stage 2) | Stage 1: 5 weeks<br>Stage 2: 6 weeks | BUP/SAM 0.5/0.5, 2/2[b], or Placebo |
| 206[c] | Placebo run-in | 297 (Group 1)<br>30 (Group 2) | Group 1: 6 weeks<br>Group 2: 10 weeks | BUP/SAM 2/2[b] or Placebo |
| 207 | SPCD | 407 (Stage 1)<br>187 (Stage 2) | Stage 1: 5 weeks<br>Stage 2: 6 weeks | BUP/SAM 1/1[b] or 2/2[b], or Placebo |

Abbreviations: BUP/SAM=buprenorphine/samidorphan; SPCD=sequential parallel comparison design.
[a] Stage 2 randomized patients are those who were randomized and received placebo in Stage 1 and did not respond.
[b] Patients received lower titration doses prior to reaching targeted BUP/SAM dose (see Table 13).
[c] Group 1 included patients with HAM-D17 scores ≥20 who entered the Placebo run-in period (N=399). Placebo non-responders were subsequently randomized (N=297) and comprised the efficacy analysis population. Group 2 included patients with HAM-D17 scores 18-19, who were excluded from the Placebo run-in and were intended to mask the presence of the Group 1 Placebo run-in. Group 2 patients were not included in the efficacy evaluation.

### 4.1.4. MDD Patient Population

#### 4.1.4.1. Major Inclusion/Exclusion Criteria

Inclusion criteria were similar across Studies 202, 205, 206, and 207. Key inclusion criteria included the following:

- Diagnosis with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).
- Inadequate response to one or two ADTs during the current major depressive episode (MDE).
- Duration of current MDE between 8 weeks and 24 months.
- Background ADT(s); selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or bupropion, taken at an adequate dose for ≥8 weeks, and at a stable dose ≥4 weeks prior to entering the double-blind treatment period.
  - Documented historically or demonstrated prospectively.
  - Patients continued on background ADT unchanged throughout study participation.
- Adults 18 to 70 years of age, with a body mass index between 18 and 40 $kg/m^2$, and otherwise healthy, as appropriate for a clinical study in MDD.

While the inclusion and exclusion criteria were similar across Studies 202, 205, 206, and 207, Study 202 had some minor differences. Key differences included:

- An upper age limit of 65 years.
- Inclusion of patients with lower HAM-D17 scores at baseline (≥16 in 202 vs ≥18 in 205, 206, and 207).

#### 4.1.4.2. Demographics and Baseline Characteristics (MDD History)

A total of 1229 patients were randomized in Studies 202, 205, 206, and 207. The majority of patients were in the United States (US, approximately 85%); the remaining patients were from sites outside the US (including sites in Australia, Bulgaria, Canada, and Germany). Across the studies, 62 to 70% of the patients were female, with a mean age of 43 to 48 years. Approximately three-quarters of the patients were White, with most of the remaining patients Black. The mean duration of the current MDE was 9 to 10 months, with a mean lifetime number of MDEs of 4 to 7. The mean MADRS-10 score at baseline was 31.0 to 32.0. All patients were required to have an inadequate response to an ADT, with inadequate response to two ADTs demonstrated in 11 to 20% of the patients across Studies 205, 206, and 207 (see Table 2). The classes of background ADTs taken during the treatment periods of Studies 202, 205, 206, and 207 are discussed in Section 4.1.4.3.

Placebo-controlled studies (202, 205, 206, and 207) had similar demographic characteristics across treatment groups, studies, and between Stage 1 and Stage 2 in SPCD studies. The demographic characteristics were also similar to the pooled Safety population presented in

Section 6.1.3 and Table 16. A summary of baseline disease characteristics for Stage 1 (202, 205, and 207) and Group 1 (206) randomized patients in the efficacy analysis population is presented in Table 2. In SPCD studies, baseline characteristics were similar across treatment groups and across studies, as well as between Stage 1 and Stage 2.

**Table 2: Patient Baseline Characteristics: BUP/SAM 2/2 and Placebo Treatment Groups**

| Parameter | | Study 202 | | Study 205 | | Study 206 | | Study 207 | |
|---|---|---|---|---|---|---|---|---|---|
| | | Placebo (N=95) | BUP/SAM 2/2 (N=20) | Placebo (N=256) | BUP/SAM 2/2 (N=59) | Placebo (N=146) | BUP/SAM 2/2 (N=142) | Placebo (N=273) | BUP/SAM 2/2 (N=63) |
| **Duration of Current MDE (month)** | | | | | | | | | |
| Mean (SD) | | 9.3 (8.24) | 8.8 (5.75) | 9.7 (5.87) | 9.2 (5.04) | 9.0 (5.81) | 8.4 (5.69) | 9.1 (5.53) | 9.0 (5.30) |
| **Lifetime Number of MDEs**[a] | | | | | | | | | |
| Mean (SD) | | 6.2 (5.84) | 6.8 (6.12) | 4.4 (3.54) | 6.2 (6.18) | 4.5 (4.94) | 4.8 (3.64) | 4.4 (3.43) | 4.3 (2.36) |
| **Number of Inadequate Responses to ADT in the Current MDE** | | | | | | | | | |
| n (%) | 1 | NA[b] | NA[b] | 206 (80.5) | 46 (78.0) | 135 (92.5) | 129 (90.8) | 241 (88.3) | 56 (88.9) |
| | 2 | | | 50 (19.5) | 12 (20.3) | 11 (7.5) | 13 (9.2) | 31 (11.4) | 7 (11.1) |
| **MADRS-10 Score at Baseline** | | | | | | | | | |
| Mean (SD) | | 31.0 (5.59) | 31.1 (5.56) | 31.9 (5.04) | 32.0 (5.72) | 27.4 (6.56) | 27.7 (6.36) | 31.7 (5.64) | 31.8 (5.64) |

Abbreviations: ADT=antidepressant therapy; BUP=buprenorphine; MADRS=Montgomery-Åsberg Depression Rating Scale; MDE=major depressive episode; NA=not applicable; SAM=samidorphan; SD=standard deviation.

Data shown are for the randomized efficacy analysis populations for Stage 1 (202, 205 and 207) and Group 1 (206). Treatment groups presented are placebo and the intended treatment dose BUP/SAM 2/2.

[a] Including the current episode of depression.

[b] As per eligibility criteria, patients in Study 202 had either one or two confirmed inadequate responses, however an individual patient's number of inadequate responses was not captured in the case report form.

#### 4.1.4.3. Background Antidepressant Therapies

In all studies, patients continued on background ADT without change throughout study participation. The classes of background ADTs taken during the treatment periods of Studies 202, 205, 206, and 207 are presented in Table 17 for Stage 1 and Studies 202, 205, and 207 are presented in Table 18 for Stage 2. The most common background ADT class was SSRI (range 52-80%). The second most common background ADT class was SNRI (range 9-33%). Background ADTs were similar across treatment groups, across studies, and across stages.

#### 4.1.4.4. Disposition

Overall study completion rates for the three SPCD studies ranged from 74% to 83%. Stage-specific completion rates for the randomized populations within each stage ranged from 86% to 92% and 86% to 93% in Stage 1 and Stage 2, respectively. AEs were the most common reasons for study discontinuation[a] from BUP/SAM 2/2. Discontinuation rates due to lack of efficacy ranged from 0 to 1%. In Study 206, completion rates were 94% and 91% for the placebo run-in and randomized treatment period, respectively. Section 6.1.5.2 summaries adverse events (AEs) leading to discontinuation. Disposition figures of participant flow for Studies 202 (Figure 27), 205 (Figure 28), 206 (Figure 29), and 207 (Figure 30) are provided in the Appendix.

Efficacy analysis populations were defined by analysis stage as randomized patients who received ≥1 dose of study drug and had ≥1 post-baseline assessment within the respective stage. Percent of available patient data at the end of the treatment period ranged from 77.8-100%. Patients who received BUP/SAM had lower retention compared to patients who received placebo as a result of higher rates of discontinuations, due largely to AEs. Few patients across all four studies reported lack of efficacy as a reason for discontinuation (5/944 patients taking placebo and 3/451 patients taking BUP/SAM 2/2).

## 4.2. Study 208: Long-term Study

Study 208 was a long-term, open-label, safety study, which included MADRS efficacy assessments, where all patients were to receive BUP/SAM 2/2 for 52 weeks in addition to background ADTs. Patients in 208 included the following:

- Patients who completed a prior BUP/SAM study (205, 206, 207, or 210 [a safety and tolerability study evaluating BUP/SAM titration]).
  - Patients in Study 205 were eligible for Study 208 after completing the follow-up period and thus were required to discontinue study drug prior to 208 enrollment.

[a] All treatment discontinuation lead to study discontinuation.

  - Patients in Studies 206, 207, and the 210 dose titration study were eligible for Study 208 after completing the treatment period and were not required to discontinue study drug prior to 208 enrollment.
- Patients who did not meet the depressive symptom related eligibility criteria for randomization in 205, 206, and 207, and were not in remission.
- *De novo* patients (ie, patients who had not participated in previous BUP/SAM clinical studies) with MDD and an inadequate response to ADT.

A total of 1454 patients were enrolled and received BUP/SAM in Study 208; 537 received BUP/SAM in a prior study and 917 received BUP/SAM for the first time in 208. Upon entering 208, some patients received titration dosing (0.5/0.5, 1/1) for the first week of treatment and 2/2 thereafter. Upon completion of the study, patients underwent abrupt discontinuation of BUP/SAM prior to follow-up, as specified in the protocol.

## 4.3. Statistical Methods in Efficacy Analysis

Efficacy analysis populations were defined as randomized patients who received ≥1 dose of study drug and had ≥1 post-baseline efficacy assessment in the relevant analysis period or stage.

### 4.3.1. Scales Used to Evaluate Efficacy

Two validated and widely-used depression rating scales, HAM-D17 (Hamilton 1960) and MADRS (Montgomery and Asberg 1979), were used to measure MDD symptom severity and to evaluate efficacy of BUP/SAM. HAM-D17, a 17-item questionnaire, was used as the primary endpoint in Study 202 and for assessment of inclusion criteria in Studies 205, 206, and 207.

Two scores derived from the 10-item MADRS questionnaire were used in the BUP/SAM development program, MADRS-10 and MADRS-6. MADRS-10 is the sum of responses to all 10 items of the MADRS; whereas, the subscale MADRS-6 is the sum of responses to six of the 10 MADRS items that are thought to represent the core symptoms of depression: reported sadness, apparent sadness, inner tension, lassitude, inability to feel, and pessimistic thoughts (Bech et al, 2002; Bech et al, 2004). MADRS items not included in the MADRS-6 score are reduced sleep, reduced appetite, concentration difficulties, and suicidal thoughts. MADRS-6 may be particularly relevant to evaluate antidepressant properties of adjunctive treatments, as all patients receive background antidepressants that may provide potential benefit on some symptoms (Nelson et al, 2017).

### 4.3.2. Overview of Analysis of Primary and Common Efficacy Endpoints

Across the four randomized, placebo-controlled studies conducted to evaluate BUP/SAM efficacy, four different primary endpoints were specified. A summary of the primary efficacy endpoints and analysis of the four placebo-controlled adjunctive BUP/SAM studies is presented in Table 3. These endpoints varied as to the MDD assessment score (HAM-D17, MADRS-10 and MADRS-6), efficacy period evaluated (baseline to end of treatment and baseline to Week 5) and number of time points used in the analysis (single and multiple time points).

**Table 3: Summary of Double-blind Placebo-controlled Studies**

| Study | Design | Primary Assessment | Primary Analysis<br>Difference BUP/SAM vs Placebo |
|---|---|---|---|
| 202 | SPCD | HAM-D17 | BUP/SAM vs placebo difference:<br>Change from baseline to end of treatment (Week 4) |
| 205 | SPCD | MADRS-10 | BUP/SAM vs placebo difference:<br>Change from baseline to Week 5 |
| 207[a] | SPCD | MADRS-6 | Average of BUP/SAM vs placebo differences: changes from baseline to Week 3 through end of treatment[b] |
| | | MADRS-10 | Average of BUP/SAM vs placebo differences: changes from baseline to Week 3 through end of treatment[b] |
| | | MADRS-10 | BUP/SAM vs placebo difference:<br>Change from baseline to end of treatment (Week 5/6) |
| 206 | Placebo Run-In | MADRS-10 | BUP/SAM vs placebo difference:<br>Change from baseline to end of treatment (Week 6) |

Abbreviations: HAM-D17=Hamilton Rating Scale for Depression-17; MADRS=Montgomery-Åsberg Depression Rating Scale; SPCD=sequential parallel comparison design.

[a] Hierarchy of endpoints tested in order presented here to control for multiplicity. Conclusion of efficacy was based on MADRS-6.

[b] BUP/SAM vs placebo difference in change from baseline calculated at each time point were averaged for Week 3 through end of treatment (Week 5/6 for Stage 1/Stage 2).

Note: In Study 205, change from baseline to Week 5 was the pre-specified primary analysis time point. This time point represents a portion of the Stage 2 treatment period (6 weeks in total duration). Week 5 was chosen with the intent of masking the primary analysis time-point.

In Study 202, HAM-D17 score was the primary efficacy endpoint. The analysis plan was finalized prior to study unblinding. Only two treatments (2/2 and 8/8) were evaluated in Study 202 and a multiplicity adjustment was not pre-specified. Given the mixed agonist/antagonist effects of BUP/SAM, the dose response was unknown and there was insufficient pharmacologic justification to support a hierarchical statistical testing procedure starting with the higher dose (8/8). A *post-hoc* Bonferroni adjustment, which is independent of prior assumptions, was performed. Conclusions were consistent with those made without multiplicity adjustment.

In Studies 205 and 206, MADRS-10 score was the primary efficacy endpoint. In Study 207, MADRS-6 score was first in the fixed sequence testing and was considered the primary efficacy endpoint. MADRS-10 score was the second and third in the fixed sequence testing. In Studies 205 and 207, multiplicity adjustment was pre-specified in the SAPs. Hypotheses were tested for BUP/SAM 2/2 followed by the lower dose. In Study 208 (long-term study), MADRS-10 was an exploratory efficacy endpoint.

Study 202 results for HAM-D17 and MADRS-10 revealed that MADRS-10 was a sensitive measure of efficacy, and for this reason subsequent studies (205, 206, and 207) used primary endpoints based on the MADRS. Additional analysis of Study 205 revealed that MADRS-6 may be a more relevant measure of efficacy for adjunctive treatment, as has been demonstrated in other clinical studies (Nelson et al, 2010; Nelson et al, 2017). Given these findings, the statistical

analysis plan for Study 207 was amended prior to unblinding to pre-specify MADRS-6 as the first primary efficacy endpoint in a sequence of three endpoints, with MADRS-10 scores pre-specified as second and third in the sequence.

*Post-hoc* analyses of Studies 202, 205, and 206 also revealed week-to-week variability in efficacy assessments, which could affect any pre-specified outcome focused on a single time point. Such variability has been noted in the literature and may result from symptomatic fluctuations over time and the subjective nature of the assessments (Rush et al, 2006). In Studies 202 and 205, BUP/SAM numerically separated from placebo over all time points beginning at Week 3 (Stage 1 and Stage 2), while effect sizes varied across week-by-week analyses. Thus, a more complete estimate of the difference between the various arms of Study 207 was achieved by utilizing data from multiple time points over treatment. This method of examining efficacy over time more comprehensively captures the patient population's experience rather than a single time point that captures only transient experience. It also guards against mischaracterization of benefit (or lack thereof) based on a specific timepoint.

The statistical analysis plan for Study 207 was amended to adopt this analysis method prior to unblinding. The primary efficacy endpoints were:

- MADRS-6 score change from baseline; calculated at each time point and those changes were averaged for Week 3 through end of treatment (MADRS-$6_{AVG}$).
- MADRS-10 score change from baseline; calculated at each time point and those changes were averaged for Week 3 through the end of treatment (MADRS-$10_{AVG}$).
- MADRS-10 score change from baseline to the end of treatment (MADRS-$10_{EOT}$).

The three endpoints were evaluated in the fixed sequence presented to adjust for multiplicity and control overall type 1 error. As pre-specified, a conclusion of efficacy was made if the efficacy endpoint in the first tier was met. Study 207 met its pre-specified primary endpoint. The analysis captured the average change from baseline depression scores for placebo compared to BUP/SAM over the final three weeks of Stage 1 (5 weeks in total duration) and the final four weeks of Stage 2 (six weeks in total duration). This method of averaging captured all of the data following the first two weeks of initiation of treatment in each stage.

Efficacy was assessed using the same two endpoints, MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$, to compare results across studies. MADRS-$10_{EOT}$ provides a conventional estimate of efficacy preferred by the FDA and used historically to support approval of MDD treatments, while MADRS-$10_{AVG}$ addresses the week-to-week variability that was observed. Together with the primary efficacy results, results using these two common endpoints provide additional insight into the consistency and robustness of BUP/SAM's efficacy.

### 4.3.3. Mixed Models Repeated Measures

In all four of the placebo-controlled studies of BUP/SAM (202, 205, 206, and 207), mixed models repeated measures (MMRM) were used to model score changes from baseline. Key covariates in the models were treatment group, visit, and treatment group-by-visit interaction as categorical fixed effects, and baseline value and baseline-by-visit interaction as covariates. For Studies 205 and 207, which were multi-national, covariates for site region and site region-by-treatment interaction were also included as categorical fixed effects. Study 206 did not include

any additional covariates. Study 202, conducted in the US only, did not include covariates for site region and only the main effect for baseline value.

For SPCD studies (202, 205, and 207), data from each stage were analyzed using separate MMRM models to calculate least squares mean differences (LSMDs) between each active arm and placebo at each visit to provide estimates and inferences for each time point. Primary analyses for the SPCD studies were based on the combined stage analysis where estimates of HAM-D17, MADRS-6, or MADRS-10 LSMD between each BUP/SAM and placebo and associated standard error were combined using pre-specified weights. Stage 1/Stage 2 weights were pre-defined as 0.6/0.4 for Study 202 and 0.5/0.5 for Studies 205 and 207.

### 4.3.4. Meta-Analysis

A meta-analysis was conducted across studies (202, 205, 206, and 207) for the primary efficacy analysis and across all studies within a single stage. Given that all studies evaluated the same population and were double-blind randomized studies, the meta-analysis serves to leverage data produced under similar conditions to increase precision in estimation. Fixed effect models of effect size were used to determine the combined estimate of the difference between BUP/SAM and placebo and its associated standard error using inverse variance weights. Hypothesis tests were based on the resulting Z statistic and were two-sided.

# 5. CLINICAL EFFICACY

Efficacy was evaluated in four randomized, double-blind, placebo-controlled studies (202, 205, 206, and 207). In all studies, patients with MDD and an inadequate response to ADT were evaluated. Patients remained on background ADT and received adjunctive treatment with BUP/SAM at doses ranging from 0.5/0.5 to 8/8. Additionally, a long-term safety study was conducted which included MADRS efficacy assessments that provided evidence of durability of effect.

Data presented are for the BUP/SAM 2/2 dose, the proposed therapeutic dose. Except for the primary endpoints, all *P*-values are nominal.

**Summary**

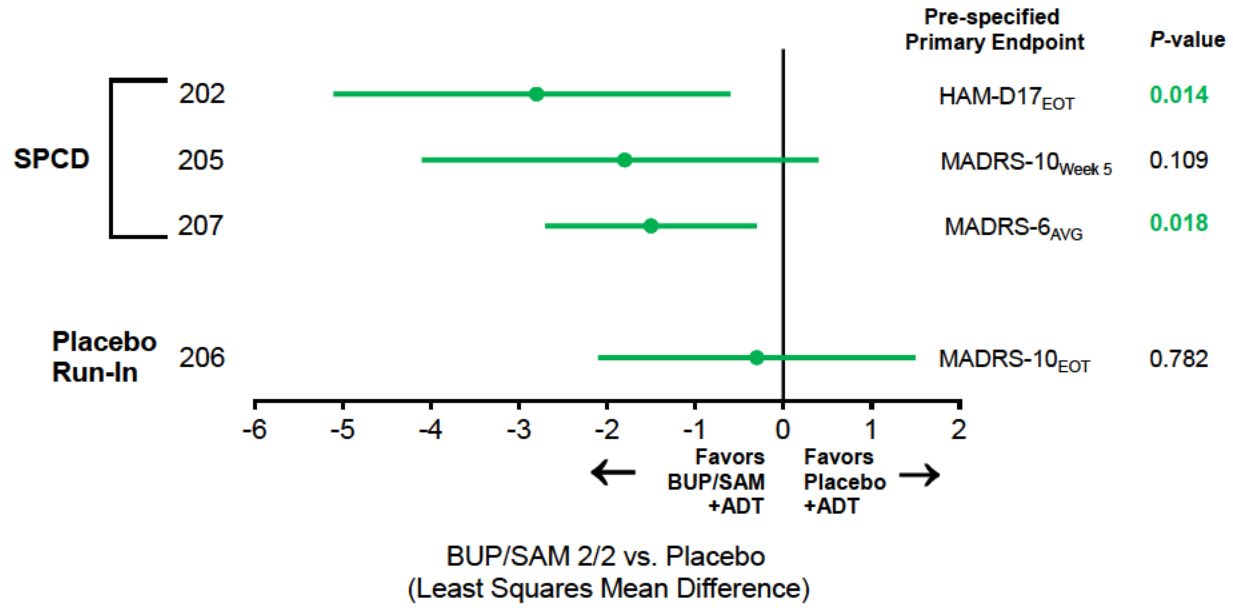
- Two of the four studies (202 and 207) had significant *P*-values for the pre-specified primary endpoint (see Section 5.1). Additional analysis of three of the four studies (202, 205, and 207) had significant *P*-values for the MADRS-10 endpoint when statistical methods were used to address week-to-week variability (see Section 5.2.6).
- These repeated, independent observations provide evidence of a consistent drug effect and demonstrate that BUP/SAM 2/2 is effective for the adjunctive treatment of MDD.
- Continued and sustained improvement was observed in MADRS scores over 1-year treatment with adjunctive BUP/SAM in patients continuing treatment in the long-term study (208).

## 5.1. Overview of Primary Efficacy Results

A summary of the primary efficacy results for the placebo-controlled studies (202, 205, 206, and 207) are presented in Figure 6. Three of the four randomized, double-blind, placebo-controlled efficacy studies had estimates for the primary endpoint that favored BUP/SAM over placebo. Two of the four studies (202 and 207) had significant *P*-values for the pre-specified primary efficacy endpoint for the BUP/SAM 2/2 dose and were positive studies.

- Study 202: HAM-D17 change from baseline to end of treatment ($HAM\text{-}D17_{EOT}$)
  - BUP/SAM vs placebo LSMD (*P*-value): -2.8 (0.014)
- Study 207: MADRS-6 average difference change from baseline to Week 3 through end of treatment ($MADRS\text{-}6_{AVG}$)
  - BUP/SAM vs placebo LSMD (*P*-value): -1.5 (0.018)

**Figure 6: Primary Efficacy Results**




Abbreviations: AVG=average; ADT=antidepressant therapy; BUP=buprenorphine; EOT=end of treatment; HAM-D17=Hamilton Rating Scale for Depression; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.

