Statistical Analysis Plan

Sponsor:	Haisco-USA Pharmaceuticals, Inc
Protocol No:	HSK3486-110
Protocol Title:	A 2-PART, DOSE-FINDING AND HUMAN ABUSE POTENTIAL STUDY OF HSK3486 INJECTION IN NONDEPENDENT, RECREATIONAL CENTRAL NERVOUS SYSTEM DEPRESSANT USERS
[redacted]	[redacted]
[redacted]	[redacted]

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative / Title:	[redacted]
Signature of Sponsor Representative / Date:	[redacted]
Name of Author / Title:	[redacted]
Signature of Author / Date:	[redacted]

[redacted]

2.0 Table of Contents

[redacted]

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under Haisco-USA Pharmaceuticals, Inc Protocol HSK3486-110.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 04-Nov-2022 (including all amendments up to this protocol date) and the final eCRF(s) dated 25-Aug-2022.

An approved and signed SAP is a requirement for database lock. An approved SAP is also required for unblinding of the study treatments.

This SAP only covers the results that will be processed by ICON Biostatistics Department.

ICON Biostatistics Department will perform the pharmacokinetic (PK), pharmacodynamic (PD), and safety and tolerability evaluation.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the second version of the SAP. In response to feedback from the FAD, the Modified Completer Set II definition has been included, and additional analysis will been conducted on this analysis set for all the PD assessment.

5.0 Study Objectives

5.1 Part 1 Primary

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

5.2 Part 1 Secondary

- To evaluate the safety and tolerability of HSK3486 in healthy, nondependent, recreational central nervous system (CNS) depressant drug users

5.3 Part 2 Primary

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

5.4 Part 2 Secondary

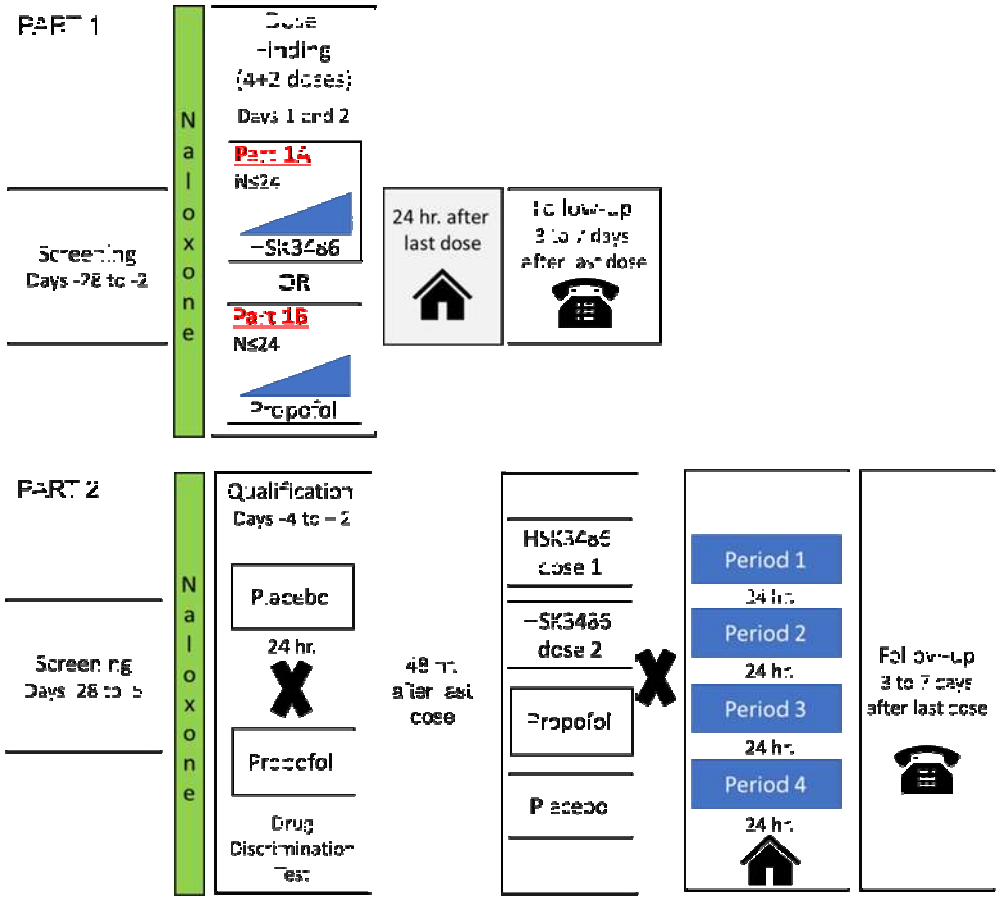
- To evaluate the safety and tolerability of HSK3486 compared to propofol when administered IV to healthy nondependent, recreational CNS depressant drug users
- To evaluate the PK profile of HSK3486 when administered IV to healthy nondependent, recreational CNS depressant drug users

6.0 Study Design

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 below figure.



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

[redacted]

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 (+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 (+5 seconds) from a syringe. The dose used for succeeding groups will be based on the 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 $\geqslant$ 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:

[redacted]

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 approximately 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.

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 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).

6.1 Sample Size Considerations

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 Emax between 0.6 mg/kg propofol and placebo that is greater than a margin of $\delta 1=15$ 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 Emax 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 Emax mean (Standard Deviation [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 $\delta 2=11$ 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 $\delta 2=11$ in a 1-sided t-test. This assumes a mean (SD) of the difference in Drug Liking Emax between HSK3486 and propofol of 0 (15).

6.2 Randomization

Part 1 of the study is non-randomized; no randomization or blinding will be conducted.

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 as outlined in table below. Subject randomization numbers for the Treatment Phase will range from 1001 to 10XX with replacement numbers ranging from 1101 to 11XX.

Sequence Number	Period 1	Period 2	Period 3	Period 4
1	A	B	D	C

2	B	C	A	D
3	C	D	B	A
4	D	A	C	B
5	A	B	D	C
6	B	C	A	D
7	C	D	B	A
8	D	A	C	B

The randomization schedules will be produced by ICON Biostatistics. The study biostatistician will create a draft randomization list and a peer biostatistician will review and approve that draft list. After the draft randomization list has been approved by the sponsor, the unblinded randomization administrator will generate and distribute the final blinded randomization to the pharmacy and kept it in a restricted area to which only unblinded team has access.

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

In response to the FDA's feedback concerning the modified completer analysis set, we have incorporated the definition for the Modified Completer Set II. Subsequently, additional analyses will be conducted utilizing the Modified Completer Set II.

7.2 Interim Analysis and Key Results

While no formal interim analysis will be performed, a dry-run of the safety tables, figures and listings (TFLs) will be provided prior to database lock to assist in review of the database. Draft TFLs will be produced using a dummy randomization scheme to keep the teams blinded. A designation of the blinded status of the study will be included in the TFLs. As a result of draft TFLs review comments; revisions will be included in the post-lock TFL delivery.

7.3 Final Analysis

Draft TFLs will be provided after database lock. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated in the first draft CSR.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the ICON Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after database lock. Only quality assured (QA'd) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

9.1.1.1 General

For summaries, the mean and median will be presented to one decimal place greater than the data, standard deviation to 2 greater than the data, and the minimum and maximum will be presented to the same number of decimal places as the data. Percentages will be presented with one decimal.

The above rule can be applied directly to collected data. For derived data rounding will occur prior to summarization (in the derived dataset as determined by the statistician) so a specific number of decimal places will have to be assumed to apply the above rounding rules for summary statistics. For data with inconsistent number of decimals in raw data the most frequently occurring numbers of decimals will be used unless that number is large and causes difficulties in presentation in which case it will be trimmed to a presentable number (2-3 decimals).

P-values will be reported to four decimal places; p-value less than 0.0001 will be reported as <0.0001.

9.1.1.2 Pharmacokinetic/Pharmacodynamic

Concentration data will be presented in listings as received by the vendor (3 significant digits). Summary statistics of concentration data will be presented to 3 significant digits with the exception of %CV which will be presented to 1 decimal place.

PK parameter data will be rounded in the listings to an appropriate number of decimal places for presentation purposes only. Unrounded values (left as received in analysis dataset) will be used for all calculations of summary statistics and analyses for the summary tables. The summary statistics will be presented to the precision listed in the table in section 16.2.2. When significant digits are used for precision, all summary statistics will be presented to the same precision. When decimal places are used for precision the rule outlined above in the General rounding section applies for summary statistics.

PD data will be follow the general rounding rules for the summary tables. The listings data will be presented with the same precision as the original PD data.

9.1.2 Imputation

Unless otherwise noted, data will not be imputed.

9.1.3 Daylight Savings Time Adjustments

In the event that clinic dates fall across Daylight Savings Time, all clinic procedures for the remainder of the treatment period will be adjusted accordingly to account for the corrected actual time-lapse between procedures. All duration calculations (ie, AE duration, relative time from dosing for PK assessments) for times post-daylight savings time that will be relative to a time prior to daylight savings will be programmatically adjusted for the hour that was gained or lost on the morning of the time change.

9.1.4 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics and nomenclature: n = number of observations or subjects, mean = arithmetic mean, SD = standard deviation, Min = minimum value, median = median value, and Max = maximum value.

[redacted]

Categorical data will be summarized and presented with the following nomenclature: n = frequency and % = percentage. Percentages by categories will be based on the number of subjects exposed within a treatment.

For categorical data, the categories will be presented in the tables exactly as they appear in the case report form (CRF) / Database.

9.1.5 Pooling

Summary statistics will be calculated by treatment (and timepoint, if applicable) for each part or each phase of the study.

9.1.6 Unscheduled Measurements

Unscheduled and early termination measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled and early termination measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline is defined as the last observation recorded before the first study drug administration for Part 1 and the last observation recorded before the first study drug administration of the Qualification Phase for Part 2. The last observation can be an unscheduled / repeated measurement.

9.2.2 Treatment/Subject Grouping

The following labels will be used to describe the study treatments throughout the SAP and TFLs.

Label	Grouping
Study Drug	HSK3486, Propofol and Placebo, Lidocaine and Naloxone
Treatment	Part 1: HSK3486 and Propofol Part 2: Qualification Phase: • Treatment X: Propofol • Treatment Y: Placebo Treatment Phase: • Treatment A: HSK3486 Dose XX • Treatment B: HSK3486 Dose XX • Treatment C: Propofol • Treatment D: Placebo
Dose Level	HSK3486 dose to be determined in Part 1

9.2.3 Common Variable Derivations

Variable	Data Type	Definition/Calculation	Note
Change from predose	All	Postdose observation minus predose observation	Per treatment period of the treatment phase

[redacted]

Variable	Data Type	Definition/Calculation	Note
Analysis Study Day (Prior to Dose)	All	Date of Measurement minus Dose Date	
Analysis Study Day (Post Dose)	All	Date of Measurement minus Dose Date +1	
Period	All	Interval of time during which treatment is constant	
Sequence	ADPD ADPDP ADPC ADPP	Randomized order in which subject is assigned to receive treatments in the Treatment Phase.	
Actual Dose (Amount)	Exposure	Percentage of infusion received times the planned dose	
TEAE	AE	AE is a TEAE if the AE Date/Time is greater than or equal to the Dose Date/Time	
Priortrt	ADPDP	Treatment received in the previous treatment period for Part 2. Example for sequence ABDC: Period 1: A -> Priortrt = "null" Period 2: B -> Priortrt = A Period 3: D -> Priortrt = B Period 4: C -> Priortrt = D	Note that this excludes treatments from the Qualification Phase. If a period is the first period of the Treatment Phase then "null" is presented.

9.2.4 QC

The analysis datasets and the TFLs will be QC'd according to the general ICON QC plan.

9.2.4.1 Critical Data

The QC plan requires datasets be classified as critical or non-critical. As the primary objective(s) of this study is (are) to characterize the pharmacokinetics and assess safety and tolerability the datasets considered critical are subject level = ADSL, pharmacodynamic = ADPD and ADPDP, pharmacokinetic = ADPC and ADPP, and adverse events = ADAE.

9.2.5 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1.

ADaM compliant datasets will be delivered to the sponsor. A define.xml file version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® (WNL) version 8.1 or higher (Certara, L.P.). Additional PK computations may be performed in SAS®.

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

Unless otherwise stated all significance testing will be 1-sided at the significance level of 0.05.

9.5 TFL Layout

Report layout will be according to the ICON – ICH E3 compliant – CSR Template. The layout of TFLs will be according to the ICON standards.

Table shells are provided with and approved as part of this SAP. Small changes to shell layout due to the nature of the data may be required after lock at the discretion of the ICON project statistician. Other changes to the shells may be out of scope. The TFLs will be provided as a single document in Adobe PDF format (in Letter format), and as individual files for each table, figure and listing in Rich Text Format (.rtf).

10.0 Analysis Sets

The following subject level Analysis Sets (populations) will be used for summaries in the study.

10.1 Part 1 Safety Set

The Safety Set will consist of subjects who receive at least one dose of propofol, HSK3486 for Part 1. This set will be used for the Part 1 safety data summaries, baseline characteristic summaries. This set will be analyzed as treated.

10.2 Part 2 Qualification Safety Set

All subjects who have received at least 1 dose of study drug during the Qualification Phase of Part 2. All safety evaluations in the Qualification Phase of Part 2 will be performed using the Qualification Safety Set. This set will be analyzed as treated.

10.3 Part 2 Treatment Safety Set

All subjects who have received at least 1 dose of study drug during the Treatment Phase of Part 2. All safety evaluations in the Treatment Phase of Part 2 will be performed using the Treatment Safety Set. This set will be analyzed as treated.

10.4 Part 2 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. All PK evaluations in the Treatment Phase will be performed using this set. This set will be analyzed as treated.

[redacted]

10.5 Part 2 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 Emax. Subjects who do not have at least 1 observation within 2 hours of the median Tmax for each active treatment and within 4 hours post dose for placebo for Drug Liking VAS will be excluded. This set will be analyzed as treated.

10.6 Part 2 Modified Completer Set I

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

1. Similar Drug Liking Emax scores (within 5 point difference) across all study treatments;

   or

2. Drug Liking Emax for placebo >60 and the difference between Emax (placebo) – Emax (positive control) $\geqslant$ 5.

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

10.7 Part 2 Modified Completer Set II

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

1. Non-responder to the positive control Emax(positive control) $\leqslant$ 55;

   or

2. Difference in Emax scores between positive control and placebo is negative Emax(placebo) − Emax(positive control) $\geqslant$ 5;

   or

3. Similar Emax scores from a completer across all study treatments including placebo Max(all Emax scores) − Min(all Emax scores) $\leqslant$ 5.

Additional analysis for all PD endpoints will be performed on this analysis set.

11.0 Subject Disposition

Part 1

The number and percentage of subjects dosed in Part 1 will be presented. The number and percentage of subjects who completed and who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented.

Part 2

The number and percentage of subjects randomized in the Qualification Phase and who discontinued prior to Treatment Phase will be presented along with a breakdown of the corresponding reasons for discontinuation. The number and percentage of subjects randomized into the Treatment Phase and members of each analysis set will be presented. The number and percentage of subjects who completed and who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented.

Analysis set and study completion data will be listed by part and subject.

12.0 Protocol Deviations

Protocol deviations will be collected and reported per ICON's Protocol Deviation Management Standard Operating Procedure (SOP) and relevant Work Instruction (WI). Subject-level deviations will be extracted and pulled into the study tabulation model (SDTM) dataset from ICON's Clinical Trial Management. Deviations that have been reported and coded as "Important" will be listed by subject.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

Subject demographics at screening will be summarized overall. The summary will include the subjects' age (years), sex, race, ethnicity, weight (kg), height (cm), and body mass index (BMI) (kg/m^2). Demographics will be summarized for the Safety Set for Part 1, Qualification Safety Set, Treatment Safety Set, PK Set, Completer Set, and Modified Completer Set I, and Modified Completer Set II for Part 2.

All demographic data as collected during the screening visit will be listed by part and subject.

13.2 Medical History

Medical history, categorized by preferred term according to MedDRA, will be listed by subject.

13.3 Other Baseline Characteristics

Substance use history will be listed by subject.

Naloxone challenge result will be listed by subject.

Non-compliance to in- or exclusion criteria (if any) will be listed by subject.

