Cover Page

**Protocol V9.0 HSK3486-309**

**TITLE OF STUDY: A Global 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**

**NCT NUMBER: NCT05486416**

**DOCUMENT DATE: 28 FEBRUARY 2023**

# Protocol

## A Global 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 Date: 28 Feb 2024
Protocol Version: 9.0

Investigational Product: HSK3486

Protocol Reference Number: HSK3486-309

[redacted]

Sponsor:
Haisco-USA Pharmaceuticals, Inc

[redacted]

Haisco-USA Pharmaceuticals, Inc.

**SUMMARY OF CHANGES**

The following is a high-level summary of changes made in protocol Version 9.0. The detailed changes (existing text and updated text) are provided in Appendix 14.

- **Inclusion 9 and Exclusion 3.d). have been updated for clarification**

## SPONSOR APPROVAL

I have read the following and approve it:

**INVESTIGATOR AGREEMENT**

I have read the following protocol and agree to conduct the study as described herein.

| | |
|---|---|
| [Name, Qualification(s)]<br>Principal Investigator | Date |

## SYNOPSIS

**Title of study:** A Global 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

**Indication:** Induction of general anesthesia in adult subjects undergoing elective surgery with endotracheal intubation

**Number of study centers:** Up to approximately 40 sites in the US and EU will be included in this study.

**Development phase:** Phase 3

**Objectives:**

**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.

**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 Objective:

- 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.

**Methodology/study design:**

This is a global 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.

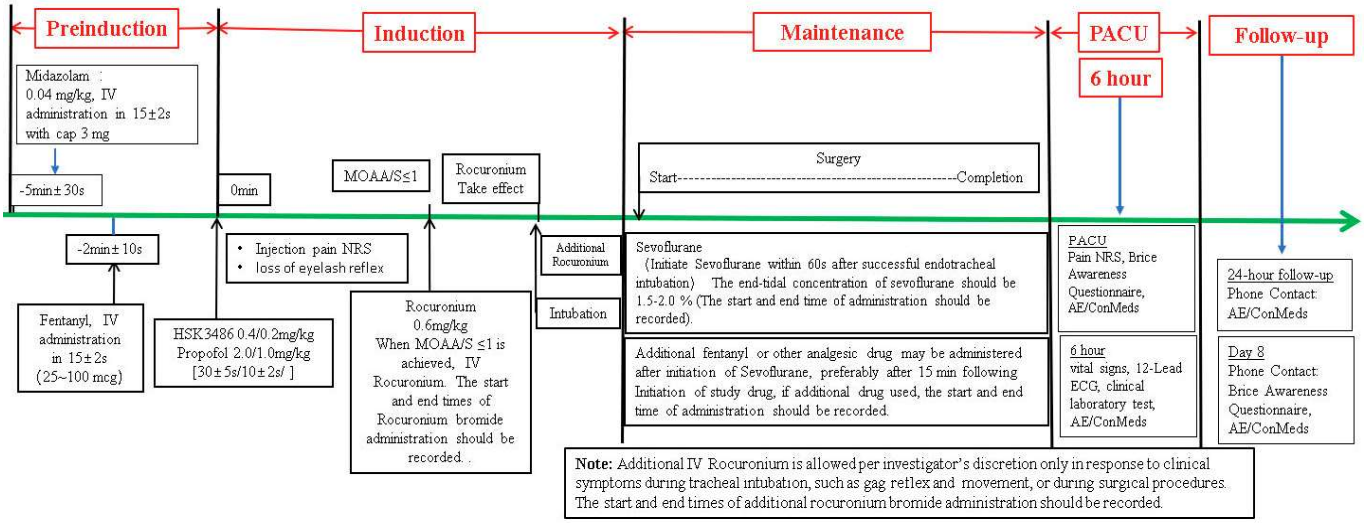
After screening, eligible subjects will be randomized in a 2:1 ratio to receive either HSK3486 0.4/0.2 mg/kg (i.e., 0.4 mg/kg IV slow injection over 30 [±5] seconds followed by an additional 0.2 mg/kg dose over 10 [±2] seconds if needed) or propofol 2.0/1.0 mg/kg (i.e., 2.0 mg/kg IV slow injection over 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 1) 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.

**Figure 1：Study design**

- **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 calculated dose of study drug 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.
- **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 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.
- **BIS:** Record the three most recent BIS values preceding midazolam administration. Record baseline BIS value prior to administering study drug. BIS will be monitored continuously. BIS values will be collected at the following timepoints post start of initial study drug administration: every 30 [±10] seconds until 5 minute, and then every 2 minutes [±30 seconds] from 5 minutes until 30 minutes. Then every 30 minutes [±2] minutes for the duration of the surgery.
- **Vital signs (HR, RR, $SpO_2$, SBP, DBP, MAP, Temp):** 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, Temp should be recorded once every 2 minutes [±30 seconds], $SpO_2$ value should be recorded once every 1 minutes [± 15 seconds] from the start of study drug administration (for every time point) for 30 minutes post start of study drug administration. RR should be recorded once every 2 minutes [±30 seconds] from the start of study drug administration until administration of rocuronium.
- **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 administration of Rocuronium bromide, evaluate and record respiratory depression. Within 15 minutes post start of study drug administration, evaluate and record cardiac depression.
- **3-lead or 5-lead and 12-lead ECG:** Monitor and records 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 end concentration of Sevoflurane should be 1.5-2.0%.



**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 2]) 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 fentanyl dose can be reduced according to patient's age and comorbidities as per the anesthetist's discretion. 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.

**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, 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. RR should be recorded once every 2 minutes [±30 seconds] from the start of study drug administration until initiation of administration of rocuronium.

  **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. Timepoints for MOAA/S ≤1 within 1 to 40 seconds should be recorded.
    - 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 calculated dose of study drug 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 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 Numeric Rating Scale (NRS; Appendix 3). 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. Timepoints for loss of eyelash reflex within 1 to 40 seconds 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 from start of initial study drug administration: every 30 [±10] seconds for 5 minutes, 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 administration of rocuronium.

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

  **Note:** For subjects with BMI ≤40 kg/m$^2$: If the exact calculated Rocuronium dose cannot be drawn, round up or down to the nearest mg (whole number) depending on investigator preference/standard of care.

  **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 start and end time of administration should be recorded).
- Information about any adverse events (AEs) and concomitant medications will be recorded.

**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] from 5 minutes until 30 minutes and then every 30 [±2] minutes for the duration of the surgery.
- Information about any adverse events (AEs) and concomitant medications will be recorded.
- Additional IV fentanyl or other analgesic drug may be administered for intraoperative analgesia only after initiation of sevoflurane, preferably after 15 minutes following. The start and end time of administration should be recorded.
- Patient management during surgery needs to follow routine best practice which includes Antiemetics Ondansetron, or other 5 HT-3 antagonists and/or Dexamethasone.

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

<u>6 hours post study drug follow-up</u>

- Assess vital signs (HR, RR, $SpO_2$, SBP, DBP, MAP, Temp) 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 PACU.

- Clinical laboratory tests (including hematology, blood chemistry, and urinalysis) will be obtained at 6 [±2] hours post start study drug administration for shipment to central laboratory.
- 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 4). 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 6 hour 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.

For the 24-hour follow-up (Day 2) phone contact

- Subjects will be evaluated by a follow-up telephone call 24 [±6] hours after study drug administration.
- 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 concomitant medications will be collected and recorded.

**Population PK study:**

- All eligible subjects in this clinical study will be required to provide venous blood samples for population PK study per time schedule planned (Appendix 5).

**Data monitoring committee:**

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 suspended 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. 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.

**Number of subjects:** A total of 399 subjects; 266 subjects in HSK3486 group and 133 subjects in propofol group.

**Diagnosis and main criteria for inclusion and exclusion:**

Inclusion criteria:

Subjects must satisfy all of the following criteria at the screening and Day 1 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 6). 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 within the screening period and 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 7.3.4 from the time of consent until 30 days post study drug administration.
6. For subjects with known hypothyroidism and/or on thyroid-hormone replacement treatment (i.e., thyroxine), or subjects suspected to have thyroid dysfunction based on clinical history and physical exam, a TSH must be drawn and be within normal levels.
7. 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.
8. Willing to comply with the site's COVID guidelines and testing requirements as applicable.
9. Patients with psychiatric/mental disorders must be considered stable on treatment (e.g., SSRIs, SNRIs, TCAs, MAOIs, psychotherapy) per investigator judgement, and no hospitalizations and urgent care due to the underlying psychiatric pathology for at least 12 months.

* Women are considered of childbearing potential until becoming post-menopausal, unless she had a documented hysterectomy or bilateral oophorectomy / salpingo-oophorectomy. A woman is considered to be post-menopausal if she had no menses for at least 12 consecutive months (without an alternative medical cause).

Exclusion criteria:

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening and Day 1 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; subjects having contraindications to propofol, opioids, and their antidotes. In cases where the only previous reaction to opioids was itching or nausea, subjects need not be excluded if the investigator believes the subject is not truly allergic to opioids.
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) Patients with psychiatric/mental disorders who have not been on a stable treatment regimen (e.g., SSRIs, SNRIs, TCAs, MAOIs, psychotherapy) per investigator judgement, for at least 12 months or who have been hospitalized or had emergent/urgent care due to the underlying psychiatric pathology within the last 12 months.
   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) History of uncontrolled diabetes in the opinion of the investigator.
   g) 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).
   h) History of drug abuse that, in the opinion of the investigator, may confound the interpretation of safety or efficacy in a study subject.
   i) For subjects with known hypothyroidism and/or on thyroid-hormone replacement treatment (i.e., thyroxine), or subjects suspected to have thyroid dysfunction based on clinical laboratory and physical exam who has a TSH value outside the normal range.

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 7]), 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 $\leq 1.5 \times 10^9$/L
   b) Platelet count $< 80 \times 10^9$/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.

**Test products, dose, and mode of administration:**

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 up to 1 minute for this population (IV slow injection over 30-60 seconds).

For ASA grade 3-4 subjects, the dose can be **reduced by 25-50% per investigator discretion**. The administration time should be extended up to 1 minute for these populations (IV slow injection over 30-60 seconds).

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: LBW = (9270 x TBW (kg)) / (6680 + (216 x BMI))
- For females: 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.

**Reference therapy, dose, dose form, and mode of administration:**

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 up to 1 minute for this population (IV slow injection over 30-60 seconds).

For ASA grade 3-4 subjects, the dose c**an be reduced by 25-50% per investigator discretion**. The administration time should be extended up to 1 minute for these populations (IV slow injection over 30-60 seconds).

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: LBW = (9270 x TBW (kg))/(6680 + (216 x BMI))
- For females: 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**, propofol,** is prepared as 100% of the initial calculated dose and administered per propofol guidelines above**.** The rescue dose administration time should be extended up to 1 minute (IV slow injection over 30-60 seconds) for elderly subjects ≥65 years of age and for ASA grade 3-4 subjects who require a dose reduction.

**Duration of subject participation in study:**

The sequence and maximum duration of the study periods per subject will be as follows:

- Screening: up to 14 days prior to the surgery and including the day of surgery (if needed)
- Treatment: on the day of surgery
- Follow-up phone contacts: 24 hours post study drug administration and 7(±2) days post-surgery

Total duration for each subject is expected to be 22 [±2] days (including screening and 1 week follow up telephone call).

**Efficacy endpoints:**

**Primary efficacy endpoint:**

- Success rate of general anesthesia induction: A successful general anesthesia induction will meet both of the following conditions:
  a) Induction success (MOAA/S ≤1) after administration of the study drug, and
  b) One or less top-up doses required without using any rescue drugs.

**Secondary efficacy endpoints:**

Key secondary endpoints:

- The proportion of subjects with any injection-site pain at time of drug administration on the Numeric Rating Scale (NRS ≥1).
- The proportion of subjects with successful induction who maintain the desired depth of anesthesia for general elective surgery, and without significant cardiac and respiratory depression within15 minutes post initiation 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 administration, defined by all the following conditions:
  a) Desired depth of anesthesia for general elective surgery is defined if all following criteria are met:
     i) No clinical signs of inadequate depth of anesthesia, such as lacrimation, movement, vomiting, coughing, laryngospasm, bucking, swallowing reflex or bronchospasm etc.
     ii) 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.
     iii) Subjects maintain desired depth of anesthesia for general elective surgery with BIS as an objective assessment (after reaching initial lowest value, BIS remains sustainable level at not more than 60).

     **Note:** Target BIS 40 to 60 for general anesthesia (Appendix 2).

     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.

**Note:** It is strongly recommended that each site have available video laryngoscopy, or an acceptable alternative, for unanticipated difficult tracheal intubation. If more than one tracheal intubation attempt is made, the start and end times of first and subsequent intubation attempts should be recorded.

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 $SpO_2$ <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.