## 5.2. Efficacy Across Studies Using Common MADRS-10 Endpoints

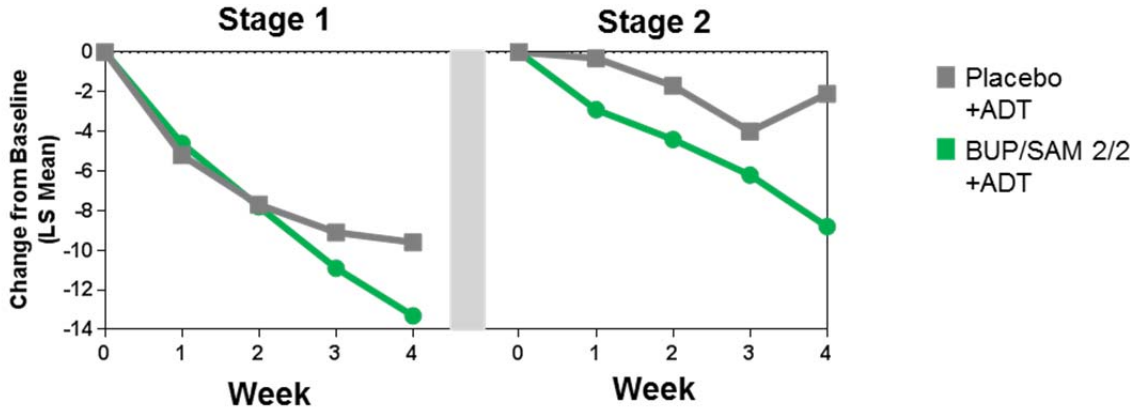
To evaluate the consistency of BUP/SAM efficacy, descriptive analysis of MADRS-10 score improvement was conducted by treatment group over time within each of the two stages of the SPCD studies (202, 205 and 207). The two-stage design of SPCD studies allows evaluations across the two randomized stages. Stage 1 represents patients who were directly randomized; whereas, Stage 2 represents an enriched population of patients who were placebo nonresponders in Stage 1, and were subsequently randomized in Stage 2.

To further evaluate the consistency of the BUP/SAM treatment effect across all four studies, efficacy endpoints and analysis methods were harmonized to allow a comparison of uniform measures. Specifically, MADRS-10 was used as the endpoint and analyzed using the same two statistical methods used for efficacy analysis in Study 207 (ie, $MADRS\text{-}10_{EOT}$ and $MADRS\text{-}10_{AVG}$) as described in Section 4.3.2. Results from individual studies using the common MADRS-10 endpoints and comparisons across studies are presented below.

### 5.2.1. Study 202

Study 202 was a Phase 2 randomized, placebo-controlled, multi-center SPCD study conducted at US sites which randomized 142 patients. Change from baseline in MADRS-10 score over time by treatment group (BUP/SAM 2/2 and placebo) and stage is presented in Figure 7. In both Stage 1 and Stage 2 and across multiple time points, patients in the BUP/SAM 2/2 treatment group had greater improvement in their MADRS-10 scores, with the greatest difference observed at the end of treatment.

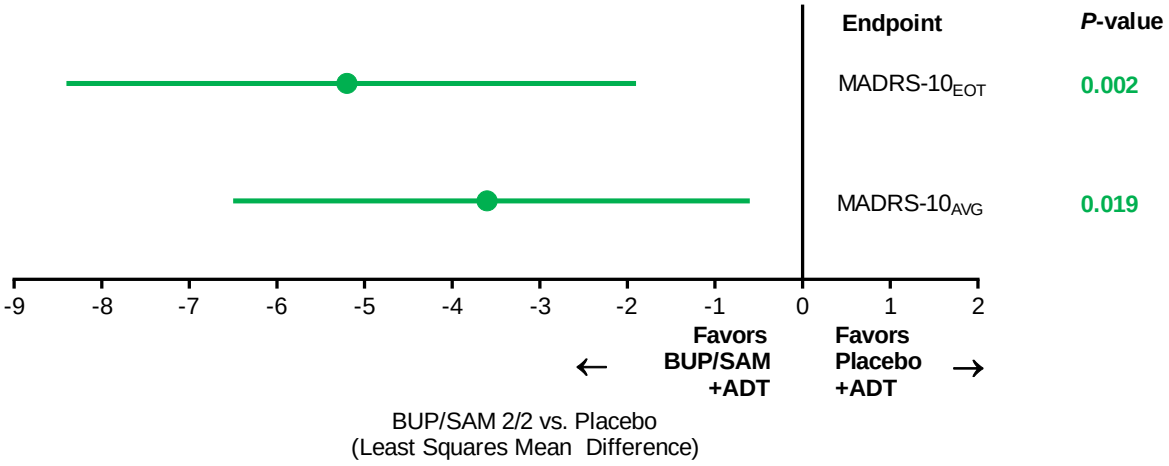
**Figure 7: MADRS-10 Change from Baseline by Treatment and Stage (Study 202)**




Abbreviations: ADT=antidepressant; BUP=buprenorphine; LS=least squares; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.

Results from the analysis using the common endpoints MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$ are presented in Figure 8. For both common endpoints, BUP/SAM 2/2 showed greater efficacy compared to placebo, with estimates favoring BUP/SAM (*P*=0.002 and 0.019 for MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$, respectively).

**Figure 8: MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$ Endpoints: BUP/SAM vs Placebo Difference (Study 202)**

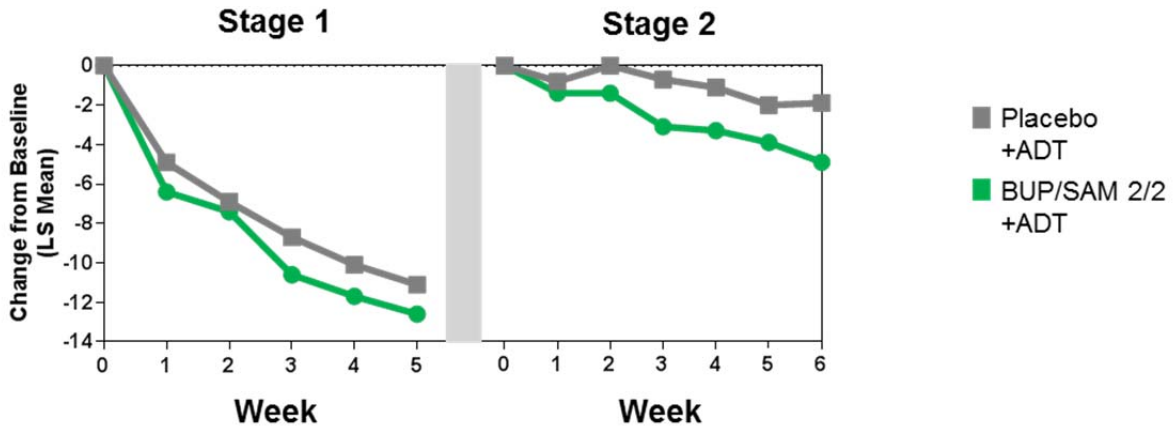



Abbreviations: ADT=antidepressant; AVG=average; BUP=buprenorphine; EOT=end of treatment; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.

### 5.2.2. Study 205

Study 205 was a Phase 3 randomized, placebo-controlled, multi-center SPCD study conducted at US and non-US sites which randomized 385 patients. Similar to what was observed in Study 202, improvement in MADRS-10 score was greater in the BUP/SAM 2/2 treatment group compared to placebo in both stages and all time points, with greatest improvement observed at the end of treatment (Figure 9).

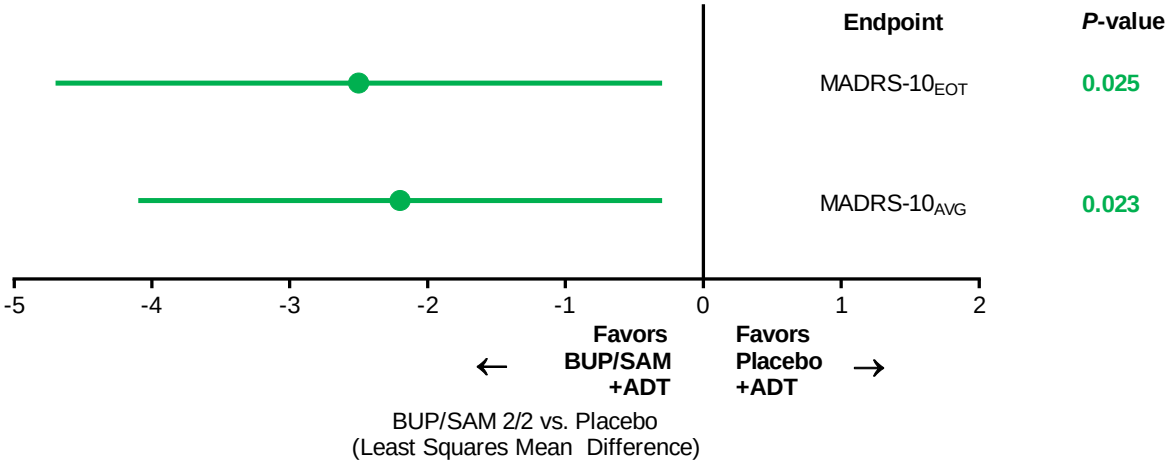
**Figure 9: MADRS-10 Change from Baseline by Treatment and Stage (Study 205)**




Abbreviations: ADT=antidepressant; BUP=buprenorphine; LS=least squares; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.

Results from the analysis using the common endpoints MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$ are presented in Figure 10. For both common endpoints, BUP/SAM 2/2 showed greater efficacy compared to placebo, with estimates favoring BUP/SAM (*P*=0.025 and 0.023 for MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$, respectively). These results from Study 205 provide supportive evidence of efficacy, even though the results for the primary endpoint did not reach statistical significance at the 0.05 level.

**Figure 10: MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$ Endpoints: BUP/SAM vs Placebo Difference (Study 205)**



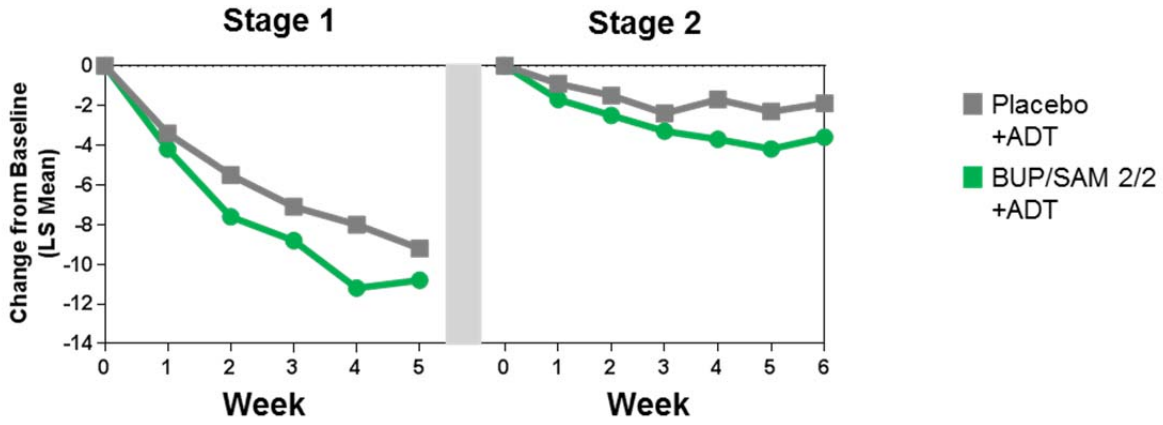

Abbreviations: ADT=antidepressant; AVG=average; BUP=buprenorphine; EOT=end of treatment; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.

### 5.2.3. Study 207

Study 207 was a Phase 3 randomized, placebo-controlled, multi-center SPCD study conducted at US and non-US which randomized 407 patients. Similar to the previous studies (202 and 205),

the BUP/SAM treatment group had greater improvement in change from baseline in MADRS-10 scores over time and within each stage compared to the placebo treatment group (Figure 11).

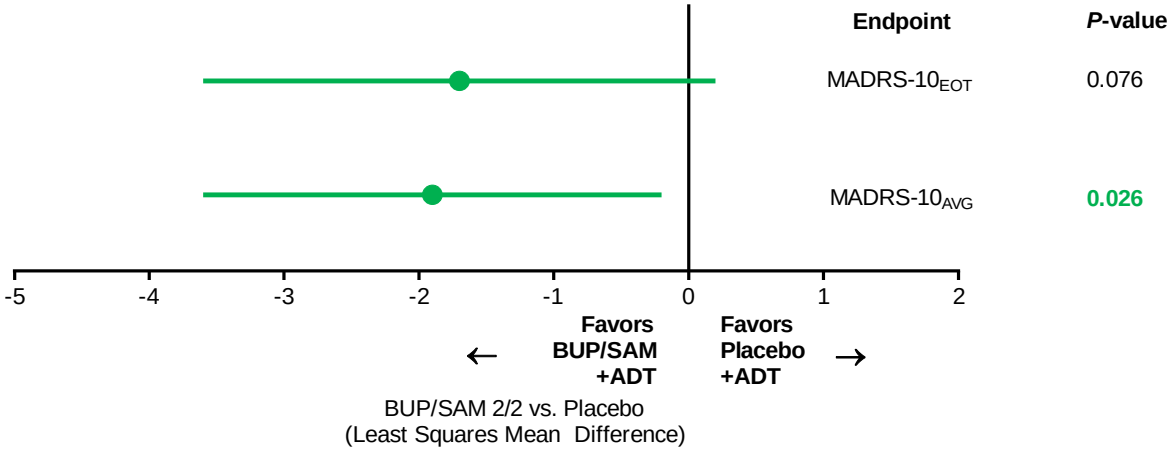
**Figure 11: MADRS-10 Change from Baseline by Treatment and Stage (Study 207)**




Abbreviations: ADT=antidepressant; BUP=buprenorphine; LS=least squares; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.

Results from the analysis using the common endpoints MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$ are presented in Figure 12. For MADRS-$10_{EOT}$, BUP/SAM 2/2 showed greater efficacy compared to placebo, with estimates favoring BUP/SAM; however, the endpoint narrowly missed significance at the 0.05 level (*P*=0.076). Results for MADRS-$10_{AVG}$ were consistent with the primary endpoint (MADRS-$6_{AVG}$), with estimates favoring BUP/SAM 2/2 over placebo (*P*=0.026 and 0.018 for MADRS-$10_{AVG}$ and MADRS-$6_{AVG}$, respectively). As described in Section 4.3.2, the common endpoints, MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$, were pre-specified and comprised part of the hierarchical primary endpoint.

**Figure 12: MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$ Endpoints: BUP/SAM vs Placebo Difference (Study 207)**

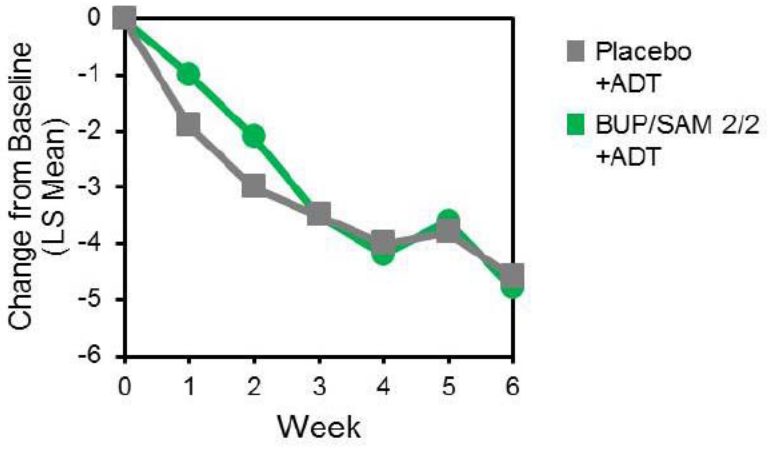



Abbreviations: ADT=antidepressant; AVG=average; BUP=buprenorphine; EOT=end of treatment; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.

### 5.2.4. Study 206

Study 206 was a Phase 3 randomized, placebo-controlled, multi-center placebo run-in study which randomized 297 patients in the efficacy population. Estimates of the difference between BUP/SAM vs placebo over time are presented in Figure 13. Study 206 pre-specified MADRS-$10_{EOT}$ as the primary endpoint.

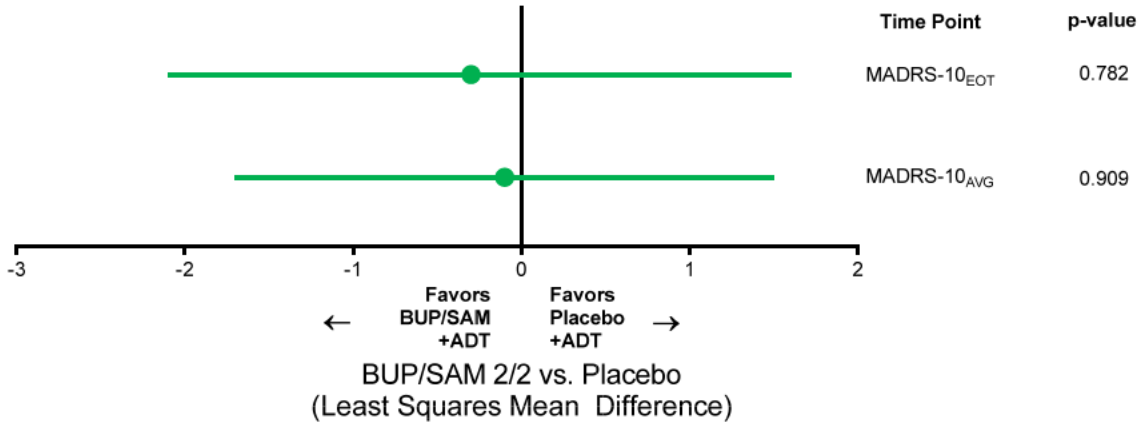
**Figure 13: MADRS-10 Change from Baseline by Treatment and Stage (Study 206)**




Abbreviations: ADT=antidepressant; BUP=buprenorphine; LS=least squares; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.

Results from the analysis using the common endpoints MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$ are presented in Figure 14. For both MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$, the estimates marginally favored BUP/SAM, but this difference was not statistically significant.

**Figure 14: MADRS-$10_{AVG}$ and MADRS-$10_{EOT}$ Endpoints: BUP/SAM vs Placebo Difference (Study 206)**



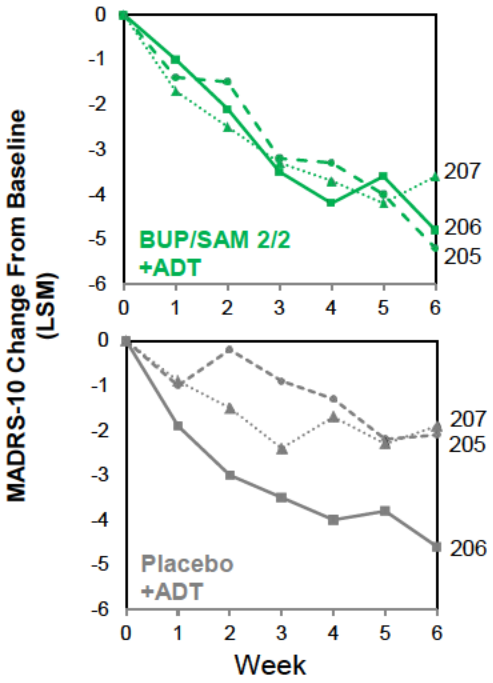

Abbreviations: ADT=antidepressant; AVG=average; BUP=buprenorphine; EOT=end of treatment; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.

The placebo response in this study was substantial. Although a placebo run-in stage was implemented in Study 206, it was of shorter duration (4 weeks in Study 206 vs 5 weeks in Studies 205 and 207) and was less effective in identifying placebo responders than Stage 1 of the

SPCD studies. Figure 15 presents results for MADRS-10 change from baseline over time in individual treatments arms (BUP/SAM and placebo) in Study 206 compared to the two other contemporaneous Phase 3 studies (205 and 207). For Studies 205 and 207, data shown are analogous to those shown for Study 206 and are from Stage 2 in patients who were placebo non-responders in Stage 1. The estimates of treatment effect are similar across all three studies (Figure 15: top panel). There is a consistent reduction in MADRS-10 scores which continues over the entire 6-week BUP/SAM 2/2 treatment period. In contrast, changes in MADRS-10 scores observed for the placebo treatment group were variable across studies, with the placebo response greatest in Study 206 (Figure 15: bottom panel). Comparison of BUP/SAM 2/2 and placebo across the 3 studies illustrates the impact of the strong, variable placebo response in Study 206 on the estimates of efficacy.

In addition to the variable magnitude of the placebo response across the three studies, week-to-week variability in the estimates in both BUP/SAM and placebo arms was observed. In Study 205, week-to-week variability contributed to the missed primary endpoint at Week 5, although there was nominal significance at end of treatment using Stage 2 Week 6. As a result of this observation, primary analysis in 207 employed statistical methods using the average of BUP/SAM vs placebo difference from multiple time points (Week 3 through end of treatment), as pre-specified in the statistical analysis plan.

**Figure 15: Difference Between BUP/SAM and Placebo Over Time (Stage 2): Phase 3 Studies 205, 206 and 207**

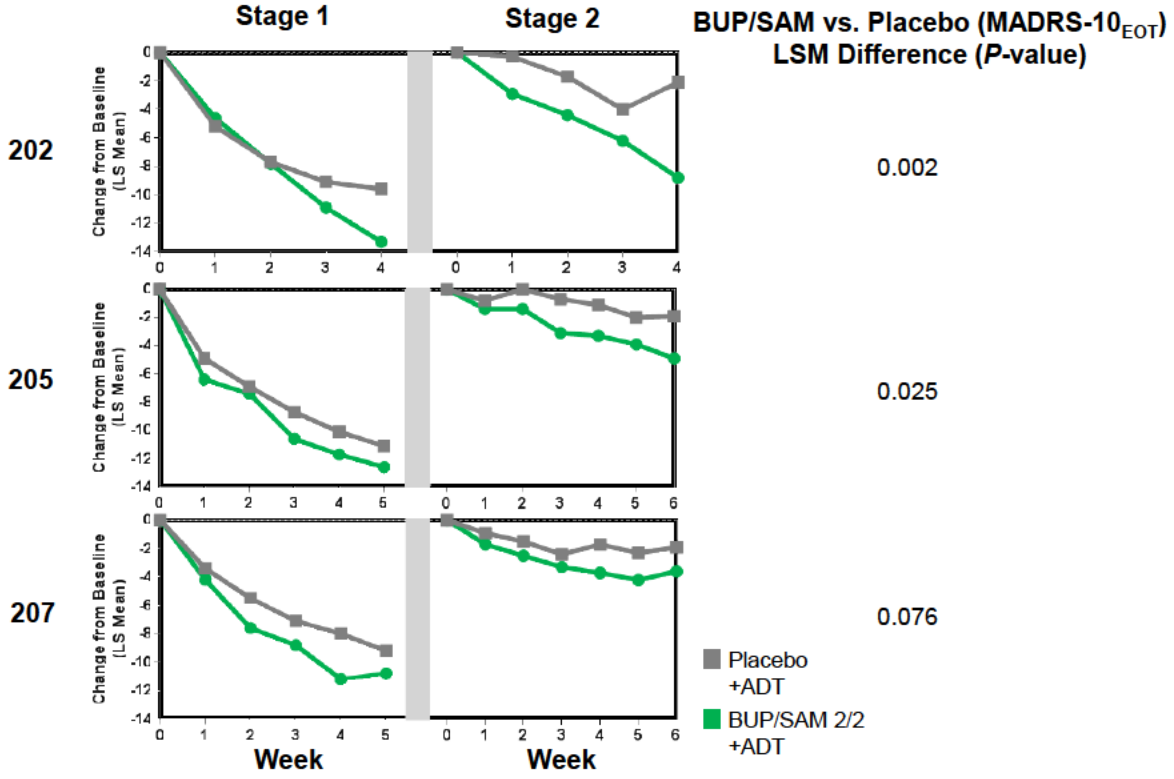



Abbreviations: ADT=antidepressant; BUP=buprenorphine; LSM=least squares mean; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.