14.0 Concomitant Medications

Concomitant medications collected on the eCRF as defined by the protocol will be categorized by medication group and subgroup according to WHO Drug Dictionary. All concomitant medications will be listed by subject. Medications with an end date prior to the first dose of any study drugs (including naloxone/lidocaine) will be considered prior medications and will be noted in the listing. If the end date (e.g. partial or missing date) does not confirm that the medication was stopped prior to first dose the medication will not be flagged as prior.

15.0 Treatment Compliance and Exposure

The number of subjects receiving each dose of study drug in Part 1 and in Part 2 Qualification and Treatment Phases of the study will be summarized by treatment.

Actual dose will be calculated as the planned dose times the ratio of volume administered (IV from a syringe) to planned volume.

Exposure data will be listed by subject.

16.0 Pharmacokinetic Analyses

16.1 Pharmacokinetic Variables

Concentrations of HSK3486 will be collected in plasma for Part 2 Treatment Phase.

PK parameters of HSK3486 will be calculated for plasma for Part 2 Treatment Phase.

16.2 Plasma Pharmacokinetic Summaries

16.2.1 Plasma Concentrations

Plasma concentrations HSK3486 below the quantifiable limit (BQL) prior to Tmax will be set to 0 in the computation of mean concentration values and the BQL values after the Tmax will be set to missing in the computation of mean concentration values. Descriptive statistics (number of subjects, mean, geometric mean, SD, coefficient of variation [%CV], median, min, and max) will be used to summarize the plasma concentrations by treatment at each scheduled timepoint.

Linear (+/-SD) and semi-logarithmic (+SD) plots of the arithmetic mean plasma concentration by scheduled sampling time will be provided by treatment. These plots will show time in hours. The plots will present all calculated means and will include a reference line for the lower limit of quantification (LLOQ).

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by subject (one subject per page). These plots will show time in hours. Individual plots will use the BQL handling procedure described below for "Plasma Pharmacokinetic Parameters".

All individual subject plasma concentration data will be listed by subject.

16.2.2 Plasma Pharmacokinetic Parameters

Plasma PK parameters for HSK3486 will be estimated using non-compartmental methods with WinNonlin® using best fit regression. The PK parameters will be estimated from the concentration-time profiles, and AUCs will be calculated using linear up / log down method. In estimating the PK parameters, BQL values will be set to zero, and the BQL values will be set to missing if they occur after C0. If an entire concentration-time profile is BQL then the profile will be excluded from PK analysis. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time is missing, the scheduled time will be substituted and flagged.

The following flags will be used to include parameters that meet the predefined criteria for summary and analysis.

Criteria Name	Criteria
Extrapolation	AUC%Extrap <= 20%
Regression	Adj Rsq >= 0.8
Lz1	Lz_Start (parent only) >= 2*Tmax
Span	Span > 2

Note: Flags will be applied to parameters prior to derivation of additional parameters in SAS and will be used to include derived parameters as well.

Parameter	Description	SAS Programming Notes	Summary Statistic Reporting Precision*
Cmax	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	Cmax from WNL	3 significant digits
C0	Initial plasma concentration. It is equal to the first observed	C0 from WNL	3 significant digits

[redacted]

Parameter	Description	SAS Programming Notes	Summary Statistic Reporting Precision*
	concentration value if that value occurs at the dose time. Otherwise, it is estimated by back-extrapolating		
Cmax/D	Dose normalized maximum plasma concentration. Expressed in concentration units per dose units.	Cmax/Dose Calculated in SAS	3 significant digits
Tmax	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	Tmax from WNL	2 decimal places
AQ	The abuse quotient as a ratio of Cmax over Tmax	Cmax/Tmax Calculated in SAS	3 significant digits
AUC0-1	Area under the plasma concentration-time curve from time 0 to 1 hour post dose	AUC0-1 from WNL To be included in analysis/summaries if the actual time for the XX hour timepoint has a time deviation < 10%.	3 significant digits
AUC0-2	Area under the plasma concentration-time curve from time 0 to 2 hour post dose	AUC0-2 from WNL To be included in analysis/summaries if the actual time for the XX hour timepoint has a time deviation < 10%.	3 significant digits
AUC0-4	Area under the plasma concentration-time curve from time 0 to 4 hour post dose	AUC0-4 from WNL To be included in analysis/summaries if the actual time for the XX hour timepoint has a time deviation < 10%.	3 significant digits
AUC0-last	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	AUClast from WNL	3 significant digits
AUC0-last/D	Dose normalized area under the concentration-time curve from time	AUC0-last/Dose Calculated in SAS	3 significant digits

[redacted]

Parameter	Description	SAS Programming Notes	Summary Statistic Reporting Precision*
	0 to the time of the last quantifiable concentration observed. Expressed as units of concentration*time per dose units.		
AUC0-inf	Area under the concentration-time curve from time 0 extrapolated to infinity.	AUCINF_obs from WNL To be included in analysis/summaries if the following criteria are met: • Extrapolation, • Regression	3 significant digits
AUC0-inf/D	Dose normalized area under the concentration-time curve from time 0 extrapolated to infinity. Expressed as units of concentration*time per dose units.	AUC0-inf/Dose Calculated in SAS Note: parameter is only calculated if AUCinf is flagged for inclusion.	3 significant digits
t1/2	Terminal elimination phase half-life expressed in time units. t1/2, will be calculated as ln(2)/Lz, where Lz is as defined below.	HL_Lambda_z from WNL To be included in analysis/summaries if the following criteria are met: • Extrapolation • Regression • Lz1 • Span	2 decimal places

*Parameters with 'decimal place' precision will follow the General rule for summary statistics rounding with the number of decimal places noted as the starting point.

Descriptive statistics (number of subjects, mean, geometric mean, SD, %CV, median, min, and max) will be used to summarize the calculated PK parameters by treatment. For Tmax, only median, min and max will be presented.

All parameters will be listed by subject, parameters that meet the inclusion criteria will be accompanied by an indication that each is criteria met.

The following parameters are used for diagnostics and thus listed but not summarized.

Parameter	Description	SAS Programming Notes
AUC%Extrap	Percentage of AUC0-inf due to extrapolation from the last quantifiable	AUC_%Extrap_obs from WNL

Parameter	Description	SAS Programming Notes
	concentration observed to infinity. AUC%Extrap = [AUC0-inf – AUC0-last]/AUC0-inf * 100	
AUC_%Back_Ext	Percentage of AUCINF that was due to back extrapolation to estimate C0 when the first measured concentration is not at dosing time.	AUC_%Back_Ext(_obs) from WNL
Adj Rsq	Goodness of fit statistic for the log-linear terminal elimination phase of the concentration-time profile identified by least-squares linear regression and adjusted for the number of points (minimum of 3) used in the estimation of Lz.	Rsq_adjusted from WNL
Lz	Terminal phase rate constant calculated by linear regression of the terminal log-linear portion of the concentration vs. time curve. Using no weighting factor, the terminal log-linear phase of the concentration-time curve is identified by least-square linear regression of at least three data points that yielded a maximum G criteria, which is also referred to as adjusted R2. Lz is the absolute value of the slope of the terminal log-linear phase. Note: In Phoenix, use Best Fit method to determine regression.	Lambda_z from WNL
Lz_Start	Lz_Start is the start time used in the regression for the determination of Lz.	Lambda_z_lower from WNL
Lz_End	Lz_End is the end time used in the regression for the determination of Lz.	Lambda_z_upper from WNL
Lz_N	Lz_N is the number of points used in the regression for the determination of Lz.	No_points_lambda_z from WNL
Span	The minimum number of half-lives needed for the Lz range to be acceptable.	Span from WNL

16.2.2.1 Pharmacokinetic Parameter Analysis

The comparison between Treatment A versus Treatment B will be performed using a linear mixed effects model with treatment, period, and sequence as fixed effects and subject nested in sequence as a random effect on the log transformed, dose normalized PK parameters (Cmax/D ,AUC0-last/D, and AUC0-inf/D for HSK3486. Estimates on the original scale of measurement will be obtained by exponentiating point estimates on the natural log scale. The geometric mean ratio, and 90% CI for the ratio of the geometric means will be reported. Geometric LS means will be provided for each treatment.

The following SAS PROC MIXED pseudo-code may be used:

```
proc mixed data = adpp;
```

[redacted]

```
    by parameter;
    class treatment period sequence subject;
    model ln(aval) = treatment period sequence/ddfm=kr;
    random subject(sequence);
    lsmeans treatment / alpha = 0.1;
    estimate "Treatment A vs Treatment B" treatment 1 -1 /e cl alpha=0.1;
run;
```

A scatter plot of individual (plus mean and median) PK parameters Cmax/D, AUC0-last/D and AUC0-inf/D by treatment for HSK3486 will be provided for Part 2 Treatment Phase.

16.2.2.2 Pharmacokinetic-Pharmacodynamic Analysis

Scatter plots for correlation evaluation between PK and PD will be provided for the following comparisons for Part 2 Treatment Phase (separate markers by treatment will be presented):

- AQ versus Drug Liking Emax;
- AUC0-1 versus Drug Liking TA_AUE0-1;

The correlation between parameters will be presented.

17.0 Pharmacodynamic Analysis

17.1 Pharmacodynamic Assessments

Assessment	Scale	Timepoints	Parameters to include in ADPDP	Notes
Balance of Effects VAS				
Drug Liking	Bipolar	Part 1: 1 minute to 24 hrs post dose Part 2: Qualification Phase: 0 (predose) to 24 hrs postdose Treatment Phase: 0 (predose) to 24 hrs postdose	Part 1: Emax Part 2: Emax, TEmax, TA_AUE0-xx, Emin, TEmin, %reduction xx=0 to 24	Since predose (time 0) is not available, for calculation of TA_AUE, create a record for time 0 (for calculation purposes only) with aval = 0. Subtract 50 from each postdose aval for all timepoints prior to calculating TA_AUE. Positive TA_AUEs indicate cumulative drug liking while negative TA_AUEs indicate cumulative drug disliking.
Overall Drug Liking	Bipolar	Part 2 only Qualification Phase: 12 and 24 hrs postdose Treatment Phase: 12 and 24 hrs postdose	Part 2: 12 and 24 hrs scores	Part 2 only

[redacted]

Assessment	Scale	Timepoints	Parameters to include in ADPDP	Notes
Take Drug Again	Bipolar	Part 2: Qualification Phase: 12 and 24 hrs postdose Treatment Phase: 12 and 24 hrs postdose	12 and 24 hrs scores	Part 2 only
Drug Effects (positive, negative, other) VAS				
Any Drug Effect	Unipolar	Part 1: 0.25 hrs to 24 hrs postdose Part 2: Qualification Phase: 0 (predose) to 24 hrs postdose Treatment Phase: 0 (predose) to 24 hrs postdose	Part 2 Qualification Phase and Treatment Phase: Emax, TEmax, TA_AUE0-1	Since predose (time 0) is not available, for calculation of TA_AUE, create a record (calculation purposes only) for time 0 with aval=0.
Good Drug Effects	Unipolar	Part 1: 0.25 hrs to 24 hrs postdose Part 2: Qualification Phase: 0 (predose) to 24 hrs postdose Treatment Phase: 0 (predose) to 24 hrs postdose	Part 2 Qualification Phase and Treatment Phase: Emax, TEmax, TA_AUE0-1	Since predose (time 0) is not available, for calculation of TA_AUE, create a record (calculation purposes only) for time 0 with aval=0.
Bad Drug Effects	Unipolar	Part 1: 0.25 hrs to 24 hrs postdose Part 2: Qualification Phase: 0 (predose) to 24 hrs postdose Treatment Phase: 0 (predose) to 24 hrs postdose	Part 2 Qualification Phase and Treatment Phase: Emax, TEmax, TA_AUE0-1	Since predose (time 0) is not available, for calculation of TA_AUE, create a record (calculation purposes only) for time 0 with aval=0.

[redacted]

Assessment	Scale	Timepoints	Parameters to include in ADPDP	Notes
Feeling High	Unipolar	Part 1: 1 minute to 24 hrs postdose Part 2: Qualification Phase: 0 (predose) to 24 hrs post dose Treatment Phase: Predose to 24 hrs postdose	Part 1: Emax Part 2: Emax	
Drowsiness/ Alertness	Bipolar	Part 1: 0 (predose) to 24 hrs postdose Part 2: Qualification Phase: 0 (predose) to 24 hrs postdose Treatment Phase: 0 (predose) to 24 hrs postdose	Part 1: Emin, TEmin, TA_AUE0-1, and TA_AUE0-2 Part 2 Qualification Phase and Treatment Phase: Emin, TEmin, TA_AUE0-1, and TA_AUE0-2	
Relaxation/ Agitation	Bipolar	Part 1: 0 (predose) to 24 hrs postdose Part 2: Qualification Phase: 0 (predose) to 24 hrs postdose Treatment Phase: 0 (predose) to 24 hrs postdose	Part 2 Qualification Phase and Treatment Phase: Emax, TEmax, Emin, TEmin, TA_AUE0-1	
Other PD Assessments				
MOAA/S	Rating 0-5 questions.	Part 1: 1 minute to 0.5 hrs postdose Part 2: Treatment Phase: 1 minute to 0.5 hrs postdose	Only in ADPD	Part 1 and Part 2 Treatment Phase only

[redacted]

Assessment	Scale	Timepoints	Parameters to include in ADPDP	Notes
Ability to complete battery of abuse potential assessment questions for 1 hour		Part 1: 1 hr post dose Part 2 Qualification Phase and Treatment Phase: 1 hrs post dose	Only in ADPD	Part 1 and Part 2 Treatment Phase only
Drug Similarity	Bipolar	Part 2 Qualification Phase and Treatment Phase: 0 (predose) to 24 hrs postdose	Only in ADPD	Part 2 only
Nausea	Unipolar	Part 2 Qualification Phase and Treatment Phase: 0 (predose) to 24 hrs postdose	Only in ADPD	Part 2 only

17.2 Pharmacodynamic Parameters

Parameter	Description	SAS Programming Notes
Emax	Peak (maximum) effect postdose obtained directly from experimental data without interpolation over the collection (peak effect).	Maximum value post dose through sampling period.
Emin	Minimum effect postdose obtained directly from experimental data without interpolation hours of collection.	Minimum value post dose through sampling period.
TEmax	Time to peak effect. First observed time to reach peak effect obtained directly from the experimental data without interpolation, expressed in time units (time to peak effect).	Time of Emax
TEmin	Time to minimum effect. First observed time to reach minimum effect obtained directly from the experimental data without interpolation, expressed in time units.	Time of Emin

Parameter	Description	SAS Programming Notes
TA_AUE0-XX	Time-averaged area under the effect curve from time 0 to XX hour. TA_AUE is calculated as the area under the effect curve (AUE), divided by the time duration from 0 hour (time of dosing) to the xx hour timepoint, where AUE is calculated using the linear trapezoidal rule on the actual time after dosing. For assessments where predose values are measured: • Bipolar scales: change from predose values are used for AUE calculation (thus time 0 change value = 0). • Unipolar scales: raw values are used for AUE calculation. For assessments where predose is not measured, a predose value of 0 will be assumed. • For bipolar scales, 50 will be subtracted from all postdose measurements prior to calculation of AUE. (time 0 change value = 0) Refer to table above for details regarding adjustments for predose by assessment.	TA_AUE from SAS using the trapezoidal rule.
%reduction	The percent reduction in effect. $\%reduction = \begin{cases} \left(\frac{C - T_i}{C - D} \times \left(1 - \frac{D - E_0}{E_0}\right)\right) 100\%, i = 1,2 \text{ if } D > E_0, \\ \frac{C - T_i}{C - D} \times 100\%, i = 1,2 \text{ if } D \leq E_0 \end{cases}$ where C, T_i, and D, are the parameter values (Drug Liking Emax) for the primary control (Treatment C), the test (T1=Treatment A or T2=Treatment B) and the placebo (Treatment D), respectively. The %reduction will only be calculated if data for the primary control, test product, and placebo are available for the given subject. If Drug liking Emax for Treatment C=50, then no %reduction will be calculated.	%reduction calculated in SAS.

17.3 Pharmacodynamic Summaries

17.3.1 Pharmacodynamic Assessments

Part 1

All PD assessment results collected over time in Part 1 will be summarized for each assessment by treatment and scheduled timepoint using descriptive statistics (n, mean, median, SD, Q1, Q3, min and max) for the Part 1 Safety Set.

Part 2

Qualification Phase: All PD assessment results collected over time in the Qualification Phase will be summarized by treatment and scheduled timepoint using descriptive statistics (n, mean, median, SD, first quartile [Q1], third quartile [Q3, min and max) for the Modified Completer Set I, and Modified Completer Set II.

Treatment Phase: All PD assessment results collected over time in the Treatment Phase will be summarized for each assessment by treatment and scheduled timepoint using descriptive statistics (n,

mean, median, SD, Q1, Q3, min and max) for the Modified Completer Set I, and Modified Completer Set II.

Linear plots of the mean (±SD) all PD assessment results over time will be provided by treatment for the Treatment Phase using the Modified Completer Set I, and Modified Completer Set II. These plots will show time in hours.

Linear plots of individual all PD assessment results over time by treatment will be provided for each subject (one subject per page) for the Treatment Phase using the Modified Completer Set I, and Modified Completer Set II. These plots will show time in hours.

Individual subject PD assessment results collected over time will be presented in the data listings for each part and study phase.

17.3.2 Pharmacodynamic Parameters for Descriptive Statistical Analysis

All PD parameters listed above will be calculated for each subject where applicable in Part 1 and Part 2 Qualification Phase and Treatment Phase.

Part 1

All PD parameters will be summarized by treatment using descriptive statistics (n, mean, median, SD, Q1, Q3, min and max) for the Part 1 Safety Set.

Part 2

Qualification Phase: All PD parameters will be summarized by treatment using descriptive statistics (n, mean, median, SD, Q1, Q3, min and max) for the Modified Completer Set I and the Modified Completer Set II.

Treatment Phase: All PD parameters will be summarized by treatment for the Modified Completer Set I and the Modified Completer Set II in the Treatment Phase using descriptive statistics (n, mean, median, SD, Q1, Q3, min and max).

All PD parameters will be presented in the data listings for each part and study phase.

17.4 Statistical Analysis of Pharmacodynamic Parameters – Part 2 Treatment Phase

All statistical analyses will be performed on Part 2 Treatment Phase using the Modified Completer Set I and the Modified Completer Set II.

The treatment comparisons to assess the abuse potential of HSK3486 compared to propofol and placebo.

Study Validity (Hypothesis #1): Treatment C (propofol) versus Treatment D (placebo)

For study validity purposes, the primary endpoint, Drug Liking Emax, will be compared between propofol (Treatment C) and placebo (Treatment D). The comparison will assess the null hypothesis that the mean difference in Drug Liking Emax is less than or equal to 15 against the alternative hypothesis that the mean is greater than 15. The hypothesis can be expressed as:

$$H0: \mu C - \mu D \leq \delta 1 \text{ vs } Ha: \mu C - \mu D > \delta 1 \quad (1)$$

where $\delta 1=15$ is called the validation margin, μC is the mean for Treatment C, and μD is the mean for Treatment D. If the treatment difference for the 1-sided (upper-tail) test is statistically significant at an alpha level of 0.05, then validity is established for the study and allows for the testing of the other pairwise comparisons shown below. 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.

[redacted]

Relative Abuse Potential (Hypothesis #2): Treatment A/Treatment B (HSK3486) versus Treatment C (propofol)

The relative abuse potential comparison between HSK3486 (Treatment A and Treatment B) and propofol (Treatment C) will test the null hypothesis that the mean difference in Drug Liking Emax between treatments is less than or equal to δ2 against the alternative hypothesis that the mean difference is greater than δ2. The hypothesis can be expressed as:

$$H0: \mu C - \mu A \leq \delta 2 \text{ vs } Ha: \mu C - \mu A > \delta 2 \quad (2)$$

$$H0: \mu C - \mu B \leq \delta 2 \text{ vs } Ha: \mu C - \mu B > \delta 2 \quad (2)$$

where μC is the mean for Treatment C, and μA and μB are the means for Treatment A and Treatment B with the margin of δ2 = 11. If the treatment difference for the 1-sided (upper-tail) test is statistically significant at an alpha level of 0.05, this will demonstrate lower relative abuse potential of HSK3486 compared to propofol. 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.

Absolute Abuse Potential (Hypothesis #3): Treatment A/Treatment B (HSK3486) versus Treatment D (placebo)

The absolute abuse potential comparison between HSK3486 (Treatment A and Treatment B) and placebo (Treatment D) will test the null hypothesis that the mean difference in Drug Liking Emax between treatments is greater than or equal to δ3 against the alternative hypothesis that the mean difference is less than δ3. The hypothesis can be expressed as:

$$H0: \mu A - \mu D \geq \delta 3 \text{ vs } Ha: \mu A - \mu D < \delta 3 \quad (3)$$

$$H0: \mu B - \mu D \geq \delta 3 \text{ vs } Ha: \mu B - \mu D < \delta 3 \quad (3)$$

where μA and μB are the means for Treatment A and or Treatment B and μD is the mean for Treatment D and the margin of δ3 = 11. If the treatment difference for the 1-sided (lower-tail) test is statistically significant at an alpha level of 0.05, this will suggest that HSK3486 does not produce a greater abuse-related response for Drug Liking compared to 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.

17.4.1 Model Selection for Primary Endpoint – Drug Liking Emax

For the primary endpoint, Drug Liking Emax, a beginning full model will be fit including fixed effects for treatment, period, treatment sequence and first-order carryover effect and a random effect for subject. The following steps will be followed to select the final model or other method of final analysis using the Modified Completer Set I, and Modified Completer Set II.

17.4.1.1 Normality Testing

The residuals from the full model of the primary endpoint will be investigated for normality using the Shapiro-Wilk W test. The null and alternative hypotheses for this analysis are shown below:

H0: distribution of residuals is normal versus Ha: distribution of residuals is not normal

The following SAS code will be applied to the residuals:

```
ods output TestsForNormality = NormTest;
proc univariate data= residualsdata normal;
    var residuals;
    histogram residuals / normal;
    QQplot resid;
run;
```

Parameters will be analyzed under the assumption of a normal distribution of errors if the p-value of the test is ≥ 0.01. Based on the Shapiro-Wilk W test, the model will be decided through the steps in the following section.

17.4.1.2 First Order Carryover Effect

If the probability value is ≥ 0.01 for the Shapiro-Wilk W test, and the carryover effect (priortrt variable) is found to be non-significant at the 25% level, this term will be dropped from the model. If carryover effect is found to be significant at the 25% level, indicator variables (one for each treatment in the model) for 'prior treatment' will be created to maintain the first-order carryover effect variable without confounding the effects of the treatment, period and sequence variables. If carryover effect is found to be significant at the 5% level, pair-wise comparisons of two sample t-tests using first-period data will be performed.

17.4.1.3 Homogeneity of Variance Testing

Levene's test will be used to evaluate potential heterogeneity of variance in the model with a one-way ANOVA including residuals as the response and treatment as a fixed effect. If the p-value is non-significant, the mixed model with equal variances will be performed.

The following SAS code may be used:

```
proc glm data= data1;
   class treatment;
   model residuals = treatment;
   means treatment/hovtest=levene welch;
run;
```

If the p-value of the Levene's test is ≤ 0.05, it will be concluded that there is a difference in variance among treatments and the model will be corrected by estimating the variances for treatment separately (unequal variance model, using Satterthwaite method and repeated statement).

The following SAS code may be used (include carryover effect if significant):

```
proc mixed data= data1;
   class subject treatment period sequence;
   model parameter= treatment period sequence/ddfm=sw;
   random subject;
   repeated/group=treatment;
run;
```

17.4.1.4 Final Model

If the normality testing concludes that the parameters should be analyzed under the assumption of a normal distribution, the mixed effects model will be used for reporting for the final analysis. Least squares (LS) means, the differences in means and 1-sided 95% confidence intervals (CIs) and the corresponding 1-sided p-values will be provided for each of the treatment comparisons. And the 2-sided 95% CIs will be also derived for the exploratory result.

