

eTable 1. Study inclusion and exclusion criteria

Inclusion criteria

- Meet DSM-5 criteria¹ for moderate or severe opioid use disorder at screening and not seeking treatment for opioid use disorder
 - Age 18–55 years
 - BMI 18–33.0 kg/m²
 - Women of childbearing potential (defined as all women who are not surgically sterile or postmenopausal for ≥1 year prior to informed consent) must have a negative pregnancy test prior to enrolment and must agree to use a medically acceptable means of contraception from screening through ≥3 months after the last dose of study drug
 - Male subjects with female partners of child-bearing potential must agree to use medically acceptable contraception from screening through ≥3 months after the last dose of study drug
 - The following methods of contraception are considered to be medically acceptable: established use of oral, injected, or implanted hormonal contraception; placement of an intrauterine device or intrauterine system; or use of a barrier method of contraception (condom or occlusive cap with use of a spermicide)
 - Male subjects must also agree not to donate sperm during the study through ≥3 months after the last dose of study drug
 - Normal or no clinically significant ECG findings at screening
 - Total bilirubin ≤1.5 × ULN, ALT ≤3 × ULN, AST ≤3 × ULN, serum creatinine ≤2 × ULN, INR ≤1.5 × ULN
 - Current or historical experience with parenteral abuse of opioids
 - Experiencing signs and symptoms of withdrawal prior to the start of buprenorphine dosing (as evidenced by a COWS score >12)
 - Agree not to take any buprenorphine products other than those administered for the current study throughout participation in the study
 - Willing to cooperate with study procedures and provide written informed consent prior to the start of any study procedures
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Exclusion criteria

- Any current diagnosis requiring chronic opioid treatment
 - History of risk factors of Torsades de Pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome) or an ECG demonstrating a QTcF >450 msec in males and >470 msec in females at screening
 - Subjects who currently meet the criteria for diagnosis of moderate or severe substance use disorder, by DSM-5 criteria,¹ for any substances other than opioids, caffeine², or nicotine
 - Subjects with uncontrolled medical or psychiatric illness or any clinically significant finding/abnormality in past medical history or at the screening physical examination that in the opinion of the principle investigator or sponsor may place the volunteer at risk or interfere with outcome variables including absorption, distribution, metabolism, and excretion of drug, including but is not limited to history or concurrent cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease
 - Subjects who have abused or used buprenorphine within 14 days prior to informed consent
 - Subjects who are currently (during the past 30 days from the signing of the informed consent) engaged in opioid agonist, partial agonist, or antagonist treatment, or require ongoing prescription or OTC medications that are clinically relevant CYP 3A4 or CYP 2C8 inducers or inhibitors (e.g., rifampicin, azole antifungals [e.g., ketoconazole], macrolide antibiotics [e.g., erythromycin]) with the exception of marijuana
 - Subjects with significant traumatic injury, major surgery, or open biopsy within the prior 4 weeks of informed consent
 - Subjects with a history of suicidal ideation within 6 months prior to informed consent as evidenced by answering “yes” to questions 4 or 5 on the suicidal ideation portion of the C-SSRS completed at the screening visit or history of a suicide attempt (per the C-SSRS) in the 6 months prior to informed consent
 - Subjects with a PHQ-9 score >15 indicating moderate or severe major depression
 - Subjects with current or history (within the 6 months prior to screening) of chest pain or palpitation on exertion or drug use, edema, clinically significant cardiovascular disease,
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including myocardial infarction, heart failure, uncontrolled hypertension, clinically significant orthostatic hypotension, endocarditis, or myocarditis