Other secondary endpoints:

- Time to successful induction of general anesthesia: Time from the end of the first administration of the study drug to MOAA/S ≤1.
- Time to the disappearance of eyelash reflex: Time from the end of the first administration of the study drug to the disappearance of eyelash reflex.
- The proportion of the subjects with any moderate injection-site pain at time of drug administration on the Numeric Rating Scale (NRS ≥4).
- The average injection site pain at time of drug administration of HSK3486 compared to propofol on NRS.

**Safety endpoints:**

- Safety assessments include Adverse events (AE), adverse events of special interest (AESI), and serious adverse events (SAE) clinical laboratory test results, vital signs (supine HR, SBP and DBP, MAP, RR, and $SpO_2$), ECG findings, physical examination findings, and administration of additional medications, or any interventions including medical interventions, e.g., administration of vasoactive drugs to treat clinically relevant changes in blood pressure.

**Pharmacokinetic endpoints:**

Plasma HSK3486 concentration at scheduled timepoints (Appendix 5).

**Sample size evaluation:**

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 patients 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 patients will give 90% power (providing the primary endpoint is statistically significant) assuming $\alpha$= 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 patients will give 90% power (providing the primary endpoint is statistically significant) to the superior testing, assuming $\alpha$= 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 patients 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).

**Statistical methods:**

**Statistical analysis sets:**

Full Analysis Set (FAS): All randomized subjects who have received any dose of the study drug (HSK3486 or propofol).

Per Protocol Set (PPS): All subjects from FAS who have completed primary efficacy endpoint measurement will be considered for 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.

Safety Set (SS): Includes all randomized subjects who have received any dose of the study drug and have post-dose safety assessment data.

**General principles:**

Continuous variables will be summarized by the standard descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Frequency of subjects or events and percentages will be summarized in categorical variables.

**Efficacy analysis:**

(a) Primary efficacy analysis

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

(b) Secondary efficacy analysis

- The 2 key secondary endpoints will be analyzed in parallel. The proportion of subjects with successful induction, who maintain desired depth of anesthesia for general elective surgery, and without significant respiratory depression (prior to administration of rocuronium bromide) and cardiac depression between the time of successful induction and 15 minutes post study drug administration in both groups and the difference between groups and 95% CI will be calculated. The p-value for comparison between groups will be obtained based on Chi-square test.
- The proportion of the subjects with any injection-site pain (NRS ≥1) and moderate injection-site pain (NRS ≥4) will be analyzed, as well as the mean NRS score for each treatment group, using the same method as stated above for the secondary composite endpoint.
- The median and its 95% CI of time to successful induction of general anesthesia will be provided by groups using the Kaplan-Meier (KM) method.
- Time to the disappearance of eyelash reflex will be analyzed using the similar statistical methods as time to successful induction of general anesthesia.
- The change of BIS during the period of anesthesia post study drug administration up to 15 minutes will be summarized descriptively by treatment group.
- Recall of awareness during surgery, assessed postoperatively, will be evaluated using the Brice Awareness Questionnaire.
- The use of study drugs and rescue drugs will be summarized descriptively by treatment group.
- 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 similar statistical methods as for the secondary composite efficacy endpoint.

**Safety analysis:**

All AEs will be coded according to the MedDRA version 25.0 or later and graded for severity according to CTCAE version 5.0. The number and percentage of subjects with treatment-emergent adverse events (TEAEs), SAEs, AEs of Special Interest (AESI), TEAEs related to study drug, SAEs related to study drug, TEAEs of Grade 2 or higher, TEAEs leading to treatment discontinuation, TEAEs leading to study discontinuation, and TEAEs

leading to death will be summarized by system organ class (SOC), preferred term (PT), and groups. In addition, the severity of TEAEs and relationship to study drug will be summarized by SOC, PT, and groups.

Laboratory test variables will be summarized by treatment group and visit using descriptive statistics. Shift tables between baseline and post-baseline time points will be presented by laboratory test and treatment group. 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.

Descriptive statistics of vital signs, pulse oximetry measurements, and ECG results at each visit will be presented.

**Note:** Since injection-site pain has been recorded and analyzed in the efficacy endpoints, it is no longer recorded in the Safety endpoints.

**Population PK analysis:**

The plasma concentration data from this study will be pooled with data from other clinical trials of HSK3486 to establish a population PK model. This model will be used to evaluate the effects of internal and external covariates on the PK of HSK3486.

**SCHEDULE OF ASSESSMENTS**

| | **Screening** | **Study treatment** | **Follow-up visit** | | **Phone contacts** | |
|---|---|---|---|---|---|---|
| | **Day -13 to Day 1[p] (prior to surgery)** | **Day 1 (day of surgery)** | **PACU and 6-hour** | | **<u>Day 2</u> 24 (±6) hours after study drug administration <u>Day 8</u> 7 (±2) days post day of surgery** | |
| | | | PACU | 6 (±2) hours | 24 (±6) hours | 7 (±2) days |
| 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] | | |
| Height, weight, and BMI | 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] | | | | |

| | **Screening** | **Study treatment** | **Follow-up visit** | | **Phone contacts** | |
|---|---|---|---|---|---|---|
| | **Day -13 to Day 1[p] (prior to surgery)** | **Day 1 (day of surgery)** | **PACU and 6-hour** | | **<u>Day 2</u> 24 (±6) hours after study drug administration <u>Day 8</u> 7 (±2) days post day of surgery** | |
| | | | PACU | 6 (±2) hours | 24 (±6) hours | 7 (±2) days |
| Instruct subject to fast minimum of 6 hours before surgery[o] | X | | | | | |
| Confirm preoperative readiness [b] | | X | | | | |
| Randomization | | X[q] | | | | |
| 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 | | | | |

| | **Screening** | **Study treatment** | **Follow-up visit** | | **Phone contacts** | |
|---|---|---|---|---|---|---|
| | **Day -13 to Day 1[p] (prior to surgery)** | **Day 1 (day of surgery)** | **PACU and 6-hour** | | **<u>Day 2</u> 24 (±6) hours after study drug administration <u>Day 8</u> 7 (±2) days post day of surgery** | |
| | | | PACU | 6 (±2) hours | 24 (±6) hours | 7 (±2) days |
| Monitor 3-lead or 5-lead ECG continuously [f] | | X | | | | |
| Administration of IV rocuronium [g] | | X | | | | |
| Endotracheal intubation [g] | | X | | | | |
| 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 6).

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 calculated 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 administrated 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. 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 minutes [±2] minutes for the duration of the surgery.

f. 12-lead ECG results collected within 30 days prior to Day 1 may be used to confirm eligibility. Obtain 12-lead ECG within the screening period only if the subject reports any cardiopulmonary symptoms that warrant an ECG, in the opinion of the investigator. 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 of should be 1.5-2.0% (The start and end 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 6 hour 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.

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, 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. RR should be recorded once every 2 minutes [± 30 seconds] from the start of study drug administration until administration of rocuronium. 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).

l. Clinical laboratory tests (Appendix 10) include hematology, blood chemistry, and urinalysis; pregnancy tests for all women of childbearing potential (Negative serum pregnancy test within the screening period and negative urine pregnancy test at baseline (Day 1)).

m. The blood collection time points for population PK analysis are listed in Appendix 5. 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. Local labs completed within 30 days prior to Day 1 may be used to confirm eligibility. In these cases, required screening laboratory samples must be drawn within the screening period and sent to the central laboratory.

q. Randomization in IXRS can occur the day prior to surgery if needed to accommodate pharmacy, research, or surgery center hours. Study drug must be administered within 12 hours of preparation.

Table of Contents

**LIST OF FIGURES**

## LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| AESI | Adverse Event of Special Interest |
| ASA-PS | American Society of Anesthesiologists Physical Status |
| BIS | bispectral index |
| BMI | body mass index |
| BP | blood pressure |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CRA | clinical research associate |
| CRO | Contract Research Organization |
| CSA | clinical study agreement |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DBP | diastolic blood pressure |
| DMC | data monitoring committee |
| DSS | Drug Safety Services |
| EC | Ethics Committee |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EEG | electroencephalogram |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| HR | heart rate |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IRB | Institutional Review Board |
| IV | intravenous |
| IXRS | Interactive Voice/Web Response Technology |
| IMP | Investigational Medicinal Products |
| kg | kilogram |
| L | Liter |
| LBW | lean body weight |
| LR | Lactated ringer's |
| ISD | Initiation of study drug |
| MAP | mean arterial pressure |
| mcg | microgram |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram |

| Abbreviation | Definition |
|---|---|
| min | minute |
| mL | milliliter |
| MOAA/S | Modified Observer's Assessment of Awareness/Sedation |
| NIM | non-inferiority Margin |
| NRS | Numeric Rating Scale |
| NS | normal saline |
| NMPA | National Medical Products Administration |
| NDA | New Drug Application |
| PACU | post-anesthesia care unit |
| PD | pharmacodynamic |
| PK | pharmacokinetic |
| PPS | Per Protocol Set |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| RBC | red blood cell |
| RR | respiratory rate |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SBP | systolic blood pressure |
| $SpO_2$ | oxygen saturation |
| SS | Safety Set |
| SUSAR | suspected unexpected serious adverse reaction |
| TBW | total body weight |
| TEAE | treatment-emergent adverse event |
| Temp | temperature |
| ULN | upper limit of normal |
| WBC | white blood cell |

# 1. INTRODUCTION

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

HSK3486 injectable emulsion (hereinafter referred to as HSK3486) is a new IV anesthetic drug developed by Sichuan Haisco Pharmaceutical Co., Ltd. HSK3486 is intended to be used in the induction of adult sedation/general anesthesia. HSK3486 has a novel structural design that provides higher potency compared to propofol, and potentially results in less site pain and cardiopulmonary instability. Clinical data to date demonstrated HSK3486 significantly reduces pain on injection and reduces hypotensive effects while still providing anesthesia induction rates equivalent to propofol.

## 1.1. Study Rationale

This is a global 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 objective of this study is to demonstrate that HSK3486 is non-inferior to propofol in the induction of general anesthesia and, furthermore, to demonstrate better anesthetic effects (i.e., desired depth of anesthesia) compared to propofol with potential for less cardiac and respiratory depression. Clinical signs of inadequate depth of sedation during endotracheal intubation include tachycardia, hypertensive response, preserved reflexes (e.g., coughing), bronchospasm, movement on painful stimuli, and a bispectral index (BIS) score >60 (Appendix 2). Cardiovascular responses have been found to be sensitive indicators of noxious stimuli (e.g., endotracheal intubation) during general anesthesia [3,4]. The primary endpoint is successful induction of anesthesia defined by Modified Observer's Assessment of Awareness/Sedation (MOAA/S) ≤1 without >1 top-up doses. A key secondary endpoint requires inducing a desired depth of anesthesia without cardiac and respiratory depression for 15 minutes post initiation of the study drug administration, which is defined by meeting all of the following: no lacrimation, movement, vomiting, coughing, laryngospasm, bucking, swallowing reflex and/or bronchospasm, etc.; no blood pressure (BP) increase >20% from baseline; and a BIS score <60. Furthermore, subjects must not exhibit a decrease in BP requiring intervention, or significant respiratory depression or apnea requiring intervention prior to pharmacologic paralysis for intubation. Incorporating these criteria into a composite endpoint provides a multidimensional approach to assessing an ideal depth of anesthesia which is clinically meaningful and relevant.

Results from the Phase 3 HSK3486-302 study showed that fewer subjects treated with HSK3486 compared to propofol demonstrated inadequate depth of anesthesia for 15 minutes post-dose as indicated by an increase in BP >20% or heart rate (HR) >30% from baseline, or BIS score >60 (HSK3486 24% compared to propofol 46%, p=0.0026). These data support using the composite secondary endpoint and thus has the ability to show a statistically significant difference between HSK3486 versus propofol in achieving the desired depth of anesthesia for induction of general anesthesia.

### 1.2. Background

Induction of general anesthesia refers to the transition in a patient's status from an awake state to an anesthesia state in which the patient can then be operated.

Propofol is widely used clinically and has become the most commonly used IV anesthetic for the induction of general anesthesia in clinical practice due to its fast onset, rapid recovery, high clearance, and convenient target-controlled IV slow injection. However, when propofol is given at its traditional induction dose (2.0-2.5 mg/kg), a single loading dose can cause severe hemodynamic fluctuations, resulting in a significant drop in the patient’s blood pressure, i.e., 15% to 40% [6,7], especially in elderly patients [8]. At the same time, the incidence of respiratory depression is also high when propofol is used; in addition, as the most common adverse reaction of propofol [5], injection-site pain increases the stress and anxiety of the patient, directly or indirectly affecting the smoothness of anesthesia induction. Due to these shortcomings, a new and more advantageous sedative/anesthetic is needed in the market.

Pain on injection is one of the key indicators in clinical trials. Methods employed in many clinical practices to alleviate pain on propofol injection have demonstrated negligible effects [1]. Pain on propofol injection is widely believed to be related to the aqueous phase concentration of the drug in the lipid emulsion formulation [9].

