CLINICAL STUDY PROTOCOL

A 2-PART, DOSE-FINDING AND HUMAN ABUSE POTENTIAL STUDY OF HSK3486 INJECTION IN NONDEPENDENT, RECREATIONAL CENTRAL NERVOUS SYSTEM DEPRESSANT USERS

CONFIDENTIAL

Sponsor code: HSK3486-110

[redacted]

Investigational product:	HSK3486
Clinical phase:	Phase 1 study
Sponsor:	Haisco-USA Pharmaceuticals, Inc [redacted]
Contract Research Organization	[redacted]
Clinical Site	[redacted]
Principal Investigator:	[redacted]

Version 2.0, 04-Nov-2022

This study will be performed in compliance with the principles of Good Clinical Practice.

SPONSOR AUTHORIZATION OF CLINICAL STUDY PROTOCOL

The Sponsor and the Contract Research Organization agree to conduct the study as outlined in this clinical study protocol. Any modification of the clinical study protocol must be agreed upon by the Sponsor and the Contract Research Organization and must be documented in writing.

Name/Position: Date: Signature:

Sponsor: Haisco-USA Pharmaceuticals, Inc

[redacted]

[redacted]

AUTHORIZATION OF CLINICAL STUDY PROTOCOL BY CONTRACT RESEARCH ORGANIZATION

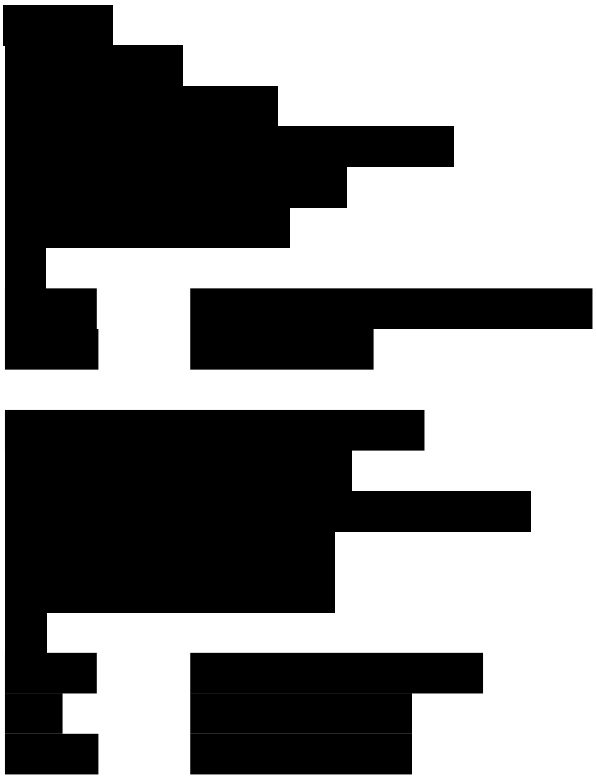
The Sponsor and the Contract Research Organization agree to conduct the study as outlined in this clinical study protocol. Any modification of the clinical study protocol must be agreed upon by the Sponsor and the Contract Research Organization and must be documented in writing.

Name/Position: Date: Signature:

[redacted]

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In case of a serious adverse event (see Appendix 8.2), the Principal Investigator will send a report within 24 hours of notification to:



SUMMARY OF CHANGES

The following changes have been introduced in this Version 2.0 of the protocol (dated 04-Nov-2022). Updates are either described below, or pictured below with double underlined/italic text for additions and ~~strikethrough~~ for deletions. Additionally, clarifications from previously approved Administrative Letters are incorporated in this protocol amendment.

- **Location:** Synopsis, Table 2 footnote n, Table 3 footnote q, and Section 3.1.3.2
  - **Addition/Deletion:** ~~approximately~~ *at least* 48 hours
  - **Rationale:** To improve the specificity of the washout verbiage used between Qualification Phase and the Treatment Phase.

- **Location:** Synopsis, Table 2: Part 2 Schedule of Assessments — Screening and Qualification Phase / Table 3: Part 2 Schedule of Assessments — Treatment Phase (Periods 1-4) and Safety Follow-up/Early Withdrawal (table body), Section 3.5.3.2
  - **Update Description:** Global VAS evaluations were planned for 8 and 24 hours postdose. The evaluation at 8 hours is changed to 12 hours
  - **Rationale:** Global VAS evaluations typically occur at 12 and 24 hours.

- **Location**: Synopsis and Section 3.3.1 (Inclusion 7)
  - **Deletion:** Remove opiates from inclusion list of ≥10 lifetime nontherapeutic experiences (i.e., for psychoactive effects) with CNS depressants.
  - **Rationale:** Inclusion of subjects with nontherapeutic experiences with opioids may decrease reliability and interpretability of the study results.

- **Location:** Synopsis, Section 3.5.3.2; Section 3.5.1.2.9
  - **Update Description:** Updated the endpoints for Part 2 of the study. The secondary endpoints for statistical hypothesis testing are: Take Drug Again VAS; High VAS; Overall Drug Liking VAS. The secondary endpoints for descriptive analysis are: Good Drug Effects; Bad Drug Effects, sick-nausea; Unknown: Any Drug Effects, Drowsiness/Alertness, and Drug Similarity.
  - **Rationale:** To clarify the secondary endpoints. These measures intend to evaluate subjective responses after peak drug effects (E_{max}) have occurred, as well as next-day responses utilizing the unipolar and bipolar VAS.

- **Location:** Synopsis, Section 3.6.3

  Update Description: Revised the power calculation for sample size**.** Changes to the Synopsis and Section 3.6.2.3 are indicated below:

  For the validity comparison, a sample size of 36 subjects will provide 95% power to detect a mean difference in the Drug Liking VAS E_{max} between 0.6 mg/kg propofol and placebo that is greater than a margin of δ_1=15 in a 1-sided, alpha=0.025 test for study validity. *And with alpha=0.05, a sample size of 36 subjects will provide at least 98% power to detect a mean difference in the Drug Liking VAS E_{max} between 0.6 mg/kg propofol and placebo that is greater than a margin of 15-point in a 1-sided test.* This assumes Drug Liking E_{max} mean (SD) of 74.4 (14.99) for propofol and 50 (0.33) for placebo, and correlation of 0.5. [5]

For the primary treatment comparison, evaluating the difference between propofol and HSK3486, a sample size of 27 will provide 95% power to reject the null hypothesis that HSK3486 has greater abuse potential than propofol, in favor of similarity with less than 11-point ~~difference~~ in a 1-sided ~~t-test,~~ alpha=0.025 *t-test*. This assumes a mean (SD) of the difference in Drug Liking E_{max} between HSK3486 and propofol of 0 (15).

- **Rationale:** The power calculation for sample size was revised based on the correct hypothesis**.**

- **Location:** Table 1: Schedule of Assessments — Screening and Qualification Phase / Table 2: Part 2 Schedule of Assessments — Screening and Qualification Phase
  - **Update Description and Additions:** Weight will be collected at Admission to the clinic in Part 1 (from the date of this protocol amendment) and Part 2. An X was added to the relevant column of the "Demographics, Height, Weight, BMI" row in Tables 1 and 2. Footnotes were added Table 1 (footnote p) and Table 2 (footnote u) to clarify that only weight will need to be redone at admission.
    - footnote *g - Weight only will be collected on Day -1.*
    - footnote *u - Weight only will be collected on Day -4.*
  - **Rationale:** Participants' weight at admission is needed to calculate the correct dose in accordance with the Pharmacy Manual. Refer to memo to file for participants' enrolled prior to this protocol amendment.

- **Location:** Table 1: Schedule of Assessments — Screening and Qualification Phase / Table 2: Part 2 Schedule of Assessments — Screening and Qualification Phase / Table 3: Part 2 Schedule of Assessments — Treatment Phase (Periods 1-4) and Safety Follow-up/Early Withdrawal / Section 3.5.1.3.7
  - **Update Description:** Pulse oximetry and telemetry measurements were planned to 8 hours postdose. This has been decreased to 4 hours postdose. For participants in Part 1, this change will apply from the date of this protocol amendment.
  - **Rationale:** This change was to decrease burden on the site staff, and given that patients who receive treatment doses of these medications in outpatient procedures are routinely discharged home within 4 hours, there is no expected increase in risk to the study subject.

- **Location:** Table 2: Part 2 Schedule of Assessments — Screening and Qualification Phase (footnotes I and k) / Table 3: Part 2 Schedule of Assessments — Treatment Phase (Periods 1-4) and Safety Follow-up/Early Withdrawal (footnotes k and n)
  - **Update Description:** Added Drug High VAS and Nausea to list of Drug Specific VAS. Added Drug Similarity to list of Other VAS.
  - **Rationale:** These parameters were inadvertently not included in the Schedules of Assessments for Part 2.

- **Location:** Table 3: Part 2 Schedule of Assessments — Treatment Phase (Periods 1-4) and Safety Follow-up/Early Withdrawal (table body and footnote j)
  - **Update Description:** The 1 min and 5 min collections will be changed to 2 min and 6 min, respectively; in footnote j the ±3 min sampling window prior to 15 min will be changed ±1 min; and an 8 hour postdose blood sampling will be added for PK collections.
  - **Rationale:** To update and expand the PK sampling window to improve accuracy of PK assessments.

- **Location:** Section 3.5.1.3.2
  - **Update Description and Addition:** Added description of Adverse Events of Special Interest (AESI).
    - *Part 2 only: AESIs are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. AESIs may be serious or nonserious. The AESIs due to pharmacological effect of an anesthetic agent include hypoxemia, bradycardia, hypotension, allergy/anaphylaxis, and cardiac arrhythmia, which are defined as follows:*
      - *Hypoxemia due to respiratory depression is defined as SpO2 <90% with duration of >30 seconds. Hypoxemia is evaluated from the initial dose of study drug until 1 hour postdose.*
      - *Symptomatic bradycardia, where bradycardia is defined as a heart rate of <45 beats/minute that lasts >30 seconds and requiring intervention. Bradycardia is evaluated from the initial dose of study drug until 1 hour postdose.*
      - *Hypotension defined as an SBP <90 mmHg that lasts >2 minutes and requiring treatment. Hypotension is evaluated from the initial dose of study drug until 1 hour postdose.*
      - *Allergy/anaphylaxis may include angioedema, bronchospasm, erythema, and hypotension. Allery/anaphylaxis is evaluated from the initial dose of study drug until 4 hours postdose.*
      - *Clinically significant cardiac arrhythmia, as judged by the Investigator. Cardiac arrhythmia is evaluated from the initial dose of study drug until 4 hours postdose.*
      - *QTc prolongation: QTc intervals of >450 ms in males and >470 ms in females occurring within 15 minutes of study drug. Participants who reach an absolute QT interval of more than 500 ms upon QTc correction for rate should be reassessed, and immediate action should be taken to correct any possible concomitant risk factors.*
    - *Start time, end time, and duration should be calculated, and treatment measures (if any) should be recorded. Additionally, AESIs will be categorized as drug related for those occurring within 15 minutes from the initial dose of study drug.*

    Rationale: To ensure proper collection and categorization of AEs associated with anesthetic agent administration.

- **Location:** Section 3.6.2.2
  - **Update Description:** Revised the relative abuse potential hypothesis testing. Changes to Section 3.6.2.2 are indicated below:

    The treatment comparison for relative abuse potential of HSK3486 will be the comparison of Drug Liking E_{max} between each dose level of HSK3486 *(Treatment A and Treatment B)* and propofol (Treatment C). The following hypothesis will be tested for each comparison:

    1. A: HSK3486 dose 1 vs. C: propofol
    2. B: HSK3486 dose 2 vs. C: propofol

    The hypothesis can be expressed as:

    $$H_o: \mu_C - \mu_T \leq \delta_2 \text{ vs. } H_a: \mu_C - \mu_T > \delta_2,$$

with δ_2 =11, ~~≥0 and~~ where μ_C is the mean *of Drug Liking E_{max}* for propofol *(Treatment C),* and μ_T is mean for *Drug Liking E_{max} for* each dose level of HSK3486 *(Treatment A and Treatment B)*. ~~Primary comparison will be the highest dose at which the subjects can complete all the assessments.~~ If the treatment difference is statistically significant *with the* ~~(less than~~11*-point (δ_2)* in a 1-sided test at a 5% level of significance, this will demonstrate that the abuse potential of *propofol is greater than that of* HSK3486 ~~is no greater than propofol~~ *by at least 11 points*. The 1-sided 95% CIs of the mean difference will be calculated. P-values will be provided for the treatment comparisons. And the 2-sided 95% CIs will be also derived for the exploratory result.

- **Rationale:** To clarify the hypothesis for comparing Drug Liking E_{max} between each dose level of HSK3486 and propofol; to clarify how statistical significance will be evaluated.

- **Location:** Section 3.6.2.2

  Update Description: Revised the hypothesis test for each dose of HSK3486 compared to placebo and provided a preselected value of margin δ_3. Changes to Section 3.6.2.2 are indicated below:

  The evaluation of absolute abuse potential of HSK3486 will be the comparison of HSK3486 versus placebo. The following hypothesis will be tested for each dose level of HSK3486 compared to placebo:

  1. A: HSK3486 dose 1 vs. D: placebo
  2. B: HSK3486 dose 2 vs. D: placebo

  The hypothesis can be expressed as:

  ~~$H_o: \mu_C - \mu_T \leq \delta_2$ vs. $H_a: \mu_C - \mu_T > \delta_2$~~

  $H_o: \mu_T - \mu_D \geq \delta_3$ vs. $H_a: \mu_T - \mu_D < \delta_3$

  With *δ_3=11* ~~$\delta_2 \geq 0$~~ and where μ_T is the mean *of Drug Liking E_{max}* for each dose level of HSK3486 *(Treatments A and B)* and μ_D is *the* mean of *Drug Liking E_{max}* for placebo *(Treatment D)***.** If the treatment difference is statistically significantly less than 11-point (δ_3) in a 1-sided test at a 5% level of significance, this will suggest that HSK3486 does not produce a greater abuse-related response than placebo. The 1-sided 95% CIs of the mean difference will be calculated. P-values will be provided for the treatment comparisons. And the 2-sided 95% CIs will be also derived for the exploratory result.

  Analyses similar to those described for the primary endpoint (Drug Liking E_{max}) will be performed on the secondary endpoints (Take Drug Again VAS 12- and 24-hour scores; High VAS E_{max}; and Overall Drug Liking VAS 12- and 24-hour scores) in the treatment phase. The same hypothesis tests and difference margins as noted above for hypotheses will be evaluated for the secondary endpoints.

  - **Rationale:** To correct the hypothesis for absolute abuse potential testing. To clarify how secondary endpoints will be evaluated.

- **Location:** Section 7

  Update Description: Added Chen and Bonson, 2013, to list of references.

  Rationale: Reference added in support of the formula used for evaluation of absolute abuse potential.

The following changes were added per Administrative Letter 1 dated 29 June 2022:

- **Location:** Table 2: Part 2 Schedule of Assessments — Screening and Qualification Phase / Table 3: Part 2 Schedule of Assessments — Treatment Phase (Periods 1-4) and Safety Follow-up/Early Withdrawal
    - **Update Description and Additions:** All 24-hour postdose assessments of Day -3 or during Periods 1, 2, and 3 can be recorded also as predose assessments of Day -2 and Periods 2, 3, and 4, respectively, without the need to redo the assessment. Clarifications will be made by adding footnote t to Table 2 and updating footnote t in Table 3. Additionally, footnote m of Table 3 is currently only used for the 24-hour assessment of drug-specific VAS but can also be applied to vital signs, the global VAS, and other VAS assessments.
        - footnote *t - The 24-hour postdose assessments of Day -3 can be recorded also as the predose assessment of Day -2 without the need to redo the assessment.*
        - footnote t - Day 2 for Periods 1, 2, and 3 will also be Day 1 for Periods 2, 3, and 4, respectively. *The 24-hour postdose assessments of Periods 1, 2, and 3 can be recorded also as predose assessments of Periods 2, 3, and 4, respectively, without the need to redo the assessment.*
    - **Rationale:** In the qualification phase of Part 2 the 24-hour postdose assessments of vital signs and all VAS assessments of Day -3 will coincide with the predose assessments of vital signs and all VAS assessments of Day -2. Similarly for the treatment phase of Part 2 the 24-hour postdose assessments of vital signs and all VAS assessments of Periods 1-3 will coincide with the predose assessments of vital signs and all VAS assessments of Periods 2-4, respectively.

The following changes were added per Administrative Letter 2 dated 23 Aug 2022:

- **Location:** Synopsis and Section 3.2.5
    - **Additions:** The Investigator and Haisco will determine the doses of HSK3486 and propofol to be used in Part 2 of the study using the following criteria *as monitored through the first hour postdose*:
        - Maximum dose at which subjects are able to adequately complete the battery of human abuse potential assessments over most of the 1-hour period
        - Level of consciousness generally remains at a MOAA/S score ≥4 (Section 3.5.1.2.3)
        - Minute ventilation does not decrease more than 30% *for one minute with verbal stimulation*
        - Oxygen saturation does not fall below 90% for more than 30 sec with verbal stimulation
    - **Rationale:** The dose determination criteria used in Part 1 for selection of doses in Part 2 were found to be unnecessarily stringent due to unclear wording in the protocol.

The following changes were incorporated per Administrative Letter 3 dated 01 September 2022:

- **Location:** Synopsis and Section 3.2.4
    - **Additions:** Dose finding will be halted*, pending discussion between sponsor and investigator,* in Part 1 if 1 subject out of 4 demonstrates 1 or more of the below changes in vital signs sustained for ≥2 minutes *with verbal stimulation as monitored through the first hour postdose*:
        - Heart rate <40 bpm
        - Systolic blood pressure (BP) <80 mmHg
        - Respiratory rate <6 breaths per minute

- Pulse oximetry O2 sat <87% with verbal stimulation
- Respiratory minute ventilation <60% of baseline
- *If the sponsor and investigator agree that the vital signs changes noted above were unlikely related to study drug and/or that there is no significant safety concern, then dose finding may proceed at an increased, decreased, or repeated dose level.*

- **Rationale:** The dose finding stopping criteria used in Part 1 were found to be unnecessarily stringent due to unclear wording in the protocol.

SYNOPSIS

Study Title

A 2-PART, DOSE-FINDING AND HUMAN ABUSE POTENTIAL STUDY OF HSK3486 INJECTION IN NONDEPENDENT, RECREATIONAL CENTRAL NERVOUS SYSTEM DEPRESSANT USERS

Study Codes

Sponsor code : HSK3486-110

[redacted]

Study Rationale

HSK3486 is a new intravenous (IV) anesthetic drug developed by Sichuan Haisco Pharmaceutical Co, Ltd. HSK3486 is intended to be used in the induction of adult sedation/general anesthesia. HSK3486 has a novel structural design that provides higher potency compared to propofol, with an anesthetic induction dose of 0.4 mg/kg for HSK3486 that has been shown comparable to the approved 2.5 mg/kg dose of propofol. This higher potency could potentially result in less site pain and cardiopulmonary instability. Substantial Phase 1 to 3 clinical trials were conducted in Australia and China. Currently, one of two pivotal Phase 3 trial is ongoing in US. This human abuse potential study is planned to address the Food and Drug Administration (FDA) requirement that any new chemical entity that targets central nervous system (CNS) needs to be evaluated on substance abuse potential in humans.