- Subjects with clinically significant measured systolic blood pressure or diastolic blood pressure, in the opinion of the investigator
- Subjects with current dyspnea, orthopnea, or tachypnea (>24 breaths per minute), and/or history (within the 90 days prior to screening) of obstructive pulmonary disease, cor pulmonale, tuberculosis, or asthma
- Subjects with other current clinically significant medical problems, such as endocrinopathies, renal or hepatic failure, myxedema, uncontrolled hypothyroidism, adrenocortical insufficiency (e.g., Addison's disease), or autoimmune disease involving the CNS
- Subjects with a history or presence of allergic or adverse response (including rash or anaphylaxis) to hydromorphone, buprenorphine, naloxone, or the Atrigel[®] Delivery System
- Subjects with clinically significant anemia or low hemoglobin at screening, or donation of >250 mL of blood or plasma, or participation in another clinical trial within 30 days prior to informed consent
- Subjects who have AIDS, acute^a hepatitis B, or acute^a hepatitis C
- Site staff or subjects affiliated with, or a family member of, site staff directly involved in the study
- Subjects who have previously received sustained-release buprenorphine
- Subjects who are unable, in the opinion of the investigator, to comply fully with the study requirements
- Subjects with a peak "Drug Liking" VAS score <40 mm (out of 100 mm) after administration of 18 mg hydromorphone during the baseline hydromorphone challenge (hydromorphone challenge on Day -17 to Day -15)
- Subjects with a <20-mm difference in peak "Drug Liking" VAS scores after administration of placebo and 18 mg hydromorphone during the baseline hydromorphone challenge (hydromorphone challenge on Day -17 to Day -15)

^a Subjects with asymptomatic hepatitis B or C infection may be enrolled.

AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CNS, central nervous system; COWS, clinical opiate withdrawal scale; C-SSRS, Columbia Suicide Severity Rating Scale; CYP, cytochrome P450; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ECG, electrocardiogram; INR, international normalized ratio; OTC, over-the-counter; PHQ-9, Patient Health Questionnaire; QTcF, Fridericia's corrected QT interval; ULN upper limit of normal; VAS, visual analogue scale.

¹American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (5th ed.). Arlington, VA: American Psychiatric Publishing; 2013.

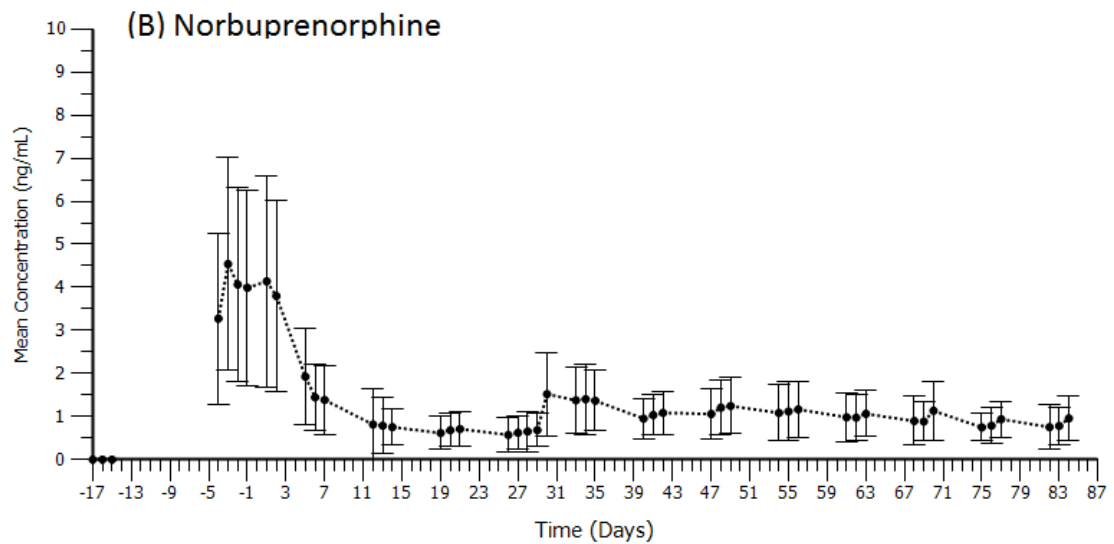
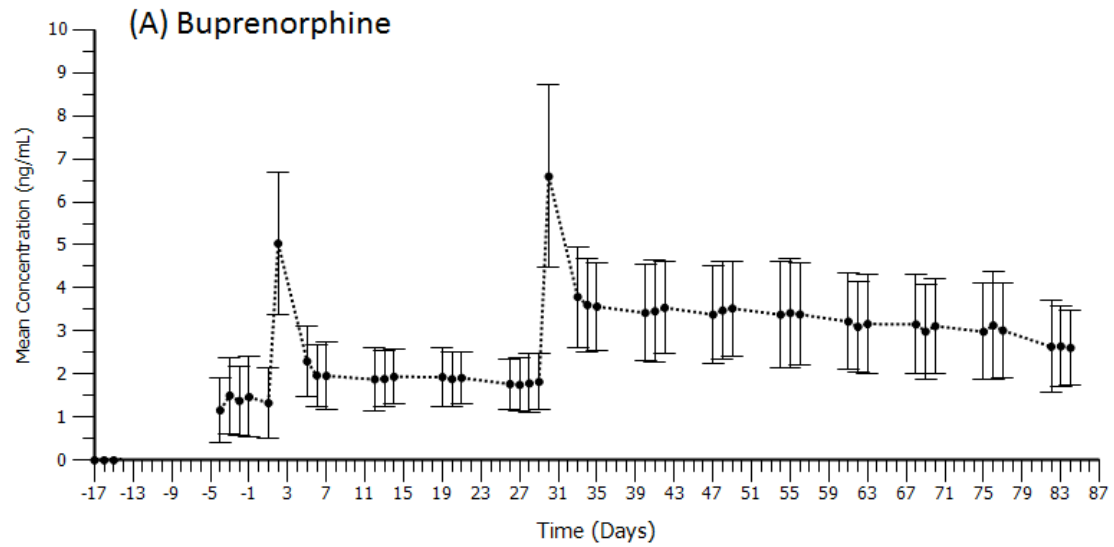
²Proposed criteria for caffeine use disorder are provided in DSM-5 as it is currently listed as a condition for further study.