The active ingredient HSK3486 is a chemical entity similar to propofol. It is a single diastereomer with 2 R-type chiral centers; the strategy in the medicinal design of HSK3486 is to realize systematic improvement in the pharmacological and physicochemical properties of the drug-receptor binding, thereby resulting in a compound that is expected to be clinically superior to propofol. HSK3486 has the pharmacodynamic (PD) characteristics of fast onset and quick stable recovery. HSK3486 has better target selectivity and higher in vitro and in vivo activities than propofol, and its potency is approximately 4 to 5 times that of propofol; the free HSK3486 concentration in water phase measured by "ultrafiltration" is lower than that of propofol (MCT Fresenius), suggesting that the injection pain of HSK3486 may be reduced or eliminated versus propofol.

The primary mechanism of action for HSK3486 is to enable chloride ion influx by enhancing the GABAA-mediated ion channel, so as to inhibit the central nervous system. This channel is also a major target of propofol action.

As of Aug 2023, 27 Phase I to III clinical studies evaluating HSK3486 have been completed and 3 are ongoing or planned. Among the 27 completed studies, a total of 1370 were enrolled in the HSK3486 group for observation (94 in Australia + 1108 in China + 168 in US), including 286 healthy subjects (including 66 elderly), 16 subjects with mild to moderate liver damage, 20 subjects with mild to moderate renal damage, 236 patients who underwent colonoscopy, 15 subjects who underwent gastroscopy, 446 subjects who underwent elective surgery, 135 subjects who underwent bronchoscopy, and 126 subjects with mechanical ventilation in ICU, and 90 subjects undergoing gynecology outpatient surgery. Results showed that HSK3486 is generally safe and well tolerated. HSK3486 featured quick onset, rapid pace of regaining consciousness, and approximately 4 to 5 times the potency of propofol. At the same time, compared with propofol the incidence of injection pain is extremely low, less respiratory depression, lower incidence of hypotension, and less impact on the circulatory system.

HSK3486 was approved by the NMPA for "Sedation in Gastrointestinal Endoscopy" and "Induction of General Anesthesia" on December 11, 2020 and February 2, 2021, respectively. The NDA registration applications for the indications of "sedation for bronchoscopy diagnosis and treatment" and "general anesthesia induction and maintenance" were accepted by the NMPA on February, 2021 and June, 2021, respectively.

For more details of clinical studies of HSK3486 conducted, please refer to the Investigator's Brochure [10].

### 1.3. Benefit-risk Assessment

To date, 27 completed Phase I to III clinical studies of HSK3486 have been carried out and a total of 1370 subjects have been exposed to HSK3486. Analysis of data from 1370 subjects have been completed. HSK3486 was generally safe and well tolerated. HSK3486 had better performance than propofol, as manifested by the following: the types of adverse reactions were generally comparable with those of propofol but with a slightly lower incidence; however, the incidence of injection-site pain was significantly lower than propofol, the incidence of dizziness and respiratory-related AEs as well as the proportion of subjects in need of airway management were lower than propofol, the incidence and extent of AEs of cardiovascular depression were comparable to those of propofol.

HSK3486 showed rapid onset of general anesthesia, less airway reactivity during endotracheal intubation (e.g., coughing), relatively stable vital signs, time to successful induction comparable to or slightly better than that of propofol (refer to Propofol US PI 2017), and potency

approximately 4 to 5 times than that of propofol in 156 enrolled subjects undergoing an elective surgery; it meets the needs of general anesthesia induction during surgery well.

To date, HSK3486 has been shown to be a safe and effective sedative/anesthetic in prior clinical trials that is suitable for induction of general anesthesia.

Phase III studies in the US will be conducted to further evaluate the efficacy and safety of HSK3486. In these Phase 3 studies, study drug will be administered preoperatively in a controlled clinical setting by healthcare providers who experience in general anesthesia. Changes in vital signs will be closely monitored during anesthesia, and corresponding risk preventions and control measures will be implemented for known drug reactions such as hypotension and sinus bradycardia, so as to ensure the safety of subjects in clinical studies. An independent data monitoring committee (DMC) will be involved in the conduct of this study to maintain the safety of all subjects dosed with the study drug.

In summary, the safety profile of propofol has been well described based on its clinical use over the past several decades. In 27 clinical studies thus far, HSK3486 has demonstrated a safety profile comparable to propofol, with potentially less cardiopulmonary instability, coupled with the additional benefit of less injection-site pain. The favorable benefit-risk assessment supports the continued evaluation of HSK3486 for induction of general anesthesia.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of HSK3486 may be found in the Investigator's Brochure [10].

# 2. OBJECTIVES AND ENDPOINTS

## 2.1. Objectives

The primary objective of this study is:

- To demonstrate HSK3486 0.4/0.2 mg/kg (0.4 mg/kg IV slow injection for the first dose, an additional 0.2 mg/kg dose 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 dose if needed) in success of induction of general anesthesia in adults undergoing elective surgery.

The secondary objectives of this study are:

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 Objective:

- 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. Endpoints

The primary efficacy endpoint is:

- Success rate of general anesthesia induction: A successful general anesthesia induction will meet both of the following conditions:
  a) Induction success (MOAA/S ≤1) after administration of the study drug, and
  b) One or less top-up dose required without using any rescue drugs.

The secondary efficacy endpoints are:

Key secondary endpoints:

- The proportion of subjects with any injection-site pain at time of drug administration on the Numeric Rating Scale (NRS ≥1).

- The proportion of subjects with successful induction who maintain the desired depth of anesthesia for general elective surgery, and without significant cardiac and respiratory depression within15 minutes post initiation 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 study drug administration, defined by all the following conditions:
  a) Desired depth of anesthesia for general elective surgery is defined if all following criteria are met:
  i) No clinical signs of inadequate depth of anesthesia, such as lacrimation, movement, vomiting, coughing, laryngospasm, bucking, swallowing reflex or bronchospasm etc.
  ii) 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.
  iii) Subjects maintain desired depth of anesthesia for general elective surgery with BIS as an objective assessment (after reaching initial lowest value, BIS remains sustainable level at not more than 60).

  **Note:** Target BIS 40-60 for general anesthesia (Appendix 2).

  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.

  **Note:** It is strongly recommended that each site have available video laryngoscopy, or an acceptable alternative, for unanticipated difficult tracheal intubation. If more than one tracheal intubation attempt is made, the start and end times of first and subsequent intubation attempts should be recorded.

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 oxygen saturation ($SpO_2$) <90% lasting >30 seconds, or life-threatening respiratory depression requiring immediate intervention.

c) No significant cardiac depression indicated by BP 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.

Other secondary endpoints:

- Time to successful induction of general anesthesia: Time from the end of the first administration of the study drug to MOAA/S ≤1.
- Time to the disappearance of eyelash reflex: Time from the end of the first administration of the study drug to the disappearance of eyelash reflex.
- The proportion of the subjects with any moderate injection-site pain at time of drug administration on the Numeric Rating Scale (NRS ≥4).
- The average injection site pain at time of drug administration of HSK3486 compared to propofol on NRS.

The safety endpoints are:

- Safety assessments include AEs, adverse events of special interest (AESI), clinical laboratory test results, vital signs (supine HR, SBP and DBP, MAP, respiratory rate [RR], and $SpO_2$), electrocardiogram (ECG) findings, physical examination findings, and administration of additional medications, or any interventions including medical interventions, e.g., administration of vasoactive drugs to treat clinically relevant changes in BP.

The PK endpoint is:

- Plasma HSK3486 concentration at scheduled time points (Appendix 5).

# 3. INVESTIGATION PLAN

## 3.1. Overall Study Design and Plan Description

This is a global 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.

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 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 if needed) in a blinded manner. Enrolled subjects will be stratified by American Society of Anesthesiologist 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 1) 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. (See Section 6.2.)

Assessments and procedures completed prior to the administration of the study drug in the operating room, the preinduction period, induction period, maintenance period and the follow-up period can be found in Section 7 – Study Assessments and Procedures.

**Population PK Study**

All eligible subjects in this clinical study will be required to provide venous blood samples for population PK study per time schedule planned (Appendix 5).

## 3.2. Discussion of Study Design, Including the Choice of Control Groups

Propofol is selected as the rescue/alternative drug (trade name: Diprivan). Given that propofol is the most common IV drug for anesthesia, should induction fail, the investigator, based on the status of the subject, should give propofol as the first choice of rescue medication; however, based on the discretion of the investigator, an alternative drug may be administered at the appropriate dose and timing as determined by the investigator.

The population in this study includes subjects undergoing elective surgeries that require endotracheal intubation under general anesthesia. For safety considerations, subjects undergoing emergency, cardiothoracic, and intracranial surgeries are excluded.

### 3.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last subject in the study.

### 3.4. Selection of Doses in the Study

#### 3.4.1. Selection of Dose for HSK3486

By analyzing the results of the dose-ascending group and the extension stage (primary) in the Phase II study of HSK3486 for induction of general anesthesia, the following can be seen that:

- Dose selection: Although the efficacy of the 0.5mg/kg HSK3486 group was comparable to that of the 2.0mg/kg propofol group, the efficacy of the 0.5mg/kg HSK3486 group was slightly better than that of the 0.3mg/kg and 0.4mg/kg HSK3486 groups, as manifested by a faster rate of successful induction and a shorter intubation time. In addition, the 0.5mg/kg HSK3486 group did not need top-up doses. However, the safety of the 0.5mg/kg HSK3486 group was slightly worse, as manifested by a larger decrease in BP, higher incidence of injection pain than 0.3 mg/kg HSK3486, and more cases of transient and prolonged QT interval. The 0.3mg/kg HSK3486 group showed better safety and a relatively small proportion of adverse drug reactions (ADRs). However, compared with the propofol group, the 0.3mg/kg group had longer time to successful induction, more obvious intubation reactions, and larger fluctuations in BP and HR, suggesting that the inhibitory effect of 0.3 mg/kg HSK3486 on intubation reactions is not strong enough. At a suitable dose, HSK3486 can be used to induce general anesthesia with a reliable efficacy and safety profile. Based on above considerations, it is reasonable to choose the dose of 0.4 mg/kg (initial dose)/0.2 mg/kg (top-up dose) as the recommended HSK3486 dose for Phase III clinical studies.
- Number of top-up doses and dosing interval: Based on the results of Phase II study for induction of general anesthesia, during induction, 1 (1/8) subject in the dose-escalation group (HSK3486 0.4/0.2mg/kg group) received 1 top-up dose of study drug, and 1 (1/22) subject in the dose-extension stage (0.3/0.15mg/kg group) received 1 top-up dose of study drug. The time to successful induction was about 0.71 to 1 minute. Therefore, in the design of Phase III study on induction of general anesthesia, the top-up dose is set at 1 minute ±10 seconds after the initial dose of the study drug. If the number of top-up doses is more than 1, the induction is considered to have failed.
- Criteria for the selection of top-up dose: The criteria for a top-up dose in the Phase III study of induction of general anesthesia are based on the results of the previous Phase II and III studies in China and are determined according to the MOAA/S score, i.e., if MOAA/S ≤1 is not reached, a top-up dose is required.
- A 25% dose reduction is required for elderly subjects ≥65 years of age for both HSK3486

and propofol. 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%. 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.

- Data from a PK study in elderly subjects (Study HSK3486-108) suggests that there are no significant differences in the PK exposures at 0.4 mg/kg between elderly (≥65 years old) and non-elderly (<65 years old), consistent with physiologically based PK modeling results. A similar efficacy and safety profile was also demonstrated between 0.3 mg/kg elderly and 0.4 mg/kg non-elderly. Of note, both propofol US and UK labels currently recommend a 25% dose reduction in subjects 65 or older.

  The HSK3486 dose will be modified for obese subjects: for subjects with BMI ≤40 $kg/m^2$, total body weight (TBW) will be used to determine dose; for subjects with BMI >40 $kg/m^2$, lean body weight (LBW) will be used to determine dose.

- Based on population PK (PopPK) modeling, subjects with BMI >45 $kg/m^2$ can be expected to have higher simulated maximum concentration ($C_{max}$) and area-under-the-curve ($AUC_{[0\text{-}24\ h]}$) than the PK exposure identified in the Phase 1 single-ascending-dose studies.
- In obese subjects, fat mass and LBW do not increase proportionately. Obese subjects have both an increased amount of fat and LBW; however, LBW accounts for as much as 20% to 40% of the excess TBW. The LBW has been shown to correlate with cardiac output, which is an important determinant in the early distribution kinetics of drugs. Based on published literature, LBW is the ideal weight scalar for drug administration in subjects with BMI >40 [11, 12].
- The anesthetic PD response in subjects with BMI >40 $kg/m^2$ is likely to be different. It has been reported that morbidly obese subjects have significantly decreased half-maximal effective concentration ($EC_{50}$) values compared to control subjects, which suggests increased brain sensitivity to propofol in the morbidly obese population [13, 14].

### 3.4.2. Selection of Dose for Propofol

Propofol has the characteristics of fast onset, rapid recovery, high clearance, and convenient target-controlled slow injection. It has become the most commonly used IV anesthetic in clinical practice. Among various propofol products, Diprivan is the most widely used both domestically and overseas; therefore, propofol is selected as the positive control drug.