Objectives - Part 1

Primary : To determine the doses of IV HSK3486 and propofol for use in Part 2, the abuse potential part of the study

Secondary : To evaluate the safety and tolerability of HSK3486 in healthy, nondependent, recreational CNS depressant drug users

Objectives - Part 2

Primary : To evaluate the abuse potential of HSK3486 compared with propofol when administered IV to healthy nondependent, recreational CNS depressant drug users

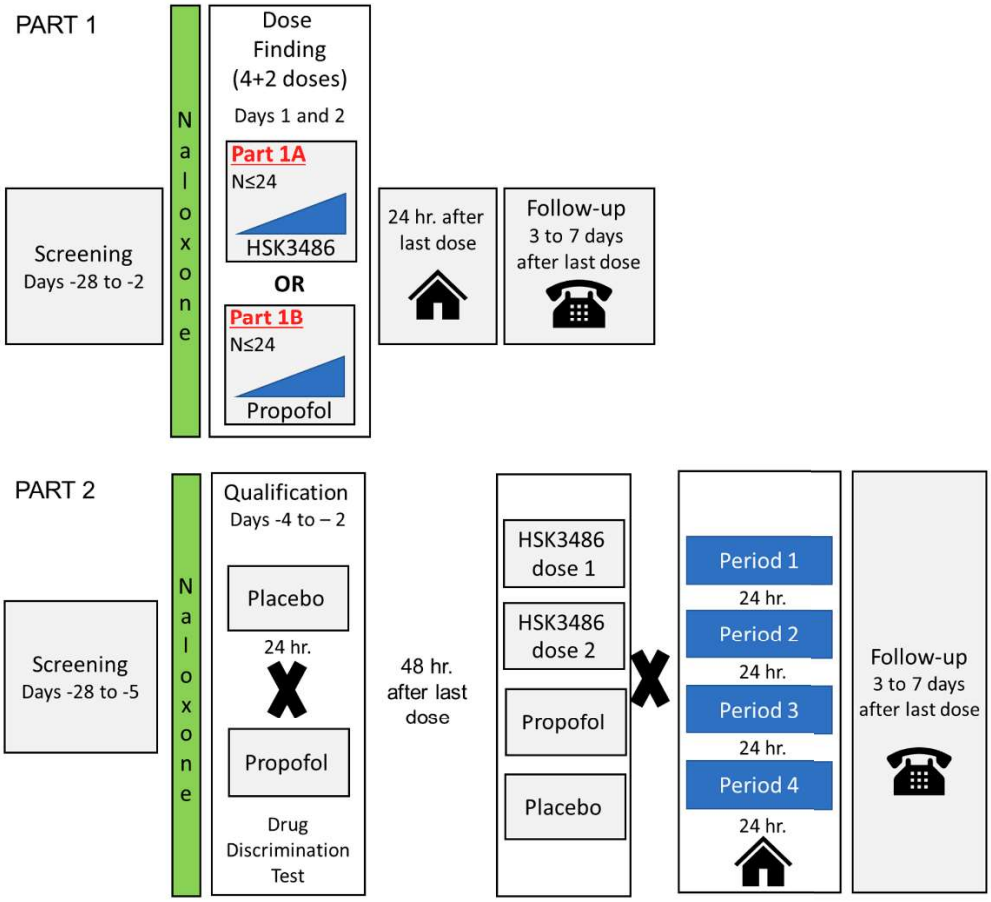
Secondary : To evaluate the safety and tolerability of HSK3486 compared to propofol when administered IV to healthy nondependent, recreational CNS depressant drug users
To evaluate the pharmacokinetic (PK) profile of HSK3486 when administered IV to healthy nondependent, recreational CNS depressant drug users

Design and Treatments

This single center study will consist of 2 parts. Part 1 will be an open-label, dose-finding study of HSK3486 and propofol conducted in up to 48 recreational users of CNS depressants to determine the appropriate doses to be used in Part 2 of the study. Part 2 will be a randomized, double-blind, placebo- and active-controlled 4-period, 4-way crossover, in approximately 42 healthy volunteers with prior recreational CNS depressant exposure. Both Part 1 and Part 2 of the study will consist of an outpatient Screening Visit, an in-clinic Treatment Phase, and Follow-up; Part 2 will also include a Qualification Phase.

A schematic summary of the study is shown in Figure 1.

Figure 1: Study Diagram



N=number of subjects

The doses to be used in Part 2 will be determined during dose finding in Part 1. Groups of 4 subjects will receive 1 dose level. Enrollment will be halted after the doses to be used in Part 2 will have been determined.

The Drug Discrimination Test will ensure subjects can differentiate between the effects of active control (propofol) and placebo.

A naloxone challenge will ensure subjects are not opioid dependent.

A naloxone challenge will be administered on the day of admission.

Part 1

Part 1 will consist of 2 separate arms: Part 1A and Part 1B. Up to 48 subjects may be enrolled to participate in Part 1 with up to 24 subjects in each arm. Screening will occur up to 28 days before drug administration. All subjects who have given their written informed consent and who satisfy all study entry criteria will be screened for eligibility to participate in the study. Subjects will be admitted to the clinic on Day -1 and administered a naloxone challenge to assess opioid dependence, on Day 1 they will be administered study drug (either HSK3486 or propofol) following a minimum 8-hour fast, and on Day 2 they will be discharged at least 24 hours after study drug administration and upon completion of study assessments. A follow-up visit will be conducted via a telephone call 3 to 7 days after study drug administration. Subjects who participate in a given group in Part 1 cannot participate in a subsequent group in Part 1; however, subjects in Part 1 may participate in Part 2 of the study at the discretion of the Investigator. If a subject is admitted to the clinic in Part 1 within the 28 day screening window of Part 2 they must be reconsented but do not need to be rescreened.

Part 1A: For HSK3486 dose determination, groups of 4 eligible subjects will receive 1 dose of study drug. On Day 1, subjects in the first group will receive IV HSK3486 0.1 mg/kg (starting dose) administered as a bolus over 30 seconds ($\pm$5 seconds) from a syringe. The dose used for succeeding groups will be based on the pharmacodynamic (PD) and safety results of the prior group. The dose used in the next group may be increased, decreased or repeated; the magnitude of change for a new dose will be no greater than 0.025 mg/kg (increase or decrease) relative to previously administered doses. It is anticipated that 4 dose levels will be sufficient to identify the doses that should be used in Part 2 of the study; however, enrollment can be halted prior to completing all planned groups once doses for Part 2 have been identified based on dose selection criteria listed below. If necessary, up to 2 additional groups of 4 subjects each may be enrolled up to a total of 24 subjects.

Part 1B: Likewise, for propofol dose determination, groups of 4 eligible subjects will receive 1 dose of propofol. On Day 1, subjects in the first group will receive IV propofol 0.5 mg/kg (starting dose) administered as a bolus over 30 seconds ($\pm$5 seconds) from a syringe. The dose used for succeeding groups will be based on the pharmacodynamic (PD) and safety results of the prior group. The dose used in the next group may be increased, decreased, or repeated; the magnitude of change for a new dose will be no greater than 0.125 mg/kg (increase or decrease) relative to previously administered doses. It is anticipated that 4 dose levels will be sufficient to identify the dose of propofol that should be used in Part 2 of the study; however, enrollment can be halted prior to completing all planned groups once the dose for Part 2 has been identified using the dose selection criteria listed below. If necessary, up to 2 additional groups of 4 subjects each may be enrolled up to a total of 24 subjects.

All subjects will receive a 2 cc pre-treatment of 1% lidocaine at the injection site to minimize pain associated with study drug administration prior to administration of either HSK3486 or propofol.

Dose finding will be halted, pending discussion between sponsor and investigator, in Part 1 if 1 subject out of 4 demonstrates 1 or more of the below changes in vital signs sustained for $\geq$2 minutes with verbal stimulation as monitored through the first hour postdose:

1) Heart rate <40 bpm
2) Systolic blood pressure (BP) <80 mmHg
3) Respiratory rate <6 breaths per minute
4) Pulse oximetry O_2 sat <87% with verbal stimulation
5) Respiratory minute ventilation <60% of baseline

If the sponsor and investigator agree that the vital signs changes noted above were unlikely related to study drug and/or that there is no significant safety concern, then dose finding may proceed at an increased, decreased, or repeated dose level.

Safety and PD assessments will be performed at defined timepoints including Drug Liking ("at this moment"), Drowsiness/Alertness visual analog scale (VAS), and the Modified Observer's Assessment of Alertness/Sedation (MOAA/S). Subjects will be rated on their ability to complete the full battery of abuse potential questions for up to 1 hour. Safety assessments will include continuous oxygen saturation, BP, and 12-lead electrocardiogram (ECG). Respiratory minute ventilation of subjects will be monitored using the ExSpiron® device. An anesthesiologist or advanced cardiovascular life support (ACLS)-certified physician capable of performing intubation will remain at the clinical research unit (CRU) to support site staff during study drug administration and for at least 0.5 hours following study drug administration.

The Investigator and Haisco will determine the doses of HSK3486 and propofol to be used in Part 2 of the study using the following criteria as monitored through the first hour postdose:

1) Maximum dose at which subjects are able to adequately complete the battery of human abuse potential assessments over most of the 1-hour period
2) Level of consciousness generally remains at a MOAA/S score ≥4
3) Minute ventilation does not decrease more than 30% for one minute with verbal stimulation
4) Oxygen saturation does not drop below 90% for more than 30 sec with verbal stimulation

For both HSK3486 and propofol, the highest doses tested in Part 1 meeting these criteria will be used in Part 2, Treatments A and C, respectively. The second dose of HSK3486 to be used in Part 2 will be the second highest dose tested in Part 1 (Treatment B) that meets these criteria.

Part 2

Part 2 will be a randomized, double-blind, placebo- and active-controlled 4-period, 4-way crossover design to assess the abuse potential of HSK3486 in nondependent, recreational CNS depressant drug (e.g., benzodiazepines, barbiturates, zolpidem, zopiclone, propofol/fospropofol, gamma-hydroxybutyrate) users. The abuse potential of single administration of 2 different presumed subtherapeutic doses of HSK3486 will be compared with that of propofol (active control) and placebo.

Screening will occur up to 28 days before drug administration. All subjects who have given their written informed consent and who satisfy all of the inclusion and exclusion criteria will be screened for eligibility to participate in the study.

Subjects will be admitted to the CRU on Day -4 for the Qualification Phase. Upon admission on Day -4, each subject will be administered a naloxone challenge to assess opioid dependence. During the Qualification Phase, subjects will undergo a Drug Discrimination Test to ensure that they can differentiate between the effects of active control (propofol) and placebo. During the Drug Discrimination Test, subjects will receive IV propofol (dose to be determined in Part 1) administered over 30 seconds (Treatment X) or matching placebo (Treatment Y) after an overnight fast in a randomized, double-blind, crossover manner with each drug administration separated by approximately 24 hours (Day -3 and Day -2). Subjects who do not meet Drug Discrimination criteria will be discharged from the CRU approximately 24 hours after the second drug administration. Subjects who successfully complete the Qualification Phase will be eligible to enter the Treatment Phase. A washout interval of at least 48 hours will be required between the last drug administration in the Qualification Phase and the first drug administration in the Treatment Phase. In both Qualification and Treatment phases of the study, the

Investigator will instruct subjects when answering questions after drug administration, not to make comparisons with previous treatments received in the study.

All subjects will be randomized to 1 of 8 treatment sequences according to two 4×4 William squares in the Treatment Phase. Subjects will receive each of the following 4 treatments in a randomized, double-blind, 4-way crossover manner following an overnight fast:

- Treatment A: HSK3486 dose 1 (IV bolus over 30 seconds [±5 seconds] from a syringe; dose to be determined in Part 1)
- Treatment B: HSK3486 dose 2 (IV bolus over 30 seconds [±5 seconds] from a syringe; dose to be determined in Part 1)
- Treatment C: Propofol (IV bolus over 30 seconds [±5 seconds] from a syringe; dose to be determined in Part 1)
- Treatment D: Placebo (Treatment A matched) (IV bolus over 30 seconds [±5 seconds] from a syringe)

To assist with blinding of subjects all study treatments in Part 2 will be administered by an unblinded dosing team, which will use a blindfold and curtain to obscure visible differences between treatments for the subject dosed, any blinded study team members, and neighboring subjects. In effort to further maintain the blind, within 5 minutes before each treatment (test, active control, or placebo; Qualification Phase and Treatment Phase) subjects will be administered 2 cc of 1% lidocaine at the injection site in order to block the stinging sensation that can occur with propofol injection.

Each treatment administration in the Treatment Phase will be separated by approximately 24 hours. Serial PD assessments will be performed, including Drug Liking, level of sedation, and ability to respond to questions. Subjects will also undergo safety assessments while housed in the CRU.

Subjects will receive a follow-up phone call approximately 3 to 7 days after either last drug administration or early withdrawal from the study.

Naloxone Challenge

During the naloxone challenge administered in Parts 1 and 2, all participants will receive IV naloxone 0.2 mg dose as an IV bolus, followed by an assessment for signs of opioid withdrawal. If there are no signs of opioid withdrawal within 30 seconds after administration, a second dose of 0.6 mg IV will be administered within 5 minutes of the first dose, followed by another assessment for signs of opioid withdrawal 5 minutes after the second naloxone dose. Only participants who do not have signs and symptoms of opioid withdrawal, as assessed by the Clinical Opioid Withdrawal Scale (COWS score <5), will be eligible to proceed with the study. Any participant demonstrating evidence of withdrawal (COWS score ≥5) on any assessment will not be eligible for further participation in the trial. The participant will be released from the study center when medically stable, as determined by the Investigator. Symptoms reported in the COWS as a consequence of opioid withdrawal will not be collected as AEs unless they meet the criteria for a new AE or serious adverse event (SAE).

Study Schedule

Part 1

Screening	: Between Day -28 and Day -2.
Confinement Period	: A single period of approximately 2 days in the clinic from Day -1 (admission) to approximately 24 hours after study drug administration.
Follow-up	: 3 to 7 days after drug administration.

Part 2

Screening	: Between Day -28 and Day -5.
Confinement Period	: An anticipated period of approximately 9 days in the clinic from Day -4 (admission) to approximately 24 hours after the last study drug administration in Period 4.
Follow-up	: 3 to 7 days after either last drug administration or early withdrawal from the study.

Subjects

Part 1

An adequate number of subjects will be screened such that up to 32 subjects (16 subjects for HSK3486 dose determination [4 groups of 4 subjects each] and 16 subjects for propofol dose determination [4 groups of 4 subjects each]) may be enrolled in Part 1 of the study. Up to an additional 16 subjects (2 groups of 4 each for HSK3486 dose determination and 2 groups of 4 each for propofol dose determination) may be enrolled in Part 1, if necessary.

Part 2

An adequate number of subjects will be screened such that a sufficient number of subjects are randomized into the Qualification Phase with the intention of qualifying and randomizing approximately 42 subjects into the Treatment Phase, with the intention of completing 36 subjects. Subjects who participated in Part 1 of the study may be eligible for Part 2 of the study at the Investigator's discretion.

Inclusion Criteria

The following criteria must be met for a subject to be eligible for inclusion in the study:

1. Willing to participate in the study, give written informed consent, and comply with the study restrictions.
2. Gender: male or female; females may be of childbearing potential, of nonchildbearing potential, or postmenopausal.
3. Age: 18 years to 55 years, inclusive, at Screening.
4. Body mass index (BMI): 18.0 kg/m^2 to 30.0 kg/m^2, inclusive.
5. Weight: ≥50 kg, inclusive.
6. Healthy subject, defined by the absence of evidence of any clinically significant, in the opinion of the Investigator, active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology, and urinalysis.
7. Subject must be a nondependent, nontreatment-seeking recreational CNS depressant user, defined as follows:
   - ≥10 lifetime nontherapeutic experiences (i.e., for psychoactive effects) with CNS depressants (e.g., benzodiazepines, barbiturates, zolpidem, zopiclone, propofol/fospropofol, gamma-hydroxybutyrate).
   - ≥1 nontherapeutic use of a CNS depressant within the 8 weeks prior to Screening.
   - ≥1 nontherapeutic use of benzodiazepines within the 12 months prior to Screening.
8. Ability and willingness to abstain from alcohol-, caffeine-, and xanthine-containing beverages or food (e.g., coffee, tea, cola, chocolate, energy drinks) from 48 hours (2 days) prior to first admission to the CRU, throughout the entire study, and until discharge.
9. All values for hematology and clinical chemistry tests of blood and urine within the normal range or show no clinically relevant deviations, as judged by the Investigator.
10. Females of childbearing potential, and males with female partner(s) of childbearing potential, as judged by the Investigator, must agree to use 2 forms of contraception, 1 of which must be a barrier method, during the study and for 90 days after the last drug administration. Acceptable barrier forms of contraception are condom, cervical cap, and diaphragm. Acceptable non barrier forms of contraception for this study are an

intrauterine device (IUD) including hormonal IUDs, oral contraceptives (used for ≥30 days prior to dosing any study treatment), and/or spermicide.
11. For females: a negative pregnancy test at Screening and Admission.
12. Postmenopausal females: defined as 12 months with no menses prior to Screening and a serum follicle-stimulating hormone (FSH) >40 IU/L at Screening.
13. All nonregular medication (including over-the-counter medication, health supplements, and herbal remedies such as St. John's Wort extract) must have been stopped at least 14 days prior to (the first) admission to the CRU. An exception is made for acetaminophen, which is allowed up to admission to the CRU.
14. All prescribed medication must have been stopped at least 30 days prior to (first) admission to the clinical research center. An exception is made for hormonal contraceptives, which may be used throughout the study.
15. Able to speak, read, and understand English sufficiently to allow completion of all study assessments.