### 5.2.5. MADRS-10 Scores Across SPCD Studies and Stages

Figure 16 presents MADRS-10 change from baseline over time for individual treatment arms for each stage from the three SPCD studies (202, 205, and 207). In six of the six randomizations, a greater change from baseline was observed with BUP/SAM 2/2 compared to placebo, demonstrating that the BUP/SAM treatment effect was consistently observed across stages as well as across studies.

**Figure 16: Consistent BUP/SAM Reduction vs Placebo in MADRS-10 Scores Across SPCD Studies**

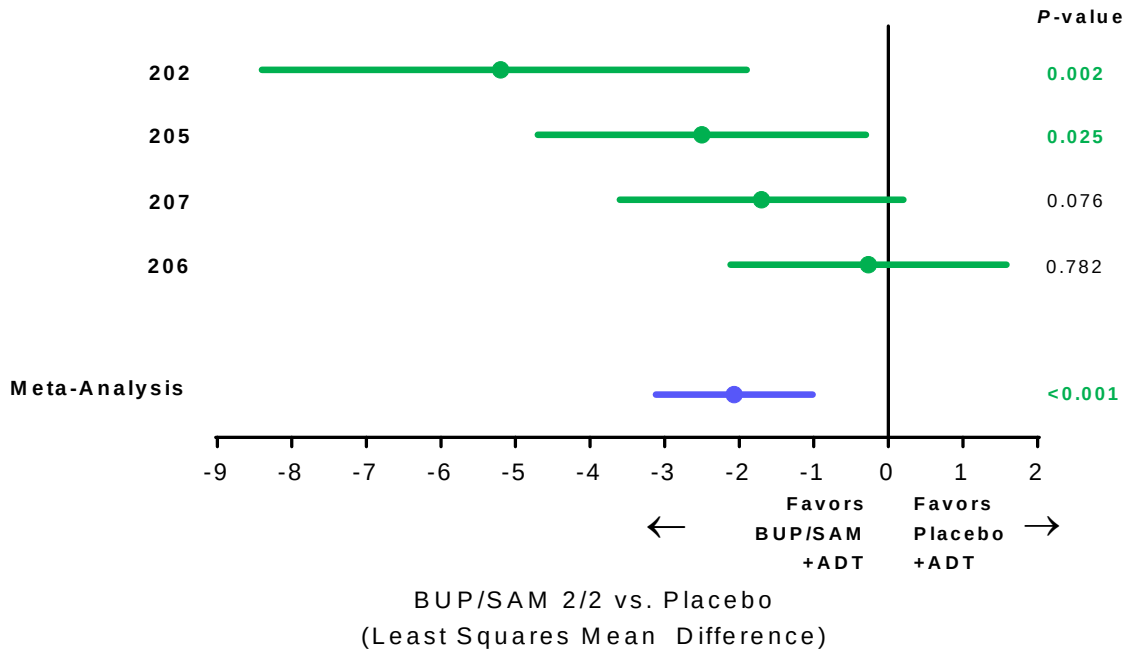



Abbreviations: ADT=antidepressant; BUP=buprenorphine; LSM=least squares mean; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.
Note: Only Stage 1 placebo non-responders are included in Stage 2. *P*-value is for the combined stage analysis of MADRS-$10_{EOT}$.

### 5.2.6. Common Endpoints Across Studies (MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$)

Using MADRS-10 end of treatment (MADRS-$10_{EOT}$) as the efficacy endpoint, three of the four studies resulted in the BUP/SAM difference vs placebo favoring BUP/SAM (Figure 17; Table 4). Two of the four studies (202 and 205) had values favoring BUP/SAM ($P$=0.002 and $P$=0.025, respectively) and one study narrowly missed the 0.05 threshold for significance (207; $P$=0.076). A meta-analysis of all four studies using the same MADRS-$10_{EOT}$ endpoint resulted in an estimate favoring BUP/SAM over placebo ($P$<0.001).

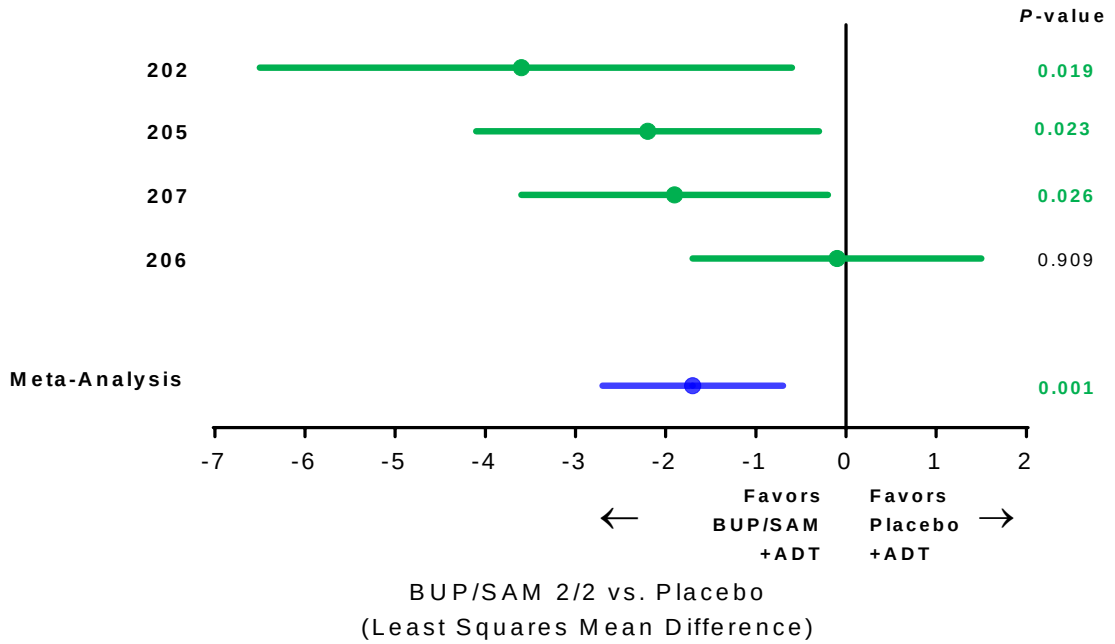
**Figure 17: Consistent BUP/SAM 2/2 Efficacy Across Studies (202, 205, 206, and 207): MADRS-10$_{EOT}$**




Abbreviations: ADT=antidepressant; BUP=buprenorphine; EOT=end of treatment; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan;

Using MADRS-10$_{AVG}$ as the efficacy endpoint, three of the four studies (202, 205, and 207) resulted in the BUP/SAM difference vs placebo favoring BUP/SAM (202; *P*=0.019, 205; *P*=0.023) including the second sequence primary endpoint for Study 207(*P*=0.026), (see Figure 18 and Table 4). The one study that did not have a substantial BUP/SAM vs placebo treatment difference was Study 206, the placebo run-in study. As discussed in Section 5.2.4, the placebo run-in design did not successfully address placebo response which impacted the ability to detect efficacy. A meta-analysis of all four studies using the MADRS-10$_{AVG}$ endpoint resulted in an estimate favoring BUP/SAM over placebo (*P*=0.001).

**Figure 18: Consistent BUP/SAM 2/2 Efficacy Across Studies (202, 205, 206, and 207): MADRS-10$_{AVG}$**




Abbreviations: ADT=antidepressant therapy; AVG=average; BUP=buprenorphine; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.

**Table 4: MADRS-10$_{EOT}$ and MADRS-10$_{AVG}$ (Studies 202, 205, 206, and 207)**

| | BUP/SAM 2/2 vs Placebo | | | |
|---|---|---|---|---|
| | **Study 202** | **Study 205** | **Study 206** | **Study 207** |
| **MADRS-10$_{EOT}$** | | | | |
| LSMD (SE) | -5.2 (1.66) | -2.5 (1.13) | -0.3 (0.95) | -1.7 (0.96) |
| 95% CI | (-8.4, -1.9) | (-4.7, -0.3) | (-2.1, 1.6) | (-3.6, 0.2) |
| *P*-value | 0.002 | 0.025 | 0.782 | 0.076 |
| **MADRS-10$_{AVG}$** | | | | |
| LSMD (SE) | -3.6 (1.52) | -2.2 (0.97) | -0.1 (0.80) | -1.9 (0.86) |
| 95% CI | (-6.5, -0.6) | (-4.1, -0.3) | (-1.7, 1.5) | (-3.6, -0.2) |
| *P*-value | 0.019 | 0.023 | 0.909 | 0.026 |
| **Number of Patients per Treatment Group and Stage** | | | | |
| BUP/SAM, Stage 1/Stage 2, n | 20/23 | 59/54 | NA/142 | 63/63 |
| Placebo, Stage 1/Stage 2, n | 95/20 | 256/54 | NA/146 | 273/60 |

Abbreviations: AVG=average; BUP=buprenorphine; CI=confidence interval; EOT=end of treatment; FAS=Full Analysis Set; LSMD=least squares mean difference; MADRS=Montgomery-Åsberg Depression Rating Scale; NA=not applicable; SAM=samidorphan; SE=standard error.

## 5.3. Efficacy Among Subgroups

Subgroup analysis was performed in the studies that provided evidence of efficacy.

### 5.3.1. Region (United States and Non-United States)

Studies 205 and 207 were global studies, and Study 202 was conducted in the US only. Efficacy analyses for US region only were performed across the studies to enable evaluation of consistency of efficacy in the same region of interest. Differences favoring BUP/SAM 2/2 over placebo were observed for MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$ in the US population across the three studies (202, 205, and 207), but not in the non-US population (Table 5). The reasons for differences in efficacy in the US and non-US subgroups cannot be known for certain. It is well established that there is variability in treatment response in different geographic regions in antidepressant clinical trials (Khin et al, 2011; Thase et al, 2016).

**Table 5: Change From Baseline in MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$, in the United States (Studies 202, 205, and 207)**

| | BUP/SAM 2/2 vs Placebo | | | | |
|---|---|---|---|---|---|
| | Study 202 | Study 205 | | Study 207 | |
| | US Study | US-only Subgroup | Non-US Subgroup | US-only Subgroup | Non-US Subgroup |
| **MADRS-$10_{EOT}$** | | | | | |
| LSMD | -5.2 | -3.5 | -1.1 | -2.4 | 0.2 |
| 95% CI | -8.4, -1.9 | -6.3, -0.8 | -6.2, 3.9 | -4.5, -0.3 | -4.2, 4.6 |
| *P*-value | 0.002 | 0.012 | 0.654 | 0.028 | 0.925 |
| **MADRS-$10_{AVG}$** | | | | | |
| LSMD | -3.6 | -2.7 | -0.8 | -2.7 | -0.1 |
| 95% CI | -6.5, -0.6 | -5.0, -0.3 | -5.1. 3.4 | -4.6, -0.8 | -4.0, 3.8 |
| *P*-value | 0.019 | 0.025 | 0.701 | 0.005 | 0.959 |
| **Number of Patients per Treatment Group and Stage** | | | | | |
| BUP/SAM, Stage 1/Stage 2, n | 20/23 | 51/43 | 8/11 | 52/52 | 11/11 |
| Placebo, Stage 1/Stage 2, n | 95/20 | 209/42 | 47/12 | 222/51 | 51/9 |

Abbreviations: AVG=average; CI=confidence interval; EOT=end of treatment; FAS=Full Analysis Set; LSMD=least squares mean difference; MADRS=Montgomery-Åsberg Depression Rating Scale; SE=standard error; US=United States.

Note: Analyses were based on stage-specific mixed models repeated measures where estimates from each stage were combined using equal weights of 0.5 for Stage 1 and 0.5 for Stage 2.

### 5.3.2. Other Subgroups

The therapeutic effect of BUP/SAM 2/2 was similar across subgroups of sex, age, race, severity of depression, duration of the current MDE, and the type of background ADT used to treat the current MDE. Subgroup analysis based on the number of inadequate ADT responses (2 inadequate responses compared to 1 inadequate response) suggested that patients with 2 inadequate responses might have had greater efficacy; however, this trend was not statistically significant and was limited due the size of the subgroup (10-20% of the population, depending on study).

## 5.4. Standardized Effect Size

The Hedges' g measure of effect size provides a standardized estimate of the magnitude of the difference in outcomes between groups and is helpful when comparing treatment effects across studies and across compounds. The Hedges' g measure is the LSMD divided by the pooled and weighted standard deviation. To evaluate the clinical significance of the magnitude of the treatment effect with BUP/SAM 2/2, effect sizes were estimated. The effect size was variable across Studies 202, 205, and 207 and ranged from 0.20 to 0.62 (0.20-0.62 based on MADRS-$10_{EOT}$ and 0.25-0.47 based on MADRS-$10_{AVG}$) (Table 6). Consistent with results from the primary efficacy analysis, effect size estimates in Study 206 did not support appreciable efficacy.

**Table 6: Summary of Standardized Effect Sizes, Stage 1 and Stage 2 Full Analysis Set (Studies 202, 205, and 207)**

| | BUP/SAM 2/2 vs Placebo | | | |
|---|---|---|---|---|
| | **Study 202** | **Study 205** | **Study 206** | **Study 207** |
| **MADRS-$10_{EOT}$** | | | | |
| Effect Size[a] | 0.62 | 0.28 | 0.01 | 0.20 |
| 95% CI | (0.23, 1.02) | (0.05, 0.52) | (-0.22, 0.24) | (-0.02, 0.43) |
| **MADRS-$10_{AVG}$** | | | | |
| Effect Size[a] | 0.47 | 0.28 | 0.01 | 0.25 |
| 95% CI | (0.07, 0.86) | (0.05, 0.52) | (-0.22, 0.24) | (0.03, 0.48) |

Abbreviations: AVG=average; BUP=buprenorphine; CI=confidence interval; EOT=end of treatment; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan

[a] Hedges' g was used to estimate effect size. The combined stage Hedges' g is defined as the average of stage-specific Hedges' g.

The effect sizes vs placebo (Hedges' g) for BUP/SAM 2/2 are consistent with those reported in the literature for approved adjunct antipsychotics for MDD, with meta-analyses ranging from 0.23 to 0.40 (Yoon et al, 2017).

## 5.5. Response and Remission Rates in Placebo-controlled Studies

Response and remission are commonly evaluated in depression studies and are desirable outcomes with long-term treatment of MDD (Kupfer 1991; Rush et al, 2006). They may also be evaluated in placebo-controlled studies that are of shorter duration. Rates of remission (MADRS-10 score ≤10) and response (MADRS-10 change from baseline >50%) were examined

as secondary, exploratory, or post-hoc endpoints across the four placebo-controlled studies. Post-hoc analysis of Study 202 data, which combined estimates across stages, demonstrated statistically significant differences between BUP/SAM 2/2 vs placebo at end of treatment for both rates of remission and response (P=0.028 and 0.005, respectively) but statistically significant results were not observed in the other studies. The observation of statistical significance in Study 202 may be due to the greater magnitude of effect vs placebo observed on MADRS-$10_{EOT}$ in this study.

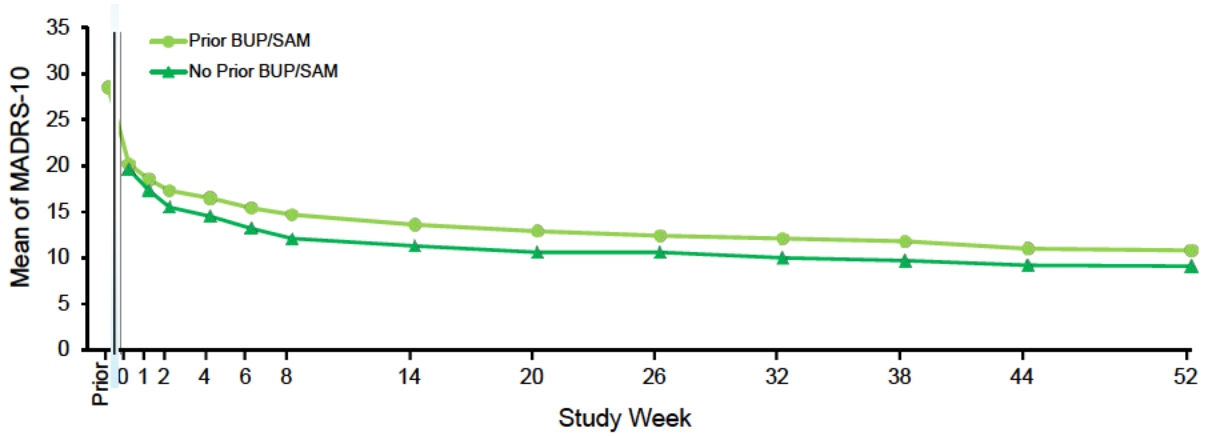
## 5.6. Efficacy Evaluation in Long-term Study

### 5.6.1. Durability of Effect

Durability of effect was assessed in Study 208. Efficacy assessments were made at each visit during the 1-year study. Figure 19 displays the mean changes from baseline in MADRS-10 score over time, with "baseline" defined as when each patient initiated BUP/SAM. Thus, baseline may have occurred in a prior BUP/SAM study (205, 206, 207, or 210) or at the start of Study 208.

Mean MADRS-10 scores show sustained improvement in depressive symptoms over the course of treatment. Improved mean MADRS-10 scores were maintained over the course of the year.

**Figure 19: Durability of Effect for Patients Who Continued Treatment**




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Prior BUP/SAM, n | 524 | 513 | 488 | 445 | 404 | 376 | 351 | 330 | 312 | 292 |
| No Prior BUP/SAM, n | 898 | 827 | 769 | 700 | 620 | 564 | 535 | 501 | 468 | 445 |

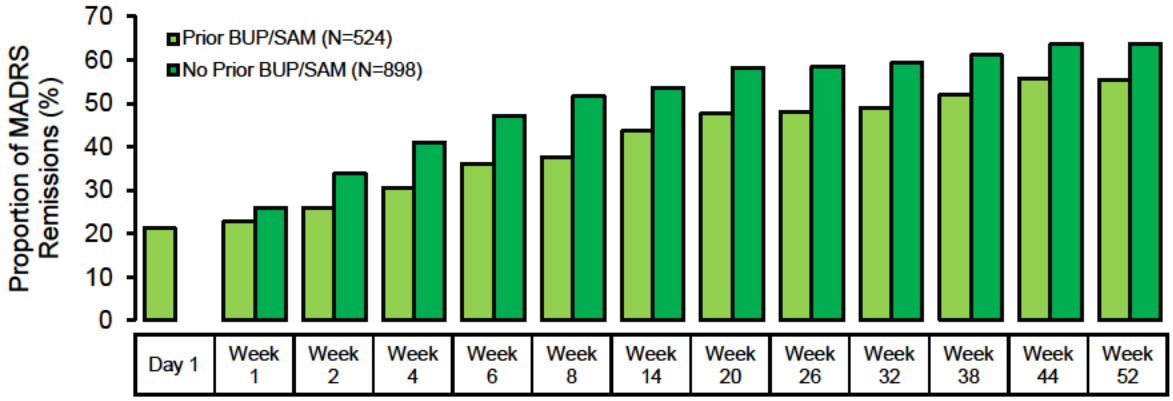
Abbreviations: BUP=buprenorphine; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan
Notes: Baseline was defined as the last non-missing assessment made on or before time of BUP/SAM initiation during either an antecedent study or Study 208. "-1" on the x-axis indicates baseline in the antecedent studies. "0" indicates Visit 2 (baseline) in Study 208 for patients who did not have any prior BUP/SAM exposure in an antecedent study.

### 5.6.2. Remission Rate

Within the long-term safety study (208), the proportion of patients who were in remission (MADRS-10 score ≤10) during each visit is presented in Figure 20 (observed cases). Remission rates increased markedly for patients during the initial weeks of Study 208. The median time to remission overall was 99 days. These analyses demonstrate that efficacy of BUP/SAM 2/2

matures over time. By the end of the study, 60.5% of all patients continuing treatment were in remission. Similar results were observed when analysis was based on Last Observation Carried Forward (LOCF), with 55.1% and 47.9% achieving remission with BUP/SAM and No Prior BUP/SAM, respectively.

**Figure 20: Remission Rate (MADRS-10 Score of ≤10) Over a 1-Year Treatment Period**




| | Day 1 | Week 1 | Week 2 | Week 4 | Week 6 | Week 8 | Week 14 | Week 20 | Week 26 | Week 32 | Week 38 | Week 44 | Week 52 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Prior Study N=524** | 524 | 524 | 519 | 513 | 503 | 488 | 445 | 404 | 376 | 351 | 330 | 312 | 292 |
| **Extension Study N=898** | - | 898 | 856 | 827 | 801 | 769 | 700 | 620 | 564 | 535 | 501 | 468 | 445 |

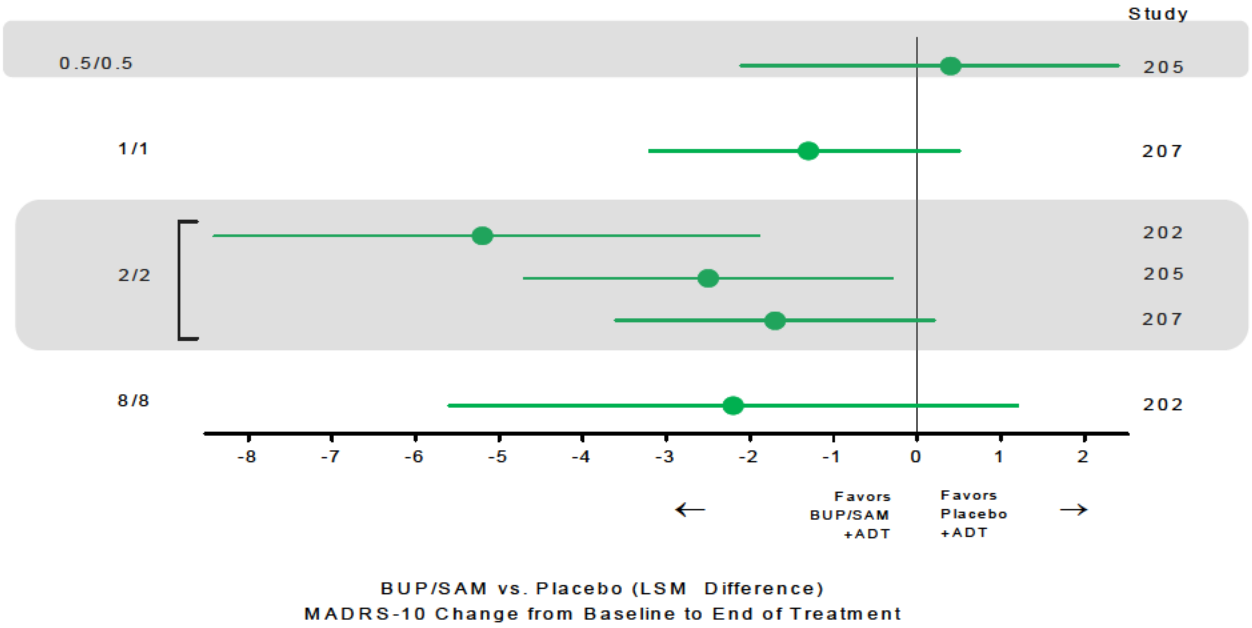
Abbreviation: BUP=buprenorphine; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan
Note: Baseline was defined as the last nonmissing assessment made on or before the time of BUP/SAM initiation during either an antecedent study or Study 208.
Note: For patients initiating BUP/SAM in Study 208, baseline was Visit 2.