Rationale for the selection of the initial and top-up doses of propofol:

In the packaging insert of propofol [9], the dose for inducing general anesthesia is 2.0 to 2.5 mg/kg. The results of the dose-ascending and extension stages of Phase II trials on induction of general anesthesia by HSK3486 showed the propofol 2.0 to 2.5mg/kg group had a 100% success

rate in induction of general anesthesia with good safety and tolerability. Among them, 2.5 mg/kg was found to have a higher incidence of ADRs during dose escalation, so 2.0 mg/kg was selected as the control dose in the extension stage; in summary, to better compare the differences in the efficacy and safety of HSK3486 and propofol, 2.0 mg/kg of propofol has been selected as the initial dose, and the top up- dose is the same as that in the design of the Phase II study on induction of general anesthesia, i.e., 1.0 mg/kg.

The propofol dose will be modified for obese subjects to match HSK3486 dosing regimens due to similar rationales as HSK3486 noted above: for subjects with BMI ≤40 kg/m$^2$, TBW will be used to determine dose; for subjects with BMI >40 kg/m$^2$, LBW will be used to determine dose.

### 3.5. Data Monitoring Committee

An independent DMC will be involved in the conduct of the study to ensure the safety and well-being of all subjects who have been administered study drug is maintained. 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 suspended 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 [CTCAE] Grade 3 and 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. 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.

# 4. SELECTION OF STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the screening and Day 1 visits:

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 6). 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 within the screening period and 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 contraception as defined in 7.3.4 from the time of consent until 30 days post study drug administration.
6. For subjects with known hypothyroidism and/or on thyroid-hormone replacement treatment (i.e., thyroxine), or subjects suspected to have thyroid dysfunction based on clinical laboratory and physical exam, a TSH must drawn and be within normal levels.
7. Capable of understanding the procedures and methods of this study, willing to sign an Informed Consent Form (ICF), and able to complete this study in strict compliance with the study protocol.
8. Willing to comply with the site's COVID guidelines and testing requirements as applicable.
9. Patients with psychiatric/mental disorders must be considered stable on treatment (e.g., SSRIs, SNRIs, TCAs, MAOIs, psychotherapy) per investigator judgement, and no hospitalization and urgent care due to the underlying psychiatric pathology for at least 12 months.

** Women are considered of childbearing potential until becoming post-menopausal, unless she

had a documented hysterectomy or bilateral oophorectomy / salpingo-oophorectomy. A woman is considered to be post-menopausal if she had no menses for at least 12 consecutive months (without an alternative medical cause).

### 4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening and Day 1 visits:

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; subjects having contraindications to propofol, opioids, and their antidotes. In cases where the only previous reaction to opioids was itching or nausea, subjects need not be excluded if the investigator believes the subject is not truly allergic to opioids.
3. Medical condition or evidence of increased sedation/general anesthesia risk as follows:
   a) Cardiovascular disorder: 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) ≥450 ms for males and ≥470 ms 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) Patients with psychiatric/mental disorders who have not been on a stable treatment regimen (e.g., SSRIs, SNRIs, TCAs, MAOIs, psychotherapy) per investigator judgement, for at least 12 months or who have been hospitalized or had emergent/urgent care due to the underlying psychiatric pathology within the last 12 months.

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) History of uncontrolled diabetes in the opinion of the investigator.

g) History of alcohol abuse within 3 months prior to screening, where alcohol abuse refers to daily alcohol drinking >2 units of alcohol (1 unit = 360 mL of beer or 45 mL of spirit with a strength of 40% or 150 mL of wine).

h) History of drug abuse that, in the opinion of the investigator, may confound the interpretation of safety or efficacy in a study subject.

i) For subjects with known hypothyroidism and/or on thyroid-hormone replacement treatment (i.e., thyroxine), or subjects suspected to have thyroid dysfunction based on clinical laboratory and physical exam who has a TSH value outside the normal range.

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 7]), 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 $\leq 1.5 \times 10^9$/L

   b) Platelet count $< 80 \times 10^9$/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.

## 4.3. Subject Discontinuation from the Study

Subject discontinuation from the study criteria will include but is not limited to the following:

1. Withdrawal of informed consent;
2. If it is believed that continued participation in the study will be detrimental to the subject's health as determined by the investigators and Sponsor's medical personnel; or
3. Other.

Subjects may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. Subjects should complete pre-withdrawal examinations as much as possible (same as the follow-up examinations) prior to withdrawal. For subjects who prematurely withdraw from the study, the investigator should ask for the reasons for withdrawal and record in the original documents and electronic Case Report Form (eCRF), and complete the test items for the end of study visit. During the study, if it is found that a female subject or the sexual partner of a male subject is pregnant, the investigator must immediately report it to the Sponsor and the Ethics Committee (EC). All relevant information must be recorded in the source file and the eCRF.

### 4.3.1. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Subjects who do not meet the criteria for participation in this study may be rescreened once within 60 days. Re-screening must be approved by the medical monitor if the screen fail reason is anything other than the screening window has elapsed. Rescreened subjects should be assigned the same subject number as for the initial screening.

### 4.3.2. Subject Discontinuation from Study Treatment

If a subject experiences an AESI of severe hypotension, bradycardia hypoxia due to respiratory depression, QTc prolongation, cardiac arrythmia, or allergy/anaphylaxis which persists despite

routine interventions and does not achieve MOAA/S ≤1 after the initial dose of study drug thus requiring a top-up dose, the subject should stop study treatment and not receive the top-up dose. It is up to the discretion of the Investigator and surgeon whether to proceed with the surgery using alternative standard-of-care medications to induce general anesthesia. Subjects who stop study treatment will remain in the study and continue to be followed for safety assessments according to the Schedule of Assessments.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. Additionally, subjects may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. Refer to the Schedule of Assessments for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Additional reasons for study treatment discontinuation can include, but are not limited to:

- Death
- Adverse event
- Sponsor determination.
- Investigator discretion

### 4.3.3. Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to complete scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to complete required study visits or declines a phone contact by study site:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

#### 4.3.4. Replacement Procedures

Subjects who discontinue or withdraw from the study will not be replaced.

#### 4.3.5. Follow-up of Subjects Prematurely Discontinued from the Study Treatment Regimen or Withdrawn from Study

Subjects who discontinue from the study will be asked to complete final study procedures and will be contacted for the Follow-up Telephone Call as described in the Schedule of Assessments. 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.

### 4.4. Study Stopping Criteria

Enrollment will be immediately stopped after one death 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, 4 or 5) 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. 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.

The determination of thresholds to suspend enrollment incorporates safety data from the prior Phase 3 study in China (Study HSK3486-302) evaluating HSK3486 compared to propofol for induction of general anesthesia in subjects undergoing elective surgery. In that study, 1 (1/176 [0.6%]) propofol-treated subject experienced an SAE of bronchospasm (deemed unlikely related to study drug), and 2 (2/176 [1%]) subjects experienced severe AESIs of hypotension (deemed related to study drug; 1 HSK3486-treated subject and 1 propofol-treated subject). However, the prior Phase 3 study in China enrolled a healthier subject population, in that only ASA-PS class I to II subjects, no elderly subjects (age >65), and no obese subjects (BMI>30) were included. Inclusion criteria for the current study includes ASA-PS class III to IV subjects, elderly subjects (age >65 years with no upper limit), and obese subjects (BMI >30 with no upper limit). It is anticipated this study will enroll a less healthy subject population with more comorbidities,

therefore, thresholds to suspend enrollment of 4 (4/399 [1%]) non-fatal SAEs related to study drug and 8 (8/399 [2%]) severe AEs of interest (CTCAE grade 3and 4) of severe hypotension, bradycardia, hypoxia due to respiratory depression or QTc prolongation occurring within 15 minutes of study drug administration or allergy/anaphylaxis have been selected using clinical judgement.

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.
Reasons for study termination may include, but are not limited to:

- Adverse events unknown to date (i.e., not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration);
- Increased frequency and/or severity and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as baseline signs and symptoms);
- Medical or ethical reasons affecting the continued performance of the study;
- Difficulties in the recruitment of subjects;
- Cancellation of drug development.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the Institutional Review Board (IRB)/EC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.

# 5. STUDY TREATMENTS

## 5.1. Treatments Administered

**Investigational drug:** HSK3486 injectable emulsion

Strength: 50 mg HSK3486 per 20 mL

Supplier: Haisco-USA Pharmaceuticals, Inc.

**Control drug:** Propofol injection

Trade name: Diprivan

Strength: 200 mg Propofol per 20 mL

Supplier: Haisco-USA Pharmaceuticals, Inc.

## 5.2. Preparation, Storage, Handling, and Accountability

HSK3486 should be stored at ≤ 25 °C (77°F) away from light and should not be frozen. Propofol should be stored between 4°C and 25°C (40°F-77°F) and should not be frozen. Both HSK3486 and propofol should be shaken well before use. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The Sponsor will provide sufficient amounts of the study drugs during the study. After the Sponsor provides the study drug to the study site, the principal investigator or authorized representative will sign for receipt upon verification and record information of the study drugs. Once receiving the study drugs, the study site should store it under the storage conditions specified in the drug label. The study drugs should be kept by a designated personnel (non-blinded) authorized by the investigator for regular accounting and record of the drug quantity. Non-blinded clinical research associates (CRAs) will supervise the drug management.

Only subjects enrolled in the study may receive study treatment and only trained and authorized site staff may supply or administer study treatment. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). The study drugs cannot be used for any purpose other than this clinical study, and it may not be sold or transferred to anyone who is not involved in this clinical study.

The use of each study drug should be recorded in a timely manner with a signature upon review. All remaining drug products, packaging, and labels are returned or destroyed at the sites after Sponsor authorization during and after the study. Remaining empty vials and packages are destroyed and recorded according to the standard operating procedures at local study sites.

Further guidance and information for the final disposition of unused study treatment are provided in the pharmacy manual.

**Drug Preparation**

On the day of drug administration, the non-blinded preparation personnel will locate the corresponding study drug according to the drug number applied by the Interactive Web Response System (IXRS) and convert the drug volume according to formula below; the drug will then be drawn into a certain number of syringes (1 initial dose + 1 top-up dose). In addition, the required alternative (propofol) rescue drug for the subjects is also prepared.

The non-blinded administration personnel will check the drug information recorded by the preparation staff and transfer the study drug to the operating room. Both the drug volume calculation and drug preparation processes should be documented in the drug dispensing record form.

Staff for drug preparation and administration are non-blinded and must not disclose subject administration information to investigators, subjects, or any other blind personnel.

Doses and method of administration for HSK3486 are as below:

Volume of initial/top-up dose = dose group (mg/kg) x baseline body weight (kg) ÷ 2.5 mg/mL.

HSK3486 is administered by using 30 [±5] seconds of slow injection. If a top-up dose is required, 50% of the initial calculated dose is given via slow injection over 10 [±2] seconds.

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 up to 1 minute for this population (IV slow injection over 30-60 seconds).

For ASA grade 3-4 subjects, the dose can be reduced by 25-50% per investigator discretion. The administration time should be extended up to 1 minute for these populations (IV slow injection over 30-60 seconds).

For subjects with BMI ≤40 kg/m$^2$, TBW will be used to determine HSK3486 dose; for subjects with BMI >40 kg/m$^2$, 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: LBW = (9270 x TBW (kg)) / (6680 + (216 x BMI))
- For females: LBW = (9270 x TBW (kg)) / (8780 + (244 x BMI))

Doses and method of administration for propofol are as below:

Volume of initial/top-up dose of propofol = dose group (mg/kg) x baseline body weight (kg) ÷ 10 mg/mL. The method of administration of propofol is the same as that of HSK3486.

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 up to 1 minute for this population (IV slow injection over 30-60 seconds).

For ASA grade 3-4 subjects, the dose can be reduced by 25-50% per investigator discretion. The administration time should be extended up to 1 minute for these populations (IV slow injection over 30-60 seconds).

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

The rescue dose, **propofol,** is prepared as 100% of the initial calculated dose and administered per propofol guidelines above. The rescue dose administration time should be extended up to 1 minute (IV slow injection over 30-60 seconds) for elderly subjects ≥65 years of age and for ASA grade 3-4 subjects who require a dose reduction.

### 5.3. Method of Treatment Assignment

The randomization of the subjects in this study is completed using the IXRS. After the subjects pass the screening, the investigator(s) or designee shall log into the IXRS and enter the general

information of each subject, such as the screening number, sex, age, height, and body weight, to obtain the randomization number. Then, the randomization number and corresponding treatment group are assigned using the IXRS and submitted to the drug preparation personnel (non-blinded) for drug preparation. The non-blinded site staff will have to log into the IXRS to obtain the kit numbers and dosages.

Study treatment will be dispensed at baseline visit (Day 1) summarized in the Schedule of Assessments.

### 5.3.1. Dose Modification

Dosage adjustments are not allowed unless these conditions are stipulated in the protocol 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. For ASA grade 3-4 subjects, the dose can be reduced by 25-50% per investigator discretion. The administration time should be extended up to 1 minute for these populations (IV slow injection over 30-60 seconds).

