Cover Page

STATISTICAL ANALYSIS PLAN V2.0 HSK3486-305

TITLE OF STUDY: A Multicenter, Randomized, Double-blinded, Propofol-controlled, Phase 3 Clinical Study to Evaluate the Efficacy and Safety of HSK3486 Injectable Emulsion for Induction of General Anesthesia in Adults Undergoing Elective Surgery

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STATISTICAL ANALYSIS PLAN
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A Multicenter, Randomized, Double-blinded, Propofol-controlled, Phase 3 Clinical Study to Evaluate the Efficacy and Safety of HSK3486 Injectable Emulsion for Induction of General Anesthesia in Adults Undergoing Elective Surgery

PROTOCOL NUMBER HSK3486-305

SPONSORED BY

Haisco-USA Pharmaceuticals, Inc

[redacted]

PREPARED BY

[redacted]

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2.0	30 October 2023	Added potential blood-compatibility AEs and changed eyelash effect measurement timepoint to the start of the drug administration

APPROVALS

Approved:

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AESI	Adverse Event of Special Interest
BIS	bispectral index
BMI	body mass index
CNS	central nervous system
DBP	diastolic blood pressure
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
HR	heart rate
KM	Kaplan-Meier
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Awareness/Sedation
NIM	non-inferiority margin
NRS	Numeric Rating Scale
PACU	post-anesthesia care unit
PK	pharmacokinetic
PT	preferred term
RR	respiratory rate
SAP	Statistical Analysis Plan
SAE	serious adverse event
SBP	systolic blood pressure
SOC	system organ class
SpO_2	oxygen saturation
Temp	temperature
WHODrugG	World Health Organization Global Drug Dictionary

LIST OF IN-TEXT TABLES

1. PURPOSE OF THE ANALYSES

This is a multicenter, randomized, double-blinded, propofol-controlled, Phase 3 clinical study to evaluate the efficacy and safety of HSK3486 for induction of general anesthesia in adults undergoing elective surgery with endotracheal intubation.

This statistical analysis plan (SAP) provides a detailed description of the strategy and statistical methodology to be used for analysis of data from the HSK3486-305 protocol.

The purpose of the SAP is to describe the pre-specified statistical approaches to the analysis of study data prior to database lock. This analysis plan is meant to supplement the study protocol. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy. Any deviations from this plan will be described in the Clinical Study Report.

2. PROTOCOL SUMMARY

2.1 Study Objectives

2.1.1 Primary objective

- To demonstrate HSK3486 0.4/0.2 mg/kg (0.4 mg/kg intravenous [IV] slow injection for the first dose, an additional 0.2 mg/kg if needed) is non-inferior to propofol 2.0/1.0 mg/kg (2.0 mg/kg IV slow injection for first dose, an additional 1.0 mg/kg if needed) in success of induction of general anesthesia in adults undergoing elective surgery.

2.1.2 Secondary objectives

Key Secondary Objectives:

- To confirm that HSK3486 0.4/0.2 mg/kg leads to statistically significant less injection-site pain in all compared to propofol 2.0/1.0 mg/kg during the induction of general anesthesia in adults undergoing elective surgery.
- To demonstrate HSK3486 0.4/0.2 mg/kg provides better anesthetic effects compared to propofol 2.0/1.0 mg/kg without significant cardiac and respiratory depression in conjunction with other routinely used preinduction and maintenance anesthetic agents in the induction of general anesthesia in adults undergoing elective surgery.

Additional Efficacy Objectives:

- To evaluate HSK3486 0.4/0.2 mg/kg induction time in general anesthesia compared to propofol.
- To evaluate HSK3486 0.4/0.2 mg/kg time to the disappearance of eyelash reflex compared to propofol.
- To confirm that HSK3486 0.4/0.2 mg/kg leads to statistically significant less moderate injection-site pain compared to propofol 2.0/1.0 mg/kg during the induction of general anesthesia in adults undergoing elective surgery.
- To better characterize that HSK3486 0.4/0.2 mg/kg leads to statistically significant less average NRS scales in injection-site pain compared to propofol 2.0/1.0 mg/kg during the induction of general anesthesia in adults undergoing elective surgery.

Safety:

- To evaluate the overall safety profile of HSK3486 compared to propofol.

Pharmacokinetic:

- To characterize the HSK3486 population pharmacokinetic (PK) profile.

2.2 Overall Study Design and Plan

This is a multicenter, randomized, double-blinded, propofol-controlled, Phase 3 clinical study to evaluate the efficacy and safety of HSK3486 for induction of general anesthesia in adults

undergoing elective surgery with endotracheal intubation. The study design is described in detail below and outlined graphically in Appendix 14.1. The schedule of assessments can be found in Appendix 14.2.

After screening, eligible subjects will be randomized in a 2:1 ratio to receive either HSK3486 0.4/0.2 mg/kg (i.e., 0.4 mg/kg IV slow injection over 30 [±5] seconds followed by an additional 0.2 mg/kg dose over 10 [±2] seconds if needed) or propofol 2.0/1.0 mg/kg (i.e., 2.0 mg/kg IV slow injection over 30 [±5] seconds followed by an additional 1.0 mg/kg dose over 10 [±2]seconds if needed) in a blinded manner. Enrolled subjects will be stratified by American Society of Anesthesiologists Physical Status (ASA-PS; I-II and III-IV), age (<65 and ≥65 years), and Body Mass Index (BMI <35 and ≥35 kg/m^2). Endotracheal intubation will be performed after adequate anesthetic induction (Modified Observer's Assessment of Awareness/Sedation [MOAA/S] ≤1) (Appendix 14.3) has been achieved and administration of neuromuscular blocking agent.

On Day 1, premedication is allowed prior to induction except for sedative-hypnotics, analgesics (e.g., opioids, NSAIDs, APAP), or any medications that relieve pain (e.g., Gabapentin), unless otherwise specified in the protocol. Premedication should be recorded if used.

Prior to administration of the study drug in the operating room, the preoperative readiness of each subject will be confirmed. Oxygen will be supplied through a facemask (oxygen flow rate: ≥4 L/min) at least 2 minutes before study drug administration. Subsequently, the investigator can adjust the oxygen flow according to the specific situation of the subject and maintenance IV solution (normal saline [NS], lactated ringer's [LR], or 5% dextrose) will be administrated through IV infusion. Throughout the preinduction and induction periods, a timing device must be used to allow accuracy and sequencing of necessary assessments.

2.2.1 Preinduction Period

- Obtain vital signs (heart rate [HR], respiratory rate [RR], oxygen saturation [SpO_2], systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial pressure [MAP]), Temperature [Temp]; baseline value will be the measurement immediately prior to initiation of study drug administration. Attach 3-lead or 5-lead electrocardiogram (ECG) to subject and monitor continuously. In the event an abnormality is noted with 3-lead or 5-lead ECG, clinical significance of an abnormality should be documented, and the investigators will decide whether to add a 12-lead ECG.
- Attach bispectral index (BIS [Appendix 14.4]) monitor to subject. Record the three most recent BIS values preceding midazolam administration.
- Subjects will receive IV midazolam at dose 0.04 mg/kg, up to 3 mg maximum over 15 [±2] seconds at 5 minutes [±30] seconds prior to initiation of induction agents as premedication. The midazolam dose can be reduced according to patient's age and comorbidities as per the anesthetist's discretion. The start and end time of midazolam administration should be recorded. The end time of midazolam administration will begin the window to start of IP.

- Subjects will receive preinduction IV fentanyl at a dose of 1 mcg/kg rounded up to the nearest 25 mcg, up to 100 mcg maximum over 15 [±2] seconds at 2 minutes [±10] seconds prior to initiation of induction agents. The start and end time of fentanyl administration should be recorded. The end time of fentanyl administration will begin the window to start of IP.

  Note: Throughout the preinduction and induction periods, a timing device must be used to allow accuracy and sequencing of necessary assessments.

- Information about any adverse events (AEs) and concomitant medications will be recorded.

2.2.2 Induction Period of General Anesthesia

The induction of general anesthesia will be performed as follows:

- Monitor vital signs (HR, RR, SpO_2, SBP, DBP, MAP, Temp) continuously. HR, RR, SBP, DBP, MAP, Temp should be recorded once every 2 minutes [±30 seconds], SpO_2 value should be recorded once every 1 minute [± 15 seconds] from the start of study drug administration (for every time point) for 30 minutes post start of study drug administration, for the judgment of key secondary endpoint.

  Note: Vital signs (HR, RR, SBP, DBP, MAP, Temp) monitor should be set to cycle every 1 minute to obtain vitals at least every 2 minutes (in case cycle requires longer than 1 minute).

- Administer IV study drug (HSK3486 0.4 mg/kg or propofol 2.0 mg/kg) into vein located on the back of right or left hand (this IV location is strongly preferred rather than mandatory) at a port closest to the IV cannula (IV injection time: 30 [±5] seconds).

- The MOAA/S will be evaluated every 30 [±10] seconds after end of study drug administration until MOAA/S ≤1 is reached.

  - If MOAA/S is still >1 at 1 minute [±10 seconds] post end of study drug administration, a top-up dose of 50% of the initial dose of study drug (either HSK3486 0.2 mg/kg or propofol 1 mg/kg depending on treatment group) will be given to the subject (IV injection time: 10 [±2] seconds). Start and end times of top-up dose administration will be recorded. The MOAA/S will be evaluated every 30 [±10] seconds post end of the top-up dose administration.

  - If MOAA/S is still >1 at 2 minutes [±10 seconds] post end of the top-up dose administration, then the rescue drug, propofol, will be given (in both treatment groups). The rescue dose is prepared as the initial calculated propofol dose (100%) and administered per propofol guidelines. The MOAA/S will be evaluated every 30 [±10] seconds post end of rescue drug administration until MOAA/S ≤1 is reached.

  - Administration of study drug must be initiated 5 minutes [±30 seconds] post midazolam preinduction medication administration stop time and at 2 minutes [±10 seconds] after preinduction fentanyl administration stop time. Top-up dose should be administered within 10 seconds once MOAA/S is evaluated >1.

- Injection-site pain is evaluated verbally by Numerical Rating Scale (NRS; Appendix 14.5). Upon initiation of study drug administration, the investigator should immediately ask the subject to rate his or her pain at injection-site. As a general guidance, the evaluation should be done multiple times with the first evaluation occurring typically within 15 seconds after initiation of study drug injection and monitored until successful induction (MOAA/S ≤1). Related information, such as the occurrence and severity of injection pain (NRS 0-10), shall be recorded. The maximum (highest value) injection-site pain will be recorded in EDC as NRS.
- Post the end of initial study drug administration, the eyelash reflex will be evaluated every 30 [±10] seconds until loss of eyelash reflex. If there is a top-up dose, eyelash reflex will be evaluated every 30 [±10] seconds post end of the top-up dose administration until loss of eyelash reflex. If there is rescue drug given, eyelash reflex will be evaluated every 30 [±10] seconds post end of the rescue drug until loss of eyelash reflex. The time of loss of eyelash reflex should be recorded.
- BIS will be monitored continuously; record baseline BIS value prior to administering study drug. BIS values will be collected at the following timepoints post start of initial study drug administration: every 30 [±10] seconds for 5 minutes, and then every 2 minutes [±30 seconds] for 30 minutes and then every 30 [±2] minutes for the duration of the surgery.
- Monitor 3-lead or 5-lead electrocardiogram (ECG) continuously. Abnormalities that are clinically significant or not clinically significant should be recorded. The investigators will decide whether to add a 12-lead ECG.
- When MOAA/S ≤1 is reached, then IV rocuronium bromide (0.6 mg/kg) is to be administered for neuromuscular blockade to perform endotracheal intubation. The start and end times of rocuronium bromide administration should be recorded. RR should be collected until initiation of administration of rocuronium.

  Note: For subjects with BMI >40 kg/m^2, the rocuronium dose may be modified per investigator discretion.

  Note: Additional IV rocuronium is allowed per investigator's discretion only in response to clinical symptoms during tracheal intubation, such as gag reflex and movement et al, or during surgical procedures. The start and end times of additional rocuronium bromide administration should be recorded.
- Intubate subject once neuromuscular blockade has taken effect; if using twitch monitor, intubate once no twitches are noted. The start and end times of first and subsequent intubation attempts should be recorded.
- During endotracheal intubation, evaluate and record clinical symptoms and/or signs for inadequate depth of anesthesia, such as lacrimation, movement, vomiting, coughing, laryngospasm, bucking, swallowing reflex and/or bronchospasm, etc. for at least 15 minutes from start of study drug administration.
- Between start of study drug administration and prior to the administration of rocuronium bromide, evaluate and record respiratory depression.

Note: Respiratory depression includes apnea, defined as absence of thoracic movement lasting >30 seconds, prior to the administration of rocuronium bromide, or hypoxia, defined as SpO_2 <90% lasting >30 seconds, or life-threatening apnea or hypoxia requiring immediate intervention.

- Evaluate and record cardiac depression from start of study drug administration until the subject leaves the operating room.

  Note: Cardiac depression is defined as SBP <90 mmHg lasting >2 minutes plus requiring medical intervention such as inotropes, vasopressors, or IV fluid resuscitation, or life-threatening hypotension requiring immediate intervention.

- Sevoflurane (an inhalation anesthetic agent) will be used for maintenance of general anesthesia. Initiate sevoflurane within 60 seconds after successful endotracheal intubation. The end-tidal concentration of sevoflurane should be 1.5-2.0 % (The initial concentration that is set and start time of administration should be recorded).
- Information about any AEs and concomitant medications will be recorded.