Exclusion Criteria

A subject who meets any of the following criteria will not be eligible for inclusion in the study:

1. An employee of the Sponsor or research site personnel directly affiliated with this study or their immediate family member (defined as a spouse, parent, child, or sibling, whether biological or legally adopted).
2. Drug or alcohol dependence within the 2 years prior to Screening (except nicotine and caffeine), as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), and/or has ever participated or plans to participate in a substance or alcohol rehabilitation program to treat their substance or alcohol dependence.
3. Opioid dependence as judged by the Investigator after a naloxone challenge.
4. Women who are pregnant, lactating, or planning to attempt to become pregnant during this study or within 90 days of last study drug administration.
5. Males with female partners who are pregnant, lactating, or planning to attempt to become pregnant during this study or within 90 days of last study drug administration.
6. Positive drug and alcohol screen (tetrahydrocannabinol [THC], morphine/opiates, methadone, oxycodone, phencyclidine, cocaine, amphetamines, methamphetamines, ecstasy, barbiturates, benzodiazepines, tricyclic antidepressants, and alcohol) at each admission to the CRU. For THC, subjects should ideally test negative. However, eligibility decision with regards to THC use will be considered on a case by case basis, at the discretion of the Investigator.
7. Treatment with an investigational drug or device within 5 times the elimination half-life, if known (e.g., a marketed product) or within 30 days (if the elimination half-life is unknown) prior to first drug administration or is concurrently enrolled in any research judged not to be scientifically or medically compatible with this study. An exception may be made for subjects who participated in Part 1 of the study.
8. History or presence of clinically significant abnormality (e.g., obstructive sleep apnea) as assessed by physical examination, medical history, ECG, vital signs, or laboratory values, which, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
9. Any disease which, in the opinion of the Investigator, poses an unacceptable risk to the subjects.
10. Mallampati intubation score >2.
11. History of clinically significant drug allergy diagnosed by a physician. Confirmatory circumstances would include treatment with epinephrine or in an emergency department.
12. Any personal or family history of issues with succinylcholine, such as malignant hyperthermia or pseudocholinesterase deficiency.
13. History of allergy, adverse reaction (including significant agitation, etc.), or hypersensitivity to propofol, lidocaine, other injected anesthetic agents, or related drugs.
14. History of allergy to eggs, egg products, soybeans or soy products.

15. Heavy smoker (>20 cigarettes per day) and/or is unable to abstain from smoking and/or the use of prohibited nicotine-containing products (including e-cigarettes, pipes, cigars, chewing tobacco, nicotine topical patches, nicotine gum, or nicotine lozenges) from 2 hours prior to dosing until at least 4 hours postdose during the in-clinic periods.
16. Routine or chronic use of more than 3000 mg of acetaminophen daily.
17. Strenuous activity (such as exercise), sunbathing, and contact sports within 48 hours (2 days) prior to admission to the CRU, during the study, and until after discharge in the last study period.
18. History of donation of more than 450 mL of blood within 60 days prior to dosing in the CRU or planned donation before 30 days has elapsed since last intake of study drug.
19. Plasma or platelet donation within 7 days of dosing and throughout the entire study.
20. Average intake of more than 14 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits). Alcohol consumption will be prohibited 48 hours prior to first admission to the CRU and throughout the entire study until the Follow-up visit (including washout period).
21. Positive screening test for hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibodies, or anti-HIV 1 and 2 antibodies.
22. History of peripheral vasculopathy, including Raynaud's phenomenon.
23. History of seizures, seizure disorder, or known electroencephalogram (EEG) abnormalities.
24. History of mental illness, which, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
25. Subject with a history of clinically significant head injury, ongoing seizure disorder, chronic tics, or diagnosis or family history of Tourette's syndrome.
26. Subjects with a history of serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, advanced arteriosclerosis, symptomatic cardiovascular disease, hypertension, or other cardiac problems.
27. Any history of clinically significant suicidality as assessed by the Investigator based upon clinical history, source documents, or scores on the Columbia-Suicide Severity Rating Scale (C-SSRS).
28. History or presence of clinically significant hepatic or renal disease.
29. History of hyperthyroidism.
30. Difficulty with venous access or unsuitable or unwilling to undergo catheter insertion.
31. Use of a cytochrome P450 (CYP)2D6-inhibiting drug or a serotonergic drug within 14 days prior to first drug administration in the Qualification Phase.
32. Consumption of any nutrients known to modulate CYP enzymes activity (e.g., grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products) within 14 days prior to administration of study medication and during the study (including washout period) until after discharge in the last study period.
33. A subject who, in the opinion of the Investigator or designee, is considered unsuitable or unlikely to comply with the study protocol for any reason.
34. A subject who has pending legal charges or is on probation.

Study Drug

Test preparation (HSK3486)

Active substance	: HSK3486 injectable emulsion
Activity	: CNS depression through gamma-aminobutyric acid receptor subtype A ($GABA_A$) mediation
In development for	: General anesthesia and sedation
Strength	: 2.5 mg/mL (total dose: 0.05 g in 20 mL)
Dosage forms	: Injection
[redacted]	[redacted]

Reference medication (Propofol injectable emulsion)

Active substance : Propofol
Activity : Positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated $GABA_A$ receptors
Indication : General anesthesia and sedation
Strength : 10 mg/mL
Dosage form : Injection
[redacted]

Placebo

Substance : Intralipid®
Activity : Not applicable
Strength : Not applicable
Dosage form : 20% IV fat emulsion
[redacted]

Masking drug (xylocaine)

Substance : Lidocaine HCl
Activity : Local anesthetic
Strength : 1%
Dosage form : Injection
[redacted]

Criteria for Evaluation

Pharmacodynamics : PD parameters in Part 1 will include:

- Drug Liking ("at this moment") VAS E_{max}
- Drug Liking ("at this moment, I feel high") E_{max} High VAS (secondary endpoint)
- Drowsiness/Alertness VAS (E_{min} [secondary endpoint], TE_{min}, TA_AUE_{0-1}, and TA_AUE_{0-2})
- MOAA/S score
- Ability to complete battery of abuse potential assessment questions for 1 hour

PD parameters in Part 2 will include:

- Drug Liking ("at this moment") VAS E_{max}
- Drug Liking ("at this moment, I feel high") E_{max} High VAS
- Drowsiness/Alertness VAS (E_{min}, TE_{min}, TA_AUE_{0-1}, and TA_AUE_{0-2})
- MOAA/S score
- Ability to complete battery of abuse potential assessment questions for 1 hour
- Overall Drug Liking VAS – 12- and 24-hour score
- Take Drug Again VAS – 12- and 24-hour score
- Drug Liking VAS (TE_{max}, TA_AUE, E_{min}, TE_{min}, and %reduction)
- Drug Effects Questionnaire (DEQ) – Any Drug Effect VAS (E_{max}, TE_{max}, and TA_AUE_{0-1})
- DEQ – Good Drug Effects VAS (E_{max}, TE_{max}, and TA_AUE_{0-1})
- DEQ – Bad Drug Effects VAS, sick-nausea (E_{max}, TE_{max}, and TA_AUE_{0-1})

- Relaxation/Agitation VAS (E_{max}, TE_{max}, E_{min}, TE_{min}, and TA_AUE_{0-1})
- Drug Similarity ("How similar is the drug you most recently received [drug 1] to drug you just took [drug 2]?") VAS

Part 2 endpoints:
The primary endpoint is Drug Liking VAS (E_{max}).

The secondary endpoints for statistical hypothesis testing are: Take Drug Again VAS (12- and 24-hour scores); High VAS (E_{max}); and Overall Drug Liking VAS (12- and 24-hour scores).

The secondary endpoints for descriptive analysis are: Good Drug Effects; Bad Drug Effects, sick-nausea; Unknown: Any Drug Effects, Drowsiness/Alertness, and Drug Similarity.

The following scale will be used for MOAA/S scoring:

5 = responds readily to name spoken in normal tone
4 = lethargic response to name spoken in normal tone
3 = responds only after name is called loudly and/or repeatedly
2 = responds only after mild prodding or shaking
1 = responds only after painful trapezius squeeze
0 = does not respond to painful trapezius squeeze

Pharmacokinetics : Plasma HSK3486 concentrations
Plasma PK parameters estimated using noncompartmental analysis, as appropriate: maximum observed plasma concentration (C_{max}), time to attain maximum observed plasma concentration (T_{max}), area under the plasma concentration-time curve (AUC) from time 0 to 1 hour postdose (AUC_{0-1}), AUC from time 0 to 2 hours postdose (AUC_{0-2}) AUC from time 0 to 4 hours postdose (AUC_{0-4}), AUC up to the last point with concentrations above the lower limit of quantification ($AUC_{last,}$), AUC from time 0 to infinity (AUC_{0-inf}), percent of estimated part for the calculation of AUC_{0-inf} ($\%AUC_{extra}$), terminal elimination rate constant (k_{el}), terminal elimination half-life ($t_{½}$), and abuse quotient (C_{max}/T_{max})

Safety : Adverse events (AEs), clinical laboratory assessments, vital signs, pulse oximetry, 12-lead ECG, continuous cardiac monitoring, physical examination, and C-SSRS. Respiratory volume of subjects will be monitored using the ExSpiron® device.

Statistical Methods

Sample size calculation : For assessment of abuse potential, the sample size will be considered the maximum of the sample sizes for the validity comparison and primary treatment comparison. Assuming a 10% dropout rate, approximately 42 subjects will be randomized to the Part 2 Treatment Phase, with the intention of completing 36 subjects.
For the validity comparison, a sample size of 36 subjects will provide 95% power to detect a mean difference in the Drug Liking VAS E_{max} between 0.6 mg/kg propofol

and placebo that is greater than a margin of δ_1=15 in a 1-sided, alpha=0.025 test for study validity. With alpha=0.05, a sample size of 36 subjects will provide at least 98% power to detect a mean difference in the Drug Liking VAS E_{max} between 0.6 mg/kg propofol and placebo that is greater than a margin of 15-point in a 1-sided test. This assumes Drug Liking E_{max} mean (SD) of 74.4 (14.99) for propofol and 50 (0.33) for placebo, and correlation of 0.5.

For the primary treatment comparison, evaluating the difference between propofol and HSK3486, a sample size of 27 will provide 95% power to reject the null hypothesis that HSK3486 has greater abuse potential than propofol, in favor of similarity with less than a margin of δ_2=11 in a 1-sided, alpha=0.025 t-test. With alpha=0.05, a sample size of 27 will provide 98% power to reject the null hypothesis that HSK3486 has greater abuse potential than propofol, in favor of similarity with less than a margin of δ_2=11 in a 1-sided t-test. This assumes a mean (SD) of the difference in Drug Liking E_{max} between HSK3486 and propofol of 0 (15).

PD parameters : PD data and derived PD parameters from the Treatment Phase will be summarized using descriptive statistics by treatment (and by time point as applicable). PD endpoints for the Treatment Phase will be analyzed using a mixed-effect model if the residuals are normally distributed. The model will include treatment, period, sequence, and first-order carryover effect (if significant) as fixed effects, baseline (where applicable) as a covariate, and subject as a random effect. Treatment variance will be evaluated and adjusted as needed. Step-wise hypothesis testing will be conducted for the treatment differences following the FDA guidance.

PK parameters : Descriptive statistics will be calculated and presented for each time point by treatment for plasma concentrations. PK parameters will be calculated and will be summarized by treatment using descriptive statistics. The natural log-transformed, dose-normalized PK exposure parameters: C_{max} and AUC, will be analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects and subject nested in sequence as a random effect. The geometric means of each treatment, geometric mean ratio of the treatment comparisons, and 90% confidence intervals will be reported. The relationship between PK and PD may be evaluated using correlational analysis or similar methodology.

Safety parameters : Descriptive statistics or incidence/frequency counts (where applicable)

Exploratory parameters : Descriptive statistics

Table 1 Part 1 Schedule of Assessments — Dose Determination

	Screening	Dose Determination Treatment Phase												FU Call
Visit:	**1**	**Visit 2**												**NA**
Day:	**-28 to -2**	**-1**	**Day 1 to 2**											**6 (±2)**
			Assessment Timepoints											**NA**
Subject Review														
Informed Consent	X													
Medical History	X	X[a]												X[a]
Medication and Recreational Drug Use History[b]	X													
Inclusion/Exclusion	X	X												
Study Restrictions Review	X	X												
Demographics, Height, Weight, BMI	X	X[p]												
Naloxone Challenge		X												
Safety														
Physical Examination	X[c]	X[d]											24h	
Serum Pregnancy (females subjects)	X													
Urine Pregnancy (female subjects)		X												
Serum FSH/Estradiol (postmenopausal subjects)	X													
HIV-1 & -2, Hepatitis B, Hepatitis C Testing	X													
Vital Signs[e]	X	X	pre	1m[f]	2m[f]	3m[f]	5m[f]	9m[f]	15m[f]	30m[f]	45m[f]	1h		24h	
Continuous Pulse Oximetry			Predose to at least 4h postdose[g]											
Electrocardiogram	X	X											8h	
Urine Drug Screen/Breath Alcohol	X	X												

	Screening	Dose Determination Treatment Phase														FU Call
Visit:	**1**	**Visit 2**														**NA**
Day:	**-28 to -2**	**-1**	**Day 1 to 2**													**6 (±2)**
			Assessment Timepoints													**NA**
Cardiac Telemetry			At least 1 h predose until at least 4h postdose													
Clinical Laboratory Tests	X[n]	X[o]													24h	
Concomitant Medications	X	X	←---------- Recorded throughout ----------→													
Adverse Event Monitoring[h]	X	X	←---------- Recorded throughout ----------→													
C-SSRS ("Baseline")	X															
C-SSR ("Since Last Visit")		X													24h	
MOAA/S					1m	3m	5m	15m	30m							
Pharmacodynamics																
Drug-Specific VAS[i]					1m[j]	5m[j]	15m	30m	45m	1h	2h	4h		8h	24h	
Other VAS[k]			pre				15m	30m	45m	1h		4h		8h	24h	
Respiratory Minute Ventilation[l]			-5m predose		1m	5m	15m	30m	45m	1h	2h	4h				
Study Administration																
Admission		X														
Drug Administration[m]				0h												
Lidocaine Administration			pre													
Discharge															24h	

AE=adverse event; BMI=body mass index; COVID-19=coronavirus disease 2019; CRU=clinical research unit; C-SSRS=Columbia-Suicide Severity Rating Scale; FSH=follicle-stimulating hormone; FU=follow-up h=hour(s); m=minute(s); HIV=human immunodeficiency virus; MOAA/S= Modified Observer's Assessment of Alertness/Sedation; NA=not applicable; pre=predose; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO_2=oxygen saturation; VAS=visual analog scale

Note: Additional COVID–19-related precautions and procedures (including SARS-CoV-2 testing/screening) may be implemented based on the prevailing situation during study conduct, at the Investigator's discretion; the instructions will be provided in a separate document. Any procedure implemented will be in accordance with the local and national regulations and shall be documented appropriately.

a Focusing on any changes since the last visit.
b Additional medical history pertaining to drug use will be collected.
c Complete physical examination.

d Symptom-directed examination performed at the Investigator's discretion. Unscheduled symptom-directed physical examinations may be conducted at any time per the Investigator's discretion.
e Vital signs will include blood pressure, heart rate, oral temperature, and respiratory rate. Oral temperature checks will be performed daily for all subjects from admission to CRU until discharge. Windows for postdose assessments are ±7m from dosing to1h postdose and ±15m from 1h to 24h postdose. Respiration rate, minute ventilation, heart rate, and SpO_2 will be monitored continuously with ExSpiron and pulse oximetry respectively.
f Blood pressure only.
g Continuous pulse oximetry will be performed for 4 hour postdose, or longer if clinically indicated at the discretion of the Investigator. Pulse oximetry will be documented at predose and 1m, 5m, 15m, 30m, 45m, 1h, 2h, and 4h postdose; additional timepoints can be documented at the Investigators discretion.
h Spontaneous AE reporting is continuous throughout the study, beginning with the time the subject gives informed consent; however, at regular intervals, AE checks will be performed using a non-leading question.
i Drug-Specific VAS includes Drug Liking VAS, Any Drug Effects VAS, Good Drug Effects VAS, and Bad Drug Effects VAS.
j At 1m and 5m postdose, only Drug Liking and Drug High VAS will be performed.
k Other VAS includes Drowsiness/Alertness VAS and Relaxation/Agitation VAS.
l Additional timepoints can be documented at the Investigators discretion.
m Subjects will be enrolled in groups of no more than 4. Subjects will receive a single dose of the assigned treatment (either HSK3486 or propofol).
n Prothrombin time/international normalized ratio, estimated creatinine clearance, and thyroid-stimulated hormone to be run at screening only.
o If safety labs completed for screening are drawn within 7 days of admission, these can be used for admission and don't require additional lab draws.
p Weight only will be collected on Day -1.

Table 2 Part 2 Schedule of Assessments — Screening and Qualification Phase

	Screening	Qualification Phase													
Visit:	**1**	**2**													
Day:	**-28 to -5**	**-4**	**Day -3 and Day -2**												
			Assessment Timepoints												
Subject Review															
Informed Consent	X														
Medical History	X	X[a]													
Medication and Recreational Drug Use History[b]	X														
Inclusion/Exclusion	X	X													
Study Restrictions Review	X	X													
Demographics, Height, Weight, BMI	X	X[t]													
Naloxone Challenge		X													
Safety															
Physical Examination	X[c]	X[d]													
Serum Pregnancy (female subjects)	X	X													
Serum FSH/Estradiol (postmenopausal subjects)	X														
HIV-1 & -2, Hepatitis B, Hepatitis C Testing	X														
Vital Signs[e]	X	X	pre	1m[f]	2m[f]	3m[f]	5m[f]	9m[f]	15m[f]	30m[f]	45m[f]	1h			24h[s]
Continuous Pulse Oximetry			Predose until at least 4h postdose[g]												
Electrocardiogram	X	X													
Urine Drug Screen/Breath Alcohol	X	X													
Cardiac Telemetry			At least 1 h predose until at least 4h postdose												
Clinical Laboratory Tests	X[p]	X[q]													
Concomitant Medications	X	X	←---------- Recorded throughout ----------→												
Adverse Event Monitoring[h]	X	X	←---------- Recorded throughout ----------→												
C-SSRS (“Baseline”)	X														

	Screening	Qualification Phase															
Visit:	**1**	**2**															
Day:	**-28 to -5**	**-4**	**Day -3 and Day -2**														
			Assessment Timepoints														
Pharmacodynamics																	
Drug-Specific VAS[i]			pre		1m[j]	5m[j]	15m	30m	45m	1h	2h	4h		8h		24h[s]	
Other VAS[k]			pre				15m	30m	45m	1h	2h	4h		8h		24h[s]	
Global VAS[l]															12h	24h[s]	
Respiratory Minute Ventilation[m]			-5m predose		1m	5m	15m	30m	45m	1h	2h	4h					
Study Administration																	
Randomization			pre[n]														
Admission		X															
Lidocaine Administration			pre														
Propofol or Placebo Administration[r]					0h												
Discharge																	X[o]

AE=adverse event; BMI=body mass index; COVID-19=coronavirus disease 2019; CRU=clinical research unit; C-SSRS=Columbia-Suicide Severity Rating Scale; FSH=follicle-stimulating hormone; h=hour(s), HIV=human immunodeficiency virus; m=minute(s); pre=predose; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO_2=oxygen saturation; VAS=visual analog scale

Note: Additional COVID–19-related precautions and procedures (including SARS-CoV-2 testing/screening) may be implemented based on the prevailing situation during study conduct, at the Investigator's discretion; the instructions will be provided in a separate document. Any procedure implemented will be in accordance with the local and national regulations and shall be documented appropriately.

a Focusing on any changes since the last visit.
b Additional medical history pertaining to drug use will be collected.
c Complete physical examination.
d Symptom-directed examination performed at the Investigator's discretion. Unscheduled symptom-directed physical examinations may be conducted at any time per the Investigator's discretion.
e Vital signs will include blood pressure, heart rate, oral temperature, and respiratory rate. Oral temperature checks will be performed daily for all subjects from admission to CRU until discharge. Windows for postdose assessments are ±7m from dosing to1h postdose and ±15m from 1h to 24h postdose. Respiration rate, minute ventilation, heart rate, and SpO_2 will be monitored continuously with ExSpiron and pulse oximetry respectively.
f Blood pressure only.
g Continuous pulse oximetry will be performed for 4 hour postdose, or longer if clinically indicated at the discretion of the Investigator. Pulse oximetry will be documented at predose and 1m, 5m, 15m, 30m, 45m, 1h, 2h, and 4h postdose; additional timepoints can be documented at the Investigators discretion.
h Spontaneous AE reporting is continuous throughout the study, beginning with the time the subject gives informed consent; however, at regular intervals, AE checks will be performed using a non-leading question.
i Drug-Specific VAS includes Drug Liking VAS, High VAS, Any Drug Effects VAS, Good Drug Effects VAS, Bad Drug Effects VAS, and Nausea.
j At 1m and 5m postdose, only Drug Liking and Drug High VAS will be performed.
k Other VAS includes Drowsiness/Alertness VAS, Relaxation/Agitation VAS, and Drug Similarity

l Global VAS includes Overall Drug Liking VAS and Take Drug Again VAS.
m Additional timepoints can be documented at the Investigators discretion.
n Subjects who meet the qualification criteria for entering Treatment Phase will remain in-house for at least 48 hours after last Qualification Phase dosing.
o Subjects who do not qualify for Treatment Phase will be discharged approximately 24 hours after the second dose (i.e., on Day -1), at the discretion of the Investigator or designee. Prior to discharge, the subjects will undergo the early termination assessments listed in Table 3.
p Prothrombin time/international normalized ratio, estimated creatinine clearance, and thyroid-stimulated hormone to be run at screening only.
q If safety labs completed for screening are drawn within 7 days of admission, these can be used for admission and don't require additional lab draws.
r One treatment, either propofol of placebo, will be administered on Day -3 and the other treatment will be administered on Day -2.
s The 24-hour postdose assessments of Day -3 can be recorded also as the predose assessment of Day -2 without the need to redo the assessment.
t Weight only will be collected on Day -4.

