

COVER PAGE – PROTOCOL V5.0 HSK3486-304

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

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Protocol

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

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Protocol Reference Number: HSK3486-304
[REDACTED]

Sponsor:

Haisco-USA Pharmaceuticals, Inc.
[REDACTED]
[REDACTED]



Haisco-USA Pharmaceuticals, Inc.

[REDACTED]
[REDACTED]

Information described herein is confidential and may be disclosed only with the express written permission of the Sponsor.

SPONSOR APPROVAL

I have read the following and approve it:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

INVESTIGATOR AGREEMENT

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

[Name, Qualification(s)]
Principal Investigator

Date

SYNOPSIS

Title of study: A Multicenter, Randomized, Double-blinded, Propofol-controlled, Phase 3 Clinical Study to Evaluate the Efficacy and Safety of HSK3486 Injectable Emulsion for Induction of General Anesthesia in Adults Undergoing Elective Surgery
Indication: Induction of general anesthesia in adult subjects undergoing elective surgery with endotracheal intubation
Number of study centers: Up to approximately 25 sites in the US will be included in this study.
Development phase: Phase 3
Objectives: Primary objective: <ul style="list-style-type: none">To demonstrate HSK3486 0.4/0.2 mg/kg (0.4 mg/kg intravenous [IV] slow injection over 30 [\pm5] seconds 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 over 30 (\pm5) seconds 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: <u>Key secondary objectives:</u> <ul style="list-style-type: none">To confirm that HSK3486 0.4/0.2 mg/kg leads to significantly less injection-site pain 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. <u>Additional Efficacy Objective:</u> <ul style="list-style-type: none">To evaluate HSK3486 0.4/0.2 mg/kg induction time in general anesthesia. <u>Safety:</u> <ul style="list-style-type: none">To evaluate the overall safety profile of HSK3486 compared to propofol. <u>Pharmacokinetic:</u> <ul style="list-style-type: none">To characterize the HSK3486 population pharmacokinetic (PK) profile.
Methodology/study design: <p>This is a multicenter, randomized, double-blinded, propofol-controlled, Phase 3 clinical study to evaluate the efficacy and safety of HSK3486 for induction of general anesthesia in adults undergoing elective surgery with endotracheal intubation.</p> <p>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 [\pm5] seconds followed by an additional 0.2</p>

mg/kg dose, if needed) or propofol 2.0/1.0 mg/kg (i.e., 2.0 mg/kg IV slow injection over 30 [\pm 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 Anesthesiologists Physical Status (ASA-PS; I-II and III-IV), age (<65 and \geq 65 years), and Body Mass Index (BMI<35 and \geq 35 kg/m²). Endotracheal intubation will be performed after adequate anesthetic induction (Modified Observer's Assessment of Awareness/Sedation [MOAA/S] \leq 1) (Appendix 5) has been achieved and administration of neuromuscular blocking agent.

Before surgery, premedication is allowed except for sedative-hypnotic or analgesic drugs.

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: \geq 4 L/min), and maintenance IV solution (normal saline [NS], lactated ringer's [LR], or 5% dextrose) will be administered through IV infusion. Any change in IV infusion should be recorded. Throughout the preinduction and induction periods, a timing device must be used to allow accuracy and sequencing of necessary assessments.

Preinduction period

- Obtain vital signs (heart rate [HR], respiratory rate [RR], oxygen saturation [SpO₂], systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial pressure [MAP], and temperature [Temp]); baseline will be the average of 2 consecutive measurements taken 2 minutes apart.
- Attach 3-lead or 5-lead electrocardiogram (ECG) to subject and monitor continuously.
- Attach bispectral index (BIS [Appendix 10]) monitor to subject.
- Subjects will receive preinduction IV fentanyl 1 mcg/kg rounded up to the nearest 25 mcg, up to 100 mcg maximum.

Induction period of general anesthesia

The induction of general anesthesia will be performed as follows:

- Monitor vital signs (HR, RR, SpO₂, SBP, DBP, MAP, and Temp) continuously and record once every 2 minutes (\pm 30 seconds) referencing the initiation of study drug administration (for every time point) for 30 minutes post initiation of study drug administration. Note: Vital sign 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) 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 [\pm 5] seconds). The MOAA/S will be evaluated every 30 (\pm 15) seconds after injection until MOAA/S \leq 1 is reached. If MOAA/S is still $>$ 1 at 1 minute (+10 seconds) post study drug administration, a top-up dose of 50% of the initial dose of study drug (either HSK3486 0.2 mg/kg or propofol 1 mg/kg depending on treatment group) will be given to the subject (IV injection time: 10 [\pm 5] seconds) and time of administration will be recorded. If MOAA/S is still at $>$ 1 at 2 minutes (+30 seconds) post end of the top-up dose, then the rescue drug, propofol, will be given (in both treatment groups). Administration of study drug must be initiated within 5 minutes post preinduction medication.
- Injection-site pain is evaluated verbally by Numeric Rating Scale (NRS; Appendix 6) upon administration of initial study drug prior to subject losing consciousness.
- After initial study drug administration, closely monitor, evaluate and record the time of loss of eyelash reflex.

- BIS will be monitored continuously; record baseline BIS value prior to administering study drug. BIS values will be collected at the following timepoints post completion of initial study drug administration: every 30 (± 10) seconds until 5 minutes, and then every 2 minutes (± 30 seconds) until 15 minutes, and then every 15 (± 5) minutes until 60 (± 10) minutes post study drug administration.
- Monitor 3-lead or 5-lead electrocardiogram (ECG) continuously.
- When MOAA/S ≤ 1 is achieved, obtain vitals (HR, BP, and RR), then IV rocuronium bromide (0.6 mg/kg) is to be administered for neuromuscular blockade to perform endotracheal intubation.
- Intubate subject once neuromuscular blockade has taken effect; if using twitch monitor, intubate once no twitches are noted.
- During endotracheal intubation, evaluate for inadequate depth of anesthesia, such as coughing, laryngospasm, and/or bronchospasm, and RR, for at least 15 minutes post study drug injection; responses should be recorded.
- Sevoflurane (an inhalation anesthetic agent) will be used for maintenance of general anesthesia. Initiate sevoflurane within 60 seconds after successful endotracheal intubation. Once sevoflurane has been initiated, monitor end-tidal sevoflurane concentration and record every 2 minutes (± 1 minute) until 30 minutes post initiation of initial study drug administration.

Note: Additional IV rocuronium is allowed per investigator's discretion only in response to clinical symptoms during tracheal intubation, such as gag reflex, movement et al, or during surgical procedures.

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. 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 and values recorded every 2 minutes (± 1 minute) until 30 minutes post initiation of initial study drug administration.
- The BIS will be monitored continuously per standard of care, and BIS values will be collected at the following timepoints post completion of initial study drug administration: every 30 (± 10) seconds until 5 minutes, and then every 2 minutes (± 30 seconds) until 15 minutes, and then every 15 (± 5) minutes until 60 (± 10) minutes post study drug administration.
- Information about any adverse events (AEs) and concomitant medications will be recorded.
- Additional IV fentanyl may be administered for intraoperative analgesia only after initiation of sevoflurane, preferably after 15 minutes following the initiation of study drug administration.
- Patient management during surgery needs to follow routine best practice which includes anti-emetics. Zofran (Ondansetron) or other 5 HT-3 antagonists and/or Dexamethasone, should be given during surgery and before subjects wake up unless otherwise contraindicated.

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

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

- After the surgery, vital signs (HR, RR, SpO₂, SBP, DBP, MAP, and Temp) will be assessed at 6 (± 2) hours post study drug administration (Note: If surgery lasts >4 hours, vital signs, clinical laboratory tests and ECG should be obtained 1 [+1] hour after completion of surgery).
- Clinical laboratory tests (including hematology, blood chemistry, and urinalysis) will be obtained at 6 (± 2) hours post study drug administration.
- Obtain 12-lead ECG at 6 (± 2) hours post 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 7).
- Information about any AEs and concomitant medications 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 and appropriate to be discharged home per the judgement of the investigator and surgeon, the subject may be released with supervision by a family member or friend, and must return to the clinic for the 24-hour follow-up visit (Day 2).

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

- 24 (± 6) hours post study drug administration (Day 2), obtain vital signs (HR, RR, SpO₂, SBP, DBP, MAP, and Temp).
- Information about any AEs and concomitant medications 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 on any AEs and associated medications will be collected.

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 8).