The following SAS code may be used for the primary endpoint analysis (include carryover effect and adjustments for unequal variances, if applicable):

```
proc mixed data= data1;
   class subject treatment period sequence;
   model parameter = treatment period sequence;
   random subject;
*validity;
lsmestimate treatment "C vs D test" 0 0 1 -1/e cl upper testvalue=15 alpha=0.05;
lsmestimate treatment "C vs D CI" 0 0 1 -1/e cl alpha=0.05;

*relative;
```

```
lsmestimate treatment "C vs A test" -1 0 1 0/e cl upper testvalue=11 alpha=0.05;
lsmestimate treatment "C vs A CI" 0 -1 0 1 0/e cl alpha=0.05;

lsmestimate treatment "C vs B test" 0 -1 1 0/e cl upper testvalue=11 alpha=0.05;
lsmestimate treatment "C vs B CI" 0 -1 1 0/e cl alpha=0.05;

*absolute;
lsmestimate treatment "A vs D test" 1 0 0 -1/e cl lower testvalue=11 alpha=0.05;
lsmestimate treatment "A vs D CI" 1 0 0 -1/e cl alpha=0.05;

lsmestimate treatment "B vs D test" 0 1 0 -1/e cl lower testvalue=11 alpha=0.05;
lsmestimate treatment "B vs D CI" 0 1 0 -1/e cl alpha=0.05;
run;
```

17.4.1.5 Final Analysis if Residuals are Not Normally Distributed

If the probability value is <0.01 for the Shapiro-Wilk W test on the residuals from the mixed model, a test of skewness will be conducted on each paired difference using PROC UNIVARIATE (Paired differences are defined using the statistical hypotheses):

```
proc univariate data=differences normal;
   var treatment_difference;
   output out=tests nobs=n skewness=skewval;
run;
```

If the distribution of the paired differences is deemed unskewed (-0.3< skewness value <0.3), then Drug Liking Emax will be analyzed using paired t-tests for each treatment comparison.

If the distribution of the paired differences is skewed, then Drug Liking Emax will be analyzed non-parametrically. The Sign Test will be used to evaluate treatment differences.

If a paired t-test is chosen for Drug Liking Emax, means, mean differences and 1-sided 95%, as well as the corresponding 1-sided p-values for the appropriate hypotheses will be presented. The following SAS PROC TTEST code for 1-sample t-test of the differences between Treatment C and D (difference defined as C – D for each subject) may be used for the comparison (similar code will be used for other comparisons):

```
proc ttest data=parm plots=(histogram qq) sides=U alpha=0.05 h0=15;
   by test param;
   var Diff_CD;
run;
```

If a Sign Test is chosen, medians from each treatment as well as the medians, 2-sided 90% CIs (equivalent to 1-sided 95% CIs) and corresponding Sign Test p-values will be provided for each treatment comparison. The following SAS PROC UNIVARIATE code may be used for comparing the differences between Treatment C and Treatment D (difference defined as C – D for each subject (similar code will be used for other comparisons):

```
proc univariate data=parm mu0=15 alpha=0.05 CIPCTLDF;
   by test;
   var Diff_CD;
   output out = tests nobs=n median = med probm = pvalues;
run;
```

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

17.4.2 Statistical Analysis of Secondary Endpoints

The secondary endpoints for statistical hypothesis testing are: Take Drug Again VAS (12- and 24-hour scores); High VAS (Emax); and Overall Drug Liking VAS (12- and 24-hour scores) for Part 2 Treatment Phase.

[redacted]

All above secondary PD parameters will be evaluated with the same steps for model selection as described for Drug Liking Emax in Section 17.4.1 using the Modified Completer Set I, and Modified Completer Set II. The same hypothesis tests and difference margins as noted above for hypotheses will be evaluated for the secondary endpoints.

The following hypotheses will be tested for all secondary PD parameters from 1-sided 95% CIs (α=0.05) using the confirmatory type of hypothesis as shown below, where δ1=15, δ2=11 and δ3=11:

- H0: μC – μD ≤ δ1 versus Ha: μC – μD > δ1 (Hypothesis #1 Propofol versus Placebo)
- H0: μC – μA ≤ δ2 versus Ha: μC – μA > δ2 (Hypothesis #2 Propofol versus HSK3486 Dose 1)
- H0: μC – μB ≤ δ2 versus Ha: μC – μB > δ2 (Hypothesis #2 Propofol versus HSK3486 Dose 2)
- H0: μA – μD ≥ δ3 versus Ha: μA – μD < δ3 (Hypothesis #3 HSK3486 Dose 1 versus Placebo)
- H0: μB – μD ≥ δ3 versus Ha: μB – μD < δ3 (Hypothesis #3 HSK3486 Dose 2 versus Placebo)

18.0 Safety Analyses

18.1 Safety Variables

- AEs
- Clinical Laboratory Evaluations
  - Clinical Chemistry
  - Hematology
  - Urinalysis
  - Coagulation
  - Serology
  - Pregnancy and FSH test
  - Alcohol breath test
- Vital Signs
  - Supine Blood Pressure
    - Systolic Blood Pressure
    - Diastolic Blood Pressure
  - Pulse rate
  - Oral body temperature
  - Respiratory rate
- Electrocardiograms (ECG)
  - Heart Rate
  - PR Interval
  - QRS-Duration
  - QT Interval
  - QTc (Friderica) Interval
- Physical examination
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Respiratory Volume and minute ventilation
- Pulse Oximetry

18.1.1 Adverse Events

Treatment emergence will be evaluated for all AEs. Treatment-emergent adverse events (TEAE) are those that occur after the first dose of study drug or any event already present that worsens in either severity or frequency following exposure to the study drug.

TEAEs occurring following dosing in a specific period but before dosing in the next period will be attributed to the treatment in that period. If the time is missing for an AE on a dosing day then the AE will be attributed to the treatment given on that day.

[redacted]

The following missing data will be imputed as defined (for calculations/summary tables only and will not be presented in listings):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively (Note: if relationship severity is not imputed a missing category should be added)
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start times for the determination of treatment assignment will be assumed to occur after treatment on the recorded date one minute after dosing
- Missing AE start date will be assumed to be after treatment for the determination of TEAE but will not be attributed to a specific treatment for summarization

A summary of number and percentage of subjects reporting TEAEs, TEAEs by severity and relationship, serious AEs (SAEs), and subjects who discontinued study drug due to an AE will be provided for Part 1, Part 2 the Qualification Phase and Treatment Phase, separately.

A summary of the number and percentage of subjects reporting each TEAE, categorized by system organ class and preferred term coded according to the MedDRA, will be presented by treatment and overall for each part and study phase. Counting will be done by subject only, not by event; subjects will only be counted once within each body system or preferred term.

A summary of the number and percentage of subjects reporting each TEAE will be presented by relationship to study drug (as recorded on the eCRF) and by treatment and overall for each part and study phase. Subjects with multiple events within a system organ class or preferred term will be counted under the category of their most drug-related event within that system organ class or preferred term.

A summary of the number and percentage of subjects reporting each TEAE will be presented by severity (as recorded on eCRF) and by treatment and overall for each part and study phase. Subjects with multiple events within a system organ class or preferred term will be counted under the category of their most severe event within that system organ class or preferred term.

All AEs (including non-treatment-emergent events) recorded on the eCRF will be listed by subject.

A separate listing of AEs leading to study drug discontinuation will be provided.

18.1.2 Deaths and Serious Adverse Events

A listing of deaths and other SAEs will be provided by subject.

18.1.3 Laboratory Data

Clinical laboratory data will be presented using units from SDTM Controlled Terminology.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, hematology, and urinalysis by treatment and scheduled time will be provided Part 1 and Part 2 Qualification Phase and Treatment Phase, separately.

All laboratory data will be listed by subject, including laboratory tests not listed in the protocol. A separate listing of out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory and will be included in the listings for reference.

18.1.4 Vital Signs

Descriptive statistics summarizing vital signs (and changes from predose) by treatment and scheduled time will be provided for Part 1 and Part 2 Qualification Phase and Treatment Phase, separately.

All vital signs will be listed by subject.

[redacted]

18.1.5 Electrocardiograms

Descriptive statistics summarizing ECG parameters by treatment and scheduled time will be provided for Part 1 and Part 2 Qualification Phase and Treatment Phase, separately.

All ECG parameters and the corresponding abnormalities will be listed by subject.

18.1.6 Other Observations Related to Safety

Respiratory volume and minute ventilation will be listed by subject.

Physical examinations conducted will be listed by subject. Any untoward findings will be reported as adverse events.

C-SSRS results will be listed by subject.

MOAA/S results will be listed by subject.

Cardiac Telemetry start and end date/time will be listed.

Follow up phone contact will be listed by subject.

Pulse oximetry data will be listed by subject.

19.0 References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

Clinical Study Protocol. A 2-part, dose-finding and human abuse potential study of HSK3486 injection in nondependent, recreational central nervous system depressant users. Version 2.0. 04 Nov 2022.

[redacted]

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
ACLS	Advanced cardiovascular life support
AE	Adverse event
ADaM	Analysis data model
ANOVA	Analysis of variance
BMI	Body mass index
BQL	Below the quantifiable limit
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence interval
COWS	Clinical Opiate Withdrawal Scale
CNS	Central nervous system
CRU	Clinical research unit
CSR	Clinical study report
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CRF	Case Report Form
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IV	intravenous
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
NCS	Not clinically significant
PD	Pharmacodynamic
PK	Pharmacokinetic
QA'd	Quality assured
QC'd	Quality controlled

[redacted]

Glossary of Abbreviations:	
SAP	Statistical analysis plan
SAE	Serious adverse event
SD	Standard deviation
SDTM	Study data tabulation model
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings
VAS	Visual analog scale
WI	Work Instruction
WNL	WinNonlin

Appendix 2: Protocol Schedule of Assessments – Part 1 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	

[redacted]

[redacted]

	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**
Continuous Pulse Oximetry			Predose to at least 8h postdose[g]												
Electrocardiogram	X	X											8h		
Urine Drug Screen/Breath Alcohol	X	X													
Cardiac Telemetry			At least 1 h predose until at least 8h 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					1	3	5	15	30m						
Pharmacodynamics															
Drug-Specific VAS[j]					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[p]			pre												

[redacted]

[redacted]

	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
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.

[redacted]

[redacted]

Appendix 3: Protocol Schedule of Assessments – Part 2 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														

[redacted]

[redacted]

	Screening		Qualification Phase														
Visit:	**1**		**2**														
Day:	**-28 to -5**	**-4**		**Day -3 and Day -2**													
				Assessment Timepoints													
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																
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]														8h	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.

[redacted]

[redacted]

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, and Bad Drug Effects VAS and 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 approximately 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 protocol **Error! Reference source not found.**.

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.

Appendix 4: Protocol Schedule of Assessments – Part 2 Treatment Phase

	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]													Approx. 24h after last Dose in Period 4	3 to 7 days after last dose
Day:	-1[a]	1												2[t]		
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]		pre		2m	6m	15m	30m	45m	1h	2h	4h						
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]		

[redacted]

[redacted]

	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]														**Approx. 24h after last Dose in Period 4**	**3 to 7 days after last dose**
Day:	**-1[a]**	**1**													**2[t]**		
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.

[redacted]

[redacted]

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.

Appendix 5: List of End of Text Outputs

List of End of Text Tables and Figures:		
Output	**Title**	**Analysis Set**
Section 14.1 – Disposition and Demographic Data		
Table 14.1.1	Summary of Analysis Sets	All Subjects
Table 14.1.2.1	Summary of Subject Disposition – Part 1	Part 1 Safety
Table 14.1.2.2	Summary of Subject Disposition – Part 2 Qualification Phase	Part 2 Qualification Safety
Table 14.1.2.3	Summary of Subject Disposition – Part 2 Treatment Phase	Part 2 Treatment Safety
Table 14.1.3.1	Summary of Demographics – Part 1	Part 1 Safety
Table 14.1.3.2	Summary of Demographics – Part 2 Qualification Phase	Part 2 Qualification Safety
Table 14.1.3.3	Summary of Demographics – Part 2 Treatment Phase	Part 2 Treatment Safety
Table 14.1.4.1	Summary of Study Drug Administration – Part 1	Part 1 Safety
Table 14.1.4.2	Summary of Study Drug Administration – Part 2 Qualification Phase	Part 2 Qualification Safety
Table 14.1.4.3	Summary of Study Drug Administration – Part 2 Treatment Phase	Part 2 Treatment Safety
Section 14.2 – Pharmacodynamic and Pharmacokinetic Data		
PD Summary		
Table 14.2.1.1.1	Summary of Drug Liking VAS Assessments – Part 1	Part 1 Safety
Table 14.2.1.1.2	Summary of Pharmacodynamic Assessments – Part 1	Part 1 Safety
Table 14.2.1.1.3	Summary of Drug Liking Pharmacodynamic Parameters – Part 1	Part 1 Safety
Table 14.2.1.1.4	Summary of Pharmacodynamic Parameters – Part 1	Part 1 Safety
Table 14.2.1.2.1a	Summary of Drug Liking VAS Assessments – Part 2 Qualification Phase	Modified Completer I
Table 14.2.1.2.1b	Summary of Drug Liking VAS Assessments – Part 2 Qualification Phase	Modified Completer II
Table 14.2.1.2.2a	Summary of Pharmacodynamic Assessments – Part 2 Qualification Phase	Modified Completer I
Table 14.2.1.2.2b	Summary of Pharmacodynamic Assessments – Part 2 Qualification Phase	Modified Completer Set II
Table 14.2.1.2.3a	Summary of Drug Liking Pharmacodynamic Parameters – Part 2 Qualification Phase	Modified Completer I
Table 14.2.1.2.3b	Summary of Drug Liking Pharmacodynamic	Modified

	Parameters – Part 2 Qualification Phase	Completer Set II
Table 14.2.1.2.4a	Summary of Pharmacodynamic Parameters – Part 2 Qualification Phase	Modified Completer I
Table 14.2.1.2.4b	Summary of Pharmacodynamic Parameters – Part 2 Qualification Phase	Modified Completer Set II
Table 14.2.1.3.1a	Summary of Drug Liking VAS Assessments – Part 2 Treatment Phase	Modified Completer I
Table 14.2.1.3.1b	Summary of Drug Liking VAS Assessments – Part 2 Treatment Phase	Modified Completer Set II
Table 14.2.1.3.2a	Summary of Pharmacodynamic Assessments – Part 2 Treatment Phase	Modified Completer I
Table 14.2.1.3.2b	Summary of Pharmacodynamic Assessments – Part 2 Treatment Phase	Modified Completer Set II
Table 14.2.1.3.3a	Summary of Drug Liking Pharmacodynamic Parameters – Part 2 Treatment Phase	Modified Completer I
Table 14.2.1.3.3b	Summary of Drug Liking Pharmacodynamic Parameters – Part 2 Treatment Phase	Modified Completer Set II
Table 14.2.1.3.4a	Summary of Pharmacodynamic Parameters – Part 2 Treatment Phase	Modified Completer I
Table 14.2.1.3.4b	Summary of Pharmacodynamic Parameters – Part 2 Treatment Phase	Modified Completer Set II
Table 14.2.1.4.1a	Statistical Analysis of Drug Liking Emax – Part 2 Treatment Phase	Modified Completer I
Table 14.2.1.4.1b	Statistical Analysis of Drug Liking Emax – Part 2 Treatment Phase	Modified Completer Set II
Table 14.2.1.4.2a	Statistical Analysis of Secondary Pharmacodynamic Parameters – Part 2 Treatment Phase	Modified Completer I
Table 14.2.1.4.2b	Statistical Analysis of Secondary Pharmacodynamic Parameters – Part 2 Treatment Phase	Modified Completer Set II
Table 14.2.1.5a	Statistical Results for Analysis Decisions – Part 2 Treatment Phase	Modified Completer I
Table 14.2.1.5b	Statistical Results for Analysis Decisions – Part 2 Treatment Phase	Modified Completer Set II
Figure 14.2.1.6.1a	Plot of Mean (±SD) Drug Liking VAS Assessments versus Time by Treatment – Part 2 Treatment Phase	Modified Completer I
Figure 14.2.1.6.1b	Plot of Mean (±SD) Drug Liking VAS Assessments versus Time by Treatment – Part 2 Treatment Phase	Modified Completer Set II
Figure 14.2.1.6.2a	Plot of Mean (±SD) Pharmacodynamic Assessment Values versus Time by Treatment – Part 2 Treatment Phase	Modified Completer I
Figure 14.2.1.6.2b	Plot of Mean (±SD) Pharmacodynamic Assessment Values versus Time by Treatment – Part 2 Treatment Phase	Modified Completer Set II

[redacted]