Table 3 Part 2 Schedule of Assessments — Treatment Phase (Periods 1-4) and Safety Follow-up/Early Withdrawal

	Treatment Phase (Period 1 to Period 4) Washout (≥24h Between Treatments)														Discharge or EW	Follow-up Call
Visit:	3															NA
		Assessment Timepoints for Each Period[s]														
		1												2[t]	Approx. 24h after last Dose in Period 4	3 to 7 days after last dose
Day:	-1[a]															
Subject Review																
Qualification/Restriction Compliance Review[a]	X															X
Medical History																X[b]
Safety																
Physical Examination															X[c]	
Urine Pregnancy (female subjects)	X															
Vital Signs[d]		pre	1m[e]	2m[e]	3m[e]	5m[e]	9m[e]	15m[e]	30m[e]	45m[e]	1h				24h[m]	X	
Continuous Pulse Oximetry		Predose until at least 4h postdose[f]															
Electrocardiogram		pre														X	
Cardiac Telemetry		At least 1h predose until at least 4h postdose															
Clinical Laboratory Tests[g]																X	
C-SSRS ("Since Last Visit")																X[h]	
MOAA/S				1m	3m	5m	15m	30m									
Concomitant Medications		←---------- Recorded throughout ----------→X															
Adverse Event Monitoring[i]		←---------- Recorded throughout ----------→X															
Pharmacokinetics																	
Blood Sampling[j u]		pre		2m	6m	15m	30m	45m	1h	2h	4h	8h					
Pharmacodynamics																	
Drug-Specific VAS[k]		pre		1m[l]	5m[l]	15m	30m	45m	1h	2h	4h		8h		24h[m]		
Other VAS[n]		pre				15m	30m	45m	1h	2h	4h		8h		24h[m]		
Global VAS[o]														12h	24h[m]		
Respiratory Minute Ventilation		-5m predose			1m	5m	15m	30m	45m	1h	2h	4h					

Study Administration																		
Randomization		pre[p]																
Admission/Continuation	X[q]																	
Lidocaine Administration		pre																
Drug Administration			0h															
Discharge																	X[r]	

AE=adverse event; COVID-19=coronavirus disease 2019; CRU=clinical research unit; C-SSRS=Columbia-Suicide Severity Rating Scale; EW=early withdrawal; h=hour(s); m=minute(s); MOAA/S= Modified Observer's Assessment of Alertness/Sedation; NA=not applicable; pre=predose; PT/INR=prothrombin time/international normalized ratio; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SpO_2=oxygen saturation; VAS=visual analog scale

Note: Additional COVID–19-related precautions and procedures (including SARS-CoV-2 testing/screening) may be implemented based on the prevailing situation during study conduct, at the Investigator's discretion; the instructions will be provided in a separate document. Any procedure implemented will be in accordance with the local and national regulations and shall be documented appropriately.

a Subjects should meet qualification criteria to qualify for Treatment Phase. Qualification criteria will be assessed after the end of Qualification Phase and before the start of Treatment Phase (Day -1).
b Focusing on any changes since the last visit.
c Symptom-directed examination performed at the Investigator's discretion. Unscheduled symptom-directed physical examinations may be conducted at any time per the Investigator's discretion.
d Vital signs will include blood pressure, heart rate, oral temperature, and respiratory rate. Oral temperature checks will be performed daily for all subjects from admission to CRU until discharge. Windows for postdose assessments are ±7m from dosing to1h postdose and ±15m from 1h to 24h postdose. Respiration rate, minute ventilation, heart rate, and SpO_2 will be monitored continuously with ExSpiron and pulse oximetry respectively.
e Blood pressure only.
f Continuous pulse oximetry will be performed for 4 hour postdose, or longer if clinically indicated at the discretion of the Investigator.
g PT/INR, estimated creatinine clearance, and thyroid-stimulating hormone will be measured at Screening only.
h On Day 2 of last Treatment Period or at early termination only.
i Spontaneous AE reporting is continuous throughout the study, beginning with the time the subject gives informed consent; however, at regular intervals, AE checks will be performed using a non-leading question.
j Pharmacokinetic blood sampling will be performed after pharmacodynamic assessments. Allowed window for collection of pharmacokinetic blood samples are ±1m prior to 15m, ±7m for 15m to 45m, and ±15m after 45m.
k Drug-Specific VAS includes Drug Liking VAS, High VAS, Any Drug Effects VAS, Good Drug Effects VAS, Bad Drug Effects VAS, and Nausea.
l At 1m and 5m postdose, only Drug Liking and Drug High VAS will be performed.
m The 24h postdose assessments for Period 1-3 will occur during the predose assessments of the following period; to accommodate this, the 24h postdose assessments collection window is ±30m.
n Other VAS includes Drowsiness/Alertness VAS, Relaxation/Agitation VAS, and Drug Similarity.
o Global VAS includes Overall Drug Liking VAS and Take Drug Again VAS.
p Treatment Period 1 only. Subjects who enter the Treatment Phase will be randomized to 1 of 8 treatment sequences.
q Subjects who successfully complete the Qualification Phase and meet the qualification criteria will remain in-house and continue in to the Treatment Phase to receive the first drug administration (Period 1) in the Treatment Phase, at least 48 hours after the last drug administration in Qualification Phase.
r Discharge occurs at the end of Period 4 (approximately 24 hours after the last study drug administration) upon completion of planned discharge procedures.
s All assessments will be repeated once for each period for a total of 4 times.
t Day 2 for Periods 1, 2, and 3 will also be Day 1 for Periods 2, 3, and 4, respectively. The 24-hour postdose assessments of Periods 1, 2, and 3 can be recorded also as predose assessments of Periods 2, 3, and 4, respectively, without the need to redo the assessment.

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LIST OF ABBREVIATIONS

ACLS	advanced cardiovascular life support
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
BP	blood pressure
CHMP	Committee for Medicinal Products for Human Use
CK	creatine kinase
CNS	central nervous system
CRO	contract research organization
CRU	clinical research unit
CSP	clinical study protocol
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DEQ	drug effects questionnaire
DSM-IV-IR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision
ECG	electrocardiogram
eCRF	electronic case report form
EDS	Early Development Services
EEG	electroencephalogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
$GABA_A$	gamma-aminobutyric acid receptor subtype A
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDL	low-density lipoprotein
LORR	loss of righting reflex
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	prothrombin time
QTc	prolonged corrected QT-interval
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure

SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TSH	thyroid stimulating hormone
VAS	visual analog scale
WMA	World Medical Association

Note: Definitions of pharmacokinetic (PK) and pharmacodynamic (PD) parameters are provided in Section 3.5.3.

1. INTRODUCTION

1.1 Background

Propofol is one of the most widely used intravenous (IV) anesthetics in clinical procedures. It induces anesthesia effectively, produces a short duration of anesthesia that allows patients to recover quickly, and it is widely used in the induction and maintenance of general anesthesia for surgery. However, propofol also comes with pronounced shortcomings, in particular, pain on injection,[1] propofol-induced decrease in diastolic blood pressure (BP) and mean arterial BP, respiratory depression,[2] and, with prolonged use, excessive lipid intake causing patients to suffer from disorders of lipid metabolism.[3]

HSK3486 is a chemical entity similar to propofol; however, is unique in that it is a single-configuration chiral compound with 1 R-designated chiral center and a terminal cyclopropyl group. HSK3486 has been engineered such that the structural design aims to enhance the pharmacological and physicochemical properties of drug-receptor binding in a systematic manner. These structural improvements result in increased potency, therefore a smaller amount of drug required, less injection-site pain, and may reduce the occurrence of side effects caused by propofol.

For further information on the investigational product, including preclinical and clinical information, refer to the HSK3486 Investigator's Brochure (IB).[4]

1.1.1 Nonclinical Summary

Nonclinical pharmacology studies, including a loss of righting reflex (LORR) study in rats and anesthesia evaluation studies in dogs and minipigs, showed that HSK3486 achieved a similar depth of anesthesia as propofol with HSK3486 having up to 6-fold higher anesthetic potency than propofol.

The results of nonclinical safety pharmacology studies showed that HSK3486 had no significant effect on central nervous system (CNS) function in rats recovered from anesthesia, suggesting that HSK3486 has no residual effect in this organ system. Observed changes in electrocardiogram (ECG), BP, respiratory rate, and body temperature after HSK3486 injection were expected changes associated with anesthetic drugs; were mild and transient; and returned to normal when the animals regained consciousness. Both HSK3486 and propofol were found to shorten action potential duration in rabbit cardiac Purkinje fibers; however, the effect of HSK3486 was found to be less than that of propofol.

Results from single- and repeat-dose toxicity and toxicokinetic studies in Sprague Dawley rats and Beagle dogs showed that the depth and duration of anesthesia in animals increased proportionally with HSK3486 dose, and multiple doses did not result in drug accumulation, with the exception of certain animals in the high-dose group which may have died from respiratory depression due to their individual sensitivity to anesthesia; this is not an unusual finding at higher doses in preclinical anesthesia studies or in other preclinical studies involving anesthesia. All other animals displayed no significant toxicity and no specific target organs were identified during the administration and recovery periods. HSK3486 was not shown to have mutagenicity. Reproductive toxicity study showed no significant toxicity to rat fertility and early embryo development by HSK3486. At 2.5 mg/kg and 5 mg/kg, fetal resorption was observed to increase due to the amplification of the pharmacological action of the test article, suggesting the need to pay attention to the respiratory management of the user population. No significant embryo-fetal developmental toxicity or teratogenicity was observed. No significant toxicity was observed in birth and lactation of F_0 females; the growth, neurobehavioral development, and fertility of F_1 generation; or the survival of F_2 generations. No significant embryo-fetal developmental toxicity or teratogenicity was observed in New Zealand White rabbits. Results of local irritation, hemolytic, and allergic tests were negative, indicating the safety of the formulation. The precipitated withdrawal test in mice, spontaneous withdrawal test in rats, and conditioned place preference tests in rats suggested that HSK3486 has no physical nor psychological dependence potential in the corresponding animal models; while in the self-administration rat model, the potential for drug dependency of HSK3486 was predicted not to be higher than that of propofol.

1.1.2 Clinical Summary

As of 30 Oct 2020, 21 Phase 1 to 3 clinical studies have been initiated or planned for HSK3486; 17 have been completed, and 4 are ongoing or planned. Among the 17 completed studies, a total of 671 subjects were exposed to HSK3486, including 228 healthy subjects, 16 subjects with hepatic impairment, 20 subjects with renal impairment, 236 subjects who underwent colonoscopy, 15 subjects who underwent gastroscopy, and 156 subjects who underwent induction of general anesthesia for elective surgery. Results showed that HSK3486 exhibited quick onset and rapid regaining of consciousness, and had approximately 4 to 5 times the potency of propofol.

The types of drug-related adverse events (AEs) in subjects exposed to HSK3486 were consistent with those in subjects exposed to propofol. Cardiovascular-related AEs including hypotension, bradycardia, and prolonged corrected QT-interval (QTc) with HSK3486 were comparable to those with propofol. However, incidences of injection-site pain and respiratory-related AEs (respiratory depression, apnea, and hypoxia), and the

proportion of subjects requiring assistance in ventilation were slightly lower with HSK3486 than propofol.

Phase 1 pharmacokinetic (PK) studies showed that HSK3486 was widely distributed after a single IV administration, the plasma exposure level increased approximately proportionally to the dose, and the clearance did not change in a dose-dependent manner. The plasma concentration of HSK3486 was characterized by 3-phase elimination, with corresponding half-lives of 0.54 min ($t_{1/2}$, α), 6.26 min ($t_{1/2}$, β), and 105 min ($t_{1/2}$, γ), similar to propofol. After a single IV administration of 0.4 mg/0.8 μCi/kg [^{14}C]HSK3486, the total recovery of radioactivity was approximately 87.24% within 10 days; the majority was excreted by kidney (84.59%), and the minority was excreted by feces (2.65%). UDP-glucuronosyltransferase and cytochrome P450 (CYP)2B6 were predicted to be the primary metabolizing enzymes of HSK3486, contributing 54.0% and 24.5%, respectively, with each of the other metabolizing enzymes contributing less than 10%.

1.2 Risk-benefit Assessment and Risk Management

Propofol has the potential for respiratory and BP depression as a common side effect, and HSK3486 has been shown to elicit lower or comparable rates, respectively, of these AEs. Risk of these AEs is low in the current study due to the planned use of subtherapeutic doses for assessment of abuse potential. Additionally, an anesthesiologist or advanced cardiovascular life support (ACLS)-certified physician capable of performing intubation will remain at the clinical research unit (CRU) to support site staff during and for an appropriate time after study drug administration, to ensure subject safety.

Due to nonclinical mutagenicity, reproductive, developmental, and fetal development studies there is no perceived risk to women of childbearing potential, who will be included in this study.

There is no expected clinical benefit for the healthy subjects who will participate in this study. The information obtained in this study can be used for the further clinical development of HSK3486.

Overall, on the basis of the available nonclinical and clinical data, and prior knowledge, the risk-benefit profile of study treatments is judged acceptable for the proposed clinical study.

1.3 Study Rationale

HSK3486 is a new IV anesthetic drug developed by Sichuan Haisco Pharmaceutical Co, Ltd. HSK3486 is intended to be used in the induction of adult sedation/general anesthesia. HSK3486 has a novel structural design that provides higher potency compared to propofol, with an anesthetic induction dose of 0.4 mg/kg for HSK3486 that has been shown comparable to the approved 2.5 mg/kg dose of propofol. This higher potency could potentially result in less site pain and cardiopulmonary instability. Substantial Phase 1 to

3 clinical trials were conducted in Australia and China. Currently, one of two pivotal Phase 3 trial is ongoing in US. This human abuse potential study is planned to address the Food and Drug Administration (FDA) requirement that any new chemical entity that targets CNS needs to be evaluated on substance abuse potential in humans.