## 5.7. Dose Response

In studies 202, 205, and 207 a second BUP/SAM dose (BUP/SAM 8/8, 0.5/0.5 and 1/1, respectively) was evaluated in addition to the therapeutic dose of BUP/SAM 2/2. Primary efficacy results from these other doses are available in Table 15.

Figure 21 presents the change from baseline in MADRS-$10_{EOT}$ for BUP/SAM 0.5/0.5 (205), BUP/SAM 1/1 (207), BUP/SAM 2/2 (202, 205, and 207) and BUP/SAM 8/8 (202). BUP/SAM 2/2 produced the greatest treatment effect, followed by BUP/SAM 1/1. BUP/SAM 0.5/0.5 was similar to placebo. Study 202 evaluated a higher dose (BUP/SAM 8/8) along with BUP/SAM 2/2 and placebo. Results indicated that BUP/SAM 2/2 had a favorable tolerability profile (Section 6.1.5.1) and that BUP/SAM 8/8 offered no additional benefit. Given that BUP/SAM 2/2 was identified as the lowest and effective dose in Study 202, subsequent studies evaluated efficacy of BUP/SAM 2/2 and lower doses. Collectively, these findings support BUP/SAM 2/2 as the therapeutic dose.

**Figure 21: BUP/SAM vs Placebo Difference: Change From Baseline in MADRS-$10_{EOT}$ (Studies 202, 205, and 207)**




Abbreviations: ADT=antidepressant; BUP=buprenorphine; CI=confidence interval; EOT=end of treatment; LSM=least squares mean; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan.
Note: Error bars represent 95% confidence intervals.
Note: The pooled results are from the pooled 205 and 207 population.

## 5.8. Efficacy Conclusions

Three of four studies (202, 205 and 207) provided evidence of efficacy. Two studies (202 and 207) were statistically significant for the pre-specified primary endpoints (HAMD-17 and MADRS-$6_{AVG}$, respectively). Studies 205 and 206 did not meet their primary endpoints (MADRS-$10_{Week\ 5}$ and MADRS-$10_{EOT}$, respectively). However, Study 205 did provide support of efficacy, while Study 206 failed to achieve its primary efficacy endpoint due to a high placebo response.

An efficacy comparison across studies was conducted using two common endpoints, MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$. MADRS-$10_{EOT}$ for two studies (202 and 205) and MADRS-$10_{AVG}$ for three studies (202, 205, and 207) had significant *P*-values. A meta-analysis combining data from all four studies (202, 205, 206, and 207) demonstrated statistically significant improvement from placebo for both common endpoints (MADRS-$10_{EOT}$ and MADRS-$10_{AVG}$). Efficacy was demonstrated to have a durable effect over a 1-year treatment period in a long-term open-label safety study (208).

# 6. SAFETY

The safety profile of BUP/SAM is derived from 2165 subjects exposed to BUP/SAM across 19 studies; 1860 subjects received the therapeutic dose of 2/2, including 1531 patients with MDD. Of these, 947 patients received BUP/SAM for at least 6 months and 743 patients for at least 1 year. The total MDD patient exposure was >1100 years.

**Summary**

- The most common AEs were gastrointestinal or sedation-related, typically mild/moderate in severity, occurred with treatment initiation, and resolved with continued treatment.
- In the placebo-controlled MDD studies, serious AEs (SAEs) were infrequent with no identified SAE pattern and none were fatal. Incidence of SAEs observed in the long-term safety study was similar to the placebo-controlled studies.
  - Other than MDD-associated events, the only SAE attributed to treatment was one event of acute opioid withdrawal following first dose of BUP/SAM in a patient who had not disclosed pre-existing opioid dependence.
  - There were 2 deaths in the long-term study, both assessed as not related to study medication by the investigator.
- No clinically meaningful changes in laboratory, vital signs, weight, or electrocardiogram (ECG) changes were observed. There was no evidence of QT prolongation in a dedicated thorough QT study.
- BUP/SAM treatment was not associated with metabolic disturbances or motor disorders, which are key safety concerns of atypical antipsychotics.
- BUP/SAM treatment was not associated with, respiratory depression, hypotension/orthostatic hypotension or hepatic injury, which are AEs commonly associated with opioids.
- Review of BUP/SAM treatment emergent adverse events (TEAEs) showed no evidence of hypomania/mania, sexual dysfunction or increased risk of suicidal ideation or behavior, which have been associated with other antidepressants.
- BUP/SAM abuse potential is low.
  - A dedicated human abuse potential study demonstrated that abuse potential with BUP/SAM 2/2 is similar to placebo;
    - 4- to 8-fold the therapeutic dose of BUP/SAM showed slightly greater abuse potential than placebo and significantly less than equivalent doses of BUP alone
  - MDD data were consistent and demonstrated;
    - Low incidences of euphoria, typically with first dose/none recurrent
    - No evidence of dependence during treatment

- Little evidence of withdrawal with abrupt discontinuation
- Abrupt discontinuation was well-tolerated

# 6.1. General Safety

## 6.1.1. Overview

The clinical studies from the BUP/SAM development program provide a comprehensive safety database that supports the overall safety profile of BUP/SAM. Safety data for BUP, along with two additional development programs in which SAM was studied as a single entity and in combination with olanzapine (ALKS 3831), serve as supplemental data in the safety assessment of BUP/SAM.

The BUP/SAM development program is comprised of 19 completed studies including one long-term safety study. There are an additional 15 studies of SAM alone or SAM combined with olanzapine.

## 6.1.2. Pooled Safety Evaluation

The study designs of the four placebo-controlled studies (202, 205, 206, and 207) evaluating adjunctive BUP/SAM in patients with MDD continuing their existing ADT are sufficiently similar to allow pooling for evaluation of safety. Pooling data increases the ability to observe potential safety differences between the intended therapeutic dose of BUP/SAM (2/2) and placebo. Studies 202, 205, and 207 used SPCD and had two stages where randomization occurred. The 5-week treatment period used for Stage 1 and Stage 2 safety evaluation of Study 202 included the 4-week efficacy treatment period and the following 1 week drug taper period. Although not a SPCD study, Study 206 was a two-stage design suitable for pooling with the other placebo-controlled studies (see Section 4.1.2). The Phase 3 program also included Studies 208 (year-long safety study) and Study 210 (to evaluate titration schedule in patients). Studies 208 and 210 were excluded from pooling due to differences in study design, including lack of a placebo arm (for study details see Table 14).

Studies 205, 206, and 207 had comparable duration of continuous treatment (10-11 weeks across both stages) followed by abrupt discontinuation of study drug and comparable off-drug follow-up (post-discontinuation) periods. The post-discontinuation period (post-last dose until the follow-up visit) of these three studies were also pooled to evaluate safety following study drug discontinuation. In contrast, Study 202 was excluded from the post-discontinuation pooling since patients did not abruptly discontinue, but were tapered off study drug, making the data unsuitable for pooled evaluation of potential withdrawal symptoms.

The three poolings of safety data (Stage 1 Period, Stage 2 Period, and Post-discontinuation Period) were further defined as follows:

1. Stage 1 Pooled Safety Population:
   - Stage 1 randomized patients from Studies 202, 205, 206, and 207
   - Received at least one dose of study drug (BUP/SAM or placebo) during the Stage 1 Period
   - 5 weeks of treatment following Stage 1 randomization

2. Stage 2 Pooled Safety Population:
    - Stage 2 randomized patients from Studies 202, 205, 206, and 207
    - Received at least one dose of study drug (BUP/SAM or placebo) during the Stage 2 Period
    - 5 or 6 weeks of treatment following Stage 2 randomization
3. Post-discontinuation Pooled Safety Population:
    - Patients in Studies 205, 206, and 207 who entered the Post-discontinuation Period following abrupt discontinuation of study drug
    - Received at least one randomized dose of study drug during double-blind treatment period

### 6.1.3. Summary of Demographic and Baseline Characteristics

Baseline demographic characteristics in the BUP/SAM clinical studies conducted in MDD (202, 205, 206, 207, 208, and 210) were similar across studies, as well as treatment groups, and were consistent with the intended patient population for whom BUP/SAM would be prescribed if approved. The majority of patients in these safety populations were female, White, and taking SSRIs, with a mean age of 43.3 to 49.7 years (depending on the treatment group).

**Stage 1: Demographics**

Demographic and baseline characteristics for the patients included in the Stage 1 Pooled Safety population are summarized in Table 16.

In the Stage 1 Pooled Safety population, 162 patients were randomized to BUP/SAM 2/2 and 658 patients were randomized to placebo:

- The majority of patients were female (66.0%), White (73.5%), and from the US (87.7%).
- Mean age was 44.9 years (range: 18-69 years).
- Mean body mass index (BMI) was 29.5 $kg/m^2$ (range: 18.3-40.0 $kg/m^2$).
- Baseline ADT use included 64.2% of patients taking SSRIs, 27.2% taking SNRIs, and 8.6% taking other ADTs (predominantly bupropion).
- Small proportions of patients reported some use of central nervous system (CNS) depressants during treatment, including benzodiazepines (11.1%), opioids (intermittent use; 3.1%), or sedating H1 antagonists (2.5%).

Demographics and baseline characteristics were comparable in the placebo group (658 patients) and other BUP/SAM dose groups (0.5/0.5, 1/1, and 8/8), with the following exception:

- The BUP/SAM 8/8 group included only patients from the US, as Study 202 (the only study with 8/8) was performed in the US only.

**Stage 2: Demographics**

The Stage 2 Pooled Safety population included 289 patients randomized to BUP/SAM 2/2, 286 patients randomized to placebo, and 140 patients randomized to other BUP/SAM doses (0.5/0.5, 1/1, or 8/8). Demographics and baseline characteristics were consistent with the Stage 1 Pooled Safety population.

### 6.1.4. Exposure

A total of 2165 subjects have been exposed to BUP/SAM across 19 clinical studies; 1860 subjects have received the therapeutic dose of 2/2, including 1531 patients with MDD. Of these, 947 patients received BUP/SAM for at least 6 months and 743 patients for at least 1 year.

A total of 1715 patients with MDD have received at least one dose (range: 0.5/0.5 to 8/8) of BUP/SAM. This includes:

- 732 patients in the placebo-controlled studies (202, 205, 206, and 207)
- 66 patients in the dose titration study (210)
- 917 patients in the long-term study (208) who had no prior exposure to BUP/SAM

### 6.1.5. Safety Profile

#### 6.1.5.1. Frequency of Common Adverse Events

TEAEs reported by ≥2% of patients in the BUP/SAM 2/2 group and greater than placebo in the Stage 1 and Stage 2 Pooled Safety populations are summarized in Table 7. During the Stage 1 Treatment Period, 68.5% of patients in the BUP/SAM 2/2 group and 54.4% of patients in the placebo group experienced at least one TEAE. Stage 1 study drug-related TEAEs with an incidence of ≥5% of patients in the BUP/SAM 2/2 treatment group and at an incidence higher than placebo were nausea, constipation, dizziness, vomiting, headache, fatigue, sedation, somnolence, and dry mouth. TEAEs reported in Stage 2 were consistent with AEs reported in Stage 1, although overall incidence rates in both BUP/SAM and placebo groups were lower in Stage 2.

**Table 7: Treatment-Emergent Adverse Events in ≥2% of Patients Treated with BUP/SAM 2/2 and a Greater Incidence Than in Placebo-Treated Patients by System Organ Class and Preferred Term – Stage 1 and Stage 2**

| System Organ Class<br>Preferred Term, n (%) | Stage 1 | | Stage 2 | |
|---|---|---|---|---|
| | BUP/SAM 2/2 (N=162) | Placebo (N=658) | BUP/SAM 2/2 (N=289) | Placebo (N=286) |
| Any TEAE | 111 (68.5) | 358 (54.4) | 137 (47.4) | 119 (41.6) |
| **Gastrointestinal disorders** | **69 (42.6)** | **135 (20.5)** | **68 (23.5)** | **26 (9.1)** |
| Nausea | 43 (26.5) | 46 (7.0) | 36 (12.5) | 5 (1.7) |
| Constipation | 20 (12.3) | 18 (2.7) | 11 (3.8) | 2 (0.7) |
| Vomiting | 16 (9.9) | 11 (1.7) | 14 (4.8) | 4 (1.4) |
| Dry mouth | 10 (6.2) | 29 (4.4) | 7 (2.4) | 4 (1.4) |
| **Nervous system disorders** | **51 (31.5)** | **116 (17.6)** | **40 (13.8)** | **22 (7.7)** |
| Dizziness | 21 (13.0) | 27 (4.1) | 9 (3.1) | 6 (2.1) |
| Headache | 17 (10.5) | 59 (9.0) | 10 (3.5) | 13 (4.5) |
| Somnolence | 11 (6.8) | 22 (3.3) | 3 (1.0) | 1 (0.3) |
| Sedation | 11 (6.8) | 6 (0.9) | 4 (1.4) | 0 |
| **Psychiatric disorders** | **29 (17.9)** | **53 (8.1)** | **15 (5.2)** | **11 (3.8)** |
| Abnormal dreams | 5 (3.1) | 12 (1.8) | 1 (0.3) | 1 (0.3) |
| Insomnia | 6 (3.7) | 10 (1.5) | 3 (1.0) | 2 (0.7) |
| Anxiety | 4 (2.5) | 7 (1.1) | 2 (0.7) | 3 (1.0) |
| **General disorders and administration site conditions** | **25 (15.4)** | **23 (3.5)** | **15 (5.2)** | **12 (4.2)** |
| Fatigue | 12 (7.4) | 10 (1.5) | 10 (3.5) | 6 (2.1) |
| **Skin and subcutaneous tissue disorders** | **14 (8.6)** | **28 (4.3)** | **14 (4.8)** | **4 (1.4)** |
| Hyperhidrosis | 6 (3.7) | 15 (2.3) | 8 (2.8) | 0 |
| **Infections and infestations** | **14 (8.6)** | **75 (11.4)** | **24 (8.3)** | **36 (12.6)** |
| Upper respiratory tract infection | 4 (2.5) | 12 (1.8) | 6 (2.1) | 10 (3.5) |
| **Metabolism and nutrition disorders** | **7 (4.3)** | **15 (2.3)** | **4 (1.4)** | **6 (2.1)** |
| Decreased appetite | 5 (3.1) | 6 (0.9) | 3 (1.0) | 2 (0.7) |

Abbreviation: BUP=buprenorphine; SAM=samidorphan; TEAE=treatment-emergent adverse event.

Table 19 and Table 20 list TEAEs in ≥2% of patients treated with BUP/SAM 2/2 and a greater incidence than in placebo-treated patients by system organ class (SOC) and preferred term (PT), Stage 1 and Stage 2, respectively, for all doses tested.

Subgroup analyses showed no clinically meaningful differences in the incidence in TEAEs across gender, age, race, background ADT type, or benzodiazepine use.

The long-term study with BUP/SAM 2/2 demonstrated a similar safety profile to that observed in the placebo-controlled studies.

### 6.1.5.2. Adverse Events Leading to Discontinuation

The incidences of AEs leading to discontinuation were low overall and numerically higher with BUP/SAM 2/2 relative to placebo. Nausea, vomiting, and dizziness were the most frequently reported AEs leading to study discontinuation in the BUP/SAM 2/2 group. During Stage 1, 22 patients (13.6%) in the BUP/SAM 2/2 group and 13 patients in the placebo group (2.0%) discontinued study participation due to an AE (Table 8). Events from the gastrointestinal (GI) disorders SOC and nervous system disorders SOC were the most common AEs resulting in discontinuation, and were reported more frequently with BUP/SAM 2/2 (7.4% and 4.9%, respectively) than placebo (0.3% and 0.6%, respectively). Incidences of AEs leading to discontinuation were lower in Stage 2. Incidences of AEs leading to discontinuation were similar in the placebo-controlled studies and the long-term study.

**Table 8: Adverse Events Leading to Study Discontinuation Reported in ≥2 Patients in the BUP/SAM 2/2 or Placebo Group - Stage 1 Pooled Safety Population**

| System Organ Class<br>Preferred Term, n (%) | Placebo (N=658) | BUP/SAM Dose | | | | |
|---|---|---|---|---|---|---|
| | | 0.5/0.5 (N=59) | 1/1 (N=63) | 2/2 (N=162) | 8/8 (N=19) | Any (N=303) |
| Any AE | 13 (2.0) | 4 (6.8) | 5 (7.9) | 22 (13.6) | 5 (26.3) | 36 (11.9) |
| **Gastrointestinal disorders** | **2 (0.3)** | **1 (1.7)** | **2 (3.2)** | **12 (7.4)** | **2 (10.5)** | **17 (5.6)** |
| Nausea | 2 (0.3) | 0 | 2 (3.2) | 8 (4.9) | 0 | 10 (3.3) |
| Vomiting | 0 | 1 (1.7) | 0 | 5 (3.1) | 2 (10.5) | 8 (2.6) |
| Abdominal pain | 0 | 0 | 0 | 2 (1.2) | 0 | 2 (0.7) |
| **Nervous system disorders** | **4 (0.6)** | **2 (3.4)** | **1 (1.6)** | **8 (4.9)** | **1 (5.3)** | **12 (4.0)** |
| Dizziness | 0 | 0 | 0 | 5 (3.1) | 0 | 5 (1.7) |
| Headache | 3 (0.5) | 1 (1.7) | 1 (1.6) | 1 (0.6) | 0 | 3 (1.0) |
| Somnolence | 2 (0.3) | 1 (1.7) | 0 | 1 (0.6) | 0 | 2 (0.7) |
| **Psychiatric disorders** | **4 (0.6)** | **0** | **1 (1.6)** | **4 (2.5)** | **0** | **5 (1.7)** |
| Insomnia | 2 (0.3) | 0 | 0 | 2 (1.2) | 0 | 2 (0.7) |
| Irritability | 0 | 0 | 0 | 2 (1.2) | 0 | 2 (0.7) |

Abbreviations: AE=adverse event; BUP=buprenorphine; SAM=samidorphan.

### 6.1.5.3. Serious Adverse Events

Serious adverse events (SAEs) were infrequent in the placebo-controlled studies and were reported at similar incidence in the BUP/SAM 2/2 and placebo groups (<2.0%); none were fatal. No pattern of SAEs with BUP/SAM 2/2 was observed in the placebo-controlled studies. There were 10 patients total with SAEs, 4 patients on BUP/SAM 2/2 and 6 patients on placebo. There

was one related SAE in Study 202, of acute opioid withdrawal precipitated by the first dose of BUP/SAM in an opioid-dependent patient who had not disclosed opioid use at the time of study entry.

In the long-term study, a total of 46 patients (3.2%) reported an SAE during the Study 208 Treatment Period, the most common being MDD disease-related events (depression and suicidal ideation, each 3 patients, 0.2%). There were two deaths, assessed as unrelated (see Section 6.1.5.4).

Three patients from the long-term study had events judged by the Investigator as at least possibly treatment-related (relapse of MDD, suicide attempt, and major depression with psychotic features).

#### 6.1.5.4. Deaths

Within the BUP/SAM clinical development program, there were two deaths, both in the long-term study (208):

- One patient died from respiratory arrest 47 days after the last reported dose of BUP/SAM.
- One patient died from a cerebral hemorrhage on Day 87 of BUP/SAM treatment. The patient had a history of hypertension, chronic heart failure functional class II and a family history of cerebral hemorrhage.

Given the sequence of the event to treatment, and the underlying medical history, neither event was judged to be treatment-related.

#### 6.1.5.5. Adverse Events of Special Interest

Adverse events of special interest (AESIs) were selected based on class effects that have been reported with BUP. These include CNS depression and sedation, respiratory depression, hypotensive and orthostatic hypotensive events, QT prolongation, hypersensitivity, hepatic effects, and potential for abuse, dependence, or withdrawal. Additionally, AEs associated with MDD or ADT therapy were assessed, including suicidal ideation and behavior, hypomania/mania, and sexual dysfunction. AESIs to evaluate abuse potential are discussed in Section 6.2.2.1. Dependence and withdrawal are discussed in Section 6.2.2.2.

In the pooled placebo-controlled studies:

- CNS depression and sedation events (namely sedation and somnolence) were more frequently reported in patients with BUP/SAM 2/2 relative to placebo. Most were mild or moderate in severity, occurred with initiation of treatment, and resolved with continued BUP/SAM treatment.
- There was no evidence of increased risk of respiratory depression, consistent with evaluations of respiratory rate and AEs across studies.
- There was no evidence of increased risk of hypotensive or orthostatic hypotensive events based on review of AEs, as well as evaluations of blood pressure.
- There was no evidence of increased risk of QTc prolongation, consistent with the negative thorough QT study (213; see Section 6.1.5.8).

- There was no evidence of increased risk of hepatic injury (safety concerns associated with BUP alone), based on review of AESIs, as well as laboratory data.
- There was no evidence of increased risk of suicidal ideation or behavior with BUP/SAM based on review of AESIs. Incidences of suicidal ideation and behavior assessed by Columbia-Suicide Severity Scale (C-SSRS) were lower with BUP/SAM 2/2 compared to placebo both in Stage 1 and Stage 2 treatment periods.
- There was no evidence of increased risk of hypomania/mania, hypersensitivity, or sexual dysfunction with the use of BUP/SAM compared to placebo with ADT.

In Study 208 (long-term safety):

- Long-term administration of open-label BUP/SAM 2/2 was associated with an AESI profile similar to what was observed with BUP/SAM 2/2 in the Stage 1 Pooled Safety population of the placebo-controlled studies.

#### 6.1.5.6. Clinical Laboratory Evaluations

Treatment with BUP/SAM 2/2 in comparison to placebo in Stage 1 and Stage 2 was not associated with clinically meaningful mean changes from baseline in the chemistry analytes[b], hematological parameters[c], or urinalysis[d] assayed over the course of treatment. Outlier analyses of these chemistry analytes or hematological parameters likewise did not reveal clinically meaningful differences in incidences between BUP/SAM 2/2 and placebo. Of the chemistry analytes, BUP/SAM treatment was not associated with disturbances in metabolic analytes. In addition, treatment-emergent outlier analyses of urinalysis[e] did not reveal excess incidences with drug. Similarly, clinical laboratory review from the long-term safety study also did not demonstrate clinically meaningful differences between treatment groups.

