COVER PAGE – STATISTICAL ANALYSIS PLAN V1.0 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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Statistical Analysis Plan

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

Haisco-USA

HSK3486-304

[redacted]

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Reviewers

The following reviews of the SAP were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
[redacted]	Lead Statistician	Draft 0.1	[redacted]
[redacted]	QC Reviewer	Draft 0.1	[redacted]
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Glossary of Abbreviations

Abbreviation	Term
AE	Adverse Event
AESI	AEs of special interest
ALT	Alanine aminotranferase
ALP	Alkaline phosphatase
ARAE	Abuse-related AEs
ASA-PS	American Society of Anesthesiologists Physical Status
AST	Aspartate aminotranferase
ATC	Anatomical Therapeutic Chemical
BIS	Bispectral index
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
CRF	Case Report Form
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
HR	Heart Rate
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Awareness/Sedation
NCI	National Cancer Institute
NRS	Numeric Rating Scale
PACU	Post-anesthesia care unit
PCS	Potentially Clinically Significant
PK	Pharmacokinetic
PPS	Per-protocol Set
PT	Preferred Term
QTcF	Fridericia corrected QT interval
RBC	Red Blood Cell
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic Blood Pressure
SD	Standard Deviation
SI	International System of Units
SOA	Schedule of Assessments

SOC	System Organ Class
SpO_2	Oxygen saturation
SS	Safety Set
TEAE	Treatment – emergent adverse event
Temp	Temperature
WBC	White Blood Cell

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	30Jul2021	5.0
eCRF	03NOV2021	5.0
DMC Charter	07May2021	2.0
IWRS	18DEC2020	1.0

2. Protocol Details

2.1 Study Objectives

The primary objective of the study is:

- To demonstrate HSK3486 0.4/0.2 mg/kg (0.4 mg/kg intravenous [IV] slow injection over 30 [±5] 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 (±5) seconds for first dose, an additional 1.0 mg/kg if needed) in success of induction of general anesthesia in adults undergoing elective surgery.

The secondary objectives of the 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 Overall Study Design

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.

Subject's screening will be started 14 days prior to study drug administration. After screening, eligible subjects will be randomized in a 2:1 ratio to receive either HSK3486 0.4/0.2 mg/kg (i.e., 0.4 mg/kg IV slow injection over 30 [±5] seconds followed by an additional 0.2 mg/kg dose if needed) or propofol 2.0/1.0 mg/kg (i.e., 2.0 mg/kg IV slow injection over 30 [±5] seconds followed by an additional 1.0 mg/kg dose if needed) in a blinded manner. Enrolled subjects will be stratified by American Society of Anesthesiologists Physical Status (ASA-PS; I to II and III to IV), age group (<65 and ≥65 years), and Body Mass Index (BMI) (<35 and ≥35 kg/m^2). Endotracheal intubation will be performed after adequate anesthetic induction (Modified Observer's Assessment of Awareness/Sedation [MOAA/S] score ≤1) (Appendix 5 of protocol) has been achieved and administration of neuromuscular blocking agent.

The randomization of the subjects in this study is completed using the Interactive Web Response System (IWRS). 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.

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, total body weight will be used to determine dose; for subjects with BMI >40, lean body weight will be used to determine dose.

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: ≥4 L/min), and maintenance IV solution (normal saline [NS], lactated ringer's [LR], or 5% dextrose) will be administrated through the 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 (SpO_2), 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 prior to initiation of study drug.
- Attach 3-lead or 5-lead electrocardiogram (ECG) to subject and monitor continuously.
- Attach Bispectral index (BIS [Appendix 10 of protocol]) 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, SpO_2, SBP, DBP, MAP, and Temp) continuously and record once every 2 minutes (±seconds) referencing the initiation of study drug administration (for every time point) for 30 minutes post initiation of study drug administration.
- Administer IV study drug (HSK3486 0.4 mg/kg or propofol 2.0 mg/kg) on the back of right or left hand vein (this IV location is strongly preferred rather than mandatory) at a port closest to the IV cannula (IV injection time: 30 [±5] seconds). The MOAA/S will be evaluated every 30 (±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 at >1 at 2 minute (+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 of protocol) 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 the 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.

- 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 end 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, SpO_2, 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 of protocol).