2. OBJECTIVES

2.1 Part 1

Primary

- To determine the doses of IV HSK3486 and propofol for use in Part 2, the abuse potential part of the study

Secondary

- To evaluate the safety and tolerability of HSK3486 in healthy, nondependent, recreational CNS depressant drug users

2.2 Part 2

Primary

- To evaluate the abuse potential of HSK3486 compared with propofol when administered IV to healthy nondependent, recreational CNS depressant drug users

Secondary

- To evaluate the safety and tolerability of HSK3486 compared to propofol when administered IV to healthy nondependent, recreational CNS depressant drug users
- To evaluate the PK profile of HSK3486 when administered IV to healthy nondependent, recreational CNS depressant drug users

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

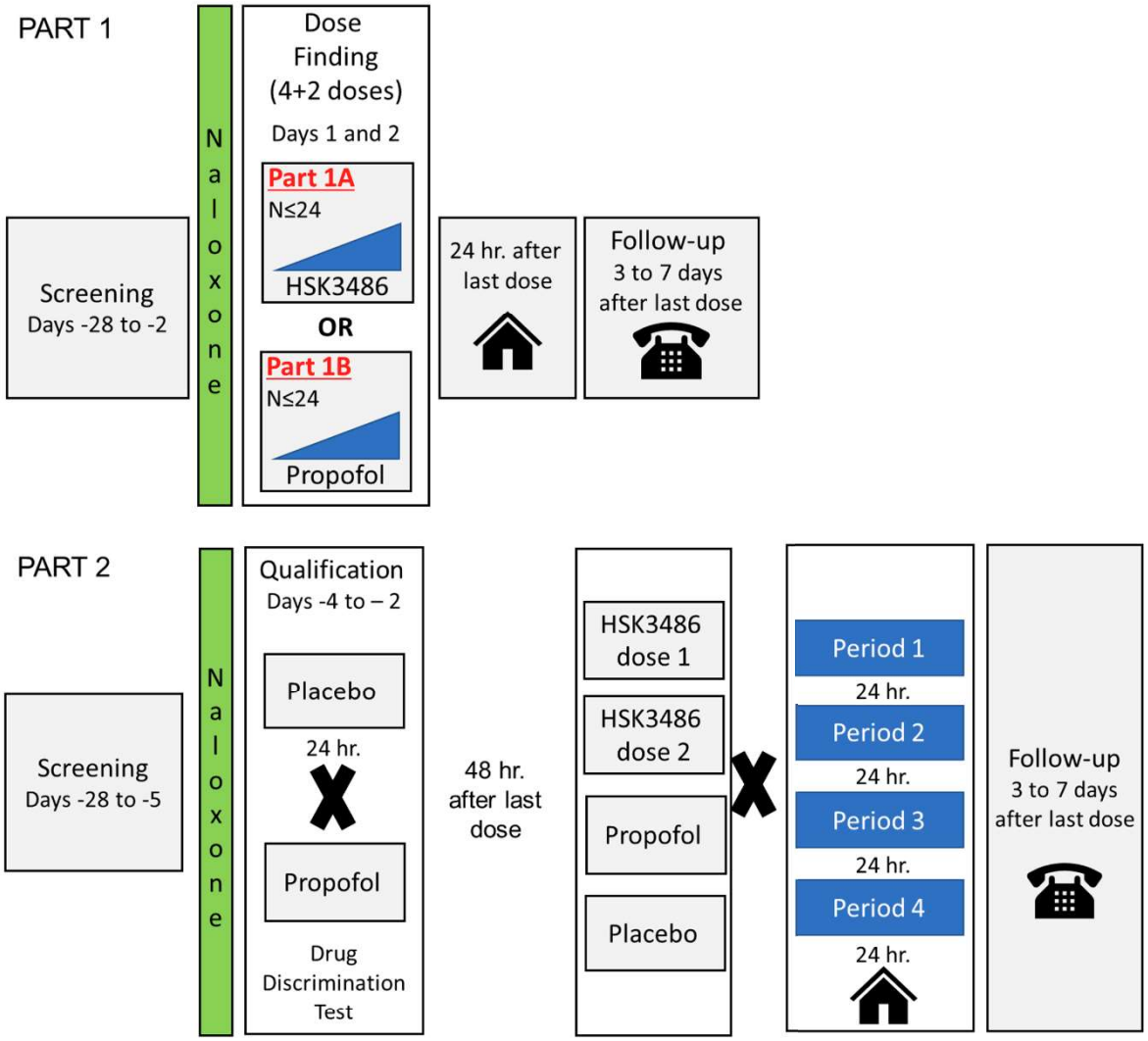
3.1.1 Type of Study

This single center study will consist of 2 parts. Part 1 will be an open-label, dose-finding study of HSK3486 and propofol conducted in up to 48 recreational users of CNS depressants to determine the appropriate doses to be used in Part 2 of the study. Part 2 will be a randomized, double-blind, placebo- and active-controlled 4-period, 4-way crossover, in approximately 42 healthy volunteers with prior recreational CNS depressant exposure. The abuse potential of single administration of 2 different presumed subtherapeutic doses of HSK3486 will be compared with a dose of propofol (active control) determined in Part 1, and placebo. Both Part 1 and Part 2 of the study will consist of an outpatient Screening Visit, an in-clinic Treatment Phase, and Follow-up; Part 2 will also include a Qualification Phase.

The treatments planned in this study are described in Section 3.4.1.

Additional coronavirus disease 2019 (COVID–19) related precautions and procedures (including SARS-CoV-2 [severe acute respiratory syndrome coronavirus 2] testing/screening) may be implemented based on the prevailing situation during study conduct, at the Investigator's discretion; the instructions will be provided in a separate document. Any procedure implemented will be in accordance with the local and national regulations and shall be documented appropriately.

Figure 2: Study Diagram



N=number of subjects
The doses to be used in Part 2 will be determined during dose finding in Part 1. Groups of 4 subjects will receive 1 dose level. Enrollment will be halted after the doses to be used in Part 2 will have been determined.
The Drug Discrimination Test will ensure subjects can differentiate between the effects of active control (propofol) and placebo.
A naloxone challenge will ensure subjects are not opioid dependent.
A naloxone challenge will be administered on the day of admission.

3.1.2 Screening Period

Subjects will report to the medical screening facility/clinical site for the eligibility screening (see Section 3.2.6 for inclusion and exclusion criteria) within 28 days prior to drug administration. If a subject participates in Part 1 and is admitted to the clinic for Part 1 within the 28 day screening window for Part 2, they will be reconsented but do not need to be rescreened.

Subjects will sign the study-specific informed consent form (ICF) prior to any study-specific screening procedures being performed. The written informed consent will be obtained for all subjects, regardless of their eligibility for the study; the signed ICFs will be retained and archived, and a copy will be provided to the subject.

Eligibility screening will consist of the assessments as presented in the schedule(s) of assessments (Table 1 or Table 2).

3.1.3 Treatment Period

3.1.3.1 Part 1

Part 1 will consist of 2 separate arms: Part 1A and Part 1B. Up to 48 subjects may be enrolled to participate in Part 1 with up to 24 subjects in each arm. Subjects will be admitted to the clinic on Day -1 and administered a naloxone challenge (Section 3.2.7) to assess opioid dependence, on Day 1 they will be administered study drug (either HSK3486 or propofol) following a minimum 8-hour fast, and on Day 2 they will be discharged at least 24 hours after study drug administration and upon completion of study assessments. Subjects who participate in a given group in Part 1 cannot participate in a subsequent group in Part 1; however, subjects in Part 1 may participate in Part 2 of the study at the discretion of the Investigator.

Part 1A: For HSK3486 dose determination, groups of 4 eligible subjects will receive 1 dose of study drug. On Day 1, subjects in the first group will receive IV HSK3486 0.1 mg/kg (starting dose) administered as a bolus over 30 seconds (±5 seconds) from a syringe. The dose used for succeeding groups will be based on the pharmacodynamic (PD) and safety results of the prior group. The dose used in the next group may be increased, decreased. or repeated; the magnitude of change for a new dose will be no greater than 0.025 mg/kg (increase or decrease) relative to previously administered doses. It is anticipated that 4 dose levels will be sufficient to identify the doses that should be used in Part 2 of the study; however, enrollment can be halted prior to completing all planned groups once doses for Part 2 have been identified based on dose selection criteria listed in Section 3.2.5. If necessary, up to 2 additional groups of 4 subjects each may be enrolled up to a total of 24 subjects. These additional groups will be used if doses have not been identified that meet the dose selection criteria, or if the Investigator and Sponsor agree that higher or intermediate doses may be of value to Part 2, even if previously tested doses meet dose selection criteria. All dose increases during dose finding are subject to stopping rules defined in Section 3.2.4.

Part 1B: Likewise, for propofol dose determination, groups of 4 eligible subjects will receive 1 dose of propofol. On Day 1, subjects in the first group will receive IV propofol 0.5 mg/kg (starting dose) administered as a bolus over 30 seconds (±5 seconds) from a syringe.[5] The dose used for succeeding groups will be based on the pharmacodynamic (PD) and safety results of the prior group. The dose used in the next group may be increased, decreased,

or repeated; the magnitude of change for a new dose will be no greater than 0.125 mg/kg (increase or decrease) relative to previously administered doses. It is anticipated that 4 dose levels will be sufficient to identify the dose of propofol that should be used in Part 2 of the study; however, enrollment can be halted prior to completing all planned groups once the dose for Part 2 has been identified based on dose selection criteria listed in Section 3.2.5. If necessary, up to 2 additional groups of 4 subjects each may be enrolled up to a total of 24 subjects. These additional groups will be used if a dose has not been identified that meets the dose selection criteria, or if the Investigator and Sponsor agree that a higher or intermediate dose may be of value to Part 2, even if previously tested doses meet dose selection criteria. All dose increases during dose finding are subject to stopping rules defined in Section 3.2.4.

All subjects will receive a 2 cc pre-treatment of 1% lidocaine at the injection site to minimize pain associated with study drug administration prior to administration of either HSK3486 or propofol.

Safety and PD assessments will be performed at defined timepoints including Drug Liking ("at this moment"), drowsiness/alertness visual analog scale (VAS), and the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) (Section 3.5.1.2.3). Subjects will be rated on their ability to complete the full battery of abuse potential questions for up to 1 hour. Safety assessments will include continuous oxygen saturation, vital signs, continuous telemetry, and 12-lead electrocardiogram (ECG). Respiratory minute ventilation of subjects will be monitored using the ExSpiron® device. An anesthesiologist or ACLS-certified physician capable of performing intubation will remain at the CRU to support site staff during study drug administration and for at least 0.5 hours following study drug administration.

Dose-finding stopping rules are described in Section 3.2.4, and Part 2 dose selection criteria are described in Section 3.2.5.

Subjects will be discharged approximately 24 hours following study drug administration. A telephone follow-up assessment will be performed 3 to 7 days after drug administration.

Assessments for follow-up will be performed as presented in Table 1 or Table 3.

3.1.3.2 Part 2

Subjects will be admitted to the CRU on Day -4 for the Qualification Phase. Upon admission on Day -4, each subject will be administered a naloxone challenge to assess opioid dependence (Section 3.2.7). During the Qualification Phase, subjects will undergo a Drug Discrimination Test to ensure that they can differentiate between the effects of active control (propofol) and placebo; qualification criteria described in Section 3.2.6. During the Drug Discrimination Test, subjects will receive IV propofol (dose to be determined in Part 1)

administered over 30 seconds (Treatment X) or matching placebo (Treatment Y) after an overnight fast in a randomized, double-blind, crossover manner with each drug administration separated by approximately 24 hours (Day -3 and Day -2). Subjects who do not meet Drug Discrimination criteria (Section 3.2.6) will be discharged from the CRU approximately 24 hours after the second drug administration. Subjects who successfully complete the Qualification Phase will be eligible to enter the Treatment Phase. A washout interval of at least 48 hours will be required between the last drug administration in the Qualification Phase and the first drug administration in the Treatment Phase. In both Qualification and Treatment phases of the study, the Investigator will instruct subjects when answering questions after drug administration, not to make comparisons with previous treatments received in the study.

All subjects will be randomized to 1 of 8 treatment sequences according to two 4×4 William squares in the Treatment Phase. Subjects will receive each of the following 4 treatments in a randomized, double-blind, 4-way crossover manner following an overnight fast:

- Treatment A: HSK3486 dose 1 (IV bolus over 30 seconds [±5 seconds] from a syringe; dose to be determined in Part 1 [Section 3.2.5])
- Treatment B: HSK3486 dose 2 (IV bolus over 30 seconds [±5 seconds] from a syringe; dose to be determined in Part 1 [Section 3.2.5])
- Treatment C: Propofol (IV bolus over 30 seconds [±5 seconds] from a syringe; dose to be determined in Part 1 [Section 3.2.5])
- Treatment D: Placebo (Treatment A matched) (IV bolus over 30 seconds [±5 seconds] from a syringe)

To assist with blinding of subjects all study treatments in Part 2 will be administered by an unblinded dosing team, which will use a blindfold and curtain to obscure visible differences between treatments for the subject dosed, any blinded study team members, and neighboring subjects. In effort to further maintain the blind, within 5 minutes before each treatment (test, active control, or placebo; Qualification Phase and Treatment Phase) subjects will be administered 2 cc of 1% lidocaine at the injection site in order to block the stinging sensation that can occur with propofol injection.

Each treatment administration in the Treatment Phase will be separated by approximately 24 hours. Serial PD assessments will be performed, including Drug Liking, level of sedation, and ability to respond to questions. Subjects will also undergo safety assessments while housed in the CRU.

Subjects will be discharged approximately 24 hours following the last dose of study drug in Period 4. A telephone follow-up assessment will be performed 3 to 7 days after either last drug adminsitration or early withdrawal from the study.

Assessments for follow-up will be performed as presented in Table 1 or Table 3.

3.2 Discussion of Study Design

See Section 3.6.3 for sample size determination.

3.2.1 Subjects and Qualification

This study will be performed in nondependent, recreational CNS depressant users. These subjects represent the population most at risk for abusing HSK3486, are familiar with the subjective effects of CNS depressants, and are able to tolerate drugs in this class, hence provide the most face-valid population for a study of abuse potential.

The Qualification Phase will ensure that subjects who proceed to the Treatment Phase are able to discriminate between propofol and placebo as well as report appropriate responses to the drug in a controlled laboratory setting.

A naloxone challenge will ensure subjects are not opioid dependent, which would confound study results.

3.2.2 Propofol as Comparator

The comparators in an abuse potential study are typically controlled substances from the same pharmacologic class as the investigational drug. HSK3486 is a unique chemical entity similar to propofol with higher potency but similar efficacy and action. Given propofol's demonstrated abuse potential, it is the appropriate comparator for the study.[5]

3.2.3 Study Design

Human abuse potential studies are typically conducted as double-blind crossovers because of inter-individual variability in subjective responses. Each subject receives each dose of study drug and acts as his/her own control.

3.2.4 Part 1 Stopping Rules for Dose Finding

Dose finding will be halted, pending discussion between sponsor and investigator, in Part 1 if 1 subject out of 4 demonstrates 1 or more of the below changes in vital signs sustained for ≥2 minutes with verbal stimulation as monitored through the first hour postdose:

1) Heart rate <40 bpm
2) Systolic BP <80 mmHg
3) Respiratory rate <6 breaths per minute
4) Pulse oximetry O_2 sat <87% with verbal stimulation
5) Respiratory minute ventilation <60% of baseline

If the sponsor and investigator agree that the vital signs changes noted above were unlikely related to study drug and/or that there is no significant safety concern, then dose finding may proceed at an increased, decreased, or repeated dose level.

3.2.5 Part 2 Dose Selection Criteria

The Investigator and Haisco will determine the doses of HSK3486 and propofol to be used in Part 2 of the study using the following criteria as monitored through the first hour postdose:

1) Maximum dose at which subjects are able to adequately complete the battery of human abuse potential assessments over most of the 1-hour period
2) Level of consciousness generally remains at a MOAA/S score ≥4 (Section 3.5.1.2.3)
3) Minute ventilation does not decrease more than 30% for one minute with verbal stimulation
4) Oxygen saturation does not fall below 90% for more than 30 sec with verbal stimulation

For both HSK3486 and propofol, the highest doses tested in Part 1 meeting these criteria will be used in Part 2, Treatments A and C, respectively. The second dose of HSK3486 to be used in Part 2 will be the second highest dose tested in Part 1 (Treatment B) that meets these criteria.

3.2.6 Qualification Criteria

Subjects must meet each of the following criteria at the end of Qualification Phase in order to be eligible for participation in the Treatment Phase:

1. Drug Liking VAS E_{max} ≥65 points for active control (IV propofol) and ≥15 points higher for active control than for placebo.
2. Acceptable placebo response based on Drug Liking VAS (score between 40 points and 60 points, inclusive).
3. Acceptable overall responses to active control (IV propofol) and placebo on all other human abuse potential PD measures, as judged by the Investigator or designee.
4. Acceptable safety and tolerability after administration of active control (IV propofol).
5. Oxygen saturation does not fall below 90% for more than 30 sec with verbal stimulation.

3.2.7 Naloxone Challenge

During the naloxone challenge administered in Parts 1 and 2, all participants will receive IV naloxone 0.2 mg dose as an IV bolus, followed by an assessment for signs of opioid withdrawal. If there are no signs of opioid withdrawal within 30 seconds after administration, a second dose of 0.6 mg IV will be administered within 5 minutes of the first dose, followed by another assessment for signs of opioid withdrawal 5 minutes after the second naloxone dose. Only participants who do not have signs and symptoms of opioid withdrawal, as assessed by the Clinical Opioid Withdrawal Scale (COWS score <5), will be eligible to proceed with the study (Appendix 8.4). Any participant demonstrating evidence of withdrawal (COWS score >5) on any assessment will not be eligible for further participation in the trial. The participant will be released from the study center when medically stable, as determined by the Investigator. Symptoms reported in the COWS as a consequence of opioid withdrawal will not be collected as AEs unless they meet the criteria for a new AE or serious adverse event (SAE).

3.3 Selection of Study Population

Subjects will be healthy male and female nondependent, nontreatment-seeking recreational CNS depressant users.

Part 1

An adequate number of subjects will be screened such that up to 32 subjects (16 subjects for HSK3486 dose determination [4 groups of 4 subjects each] and 16 subjects for propofol dose determination [4 groups of 4 subjects each]) may be enrolled in Part 1 of the study. Up to an additional 16 subjects (2 groups of 4 each for HSK3486 dose determination and 2 groups of 4 each for propofol dose determination) may be enrolled in Part 1, if necessary.

Part 2

An adequate number of subjects will be screened such that a sufficient number of subjects are randomized into the Qualification Phase with the intention of qualifying and randomizing approximately 42 subjects into the Treatment Phase, with the intention of completing 36 subjects. Subjects who participated in Part 1 of the study may be eligible for Part 2 of the study at the Investigator's discretion.

3.3.1 Inclusion Criteria

Note: Restrictions that apply to the period after admission are described in Section 3.4.8, except when they concern a statement of willingness.

The following criteria must be met for a subject to be eligible for inclusion in the study:

1) Willing to participate in the study, give written informed consent, and comply with the study restrictions.
2) Gender: male or female; females may be of childbearing potential, of nonchildbearing potential, or postmenopausal.
3) Age: 18 years to 55 years, inclusive, at Screening.
4) Body mass index (BMI): 18.0 kg/m^2 to 30.0 kg/m^2, inclusive.
5) Weight: ≥50 kg, inclusive.
6) Healthy subject, defined by the absence of evidence of any clinically significant, in the opinion of the Investigator, active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, serology, and urinalysis.
7) Subject must be a nondependent, nontreatment-seeking recreational CNS depressant user, defined as follows:
   a. ≥10 lifetime nontherapeutic experiences (i.e., for psychoactive effects) with CNS depressants (e.g., benzodiazepines, barbiturates, zolpidem, zopiclone, propofol/fospropofol, gamma-hydroxybutyrate).
   b. ≥1 nontherapeutic use of a CNS depressant within the 8 weeks prior to Screening.
   c. ≥1 nontherapeutic use of benzodiazepines within the 12 months prior to Screening.

8) Ability and willingness to abstain from alcohol-, caffeine-, and xanthine-containing beverages or food (e.g., coffee, tea, cola, chocolate, energy drinks) from 48 hours (2 days) prior to first admission to the CRU, throughout the entire study, and until discharge.
9) All values for hematology and clinical chemistry tests of blood and urine within the normal range or show no clinically relevant deviations, as judged by the Investigator.
10) Females of childbearing potential, and males with female partner(s) of childbearing potential, as judged by the Investigator, must agree to use 2 forms of contraception, 1 of which must be a barrier method, during the study and for 90 days after the last drug administration. Acceptable barrier forms of contraception are condom, cervical cap, and diaphragm. Acceptable non barrier forms of contraception for this study are an intrauterine device (IUD) including hormonal IUDs, oral contraceptives (used for ≥30 days prior to dosing any study treatment), and/or spermicide.
11) For females: a negative pregnancy test at Screening and Admission.
12) Postmenopausal females: defined as 12 months with no menses prior to Screening and a serum follicle-stimulating hormone (FSH) >40 IU/L at Screening.
13) All nonregular medication (including over-the-counter medication, health supplements, and herbal remedies such as St. John's Wort extract) must have been stopped at least 14 days prior to (the first) admission to the CRU. An exception is made for acetaminophen, which is allowed up to admission to the CRU.
14) All prescribed medication must have been stopped at least 30 days prior to (first) admission to the clinical research center. An exception is made for hormonal contraceptives, which may be used throughout the study.
15) Able to speak, read, and understand English sufficiently to allow completion of all study assessments.