#### 6.1.5.7. Electrocardiogram Parameters

No clinically meaningful trends were seen in ECG parameters over time, and no significant differences were observed between treatment groups.

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[b] Sodium, chloride, potassium, bicarbonate, calcium, phosphorus, magnesium, blood urea nitrogen, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase, total bilirubin, total protein, albumin, random glucose, HbA1c, random total cholesterol, random low density lipoprotein (LDL), random high-density lipoprotein (HDL), random triglycerides, uric acid, creatine kinase (CK), lactate dehydrogenase (LDH), and prolactin.
[c] Red blood cell, hematocrit, hemoglobin, white blood cell, neutrophils, lymphocytes, monocytes, eosinophils or basophils.
[d] Urine specific gravity or pH.
[e] Urine specific gravity, pH, glucose, and protein

#### 6.1.5.8. Effects of QT Interval

In a thorough QT study (213) designed in accordance with the FDA Guidance (Center for Drug Evaluation and Research 2005), BUP/SAM titrated to a supratherapeutic dose of 8/8 (four times the intended therapeutic dose) did not prolong the QT interval and was not associated with any other abnormalities of cardiac repolarization. Additionally, there was no relationship evident between plasma parent or metabolite concentrations and the ΔΔQTcF based on linear mixed-effects modeling. The projected QTcF change at the mean maximal concentration ($C_{max}$) of BUP/SAM for the supratherapeutic dose (ie, 8/8) was less than 3 msec, and the maximum one-sided 95% confidence interval (CI) was 4.23 msec. For more information on Study 213 see Table 14.

#### 6.1.5.9. Vital Signs (Heart Rate, Blood Pressure, Respiratory Rate, Body Temperature, and Body Weight)

Vital sign parameters (heart rate, blood pressure, respiratory rate, and temperature) and weight were recorded for patients with MDD in the clinical studies of BUP/SAM.

There were no clinically meaningful mean changes from baseline over time in vital signs or weight between treatment groups. The incidences of treatment-emergent outliers for these parameters were similar between treatment groups.

#### 6.1.5.10. Suicidal Ideation and Behavior

There was no evidence of increased treatment-emergent suicidal ideation or behavior with adjunctive BUP/SAM as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) scores in Stage 1 or Stage 2 of the controlled studies or in the long-term study. Review of AE reporting also provided no evidence of increased suicidal ideation or behavior with treatment.

##### 6.1.5.10.1. Columbia-Suicide Severity Rating Scale

No patient treated with BUP/SAM reported worsening of suicidal behavior as assessed using the C-SSRS for the Stage 1 Pooled Safety Population. At any post-baseline visit in the Treatment Period for the Stage 1 Pooled Safety population, 2 patients in the placebo group (0.3%) reported suicidal behavior (“preparatory acts or behavior”).

At baseline, suicidal ideation was reported in 16.7% of patients in the BUP/SAM 2/2 group vs 12.6% in the placebo group. At any post-baseline visit:

- The proportion of patients with post-baseline suicidal ideation or behavior reported on the C-SSRS in the BUP/SAM 2/2 group was 9.9%, compared to 16.3% for placebo

A summary of the post-baseline C-SSRS categories in Stage 1 is provided in Table 9.

**Table 9: Less Suicidal Ideation or Behavior with BUP/SAM Treatment vs Placebo**

| Post-Baseline C-SSRS Categories (Stage 1) | BUP/SAM 2/2 (N=162) n (%) | Placebo (N=658) n (%) |
|---|---|---|
| Suicidal Behavior | 0 | 2 (0.3) |
| Suicidal Ideation | 16 (9.9) | 107 (16.3) |
| Self-injurious behavior without suicidal intent | 0 | 2 (0.3) |

Abbreviations: BUP=buprenorphine; C-SSRS=Columbia-Suicide Severity Scale; SAM=samidorphan.

A similar trend was observed in Stage 2. The prevalence of suicidal ideation and behavior in the long-term study was similar to that observed with BUP/SAM in the placebo-controlled studies.

#### 6.1.5.10.2. Adverse Events of Special Interest to Evaluate Suicidal Ideation and Behavior

Monitoring of AEs revealed no evidence of increased treatment-emergent suicidal ideation or behavior. The only occurrences of treatment-emergent suicidal behavior or treatment-emergent serious suicidal ideation during the Stage 1 Treatment Period were both reported in the placebo group (0.3% and 0.2%, respectively). One additional placebo patient reported non-serious suicidal ideation. A similar low incidence of AEs of suicidal ideation was observed in the long-term study.

## 6.2. Abuse Potential Assessment

An abuse potential assessment was undertaken across the BUP/SAM program. A dedicated HAP study was conducted with BUP/SAM as well as BUP alone compared to placebo. In addition, abuse potential terms were queried across the BUP/SAM clinical dataset (see Table 21). All data provide consistent evidence of low abuse potential for BUP/SAM. There were no reports of drug abuse across the developmental program. In addition, there was no evidence of dependence observed during BUP/SAM treatment and there was little evidence of withdrawal upon abrupt discontinuation of BUP/SAM.

BUP is a Schedule III (CIII) narcotic. The purpose of SAM, a μ-opioid receptor antagonist, in BUP/SAM is to reduce the abuse and dependence potential of BUP. The subjective and objective PD effects of SAM alone have been assessed in two dedicated HAP studies (33-012 and 33-B109). In these studies, SAM demonstrated no abuse potential at doses ranging from 2.5 mg to 30 mg (ie, abuse potential similar to placebo). Comparisons between SAM and placebo, as assessed by the within-subject differences on $E_{max}$ Drug Liking VAS scores, showed no dose response, with medians equal to 0.

### 6.2.1. Clinical Abuse Potential Studies

#### 6.2.1.1. Buprenorphine

BUP has the potential to be abused, which may pose a risk of overdose and death (Subutex USPI, 2018). The abuse liability of BUP has been described extensively in the scientific literature (Lofwall and Walsh 2014).

#### 6.2.1.2. Buprenorphine and Samidorphan Combination

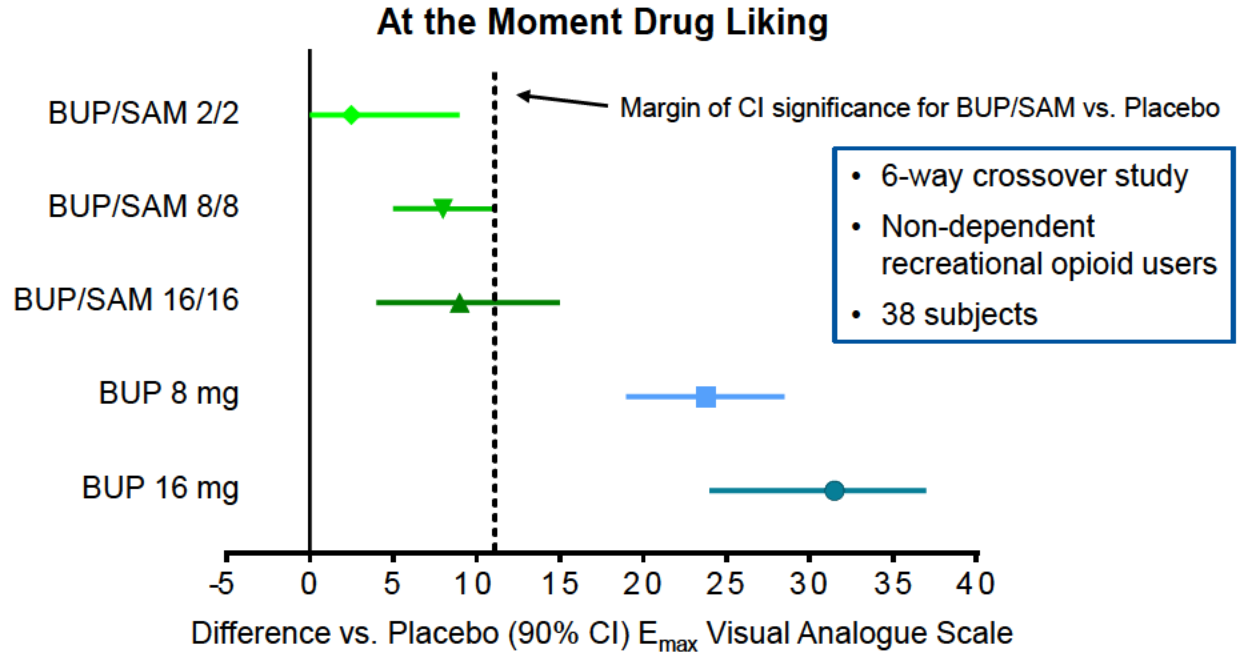
BUP/SAM was evaluated in a dedicated HAP study (212). The study was consistent with the FDA guidance for the assessment of abuse potential (Center for Drug Evaluation and Research 2017).

**Study 212 (Single Dose, Human Abuse Potential; BUP/SAM 2/2–16/16)**

A Phase 1 HAP study (212) was conducted in a population of nondependent, recreational opioid users. The primary objective of this study was to evaluate the abuse potential of a single dose of BUP/SAM at the therapeutic dose of 2/2, and at 4-fold and 8-fold doses of 8/8 and 16/16, compared to placebo and a positive control, BUP (doses of 8 mg and 16 mg). Prior to entry into the double-blinded six-way cross-over study (treatment phase), subjects were first assessed to determine if they could discriminate between the effects of BUP and placebo in a double-blinded cross-over qualification phase. Only subjects who were able to discriminate BUP from placebo on the Drug Liking VAS $E_{max}$ scores were included in the treatment phase of the study.

Maximum effect ($E_{max}$) Drug Liking VAS scores (the primary endpoint) for BUP/SAM 2/2 was similar to placebo with the 90% confidence interval (CI) upper boundary less than the pre-specified 11 point threshold of clinical significance. Supra-therapeutic doses of BUP/SAM 8/8 and 16/16 resulted in slightly greater Drug Liking $E_{max}$ scores than placebo (with the 8/8 dose just reaching the 90% upper CI of 11, and the 16/16 dose 90% upper CI exceeding 11, see Figure 22). These BUP/SAM vs placebo differences were significantly less than those observed for equivalent doses of BUP alone vs placebo.

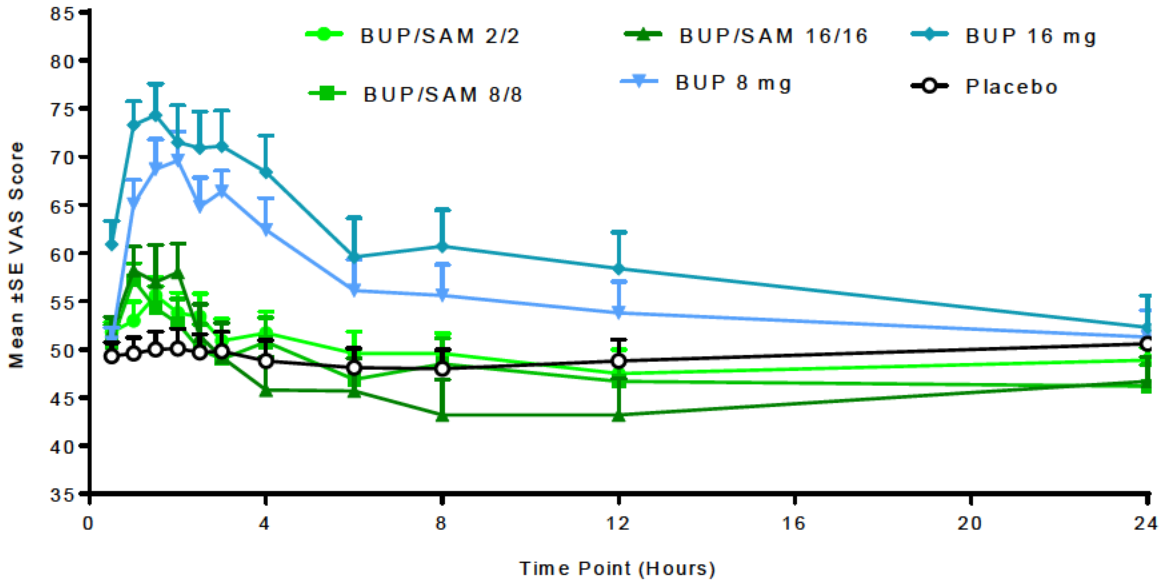
**Figure 22: $E_{max}$ Drug Liking: Difference and 90% Confidence Interval**




Abbreviations: BUP=buprenorphine; CI=confidence interval; SAM=samidorphan; VAS=visual analog scale

Mean scores for "At the Moment Drug Liking" VAS over time are presented in Figure 23, which shows consistently lower "At the Moment Drug Liking" VAS scores for BUP/SAM compared to BUP alone over a 24 hour period.

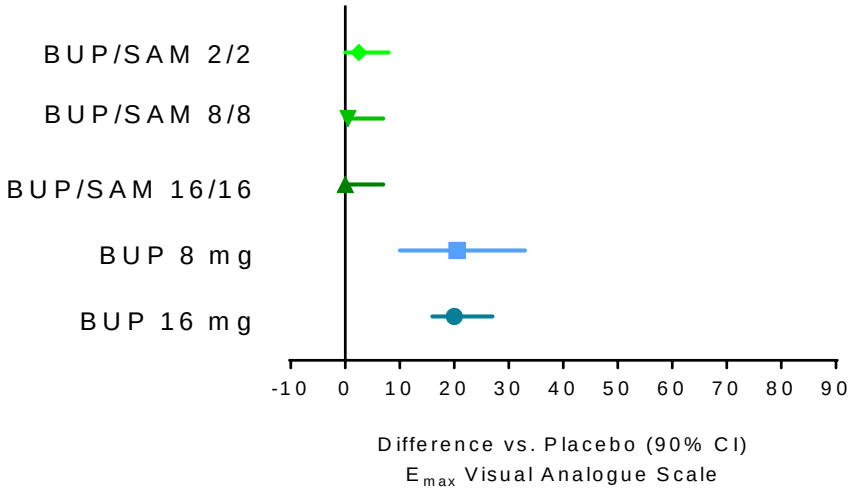
**Figure 23: At the Moment Drug Liking VAS Scores Over Time**




Abbreviations: BUP=buprenorphine; SAM=samidorphan; SE=standard error; VAS=visual analog scale.
Note: When completing the At the Moment Drug Liking VAS, subjects were asked "At this moment, my liking for this drug is," and response anchors for this scale were as follows: 0="Strong disliking," 50="Neither like nor dislike," and 100="Strong liking.

For the secondary endpoint of "Overall Drug Liking" mean $E_{max}$ VAS scores were higher for BUP compared to placebo ($P$<0.001). In contrast, $E_{max}$ VAS scores for all doses of BUP/SAM were similar compared to placebo ($P$=0.341, $P$=0.999 and $P$=0.513 for BUP/SAM 2/2, 8/8, and 16/16, respectively), and were lower compared to BUP ($P$<0.001) Figure 24.

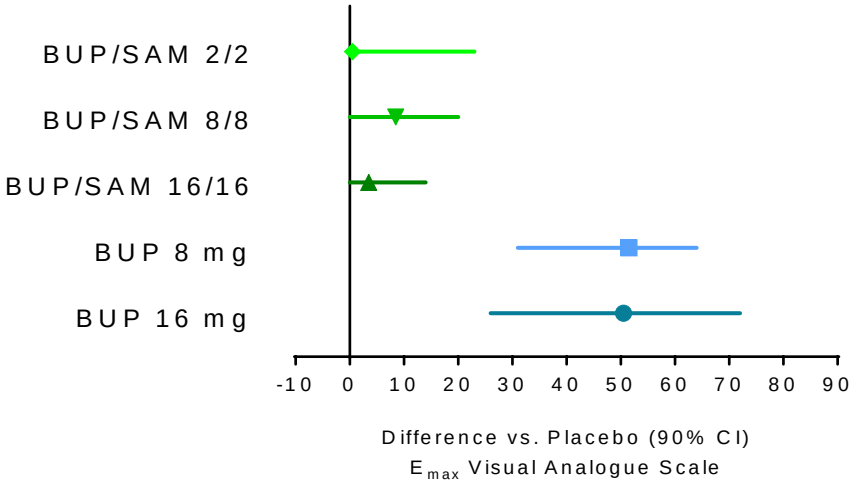
**Figure 24: Overall Drug Liking VAS vs Placebo**




Abbreviations: BUP=buprenorphine; CI=confidence interval; SAM=samidorphan; VAS=visual analog scale

Similarly, for the secondary endpoint "Take Drug Again", $E_{max}$ VAS scores were higher with BUP than with placebo (P<0.001), and $E_{max}$ VAS scores for both doses of BUP were higher than all doses of BUP/SAM (P<0.001). "Take Drug Again" $E_{max}$ VAS scores for BUP/SAM 2/2 and 8/8 were similar to placebo (Figure 25).

**Figure 25: Take Drug Again VAS vs Placebo**

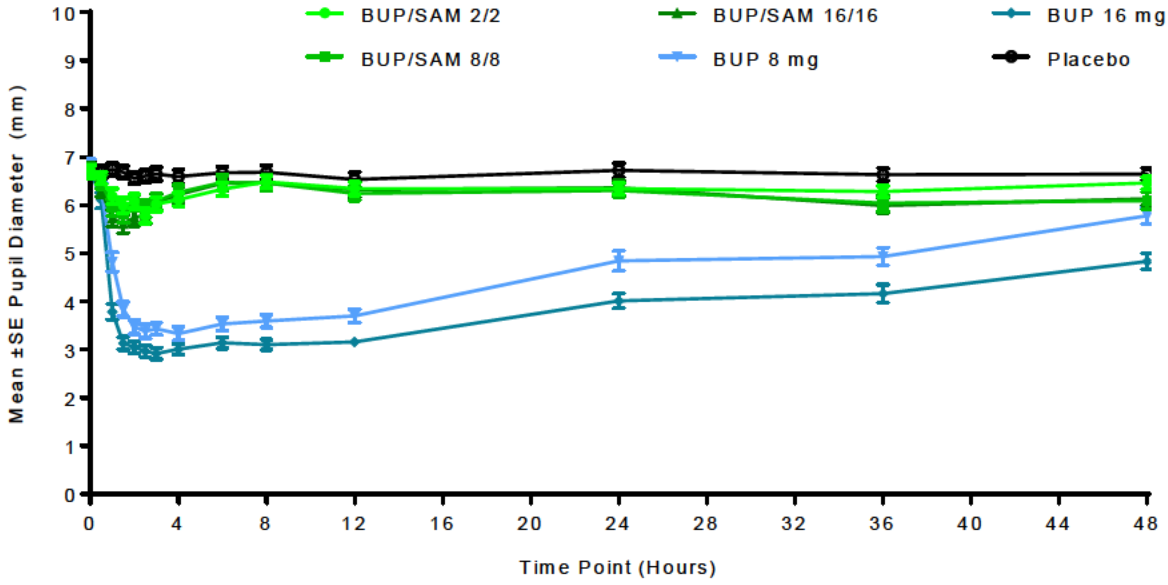



Abbreviations: BUP=buprenorphine; CI=confidence interval; SAM=samidorphan; VAS=visual analog scale

*Pupillometry Assessments*

The largest mean changes in pupil constriction were observed with BUP 8 mg and 16 mg relative to placebo (Figure 26). BUP/SAM did elicit pupil constriction compared to placebo; however, the changes from baseline were slight compared to BUP 8 mg and 16 mg ($P$<0.001) (Figure 26).

**Figure 26: Pupil Diameter Over Time**




Abbreviations: BUP=buprenorphine; PBO=placebo; SAM=samidorphan; SE=standard error.

*TEAEs*

TEAEs seen at ≥5% during the treatment period in Study 212 were euphoric mood (all treatment groups except placebo), irritability (BUP/SAM 16/16), vomiting (all treatment groups except BUP/SAM 2/2 and placebo), nausea, paraesthesia oral (BUP 16 mg), dry mouth (BUP 16 mg), somnolence, dizziness (BUP/SAM 16/16, BUP 8 mg, BUP 16 mg), headache (BUP 16 mg), sedation (BUP 8 mg, BUP 16 mg), feeling abnormal (BUP/SAM 16/16), feeling hot (BUP/SAM 8/8, BUP 8 mg, BUP 16 mg), pruritus (BUP/SAM 2/2, BUP 8 mg, BUP 16 mg), pruritus generalized (BUP 16 mg), and hot flush (BUP 16 mg).

In summary, the abuse potential of BUP/SAM was low as assessed in the HAP study (212):

- The abuse potential of the therapeutic dose of BUP/SAM (2/2) as measured by the primary endpoint ($E_{max}$ Drug Liking VAS) was similar to placebo.
- At four-fold (8/8) and eight-fold (16/16), the therapeutic doses of BUP/SAM resulted in $E_{max}$ Drug Liking VAS scores that were greater than placebo. The magnitude of these differences was small and significantly less than that of equivalent doses of BUP alone. All BUP/SAM doses were similar to placebo on secondary endpoints of $E_{max}$ Overall Drug Liking and Take Drug Again VAS scores.

### 6.2.2. Abuse Potential in MDD

#### 6.2.2.1. Adverse Events of Special Interest to Evaluate for Abuse Potential

Consistent with the findings of the HAP study (see Section 6.2.1.2), BUP/SAM demonstrated low evidence of abuse potential in patients with MDD when AESIs to evaluate for abuse potential were assessed, these included the three categories of euphoria-related events, abuse behavior events, and non-specific events (see Table 21).

In both Stage 1 and Stage 2, the majority of MedDRA query terms used to assess for abuse potential of BUP/SAM were nonspecific events (ie, events also seen in drugs not associated with abuse potential), occurring with a higher incidence among patients randomized to BUP/SAM compared to placebo. The incidence of these events was higher in Stage 1 than Stage 2 and did not increase with increased exposure.

In the Stage 1 Pooled Safety population, the most common AESI was nonspecific, dizziness (13.0% of BUP/SAM 2/2 patients vs 4.1% of placebo patients). Other common nonspecific AESIs were somnolence and sedation (each 6.8% of BUP/SAM 2/2 patients vs 3.3% and 0.9% of placebo patients, respectively). No patient randomized to BUP/SAM reported abuse behavior.

Euphoria-related AESIs had higher incidence in patients randomized to BUP/SAM 2/2 treatment compared to placebo (4.3% vs 0.2%, respectively) in the placebo-controlled studies in Stage 1 (see Table 10). These events typically were reported with treatment initiation and did not reoccur with continued treatment. In Stage 2, there were no reports of euphoria in 289 BUP/SAM or 286 placebo-treated patients.