- Information about any AEs and concomitant mediations will be collected and recorded.

- After the surgery, subjects may remain in the hospital or observation unit if required based on standard of care and the clinical situation; however, if the subject is clinically stable 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, SpO_2, SBP, DBP, MAP, and Temp).

- Information about any AEs and concomitant mediations will be collected and recorded.

Day 8: Phone Contact

- Subjects will be evaluated by a follow-up telephone call 7 (±2) days after surgery.
- Surgical awareness with recall will be re-assessed using the Brice Awareness Questionnaire.
- Information on any AEs and associated medications will be collected.

End of Study

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

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 event (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 minutes duration despite routine interventions. If these criteria are met, enrollment will be temporarily suspended while the Data Monitoring Committee (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.

Reasons for study termination may include, but are not limited to:

- adverse events (AEs) 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,
- medical or ethical reasons affecting the continued performance of the study,
- difficulties in the recruitment of subjects, or
- 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)/Ethics committee (EC) or local health authorities, the Sponsor's procedures, or Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of participants by the investigator.

2.3 Sample Size and Power

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 is -8%.
- For the key secondary endpoint of incidence of injection-site pain, a sample size of 176 patients will give 90% power assuming α=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 225 patients will give at least 80% power (providing the first primary endpoint is statistically significant) to the superior testing, assuming α=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.

3. Efficacy and Safety Variables

3.1 Primary Efficacy Endpoint

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

A successful general anesthesia induction will meet both of the following conditions:

I. Induction success (MOAA/S ≤1) after administration of the study drug, and

II. One or less top-up dose required without using any rescue drugs.

	Situation	Measurement
MOAA/S will be evaluated every 30 (±15) seconds after injection until MOAA/S ≤1	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)
	MOAA/S is still at >1 at 2 minutes (+30 seconds) post end of the top-up dose	the rescue drug, propofol, will be given (in both treatment groups)

In all instances, subjects that receive rescue medication will be considered induction failures, even in the instance where the time rescue medication is started coincides or is after the time noted where MOAA/S ≤1.

3.2 Secondary Efficacy Endpoints

Key secondary endpoints:

- The proportion of subjects with any injection-site pain at the 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. See Appendix 10 of protocol.

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

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

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

Other secondary endpoints:

- Time to successful induction of general anesthesia: Time from the end of the first administration of the study drug to MOAA/S ≤1.
- Time to the disappearance of eyelash reflex: Time from the end of the first administration of the study drug to the disappearance of eyelash reflex.
- Use of the top-up study drug and rescue/remediation drugs.

3.3 Safety Endpoints

Safety assessments include AEs, clinical laboratory test results, vital signs (supine HR, SBP and DBP, MAP, RR, Temp, and SpO_2), 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.

See Section 7.7 for a detailed explanation.

4. Pharmacokinetic Endpoints

Plasma HSK3486 concentration will be collected at scheduled time points (see Appendix 8 of protocol).

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. PK analysis of concentration data is not included in this SAP. It will be performed by an appointed contract research organization/entity by Haisco-USA and will be reported separately from the main clinical study report.

5. Analysis populations

Definitions of the Full Analysis Set (FAS), Per Protocol Set (PPS) and Safety Set (SS) are provided bellow.

5.1 Full Analysis Set (FAS)

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

The FAS will be the primary analysis population for efficacy. Subjects will be analyzed according to the study drug to which they are randomized.

5.2 Per Protocol Set (PPS)

All subjects from FAS who have completed primary efficacy endpoint data, and have no important study protocol deviations during the study as determined by review of Haisco-USA. Subjects with any protocol deviations will be reviewed after database lock and prior to study unblinding and may be excluded from PPS if these important deviations will impact the efficacy evaluations.

This population will be the supportive analysis population for efficacy analysis. Subjects will be analyzed according to the study drug to which they are randomized.

Protocol deviations are defined as any untoward change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Section 5.3.1 of SAP details the deviations.

5.3 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.

Safety endpoints will be analyzed using the SS. Subjects will be analyzed according to the study drug to which they are actually treated.

5.3.1 Important Protocol Deviations Leading to Exclusion from the PPS Analysis

Only those important protocol deviations considered to have a major effect on efficacy will lead to complete exclusion of the subject from the PPS. For the purposes of this study, the following criteria have been identified as important protocol deviations as it is considered that the occurrences of any of these criteria might have an important influence on the primary efficacy endpoint. Subjects will be assessed purely by comparison of their CRF data with the criteria below; protocol waivers will not be taken into consideration.

Type	Important Protocol Deviation Leading to Exclusion from the PPS	Method of Identification
Pregnancy	Pregnant female subject during the study period should withdraw from the study	**programmable** check from CRF page "Pregnancy Test"
Inclusion Criteria 3	Subject BMI is not 18 or more	**Programmable** check from CRF page "Height, Weight and BMI"
Prohibited Therapies	Any subject who went through prohibited therapies	**Non-programmable** subjects went through therapies listed in section 6.2 of protocol
Study Medication	Partially dosing of study medication administration	**Non-programmable** unblinded CRA will identify patients who had been partially dosed of study medication

Important protocol deviations occurring during the study will be reviewed by Haisco-USA prior to database lock or unblinding. At this time, important deviations that will lead to exclude from the PPS will be identified. Additional important protocol deviations leading to exclusion from the PPS, not anticipated at the time of preparing this SAP, but identified during the study will be documented in an SAP amendment or other document and included in all relevant protocol deviation reviews and approvals.

5.4 Special Subpopulations

Not applicable.

6. DATA Handling

6.1 Time points and Visit Windows

Day 1 is defined as the day of first dose of study drug. Relative days after Day 1 are calculated as

Study day = (assessment date – first dose of study drug) + 1.

Relative days prior to Day 1 are calculated as

Study day = (assessment date – first dose of study drug).

The day prior to Day 1 is Day -1.

Unless otherwise specified, data will be analyzed using nominal study visits as defined in the SOA of protocol. Analysis windows will be applied for data collected continuously during the conduct of the surgery (i.e. BIS monitoring and vital signs).

Multiple visits within the same window will be dealt with as follows:

- If both scheduled and unscheduled visits fall within the same visit window, the scheduled visit will be used for analysis.

- If multiple scheduled visits occur within a single visit window then the visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later visit will be used in the analysis

- If multiple unscheduled visit occurs within a single visit window (with no scheduled visit within the window) then the unscheduled visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later unscheduled visit will be used in the analysis.

6.2 Handling of Dropouts, Missing Data, and Outliers

See Section 7.6.1 for imputation of the primary efficacy endpoint. All other safety and efficacy analysis will be carried out on observed data. No imputation is planned for missing or partially collected data except for start and end dates of adverse events and concomitant medications, which will be based on following algorithm.

1. If year is missing;
    - No imputation.
2. If both day and month are missing;
    - If year is same as the year of first dose of study drug, set both day and month to first dose of study drug.
    - If year is prior to the year of first dose of study drug, set to 31 December.
    - If year is after the year of first dose of study drug, set to 01 January.
3. If only month is missing;
    - If year is same as the year of first dose of study drug, set both day and month to first dose of study drug.
    - If year is prior to the year of first dose of study drug, set both day and month to 31 December.
    - If year is after the year of first dose of study drug, set both day and month to 01 January.
4. If day is missing;

- If month and year are same as first dose of study drug, set to day of first study drug dose.
- If month and/or year is prior to first dose of study drug, set to last day of the month.
- If month and/or year is after first dose of study drug, set to first day of the month.

If an imputed start date is after the end date of the event (AE or medication), then the earliest of the first dose date of study drug and end date of the event will be assigned as the start date.

If an imputed end date is after the death date, then the date of death will be assigned to the end date.

No rules for outlier detection are planned.

7. Statistical Methods

7.1 General Principles

All data processing, summarization and analyses will be performed using [redacted] SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

Unless otherwise specified, baseline is defined as the last non-missing data assessed/performed on or before the first dose of study drug administration.

The following principles will be applied to all TFLs unless otherwise stated:

Principle	Value	Suggested Alternative Values
Treatment group labels and order	HSK3486 0.4 mg/kg/0.2 mg/kg Propofol 2 mg/kg/1 mg/kg	
Tables	Data in summary tables will be presented by study drug, assessment and visit (where applicable).	
Listings	All data collected presented by study drug, subject ID, assessment and visit (where applicable), unless otherwise specified.	
Descriptive summary statistics for continuous variables	Number of subjects/observations (N), mean, standard deviation (SD), median, minimum and maximum.	
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]	

Principle	Value	Suggested Alternative Values
Denominator for percentages	Number of subjects in the analysis population by study drug, unless stated otherwise in table shell.	
Include "Missing" as category	Yes, When the number missing is greater than zero for at least one study drug.	
Display for 0 percentages	Blank	0
Display to one more decimal place than collected value	Mean Median	
Display to two more decimal places than collected value	Standard Deviation Confidence Interval (CI)	
Limit of precision for displays	3 decimal places	
Date Format	DDMMMYYYY	

7.2 Subject Disposition and Data Sets Analyzed

Subject disposition will be listed and summarized by study drug and overall for all subjects and will include the number and percentage of subjects:

- screened;
- screen failure (including reason for failure);
- randomized;
- randomized and not treated;
- treated;
- included in each study population (FAS, SS and PPS);
- completed study;
- discontinued study (including primary reason for study discontinuation).

A summary of patient enrollment by site will also be provided by overall for all randomized subjects.

7.3 Protocol Deviations

All protocol deviations will be listed, and important deviations will be summarized by study drug for the FAS population.

All important protocol deviations will be reviewed for the determination of PPS population. Those important protocol deviations leading to exclusion from the PPS population (see Section 5.3.1) will be listed and summarized by study drug for the FAS population.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed for the FAS population and summarized by study drug and overall for all analysis populations (FAS, SS and PPS). Standard descriptive statistics will be presented for the continuous variables of:

- age (years);
- weight (kg);
- height (cm);
- body mass index (kg/m^2),
- Pre-dose BIS.

The total counts and percentages of subjects will be presented for the categorical variables of:

- age group (years) (grouped as <65, and ≥65);
- gender;
- race;
- ethnicity;
- BMI group (kg/m2) (grouped as <35, and ≥35);
- ASA-PS (grouped as I to II and III to IV);
- Modified Mallampati Score.

No formal tests of statistical significance will be performed on the demographic data.

Other baseline measurements, such as vital signs, laboratory, ECG, will be summarized by study drug with the post-baseline measurements and are detailed in later sections.

7.4.1 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 (or a later version if updated during the study). All medical history will be listed, and the number and percentage of subjects with any

medical history will be summarized for the FAS population by system organ class (SOC) and preferred term (PT) for each study drug and overall.

7.4.2 Previous and Concomitant Medications

Medications received prior to or concomitantly with study drug will be coded by [redacted] using the WHO Drug Dictionary Global Sep 2020 B3 (or a later version if updated during the study) Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are those taken prior to study with a stop date prior to the date of surgery.

Concomitant medications are those with a start date on or after the date of surgery, or those with a start date prior to the date of surgery and continuing through the study with a stop date on or after the date of surgery or ongoing at the end of the study.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications and concomitant medications will be listed together and summarized separately for the FAS population.

The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication within each ATC-Level 4, and PT.

7.4.3 Study surgery, procedures and other administrations

A detailed list of study surgery performed, administration of rocuronium bromide, administration of fentanyl, endotracheal Intubation, and End-tidal sevoflurane monitoring will be presented.

7.5 Measurements of Treatment Compliance

Study drugs will be administered at the site by site personnel as a single injection. Therefore, only exposure will be summarized.

See Section 7.7.1 of SAP for exposure of study drug.

7.6 Efficacy

7.6.1 Primary Efficacy Analysis

The primary efficacy endpoint of this study is Success Rate of Anesthesia Induction, which is the proportion of subjects with successful anesthesia. A subject is considered successful for anesthetic induction if he/she meets the following criteria.

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

MOAA/S ≤ 1 (see Appendix 5 of protocol) represents subjects that do not respond to the light stimulus or shaking but respond to painful stimulation.

The statistical hypothesis of non-inferiority will be tested, that is:

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

against

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

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

A summary table of frequency counts and percentages of success of general anesthesia induction, failure of general anesthesia induction and reason for failure (MOAA/S > 1 or use of rescue medication) will be displayed. Success rate of general anesthesia induction in both treatment groups and rate difference and its 95% confidence interval (CI), estimated by Farrington-Manning method with the stratification factors included in the analysis will be displayed for the FAS and PPS populations. If the response rate is 100% for either treatment group, then the exact Farrington-Manning method will be used. In this case, both the exact and asymptotic CIs will be reported, but the exact CI will be used for the primary analysis.

The lower limit of the 95% CI for difference in rates of successful induction will be compared with the non-inferiority margin of -8% to confirm the establishment of non-inferiority. The FAS subjects who are not evaluable for anesthesia success will be counted as treatment failures.

See Appendix 2 of SAP for SAS syntax of Farrington-Manning method.

7.6.2 Secondary Efficacy Analysis

7.6.2.1 Injection pain score

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

A summary with standard descriptive statistics will be provided for the NRS pain score collected at the time of study drug administration for the FAS and PPS populations. A separate summary of the subject's NRS recall of pain score assessed in the PACU once the subject is alert and fully oriented will be provided.

The proportion of subjects with any injection site pain (NRS ≥ 1) during IP administration for each treatment group and the difference between the 2 treatment groups and 95% CI will be calculated. Statistical testing will be done using the Cochran-Mantel-Haenszel test stratified for ASA-PS (I to II and III to IV), age group (<65 and ≥65 years) and BMI (<35 and ≥35 kg/m^2).

The same analysis methods as stated above will be provided for any injection site pain (NRS≥ 1) in PACU, moderate pain (NRS ≥ 4) during IP administration, moderate pain (NRS ≥ 4) in PACU, any injection site pain (NRS ≥ 1) either during IP administration or in PACU, and moderate pain (NRS ≥ 4) either during IP administration or in PACU, as well as the mean NRS pain score (during IP administration, in PACU, either during IP administration or in PACU) for each treatment group as supportive evidence.

A list of observed NRS score will be presented for each visit timepoint.

7.6.2.2 Desired depth of anesthesia for general elective surgery

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

- No clinical symptoms in response to tracheal intubation, such as coughing, laryngospasm, or bronchospasm.
- No BP (SBP, DBP, or MAP) increase of more than 20% from baseline on 2 consecutive readings in response to noxious stimulus 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 at a level of not more than 60 for the 15 minutes post initiation of study drug administration).

Note: Target BIS 40 to 60 for general anesthesia (see Appendix 10 of protocol 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 SpO_2 <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.

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) will be calculated for both treatment groups and the difference in proportions between the treatment groups and 95% CI for difference will be calculated for the FAS and PPS populations. The Cochran-Mantel-Haenszel test stratified by ASA-PS (I to II and III to IV), age group (<65 and ≥65 years) and BMI (<35 and ≥35 kg/m^2), will be used to calculate the p-value for superiority of HSK3486 over propofol.

The summary of proportion of subjects with successful induction without non-optimal anesthetic effects within 15 minutes post administration of study drugs will also be analyzed using the similar statistical methods as for the secondary composite efficacy endpoint.

7.6.2.3 Time to successful induction of general anesthesia

Time to successful induction of general anesthesia 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. For subjects who did not achieve

successful induction of general anesthesia, it will be censored at the start time of rescue medication.

Time to successful induction of general anesthesia = (date and time of event/censor – date and time of end of the first administration of study drug)

The Kaplan-Meier method will be used for analyses. The median time with 95% two-sided confidence intervals will be estimated for each treatment group for the FAS populations. A graphic presentation of the Kaplan-Meier estimates by study drug will also be included.

See Appendix 3 of SAP for SAS syntax of time to event endpoint.

7.6.2.4 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. For subjects who did not achieve loss of eyelash reflex during the induction phase, it will be censored at the start time of rescue medication.

Time to Loss of Eyelash Reflex = (date and time of event/censor – date and time of end of the first administration of study drug)

The Kaplan-Meier method will be used for analyses. The median time with 95% two-sided confidence intervals will be estimated for each treatment group for the FAS populations. A graphic presentation of the Kaplan-Meier estimates by study drug will also be included.

A list of observed loss of eyelash reflex will be presented.

See Appendix 3 of SAP for SAS syntax of time to event endpoint.

7.6.2.5 Bispectral Index

The change of BIS during the period of anesthesia post study drug administration up to 15 minutes will be summarized descriptively by treatment group. For this summary, BIS values will be windowed as shown below.

	Time post completion of initial study drug administration	Collection timepoints and window
BIS collection timepoints and windows	Until 5 minutes	every 30 (±10) seconds
	Until 15 minutes	every 2 minutes (± 30 seconds)
	until 60 (±10) minutes	every 15 (±5) minutes

7.6.2.6 Brice Awareness Questionnaire

Summary of Brice Awareness Questionnaire (see Appendix 7 of protocol) results will be provided by treatment group and overall for the Safety Set. A list will also be provided.

7.6.2.7 Remediation

The use of study drugs and remediation drugs will be summarized descriptively by treatment group.

A detailed list of study drugs and remediation drugs will also be presented.

7.6.3 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 (i.e., the null hypothesis of no difference is rejected) 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 the α=0.05 level. If the first test of injection-site pain is rejected (i.e., the null hypothesis of no difference is accepted), then the testing stops. This procedure controls the familywise Type I error rate at the overall α=0.05 level for the key secondary endpoints. The analyses for all other secondary endpoints will be descriptive, and any testing that may be done will not be adjusted to maintain Type I error.

7.6.4 Sensitivity Analysis

A sensitivity analysis of Success Rate of Anesthesia Induction using the same methodology as the primary endpoint will be conducted considering all subjects taking propofol with missing criteria as successful anesthetic induction.

7.6.5 Subgroup Analysis

Subgroup analysis of Success Rate of Anesthesia Induction for ASA-PS (I to II and III to IV), age group (<65 and ≥65 years) and BMI (<35 and ≥35 kg/m^2) will be conducted using the same methodology as the primary endpoint.

7.6.6 Exploratory Analysis

Not applicable.

7.7 Safety

7.7.1 Extent of Exposure

Frequency counts and percentages will be calculated for the number of doses received (including top-up and rescue medication), the number of subjects receiving a top-up dose, and the number of subjects receiving rescue medication. Duration will be summarized using standard descriptive statistics, and the frequency and percentage for anatomical location and laterality will also be provided. The Safety Set will be used for all summaries.

7.7.2 Adverse Events

All adverse events (AEs) recorded on the CRF will be coded using the MedDRA dictionary Version 23.1 (or a later version if updated during the study) and classified as either pre-treatment AEs or treatment – emergent AEs (TEAEs) as follows:

- Pre-treatment AEs are events that start prior to the date and time of first dose of study drug.
- TEAE is any event that is not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

All AE data will be listed by study drug. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of serious AEs (SAEs), AEs leading to discontinuation of study drug, AEs resulting in death, Adverse Events of Special Interest (AESI) and Abuse-related AEs (ARAE) of interest will be produced. A separate list of Preferred Terms of AESIs and ARAEs of interest will also be presented.

Summary tables of TEAEs by treatment group and overall will be produced for the Safety Set.

Assessment of AE severity will be based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

The relationship between an AE and study drug is assessed by investigator using a 4-category system as definitely related, likely related, unlikely related, or not related.

An overview table will summarize the number and percentage of subjects with at least one of the following TEAEs, where subjects with more than one TEAE in a particular category are counted only once in that category:

- any TEAE;
- any TEAE by severity (mild, moderate, severe, life-threatening, death);
- study drug-related TEAE;
- Adverse Events of Special Interest (AESI);

- Abuse-related AEs (ARAE) of Interest;
- TEAE causing study drug discontinuation;
- TEAE causing discontinuation from the study;
- TEAE leading to death;
- Study drug-related TEAE leading to death;
- Serious TEAE;
- Study drug-related serious TEAE;
- Serious TEAE causing study drug discontinuation;
- Serious TEAE causing discontinuation from the study.

The number and percentage of subjects reporting each TEAE and the number of events for each TEAE will be summarized by System Organ Class (SOC) and Preferred Term (PT) for the Safety Set. SOCs and PTs will be sorted by descending overall total in summary tables. The following summaries will be produced:

- TEAEs, by SOC and PT;
- TEAEs, by PT;
- TEAEs with incidence ≥ 5%, by PT;
- TEAEs related to study drug, by SOC and PT;
- TEAEs related to study drug, by PT;
- TEAEs by relationship to study drug, by SOC and PT;
- TEAEs by maximum severity, by SOC and PT;
- TEAEs severity grade 3 or higher, by SOC and PT;
- TEAEs related to study drug by maximum severity, by SOC and PT;
- TEAEs severity grade 3 or higher related to study drug, by SOC and PT;
- AESIs and ARAEs of interest, by SOC and PT;
- TEAEs causing discontinuation from study drug, by SOC and PT;
- TEAEs related to study drug causing discontinuation from study drug, by SOC and PT;
- TEAEs causing discontinuation from study, by SOC and PT;

- TEAEs related to study drug causing discontinuation from study drug, by SOC and PT;
- Serious TEAEs, by SOC and PT;
- Serious TEAEs related to study drug, by SOC and PT;

In the above summaries, subjects with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one TEAE within a particular PT are counted only once for that PT. For summaries by maximum severity, subjects with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. Similarly, for summaries by relationship, subjects with multiple TEAEs within a particular SOC or PT will be counted under the category of their most related AE within that SOC or PT. A study drug-related TEAE is an TEAE considered by the investigator as definitely or likely related to study drug. If any AE relationship is missing/unknown to study drug, it is considered as definitely related to study drug. For event counts, the count will represent the number of occurrences of the SOC or PT.

Along with all the above summaries, duration of AESI and ARAE of interest will be displayed using descriptive statistics for the Safety Set.

No statistical comparisons of AEs between treatment groups will be performed.

7.7.3 Laboratory Evaluations

Data for the following hematology, blood chemistry, and urinalysis analytes received from central laboratory will be listed and summarized by treatment group and visit. If data for any additional analytes are also received, then these will be listed only.

Hematology	Serum Chemistry	Urinalysis
White Blood Cell (WBC) Count, Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils, Red Blood Cell (RBC) Count, Hemoglobin, Hematocrit, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Mean corpuscular volume, Platelet count, Serum pregnancy test (for females only).	Aspartate aminotranferase (AST), Alanine aminotranferase (ALT), Alkaline phosphatase (ALP), Gamma-Glutamyltransferase (GGT), Total Bilirubin, Total protein, Albumin, Lactate dehydrogenase, Triglycerides, Total Cholesterol, Low-density lipoprotein, High-density lipoprotein, Sodium, Potassium, Chloride, Calcium, Phosphorus, Bicarbonate, Uric acid, Blood Urea Nitrogen, Creatinine, Blood glucose.	Color and appearance, Urinary protein, Urinary glucose, Urinary WBCs, Urinary RBCs, Urinary ketone bodies, pH, Specific gravity, Leukocytes, Bilirubin, Nitrite, Occult blood, Urine pregnancy test (for females only).

All laboratory data will be reported in International System of Units (SI)/Conventional units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory data (both categorical and continuous) will be summarized by timepoint using standard descriptive statistics for the Safety Set. Changes from baseline will also be summarized for continuous data.

For hematology and serum chemistry, shift tables presenting from baseline to worst post-baseline visit (including unscheduled visits) will be provided for each treatment group.

For each laboratory analyte, the baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of study drug. Assessments carried out on the day of first study drug administration are considered to have taken place before the study drug administration if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

A list of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will also be provided.

7.7.4 Vital Signs

The following vital signs will be listed and summarized by treatment group and visit timepoint.

- systolic and diastolic blood pressure (mmHg);
- heart rate (beats/min);
- respiratory rate (breaths/min);
- oxygen saturation (SpO_2) (%);
- mean arterial pressure (MAP) (mmHg);
- body temperature (°C);

Subjects will be assessed for Potentially Clinically Significant (PCS) criteria and summary of frequency counts and percentages will be displayed by study drug for the Safety Set. A subject is considered as PCS if any of the following criteria is met;

- Systolic Blood Pressure (<90 mmHg or >180 mmHg);
- Diastolic Blood Pressure (<50 mmHg or >100 mmHg);
- Temperature (<36 °C or >38 °C);
- Heart Rate (<40 beats/min or >100 beats/min);
- Respiratory Rate (<8 breaths/min or >20 breaths/min).

Vital signs data and changes from baseline in vital signs will be summarized by timepoint using standard descriptive statistics for the Safety Set. For vital signs collected during the induction and general maintenance period of anesthesia, the following windows will be used for analysis.

	Time post completion of initial study drug administration	Collection timepoints and window
Vital sign collection timepoints and windows during surgery	Until 30 minutes	every 2 minutes (±30) seconds

The baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of study drug administration. Assessments carried out on day of first study drug administration are considered to have taken place before the study drug administration if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

7.7.5 Electrocardiograms

The following quantitative ECG measurements will be taken during the study:

- RR interval (msec);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- Fridericia corrected QT (QTcF) interval (msec);

An overall Investigator assessment of ECG will be provided (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant").

Subjects will be assessed for PCS criteria and summary of frequency counts and percentages will be displayed by study drug for the Safety Set. A subject is considered as PCS if any of the following criteria is met;

- HR (<40 bpm or >150 bpm)
- PR interval (>240 msec);
- QRS duration (>120 msec);
- QTcF interval (<320 msec or >500 msec or increase of >45 msec from baseline).

The ECG measurements and changes from baseline in ECG will be listed and summarized using standard descriptive statistics and investigator assessment will be listed and the frequency counts and percentage of subjects within each assessment category will be tabulated by treatment group and visit for the Safety Set.

Shifts from baseline (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) to worst post-baseline visit (including unscheduled visits) will be presented.

The baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of study drug. Assessments carried out on day of first study drug administration are considered to have taken place before the study drug administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables. For shift from baseline to worst post-baseline, all scheduled and unscheduled visits will be included to find the worst post-baseline result.

7.7.6 Physical Examination

A list of Physical examination results for each body system (normal/ abnormal, not clinically significant/ abnormal, clinically significant) will be provided.

Separate list of ASA-PS Score (Appendix 4 of protocol) and Modified Mallampati Score (Appendix 11 of protocol) will also be provided.

7.7.7 Other Safety Variables

- 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.

7.8 Interim Analysis

No interim analysis will be performed for this study.

8. Changes in Planned Analysis

9. Data Issues

Any Data Issues will be described in the Clinical Study Report.

10. References

1 ICH. *Statistical Principles for Clinical Trials*, Guideline E9, 1998. Available at http://www.emea.eu.int/pdfs/human/ich/036396en.pdf

2 CPMP. *Points to Consider on Missing Data*. EMEA: London, 2001. Available at http://www.emea.eu.int/pdfs/human/ewp/177699EN.pdf

3 Phillips A and Haudiquet V. *ICH E9 guideline "Statistical principles for clinical trials": a case study*. Statistics in Medicine 2003; 22:1-11

4 Brown D J. *ICH E9 guideline "Statistical principles for clinical trials": a case study. Response to A. Phillips and V. Haudiquet.* Statistics in Medicine 2003; 22:13-17

5 Phillips A, Ebbutt A, France L, Morgan D, Ireson M, Struthers L and Heimann G. *Issues in applying recent CPMP "Points to Consider" and FDA guidance documents with biostatistical implications.* Pharmaceutical Statistics 2003; 2:241-251

6 Senn S. *Statistical Issues in Drug Development*. John Wiley & sons (Chichester), 1997.

7 Chow S-C and Liu J-P. *Design and Analysis of Clinical Trials: Concepts and Methodologies*. John Wiley & sons (New York), 1998.

8 Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine 2009; 28: 586-604.

9 CPMP. *Points to Consider on Adjustment for Baseline Covariates*. EMEA: London, 2003

10 ICH. *ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers*, 2012. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf

11. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary/Reason for Changes
Version 1, Final, 22 Nov 2021	Not applicable; the first version

Appendix 2: Primary endpoint SAS syntax

```
proc freq data=<input dataset> order=data;
        tables <treatment variable>*<response variable>/ alpha= 0.025
                riskdiff(noninf margin=0.08 method=fm cl=fm norisks);
        [exact riskdiff(method=fmscore);]
        weight <frequency variable>;
run;
```

Appendix 3: Time to event endpoint SAS syntax

```
proc lifetest data=<input dataset> method=km conftype=loglog atrisk
alphaqt=0.05 ;
        time <AVAL variable in minutes>*cnsr(<censored number>);
        strata <strata variables>;
run;
```