Both the HSK3486 and the propofol doses will be modified for morbidly obese subjects: For subjects with BMI ≤40 kg/$m^2$, TBW will be used to determine dose; for subjects with BMI >40 kg/$m^2$, LBW will be used to determine dose. LBW should be calculated using the Janmahasatian formula included in section 5.2.

## 5.4. Blinding

This is a double-blind study. The IXRS will be programmed with blind-breaking instructions. The study blind may be broken if, in the opinion of the investigator, it is in the subject's best interest to know the study treatment assignment. Sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the subject's condition (e.g., antidote is available). In this case, Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

The study staff are divided into 2 groups: blinded and non-blinded. The study ensures that the investigators, subjects, and the entire operating process of the study are blinded.

Blinded staff include the principal investigator, study nurse, clinical research coordinator, blinded CRA, and all the other personnel involved in the documentation, assessment, analysis, and review of efficacy/safety endpoint data. These staff are primarily responsible for all study

procedures other than drug management (such as subject screening, documentation, assessment, analysis, and review of efficacy and safety endpoints).

The non-blinded staff are responsible for the management, preparation, and administration of the study drug. Detailed descriptions of blinding procedures are described in the Blinding Plan.

Once the study is started, both the blinded and non-blinded study staff ensure that their respective responsibilities are performed in strict accordance with protocol requirements. The blinded and non-blinded staff ensure that no communication related to study drug groups takes place to avoid unintentional unblinding. Once assigned, blinded and non-blinded staff must remain in their respective role for the duration of study participation.

## 5.5. Treatment Compliance

All study drugs will be administered at the site by site personnel; therefore, subject compliance will not be measured.

## 5.6. Preinduction Drugs

***Fentanyl and Midazolam***

All subjects will receive preinduction IV midazolam at dose 0.04 mg/kg, up to 3 mg maximum per subject over 15 [±2] seconds at 5 minutes [±30 seconds] prior to initiating study drug. And all subjects will receive preinduction IV fentanyl 1 mcg/kg rounded up to the nearest 25 mcg, up to 100 mcg maximum per subject over 15 [±2] seconds at 2 minutes [±10 seconds] prior to initiating study drug. Fentanyl and midazolam doses can be reduced according to the patient's age and comorbidities as per the anesthetist's discretion.

# 6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

## 6.1. Concomitant Therapies

The investigator will review all medications and therapies taken by the subject (or are intended to be taken during the study) during screening and will assess whether or not the medications or therapies will impact the study.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Any medications/supplements/vitamins used by the subjects during Day of Surgery and after surgery until the end of the study (Day 8) are classified as concomitant medication except for study drugs and combination drugs.

Any medications/supplements/vitamins used before the Day of Surgery are classified as previous medications. All previous medications used by the subjects within 1 month before screening should be recorded in the source medical record and the eCRF.

A record of concomitant medication should consist of drug name (generic name), dose and number of daily doses, method of administration, start and end time of administration, and reason for use.

Prior to, during, and after surgery, antiemetics, hemostatics and antibiotics can be used according to the clinical situation of the subjects. Postoperative use of analgesics can be determined by the investigators when needed.

During the study, drugs that may affect the QT interval should be used with caution (Appendix 8); in case of an emergency where such drugs must be used, please record the use of the drugs and the reason.

### 6.2. Prohibited Therapies

No sedative hypnotics, anesthetic drugs, analgesics, systemic neuromuscular blocking agents or any medications that relieve pain other than those prescribed in the protocol are allowed on Day 1 until the completion of endotracheal intubation, including but not limited to the following:

- Inhalation anesthetics: isoflurane, enflurane, desflurane, halothane, anesthetic ether, nitrous oxide

  **Note:** Sevoflurane will be used for maintenance of general anesthesia upon the completion of endotracheal intubation.
- Intravenous anesthetics: thiopental sodium, ketamine, etomidate, sodium oxybate, lidocaine
- Systemic neuromuscular blocking agents (other than protocol-prescribed rocuronium): atracurium, cisatracurium, mivacurium, succinylcholine, vecuronium, pancuronium

  **Note:** Regional and local neuromuscular blocking agents and anesthetics are permitted if not involving the upper extremity where study drug is administered.
- Analgesics : morphine, methadone, codeine, pentazocine, tramadol, NSAIDs, APAP, etc.

  **Note:** Additional IV fentanyl may be administered for intraoperative analgesia only after initiation of sevoflurane, preferably after 15 minutes following the end of study drug administration.
- Other drugs that relieve pain: Gabapentin
- Benzodiazepines: Valium, Ativan, etc.

**Note:** spinal and epidural blocks are not permitted at any time on Day 1.

# 7. STUDY ASSESSMENTS AND PROCEDURES

## 7.1. Study Procedures

### 7.1.1. Screening Period (Day -13 to Day 1)

During the screening period and before the investigator conducts any study procedures, he/she will discuss with subjects their clinical condition, the commonly used anesthesia methods, the characteristics of the study drug, and the possible adverse reactions that can be caused by the study drug. The subjects will sign the ICF and receive a signed copy.

After signing the ICF, the subject will be assigned a screening number, and the following procedures/evaluations will be conducted as indicated in the Schedule of Assessments:

- Assess inclusion/exclusion criteria.
- Demographics.
- Collect medical history (disease history, allergy history, alcohol history and surgical anesthesia history, etc.).
- Prior medications.
- Modified Mallampati score assessment (Appendix 7).
- Physical examination, including ASA-PS score (Appendix 6).
- Vital signs (HR, RR, $SpO_2$, SBP, DBP, MAP, Temp) after the subject has been resting supine for ≥5 minutes.
- Height, weight, and calculated BMI.
- 12-lead ECG. ECG results collected within 30 days of Day 1 are acceptable for eligibility.
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis, etc.). Lab results collected within 30 days of Day 1 are acceptable for eligibility. Required screening laboratory samples must be collected and sent to the central laboratory within the screening period.
- Conduct serum human chorionic gonadotropin (HCG) test (for women of childbearing potential only).
- Instruct subject to fast at least 6 hours before surgery. 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.
- Document AEs (after signing informed consent).

**Note:** This study only collects the subjects' disease history within 6 months before screening and all previous medications used within 1 month before screening, and the above information should be recorded in the source medical record and the eCRF.

### 7.1.2. Day of Surgery (Day 1)

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/m2).

The screening BMI will be used to calculate study drug dose. 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 IV top-up dose if needed) or propofol 2.0/1.0 mg/kg (i.e., 2.0 mg/kg IV slow injection over 10 [±2] seconds followed by an additional 1.0 mg/kg top-up dose if needed) in a blinded manner.

All throughout the preinduction and induction periods a timing device must be used to allow accuracy and sequencing of necessary assessments.

On the day of surgery, the following procedures as indicated in the Schedule of Assessments will occur:

Prior to entering the operating room:

- Refer to 7.1.1 to ensure required screening laboratory samples have been collected and sent within the screening period to the central laboratory.
- Measure vital signs (HR, RR, $SpO_2$, SBP, DBP, MAP, Temp) to confirm consistent with eligibility criteria (after the subject has been resting supine for ≥5 minutes).
- Conduct urine human chorionic gonadotropin (HCG) test (for women of childbearing potential only).
- Obtain 12-lead ECG at Day 1 visit only if the subject reports any cardiopulmonary symptoms that warrant an ECG, in the opinion of the investigator. The 12-lead ECG should be repeated to assess its compliance with the inclusion/exclusion criteria.
- Verify inclusion/exclusion criteria.
- Premedication allowed except sedative-hypnotics, analgesic drugs or any medications that relieve pain.
- Orient subject to the use of the NRS pain assessment.

Preinduction period:

- Confirm preoperative readiness (subject is hemodynamically stable and has followed

preoperative instructions, and there is no evidence of acute illness such as fever).

- 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.
- Start maintenance IV infusion (NS, LR, or 5% dextrose solution).
- 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.
- Administer oxygen via face mask (≥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.
- Attach BIS monitor to subject (either in preoperative anesthesia unit or in operating room, depending on local practice). 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 per subject 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 fentanyl dose can be reduced according to patient's age and comorbidities as per the anesthetist's discretion. 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.
- Information about any adverse events (AEs) and concomitant medications will be recorded.
- Note: Throughout the preinduction and induction periods, a timing device must be used to allow accuracy and sequencing of necessary assessments.

<u>Induction period of general anesthesia:</u>

- Monitor vital signs (HR, RR, $SpO_2$, SBP, DBP, MAP, Temp) continuously. HR, 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. RR should be recorded once every 2 minutes [± 30 seconds] from the start of study drug administration until administration of rocuronium.

**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. Timepoints for MOAA/S ≤1 within 1 to 40 seconds should be recorded.
- 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 calculated dose of study drug 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 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 at 5 minutes [±30 seconds] post midazolam preinduction medication administration stop time. Top-up doses should be administrated within 10 seconds once MOAA/S is evaluated >1.
- Injection-site pain is evaluated verbally by Numeric Rating Scale (NRS; Appendix 3). Upon administration 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. 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.
- 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. Timepoints for loss of eyelash reflex within 1 to 40 seconds 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 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 duration of the surgery.
- Monitor 3-lead or 5-lead electrocardiogram (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.
- 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 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:** For subjects with BMI ≤40 kg/$m^2$: If the exact calculated Rocuronium dose cannot be drawn, round up or down to the nearest mg (whole number) depending on investigator preference/SOC.

  **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 start and end time of administration should be recorded).
- Information about any adverse events (AEs) and concomitant medications will be recorded.

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 post 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.
- 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.
- Blood sample for population PK study will be collected at the time points as indicated in (Appendix 5).
- Information about any adverse events (AEs) and concomitant medications will be recorded.

#### 7.1.3. Follow-up Period 6 (±2) hour Post Study Drug and 24-hour Post Study Drug Phone Contact [Day 2]

For the first 6 (±2) hour post study drug evaluation, study assessments and procedures will be assessed as indicated in Schedule of Assessments:

- Postoperatively, the subject will be monitored per facility/institution standard of care in the PACU until the 6 (±2) hour follow-up assessments. However, when deemed discharge ready per institution/facility policy, inpatients may be transferred to their rooms where the 6 hour follow up assessments can be performed. For subjects undergoing outpatient surgery, upon discharge readiness they may be released from the PACU but must remain in the facility/institution as well as be accompanied by a responsible individual until the 6 (±2) hour follow-up assessments. The responsible party can be either a personal acquaintance or personnel from the institution.
- In the 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 4).
- After the surgery, vital signs (HR, RR, $SpO_2$, SBP, DBP, MAP, Temp) will be assessed at 6 (±2) hours post study drug administration.
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis) will be obtained at 6 (±2) hours post administration of study drug for shipment to central laboratory.
- Obtain 12-lead ECG at 6 (±2) hours post study drug administration, and as clinically indicated.

Note: If surgery lasts >4 hours, vital signs, clinical laboratory tests, and 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 PACU.

- Document AEs and concomitant medications.
- 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.

24-hour follow-up: Phone Contact

- Subjects will be evaluated by a follow-up telephone call 24 [±6] hours after study drug administration.
- Information about any AEs and concomitant mediations will be collected and recorded.

### 7.1.4. Phone Contact (Day 8)

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.

## 7.2. Efficacy Assessments

### 7.2.1. Success Rate of Anesthesia Induction

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 1), observation and evaluation are carried out stepwise, and the cross-level evaluation should not be carried out**.

MOAA/S scoring: The subject's name is called during induction to observe the subject's response to name calling with a normal tone. Lightly stimulate or shake the subject after the subject falls asleep and observe the subject's response to painful stimulation. 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 should be recorded.

### 7.2.2. Composite Endpoint to Evaluate Desired Depth of Anesthesia

Composite endpoint of desired depth of anesthesia for general elective surgery is defined if all following criteria are met:

- Proportion of successfully induced subjects treated with HSK3486 compared to propofol with no any clinical symptoms in response to tracheal intubation, such as lacrimation, movement, vomiting, coughing, laryngospasm, bucking, swallowing reflex or bronchospasm, or an event where no SBP, DBP, or MAP increases more than 20% from baseline in response to any major operational procedures or noxious stimulus in defined period ,within 15 minutes post initiation start of study drug administration or up to the start of second tracheal intubation attempt.
- Subjects maintain desired depth of anesthesia for general elective surgery within 15 minutes post initiation of study drug administration with BIS as an objective assessment (after reaching the initial lowest value, BIS remains sustainable level at not more than 60 during 15 minutes after study drug administration).

  **Note:** Target BIS 40 to 60 for general anesthesia (see Appendix 2 for BIS guidance).

  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.

- 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 $SpO_2$ <90% lasting >30 seconds, or life-threatening apnea or hypoxia requiring immediate intervention.

- 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.

### 7.2.3. 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 3). 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 should be oriented to the NRS for the evaluation of injection-site pain. 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 administration 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.