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 20% enrollment. Additionally, 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 3 (3/255 [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 5 (5/255 [2%]) severe AEs of special interest (AESIs; Common Terminology Criteria for Adverse Events [CTCAE] Grade 3, 4 or 5) of hypotension, bradycardia, or hypoxia (i.e., respiratory depression) 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 255 subjects; 170 subjects in HSK3486 group and 85 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 visit:

1. Subjects undergoing elective surgery (nonemergency, noncardiothoracic, and nonintracranial 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 4). 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/m².
4. Vital signs at screening: RR ≥ 10 and ≤ 24 breaths/min; SpO₂ $\geq 95\%$ 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 females of childbearing potential, negative serum pregnancy test at screening (if results available) and must have negative urine pregnancy test at baseline (Day 1). Additionally, females of childbearing potential must agree to use birth control (such as condom, intrauterine device [IUD], abstinence) from the time of consent until 30 days post study drug administration.
6. Capable of understanding the procedures and methods of this study, willing to sign an Informed Consent Form, and able to complete this study in strict compliance with the study protocol.

Exclusion criteria:

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

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

2. Known to be allergic to eggs, soy products, opioids and their antidotes, or propofol; subject having contraindications to propofol, opioids, and their antidotes.
3. Medical condition or evidence of increased sedation/general anesthesia risk as follows:
 - a) Cardiovascular disorders: uncontrolled hypertension (SBP >160 mmHg and/or DBP >100 mmHg) with or without antihypertensive therapy (antihypertensive therapy should be stable for 1 month prior to screening), serious arrhythmia (including the subjects with implanted pace makers), unstable heart failure, Adams-Stokes syndrome (i.e., syncope or near-syncope due to cardiac arrhythmia), 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.
 - b) Respiratory system disorders: respiratory insufficiency (except mild respiratory insufficiency not requiring O₂ to achieve SpO₂ >92 could be permitted), history of severe obstructive lung disease (i.e., forced expiratory volume in 1 second [FEV₁] <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 1 week 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) Psychiatric disease: history of schizophrenia, mania, long-term (more than 1 year) administration of psychoactive drug, or cognitive impairment.
 - e) Uncontrolled clinically significant conditions of liver (e.g., severe hepatic insufficiency defined as Childs-Pugh class C), kidney, gastrointestinal tract, blood system, nervous system, or metabolic system diseases, judged by the investigator to be unsuitable for involvement in the study.
 - f) Known glycated hemoglobin (HbA_{1c}) greater than or equal to 10%.
 - g) Known thyroid-stimulating hormone (TSH) value outside the normal range or on thyroid -replacement therapy with a known free T₄ level outside the normal range.
 - h) History of alcohol abuse within 3 months prior to screening, where alcohol abuse refers to daily alcohol drinking >2 units of alcohol (1 unit = 360 mL of beer or 45 mL of spirit with a strength of 40% or 150 mL of wine).
 - i) History of drug abuse within 3 months prior to screening.
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 1 year, no requirement for rescue inhalers or oral steroids within past 1 year, not evaluated in emergency department, urgent care, or hospitalized for an asthma attack within past 5 years.
 - 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 11), 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 enrollment.
 6. Taking valproic acid (Depakote) within 1 week prior to enrollment; taking UGT1A9 inhibitors, including but not limited to phenytoin, fosphenytoin, mefenamic acid, sorafenib, deferasirox, rifampicin, within 1 week prior to enrollment.
 7. 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 $< 90 \text{ g/L}$ (without blood transfusion within 14 days)
 - d) Alanine transaminase and/or aspartate transaminase $\geq 2.0 \times$ upper limit of normal (ULN)
 - e) Total bilirubin $\geq 2.0 \times$ ULN
 - f) Severe renal impairment defined by creatinine clearance (CrCl) $\leq 30 \text{ mL/min}$
 8. Female subjects with a positive pregnancy test (serum or urine) at screening or baseline; lactating subjects; any subject planning to get pregnant within 1 month after the study (including the male subject's partner).
 9. 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: 0.4/0.2 mg/kg, IV slow injection over 30 (± 5) seconds, preoperatively; 1 top--up dose (0.2 mg/kg) permitted, if needed. Dose will be adjusted with a 25% dose reduction for elderly subjects ≥ 65 years of age.

For subjects with BMI ≤ 40 , total body weight (TBW) will be used to determine HSK3486 dose; for subjects with BMI > 40 , lean body weight (LBW) will be used to determine HSK3486 dose.

HSK3486 injectable emulsion will be stored at $\leq 25 \text{ }^\circ\text{C}$ away from light and should not be frozen.

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

Name: Propofol injection

Dose, route, frequency: 2.0/1.0 mg/kg, IV slow injection over 30 (± 5) seconds, preoperatively; 1 top--up dose (1 mg/kg) permitted, if needed. Dose will be adjusted with a 25% dose reduction for elderly subjects ≥ 65 years of age.

For subjects with BMI ≤ 40 , TBW will be used to determine propofol dose; for subjects with BMI > 40 , LBW will be used to determine propofol dose.

Propofol will be stored at 4°C to 25°C away from light and should not be frozen.

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
- Treatment: on the day of surgery
- Follow-up: 24 hours post study drug administration
- Phone contact: 1 week (± 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:
 - Induction success (MOAA/S ≤ 1) after administration of the study drug, and
 - 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 between the time of successful induction and 15 minutes post initiation of study drug administration, or up to the beginning 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:
 - Desired depth of anesthesia for general elective surgery is defined if all following criteria are met:
 - No clinical signs of inadequate depth of anesthesia, such as coughing, laryngospasm, or bronchospasm and no additional IV rocuronium bromide after routine rocuronium bromide 0.6 mg/kg in response to clinical symptoms, such as gag reflex, movement et al, due to first tracheal intubation.
 - No event where any of the SBP, DBP, or MAP increases more than 20% from baseline on 2 consecutive readings in response to any major operational procedures or noxious stimulus in defined period.

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

Note: Target BIS 40 to 60 for general anesthesia (Appendix 10).

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

Video laryngoscopy is strongly recommended during tracheal intubation. Timing of second intubation attempt needs to be recorded.

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

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

- 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.
- Use of the top-up study drug and rescue/remediation drugs.

Safety endpoints:

- Safety assessments include AEs, clinical laboratory test results, vital signs (supine HR, SBP and DBP, MAP, RR, Temp, and SpO₂), ECG findings, physical examination findings, administration-site pain, and administration of additional fluids, 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 8).

Sample size evaluation:

A total of 255 subjects (170 in HSK3486 0.4/0.2 mg/kg group and 85 in propofol 2.0/1.0 mg/kg group) need to be enrolled 2:1 into this study given a drop-out rate of 3% based on the following assumptions:

- For the primary endpoint, a sample size of 215 patients 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 176 patients will give 90% power assuming $\alpha=0.05$ (2-sided) and the proportion of subjects who meet the endpoint criteria of any injection-site pain are 20% and 45% for HSK3486 and propofol, respectively.
- For the key secondary composite endpoint, a sample size of 255 patients will give at least 80% power (providing the primary endpoint is statistically significant) to the superior testing, assuming $\alpha=0.05$ (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 study drug administration observation period (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, about 255 patients will be randomized and treated in this study.

Statistical methods:

Statistical analysis sets:

Full Analysis Set (FAS): All randomized subjects who have received at least 1 dose of the study drug (HSK3486 or propofol).

Per Protocol Set (PPS): All subjects from FAS who have completed primary efficacy endpoint data and no major study protocol violations during the study. Subjects with any major protocol deviations will be reviewed after database lock and prior to study unblinding, and may be excluded from PPS if these major deviations will impact the efficacy evaluations.

Safety Set (SS): Includes all randomized subjects who have received at least 1 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 using an ordered fixed-sequence step-down procedure. The proportion of subjects with any injection-site pain at time of drug administration on the NRS will be tested first, and if successful then will the composite endpoint of successful induction be tested. For each key secondary endpoint, the comparison between HSK3486 and propofol arms will be conducted at $\alpha=0.05$ level. If the first test of injection-site pain is rejected, then the testing stops. 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 ($NRS \geq 1$) and moderate injection-site pain ($NRS \geq 4$) will be analyzed, as well as the mean NRS score for each treatment group.
- 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.
- The use of study drugs and remediation drugs will be summarized descriptively by treatment group.

Safety analysis:

All AEs will be coded according to the MedDRA version 23.0 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 (AESIs), TEAEs related to study drug, SAEs related to study drug, TEAEs of Grade 3 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 postbaseline timepoints 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. Data obtained from laboratory tests not required by the protocol will not be summarized 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.