2.2.3 Maintenance Period of General Anesthesia

- During the maintenance period of general anesthesia, the inhalational anesthetic agent sevoflurane will be used according to routine clinical practice, and the end-tidal concentration of sevoflurane should be 1.5-2.0 % within 15 minutes after initiation of study drug administration and can be adjusted to the desired effect after that. Propofol should not be used at any time all throughout the maintenance period.
- During the maintenance period, end-tidal sevoflurane concentration will be monitored per standard of care.
- The BIS will be monitored continuously per standard of care, and BIS values will be collected at the following timepoints from start of initial study drug administration: every 30 [±10] seconds until 5 minutes, then every 2 minutes [±30 seconds] until 30 minutes and then every 30 [±2] minutes for the duration of the surgery.
- Additional IV fentanyl or other analgesic drug may be administered for intraoperative analgesia only after initiation of sevoflurane, preferably after 15 minutes following the initiation of study drug administration, start time and end time of initial study drug administration should be recorded; if additional drug used, the start and end time of administration should be recorded.
- Subject management during surgery needs to follow routine best practice which includes Antiemetics Ondansetron, or other 5 HT-3 antagonists and/or Dexamethasone**.** Antiemetics should be given during surgery and before subjects wake up unless otherwise contraindicated. The use of antiemetics should be recorded in concomitant medications.
- Monitor 3-lead or 5-lead ECG continuously. Abnormalities of clinical significance and non-clinical significance should be recorded. The investigators decide whether to add a 12-lead ECG based on the Subject's condition. Information about any adverse events (AEs) and concomitant medications will be recorded.

- Information about any adverse events (AEs) and concomitant medications will be recorded.

2.2.4 Follow-up period (6 hours Post Study Drug and 24-hours Post Study Drug Administration (Day 2); Day 8 Phone Contact)

Day 1 Visit:

For the first 6 hours post study drug evaluation, study assessments and procedures will be assessed as indicated in the Schedule of Assessments:

- After the surgery, vital signs (HR, RR, SpO_2, SBP, DBP, MAP, Temp) will be assessed at 6 [±2] hours post start study drug administration.

  Note: If surgery lasts >4 hours, vital signs, clinical laboratory tests and 12-ECG should be obtained 1[+1] hour after completion of surgery. Duration of surgery is defined as time from study drug administration to time of transfer from operating room to recovery room or post-anesthesia care unit (PACU).

- Clinical laboratory tests (including hematology, blood chemistry, and urinalysis) will be obtained at 6[±2] hours post start study drug administration.
- Obtain 12-lead ECG at 6 [±2] hours post start study drug administration.
- In the post-anesthesia care unit (PACU), once the subject is alert and oriented, repeat NRS for recall of pain at time of study drug administration and assess surgical awareness with recall using the Brice Awareness Questionnaire (Appendix 14.6). The assessment time and result should be recorded.
- Information about any AEs and concomitant mediations will be collected and recorded.
- After the surgery, subjects may remain in the hospital or observation unit if required based on standard of care and the clinical situation; however, if the subject is clinically stable after the Day 1 follow-up assessments and appropriate to be discharged home per the judgement of the investigator and surgeon, the subject may be released with supervision by a family member or friend, and must return to the clinic for the 24-hour follow-up visit (Day 2).

Day 2 Visit:

For the 24-hour follow-up (Day 2) visit, study assessments and procedures will be assessed as indicated in the Schedule of Assessments:

- 24 [±6] hours post study drug administration (Day 2), obtain vital signs (HR, RR, SpO_2, SBP, DBP, MAP, Temp).
- Information about any AEs and concomitant mediations will be collected and recorded.

Day 8 Phone Contact:

- Subjects will be evaluated by a follow-up telephone call 7 [±2] days after surgery.

- Surgical awareness with recall will be re-assessed using the Brice Awareness Questionnaire.
- Information about any AEs and associated medications will be collected and recorded.

2.3 Study Population

Inclusion criteria:

Subjects must satisfy all of the following criteria at the screening visit:

1. Subjects undergoing elective surgery (non-emergency, non-cardiothoracic, and non-intracranial surgery, anticipated to last at least 1 hour) requiring endotracheal intubation and inhalation general anesthesia during the maintenance period. Duration of surgery is defined as time from study drug administration to time of transfer from operating room to recovery room or PACU.

2. Males or females, aged ≥18 years old, with ASA-PS I to IV (Appendix 14.8). For ASA-PS IV subjects, clinical status must be optimized at time of preoperative anesthesia evaluation per judgement of the anesthesiologist.

3. BMI ≥18 kg/m^2.

4. Vital signs at screening: RR ≥10 and ≤24 breaths/min; SpO_2≥92% in ambient air; SBP ≥90 and ≤160 mmHg; DBP ≥55 and ≤100 mmHg; HR ≥55 (or ≥50 if subjects are on beta blockers) and ≤100 beats/min.

5. For all women of childbearing potential, negative serum pregnancy test at screening and must have negative urine pregnancy test at baseline (Day 1). Additionally, women of childbearing potential* and male subjects with female partners of childbearing potential must agree to use effective contraception as defined in the study protocol from the time of consent until 30 days post study drug administration.

6. Capable of understanding the procedures and methods of this study, willing to sign an Informed Consent Form, and able to complete this study in strict compliance with the study protocol.

7. Willing to comply with the site's COVID guidelines and testing requirements as applicable.

8. Subjects with psychiatric diseases (schizophrenia, mania) must be considered stable on treatment (with SSRIs, SNRIs, TCAs, and MAOIs) and no hospitalizations and urgent care for at least 1 year.

*Women NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral salpingo-oophorectomy) or who are postmenopausal (defined 12 months since last regular menses).

Exclusion criteria:

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening visit:

1. Contraindications to deep sedation/general anesthesia or a history of adverse reaction to sedation/general anesthesia.

2. Known to be allergic to eggs, soy products, opioids and their antidotes, or propofol; subject having contraindications to propofol, opioids, and their antidotes.

3. Medical condition or evidence of increased sedation/general anesthesia risk as follows:
   a) Cardiovascular disorders: uncontrolled hypertension (SBP>160 mmHg and/or DBP >100 mmHg) with or without antihypertensive therapy (antihypertensive therapy should be stable for 1 month prior to screening), serious arrhythmia (including the subjects with implanted pace makers), unstable heart failure, Adams-Stokes syndrome (i.e., syncope or near syncope due to cardiac arrythmia), unstable angina, myocardial infarction occurring within 6 months prior to screening, history of tachycardia/bradycardia requiring medications, third degree atrioventricular block or QT interval corrected for HR using Fridericia's formula (QTcF)≥450ms for males and ≥470ms for females.
   b) History of severe obstructive lung disease (i.e., forced expiratory volume in 1 second [FEV_1] <50% predicted), history of bronchospasm requiring treatment in a hospital emergency room or hospitalization occurring within 3 months prior to screening, developing acute respiratory tract infection within 2 weeks prior to baseline (such as symptoms of fever, shortness of breath, wheezing, nasal congestion, and cough).
   c) Cerebrovascular disease: subject with a history of serious craniocerebral injury, convulsion, seizure disorder, intracranial hypertension, cerebral aneurysm, or stroke.
   d) Subjects with psychiatric diseases (schizophrenia, mania) who have not been on a stable treatment regimen (with SSRIs, SNRIs, TCAs, MAOIs) for at least 1 year or who have been hospitalized or had emergent/urgent care within the past year.
   e) Uncontrolled clinically significant conditions of liver (e.g., severe hepatic insufficiency defined as Childs-Pugh class C), kidney, gastrointestinal tract, blood system, nervous system, or metabolic system diseases, judged by the investigator to be unsuitable for involvement in the study.
   f) Known glycosylated hemoglobin (HbA1c) greater than or equal to 10%.
   g) Known thyroid-stimulating hormone (TSH) value 10% outside the normal range or on thyroid replacement therapy with a known free T-4 level outside the normal range.
   h) History of alcohol abuse within 3 months prior to screening, where alcohol abuse refers to daily alcohol drinking >2 units (1 unit = 360 mL of beer or 45 mL of spirit with a strength of 40% or 150 mL of wine).
   i) History of drug abuse that, in the opinion of the investigator, may confound the interpretation of safety or efficacy in a study subject.

4. Management risks of respiratory tract and judged by the investigator to be unsuitable for inclusion in the study as follows:

a) Asthma must be stable: stable doses of asthma medications for the past 6 months, no requirement for rescue inhalers or oral steroids within past 6 months, not evaluated in emergency department, urgent care, or hospitalized for an asthma attack within past 1 year.

b) History (or family history) of malignant hyperthermia.

c) Any previous failure of tracheal intubation.

d) Judged to have a difficult airway for endotracheal intubation in the opinion of the Investigator based on parameters such as modified Mallampati score (Grade III or IV [Appendix 14.9], neck mobility, short thyromental distance, and/or history of difficult intubation).

5. Any medication that has the potential to interact synergistically with propofol or HSK3486, including but not limited to all sedatives and hypnotics (e.g., benzodiazepines and opioids) taken within 5 half-lives prior to Day 1.

6. Laboratory parameters measured at screening with the following levels:
   a) Neutrophil count ≤1.5 x 10^9/L
   b) Platelet count <80 x 10^9/L
   c) Hemoglobin <90 g/L (without blood transfusion within 14 days)
   d) Alanine transaminase and/or aspartate transaminase ≥2.0 x upper limit of normal (ULN)
   e) Total bilirubin ≥2.0 x ULN
   f) Severe renal impairment defined by creatinine clearance (CrCl) ≤30 mL/min

7. Female subjects with a positive pregnancy test at screening (serum) or baseline (urine); lactating subjects; any subject planning to get pregnant within 1 month after the study (including the male subject's partner).

8. Judged by the investigator to have any other factors that make the subject unsuitable for participation in the study.

2.4 Treatment Regimens

2.4.1 Test Product

Name: HSK3486 injectable emulsion

Dose, route, frequency: 0.4 mg/kg, IV slow injection over 30 [±5] seconds, preoperatively; 1 top up dose (0.2 mg/kg), IV injection over 10 [±2] seconds permitted if needed.

For elderly subjects ≥65 years of age, the dose will be automatically adjusted to a 25% dose reduction. According to the judgment of the investigator, the dose can be further reduced up to 50% of the calculated dose. The administration time should be extended to 1 minute for this population.

For ASA grade 3-4 subjects, the dose can be reduced by 25-50% per investigator discretion. The administration time should be extended to 1 minute for these populations.

For subjects with BMI ≤40 kg/m^2, total body weight (TBW) will be used to determine HSK3486 dose; for subjects with BMI >40 kg/m^2, lean body weight (LBW) will be used to determine HSK3486 dose, and rescue dose. LBW should be calculated using the Janmahasatian formula included below.

The Janmahasatian Formula:

- For males: estimated LBW = (9270 x TBW (kg))/ (6680 + (216 x BMI))
- For females: estimated LBW = (9270 x TBW (kg))/ (8780 + (244 x BMI))

HSK3486 injectable emulsion will be stored at ≤ 25 °C (77°F) away from light and should not be frozen. It should be shaken well before use.

2.4.2 Reference Therapy

Name: Propofol injection

Dose, route, frequency: 2.0 mg/kg, IV slow injection over 30[±5] seconds, preoperatively; 1 top up dose (1 mg/kg), IV injection over 10 [±2] seconds is permitted if needed.

For elderly subjects ≥65 years of age, the dose will be automatically adjusted to a 25% dose reduction. According to the judgment of the investigator, the dose can be further reduced by up to 50% of the calculated dose. The administration time should be extended to 1 minute for this population.

For ASA grade 3-4 subjects, the dose can be reduced by 25-50% per investigator discretion. The administration time should be extended to 1 minute for these populations.

For subjects with BMI ≤40 kg/m^2, TBW will be used to determine propofol dose; for subjects with BMI >40 kg/m^2, LBW will be used to determine propofol dose, and Rescue dose. LBW should be calculated using the Janmahasatian formula included below.

The Janmahasatian Formula:

- For males: estimated LBW = (9270 x TBW (kg))/ (6680 + (216 x BMI))
- For females: estimated LBW = (9270 x TBW (kg))/ (8780 + (244 x BMI))

Propofol will be stored between 4°C and 25°C (40° to 77°F) away from light and should not be frozen. It should be shaken well before use.

The rescue dose is prepared as 100% of the initial calculated dose and administered per propofol guidelines above.

2.5 Sample Size Determination

A total of 399 subjects (266 in HSK3486 0.4/0.2 mg/kg group and 133 in propofol 2.0/1.0 mg/kg group) need to be enrolled 2:1 into this study based on the following assumptions:

- For the primary endpoint, a sample size of 215 subjects will give at least 90% power (providing the primary endpoint is statistically significant) assuming that type I error is 0.025 (1-sided), the success rate of general anesthesia induction of HSK3486 and propofol are both 97%, and non-inferiority margin (NIM) is -8%.

- For the key secondary endpoint of incidence of injection-site pain, a sample size of 365 subjects will give 90% power (providing the primary endpoint is statistically significant) assuming α= 0.015 (2-sided) and the proportion of subjects who meet the endpoint criteria of any injection-site pain are 6.8% and 20.5% for HSK3486 and propofol, respectively.

