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INhaled Sedation versus Propofol in REspiratory failure in the Intensive Care Unit (INSPiRE-ICU1): protocol for a randomised, controlled trial

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ABSTRACT

Introduction Sedation in mechanically ventilated adults in the intensive care unit (ICU) is commonly achieved with intravenous infusions of propofol, dexmedetomidine or benzodiazepines. Significant limitations associated with each can impact their usage. Inhaled isoflurane has potential benefit for ICU sedation due to its safety record, sedation profile, lack of metabolism and accumulation, and fast wake-up time. Administration in the ICU has historically been restricted by the lack of a safe and effective delivery system for the ICU. The Sedaconda Anaesthetic Conserving Device-S (Sedaconda ACD-S) has enabled the delivery of inhaled volatile anaesthetics for sedation with standard ICU ventilators, but it has not yet been rigorously evaluated in the USA. We aim to evaluate the efficacy and safety of inhaled isoflurane delivered via the Sedaconda ACD-S compared with intravenous propofol for sedation of mechanically ventilated ICU adults in USA hospitals.

Methods and analysis INhaled Sedation versus Propofol in REspiratory failure in the ICU (INSPiRE-ICU1) is a phase 3, multicentre, randomised, controlled, open-label, assessor-blinded trial that aims to enrol 235 critically ill adults in 14 hospitals across the USA. Eligible patients are randomised in a 1.5:1 ratio for a treatment duration of up to 48 (±6) hours or extubation, whichever occurs first, with primary follow-up period of 30 days and additional follow-up to 6 months. Primary outcome is percentage of time at target sedation range. Key secondary outcomes include use of opioids during treatment, spontaneous breathing efforts during treatment, wake-up time at end of treatment and cognitive recovery after treatment.

Ethics and dissemination Trial protocol has been approved by US Food and Drug Administration (FDA) and central (Advarra SSU00208265) or local institutional review boards ((IRB), Cleveland Clinic IRB FWA 00005367, Tufts HS IRB 20221969, Houston Methodist IRB PR000035247, Mayo Clinic IRB Mod22-001084-08, University of Chicago IRB21-1917-AM011 and Intermountain IRB 033175). Results will be presented at scientific conferences, submitted for publication, and provided to the FDA.

Trial registration number NCT05312385.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is a multicentre, randomised, controlled, open-label, assessor-blinded trial to evaluate the efficacy and safety of inhaled isoflurane delivered via the Sedaconda Anaesthetic Conserving Device-S compared with intravenous propofol for sedation of mechanically ventilated adults intensive care unit (ICU) patients.
⇒ The inclusion of a diverse group of medical and surgical mechanically ventilated adult ICU patients requiring continuous sedation across a large number of geographically diverse US ICUs enhances generalisability of the trial results.
⇒ The use of guideline-driven best sedation practices, including the ABCDEF bundle, in all participating ICUs ensures the trial results are applicable to modern, evidence-based care environments.
⇒ Although outcome assessors are blinded to treatment group assignment, patients, families and clinicians are not; clinician knowledge of sedation strategy assignment may potentially influence clinical decision-making and reporting.

INTRODUCTION

Pain, agitation and delirium are commonly experienced by critically ill adults, especially those requiring invasive mechanical ventilation.[1] A significant proportion of mechanically ventilated adults admitted to the intensive care unit (ICU) require sedation, and often analgesia, to optimise their comfort, safety and clinical management. This therapy is most commonly achieved with intravenous infusions of propofol, dexmedetomidine or benzodiazepines (eg, midazolam). These sedatives, even when titrated to an established sedation goal, have significant limitations and potential harmful effects in

the critically ill—a population with frequent underlying comorbidity and end-organ dysfunction that impact drug response and clearance. Propofol can cause hypotension, hyperlipidaemia, respiratory depression, is immunosuppressive, and carries the risk of propofol-related infusion syndrome, a potentially lethal side effect.[2–4] Dexmedetomidine has been associated with bradycardia and hypotension, potentially increased mortality in younger adults, and may be insufficient when deeper levels of sedation are required.[5–8] Midazolam infusions are associated with drug accumulation leading to coma, prolonged wake-up times, increased length of mechanical ventilation and hospital stay, tolerance necessitating dose-escalation, pharmacogenomic variability, dose-related incident delirium, withdrawal symptoms after discontinuation, and increased mortality.[9–15]