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 visits			Phone contact
	Day -13 to Day 0	Day 1 (day of surgery)	6-hour and 24-hour (Day 2) ¹ follow-up after study drug administration			Day 8 1 week (±2 days) post day of surgery
			PACU	6 (±2) hours	24 (±6) hours (Day 2)	
Written informed consent	X					
Inclusion/exclusion criteria	X	Verify				
Demographics	X					
Medical history	X					
Modified Mallampati score assessment	X					
Physical exam ^b	X					
Vital signs	X	X ^{c,j}		X ^j	X ^j	
Height, weight, and BMI	X	X				
12-lead ECG	X	X ^m		X ^m		
Clinical laboratory tests ^d	X	X ^{d,j}		X ^j		
Serum pregnancy test (females) ^d	X					
Urine pregnancy test (females) ^d		X				
Instruct subject to fast minimum of 6 hours before surgery	X					
Confirm preoperative readiness ^a		X				

	Screening	Study treatment	Follow-up visits			Phone contact
	Day -13 to Day 0	Day 1 (day of surgery)	6-hour and 24-hour (Day 2) ^l follow-up after study drug administration			Day 8 1 week (± 2 days) post day of surgery
			PACU	6 (± 2) hours	24 (± 6) hours (Day 2)	
Start maintenance IV infusion (NS, LR, or 5% dextrose)		X				
Administration of preinduction IV fentanyl		X				
Administer oxygen via face mask (≥ 4 L/min)		X				
Administration of study drug ^e		X				
Pain NRS ^g		X	X			
Monitor BIS ^f		X				
Monitor eyelash reflex		X				
Monitor MOAA/S		X				
Monitor 3-lead or 5-lead ECG continuously		X ^m				
Administration of IV rocuronium ^h		X				
Endotracheal intubation ^h		X				

	Screening	Study treatment	Follow-up visits			Phone contact
	Day -13 to Day 0	Day 1 (day of surgery)	6-hour and 24-hour (Day 2) ^l follow-up after study drug administration			Day 8 1 week (±2 days) post day of surgery
			PACU	6 (±2) hours	24 (±6) hours (Day 2)	
General anesthesia maintenance per routine practice (sevoflurane must be used as inhalational agent; record use of any alternative drugs) ⁱ		X				
Blood sample collection for population PK study		X				
Brice Awareness Questionnaire			X ^k			X
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; SpO₂ = peripheral capillary oxygen saturation; Temp = temperature.

- a. Subject is hemodynamically stable and has followed preoperative instructions, and there is no evidence of acute illness such as fever.
- b. Physical examination will include ASA-PS score.
- c. 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, SpO₂, SBP, DBP, MAP, Temp) will be collected. During preinduction, obtain baseline vital signs (baseline value will be the average of 2 consecutive measurements at least 2 minutes apart). During the induction of general anesthesia and maintenance period, HR, RR, SpO₂, SBP, DBP, MAP, and Temp will be monitored continuously and recorded once every 2 minutes (±30 seconds) referencing the initiation of study drug administration (for every time point) for 30 minutes post initiation of study drug

- administration. After the surgery, vital signs (HR, RR, SpO₂, SBP, DBP, MAP, and Temp) will be assessed at 6 (±2) hours post study drug administration.
- d. Clinical laboratory tests include hematology, blood chemistry, and urinalysis; pregnancy tests for all females of childbearing potential (serum at screening and urine at baseline). If screening laboratory tests were obtained ≥7 days prior to enrollment, laboratory tests should be repeated on Day 1 prior to study drug administration.
 - e. Administer IV study drug (HSK3486 0.4 mg/kg or propofol 2.0 mg/kg) in 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 (±15) seconds after injection until MOAA/S ≤1 is reached. If MOAA/S >1 at 1 minute (+10 seconds) post study drug administration, a top-up dose of 50% of the initial dose of study drug (either HSK3486 0.2 mg/kg or propofol 1 mg/kg depending on treatment group) will be given to the subject (IV injection time: 10 [±5] seconds) and time of administration will be recorded. If MOAA/S is still >1 at 2 minutes (+30 seconds) post end of the top-up dose injection, then the rescue drug propofol will be given (in both treatment groups). Administration of study drug must be initiated within 5 minutes post preinduction fentanyl.
 - f. At preinduction, attach BIS monitor to subject. Record baseline BIS value prior to administering study drug. The BIS values will be collected at the following timepoints post completion of initial study drug administration: every 30 (±10) seconds until 5 minutes, and then every 2 minutes (± 30 seconds) until 15 minutes, and then every 15 (±5) minutes until 60 (±10) minutes post study drug administration.
 - g. Prior to entering the OR, orient the subject to the use of the NRS assessment. The NRS pain score will be obtained upon administration of initial study drug injection prior to subject losing consciousness. In the PACU, once subject is alert and oriented, pain NRS is repeated for recall of pain at time of study drug administration.
 - h. When MOAA/S ≤1 is achieved, IV rocuronium bromide (0.6 mg/kg) is administered for neuromuscular blockade to ensure a smooth intubation. Perform endotracheal intubation and record the time and response.
 - i. An inhalational anesthetic agent, sevoflurane, will be used for maintenance of general anesthesia. Initiate sevoflurane within 60 seconds after successful endotracheal intubation. Once sevoflurane has been initiated, monitor end-tidal sevoflurane concentration and record every 2 minutes (±1 minute) until 30 minutes post initiation of initial study drug administration.
 - j. At 6 (±2) hours post study drug administration, obtain vital signs (HR, RR, SpO₂, SBP, DBP, MAP, and Temp) and clinical laboratory tests (including hematology, blood chemistry, and urinalysis). At 24 (±6) hours post study drug administration (Day 2), obtain vital signs (HR, RR, SpO₂, SBP, DBP, MAP, and Temp).
 - k. The Brice Awareness Questionnaire is administered in the PACU once the subject is alert and oriented. The questionnaire is repeated at Day 8.
 - l. 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 and appropriate to be discharged home per the judgement of the investigator and surgeon, the subject may be released with supervision by a family member or friend, and must return to the clinic for the 24-hour follow-up visit (Day 2).
 - m. During the surgery, 3-lead or 5-lead ECG will be monitored continuously. A 12-lead ECG will be obtained at 6 hours (±2 hours) post study drug administration and as clinically indicated.

TABLE OF CONTENTS

SPONSOR APPROVAL2
INVESTIGATOR AGREEMENT3
SYNOPSIS4
SCHEDULE OF ASSESSMENTS16
TABLE OF CONTENTS20
LIST OF FIGURES23
LIST OF ABBREVIATIONS24
1. INTRODUCTION26
1.1. Study Rationale26
1.2. Background27
1.3. Benefit-risk Assessment28
2. OBJECTIVES AND ENDPOINTS30
2.1. Objectives30
2.2. Endpoints30
3. INVESTIGATION PLAN33
3.1. Overall Study Design and Plan Description33
3.2. Discussion of Study Design, Including the Choice of Control Groups33
3.3. End of Study Definition34
3.4. Selection of Doses in the Study34
3.4.1. Selection of Dose for HSK348634
3.4.2. Selection of Dose for Propofol35
3.5. Data Monitoring Committee36
4. SELECTION OF STUDY POPULATION37
4.1. Inclusion Criteria37
4.2. Exclusion Criteria37
4.3. Subject Discontinuation from the Study39
4.3.1. Screen Failures40
4.3.2. Subject Discontinuation from Study Treatment40
4.3.3. Lost to Follow-up41
4.3.4. Replacement Procedures41
4.3.5. Follow-up of Subjects Prematurely Discontinued from the Study Treatment
Regimen or Withdrawn from Study41
4.4. Study Stopping Criteria41
5. STUDY TREATMENTS44
5.1. Treatments Administered44
5.2. Preparation, Storage, Handling, and Accountability44
5.3. Method of Treatment Assignment46
5.3.1. Dose Modification46
5.4. Blinding46
5.5. Treatment Compliance47
5.6. Preinduction Fentanyl47
6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS49
6.1. Concomitant Therapies49
6.2. Prohibited Therapies49