- For the key secondary composite endpoint, a sample size of 338 subjects will give 90% power (providing the primary endpoint is statistically significant) to the superior testing, assuming α= 0.035 (2-sided), the proportion of subjects with successful induction, maintained desired depth of anesthesia for general elective surgery, without significant cardiac depression within the 15-minute post initiation start of study drug administration observation period and no significant respiratory depression (prior to administration of rocuronium bromide) of HSK3486 and propofol are 82% and 65%, respectively (i.e., 17% treatment effect).

To power statistical testing for all three endpoints at 90% and provide sufficient safety data, it is decided that 399 subjects will be randomized and treated in this study (266 in HSK3486 0.4/0.2 mg/kg group and 133 in propofol 2.0/1.0 mg/kg group).

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied for this study.

- Categorical variables will be summarized using the frequency of subjects/events and percentages. Percentages will be reported to one decimal place.

- Continuous variables will be summarized descriptively, including the number of subjects (n), mean, standard deviation, median, minimum, and maximum.

- The minimum and maximum will be reported to the same level of precision as the original observations. The mean and median will be reported to 1 more significant digit than the precision of the original observations. Standard deviation will be reported to 2 more significant digits than the precision of the original observations.

- *P* values will be reported to 3 decimal places if greater than 0.001. *P* values less than 0.001 will be reported as '<0.001'. Report *P* values and significant levels as 0.05 (with leading zero) rather than .05.

- No preliminary rounding will be performed; rounding will only occur after analysis. To round, consider the digit to the right of the last significant digit: if < 5 then round down, if ≥5 then round up.

- All listings will be sorted in order of treatment group (i.e., HSK3486, propofol), subject identifier, and time of assessment (e.g., visit, date, time, and/or event). Dates in listings will be displayed as YYYY-MM-DD (e.g., 2022-01-22).

- All analysis will be performed using the SAS System version 9.4 or higher.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

4. ANALYSIS POPULATIONS

4.1 Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects who receive any dose of the study drug (HSK3486 or propofol). The FAS will be the primary population used for all efficacy endpoints. Subjects will be analyzed according to the study drug to which they are randomized.

4.2 Per Protocol Set

All subjects from the FAS who have completed the primary efficacy endpoint measurement will be considered for the Per Protocol Set (PPS). Subjects with any important protocol deviations will be reviewed after database lock and prior to study unblinding and may be excluded from PPS if these important deviations will impact the efficacy evaluations. The PPS will be a secondary efficacy population, used only for certain efficacy analyses. Subjects will be analyzed according to the study drug to which they are randomized.

4.3 Safety Set

The Safety Set (SS) will include all randomized subjects who receive any dose of the study drug and have post-dose safety assessment data. The SS will be the primary population used for all safety analyses. Subjects will be analyzed according to the study drug actually administered, regardless of the randomized assignment. Note that only the initial study drug administration will be taken into account, while rescue propofol will be ignored for the purposes of classification of treatment groups in safety analyses.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

The number and percentage of subjects in each of the following categories will be summarized by treatment group and overall:

- Screen Failures (with reason for screen failure)
- Enrolled (signed informed consent)
- Randomized (has randomization record in the Interactive Web Randomization System)
- Received Study Drug
- Completed Primary Efficacy Measurement
- Completed Study
- Discontinued Study (with primary reason for discontinuation)

Disposition information will also be presented in a by-subject listing, including the variables listed above. Randomization information will be presented in a separate by-subject listing, including the randomization date and time, randomization number, and stratification factors)

In addition, the number and percentage of subjects in each analysis population (FAS, PPS, SS) will be summarized by treatment group and overall. The analysis populations will also be presented in a by-subject listing, including the reason for exclusion when appropriate.

5.2 Protocol Deviations

All protocol deviations in this study will be reported in CTMS, as determined by clinical research associates during site monitoring or by medical reviewers. The CTMS can be exported as an Excel listing.

No additional programmatic deviations will be derived. Subjects with any important protocol deviations will be reviewed after database lock and prior to study unblinding and may be excluded from PPS if these important deviations will impact the efficacy evaluations.

The number and percentage of subjects with any protocol deviation will be summarized by treatment group and overall for the SS. The display will be sorted by descending frequency of overall subjects who incurred each deviation. The same summary will be repeated separately for non-important deviations only and for important deviations only. All protocol deviations will also be presented in a by-subject listing, including a column to indicate whether the deviation was considered important or not.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The demographic variables and baseline characteristics listed below will be summarized by treatment group and overall for each of the FAS, PPS, and SS. For categorical variables, the possible responses are listed in parentheses. Demographics and baseline characteristics will also be presented in a by-subject listing.

- Age, in years (from electronic Case Report Form [eCRF]; will not be re-derived)
- Age Stratification Factor (<65 years, ≥65 years)
- Sex (female, male)
- Childbearing Potential (yes, no)
  Note: Denominator for percentages will exclude male subjects.
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, unknown)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported)
- ASA-PS Score (I, II, III, IV, V)
- ASA-PS Stratification Factor (I-II, III-IV)
- Modified Mallampati Score (I, II, III, IV)
- Ever Consumed Alcohol (never, current, former)
- History of Drug Abuse in Last 3 Months (yes, no)
- Any Relevant Anesthesia History (yes, no)
- Post-Op Nausea and Vomiting (yes, no)
- High Fevers with Anesthesia (yes, no)
- History of Malignant Hyperthermia (yes, no)
- Height, in cm
- Weight, in kg
- BMI, in kg/m^2
- BMI Stratification Factor (<35 kg/m^2, ≥35 kg/m^2)

6.1 Medical History

Medical history data for this study consists of log lines of self-reported medical conditions. Each event reported will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 system organ class (SOC) and preferred term (PT). Events will then be summarized by MedDRA SOC and PT, by treatment group and overall for the SS. The display will be sorted by descending frequency of overall subjects who incurred each SOC, and by descending frequency of PT within each SOC.

The medical history data will also be presented in a by-subject listing, including the verbatim investigator description of the relevant medical condition, the coded terms (SOC, PT), start date, end date, and whether the condition is ongoing.

6.2 Surgical History

Surgical history data for this study consists of log lines of self-reported surgical conditions. Each condition reported will be coded using the MedDRA version 25.0 system organ class (SOC) and preferred term (PT). Conditions will then be summarized by MedDRA SOC and PT, by treatment group and overall for the SS. The display will be sorted by descending frequency of overall subjects with a condition reported under each SOC, and by descending frequency of PT within each SOC.

The surgical history data will also be presented in a by-subject listing, including the verbatim investigator description of the relevant condition, the coded terms (SOC, PT), whether the condition is controlled, date of first diagnosis, date of resolution, and whether the subject is taking any ongoing medications for the condition.

6.3 Allergy History

Allergy history data will not be summarized, as the names of the allergic medicines/substances will not be coded. Allergy history data will be presented in a by-subject listing, including the allergen category, name of the allergic medicine/substance, name of the allergy condition, date of first diagnosis, whether the allergy is ongoing, and the severity of symptoms.

6.4 Planned Study Surgery

Details of the planned study surgery will be summarized by treatment group and overall for the SS. The summary will include the number of subjects on whom surgery was performed, whether the subject fasted for 6 hours prior, type of surgery (Abdominal/Pelvic, Cosmetic and Reconstructive, Head and Neck, Orthopedic, or Other), location of surgery (Head and Neck, Upper Extremity, Lower Extremity, Abdomen, Chest/Thorax, Pelvis/Urogenital, Buttocks, Back/Spine, or other). Study surgery data will also be presented in a by-subject listing.

6.5 Prior and Concomitant Medications/Therapies

Protocol-specified medications administered in the operating room (such as fentanyl, rocuronium, midazolam) will not be considered concomitant medications, and will instead be summarized along with the study drug and rescue medications, as described in Section 9.2.

All other medications and therapies recorded will be divided into 4 categories for the purposes of analysis:

- **Prior Medications** will be any medications/supplements/vitamins used before the Day of Surgery, within 1 month before screening.
- **Intraoperative Analgesics** will be any analgesic drugs administered in the operating room, excluding protocol-specified medications (collected via eCRF form "Intraoperative Administration").
- **Concomitant Medications** will be any medications/supplements/vitamins used by the subjects during Day of Surgery and after surgery until the end of the study (Day 8) (collected via eCRF page "Prior and Concomitant Medications"). Note that some medications can be considered both prior and concomitant if initiated before the Day of Surgery and continued on or past the Day of Surgery.
- **Concomitant Therapies** will be any non-medication therapies used by the subjects during Day of Surgery and after surgery until the end of the study (collected via eCRF page "Concomitant Non-Medications Therapy").

All prior & concomitant medications/therapies will be coded to the World Health Organization Global Drug Dictionary (WHODrugG), March 2022 version. For prior and concomitant medications and therapies, the number and percentage of subjects receiving each medication/therapy will be summarized by WHODrug Anatomical Therapeutic Class (ATC) Level 4 Term, by treatment group and overall for the SS.

In order to define concomitant medications, the start and end dates of each medication will be imputed as follows. The date of surgery will be compared to the start and end dates of medication in order to determine whether the medication was concomitant; therefore, times are not relevant for this comparison, and will not be imputed.

Medication Start Dates:

- If the medication start date is completely missing, then impute using the Date of Surgery.
- If the year of medication start is available, but the month and day are missing:
    - If year of medication start is the same as year of Date of Surgery, then impute as the month and day or Date of Surgery.
    - If year of medication start is prior to year of Date of Surgery, then impute as December 31.
    - If year of medication start is after year of Date of Surgery, then impute as January 01.
- If the year and month of medication start are available, but the day is missing:
    - If year/month of medication start is the same as year/month of Date of Surgery then impute as the Date of Surgery.
    - If year/month of medication start is prior to year/month of Date of Surgery then impute as the last day of the month.

- If year/month of month is after year/month of Date of Surgery, then impute as the first day of the month.

Medication Stop Dates:

- If the medication stop date is completely missing or if the medication is ongoing, then impute using the subject's last contact date.
- If the year of medication stop is available, but the month and day are missing:
  - If year of medication stop is the same as year of Date of Surgery, then impute as the subject's last contact date.
  - If year of medication stop is prior to or after year of Date of Surgery, then impute as December 31.
- If the year and month of medication stop are available, but the day is missing:
  - If year/month of medication stop is the same as year/month of Date of Surgery then impute as the subject's last contact date.
  - If year/month of medication stop is prior to or after year/month of Date of Surgery then impute as the last day of the month.

Medication/therapy data will also be presented in four by-subject listings, in accordance with the categories specified above.

7. MEASUREMENTS OF TREATMENT COMPLIANCE

Treatment compliance is not applicable for this protocol. Analyses of study drug exposure, doses, and durations are described in Section 9.2.

8. EFFICACY EVALUATION

8.1 Overview of Efficacy Analysis Issues

8.1.1 Handling of Dropouts or Missing Data

Handling of missing data for each endpoint is discussed in the specific sections for those endpoints.

8.1.2 Multicenter Studies

The success rate of general anesthesia induction in both treatment groups (counts and proportions) will be reported in a separate display by site (out of the FAS population at that site). No inferential statistics will be reported at the site level due to expected small sample sizes. For all other analyses described in this document, data from all sites will be pooled for the purpose of analyses.

8.1.3 Assessment Time Windows

No analysis windowing will be performed.

8.1.4 Multiple Comparisons/Multiplicity

The primary endpoint of non-inferiority to propofol for successful induction of general anesthesia will be tested first. If the null hypothesis fails to be rejected, the testing will stop. If the primary endpoint is statistically significant, then the key secondary endpoints will be tested in parallel using a weighted Bonferroni-Holm step-down approach with weights w_1=0.7 for the proportion of subjects who maintain the desired depth of anesthesia, and w_2=0.3 for the incidence of injection-site pain. In this procedure, the p-values for the secondary endpoints are divided by their respective alpha levels, then the endpoint for which this calculation is smaller (i.e., test $p_j < \alpha_j$ for j=arg min (p_1/0.035, p_2/0.015)) is tested. If the first test is rejected, then the other endpoint will be tested at α=0.05; otherwise testing will stop. This procedure controls the familywise Type I error rate at the overall α=0.05 level for the key secondary endpoints. The analyses for all other secondary endpoints will be descriptive, and any testing that may be done will not be adjusted to maintain Type I error [4].

8.2 Efficacy Variables

Table 8-1 below presents a summary of the study efficacy variables and types of analyses used to evaluate them.

Table 8-1 Efficacy Variables and Analysis Methods

Efficacy Variables	NI[a]	CMH[b]	KM[c]	ANOVA[d]	Descriptive[e]
Primary					
Proportion of Subjects with Successful Induction	X				
Secondary					
Proportion of Subjects Meeting Successful Induction Secondary Composite Endpoint		X			
Proportion of Subjects with Any Injection Site Pain (NRS ≥1)		X			
Proportion of Subjects with Moderate Injection Site Pain (NRS ≥4)		X			
Mean NRS Pain Score				X	
Time to Successful Induction of General Anesthesia			X		
Time to Disappearance of Eyelash Reflex			X		
Proportion of Subjects with Successful Induction of General Anesthesia without Non-optimal Anesthetic Effects		X			
Change of BIS During the Period of Anesthesia Post Study Drug Administration up to 15 Minutes					X
Brice Awareness Questionnaire					X

ANOVA = analysis of variance; ASA-PS = American Society of Anesthesiologists Physical Status; BIS = bispectral index; BMI = body mass index; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; KM = Kaplan Meier; NI = Non-inferiority; NRS = numerical rating scale.