### 7.2.4. 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 end of the first administration of the study drug to the time when MOAA/S ≤1.

#### 7.2.5. 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 end of the first administration of the study drug to the time when eyelash reflex is lost.

#### 7.2.6. Successful induction without non-optimal anesthetic effects

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 similar statistical methods as for the secondary composite efficacy endpoint.

#### 7.2.7. 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 2) for BIS guidance).

#### 7.2.8. Brice Awareness Questionnaire

Recall of awareness during surgery, assessed postoperatively, will be evaluated using the Brice Awareness Questionnaire (see Appendix 4).

#### 7.2.9. Use of Study Drugs and Alternative Drugs

The use of HSK3486 (including the time and the amount of top-up dose) is evaluated from the end of study drug administration to the time of successful induction. The use of propofol (including the time and the amount of top-up dose) is evaluated from the end of study drug administration to the time of successful induction. The proportion of subjects using the alternative drug (propofol) will also be calculated for each dose group.

### 7.3. Safety and Tolerability Assessments

#### 7.3.1. Adverse Events

Adverse event definitions and assignment of severity and causality are detailed in (Appendix 9).

Adverse events will be elicited from the subject (or, when appropriate, from a caregiver, surrogate, or the subject's legally authorized representative) by the study site staff using a non-leading question such as "How are you feeling today?" or "Have you had any health concerns since your last visit?"

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue the HSK3486 (see Section 4.3.2).

When possible, AEs should be reported as the unifying diagnosis rather than individual signs and symptoms of an underlying condition (e.g., fever, cough, and elevated white blood cells [WBC] associated with pneumonia should be reported as pneumonia). Laboratory values themselves are usually not AEs, especially when a component of the underlying AE (e.g., an elevated WBC associated with pneumonia should not be reported as a separate AE).

If arterial blood pressure is <90 mmHg and greater than a 30% decrease from baseline, an adverse event will be recorded.

**AEs Do Not Include the Following:**

- Anesthetic effect-related sleepiness, somnolence, or even loss of consciousness occurring during administration (i.e., the intended therapeutic effect of the drug under study)
- Chronic diseases that are present before participating in the clinical study
- Elective medical examination or surgery scheduled prior to enrollment into the study
- Overdose of the study drug or concomitant medication not resulting in any signs or symptoms
- Lack of efficacy should be captured as a treatment failure for clinical efficacy, not as an AE.

### 7.3.2. Reporting Serious Adverse Events

For the definition of an SAE please see Appendix 9. All SAEs, occurring after the signing of the ICF until the end of study and regardless of study drug relationship, must be reported by SAE Electronic Case Report Form (eCRF) form within the clinical database (Medidata RAVE) within 24 hours of obtaining knowledge of the event. The Investigator will be responsible for reporting serious adverse events to the IRB/EC.

In the case of clinical database outage or the site is unable to access the system, the investigators will be requested to complete a Safety Event Report Form in English and report it by facsimile or email to Rho. The facsimile report should include all available information requested on the SAE Form. Initial reports of SAEs should never be left on telephone voicemails. Always email or fax SAE reports and follow with a telephone call if needed.

**Serious Adverse Event Reporting Contact Information:**

[redacted]

The SAE Form will collect data surrounding the event (e.g., the nature of the symptom[s], time of onset in relation to initiation of therapy, duration, intensity, and whether or not therapy was interrupted or discontinued). The investigator's assessment of the probable cause of the event will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic tests reports, and procedures as well as all pertinent medical information related to the event will also be collected.

Rho will forward SAE queries requesting incomplete or missing information directly to the investigator. It is the investigator's responsibility to be diligent in providing this information back to Rho as soon as it is available.

If an Investigator becomes aware of a serious adverse event within 30 days after the last dose of study drug and it is considered by him/her to be caused by the study drug with a reasonable possibility, the event must be documented and reported through completion of the adverse event eCRF.

### 7.3.3. Adverse Events of Special Interest

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

- Hypoxemia due to respiratory depression is defined as $SpO_2$ <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 and 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 Day 2 phone contact.
- 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 6 (±2) hours post study drug.
- QTc prolongation: QTc intervals of ≥ 450 ms in males and ≥ 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 [15, 16].
- Adverse events of thrombogenicity/hemolytic disorders will be considered an AESI.

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 7.2.3) for injection-site pain evaluation.

#### *7.3.3.1. Abuse-related AEs of Interest*

Both HSK3486 and propofol cross the blood-brain barrier and have 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 should be reported as an AE. Investigators and site personnel should 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.

For all abuse-related AEs of interest, the time of onset and duration of the event, dose administered, severity and outcome should be recorded.

While not AEs, any subject dropouts and lost or unaccounted for drug product (which could be indicative of abuse-related aberrant behavior) needs to be documented and recorded by site personnel.

### 7.3.4. Contraception and Pregnancy

Currently, the effects of HSK3486 on the fetus are still unknown. Therefore, female subjects of childbearing potential and male subjects with female partners of childbearing potential are required to adopt appropriate contraceptive measures before (from screening) and during the study (30 days post study drug administration). For male subjects who have not been sterilized, their female partners of childbearing potential must also use appropriate contraception. Effective contraceptive measures include female bilateral tubal ligation, male vasectomy, hormone contraceptives (oral, implanted, injected and transdermal), the combination of intrauterine contraceptive device and barrier contraceptive (condoms, cervical caps) or abstinence. Male subjects should refrain from donating sperm from Day 1 to 30 days post study drug administration.

If a female subject or a female sexual partner of a male subject who has taken the study drug becomes pregnant during the study period (from signing ICF to 30 days post study drug administration), the investigator should immediately record the pregnancy information and fill out a pregnancy-specific report and notify the Contract Research Organization (CRO) designated by the Sponsor within 24 hours of being informed of the event. The investigator should also report the event to the IRB/EC in accordance with the ethical requirements of each study site.

The pharmacovigilance personnel of the CRO should review the pregnancy report form in accordance with the standard operating procedures and report it to the Sponsor within one business day of being informed of the event. If the event occurs during the study period, the pregnant female subject should withdraw from the study for reasons of protocol deviation.

A pregnancy event should be followed up to the end of pregnancy or 8 weeks after the fetus is born. The follow-up information of pregnancy events is recorded in the source file.

If pregnancy results meet SAE criteria, i.e., spontaneous abortion, induced abortion, stillbirth, neonatal death, and congenital malformations (including deformities in aborted babies), the investigator shall report in accordance with the SAE reporting procedure.

### 7.3.5. Clinical Laboratory Evaluations

Laboratory tests include the following:

- Blood routine (Hematology) (about 2 mL of blood sample): WBC count with differential (% and absolute count) including neutrophils, lymphocytes, monocytes, basophils, eosinophils; red blood cell (RBC) count, Hb, hematocrit (HCT), MCH, MCHC, MCV and platelet count (PLT).
- Blood biochemistry (about 5 mL of blood sample): liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], total bilirubin [TBIL], total protein [TP], albumin [ALB], lactate dehydrogenase [LDH]), blood lipids (triglycerides [TG], cholesterol [TC], low-density lipoprotein [LDL], high-density lipoprotein [HDL]), electrolytes (sodium [Na], potassium [K]), chloride [Cl], calcium [Ca], phosphorus [P], bicarbonate [HCO3], renal function (uric acid [UA], blood urea nitrogen [BUN], creatinine [Cr]), blood glucose (Glu), and thyroid stimulating hormone (TSH).
- Urinalysis (about 7 mL of fresh urine sample): color and appearance, urinary protein (PRO), urinary glucose (GLU), microscopic exam including urinary WBCs and RBCs, urinary ketone bodies (KET), pH and specific gravity, leukocytes, bilirubin, nitrite, and occult blood.

Laboratory tests are performed in the screening period and 6 (±2) hours post administration of study drug except for TSH. TSH is only drawn at the screening visit for subjects with known hypothyroidism and/or on thyroid-hormone replacement treatment (i.e., thyroxine), or subjects suspected to have thyroid dysfunction based on clinical laboratory and physical exam. In those cases where local laboratory results are utilized to confirm eligibility, required screening laboratory samples must be drawn and sent to the central laboratory within the screening period. Local laboratory results will be maintained in the source documents but not be entered into the eCRF.

For cases where central and local labs are drawn within the screening period to confirm eligibility, blood volumes noted above in bullets 1 and 2 will be increased up to approximately 15 mL total. Urine volume noted in bullet 3 will be increased up to approximately 15 mL.

### 7.3.6. Vital Signs, Physical Examination, and Other Safety Evaluations

#### *7.3.6.1. Vital Signs*

Vital signs include RR, HR, $SpO_2$, Temp, BP (SBP, DBP, and MAP).

During screening, vital sign examination should be performed after resting for at least 5 minutes. If the results exceed the inclusion/exclusion criteria and are confirmed after repeated tests, the subject shall not be enrolled.

For the pre-anesthetic preparation period, after the anesthetic monitor is mounted, baseline vital signs values will be the measurement immediately prior to initiation of study drug administration.

During anesthesia induction period, RR should be recorded once every 2 minutes [±30 seconds] from the start of study drug administration until administration of rocuronium. During anesthesia induction and maintenance period, vital signs are continuously monitored, and values are recorded once every 2 minutes [±30 seconds] (including vital signs monitored at the start of medication) for 30 minutes post study drug administration ($SpO_2$ value should be recorded once every 1 minute [±15 seconds]), and then at 6 [±2] hours post study drug administration.

If arterial blood pressure is <90 mmHg and greater than a 30% decrease from baseline, an adverse event will be recorded.

#### *7.3.6.2. Physical Examinations*

Physical examinations include skin, head, and neck, cardiovascular system, respiratory system, gastrointestinal system, psychological and neurological system, and musculoskeletal system. ASA-PS and Mallampati (oropharyngeal exam) classifications will also be evaluated. These assessments will be completed at screening, and a focused physical exam will be repeated as needed to assess AEs.

#### *7.3.6.3. 12-lead ECG and 3-lead/5-lead ECG*

In the 12-lead ECG examination, the values of QT interval, QTcF interval, PR interval, QRS interval, RR interval and their clinical significance determinations are recorded. The 12-lead ECG examination is done during the screening period. 12-lead ECG results collected within 30 days prior to Day 1 may be used to confirm eligibility. Obtain 12-lead ECG within the screening period only if the subject reports any cardiopulmonary symptoms that warrant an ECG, in the opinion of the investigator. A 12-lead ECG will be obtained at 6 [±2] hours post study drug administration and as clinically indicated. During the surgery, a 3-lead or 5-lead ECG (i.e., rhythm strip) is monitored continuously. If the 3-lead ECG shows clinically significant abnormalities, the investigators will decide whether to add a 12-lead ECG based per investigator's discretion.

### 7.3.7. Use of Additional Medication or Any Interventions

Administration of additional medication or any interventions including medical interventions, e.g., administration of vasoactive drugs, necessary due to a clinically relevant change in BP, should be documented.

### 7.4. Pharmacokinetic Analysis

To maintain the blind, all subjects should undergo PK blood sampling regardless of their groups. However, only the blood samples in the HSK3486 group are tested and analyzed; unless requested by the Sponsor or its designated personnel, the propofol group may also be analyzed.

To ensure the accuracy of the PK data, it is necessary to accurately record the actual start and end time of dosing, the dose, and the blood sampling time of each subject.

The blood collection time points are listed in Appendix 5. Approximately 2 mL of venous blood is collected at each time point.

For the requirements of collection, processing, transportation, and analysis of blood samples, please see “Central Laboratory Manual”.

# 8. SAMPLE SIZE AND DATA ANALYSES

## 8.1. Determination of Sample Size

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 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 first primary endpoint is statistically significant) assuming $\alpha$=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 first primary endpoint is statistically significant) to the superior testing, assuming $\alpha$=0.035 (2-sided), the proportion of subjects with successful induction, maintained desired depth of anesthesia for general elective surgery, without significant cardiac and respiratory 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, 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).

Enrolled subjects will be stratified between the 2 treatment groups by ASA-PS grade I to II and III to IV; age <65 and ≥65 years; and BMI <35 and ≥35 kg/$m^2$. The stratification schema will be described in the Statistical Analysis Plan.

## 8.2. Analysis Populations

**Full Analysis Set (FAS)**: All randomized subjects who have received any dose of the study drug (HSK3486 or propofol).

**Per Protocol Set (PPS)**: All subjects from FAS who have completed primary efficacy endpoint measurement will be considered for 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.

**Safety Set (SS)**: Includes all randomized subjects who have received any dose of the study drug and have post-dose safety assessment data.

The FAS will be the primary analysis population for efficacy and PPS will be the supportive analysis population for efficacy analysis. Safety endpoints will be analyzed using the SS.

## 8.3. General Considerations

Continuous variables will be summarized by the standard descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Frequency of subjects or events and percentages will be summarized in categorical variables. Details of the statistical analyses will be given in a separated Statistical Analysis Plan (SAP).