3.3.2 Exclusion Criteria

Note: Restrictions that apply to the period after admission are described in Section 3.4.8, except when they concern a statement of willingness.

A subject who meets any of the following criteria will not be eligible for inclusion in the study:

1. An employee of the Sponsor or research site personnel directly affiliated with this study or their immediate family member (defined as a spouse, parent, child, or sibling, whether biological or legally adopted).
2. Drug or alcohol dependence within the 2 years prior to Screening (except nicotine and caffeine), as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), and/or has ever participated or plans to participate in a substance or alcohol rehabilitation program to treat their substance or alcohol dependence.
3. Opioid dependence as judged by the Investigator after a naloxone challenge.
4. Women who are pregnant, lactating, or planning to attempt to become pregnant during this study or within 90 days of last study drug administration.

5. Males with female partners who are pregnant, lactating, or planning to attempt to become pregnant during this study or within 90 days of last study drug administration.
6. Positive drug and alcohol screen (tetrahydrocannabinol [THC], morphine/opiates, methadone, oxycodone, phencyclidine, cocaine, amphetamines, methamphetamines, ecstasy, barbiturates, benzodiazepines, tricyclic antidepressants, and alcohol) at each admission to the CRU. For THC, subjects should ideally test negative. However, eligibility decision with regards to THC use will be considered on a case by case basis, at the discretion of the Investigator.
7. Treatment with an investigational drug or device within 5 times the elimination half-life, if known (e.g., a marketed product) or within 30 days (if the elimination half-life is unknown) prior to first drug administration or is concurrently enrolled in any research judged not to be scientifically or medically compatible with this study. An exception may be made for subjects who participated in Part 1 of the study.
8. History or presence of clinically significant abnormality (e.g., obstructive sleep apnea) as assessed by physical examination, medical history, ECG, vital signs, or laboratory values, which, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
9. Any disease which, in the opinion of the Investigator, poses an unacceptable risk to the subjects.
10. Mallampati intubation score >2.
11. History of clinically significant drug allergy diagnosed by a physician. Confirmatory circumstances would include treatment with epinephrine or in an emergency department.
12. Any personal or family history of issues with succinylcholine, such as malignant hyperthermia or pseudocholinesterase deficiency.
13. History of allergy, adverse reaction (including significant agitation, etc.), or hypersensitivity to propofol, lidocaine, other injected anesthetic agents, or related drugs.
14. History of allergy to eggs, egg products, soybeans or soy products.
15. Heavy smoker (>20 cigarettes per day) and/or is unable to abstain from smoking and/or the use of prohibited nicotine-containing products (including e-cigarettes, pipes, cigars, chewing tobacco, nicotine topical patches, nicotine gum, or nicotine lozenges) from 2 hours prior to dosing until at least 4 hours postdose during the in-clinic periods.
16. Routine or chronic use of more than 3000 mg of acetaminophen daily.
17. Strenuous activity (such as exercise), sunbathing, and contact sports within 48 hours (2 days) prior to admission to the CRU, during the study, and until after discharge in the last study period.
18. History of donation of more than 450 mL of blood within 60 days prior to dosing in the CRU or planned donation before 30 days has elapsed since last intake of study drug.
19. Plasma or platelet donation within 7 days of dosing and throughout the entire study.
20. Average intake of more than 14 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits). Alcohol consumption will be prohibited 48 hours prior to first admission to the CRU and throughout the entire study until the Follow-up visit (including washout period).

21. Positive screening test for hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibodies, or anti-HIV 1 and 2 antibodies.
22. History of peripheral vasculopathy, including Raynaud's phenomenon.
23. History of seizures, seizure disorder, or known electroencephalogram (EEG) abnormalities.
24. History of mental illness, which, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
25. Subject with a history of clinically significant head injury, ongoing seizure disorder, chronic tics, or diagnosis or family history of Tourette's syndrome.
26. Subjects with a history of serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, advanced arteriosclerosis, symptomatic cardiovascular disease, hypertension, or other cardiac problems.
27. Any history of clinically significant suicidality as assessed by the Investigator based upon clinical history, source documents, or scores on the Columbia-Suicide Severity Rating Scale (C-SSRS).
28. History or presence of clinically significant hepatic or renal disease.
29. History of hyperthyroidism.
30. Difficulty with venous access or unsuitable or unwilling to undergo catheter insertion.
31. Use of a cytochrome p450 (CYP)2D6-inhibiting drug or a serotonergic drug within 14 days prior to first drug administration in the Qualification Phase.
32. Consumption of any nutrients known to modulate CYP enzymes activity (e.g., grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products) within 14 days prior to administration of study medication and during the study (including washout period) until after discharge in the last study period.
33. A subject who, in the opinion of the Investigator or designee, is considered unsuitable or unlikely to comply with the study protocol for any reason.
34. A subject who has pending legal charges or is on probation.

3.3.3 Removal of Subjects from Assessment

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time for any reason.

The Investigator has the right to terminate participation of a subject for any of the following reasons: difficulties in obtaining blood samples, violation of the protocol, severe AEs or SAEs, or for any other reason relating to the subject's safety or integrity of the study data.

If a subject is withdrawn from the study, the Sponsor will be informed immediately. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned.

After signing informed consent, subjects who drop out or withdraw for any reason without completing all screening evaluations successfully as well as subjects who drop out or withdraw prior to the first dose of study drug will be considered screening failures.

A subject who is withdrawn or voluntarily withdraws from the study for any reason, whether related to the study drug or not, after having received the first dose of study drug, will be considered an early-termination subject. If a subject is withdrawn for a reason related to the study drug, according to the judgment of the Investigator, the early-termination subject will not be replaced. If a subject does not complete the study for a reason not related to the study drug, the early-termination subject may be replaced after mutual agreement between the Sponsor and site.

The decision regarding the replacement of subjects will be documented.

Every effort will be made to ensure that early-termination subjects who have received study drug complete the early-termination assessments/safety follow-up assessments.

3.4 Treatments

3.4.1 Treatments Administered

In Part 1 subjects will be administered either propofol or HSK3486 at a starting dose of 0.5 mg/kg and 0.1 mg/kg, respectively. In between each group the dose can be increased or decreased by no more than 0.125 mg/kg (propofol) or 0.025 mg/kg (HSK3486) relative to any previously tested dose.

In Part 1, subjects will receive a treatment of 2 cc of 1% lidocaine at the injection site to minimize pain associated with study drug administration prior to administration of either HSK3486 or propofol.

In the Qualification Phase of Part 2, subjects will undergo a Drug Discrimination Test. Each subject will be administered one of the follow treatments:

- Treatment X: IV propofol (dose determined in Part 1)
- Treatment Y: Matching placebo

In the Treatment Phase of Part 2, subjects will receive each of the following treatments:

- Treatment A: HSK3486 dose 1 (IV bolus over 30 seconds [±5 seconds] from a syringe; dose to be determined in Part 1)
- Treatment B: HSK3486 dose 2 (IV bolus over 30 seconds [±5 seconds] from a syringe; dose to be determined in Part 1)
- Treatment C: Propofol (IV bolus over 30 seconds [±5 seconds] from a syringe; dose to be determined in Part 1)
- Treatment D: Placebo (IV bolus over 30 seconds [±5 seconds] from a syringe)

In order to maintain the blind in Part 2, subjects will be administered 2 cc of 1% lidocaine at the injection site within 5 minutes before each treatment (test, active control, or placebo;

Qualification Phase and Treatment Phase) in order to block the stinging sensation that can occur with propofol injection. Additionally a blindfold and curtain will be used to hide visible differences between the separate treatments, and a unblinded dosing team will be used to maintain the blind of the site staff performing the study assessments. Further details are provided in the Pharmacy Manual.

3.4.2 Identity of Investigational Products

Test preparation (HSK3486)

Active substance : HSK3486 injectable emulsion
Activity : CNS depression through gamma-aminobutyric acid receptor subtype A ($GABA_A$) mediation
In development for: General anesthesia and sedation
Strength : 2.5 mg/mL (total dose: 0.05 g in 20 mL)
Dosage forms : Injection
[redacted]

Reference medication (Propofol injectable emulsion)

Active substance : Propofol
Activity : Positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated $GABA_A$ receptors
Indication : General anesthesia and sedation
Strength : 10 mg/mL
Dosage form : Injection
[redacted]

Placebo

Substance : Intralipid®
Activity : Not applicable
Strength : Not applicable
Dosage form : 20% IV fat emulsion
[redacted]

Masking drug (xylocaine)

Substance : Lidocaine HCl
Activity : Local anesthetic
Strength : 1%
Dosage form : Injection
[redacted]

The test preparation will be provided by the Sponsor. The reference medication, placebo, and masking drug will be commercially obtained by the Pharmacy.

For details concerning drug storage and drug accountability see Appendix 8.1.

3.4.3 Method of Assigning Subjects to Treatment Groups

Part 1 of the study is non-randomized.

In Part 2 of the study, subjects enrolled in the Qualification Phase will be randomized to 1 of 2 treatment sequences (XY or YX) in a 1:1 ratio. Randomization numbers will begin with 2001.

Subjects who successfully complete the Qualification Phase and continue to be enrolled in the Treatment Phase of Part 2 will be randomized to 1 of 8 treatment sequences (with equal allocation) according to two 4×4 William's design Latin squares. Subject randomization numbers for the Treatment Phase will range from 1001 to 10XX with replacement numbers ranging from 1101 to 11XX.

The randomization schedules will be produced by [redacted] Biostatistics. The study biostatistician will create a draft randomization list and a peer biostatistician will review and approve that draft list. After the final randomization list has been approved, it will be transferred to the pharmacy and kept in a restricted area to which only the pharmacy has access.

3.4.4 Selection of Doses in the Study

To ensure all subjects can complete the necessary assessments in the study a nonsedating dose of both HSK3486 and propofol is needed.

The starting dose of propofol in Part 1 is 0.5 mg/kg, which is similar to a dose of 0.6 mg/kg that demonstrated abuse potential in previous work.[5] A single-ascending dose study with HSK3486 has shown MOAA/S and Richmond agitation-sedation scale scores of 4 and -2, respectively, at 0.128 mg/kg,[6] which is expected to be slightly too much sedation for the assessments in the current study. A dose of 0.1 mg/kg was chosen as an appropriate starting dose for HSK3486 in Part 1

The doses used in Part 2 of the study will be determined based on selection criteria outlined in Section 3.2.5 from results obtained in Part 1.

3.4.5 Timing of Doses in the Study

All study treatments will be administered after a minimum of an 8-hour fast. During fasting, no fluids are allowed except water, excluding the 2 hours prior to dosing when all fluids including water are restricted. Water can be resumed after dosing is complete.

In Part 2 (Qualification Phase and Treatment Phase), a single treatment will be administered each day separated by approximately 24 hours each.

All study drug will be administered with the subject in the upright position as an IV bolus over 30 seconds (±5 seconds).

Fasting will continue for a period of at least 4 hours after drug administration. When not fasting, noncaffeinated fluids are allowed ad libitum.

3.4.6 Meals During the Study

A fasting period of at least 4 hours is required before obtaining clinical laboratory blood samples at all time points (Table 1, Table 2, and Table 3).

With the exception of the restrictions with respect to methylxanthine- and alcohol-containing beverages or food as described in Section 3.4.8 and what has been described in Section 3.4.5, there are no special requirements related to food and beverage intake. When not fasting, meals and snacks (such as decaffeinated coffee, herbal tea, fruit, biscuits) will be provided according to site standard operating procedures (SOPs). A standard dinner will be provided on the evening before those days where fasting is required until fasting is complete.

3.4.7 Blinding

Part 1 is open-label (not applicable).

In Part 2, all subjects will be randomized to 1 of 8 treatment sequences according to two 4×4 William squares. The following controls will be employed to maintain the double-blind status of the study:

- Due to visible differences between study treatments, a blindfold will be used to hide the treatment administered to each subject, and a curtain will be used to hide difference in treatment for subjects dosed, any blinded study team members, and neighboring subjects.
- An unblinded dosing team will be used to ensure the remainder of the site staff will be blinded during study assessments.
- Within 5 minutes before each treatment (test, active control, or placebo; Qualification Phase and Treatment Phase) subjects will be administered 2 cc of 1% lidocaine at the injection site in order to block the stinging sensation that can occur with propofol injection.
- The randomization code will be provided to the pharmacist for dispensing purposes and kept in the pharmacy, accessible to the pharmacist and the pharmacy technician only.

The laboratory where the PK samples will be analyzed will be provided a copy of the randomization code by the pharmacy since only samples of subjects who have received the active drug HSK3486 will be analyzed.

3.4.8 Concomitant Medication and Other Restrictions During the Study

Note: Restrictions that apply to the period before admission are described in Section 3.3.1 and Section 3.3.2.

The use of all prescribed medication is not allowed from at least 30 days prior to admission to the clinical research center until follow-up. The use of all over-the-counter medication, vitamin preparations and other food supplements, or herbal medications (e.g., St. John's wort) is not allowed from at least 14 days prior to admission to the clinical research center until follow-up. An exception is made for:

- Acetaminophen: from admission onwards, the Investigator may permit a limited amount of acetaminophen for the treatment of headache or any other pain.
- Hormonal contraceptives, which are allowed throughout the study.
- Lidocaine.
- Intralipid.

Other medication to treat AEs may only be prescribed if deemed necessary by the Investigator. If medication is used, the name of the drug, the dose, and dosage regimen will be recorded in the electronic case report form (eCRF). All medications (prescription and over-the-counter) taken within 30 days of study screening or during the study will be recorded in the appropriate section of the eCRF and in the source documents.

The use of methylxanthine-containing beverages or food (coffee, tea, cola, chocolate, energy drinks) is not allowed from 48 hour prior to admission until discharge. The use of grapefruit (juice) is not allowed from 14 days prior to admission until discharge. Restrictions to nicotine-containing products are described in Section 3.3.2.

The use of alcohol is not allowed during the stay in the clinical research center.

Subjects will not be allowed to smoke for 2 hours prior to dosing until at least 4 hours postdose during the in-clinic periods.

Strenuous exercise is not allowed within 48 hours (2 days) prior to admission. Strenuous exercise is also not allowed during the stay in the clinical research center and until after discharge.

Subjects should not consume any foods containing poppy seeds within 48 hours (2 days) prior to admission to the clinical research center as this could cause a false positive drug screen result.

Contraceptive requirements for males and females are described in Section 3.3.1.

3.4.9 Treatment Compliance

Study drug will be administered in the clinical research center by the Investigator or authorized designee (Part 1 and Part 2) or an unblinded dosing team (Part 2). Compliance will be further confirmed for HSK3486 by bioanalytical assessment in plasma samples (see Section 3.5.4).

The exact times of study drug administration and the number of units administered will be recorded in the eCRF.

3.5 Pharmacokinetic, Pharmacodynamic, and Safety Variables

3.5.1 Pharmacokinetic, Pharmacodynamic, and Safety Assessed

Schedules of assessments are presented in Table 1, Table 2, and Table 3.

3.5.1.1 Pharmacokinetic Measurements

The samples obtained for PK analysis may be used for analysis of metabolites of the study drug in the future.

3.5.1.1.1 Blood Sampling

At the time points defined in the schedule of assessments, blood samples of 2 mL each will be taken for the analysis of HSK3486 in plasma samples. The blood samples will be taken via an indwelling IV catheter or by direct venipuncture. The exact times of blood sampling will be recorded in the eCRF.

Details on sample collection, handling, storage, and shipping will be described in the laboratory manual.

3.5.1.2 Pharmacodynamic Measurements

All measures will be taken to prevent missing data due to subjects falling asleep and/or impairment of their ability to respond adequately. Missing data will not be imputed for statistical summary and analysis.

3.5.1.2.1 Drug Liking (“at this moment”) VAS

Drug Liking assesses the degree that a subject likes a drug effect at the time the question is being asked (that is, “at this moment”). Subjects respond to the statement “At this moment, my liking for this drug is.” The answer is scored using a 0 to 100-point bipolar VAS anchored in the center with a neutral anchor of "neither like nor dislike" (score of 50), on the left with "strong disliking" (score of 0) and on the right with "strong liking" (score of 100).

3.5.1.2.2 Drowsiness/Alertness VAS

This scale assesses the subject’s mental state at the time the question is being asked (that is, at the moment). Subjects respond to the statement “At this moment, my mental state is:” The question is scored using a 0 to 100-point bipolar VAS anchored on the left with “very drowsy” (score of 0); “neither drowsy nor alert” (score of 50) in the middle; and anchored on the right with “very alert” (score of 100).

3.5.1.2.3 MOAA/S Score

The following scale will be used for MOAA/S scoring:
5 = responds readily to name spoken in normal tone

4 = lethargic response to name spoken in normal tone
3 = responds only after name is called loudly and/or repeatedly
2 = responds only after mild prodding or shaking
1 = responds only after painful trapezius squeeze
0 = does not respond to painful trapezius squeeze

3.5.1.2.4 Ability to Complete Battery of Abuse Potential Assessment Questions for 1 Hour

The Investigator will assess if the subject was able to complete the required questions within the 1-hour period after study treatment administration.

3.5.1.2.5 Overall Drug Liking VAS

This scale assesses the subject's global perception of Drug Liking (i.e., the subjective effects over the whole course of the drug experience including any carryover effects). Subjects respond to the statement "Overall, my liking for this drug is:" The question is scored using a 0 to 100-point bipolar VAS anchored on the left with "strong disliking" (score of 0); "neither like nor dislike" (score of 50) in the middle; and anchored on the right with "strong liking" (score of 100). This scale has the advantage of the subject being relatively less affected or unaffected by acute study drug effects (if any) by the time of the assessment.

3.5.1.2.6 Take Drug Again VAS

This test is a subjective assessment of the degree to which a subject would desire to take the drug again if given the opportunity. Subjects respond to the statement "Would you want to take the drug you just received again, if given the opportunity?" The question is scored using a 0 to 100-point bipolar VAS anchored on the left with "definitely would not" (score of 0); "do not care" (score of 50); and anchored on the right with "definitely would" (score of 100).

3.5.1.2.7 Drug Effects Questionnaire

The drug effects questionnaire (DEQ) is a series of scales used to evaluate subjective responses at the time the question is being asked to general and specific drug effects following acute administration of study treatments. Subjects respond to statements assessing the following: any drug effects, good drug effects, and bad drug effects. The answer is scored using a 0 to 100-point unipolar VAS anchored on the left by "not at all" (score of 0) and on the right by "extremely" (score of 100).