[a] The lower limit of the Farrington-Manning 95% CI for the risk difference will be compared with the NI margin of -8%.

[b] CMH Chi-squared test controlling for the stratification factors in the study randomization.

[c] The median time and its 95% CI will be provided by treatment group using the Kaplan-Meier (KM) method. The KM estimates and 95% CIs at selected time points will also be reported. A Cox regression model controlling for the stratification factors in the study randomization will be used to compare treatment groups.

[d] Mean treatment differences will be compared via ANOVA, controlling for the stratification factors in the study randomization.

[e] Endpoints will be summarized descriptively, with no inferential statistics computed.

8.2.1 Primary Efficacy Endpoint

Success rate of anesthesia induction: The proportion of subjects with successful anesthesia induction in all subjects of the group.

A successful anesthetic induction should meet both of following conditions:

1. Successful induction of anesthesia (MOAA/S ≤ 1) after the dosing of the study drug, and
2. One or less top-up dose required without using any rescue drugs.

Scoring criteria: According to the MOAA/S scale (Appendix 14.3), observation and evaluation will be carried out stepwise, and the cross-level evaluation will not be carried out.

MOAA/S scoring: The subject's name will be called during induction to observe the subject's response to name calling with a normal tone. The subject will be lightly stimulated or shaken after the subject falls asleep, and the subject's response to painful stimulation will be observed. If the subject does not respond to the light stimulus or shaking but responds to painful stimulation (by squeezing the trapezius muscle), the MOAA/S score is 1 and the time from the end of the dosing of the study drug to when MOAA/S is ≤1 will be recorded.

8.2.1.1 Primary Efficacy Analysis

The primary efficacy analysis will compare the success rate of anesthesia induction (defined as the proportion of subjects with MOAA/S ≤ 1 after the dosing of the study drug, with one or less top-up dose required, and without using any rescue drugs) between the HSK3486 group and the propofol group using a difference of proportions (HSK3486 minus propofol) among all subjects in the FAS (all randomized subjects who receive any dose of the study drug), analyzed as randomized. The FAS subjects who are non-evaluable for anesthesia success will be counted as treatment failures in the primary analysis. No additional sensitivity analysis is planned, as minimal missing data is expected for this study design.

The statistical null hypothesis to be tested is:

$$H_0: p_t - p_c \leq \delta$$

With the alternative hypothesis:

$$H_1: p_t - p_c > \delta$$

Where p_t and p_c are the anesthesia success rates for the HSK3486 and propofol arms, respectively, and δ is the NIM. This hypothesis will be tested at the 1-sided α=0.025 level.

Success rate of general anesthesia induction in both groups and rate difference between groups and its 95% confidence interval (CI) will be estimated by Farrington-Manning method in the FAS. The lower limit of 95% CI of rate difference will be compared with the NIM of -8% to confirm the establishment of non-inferiority. The FAS subjects who are non-evaluable for anesthesia success will be counted as treatment failures in the primary analysis.

In addition, the primary endpoint analysis described above will be repeated using the PPS to test the robustness of the primary endpoint when removing subjects with important protocol deviations.

Grades and times from all MOAA/S assessments will also be presented in a by-subject listing, including the datetime of induction of anesthesia, and the datetime of loss of eyelash reflex.

8.2.1.2 Justification of the Non-inferiority Margin

The NIM for this study is based on the expectation that the active control, propofol, and HSK3486 will both perform similarly to historical evidence, achieving ≥97% efficacy for induction of general anesthesia, defined as achieving MOAA/S ≤1 after 1 dose, with no more than 1 top-up dose if needed. Since the expected response rates are ≥97%, there is little concern for loss of assay sensitivity (i.e., loss of efficacy) from historical performance or loss of the "constancy assumption." Furthermore, the exercise of attempting to identify the M1 based on historical literature would lead to an unacceptably large margin, then applying clinical judgement to establish the M2 (often 50% of the M1) (Food and Drug Administration Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness, 2016) would lead to a NIM >10%, which permits too much uncertainty to be acceptable or useful. Using a NIM of 8% is clinically relevant and meaningful for this indication.

8.2.2 Key Secondary Efficacy Analyses

8.2.2.1 Composite Endpoint to Evaluate Desired Depth of Anesthesia

Successfully induced subjects treated with HSK3486 compared to propofol who maintain the desired depth of anesthesia for general elective surgery, and without significant cardiac and respiratory depression within 15 minutes post initiation of start of study drug administration, or up to the start of second tracheal intubation attempt if it is a difficult condition and not beyond 15 minutes post initiation start study drug initiation are defined as meeting all of the following criteria:

a) Desired depth of anesthesia for general elective surgery is defined if all following criteria are met:
   - No clinical signs of inadequate depth of anesthesia, such as lacrimation, movement, vomiting, coughing, laryngospasm, bucking, swallowing reflex or bronchospasm etc.
   - No blood pressure (SBP, DBP, or MAP) increases more than 20% from baseline in response to any major operational procedures or noxious stimulus in defined period.
   - Subjects maintain desired depth of anesthesia for general elective surgery with BIS as an objective assessment (after reaching the initial lowest value, BIS remains sustainable level at not more than 60)

     Note: Target BIS 40 to 60 for general anesthesia (see Appendix 14.4).

   The BIS sustainable level at not more than 60 is defined as not more than 1 episode with BIS value observed >60 after reaching initial lowest value, in defined period.

b) No significant respiratory depression, such as apnea, prior to the administration of rocuronium bromide.

Note: For the composite endpoint, respiratory depression includes apnea, defined as absence of thoracic movement lasting >30 seconds, or hypoxia, defined as SpO2 <90% lasting >30 seconds, or life-threatening apnea or hypoxia requiring immediate intervention.

c) No significant cardiac depression indicated by blood pressure decrease that requires intervention, i.e., vasopressors and/or IV fluid resuscitation.

Note: For the composite endpoint, cardiac depression is defined as SBP <90 mmHg lasting >2 minutes plus requiring medical intervention such as inotropes, vasopressors, or IV fluid resuscitation, or life-threatening hypotension requiring immediate intervention.

The proportion of FAS subjects meeting the composite endpoint criteria for the proportion of successfully induced subjects will be calculated for both groups. The FAS subjects who are non-evaluable for anesthesia success will be counted as treatment failures in the secondary composite endpoint. The difference between groups will be calculated as the difference in proportions (HSK3486 minus propofol). The same analysis will be repeated for the PPS subjects.

The 95% CI will also be reported. The p-value for comparison between groups will be obtained based on the Cochran-Mantel-Haenszel (CMH) test using the stratification factors American Society of Anesthesiologists Physical Status (ASA-PS; I-II and III-IV), age (<65 and ≥65 years), and Body Mass Index (BMI <35 and ≥35 kg/m^2).

8.2.2.2 Injection-site Pain

Injection-site pain is evaluated verbally during study drug administration using the NRS, ranging from 0 (no pain) to 10 (worse imaginable pain) (see Appendix 14.5). Recollection of pain during study drug administration will be assessed in the PACU once the subject is awake and oriented.

During the baseline visit, the subject will be oriented to the NRS for the evaluation of injection-site pain. Upon initiation of study drug administration, the investigator will immediately ask the subject to rate his or her pain. As a general guidance, the evaluation will be done multiple times with the first evaluation occurring typically within 15 seconds after initiation of study drug administration and monitored until successful induction (MOAA/S ≤1). Related information such as the occurrence and severity of injection pain (NRS 0-10) will be recorded. The maximum (highest value) injection-site pain will be recorded. Pain during the injection of study drug in the hand/arm will be distinguished from unrelated puncture pain from the IV site or due to adhesive tape at the IV site. When injection pain occurs, the subject's pain will be graded verbally using the NRS (0-10) and will be recorded. The subject will be asked to rate the pain on a scale from 0, which is no pain, to 10, which is the worst pain imaginable. The subject will point to the number on the scale that best represents the intensity of the pain now. In the PACU, once the subject is alert and oriented, the NRS for recall of pain at time of study drug administration will be repeated.

During induction of anesthesia, the maximum NRS pain score collected will be used for all analysis detailed below. If no NRS pain score is collected during this time, the NRS recall pain score collected in the PACU will be used for analysis. All injection site pain analyses will be based on the FAS and repeated in the PPS.

The proportion of subjects with any injection-site pain (NRS ≥1) will be analyzed using the same CMH methods described in Section 8.2.2.1 for the composite secondary endpoint.

The proportion of subjects with moderate injection-site pain (NRS ≥4) will be analyzed using the same CMH methods described in Section 8.2.2.1 for the composite secondary endpoint.

The mean injection-site NRS pain score will be analyzed using an analysis of variance (ANOVA). The model will contain treatment as a fixed effect, with the stratification factors in the study randomization included as factors. Descriptive statistics will be provided for the NRS pain scores by treatment group, along with the least squares (LS) means, standard errors, 95% CIs by treatment group, and LS means, standard errors, and 95% CIs for the difference between treatment groups. The difference between groups will be calculated as the difference in LS means (HSK3486 minus propofol).

All injection-site NRS pain scores will also be presented in a by-subject listing.

8.2.3 Other Secondary Efficacy Endpoints

8.2.3.1 Time to Successful Anesthesia Induction

The time to successful anesthesia induction is evaluated during the induction period and is defined as the time from the start of the first administration of the study drug to the time when MOAA/S ≤1. If anesthesia induction requires rescue medication, the subject will be counted as an anesthesia induction failure at the time of the rescue medication. If the subject dies prior to successful anesthesia induction, the subject will be censored at the time of death. The median and its 95% CI of time to successful induction of general anesthesia will be provided by treatment group using the KM method. The KM estimates and 95% CIs at selected time points will also be reported.

In addition, a Cox proportional hazards model will be utilized to compare the time to successful anesthesia between treatment groups. The model will control for the stratification factors in the study randomization. The hazard ratio (HSK3486/propofol) will be reported, along with the 95% CI for the hazard ratio, and the p-value to test if the hazard ratio is equal to 1.

The time to successful anesthesia induction will also be displayed in a KM plot by treatment group.

8.2.3.2 Time to Loss of Eyelash Reflex

The time to loss of eyelash reflex is evaluated during the induction period and defined as the time from the start of the first administration of the study drug to the time when eyelash reflex is lost. Analyses will use the same KM and Cox methods described for the time to successful anesthesia induction in Section 8.2.3.1. If rescue medication is required, the subject will be

counted as a failure for time to loss of eyelash reflex at the time of the rescue medication. If the subject dies prior to successful anesthesia induction, the subject will be censored at the time of death.

The time to loss of eyelash reflex will also be displayed in a KM plot by treatment group.

8.2.3.3 Successful Induction without Non-optimal Anesthetic Effects

Non-optimal anesthetic effects are defined as those subjects experiencing any of the following:

a) Any clinical symptoms in response to tracheal intubation, such as lacrimation, movement, vomiting, coughing, laryngospasm, bucking, swallowing reflex or bronchospasm etc.

b) An event where blood pressure (SBP, DBP, or MAP) increases more than 20% from baseline in response to any major operational procedures or noxious stimulus in defined period.

c) Subjects do not maintain desired depth of anesthesia for general elective surgery with BIS as an objective assessment (i.e., after reaching initial lowest value, BIS sustainable level at more than 60).

d) Significant respiratory depression.

e) Cardiac depression indicated by blood pressure decreases that requires intervention (i.e., vasopressors and/or IV fluid resuscitation).

The proportion of subjects with successful induction without non-optimal anesthetic effects within 15 minutes post initiation of administration of study drugs will be analyzed using the same CMH methods described for the secondary composite efficacy endpoint in Section 8.2.2.1.

8.2.3.4 Changes in the Bispectral Index

From the start of study drug administration to the end of the surgery, the subjects are continuously monitored for their BIS, which is recorded at specified time points to understand the changes in the BIS of the subjects throughout the entire anesthesia period (see Appendix 14.4) for BIS guidance). The BIS is measured prior to midazolam administration, prior to study drug administration, every 30 (±10) seconds from study drug administration until 5 minutes post study drug administration, and every 2 minutes (±30 seconds) from 5 minutes post study drug administration until 30 minutes post study drug administration.

The BIS values and changes from baseline will be summarized descriptively by treatment group for all timepoints collected prior to administration of rescue medication. The average of 3 BIS measurements collected immediately prior to study drug administration (after midazolam administration) will be considered the baseline value for analysis purposes. Any values collected within the appropriate time windows will be included in analysis. No timepoint windowing will be performed. Values collected outside of the appropriate time windows will be excluded from analysis. If multiple measurements are collected within any given time window for post-baseline timepoints, the average measurement within said window will be used for analysis.

The BIS values will also be presented in a by-subject listing, including a column to indicate which values were collected after administration of rescue medication Additionally, figures will be constructed providing the BIS actual values and mean change from baseline over time per treatment arm.

8.2.3.5 Brice Awareness Questionnaire

Recall of awareness during surgery, assessed postoperatively, will be evaluated using the Brice Awareness Questionnaire (see Appendix 14.6). The questionnaire will be administered in the PACU once the subject is alert and oriented. The questionnaire is repeated at Day 8. The results of each question will be summarized descriptively by treatment group and timepoint, for all timepoints collected prior to administration of rescue medication.

The Brice Awareness Questionnaire scores will also be presented in a by-subject listing.