**Table 10: Overview of Categorized Adverse Events of Special Interest to Evaluate for Abuse Potential – Placebo-controlled Studies in MDD (202, 205, 206, and 207)**

| Ad hoc System Organ Class, n (%) | Placebo | Randomized BUP/SAM Dose | | | | |
|---|---|---|---|---|---|---|
| | | 0.5/0.5 | 1/1 | 2/2 | 8/8 | Any |
| **Stage 1 Pooled Safety Population** | | | | | | |
| Number of patients | 658 | 59 | 63 | 162 | 19 | 303 |
| Any AESI | 54 (8.2) | 9 (15.3) | 12 (19.0) | 42 (25.9) | 12 (63.2) | 75 (24.8) |
| Abuse behavior | 1 (0.2) | 0 | 0 | 0 | 0 | 0 |
| Euphoria related | 1 (0.2) | 0 | 1 (1.6) | 7 (4.3) | 1 (5.3) | 9 (3.0) |
| Nonspecific[a] | 53 (8.1) | 9 (15.3) | 11 (17.5) | 37 (22.8) | 12 (63.2) | 69 (22.8) |
| **Stage 2 Pooled Safety Population** | | | | | | |
| Number of patients | 286 | 56 | 62 | 289 | 22 | 429 |
| Any AESI | 7 (2.4) | 5 (8.9) | 1 (1.6) | 14 (4.8) | 8 (36.4) | 28 (6.5) |
| Nonspecific[a] | 7 (2.4) | 5 (8.9) | 1 (1.6) | 14 (4.8) | 8 (36.4) | 28 (6.5) |

Abbreviations: AESI=adverse event of special interest.

[a] Note: "nonspecific" are noneuphoria related terms that may be associated with abuse of a particular drug, but are not necessarily indicative of abuse of the drug of interest. These include terms indicative of impaired attention, cognition, mood, dissociative/psychotic terms, and related terms not captured elsewhere.

Across Stage 1 and Stage 2 of the controlled studies, euphoria-related events occurred infrequently, with the combined stage incidence higher with the 2/2 dose (1.6%) compared to placebo (0.2%). Similarly, in the long-term safety study (208), the incidence of euphoria-related AESIs was low (1.2%), there was no abuse behavior, and the non-specific events were similar to that seen in the placebo-controlled studies.

Most euphoria-related AEs in MDD studies were reported with treatment initiation and none reoccurred with continued treatment. There did not appear to be a correlation of euphoria-related events and dose of BUP/SAM. A similar number of euphoria-related events were reported on 0.5/0.5 (initial titration dose) and 2/2. There were no euphoria-related AEs on 8/8 (Table 11). There were no euphoria-related AEs in Stage 2.

**Table 11: Euphoria-related Events Pooled and Long-Term MDD Studies**

| | **Pooled Placebo Controlled Studies (Stage 1)** | | | | | **Study 208 Safety Population** |
|---|---|---|---|---|---|---|
| | | **BUP/SAM Arms** | | | | |
| | **Placebo** | **0.5/0.5** | **1/1** | **2/2** | **8/8** | |
| Number of Patients (N) | **N=658** | **N=59** | **N=63** | **N=162** | **N=19** | **BUP/SAM N=1454** |
| Incidence % (n) | 0.2% (1) | 0 | 1.6% (1) | 4.3% (7) | 5.3% (1) | 1.2% (18) |
| Actual dose when event occurred (n)[a] | Placebo | N/A | 0.5/0.5 (1) | 2/2 (4)<br>0.5/0.5 (3) | 4/4 (1) | 0.5/0.5 (11)<br>2/2 (7) |

Abbreviations: BUP=buprenorphine; MDD=major depressive disorder; SAM=samidorphan.
[a] Due to titration, actual dose that patient was taking at time of euphoria-related event.

### 6.2.2.2. Dependence and Withdrawal

To assess dependence and withdrawal, post-discontinuation-emergent AEs are summarized for patients who were exposed to ≥4 weeks of study drug. In each of the studies described here, post-discontinuation AEs that can be associated with withdrawal were evaluated over the period of 3 to 16 days after the last dose of BUP/SAM (a period of time that is consistent with approximately 5 times the half-life of the slowest metabolized metabolites of both BUP and SAM, and when withdrawal would be expected to emerge). Similarly, objective evaluation of withdrawal was performed using COWS assessments while on treatment (baseline), as well as within this post-discontinuation period.

For the COWS analysis, patients were required to have an adequate baseline COWS assessment (within 2 days of the last dose, [ie, before the potential onset of withdrawal]), ≥4 weeks of exposure, and a subsequent post-discontinuation assessment within the same 3- to 16-day window following last dose of drug evaluated for the AESI analysis (Tompkins et al, 2009).

#### 6.2.2.2.1. Dependence

There was no evidence of dependence in either placebo-controlled or long-term studies of BUP/SAM by review of AE event terms that can be associated with dependence. This assessment was performed using a standard query for drug dependence consistent with FDA

guidance for abuse potential assessment (Center for Drug Evaluation and Research 2017) (see Appendix Table 21).

#### 6.2.2.2.2. Withdrawal

There was no evidence of withdrawal in the placebo-controlled studies following abrupt discontinuation of BUP/SAM as evaluated by assessment of withdrawal symptoms using the COWS scale and AESI review. For a list of preferred terms used to assess withdrawal see Table 21. In the long-term safety study (208), following treatment of up to one year, the incidence of COWS scores from no withdrawal baseline to mild COWS scores were higher than observed in the placebo-controlled studies (4.9% vs 2.7%), however the number of COWS assessments performed was more frequent in the long-term study, limiting direct comparability, and there was no placebo group. Similarly, the reported event of drug withdrawal was uncommon (0.4%), mild or moderate in severity and typically did not require medical intervention.

##### 6.2.2.2.2.1. Clinical Opiate Withdrawal Scale (COWS)

COWS assessments were systematically performed in both the placebo-controlled as well as in the long-term MDD studies. Across the BUP/SAM development program, there was little evidence of withdrawal upon abrupt discontinuation of BUP/SAM by review of COWS assessments. Patients who had received at least 4 weeks of study treatment were included in these analyses, so long as they had a baseline COWS assessment and at least 1 COWS assessment in the Day 3 through Day 16 post-discontinuation period. Only patients in the controlled Studies 205, 206, and 207 were included in this assessment since study drug was abruptly discontinued in these studies. Study 202 had included a week taper of study drug at end of study so was not included in this analysis. In this population, there was no association of BUP/SAM 2/2 with withdrawal compared to placebo. The median COWS change from baseline in all BUP/SAM treatment groups was 0.0 (COWS scores <5.0 are defined as no withdrawal). A slight increase in mean post-discontinuation COWS score was observed with BUP/SAM 2/2 compared to placebo patients (placebo-adjusted difference of 0.2). This change is not considered clinically meaningful. Equivalent proportions of patients in the BUP/SAM 2/2 and placebo groups had an increased COWS score category from no withdrawal (baseline) to mild withdrawal (2.7%) post discontinuation. One BUP/SAM 2/2 patient (0.9%) worsened to moderate withdrawal by COWS score from no withdrawal at baseline.

In the long-term study (208) the incidence of categorical COWS score worsening was low (5.6%), and the majority of such worsening was from no withdrawal to mild withdrawal (4.9%). Mean post-baseline changes in COWS scores were <1 (0.0-0.4), including visits at 7, 14, and 28 days post-discontinuation. These mean changes are similar to those observed in the Pooled Post-discontinuation Safety population for BUP/SAM 2/2 patients. Mean post-baseline scores across visits ranged from 0.5 to 0.9. In contrast, withdrawal from BUP alone mean COWS scores are typically higher, eg, ~5-6 (Derbel et al, 2016).

There were 6 of 831 patients (0.7%) in Study 208 who had scores of moderate withdrawal by COWS assessment during the post-discontinuation period. Of these patients:

- One patient had moderate COWS score 1 week after last dose, the rest had this (their highest) score 2 weeks after last dose. One of the five with moderate at week 2 continued to have a moderate score ≥28 days after the last dose of BUP/SAM.
- Only one of the 6 patients had more than two AESIs to evaluate the potential for withdrawal following discontinuation, however, they were ongoing at study end. None of these patients had an AE of "drug withdrawal."

Post-discontinuation change in COWS scores for the placebo-controlled and long-term studies are presented in Table 12.

**Table 12: Post-discontinuation Change in COWS Scores**

| COWS Score Category[a] | Placebo-controlled Studies | | Long-term Study |
|---|---|---|---|
| | BUP/SAM 2/2 (N=113) | Placebo (N=148) | BUP/SAM 2/2 (N=831) |
| No Withdrawal (0-4) | 96.5% | 97.3% | 94.3% |
| Mild Withdrawal (5-12) | 2.7% | 2.7% | 4.9% |
| Moderate Withdrawal (13-24) | 0.9% | 0 | 0.7% |
| Moderate-severe or Severe Withdrawal (25-48) | 0 | 0 | 0 |

Abbreviations: COWS=Clinical Opioid Withdrawal Scale

[a] Patients with score of "No Withdrawal" at end of treatment period, baseline assessment.

#### 6.2.2.2.2.2. Adverse Events of Special Interest of Withdrawal

Little evidence of withdrawal was observed upon abrupt discontinuation of BUP/SAM by review of AESIs.

In the pooled placebo controlled studies (205, 206, and 207), there was no evidence of withdrawal:

- The incidence of AESIs to evaluate the potential for withdrawal was low in patients post-discontinuation with study drug exposure ≥4 weeks (4 BUP/SAM 2/2 patients [3.1%] and 3 placebo patients [1.8%]).
- AESI to evaluate the potential for withdrawal were varied event terms and none was reported in more than 1 BUP/SAM 2/2 patient.
- No patient had a cluster of more than 2 AESIs events used to evaluate the potential of withdrawal.

In the long-term safety study, there was little evidence of withdrawal across 1013 patients with ≥4 weeks of BUP/SAM exposure:

- No AESI to evaluate the potential for withdrawal was reported in ≥5% of patients regardless of prior exposure to BUP/SAM.

- There were four patients reporting drug withdrawal. Two of these patients had objective COWS scores of no withdrawal during the evaluated post-discontinuation period, one had mild withdrawal, and one patient had no COWS assessments conducted in the 3 to 16 day post-discontinuation period, limiting objective assessment of this patient. All events were mild or moderate in severity, and typically did not require medical management (one received clonidine).

The profile of post-discontinuation-emergent AESIs associated with BUP/SAM is different from what has been associated with BUP discontinuation. BUP withdrawal has been described as comprising multiple concurrent symptoms, including insomnia accompanied by GI events, and/or muscle aches and pains, occurs in most patients, and requires symptomatic treatment (Dunn et al, 2015). Unlike BUP, there was no clustering of events, few patients had any withdrawal related-symptoms or required treatment.

There was no evidence of withdrawal in the placebo-controlled studies and in the long-term study there was little evidence of withdrawal observed upon abrupt discontinuation of BUP/SAM by review of AESIs, as well as objective COWS assessments.

## 6.3. Safety Conclusions

In summary, common AEs with BUP/SAM were GI or sedation-related, generally mild or moderate in severity, and typically occurred with treatment initiation. There were no clinically meaningful post-baseline changes in laboratory, vital signs, weight, or ECGs. In addition, there was no evidence of increased treatment-emergent suicidal ideation or behavior. BUP/SAM abuse potential was low across the clinical development program. A dedicated human abuse potential study showed that BUP/SAM 2/2 is similar to placebo. At 4- to 8-times the therapeutic dose of BUP/SAM, drug liking was slightly greater than placebo and significantly lower than equivalent dose of BUP alone. Data from MDD patients were consistent with further evidence of low abuse potential with BUP/SAM with low incidence of euphoria, no evidence of dependence, and little evidence of withdrawal upon abrupt discontinuation even following a year of treatment.

# 7. CLINICAL PHARMACOLOGY

## 7.1. Background

An evaluation of the clinical pharmacology profile of BUP/SAM has been completed that involved a total of 20 Phase 1 studies, a population pharmacokinetics (PK) analysis using integrated data from the Phase 1 studies, one Phase 2 study (202) and three Phase 3 studies (205, 206, and 207), and physiologically-based PK (PBPK) modeling and simulations. The studies included evaluations in healthy subjects, healthy opioid-experienced subjects, and patients with MDD. Of the 20 Phase 1 studies, 13 studies were conducted with BUP/SAM or co-administered BUP and SAM; whereas, the other 7 studies were conducted with SAM alone.

The clinical pharmacology program for BUP/SAM was designed to establish the single- and multiple-dose PK profiles of BUP and SAM in healthy subjects and in patients with MDD, to investigate potential clinical drug-drug interactions (DDI), to determine the effects of intrinsic and extrinsic factors on PK, and to evaluate exposure-response relationships related to abuse potential and cardiac repolarization.

The population PK analysis characterized the PK of BUP and SAM with BUP/SAM administration in MDD patients and identified covariates that could explain between-patient variability in PK. Furthermore, PBPK modeling and simulations were also completed to evaluate potential for DDI, impact of mild to moderate renal impairment, and food effect on PK.

## 7.2. Overview of Clinical Pharmacology Findings

A summary of key clinical pharmacology findings are as follows:

- BUP and SAM are rapidly absorbed following BUP/SAM SL administration:
  - Peak plasma exposures for BUP and SAM are observed within 1 to 2 hours postdose.
  - Absolute bioavailability of a single BUP/SAM 2/2 SL dose is estimated to be 29% for BUP and 74% for SAM.
  - SL administration of BUP/SAM doses 0.5/0.5, 1/1, 2/2, and 8/8 result in dose-proportional increases in plasma exposures of BUP and SAM.
  - PBPK analysis indicated that post-prandial increases in splanchnic blood flow are not expected to affect SL bioavailability of BUP/SAM.
  - Consumption of water <10 min following SL dose of BUP/SAM resulted in ≥50% and ≥36% decrease in $C_{max}$ and AUC of BUP, with no effect on SAM plasma exposures. Therefore, it is recommended to avoid eating or drinking at least 15 min after SL administration of BUP/SAM.
- Following SL administration of BUP/SAM, BUP has a mean terminal elimination half-life of 19 to 26 hours and SAM has a mean terminal elimination half-life of 5 to 7 hours. However, the PD results related to subjective effects and miosis from a HAP study (212) indicated that the PD half-life is shorter for the BUP/SAM combination.

- BUP is eliminated primarily through hepatic metabolism and biliary excretion, with minimal renal excretion (<1%) (Subutex USPI, 2018); SAM is primarily eliminated through hepatic metabolism and renal excretion.
- BUP undergoes N-dealkylation to nBUP via CYP3A4 (Subutex USPI, 2018); SAM undergoes N-dealkylation to RDC-9986 and N-oxidation to RDC-1066, primarily also via CYP3A4.
- The major BUP and SAM metabolites (nBUP, RDC-9986, and RDC-1066) do not contribute to the pharmacological response of BUP/SAM.
- Age, body weight, gender, race, and disease status (MDD) do not impact the PK of BUP or SAM after SL administration of BUP/SAM.
- Moderate to severe hepatic impairment (Child-Pugh Class B and C) resulted in significant increases (2- to 4-fold) in plasma exposures of BUP and SAM; whereas, mild hepatic impairment (Child-Pugh Class A) resulted in <2-fold increases in plasma exposures. Therefore, for patients with moderate to severe hepatic impairment, an initial maintenance dose of 1/1 should be considered and the patient monitored for clinical response. No dose adjustment is recommended for patients with mild hepatic impairment.
- Severe renal impairment (eGFR < 30 mL/min/1.73 $m^2$) resulted in approximately 2-fold increases in plasma exposures of BUP and SAM. The impact of mild to moderate renal impairment estimated using PBPK modeling and simulation suggested a modest increase in plasma exposures (range: 49-76%) of SAM, but only up to a 17% increase in BUP exposures. Therefore, for patients with severe renal impairment, an initial maintenance dose of 1/1 should be considered and the patient monitored for clinical response. No dose adjustment is recommended for patients with mild to moderate renal impairment.
- The concomitant use of BUP/SAM with itraconazole, a strong CYP3A4 inhibitor, resulted in mild increases (approximately 50%) in exposures to BUP and SAM. Therefore, no dose adjustment is required for the concomitant use of CYP3A4 inhibitors.
- The concomitant use of BUP/SAM with rifampin, a potent CYP3A4 inducer, decreased the total exposures of BUP and SAM by 50% and 70%, respectively, compared to the use of BUP/SAM alone. Therefore, BUP/SAM is not recommended to be dosed with strong inducers of CYP3A4.
- Population PK analysis indicated no influence of any concomitant ADT on the PK of BUP or SAM.
- *In vitro* studies supported by PBPK modeling indicated that BUP/SAM 2/2 is not expected to cause any clinically significant interactions when coadministered with drugs that the substrates of any CYP450 enzymes or key drug transporters.
- BUP/SAM at doses up to 8/8 demonstrated no effect on QTc interval or any other ECG parameters (see Section 6.1.5.8).

- Clinical studies conducted with BUP/SAM to evaluate human abuse potential demonstrated a low potential of abuse. Clinical study findings are discussed in Section 6.2.

# 8. POSTMARKETING AND RISK EVALUATION AND MITIGATION STRATEGY (REMS) FOR BUP/SAM

## 8.1. Post-marketing Surveillance Plan

Alkermes proposes a robust post-marketing safety surveillance plan that includes active surveillance for on-going assessment for any evidence of misuse, abuse or accidental exposure with BUP/SAM. This plan is further described below.

Alkermes has a validated safety database and pharmacovigilance system and actively monitors and continually assesses the evolving safety profile of all Alkermes investigational and marketed products. Routine pharmacovigilance includes individual, as well as aggregate review of AE reports using regular signaling activities to assess for any changes in the known safety profiles of the products. Routine pharmacovigilance also includes monitoring the scientific literature, as well as labeling and regulatory actions, for products in the same drug class to ensure that any new safety issues are identified and managed in a timely manner.

In addition to routine pharmacovigilance, Alkermes proposes to utilize active monitoring from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) national monitoring service following marketing approval. RADARS is commonly used by industry, as well as the FDA to monitor for evidence of diversion, misuse, abuse, or overdose associated with a given drug. RADARS uses a matrix of nationwide data sources, which include poison control centers, drug treatment center surveys, and law enforcement, as well as internet sites, to perform ongoing assessments for misuse, abuse and accidental exposure. BUP/SAM specific RADARS data will be shared with FDA and will inform our understanding of any potential risk for misuse and abuse. Alkermes will use any evolving data to modify education or other interventions as appropriate.

## 8.2. Risk Evaluation and Mitigation Strategy (REMS) for BUP/SAM

### 8.2.1. REMS Content

All BUP containing products are approved with a REMS. The proposed REMS for BUP/SAM is designed to mitigate the risks of misuse and accidental exposure and is modeled after BUP REMS, yet specific for adjunctive treatment of MDD. These elements include:

- Informing healthcare providers of these risks through the use of a:
  - Dear Healthcare Provider (HCP) Letter
  - HCP Education Brochure and Appropriate Use Checklist
  - REMS website available for HCP access
- Informing patients of these risks through use of a Medication Guide

### 8.2.2. REMS Assessments

As a part of the proposed BUP/SAM REMS program, routine pharmacovigilance activities will be combined with active surveillance to assess for any evidence of diversion, misuse, or abuse of

BUP/SAM using RADARS (see Section 8.1). This information will be used by Alkermes and FDA to evaluate the success of existing risk mitigation efforts and aid in informing further modification with evolving data, if needed. As a part of the proposed REMS program, Alkermes will perform knowledge assessment surveys to prescribers to assess their understanding of the REMS, along with other measures at agreed upon time points following product approval according to what may be agreed with FDA at the time of product approval.

# 9. RISK/BENEFIT PROFILE OF BUP/SAM IN THE ADJUNCTIVE TREATMENT OF MAJOR DEPRESSIVE DISORDER

## 9.1. Benefits of Treatment with BUP/SAM

BUP/SAM 2/2 provides clinically meaningful efficacy in the adjunctive treatment of patients with MDD with a history of inadequate response to standard ADTs. Alkermes conducted four placebo-controlled studies of daily BUP/SAM in MDD patients, who received a therapeutic dose of background ADT (SSRI, SNRI, or bupropion), to demonstrate efficacy, two of which met their pre-specified primary endpoints.

- Two of the four studies (202 and 207) had significant *P*-values for the pre-specified primary endpoint
- Three of the four studies (202, 205, and 207) demonstrated evidence of efficacy
  - *P*-values for the MADRS-10 endpoint were significant when statistical methods were used to address week-to-week variability by evaluating BUP/SAM vs placebo at multiple time points.
- Importantly, clinically meaningful efficacy was demonstrated in patients in the US across three independent studies (202, 205, and 207).

BUP/SAM 2/2 showed continued improvement in MADRS scores over a 1-year treatment period in the long-term open-label safety study in those patients continuing treatment.

The strength of the BUP/SAM evidence derives from the effects across multiple studies and across multiple randomizations and multiple measures of effect within studies. This totality of data, considered along with the results of individual studies, provides substantial evidence of efficacy for BUP/SAM 2/2 in the adjunctive treatment of MDD.

## 9.2. Risks of Treatment with BUP/SAM

The common AEs associated with BUP/SAM included mild to moderate nausea, dizziness, constipation, vomiting, fatigue, somnolence, headache, and sedation. These events typically occurred with initiation of treatment, resolved with continued treatment, and did not lead to discontinuation. Other than the precipitation of acute opioid withdrawal with first dose of BUP/SAM in one patient who had not shared that they were receiving chronic opioid treatment, SAEs occurred with no identifiable pattern and at low incidence (Section 6.1.5.3). Long-term treatment (approximately one year) did not demonstrate evidence of any new safety findings.

CNS depression and sedation events were more frequently observed in patients with BUP/SAM 2/2 relative to placebo. There was no evidence of increased risk of respiratory depression, hypotensive and orthostatic hypotensive events, hypersensitivity, QT prolongation, hepatic effects, hypomania/mania or sexual dysfunction with the use of BUP/SAM.

The risk of suicide among patients who do not respond to treatment is significant. There was no evidence of increased suicidal ideation observed across pooled placebo-controlled studies in which patients received BUP/SAM 2/2 and remained on background ADT, which further supports efficacy of this agent with a distinct mechanism of action.

BUP/SAM was not associated with clinically meaningful changes over time in laboratory tests, vital signs, weight, or ECG parameters, including metabolic parameters.

The abuse potential for BUP/SAM is low based on data collected throughout the development program. Thorough evaluation of abuse potential of BUP/SAM included a HAP study (212) in opioid-experienced, recreational users, which demonstrated that the $E_{max}$ Drug Liking VAS (primary endpoint) score of the therapeutic dose of BUP/SAM (2/2) was comparable to placebo. Four-fold (8/8) and eight-fold (16/16) super-therapeutic doses of BUP/SAM showed higher $E_{max}$ Drug Liking VAS scores vs placebo, but the magnitude of differences was small and significantly less than those of equivalent doses of BUP alone. Additionally, a detailed review of AESIs was undertaken to evaluate abuse, dependence, and withdrawal (and systematic use of COWS assessments) in over 1000 patients. There was little evidence of withdrawal with BUP/SAM with these two analyses. There was no abuse behavior or dependence observed in the development program. Taken together, the findings support the conclusion that the risk of abuse with BUP/SAM is low.

BUP/SAM has a favorable safety profile. The common adverse events were mild, transient, related to tolerability, and should be easily managed by patients and physicians. Potential risks associated with BUP/SAM can be addressed with precautions (ie, contraindicating use in patients who are opioid dependent or receiving chronic opioid treatment) which would be contained in product labeling and the proposed active pharmacovigilance and REMS plans.