## 8.4. Efficacy Analysis

### 8.4.1. Primary Efficacy Outcome Measure

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 $\delta$ 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) are estimated by Farrington-Manning method in the FAS. The stratification factors will be included in the analysis. 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.

### 8.4.2. 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 [FDA] 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.

### 8.4.3. Secondary Efficacy Outcome Measures

The proportion of subjects with successful induction, who maintain desired depth of anesthesia for general elective surgery, and without significant cardiac and respiratory depression between the time of successful induction and 15 minutes post initiation of study drug administration (prior to administration of rocuronium bromide) in both groups and difference between groups and 95% CI will be calculated. The p-value for comparison between groups will be obtained based on the Cochran-Mantel-Haenszel Chi-squared test using the stratification factors in the study randomization.

The proportion of the subjects with any injection-site pain (NRS ≥1) and moderate pain (NRS ≥4) will be analyzed, as well as the mean NRS pain score for each treatment group.

The median and its 95% CI of time to successful induction of general anesthesia and time to the disappearance of eyelash reflex will be provided by groups using the Kaplan-Meier (KM) method. The KM estimates and 95% Cis at selected time points will also be reported.

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 similar statistical methods as for the secondary composite efficacy endpoint.

The change of BIS during the period of anesthesia post study drug administration up to 15 minutes will be summarized descriptively by treatment group.

The Brice Awareness Questionnaire results will be summarized descriptively by treatment group.

The use of study drugs and remediation drugs will be summarized descriptively by treatment group and between-group p-values.

### 8.4.4. Methods for the Control of Type I Error

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 stops. 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 is tested at $\alpha=0.05$; otherwise testing stops. This procedure controls the familywise Type I error rate at the overall $\alpha=0.05$ 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.

### 8.5. Safety Analysis

Safety endpoints include Aes, clinical laboratory test results, vital signs (supine) HR, SBP and DBP, RR, and $SpO_2$, ECG findings, physical examination findings, and administration of additional medication or any interventions including medical interventions, e.g., administration of vasoactive drugs, necessary due to a clinically relevant change in BP. No formal statistical analysis of the safety data will be performed.

All Aes will be coded according to the MedDRA version 25.0 or later and graded for severity according to CTCAE version 5.0. The number and percentage of subjects with treatment-emergent adverse events (TEAEs), SAEs, AESIs (Section 7.3.3), TEAEs related to study drug, SAEs related to study drug, TEAEs of Grade 2 or higher, TEAEs leading to treatment discontinuation, TEAEs leading to study discontinuation, and TEAEs leading to death will be summarized by system organ class (SOC), preferred term (PT), and groups. In addition, the severity of TEAEs and relationship to study drug will be summarized by SOC, PT, and treatment groups.

Laboratory test variables will be summarized by treatment group and visit using descriptive statistics. Shift tables between baseline and post-baseline time points will be presented by laboratory test and treatment group. 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.

Descriptive statistics of vital signs, pulse oximetry measurements, site pain on study drug administration with intensity rating on a verbal score, and ECG results at each visit will be presented.

**Note:** Since injection-site pain has been recorded and analyzed in the efficacy endpoints, it is no longer recorded in the Safety endpoints.

An independent DMC will be involved in the review of all safety data at approximately 30% enrollment, and on an ad hoc (as needed) basis as described in Section 3.5, as well as described in the DMC Charter.

### 8.6. Pharmacokinetic Analysis

The plasma concentration data from this study will be pooled with those from other clinical trials of HSK3486 to establish a population PK model. This model will be used to evaluate the effects of internal and external covariates on the PK of HSK3486.

### 8.7. Interim Analysis

No formal interim analyses will be conducted.

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# 10. APPENDICES

## Appendix 1 Modified Observer's Assessment of Awareness/Sedation (MOAA/S) Scale

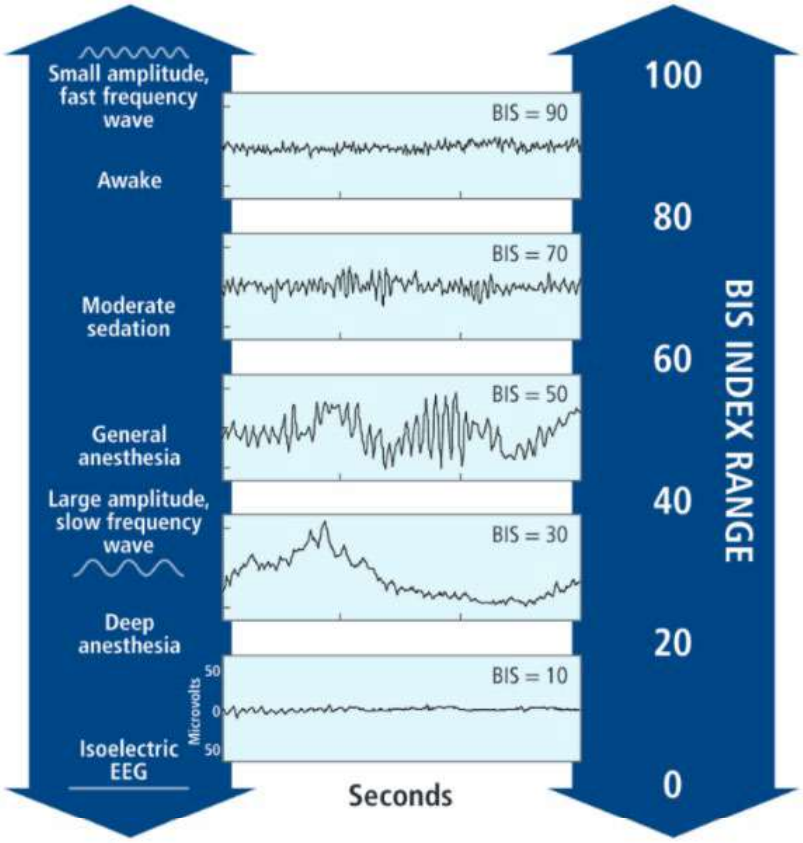
The assessment for MOAA/S is performed stepwise and skipping of any grade is not allowed. The judgment of recovery can be based on a reverse order of scoring.

| 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) |

## Appendix 2 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).

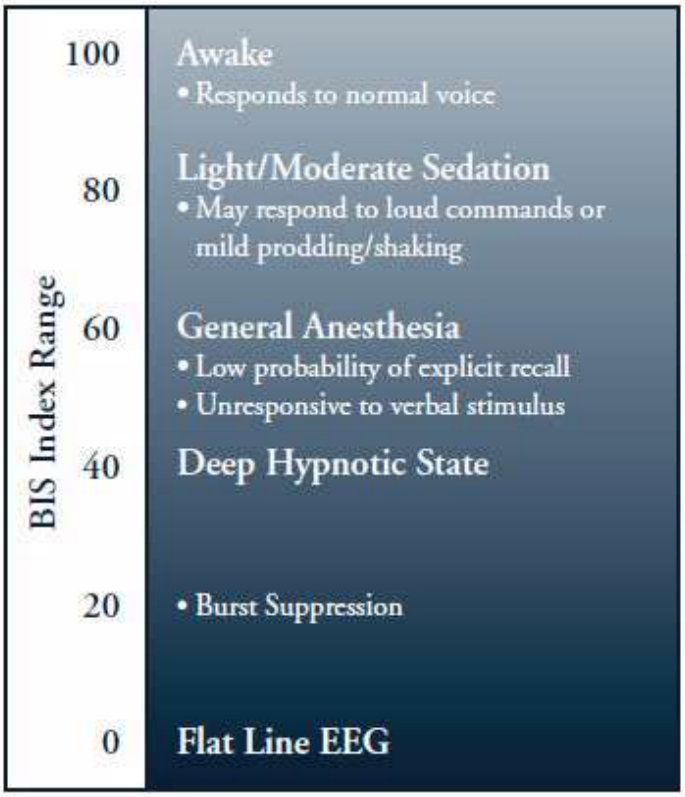
**Figure 2 The BIS Index is scaled to correlate with important clinical endpoints during administration of anesthetic agent.**



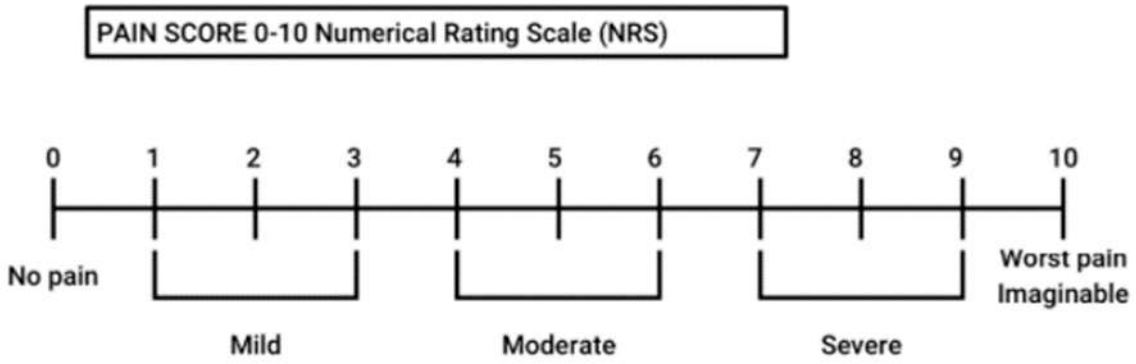

It should be noted that the BIS Index range represents a continuum that correlates to the clinical state and expected responses (Figure 3).

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**




**Appendix 3 Numerical Rating Scale (NRS) for Grading of Injection-site Pain**



**Appendix 4 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]:

**Appendix 5 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 |

Note:

1. Up to 1 top-up dose of study drug is allowed. "The end of last dose of study drug" refers to the last dose of study drug for induction of general anesthesia. This is calculated from post study drug administration. For example, if the subject only receives the initial dose of study drug and has achieved successful anesthesia induction, then "the end of last dose of study drug" means the initial dose of study drug. If the subject receives an additional top-up dose in the anesthesia induction, "the end of last dose of study drug" means the last top-up dose of study drug.
2. All subjects are required to provide venous PK blood samples. The blood volume is approximately 2 mL per sample. The PK blood samples will be taken from a second IV.
3. For subjects requiring rescue medication, the 2-minute PK sample must be taken prior to rescue medication being administered.

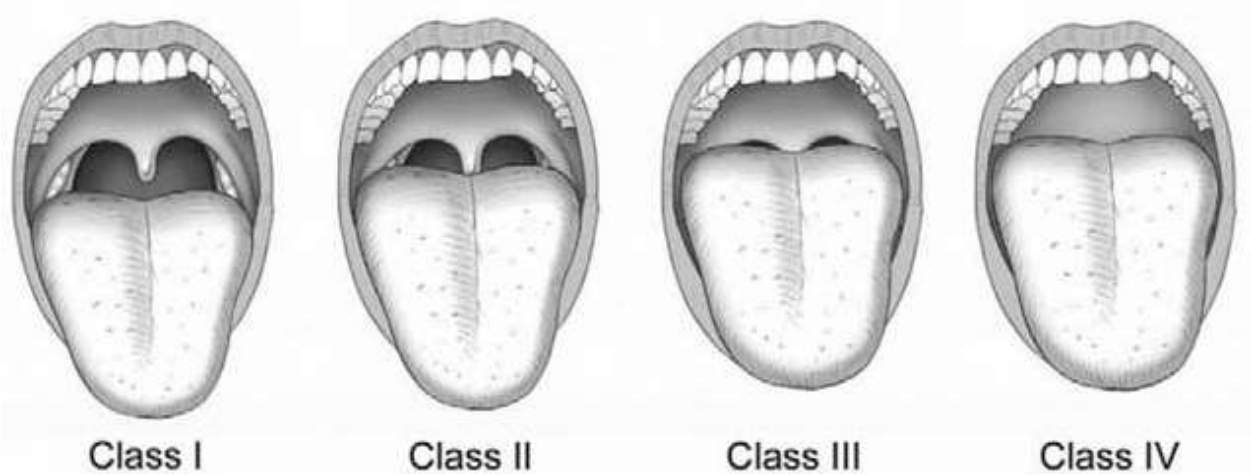
## Appendix 6 American Society of Anesthesiologists (ASA) Physical Status Grade

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.