Current guidelines[1] recommend the use of non-benzodiazepine sedatives, such as propofol or dexmedetomidine, when continuous sedation is required based on several studies demonstrating more favourable short- and long-term outcomes with their use.[12–14 16] Recent trials evaluating propofol and dexmedetomidine, however, have found patients frequently require the administration of additional sedatives (each with their own safety concerns) and spend significant time outside of the desired sedation target despite the protocolised use of daily spontaneous awakening studies and the prioritisation of light sedation goals.[17–19] While multidomain approaches like the ABCDEF bundle[20] have been shown to reduce delirium and coma, facilitate mechanical ventilation and ICU liberation, and reduce mortality, they can be challenging to adopt on a routine basis, particularly during surges of ICU care as was recently experienced during the COVID-19 pandemic.[21–23] None of the currently available intravenous sedatives in the USA meet all the criteria for the ideal sedative in mechanically ventilated ICU adults, and, thus, there remains an unmet medical need for additional safe and highly efficacious sedative agents for this population.

Inhaled volatile anaesthetics, such as isoflurane, have long been used for general anaesthesia in operating rooms and possess many advantageous properties for ICU sedation in mechanically ventilated adults including the ability to be titrated to a full range of sedation depths, perform rapid wake-ups, avoid drug tolerance and withdrawal, provide analgesia, reduce respiratory depression and avoid drug accumulation, even in the setting of end-organ dysfunction given their minimal metabolism and lack of renal clearance.[24–27] Use of inhaled volatile agents in the ICU has traditionally been limited to rescue scenarios (eg, refractory bronchospasm, status asthmaticus and status epilepticus) due to the requirement of anaesthesia personnel and machines for administration.

Recent technological advances, however, have greatly simplified the administration of inhaled volatile anaesthetics in the ICU through the introduction of volatile anaesthetic reflection filters to minimise anaesthetic vapour loss and enable inhaled sedation to be performed with standard ICU ventilators. The Sedaconda Anaesthetic Conserving Device-S (Sedaconda ACD-S, Sedana Medical AB, Danderyd, Sweden) is a small, disposable, volatile anaesthetic agent delivery and reflection system, developed for the administration of isoflurane (or sevoflurane) primarily for ICU sedation by non-anaesthesia personnel (figure 1). The anaesthetic is continuously infused via a syringe pump by the bedside nurse into the ACD-S device, and titration to the targeted sedation goal is achieved by changing the syringe pump infusion rate. The ACD-S device is inserted into the ventilator circuit between the patient's endotracheal tube or tracheostomy and the Y-piece in place of a passive heat and moisture exchanger. The small amount of isoflurane that is not reflected by the ACD-S device is captured by gas scavenging on the ventilator exhaust port, resulting in a closed administration circuit shown to result in minimal environmental release of isoflurane and at an amount that is far below current US Occupational Safety and Health Administration exposure limits.[28]

The Sedaconda ACD-S has been approved and used for inhaled sedation in the ICU in over 40 countries in Europe, Asia and South America for several years. Isoflurane via the Sedaconda ACD-S was recently approved for sedation of mechanically ventilated adults in 17 European countries. Growing evidence and clinical experience from this increased use within the ICU indicate sedation efficacy reduced opioid requirements, ability to maintain spontaneous breathing, fast predictable wake-up regardless of sedation depth, limited side effects and less need for additional sedatives.[29–33] Clinically insignificant drug accumulation and rapid wake-up suggest isoflurane may potentially improve delirium in the ICU and long-term cognition afterwards,[34] and inhaled anaesthetics in critically ill patients have been associated with fewer hallucinations and faster psychomotor recovery.[35] However, most studies to date are small, and the impact of inhaled anaesthetics on delirium and cognitive outcomes in ICU populations remain unclear. Isoflurane administered via the Sedaconda ACD-S for inhaled sedation in the ICU is currently not approved by the US Food and Drug Administration (FDA) and has not been evaluated within the US healthcare system where ICU personnel and management practices are different from Europe.[36 37] Therefore, the INhaled Sedation versus Propofol in REspiratory failure in the ICU 1 trial (INSPiRE-ICU1, NCT05312385) was designed to evaluate the efficacy and safety of inhaled isoflurane delivered via the Sedaconda ACD-S compared with intravenous propofol for sedation of mechanically ventilated ICU adult patients in the USA.

METHODS AND ANALYSIS

Trial design, setting and registration

Trial design

INSPiRE-ICU1 is a phase 3, multicentre, randomised, controlled, open-label, assessor-blinded trial evaluating the efficacy and safety of inhaled isoflurane delivered

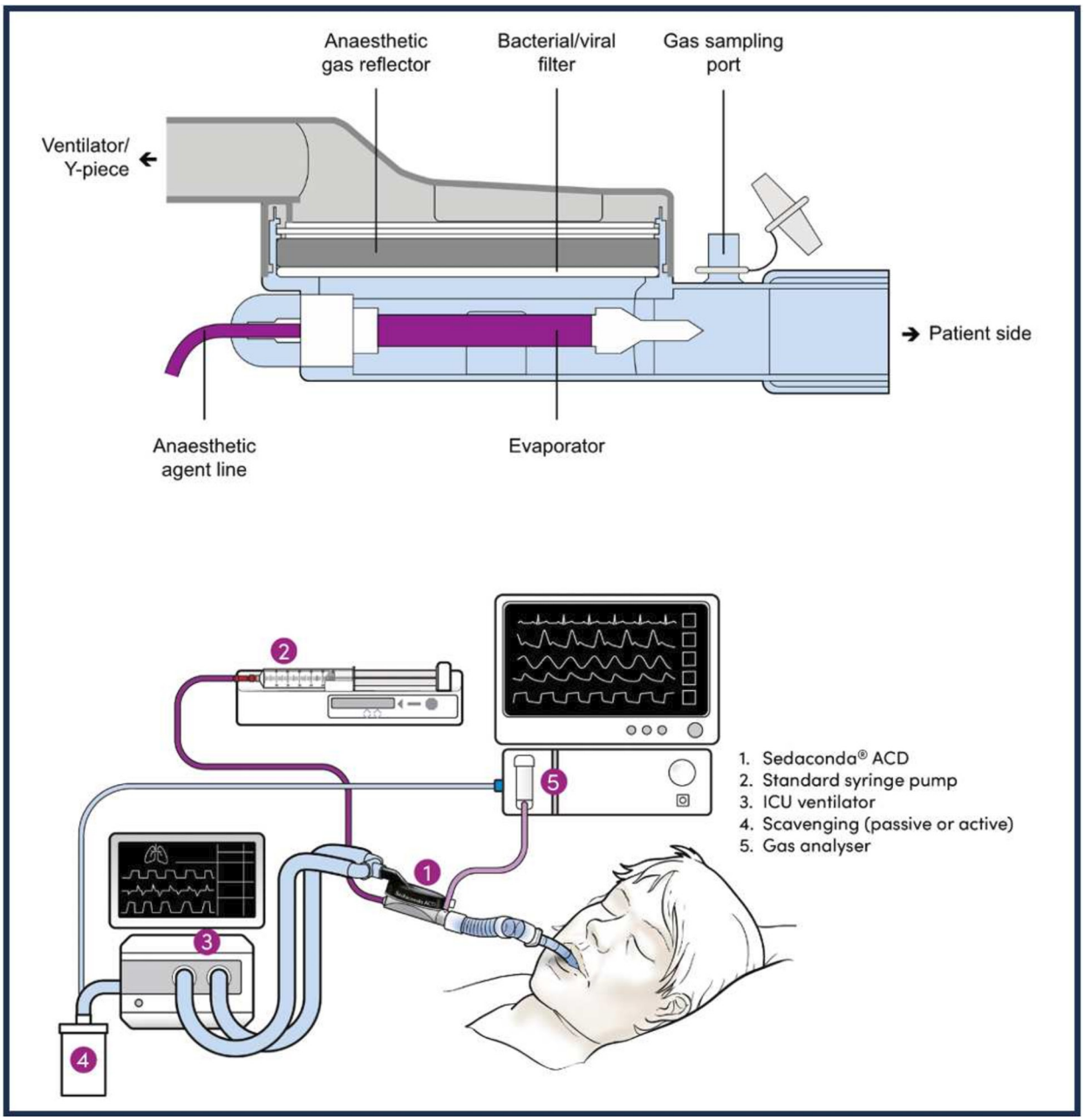

Figure 1 The Sedaconda Anaesthetic Conserving Device-S (Sedaconda ACD-S) is a small, disposable volatile anaesthetic agent delivery and reflection system capable of administering isoflurane to mechanically ventilated patients. Standard placement is integrated into the ventilator circuit in place of the commonly used passive heat and moisture exchanger, between the patient's endotracheal tube or tracheostomy and the Y-piece of the ventilator tubing. The evaporator is a porous plastic rod with a large surface area that vaporises isoflurane with the airflow. Isoflurane exhaled by the patient enters the reflection medium, is absorbed to the active carbon filter, and is desorbed and returned to the patient in the next breath with approximately 90% reflection. The syringe is a standard 50–60 mL syringe with a unique connector system to prevent unintentional intravenous administration. Sedation depth is adjusted by increasing or decreasing the syringe pump rate. A FlurAbsorb active carbon filter is used to scavenge the small amounts of exhaled isoflurane not reflected by the ACD-S device to create a closed administration circuit. End-tidal carbon dioxide (CO_2) concentration is measured with standard gas analyser and presented with capnography. ICU, intensive care unit.

via the Sedaconda ACD-S compared with intravenous propofol for the sedation of mechanically ventilated adults ICU patients. INSPiRE-ICU1 is the first of two, methodologically identical, parallel phase 3 trials (INSPiRE-ICU1 and INSPiRE-ICU2). Reporting of the INSPiRE-ICU1 protocol herein adheres to the Standard Protocol Items for Randomised Trials (SPIRIT)[38] statement as delineated in online supplemental materials, SPIRIT checklist.

Patient and public involvement

Patients or the public were not involved in trial design, conduct or dissemination plans of our research.

Setting

INSPiRE-ICU1 will include 235 adult patients (≥18 years) from 14 academic hospital systems in the USA.

Trial registration

The trial is registered on ClinicalTrials.gov and under FDA Investigational New Drug Application Number 141407.

Population, eligibility, screening and consent

Study population and eligibility

The target population includes adults in the ICU anticipated to require invasive mechanical ventilation and continuous sedation to achieve a clinically indicated Richmond Agitation Sedation Scale score (RASS)[39] range of −1 to −4 for >12 hours without concomitant conditions or considerations that confound assessment of sedation depth. Eligible patients include those admitted to an ICU with an anticipated need for mechanical ventilation and continuous sedation or whom have upcoming planned surgery and a similar anticipated need for postoperative continuous sedation and mechanical ventilation. Exclusion criteria included severe neurological condition causing inability to participate in the trial or contraindication to propofol or isoflurane including severe haemodynamic compromise defined by norepinephrine >0.3 µg/kg/min or equivalent as defined in online supplemental appendix A. Full inclusion and exclusion criteria are delineated in box 1.

Screening and consent

Patients in the ICU fulfilling all inclusion criteria and no exclusion criteria are considered for enrolment. Initial informed consent is most commonly obtained from a legally authorised representative and then re-confirmed with the patient when their clinical condition permits. Initial screening is permitted up to 30 days prior to any study treatments to allow for the identification and potential enrolment of patients with planned postoperative mechanical ventilation. In such instances, informed consent is obtained initially from the patient.

Timeline, sample size and recruitment

Study timeline and flow

The study timeline and participant flow are summarised in figure 2.

Sample size

The trial is powered to evaluate the non-inferiority of inhaled isoflurane via the Sedaconda ACD-S compared with intravenous propofol in maintaining the depth of sedation within the target RASS range of −1 to −4. Based on previous studies and accounting for lack of familiarity in the USA with inhaled sedation in the ICU, anticipated time spent in the target RASS range is on average 70% with isoflurane and 75% with propofol with an SD of approximately 20%.[32 40] Assuming an attrition rate of 5%, a total of 235 randomised patients will provide 95% power for a non-inferiority test with a one-sided alpha of 0.025.

Box 1 Inclusion and exclusion criteria

Inclusion criteria

⇒ Adults ≥18 years of age.
⇒ Anticipated to require >12 hours of invasive mechanical ventilation and continuous sedation in the ICU.
⇒ Receipt of continuous sedation due to clinical need for sedation to RASS<0.

Exclusion criteria

⇒ Need for RASS −5.
⇒ Sedation for invasive mechanical ventilation for >72 hours.[1]
⇒ Severe neurological condition causing inability to participate in the trial, namely inability to assess RASS and CPOT.[2]
⇒ Ventilator tidal volume <200 or >1000 mL.
⇒ Need for ECMO, $ECCO_2R$, HFOV or HFPV.
⇒ Comfort care only (ie, end of life care).
⇒ Contraindication to propofol or isoflurane, including:
  ⇒ Severe haemodynamic compromise, defined as the need for norepinephrine ≥0.3 µg/kg/min (or equivalents) to maintain blood pressure within a clinically acceptable range (eg, ≥65 mm Hg).[3]
  ⇒ Known or suspected personal/family MH history, high MH risk or acute drug-induced muscle injury.
  ⇒ Allergy to isoflurane or propofol, or propofol infusion syndrome.
⇒ History of ventricular tachycardia and/or long QT syndrome.
⇒ Intravenous benzodiazepine or barbiturate requirements for seizures or dependencies, including alcohol withdrawal.
⇒ Neuromuscular disease that impairs spontaneous ventilation.[4]
⇒ Concurrent enrolment in another study that, in the investigator's opinion, would impact the patient's safety or study assessments.
⇒ Participation in another study involving investigational drug(s) or devices(s) within 30 days.
⇒ Previous randomisation or receipt of treatment in INSPiRE-ICU1 or 2.
⇒ Anticipated requirement of treatment with continuous infusion of an NMBA for >4 hours.
⇒ Female patients who are pregnant or breastfeeding.
⇒ Imperative need for continuous active humidification through mechanical ventilation circuit.
⇒ Attending physician's refusal to include the patient.
⇒ Inability to obtain informed consent.

CPOT, Critical Care Pain Observation Tool score; $ECCO_2R$, extracorporeal CO_2 removal; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillation ventilation; HFPV, high-frequency percussive ventilation; ICU, intensive care unit; MH, malignant hyperthermia; NMBA, neuromuscular blocking agent; RASS, Richmond Agitation Sedation Scale score.
[1]For patients extubated ≥24 hours and subsequently re-intubated, the start time of sedation for invasive mechanical ventilation is considered the time of re-intubation. For patients extubated and re-intubated within 24 hours, the start time of sedation for invasive mechanical ventilation is considered to be the time of the original intubation. [2]Examples include acute stroke, severe head trauma, meningitis, suspected or known intracranial pressure elevation, or the need for intracranial pressure monitoring. [3]Vasopressor doses are summed into norepinephrine equivalents according to the approach delineated in online supplemental appendix A. [4]Examples include C5 or higher spinal cord injury, amyotrophic lateral sclerosis, etc.

Recruitment

Recruitment started 28 April 2022 with completion of recruitment expected in 2024. Queries to investigators, data cleaning and closure of the database will follow. Data analysis, manuscript preparation and submission for publication are anticipated to occur in 2025.