8.3 Examination of Subgroups

The primary endpoint for success rate of general anesthesia induction will be repeated for each of the following subgroups in the FAS:

- Age Stratification Factor (<65 years, ≥65 years)
- ASA-PS Stratification Factor (I-II, III-IV)
- BMI Stratification Factor (<35 kg/m^2, ≥35 kg/m^2)
- Sex (female, male)
- Race (Asian, Black or African American, White, or Other)
- Surgery Type (abdominal/pelvic, cosmetic and reconstructive, head and neck, orthopedic, or other)

9. SAFETY EVALUATION

9.1 Overview of Safety Analysis Methods

The following assessments will be used to evaluate the safety of HSK3486 injectable emulsion in adults undergoing elective surgery:

- AEs
- Clinical laboratory evaluations
- Vital signs
- Physical examinations
- 12-lead ECG and 3-lead/5-lead ECG
- Administration of additional medication or any interventions including medical interventions

All safety analyses will be performed using the SS, according to the study drug actually administered, regardless of the randomized assignment. Note that only the initial study drug administration will be taken into account, while rescue propofol will be ignored for the purposes of classification of treatment groups in safety analyses. All safety endpoints will be summarized by treatment group (and by timepoint as appropriate). Listings will also be produced for all safety endpoints.

9.2 Extent of Exposure

The details of each protocol-specified exposure administered in the operating room will be summarized by treatment group and overall. Table 9-1 below lists the specific exposures that will each be summarized separately, as well as which components will be summarized for each.

Table 9-1 Exposure Variables

Infusion Type	Categorical Variables	Continuous Variables
Maintenance IV Solution	▪ Number of Subjects ▪ Type of Solution	
Midazolam	▪ Number of Subjects	▪ Duration of Infusion ▪ Planned Dose ▪ Dose Administered
Fentanyl	▪ Number of Subjects	▪ Duration of Infusion ▪ Planned Dose ▪ Dose Administered
Oxygen	▪ Number of Subjects	▪ Oxygen Flow Rate
Initial Study Drug	▪ Number of Subjects ▪ Anatomical Location ▪ Laterality	▪ Duration of Infusion ▪ Dose Administered
Top-Up Dose	▪ Number of Subjects ▪ Anatomical Location ▪ Laterality	▪ Duration of Infusion ▪ Dose Administered
Rescue Medication	▪ Number of Subjects	▪ Duration of Infusion ▪ Dose Administered

Rocuronium	▪ Number of Subjects	▪ Duration of Infusion ▪ Planned Dose ▪ Dose Administered
Sevoflurane	▪ Number of Subjects	▪ Duration of Administration ▪ Initial Concentration

For continuous variables, the treatment difference will be analyzed using an ANOVA, controlling for the stratification factors in the study randomization. Descriptive statistics will be provided by treatment group, along with the least squares (LS) means, standard errors, 95% CIs by treatment group, and LS means, standard errors, and 95% CIs for the difference between treatment groups. The difference between groups will be calculated as the difference in LS means (HSK3486 minus propofol).

For categorical variables, the count and percentage of subjects in each category will be presented.

In addition, to assess the protocol-specified dose adjustments, the summaries of initial study drug, top-up dose, and rescue medication will be repeated for the following subgroups:

- Age (<65 years, ≥65 years)
- ASA-PS (I-II, III-IV)
- BMI (<40 kg/m^2, ≥40 kg/m^2)

The timing and dosing information for all exposures listed above will also be presented in a by-subject listing.

9.3 Adverse Events

Protocol-specific adverse event definitions and classifications are briefly outlined below and are detailed in Appendix 14.10. An AE is defined as any untoward medical occurrence in a study subject, regardless of whether or not considered drug related.

In this study, only those AEs classified as treatment emergent adverse events (TEAEs) will be included in summary tables. Per protocol, a TEAE is defined as an AE that occurs after the subject starts treatment with the Investigational Medicinal Products (IMP). The date and time of onset for each AE will be compared to the date and time of initial study drug administration (HSK3486 or propofol) to determine whether the AE is treatment emergent. Any AE with onset date and time on or after the date and time of initial study drug administration will be considered a TEAE.

Missing and partial AE onset dates and times will be imputed for the purposes of defining TEAEs as follows:

- If the AE onset date and time are completely missing, then impute using the date and time of initial study drug administration.
- If the year of AE onset is available, but the month, day, and time are missing:
    - If year of onset is the same as year of initial study drug administration, then impute as the month, day, and time of initial study drug administration.

  - If year of onset is prior to year of initial study drug administration, then impute as December 31 at 11:59:59pm.
  - If year of onset is after year of initial study drug administration, then impute as January 01 at 12:00:01am.

- If the year and month of AE onset are available, but the day and time are missing:
  - If year/month of onset is the same as year/month of initial study drug administration, then impute as the day and time of initial study drug administration.
  - If year/month of onset is prior to year/month of initial study drug administration, then impute as the last day of the month at 11:59:59pm.
  - If year/month of onset is after year/month of initial study drug administration, then impute as the first day of the month at 12:00:01am.
- If the date of AE onset is available, but the time is completely missing:
  - If date of onset is the same as date of initial study drug administration, then impute as the time of initial study drug administration.
  - If date of onset is prior to date of initial study drug administration, then impute as 11:59:59pm.
  - If date of onset is after date of initial study drug administration, then impute as 12:00:01am.
- If the date and hour of AE onset are available, but the minutes are missing:
  - If date/hour of onset is the same as date/hour of initial study drug administration, then impute as the time of initial study drug administration.
  - If date/hour of onset is prior to date/hour of initial study drug administration, then impute minutes:seconds as :59:59.
  - If date/hour of onset is after date/hour of initial study drug administration, then impute minutes:seconds as 00:01.
- If the date, hour, and minute of AE onset are available, but the seconds are missing:
  - If date/hour/minute of onset is the same as date/hour/minute of initial study drug administration, then impute as the time of initial study drug administration.
  - If date/hour/minute of onset is prior to date/hour/minute of initial study drug administration, then impute seconds as :59.
  - If date/hour/minute of onset is after date/hour/minute of initial study drug administration, then impute seconds as :01.

Note that AE stop dates/times will not be imputed since the stop date does not affect the determination of treatment emergence. Note also that any listings of AEs will display onset dates as collected in the EDC system but will not display imputed dates.

All AEs will be coded according to the MedDRA version 25.0 and graded for severity according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

A tabular overview of adverse events will be presented by treatment group and overall, including a row for each of the following categories:

- Number of subjects with any TEAE
- Total number of TEAEs
- Number of subjects with any serious TEAE
- Total number of serious TEAEs
- Number of subjects with any TEAE of CTCAE grade 2 or higher
- Total number of TEAEs of CTCAE grade 2 or higher
- Number of subjects with any AESIs
- Total number of AESIs
- Number of subjects with any TEAE related to study drug
- Total number of TEAEs related to study drug
- Number of subjects with any TEAE leading to treatment discontinuation
- Number of subjects with any TEAE leading to study discontinuation
- Number of subjects with any TEAE leading to death

In addition, the incidence of TEAEs will be summarized by treatment group and overall, for the following categories of AEs:

- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- TEAEs related to study drug by SOC and PT
- Serious TEAEs related to study drug by SOC and PT
- TEAEs of CTCAE grade 2 or higher by SOC, PT
- TEAEs leading to treatment discontinuation by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT
- TEAEs by SOC, PT, and maximum severity
- TEAEs by SOC, PT, and maximum relationship to study drug
- Common TEAEs (≥2% of subjects in any treatment group) by PT
- TEAEs of special interest (hypoxemia, bradycardia, hypotension) by PT
- Abuse-related TEAEs of interest by PT

If a subject experiences more than one episode of an AE, the subject will be counted once for the given PT. If a subject has more than 1 AE in a SOC, the subject will be counted only once in that SOC. The summary tables will include incidence estimates for overall SOC, as well as for PTs within each SOC. The displays will be sorted by descending frequency of overall subjects with an AE reported under each SOC, and by descending frequency of PT within each SOC.

The AE data will also be presented in by-subject listings. Separate by-subject listings will be generated for each of the following categories of AEs, with a column to indicate whether each AE was treatment emergent:

- All AEs
- Serious AEs (SAEs)
- AEs leading to treatment discontinuation
- AEs leading to study discontinuation
- AEs leading to death
- AEs of special interest (AESIs)

9.4 Abuse-related AEsDeaths, Serious Adverse Events, and Other Significant Adverse Events

Deaths, SAEs, AESIs and abuse-related AEs of interest will be summarized and listed as described in Section 9.3. The type of events that will fall into these categories are described in more detail below.

In addition, any potential blood compatibility-related AEs will be summarized in the same manner.

9.4.1 Serious Adverse Events

An SAE is any AE occurring at any dose that meets 1 or more of the following criteria:

- Results in death
- Is life-threatening
- Requires subject hospitalization or prolongation of an existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Results in an important medical event.

9.4.2 Adverse Events of Special Interest

The AESIs due to pharmacological effect of an anesthetic agent include hypoxemia, bradycardia, severe hypotension, allergy/anaphylaxis, cardiac arrhythmia and QTc prolongation which are defined as follows:

- Hypoxemia due to respiratory depression is defined as SpO2 <90% with duration of >30 seconds. Hypoxemia is evaluated from the initial dose of study drug until the subject leaves the operating room. Those occurring within 15 minutes from the end of the last dose of study drug will be categorized as drug related unless an obvious cause is ascertained.

- Bradycardia is defined as a heart rate of <45 beats/minute that lasts >30 seconds requires intervention (treatment). Bradycardia is evaluated from the initial dose of study drug until the subject leaves the operating room. Those occurring within 15 minutes from the end of the last dose of study drug will be categorized as drug related unless an obvious cause is ascertained.

- Severe hypotension is defined as an SBP <90 mmHg that lasts >2 minutes requiring treatment. Severe hypotension is evaluated from the initial dose of study drug until the subject leaves the operating room. Those occurring within 15 minutes from the end of the last dose of study drug will be categorized as drug related unless an obvious cause is ascertained.
- Allergy/anaphylaxis may include angioedema, bronchospasm, erythema, and hypotension. Allergy/anaphylaxis is evaluated from the initial dose of study drug until visit Day 2.
- Cardiac arrhythmia is any rhythm not arising from the sinus node (atrial fibrillation, atrial flutter, Torsade de pointes). Cardiac arrythmia is evaluated from the initial dose of study drug until visit Day 2.
- QTc prolongation: QTc intervals of $\geq$ 450 ms in males and $\geq$ 470 ms in females occurring within 15 minutes from the end of the last dose of study drug are considered QTc prolongation. Patients who reach an absolute QT interval of more than 500 ms upon QTc correction for rate should be reassessed, and immediate action should be taken to correct any possible concomitant risk factors [2, 3].

AESI start time, end time (both should be accurate to the second and the duration should be calculated) and treatment measures should be recorded (if any).

Note: Vital sign values out of range (or suspected as being erroneous) should be confirmed with a second measurement before recording as the confirmed value.

Note: Since injection-site pain has been recorded and analyzed in the efficacy endpoints, it is no longer recorded in the Safety endpoints (see section 2.1.2) for injection-site pain evaluation.

Note: The list and definitions of AESIs as modified in protocol version 5.0 will be implemented retroactively to include applicable events for all study subjects. The list and definitions were modified primarily based on the background rates of adverse events in previously completed studies and include those events that were uncommon, rare, or very rare (> 1/1,000; >1/10,000; <1/10,000 respectively) that are clinically significant.

9.4.3 Abuse-Related Adverse Events of Interest

Both HSK3486 and propofol cross the blood-brain barrier and have central nervous system (CNS) effects, which are the intended pharmacological action of the drug (e.g., sedation, anesthesia/unconsciousness). Any untoward change from baseline that is not the intended or desired effect of the study drug will be reported as an AE. Investigators and site personnel will monitor for and report abuse-related AEs of interest, which include: euphoria, dissociative effects, hallucinations, psychosis, changes in mood, impaired cognition, attention and psychomotor effects, and inappropriate affect; overdoses, abuse, and misuse.

9.5 Clinical Laboratory Evaluations

The laboratory analytes to be assessed in this study are listed in Appendix 14.11. Blood draws for central laboratory evaluations are collected at Screening and at 6 (±2) hours post administration of study drug. Summaries of actual values and the changes from baseline to each time point will be presented by treatment group and overall for all quantitative laboratory parameters (e.g., white blood cell count, lymphocyte count). Summary laboratory values will be reported using the International System of Units only. Only data from the central laboratory will be summarized. Data collected from local labs will be utilized to address eligibility concerns and otherwise at investigators' discretion but will not be included in summaries.

Baseline is defined as the last measurement taken on or prior to the initial study drug administration. Note that the Day 1 assessment can be included in the evaluation of baseline if the sample is drawn prior to dosing. Otherwise, the baseline value would come from the screening assessment.

Quantitative laboratory test results will be classified by the central lab according to whether the value was below (L), within (N), or above (H) the laboratory parameter reference range. A summary of treatment-emergent shifts will compare the baseline L/N/H classification for each laboratory test to the highest and/or lowest L/N/H classification obtained after initial administration of study drug.

Qualitative laboratory test results will be reported using categories such as Abnormal/Normal, Positive/Negative, etc. A summary of treatment-emergent shifts will compare the baseline classification for each laboratory test to the worst classification obtained after initial administration of study drug.

Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries but will be listed.

All laboratory evaluation data will be presented in by-subject listings, separated into the following 4 groups of analytes:

- Chemistry (including Glycosylated Hemoglobin and Hormones)
- Hematology
- Urinalysis

- Pregnancy Test Results

9.6 Vital Signs, Physical Findings, and Other Observations Related to Safety

9.6.1 Vital Signs

The vital signs collected in this study include RR, HR, SpO_2, Temp, SBP, DBP, and MAP. Vital signs are assessed at screening, at Day 1 preinduction, continuously during the induction of general anesthesia, as well as 6 (±2) hours and 24 (±6) hours post administration of study drug. Summaries of actual values and the changes from baseline to each time point will be presented by treatment group and overall.

Baseline is defined as the last measurement taken on or prior to the initial study drug administration. Note that the Day 1 assessment will be included in the evaluation of baseline if the assessment is performed prior to dosing. Otherwise, the baseline value will come from the screening assessment.

The number of subjects with blood pressure (SBP, DBP, or MAP) with ≥30% decrease from baseline will be summarized for each post-baseline time point by treatment group and overall.

Vital sign data will also be presented in a by-subject listing. Mean change from baseline over time for vital sign data will also be presented in a figure for 1) baseline to 30 minutes on Day 1 and 2) baseline to 6 hours and 24 hours.

9.6.2 Physical Examinations

Physical examinations include skin, head, neck, cardiovascular system, respiratory system, gastrointestinal system, psychological and neurological system, and musculoskeletal system. These assessments will be completed at screening, and a focused physical exam will be repeated as needed to assess AEs. Physical examination data will not be tabulated but will be presented in a by-subject listing.

9.6.3 12-lead ECG and 3-lead/5-lead ECG

The 12-Lead ECG parameters collected in this study include PR, QRS, QT, QTcF, and RR. These measurements are collected via 12-Lead ECG at screening, at 6 hours (±2 hours) post study drug administration, and as clinically indicated. Summaries of actual values and the changes from baseline to each time point will be presented by treatment group and overall.

In addition, 3-Lead or 5-Lead ECGs are monitored continuously during the surgery. Using the normality assessment from all 12-Lead, 3-Lead, and 5-Lead ECGs collected during the course of the study, a summary of treatment-emergent shifts will compare the baseline ECG normality assessment to the worst ECG normality assessment obtained after initial administration of study drug. Normality assessments will be categorized by the PIs at each site as normal, abnormal clinically significant, or abnormal not clinically significant.

All 12-Lead, 3-Lead, and 5-Lead ECG data will also be presented in a by-subject listing.

10. OTHER ANALYSES

Not applicable.

11. INTERIM ANALYSES AND DATA MONITORING

No formal interim analyses will be conducted.

An independent data monitoring committee (DMC) will be involved in the conduct of the study to ensure the safety of all subjects who have been administered study drug. The DMC will consist of 3 unblinded members: 2 anesthesiologists with appropriate clinical expertise and 1 statistician. The DMC will review all available unblinded safety information at approximately 30% enrollment. Additionally, enrollment will be immediately stopped after one death during the study where a clear alternative cause is not readily apparent (i.e., deemed definitely or likely related to study drug); after 4 (4/399 [1%]) non-fatal serious adverse events (SAEs) where a clear alternative cause is not readily apparent (i.e., deemed definitely or likely related to study drug); or after 8 (8/399 [2%]) severe AEs of special interest (AESIs; Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or 4) of severe hypotension, bradycardia, hypoxia due to respiratory depression, or QTc prolongation occurring within 15 minutes of study drug administration, where a clear alternative cause is not readily apparent (i.e., deemed definitely or likely related to study drug), and lasting ≥10 minute duration despite routine interventions. AESIs of allergy/anaphylaxis or cardiac arrhythmia occurring from the initial dose of study drug until Day 2 where a clear alternative cause is not readily apparent will be evaluated as part of the stopping criteria. If these criteria are met, enrollment will be temporarily suspended while the DMC convenes to review all available unblinded data. Based on recommendations from the DMC, the Sponsor can terminate the study or resume enrollment if measures can be taken to effectively address (i.e., mitigate) the risk to safely continue the study, such as revising inclusion/exclusion criteria or study procedures. The final decision to suspend enrollment or proceed will be made by the Sponsor after consultation with the DMC members and taking into consideration their recommendations. Conduct of the DMC is described in the DMC Charter.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

In order to avoid using negative numbers in the analysis, the definition of time to successful anesthesia induction has been changed from the end of the first administration of the study drug to the start of the first administration of the study drug. The ending point of the measurement, MOAA/S ≤1, remains unchanged.

A corresponding change has been made in the definition of the time to loss of eyelash reflex. It will be measured from the start of the first administration of the study drug, instead of the end of the administration.

An additional summary table will be added to the analysis, containing any potential blood compatibility-related AEs. The PT terms of the AEs will be summarized in the table in a similar manner to the AESI output.

13. REFERENCES

1. Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness. Food and Drug Administration, November 2016.

2. Kishida H, Cole JS, Surawicz B. Negative U wave: a highly specific but poorly understood sign of heart disease. Am J Cardiol. 1982 Jun;49(8):2030-6. doi: 10.1016/0002-9149(82)90225-9. PMID: 6211085.

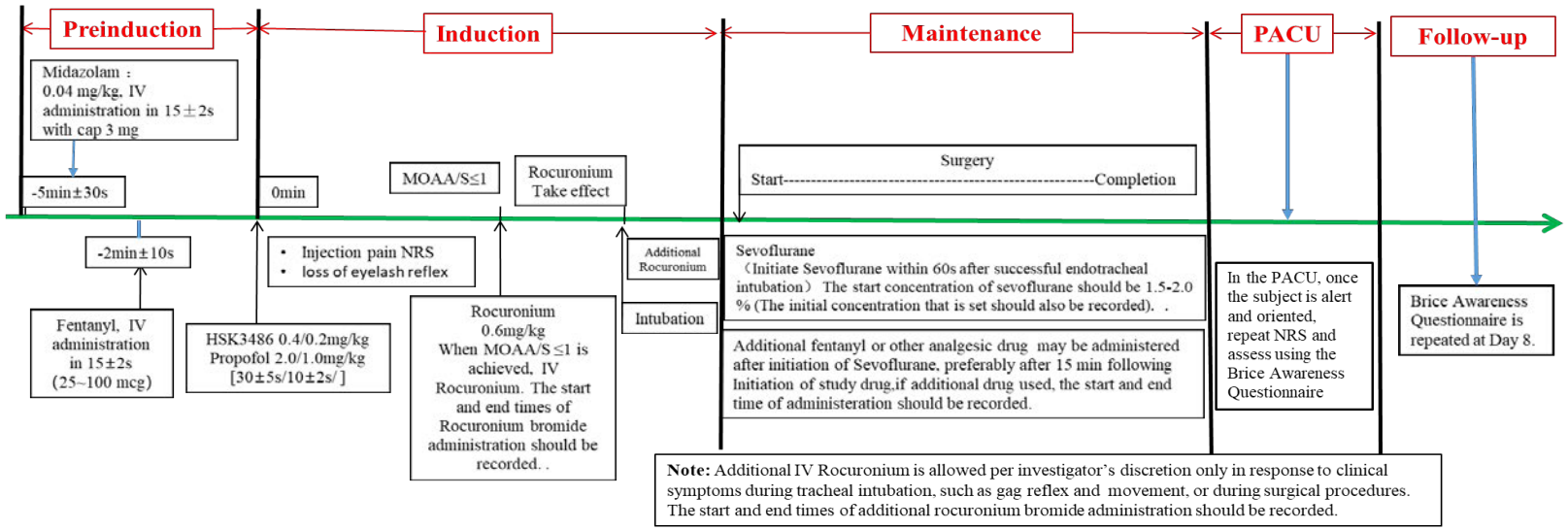
3. Document E 14: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Non-Antiarrhythmic Drugs, Rockville, Md: US Department of Health and Human Services, Food and Drug Administration; October 2005.

4. Zhang J, Quan H, Nh J, Stepanavage ME. Some Statistical Methods for Multiple Endpoints in Clinical Trials. Elsevier Science Inc. 1997.

14. APPENDICES

14.1 Study Flow Chart

- **MOAA/S :**The MOAA/S will be evaluated every 30 [±10] seconds after end of study drug administration until MOAA/S ≤1 is reached. If MOAA/S is still >1 at 1 minute [±10] seconds post end of study drug administration, a top-up dose of 50% of the initial dose of study drug (either HSK3486 0.2 mg/kg or Propofol 1 mg/kg depending on treatment group) will be given to the subject (IV injection time: 10 [±2] seconds. Start and end times of top-up dose administration will be recorded. The MOAA/S will be evaluated every 30 [±10] seconds post end of the top-up dose administration. If MOAA/S is still >1 at 2 minutes [±10]seconds post end of the top-up dose administration, then the rescue drug, propofol, will be given (in both treatment groups). The MOAA/S will be evaluated every 30 [±10] seconds post end of rescue drug administration until MOAA/S ≤1 is reached.
- **Evaluation of eyelash reflex**: Post the end of initial study drug administration, the eyelash reflex will be evaluated every 30 [±10] seconds until loss of eyelash reflex. If there is a top-up dose, eyelash reflex will be evaluated every 30 [±10] seconds post end of the top-up dose administration until loss of eyelash reflex. If there is rescue drug given, eyelash reflex will be evaluated every 30 [±10] seconds post end of the rescue drug until loss of eyelash reflex. The time of loss of eyelash reflex should be recorded.
- **Evaluation of injection pain**: Injection-site pain is evaluated verbally by Numeric Rating Scale .Upon initiation of study drug injection, the investigator should immediately ask the subject to rate his or her pain at injection-site. As a general guidance, the evaluation should be done multiple times with the first evaluation occurring typically within 15 seconds after initiation of study drug injection and monitored until successful induction (MOAA/S ≤1). Related information, such as the occurrence and severity of injection pain (NRS 0-10), shall be recorded. The maximum (highest value) injection-site pain will be recorded in EDC as NRS.
- **BIS:** Preinduction period:Record the three most recent BIS values preceding Midazolam administration, Induction period of general anesthesia& Maintenance period of general anesthesia:BIS will be monitored continuously; record baseline BIS value prior to administering study drug. BIS values will be collected at the following timepoints post start of initial study drug administration: every 30 [±10] seconds for 5 minutes, and then every 2 minutes [±30] seconds for 30 minutes.
- **Vital signs (HR, RR, SpO_2, SBP, DBP, MAP):**Baseline value will be the measurement immediately prior to initiation of study drug administration. During the induction of general anesthesia monitor vital signs continuously.HR, RR,SBP, DBP, MAP should be recorded once every 2 minutes [±30] seconds ,SpO_2 value should be recorded once every 1 minutes from the start of study drug administration (for every time point) for 30 minutes post start of study drug administration.
- **Clinical symptoms and/or signs for inadequate depth of anesthesia**:During endotracheal intubation, evaluate and record clinical symptoms and/or signs for inadequate depth of anesthesia, such as lacrimation, movement, vomiting reflection, coughing, laryngospasm, bucking, swallowing reflex and/or bronchospasm, etc. for at least 15 minutes post start of study drug injection.
- **Endotracheal intubation:** Intubate subject once neuromuscular blockade has taken effect; if using twitch monitor, intubate once no twitches are noted. The start and end times of first and subsequent intubation attempts should be recorded.
- **Respiratory and cardiac depression**:Between start of study drug administration and prior to the administration of Rocuronium bromide, evaluate and record respiratory depression. Within15 minutes post start of study drug administration, evaluate and record cardiac depression.
- **3-lead or 5-lead and 12-lead ECG:** Monitor and record ECG according to Study Procedures.
- **Use of Sevoflurane:** Sevoflurane (an inhalation anesthetic agent) will be used for maintenance of general anesthesia. Initiate Sevoflurane within 60 seconds after successful endotracheal intubation. The start concentration of Sevoflurane should be 1.5-2.0 % ((The initial concentration that is set and start time of administration should be recorded).