**Appendix 7 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.

## Appendix 8 Drugs that May Prolong the QT Interval

*use with caution only if medically necessary

| **Drugs that prolong QT interval (including but not limited to the following)** | |
|---|---|
| **Antibiotics** | Clarithromycin<br>Azithromycin<br>Erythromycin<br>Roxithromycin<br>Metronidazole<br>Moxifloxacin |
| **Antiarrhythmics** | Quinidine<br>Sotalol<br>Amiodarone<br>Disopyramide<br>Procainamide |
| **Antipsychotics** | Fluphenazine<br>Droperidol<br>Haloperidol<br>Thioridazine<br>Pimozide<br>Clozapine<br>Olanzapine<br>Chlorpromazine<br>Quetiapine |
| **Antifungals** | Fluconazole<br>Ketoconazole<br>Itraconazole |
| **Antimalarial drugs** | Mefloquine<br>Chloroquine |
| **Antidepressants** | Amitriptyline<br>Imipramine<br>Clomipramine<br>Dosulepin<br>Doxepin<br>Floxitine<br>Paroxetine |

| | |
|---|---|
| | Sertralin<br>Citalopram<br>Fluvoxamine |
| **Anti-tumor drugs** | Anthracyclines<br>5-fluoropyrimidine |
| **Antihistamines** | Diphenhydramine<br>Terfenadine<br>Astemizole |
| **Other drugs** | Indapamide<br>Cisapride |

## Appendix 9 Adverse Event Definitions

### Definitions

An adverse event (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 electronic Case Report Form (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 Common Terminology Criteria for Adverse Events (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 patient 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 Relate**d: Underlying or concurrent disease or other drugs/exposures provide plausible alternative explanations. Temporal relationship to study drug administration makes a causal relationship improbable.
- **Likely Relate**d: 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 Relate**d: 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 change**d: The medication schedule was not changed.
- **Dose reduce**d: The medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
- **Drug interrupte**d: The medication schedule was modified by temporarily terminating the prescribed regimen of medication.
- **Drug withdraw**n: The medication schedule was modified through termination of the prescribed regimen of medication.
- **Not applicable**
- **Unknown**

**Follow-up of Adverse Events**

All serious Aes (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.

## Appendix 10 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 → local laboratory only (For females only) |
| Uric acid | Serum pregnancy test (For females only) |
| | TSH* |
| | |
| **Complete Urinalysis (UA):** | |
| Color and appearance | |
| 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; WBC = white blood cell.
*TSH test will only be done during the screening period. TSH is only drawn for subjects with known hypothyroidism and/or on thyroid-hormone replacement treatment (i.e., thyroxine), or subjects suspected to have thyroid dysfunction based on clinical laboratory and physical exam.

## Appendix 11 Regulatory, Ethical, and Study Oversight Considerations

### Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Ethics Committee (EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

- Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

### Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

### Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the investigator (or designee) and that their participation is voluntary, and they are free to withdraw from the study at any time.

Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable. The subject will be given a copy of the signed ICF, and the original will be maintained with the subject's records.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

**Subject Data Protection**

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Subject and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her medical records may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the **S**ponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

**Disclosure**

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

**Data Quality Assurance**

The following data quality steps will be implemented:

- All subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Pre-defined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in accordance with 21 CFR 312.6I) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

**Investigator Documentation Responsibilities**

All individual, subject-specific study data will be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion. All data generated from external sources (e.g., central laboratory, pharmacokinetics, pharmacodynamics, electrocardiogram central readers) and transmitted to the Sponsor or designee electronically will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each subject who signs an ICF and undergoes any pre-screening or screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, the data queries, and the site notifications.

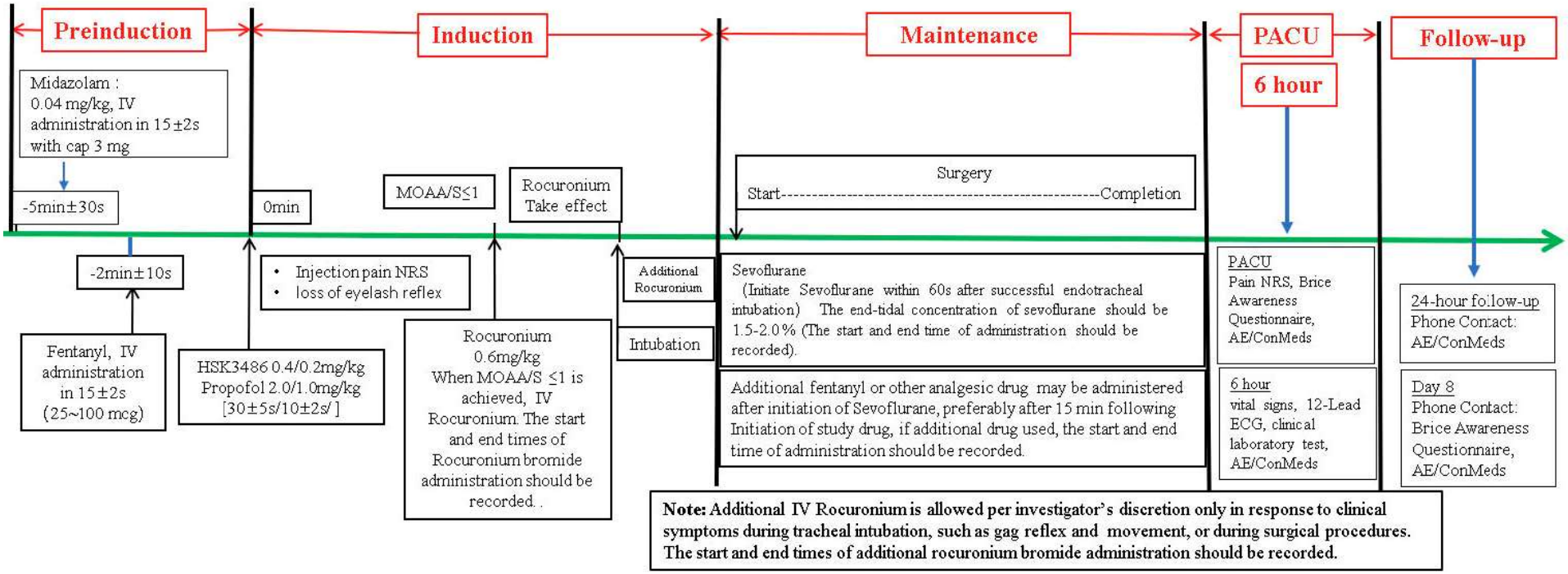
**Publications**

If on completion of the study the data warrant publication, the investigator may publish the results in recognized (referred) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process shall occur:

The institution and investigator shall not publish or present data from an individual study center until the complete multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the investigator expects to participate in the publication of data generated from this site, the institution and investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor shall have 60 days to respond with any requested revisions, including (without limitation) the deletion of confidential information. The investigator shall act in good faith upon requested revisions, except the investigator shall delete any confidential information from such proposed publications. The investigator shall delay submission of such publication or presentation materials for up to an additional 90 days to have a patent application(s) filed.

## Appendix 12 Study design (a larger version)

- **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 calculated dose of study drug 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.
- **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 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.
- **BIS:** Record the three most recent BIS values preceding midazolam administration. Record baseline BIS value prior to administering study drug. BIS will be monitored continuously. BIS values will be collected at the following timepoints post start of initial study drug administration: every 30 [±10] seconds until 5 minute, and then every 2 minutes [±30 seconds] from 5 minutes until 30 minutes. Then every 30 minutes [±2] minutes for the duration of the surgery.
- **Vital signs (HR, RR, $SpO_2$, SBP, DBP, MAP, Temp):** 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, Temp should be recorded once every 2 minutes [±30 seconds], $SpO_2$ value should be recorded once every 1 minutes [± 15 seconds] from the start of study drug administration (for every time point) for 30 minutes post start of study drug administration. RR should be recorded once every 2 minutes [±30 seconds] from the start of study drug administration until administration of rocuronium.
- **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 administration of Rocuronium bromide, evaluate and record respiratory depression. Within 15 minutes post start of study drug administration, evaluate and record cardiac depression.
- **3-lead or 5-lead and 12-lead ECG:** Monitor and records 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 end concentration of Sevoflurane should be 1.5-2.0%.


Preinduction
Induction
Maintenance
PACU
6 hour
Follow-up
Midazolam :
0.04 mg/kg, IV
administration in 15±2s
with cap 3 mg
-5min±30s
-2min±10s
Fentanyl, IV
administration
in 15±2s
(25~100 mcg)
0min
HSK3486 0.4/0.2mg/kg
Propofol 2.0/1.0mg/kg
[30±5s/10±2s/ ]
• Injection pain NRS
• loss of eyelash reflex
MOAA/S≤1
Rocuronium
0.6mg/kg
When MOAA/S ≤1 is
achieved, IV
Rocuronium. The start
and end times of
Rocuronium bromide
administration should be
recorded. .
Rocuronium
Take effect
Additional
Rocuronium
Intubation
Surgery
Start----------Completion
Sevoflurane
(Initiate Sevoflurane within 60s after successful endotracheal intubation) The end-tidal concentration of sevoflurane should be 1.5-2.0% (The start and end time of administration should be recorded).
Additional fentanyl or other analgesic drug may be administered after initiation of Sevoflurane, preferably after 15 min following Initiation of study drug, if additional drug used, the start and end time of administration should be recorded.
PACU
Pain NRS, Brice Awareness Questionnaire, AE/ConMeds
6 hour
vital signs, 12-Lead ECG, clinical laboratory test, AE/ConMeds
24-hour follow-up
Phone Contact:
AE/ConMeds
Day 8
Phone Contact:
Brice Awareness Questionnaire,
AE/ConMeds
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, or during surgical procedures. The start and end times of additional rocuronium bromide administration should be recorded.

## Appendix 13 IMP/AxMP designation

| Active Substance | Product Name | IMP/AxMP Designation | Marketing Authorization Status in EEA | Used within Marketing Authorization |
|---|---|---|---|---|
| HSK3486 | HSK3486 2.5 mg/ml injectable emulsion 20 ml vial | IMP (test product) | No | N/A |
| Propofol | Propofol 10 mg/ml injectable emulsion 20 ml vial | IMP (comparator) AxMP (rescue medicine) | Authorized | Yes |
| Midazolam | Midazolam solution for injection/infusion | AxMP (background therapy) | Authorized | Yes |
| Fentanyl | Fentanyl solution for injection | AxMP (background therapy) | Authorized | Yes |
| Rocuronium | Rocuronium solution for injection/infusion | AxMP (background therapy) | Authorized | Yes |
| Sevoflurane | Sevoflurane inhalation vapour, liquid | AxMP (background therapy) | Authorized | Yes |

IMP = Investigational Medicinal Product; AxMP = Auxiliary Medicinal Product; EEA = European Economic Area

## Appendix 14 Detailed Summary of Changes

The below reflects changes made from protocol Version 8.0 to Version 9.0. Minor clarifications, formatting, grammatical and spelling errors have been corrected throughout Version 9.0 as needed and may not be outlined below. Corresponding updates have been reflected in the synopsis, appendices and figures as applicable.

**Section (s) affected**
**4.1 Inclusion Criteria**

Existing text

9. Patients with psychiatric/mental disorders must be considered stable on treatment (e.g., SSRIs, SNRIs, TCAs, MAOIs, psychotherapy) and no hospitalization and urgent care for at least 1 year.

Updated text

9. Patients with psychiatric/mental disorders must be considered stable on treatment (e.g., SSRIs, SNRIs, TCAs, MAOIs, psychotherapy) ***per investigator judgement,*** and no hospitalization and urgent care ***due to the underlying psychiatric pathology*** for at least ***12 months***.

**Section (s) affected**
**4.2 Exclusion Criteria**

Existing text

3. d). Patients with psychiatric/mental disorders who have not been on a stable treatment regimen (e.g., SSRIs, SNRIs, TCAs, MAOIs, psychotherapy) for at least 1 year or who have been hospitalized or had emergent/urgent care within the past year.

Updated text

3. d). Patients with psychiatric/mental disorders who have not been on a stable treatment regimen (e.g., SSRIs, SNRIs, TCAs, MAOIs, psychotherapy) ***per investigator judgement,*** for at least ***12 months*** or who have been hospitalized or had emergent/urgent care ***due to the underlying psychiatric pathology*** within the ***last 12 months***.

**Section (s) affected**
**7.3.2 Reporting Serious Adverse Events**

Existing text

**Serious Adverse Event Reporting Contact Information:**

Rho, Inc. Safety Group Email: rho_productsafety@rhoworld.com

Serious Adverse Event Help Line: 1-888-746-7231

Serious Adverse Event Fax Line: 1-888-746-3293

**Medical Monitor Contact Information:**
Rho, Inc. Medical Monitor
Anna Pinsky, MD
Telephone: 919-595-6461 (Medical Monitor Line)
Email: MedicalMonitorSupport@rhoworld.com AND jamie_chang@rhoworld.com

Updated text

**Serious Adverse Event Reporting Contact Information:**

Rho, Inc. Safety Group Email: rho_productsafety@rhoworld.com

Serious Adverse Event Help Line: 1-888-746-7231

Serious Adverse Event Fax Line: 1-888-746-3293

**Medical Monitor Contact Information:**

Rho, Inc. Medical Monitor
Anna Pinsky, MD
Telephone: 919-595-6461 (Medical Monitor Line)
Email: MedicalMonitorSupport@rhoworld.com AND ***Anna_Pinsky@rhoworld.com***

**Section (s) affected**
**7.1.2 Day of Surgery (Day 1)**

Existing text

Administration of study drug must be initiated within 5 minutes [±30 seconds] post midazolam preinduction medication administration stop time.

Updated text

Administration of study drug must be initiated ***at*** 5 minutes [±30 seconds] post midazolam preinduction medication administration stop time.