## 9.3. Conclusions of Benefit Risk Assessment

MDD is a prevalent and disabling disorder which is associated with significant morbidity and mortality. The majority of patients treated with existing antidepressant medication do not achieve adequate symptom relief. All existing antidepressant medications work via monoamine pathways and all approved adjunctive antidepressants are associated with side effects that limit tolerability. To achieve better outcomes, new treatments with novel mechanisms of action, and favorable safety profiles, are urgently needed.

Two placebo-controlled clinical trials (202 and 207) demonstrated efficacy of BUP/SAM 2/2 and another placebo-controlled trial (205) was strongly supportive of the positive studies. The clinical trials specifically focused on patients continuing therapeutic doses of ADTs who had an inadequate response to treatment. All patients, including patients randomized to placebo treatment, remained on background ADT throughout the treatment period. BUP/SAM was generally well-tolerated with no unexpected safety findings. Common AEs associated with BUP/SAM included nausea, dizziness, constipation, vomiting, fatigue, somnolence, and sedation. These AEs occurred primarily with treatment initiation and were generally self-limited. SAEs with BUP/SAM occurred at low incidence like that of placebo with no observable pattern. Long-term treatment showed no evidence of any additional safety findings.

There was no evidence of increased risk of suicide with BUP/SAM, and suicidal ideation showed greater decreases with BUP/SAM vs placebo in controlled studies.

BUP/SAM was not associated with metabolic disturbances or motor disorders, which are key safety concerns of atypical antipsychotics currently used as adjunctive treatments for MDD.

Extensive evaluations across the clinical development program indicate that the risk of abuse with BUP/SAM is low. There was no evidence of dependence and there was little evidence of withdrawal with abrupt discontinuation of treatment.

Based on the high clinical need for new agents to treat major depressive disorder, efficacy demonstrated in the clinical development program, and the favorable safety profile including a low potential for abuse, it is concluded that the benefits of BUP/SAM outweigh its risks. BUP/SAM has the potential to serve as an important therapeutic option for the treatment of depression in patients who do not adequately respond to standard ADT.

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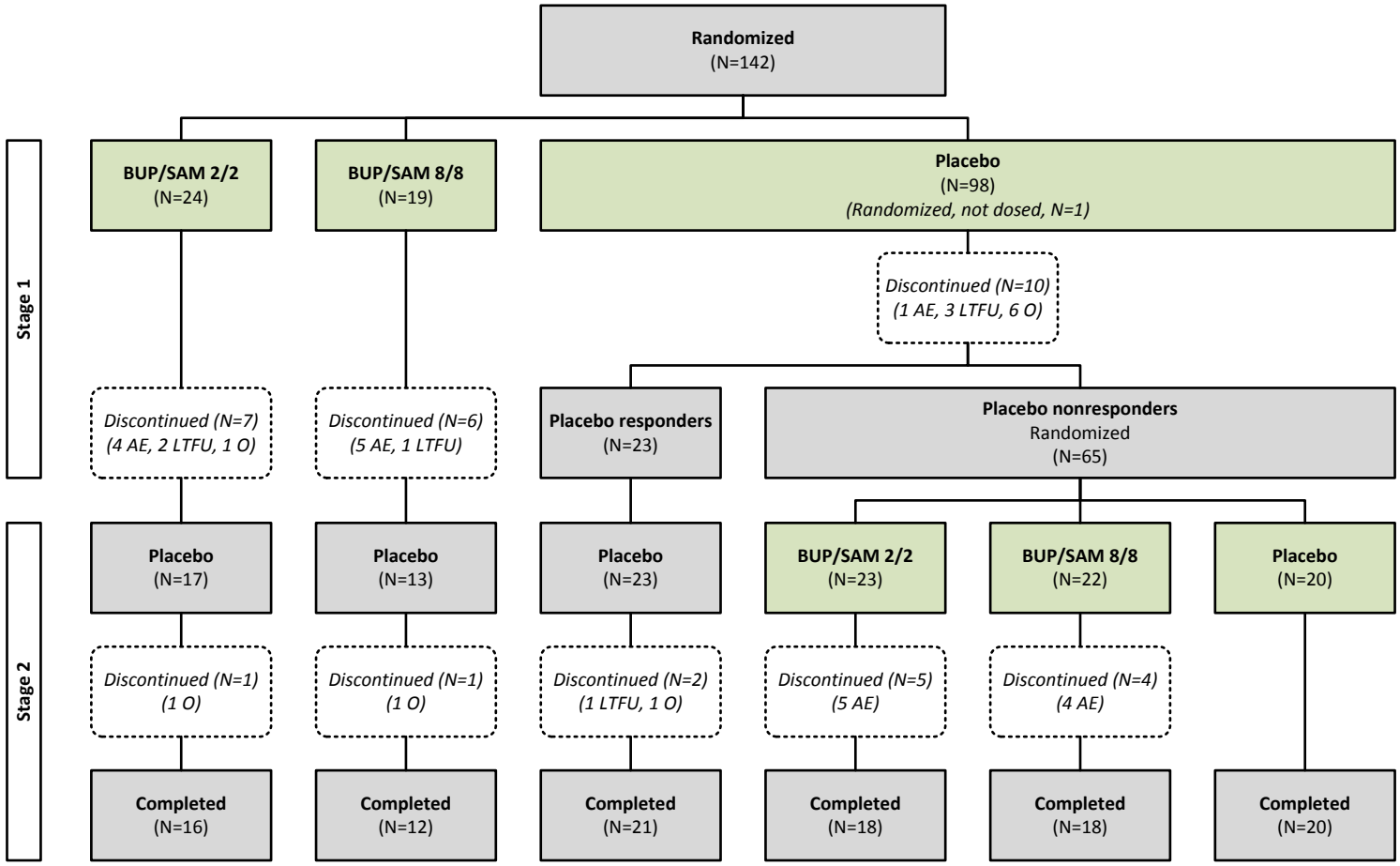
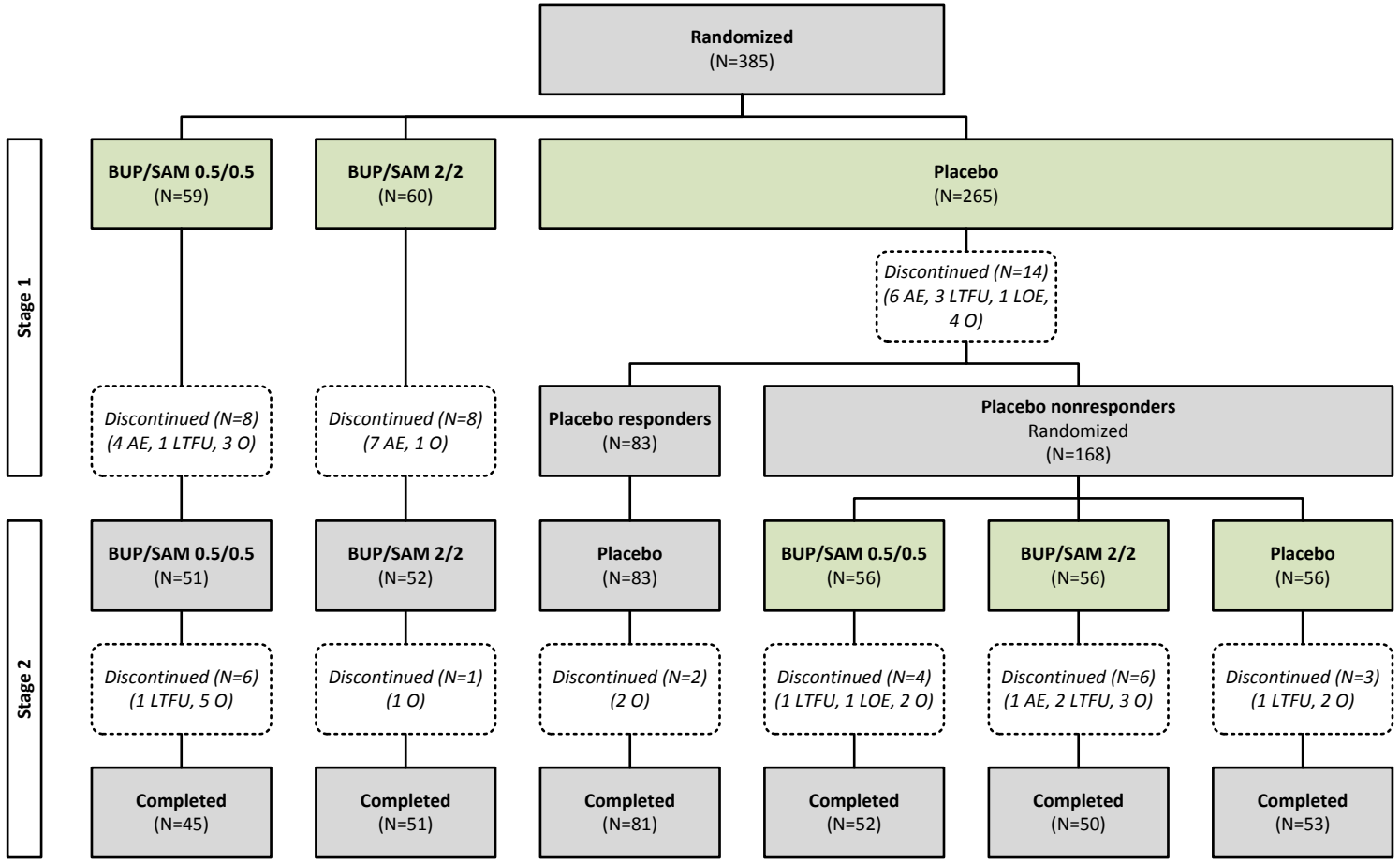
# APPENDIX

**Figure 27: Disposition: Study 202**



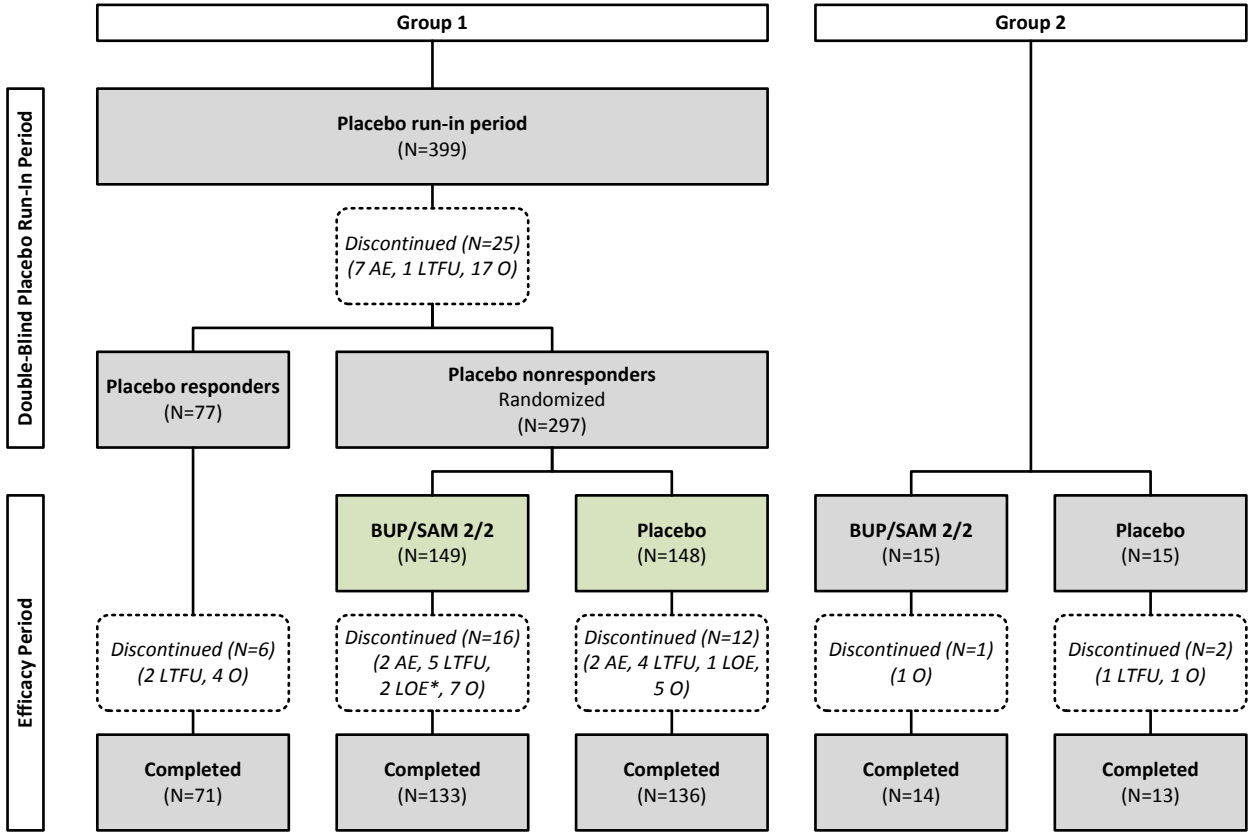

Abbreviations: AE=adverse event; BUP=buprenorphine; LTFU=lost to follow-up; O=other; SAM=samidorphan.

**Figure 28: Disposition: Study 205**



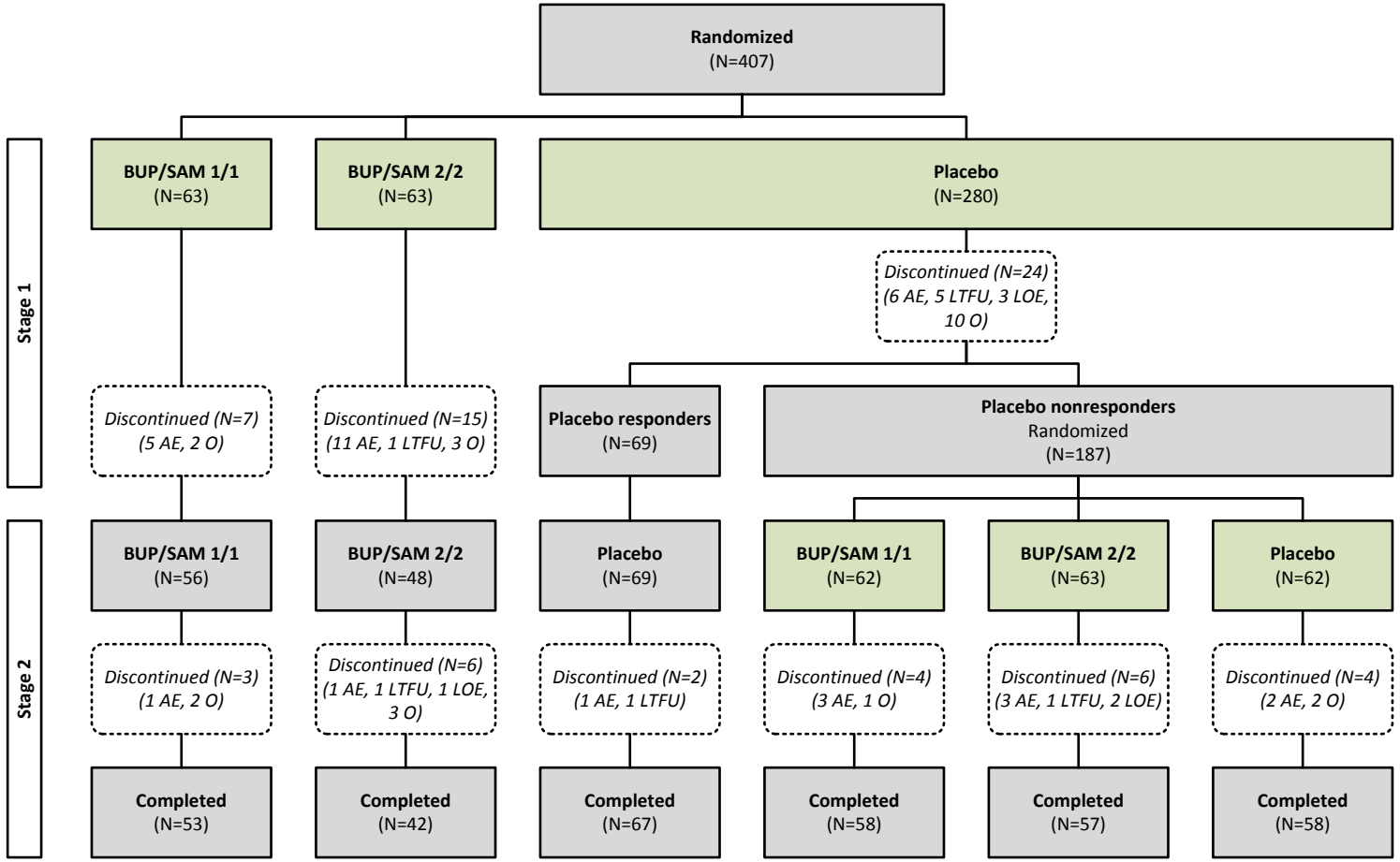

Abbreviations: AE=adverse event; BUP=buprenorphine; LOE=lack of efficacy; LTFU=lost to follow-up; O=other; SAM=samidorphan.
Note: "Other" reasons for discontinuation were nonadherence with study visits; psychiatrist decision to try new treatment; and work schedule change.
Note: Non-compliance with study drug was defined as a lack of adherence to study drug regimen.
Note: Patients who had previously or concurrently participated in the program at another center were excluded from the efficacy analysis population.

**Figure 29: Disposition: Study 206**




Abbreviations: AE=adverse event; BUP=buprenorphine; LOE=lack of efficacy; LTFU=lost to follow-up; O=other; SAM=samidorphan.
Note: Two placebo nonresponders (BUP/SAM 2/2) discontinued after randomization but prior to receiving randomized treatment: One patient discontinued due to lack of efficacy (during placebo run-in) and one patient withdrew from the study because he moved to another state

**Figure 30: Disposition: Study 207**




Abbreviations: AE=adverse event; BUP=buprenorphine; LOE=lack of efficacy; LTFU=lost to follow-up; O=other; SAM=samidorphan.
Note: In Stage 1, one patient was randomized to placebo but never received study drug due to failure to meet randomization criteria and therefore is not included in figure
Note: Patients who had previously or concurrently participated in the program at another center were excluded from the efficacy analysis population.

**Table 13: BUP/SAM Titration Schedules and Doses**

| Study | Treatment Duration | Dose(s) | Titration Schedule |
|---|---|---|---|
| *Phase 2* | | | |
| 202 | Stage 1: 4 weeks;<br>Stage 2: 4 weeks | 2/2, 8/8 | 2/2 (2 d), 4/4 (1 d)[a] |
| *Phase 3* | | | |
| 205 | Stage 1: 5 weeks;<br>Stage 2: 6 weeks | 0.5/0.5, 2/2 | 0.5/0.5 (3 d), 1/1 (4 d)[b] |
| 206 | 10 weeks | 2/2 | 0.5/0.5 (3 d), 1/1 (4 d) |
| 207 | Stage 1: 5 weeks;<br>Stage 2: 6 weeks | 1/1, 2/2 | 0.5/0.5 (3 d), 1/1 (4 d)[c] |
| 208 | 52 weeks | 2/2 | 0.5/0.5 (3 d), 1/1 (4 d) |
| 210 | 8 weeks | 2/2 | 0.5/0.5 (3 d or 7 d), 1/1 (4 d or 7 d) |

[a] 8/8 dose only. No titration for 2/2.
[b] 2/2 dose only.
[c] 1/1 titration was 3 days at 0.5/0.5, 1-week dose titration for patients receiving 2/2.

**Table 14: List of Clinical Studies**

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Enrolled[a] | Healthy Subjects or Diagnosis of Patients | Duration of Treatment[b] | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| **Phase 2 Studies – Buprenorphine + Samidorphan** | | | | | | | | |
| Efficacy/ Safety | 202 | Efficacy of BUP/SAM for treatment of MDD, safety, and tolerability | R, DB, two-stage, PC, SPCD study | *Stage 1:* BUP/SAM 2/2, titration dosing of BUP/SAM (2/2 or 8/8), or PBO; once daily for 4 weeks, followed by 1-week dose tapering; SL *Stage 2 (following PBO non-responder re-randomization):* BUP/SAM 2/2, titration dosing BUP/SAM 2/2, or 8/8, or PBO; once daily for 4 weeks, followed by 1-week dose tapering; SL | 142 | Adult patients with MDD and inadequate response to ADT | 10 weeks (2 phases, each phase 4-week treatment followed by 1-week dose tapering) | Complete; Full (Fava et al, 2016) |
| **Phase 3 Studies – Buprenorphine + Samidorphan: Double-Blind, Placebo-Controlled** | | | | | | | | |
| Efficacy | 205 | Efficacy of BUP/SAM for treatment of MDD, safety, and tolerability | R, DB, two-stage, PC, SPCD study | BUP/SAM (0.5/0.5 or 2/2[m]) or PBO; once daily for 11 weeks; SL | 385 | Adult patients with MDD and inadequate response to ADT | 11 weeks | Complete; Full |
| Efficacy | 206 | Efficacy of BUP/SAM for treatment of MDD, safety, and tolerability | R, DB, PC, two-stage, PG study | BUP/SAM titration dosing (2/2[m]) or PBO; once daily for 10 weeks; SL | 327 | Adult patients with MDD and inadequate response to ADT | Group 1: 6 weeks Group 2: 10 weeks | Complete; Full |
| Efficacy | 207 | Efficacy of BUP/SAM for treatment of MDD, safety, and tolerability | R, DB, two-stage, PC, SPCD study | BUP/SAM titration dosing (1/1[n] or 2/2[m]) or PBO; once daily for 11 weeks; SL | 407 | Adult patients with MDD and inadequate response to ADT | 11 weeks | Complete; Full |

**Table 14: List of Clinical Studies (Continued)**

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Enrolled[a] | Healthy Subjects or Diagnosis of Patients | Duration of Treatment[b] | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| **Phase 3 – Buprenorphine + Samidorphan: Short-Term Open-Label** | | | | | | | | |
| Safety | 210 | Safety and tolerability | R, DB, PG | BUP/SAM 1-week[o] or 2-week[p] titration dosing (0.5/0.5, 1/1, 2/2); once daily for 8 weeks; SL | 66 | Adult patients with MDD and inadequate response to ADT | 8 weeks | Complete; Full |
| **Phase 3 – Buprenorphine + Samidorphan: Long-Term Open-Label** | | | | | | | | |
| Long-term safety | 208 | Long-term safety and tolerability | OL | BUP/SAM (2/2)[q] ; SL | 1486 | Adult patients with MDD and inadequate response to ADT | 52 weeks | Complete; CSR pending |
| **Phase 1 Studies – Samidorphan Alone** | | | | | | | | |
| PK/ Safety | 33-012 | Evaluate the abuse potential, PK, and safety of PO administered SAM relative to OXY | DB, R, PC and positive controlled, SD six way crossover study | Multiple dose SAM (2.5 mg, 10 mg, and 20 mg), multiple dose oxycodone (15 mg and 30 mg) and PBO; one treatment per day over 6 treatment days; PO | 55 | Healthy, nondependent, opioid-experienced adult subjects | 3 days (5-day washout between treatments) | Complete; Full |
| PK/ Safety | B109 | Evaluate the abuse potential of SAM compared with PBO, OXY, PEN, and naltrexone<br>Safety and tolerability of SAM in healthy opioid users | DB, R, PC and AC, SD six way crossover study | Single doses of SAM (10 mg and 30 mg); PO<br>single dose oxycodone (40 mg); PO<br>single dose pentazocine (30 mg); IV<br>single dose naltrexone (100 mg); PO<br>and PBO; PO and/or IV | 69[d] | Healthy, nondependent, opioid-experienced adult subjects | 2 days (10-day washout between treatments) | Complete; Full |