14.2 Schedule of Assessments

	Screening	**Study treatment**	**Follow-up visits**			**Phone contact**
	Day -13 to Day 1[p] (prior to surgery)	**Day 1 (day of surgery)**	**6-hour and 24 hour (Day 2) [i] follow-up after study drug administration**			**Day 8 1 week (±2 days) post day of surgery**
			PACU	6 (±2) hours	24 (±6) hours (Day 2)	
Written informed consent	X					
Inclusion/exclusion criteria	X	Verify				
Demographics	X					
Medical history	X					
Modified Mallampati score assessment	X					
Physical exam [a]	X					
Vital signs	X	X [j]		X [k]	X [k]	
Height, weight, and BMI	X	X				
12-lead ECG	X	X [f]		X [f]		
Clinical laboratory tests	X [lp]			X [k]		
Serum pregnancy test (females)	X [lp]					
Urine pregnancy test (females)		X [l]				
Instruct subject to fast minimum of 6 hours before surgery[o]	X					
Confirm preoperative readiness [b]		X				

	Screening	**Study treatment**	**Follow-up visits**			**Phone contact**
	Day -13 to Day 1[p] (prior to surgery)	**Day 1 (day of surgery)**	**6-hour and 24 hour (Day 2) [i] follow-up after study drug administration**			**Day 8 1 week (±2 days) post day of surgery**
			PACU	6 (±2) hours	24 (±6) hours (Day 2)	
Randomization		X				
Start maintenance IV infusion (NS, LR, or 5% dextrose)		X				
Administration of preinduction IV midazolam		X				
Administration of preinduction IV fentanyl		X				
Administer oxygen via face mask (⩾4 L/min)		X				
Administration of study drug [c]		X				
Pain NRS [d]		X	X			
Monitor BIS [e]		X				
Monitor eyelash reflex		X				
Monitor MOAA/S		X				
Monitor 3-lead or 5-lead ECG continuously [f]		X				
Administration of IV rocuronium [g]		X				
Endotracheal intubation [g]		X				

	Screening	Study treatment	Follow-up visits			Phone contact
	Day -13 to Day 1[p] (prior to surgery)	Day 1 (day of surgery)	6-hour and 24 hour (Day 2) [i] follow-up after study drug administration			Day 8 1 week (±2 days) post day of surgery
			PACU	6 (±2) hours	24 (±6) hours (Day 2)	
General anesthesia maintenance per routine practice (sevoflurane must be used as inhalational agent; record use of any alternative drugs) [h]		X				
Blood sample collection for population PK study		X [m]				
Brice Awareness Questionnaire			X [n]			X [n]
Adverse events and prior/concomitant medications	X	X	X	X	X	X

Abbreviations: ASA-PS = American Society of Anesthesiologists Physical Status; BIS = bispectral index; BMI = body mass index; DBP = diastolic blood pressure; ECG = electrocardiogram; HR = heart rate; IV = intravenous; LR = lactated ringer's; MAP = mean arterial pressure; MOAA/S = Modified Observer's Assessment of Awareness/Sedation; NRS = Numeric Rating Scale; NS = normal saline; OR = operating room; PACU = post-anesthesia care unit; PK = pharmacokinetic; RR = respiratory rate; SBP = systolic blood pressure; SpO_2 = peripheral capillary oxygen saturation.

a. Physical examination will include ASA-PS score (Appendix 14.8).

b. Subject is hemodynamically stable and has followed preoperative instructions, and there is no evidence of acute illness such as fever.

c. Administer IV study drug (HSK3486 0.4 mg/kg or propofol 2.0 mg/kg) on the back of right or left hand vein (this IV location is strongly preferred rather than mandatory) at a port closest to the IV cannula (IV injection time: 30 [±5] seconds). The MOAA/S will be evaluated every 30 [±10] seconds after end of injection until MOAA/S ≤1 is reached. If MOAA/S is still >1 at 1 minute [±10 seconds] post end of study drug administration, a top-up dose of 50% of the initial dose of study drug (either HSK3486 0.2 mg/kg or propofol 1 mg/kg depending on treatment group) will be given to the subject (IV injection time: 10 [±2] seconds) and start and end time of administration will be recorded. The MOAA/S will be evaluated every 30 [±10] seconds post end of

the top-up dose. If MOAA/S is still >1 at 2 minutes [±10 seconds] post end of the top-up dose, then the rescue drug, propofol (100% of the initial calculated dose), will be given (in both treatment groups). The MOAA/S will be evaluated every 30 [±10] seconds post end of rescue drug administration until MOAA/S ≤1 is reached. Administration of study drug must be initiated 5 minutes [±30 seconds] post midazolam preinduction medication administration stop time. Top-up doses should be administered within 10 seconds once MOAA/S is evaluated >1.

d. Prior to entering the OR, orient the subject to the use of the NRS assessment. Upon initiation of study drug administration, the investigator should immediately ask the subject to rate his or her pain. As a general guidance, the evaluation should be done multiple times with the first evaluation occurring typically within 15 seconds after initiation of study drug injection and monitored until successful induction (MOAA/S ≤1). Related information such as the occurrence and severity of injection pain (NRS 0-10) shall be recorded. The maximum (highest value) injection-site pain should be recorded. Pain during the injection of study drug in the hand/arm should be distinguished from unrelated puncture pain from the IV site or due to adhesive tape at the IV site. When injection pain occurs, the subject's pain should be graded verbally using the NRS (0-10) and should be recorded. The subject should be asked to rate the pain on a scale from 0, which is no pain, to 10, which is the worst pain imaginable. Ask the subject to point to the number on the scale that best represents the intensity of the pain now. In the PACU, once the subject is alert and oriented, repeat NRS for recall of pain at time of study drug administration.
e. At preinduction, attach BIS monitor to subject. Record the three most recent BIS values before midazolam administration. Also, record baseline BIS value prior to administering study drug. The BIS values will be collected at the following timepoints at start of initial study drug administration: every 30 [±10] seconds until 5 minutes, then every 2 minutes [± 30 seconds] until 30 minutes and then every 30 [±2] minutes for the duration of the surgery.
f. Obtain 12-lead ECG at Day 1 visit only if the screening ECG is more than 1 week from the Day 1 visit. During the surgery, 3-lead or 5-lead ECG will be monitored continuously and the investigators will decide whether to add a 12-lead ECG. A 12-lead ECG will be obtained at 6 [±2] hours post study drug administration and as clinically indicated.
g. When MOAA/S ≤1 is reached, IV rocuronium bromide (0.6 mg/kg) is to be administered for neuromuscular blockade to perform endotracheal intubation. RR collected until initiation of administration of rocuronium. Intubate subject once neuromuscular blockade (rocuronium) has taken effect; if using twitch monitor, intubate once no twitches are noted. The start and end of first and subsequent intubation attempt time should be recorded.
h. An inhalational anesthetic agent, Sevoflurane (an inhalation anesthetic agent) will be used for maintenance of general anesthesia. Initiate sevoflurane within 60 seconds after successful endotracheal intubation. The end-tidal concentration of sevoflurane should be 1.5-2.0% (The initial concentration that is set and start time of administration should be recorded).
i. After the surgery, subjects may remain in the hospital or observation unit if required based on standard of care and the clinical situation; however, if the subject is clinically stable after the Day 1 follow-up assessments and appropriate to be discharged home per the judgement of the investigator and surgeon, the subject may be released with supervision by a family member or friend, and must return to the clinic for the 24-hour follow-up visit (Day 2).
j. On the day of surgery prior to entering the operating room (after the subject has been resting supine for ≥5 minutes), vital signs (HR, RR, SpO_2, SBP, DBP, MAP, Temp) will be collected. During preinduction, obtain

baseline vital signs (baseline value will be the measurement immediately prior to initiation of study drug administration). During the induction of general anesthesia, monitor vital signs (HR, RR, SpO_2, SBP, DBP, MAP, Temp) continuously. HR, RR, SBP, DBP, MAP, Temp should be recorded once every 2 minutes [±30] seconds, SpO_2 value should be recorded once every 1 minute [± 15 seconds] from the start of study drug administration (for every time point) for 30 minutes post start of study drug administration, for the judgment of key secondary endpoint. After the surgery, vital signs (HR, RR, SpO_2, SBP, DBP, MAP, Temp) will be assessed at 6 [±2] hours post study drug administration.

k. At 6 [±2] hours post study drug administration, obtain vital signs (HR, RR, SpO_2, SBP, DBP, MAP, Temp) and clinical laboratory tests (including hematology, blood chemistry, and urinalysis). At 24 [±6] hours post study drug administration (Day 2), obtain vital signs (HR, RR, SpO_2, SBP, DBP, MAP, Temp).

l. Clinical laboratory tests (Appendix 14.12) include hematology, blood chemistry, and urinalysis; pregnancy tests for all women of childbearing potential (serum sample at screening and urine sample at baseline. If screening and baseline are both conducted on Day 1, a urine sample for pregnancy testing is not required if serum pregnancy eligibility is confirmed with an approved local lab as per footnote p). HbA1c and TSH test (with free T-4 if TSH abnormal) will only be done during the screening period.

m. The blood collection time points for population PK analysis are listed (Appendix 14.7). Approximately 2 mL of venous blood is collected at each time point.

n. The Brice Awareness Questionnaire is administered in the PACU once the subject is alert and oriented. The questionnaire is repeated at Day 8.

o. Per investigator discretion, in otherwise healthy patients, clear liquids may be ingested for up to 2 hours prior to surgery. These liquids should not include alcohol. Examples of clear liquids include, but are not limited to, water and fruit juices without pulp, carbonated beverages, carbohydrate-rich nutritional drinks, clear tea, and black coffee.

p. In cases where a separate screening visit is not feasible, or the central laboratory results are not available on Day 1, screening activities may be conducted on Day 1 prior to surgery. A study approved local laboratory may be used to confirm eligibility. In these cases, required screening laboratory samples must be drawn in parallel and sent to the central laboratory.

14.3 Modified Observer's Assessment of Awareness/Sedation (MOAA/S) Scale

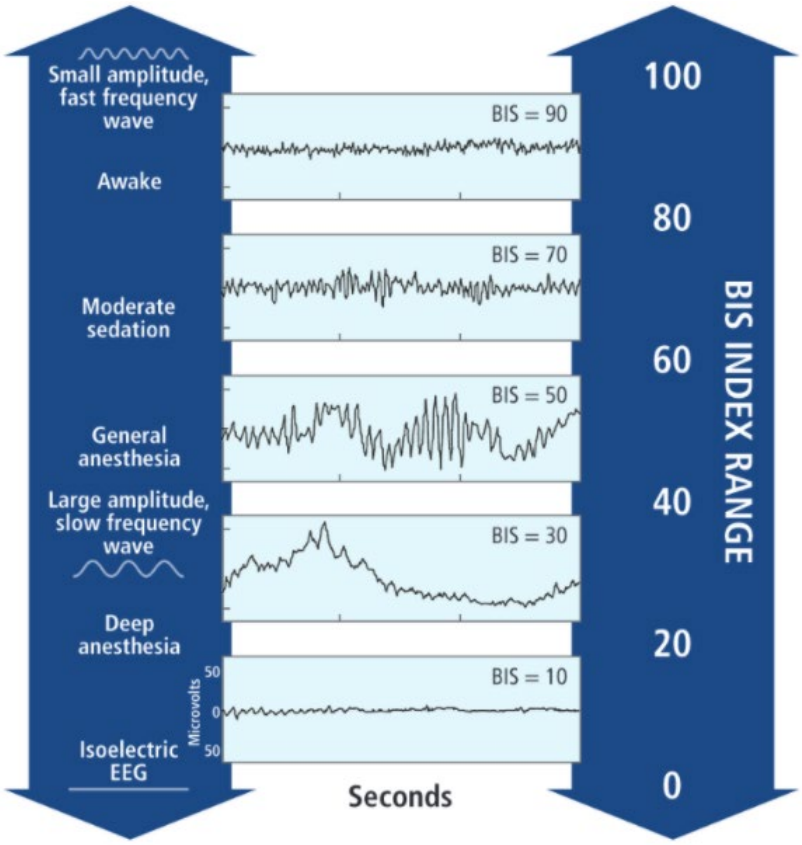
The assessment for MOAA/S is performed stepwise and skipping of any grade is not allowed. The judgment of recovery can be based on a reverse order of scoring.

Grade	Description
Grade 5	Completely awake; responds readily to name spoken in normal tone
Grade 4	Lethargic response to name spoken in normal tone
Grade 3	Responds only after name is called loudly and repeatedly
Grade 2	Responds only after mild prodding or shaking
Grade 1	Responds only after painful trapezius squeeze (including active and reflex withdrawals)
Grade 0	No response after painful stimulus (trapezius squeeze)

14.4 Bispectral Index (BIS)

The BIS Index is a number between 0 and 100 scaled to correlate with important clinical endpoints and electroencephalogram (EEG) states during administration of anesthetic agents (Figure 2). The BIS values near 100 represent an "awake" clinical state while 0 denotes the maximal electroencephalogram (EEG) effect possible (i.e., an isoelectric EEG).

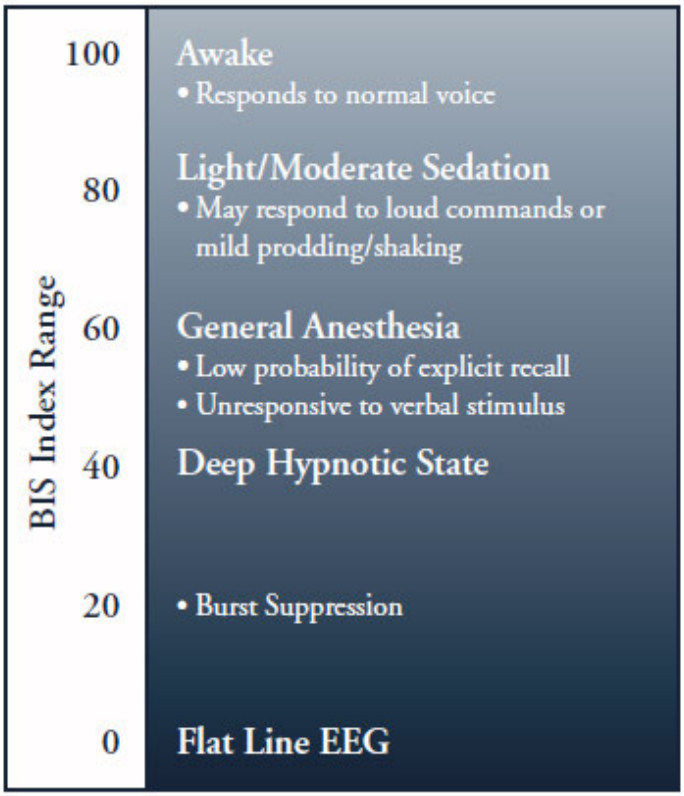
Figure 2 The BIS Index is scaled to correlate with important clinical endpoints during administration of anesthetic agent.



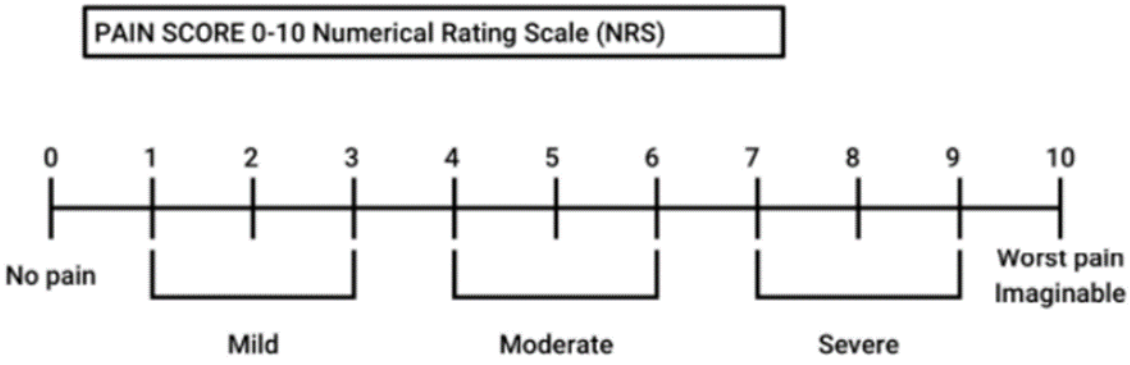
It should be noted that the BIS Index range represents a continuum that correlates to the clinical state and expected responses (Figure 3).

This chart below reflects a general association between clinical state and BIS values. Ranges are based on results from a multicenter study of the BIS involving the administration of specific anesthetic agents. The BIS values and ranges assume that the EEG is free of artifacts that can affect its performance. Titration of anesthetics to BIS ranges should be dependent upon the individual goals established for each subject. These goals and associated BIS ranges may vary over time and in the context of subject status and treatment plan.

Figure 3 BIS Index Range: A Continuum of Clinical State and EEG Changes



14.5 Numerical Rating Scale (NRS) for Grading of Injection-site Pain



14.6 Brice Awareness Questionnaire

1) What is the last thing you remember before going to sleep?

-Being in the pre-op area
-Seeing the operating room
-Being with family
-Hearing voices
-Feeling mask on face
-Smell of gas
-Burning or stinging in the IV line
-Other [Free Text]:

2) What is the first thing you remember after waking up?

-Hearing voices
-Feeling breathing tube
-Feeling mask on face
-Feeling pain
-Seeing the operating room
-Being in the recovery room
-Being with family
-Being in ICU
-Nothing
-Other [Free Text]:

3) Do you remember anything between going to sleep and waking up?

-No
-Yes:
    -Hearing voices
    -Hearing events of the surgery
    -Unable to move or breathe
    -Anxiety/stress
    -Feeling pain
    -Sensation of breathing tube
    -Feeling surgery without pain
    -Other [Free Text]:

4) Did you dream during your procedure?

-No
-Yes:
    -What about [Free Text]:

5) Were your dreams disturbing to you?

-No
-Yes

6) What was the worst thing about your operation?

-Anxiety

-Pain
-Recovery process
-Functional limitations
-Awareness
-Other [Free Text]

14.7 Pharmacokinetic (PK) Blood Samples Collection Timetable

Phase	Time	Allowed Time Window	PK Blood Sample Collection[2]
Before dosing study drug			
	Before the 1st dose of study drug administration	Within 10 minutes prior to study drug administration	X
After the end of last dose of study drug[1]			
	2 minutes[3]	±30 seconds	X
	3 ~ 30 minutes	Not applicable	X
	60 ~ 120 minutes	Not applicable	X

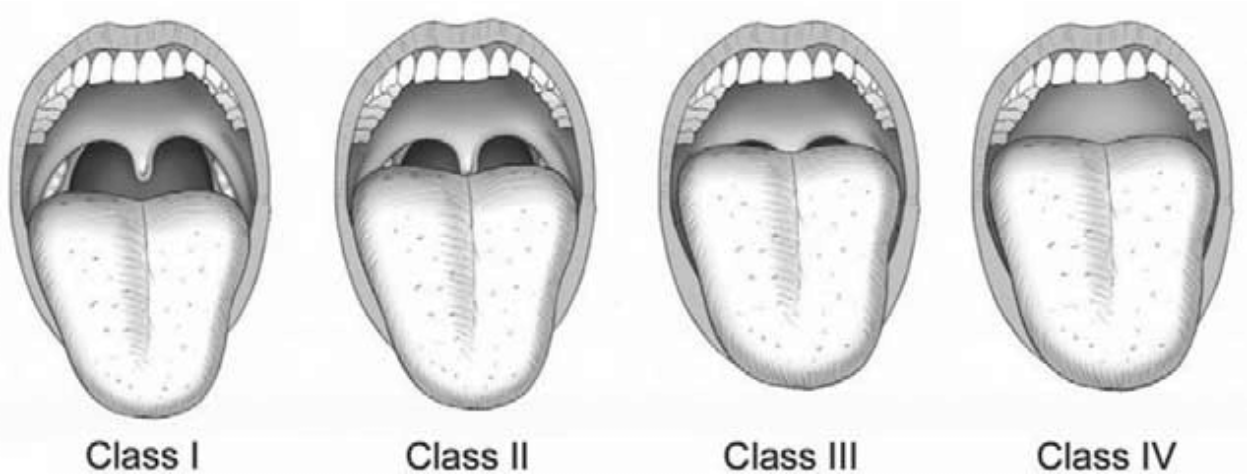
14.8 American Society of Anesthesiologists (ASA) Physical Status Grade

Before anesthesia, the ASA classifies subjects into 5 grades according to their physical conditions and the risk of surgery:

- **ASA I**: Normal and healthy. No systemic diseases other than local lesions.
- **ASA II**: A subject with mild systemic disease.
- **ASA III**: A subject with severe systemic disease that results in functional limitations but not incapacity.
- **ASA IV**: A subject with severe systemic disease that is a constant threat to life and results in incapacity.
- **ASA V**: A moribund subject who is not expected to survive without the operation. If it is an emergency surgery, mark "Emergency" or "E" before the evaluated level shown above.

Subjects assessed as ASA I or ASA II have good tolerability to anesthesia and surgery, and the process of anesthesia is smooth. Subjects assessed as ASA III are under certain risks of anesthesia. The pre-anesthetic preparation should be adequate. Effective measures should be taken to prevent complications that may occur during anesthesia. Subjects assessed as ASA IV are under particularly high risks of anesthesia. Subjects assessed as ASA V are under extremely high risks of anesthesia and surgery for their extremely critical conditions, extremely poor tolerability to anesthesia, and death that may occur at any time. Thus, pre-anesthetic preparation is more important and shall be adequate, careful, and comprehensive.

14.9 Mallampati Classification



The Modified Mallampati classification is a simple scoring system to help predict difficult intubation. It relates the amount of mouth opening to the size of the tongue and provides an estimate of space available for oral intubation by direct laryngoscopy. Class I is present when the soft palate, uvula, and pillars are visible; Class II when the soft palate and uvula are visible; Class III when only the soft palate and base of the uvula are visible; and Class IV when only the hard palate is visible. Mallampati Class I and II predict easy laryngoscopy, Class III predicts difficulty, and Class IV predicts extreme difficulty.

14.10 Adverse Event Definitions

Definitions

An AE is:

- Any untoward medical occurrence in a study subject, regardless of whether or not considered drug-related. The examples are as follows:
- Any clinically significant recurrence or worsening of a pre-existing condition.
- An AE occurring from overdose of a Sponsor study drug whether accidental or intentional (i.e., a dose higher than that prescribed by a healthcare professional for clinical reasons).
- A treatment-emergent AE is defined as：an AE that occurs after the subject starts treatment with the IMP.

A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the subject signs the Informed Consent Form and that is documented as part of the subject's medical history.

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

The diagnosis should be recorded, in preference to listing the individual signs and symptoms. For example, symptoms of fever, cough, and elevated white blood cells should be reported as pneumonia rather than the individual signs and symptoms. Abnormal laboratory values are typically not reported as AEs by themselves, but rather are included with the underlying diagnosis. For example, a low serum hemoglobin value associated with gastrointestinal bleeding should not be reported separately from the underlying diagnosis of gastrointestinal hemorrhage.

Reporting of Adverse Events

At each visit, the investigator, or delegate, will determine whether or not any AEs have occurred. Non-leading questions such as "How are you feeling today?" or "Have you had any health concerns since your last visit?" should be used to elicit the subject to report any possible AEs. If any AEs have occurred, they will be recorded in the AE section of the eCRF and in the subject's source documents.

AEs will be collected from the time of informed consent until the final study visit. AEs that are related to the investigational drug and continue beyond the normal collection period (i.e., are ongoing at the time a subject exits the study) will be followed until resolution or stabilization.

Assessment of Severity

The investigator will be asked to provide an assessment of the AE severity using the CTCAE Version 5.0 classification. This study will enroll subjects undergoing elective surgeries requiring

general anesthesia using endotracheal intubation; however, not all subjects will be healthy volunteers. Elective surgery does not necessarily mean optional surgery. Elective means the surgery can be scheduled in advance, and it can still be associated with serious conditions. The intent is to exclude emergent surgeries for life-threatening conditions, while still including a diverse, heterogenous subject population such as ASA-PS III-IV, elderly and morbidly obese subjects with comorbidities. The CTCAE Version 5 severity classification is as follows:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money).
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE.

Relationship to Study Treatment

The investigator will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- **Not related**: When the AE is definitely caused by the subject's clinical state, or the study procedure/conditions. There is no association between the study drug and the reported event; there is a clear alternative explanation; a causal relationship is non plausible.
- **Unlikely Related**: Underlying or concurrent disease or other drugs/exposures provide plausible alternative explanations. Temporal relationship to study drug administration makes a causal relationship improbable.
- **Likely Related**: There is a reasonable possibility that the drug caused the AE; the event is unlikely attributed to underlying or concurrent disease or other drugs/exposures (i.e., alternative explanation). There is a reasonable time sequence to administration of the study drug.
- **Definitely Related**: A definite causal relationship exists between the drug administration and the AE; including a plausible time relationship to drug administration, and it cannot be explained by underlying or concurrent disease or other drugs/exposures; abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Action Taken for Adverse Events

The investigator or designee will record the action taken for the AE in the eCRF. Actions taken will include:

- **Dose increased**: The medication schedule was modified by addition, either by changing the frequency, strength, or amount.
- **Dose not changed**: The medication schedule was not changed.
- **Dose reduced**: The medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
- **Drug interrupted**: The medication schedule was modified by temporarily terminating the prescribed regimen of medication.
- **Drug withdrawn**: The medication schedule was modified through termination of the prescribed regimen of medication.
- **Not applicable**
- **Unknown**

Follow-up of Adverse Events

All SAEs that are ongoing at the time of discontinuation, or that develop prior to the final Follow-up Telephone Call, will be followed for 30 days, or until resolution or stabilization.

Serious Adverse Events

An SAE is any AE occurring at any dose that meets 1 or more of the following criteria:

- Results in death
- Is life-threatening (see below)
- Requires subject hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in a congenital anomaly or birth defect
- Results in an important medical event (see below).

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room, blood dyscrasias or convulsions that do not require hospitalization, or development of drug dependency or drug abuse.

A **life-threatening adverse event** is any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though drug-induced hepatitis of a more severe nature can be fatal. Hospitalization is to be considered only as an overnight admission.

Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious.

The following circumstances should not be considered an AE/SAE:

- Planned hospitalization for the surgery required for study participation.
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for surgical follow-up required as routine standard of care.

In addition, a hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions (i.e., the AE resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the subject's bodily function/structure, physical activities, or quality of life).

Medical and scientific judgment should be exercised in deciding whether a case is serious in those situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability, or incapacity. These include events that may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. Such events should usually be considered as serious.

14.11 Clinical Laboratory Evaluations

The following clinical laboratory analytes will be assessed:

Chemistry (Chem-20):	**Hematology (CBC):**
Albumin	Hematocrit
ALP	Hemoglobin
ALT	MCH
AST	MCHC
BUN	MCV
Calcium	Platelet count
Chloride	RBC count
Cholesterol (TC, LDL, HDL, TG)	WBC count
Creatinine	WBC differential
GGT	(% & ABS count)
Glucose	Basophils
LDH	Eosinophils
Phosphorus	Lymphocytes
Potassium	Monocytes
Sodium	Neutrophils
Bilirubin (Total and Indirect)	
Total CO_2 (measured as bicarbonate)	**Hormone:**
Total protein	Urine pregnancy test [redacted] local laboratory only (For females only)
Uric acid	Serum pregnancy test (For females only)
	TSH* (free T-4 if TSH abnormal)
Complete Urinalysis (UA):	**Glycosylated Hemoglobin**
Color and appearance	HbA1c*
pH and specific gravity	
Bilirubin	
Glucose	
Ketones	
Leukocytes	
Nitrite	
Occult blood	
Protein	
Microscopic (including RBCs and WBCs)	

Abbreviations: ABS = absolute; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CO_2 = carbon dioxide; GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; TSH = thyroid stimulating hormone; WBC = white blood cell.

*: HbA1c and TSH test (with free T-4 if TSH abnormal) will only be done during the screening period.