eTable 2. Sustained-release buprenorphine dosing criteria

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- Subjects who do not meet any of the following criteria on Day 1 (prior to sustained-release buprenorphine dose) will be excluded from being dosed with sustained-release buprenorphine and continuing in the study
 - Subjects must be able to tolerate the induction and stabilization with buprenorphine
 - Subjects must be stable on a daily dose of buprenorphine between 8 mg and 24 mg by Day –9 and continue on that dose through Day –1. Subjects are stable if they have a COWS score of ≤ 12 and an Opioid Craving VAS score of ≤ 20 mm from Day –9 through Day 1 predose
 - No suicidal ideation or suicide attempt (per the C-SSRS) from Day –14 through Day 1 predose
 - No moderate or severe major depressive symptoms as indicated by a PHQ-9 score < 15
 - Normal or no clinically significant ECG findings through predose on Day 1, and an ECG demonstrating QTcF ≤ 450 msec in males and QTcF ≤ 470 msec in females prior to administration of sustained-release buprenorphine
 - Subjects must be able, in the opinion of the investigator, to comply fully with the study requirements

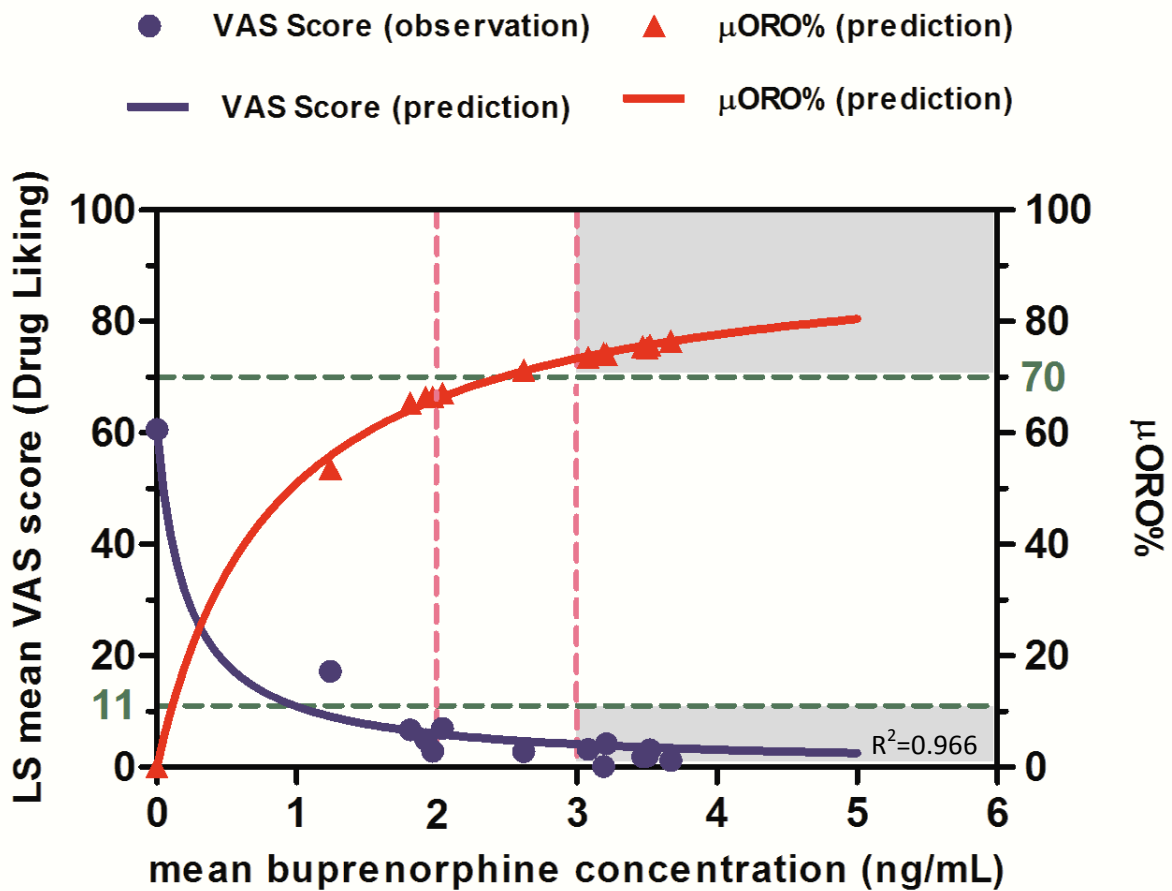
^a Subjects with asymptomatic hepatitis B or C infection may be enrolled.

COWS, clinical opiate withdrawal scale; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; PHQ-9, Patient Health Questionnaire; QTcF, Fridericia's corrected QT interval; VAS, visual analogue scale.



eFigure 1. (A) Mean \pm SD buprenorphine plasma concentrations; (B) Mean \pm SD norbuprenorphine plasma concentrations (before and 24 hr after sustained-release buprenorphine on Day 1, immediately before hydromorphone administration on Days -17, -16, -15, -3, -2, -1, 5–7, etc) (ITT population). ITT, intent-to-treat; SD, standard deviation.

eFigure 2. Correlation between mean buprenorphine concentration and clinical effect



A saturable Emax model was used for predicting the μ ORO using mean buprenorphine plasma concentrations as presented in equation 1 (Nasser AF, et al. Clin Pharmacokinet. 2014;53:813-824):

$$\mu\text{ORO} = \frac{E_{\text{max}} * C}{EC_{50} + C} \quad (1)$$

Where C is buprenorphine plasma concentration and EC50 is buprenorphine plasma concentration expected to achieve 50% of the maximal μ ORO (Emax).

An Emax inhibitory model was used for describing the relationship between Drug Liking VAS scores and buprenorphine plasma concentrations after 18mg hydromorphone challenge as presented in equation 2:

$$E = E_0 * \left(1 - \frac{C}{C + IC_{50}}\right) \quad (2)$$

Where C is buprenorphine plasma concentration and IC50 is buprenorphine plasma concentration that results in 50% of the Drug Liking VAS scores at baseline (E0).

The estimated value for E0 (standard error) was 60.71 (2.99) and the estimated value for IC50 (standard error) was 0.22 (0.04) (ng/mL).