**Table 14: List of Clinical Studies (Continued)**

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Enrolled[a] | Healthy Subjects or Diagnosis of Patients | Duration of Treatment[b] | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| **Phase 1 Studies - Buprenorphine + Samidorphan** | | | | | | | | |
| PK/PD | 33-008 | PD of SAM when coadministered with BUP.<br>PK, safety and tolerability of SAM when coadministered with BUP | R, DB, PC, two-cohort, SD, three-way crossover, DDI study of BUP and SAM | *Cohort 1:*<br>Multiple dose SAM (1 mg, 4 mg) and PBO, coadministered with BUP (8 mg); one treatment per visit over 3 visits; SL<br>*Cohort 2:*<br>Multiple dose SAM (8 mg, 16 mg) and PBO, coadministered with BUP (8 mg); one treatment per visit over 3 visits; SL | 13 | Healthy, nondependent, opioid-experienced adult subjects | 3 days (7- to 12-day washout between treatments) | Complete; Full<br>(Ehrich et al, 2015) |
| PK/ Safety | 33 BUP-201 | Safety and tolerability of BUP/SAM over a range of dose levels in MDD patients.<br>Multiple dose PK of BUP/SAM in MDD patients | R, DB, PC, MD, two cohort, PG study | *Cohort A:*<br>Multiple dose BUP-SAM 8:1 BUP:SAM (2/0.25, 4/0.5[e]) or PBO; once daily for 7 days; SL<br>*Cohort B:*<br>Multiple dose BUP-SAM 1:1 BUP:SAM (4/4, 8/8[e]) or PBO; once daily for 7 days; SL | 32 | Adult patients with MDD and inadequate response to ADT | Up to 7 days | Complete; Full<br>(Ehrich et al, 2015) |

**Table 14: List of Clinical Studies (Continued)**

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Enrolled[a] | Healthy Subjects or Diagnosis of Patients | Duration of Treatment[b] | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| PK/ Safety | 213 | Evaluate the QTc effect of BUP/SAM at super-therapeutic doses of 8/8 mg.<br>Evaluate the QTc effect of BUP/SAM 0.5/0.5, 2/2, 4/4 mg and (super-therapeutic) 8/8 mg doses.<br>Evaluate the effect of escalating doses of BUP/SAM on HR, PR, QRS, and ECG morphology.<br>Evaluate concentration-QTc relationship.<br>Evaluate assay sensitivity of the study by assessment of the QTc effect of moxifloxacin 400 mg.<br>Evaluate PK of SAM, BUP and respective primary metabolites. | R, DB, PC and moxifloxacin-controlled, three-sequence, crossover, PG, TQT study | *Group 1:*<br>MOXI PBO; once daily at beginning and end of study; PO<br>BUP/SAM titration dosing (0.5/0.5, 1/1, 2/2, 4/4, 8/8); once daily for 12 days; SL<br>*Groups 2 and 3:*<br>2-way crossover MOXI (400 mg) or MOXI PBO, once daily at beginning and end of study; PO<br>BUP/SAM PBO; once daily for 12 days; SL | 128 | Healthy adult subjects | 12 days | Complete; Full |

**Table 14: List of Clinical Studies (Continued)**

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Enrolled[a] | Healthy Subjects or Diagnosis of Patients | Duration of Treatment[b] | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|
| PK/ Safety | 212 | Evaluate abuse potential of BUP/SAM, safety, tolerability, and PK | R, DB, PC and active-controlled, SD, 6 way crossover abuse potential study | Multiple dose BUP/SAM (2/2, 8/8, and 16/16), multiple dose BUP (8 mg and 16 mg), and PBO; one treatment per visit over 6 visits; SL | 56 | Healthy, non-dependent, opioid-experienced adult subjects | 3 days (≥10-day washout between treatments) | (Pathak et al, 2018) |

ADT=antidepressant therapy; AUD=alcohol use disorder; BA=bioavailability; BE=bioequivalence; BED=binge eating disorder; BUP=buprenorphine; CYP3A4=cytochrome P450 3A4; DB=double-blind; DDI=drug-drug interaction; ECG=electrocardiogram; HR=heart rate; ITZ=itraconazole; MD=multiple dose; MDD=Major Depressive Disorder; MOXI=moxifloxacin; NA=not applicable; OL=open-label; OLZ=olanzapine; PBO=placebo; PC=placebo-controlled; PD=pharmacodynamics; PG=parallel group; PI =principal investigator; PK=pharmacokinetics; PO=oral; PR=pulse rate; R=randomized; REMI=remifentanil; SAM=samidorphan; SB=single-blind; SD=single dose; SL=sublingual; SPCD=sequential parallel comparative design

[a] For placebo-controlled studies, the total N enrolled indicates the number of subjects randomized.

[b] Number of days dosing with investigational study drug (BUP/SAM [BUP + SAM], SAM, or ALKS 3831 [OLZ + SAM]).

[d] One additional subject was randomized, but never dosed.

[e] In clinical studies, doses of BUP-SAM and BUP/SAM are expressed as ratios by weight of BUP to SAM (ie, ALKS 33) (eg, a 8 mg BUP:8 mg SAM dose is expressed as BUP-SAM 8/8).

[m] Subjects randomized to the 2/2 dose went through titration dosing (0.5/0.5, 1/1) for the first week of treatment and 2/2 thereafter.

[n] Subjects randomized to the 1/1 dose went through titration dosing (0.5/0.5) for the first three days of treatment and 1/1 thereafter.

[o] Subjects randomized to the 1-week titration group went through titration dosing (0.5/0.5, 1/1) for the first week of treatment and 2/2 thereafter.

[p] Subjects randomized to the 2-week titration group went through titration dosing (0.5/0.5) for the first week of treatment, (1/1) for the second week of treatment, and 2/2 thereafter.

[q] Some subjects underwent titration dosing (0.5/0.5, 1/1) for the first week of treatment and 2/2 thereafter. Subjects that could not tolerate the 2/2 dose were allowed to drop down to the 1/1 dose if needed.

**Table 15: Primary Efficacy Analysis of BUP/SAM Doses 0.5/0.5, 1/1 and 8/8 vs Placebo**

| Study | Design | Primary Assessment | Primary Analysis Difference BUP/SAM vs Placebo | BUP/SAM Dose | BUP/SAM vs Placebo LSMD (95% CI) *P*-value |
|---|---|---|---|---|---|
| 205 | SPCD | MADRS-10 | BUP/SAM vs placebo difference:<br>Change from baseline to Week 5 | 0.5/0.5 | 0.0 (1.17)<br>0.975 |
| 207 | SPCD | MADRS-6 (Tier 1) | Average of BUP/SAM vs placebo differences: changes from baseline to Week 3 through end of treatment | 1/1 | -0.6 (0.62)<br>0.329 |
| | | MADRS-10 (Tier 2) | Average of BUP/SAM vs placebo differences: changes from baseline to Week 3 through end of treatment | | -0.9 (0.85)<br>0.277 |
| | | MADRS-10 (Tier 3) | BUP/SAM vs placebo difference:<br>Change from baseline to end of treatment (Week 5/6) | | -1.3 (0.95)<br>0.165 |
| 202 | SPCD | HAM-D17 | BUP/SAM vs placebo difference:<br>Change from baseline to end of treatment (Week 4) | 8/8 | -0.5 (1.2)<br>0.699 |

Abbreviations: BUP=buprenorphine; HAM-D17= Hamilton Rating Scale for Depression-17; MADRS=Montgomery-Åsberg Depression Rating Scale; SAM=samidorphan; SPCD= Sequential parallel comparison design.

**Table 16: Demographics and Baseline Characteristics - Stage 1 Pooled Safety Population**

| Category | Placebo (N=658) | BUP/SAM Dose | | | | |
|---|---|---|---|---|---|---|
| | | 0.5/0.5 (N=59) | 1/1 (N=63) | 2/2 (N=162) | 8/8 (N=19) | Any (N=303) |
| **Age (years)** | | | | | | |
| Mean (SD) | 45.9 (12.01) | 45.0 (13.89) | 45.1 (11.46) | 44.9 (12.98) | 45.8 (11.93) | 45.0 (12.74) |
| **Gender, n (%)** | | | | | | |
| Female | 450 (68.4) | 38 (64.4) | 42 (66.7) | 107 (66.0) | 11 (57.9) | 198 (65.3) |
| **Primary race, n (%)** | | | | | | |
| White | 476 (72.3) | 42 (71.2) | 44 (69.8) | 119 (73.5) | 13 (68.4) | 218 (71.9) |
| Black or African American | 169 (25.7) | 16 (27.1) | 17 (27.0) | 39 (24.1) | 6 (31.6) | 78 (25.7) |
| **Region, n (%)** | | | | | | |
| US | 557 (84.7) | 53 (89.8) | 54 (85.7) | 142 (87.7) | 19 (100.0) | 268 (88.4) |
| NonUS | 101 (15.3) | 6 (10.2) | 9 (14.3) | 20 (12.3) | 0 | 35 (11.6) |
| **Body mass index ($kg/m^2$)** | | | | | | |
| Mean (SD) | 29.6 (5.6) | 30.1 (5.5) | 29.9 (6.0) | 29.5 (5.6) | 30.9 (6.1) | 29.8 (5.7) |
| **ADT type for current ADT, n (%)** | | | | | | |
| SSRI | 419 (63.7) | 40 (67.8) | 32 (50.8) | 104 (64.2) | 18 (94.7) | 194 (64.0) |
| SNRI | 179 (27.2) | 10 (16.9) | 22 (34.9) | 44 (27.2) | 1 (5.3) | 77 (25.4) |
| Other | 60 (9.1) | 9 (15.3) | 9 (14.3) | 14 (8.6) | 0 | 32 (10.6) |
| **Benzodiazepine use, n (%)** | | | | | | |
| No | 582 (88.4) | 58 (98.3) | 58 (92.1) | 140 (86.4) | 16 (84.2) | 272 (89.8) |
| Yes | 63 (9.6) | 1 (1.7) | 3 (4.8) | 18 (11.1) | 3 (15.8) | 25 (8.3) |
| Other[a] | 13 (2.0) | 0 | 2 (3.2) | 4 (2.5) | 0 | 6 (2.0) |
| **Opioid use, n (%)[b]** | | | | | | |
| No | 651 (98.9) | 58 (98.3) | 63 (100.0) | 157 (96.9) | 19 (100.0) | 297 (98.0) |
| Yes | 7 (1.1) | 1 (1.7) | 0 | 5 (3.1) | 0 | 6 (2.0) |
| **Sedating $H_1$ antagonist use, n (%)** | | | | | | |
| No | 644 (97.9) | 59 (100.0) | 60 (95.2) | 158 (97.5) | 19 (100.0) | 296 (97.7) |
| Yes | 14 (2.1) | 0 | 3 (4.8) | 4 (2.5) | 0 | 7 (2.3) |

Abbreviations: ADT=antidepressant therapy; Max=maximum; Min=minimum; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

[a] "Other" is defined as subjects taking sedating $H_1$ antagonist but not taking benzodiazepine group concomitant medications.

[b] Opioid use was excluded as part of study criteria.

**Table 17: Background Antidepressant Therapy Class (Placebo and BUP/SAM 2/2 Doses), Stage 1 (Studies 202, 205, 206, and 207)**

| ADT Type for Current MDE, n (%) | Study 202 | | Study 205 | | Study 206[a] | | Study 207 | |
|---|---|---|---|---|---|---|---|---|
| | Placebo (N=95) | BUP/SAM 2/2 (N=20) | Placebo (N=256) | BUP/SAM 2/2 (N=59) | Placebo (N=148) | BUP/SAM 2/2 (N=147) | Placebo (N=273) | BUP/SAM 2/2 (N=63) |
| SSRI | 75 (78.9) | 16 (80.0) | 151 (59.0) | 35 (59.3) | 98 (66.2) | 103 (70.1) | 172 (63.0) | 35 (55.6) |
| SNRI | 20 (21.1) | 4 (20.0) | 79 (30.9) | 18 (30.5) | 35 (23.6) | 31 (21.1) | 71 (26.0) | 21 (33.3) |
| Other[b] | 3 (3.2) | 1 (5.0) | 26 (10.2) | 6 (10.2) | 16 (10.8) | 13 (8.8) | 30 (11.0) | 7 (11.1) |

Abbreviations: ADT=antidepressant therapy; MDE=major depressive episode; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

[a] Group 1 only.

[b] The ADTs listed as other for Study 202 included bupropion and trazodone (protocol violations).

**Table 18: Background Antidepressant Therapy Class (Placebo and BUP/SAM 2/2 Doses), Stage 2 Full Analysis Set (Studies 202, 205, and 207)**

| ADT Type for Current MDE, n (%) | Study 202 | | Study 205 | | Study 207 | |
|---|---|---|---|---|---|---|
| | Placebo (N=20) | BUP/SAM 2/2 (N=23) | Placebo (N=54) | BUP/SAM 2/2 (N=54) | Placebo (N=60) | BUP/SAM 2/2 (N=63) |
| SSRI | 16 (80.0) | 21 (91.3) | 37 (68.5) | 30 (55.6) | 31 (51.7) | 40 (63.5) |
| SNRI | 4 (20.0) | 2 (8.7) | 15 (27.8) | 18 (33.3) | 21 (35.0) | 17 (27.0) |
| Other[a] | 1 (5.0) | 0 | 2 (3.7) | 6 (11.1) | 8 (13.3) | 6 (9.5) |

Abbreviations: ADT=antidepressant therapy; MDE=major depressive episode; PBO=placebo; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

[a] The ADT listed as other for Study 202 was trazodone (protocol violation).

**Table 19: Treatment-Emergent Adverse Events in ≥2% of Patients Treated with BUP/SAM 2/2 and a Greater Incidence than in Placebo-Treated Patients by System Organ Class and Preferred Term - Stage 1**

| System Organ Class<br>Preferred Term, n (%) | Placebo (N=658) | BUP/SAM Dose | | | |
|---|---|---|---|---|---|
| | | 0.5/0.5 (N=59) | 1/1 (N=63) | 2/2 (N=162) | 8/8 (N=19) |
| Any TEAE | 358 (54.4) | 34 (57.6) | 37 (58.7) | 111 (68.5) | 18 (94.7) |
| **Gastrointestinal disorders** | **135 (20.5)** | **21 (35.6)** | **19 (30.2)** | **69 (42.6)** | **11 (57.9)** |
| Nausea | 46 (7.0) | 14 (23.7) | 9 (14.3) | 43 (26.5) | 9 (47.4) |
| Constipation | 18 (2.7) | 4 (6.8) | 9 (14.3) | 20 (12.3) | 1 (5.3) |
| Vomiting | 11 (1.7) | 4 (6.8) | 3 (4.8) | 16 (9.9) | 8 (42.1) |
| Dry mouth | 29 (4.4) | 2 (3.4) | 2 (3.2) | 10 (6.2) | 2 (10.5) |
| **Nervous system disorders** | **116 (17.6)** | **16 (27.1)** | **17 (27.0)** | **51 (31.5)** | **16 (84.2)** |
| Dizziness | 27 (4.1) | 4 (6.8) | 6 (9.5) | 21 (13.0) | 9 (47.4) |
| Headache | 59 (9.0) | 7 (11.9) | 4 (6.3) | 17 (10.5) | 5 (26.3) |
| Somnolence | 22 (3.3) | 5 (8.5) | 4 (6.3) | 11 (6.8) | 2 (10.5) |
| Sedation | 6 (0.9) | 2 (3.4) | 3 (4.8) | 11 (6.8) | 5 (26.3) |
| **Psychiatric disorders** | **53 (8.1)** | **5 (8.5)** | **8 (12.7)** | **29 (17.9)** | **2 (10.5)** |
| Abnormal dreams | 12 (1.8) | 3 (5.1) | 2 (3.2) | 5 (3.1) | 0 |
| Insomnia | 10 (1.5) | 1 (1.7) | 2 (3.2) | 6 (3.7) | 0 |
| Anxiety | 7 (1.1) | 0 | 1 (1.6) | 4 (2.5) | 1 (5.3) |
| **General disorders and administration site conditions** | **23 (3.5)** | **4 (6.8)** | **7 (11.1)** | **25 (15.4)** | **3 (15.8)** |
| Fatigue | 10 (1.5) | 3 (5.1) | 5 (7.9) | 12 (7.4) | 2 (10.5) |
| **Skin and subcutaneous tissue disorders** | **28 (4.3)** | **3 (5.1)** | **3 (4.8)** | **14 (8.6)** | **4 (21.1)** |
| Hyperhidrosis | 15 (2.3) | 0 | 2 (3.2) | 6 (3.7) | 1 (5.3) |
| **Infections and infestations** | **75 (11.4)** | **3 (5.1)** | **3 (4.8)** | **14 (8.6)** | **1 (5.3)** |
| Upper respiratory tract infection | 12 (1.8) | 1 (1.7) | 1 (1.6) | 4 (2.5) | 0 |
| **Metabolism and nutrition disorders** | **15 (2.3)** | **2 (3.4)** | **2 (3.2)** | **7 (4.3)** | **1 (5.3)** |
| Decreased appetite | 6 (0.9) | 0 | 1 (1.6) | 5 (3.1) | 1 (5.3) |

Abbreviation: BUP=buprenorphine; SAM=samidorphan; TEAE=treatment-emergent adverse event

**Table 20: Treatment-Emergent Adverse Events in ≥2% of Patients in the BUP/SAM 2/2 and a Greater Incidence than in Placebo-Treated Patients by System Organ Class and Preferred Term - Stage 2**

| System Organ Class<br>Preferred Term, n (%) | Placebo (N=286) | BUP/SAM Dose | | | |
|---|---|---|---|---|---|
| | | 0.5/0.5 (N=56) | 1/1 (N=62) | 2/2 (N=289) | 8/8 (N=22) |
| Any TEAE | 119 (41.6) | 27 (48.2) | 29 (46.8) | 137 (47.4) | 19 (86.4) |
| **Gastrointestinal Disorders** | **26 (9.1)** | **12 (21.4)** | **7 (11.3)** | **68 (23.5)** | **12 (54.5)** |
| Nausea | 5 (1.7) | 5 (8.9) | 2 (3.2) | 36 (12.5) | 5 (22.7) |
| Vomiting | 4 (1.4) | 2 (3.6) | 0 | 14 (4.8) | 3 (13.6) |
| Constipation | 2 (0.7) | 1 (1.8) | 2 (3.2) | 11 (3.8) | 3 (13.6) |
| Dry mouth | 4 (1.4) | 0 | 1 (1.6) | 7 (2.4) | 1 (4.5) |
| **Nervous System Disorders** | **22 (7.7)** | **7 (12.5)** | **2 (3.2)** | **40 (13.8)** | **15 (68.2)** |
| Dizziness | 6 (2.1) | 4 (7.1) | 1 (1.6) | 9 (3.1) | 4 (18.2) |
| **Skin and Subcutaneous Tissue Disorders** | **4 (1.4)** | **3 (5.4)** | **0** | **14 (4.8)** | **3 (13.6)** |
| Hyperhidrosis | 0 | 0 | 0 | 8 (2.8) | 1 (4.5) |
| **General Disorders and Administration Site Conditions** | **12 (4.2)** | **1 (1.8)** | **0** | **15 (5.2)** | **2 (9.1)** |
| Fatigue | 6 (2.1) | 0 | 0 | 10 (3.5) | 1 (4.5) |

Abbreviation: BUP=buprenorphine; SAM=samidorphan; TEAE=treatment-emergent adverse event.

**Table 21: Preferred Terms Used to Evaluate Abuse Behavior, Nonspecific Abuse Potential, Euphoria, Potential for Dependence, and Potential for Withdrawal**

| **Preferred Terms Used to Evaluate Abuse Potential** | |
|---|---|
| Accidental overdose | Drug abuser |
| Drug diversion | Drug level above therapeutic |
| Drug level increased | Drug screen |
| Drug screen positive | Intentional overdose |
| Intentional product misuse | Intentional product use issue |
| Maternal use of illicit drugs | Needle track marks |
| Neonatal complications of substance abuse | Overdose |
| Prescription drug used without a prescription | Prescription form tampering |
| Product tampering | Substance abuse |
| Substance abuser | Substance use |
| Substance-induced mood disorder | Substance-induced psychotic disorder |
| Toxicity to various agents | |
| **Preferred Terms Used to Evaluate Nonspecific Abuse Potential** | |
| Acute psychosis | Emotional disorder |
| Aggression | Flight of ideas |
| Cognitive disorder | Medication overuse headache |
| Confusional state | Mental impairment |
| Delirium | Mood altered |
| Delusional disorder, unspecified type | Mood swings |
| Depersonalisation/derealisation disorder | Narcotic bowel syndrome |
| Disorientation | Paranoia |
| Dissociation | Psychotic behaviour |
| Disturbance in attention | Psychotic disorder |
| Disturbance in social behavior | Sedation |
| Dizziness | Somnolence |
| Dopamine dysregulation syndrome | Stupor |

**Table 21: Preferred Terms Used to Evaluate Abuse Behavior, Nonspecific Abuse Potential, Euphoria, Potential for Dependence, and Potential for Withdrawal (Continued)**

| | | | |
|---|---|---|---|
| **Preferred Terms Used to Evaluate Euphoria** | | | |
| Euphoric mood | | Hallucination, mixed | |
| Feeling abnormal | | Hallucination, olfactory | |
| Feeling drunk | | Hallucination, synaesthetic | |
| Feeling of relaxation | | Hallucination, tactile | |
| Hallucination | | Hallucination, visual | |
| Hallucination, auditory | | Inappropriate affect | |
| Hallucination, gustatory | | Thinking abnormal | |
| **Preferred Terms Used to Evaluate Potential for Dependence** | | | |
| Dependence | | Drug tolerance | |
| Drug dependence | | Drug tolerance decreased | |
| Drug dependence, antepartum | | Drug tolerance increased | |
| Drug dependence, postpartum | | Substance dependence | |
| **Preferred Terms Used to Evaluate Potential for Withdrawal** | | | |
| Drug withdrawal syndrome | Anhedonia | Poor quality sleep | Vomiting |
| Drug withdrawal convulsions | Depressed mood | Syncope | Abdominal pain |
| Drug withdrawal syndrome neonatal | Depression | Terminal insomnia | Arthralgia |
| Drug withdrawal maintenance therapy | Dysphoria | Agitation | Diarrhoea |
| Drug withdrawal headache | Feeling of despair | Irritability | Mydriasis |
| Withdrawal arrhythmia | Morose | Anxiety | Piloerection |
| Withdrawal syndrome | Negative thoughts | Chills | Restlessness |
| Drug rehabilitation | Persistent depressive disorder | Hyperhidrosis | Rhinorrhoea |
| Rebound effect | Dyssomnia | Nausea | Tachycardia |
| Steroid withdrawal syndrome | Headache | Nervousness | Yawning |
| Drug detoxification | Insomnia | Pain | |
| Reversal of opiate activity | Obsessive thoughts | Tremor | |