3.5.1.2.8 Relaxation/Agitation VAS

This scale assesses the subject's mood at the time the question is being asked (that is, at the moment). Subjects respond to the statement "At this moment, my mood is:" The question is scored using a 0 to 100-point bipolar VAS anchored on the left with "very relaxed" (score of 0); "neither relaxed nor agitated" (score of 50) in the middle; and anchored on the right with "very agitated" (score of 100).

3.5.1.2.9 Drug Similarity VAS

This scale assesses the subject's perception of drug similarity (i.e., the subjective opinion of whether the drugs are similar). Subjects respond to the statement "[How similar is the drug you most recently received [drug 1] to drug you just took [drug 2]?" The question is scored using a 0 to 100-point bipolar VAS anchored on the left with "Not at all similar" (score of 0) and anchored on the right with "Extremely similar" (score of 100).

3.5.1.3 Safety and Tolerability Measurements

Safety and tolerability assessments will consist of AEs, clinical laboratory, vital signs, pulse oximetry, respiratory volume, 12-lead ECG, continuous cardiac monitoring, physical examination, and C-SSRS. Assessments will be performed in accordance with the schedules of assessments presented in Table 1, Table 2, and Table 3.

3.5.1.3.1 Adverse Events

Adverse events will be recorded from signing of the ICF until completion of the follow-up visit. Any clinically significant observations, as determined by the Investigator, in results of clinical laboratory, 12-lead ECGs, continuous cardiac monitoring, vital signs, pulse oximetry, physical examinations, or C-SSRS will be recorded as AEs.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the first administration of study drug or any event already present that worsens in either severity or frequency following exposure to the study drug.

At several time points before and after drug administration, subjects will be asked nonleading questions to determine the occurrence of AEs. Subjects will be asked in general terms about any AEs at regular intervals during the study. In addition, all AEs reported spontaneously during the course of the study will be recorded. All answers will be interpreted by the Investigator using the Medical Dictionary for Regulatory Activities (MedDRA; most recent version) for AEs and will be recorded in the eCRF as reported terms.

The severity of the AEs will be rated as mild, moderate, or severe; the relationship between the AEs and the study drug will be indicated as none, unlikely, possibly, likely, or definitely. Adverse events assessed as possibly, likely, or definitely will be considered related to the study drug; AEs assessed as none or unlikely will be considered not related to the study drug. Details on rating the severity of AEs and relationship to study treatment are given in Appendix 8.2.

Pregnancy of female subjects and female partners of male subjects will be monitored along with follow-up, if warranted (see Appendix 8.3).

3.5.1.3.2 Adverse Events of Special Interest

Part 2 only: AEs of special interest (AESIs) are AEs for a particular product or class of products that a Sponsor may wish to monitor carefully. AESIs may be serious or nonserious. The AESIs due to pharmacological effect of an anesthetic agent include hypoxemia, bradycardia, hypotension, allergy/anaphylaxis, and cardiac arrhythmia, which are defined as follows:

- Hypoxemia due to respiratory depression is defined as SpO2 <90% with duration of >30 seconds. Hypoxemia is evaluated from the initial dose of study drug until 1 hour postdose.
- Symptomatic bradycardia, where bradycardia is defined as a heart rate of <45 beats/minute that lasts >30 seconds and requiring intervention. Bradycardia is evaluated from the initial dose of study drug until 1 hour postdose.
- Severe hypotension defined as an SBP <90 mmHg that lasts >2 minutes and requiring treatment. Hypotension is evaluated from the initial dose of study drug until 4 hours postdose.
- Allergy/anaphylaxis may include angioedema, bronchospasm, erythema, and hypotension. Allery/anaphylaxis is evaluated from the initial dose of study drug until 4 hours postdose.
- Clinically significant cardiac arrhythmia, as judged by the Investigator. Cardiac arrythmia is evaluated from the initial dose of study drug until 4 hours postdose.
- QTc prolongation is a QTc interval of >450 ms in males and >470 ms in females occurring within 15 minutes of study drug. Patients who reach an absolute QT interval of more than 500 ms upon QTc correction for rate should be reassessed, and immediate action should be taken to correct any possible concomitant risk factors.

Start time, end time, and duration should be calculated, and treatment measures (if any) should be recorded. Additionally, AESI's will be categorized as drug related for those occurring within 15 minutes from the initial dose of study drug.

3.5.1.3.3 Clinical Laboratory

Blood and urine samples for clinical laboratory assessments will be collected according to site SOPs. All blood and urine specimens will be sent to a local reference laboratory for analysis and testing.

The following parameters will be measured:

- Hematology: erythrocytes (red blood cells), leukocytes (white blood cells) with differential (neutrophils, eosinophils, lymphocytes, monocytes, and basophils), hemoglobin, hematocrit, and platelet count.
- Coagulation: prothrombin time/international normalized ratio (PT/INR) will be measured at screening only.
- Blood chemistry: sodium, potassium, chloride, bicarbonate, creatinine, creatine kinase (CK), amylase, lipase, glucose (fasting), urea, albumin, calcium, magnesium, inorganic phosphorus, alkaline phosphatase, aspartate aminotransferase (AST), alanine

aminotransferase (ALT), total bilirubin, total protein, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and uric acid. Estimated creatinine clearance (Cockroft Gault formula) and thyroid stimulating hormone (TSH) will be measured at screening only.

- Urinalysis: A midstream, clean-catch urine specimen will be collected for dipstick analysis of protein, blood, glucose, leukocyte esterase, and pH (to be captured in the database).

The following parameters will also be measured:

- Alcohol breath test.
- Urine will be collected for the assessment of the following drugs of abuse: THC, amphetamines, methamphetamines, 3,4-methylenedioxy-N-methylamphetamine (ecstasy), opiates/morphine, methadone, oxycodone, phencyclidine, cocaine, benzodiazepines, tricyclic antidepressants, and barbiturates. Results must be available and reviewed before dosing on Day 1.
- Serology will be collected for the measurement of HIV-1 and -2 antibodies, HBsAg, , and HCV antibody.
- For all females, a serum and/or urine pregnancy test will be collected. Results must be available and reviewed before dosing.
- A FSH and estradiol panel will be performed on all postmenopausal females.

In case of unexplained or unexpected clinical laboratory test values for enrolled subjects, the tests will be repeated as soon as possible and followed up until the results are considered not clinically significant, as determined by the Investigator and/or an adequate explanation for the abnormality is found. The clinical laboratory will clearly mark all laboratory test values that are outside the reference range, and the Investigator will indicate which of these deviations are clinically significant. These clinically significant laboratory result deviations will then be recorded as AEs, and the relationship to the treatment will be indicated (see also Appendix 8.2).

The procedures for the collection, handling, and shipping of laboratory samples are specified in the laboratory manual(s) provided to the study site.

3.5.1.3.4 Vital Signs

Systolic and diastolic BP and pulse will be recorded after the subject has been resting for at least 5 minutes in the semirecumbant position; subjects can be moved to an upright position temporarily for dosing. These assessments will be made using an automated device whenever possible. Body temperature and respiratory rate will also be measured.

3.5.1.3.5 Pulse Oximetry

Pulse oximetry will be assessed using and automated device.

3.5.1.3.6 Respiratory Volume

Respiratory volume and minute ventilation will be measured using the ExSpiron® device.

3.5.1.3.7 Electrocardiogram

A standard 12-lead ECG will be recorded after the subject has been resting for at least 5 minutes in the semirecumbant position; subjects can be moved to an upright position temporarily for dosing. The ECG will be recorded using an ECG machine equipped with computer-based interval measurements. The following ECG parameters will be recorded: heart rate, PR-interval, QRS-duration, QT-interval, QTc-interval (Fridericia's), and the interpretation of the ECG profile by the Investigator.

3.5.1.3.8 Continuous Cardiac Monitoring

A 12-lead ECG will be recorded continuously by telemetry from at least 1 hour before to at least 4 hours after each drug administration. Subjects will remain quietly semirecumbant (with minimal disturbance by procedures) for 15 minutes just prior to any PK sampling during telemetry and at 3 time points between -1 and -0.25 hours predose (15 minutes each; for baseline). Subjects can be moved to an upright position temporarily for dosing.

All relevant or significant arrhythmic events will be recorded in rhythm strips (10 seconds). The ECG will be evaluated by the Investigator for clinically significant events.

During days with telemetry, meals will be standardized. Start and stop time of the (in total) 15-minute periods will be recorded.

The telemetry will be monitored continuously by a staff member until at least 1 hour postdose.

3.5.1.3.9 Physical Examination

As indicated in the schedules of assessments (Table 1, Table 2, and Table 3), a complete physical examination will be performed consisting of all body systems (with the exception of genitalia, anus/rectal, and breast examinations, which will only be performed if medically indicated). Unscheduled symptom-driven physical examinations may be conducted at any time per the Investigator’s discretion.

3.5.1.3.10 Columbia-Suicide Severity Rating Scale

Suicide-related thoughts and behaviors will be assessed using the C-SSRS. Regulatory agencies have been interested in examining suicide-related thoughts and behaviors in patients receiving antidepressant and other drugs used in psychiatric illnesses. In Feb 2009, the FDA’s Division of Psychiatry Products communicated that information regarding suicide-related thoughts and behaviors should be prospectively collected in a standardized format (Columbia Classification Algorithm or Suicide Assessment) from all clinical studies, including Phase 1 studies, for all drugs in development to enable the analysis of

suicide-related thoughts and behaviors in an aggregated fashion.[7] The tool was developed by a National Institute of Mental Health trial group for the purpose of being a counterpart to the FDA's categorization of suicidal events.

The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period.[7, 8, 9] The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The C-SSRS will be administered by appropriately trained site personnel. A referral to a psychiatrist will be made in case of a significant finding on the C-SSRS.

All AEs obtained through the questionnaire are recorded. The Sponsor or its designee will be alerted within 24 hours of the Investigator's awareness of any SAEs from these questionnaires.

3.5.1.3.11 Mallampati Score

The ease of intubation will be assessed using the Mallampati score and the Investigator or designee judgement. The Investigator, or designee, will visualize the anatomy of the oral cavity, specifically noting whether the base of the uvula, faucial pillars, and soft palate are visible.

1. Soft palate, uvula, faucial pillars visible
2. Soft palate, faucial pillars visible but uvula masked by the base of the tongue
3. Soft palate only visible

3.5.1.4 Total of Blood Volume

Table 4 and Table 5 present the number and volume of blood samples and the total volume of blood that will be collected throughout the study per subject.

If deemed necessary by the Investigator or the Sponsor, the number and/or volume of blood samples per assessment may be increased, as long as the total volume of blood drawn for a subject does not surpass 500 mL (except when extra blood samples need to be taken for safety reasons).

Table 4 Number and Volume of Blood Samples and Total Blood Volume Collected per Subject - Part 1

Assessment	Maximum # Samples	Volume of Blood per Sample (mL)	Total Volume of Blood (mL)
Clinical Chemistry	3	8.5	25.5
Hematology	3	4	12
Coagulation	1	2.7	2.7
Serology	1	8.5	8.5
Total Volume of Blood Drawn			48.7

Table 5 Number and Volume of Blood Samples and Total Blood Volume Collected per Subject - Part 2

Assessment	Maximum # Samples	Volume of Blood per Sample (mL)	Total Volume of Blood (mL)
Pharmacokinetic	36	2	72
Clinical Chemistry	3	8.5	25.5
Hematology	3	4	12
Coagulation	1	2.7	2.7
Serology	1	8.5	8.5
Total Volume of Blood Drawn			120.7

3.5.2 Appropriateness of Measurements

The assessments that will be made in this study are standard and generally recognized as reliable, accurate, and relevant.

3.5.2.1 Timing of Assessments

If more than one procedure is required at the same time point, the procedures will be conducted as close as possible to the nominal time point, with the order of procedures determined at the Investigator's discretion. Specific sampling windows for individual assessments are outlined in the schedule of assessments (Table 1, Table 2, and Table 3).

3.5.3 Pharmacokinetic, Pharmacodynamic, and Safety Variables

3.5.3.1 Pharmacokinetic Variables

PK variables will be the plasma concentrations of HSK3486 and associated PK parameters. The PK parameters to be determined or calculated using noncompartmental analysis from the plasma concentration-time data for HSK3486 include, but are not limited to, the parameters as given in Table 6. A complete list of PK parameters will be provided in the statistical analysis plan (SAP).

Table 6 Pharmacokinetic Parameters

Parameter	Description
C_{max}	Maximum observed plasma concentration
T_{max}	Time to attain maximum observed plasma concentration
C_{max}/T_{max}	The abuse quotient as a ratio of C_{max} over T_{max}
AUC_{0-1}	Area under the plasma concentration-time curve from time 0 to 1 hour postdose
AUC_{0-2}	Area under the plasma concentration-time curve from time 0 to 2 hours postdose
AUC_{0-4}	Area under the plasma concentration-time curve from time 0 to 4 hours postdose

Parameter	Description
$AUC_{0\text{-last}}$	Area under the plasma concentration-time curve up to the last point with concentrations above the lower limit of quantification (LLOQ)
$AUC_{0\text{-inf}}$	Area under the plasma concentration-time curve from time 0 to infinity calculated as: $AUC_{0\text{-inf}}=AUC_{0\text{-t}}+C_{last}/k_{el}$, where C_{last} is the last measurable plasma concentration
$\%AUC_{extra}$	Percentage of estimated part for the calculation of $AUC_{0\text{-inf}}$ $([AUC_{0\text{-inf}}-AUC_{0\text{-t}}]/AUC_{0\text{-inf}})*100\%$
k_{el}	Terminal elimination rate constant
$t_{1/2}$	Terminal elimination half-life, calculated as $0.693/k_{el}$

3.5.3.2 Pharmacodynamic Variables

The PD parameters to be measured include, but are not limited to, the parameters as given below. PD parameters are defined in Table 6. A complete list of PD parameters will be provided in the SAP.

- PD parameters in Part 1 will include:
  - Drug Liking ("at this moment") VAS E_{max}
  - Drug Liking ("at this moment, I feel high") E_{max} High VAS (secondary endpoint)
  - Drowsiness/Alertness VAS (E_{min} [secondary endpoint], TE_{min}, $TA\_AUE_{0\text{-}1}$, and $TA\_AUE_{0\text{-}2}$)
  - MOAA/S score
  - Ability to complete battery of abuse potential assessment questions for 1 hour
- PD parameters in Part 2 will include:
  - Drug Liking ("at this moment") VAS E_{max}
  - Drug Liking ("at this moment, I feel high") E_{max} High VAS
  - Drowsiness/Alertness VAS (E_{min}, TE_{min}, $TA\_AUE_{0\text{-}1}$, and $TA\_AUE_{0\text{-}2}$)
  - MOAA/S score
  - Ability to complete battery of abuse potential assessment questions for 1 hour
  - Overall Drug Liking VAS – 12- and 24-hour score
  - Take Drug Again VAS – 12- and 24-hour score
  - Drug Liking VAS (TE_{max}, TA_AUE, E_{min}, TE_{min}, and %reduction)
  - DEQ – Any Drug Effect VAS (E_{max}, TE_{max}, and $TA\_AUE_{0\text{-}1}$)
  - DEQ – Good Drug Effects VAS (E_{max}, TE_{max}, and $TA\_AUE_{0\text{-}1}$)
  - DEQ – Bad Drug Effects VAS (E_{max}, TE_{max}, and $TA\_AUE_{0\text{-}1}$)
  - Relaxation/Agitation VAS (E_{max}, TE_{max}, E_{min}, TE_{min}, and $TA\_AUE_{0\text{-}1}$)
  - Drug Similarity ("How similar is the drug you most recently received [drug 1] to drug you just took [drug 2]?") VAS

Part 2 Endpoints:
The primary endpoint for Part 2 is Drug Liking VAS (E_{max}).

The secondary endpoints for statistical hypothesis testing are: Take Drug Again VAS (12- and 24-hour scores); High VAS (E_{max}); and Overall Drug Liking VAS (12- and 24-hour scores).

The secondary endpoints for descriptive analysis are: Good Drug Effects; Bad Drug Effects, sick-nausea; Unknown: Any Drug Effects, Drowsiness/Alertness, and Drug Similarity.

Table 7 Pharmacodynamic Parameters

Parameter	Description
E_{max}	Maximum effect
E_{min}	Minimum effect
TE_{max}	Time to maximum effect
TE_{min}	Time to minimum effect
TA_AUE	Time-averaged area under the effect curve
TA_AUE_{0-1}	Time-averaged area under the effect curve from time 0 to 1 hour postdose
TA_AUE_{0-2}	Time-averaged area under the effect curve from time 0 to 2 hour postdose
%reduction	Percent reduction in E_{max}

3.5.3.3 Safety Variables

The safety variables to be measured include, but are not limited to, the variables as given below. A complete list of safety variables will be provided in the SAP.

- AEs
- Clinical laboratory
- Vital signs
- Pulse oximetry
- 12-lead ECG
- Continuous cardiac monitoring
- Physical examination
- C-SSRS
- Respiratory Volume

3.5.4 Drug Concentration Measurements

The analysis of HSK3486 in plasma samples will be performed with a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method. The bioanalytical report for the determinations will be included in the clinical study report (CSR).

3.5.5 Retention of Blood and Urine Samples

Blood and urine samples remaining after clinical laboratory assessments have been performed will not be stored for future use and will be destroyed after analysis as per laboratory procedure.

3.6 Statistical Procedures and Determination of Sample Size

3.6.1 Analysis Sets

3.6.1.1 Safety Set

All subjects who have received at least 1 dose of propofol, HSK3486, or placebo.

3.6.1.2 Qualification Safety Set

All subjects who have received at least 1 dose of study drug during the Qualification Phase of Part 2.

3.6.1.3 Pharmacokinetic Set

All subjects who have received at least 1 dose of propofol or HSK3486 in the Treatment Phase of Part 2 and provided sufficient bioanalytical assessment results to calculate reliable estimates of the PK parameters.

3.6.1.4 Completer Set

All subjects who complete all treatment periods in Part 2 Treatment Phase and have sufficient data for evaluation of the primary endpoint, Drug Liking E_{max}. Subjects who do not have at least 1 observation within 2 hours of the median T_{max} for each active treatment and within 4 hours postdose for placebo for Drug Liking VAS will be excluded.

3.6.1.5 Modified Completer Set

All subjects in the Completer Set, excluding subjects with unreliable responses based on the following prespecified criteria:

1. Similar Drug Liking E_{max} scores (within 5 point difference) across all study treatments; or
2. Drug Liking E_{max} for placebo >60 and the difference between E_{max} (placebo) – E_{max} (positive control) $\geq$ 5.

This set will be the primary analysis set for all PD endpoints.

3.6.2 Statistical and Analytical Plan for Pharmacokinetic, Pharmacodynamic, and Safety Evaluation

A SAP will be generated and finalized prior to database lock (and unblinding of study treatment codes). Full details of the analysis to be performed will be included in the SAP.

Any deviation from the SAP will be reported in the section “Changes in Planned Analysis” in the CSR.

3.6.2.1 Pharmacokinetic Evaluation

The PK parameters and their statistical evaluation will be included in the CSR for this study.