7.	STUDY ASSESSMENTS AND PROCEDURES	51
7.1.	Study Procedures	51
7.1.1.	Screening Period (Day -13 to Day 0)	51
7.1.2.	Day of Surgery (Day 1)	52
7.1.3.	Follow-up Period (6-hour Post Study Drug and 24-hour Post Study Drug Visit [Day 2])	55
7.1.4.	Phone Contact (Day 8)	56
7.2.	Efficacy Assessments	56
7.2.1.	Success Rate of Anesthesia Induction	56
7.2.2.	Composite Endpoint to Evaluate Desired Depth of Anesthesia	56
7.2.3.	Injection-site Pain	57
7.2.4.	Time to Successful Anesthesia Induction	57
7.2.5.	Time to Loss of Eyelash Reflex	58
7.2.6.	Changes in the Bispectral Index	58
7.2.7.	Brice Awareness Questionnaire	58
7.2.8.	Use of Study Drugs and Alternative Drugs	58
7.3.	Safety and Tolerability Assessments	58
7.3.1.	Adverse Events	58
7.3.2.	Reporting Serious Adverse Events	59
7.3.3.	Adverse Events of Special Interest	60
7.3.3.1.	Abuse-related AEs of Interest	60
7.3.4.	Contraception and Pregnancy	61
7.3.5.	Clinical Laboratory Evaluations	61
7.3.6.	Vital Signs, Physical Examination, and Other Safety Evaluations	62
7.3.6.1.	Vital Signs	62
7.3.6.2.	Physical Examinations	62
7.3.6.3.	12-lead ECG and 3-lead/5-lead ECG	63
7.3.7.	Use of Additional Fluids or Medication or Any Interventions	63
7.4.	Pharmacokinetic Analysis	63
8.	SAMPLE SIZE AND DATA ANALYSES	64
8.1.	Determination of Sample Size	64
8.2.	Analysis Populations	64
8.3.	General Considerations	65
8.4.	Efficacy Analysis	65
8.4.1.	Primary Efficacy Outcome Measure	65
8.4.2.	Justification of the Non-inferiority Margin	65
8.4.3.	Secondary Efficacy Outcome Measures	66
8.4.4.	Methods for the Control of Type I Error	66
8.5.	Safety Analysis	67
8.6.	Pharmacokinetic Analysis	67
8.7.	Interim Analysis	68
9.	REFERENCES	69
10.	APPENDICES	70
Appendix 1	Adverse Event Definitions	70
Appendix 2	Clinical Laboratory Evaluations	74
Appendix 3	Regulatory, Ethical, and Study Oversight Considerations	75

Appendix 4	American Society of Anesthesiologists (ASA) Physical Status Grade.....	79
Appendix 5	Modified Observer’s Assessment of Awareness/Sedation (MOAA/S) Scale	80
Appendix 6	Numerical Rating Scale (NRS) for Grading of Injection-site Pain.....	81
Appendix 7	Brice Awareness Questionnaire.....	82
Appendix 8	Pharmacokinetic (PK) Blood Samples Collection Timetable	84
Appendix 9	Drugs that May Prolong the QT Interval	85
Appendix 10	Bispectral Index (BIS).....	87
Appendix 11	Mallampati Classification.....	89

LIST OF FIGURES

Figure 1 The BIS Index is scaled to correlate with important clinical endpoints during administration of anesthetic agent. 87
Figure 2 BIS Index Range: A Continuum of Clinical State and EEG Changes 88

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
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
IWRS	Interactive Web Response System
kg	kilogram
L	Liter
LBW	lean body weight
LR	Lactated ringer's
MAP	mean arterial pressure
mcg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mL	milliliter
MOAA/S	Modified Observer's Assessment of Awareness/Sedation
NIM	non-inferiority Margin

Abbreviation	Definition
NRS	Numeric Rating Scale
NS	normal saline
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
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 outpatient 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 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 10). 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 dosing of study drug, which is defined by meeting all of the following: no coughing, laryngospasm, or bronchospasm; 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 a large number of 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 May 2020, 13 Phase I to III clinical studies evaluating HSK3486 have been completed. The ongoing studies are (i) Phase III General Anesthesia Induction Study of HSK3486 (HSK3486-303), which is enrolling patients (170 patients have been enrolled at present), and (ii) Phase I Continuous Infusion Study for 4h and 12h in healthy patients (HSK3486-102), which has completed enrollment and is currently in the data analysis stage. The study under ethical review is on induction and maintenance of general anesthesia (HSK3486-204).

Among the 13 completed studies, a total of 568 patients were enrolled in the HSK3486 group for observation, including 161 healthy individuals, 236 patients who underwent colonoscopy, 15 patients who underwent gastroscopy, and 156 patients who underwent elective surgery. Results showed that HSK3486 featured quick onset, rapid pace of regaining consciousness, and approximately 4 to 5 times the potency of propofol. When used to induce general anesthesia in elective surgery, HSK3486 showed quick onset, reduced response to tracheal intubation and stable vital signs in patients, with a similar or slightly longer duration of successful induction as compared with propofol. When used for diagnostic and therapeutic gastroscopy, data demonstrated that anesthesiologists were at least satisfied, if not more, with HSK3486 compared to propofol. In addition, patients who underwent gastroscopy enjoyed improved levels of comfort and had lower levels of awareness as compared with sessions in which propofol was used. The types of drug-related adverse events (AEs) caused by HSK3486 was consistent with that of propofol. Cardiovascular-related AEs (including hypotension, bradycardia, and prolonged QTc interval) caused by HSK3486 are comparable to those caused by propofol. However, incidences of pain on injection and respiratory-related AEs (respiratory depression, apnea, and hypoxia), and the proportion of patients requiring assisted ventilation when HSK3486 was administered were lower than those of propofol. In particular, HSK3486 appeared to have a significant advantage with regards to pain on injection, in that these were not as common versus propofol.

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

1.3. Benefit-risk Assessment

To date, 13 completed Phase I to III clinical studies of HSK3486 have been carried out and a total of 568 subjects have been exposed to HSK3486. Analysis of data from 568 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 consistent with those of propofol but with a slightly lower incidence; however, the incidence of injection-site pain was significantly lower than that of propofol, the incidence of

dizziness and respiratory-related AEs as well as the proportion of subjects in need of airway management were lower than those of 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 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 and Europe 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 experienced 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 study drug.

In summary, the safety profile of propofol has been well described based on its clinical use over the past several decades. In 13 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 over 30 (\pm 5) seconds 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 over 30 (\pm 5) seconds 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 significantly less injection-site pain 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.

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 ($MOAA/S \leq 1$) 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 between the time of successful induction and 15 minutes post initiation of study drug administration, or up to the beginning of second tracheal intubation attempt if it is a difficult condition and not beyond 15 minutes post initiation of 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 coughing, laryngospasm, or bronchospasm and no additional IV rocuronium bromide after routine rocuronium bromide 0.6 mg/kg in response to clinical symptoms, such as gag reflex, movement et al, due to first tracheal intubation.
 - ii) No event where any of the SBP, DBP, or MAP increases more than 20% from baseline on 2 consecutive readings 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 10).
The BIS sustainable level at not more than 60 is defined as not more than 1 episode with BIS value observed >60 in defined period.
Video laryngoscopy is strongly recommended during tracheal intubation. Timing of second intubation attempt needs to 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 (SpO₂) $<90\%$ 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.
- Use of the top-up study drug and rescue/remediation drugs.

The safety endpoints are:

- Safety assessments include AEs, clinical laboratory test results, vital signs (supine HR, SBP and DBP, MAP, respiratory rate [RR], temperature [Temp], and SpO₂), electrocardiogram (ECG) findings, physical examination findings, administration site pain, and administration of additional fluids, 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 timepoints (Appendix 8).

3. INVESTIGATION PLAN

3.1. Overall Study Design and Plan Description

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

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 [\pm 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 [\pm 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 Anesthesiologists Physical Status (ASA-PS; I-II and III-IV), age (<65 and \geq 65 years), and Body Mass Index (BMI<35 and \geq 35 kg/m²). Endotracheal intubation will be performed after adequate anesthetic induction (Modified Observer's Assessment of Awareness/Sedation [MOAA/S] \leq 1) (Appendix 5) has been achieved and administration of neuromuscular blocking agent.

Before surgery, premedication is allowed except for sedative hypnotic or analgesic drugs.

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 8).

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 0.5-mg/kg HSK3486 group was comparable to that of the 2.0-mg/kg propofol group, the efficacy of the 0.5-mg/kg HSK3486 group was slightly better than that of the 0.3-mg/kg and 0.4-mg/kg HSK3486 groups, as manifested by a faster rate of successful induction and a shorter intubation time. In addition, the 0.5-mg/kg HSK3486 group did not need top-up doses. However, the safety of the 0.5-mg/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 0.3-mg/kg HSK3486 group showed better safety and a relatively small proportion of adverse drug reactions (ADRs). However, compared with the propofol group, the 0.3-mg/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 0.4/0.2-mg/kg group) received 1 top-up dose of study drug, and 1 (1/22) subject in the dose-extension stage (0.3/0.15-mg/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 \pm 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 \leq 1 is not reached, a top-up dose is required.
- A 25% dose reduction is required for elderly subjects \geq 65 years of age for both HSK3486

and propofol.

Preliminary 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 , total body weight (TBW) will be used to determine dose; for subjects with BMI > 40 , lean body weight (LBW) will be used to determine dose.

- Based on population PK (PopPK) modeling, subjects with BMI > 45 can be expected to have higher simulated maximum concentration (C_{max}) and area-under-the-curve (AUC[0-24 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 is likely to be different. It has been reported that morbidly obese patients have significantly decreased half-maximal effective concentration (EC₅₀) values compared to control patients, 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 2.5-mg/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 , TBW will be used to determine dose; for subjects with BMI >40 , 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 20% enrollment. Additionally, 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 3 (3/255 [1%]) nonfatal 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 5 (5/255 [2%]) severe AEs of special interest (AESIs; Common Terminology Criteria [CTCAE] Grade 3, 4 or 5) of hypotension, bradycardia, or hypoxia (i.e., respiratory depression) 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 visit:

1. Subjects undergoing elective surgery (nonemergency, noncardiothoracic, and nonintracranial 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.
1. Males or females, aged ≥ 18 years old, with ASA-PS I to IV (Appendix 4). For ASA-PS IV subjects, clinical status must be optimized at time of preoperative anesthesia evaluation per judgement of the anesthesiologist.
2. BMI ≥ 18 kg/m².
3. Vital signs at screening: RR ≥ 10 and ≤ 24 breaths/min; SpO₂ $\geq 95\%$ 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.
4. For all females of childbearing potential, negative serum pregnancy test at screening (if results available) and must have a negative urine pregnancy test at baseline (Day 1). Additionally, females of childbearing potential must agree to use birth control (such as condom, intrauterine device [IUD], abstinence) from the time of consent until 30 days post study drug administration.
5. 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.

4.2. Exclusion Criteria

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

1. Contraindications to deep sedation/general anesthesia or a history of adverse reaction to sedation/general anesthesia.
2. Known to be allergic to eggs, soy products, opioids and their antidotes, or propofol; subject having contraindications to propofol, opioids, and their antidotes.
3. Medical condition or evidence of increased sedation/general anesthesia risk as follows:

- a) Cardiovascular 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 arrhythmia), 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.
 - b) Respiratory system disorders: respiratory insufficiency (except mild respiratory insufficiency not requiring O₂ to achieve SpO₂ >92 could be permitted), history of severe obstructive lung disease (i.e., forced expiratory volume in 1 second [FEV₁] <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 1 week 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) Psychiatric disease: history of schizophrenia, mania, long-term (more than 1 year) administration of psychoactive drug, or cognitive impairment.
 - e) Uncontrolled clinically significant conditions of liver (e.g., severe hepatic insufficiency defined as Childs-Pugh class C), kidney, gastrointestinal tract, blood system, nervous system, or metabolic system diseases, judged by the investigator to be unsuitable for involvement in the study.
 - f) Known glycosylated hemoglobin (HbA1c) greater than or equal to 10%.
 - g) Known thyroid-stimulating hormone (TSH) value outside the normal range or on thyroid-replacement therapy with a known free T4 level outside the normal range.
 - h) History of alcohol abuse within 3 months prior to screening, where alcohol abuse refers to daily alcohol drinking >2 units of alcohol (1 unit = 360 mL of beer or 45 mL of spirit with a strength of 40% or 150 mL of wine).
 - i) History of drug abuse within 3 months prior to screening.
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 1 year, no requirement for rescue inhalers or oral steroids within past 1 year, and not evaluated in emergency department, urgent care, or hospitalized for an asthma attack within past 5 years.
 - 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 11), 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 enrollment.
6. Taking valproic acid (Depakote) within 1 week prior to enrollment; taking UGT1A9 inhibitors, including but not limited to phenytoin, fosphenytoin, mefenamic acid, sorafenib, deferasirox, rifampicin, within 1 week prior to enrollment.
7. 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 $< 90 \text{ g/L}$ (without blood transfusion within 14 days)
 - d) Alanine transaminase and/or aspartate transaminase $\geq 2.0 \times$ upper limit of normal (ULN)
 - e) Total bilirubin $\geq 2.0 \times$ ULN
 - f) Severe renal impairment defined by creatinine clearance (CrCl) $\leq 30 \text{ mL/min}$
8. Female subjects with a positive pregnancy test (serum or urine) at screening or baseline; lactating subjects; any subject planning to get pregnant within 1 month after the study (including the male subject's partner).
9. 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 maybe rescreened once within 60 days. 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 or hypoxia (i.e., respiratory depression) 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

4.3.3. Lost to Follow-up

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

The following actions must be taken if a subject fails to return to the clinic for a required study visit or declines a phone contact (phone visit) 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 3 (3/255 [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 5 (5/255 [2%]) severe AEs of special interest (AESIs; Common Terminology Criteria for Adverse Events [CTCAE] Grade 3, 4, or 5) of hypotension, bradycardia, or hypoxia (i.e., respiratory depression) 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 patient population, in that only ASA-PS class I to II patients, no elderly patients (age >65), and no obese subjects (BMI>30) were included. Inclusion criteria for the current study includes ASA-PS class III to IV patients, elderly patients (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 patient population with more comorbidities, therefore, thresholds to suspend enrollment of 3 (3/255 [1%]) nonfatal SAEs related to study drug and 5 (5/255 [2%]) severe AEs of interest (CTCAE grade 3, 4, or 5) of hypotension, bradycardia or hypoxia occurring within 15 minutes of study drug administration 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

Specification: 20 mL: 0.05 g

Supplier: Sichuan Haisco Pharmaceutical Co., Ltd.

Control drug: Propofol injection

Trade name: Diprivan

Strength: 20 mL: 0.2 g

Supplier: Sichuan Haisco Pharmaceutical Co., Ltd.

Before the study drugs are delivered to the study site, the drug packaging unit (nonblinded) and other non-blinded personnel are responsible for packaging and labeling the study drugs based on the maximum quantity of study drug that each site might require during the induction of general anesthesia to avoid the need to request more drugs during the course of the study. The study drugs for each subject shall be packaged individually.

5.2. Preparation, Storage, Handling, and Accountability

Study drugs should be stored at 4°C to 25°C away from light and should not be frozen. 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 designated personnel (nonblinded) authorized by the investigator for regular accounting and record of the drug quantity. Nonblinded clinical research associates (CRAs) will supervise the drug management.

Only subjects enrolled in the study may receive study treatment and only 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 package 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 nonblinded preparation personnel will locate the corresponding study drug according to the drug number applied by the Interactive Web Response System (IWRS) 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 (rescue) drug for the subjects is also prepared.

The nonblinded 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 nonblinded 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 dose is given via slow injection over 10 (±5) seconds.

For elderly subjects ≥65 years of age, dose will be reduced by 25%.

For subjects with BMI ≤40, TBW will be used to determine HSK3486 dose; for subjects with BMI >40, LBW will be used to determine HSK3486 dose.

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, dose will be reduced by 25%.

For subjects with BMI ≤ 40 , TBW will be used to determine propofol dose; for subjects with BMI > 40 , LBW will be used to determine propofol dose.

5.3. Method of Treatment Assignment

The randomization of the subjects in this study is completed using the IWRS. After the subjects pass the screening, the investigator(s) or designee shall log into the IWRS 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 IWRS and submitted to the drug preparation personnel (nonblinded) for drug preparation. The non-blinded site staff will have to log into the IWRS to obtain the kit numbers and dosages.

Study treatment will be dispensed at baseline visit summarized in the Schedule of Assessments.

5.3.1. Dose Modification

Dose reductions will not be allowed unless the subjects are ≥ 65 years of age. A 25% dose reduction is required for elderly subjects ≥ 65 years of age.

Both the HSK3486 and the propofol dose will be modified for morbidly obese subjects: For subjects with BMI ≤ 40 , TBW will be used to determine dose; for subjects with BMI > 40 , LBW will be used to determine dose.

5.4. Blinding

This is a double-blind study. The IWRS 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.

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 Fentanyl

All subjects will receive preinduction IV fentanyl 1 mcg/kg rounded up to the nearest 25 mcg, up to 100 mcg maximum. Note: Administration of study drug must be initiated within 5 minutes after preinduction fentanyl.

Fentanyl is given for analgesia as standard of care prior to endotracheal intubation. Introduction of a foreign body into the trachea is a highly noxious procedure and providing analgesia prior to intubation is aligned with standard of care, aimed to limit unnecessary discomfort to subjects.

In the HSK3486-301 study in China evaluating HSK3486 compared to propofol for procedural sedation in subjects undergoing colonoscopy or gastroscopy, all subjects received fentanyl (50 µg IV) 1 minute prior to study drug injection. Even with the use of fentanyl immediately prior to study drug administration, the incidence of injection-site pain was significantly higher in the propofol treated group at 52.4% (76/145), which is consistent with literature reports, compared to only 4.9% (7/144) in the HSK3486 group.

In the HSK3486-302 study in China evaluating HSK3486 compared to propofol for induction of general anesthesia in subjects undergoing elective surgery requiring endotracheal intubation, all subjects received preinduction midazolam (0.04 mg/kg IV) and sufentanil (0.3 µg/kg IV) 2

minutes prior to receiving study drug. The incidence of pain on injection was significantly higher for propofol at 20.5% (18/88) compared to HSK3486 at 6.8% (6/88). The blunted effect of injection-site pain for propofol was likely due to preinduction midazolam.

Based on these data, a difference of $\geq 20\%$ injection-site pain between the treatment groups is anticipated for this study, noting also that midazolam will not be used in this study. Both treatment groups equally will receive fentanyl (1 $\mu\text{g}/\text{kg}$ IV rounded up to the nearest 25 mcg, up to 100 mcg maximum) for analgesia within 5 minutes prior to study drug, so any difference in incidence of injection-site pain will be interpretable and likely due to the effect of study drugs. The incidence of any pain (NRS >0) and moderate pain (NRS ≥ 4) for each treatment group will be reported, and well as the mean NRS score for each group.

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 are classified as concomitant medication except for study drugs and combination drugs; any medications/supplements/vitamins used before the baseline period 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 to use.

Before the end of the surgery, antiemetics and hemostatics can be used according to the clinical situation of the subjects, and postoperative use of antibiotics, hemostatics, antiemetics, and 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 9); 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-hypnotic, anesthetic drugs, analgesics, and systemic neuromuscular blocking agents other than those prescribed in the protocol are allowed from when the subjects are given

pre-anesthetic medications 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
- 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, 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.

IV acetaminophen is permitted.

- Benzodiazepines: Valium, Ativan, etc.

Valproic acid (Depakote) and UGT1A9 inhibitors, including but not limited to phenytoin, fosphenytoin, mefenamic acid, sorafenib, deferasirox, rifampicin, are prohibited within 1 week prior to enrollment until the end of study visit.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Study Procedures

7.1.1. Screening Period (Day -13 to Day 0)

During the screening period and before the investigator conducts any study procedures, he/she will explain to the subjects about 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, and surgical anesthesia history, etc.).
- Prior medications.
- Modified Mallampati score assessment (Appendix 411).
- Physical examination (including ASA-PS score, see Appendix 4).
- Vital signs (HR, RR, SpO₂, SBP, DBP, MAP, and Temp) after the subject has been resting supine for ≥ 5 minutes.
- Height, weight, and calculated BMI.
- 12-lead ECG.
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis).
- Conduct serum human chorionic gonadotropin (HCG) test (for females of childbearing age only).
- Instruct subject to fast at least 6 hours before surgery.
- Document AEs (after signing informed consent).

During screening, laboratory tests will be processed centrally. Central laboratory results should be used to confirm enrollment. However, in cases where central results are not yet available, results from local laboratories may be used. Screening laboratory tests obtained ≥ 7 days prior to enrollment should be repeated on Day 1 prior to study drug administration using the central laboratory. If any local screening laboratory tests are carried out in an external laboratory, the data must be judged by the investigator(s) as reliable before it can be deemed valid.

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)

Height, weight, and BMI will be obtained prior to dosing study drug. The most recent 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 (\pm 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 30 (\pm 5) 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.

If screening clinical laboratory tests were obtained \geq 7 days prior to enrollment, clinical laboratory tests (hematology, blood chemistry, and urinalysis) should be repeated on Day 1 prior to study drug administration.

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

Prior to entering the operating room:

- Measure vital signs (HR, RR, SpO₂, SBP, DBP, MAP, and Temp) to confirm consistent with eligibility criteria (after the subject has been resting supine for \geq 5 minutes).
- Conduct urine human chorionic gonadotropin (HCG) test (for females of childbearing age only).
- Obtain 12-lead ECG – only if the screening ECG is more than 1-week from the baseline visit, the 12-lead ECG should be repeated to assess its compliance with the inclusion/exclusion criteria.
- Verify inclusion/exclusion criteria.
- Height, weight, and calculated BMI.
- Premedication allowed except sedative-hypnotic or analgesic drugs.
- 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 (HR, RR, SpO₂, SBP, DBP, MAP, and Temp); baseline vital signs will be the average of 2 consecutive measurements taken 2 minutes apart.
- Start maintenance IV infusion (NS, LR, or 5% dextrose solution).
- Attach 3-lead or 5-lead electrocardiogram (ECG) to subject and monitor continuously.
- Subjects will receive preinduction treatment with IV fentanyl 1 mcg/kg rounded up to the nearest 25 mcg, up to 100 mcg maximum.
- Administer oxygen via face mask (≥ 4 L/min) after baseline vital sign values are determined.
- Attach BIS monitor to subject (either in preoperative anesthesia unit or in operating room, depending on local practice).

Induction period of general anesthesia:

- Monitor vital signs (HR, RR, SpO₂, SBP, DBP, MAP, and Temp) continuously and record once every 2 minutes (± 30 seconds) referencing the initiation of study drug administration (for every time point) for 30 minutes post initiation of study drug administration. Note: Vital sign monitor should be set to cycle every 1 minute, in order 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) on the back of right or left hand vein (this IV site 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 (± 15) seconds after injection until MOAA/S ≤ 1 is reached. If MOAA/S is still > 1 at 1 minute (+10 seconds) post study drug administration, a top-up dose of 50% of the initial dose of study drug (either HSK3486 0.2 mg/kg or propofol 1 mg/kg depending on treatment group) will be given to the subject (IV injection time: 10 [± 5] seconds) and time of administration will be recorded. If MOAA/S is still > 1 at 2 minutes (+30 seconds) post end of the top-up dose, then the rescue drug, propofol, will be given (in both treatment groups). Administration of study drug must be initiated within 5 minutes post preinduction IV fentanyl.
- Injection-site pain is evaluated verbally by Numeric Rating Scale (NRS; Appendix 46) upon administration of initial study drug prior to subject losing consciousness.
- After initial study drug administration, closely monitor, evaluate and record the time of loss of eyelash reflex.
- BIS will be monitored continuously; record baseline BIS value prior to administering study drug. BIS values will be collected at the following timepoints post completion of initial study drug administration: every 30 (± 10) seconds until 5 minutes, and then every 2 minutes (± 30 seconds) until 15 minutes, and then every 15 (± 5) minutes until 60 (± 10) minutes post study drug administration.
- Monitor 3-lead or 5-lead electrocardiogram (ECG) continuously.

- When MOAA/S ≤ 1 is achieved, obtain vital signs (HR, BP and RR), then IV rocuronium bromide (0.6 mg/kg) is administered for neuromuscular blockade to perform endotracheal intubation.
- Intubate subject once neuromuscular blockade has taken effect; if using twitch monitor, intubate once no twitches are noted; time of intubation should be recorded.
- During endotracheal intubation, evaluate for inadequate depth of anesthesia, such as coughing, laryngospasm and/or bronchospasm, and RR, for at least 15 minutes post study drug injection; responses should be recorded.
- Sevoflurane (an inhalation anesthetic agent) will be used for maintenance of general anesthetic. Initiate sevoflurane within 60 seconds after successful endotracheal intubation. Once sevoflurane has been initiated, monitor end-tidal sevoflurane concentration and record every 2 minutes (± 1 minute) until 30 minutes post initiation of initial study drug administration.

Note: Additional IV rocuronium is allowed per investigator's discretion only in response to clinical symptoms during tracheal intubation, such as gag reflex, movement et al, or during surgical procedures.

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. Propofol should not be used at any time all throughout the maintenance period.
- Additional IV fentanyl may be administered for intraoperative analgesia only after initiation of sevoflurane, preferably after 15 minutes following the initiation of study drug administration.
- Patient management during surgery needs to follow routine best practice which includes anti-emetics. Zofran (Ondansetron) or other 5 HT-3 antagonists and/or Dexamethasone, should be given during surgery and before subjects wake up unless otherwise contraindicated.
- The BIS will be monitored continuously per standard of care, and BIS values will be collected at the following timepoints post completion of initial study drug administration: every 30 (± 10) seconds until 5 minutes, then every 2 minutes (± 30 seconds) until 15 minutes, and then every 15 (± 5) minutes until 60 (± 10) minutes post study drug administration.
- Monitor end-tidal sevoflurane concentration per standard of care and record values once every 2 minutes (± 1 minute) until 30 minutes post initiation of initial study drug administration.
- Monitor 3-lead or 5-lead ECG continuously.
- Administer sevoflurane through maintenance period.

- Document AEs and concomitant medications.
- Blood sample for population PK study will be collected at the timepoints as indicated in Appendix 8.

7.1.3. Follow-up Period (6-hour Post Study Drug and 24-hour Post Study Drug Visit [Day 2])

For the 6-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-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. 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 7).
- After the surgery, vital signs (HR, RR, SpO₂, SBP, DBP, MAP, and Temp) will be assessed at 6 (± 2) hours post study drug administration. Note: If surgery lasts >4 hours, vital signs, clinical laboratory tests, and ECG should be obtained 1 (+1) hour after completion of surgery.
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis) will be obtained at 6 (± 2) hours post administration of study drug.
- Obtain 12-lead ECG at 6 (± 2) hours post study drug administration, and as clinically indicated.
- 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 and appropriate to be discharged home per the judgement of the investigator and surgeon, the subject may be released with supervision by a family member or friend, and must return to the clinic for the 24-hour follow-up visit (Day 2).

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

- 24 (± 6) hours post study drug administration (Day 2), obtain vital signs (HR, RR, SpO₂, SBP, DBP, MAP, and Temp).
- 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 on any AEs and associated medications will be collected.

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 ($MOAA/S \leq 1$) 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 5), 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 start 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 any clinical symptoms in response to tracheal intubation, such as coughing, laryngospasm, or bronchospasm, or an event where any of SBP, DBP, or MAP increases more than 20% from baseline on 2 consecutive readings in response to any noxious stimuli within 15 minutes post initiation of study drug administration.
- 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 10 for BIS guidance).

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

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

- 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.

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 6). Recollection of pain during study drug administration will be assessed in the PACU once the subject is awake and oriented.

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

In the PACU, once the subject is alert and oriented, repeat NRS for recall of pain at time of study drug administration.

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 is ≤ 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. 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 timepoints to understand the changes in the BIS of the subjects throughout the entire anesthesia period (see Appendix 10) for BIS guidance).

7.2.7. Brice Awareness Questionnaire

Recall of awareness during surgery, assessed postoperatively, will be evaluated using the Brice Awareness Questionnaire (see Appendix 7).

7.2.8. Use of Study Drugs and Alternative Drugs

The use of HSK3486 and propofol (including the time and use of top-up dose, the amount of top-up dose, and the total dose) is evaluated from the end of study drug administration to the time of successful induction. The use of alternative drug (propofol) (including the time and use of top-up dose, the amount of top-up dose, and the total dose), as well as the proportion of subjects using the rescue/remedial drug (propofol), is evaluated from the beginning of the dosing of the study drug to the time of successful induction. The proportion of subjects using the alternative drug (propofol) is also 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 1.

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 nonleading 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).

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 1. All SAEs, occurring after the signing of the ICF until the end of study and regardless of study drug relationship, must be reported by facsimile or email to [REDACTED] within 24 hours of obtaining knowledge of the event. 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 fax SAE reports and follow with a telephone call, if needed.

[REDACTED]

[REDACTED]

[REDACTED]

[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.

██████████ 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 ██████████ as soon as it is available.

7.3.3. Adverse Events of Special Interest

The AESIs due to pharmacological effect of an anesthetic agent include hypoxemia, bradycardia, hypotension, and injection-site pain are defined as follows:

- Hypoxemia is defined as SpO₂ <90% with duration of >30 seconds. Hypoxemia is evaluated from the initial dose of study drug until the subject leaves the operating room. For hypoxemia occurring after the dosing of study drugs, its start time and end time (both should be accurate to the second and the duration should be calculated), and treatment measures should be recorded (if any).
- Bradycardia is defined as a heart rate of <45 beats/minute that lasts >30 seconds. Bradycardia is evaluated from the initial dose of study drug until the subject leaves the operating room. For bradycardia occurring after the dosing of study drugs, its start time and end time (both should be accurate to the second and the duration should be calculated), and treatment measures should be recorded (if any).
- Hypotension is defined as an SBP <90 mmHg that lasts >2 minutes. Hypotension is evaluated from the initial dose of study drug until the subject leaves the operating room. For hypotension occurring after the dosing of study drugs, its start time and 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.

- 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, male and female subjects of childbearing age are required to adopt appropriate contraceptive measures before (from screening) and during the study. Effective contraceptive measures include female sterilization (such as bilateral tubal ligation), hormone contraceptives (oral, implanted, and transdermal), and the combination of intrauterine contraceptive device and barrier contraceptive (condoms, cervical caps).

If a female subject or a female sexual partner of a male subject who has used at least once the study drug becomes pregnant during the study period (from signing ICF to the end of the follow-up period), the investigators should immediately record the pregnancy information as a special AE 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 investigators should also report the event to the 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 24 hours 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 violation.

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]), and blood glucose (Glu).
- 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 (\pm 2) hours post administration of study drug. If the screening laboratory tests are \geq 7 days old at the time of randomization, they should be repeated on Day 1 before study drug administration. Screening laboratory tests used for enrollment will be based on local results if central results are not available yet.

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

7.3.6.1. Vital Signs

Vital signs include RR, HR, SpO₂, BP (SBP, DBP, and MAP), and Temp.

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 average of 2 consecutive measurements at least 2 minutes apart.

During anesthesia induction and maintenance period, vital signs are continuously monitored and values are recorded once every 2 minutes (\pm 30 seconds) (including vital signs monitored at the start of medication) for 30 minutes post study drug administration, and then at 6 (\pm 2) hours post study drug administration, and at the 24-hour (Day 2) visit.

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. The 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. At baseline, if the screening ECG is more than 1-week from the baseline visit, the 12-lead ECG should be repeated to assess its compliance with the inclusion/exclusion criteria (the result is also used as the baseline value). 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, a 12-lead ECG should be performed for verification.

7.3.7. Use of Additional Fluids or Medication or Any Interventions

Administration of additional fluids or 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 timepoints are listed in Appendix 8. Approximately 3 mL of venous blood are collected at each timepoint.

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 255 subjects (170 in HSK3486 0.4/0.2 mg/kg group and 85 in propofol 2.0/1.0 mg/kg group) need to be enrolled 2:1 into this study given a drop-out rate of 3% based on the following assumptions:

- For the primary endpoint, a sample size of 215 patients 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 176 patients will give 90% power assuming $\alpha=0.05$ (2-sided) and the proportion of subjects who meet the endpoint criteria of any injection-site pain are 20% and 45% for HSK3486 and propofol, respectively.
- For the key secondary composite endpoint, a sample size of 255 patients will give at least 80% power (providing the first primary endpoint is statistically significant) to the superior testing, assuming $\alpha=0.05$ (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 15 minutes post study drug administration observation period (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, about 255 patients will be randomized and treated in this study.

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/m². 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 at least 1 dose of the study drug (HSK3486 or propofol).

Per Protocol Set (PPS): All subjects from FAS who have completed primary efficacy endpoint data, and no major study protocol violations during the study. Subjects with any major protocol deviations will be reviewed after database lock and prior to study unblinding, and may be excluded from PPS if these major deviations will impact the efficacy evaluations.

Safety Set (SS): Includes all randomized subjects who have received at least 1 dose of the study drug and have postdose 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 δ is the NIM. This hypothesis will be tested at the 1-sided $\alpha=0.025$ 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 noninferiority. The FAS subjects who are nonevaluable 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 $\geq 97\%$ 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 $\geq 97\%$, 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 proportion of subjects with successful induction without nonoptimal 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 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 timepoints will also be reported.

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 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 primary endpoint is statistically significant, then the key secondary endpoints will be tested using an ordered fixed-sequence step-down procedure. The proportion of subjects with any injection-site pain at time of drug administration on the NRS will be tested first, and if successful then will the composite endpoint of successful induction be tested. For each key secondary endpoint, the comparison between HSK3486 and propofol arms will be conducted at $\alpha=0.05$ level. If the first test of injection-site pain is rejected, then the 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, Temp, and SpO₂), ECG findings, physical examination findings, site pain on study drug administration with intensity rating on NRS, and administration of additional fluids or 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 23.0 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 (see Section 7.3.3), TEAEs related to study drug, SAEs related to study drug, TEAEs of Grade 3 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 postbaseline timepoints 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. Data obtained from laboratory tests not required by the protocol will not be summarized 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.

An independent DMC will be involved in the review of all safety data at approximately 20% 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 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.
- 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 any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

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.

Adverse event reporting begins from the time of informed consent and ends 30 days after the last dose of study drug.

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 Related:** Underlying or concurrent disease or other drugs/exposures provide plausible alternative explanations. Temporal relationship to study drug administration makes a causal relationship improbable.
- **Likely Related:** There is a reasonable possibility that the drug caused the AE; the event is unlikely attributed to underlying or concurrent disease or other drugs/exposures (i.e., alternative explanation). There is a reasonable time sequence to administration of the study drug.
- **Definitely Related:** A definite causal relationship exists between the drug administration

and the AE; including a plausible time relationship to drug administration, and it cannot be explained by underlying or concurrent disease or other drugs/exposures; abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Action Taken for Adverse Events

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

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

Follow-up of Adverse Events

All 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 2 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)	
Total CO ₂ (measured as bicarbonate)	For Females Only:
Total protein	Urine pregnancy test → local laboratory only
Uric acid	Serum pregnancy test
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; CO₂ = 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.

Appendix 3 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 Sponsor, 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 312.62(c) 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 (refereed) 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 4 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.

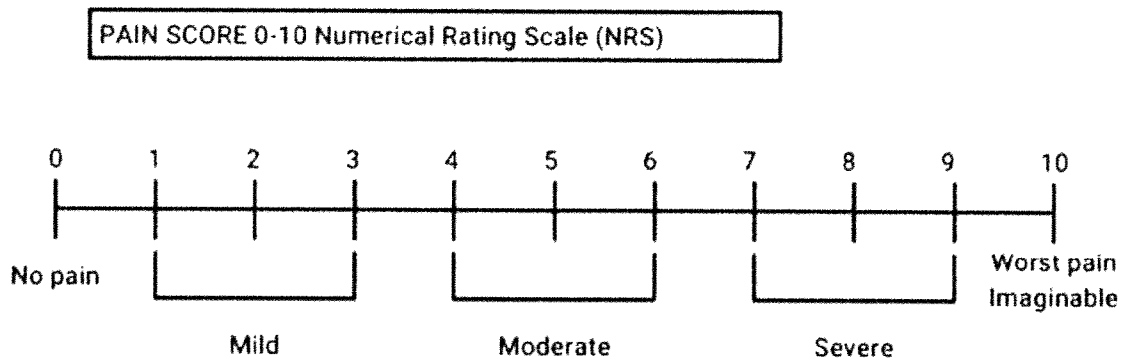
Subjects assessed as ASA I or ASA II have good tolerability to anesthesia and surgery, and the process of anesthesia is smooth. Subjects assessed as ASA III are under certain risks of anesthesia. The pre-anesthetic preparation should be adequate. Effective measures should be taken to prevent complications 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 5 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 6 Numerical Rating Scale (NRS) for Grading of Injection-site Pain



Appendix 7 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 8 Pharmacokinetic (PK) Blood Samples Collection Timetable

Phase	Time	Allowed Time Window	PK Blood Sample Collection ²
Before dosing study drug			
	Before the 1 st 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	±30 seconds	X
	3 ~ 30 minutes	Not applicable	X
	60 ~ 120 minutes	Not applicable	X

Note:

- 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 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 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.
- All the subjects are required to provide venous PK blood samples. The blood volume is approximately 3 mL per sample. The PK blood samples will be taken from a second IV.

Appendix 9 Drugs that May Prolong the QT Interval

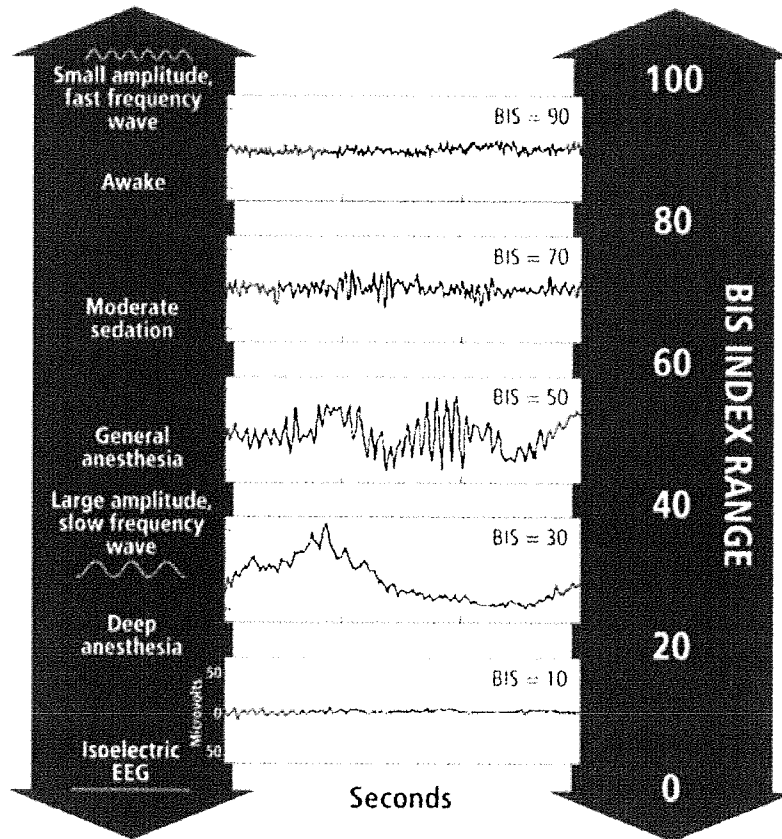
Drugs that prolong QT interval (including but not limited to the following)	
Antibiotics	Clarithromycin Azithromycin Erythromycin Roxithromycin Metronidazole Moxifloxacin
Antiarrhythmics	Quinidine Sotalol Amiodarone Disopyramide Procainamide
Antipsychotics	Fluphenazine Droperidol Haloperidol Thioridazine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

Anti-tumor drugs	Anthracyclines 5-fluoropyrimidine
Antihistamines	Diphenhydramine Terfenadine Astemizole
Other drugs	Indapamide Cisapride

Appendix 10 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 1). The BIS values near 100 represent an “awake” clinical state while 0 denotes the maximal electroencephalogram (EEG) effect possible (i.e., an isoelectric EEG).

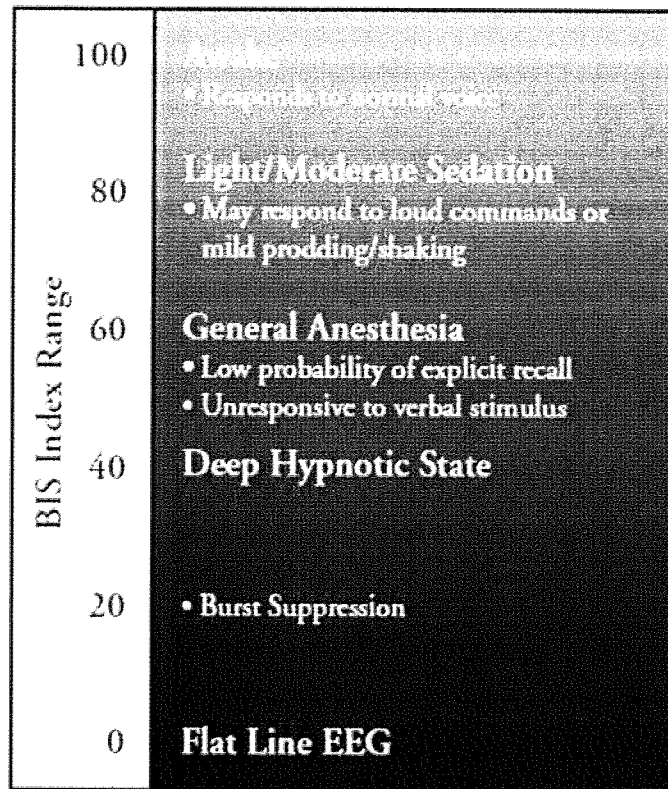
Figure 1 The BIS Index is scaled to correlate with important clinical endpoints during administration of anesthetic agent.



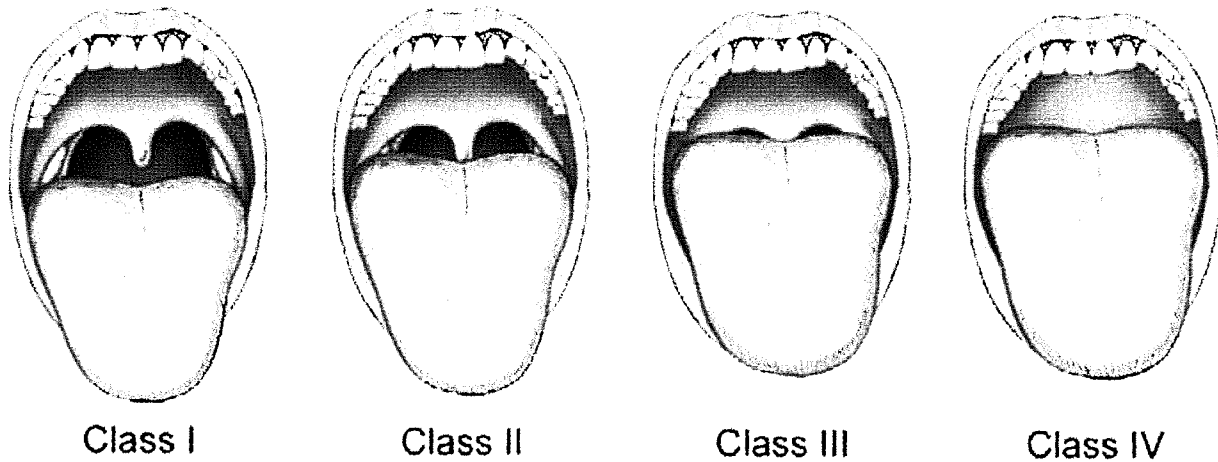
It should be noted that the BIS Index range represents a continuum that correlates to the clinical state and expected responses (Figure 2).

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



Appendix 11 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.