Figure 14.2.1.7.1a	Plot of Individual Drug Liking VAS Assessments versus Time by Treatment – Part 2 Treatment Phase	Modified Completer I
Figure 14.2.1.7.1b	Plot of Individual Drug Liking VAS Assessments versus Time by Treatment – Part 2 Treatment Phase	Modified Completer Set II
Figure 14.2.1.7.2a	Plot of Individual Pharmacodynamic Assessment Values versus Time by Treatment – Part 2 Treatment Phase	Modified Completer I
Figure 14.2.1.7.2b	Plot of Individual Pharmacodynamic Assessment Values versus Time by Treatment – Part 2 Treatment Phase	Modified Completer Set II
PK Summary		
Table 14.2.2.1	Summary of HSK3486 Plasma Concentrations – Part 2 Treatment Phase	PK
Table 14.2.2.2	Summary of HSK3486 Plasma Pharmacokinetic Parameters – Part 2 Treatment Phase	PK
Table 14.2.2.3	Statistical Analysis of Treatment Comparison for Dose Normalized Pharmacokinetic parameters – Part 2 Treatment Phase	PK
Figure 14.2.2.4.1	Plot of Mean (± SD) HSK3486 Plasma Concentrations Versus Time on a Linear Scale – Part 2 Treatment Phase	PK
Figure 14.2.2.4.2	Plot of Mean (+SD) HSK3486 Plasma Concentrations Versus Time on a Semi-Log Scale – Part 2 Treatment Phase	PK
Figure 14.2.2.5.1	Plot of Individual HSK3486 Plasma Concentrations Versus Time on a Linear Scale – Part 2 Treatment Phase	PK
Figure 14.2.2.5.2	Plot of Individual HSK3486 Plasma Concentrations Versus Time on a Semi-Log Scale – Part 2 Treatment Phase	PK
Figure 14.2.2.6	Scatter Plot of Individual Plasma Dose Normalized Pharmacokinetic Parameters – Part 2 Treatment Phase	PK
Figure 14.2.2.7	Scatter Plot of Pharmacokinetic-Pharmacodynamic Parameters – Part 2 Treatment Phase	PK
Section 14.3 – Safety Data		
Table 14.3.1.1.1	Summary of Adverse Events – Part 1	Part 1 Safety
Table 14.3.1.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Part 1	Part 1 Safety
Table 14.3.1.1.3	Summary of Treatment Emergent Adverse Events by Relationship to Study Drug – Part 1	Part 1 Safety
Table 14.3.1.1.4	Summary of Treatment Emergent Adverse Events by Severity – Part 1	Part 1 Safety

[redacted]

Table 14.3.1.2.1	Summary of Adverse Events – Part 2 Qualification Phase	Part 2 Qualification Safety
Table 14.3.1.2.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Part 2 Qualification Phase	Part 2 Qualification Safety
Table 14.3.1.2.3	Summary of Treatment Emergent Adverse Events by Relationship to Study Drug – Part 2 Qualification Phase	Part 2 Qualification Safety
Table 14.3.1.2.4	Summary of Treatment Emergent Adverse Events by Severity – Part 2 Qualification Phase	Part 2 Qualification Safety
Table 14.3.1.3.1	Summary of Adverse Events – Part 2 Treatment Phase	Part 2 Treatment Safety
Table 14.3.1.3.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Part 2 Treatment Phase	Part 2 Treatment Safety
Table 14.3.1.3.3	Summary of Treatment Emergent Adverse Events by Relationship to Study Drug – Part 2 Treatment Phase	Part 2 Treatment Safety
Table 14.3.1.3.4	Summary of Treatment Emergent Adverse Events by Severity – Part 2 Treatment Phase	Part 2 Treatment Safety
Table 14.3.2	Listing of Deaths and Other Serious Adverse Events	All Subjects
Table 14.3.3	Not part of TFL – Reserved for Narratives in CSR	
Table 14.3.4	Listing of Abnormal Laboratory Values	All Subjects
Table 14.3.5.1	Summary of Laboratory Results – Part 1	Part 1 Safety
Table 14.3.5.2	Summary of Laboratory Results – Part 2 Qualification Phase	Part 2 Qualification Safety
Table 14.3.5.3	Summary of Laboratory Results – Part 2 Treatment Phase	Part 2 Treatment Safety
Table 14.3.6.1	Summary of Vital Signs – Part 1	Part 1 Safety
Table 14.3.6.2	Summary of Vital Signs – Part 2 Qualification Phase	Part 2 Qualification Safety
Table 14.3.6.3	Summary of Vital Signs – Part 2 Treatment Phase	Part 2 Treatment Safety
Table 14.3.7.1	Summary of 12-Lead Electrocardiogram Results – Part 1	Part 1 Safety
Table 14.3.7.2	Summary of 12-Lead Electrocardiogram Results – Part 2 Qualification Phase	Part 2 Qualification Safety
Table 14.3.7.3	Summary of 12-Lead Electrocardiogram Results – Part 2 Treatment Phase	Part 2 Treatment Safety

[redacted]

List of End of Text Listings:	
Output	**Title**
Section 16.2.1 – Disposition	
Listing 16.2.1	Subject Disposition
Listing 16.2.2	Important Protocol Deviations
Section 16.2.3 – Excluded Subjects	
Listing 16.2.3.1	Analysis Sets
Listing 16.2.3.2	Eligibility Criteria
Section 16.2.4 – Demographics and Baseline Characteristics	
Listing 16.2.4.1	Subject Demographics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Prior and Concomitant Medications
Listing 16.2.4.4	Recreational Drug Use History
Listing 16.2.4.5	Naloxone Challenge Result
Section 16.2.5 - Compliance	
Listing 16.2.5.1	Study Drug Administration
Listing 16.2.5.2	Lidocaine Administration
Section 16.2.6.1 – Pharmacodynamic Data	
Listing 16.2.6.1.1	Pharmacodynamic Assessments
Listing 16.2.6.1.2	Pharmacodynamic Parameters
Section 16.2.6.2 – Pharmacokinetic Data	
Listing 16.2.6.2.1	HSK3486 Plasma Concentrations
Listing 16.2.6.2.2	HSK3486 Pharmacokinetic Parameters
Listing 16.2.6.2.3	HSK3486 Pharmacokinetic Diagnostic Parameters
Section 16.2.7 – Adverse Events Data	
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Adverse Events Leading To Study Drug Discontinuation
Section 16.2.8 – Laboratory Data	
Listing 16.2.8.1	Clinical Laboratory Results – Chemistry
Listing 16.2.8.2	Clinical Laboratory Results – Hematology
Listing 16.2.8.3	Clinical Laboratory Results – Coagulation
Listing 16.2.8.4	Clinical Laboratory Results – Urinalysis
Listing 16.2.8.5	Clinical Laboratory Results – Additional Assessments
Section 16.2.9-12– Other Safety Data	
Listing 16.2.9	Vital Signs

[redacted]

Listing 16.2.10	12-Lead Electrocardiogram Results
Listing 16.2.11	Physical Examinations
Listing 16.2.12	Columbia-Suicide Severity Rating Scale
Listing 16.2.13	Respiratory Volume and Minute Ventilation
Listing 16.2.14	Pulse Oximetry Result
Listing 16.2.15	Follow Up Contact
Listing 16.2.16	Modified Observer's Assessment of Alertness/Sedation Scale
Listing 16.2.17	Cardiac Telemetry Date Time

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.9.2.1a	Statistical Methods and Analysis Output Supporting Table 14.2.1.4.1a
Appendix 16.1.9.2.1b	Statistical Methods and Analysis Output Supporting Table 14.2.1.4.1b
Appendix 16.1.9.2.2a	Statistical Methods and Analysis Output Supporting Table 14.2.1.4.2a
Appendix 16.1.9.2.2b	Statistical Methods and Analysis Output Supporting Table 14.2.1.4.2b
Appendix 16.1.9.2.3a	Statistical Methods and Analysis Output Supporting Table 14.2.1.5a
Appendix 16.1.9.2.3b	Statistical Methods and Analysis Output Supporting Table 14.2.1.5b
Appendix 16.1.9.2.4	Statistical Methods and Analysis Output Supporting Table 14.2.2.3

[redacted]

Appendix 6: Shells for Post-Text Tables, Figures and Listings

Shells are provided in a separate document.

20.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
22-Nov-2022	[redacted]	Created from EDSREP 009 T 01 G.
04-Oct-2023	[redacted]	The Modified Completer Set II has been incorporated in response to FAD comment, Additional analysis will be performed on the Modified Completer Set II for the PD analysis.