Descriptive statistics will be calculated and presented for each time point by treatment for plasma concentrations.

PK parameters will be calculated and will be summarized by treatment using descriptive statistics and will be listed and summarized in tabular and/or graphical form.

The natural log transformed PK exposure parameters: C_{max} and AUC, will be analyzed using a mixed-effect model with treatment, period, and sequence as fixed effects and subject nested in sequence as a random effect. The geometric means of each treatment, geometric mean ratio of the treatment comparisons, and 90% confidence intervals will be reported. The relationship between PK and PD may be evaluated using correlational analysis or similar methodology.

3.6.2.2 Pharmacodynamic Evaluation

The PD parameters and their statistical evaluation will be included in the CSR for this study.

PD data and derived PD parameters from Part 1 and Part 2 Treatment Phases will be summarized using descriptive statistics by treatment (and by time point as applicable).

For Part 2, the following sequential hypotheses will be used to evaluate the abuse potential of HSK3486 compared to propofol and placebo.

For study validity, the primary endpoint, Drug Liking E_{max}, will be compared between propofol (Treatment C) and placebo (Treatment D), the following hypothesis will be tested:

$$H_o: \mu_C - \mu_D \leq 15 \text{ vs. } H_a: \mu_C - \mu_D > 15 \quad (1)$$

where μ_C is the mean for propofol and μ_D is mean for placebo. If the treatment difference is statistically significant with a margin of 15 points in a 1-sided test at a 5% level of significance, validity is established for the study. The 1-sided 95% CIs of the mean difference will be calculated. P-values will be provided for the treatment comparisons. And the 2-sided 95% CIs will be also derived for the exploratory result.

The treatment comparison for relative abuse potential of HSK3486 will be the comparison of Drug Liking E_{max} between each dose level of HSK3486 (Treatment A and Treatment B) and propofol (Treatment C). The following hypothesis will be tested for each comparison:

3. A: HSK3486 dose 1 vs. C: propofol
4. B: HSK3486 dose 2 vs. C: propofol

The hypothesis can be expressed as:

H_o: $\mu_C - \mu_T \leq \delta_2$ vs. H_a: $\mu_C - \mu_T > \delta_2$,

with δ_2 =11, where μ_C is the mean of Drug Liking E_{max} for propofol (Treatment C),and μ_T is mean for Drug Liking E_{max} for each dose level of HSK3486 (Treatment A and Treatment B). If the treatment difference is statistically significant with the 11-point (δ_2) in a 1-sided test at a 5% level of significance, this will demonstrate that the abuse potential of propofol is greater than that of HSK3486 by at least 11 points. The 1-sided 95% CIs of the mean difference will be calculated. P-values will be provided for the treatment comparisons. And the 2-sided 95% CIs will be also derived for the exploratory result.

The evaluation of absolute abuse potential of HSK3486 will be the comparison of HSK3486 versus placebo. The following hypothesis will be tested for each dose level of HSK3486 compared to placebo:

1. A: HSK3486 dose 1 vs. D: placebo
2. B: HSK3486 dose 2 vs. D: placebo

The hypothesis can be expressed as:

H_o: $\mu_T - \mu_D \geq \delta_3$ vs. H_a: $\mu_T - \mu_D < \delta_3$,

with δ_3 =11 and where μ_T is the mean of Drug Liking E_{max} for each dose level of HSK3486 (Treatments A and B) and μ_D is the mean of Drug Liking E_{max} for placebo (Treatment D). [10] If the treatment difference is statistically significantly less than 11-point (δ_3) in a 1-sided test at a 5% level of significance, this will suggest that HSK3486 does not produce a greater abuse-related response than placebo. The 1-sided 95% CIs of the mean difference will be calculated. P-values will be provided for the treatment comparisons. And the 2-sided 95% CIs will be also derived for the exploratory result.

The above hypotheses will be tested sequentially, and no adjustments will be made for multiplicity.

A linear mixed-effects model will be fit to each parameter. The model will have treatment, period, sequence, and first-order carryover effect (if significant at alpha=0.25) as fixed effects, baseline (predose) measurements as a covariate (where applicable), and subject as a random effect. If the variance among the treatments is homogeneous, an equal variance model will be conducted; if the variance among treatments is heterogeneous, the model will be corrected by estimating the variances for treatment separately (an unequal variance model, using Satterthwaite method and repeated statement heteroscedasticity will be adjusted using the repeated statement with subject nested in sequence as a random factor with the cross-over design). The residuals from the mixed-effects model will be investigated for normality using the Shapiro-Wilk W test. If the normality assumption of the model is satisfied (p-value ≥0.01), least square means and 95% confidence intervals for

treatment differences will be computed from the linear mixed model, along with the statistical significances of all treatment differences.

If the normality assumption of the model is not satisfied, the distribution of the treatment differences will be examined for skewness. If the distribution is slightly skewed, a t-test may be used for analysis; otherwise, the sign test will be conducted.

Analyses similar to those described for the primary endpoint (Drug Liking E_{max}) will be performed on the secondary endpoints (Take Drug Again VAS 12- and 24-hour scores; High VAS E_{max}; and Overall Drug Liking VAS 12- and 24-hour scores) in the treatment phase. The same hypothesis tests and difference margins as noted above for hypotheses will be evaluated for the secondary endpoints.

3.6.2.3 Evaluation of Safety and Tolerability

Safety and tolerability will be assessed through AEs, clinical laboratory, vital signs, pulse oximetry, respiratory volume, ECGs, continuous cardiac monitoring, physical examination findings, C-SSRS, and any other parameter that is relevant for safety assessment.

3.6.2.3.1 Adverse Events

Summary tables of TEAEs will be presented by system organ class based on the MedDRA terminology list (preferred terms): a table containing the number of subjects experiencing the AE by treatment, a table by treatment and relationship, and a table by treatment and severity.

3.6.2.3.2 Clinical Laboratory

Clinical laboratory data will be listed accompanied by an indication if the parameter is outside the reference range. A summary of all data outside the reference range of the clinical laboratory will be provided. Clinical laboratory data will be presented descriptively, where applicable.

3.6.2.3.3 Vital Signs, Pulse Oximetry, Respiratory Volume, and Electrocardiograms

Vital signs, pulse oximetry, respiratory volume, and ECG parameters will be listed, and they will be presented descriptively, where applicable.

3.6.2.3.4 Continuous Cardiac Monitoring

Continuous cardiac monitoring will be performed and monitored in the clinic by the Investigator for subject safety. No formal analysis will be performed. All findings will be reported as AEs.

3.6.2.3.5 Physical Examination

Changes from baseline for physical examination will be described and listed.

3.6.2.3.6 Columbia-Suicide Severity Rating Scale

C-SSRS findings will be listed.

3.6.3 Determination of Sample Size

For assessment of abuse potential, the sample size will be considered the maximum of the sample sizes for the validity comparison and primary treatment comparison. Assuming a 10% dropout rate, approximately 42 subjects will be randomized to the Part 2 Treatment Phase, with the intention of completing 36 subjects.

For the validity comparison, a sample size of 36 subjects will provide 95% power to detect a mean difference in the Drug Liking VAS E_{max} between 0.6 mg/kg propofol and placebo that is greater than a margin of δ_1=15 in a 1-sided, alpha=0.025 test for study validity. With alpha=0.05, a sample size of 36 subjects will provide at least 98% power to detect a mean difference in the Drug Liking VAS E_{max} between 0.6 mg/kg propofol and placebo that is greater than a margin of 15-point in a 1-sided test. This assumes Drug Liking E_{max} mean (SD) of 74.4 (14.99) for propofol and 50 (0.33) for placebo, and correlation of 0.5.[5]

For the primary treatment comparison, evaluating the difference between propofol and HSK3486, a sample size of 27 will provide 95% power to reject the null hypothesis that HSK3486 has greater abuse potential than propofol, in favor of similarity with less than a margin of δ_2=11 in a 1-sided alpha=0.025 t-test. With alpha=0.05, a sample size of 27 will provide 98% power to reject the null hypothesis that HSK3486 has greater abuse potential than propofol, in favor of similarity with less than a margin of δ_2=11 in a 1-sided t-test. This assumes a mean (SD) of the difference in Drug Liking E_{max} between HSK3486 and propofol of 0 (15).

3.7 Data Quality Assurance

The study may be audited to assess adherence to the clinical study protocol (CSP). During the conduct of the study, process-related audits may be performed. An audit certificate will be provided in the appendices of the final CSR outlining any audits and other related activities performed.

The clinical research site will be monitored by the study monitor to ensure correct performance of the study procedures and assure that the study is conducted according to the relevant regulatory requirements. The eCRF entries will be verified with the source documentation, if applicable (in some cases data are captured directly on the eCRF, therefore source data verification is not necessary).

Regulatory authorities, the Institutional Review Board (IRB), and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study. Review procedures will be followed for all documents that are generated in relation with the study.

An explanation will be given for all missing, unused, and spurious data in the relevant sections of the CSR.

4. ETHICS

4.1 Institutional Review Board

The CSP and the ICFs will be submitted for review and approval by an IRB prior to the eligibility screening. The composition of the IRB will be in accordance with the recommendations of the International Council for Harmonisation (ICH) E6(R2) Guideline for Good Clinical Practice (GCP).[10]

The contract research organization (CRO) conducting the study will keep the IRB informed about the progress of the study. All changes in research activities and all unanticipated problems involving risks to human subjects will be immediately reported in accordance with IRB requirements. The CRO conducting the study will inform the subjects and the IRB if anything occurs on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal, or if further recruitment of subjects in the study has been put on hold for that reason, whichever occurs first. The study may be suspended pending further review by the IRB, except insofar as suspension would jeopardize the subjects' health. The CRO conducting the study will take care that all subjects are kept informed.

No changes will be made in the study without IRB approval, except when required to eliminate apparent immediate hazards to human subjects.

Notification of the end of the study will be sent to the IRB within 90 days after completion of follow-up for the last subject. In case a study is temporarily halted, the site or Sponsor will notify the IRB immediately, including the reason for this. In case a study is ended prematurely, the IRB will be notified within 15 days, including the reasons for the premature termination. The end of the study is defined as the date of receipt of the last data point for statistical analysis of the last subject participating in the study.

4.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, Jun 1964, and subsequent amendments.[12]

This study is also designed to comply with ICH E6(R2) Guideline for GCP (European Medicines Agency [EMA]/Committee for Medicinal Products for Human Use [CHMP]/ICH/135/1995)[11] and any applicable national and local laws and regulations (e.g., Code of Federal Regulations Title 21, Parts 50, 54, 56, 312, and 314).

Guidelines adopted by the ICH and other relevant international guidelines, recommendations, and requirements will be taken into account as comprehensively as possible, as long as they do not violate local law.

Whenever the term “Investigator” is noted in the CSP text, it may refer to either the Investigator at the site or an appropriately qualified, trained, and delegated individual of the investigational site.

4.3 Subject Information and Consent

All subjects will be informed verbally and in writing regarding the objectives, procedures, and risks of study participation. The subjects will sign the ICF that contains information about the objectives of the study, the procedures followed during the study, and the risks and restrictions of the study, with special reference to possible side effects of the study drug and potential interactions.

4.4 Privacy

All personal details of subjects will be treated as confidential by the Investigator and staff at the CRO conducting the study, and handling of personal data will be in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996.[13]

5. STUDY DOCUMENTATION

5.1 Archiving

The Investigator shall retain essential documents for a period of at least 2 years after the last approval of a marketing application in an ICF region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the investigational product. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor will inform the Investigator/institution as to when these documents no longer need to be retained.

5.2 Recording of Data in Source Documents and Electronic Case Report Forms

All data will be collected on source documents and then entered in the eCRFs.

6. CONFIDENTIALITY AND PUBLICATION POLICY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB personnel, the Sponsor and its authorized representatives are allowed full access to the records.

All study subjects must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject, who will be required to give consent for their data to be used as described in the ICF. The subjects must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Identification of subjects and eCRFs shall be by unique subject numbers only.

All personal details will be treated as confidential by the Investigator and site staff.

All relevant aspects regarding publication will be part of the contract (or similar document) between the Sponsor and CRO conducting the study.

7. REFERENCES

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8. APPENDICES

8.1 Drug Accountability

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Accountability Forms) and disposition (e.g., Drug Dispensing Forms) of the study drug must be maintained. The Drug Dispensing Form(s) must be kept current and should contain the following information:

- The identification of the subject to whom the study drug was administered
- The date(s) and quantity of the study drug administered to the subject (when applicable)
- The date(s) and quantity of the study drug returned by the subject (when applicable)

All records and drug supplies must be available for inspection by the monitor at every monitoring visit. Unused medication will be returned to the Sponsor at the end of the study or will be locally destroyed according to study site procedures. The site will retain the original, completed Drug Dispensing Form(s) and Drug Accountability Form(s), and copies will be returned to the Sponsor upon request. The Investigator's copy of the Drug Accountability Form(s) must accurately document the return of all study drug supplies to the Sponsor if applicable.

8.2 Adverse Events and Serious Adverse Events Evaluation and Reporting

8.2.1 Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. AE definitions will be followed as stated in the "Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (International Council of Harmonisation [ICH] topic E2A).[13]

All AEs reported by the subjects or apparent from their physical appearance during the clinical study will be reported on the AE electronic case report form (eCRF) page.

The severity of AEs will be graded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA):

- **Mild**: An AE that is easily tolerated by the subject, causes minimal discomfort, does not interfere with everyday activities, and does not require intervention.
- **Moderate**: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- **Severe**: An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If an AE has multiple aspects, the aspect with the highest severity will be graded.

It is emphasized that the term severe is a measure of severity; thus, a severe AE is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., laboratory, x-ray, electrocardiogram [ECG]) should also be recorded as AEs. Test findings and physical examination findings can result in AEs if they:

- Are associated with accompanying symptoms, and/or
- Require additional diagnostic testing or medical/surgical intervention, and/or
- Lead to a change in study dosing or discontinuation from the study; result in the addition of significant additional concomitant drug treatment or other therapy, and/or
- Lead to any of the outcomes included in the definition of a serious adverse event (SAE), and/or
- Are considered to be an AE by the Investigator or Sponsor.

Reporting as an AE should not be triggered by:

- Merely repeating an abnormal test, or
- Any abnormal test result that is determined to be an error.

The relationship of any AE to the study drug will be assessed and graded on a 5-point scale: none, unlikely, possibly, likely, or definitely.

Relationship between use of study drug and AE (Causality)					
AE (is)	**None**	**Unlikely**	**Possibly**	**Likely**	**Definitely**
Clearly the result of an external factor	Yes	No	No	No	No
Probably/possibly the result of another factor	No	Yes	Yes	No	No
Has a chronological relationship with the time of study drug administration and/or represents a known reaction to study drug	No	No	Yes	Yes	Yes
Disappears or decreases after discontinuation of the study drug	NA	NA	NA	Yes	Yes
Recurs on renewed administration (re-challenge)	No	No	NA	NA	Yes or NA*

AE=adverse event; NA=not applicable

* A rechallenge is not required; if done, rechallenge would be expected to be positive.

8.2.2 Serious Adverse Events

An SAE is any untoward medical occurrence that, on the basis of medical and scientific judgment:

- Results in death, or
- Is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), or
- Requires inpatient hospitalization for a medical reason or prolongation of existing hospitalization (this refers to hospital admission required for treatment of the AE). (Note: this does not include confinement in, for example, a respite unit; a skilled nursing unit; rehabilitation facility; the clinical research center; or confinement due to planned or unplanned reason unrelated to study), or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

SAEs will be collected from the time of informed consent until the final study visit. SAEs that are related to the investigational drug and continue beyond the normal collection period (i.e., are ongoing at the time a subject exits the study) will be followed until resolution or until stabilized with sequelae. SAEs that begin after the subject's participation in the study is complete, but that the Investigator considers to be related to study drug, may be reported at any time.

The Investigator or clinical site personnel must notify [redacted] of all SAEs, regardless of relationship to the investigational drug, within 24 hours of clinical site personnel becoming aware of the event. The Investigator will provide the initial notification by sending a completed "SAE Notification Form," which must include the Investigator's assessment of the relationship of the event to investigational drug and must be signed by the Investigator.

In addition, notification is sent to the Institutional Review Board (IRB).

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to [redacted].

All SAE reports should be sent to the contacts provided on Page 4: SAE Contact Information.

8.2.3 Suspected Unexpected Serious Adverse Reactions

An SAE that is also an unexpected adverse drug reaction is called a suspected unexpected serious adverse reaction (SUSAR). Unexpected adverse reactions are adverse reactions of which the nature or severity is not consistent with the applicable product information (e.g., IB for an unapproved investigational medicinal product or the Summary of Product Characteristics for an authorized medicinal product).

The Sponsor or its representative (e.g., the contract research organization [CRO] conducting the study if agreed to before start of the study) will promptly report (expedited reporting) the following SUSARs to the IRB:

- SUSARs that have arisen in the current clinical study that was assessed by the IRB
- SUSARs that have arisen in other clinical studies of the same Sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the current clinical study that was assessed by the IRB

Expedited reporting will occur no later than 15 calendar days after the Sponsor or its representative has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be maximally 7 calendar days for a preliminary report with another 8 days for completion of the report.

8.2.4 Follow-up of Adverse Events

Follow-up of AEs will continue until resolution, stabilization, or death. In case of ongoing AEs at database closure, the data obtained at database closure will be used in the statistical analysis. The follow-up of the AE will be documented in the source documents and will be described in the final clinical study report (CSR) only if considered relevant by the Investigator.

8.3 Pregnancy

A female clinical study subject must be instructed to stop taking the study drug and immediately inform the Investigator if she becomes pregnant during the study. Pregnancies occurring up to 90 days after the last dose of study drug must also be reported to the Investigator. The Investigator will make arrangements for the subject to be counseled by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until the outcome of the pregnancy is known.

The Investigator should report all pregnancies of female clinical study subjects to the Sponsor within 1 working day of becoming aware of them.

If the Investigator becomes aware of a pregnancy occurring in the partner of a male subject participating in the study up to 90 days after the last dose of study drug of the male subject, the pregnancy should be reported to the Sponsor within 1 working day of obtaining written

consent from the pregnant partner. The Investigator may make arrangements for the partner to be counseled by a specialist, to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the partner should continue until the outcome of the pregnancy is known.

8.4 Clinical Opioid Withdrawal Scale

For each item, circle the number that best describes the patient' s signs or symptoms. Rate on just the apparent relationship to opiate withdrawal. For example, if pulse rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Subject's Name:	Date and Time:
Reason for this assessment:	
Resting Pulse Rate: beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset:** *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by roomtemperature or patient activity* 0 no report of chills or flushing 1 participant report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *if patient was having pain previously, only the additional component attributed toopiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerection of skin can be felt or hairsstanding up on arms 5 prominent piloerection

Runny nose or tearing *Not accounted for by cold -symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____ _____ _____
Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal	