CLINICAL STUDY PROTOCOL

A Phase 3, Multicenter, Randomized, Controlled, Open-Label, Assessor-Blinded Study to Evaluate the Efficacy and Safety of Inhaled Isoflurane Delivered via the Sedaconda ACD-S Compared to Intravenous Propofol for Sedation of Mechanically Ventilated Intensive Care Unit Adult Patients (INSPiRE-ICU1)

Investigational Product: Isoflurane delivered via the Sedaconda ACD-S

Protocol Number: SED003

Investigational New Drug Application Number: [redacted]

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SIGNATURE PAGE

STUDY TITLE: A Phase 3, Multicenter, Randomized, Controlled, Open-Label, Assessor-Blinded Study to Evaluate the Efficacy and Safety of Inhaled Isoflurane Delivered via the Sedaconda ACD-S Compared to Intravenous Propofol for Sedation of Mechanically Ventilated Intensive Care Unit Adult Patients (INSPiRE-ICU1)

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
Peter Sackey *Electronically signed by: Peter Sackey Reason: Approved Date: Oct 8, 2023 09:13 GMT+2*	08-Oct-2023

Peter Sackey, MD, PhD,
Chief Medical Officer
Sedana Medical AB

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Sedana Medical AB to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Sedana Medical AB and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Sedana Medical AB, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 3, Multicenter, Randomized, Controlled, Open-Label, Assessor-Blinded Study to Evaluate the Efficacy and Safety of Inhaled Isoflurane Delivered via the Sedaconda ACD-S Compared to Intravenous Propofol for Sedation of Mechanically Ventilated Intensive Care Unit Adult Patients (INSPiRE-ICU1)

PROTOCOL NUMBER: SED003

INVESTIGATIONAL PRODUCT: Isoflurane delivered via the Sedaconda Anaesthetic Conserving Device - S (Sedaconda ACD-S)

PHASE: 3

INDICATION: Sedation of mechanically ventilated patients in the intensive care unit (ICU)

OBJECTIVES AND ENDPOINTS:

Objectives	Endpoints
Primary	
To compare the percentage of time sedation depth is maintained within the target range, in absence of rescue sedation, as assessed according to the RASS scale, in isoflurane- vs propofol-treated patients	The percentage of time sedation depth is maintained within the prescribed RASS interval through end of study drug treatment
Key secondary	
1. To compare the effect of isoflurane vs propofol on use of opioids during the study drug treatment period	Change in mean fentanyl-equivalent opioid dose during the study drug treatment period compared to mean opioid dose during the 60 minutes prior to randomization
2. To compare the effect of isoflurane vs propofol on the wake up time at end of study drug treatment	Time from stop of study drug treatment to RASS ≥0, up to 4 hours
3. To compare the effect of isoflurane vs propofol on cognitive recovery after EOT	Delirium by CAM-ICU-7 assessments 60 minutes (±10 minutes) after EOT in patients not re-sedated with benzodiazepine or propofol infusions
4. To compare the effect of isoflurane vs propofol on spontaneous breathing effort during the study drug treatment period	Proportion of ventilator parameter observations with spontaneous breathing efforts during the study drug treatment period
Other secondary	
To compare the effect of isoflurane vs propofol on time from sedation termination to extubation in patients for whom study drug is terminated for extubation	Time from EOT to extubation if study drug is terminated for extubation
To compare the effect of isoflurane vs propofol on days alive and free of mechanical ventilation through Study Day 30	Days alive and free of mechanical ventilation[1] through Study Day 30
To compare the effect of isoflurane vs propofol on days alive and free of the ICU	Days alive and free of the ICU[2] through Study Day 30
To compare the effect of isoflurane vs propofol on delirium and coma free days until 7 days after EOT	Delirium and coma free days from start of study drug until 7 days after EOT, as assessed with CAM-ICU-7 and RASS
To compare the effect of isoflurane vs propofol on mortality at 30 days after randomization	Mortality rate at 30 days after randomization
To compare the effect of isoflurane vs propofol on mortality at 3 months after randomization	Mortality rate at 3 months after randomization

Objectives	Endpoints
Other secondary (Continued)	
To compare the effect of isoflurane vs propofol on mortality at 6 months after randomization	Mortality rate at 6 months after randomization
To compare the safety of isoflurane vs propofol	AEs, clinical laboratory assessments, vital signs, physical examination, blood gases, organ function, and ventilator parameters
To assess Sedaconda ACD-S device deficiencies in patients receiving isoflurane	Frequency and type of Sedaconda ACD-S device deficiencies in patients receiving isoflurane
To compare the use of restraints in patients receiving isoflurane vs propofol	Proportion of patients using restraint during the study drug treatment period
Exploratory	
To assess isoflurane dose over time	• Isoflurane dose in mL/hour; • Isoflurane dose in mL/hour/L minute ventilation; and • End-tidal isoflurane concentration every 4 hours.
To compare the effect of isoflurane vs propofol on major ICU interventions through Study Day 30 or until ICU discharge, whichever comes first	Need for: • Renal replacement therapy; • ECLS; • Tracheostomy; and • Non-invasive ventilation.
To compare the effect of isoflurane vs propofol on level of care up to 30 days after randomization	Level of care: • Patient deceased; • Still in ICU; • Intermediary care unit; • General ward; • Another ICU (within or outside the hospital); • Another hospital (unknown ward); • Rehabilitation unit; • Nursing home; • Hospice; and • Home.
To assess the end-tidal isoflurane concentration and relation to RASS scores	End-tidal isoflurane concentration over time and relation to RASS scores
To compare oxygenation (PaO_2/FiO_2) over time during the study drug treatment period, in patients with ARDS/AHRF, in isoflurane vs propofol-treated patients	Oxygenation (PaO_2/FiO_2) in patients with ARDS/AHRF over time during the study drug treatment period
To compare memory panorama from time in the ICU in isoflurane- vs propofol-treated patients	Number of factual memories, memories of feelings, or delusional memories, as assessed by the ICU Memory Tool, collected at 3 months follow-up
To compare physical outcomes at 3 and 6 months post-randomization in isoflurane- vs propofol-treated patients	Activities of daily living, as assessed by the Katz ADL and Pfeffer FAQ, at 3 and 6 months post-randomization
To compare psychological outcomes at 3 and 6 months post-randomization in isoflurane- vs propofol-treated patients	Depression, anxiety, and post-traumatic stress symptoms, as assessed by IES-R and PROMIS Depression and Anxiety questionnaires, at 3 and 6 months post-randomization
To compare cognitive function 3 and 6 months post-randomization in isoflurane- vs propofol-treated patients	Cognitive function, as assessed by TICS, WAIS IV-Digit Span, Hayling Sentence Completion Test, Controlled Oral Word Association, WMS-IV – Immediate Memory (Adult/Older Adult), WMS-IV – Delayed Memory (Adult/Older Adult), and PROMIS Cognitive Function questionnaire, at 3 and 6 months post-randomization
To compare quality of life at 3 and 6 months post-randomization in isoflurane- vs propofol-treated patients	Quality of life at 3 and 6 months post-randomization, as assessed by WHODAS 2.0 and BPI
To compare the need for rescue, other sedatives, and antipsychotics in isoflurane- vs propofol-treated patients	Use of rescue sedatives, other sedatives, and antipsychotics from randomization to EOT
To compare the hemodynamic instability in isoflurane- vs propofol-treated patients	Change from Baseline in highest daily vasoactive drug requirements during study drug treatment

Objectives	Endpoints
Exploratory (Continued)	
To compare duration of mechanical ventilation in isoflurane- vs propofol-treated patients	Duration of mechanical ventilation
To compare ICU length of stay in isoflurane- vs propofol-treated patients	ICU length of stay
To compare minute ventilation in isoflurane- vs propofol-treated patients	Change in minute ventilation every 8 hours during the study drug treatment period

1. For Days alive and free of mechanical ventilation, only invasive ventilation will be taken into account. Successful ventilator discontinuation is defined as being alive and free of ventilation for 48 hours (inclusive) following discontinuation. For example, if a patient was discontinued from mechanical ventilator and ventilation was initiated again within the next 48 hours or the patient died within the next 48 hours, then the time (less than 48 hours) that was off ventilation did not count as Days alive and free of mechanical ventilation.
2. The Days alive and free of the ICU is defined similarly to the Days alive and free of mechanical ventilation. Successful ICU discharge is defined as being alive and out of ICU for 48 hours (inclusive) following discharge.

AE = adverse event; AHRF = acute hypoxemic respiratory failure; ARDS = acute respiratory distress syndrome; BPI = Brief Pain Inventory; CAM-ICU-7 = 7-point scale of the Confusion Assessment Method for the Intensive Care Unit; ECLS = extracorporeal life support; EOT = end of treatment; FAQ = functional activities questionnaire; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; IES-R = impact of event scale; Katz ADL = Katz Index of Independence in Activity of Daily Living; PaO_2 = partial pressure of oxygen; PROMIS = Patient-Reported Outcomes Measurement Information System; RASS = Richmond Agitation Sedation Scale; Sedaconda ACD-S = Sedaconda Anaesthetic Conserving Device - S; SOC = standard of care; TICS = Telephone Interview for Cognitive Status; vs = versus; WAIS = Wechsler adult intelligence scale; WHODAS 2.0 = World Health Organization Disability Assessment Schedule 2.0; WMS = Wechsler memory scale.

POPULATION:

Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Adults ≥18 years of age;
2. Patients who are anticipated to require >12 hours of invasive mechanical ventilation and continuous sedation in the ICU; and
3. Receipt of continuous sedation due to clinical need for sedation to Richmond Agitation Sedation Scale (RASS) <0.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Need for RASS -5;
2. Sedation for invasive mechanical ventilation immediately prior to Baseline for >72 hours (patients who have been extubated for at least 24 hours and subsequently re-intubated will have sedation for invasive mechanical ventilation starting from when they were re-intubated);
3. Severe neurological condition that causes the patient to lack ability to participate in the study (ie, unable to be assessed for RASS and Critical Care Pain Observation Tool), including, but not restricted to, patients with acute stroke, severe head trauma, meningitis, suspected of having elevated intracranial pressure (ICP), or the need for ICP monitoring;
4. Ventilator tidal volume <200 or >1000 mL at Baseline;
5. Need for extracorporeal membrane oxygenation, extracorporeal carbon dioxide removal, high frequency oscillation ventilation, or high frequency percussive ventilation at Screening;
6. Comfort care only (end of life care);

7. Contraindication to propofol or isoflurane, including:
    a. Known or suspected personal or family history of malignant hyperthermia (MH) or high risk for MH or acute drug-induced muscle injury (eg, muscular dystrophies);
    b. Severe hemodynamic compromise, defined as the need for norepinephrine ≥0.3 mcg/kg/min (or equivalent vasopressor dose) to maintain blood pressure within acceptable range, assumed to be mean arterial pressure ≥65 mmHg unless prescribed clinically; or
    c. Allergy to isoflurane or propofol, or have propofol infusion syndrome.
8. History of ventricular tachycardia/Long QT Syndrome;
9. Requirement of intravenous (IV) benzodiazepine or barbiturate administration for seizures or dependencies, including alcohol withdrawal;
10. Neuromuscular disease that impairs spontaneous ventilation (eg, C5 or higher spinal cord injury, amyotrophic lateral sclerosis, etc);
11. Concurrent enrollment in another study that, in the Investigator's opinion, would impact the patient's safety or assessments of this study;
12. Participation in other study involving investigational drug(s) or devices(s) within 30 days prior to randomization;
13. Previous randomization or receipt of treatment in this study or in SED004;
14. Anticipated requirement of treatment with continuous infusion of a neuromuscular blocking agent for >4 hours;
15. Female patients who are pregnant or breast-feeding;
16. Imperative need for continuous active humidification through mechanical ventilation circuit;
17. Attending physician's refusal to include the patient; or
18. Inability to obtain informed consent.

STUDY DESIGN AND DURATION:

This is a therapeutic confirmatory (Phase 3), multicenter, randomized, controlled, open-label, assessor-blinded study. Approximately 235 patients receiving mechanical ventilation and requiring continuous sedation at approximately 15 to 20 sites in the United States (US) will be randomized in a 1.5:1 ratio to inhaled isoflurane (administered via the Sedaconda ACD-S device) or propofol (administered via IV infusion) for sedation, respectively. In addition, approximately 3 to 5 run-in training patients per site will be enrolled. The treatment duration in this study is expected to be at least 12 hours and may last up to 48 (±6) hours or to the time for extubation, whichever occurs first, with a follow-up period of 6 months.

Patients eligible for the study will either have planned surgery with anticipated need for sedation and mechanical ventilation in the ICU (ie, postoperative patients) for >12 hours or have already been admitted to the ICU and anticipate needing sedation and mechanical ventilation for >12 hours.

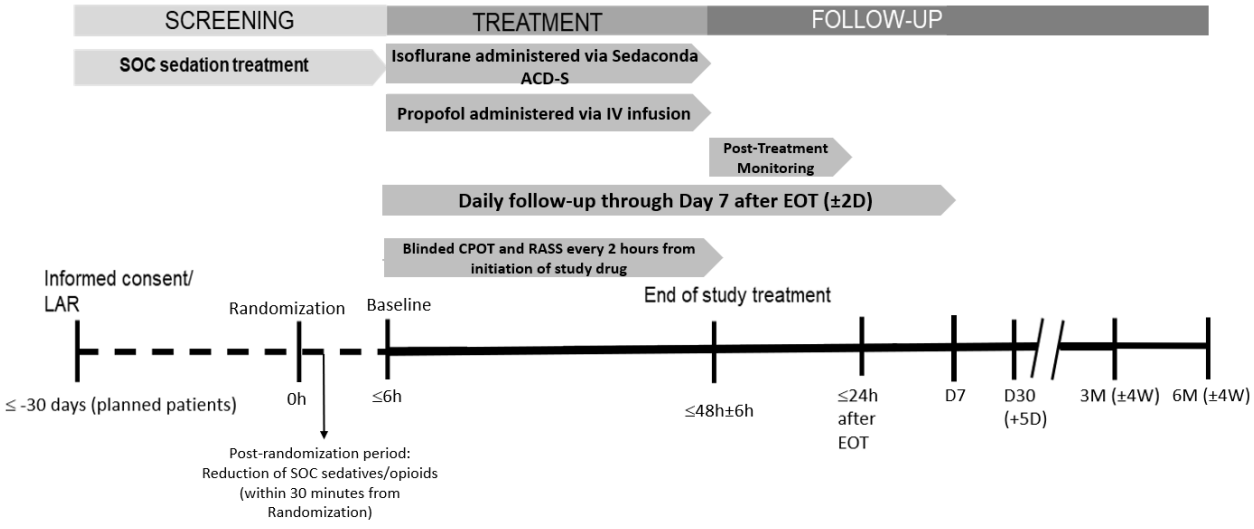
Informed consent must be obtained from the patient or patient's legally authorized representative for all patients.

The study will comprise the following key study periods:

- Screening period: Day -30 to randomization;
  - Initial Screening: Day -30 to randomization;
  - Complete Screening: -24 hours to randomization;
  - Randomization; and
  - Baseline: Randomization to initiation of study drug treatment (up to 6 hours).
- Treatment period: initiation of study drug administration to the end of treatment (EOT) (up to 48 [±6] hours); and
- Follow-up period: EOT to 6 months (±4 weeks) after randomization.
  - Post-treatment monitoring phase: until 24 hours after EOT;
  - 24 hours after EOT until 7 days after EOT: daily follow-up from the time of randomization until 7 days after EOT;
  - Follow-up: at Study Day 30 (+5 days) after randomization;
  - 3-month centralized telephone follow-up: 3 months (±4 weeks) after randomization; and
  - 6-month centralized telephone follow-up: 6 months (±4 weeks) after randomization.

A schematic of the study flow is shown in Figure S1.

Figure S1. Study Scheme



CPOT = Critical Care Pain Observation Tool; D = day(s); EOT = end of treatment; h = hour(s); IV = intravenous; LAR = legally authorized representative; M = month; RASS = Richmond Agitation Sedation Scale; Sedaconda ACD-S = Sedaconda Anaesthetic Conserving Device - S; SOC = standard of care; W = week(s).

For training purposes in the use of Sedaconda ACD-S, approximately 3 to 5 patients at each site will be assigned to receive isoflurane via Sedaconda ACD-S in a non-blinded fashion, before any patients are randomized.

An independent Data Safety Monitoring Board (DSMB) will be assembled to safeguard the safety of study patients per the DSMB Charter. This DSMB will serve jointly for both this study and the SED004 study, a confirmatory study identical to SED003.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Isoflurane for inhalation will be administered via the Sedaconda ACD-S device.

Propofol will be administered via IV infusion.

Study drug will be titrated and adjusted by the clinical team throughout the study drug treatment period according to the protocol-directed dose titration guide to achieve and maintain the desired sedation depth.

STATISTICAL ANALYSES:

All efficacy analyses will be performed using both the Intent-to-Treat (ITT) and the modified ITT Analysis Sets. Analysis of the ITT Analysis Set will be considered primary. The hypothesis test for the primary efficacy endpoint is a non-inferiority test. Hypothesis tests for the other efficacy endpoints are superiority tests.

SAMPLE SIZE:

A total of 235 randomized patients and approximately 3 to 5 run-in training patients per site will be enrolled in the study.

SITES: Approximately 15 to 20 sites in the US

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
21 CFR	Title 21 of the Code of Federal Regulations
ABG	Arterial blood gas
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BPI	Brief Pain Inventory
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CAM-ICU-7	7-point scale of the Confusion Assessment Method for the Intensive Care Unit
CIBS	Critical Illness, Brain Dysfunction, and Survivorship
CO_2	Carbon dioxide
COVID-19	Coronavirus Disease 2019
CPAP	Continuous positive airway pressure
CPOT	Critical Care Pain Observation Tool
CRA	Clinical Research Associate
CSR	Clinical Study Report
CTIRT	[redacted] Interactive Response Technology
DILI	Drug-induced liver injury
DSMB	Data Safety Monitoring Board
$ECCO_2R$	Extracorporeal carbon dioxide removal
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EOT	End of treatment
$EtCO_2$	End-tidal carbon dioxide
FAQ	Functional activities questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HFOV	High frequency oscillation ventilation
HFPV	High frequency percussive ventilation
HME	Heat and moisture exchanger
ICF	Informed consent form
ICH	International Council for Harmonisation
ICP	Intracranial pressure

Abbreviation	Definition
ICU	Intensive care unit
IES-R	Impact of event scale
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
Katz ADL	Katz Index of Independence in Activity of Daily Living
LAR	Legally authorized representative
LTO	Long-Term Outcomes
MAC	Minimal alveolar concentration
MDR	Medical Device Regulation
MH	Malignant hyperthermia
mITT	Modified Intent-to-Treat
NMBA	Neuromuscular blocking agent
P0.1	Airway occlusion pressure
PaO_2	Partial pressure of oxygen
PC	Pressure assist/control
pCO_2	Partial pressure of carbon dioxide
PEEP	Positive end-expiratory pressure
PETAL	Prevention and Early Treatment of Acute Lung Injury
PP	Per-Protocol
PRIS	Propofol-related infusion syndrome
PROMIS	Patient-Reported Outcomes Measurement Information System
PRVC	Pressure-regulated volume control
PS	Pressure support
PSV	Pressure support ventilation
PTSD	Post-traumatic stress disorder
RASS	Richmond Agitation Sedation Scale
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAPS	Simplified Acute Physiology Score
SAT	Spontaneous Awakening Trial
SBT	Spontaneous breathing test
SD	Standard deviation
Sedaconda ACD	Sedaconda Anaesthetic Conserving Device
Sedaconda ACD-S	Sedaconda Anaesthetic Conserving Device - S
SIMV	Synchronized intermittent mandatory ventilation
SOC	Standard of care
SOFA	Sequential organ failure assessment
SpO_2	Peripheral capillary oxygen saturation

Abbreviation	Definition
SUSAR	Suspected Unexpected Serious Adverse Reaction
TICS	Telephone Interview for Cognitive Status
ULN	Upper limit of normal
US	United States
VC	Volume control
WAIS	Wechsler adult intelligence scale
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule
WMS	Wechsler memory scale

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background

Invasive mechanical ventilation (later referred to as mechanical ventilation) is life supporting and commonly used to support pulmonary gas exchange and/or unload the respiratory muscles in critically ill patients.[1] Pain, agitation, and delirium are commonly experienced by critically ill intensive care unit (ICU) patients.[2,3] A significant proportion of intubated, mechanically ventilated patients require sedation, in addition to analgesia, to manage these clinical problems for their comfort and safety.

Sedation in mechanically ventilated ICU patients is commonly achieved with the infusion of propofol, benzodiazepines, or dexmedetomidine.

These sedatives used in the ICU are often useful to achieve comfort and safety, but they also have significant limitations. Prolonged infusions of benzodiazepines in critically ill patients are associated with drug accumulation, prolonged wake-up times, tolerance development, withdrawal symptoms, and delirium after discontinuation.[3,4,5] Propofol, as an ICU sedative, reduces blood pressure and is also associated with hyperlipidemia and the risk of propofol-related infusion syndrome (PRIS), a potentially lethal side effect.[3] The risk of propofol infusion syndrome is higher with high doses and long-term (>48 hours) sedation.[6] For this reason, the maximum propofol infusion rate in the United States (US) has been limited to 4 mg/kg/hour, which is a dose limit that leads to some patients being insufficiently sedated with propofol alone. It is lipophilic and can have drug accumulation with longer durations of use leading to delayed arousal.[7]

Recent US Society of Critical Care Medicine guidelines[2,3] recommend non-benzodiazepine sedatives, such as propofol or dexmedetomidine when sedation is required, based on several studies demonstrating more favorable short- and long-term outcomes with non-benzodiazepine sedatives. The recommendations include cautionary statements regarding potential side effects and negative long-term consequences of ICU sedation.[3]

Dexmedetomidine as an ICU sedative is useful in certain patients and situations, such as patients in distress during noninvasive ventilation[8] and patients suffering from agitated delirium at the time of extubation.[9] Dexmedetomidine appears to be insufficient as a sedative for a proportion of mechanically ventilated patients early on during mechanical ventilation, does not induce amnesia if deep sedation or neuromuscular blockade is required, and has been associated with a higher incidence of bradycardia, hypotension, and asystole than other intravenous (IV) sedatives.[3,10]

Thus, there is currently no palatable alternative to propofol for mechanically ventilated patients requiring deeper sedation. Safe alternatives to propofol are needed to support patients with contraindications to propofol, and to diversify therapeutic options during drug shortages, as has occurred several times with propofol over the last decade. Efforts to limit the complications of currently available sedatives include strategies such as daily wake-up procedures and light sedation strategies, as well as monitoring for PRIS.[11,12]

A sedative agent that could achieve the full range of sedation depths and permit rapid wake-up, without tolerance development, withdrawal, clinically significant accumulation, or active metabolites, suitable for patients with hepatic and renal dysfunction, would be appealing.

Volatile anesthetics suppress consciousness but leave many autonomic functions intact. In the absence of disturbed information processing, the number of adverse experiences in patients during

and after treatment should be lower, as indicated in follow-up studies after volatile anesthetic sedation in ICU patients.[13,14] In studies so far, wake-up after inhaled sedation has been short and predictable,[15] which implies that extubation can be planned and organized, and the time during which the patient needs very close observation between termination of sedative treatment and extubation is short.

1.2 Inhaled Isoflurane as an ICU Sedative

Isoflurane has been used for general anesthesia in operating rooms since the early 1980s. Its efficacy and safety as a general anesthetic have been evaluated extensively. It is considered one of the safest anesthetic drugs and has often been used in clinical practice for patients with marginal renal or liver function. Isoflurane is eliminated almost exclusively in unchanged form via exhalation after discontinued administration; thus, elimination is independent of renal or liver function with only 0.2% of isoflurane being metabolized.[16]

Dose recommendations for approved indications of isoflurane with average end-tidal concentrations (minimal alveolar concentration [MAC]) required for pain-free general anesthesia during surgical stimulation in adults (50 to 70 years of age) are 1.15% and 1.10%, respectively, with isoflurane administered in 100% oxygen.[16] For sedation, the end-tidal anesthetic gas concentration is typically slightly more than one-third of the MAC, ie, slightly above MAC-awake, and 0.3% to 0.5% expired volume provides acceptable sedation in adults.[15,17,18]

As an alternative to ICU IV sedation, inhaled sedation using isoflurane started during the late 1980s.[19] Isoflurane was used successfully in sedation studies where isoflurane was administered via vaporizers using specially adapted high-flow ICU ventilators. While comparisons with midazolam and propofol in adults showed acceptable sedation effects and faster emergence, without reported tolerance or withdrawal symptoms,[15,19] the non-standard delivery of anesthetic agent via non-standard adaptations and scavenging issues were stated as major hurdles for more widespread use in the ICU environment. Recent technological advances, however, have greatly simplified the application of inhalational anesthetics in the ICU. The introduction of a volatile anesthetic reflection filter, the Sedaconda Anaesthetic Conserving Device (Sedaconda ACD) in 2005 enabled the concept of inhalational sedation to be performed in any ICU with standard ICU ventilators.

Isoflurane has been used as an inhaled ICU sedative for over a decade in some clinical centers in Europe, and Sedaconda was recently approved for sedation of mechanically ventilated adult patients during intensive care in Europe. Inhaled sedation has been one of the suggested options for ICU sedation in Germany[20] and more recently, it has been included in the Pan-American sedation guidelines, as well as suggested as a treatment in acute respiratory distress syndrome (ARDS)[21] and Coronavirus Disease 2019 (COVID-19).[22,23] To date, the growing body of study data and clinical experience indicate good sedative properties without significant side effects.[17,18,24,25] A commonly described feature of inhaled sedation is a short and reliable wake-up, regardless of sedation depth.[15,17] Other findings in small clinical trials have found a shorter time to adequate communication and cooperation and the ability to maintain spontaneous breathing, even during deeper levels of sedation.[26,18]

1.3 The Sedaconda ACD-S

The Sedaconda Anaesthetic Conserving Device - S (Sedaconda ACD-S) is a small, disposable volatile anesthetic agent delivery and reflection system, developed for the administration of

isoflurane and sevoflurane to mechanically ventilated patients, without the need for an anesthesia machine. The Sedaconda ACD is previously known as the AnaConDa. The Sedaconda ACD-L (100 mL) and Sedaconda ACD-S (50 mL) are CE-certified, according to European Medical Device Regulation 2017/745 (as Risk Classification IIa products according to Annex 9), approved for the administration of isoflurane and sevoflurane in mechanically ventilated patients, and have been on the market outside the US since 2005 and 2017, respectively. In the planned clinical studies in the US, only Sedaconda ACD-S will be used.

Figure 1. Sedaconda ACD Schematic

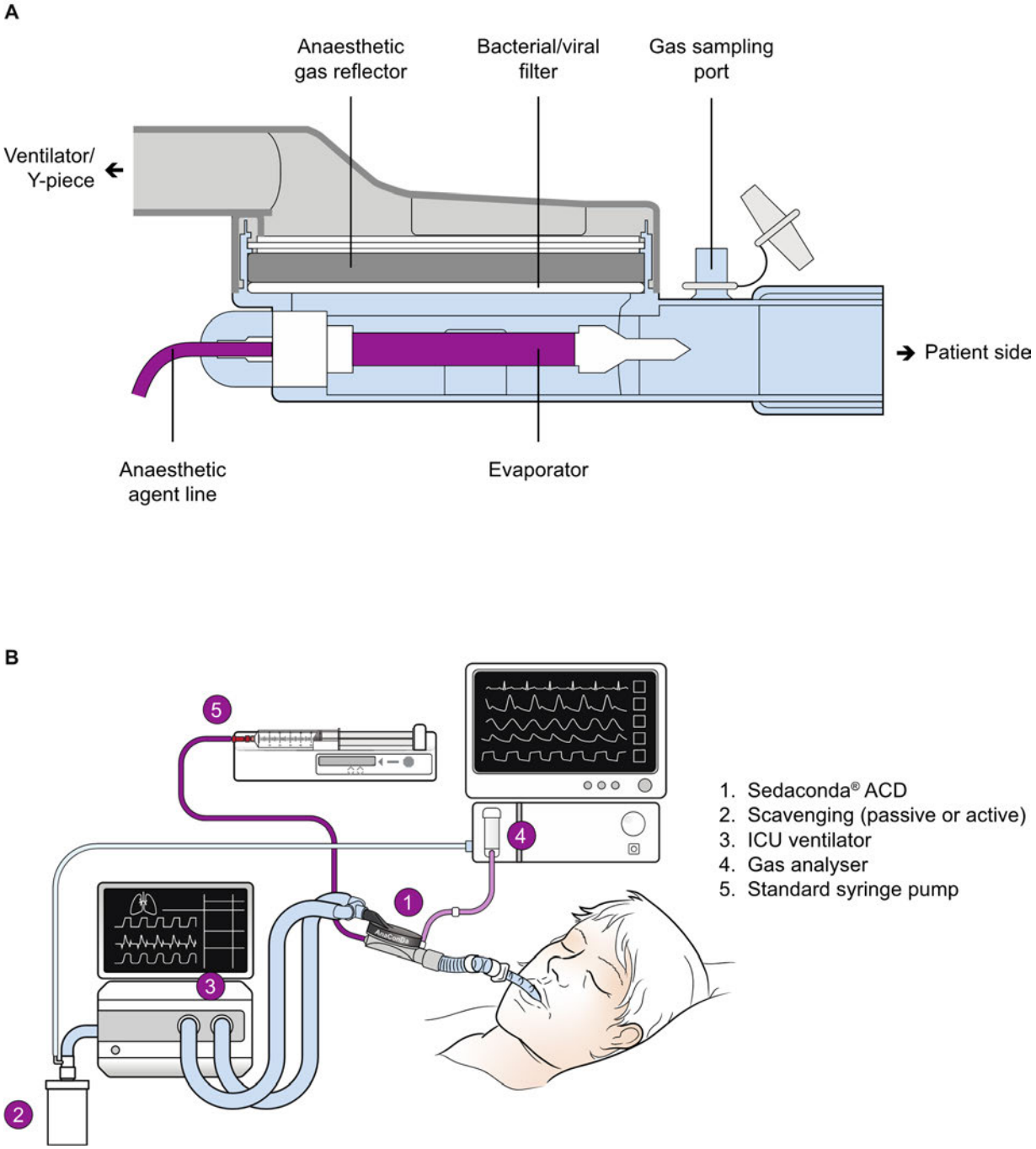


Figure 1. Sedaconda ACD Schematic (Continued)

Sedaconda ACD = Sedaconda Anaesthetic Conserving Device; ICU = intensive care unit.

The Sedaconda ACD-S standard placement is to be integrated into the ventilator circuit in place of the commonly used passive heat and moisture exchanger (HME), between the patient's endotracheal tube or tracheostomy and the Y-piece of the ventilator tubing. It contains a miniature vaporizer and conserving medium consisting of an interwoven lipophilic active carbon filter that also exerts HME properties. The volatile anesthetic is administered continuously via a syringe pump into the miniature vaporizer. The evaporator is a porous plastic rod with a large surface area that will vaporize isoflurane or sevoflurane with the airflow, due to the volatility of both agents.

The anesthetic exhaled by the patient enters the reflection medium, is adsorbed to the active carbon filter, and is desorbed and returned to the patient in the next breath. Approximately 90% of the anesthetic/sedative agent administered will be reflected when the Sedaconda ACD-S is placed at the Y-piece of the respiratory circuit.

The syringe is a standard 50 to 60 mL syringe, coupled with a unique connector system to prevent unintentional IV administration of volatile sedatives. Sedation depth can be adjusted by increasing or decreasing the syringe pump rate, or by giving a small bolus (0.3 to 0.5 mL) of isoflurane.

In contrast to an anesthesia machine, there is no need for additional equipment to maintain operation of the Sedaconda ACD-S besides the use of a FlurAbsorb filter, the availability of an anesthetic gas monitor, and standard ICU equipment. With the gas monitor, the patients end-tidal concentration can be measured whenever necessary. There is also no carbon dioxide (CO_2) absorber to manage, which is a critical element of an anesthesia machine. The Sedaconda ACD-S is intended for single use and needs to be replaced every 24 hours or when needed, eg, in patients with mobilization of copious airway secretions.

When a device such as a Sedaconda ACD-S (which is a modified HME) is placed in the breathing circuit it adds volume to the circuit that the patient rebreathes, so-called dead space. The physician must, as with the introduction of any HME, determine if the patient's breathing capacity (tidal volume and respiratory status [eg, partial pressure of carbon dioxide (pCO_2)/end-tidal carbon dioxide ($EtCO_2$) level]) is such that the patient can tolerate the additional dead space.

The first Sedaconda ACD marketed in Europe had a dead space of 100 mL which occasionally led to increases in CO_2. The 50 mL Sedaconda ACD-S was developed as a smaller dead space device to mitigate the risk of increases in CO_2. Preliminary clinical experience and bench testing suggests that this device, when attached in the standard mode at the Y-piece of the respiratory circuit, can be used in patients with tidal volumes above 200 mL. Due to the 50 mL dead space of the Sedaconda ACD-S, clinically significant rebreathing may occur when used in patients with tidal volumes below 200 mL, previously demonstrated for the original 100 mL Sedaconda ACD-S.[27]

In the current study, only the Sedaconda ACD-S will be used and patients with tidal volumes below 200 mL will not be included. All sites will receive in-person, discipline-specific device training by Sponsor staff (Clinical Education Specialists), who will be available to respond to questions and for retraining throughout the study, as needed. The training will include all therapy-related standard procedures and troubleshooting and will also cover the pharmacokinetics, pharmacodynamics, dosing, and safety of the study drug isoflurane. Access will be given to online training materials, such as e-learning and setup videos as well as paper manuals and checklists. Local clinical educators will be trained to support staff and respond to basic therapy-related questions during patient inclusion.

1.4 Sedana Medical Clinical Studies on Isoflurane and Sedaconda ACD

SED001 was a Phase 3, multicenter, randomized, controlled, open-label study in 301 adults with up to 48 (±6) hours of treatment of isoflurane administered via Sedaconda ACD and 30 days of follow-up. The study was conducted in Germany and Slovenia. The last patient completed the study on 11 February 2020.[18]

The results from this randomized controlled trial demonstrated that isoflurane delivered via the Sedaconda ACD was non-inferior to propofol for sedation (at the prescribed range of Richmond Agitation Sedation Scale [RASS] -1 to -4) of invasively ventilated patients with some other merits. Opioid doses were lower and spontaneous breathing more common in the isoflurane group compared to the propofol group. Its use was associated with short and predictable emergence and with an acceptable safety profile, with no new safety signals compared to the anesthesia indication. Please refer to the current version of the Investigator's Brochure for details.

SED002 is a Phase 3, multicenter, randomized, controlled, open-label study in children between 3 to 17 years old, with a minimum of 12 hours and up to 48 (±6) hours of treatment of isoflurane administered via Sedaconda ACD-S compared with IV midazolam, and a follow-up period of 48 hours after discontinuation of study drug administration and a second longer-term follow-up of 30 days. SED002 was initiated early 2021 and patient enrollment was completed in January 2023.

SED003 (this study) and SED004 will be two Phase 3 studies planned to be conducted in the US, with a goal to demonstrate non-inferiority of isoflurane administered via Sedaconda ACD-S to the current standard of care (SOC), IV propofol infusion, in patients requiring sedation and mechanical ventilation in the ICU. In the pre-Investigational New Drug Application feedback from the Food and Drug Administration (FDA) [redacted], the Agency stated that as the proposed use is a

new indication for isoflurane, two well-controlled studies are required. The Agency noted that SED001 may not satisfy the US regulatory requirements for an adequate and well-controlled study due to its open-label design and therefore, two registration studies in the US are proposed. A joint Data Safety Monitoring Board (DSMB) will be convened to serve on both clinical studies, and data generated from these studies will be subject to study-specific and pooled analyses.

1.5 Rationale

1.5.1 Study Rationale

Based on SED001 and previous literature, isoflurane has recently been approved for ICU sedation in 17 European countries. The Sedaconda ACD-L/ACD-S is approved in Europe, Australia, Canada, Japan, Mexico, South Korea, and other countries for the administration of volatile anesthetics for mechanically ventilated patients. Neither the Sedaconda ACD nor isoflurane is currently approved for ICU sedation in the US. As part of a New Drug Application seeking approval for use, this study will seek to establish the non-inferiority of isoflurane delivered via the Sedaconda ACD-S for ICU sedation for a period up to 48 (±6) hours compared to IV propofol, a SOC sedative.

1.5.2 Study Design Rationale

Due to the medical need for sedation in the study population, a placebo-controlled study is not feasible. IV propofol is the most commonly used sedative in mechanically ventilated adult patients in the US.[10] It is approved and recommended for use in intensive care sedation and therefore is the most appropriate active control for this study. A non-inferiority design is chosen based on known sedative properties of isoflurane and propofol.

A randomized, active-controlled, open-label design with a blinded assessment strategy will be used in this study. The many differences between the two treatments in route of administration, adjustment and pharmacologic effects, as well as blinding challenges for bedside treating staff related to the products, make it impractical to conduct a fully double-blind study with acceptable quality in the complex setting of the ICU with critically ill patients. An assessor blinding approach will be utilized to minimize bias. Treating staff will be unblinded to patient treatment assignments but treatment allocation will not be disclosed to potential blinded assessors nor to other members of the clinical team not directly involved in the patient's care.

The primary objective is to compare the percentage of time sedation depth is maintained within the target range, in absence of rescue sedation, as assessed according to the RASS scale, in isoflurane- versus propofol-treated patients. The sedation depth will be assessed using the blinded RASS assessments every 2 hours throughout the study drug treatment period.

Clinical staff will be trained by the Investigator in standardized assessment of the RASS and Critical Care Pain Observation Tool (CPOT). These individuals will be delegated the task of performing the blinded RASS and CPOT assessments during the study drug treatment period for each patient per Sections 7.1.1 and 7.1.2.

1.5.2.1 RASS target rationale

For mechanically ventilated patients, sedative requirements change over time. In the first days of mechanical ventilation, a significant proportion of patients are sedated to moderate or deep levels of sedation (RASS -3 or below).[10,28] The need for ventilator tolerance and multiple diagnostic and

therapeutic procedures may make moderate or sometimes even deep sedation necessary. This is especially true for patients with ARDS caused by sepsis (eg, COVID-19, bacterial pneumonia) or trauma.[25,26]

Similar to several previous sedation studies with RASS range targets,[10,29,30] a sedation target including 4 steps on the RASS scale is planned to be used, with one step deeper sedation than in the PRODEX and MIDEX studies[31,32], ie, RASS -1 to -4 compared to RASS 0 to -3.[29] The inclusion criterion "Receipt of continuous sedation due to clinical need for sedation RASS <0" identifies patients in need of continuous sedation and who cannot be managed at RASS 0.

1.5.2.2 Rationale for 48-hour study drug treatment period

As discussed with the FDA ([redacted] efficacy and safety data to support the proposed dose and duration of isoflurane via the Sedaconda ACD-S should be provided.

The maximum sedation time planned with the study drug is 48 (±6) hours. The sedation period of up to 48 hours has been chosen because a large proportion of patients that are anticipated to require mechanical ventilation and sedation for more than 12 hours will likely require sedation for an additional 24 to 48 hours. Several published, randomized, controlled studies have a median sedation time of about 2 days,[3,33] and the most common durations of mechanical ventilation in ICU patients in the US were 48 to 72 hours.[34] The duration of isoflurane sedation described in the literature ranges from a few hours[35,36] to several weeks.[37,38,39] A significant proportion of patients can be managed with light sedation after the first days of mechanical ventilation, at which timepoint opioid analgesia or other sedatives, promoting greater degree of wakefulness, may be preferable.[10,18]

The time span for ending study drug treatment permits the treatment to be terminated at an appropriate timepoint in relation to other activities, including potential extubation planned in the first hours after 48 hours, and also allows a practicable time for the study team to perform end of treatment (EOT) assessments.

Having a fair proportion of patients that are sedated for the full length of the 48-hour study drug treatment period is important from a safety evaluation perspective. In parallel, it is important for the evaluation of emergence variables that a proportion of patients will be extubated during the course of the 48-hour study drug treatment period.

In SED001, approximately 66% of patients needed more than 24 hours of sedation. In SED003, a pre-randomization duration of mechanical ventilation of 0 up to 72 hours is permitted and the anticipated need for mechanical ventilation is required to be >12 hours or longer to be eligible. These criteria imply that another 24 to 48 (±6) hours of study sedation is clinically likely for an estimated proportion of approximately 50% of patients. A proportion in this range would give a reasonable body of data on both longer durations of isoflurane exposure and wake-up and long-term follow-up data from a fair proportion of patients awoken directly from the study drug.

1.5.2.3 Rationale for CAM-ICU-7 assessment 60 minutes post EOT

After ending sedation in ICU from different levels of sedation, early restoration of cognitive functions is desirable. This makes it safer and easier to prepare for and perform an extubation. The patient can cooperate better with the bedside care team in understanding instructions, improve secretion clearance, and acceptance of non-invasive ventilation or high flow nasal oxygen. A

confused or delirious patient makes liberation from mechanical ventilation complicated and potentially unsafe.[27]

In study SED001, the majority of patients had reached sufficient RASS levels to permit a Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) assessment within 60 minutes.

Therefore, 60 minutes after completion of study sedation is considered adequate for cognitive follow-up by evaluation of delirium with 7-point scale of the CAM-ICU (CAM-ICU-7).

1.5.2.4 Rationale for run-in training patients

Unlike in Europe, where the Sedaconda ACD has been marketed for several years, it is a novel device in the US and the proficiency in managing the therapy from an efficacy perspective is expected to improve through clinical experiences. At each site, approximately 3 to 5 run-in training patients will be enrolled. The final number of run-in training patients at each site will be set in dialogue between the Sponsor's clinical educator and the clinical staff. Each ICU will start with run-in training patients before any patients are randomized. These training patients will not be randomized, and treatment with isoflurane via Sedaconda ACD-S will be open-label in order to familiarize the larger clinical staff group who will manage patients in the study. For training purposes, patients with expected longer exposure times (ie, 12 to 48 [±6] hours) are preferable. Inclusion and exclusion criteria will be the same for these patients as for randomized patients. All assessments will be the same for the run-in training patients as for the randomized patients, but they will be performed in a non-blinded fashion. The efficacy analyses will not include the data from these patients but the safety data from these patients will be included in the safety reporting from the study. The power calculation of sample size for the primary endpoint will not include these run-in training patients.

1.5.2.5 Rationale for adaptive expected exposure duration

When enrolling a patient into a clinical trial, predicting with certainty the remaining duration of mechanical ventilation and sedation can be difficult and may not reflect the actual later exposure. In clinical practice, deterioration with subsequently longer time on mechanical ventilation is more common than rapid improvement and shorter time than anticipated. Hence, the anticipated minimum duration of mechanical ventilation is set to 12 hours in this clinical trial, despite the need for a substantial proportion of patients exposed to longer periods of isoflurane sedation to support the intended 48-hour duration of use.

Data on cognitive recovery and extubation times in patients on study medication when mechanical ventilation is stopped are important to address and therefore, it is desirable to balance long-term exposures with shorter exposures times, rendering wake-up data.

Given the above, predicted remaining time on the ventilator for each patient will be collected at enrollment. Actual exposure durations and number of patients exposed to the maximum duration will be assessed regularly in the study as part of the risked-based monitoring. Based on the cumulative exposure times observed as the studies progress, a restriction in enrollment may be prospectively imposed to only include patients with anticipated longer (>24 hours) remaining duration of mechanical ventilation in recruitment, in order to balance long-term and short-term exposures.

1.6 Risk/Benefit

Patients enrolled in this study will be those who are anticipated to require sedation during mechanical ventilation for >12 hours. The study is designed to ensure all patients are provided adequate sedation for safety and comfort through administration of study drug and SOC. After randomization, patients will be sedated with IV propofol infusion, which is SOC in the vast majority of ICUs,[10] or the study drug, isoflurane administered via the Sedaconda ACD-S device. Isoflurane has been widely used clinically for this indication at the dose proposed.[15,20,22,24,40] In both treatment groups, patients who are not adequately sedated will receive rescue sedation. Patients that experience adverse reactions that require discontinuation of the treatment, or meet any other withdrawal criteria as outlined in Section 4.4, will be removed from the study drug with sedative choice and sedation management returned to the treating physician for SOC. Unless the patient withdraws consent, the patient will continue in the study for assessment and follow-up, per the Schedule of Procedures in Appendix A, even if the study drug is discontinued.

In any ICU study, there is the risk that data collection for the purpose of assessing efficacy and safety could interfere with patient safety and comfort. In this study, the risk has been mitigated by allowing unblinded treatment of the patient with open-label adjustment of sedation by bedside staff caring for the patient, combined with periodic blinded assessment of the primary endpoint by a healthcare professional not directly involved in the patient's ICU care.

The risks of ICU sedation with IV propofol infusion are well described in the literature[3] and outlined in the Background (Section 1.1). While no inhaled agent has been approved for ICU sedation in the US, there is significant experience with the prolonged use of isoflurane in the literature, with no time limit for the duration of anesthesia. The clinical use of isoflurane for sedation has expanded vastly since the introduction of the Sedaconda ACD device in Europe and other markets where the device is available. No previously unknown side effects have been reported, as side effects seen in the ICU are similar to those seen with isoflurane use for general anesthesia. This is also the case for SED001, where safety data from 150 patients treated with isoflurane via the Sedaconda ACD has been analyzed. Isoflurane sedation using the Sedaconda ACD device for up to several days has been described in a number of studies.[15,24]

Adverse reactions encountered in the administration of isoflurane are, in general, dose-dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension, and arrhythmias. Potential, serious, undesirable effects include malignant hyperthermia (MH), anaphylactic reactions, and liver adverse reactions.

Minimally raised levels of serum inorganic fluoride can occur during and after isoflurane anesthesia due to biodegradation of the agent. No cases of isoflurane-related polyuric renal failure have been reported after isoflurane sedation with durations beyond that planned in SED003.[15,24,38,40] It is unlikely that the low levels of serum inorganic fluoride observed (mean serum inorganic fluoride level of 25 µmol/L reported in one study[41]) could cause renal toxicity, as these are well below proposed and conservative threshold levels for kidney toxicity (mainly based on methoxyflurane-related renal toxic effects). There are no reports of isoflurane sedation-related renal dysfunction.

There are risks with the introduction of a novel device and therapy in critically ill patients. Therefore, device- and therapy-specific user-related risks are being mitigated via Human Factors engineering, focusing on optimizing design, training, and controls. All participating ICUs will be trained and the Sponsor will provide support in this through dedicated clinical educators. The

proficiency in providing adequate sedation will also be optimized by the inclusion of approximately 3 to 5 run-in training patients per site that will be treated with the support of the Sponsor's clinical educator.

The Sedaconda ACD-S has a dead space of 50 mL. This dead space is within the range of standard HMEs that commonly have a dead space of 29 to 95 mL.[42] Training regarding the HME function and the dead space of Sedaconda ACD-S will be performed prior to the study.

As with all standard HMEs, heavy secretions that reach the Sedaconda ACD may increase the resistance to flow. Very frequent nebulization may also increase the resistance to flow within the Sedaconda ACD. Any of these events would, in turn, lead to increased pressure drop across the device, which may affect the ventilation of the patient, either by increased ventilator pressures (if a volume-controlled ventilation mode is used) or by reduced tidal volumes (if the patient is on a pressure control ventilation mode). Besides standard ventilator alarms indicating such an eventuality, the handling of nebulization and secretions is explained in the device instructions for use and training. These aspects and other user-related risks have been evaluated in recent Human Factors evaluations and are addressed in training, instructions for use, and through controls such as ventilator alarms. All study sites will receive specific training in the use of Sedaconda ACD-S prior to the study, including the risks of volume or pressure changes due to changes in filter resistance.

1.7 The Coronavirus Disease

In March 2020, COVID-19, caused by infection with severe acute respiratory syndrome coronavirus 2, was characterized as a pandemic by the World Health Organization (WHO). The COVID-19 pandemic has impacted clinical studies worldwide due to quarantines, site closures, travel limitations, diversion of resources, and/or general interruptions in study-related procedures.

Coronavirus vaccinations are underway in the US and other countries. The clinical trial is planned to be initiated earliest Quarter 1, 2022.

This study protocol does not include contingency plans to manage disruptions due to COVID-19 control measures. Any protocol deviations that result from COVID-19 illness and/or COVID-19 control measures will be discussed in the Clinical Study Report (CSR).

2 STUDY OBJECTIVES AND ENDPOINTS

The objectives and endpoints for this study are presented below in Table 1.

Table 1. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the percentage of time sedation depth is maintained within the target range, in absence of rescue sedation, as assessed according to the RASS scale, in isoflurane- vs propofol-treated patients	The percentage of time sedation depth is maintained within the prescribed RASS interval through end of study drug treatment
Key secondary	
1. To compare the effect of isoflurane vs propofol on use of opioids during the study drug treatment period	Change in mean fentanyl-equivalent opioid dose during the study drug treatment period compared to mean opioid dose during the 60 minutes prior to randomization
2. To compare the effect of isoflurane vs propofol on the wake up time at end of study drug treatment	Time from stop of study drug treatment to RASS ≥0, up to 4 hours
3. To compare the effect of isoflurane vs propofol on cognitive recovery after EOT	Delirium by CAM-ICU-7 assessments 60 minutes (±10 minutes) after EOT in patients not re-sedated with benzodiazepine or propofol infusions
4. To compare the effect of isoflurane vs propofol on spontaneous breathing effort during the study drug treatment period	Proportion of ventilator parameter observations with spontaneous breathing efforts during the study drug treatment period
Other secondary	
To compare the effect of isoflurane vs propofol on time from sedation termination to extubation in patients for whom study drug is terminated for extubation	Time from EOT to extubation if study drug is terminated for extubation
To compare the effect of isoflurane vs propofol on days alive and free of mechanical ventilation through Study Day 30	Days alive and free of mechanical ventilation[1] through Study Day 30
To compare the effect of isoflurane vs propofol on days alive and free of the ICU	Days alive and free of the ICU[2] through Study Day 30
To compare the effect of isoflurane vs propofol on delirium and coma free days until 7 days after EOT	Delirium and coma free days from start of study drug until 7 days after EOT, as assessed with CAM-ICU-7 and RASS
To compare the effect of isoflurane vs propofol on mortality at 30 days after randomization	Mortality rate at 30 days after randomization
To compare the effect of isoflurane vs propofol on mortality at 3 months after randomization	Mortality rate at 3 months after randomization
To compare the effect of isoflurane vs propofol on mortality at 6 months after randomization	Mortality rate at 6 months after randomization
To compare the safety of isoflurane vs propofol	AEs, clinical laboratory assessments, vital signs, physical examination, blood gases, organ function, and ventilator parameters
To assess Sedaconda ACD-S device deficiencies in patients receiving isoflurane	Frequency and type of Sedaconda ACD-S device deficiencies in patients receiving isoflurane
To compare the use of restraints in patients receiving isoflurane vs propofol	Proportion of patients using restraint during the study drug treatment period
Exploratory	
To assess isoflurane dose over time	• Isoflurane dose in mL/hour; • Isoflurane dose in mL/hour/L minute ventilation; and • End-tidal isoflurane concentration every 4 hours.
To compare the effect of isoflurane vs propofol on major ICU interventions through Study Day 30 or until ICU discharge, whichever comes first	Need for: • Renal replacement therapy; • ECLS; • Tracheostomy; and • Non-invasive ventilation.

Table 1. Study Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory (Continued)	
To compare the effect of isoflurane vs propofol on level of care up to 30 days after randomization	Level of care: • Patient deceased; • Still in ICU; • Intermediary care unit; • General ward; • Another ICU (within or outside the hospital); • Another hospital (unknown ward); • Rehabilitation unit; • Nursing home; • Hospice; and • Home.
To assess the end-tidal isoflurane concentration and relation to RASS scores	End-tidal isoflurane concentration over time and relation to RASS scores
To compare oxygenation (PaO_2/FiO_2) over time during the study drug treatment period, in patients with ARDS/AHRF, in isoflurane vs propofol-treated patients	Oxygenation (PaO_2/FiO_2) in patients with ARDS/AHRF over time during the study drug treatment period
To compare memory panorama from time in the ICU in isoflurane- vs propofol-treated patients	Number of factual memories, memories of feelings, or delusional memories, as assessed by the ICU Memory Tool, collected at 3 months follow-up
To compare physical outcomes at 3 and 6 months post-randomization in isoflurane- vs propofol-treated patients	Activities of daily living, as assessed by the Katz ADL and Pfeffer FAQ, at 3 and 6 months post-randomization
To compare psychological outcomes at 3 and 6 months post-randomization in isoflurane- vs propofol-treated patients	Depression, anxiety, and post-traumatic stress symptoms, as assessed by IES-R and PROMIS Depression and Anxiety questionnaires, at 3 and 6 months post-randomization
To compare cognitive function 3 and 6 months post-randomization in isoflurane- vs propofol-treated patients	Cognitive function, as assessed by TICS, WAIS IV-Digit Span, Hayling Sentence Completion Test, Controlled Oral Word Association, WMS-IV – Immediate Memory (Adult/Older Adult), WMS-IV – Delayed Memory (Adult/Older Adult), and PROMIS Cognitive Function questionnaire, at 3 and 6 months post-randomization
To compare quality of life at 3 and 6 months post-randomization in isoflurane- vs propofol-treated patients	Quality of life at 3 and 6 months post-randomization, as assessed by WHODAS 2.0 and BPI
To compare the need for rescue, other sedatives, and antipsychotics in isoflurane- vs propofol-treated patients	Use of rescue sedatives, other sedatives, and antipsychotics from randomization to EOT
To compare the hemodynamic instability in isoflurane- vs propofol-treated patients	Change from Baseline in highest daily vasoactive drug requirements during study drug treatment
To compare duration of mechanical ventilation in isoflurane- vs propofol-treated patients	Duration of mechanical ventilation
To compare ICU length of stay in isoflurane- vs propofol-treated patients	ICU length of stay
To compare minute ventilation in isoflurane- vs propofol-treated patients	Change in minute ventilation every 8 hours during the study drug treatment period

1. For Days alive and free of mechanical ventilation, only invasive ventilation will be taken into account. Successful ventilator discontinuation is defined as being alive and free of ventilation for 48 hours (inclusive) following discontinuation. For example, if a patient was discontinued from mechanical ventilator and ventilation was initiated again within the next 48 hours or the patient died within the next 48 hours, then the time (less than 48 hours) that was off ventilation did not count as Days alive and free of mechanical ventilation.
2. The Days alive and free of the ICU is defined similarly to the Days alive and free of mechanical ventilation. Successful ICU discharge is defined as being alive and out of ICU for 48 hours (inclusive) following discharge.

AE = adverse event; AHRF = acute hypoxemic respiratory failure; ARDS = acute respiratory distress syndrome; BPI = Brief Pain Inventory; CAM-ICU-7 = 7 point scale of the Confusion Assessment Method for the Intensive Care Unit; ECLS = extracorporeal life support; EOT = end of treatment; FAQ = functional activities questionnaire; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; IES-R = impact of event scale; Katz ADL = Katz Index of Independence in Activity of Daily Living; PaO_2 = partial pressure of oxygen; PROMIS = Patient Reported Outcomes Measurement Information System; RASS = Richmond Agitation Sedation Scale; Sedaconda ACD-S = Sedaconda Anaesthetic Conserving Device - S; SOC = standard of care; TICS = Telephone Interview for Cognitive Status; vs = versus; WAIS = Wechsler adult intelligence scale; WHODAS 2.0 = World Health Organization Disability Assessment Schedule 2.0; WMS = Wechsler memory scale.

3 STUDY DESCRIPTION

3.1 Study Indication

The indication of this study is for sedation of mechanically ventilated patients in the ICU.

3.2 Summary of Study Design

This is a therapeutic confirmatory (Phase 3), multicenter, randomized, controlled, open-label, assessor-blinded study. Approximately 235 patients receiving mechanical ventilation and requiring continuous sedation at approximately 15 to 20 sites in the US will be randomized in a 1.5:1 ratio to inhaled isoflurane (administered via the Sedaconda ACD-S device) or propofol (administered via IV infusion) for sedation, respectively. In addition, approximately 3 to 5 run-in training patients per site will be enrolled. The treatment duration in this study is expected to be at least 12 hours and may last up to 48 (±6) hours or to the time for extubation, whichever occurs first, with a follow-up period of 6 months.

Patients eligible for the study will either have planned surgery with anticipated need for sedation and mechanical ventilation in the ICU (ie, postoperative patients) for >12 hours or have already been admitted to the ICU and anticipate needing sedation and mechanical ventilation for >12 hours.

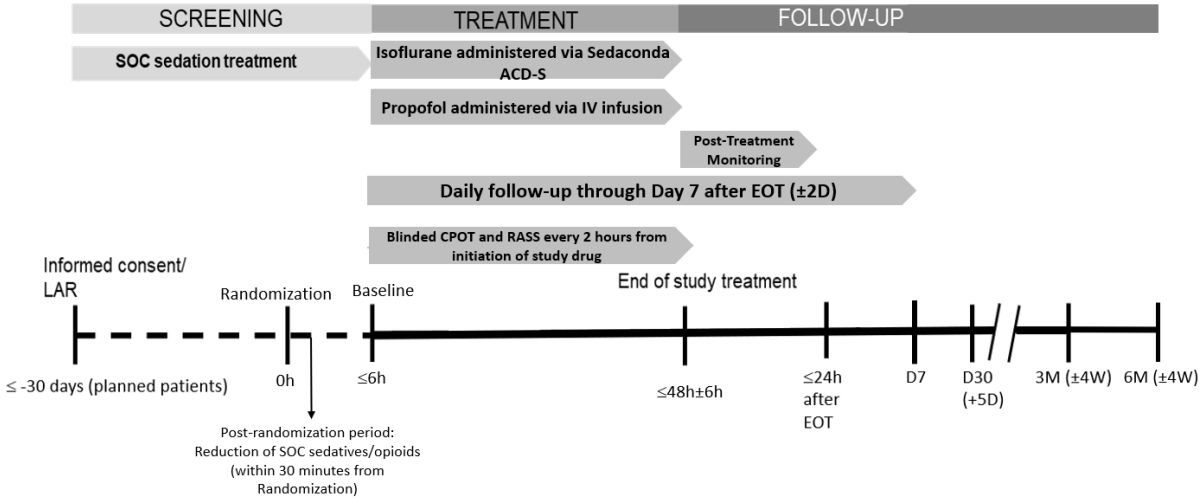
Informed consent must be obtained from the patient or patient's legally authorized representative (LAR) for all patients according to Section 6.1.

The study will comprise the following key study periods:

- Screening period: Day -30 to randomization;
  - Initial Screening: Day -30 to randomization;
  - Complete Screening: -24 hours to randomization;
  - Randomization; and
  - Baseline: Randomization to initiation of study drug treatment (up to 6 hours).
- Treatment period: initiation of study drug administration to the EOT (up to 48 [±6] hours); and
- Follow-up period: EOT to 6 months (±4 weeks) after randomization.
  - Post-treatment monitoring phase: until 24 hours after EOT;
  - 24 hours after EOT until 7 days after EOT: daily follow-up from the time of randomization until 7 days after EOT;
  - Follow-up: at Study Day 30 (+5 days) after randomization;
  - 3-month centralized telephone follow-up: 3 months (±4 weeks) after randomization; and
  - 6-month centralized telephone follow-up: 6 months (±4 weeks) after randomization.

A schematic of the study flow is shown in Figure 2.

Figure 2. Study Scheme



CPOT = Critical Care Pain Observation Tool; D = day(s); EOT = end of treatment; h = hour(s); IV = intravenous; LAR = legally authorized representative; M = month; RASS = Richmond Agitation Sedation Scale; Sedaconda ACD-S = Sedaconda Anaesthetic Conserving Device - S; SOC = standard of care; W = week(s).

Patients will be screened between Day -30 to randomization to determine study eligibility.

At randomization, ongoing sedation and opioid infusions will be reduced to half as described in Section 3.7. Baseline values will be obtained during the baseline phase (ie, from randomization to initiation of study drug administration) as specified in Appendix A and Section 6.1.3.

Initiating study drug treatment must be performed as close to randomization as possible, and no later than 6 hours after randomization. It is recommended to start study drug treatment at the full hour to simplify data collection timepoints. The target sedation depth (ie, RASS range of -1 to -4) will be valid from randomization.

Study drug dose titration will be performed by the clinical team to reach the targeted sedation depth (ie, RASS range -1 to -4, as set by the clinical team) based on unblinded RASS assessments during initial titration and thereafter based on blinded assessments every 2 hours until the patient reaches EOT. Sedation will also be adjusted based on non-blinded RASS assessments by bedside staff between formal blinded assessments; see Section 7.1.1 for further details.

Pain level will be assessed using the CPOT, assessed in parallel with the RASS assessment, to ensure that pain and sedation are managed properly.

Study drug treatment will be stopped when the patient is planned to be extubated or reaches the maximum treatment duration of 48 (±6) hours, as specified in Section 6.2.5, at which time the patient will be transitioned to SOC sedation when clinically indicated.

Patients will be monitored until 24 hours after EOT, followed-up until Day 7 and at Study Day 30 (+5) days, and a consecutive subset of patients still alive will receive a telephone call from the Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center in Nashville at 3 months (±4 weeks) and 6 months (±4 weeks), respectively, after randomization to assess long-term outcomes (LTO).

For training purposes in the use of Sedaconda ACD-S, approximately 3 to 5 patients at each site will be assigned to receive isoflurane via Sedaconda ACD-S in a non-blinded fashion according to Section 3.5, before any patients are randomized.

An independent DSMB will be assembled to safeguard the safety of study patients per the DSMB Charter. This DSMB will serve jointly for both this study and the SED004 study, a confirmatory study identical to SED003, see Section 8.8.

3.3 Time Portion of Adequate Sedation Depth

The primary objective of this study is to compare the percentage of time sedation depth is maintained within the target range, in absence of rescue sedation, as assessed according to the RASS scale, in isoflurane- versus propofol-treated patients. This parameter will be derived for each patient, as follows:

$$\%\ adequate\ sedation = \frac{success\ time}{success\ time + failure\ time}$$

'Success time' is the time during study drug treatment when blinded RASS falls within -1 to -4.

'Failure time' is counted if:

1. Blinded RASS is outside the target range (ie, less than -4 or greater than -1);
2. Rescue sedation is needed, ie, RASS target is not achieved, despite use of study drug; or
3. 'Treatment failure', as defined in Section 5.4.1.2.

If a blinded RASS assessment is not performed per study schedule (missed assessment), the missed assessment will not be accounted for in the primary endpoint, but will be counted as failure in a sensitivity analysis.

When SOC procedures imply significant change to sedation level, blinded assessments will not be performed. The rules for when not to perform blinded RASS and CPOT assessments due to such changes of sedation level are described in Section 7.1.3. Such omitted blinded RASS assessments due to SOC procedures in or outside the ICU, as described in Section 7.1.3, are not considered protocol deviations and are not counted as failure time.

3.4 SOC and ABCDEF Bundle

ICU care for patients will be managed per SOC during the study using the ABCDEF bundle as a guide,[43] see Appendix C.

Regarding screening for unassisted breathing readiness and extubation, additional recommendations are provided in Appendix D. The strategy for performing the spontaneous breathing test (SBT) readiness screening and subsequent SBT will adhere to current SOC (ie, mandated daily screening and, when criteria met, SBT initiation) while allowing for local practice variation that reflects usual care. For any sites without an existing clinical SBT protocol, recommendations are provided in Appendix D.

3.5 Run-In Training Patients

For training purposes in the use of Sedaconda ACD-S, approximately 3 to 5 run-in training patients per site will be assigned to receive isoflurane via Sedaconda ACD-S in an unblinded setting. Each

site will start with run-in training patients before any patients are randomized. The number of run-in training patients at each site will be set in dialogue between the Sponsor and the local study team. The run-in training patients will be assigned a unique identification number but will not be randomized. Run-in training patients will perform all assessments according to Appendix A, including the long-term follow-up assessments at 3 and 6 months.

Additional run-in patients will not be allowed at a given site after the first patient is randomized.

3.6 Randomization and Blinding

Patients will be randomized in a 1.5:1 ratio to receive isoflurane (administered via the Sedaconda ACD-S device) or propofol (administered via IV infusion), respectively.

3.6.1 Stratified Randomization

Randomization will be stratified by Simplified Acute Physiology Score (SAPS) III (SAPS 0 to <40, 40 to <60, and ≥60) and patient type (medical and surgical [including trauma]) assessed at Screening. Surgical patient will be defined as patients who meet either of the following criteria:

1. Have undergone surgery within the prior 2 weeks and for whom the current respiratory failure episode is related to that surgery or surgical disease process, or a complication thereof; or
2. Patients anticipated to undergo surgery within the next 2 days for a condition that is related to etiology of respiratory failure.

3.6.2 Blinding

Bedside treating staff, taking care of the study patient will not be blinded to treatment assignment. Besides this group, treatment allocation will not be disclosed unless clinically motivated. The blinded RASS and CPOT assessment results will be documented without the blinded assessor and the bedside staff discussing study treatment or sedation. After documentation, the scores will be communicated to the bedside staff.

Each patient will have a double drug delivery set-up, 1 for active treatment and 1 nonfunctional set-up, to maintain blinding for staff not directly involved in the care of the patient. Measures will be taken to visually obscure both drug delivery set-ups.

The blinded assessors will not have access to the patient during the study drug treatment period unless the blinding measures are in place.

Detailed blinding instructions will be provided, with the option for local optimizations.

3.6.3 Blinded Assessment of RASS and CPOT

Clinical staff will be trained by the Investigator or designee in standardized assessment of the RASS and CPOT.

Blinded assessors will have limited interaction with treating staff and will not participate in treatment discussions or decisions. Staff treating the patient should avoid revealing the study treatment to other staff members. Unless medically indicated, discussions regarding study patients between staff not directly involved in the care of the patient should be avoided until all blinded

assessments are completed. These individuals will be delegated the task of performing the blinded RASS and CPOT assessments for each patient, with the following guidance:

- At the time of enrollment, and before each new shift, potential assessors (previously experienced or trained in RASS and CPOT) among staff on duty will be notified. At the time of blinded assessment, any of these assessors will be asked to perform the blinded assessments;
- Prior to the blinded assessment, bedside staff will ensure that all devices and equipment are covered according to the blinding instruction;
- Additionally, prior to the blinded assessment, the assessor will confirm the period is eligible for assessment, as described in Section 7.1.3. Thereafter, the blinded assessor will have access to the patient;
- At the time of documentation of RASS and CPOT scores, the assessor will certify in writing that he/she was not aware of the study drug treatment given;
- In case the assessor becomes unblinded, a new assessor will be selected among the trained clinical staff; and
- After documenting the RASS and CPOT scores, the results will be relayed to bedside staff for consideration of a possible need to titrate sedative and analgesic drugs.

3.6.4 Breaking the Blind

This is an open-label study with blinded assessments. Bedside staff will be unblinded to patient treatment assignments. There is no provision for breaking the blind for the blinded assessors. If a potential blinded assessor is unintentionally informed of or learns of a patient's treatment assignment, this assessor will not make any further assessments and other assessors, still blinded to treatment arm, will conduct the remaining assessments during the study drug treatment period.

3.7 Reduction of SOC Sedatives and Opioids After Randomization

To minimize the effects of different SOC drugs at initiation of study drug treatment, both sedative and opioid infusions will be reduced to half, as soon as possible after randomization and prior to study drug initiation, unless the patient is agitated or shows signs of ongoing pain (see Section 6.1.3).

If clinically indicated after the dose reductions and prior to the start of study drug treatment, titration of SOC sedatives and/or opioid analgesics is permitted.

3.8 Study Drug Treatment

Study treatments will be administered as detailed in Section 5.

Throughout the study drug treatment period, the study drug dose (isoflurane or propofol) should be adjusted to maintain the target RASS range of -1 to -4. Sedation may be paused for clinical purposes (eg, decreased sedation for neurological examinations and daily Spontaneous Awakening Trials [SATs]). If additional sedation is needed for routine ICU care per SOC (eg, repositioning the patient), study drug should primarily be used for this purpose.

Procedural sedation for procedures within and outside the ICU is discussed in Section 5.5.2.1. Study drug may not be administered outside of the ICU. Re-initiation of study drug, if it is paused for procedures, is detailed in Section 5.3.4.

If adjustments of the study drug are insufficient to reach or maintain the target RASS range, rescue sedative agents may be given, as detailed in Section 5.4.

3.9 End of Treatment

EOT is achieved when the patient reaches one of the following scenarios:

- Study drug administration is stopped for extubation;
- Reaching 48 (±6) hours of study drug treatment; or
- Any medical condition that indicates to the Investigator that continued treatment is not in the best interest of the patient.

EOT due to transfer from ICU (to other ICU or for procedure outside the ICU with return to the ICU >42 hours after initiation of study drug treatment) constitutes a special scenario. In this situation, all EOT assessments that are applicable and feasible should be performed prior to transfer.

3.10 Extubation

Extubation will be performed per SOC. For any sites without an existing screening for extubation readiness protocol, recommendations are provided in Appendix D.

Patients for whom extubation is attempted but unsuccessful (ie, requiring re-intubation) and any EOT assessments have been initiated (wake-up test or CAM-ICU-7 after 60 minutes) will not receive further study drug. If sedation is required upon re-intubation, only SOC sedation is permitted.

3.11 Long-Term Outcomes Assessment

In drug studies of critically ill patients, outcomes may be assessed at remote timepoints and not merely in the ICU. This is because the “success” of interventions is not defined merely by their impact in the hospital but also by their persistent effects. The CIBS Center at Vanderbilt University Medical Center, LTO Core will conduct the LTO assessments for a consecutive subset of patients in this trial.

Appropriate performance of cognitive assessments, in particular as clinical trial outcomes, requires specially trained neuropsychology professionals and standardization of test administration. Results from in-person assessment strategies may suffer from bias due to higher loss to follow-up, missing and/or partial data (which is not random), and testing in an unfamiliar or uncomfortable environment, which will be exacerbated by these assessments being conducted at 30 to 40 individual sites (ie, de-centralized) by less experienced assessors in the specific test battery. To achieve scientific rigor and standardization of assessments and higher rates of complete follow-up, validated remote assessments performed by one single centralized team will be utilized for both clinical trials. This technique is especially important for multicenter trials where neuropsychology resources will vary by center and in-person assessments are often not feasible, practical, or reliable. Remote, centralized cognitive assessments have been performed in many landmark trials in

critically ill patients, including recent sedation trials and several studies conducted under FDA Investigational New Drug applications.[10,28,44,45,46] The Vanderbilt CIBS Center (www.icudelirium.org) is an internationally recognized center for its work in acute and long-term brain dysfunction from critical illness, including landmark studies on delirium, cognitive impairment, and sedation.[28,44,47,48,49,50,51] The LTO Core within the CIBS Center, comprised of neuropsychology professionals, has been responsible for cognitive assessments performed in CIBS Center studies, along with multiple other multicenter trials including several Prevention and Early Treatment of Acute Lung Injury (PETAL) network studies in critically ill patients.

A comprehensive battery slightly less than an hour in duration will be employed, which is significantly more sensitive than a brief screening test but less cumbersome than a lengthy clinically oriented neuropsychological assessment. This battery combines tests from diverse and relevant domains of functioning and balances the need to be sufficiently challenging to patients as well as the need to be feasibly administered and well tolerated. Crucially, this battery can be given by telephone or videophone, which allows for it to be administered by the CIBS Center's LTO Core to individuals from around the country, regardless of which enrollment sites they are from. A description of these Cognitive Assessments, Mental Health, Functioning, and Quality of Life Assessments are provided in Section 7.3.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Adults ≥18 years of age;
2. Patients who are anticipated to require >12 hours of invasive mechanical ventilation and continuous sedation in the ICU; and
3. Receipt of continuous sedation due to clinical need for sedation to RASS <0.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Need for RASS -5;
2. Sedation for invasive mechanical ventilation immediately prior to Baseline for >72 hours (patients who have been extubated for at least 24 hours and subsequently re-intubated will have sedation for invasive mechanical ventilation starting from when they were re-intubated);
3. Severe neurological condition that causes the patient to lack ability to participate in the study (ie, unable to be assessed for RASS and CPOT), including, but not restricted to, patients with acute stroke, severe head trauma, meningitis, suspected of having elevated intracranial pressure (ICP), or the need for ICP monitoring;
4. Ventilator tidal volume <200 or >1000 mL at Baseline;
5. Need for extracorporeal membrane oxygenation (ECMO), extracorporeal CO_2 removal ($ECCO_2R$), high frequency oscillation ventilation (HFOV), or high frequency percussive ventilation (HFPV) at Screening;
6. Comfort care only (end of life care);
7. Contraindication to propofol or isoflurane, including:
    a. Known or suspected personal or family history of MH or high risk for MH or acute drug-induced muscle injury (eg, muscular dystrophies);
    b. Severe hemodynamic compromise, defined as the need for norepinephrine ≥0.3 mcg/kg/min (or equivalent vasopressor dose[52] [Appendix K]) to maintain blood pressure within acceptable range, assumed to be mean arterial pressure ≥65 mmHg unless prescribed clinically; or
    c. Allergy to isoflurane or propofol, or have propofol infusion syndrome.
8. History of ventricular tachycardia/Long QT Syndrome;
9. Requirement of IV benzodiazepine or barbiturate administration for seizures or dependencies, including alcohol withdrawal;
10. Neuromuscular disease that impairs spontaneous ventilation (eg, C5 or higher spinal cord injury, amyotrophic lateral sclerosis, etc);

11. Concurrent enrollment in another study that, in the Investigator's opinion, would impact the patient's safety or assessments of this study;
12. Participation in other study involving investigational drug(s) or devices(s) within 30 days prior to randomization;
13. Previous randomization or receipt of treatment in this study or in SED004;
14. Anticipated requirement of treatment with continuous infusion of a neuromuscular blocking agent (NMBA) for >4 hours;
15. Female patients who are pregnant or breast-feeding;
16. Imperative need for continuous active humidification through mechanical ventilation circuit;
17. Attending physician's refusal to include the patient; or
18. Inability to obtain informed consent.

4.3 Criteria for Early Study Drug Discontinuation

A patient should be discontinued from the study drug prior to EOT for any of the following reasons:

- Treatment failure, ie, clinical failure for the patient to be adequately sedated with study drug as specified in Section 5.4.1.2;
- New onset of coma due to structural brain disease such as stroke, intracranial hemorrhage, cranial trauma, malignancy, anoxic brain injury, or cerebral edema;
- Severe or serious adverse events (SAEs):
  - Development of an adverse event of special interest (AESI) that qualifies as a severe adverse event (AE) or SAE at least possibly related to study drug, without a clear alternate explanation;
  - For any other severe AEs, the decision on whether to continue with study drug will be made at the site level by the Investigator and clinical team in accordance with whether continuation/reintroduction of study treatment is in the best interest of the patient for the first severe AE; or
  - A second severe AE or any SAE without a clear alternate explanation will lead to discontinuation of study treatment.
- Unresolved Sedaconda ACD-S device-related issues; see Section 8.7;
- Any medical condition that indicates to the Investigator that continued study drug treatment is not in the best interest of the patient;
- Transition to comfort care;
- Death;
- Requirement of prohibited concomitant medication; see Section 5.5.1;

- Need for ECMO, $ECCO_2R$, HFOV, or HFPV; or
- Withdrawal of consent to receive study drug.

See Section 6.2.5 for applicable procedures at the time of study drug discontinuation.

4.4 Criteria for Study Withdrawal

A patient should be withdrawn from the study for any of the following reasons:

- Any medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient;
- Withdrawal of consent by the patient or LAR or request for discontinuation from the study for any reason;
- Withdrawal of the site by the Sponsor due to Investigator failure to comply with protocol requirements or study-related procedures; and
- Termination of the study by the Sponsor or the regulatory authority.

See Section 6.4 for related procedures at the time of study withdrawal.

5 STUDY TREATMENTS

5.1 Drug and Device Supplies

5.1.1 Formulation and Packaging

Commercially available isoflurane and propofol will be provided by the Sponsor through an authorized service provider.

Isoflurane will be provided in 100 or 250 mL bottles containing 100% v/v of isoflurane for inhalation.

Propofol will be provided as an IV solution for infusion at the dose of 1% w/v (1 g, 10 mg/ml) or 2% w/v (2 g, 20 mg/mL).

Study-specific isoflurane and propofol will be labeled in accordance with Good Manufacturing Practice and local regulatory guidelines.

5.1.2 Storage and Accountability

All study drugs shall be kept in a secure place with limited access under appropriate storage conditions and in accordance with local regulations. See Instructions-For-Use provided for additional information on isoflurane storage.

Isoflurane shall be stored between 20°C to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F), in order to avoid gas volume expansion upon warming. The bottles should be stored in the outer carton to protect from light. Refer to the Pharmacy Manual for detailed instructions.

Propofol shall be stored between 4°C to 25°C (40°F to 77°F). Propofol shall not be frozen. Shake well before use.

Temperature logs shall be kept for the storage room where the study drugs are stored prior to dispensing. The minimum and maximum temperature should be noted daily on business days (unless automatic temperature readings are available).

The Investigator is responsible for establishing routines for correct handling of the study drugs at the site to ensure the following:

- Study drugs are correctly received, accounted for, and logged by a designated person;
- Accurate records are maintained, accounting for the receipt and disposition of the study drugs;
- Study drugs are handled and stored safely, properly, and in agreement with the given handling and storage instructions;
- Study drugs are prescribed only by the Investigator or designee;
- Study drugs are only dispensed by designated site staff;

- Study drug dispensing is recorded on an appropriate Drug Dispensing Log. At least the following information will be documented: patient identification number, the study drug and quantity dispensed, date and time of dispensing, and any leftover study drug from the dispensed unit returned to storage after patient has completed the study. This record must be kept in addition to any study drug administration information recorded in the electronic case report form (eCRF) or the patient's medical chart/source documents; and
- All unused study drugs and empty containers are stored until they have been checked by the Clinical Research Associates (CRAs).

After verifying drug accountability, all unused study drugs and all empty bottles will be returned to the Sponsor or designee for destruction or be destroyed locally upon agreement with, and approval from, the Sponsor or designee.

5.1.3 Sedaconda ACD-S Supply, Storage, and Accountability

The Sedaconda ACD-S devices will be manufactured under the responsibility of Sedana Medical Limited (Unit 2A, The Village Centre, TwoMileHouse, Naas, Co. Kildare, W91 PWH5, Ireland). The Sedaconda ACD-S devices and applicable auxiliaries will be provided and labelled with a unique device identifier together with the instructions for use. The Sedaconda ACD-S devices and auxiliaries provided for this study will only be used during the study drug treatment period. The use of the Sedaconda ACD-S devices will be accounted for during the study using a device accountability log.

In addition to the Sedaconda ACD-S, the study sites will be provided with auxiliary supplies required for the use of the Sedaconda ACD-S, such as the unique Sedaconda syringes, gas sampling connector, isoflurane filling adapter, FlurAbsorb, and FlurAbsorb accessory kit. FlurAbsorb is used for scavenging of waste anesthetic gases from the exhaust port of the ventilator. The Sedaconda ACD-S and auxiliaries should be stored at room temperature.

5.2 Study Drug Preparation and Dispensing

Patients will be randomized in a 1.5:1 ratio to receive isoflurane (administered via the Sedaconda ACD-S device) or propofol (administered via IV infusion), respectively. The duration of the study drug treatment will be up to 48 (±6) hours.

Study drug will be prepared and dispensed by unblinded study site personnel according to the research Pharmacy Manual provided in conjunction with this protocol.

5.3 Study Drug Dosing

5.3.1 Isoflurane Dosing

The initial dose of isoflurane in this study is 3.0 mL/hour, and dose titration based on frequent assessments of the patient's clinical sedation depth and hemodynamics will occur at dose increments or decrements of 0.5 to 1.0 mL/hour. In deeply sedated, hypovolemic or hypotensive patients receiving vasopressors, lower doses may be considered. The dose titration is performed by the clinical team. During initiation, bolus doses of 0.3 to 0.5 mL can be given, as clinically indicated, to obtain rapid deepening of sedation when required to achieve RASS target. Isoflurane pump rate should not exceed 15 mL/hour. The dosing schedule is based on clinical experience,

dosing from SED001, and pharmacokinetic bench studies on isoflurane dosing for anesthesia.[33] See Table 2 below.

Table 2. Isoflurane/Sedaconda ACD-S Starting Dose and Titration Schedule

Starting Dose[1]	Dose Titration Schedule[1]
3.0 mL/hour[2]	Stepwise titration[2] by 0.5 to 1.0 mL/hour until desired clinical effect is achieved. Peak clinical effects are typically noticeable within 10 to 15 minutes.
	Bolus dose of 0.3 to 0.5 mL
1. Before initiating the starting dose, the Sedaconda ACD-S will be primed with 1.2 mL isoflurane. 2. In deeply sedated, hypovolemic or hypotensive patients receiving vasopressors, lower doses may be considered. ACD-S = Sedaconda Anaesthetic Conserving Device – S.	

5.3.2 Propofol Dosing

In most patients, the initial infusion should be approximately 10 to 25 µg/kg/minute (0.6 to 1.5 mg/kg/hour) for at least 5 minutes. Subsequent adjustment may occur in increments or decrements of 5 to 10 µg/kg/minute (0.3 to 0.6 mg/kg/h) every 5 to 10 minutes until the target sedation depth is achieved. Maintenance doses of 5 to 50 µg/kg/minute (0.3 to 3 mg/kg/hour) or higher may be required. Propofol dose should not exceed 66 µg/kg/minute (ie, 4.0 mg/kg/hour) according to label instructions.[53]

Propofol will be administered via IV infusion.

The starting dose and titration schedule specified in Table 3 will be followed, unless the patient is receiving propofol prior to randomization and is within RASS target range. In such cases, the same dose as prior to randomization is recommended as the starting dose.

Table 3. Propofol IV Infusion Starting Dose and Titration Schedule

Starting Dose	Dose Titration Schedule
0.6 to 1.5 mg/kg/hour, or the pre-randomization dose in patients already receiving SOC propofol and within the targeted RASS range	Stepwise titration by 0.3 to 0.6 mg/kg/hour every 5 to 10 minutes
	Bolus dose of 0.3 to 0.5 mg/kg
IV = intravenous; RASS = Richmond Agitation Sedation Scale; SOC = standard of care.	

5.3.3 Initiation of Study Drug Treatment

The SOC sedatives and opioid analgesics will be reduced to half as soon as possible after randomization and prior to study drug initiation, unless the patient is agitated or shows signs of ongoing pain, as described in Section 6.1.3. If clinically indicated after the dose reductions and prior to the start of study drug treatment, titration of SOC sedatives and/or opioid analgesics is permitted.

As soon as the study drug treatment has been initiated, the SOC sedative should be stopped (ie, slow weaning will not be permitted) to limit the impact of residual SOC sedation.

Once study drug treatment has been initiated, titration will be based on frequent assessments of the patient's sedation depth, hemodynamics, and end-tidal isoflurane concentration (for isoflurane group) by the clinical staff who are unblinded to study drug assignment. The patient's level of pain will also be assessed to inform opioid dose titration.

Isoflurane administered via Sedaconda ACD-S

The Sedaconda ACD-S is set up according to the Instruction-For-Use together with a gas monitor and scavenging system and should be used according to the Instruction-For-Use provided.

The syringe is filled with 50 mL of isoflurane and put into the syringe pump. Isoflurane syringes will be prepared according to the instructions for use and local drug guidelines when a patient is randomized to isoflurane and delivered to the local drug storage facility at the ICU. Sedation will start after priming of the Sedaconda ACD-S agent line with 1.2 mL isoflurane.

The starting dose and titration schedule are specified in Table 2.

Propofol IV

Propofol is set up according to local guidelines. The starting dose and titration schedule are provided in Table 3.

5.3.4 Study Drug Treatment Maintenance

Throughout the study drug treatment period, the study drug dose (isoflurane or propofol) should be titrated to maintain RASS between -1 to -4.

If study drug is insufficient to reach or maintain the target RASS range, rescue sedative agents should be given in accordance with Section 5.4.

Sedation may be paused for clinical purposes (eg, decreased sedation for neurological examinations, or conduct of a SAT and SBT consistent with best practice in accordance with Section 3.4).

Management of procedural sedation is discussed in Section 5.5.2.1.

Study drug may not be administered outside of the ICU. In the case of procedures outside the ICU, study drug must be stopped (removal of Sedaconda ACD-S, or replacement of propofol dispensed as study drug). Study drug should be re-initiated as soon as possible after returning to the ICU, at a dose between 50% and 100% of the previously administered dose at the time of treatment interruption, and titrated to reach the target RASS range.

Patients who return to the ICU prior to 42 hours from start of study drug treatment (the earliest timepoint for end of study drug treatment) should resume study drug.

Patients who return to the ICU later than 42 hours from start of study drug treatment, should transition to SOC sedation and medical care at the discretion of the treating physician. See Section 6.2.6 for related procedures at EOT.

Isoflurane via the Sedaconda ACD-S

The syringe pump rate for a given sedation target may need to be adjusted to match the patient's minute ventilation. Significant increases in minute ventilation may require an increase in pump rate to maintain the sedation level. Similarly, significant decreases in minute ventilation may require a decrease in pump rate to maintain the same sedation depth.

In absence of other sedatives, but with ongoing IV opioid administration, typical maintenance pump rates to achieve RASS -1 to -4 are approximately 0.4 mL/hour isoflurane/L minute ventilation, translating to a pump rate of approximately 3 mL/hour for a patient with a minute ventilation of 7 L/min. Pump rate should be adjusted to achieve the intended sedation target,

considering the patient's age and medical condition, as well as concomitant centrally acting medications. Pump rates of up to 15 mL/hour are allowed. For short procedures or to increase sedation quickly, a programmed bolus of 0.3 to 0.5 mL can be given via the pump, see Section 5.3.1.

Long-term end-tidal concentration assessed every 4 hours should not exceed 1%. If end-tidal concentration should exceed 1% at 2 consecutive 4-hour end-tidal concentration measurements, the isoflurane pump rate should be reduced, and no bolus doses of isoflurane should be used until the patient reaches an isoflurane end-tidal concentration below 1%.

The Sedaconda ACD-S device may be changed as needed or at least after 24 (±4) hours of study drug administration. The time for the Sedaconda ACD-S device change should be recorded in the eCRF.

When stopping isoflurane administration, the Sedaconda ACD-S must be removed and replaced with a standard HME or active humidifier. Removal of the ACD-S is necessary to facilitate rapid elimination of isoflurane from the body.

Propofol

The propofol and the propofol line or syringe may be changed as needed according to local guidelines.

5.3.5 Post-Study Drug Treatment

After EOT or early discontinuation of study drug, study drug should not be resumed or re-initiated, and SOC sedatives should be initiated as needed to ensure patients are not restless or agitated for any length of time. Patients will transition to medical care per SOC at the discretion of the treating physician. The isoflurane, propofol, and Sedaconda ACD-S provided for the study may not be used after the completion of the study drug treatment period.

5.4 Rescue Medication

5.4.1 Rescue Sedation and Treatment Failure

Whenever possible, the patient's sedative requirements should be met using only the assigned study drug, which may be titrated as necessary in accordance with Section 5.3. If study drug is insufficient to reach or maintain the target RASS range or if the patient requires additional sedation due to a medical procedure, action may be taken as outlined below.

5.4.1.1 Per-protocol rescue sedation

Rescue sedation is defined as sedative agents, other than the study drug, that are allowed in case of inadequate sedation, due to reasons such as observed acute agitation or immediate risk of extubation that is not controlled by administration of study drug and despite adequate analgesia (pain management assessed by CPOT).

The use of rescue sedation in this study should be stepwise in the following order:

First-line rescue: bolus of study sedative drug

The following rescue medications, with dose ranges, can be given:

- Bolus doses of the assigned study drug patient is receiving:
  - Propofol 0.3 to 0.5 mg/kg, or isoflurane 0.3 to 0.5 mL; and
  - Maximum 2 bolus doses/hour before use of second-line rescue medication (when used as rescue rather than procedural).

Second-line rescue: rescue sedatives if study sedation is not sufficient

These medications should not be used routinely. The choice of medications used for second-line rescue sedation depends on the clinical scenario and anticipated need for additional sedation.

The following rescue medications, with dose ranges, can be given:

- Dexmedetomidine infusion: 0.15 to 0.7 mcg/kg/hour for a maximum of 3 hours accumulated per 24 hours; and/or
- Midazolam bolus: 0.5 to 5 mg per dose, at a maximum of 3 boluses per 24 hours.

5.4.1.2 Treatment failure

Treatment failure is defined as when study drug is deemed insufficient to reach or maintain the target RASS range for sedation, and the resulting amount of rescue sedation meets either of the following criteria:

- There is a clinical need for infusion of dexmedetomidine for >3 hours per 24 hours; and/or
- There is a clinical need for >3 midazolam boluses per 24 hours.

As soon as possible after treatment failure occurs, the patient should discontinue study drug and transition to medical care per SOC at the discretion of the treating physician. See Section 6.2.5 for related procedures at the time of study drug discontinuation.

5.5 Prohibited and Restricted Medications

5.5.1 Prohibited Medications

Medications for purposes of sedation other than the allocated study drug are prohibited throughout the study drug treatment period, unless used for procedures outside the ICU. Such prohibited medications include the following:

- Chlorpromazine;
- Chloral hydrate;
- Barbiturates;
- Gamma-hydroxybutyrate;
- Clonidine;

- Ketamine; and
- Continued treatment with a NMBA for >4 hours during the study drug treatment period.

If prohibited medications specified above are deemed required for patient safety during the study drug treatment period, the patient should discontinue study drug and transition to medical care per SOC at the discretion of the treating physician. See Section 6.2.5 for related procedures at the time of study drug discontinuation.

5.5.2 Restricted Medications

The following medications are restricted during the study treatment period when in the ICU:

- Propofol;
  - Non-study drug propofol infusions are not permitted in either of the treatment arms for sedation with the exception of procedures inside or outside the ICU, as outlined in Section 5.5.2.1.
- Benzodiazepines (see Section 7.1.6) may only be used as rescue sedatives if study sedation is not sufficient;
- α2-adrenergic agonists (see Section 7.1.6) may only be used as rescue sedatives if study sedation is not sufficient and during SATs and the EOT wake-up test (see Section 6);
- Antipsychotics, eg, haloperidol, quetiapine, olanzapine, or chlorpromazine should not be used during study sedation unless the patient has been on these medications before ICU admission, except during SATs (see Section 5.5.2.1) and during the EOT wake-up test (see Section 6); and
- NMBAs.
  - Continuous infusions of NMBAs for study drug treatment periods >4 hours are not permitted. Shorter infusions of NMBA may be used as indicated for medical procedures as described in Section 5.5.2.1. Any infusions of NMBAs ≤4 hours must be identified and recorded by site staff. If a NMBA is given as a bolus, no assessments of RASS, CPOT, or spontaneous breathing efforts can be performed until at least 2 hours after the last bolus. If a NMBA is given as a continuous infusion (<4 hours), no assessments of RASS, CPOT, or spontaneous breathing efforts can be performed until 4 hours after termination of continuous infusion.

5.5.2.1 Procedural sedation

Sedation for procedures within the ICU

The infusion rate of study drug may be increased pre-emptively in anticipation of increased requirement of sedation due to, or during, a planned minor procedure in the ICU (eg, changing dressings, washing or repositioning the patient, bronchoscopy, IV-line placement, radiological examination). This is considered a change in sedation level per SOC and should be recorded as any other changes in study drug administration.

Pre-emptive increase of the study drug and/or additional bolus sedation is permitted during minor ICU procedures, as specified below:

- For procedures not involving the airway;
  - Bolus doses of study drug/temporary increase of study drug dose are allowed.
    - For isoflurane, pump rate may temporarily be increased up to 50% above the sedation maintenance pump rate for short periods (eg, up to 30 minutes) during short surgical procedures.
- For airway-related procedures (ie, bronchoscopy and suctioning in the endotracheal tube); and
  - Bolus doses of propofol, 1 to 2 mg/kg, or continuous infusion up to 4 mg/kg/hour (66 mcg/kg/min), are allowed in either treatment group; and
  - Additional analgesia is permitted, such as fentanyl and alfentanil.

  Administration of these medications may be repeated, as needed, during the procedure.
- During daily SATs or during the EOT wake-up test, antipsychotics and/or medications (analgesics or α2-adrenergic agonists) intended to reduce autonomic stress are permitted at the lowest effective dose and only if the patient does not tolerate the procedure without such drugs. α2-adrenergic agonists must not be started earlier than 60 minutes before initiating the SAT or EOT wake-up test. If the patient needs re-sedation after a daily SAT, bolus doses of the assigned study drug may be given for rapid deepening of sedation.

Sedation or anesthesia procedures outside the ICU

In the case of surgical or diagnostic procedure (eg, radiological examination) outside the ICU, study drug should be replaced by other medications as indicated regardless of the RASS score, at the discretion of the clinical team. The time for leaving and returning to the ICU must be recorded in the eCRF.

Anesthesia and analgesia for these purposes shall be given according to SOC.

See Section 5.3.4 regarding re-initiation of study drug when the patient returns to the ICU.

5.5.3 Restricted Procedures

Soft physical restraints should be used only after closely weighing the risks and benefits of their use in the individual patients. During the study drug treatment period, the use of restraints should be assessed and documented in the eCRF.

5.5.4 Analgesic Treatment

Opioids and other analgesic drugs (eg, acetaminophen, ketorolac, ibuprofen) are permitted throughout the study to treat pain.[54] Study drug and rescue sedation should not be used to treat pain; rather, a pain medication should be used. All pain treatment should be used per SOC.

All study patients should receive adequate analgesia throughout the study at the discretion of the Investigator and treating clinical team. Continuous opioid infusions as per SOC are allowed throughout the study drug treatment period but should be adjusted as clinically appropriate primarily after CPOT assessments.

The majority of study patients are anticipated to be receiving SOC opioids in parallel with sedatives, as opioids are indicated to manage pain, which most mechanically ventilated patients experience. As in clinical practice, CPOT scores and other clinical parameters (eg, breathing effort, gut mobility) guide dosing. It is recommended to use the lowest possible opioid maintenance dose to reach analgesia and comfort goals and minimize opioid side effects. Non-opioid analgesia can be considered, when appropriate.

6 STUDY PROCEDURES

Study procedures will follow the Schedule of Procedures in Appendix A. See Section 7 (Study Assessments) and Section 8 (Safety Assessments) for additional information on each assessment.

6.1 Screening Period

6.1.1 Screening (Day -30 to Randomization)

The participating patients will be recruited at the study sites. Due to the nature of the study patient population, ie, necessitating consent by the study patient or LAR, sedated patients admitted to the ICUs will be pre-screened on available clinical data prior to obtaining informed consent. Assessments taken in SOC may be used even if they are taken before the informed consent procedure.

The study sites are advised to designate a person responsible for daily pre-screening. Potential candidates or their LARs will be contacted and invited to receive written and oral information about the study. Thereafter, formal screening will follow.

Investigators should keep an anonymized record (eg, a patient pre-screening log) of patients who entered the pre-study screening and were considered for enrollment, even if they were not subsequently enrolled. This information is necessary to verify that the patient population was selected without bias (in accordance with International Council for Harmonisation [ICH]-Good Clinical Practice [GCP]). The reasons for non-eligibility are to be defined in terms of 1 or more of the eligibility criteria.

A unique patient identification number will be assigned to each patient for whom informed consent has been obtained (refer to Section 3.6.1).

The Screening period may begin up to 30 days prior to initiation of study drug administration to allow for postsurgical patients to be assessed preoperatively. Initiation of study drug treatment should occur ideally as close to randomization as possible and no later than 6 hours after randomization.

6.1.1.1 Initial Screening (Day -30 to randomization)

To allow for patient consent, the Initial Screening can be performed up to 30 days prior to randomization.

The following will be performed at the Initial Screening:

- Informed consent;
- Inclusion/exclusion criteria;
- Demographic information;
- Medical/surgical history;
- Physical function and outcomes (Katz Index of Independence in Activity of Daily Living [Katz ADL] and Pfeffer functional activities questionnaire [FAQ]); and
    - Screening Katz ADL and Pfeffer FAQ data can be collected until 48 hours after initiation of study drug treatment as the time period of interest is not synonymous with when data needs to be captured.

- Cognitive function and outcomes (Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE]).
    - Screening IQCODE data can be collected until 48 hours after initiation of study drug treatment as the time period of interest is not synonymous with when data needs to be captured.

6.1.1.2 Complete Screening (-24 hours to randomization)

The Complete Screening shall be performed within 24 hours prior to randomization.

If the Initial Screening is performed more than 24 hours prior to randomization, the following assessments need to be re-assessed:

- Inclusion/exclusion criteria; and
- Medical/surgical history.

For all patients, the Complete Screening will include the following:

- Prior relevant medications, including the mean opioid dose assessment at 60 minutes prior to randomization (see Section 7.2.1);
- Weight and height;
- Physical examination;
- Clinical laboratory assessments;
    - Screening/Baseline clinical laboratory tests, other than those pertaining to trial eligibility, may be collected at any time during the Complete Screening or post-randomization period prior to initiation of study drug treatment.
- Pregnancy test (female patients of childbearing potential);
- Patient characteristics, including SAPS III (see Appendix J); and
- Anticipated remaining time on the ventilator (at time of randomization).

6.1.2 Randomization

Each eligible patient will be assigned a unique identification number. The Investigator or designee must contact the [redacted] Interactive Response Technology (CTIRT) to acquire the unique identification number for each patient. Patient numbers will consist of 6 digits. The first 3 digits will reflect the site number assigned, followed by a 3-digit patient number. The patient number will be used to identify the patient throughout the study.

If a patient is not eligible to receive treatment or if the patient discontinues from the study, the unique patient number cannot be reassigned to another patient.

The run-in training patients will be assigned a unique identification number but will not be randomized.

Randomization will be stratified by SAPS III (Total score 0 to <40, 40 to <60, and ≥60) and patient type (medical and surgical [including trauma]) assessed at Screening. Surgical patient will be defined as patients who meet either of the following criteria:

1. Have undergone surgery within the prior 2 weeks and for whom the current respiratory failure episode is related to that surgery or surgical disease process, or a complication thereof; or
2. Patients anticipated to undergo surgery within the next 2 days for a condition that is related to etiology of respiratory failure.

Treatment assignments for the individual patients will be determined through a computer generated randomization list and accessed using the CTIRT. Instructions for access and use of the system are provided in the study manual.

6.1.3 Baseline (Randomization to Initiation of Study Drug Treatment)

As soon as possible after randomization, and no later than 6 hours after randomization, the study equipment will be set-up and study drug treatment shall be initiated.

SOC sedative and opioid infusion doses should be reduced to half as soon as possible after randomization and prior to study drug initiation unless the patient is agitated or showing signs of ongoing pain.

As soon as the study drug treatment has been initiated, the SOC sedative should be stopped (ie, slow weaning will not be permitted) to limit the impact of residual SOC sedation. Note that Baseline procedures should be performed prior to the start of study drug administration.

The following will be performed:

- Reduction of SOC sedative and opioid infusion doses to half;
- Unblinded RASS and CPOT within 30 minutes prior to the initiation of study drug administration;
- Vital signs within 60 minutes prior to the start of study drug administration;
- Ventilator parameters;
- Blood gases;
- Organ function (sequential organ failure assessment [SOFA] on the date of randomization); and
- Concomitant relevant medications (see Section 7.2.1).

6.2 Treatment Period

From start of study drug and throughout the study drug treatment period, the following will be performed:

- Concomitant relevant medications (see Section 7.2.1);
- Study drug administration;
- Sedaconda ACD-S device deficiencies; and
- AEs.

Data related to study drug administration, including doses, dose changes, start and stop times, and occurrence of any interruptions in study drug administration, will be recorded. The dose of isoflurane (mL/hour) and propofol (mg/kg/hour or mcg/kg/min) should be recorded throughout study drug treatment and every time study drug dose is adjusted.

The patient's sedation level and opioid doses will be assessed frequently by the clinical staff who are unblinded to the study drug assignment. Unblinded RASS and CPOT assessments to guide titration will, however, not be documented in the study eCRF.

6.2.1 Every 2 (±0.5) Hours From Start of Study Drug

From start of study drug and throughout the study drug treatment period, the following will be performed every 2 hours:

- RASS (blinded assessments); and
- CPOT (blinded assessments).

6.2.2 Every 4 (±0.5) Hours For Isoflurane Patients Only

From start of study drug and throughout the study drug treatment period the following will be performed every 4 hours:

- Isoflurane end-tidal concentration measurement.

6.2.3 Every 8 (±2) Hours

From start of study drug and throughout the study drug treatment period, the following will be performed every 8 hours:

- Ventilator parameters;
- Vital signs; and
- Blood gases (if arterial line is available).

Note: These assessments will be performed more frequently when clinically indicated (as patients will often be observed continuously or more frequently than every 8 hours in clinical practice).

6.2.4 Daily

The following will be performed daily after the initiation of study drug:

- Non-blinded CAM-ICU-7 (together with non-blinded RASS) according to Section 7.2.3;

  Note: More frequent assessments will be performed when clinically indicated.
- Clinical laboratory assessments;
- Organ function (SOFA) (excluding the date of randomization, which is captured in the Baseline procedures; see Section 6.1.3); and
- Restraints assessment.

6.2.5 Early Study Drug Discontinuation

If study drug is discontinued for any of the reasons listed in Section 4.3, the following assessments will be performed at the time of study drug discontinuation:

- The date, time, and reason(s) for early discontinuation of study drug;
- Physical examination (unless already performed this calendar date and not required for patients transitioned to comfort care);
- Clinical laboratory assessments (unless already performed this calendar date prior to study drug discontinuation. Not required for patients transitioned to comfort care);
- Organ function (SOFA); and
- Restraints assessment.

If patients are discontinued early from study drug, patients will transition to medical care per SOC at the discretion of the treating physician.

Unless the patient or LAR withdraws consent, the patient should continue in the study for safety assessments and follow-up even if the study drug is discontinued. All visits and assessments required for the rest of the study will be conducted and recorded in the eCRF, if possible. Wake-up test and CAM-ICU-7 at EOT per Section 6.2.6 should not be performed.

6.2.6 End of Treatment

The following will be performed at EOT due to end of study treatment or extubation:

- Wake-up test;
  - Blinded RASS assessments until 4 hours after EOT.
- Blinded CAM-ICU-7 (not required for patients reaching EOT due to treatment failure, patients transitioned to comfort care, or patients continued onto benzodiazepines or propofol sedation due to clinical need before 60 minutes after EOT); and
  - Assessment at 60 minutes (±10 minutes) after EOT.
- Physical examination.

Patients will thereafter transition to medical care per SOC at the discretion of the treating physician.

6.3 Follow-Up Period

6.3.1 Post-Treatment Monitoring

The following will be performed once until 24 hours after EOT:

- Physical examination;
- Vital signs;

- Clinical laboratory assessments;
  - To be performed if patient is still in the ICU at 18 hours after EOT. Analyses performed with an 18- to 48-hour window after EOT per SOC can be used.
- Time of extubation;
  - For patients who are extubated on study drug only.
- Concomitant relevant medications (see Section 7.2.1); and
- AEs.

6.3.2 Follow-Up Contact

6.3.2.1 Until Day 7 after EOT (±2 days)

The following will be performed from EOT until Day 7 after EOT:

- Concomitant relevant medications (see Section 7.2.1); and
- AEs.

The following will be performed daily until Day 7 after EOT or until discharge, whichever comes first:

- Organ function (SOFA) until ICU discharge; and
- Delirium and coma assessment with RASS and CAM-ICU-7 until hospital discharge.

6.3.2.2 Study Day 30 (+5 days) after randomization

The following will be performed at Study Day 30 or at ICU discharge, whichever comes first:

- Major ICU interventions (see Section 7.2.13); and
- Concomitant relevant medications (see Section 7.2.1).

The following will be performed through telephone call if not possible to retrieve information through medical records at Study Day 30 (regardless of ICU discharge status):

- Level of care (can be collected retrospectively for the whole study period);
- Duration of mechanical ventilation;
- Late onset drug-induced liver injury;
- Mortality; and
- Follow-up of any unresolved AEs.

Evidence of late onset hepatitis or drug-induced liver injury (DILI) attributable to study drug treatment, as assessed via medical records, laboratory assessments, or diagnosis review should be performed at Study Day 30. Any findings should be recorded as AEs.

6.3.2.3 3 months (±4 weeks) – telephone call

The following will be performed through telephone call at 3 months:

- LTO assessments; and
  - A detailed description of the LTO assessments performed at the 3-month follow-up visit in a consecutive subset of patients are described in Section 7.3.
- Mortality.

6.3.2.4 6 months (±4 weeks) – telephone call

The following will be performed through telephone call at 6 months in a consecutive subset of patients:

- LTO assessments; and
  - A detailed description of the LTO assessments performed at the 6-month follow-up visit are described in Section 7.3.
- Mortality.

6.4 Early Withdrawal From Study

For patients who are withdrawn from the study prior to completion, all applicable study procedures will be performed at an early withdrawal visit. Any assessments done within 2 hours prior to the withdrawal can be used as the early withdrawal assessment.

If a patient withdraws consent, the patient will be encouraged to complete the early withdrawal visit, if possible.

Patients who have discontinued their participation in the study cannot re-enter into the study. Withdrawn patients will not be replaced. Patients will transition to medical care per SOC at the discretion of the treating physician.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's records.

6.4.1 Study Withdrawal Prior to EOT

If patient is withdrawn and study drug is discontinued prior to EOT, see Section 6.2.5 for related procedures at the time of study drug discontinuation.

6.4.2 Early Withdrawal After EOT

When study withdrawal occurs after EOT and before the Study Day 30 follow-up, the following will be performed, if accepted despite consent withdrawal:

- The date, time, and reason(s) for study withdrawal;
- Physical examination (until 24 hours after EOT);
- Vital signs (until 24 hours after EOT);
- Level of care (until Study Day 30);

- Time of extubation and duration of mechanical ventilation (until Study Day 30);
- AE collection (until Day 7 after EOT, or unresolved AE until Study Day 30); and
- LTO assessments at 3 and 6 months.
    - ICU Memory Tool will be assessed at 3 months follow-up only.

7 STUDY ASSESSMENTS

7.1 Blinded Efficacy Assessments

Blinded assessments of RASS, CPOT, and CAM-ICU-7 will be performed, as indicated in Appendix A, by designated assessors.

7.1.1 Richmond Agitation Sedation Scale

The RASS[a,b] shown in Figure 3 will be used to assess agitation and sedation throughout the study.

Figure 3. Richmond Agitation Sedation Scale

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to *voice* **(≥10 seconds)**	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to *voice* **(<10 seconds)**	
-3	Moderate sedation	Movement or eye opening to *voice* **(but no eye contact)**	
-4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation	Physical Stimulation
-5	Unarousable	No response to *voice or physical* stimulation	

Procedure for RASS Assessment

1. Observe patient
   a. Patient is alert, restless, or agitated. **(score 0 to +4)**
2. If not alert, state patient's name and *say* to open eyes and look at speaker.
   b. Patient awakens with sustained eye opening and eye contact. **(score –1)**
   c. Patient awakens with eye opening and eye contact, but not sustained. **(score –2)**
   d. Patient has any movement in response to voice but no eye contact. **(score –3)**
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   e. Patient has any movement to physical stimulation. **(score –4)**
   f. Patient has no response to any stimulation. **(score –5)**

Clarification regarding procedure for RASS Assessment item #3: When no response to verbal stimulation, physically stimulate the patient by shaking the shoulder. Rubbing the sternum will NOT be used in the study.
RASS = Richmond Agitation Sedation Scale.

In training and written bedside instructions, shaking the patient's shoulder (not rubbing the sternum) will be stated as the method to discriminate between RASS -4 to -5.

For the primary endpoint, blinded efficacy assessment of RASS will begin 2 hours after initiation of study drug administration and every 2 hours thereafter until EOT per Appendix A. In accordance with the instructions defined for the instrument, the assessor should observe the patient

Sources:
[a.] Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* 2002;166(10):1338-1344.
[b.] Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: the reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA*. 2003;289(22):2983-2991.

for at least 30 to 60 seconds[55] and score the most distressed or painful behavior (ie, the lightest RASS) shown during the observation period.

7.1.2 Critical Care Pain Observation Tool

Pain will be assessed using the CPOT every 2 hours until EOT and recorded together with the blinded RASS assessment by the blinded assessor. The CPOT is included in Appendix E.

For the purpose of the study, where the baseline opioid infusion is primarily aimed at alleviating pain at rest, the blinded CPOT assessments will be performed when the patient is at rest. Blinded CPOT assessments will not be performed during turning or active stimulation, nor to evaluate the effect of bolus doses of analgesics.

7.1.3 Periods When Blinded RASS and CPOT Assessments Should Not Be Performed

Blinded RASS and CPOT assessments should not be performed during or shortly after periods of intentional deepening of sedation for procedures, nor during SAT. The earliest blinded RASS and CPOT assessments allowed after intentional changes in sedation level are as follows:

- 1 hour after intentional deepening of sedation for an in-ICU procedure (eg, following bronchoscopy, prone-positioning, or wound dressing);
- 1 hour after resuming study sedation after a procedure outside the ICU (eg, CT scan, endoscopy, surgery, etc);
- 1 hour after an SAT;
- 2 hours after a bolus of NMBA; or
- 4 hours after the end of an infusion of NMBA.

If a clinical event meets more than one scenario with different exclusion periods, then the longer time period applies. For example, a patient who undergoes a procedure outside the ICU that requires NMBA infusion would have no blinded assessments done for 4 hours after the end of the NMBA.

After the excluded period, blinded assessments should resume per the original schedule (see Section 7.1.5).

7.1.4 Communication of Blinded RASS and CPOT to Bedside Staff

The blinded assessor will assess and document the RASS and CPOT scores without any interference by the clinical team. After the documentation of RASS and CPOT, the assessor will certify in writing that he/she was not aware of the study drug treatment given. Once the blinded assessor has left the room, bedside staff should access the documented RASS and CPOT scores and adjust the study drug and analgesia, if appropriate.

The date, time, and result of each blinded RASS and CPOT assessment performed shall be recorded in the eCRF.

7.1.5 Handling of Interrupted and/or Missing RASS Assessments

The time frame (every 2 [±0.5] hours) for blinded RASS and CPOT gives some flexibility in the planning of the blinded assessments in relation to procedures or unexpected events affecting the

ability to perform the blinded RASS and CPOT assessments. If it is not possible to perform a blinded RASS assessment due to a procedure during the subsequent periods listed in the above Section 7.1.3, then that assessment will be skipped and the next assessment (ie, in another 2 [±0.5] hours) will be performed per the original schedule.

Missed blinded RASS assessments due to procedures per SOC are not considered protocol deviations and are not counted as failure time. All missed RASS assessments will be documented, with reason for not being done, in the eCRF.

7.1.6 Wake-Up Test

Prior to EOT, a safety screen[51] (see Appendix D) will be conducted if RASS <0 to evaluate if it is safe to pause or discontinue sedation and allow the patient to wake up. Time to wake-up shall be measured for all patients after EOT unless prohibited by patient safety considerations in the judgment of the clinical team and Investigator.

Immediately prior to stopping study drug (within 15 minutes prior to EOT), a blinded RASS assessment should be performed and documented.

Patients whose blinded RASS is 0 or higher will not undergo wake-up testing.

During the EOT wake-up test, antipsychotics and/or medications (analgesics or α2-adrenergic agonists) intended to reduce autonomic stress during wake-up are permitted at the lowest effective dose and only if the patient does not tolerate the wake-up test without such drugs. Opioid analgesics infusions should be paused, or reduced to a minimum level ensuring comfort (CPOT ≤2). Use of such medications during the wake-up test should be recorded in the eCRF. The use of study drug or benzodiazepines is not allowed during the EOT wake-up test.

The wake-up test starts when study drug is stopped and Sedaconda ACD removed (in isoflurane arm). Study drug should not be resumed after this timepoint, and SOC sedatives should instead be initiated if needed to ensure patients are not restless or agitated for any length of time.

Sedation depth will be assessed by a blinded assessor until RASS 0 or lighter is achieved, at a minimum frequency of:

- Every 15 (±5) minutes for hour 1;
- Every 30 (±10) minutes for hours 2 to 4; and
- Earlier, as needed, for safety (eg, patient potential harm to self/others, pulling at devices, etc).

The blinded assessor may remain at bedside after a prior RASS assessment, if it is deemed likely by the blinded assessor that RASS 0 may be achieved within a short time, and if it is agreed with bedside staff that the blinding will not be compromised by doing so.

The wake-up test ends at the first occurrence of the following:

- RASS 0 or lighter is confirmed by blinded assessment;
- 4 hours after EOT;
- Time of re-sedation before RASS ≥0 due to respiratory distress, cardiovascular events, or other clinical indication; or

  Note: Details of re-sedation with SOC sedative should be recorded as concomitant medication.

- New-onset neurological deficit or detection of intracranial event.

  Note: The diagnosis of neurological deficit or intracranial event should be recorded as an adverse event. The time for leaving ICU for diagnostic testing of neurological deficit or intracranial event should be recorded as a procedure.

7.1.7 CAM-ICU-7 at 60 Minutes After EOT

Cognitive recovery will be assessed by the 7-point scale of the CAM-ICU-7 at 60 (±10) minutes after EOT by a blinded assessor, on all patients except those already re-sedated with benzodiazepines or SOC propofol. If a planned assessment cannot be performed due to extubation procedure, the assessment should be performed as soon as possible after extubation.

RASS is an integral part of the CAM-ICU-7 assessment and will be assessed first. If RASS is ≥-3, CAM-ICU-7 will be performed. If RASS is -4 or -5, CAM-ICU-7 will not be performed.

The CAM-ICU-7 is provided in Appendix F.

7.2 Other Assessments

In clinical practice, some assessments may be documented frequently. For purposes of data entry, it is recommended to utilize the first available data point within the given time frame. However, apparently erroneous data should not be used.

7.2.1 Prior and Concomitant Medications

From ICU admission, but not before 24 hours prior to initiation of study drug, until 24 hours after EOT all relevant prior and concomitant medications taken by the patient are to be recorded.

Relevant medications include the following:

- Opioids and other analgesics;
- Sedative agents (including prohibited and restricted medications);
- Antipsychotics/neuroleptics;
- NMBAs;
- Vasopressors and inotropes;

  Note: Data on vasopressors and inotropes will be recorded, as highest continuous dose for specified medications, per pre-defined time intervals. Bolus doses of vasopressors or inotropes will not be accounted for.

- Any medications used to reverse the effects of the above medications; and
- Any medications associated with an AE.

Except for vasopressors and inotropes, data to be recorded are the dose, unit, frequency, route, and start and end time. For concomitant sedative and antipsychotics, the indication for administration (procedural sedation, rescue sedation, SAT, EOT, other reason) will also be recorded during the treatment period only.

Specified vasopressors and inotropes (highest continuous dose) include the following:

- Angiotensin-II (ng/kg/min);
- Dobutamine (mcg/kg/min);
- Dopamine (mcg/kg/min);
- Epinephrine (mcg/kg/min);
- Norepinephrine (mcg/kg/min);
- Milrinone (mcg/kg/min);
- Phenylephrine (mcg/kg/min); and
- Vasopressin (units/min).

Pre-defined time intervals for highest continuous dose of vasopressors and inotropes include the following:

- Pre-initiation: during the 24 hours in ICU prior to initiation of study drug (only administration in ICU will be considered);
- Day 1: during the first 24 hours of study drug administration, or until EOT, if EOT occurs within the first 24 hours;
- Day 2 until EOT: during hours 24 to 48 (±6 hours) or until EOT, if EOT occurs during hours 24 to 48 (±6 hours); and
- From EOT until 24 hours after EOT.

Receipt (Yes/No) per calendar day of selected medications will be collected in a separate form, from 24 hours after EOT until Study Day 30 or ICU discharge, whichever comes first:

- Opioids and other analgesics;
- Sedative agents; and
- Antipsychotics/neuroleptics.

Medications associated with an AE:

Any medications associated with an AE should be recorded at the same level of detail as for relevant medications before end of the 24 hour post-treatment monitoring period.

Medications associated with an AE are those that meet either of the following:

- The medication is at least possibly related to the AE; or
- The medication is given as treatment for the AE.

Note that vasopressors and inotropes associated with an AE will be recorded both as highest continuous dose and at the more detailed level required for AEs in a standard concomitant medication eCRF.

7.2.2 Non-Blinded RASS and CPOT

Sedation and analgesia will be adjusted based on non-blinded RASS and CPOT by bedside staff between formal blinded assessments; however, these non-blinded clinical assessments will not be documented in the eCRF.

7.2.3 Non-Blinded CAM-ICU-7

Delirium and coma free days from the start of study drug treatment and up to 7 days after EOT or up to hospital discharge, whatever comes first, will be assessed by daily (at a minimum) CAM-ICU-7 and RASS as specified in Appendix A. However, more frequent assessments will be performed when clinically indicated. RASS will be assessed first. If RASS is ≥-3, CAM-ICU-7 will be assessed. If RASS is -4 or -5, CAM-ICU-7 will not be assessed.

If a patient's RASS is -3 or lighter and negative for delirium per CAM-ICU-7, then the patient will be considered delirium and coma free for that assessment timepoint.

The CAM-ICU-7 is provided in Appendix F.

7.2.4 Spontaneous Breathing

Spontaneous breathing effort is present if any of the following is met:

- Airway occlusion pressure (P0.1) >0 cmH_2O (if available);
- Pressure support (PS) or other spontaneous ventilator mode is being used; or
- Observed respiratory rate exceeds set respiratory rate.

7.2.5 Restraints

During the study drug treatment period, the use of restraints should be assessed daily. Soft physical restraints should be used only after closely weighing the risks and benefits of their use in the individual patients.

7.2.6 Organ Failure, SOFA

Organ failures will be assessed using SOFA.[56] The individual scores will be recorded and total score for all organs will be calculated; see Appendix H for calculator to be used.

The function of several organs requires laboratory assessments. The routine laboratory values can be used, if available.

7.2.7 Clinical Laboratory Evaluations

Clinical laboratory assessments should be performed at Screening and daily after the start of study drug administration. Assessments should also be performed on the calendar day after EOT, if the patient is still in the ICU. See Appendix A.

Local hospital laboratories will be used to assess the safety laboratory parameters (including clinical chemistry, lipid profile, hematology, and coagulation). A list of laboratory analyses is presented in Appendix B.

Any significant abnormalities, as assessed by the Investigator, will be followed according to clinical practice. Additional tests and other evaluations required to establish the significance or

etiology of an abnormal result or to monitor the course of an AE will be obtained when clinically indicated.

7.2.8 Physical Examinations

A physical examination will be performed at Screening, at the end of the study drug treatment period, and 24 hours after EOT and should be performed, as appropriate, for the patient's condition.

During the physical examination, the Investigator will also consider results available from examinations such as ultrasound, radiology examinations, or laboratory tests and document his/her integrated assessment.

Prespecified examinations will be evaluated as "not clinically significant" or "clinically significant" (abnormal). Other examinations and findings can also be recorded. Findings at Baseline must be reported in the medical history eCRF and findings at EOT should be reported as an AE.

Pre-specified examinations include the following:

- Neurologic examination (upper limb motor deficit, lower limb motor deficit, focal deficit);
- Cardiac examination (heart rate irregular, arrhythmia, cardiac murmur);
- Pulmonary examination (rhonchi, decreased breath sounds, wheezing, stridor);
- Abdominal examination (abdominal tenderness, central obesity, scaphoid abdomen, bowel sounds decreased, bowel sounds increased); and
- Extremity examination (peripheral coldness, pulse absent, oedema peripheral).

7.2.9 Pregnancy Test

Female patients of childbearing potential must have a negative (serum or urine) pregnancy test prior to randomization. A pregnancy test obtained previously as part of usual care during this hospital episode that is documented in the patient's medical record will suffice. Female patients not of childbearing potential are defined as female patients who have been postmenopausal for at least 1 year, have been surgically sterilized, or are ≥60 years of age. If possible, a urine dipstick will be used preferentially. If the urine test is positive, a serum chorionic gonadotropin pregnancy test must be performed to rule out pregnancy.

7.2.10 Vital Signs

Vital signs are to be collected at Baseline and every 8 (±2) hours until 24 hours after EOT. However, vital signs will be performed more frequently when clinically indicated. Vital signs will include the following:

- Systolic, diastolic, and mean arterial blood pressure;
- Heart rate;
- Peripheral capillary oxygen saturation (SpO_2), measured by pulse oximetry;
    - For patients not receiving ventilator treatment (for patients on ventilator support, SpO_2 will be captured as part of the ventilator parameters).

- Respiratory rate; and

  Note: Respiratory rate will not be recorded as part of vital sign assessments while patient is on ventilator support, as it will be captured in the ventilator parameter records as observed breathing rate.

- Body temperature.

7.2.11 Ventilator Parameters

Ventilator parameters will be captured at Baseline and, at a minimum, every 8 hours until EOT. Ventilator parameter assessments will be performed more frequently when clinically indicated (as patients will often be observed continuously or more frequently than every 8 hours in clinical practice).

The following parameters will be recorded, if available, per ventilator type, mode, and settings:

- End-tidal concentration of isoflurane for patients randomized to isoflurane (% volume);
- Ventilator mode, (select one of the below categories):
  - Volume assist/control or volume control (VC);
  - VC with autoflow;
  - Pressure assist/control (PC);
  - Pressure-regulated volume control (PRVC) or volume-targeted pressure control;
  - Pressure support ventilation (PSV);
  - Volume Support;
  - Volume synchronized intermittent mandatory ventilation (SIMV);
  - Pressure SIMV;
  - PRVC SIMV;
  - Airway pressure release ventilation;
  - Bivent or Bilevel;
  - Neurally adjusted ventilatory assist;
  - Adaptive support ventilation;
  - Mandatory minute ventilation; and

    Note: Changes in minute ventilation will be displayed continuously on the ventilator, available for bedside staff and for assessment by the clinical team. The documented minute ventilation will be based on the actual minute ventilation, including spontaneous breathing efforts.

  - Other (includes dual and alternative modes).
- Set tidal volume (mL) (for volume-targeted modes only);
- Observed tidal volume (mL);

- Set rate (breaths/minute) (for modes with preset rates only);
- Observed rate (breaths/minute);
- Observed minute volume (L/minute);
- Set positive end-expiratory pressure (PEEP) (cmH_2O);
- PS above PEEP (cmH2O) (for PSV mode only);
- PC above PEEP (cmH_2O) (for PC mode only);
- Peak inspiratory pressure (cmH_2O);
- Plateau pressure, with a 0.5 second end-inspiratory cause (cmH_2O) (if available);
- Mean airway pressure (cmH_2O);
- Fraction of inspired oxygen (%);
- SpO_2 (%);
- $EtCO_2$;
- Ventilator trigger (select 1 of the below):
  - Pressure (cmH_2O); or
  - Flow (L/minute).
- P0.1 (if available);
- Arterial blood gas (ABG) since last evaluation (if available);
- PCO_2 (mmHg); and
- Partial pressure of oxygen (PaO_2) (mmHg).

7.2.12 Blood Gas Analyses

Blood gas analyses will be performed at Baseline and every 8 hours until EOT, if arterial line is available. Blood gas analyses will be performed more frequently when clinically indicated.

If arterial line is available, the following parameters will be obtained from arterial blood samples as specified in Appendix A:

- Arterial pH;
- Base excess in mmol/L (mEq/L);
- PCO_2 (mmHg); and
- PaO_2 (mmHg).

7.2.13 Major ICU Interventions

Major ICU interventions will be assessed through Study Day 30 or until ICU discharge, whichever comes first. New renal replacement therapy or extracorporeal support occurring prior to Study Day 7 from the start of study drug should also be reported as AEs. Extubation, tracheostomy, non-invasive ventilation, or re-admission to the ICU should, however, not be reported as AEs.

The following specific events are major ICU interventions:

- Renal replacement therapy;
- Extracorporeal life support;
- Extubation;
- Tracheostomy; and
- Non-invasive ventilation.

7.2.14 Level of Care

The level of care will be assessed as specified in Appendix A and will include the following:

- Still in ICU;
- Patients deceased in the ICU;
- Intermediary care unit;
- General ward;
- Another ICU (within or outside the hospital);
- Another hospital (unknown ward);
- Rehabilitation unit;
- Nursing home;
- Hospice; or
- Home.

7.2.15 Late Onset Drug-Induced Hepatitis

At Study Day 30, sites should assess for evidence of late onset hepatitis or DILI attributable to study drug treatment. This assessment can be done via medical records, laboratory assessments, or diagnosis review. Any findings should be recorded as AEs.

7.3 Long-Term Outcomes Assessment

Cognitive, Mental Health, Functioning, and Quality of Life Assessments will be conducted at 3 and 6 months post-randomization as specified in Section 3.11 and Appendix A. Baseline assessments will be conducted by the IQCODE, Katz ADL, and Pfeffer FAQ as specified in Appendix A.

7.3.1 Cognitive Long-Term Outcomes

Cognitive LTO will be assessed by:

- Telephone Interview for Cognitive Status (TICS).

  The TICS is a brief, standardized test developed for use in situations where in-person cognitive screening is impractical or inefficient (eg, large-scale population screening, epidemiological surveys, with patients who are unable to appear in person for clinical follow-up).

- Hayling Sentence Completion Test.

  The Hayling Sentence Completion Test is a measure of executive function consisting of two sets of 15 sentences; the examiner reads the questions aloud and patient completes the sentences.

- Wechsler adult intelligence scale (WAIS) IV-Digit Span.

  The WAIS IV-Digit Span involves the recitation of a string of numbers as a measure of attention.

- Controlled Oral Word Association.

  The Controlled Oral Word Association involves generating a list of as many words that start with “F,” “A,” and “S” in 60 seconds to measure verbal fluency.

- Wechsler memory scale (WMS)-IV – Immediate Memory (Adult/Older Adult).

  The WMS-IV – Immediate Memory (Adult/Older Adult) is a test in which a patient immediately recalls a short story. The WMS-IV (Adult) is used for adults under the age of 65 and the WMS-IV (Older Adult) is used for adults 65 and older. The Logical Memory I subtest is used to test Immediate Memory on the WMS-IV (both Adult and Older Adult).

- WMS-IV – Delayed Memory (Adult/Older Adult).

  The WMS-IV – Delayed Memory (Adult/Older Adult) is a test in which a patient recalls a short story 20 minutes later. The WMS-IV (Adult) is used for adults under the age of 65 and the WMS-IV (Older Adult) is used for adults 65 and older. The Logical Memory II subtest is used to test Delayed Memory on the WMS-IV (both Adult and Older Adult).

- Patient-Reported Outcomes Measurement Information System (PROMIS) Cognitive Function questionnaire.

  The PROMIS Cognitive Function questionnaire is a set of person-centered measures that evaluates and monitors physical, mental, and social health.

- ICU Memory Tool.

  The ICU Memory Tool is a brief tool that evaluates memories during critical illness/intensive care.

7.3.2 Physical Long-Term Outcomes

Physical LTO will be assessed by:

- Katz ADL.

  The Katz ADL is a brief measure of basic activities of daily living.

- Pfeffer FAQ.

  The Pfeffer FAQ is a brief measure of "higher order" abilities (eg, driving, managing money, cooking, understanding the news, etc).

7.3.3 Psychological Long-Term Outcomes

Psychological LTO will be assessed by:

- Impact of event scale (IES-R).

  The IES-R is a brief screening tool that measures post-traumatic stress disorder (PTSD) and PTSD symptoms.

- PROMIS Depression and Anxiety Questionnaires.

  The PROMIS Depression and Anxiety questionnaires are a set of person-centered measures that evaluates and monitors depression and anxiety.

7.3.4 Long-Term Quality of Life Outcomes

Quality of life will be assessed by:

- WHO Disability Assessment Schedule 2.0 (WHODAS).

  The WHODAS is a generic assessment instrument for health and disability.

- Brief Pain Inventory (BPI).

  The BPI is an assessment tool used in pain management.

8 SAFETY ASSESSMENTS

8.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product. All AEs as described below, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

In this study of critically ill patients, AEs should be defined in relation to the patient's condition. Fluctuations in clinical state or typical medical occurrences expected in this setting need not be recorded as AEs. Some examples of relevant AEs are provided in Appendix G. Note that these are examples and not an exhaustive list, so the Investigator should exercise judgment in the collection of AEs in the study.

AEs, which include clinical laboratory test variables, will be monitored and documented from the initiation of study drug administration until the 7-day post EOT follow-up. AEs occurring during the clinical study will be followed until returned to normal, stabilized, or are no longer clinically significant. If remaining clinically significant at the Day 7 follow-up, the patient will be referred to an appropriate clinical consultant. Such referrals will be followed-up at Study Day 30 and outcomes documented.

Instructions should be provided to the Investigator and his/her designees to report any AE that patients experience, whether or not they think the event is related to study drug. From the start of study drug administration, Investigators should continuously monitor for AEs until the end of the 7-day after EOT follow-up and record the AEs in the eCRF.

Wherever possible, AEs should be reported as specific diseases or syndromes rather than individual associated signs and symptoms. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator or designee, it should be recorded as a separate AE in the eCRF. Additionally, the condition (eg appendicitis, gastrointestinal bleeding, or hemolytic anemia) that led to a medical or surgical procedure (such as surgery, endoscopy, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at the start of study drug administration should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at Baseline changes in severity, frequency, or seriousness later during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination findings that are detected during the study or worsen significantly from Baseline during the course of study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Abnormal test results that are determined to be an error (eg, followed up with a normal value shortly after a suspected spurious value) should not be reported as an AE. Laboratory

abnormalities or abnormal clinical assessments should be reported as an AE if any of the following are applicable:

- If action taken with the study drug is required as a result of the abnormality;
- The abnormality deviates from the anticipated critical care course; or
- Based on the clinical judgment of the Investigator.

All AEs from patients treated with isoflurane via the Sedaconda ACD-S will be reported together with the current isoflurane pump rate, all recorded isoflurane end-tidal concentrations, and total exposure time. The use of volatile anesthetics in the 24 hours prior to inclusion is also captured in the eCRF.

AEs and SAEs that result from the Sedaconda ACD-S (defined in Section 8.7) will also be considered device deficiencies. Device deficiencies should be reported during the time Sedaconda ACD-S is used and recorded on the appropriate eCRF.

8.1.1 Adverse (Drug) Reaction

All harmful and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction (ADR). “Responses” to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected ADR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.1.3 Assessment of AEs by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug and device using the categories described below.

Assessment of severity

Mild – An event that is easily tolerated and generally not expected to interfere with critical care course.

Moderate – An event that is sufficiently discomforting to interfere with critical care course.

Severe – An event that is incapacitating, leads to major intervention, significantly alters current critical care course.

Causality assessment

The relationship of an AE to the administration of the study drug and the use of device is to be assessed according to the following definitions:

Not considered causally related – All AEs determined to be not related or unlikely related according to Table 4.

Considered causally related – All AEs determined to be at least possibly related according to Table 4.

The following factors should be considered when determining the causality of an AE:

- Underlying, concomitant, intercurrent diseases;
  - The natural history and course of the disease being treated and any other comorbid disease the patient may have, as well as prehospital and pre-ICU exposures.
- Concomitant drug(s) and therapies;
  - The other drug(s) and therapies the patient is receiving should be examined to determine whether any of them might be recognized to cause the event in question.
- The temporal sequence from study drug administration/use of device to the event;
  - The event should occur after the study drug is given/while using the device. The length of time from study drug exposure/use of device to event should be evaluated in the clinical context of the event.
- The pharmacology and pharmacokinetics of the study drug; and
  - The known pharmacologic properties (absorption, distribution, metabolism, excretion and known ADRs) of the study drug should be considered.
- Known response pattern for this class of study drug.
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

Table 4. AE Causality Assessment Criteria

Causality Assessment	Causality Criteria
Not considered causal	
Not related	• The AE follows a temporal sequence different from study drug administration; and • The AE is clearly produced by the patient´s clinical condition or by other modes of therapy administered to the patient.
Unlikely to be related	• The temporal sequence between the AE and the study drug administration is such that the study drug is not likely to be associated with the observed event; and • The AE could easily and more likely have been produced by the patient´s clinical condition or by other modes of therapy administered to the patient.
Considered causal	
Possibly related	• The AE follows a reasonable temporal sequence from study drug administration; and • The AE could have been, but is equally or less likely produced by the patient´s state or by other modes of therapy administered to the patient.
Probably related	• The AE follows a reasonable temporal sequence from study drug administration; • The AE abates upon discontinuation of the study drug (de-challenge); • The AE is likely a reaction to an agent or chemical group, or predicted by known pharmacology; and • The AE cannot be reasonably explained by the known characteristics of the patient´s clinical state or by other modes of therapy administered to the patient.
Definitely related	• The AE follows a reasonable temporal sequence from study drug administration; • The AE is a known reaction to agent or chemical group, or predicted by known pharmacology; • The AE cannot be explained by patient´s clinical state or other factors; • The AE abates upon discontinuation of the study drug (de-challenge); and • The AE is confirmed by reappearance of the reaction on repeat exposure (re-challenge).
AE = adverse event.	

AEs that are categorized as being at least possibly related to the study treatment will be considered to have a reasonable causal relationship to the investigational intervention.

8.1.4 AEs of Special Interest

The Investigator will monitor each patient for clinical and laboratory evidence for pre-defined AESIs throughout the patient's participation in this study. These AESIs are specific AEs, potentially associated with the clinical use of one or both study drugs. Most AESIs are however not per se causally related with the study drugs and causality assessment must be done for AESIs as with all AEs.

The Investigator will assess and record any additional information on the AESI in detail on an AE form, which must be submitted within 24 hours of awareness of the event.

The definitions for each AESI grade are described in Appendix G.

For this study, AESIs include the following:

- MH[c] suspected by the Investigator in a patient recently exposed to volatile anesthetic or succinylcholine. No consensus diagnostic criteria exist for MH, but manifestations may include muscle rigidity; unexplained hypercapnia resistant to increasing minute ventilation; elevated creatine kinase or urine myoglobin suggesting rhabdomyolysis; acute hyperkalemia >6 mmol/L potentially resulting in electrocardiogram changes of peaked T-waves, increased ventricular ectopy, ventricular tachycardia, or ventricular fibrillation; and hyperthermia;
- PRIS suspected by the Investigator in a patient recently exposed to propofol. PRIS is defined as the development of metabolic acidosis and cardiac dysfunction along with at least one of rhabdomyolysis, hypertriglyceridemia, or renal failure after the initiation of propofol therapy;[57]
- Hypoxemia;
- Hypercapnia;
- Hypotension;
- Liver injury, defined as:
  - Alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN);
  - Aspartate aminotransferase (AST) ≥3 × ULN;
  - Total bilirubin >2 × ULN;
  - Alkaline phosphatase >2 × ULN;
  - Hy's Law criteria (ALT or AST ≥3 × ULN and total bilirubin >2 × ULN);
- Accidental self-extubation during active study drug administration;
- Hyperkalemia; and
- Rhabdomyolysis independent of MH.

During the course of the study, additional AESIs may be identified by the Sponsor.

c. Will be collected for 24 hours post EOT.

A severe AESI or SAE deemed as possibly, probably, or definitively related to the study drug should lead to discontinuation of study drug.

8.2 SAEs

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations;

  For the purpose of this study, all patients are hospitalized at the start of the study and hospitalization is in itself does therefore not define an SAE. However, if prolongation of hospitalization is necessary, the reason for this prolongation may contribute to the categorization of an SAE.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Requires medical or surgical intervention to preclude permanent impairment or prevent permanent damage to a body structure; and
- An important medical event. Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient's health and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.3 SAE Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from initiation of study drug administration until 7 days after the completion of study drug administration must be reported to [redacted] Clinical Safety within 24 hours of the knowledge of the occurrence. After the 7-day post EOT reporting window, any SAE that the Investigator considers related to study drug must be reported to the [redacted] Clinical Safety or the Sponsor/designee.

To report the SAE, the Investigator or designee will complete the SAE form electronically in the study eCRF. When the form is completed, [redacted] Safety personnel will be notified electronically by the electronic data capture system and will retrieve the form. If the event meets serious criteria and it is not possible to access the eCRF, send an email to [redacted] Safety at [redacted] or call the [redacted] SAE reporting line (telephone number listed below), and fax/email the completed paper SAE form to [redacted] (contact information listed in Section 8.6) within 24 hours of awareness. When the eCRF becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the eCRF for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to [redacted] Clinical Safety via fax or email. If it is not possible to access the eCRF, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

Due to the nature of the patient population and testing prior to enrollment, it is not anticipated that pregnancy will be detected during the 48-hour study drug treatment period in the ICU and at the 7-day follow-up after EOT. However, if pregnancy is detected during this period, applicable procedures will be followed to report the outcome of the pregnancy.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA, and in any case no later than 7 calendar days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 calendar days.

All other SUSARs will be reported to the FDA as soon as possible but within a maximum of 15 calendar days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in US legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The Sponsor/designee will also inform all reviewing Institutional Review Boards (IRBs) and participating Investigators per local regulations.

8.6 Special Situation Reporting Requirements Related to Study Drug

Occurrences of events of overdose and medication error must be reported to the Sponsor or designee. Any AEs/SAEs associated with either an overdose or medication error should be reported, as appropriate.

- Overdose: Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied.
- Medication error: A medication error is defined as an error made in prescribing, dispensing, administration, and/or use of study drug. The administration and/or use of expired study drug should be considered as a reportable medication error.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to [redacted] Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation Reports

should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available. FDA will be informed of any unexpected, serious, or life-threatening AEs.

Safety Contact Information: [redacted] Clinical Safety
[redacted] SAE reporting line – US:
[redacted]

8.7 Sedaconda ACD-S Deficiencies Reporting

The Sedaconda ACD-S will be used according to its instructions for use and as also outlined within the Investigator's Brochure and will be recorded as specified in Appendix A.

A device deficiency is defined as any inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors, or inadequacy in information supplied by the manufacturer.

Deficiencies observed with the Sedaconda ACD-S will be recorded in the eCRF immediately (within 24 hours of becoming aware of it). The information recorded will include a description of the device deficiency as well as information about whether there was an AE or SAE as a result of the deficiency. If an AE or SAE occurred, the AE or SAE should be recorded in the eCRF related to the device as described in Section 8.1.

All device deficiencies reported in the eCRF will lead to an email alert sent directly to the Sponsor. The Sponsor will review all device deficiencies during the study and determine and document in writing whether they could have led to a SAE.

If the Investigator or Sponsor judges that the device deficiency could have led to a SAE, the device deficiency may be subject to medical device vigilance safety reporting procedures.

Reporting of deficiencies to competent authorities will follow the Sponsor's standard operating procedure for incident reporting and the applicable regulation on device vigilance, ie, European Commission Guidelines on a medical device vigilance system MEDDEV 2.12-1 Revision 8[58] and Medical Device Regulation (MDR) 2017/745.[59] In case requirements are discrepant, the requirements stipulated by the MDR will be followed.

8.7.1 Unresolved Sedaconda ACD-S Device-Related Issues

If a device-related issue occurs and is unresolved, the patient will be discontinued from study drug treatment and converted to SOC sedation. Any device-related issues shall be documented in the eCRF, regardless of whether the error resulted in an AE.

8.8 Data Safety Monitoring Board and Study Stopping Criteria

An independent DSMB will be formed to monitor safety during the study. This DSMB will serve on both this study and the SED004 study. The DSMB will review relevant safety data for all patients. The DSMB will not analyze data for efficacy. The DSMB will comprise at least 3 members with appropriate expertise who are all independent of the Sponsor. Study sites will be notified of any relevant safety findings that may jeopardize patient safety. The DSMB will have planned meetings after approximately 25% of the randomized patients in the 2 trials combined

have completed the 30-day follow-up period. The run-in patients will also be included in the analyses. Subsequent planned meetings will occur at an appropriate time after 50% and 75% of patients in the 2 trials combined have completed the 30-day follow-up.

Accrued and cumulative moderate AEs, severe AEs, and SAEs will be monitored throughout the conduct of the study. The causality and expectedness of SAEs, as evaluated by the Sponsor based on aggregate data, will also be reviewed.

If stopping criteria described are met (Appendix I), recruitment into both studies will be paused, and an ad hoc DSMB meeting will be held within 10 working days for the DSMB to cumulatively review AEs in both studies. The DSMB will provide recommendations to the Sponsor concerning any actions that may be necessary in the light of their assessment (eg, the studies may be continued without amendment, paused and recruitment temporarily suspended, amended, or stopped completely). Given the similar exposures to the study drug in the studies SED003 and SED004, the DSMB recommendations will apply to both studies. The Sponsor will notify the FDA of any DSMB recommendations related to the safety of the study drug, leading to any changes in the conduct of the study.

The DSMB will receive all SUSARs and SAEs with the outcome of “death” with determined causality related to study drug for ad hoc review.

A DSMB charter will be established to outline the DSMB’s responsibilities and procedures.

9 STATISTICS

9.1 Analysis Populations

Detailed statistical analyses will be provided in the Statistical Analysis Plan (SAP).

9.1.1 Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) Analysis Set will include all randomized patients who receive any amount of study drug. The ITT Analysis Set will follow the intention-to-treat principle, ie, patients will be analyzed according to the treatment group assigned at randomization. The primary efficacy analysis will be performed using the ITT Analysis Set.

9.1.2 Modified Intent-to-Treat Analysis Set

The modified Intent-to-Treat (mITT) Analysis Set will include all patients in the ITT Analysis Set who have at least a 6-hour sedation period and at least 3 blinded RASS assessments. All efficacy analyses will be performed on the mITT Analysis Set in addition to the ITT Analysis Set.

9.1.3 Per-Protocol Analysis Set

The Per-Protocol (PP) Analysis Set will include all patients in the ITT Analysis Set without any major protocol deviation affecting the primary efficacy analysis.

In order to be included in the PP Analysis Set, patients need to have been sedated for at least 8 hours, with at least 50% of the planned RASS assessments performed. Additional criteria for inclusion in the PP Analysis Set will be specified in the SAP. The main statistical analysis for primary efficacy endpoint will be repeated on the PP Analysis Set.

9.1.4 Safety Analysis Set

The Safety Analysis Set will include all patients who receive any amount of study drug including the run-in training patients and will be analyzed in accordance with the actual treatment received.

9.2 Statistical Methods

Categorical data will generally be summarized with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation (SD), minimum, and maximum.

A fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the primary efficacy endpoint will be tested at the 1-sided 0.025 level first (non-inferiority test), followed by testing the key secondary efficacy endpoints at the 2-sided 0.05 level (superiority test) in the following hierarchical manner:

1. Change in mean fentanyl-equivalent opioid dose during the study drug treatment period compared to mean opioid dose during the 60 minutes prior to randomization;
2. Time from stop of study drug treatment to RASS ≥0, up to 4 hours;

3. Delirium by CAM-ICU-7 assessments 60 (±10) minutes after EOT in patients not re-sedated with benzodiazepine or propofol infusions; and
4. Proportion of ventilator parameter observations with spontaneous breathing efforts during the study drug treatment period.

Inferential conclusions about these efficacy endpoints will require statistical significance of the previous endpoints (in favor of the isoflurane-treated patients) and the primary efficacy endpoint.

Only the primary efficacy endpoint analysis will use non-inferiority test; the other efficacy endpoints analyses will all use superiority test.

9.2.1 Analysis of Efficacy

All efficacy analyses will be performed using both the ITT and the mITT Analysis Sets. Analysis of the ITT Analysis Set will be considered primary.

9.2.1.1 Primary efficacy analysis

The primary efficacy analysis will be performed on the ITT Analysis Set. The primary analysis on the primary efficacy endpoint will be performed based on an analysis of variance (ANOVA) model, including treatment group and stratification factor (SAPS III [0 to <40, >40 to <60, and ≥60] and patient type [medical and surgical (including trauma)]) as fixed effects. Surgical patient will be defined as patients who meet either of the following criteria:

- Have undergone surgery within the prior 2 weeks and for whom the current respiratory failure episode is related to that surgery or surgical disease process, or a complication thereof; or
- Patients anticipated to undergo surgery within the next 2 days for a condition that is related to etiology of respiratory failure.

The treatment comparisons will be estimated together with a one-sided 97.5% confidence interval and p-value for the hypothesis testing. Least squares mean for each treatment group will also be provided. The hypothesis test for primary efficacy endpoint analysis is based on a 1-sided significance level of 0.025. The primary efficacy endpoint will be summarized by stratification factor. ANOVA model will be used to analyze the primary efficacy endpoint for each subgroup, which will include randomized treatment group as a fixed effect. Sensitivity analyses will be performed if more than 20% (inclusive) of the total number of patients are included at one study site.

The detail of the analysis and the description of the estimand and missing data handling will be provided in the SAP.

9.2.1.2 Secondary efficacy analysis

The analyses of the key secondary efficacy endpoints will be performed on both the ITT and mITT Analysis Sets (superiority analysis), unless otherwise specified. The hypothesis test for the key secondary endpoint analyses is based on a 2-sided significance level of 0.05.

9.2.1.3 Other efficacy analysis

The detail of the analyses for the exploratory efficacy endpoints will be described in detail in the final SAP.

9.2.2 Analysis of Safety

All safety analyses will be performed on the Safety Analysis Set. Patients will be analyzed by the treatment received.

Safety measures will be summarized descriptively. Qualitative variables will be summarized using counts and percentages by treatment group at each study visit.

Laboratory and vital sign parameters will be presented using descriptive statistics for observed values at each visit and changes from Baseline, as appropriate. Abnormal physical examination findings will be presented in a by-patient data listing. Details of any abnormalities will be included in patient listings.

9.2.3 Interim Analysis

No interim analysis of outcome data is planned for this study; however, a primary analysis will be performed to evaluate the primary and key secondary efficacy endpoints as well as safety data and all outcomes related to the first 30 days when all patients complete the Study Day 30 visit, or would have completed the Study Day 30 visit, in the case of patients who discontinue the study early. The study (blinded RASS assessment results) will be unblinded at that time.

A separate analysis and study report will be performed for the LTO (3 and 6 months), once all patients have performed the 6-month follow-up.

9.2.4 Sample Size Determination

The study will be powered for a non-inferiority test of isoflurane via Sedaconda ACD-S compared to propofol via IV infusion in maintaining a target depth of sedation.

The proposed non-inferiority margin in the planned clinical trials is 15%. In clinical sedation trials such as the PRODEX, MIDEX, and SED001 studies, as well as in the proposed US clinical trials, sedation level is commonly assessed at approximately 2-hour intervals. A 15% absolute difference is equal to a difference of 3.6 hours in a 24-hour period. This is roughly the time span of 2 routine assessments of sedation and is therefore likely to be detectable and is clinically relevant. In the planned clinical trials, a 15% non-inferiority margin would imply that failing to reach the RASS target at 2 or more occasions in the isoflurane arm compared to the propofol arm in a 24 hour period would signify inferiority.

Previous studies assessing sedation success in mechanically ventilated patients with propofol have shown varying proportions of time within target sedation level. Targets have been defined as a 4-step range on the RASS score between 0 to -3 (PRODEX, MIDEX) or -1 to -4 (SED001). Proportions of time within target range during propofol sedation in these studies were between 64.7% (PRODEX) and 92% (SED001).

In SED001, the proportion of time within target RASS range for isoflurane was approximately 91%, with a SD of 12.4%. In SED001, staff in all participating European ICUs were familiar with both sedation methods since Sedaconda ACD had been available in Europe for many years and only sites with prior experience administering sedation with Sedaconda ACD participated in the study.

In the planned US clinical trials, patients are anticipated to be in the target RASS range on average 75% of the time when receiving standard sedative treatment, and on average 70% with isoflurane

via the Sedaconda ACD-S with an SD of approximately 20%. A total of 235 randomized patients will provide 95% power for the non-inferiority test with 1-sided α 0.025 assuming attrition rate of 5%.

Generally, the estimated proportions and higher variance compared to what was found in SED001 are due to assessor blinding. Further, in SED003, the experience with the Sedaconda ACD-S will be very limited prior to and during the trial, as the Sedaconda ACD-S is not approved for use in the US, and we anticipate a recruitment rate of approximately 2 to 3 patients/month at each study site. Hence, a slightly lower success rate for the isoflurane/Sedaconda ACD-S group and a larger variance in both groups is anticipated compared to the European SED001 trial.

10 STUDY MANAGEMENT

10.1 Clinical Monitoring

Before the initiation of the study at the study site, the study monitor will:

- Determine the adequacy of the facilities; and
- Discuss with the Investigator (and study personnel if applicable) their responsibilities with regards to GCP, protocol adherence, and local regulations.

At an initiation meeting, the study monitor will review the study procedures with the Investigator (and the study personnel, as applicable) and document this in compliance with the ICH-GCP guidelines.

During the study, the monitor will pay visits to the study site in order to complete the following:

- Provide information and support to the Investigator;
- Confirm that facilities remain acceptable;
- Confirm that the study team is adhering to the protocol;
- Confirm that data are being accurately recorded in the eCRF;
- Ensure that accountability checks for the study drug and device are being performed; and
- Conduct source data verification, which will require direct access to all original records for each patient (eg, medical records). Definition of key variables to be source data verified will be described in the Monitoring Plan.

The frequency of the monitoring visits per site will be determined through a risk-based approach depending on recruitment rate, observed data quality, and overall site performance. The monitor will be available (by telephone and email) between visits if the Investigator or other study personnel at the study site needs information, advice or help.

10.2 Audits and Inspections

The purpose of an audit or inspection is to systematically and independently examine all study-related activities to document that they were conducted, recorded, analyzed, and accurately reported according to the study protocol, ICH-GCP including the Declaration of Helsinki, and all other relevant regulations.

Audits or inspections may therefore be performed by authorized representatives of the Sponsor, the CRO, or a competent authority at the study site during or after the study. These visits may include source data verification, and confidentiality documents are therefore created. This implies that auditors/inspectors will have the right to inspect the study sites at any time during and/or after completion of the study and will have direct access to source documents, including patients' medical records. By participating in this study, the Investigator agrees to this requirement.

The Investigator should contact the monitor and/or Sponsor immediately if they are contacted by a competent authority about an inspection at their study site.

10.3 Training of Study Personnel

The Investigator will maintain records of all individuals involved in the study (medical, nursing, and other personnel). The Investigator will ensure that appropriate training relevant to the study is given to the personnel involved in the study, and that any new information of relevance to the conduct of the study is forwarded to the persons involved.

10.4 Protocol Deviations

Deviations from the protocol should not occur. If a deviation occurs, the Investigator (or designee) will inform the monitor about the deviation, and the implications of the deviation must be reviewed and discussed. The deviation will be logged by the monitor, including documentation of the reason and date for the deviation.

10.5 Study Timetable

The recruitment period is planned to proceed until approximately 3 to 5 run-in training patients per site and 235 randomized patients have been enrolled, where the intended first patient's first visit is in Q1 2022 and the intended last patient's last visit in Q4 2023.

10.6 Declaration of End of Study

The end of the study is defined as the last patient's last visit.

The competent authority and the IRB will be informed that the clinical study has ended within 90 days of the end of the clinical study. If the study has to be terminated early, this period will be reduced to 15 days and the reasons will be clearly explained.

10.7 Study Reporting

The data and information collected during this study will be reported in a CSR prepared by the Sponsor. The final study summary results shall be submitted to the regulatory authority as well as to the IRB as required by local legislations, within 12 months after completion of the study. The trial and a summary of the trial results will be made publicly available at clinicaltrials.gov. Trial registration may occur in other registries in accordance with local regulatory requirements.

Any confidential information relating to the study drug or the study, including any data and results from the study, will be the exclusive property of the Sponsor. The Investigators and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to the Sponsor.

10.8 Archiving

After the end of the study, the Investigator shall keep records of the study for the period mandated by local requirements or as specified in the clinical trial agreement. This includes any original source documents related to the study, including the Patient Identification List, which provides the link between the named patient source records and pseudonymous eCRF data; the original signed informed consent forms (ICFs); and detailed records of administration of study drug. The Sponsor should be contacted before any study related documentation is planned for destruction.

10.9 Patient Confidentiality

The Investigator will ensure that the confidentiality of the patients' data is preserved; any documents identifying the patient, such as the signed ICF, will be maintained by the Investigator in strict confidence. Patients will be assigned a unique identifier. Any records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient will 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 patient who will be required to give consent for their data to be used as described in the informed consent. The patient must be informed that his/her medical records may be examined by auditors or other authorized personnel appointed by the Sponsor and by inspectors from regulatory authorities.

10.10 Study Agreements

The Investigator at the study site must comply with all the terms, conditions, and obligations of the clinical study agreement for this study. In the event of any inconsistency between this protocol and the clinical study agreement, the protocol shall prevail.

Agreements between the Sponsor and the Investigator must be in place before any study-related procedures can take place.

10.11 Publication

The Sponsor is the sole owner of the results from the study. No data can be shared or published before written approval has been received from the Sponsor.

By signing the protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor.

The information obtained during the conduct of this study is considered confidential and will be used by the Sponsor for registration purposes and for the general development of the study drug. Data will not be made available to any third party other than the authorized representatives of relevant authorities. Study progress and results of the project will be summarized in a CSR as described in Section 10.7. The report will also form the basis for scientific publications at the appropriate time.

All information supplied by the Sponsor in connection with this study shall remain the sole property of the Sponsor and is to be considered confidential information. No confidential information shall be disclosed to others without prior written consent from the Sponsor and shall not be used except in the performance of this study. The information obtained during this study may be made available to other physicians who are conducting other clinical studies with the study drug, if deemed necessary by the Sponsor.

Results from the study may be published, and then authorship of a manuscript for publication in a peer-reviewed journal will be offered in compliance with the Vancouver guidelines.

The Sponsor determines when to publish. No other publications or presentations resulting from the study may be made until the study is completed and the primary study results have been published.

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

Data will be recorded at the site in eCRFs and reviewed by the CRAs during monitoring visits. The CRAs will verify data recorded in the eCRF with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the eCRF.

11.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

11.1.3 Data Entry

Data must be recorded using the eCRF as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR) Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

11.1.4 Medical Information Coding

For medical information, the latest version of the following thesauri will be used:

- Medical Dictionary for Regulatory Activities for medical history and AEs; and
- WHO Drug Dictionary for prior and concomitant medications and coding of procedures.

11.1.5 Data Validation

Validation checks programmed within the eCRF, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

11.2 Source Data

Records of patients, source documents, delegation logs, training logs, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12 ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical Conduct of the Study

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

12.2 Institutional Review Board

The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and ICH Guidelines require that approval be obtained from an IRB prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, and any other written information regarding this study to be provided to a patient or patient's LAR must be approved by the IRB.

No study drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

12.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient or LAR is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient or LAR before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the patient and LAR. If the initial informed consent is given by the LAR, then the information about the study will be given to, and consent obtained from, the patient as soon as the patient's condition allows.

12.4 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by [redacted] or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been submitted to FDA for review and approved by the IRB, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to FDA and the IRB within 5 working days.

12.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB, as appropriate. Patients or their LAR may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

12.6 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators should commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12.7 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out patient liability insurance for all patients who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 5. Schedule of Procedures (Screening Period and Treatment Period)

	Screening Period				Treatment Period				
	Screening/Randomization			Baseline					
Hour, Day, or Month (± Window)	Initial Screening D -30 to Randomization	Complete Screening -24h to Randomization	Randomization	Randomization to Initiation of Study Drug (up to 6 hours)	Q2h (±0.5h)	Q4h[nn] (±0.5h)	Q8h (±2h)	Daily	EOT/ Up to 48h (±6h)
Informed consent[d]	X								
Inclusion/exclusion criteria	X	X[e]							
Demographic information	X								
Medical/surgical history	X	X[e]							
Prior/concomitant relevant medications[f]		X		X			X		
Weight and height[g]		X							
Physical examination[h]		X							X
Clinical laboratory assessments[i]		X						X	
Pregnancy test[l]		X							
Physical function and outcomes[m]	X[kk]								
Cognitive function and outcomes[n]	X[kk]								
Reduction of SOC sedation and opioids to half				X[o]					
Discontinuation of SOC sedatives and opioids				X[ll]					
Patient characteristics[p]		X							
Predicted time remaining on ventilator[q]		X							
Ventilator parameters[r]				X			X[s]		
Blood gases[t]				X			X[s]		
Organ function (SOFA)[u]				X				X	
Randomization[v]			X						
Vital signs[w]				X[x]			X[s]		
RASS				X[x]	X[y]			X[z]	X[y]
CPOT				X[x]	X[y]				
Study drug administration[v]				X			X		

	Screening Period				Treatment Period				
	Screening/Randomization			Baseline					
Hour, Day, or Month (± Window)	**Initial Screening D -30 to Randomization**	**Complete Screening -24h to Randomization**	**Randomization**	**Randomization to Initiation of Study Drug (up to 6 hours)**	**Q2h (±0.5h)**	**Q4h[nn] (±0.5h)**	**Q8h (±2h)**	**Daily**	**EOT/ Up to 48h (±6h)**
Isoflurane end-tidal concentration measurement[aa]						X			
Sedaconda ACD-S device deficiencies					X				
Adverse events[cc]					X				
Restraints								X	
CAM-ICU-7[ee]								X[z]	X[ee]
Wake-up test[ff]									X

Footnotes appear at the end of Table 6.

Table 6. Schedule of Procedures (Follow-Up Period and Early Withdrawal)

	Follow-Up Period					
	Post-Treatment Monitoring	Follow-Up Contact		3-Month Phone Call	6-Month Phone Call	EW[c]
Hour, Day, or Month (± Window)	Until 24h after EOT	Until D7 after EOT (±2D)	D30 (+5D)[a]	3M (±4W)[b]	6M (±4W)[b]	UNS
Prior/concomitant relevant medications[f]	X	X[f]	X[f]			
Physical examination[h]	X					X
Clinical laboratory assessments[i]	X[j]					X[k]
Physical function and outcomes[m]				X	X	X[oo]
Cognitive function and outcomes[n]				X	X	X[oo]
Organ function (SOFA)[u]		X				
Vital signs[w]	X					X
RASS		X[z]				
Major ICU interventions[bb]			X			
Adverse events[cc]	X	X	X[dd]			X
CAM-ICU-7[ee]		X[z]				
Time of extubation[gg]	X					
Duration of mechanical ventilation			X			X[hh]
Level of care			X			X
Mortality			X	X	X	
ICU Memory Tool				X[ii]		X[oo]
Psychological outcomes[jj]				X	X	
Late onset of drug-induced liver injury			X			
Quality of life[kk]				X	X	

a. Major ICU interventions, information on ICU care, and relevant concomitant medications are to be collected at Study Day 30 or at ICU discharge, whichever comes first. Level of care (can be collected retrospectively for the whole study period), duration of mechanical ventilation, late onset drug-induced liver injury, mortality, and follow-up of any unresolved AEs are to be performed through telephone call if not possible to retrieve information through medical records at Study Day 30 (regardless of ICU discharge status).
b. Patients will be followed-up via telephone call at 3 and 6 months (±4 weeks).
c. Unless consent is withdrawn, the patient should continue in the study for assessment and follow-up even if study drug is discontinued. If consent is withdrawn, patients will be encouraged to complete the EW visit, if possible.
d. Informed consent must be obtained from patient or patient's LAR before any study-related procedures are performed. If the patient is unable to consent at the time of Screening, informed consent may be obtained from the patient's LAR; however, information about the study will be given to, and consent obtained from, the patient as soon as the patient's condition allows.
e. To be assessed only if Initial Screening is performed more than 24 hours prior to the Complete Screening.
f. All relevant prior and concomitant medications (see Section 7.2.1) are recorded from ICU admission or 24 hours prior to initiation of study drug treatment, whichever is shortest, until the end of the 24-hour post-treatment monitoring period. After this, only receipt of specific sedative, antipsychotic, and analgesic medications and relevant concomitant medications associated with ongoing AEs will be collected from 24 hours after EOT until Study Day 30 or ICU discharge, whichever comes first. All administered opioids, including the mean opioid dose assessment at 60 minutes prior to randomization, are to be collected also during Screening (Section 3.7).
g. Body weight (lb) and height (inch) should be measured when possible or be estimated. Weight and height available in patient's records can be used if measured within the last 7 days.

h. Physical examinations should be performed appropriately, per the patient's condition. Any findings should be recorded on the physical examination eCRF.
i. Includes clinical chemistry, lipid profile, hematology, and coagulation. See Appendix B for a list of clinical laboratory analytes. Screening/Baseline clinical laboratory tests, other than those pertaining to trial eligibility, may be collected at any time during the Complete Screening (-24 hours to 0 hour) or post-randomization period (0 hour to +6 hours) prior to initiation of study drug treatment.
j. Assessment should be performed once during post-treatment monitoring period, if the patient is still in the ICU. Analyses performed per SOC with an 18-to-48-hour window after EOT can be used.
k. Only applicable if EW is during study drug treatment period.
l. Female patients of childbearing potential must have a negative (serum or urine) pregnancy test prior to randomization. A pregnancy test obtained previously as part of usual care during this hospital episode that is documented in the patient's medical record will suffice. Female patients not of childbearing potential are defined as female patients who have been postmenopausal for at least 1 year, have been surgically sterilized, or are ≥60 years of age.
m. Physical outcomes assess activities of daily living by the Katz ADL and Pfeffer FAQ.
n. Cognitive baseline will be assessed by the IQCODE. LTO will be assessed by TICS, WAIS IV-Digit Span, Hayling Sentence Completion Test, Controlled Oral Word Association, WMS-IV – Immediate Memory (Adult/Older Adult), WMS-IV – Delayed Memory (Adult/Older Adult), and PROMIS Cognitive Function questionnaire.
o. To be performed within 30 minutes from randomization; see Section 3.7.
p. SAPS III, reasons for ICU admission, ICU diagnosis criteria, hospital and ICU admission, time for intubation, and exposure of volatile anesthetics in the past 24 hours (and if yes, what drug [sevoflurane/isoflurane/desflurane]) to be assessed at Complete Screening.
q. Predicted remaining time on the ventilator for each patient to be collected just shortly before randomization in order to monitor the proportion of patients with longer (>24 hours) versus shorter (12 to 24 hours) exposure times.
r. Ventilator parameters include ventilator mode, set tidal volume, observed tidal volume, set rate, observed rate, observed minute volume, set PEEP, PS above PEEP, PC above PEEP, PIP, plateau pressure (once daily only), mean airway pressure, FiO_2, SpO_2, $EtCO_2$, ventilator trigger, P0.1, and ABG.
s. These assessments will be performed more frequently when clinically indicated (as patients will often be observed continuously or more frequently than every 8 hours in clinical practice).
t. Only applicable when arterial line is available.
u. Organ function will be assessed by SOFA once daily at Baseline, during the study drug treatment period, the 24-hour post-treatment period, and until 7 days after EOT.
v. After randomization, the study equipment will be set-up and study drug treatment shall be initiated as close to randomization as possible and no later than 6 hours after randomization.
w. Vital signs include systolic, diastolic, and mean arterial blood pressure, heart rate, SpO_2, (measured by pulse oximetry; will not be assessed while patients are on ventilator support, as it will be captured as a ventilator parameter), respiratory rate (will not be recorded as part of vital sign assessments while patient is on ventilator support, as it will be captured in the ventilator parameter records as observed breathing rate), and body temperature.
x. Unblinded baseline assessment for RASS and CPOT should be performed within 30 minutes prior to initiation of study drug administration. Vital signs should be performed within 60 minutes prior to initiation of study drug administration.
y. Assessment will be performed in a blinded manner by a blinded assessor.
z. CAM-ICU-7 and RASS will be performed daily (at a minimum) during the study drug treatment period and until 7 days after EOT or until hospital discharge, whichever comes first. However, more frequent assessments will be performed when clinically indicated. RASS will be assessed first. If RASS is ≥-3, CAM-ICU-7 will be assessed. If RASS is -4 or -5, CAM-ICU-7 will not be assessed.
aa. A separate gas monitor will be readily available during the study drug treatment period for measurement of end-tidal isoflurane concentrations. Only applicable for isoflurane-treated patients.
bb. Major ICU interventions through Study Day 30 or until ICU discharge, whichever comes first, include the following: renal replacement therapy, ECLS, tracheostomy, non-invasive ventilation, and re-admission to the ICU.
cc. Recording of AEs will start at the initiation of study drug administration and continue until Day 7 post EOT.
dd. Only AEs unresolved at D7 to be followed-up.
ee. CAM-ICU-7 will be assessed 60 (±10) minutes after EOT in all patients by a blinded assessor. CAM-ICU-7 will not be required for patients reaching EOT due to treatment failure, patients transitioned to comfort care, or patients continued onto benzodiazepines or propofol sedation due to clinical need before 60 minutes after EOT.
ff. Wake-up test will be assessed through blinded RASS assessments.
gg. To be collected for patients who are extubated on study drug only.

hh. Only applicable if EW is after EOT.
ii. Memory panorama from time in the ICU will be assessed by the ICU Memory Tool at the 3-month follow-up visit only.
jj. Psychological outcomes will be assessed by the PROMIS Depression and Anxiety questionnaires and IES-R.
kk. Quality of life will be assessed by the WHODAS 2.0 and BPI questionnaires.
ll. Baseline data can be collected until 48 hours after initiation of study drug treatment as the time period of interest is not synonymous with when data needs to be captured.
mm. As soon as the study drug treatment has been initiated, the SOC sedative should be stopped (ie, slow weaning will not be permitted) to limit the impact of residual SOC sedation.
nn. For isoflurane-treated patients only.
oo. LTO assessments will be completed at 3 and 6 months. ICU Memory Tool will be assessed at 3 months follow-up only.

ABG = arterial blood gas; AE = adverse event; BPI = Brief Pain Inventory; CAM-ICU-7 = 7-point scale of the Confusion Assessment Method for the Intensive Care Unit; CPOT = Critical Care Pain Observation Tool; D = day; ECLS = extracorporeal life support; eCRF = electronic case report form; EOT = end of treatment; $EtCO_2$ = end-tidal carbon dioxide; EW = early withdrawal; FAQ = functional activities questionnaire; FiO_2 = fraction of inspired oxygen; h = hour; ICU = intensive care unit; IES-R = impact of event scale; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; Katz ADL = Katz Index of Independence in Activity of Daily Living; LAR = legally authorized representative; LTO = Long-Term Outcomes; M = month; P0.1 = airway occlusion pressure; PC = pressure assist/control; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; PROMIS = Patient-Reported Outcomes Measurement Information System; PS = pressure support; Q = every; RASS = Richmond Agitation Sedation Scale; SAPS = Simplified Acute Physiology Score; Sedaconda ACD-S = Sedaconda Anaesthetic Conserving Device - S; SOC = standard of care; SOFA = sequential organ failure assessment; SpO_2 = peripheral capillary oxygen saturation; TICS = Telephone Interview for Cognitive Status; UNS = unscheduled; W = week(s); WAIS = Wechsler adult intelligence scale; WHODAS 2.0 = World Health Organization Disability Assessment Schedule 2.0; WMS = Wechsler memory scale.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Clinical Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate (calculated)
Glucose	Inorganic phosphorus
Potassium	Sodium
Total bilirubin	Total protein
Uric acid	

Coagulation

International normalized ratio (INR)	Partial thromboplastin time (PTT)
Prothrombin time (PT)	

Lipid Profile

High-density lipoprotein-cholesterol	Low-density lipoprotein-cholesterol
Total cholesterol	Triglycerides

Hematology

Hematocrit	Hemoglobin
Platelets	White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Other Tests

Blood gas analysis [1]	Serum and urine pregnancy test [2]

1. If arterial line is available.
2. Female patients of childbearing potential must have a negative serum or urine pregnancy test prior to randomization.

APPENDIX C: THE ABCDEF BUNDLE

The care for patients in the intensive care unit (ICU) will be managed per standard of care during the study using the ABCDEF bundle as a guide.[1] Study personnel will be encouraged to emphasize and follow the ABCDEF bundle.

The ABCDEF bundle includes the following components:

a. **A**BCDEF (assess and monitor pain). Monitor and manage pain level in all patients daily with the validated pain scales (ie, Critical Care Pain Observation Tool), in accordance with practice guidelines and local ICU policies;

b. A**B**CDEF (both awakening and breathing trials). This component includes standardized Spontaneous Awakening Trials (SATs) (ie, daily interruption of sedation) paired with spontaneous breathing tests, both administered only when specific safety criteria are met. Sedation held for the SAT will be restarted, if needed, at the lowest possible rate that is needed to achieve the target Richmond Agitation Sedation Scale score. All study centers will use validated sedation scales to facilitate goal-directed sedation, a practice that will continue throughout the study. Ventilator management will be standardized according to each institution's approved protocols;

c. AB**C**DEF (choice of analgesia and sedation). To improve patient outcomes, choice of sedatives and analgesic medications, as well as careful consideration regarding medication doses, titration, and discontinuation, should be continually assessed. Decreased exposure to sedatives, particularly benzodiazepines, to achieve target sedation scores should be recommended. Sedation should be continually monitored and documented;

d. ABC**D**EF (delirium monitoring and management). The delirium component will include nonpharmacologic strategies, given that the majority of delirium in the ICU is the hypoactive subtype. The protocol includes nonpharmacologic strategies that have been shown to reduce delirium in non-ICU settings. Study personnel will encourage members of the ICU team to perform the following tasks:

   - Reorient and cognitively stimulate patients by conveying the day, date, place, and reason for hospitalization; updating whiteboards with caregiver names; requesting placement of a clock and calendar in the room; and discussing current events;
   - Determine the need for hearing aids and/or eyeglasses from the surrogate and request that the surrogate provide these to the patient when appropriate; and
   - Maintain sleep preservation using techniques including noise reduction strategies (eg, minimize noise outside the room and offer white noise or earplugs), normalizing day-night variation in illumination, minimizing interruptions during normal sleeping hours via a "time out" strategy, maintaining ventilator synchrony, and promoting comfort and relaxation (eg, back care, massage, oral care, washing face/hands, and daytime bath).

1. Marra A, Ely EW, Pandharipande PP, et al. The ABCDEF bundle in critical care. *Crit Care Clin*. 2017;33(2):225-243.

e. ABCD**E**F (early mobility and exercise). The exercise component of the ABCDEF bundle will include strategies to promote mobility and exercise in the earliest phases of critical illness. Early physical/occupational therapy have been shown to significantly reduced delirium duration for mechanically ventilated ICU patients. Study personnel will encourage members of the ICU team to evaluate each patient's readiness for mobility and exercise and coordinate the following activities: removal of restraints, active range of motion, sitting on the side of the bed, sitting in a chair, standing in place, and ambulation; and

f. ABCDE**F** (family engagement). Family members and surrogate decision makers should be encouraged to become active partners in multi-professional decision-making and treatment planning. Active family involvement has been shown to increase both provider and family satisfaction within the ICU without interfering with patient care or provider education.

APPENDIX D: SCREENING FOR SPONTANEOUS AWAKENING TRIAL (SAT) AND SPONTANEOUS BREATHING TEST (SBT)

Eligibility: Patients are candidates if they are on mechanical ventilation.

Step 1: Spontaneous Awakening Test (SAT) Safety Screen- pass/fail

If the patient has any of the following criteria, he/she fails the safety screen and should not have an SAT at that time.

The SAT safety screen criteria include the following:

- Active seizures- the patient is currently receiving medications for active seizures;
- Alcohol withdrawal- the patient is currently receiving medications for alcohol withdrawal;
- Agitation- the patient is currently or has recently (in the last 2 hours) receiving medications for agitation (Richmond Agitation Sedation Scale [RASS] ≥2);
- Paralytics- the patient is currently on a paralytic infusion;
- Myocardial ischemia- the patient has documentation of myocardial ischemia in the last 24 hours;
- High ICP- there is evidence of elevated ICP (ICP >20); and
- Patient off the unit- effort should be made to attempt the safety screen when the patient returns to unit.

<u>If the patient fails the SAT safety screen</u>

If the patient does not pass the safety screen, it is not considered safe to turn off the sedatives. No further action is needed. Bedside staff should try the safety screen again in 24 hours; bedside staff can reassess safety criteria before 24 hours if the patient's condition has changed and bedside staff or the clinical team think the patient would pass the safety screen.

<u>If the patient passes the SAT safety screen</u>

Perform SAT (**Step 2**).

Step 2: Perform the SAT

The SAT is defined as the discontinuation of all sedatives being given for sedation; administration of medications being used for the purpose of analgesia should continue.

<u>If the patient fails the SAT</u>

Bedside staff should restart at the lowest possible infusion rate that is needed to achieve target RASS. Typically start at ½ of the most recent dose and titrate, as needed.

The SAT failure criteria include the following:

- Sustained anxiety or agitation;
- Respiratory rate >35 breaths/minute for 5 minutes;
- Peripheral capillary oxygen saturation (SpO_2) <88% for 5 minutes;

- Respiratory distress; and
- Acute cardiac dysrhythmia.

If the patient passes the SAT

If the patient exhibits either of the pass criteria below and no failure criteria, he/she is advanced to **Step 3** (SBT Safety Screen).

The SAT pass criteria include the following:

- The patient opens their eyes to voice (RASS ≥-3) and is tolerating sedative cessation for any amount of time; or
- The patient is comatose and tolerating sedative cessation for >4 hours.

Step 3: Spontaneous Breathing Trial (SBT) Safety Screen- pass/fail

If the patient has any of the following criteria, he/she fails the safety screen and should not have an SBT at that time.

The SBT safety screen criteria include the following:

- Agitation- the patient is currently agitated (RASS ≥+2);
- Oxygen saturation <88%;
- Fraction of inspired oxygen (FiO_2) >50%;
- Positive end-expiratory pressure (PEEP) >7.5 cmH_2O;
- Myocardial ischemia- the patient has documentation of myocardial ischemia in the last 24 hours;
- Vasopressor use- the patient has documented significant use of vasopressors, including the following:
  - Dopamine or dobutamine infusion >5 mcg/kg/minute;
  - Norepinephrine or epinephrine infusion >2 mcg/minute; or
  - Vasopressin or milrinone at any dose.
- Patient off the unit- effort should be made to attempt the safety screen when the patient returns to unit.

If the patient fails the SBT safety screen

Bedside staff should try the safety screen again in 24 hours; bedside staff can reassess safety criteria before 24 hours if the patient remains off sedatives, his/her condition has changed, and bedside staff or the clinical team think the patient would pass the safety screen.

If the patient passes the SBT safety screen

Perform SBT (**Step 4**).

Step 4: Perform the SBT

The SBT is defined as discontinuation of active ventilator support so that the patient is allowed to breathe through a T-tube circuit or the ventilator circuit with continuous positive airway pressure (CPAP)/PEEP ≤7.5 cmH_2O and pressure support of ≤7 cmH_2O.

If the patient fails the SBT

Bedside staff should return the ventilatory support to the previous settings.

The SBT failure criteria include the following:

- Sustained respiratory rate >35/minute;
- Sustained respiratory rate <8/minute;
- Sustained SpO_2 <88%;
- Respiratory distress;
- Mental status change; or
- Acute cardiac arrhythmia.

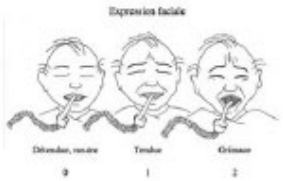
If the patient passes the SBT

Passing the SBT is defined as the patient exhibiting no failure criteria for 2 hours. At this end of the 2 hours, the clinical team should consider extubation.

APPENDIX E: CRITICAL CARE PAIN OBSERVATION TOOL (CPOT)

The Critical-Care Pain Observation Tool (CPOT)

(Gélinas et al., 2006)

Indicator	Score		Description
Facial expression  Caroline Arbour, RN, B.Sc., PhD(student) School of Nursing, McGill University	Relaxed, neutral	0	No muscle tension observed
	Tense	1	Presence of frowning, brow lowering, orbit tightening and levator contraction or any other change (e.g. opening eyes or tearing during nociceptive procedures)
	Grimacing	2	All previous facial movements plus eyelid tightly closed (the patient may present with mouth open or biting the endotracheal tube)
Body movements	Absence of movements or normal position	0	Does not move at all (doesn't necessarily mean absence of pain) or normal position (movements not aimed toward the pain site or not made for the purpose of protection)
	Protection	1	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements
	Restlessness/Agitation	2	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed
Compliance with the ventilator (intubated patients)	Tolerating ventilator or movement	0	Alarms not activated, easy ventilation
	Coughing but tolerating	1	Coughing, alarms may be activated but stop spontaneously
	Fighting ventilator	2	Asynchrony: blocking ventilation, alarms frequently activated
OR			
Vocalization (extubated patients)	Talking in normal tone or no sound	0	Talking in normal tone or no sound
	Sighing, moaning	1	Sighing, moaning
	Crying out, sobbing	2	Crying out, sobbing
Muscle tension Evaluation by passive flexion and extension of upper limbs when patient is at rest or evaluation when patient is being turned	Relaxed	0	No resistance to passive movements
	Tense, rigid	1	Resistance to passive movements
	Very tense or rigid	2	Strong resistance to passive movements or incapacity to complete them
TOTAL	___ / 8		

Brief description of each CPOT behavior:

Facial expression: The facial expression is one of the best behavioral indicators for pain assessment. A score of 0 is given when there is no muscle tension observable in the patient's face. A score of 1 consists of a tense face which is usually exhibited as frowning or brow lowering. A score of 2 refers to grimacing, which is a contraction of the full face including eyes tightly closed and contraction of the cheek muscles. On occasion, the patient may open his or her mouth, or if intubated, may bite the endotracheal tube. Any other change in facial expression should be described in the chart, and given a score of 1 if different from a relaxed (0) or grimacing (2) face.

Body movements: A score of 0 is given when a patient is not moving at all or remains in a normal position as per the nurse's clinical judgment. A score of 1 refers to protective movements, meaning that the patient performs slow and cautious movements, tries to reach or touch the pain site. A score of 2 is given when the patient is restless or agitated. In this case, the patient exhibits repetitive movements, tries to pull on tubes, tries to sit up in bed, or is not collaborative. Of note, body movements are the less specific behaviors in relation with pain, but are still important in the whole evaluation of the patient's pain.

Compliance with the ventilator: Compliance with the ventilator is used when the patient is mechanically ventilated. A score of 0 refers to easy ventilation. The patient is not coughing nor activating the alarms. A score of 1 means that the patient may be coughing or activating the alarms but this stops spontaneously without the nurse having to intervene. A score of 2 is given when the patient is fighting the ventilator. In this case, the patient may be coughing and activating the alarms, and an asynchrony may be observed. The nurse has to intervene by talking to the patient for reassurance or by administering medication to calm the patient down.

Vocalization: Vocalization is used in non-intubated patients able to vocalize. A score of 0 refers to the absence of sound or to the patient talking in a normal tone. A score of 1 is given when the patient is sighing or moaning, and a score of 2 when the patient is crying out (Aïe! Ouch!) or sobbing.

Muscle tension: Muscle tension is also a very good indicator of pain, and is considered the second best one in the CPOT. When the patient is at rest, it is evaluated by performing a passive flexion and extension of the patient's arm. During turning, the nurse can easily feel the patient's resistance when she is participating in the procedure. A score of 0 is given when no resistance is felt during the passive movements or the turning procedure. A score of 1 refers to resistance during movements or turning. In other words, the patient is tense or rigid. A score of 2 consists of strong resistance. In such cases, the nurse may be unable to complete passive movements or the patient will resist against the movement during turning. The patient may also clench his/her fists.

Directives of use of the CPOT

1. The patient must be observed at rest for one minute to obtain a baseline value of the CPOT.
2. Then, the patient should be observed during nociceptive procedures (e.g. turning, wound care) to detect any changes in the patient's behaviors to pain.
3. The patient should be evaluated before and at the peak effect of an analgesic agent to assess whether the treatment was effective or not in relieving pain.
4. For the rating of the CPOT, the patient should be attributed the highest score observed during the observation period.
5. The patient should be attributed a score for each behavior included in the CPOT and muscle tension should be evaluated last, especially when the patient is at rest because the stimulation of touch alone (when performing passive flexion and extension of the arm) may lead to behavioral reactions.

Observation of patient at rest (baseline).

The nurse looks at the patient's face and body to note any visible reactions for an observation period of one minute. She gives a score for all items except for muscle tension. At the end of the one-minute period, the nurse holds the patient's arm in both hands – one at the elbow, and uses the other one to hold the patient's hand. Then, she performs a passive flexion and extension of the upper limb, and feels any resistance the patient may exhibit. If the movements are performed easily, the patient is found to be relaxed with no resistance (score 0). If the movements can still be performed but with more strength, then it is concluded that the patient is showing resistance to movements (score 1). Finally, if the nurse cannot complete the movements, strong resistance is felt (score 2). This can be observed in patients who are spastic.

Observation of patient during turning.

Even during the turning procedure, the nurse can still assess the patient's pain. While she is turning the patient on one side, she looks at the patient's face to note any reactions such as frowning or grimacing. These reactions may be brief or can last longer. The nurse also looks out for body movements. For instance, she looks for protective movements like the patient trying to reach or touching the pain site (e.g. surgical incision, injury site). In the mechanically ventilated patient, she pays attention to alarms and if they stop spontaneously or require that she intervenes (e.g. reassurance, administering medication). According to muscle tension, the nurse can feel if the patient is resisting to the movement or not. A score 2 is given when the patient is resisting against the movement and attempts to get on his/her back.

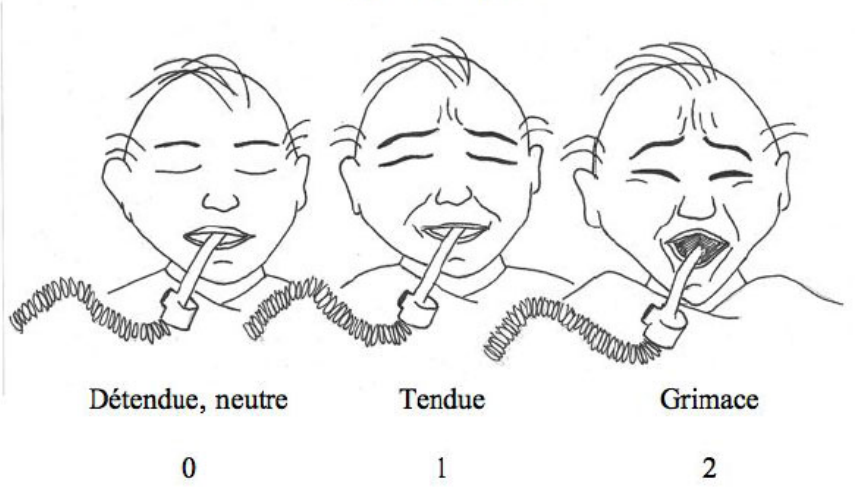
Facial expressions

0
Relaxed, neutral
(no muscle tension)

1*
Tense
(frowning, brow lowering, orbit tightening, little levator contraction)

2
Grimacing
(contraction of the whole face: frowning, brow lowering, eyes tightly closed, levator contraction – mouth may be opened or the patient may be biting the endotracheal tube)

Expression faciale



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* A score of 1 may be attributed when a change in the patient's facial expression is observed compared with rest assessment (e.g. open eyes, tearing).

Inspired by : Prkachin, K. M. (1992). The consistency of facial expressions of pain : a comparison across modalities. *Pain, 51*, 297-306.

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APPENDIX F: 7-POINT SCALE OF THE CONFUSION ASSESSMENT METHOD FOR THE INTENSIVE CARE UNIT (CAM-ICU-7)

The CAM-ICU-7 Delirium Severity Scale

CAM-ICU		
Items	**Grading**	**Score**
1. Acute Onset or Fluctuation of Mental Status Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	0 absent 1 present	
2. Inattention Say to the patient, "*I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand.*" Read letters from the following letter list in a normal tone 3 seconds apart. SAVEAHAART (Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A")	0 absent (correct ≥ 8) 1 for inattention (correct 4-7) 2 for severe inattention (correct 0-3)	
3. Altered Level of Consciousness Present if the Actual RASS score is anything other than alert and calm (zero)	0 absent (RASS 0) 1 for altered level (RASS 1, −1) 2 for severe altered level (RASS >1, < −1)	
4. Disorganized Thinking Yes/No Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. Command: Say to patient "Hold up this many fingers" (Hold two fingers in front of patient). "Now do the same with the other hand" (Do not repeat number of fingers) An error is counted if patient is unable to complete the entire command.	0 absent (correct ≥ 4) 1 for disorganized thinking (correct 2, 3) 2 for severe disorganized thinking (correct 0, 1)	
	Total Score	

CAM-ICU: Confusion Assessment Method for the Intensive Care Unit; RASS: Richmond Agitation Sedation Scale; SAS: Sedation-Agitation Scale; GCS: Glasgow Coma Scale

APPENDIX G: ADVERSE EVENT REPORTING GUIDANCE

Most intensive care unit (ICU) patients have ongoing and fluctuating variations in their vital parameters and laboratory values. A typical ICU patient will experience multiple such variations on a daily basis, of which many are minor and routinely managed.

In parallel there is a need to establish the safety profile of the sedative drugs in the clinical trial, using adverse event (AE) reporting.

AE reporting should be based on events and results from assessments that indicate new-onset pathology and that require more than minor routine adjustments of slight physiologic deviations.

The list below is not to be seen as a complete list of reportable AEs but may aid in exemplifying some of the AEs that should be recorded. Similar events not listed here should also be recorded.

Neurological

- New-onset ischemic or hemorrhagic stroke;
- New-onset neurological deficits; or
- Seizures.

Cardiovascular

- New-onset arrhythmia (atrial fibrillation, supraventricular or ventricular tachycardia, bradycardia, or other) leading to intervention (eg, cardioversion, defibrillation, pacemaker, or drug treatment);
- New-onset electrocardiogram abnormalities requiring specific monitoring, treatment or follow-up;
- Myocardial ischemia, clinical angina pectoris, or myocardial infarction;
- New-onset regional or global myocardial dysfunction, visualized by echocardiogram;
- Circulatory shock, regardless of relation/causality to study drug; or
- Pericardial effusion.

Respiratory

- Hypoxia;
- New-onset increase of oxygen requirements of more than 20%;
- Self-extubation;
- Respiratory acidosis;
- Pneumothorax; or
- Aspiration.

Gastrointestinal

- Gastrointestinal bleeding;
- Gastric or duodenal ulcer;
- Ileus; or
- Worsening of liver function tests requiring intensified/follow-up monitoring or consultation.

Renal

- Polyuric renal failure; or
- New-onset anuria or oliguria.

Hematology

- Anemia not explained by recent trauma or surgery;
- New-onset thrombocytopenia; or
- New-onset thrombocytosis.

Infection

- New-onset verified infection (eg, urinary tract infection, pneumonia, sepsis, or other) requiring treatment.

THIS IS NOT TO BE VIEWED AS A CHECKLIST, MERELY A GUIDANCE ON SOME POTENTIAL AEs, AIMED TO GUIDE AE REPORTING.

Other AEs not listed here but that are similar in type, severity, or out of the normal fluctuations of physiological variability seen in an ICU patient should be reported.

If in doubt, the Investigator should report.

Table 7. AE Severity Assessment Definitions

Assessed from the initiation of study drug administration and until 7 days post EOT	Mild AE	Moderate AE	Severe AE	Serious AE
Definitions	An event that is easily tolerated and generally not expected to interfere with critical care course.	An event that is sufficiently discomforting to interfere with critical care course.	An event that is incapacitating, leads to major intervention, significantly alters current critical care course.	Death; prolonged hospitalization; persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions; congenital anomaly/birth defect; requires medical or surgical intervention to preclude permanent impairment or prevent permanent damage to a body structure; medical event eg, convulsions, asthma requiring acute treatment to prevent an outcome above.

AE = adverse event; EOT = end of treatment.

Table 8. AE Causality Assessment Criteria

Causality Assessment	Causality Criteria
Not considered causal	
Not related	• The AE follows a temporal sequence different from study drug administration; and • The AE is clearly produced by the patient´s clinical condition or by other modes of therapy administered to the patient.
Unlikely to be related	• The temporal sequence between the AE and the study drug administration is such that the study drug is not likely to be associated with the observed event; and • The AE could easily and more likely have been produced by the patient´s clinical condition or by other modes of therapy administered to the patient.
Considered causal	
Possibly related	• The AE follows a reasonable temporal sequence from study drug administration; and • The AE could have been, but is equally or less likely produced by the patient´s state or by other modes of therapy administered to the patient.
Probably related	• The AE follows a reasonable temporal sequence from study drug administration; • The AE abates upon discontinuation of the study drug (de-challenge); • The AE is likely a reaction to an agent or chemical group, or predicted by known pharmacology; and • The AE cannot be reasonably explained by the known characteristics of the patient´s clinical state or by other modes of therapy administered to the patient.
Definitely related	• The AE follows a reasonable temporal sequence from study drug administration; • The AE is a known reaction to agent or chemical group, or predicted by known pharmacology; • The AE cannot be explained by patient´s clinical state or other factors; • The AE abates upon discontinuation of the study drug (de-challenge); and • The AE is confirmed by reappearance of the reaction on repeat exposure (re-challenge).

AE = adverse event.

Table 9. List of AESIs

List of AESIs	Mild	Moderate	Severe	SAE
Hypoxemia	Oxygen desaturation event that requires an increase in FiO_2 of >10% or any increase in PEEP for >60 minutes to maintain SpO_2 of at least 88%, despite ventilator optimization.	Oxygen desaturation event that requires an increase in FiO_2 >20% or increase in PEEP of >5 cmH_2O for >60 minutes to maintain SpO_2 of at least 88%, despite ventilator optimization.	Refractory hypoxemia, defined as SpO_2 <88% lasting for 30 minutes or longer, despite ventilator optimization.	Need for respiratory rescue therapy, defined as ECMO, $ECCO_2R$, inhaled nitric oxide, or inhaled epoprostenol initiated for life threatening refractory hypoxemia, or other life-threatening manifestations of hypoxemia.
Hypercapnia	PCO_2 10 to 15 mmHg above baseline on 2 consecutive blood gases at least 60 minutes apart, despite ventilator optimization.	pCO_2 16 to 20 mmHg above baseline on 2 consecutive blood gases at least 60 minutes apart, despite ventilator optimization.	pCO_2 >20 mmHg above baseline on 2 consecutive blood gases at least 60 minutes apart, despite ventilator optimization.	ECMO support or life-threatening manifestations of respiratory acidosis.
MH				Any episode of MH, which may be characterized by muscle rigidity; unexplained hypercapnia resistant to increasing minute ventilation; elevated CK or urine myoglobin suggesting rhabdomyolysis; acute hyperkalemia >6 mmol/L potentially resulting in ECG changes of peaked T-waves, increased ventricular tachycardia, or ventricular fibrillation and hyperthermia in a patient exposed to volatile anesthetic or succinylcholine.

Table 9. List of AESIs (Continued)

List of AESIs	Mild	Moderate	Severe	SAE
PRIS suspected by the Investigator in a patient recently exposed to propofol				Any episode of PRIS, characterized by the development of otherwise unexplained metabolic acidosis and cardiac dysfunction with at least 1 of rhabdomyolysis, hypertriglyceridemia, or renal failure after initiation of propofol.
Accidental self-extubation	Accidental self-extubation will be recorded as an AESI, but grading is unnecessary, per FDA guidance			
Hypotension	New episode of SBP <90* mmHg or MAP <65* mmHg lasting at >60 minutes **OR** fluid bolus ≥1000 mL over <60 minutes **OR** new low dose vasopressor <0.05 mcg/kg/min norepinephrine equivalent >60 minutes **OR** increase of existing vasopressor by 0.05 to 0.1 mcg/kg/min norepinephrine equivalent over from baseline and increase lasting >60 minutes.	New low dose vasopressor 0.05 to <0.2 mcg/kg/min norepinephrine equivalent OR increase over <60 minutes of vasopressor(s) by 0.1 to <0.2 mcg/kg/min norepinephrine equivalent and lasting >60 minutes, to maintain SBP ≥90* mmHg or MAP ≥65* mmHg.	New vasopressor ≥0.2 mcg/kg/min norepinephrine equivalent or increase over <60 minutes of vasopressor(s) by ≥0.2 mcg/kg/min norepinephrine equivalent and lasting >60 minutes, to maintain SBP ≥90* mmHg or MAP ≥65* mmHg.	Immediate life-threatening hypotension, requiring intervention eg, CPR, mechanical circulatory support.
Liver injury	1) ALT ≥3 × ULN; or 2) AST ≥3 × ULN; or 3) Total bilirubin >2 × ULN; or 4) Alkaline phosphatase >2 × ULN.	Hy's Law criteria (ALT or AST 3 × ULN and total bilirubin >2 × ULN).	Mild encephalopathy and Hy's Law criteria (ALT or AST 3 × ULN and total bilirubin >2 × ULN).	Life-threatening consequences; moderate to severe encephalopathy; coma and Hy's Law criteria (ALT or AST >3 × ULN and total bilirubin >2 × ULN).
Hyperkalemia	>5.5 mEq/L (>5.5 mmol/L) in a non-hemolyzed sample and in absence of respiratory acidosis.	>6.0 to 6.5 mEq/L (6.0 to 6.5 mmol/L) in a non-hemolyzed sample for which a medication or dialysis to lower potassium was prescribed.	>6.5 to 7.0 mEq/L (>6.5 to 7.0 mmol/L) in a non- hemolyzed sample for which a medication or dialysis to lower potassium was prescribed.	>7.0 mEq/L (>7.0 mmol/L) in a non-hemolyzed sample for which a medication or dialysis to lower potassium was prescribed, or life-threatening arrhythmia due to hyperkalemia.

Table 9. List of AESIs (Continued)

List of AESIs	Mild	Moderate	Severe	SAE
Rhabdomyolysis independent of MH	CK 10,000 to 20,000 U/L	CK >20.000 U/L with moderate renal failure graded as AKIN[1] Stage 3.	CK >20.000 U/L requiring dialysis.	Life-threatening consequences of rhabdomyolysis.

* Unless a different clinical target is selected by the clinical team prior to randomization.
AESI = adverse event of special interest; AKIN = Acute Kidney Injury Network; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; CPR = cardiopulmonary resuscitation; $ECCO_2R$ = extracorporeal carbon dioxide removal; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; FDA = Food and Drug Administration; FiO_2 = fraction of inspired oxygen; MAP = mean arterial pressure; MH = malignant hyperthermia; pCO_2 = partial pressure of carbon dioxide; PEEP = positive end-expiratory pressure; PRIS = propofol-related infusion syndrome; SAE = serious adverse event; SBP = systolic blood pressure; SpO_2 = peripheral capillary oxygen saturation; ULN = upper limit of normal.

1. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. *Clin Kidney J*. 2013;6(1):8-14.

APPENDIX H: ORGAN FAILURE, SEQUENTIAL FAILURE ASSESSMENT (SOFA)

The SOFA Score*

Organ System, Measurement	SOFA Score				
	0	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	Normal	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation Platelets $x10^3/mm^3$	Normal	<150	<100	<50	<20
Liver Bilirubin, mg/dL (µmol/l)	Normal	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (<204)
Cardiovascular Hypotension	Normal	MAP<70 mmHg	Dopamine ≤5 or dobutamine (any dose)**	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System Glasgow Coma Score	Normal	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL (µmol/l) or Urine output	Normal	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or <500 mL/day	>5.0 (>440) or <200 mL/day

* Source: Vincent et al., 1996.

**Adrenergic agents administered for at least 1 hour (doses given are in mcg/kg/min).

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Sequential Organ Failure Assessment (SOFA) Score

Introduction: The SOFA score predicts mortality risk for patients in the intensive care unit based on lab results and clinical data.

Points & Pearls

- The Sequential Organ Failure Assessment (SOFA) is a mortality prediction score that is based on the degree of dysfunction of 6 organ systems.
- The score is calculated at admission and every 24 hours until discharge, using the worst parameters measured during the prior 24 hours.
- The scores can be used in several ways, including:
  - As individual scores for each organ to determine the progression of organ dysfunction.
  - As a sum of scores on a single intensive care unit (ICU) day.
  - As a sum of the worst scores during the ICU stay.
- The SOFA score stratifies mortality risk in ICU patients without restricting the data used to admission values.

Critical Actions

Clinical prediction scores such as the SOFA and the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE II) can be measured on all patients who are admitted to the ICU, to determine the level of acuity and mortality risk. This information can then be used in various ways, such as to provide the family with a prognosis, for clinical trials, and/or for quality assessment.

The SOFA score is not designed to influence medical management. It should not be used dynamically or to determine the success or failure of an intervention in the ICU.

CALCULATOR REVIEW AUTHOR

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Why to Use

The SOFA score can be used to determine the level of organ dysfunction and mortality risk in ICU patients.

When to Use

- The SOFA can be used on all patients who are admitted to an ICU.
- It is not clear whether the SOFA is reliable for patients who were transferred from another ICU.

Instructions

Calculate the SOFA score using the worst value for each variable in the preceding 24-hour period.

Next Steps

Even though it is calculated sequentially based on the worst value for each variable in the past 24 hours, the SOFA score is not meant to indicate the success or failure of interventions or to influence medical management.

Abbreviations: ICU, intensive care unit; SOFA, sequential organ failure assessment.

Evidence Appraisal

The SOFA variables were selected by a working group of the European Society of Intensive Care Medicine (Vincent 1996). In the initial validation study, 1449 patients were enrolled over a period of 1 month from 40 ICUs in 16 countries (Vincent 1998). The study found that the SOFA score had a good correlation to organ dysfunction/failure in critically ill patients.

The SOFA score was also prospectively validated in an observational cohort study conducted by Ferreira et al (2001) at the ICU of a university hospital in Belgium. The study included 352 patients and found that the SOFA score was a good indicator of prognosis.

Use the Calculator Now

Click here to access the calculator.

Calculator Creator

Jean-Louis Vincent, MD, PhD
Click here to read more about Dr. Vincent.

References

Original/Primary Reference

- Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-710. **https://www.ncbi.nlm.nih.gov/pubmed/8844239**

Validation References

- Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med*. 1998;26(11):1793-1800. **https://www.ncbi.nlm.nih.gov/pubmed/9824069**
- Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286(14):1754-1758. **DOI: https://doi.org/10.1001/jama.286.14.1754**

Additional Reference

- Cárdenas-Turanzas M, Ensor J, Wakefield C, et al. Cross-validation of a Sequential Organ Failure Assessment score-based model to predict mortality in patients with cancer admitted to the intensive care unit. *J Crit Care*. 2012;27(6):673-680. **DOI: https://doi.org/10.1016/j.jcrc.2012.04.018**

APPENDIX I: STUDY STOPPING CRITERIA

Table 10. Criteria in the Isoflurane Group Triggering an Ad Hoc DSMB Meeting

Occurrence of moderate or severe AEs related to isoflurane or the device (no plausible alternative explanation; assessed as being possibly, probably, or definitely related to the study drug by Investigator or Sponsor)	**Events observed in the isoflurane group**
SAE – death	>1 patient
SAE (events listed in the reference safety information)*	≥5 patients
SUSAR (events **not** listed in the reference safety information)*	≥3 patients
Malignant hyperthermia	>2 patients
Hypoxemia – moderate	>10 patients
Hypoxemia – severe	>5 patients
Hypercapnia – moderate	>10 patients
Hypercapnia – severe	>5 patients
Accidental self-extubation	≥10 patients
Hypotension – moderate	>10 patients
Hypotension – severe	>5 patients
Drug-induced liver injury – moderate and severe	≥2 patients
Hyperkalemia – moderate	>10 patients
Hyperkalemia – severe	>5 patients
Rhabdomyolysis independent of malignant hyperthermia – moderate	≥5 patients
Rhabdomyolysis independent of malignant hyperthermia – severe	≥2 patients

*The reference safety information is defined in the IB (Section 7.7, Reference Safety Information).
AE = adverse event; DSMB = Data Safety Monitoring Board; IB = Investigator's Brochure; SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction.

No action will be taken on a study level for any of the expected adverse drug reactions (ADRs) labelled in the propofol United States product info. The action taken at a patient level for these ADRs is at the discretion of the Investigator.

If >5 reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) concerning the same type of medical event (ie, unlabeled events with a suspected relationship to treatment), there will be an ad hoc Data Safety Monitoring Board meeting.

Definitions and grading of each AE of special interest is described in Appendix G.

APPENDIX J: SIMPLIFIED ACUTE PHYSIOLOGY SCORE

For additional details on Simplified Acute Physiology Score (SAPS) III scoring and evaluation, reference the publications provided on the main SAPS III website: https://www.saps3.org/archive/publications/.

SAPS III will be calculated using the [redacted] online calculator available at the following website: [redacted]

APPENDIX K: EQUIVALENT VASOPRESSOR DOSE

The vasopressor equivalent dose will be calculated using the conversion factors presented in Table 11.

Table 11. Vasopressor Conversion Ratios

Vasopressor	Range of Ratios[a]	Suggested Ratio[a]	Equivalent Dose
Norepinephrine	1	1	0.1 mcg/kg/min
Epinephrine	0.7-1.4	1	0.1 mcg/kg/min
Dopamine	75.2-144.4	100	10 mcg/kg/min
Metaraminol	8.3	8	0.8 mcg/kg/min
Phenylephrine	1.1-16.3	10	1 mcg/kg/min
Vasopressin	0.3-0.4	0.4	0.04 units/min
Angiotensin II	0.07-0.13	0.1	0.01 mcg/kg/min

Formula: norepinephrine equivalents = norepinephrine + epinephrine + phenylephrine/10 + dopamine/100 + metaraminol/8 + vasopressin × 2.5 + angiotensin II × 10.

a. Reported in reference to 1 unit of norepinephrine. For calculations, all doses are in mcg/kg/min with the exception of vasopressin in units/min. Angiotensin II is usually dose in ng/kg/min and must be converted to mcg/kg/min for calculations.

Source: Goradia S, Sardaneh AA, Narayan SW, et al. Vasopressor dose equivalence: A scoping review and suggested formula. *J Crit Care*. 2021;61:233-240.