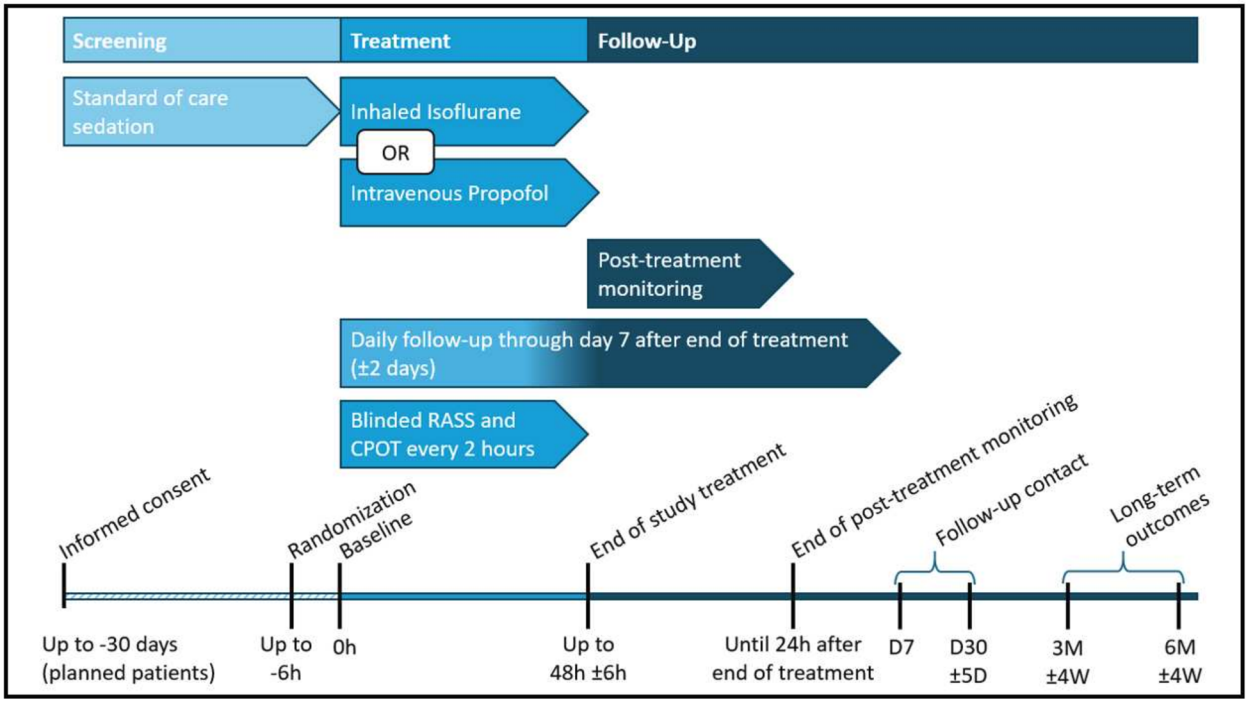

Figure 2 Trial scheme for patient progression. Patients are screened between days −30 and 0 hours prior to initiation of study drug administration to determine trial eligibility. Baseline values are obtained during the baseline phase. At randomisation, ongoing sedation and opioid infusions are reduced to half. Initiating study drug treatment is performed as close to randomisation as possible, no later than 6 hours after randomisation. Study drug titration is performed by the clinical team to reach targeted sedation depth. Blinded RASS assessments occur every 2 hours with pain levels assessed in parallel with CPOT assessments. Study drug treatment is stopped when patient is planned for extubation or reaches maximum treatment duration of 48 (±6) hours, whichever occurs first. Patients are monitored until 24 hours after end of treatment, followed-up until day 7 and day 30, and receive long-term assessments at 3 and 6 months. COPT, Critical Care Pain Observation Tool; RASS, Richmond Agitation Sedation Scale.

Assignment of interventions, blinding and masking

Randomisation

Owing to the novelty of inhaled sedation in the US ICUs, sites are allowed approximately 3–5 run-in training patients per the full inclusion and exclusion criteria who receive isoflurane in a manner consistent with the remainder of the trial protocol, with the exception that all assessments are non-blinded. These patients are not included in the power calculation of sample size, and data from the run-in patients will not contribute to efficacy analyses. Patients are otherwise randomised in a 1.5:1 ratio to receive isoflurane or propofol as determined by a computer-generated sequence using a central online management system. The approach to randomisation is stratified according to the Simplified Acute Physiology Score (SAPS) III score[41] and patient type. SAPS is categorised as 0 to <40, 40 to <60 or ≥60 and patient type is categorised as medical or surgical, as assessed at the time of screening. Surgical patients are considered those falling into at least one of the following categories: trauma; surgery within the two prior weeks and for whom respiratory failure is related to that surgery, surgical disease process or a complication thereof; and patients anticipated to undergo surgery within the next 2 days for a condition that is related to the aetiology of respiratory failure. Study drug is then provided according to randomisation by the local investigational pharmacy.

Blinding and masking

Owing to the complexity of clinical care in the ICU, differing routes and mechanisms of study drug administration (ie, inhaled vs intravenous), and differing pharmacological effects of the study drugs, including their onset and offset, bedside staff are not blinded to the treatment assignment. Treatment assignments are not disclosed to members of the care team not involved in the direct care of the patient. Key study assessments are conducted by blinded assessors trained in the standardised assessment of RASS and Critical Care Pain Observation Tool (CPOT)[42] to mitigate the risk of bias. As such, the trial is open-label with blinded assessments. Masking is accomplished by establishing both an inhaled and intravenous drug delivery setup with one being active and the other being non-functional according to treatment assignment. Recognisable components of both setups are physically concealed to mitigate the risk of assessors becoming aware of the treatment assessment (ie, unblinded). Additionally, the standalone gas monitor (see next section for details) is configured to display only capnography, with end-tidal agent concentrations obscured by default but available to the treating clinical team on-demand. If a potential assessor becomes unblinded, this assessor will not participate in further assessments.

Treatment approach, intervention, control and concomitant care

Treatment approach

After randomisation but before study drug initiation, standard of care (SOC) sedative and opioid analgesics are reduced by half unless contraindicated by agitation or pain. Sedative agents are then stopped on initiation of the study drug (isoflurane or propofol) to further minimise confounding of sedation depth assessments and other measures by residual SOC sedative agent use. Opioid medications for analgesia are allowed throughout the study drug treatment period per unit standard pain assessment protocols. All patients receive the allocated study drug for up to 48±6 hours as the primary sedative agent, titrated to achieve the target RASS range of −1 to −4 based on clinical assessments. A standalone end-tidal carbon dioxide and anaesthetic agent monitor (BeneVision N12, Mindray, China) is used for monitoring of exhaled gasses in both arms of the trial alongside SOC physiologic and clinical monitoring.

Intervention: inhaled isoflurane

Inhaled isoflurane is administered via the Sedaconda ACD-S, previously known as the AnaConDa-S. The Sedaconda ACD-S contains a porous plastic evaporator rod, facilitating isoflurane vaporisation and an interwoven lipophilic active carbon filter, facilitating agent conservation as well as heat and moisture exchange. The Sedaconda ACD-S is placed in the ventilator circuit between the tracheal tube and the Y-piece, and isoflurane is delivered to the Sedaconda ACD-S continuously via a syringe pump (figure 1). Unique connectors and fittings on the isoflurane syringe and delivery tubing are designed to prevent unintentional intravenous drug delivery, and the low priming volume (1.2 mL) delivery tubing is permanently fused to the Sedaconda ACD-S. Scavenging of exhaled gasses is accomplished by diverting exhaled gasses from the ventilator exhaust port through an active carbon filter (FlurAbsorb, Sedana Medical AB, Sweden) before exhausting to the ambient atmosphere. The Sedaconda ACD-S introduces approximately 50 mL of dead space into the ventilator circuit; therefore, patients with tidal volumes <200 mL are excluded from the trial given their risk for clinically significant rebreathing. The Sedaconda ACD-S is changed every 24 hours or more often when clinically indicated (eg, secretion burden).

After priming the Sedaconda ACD-S, isoflurane is administered at a starting dose up to 3 mL/hour, and a lower starting dose may be used when clinically indicated (eg, deep sedation or hypotension at baseline). Isoflurane is then titrated according to clinical assessment of sedation depth based on RASS score assessment in recommended increments of 0.5–1 mL/hour to reach the RASS score target. Peak clinical effects are typically noticeable within 10–15 min after an isoflurane dose change. Isoflurane is administered up to a maximum dose of 15 mL/hour, and bolus doses are administered at 0.3–0.5 mL to rapidly deepen sedation when clinically indicated.

Control: intravenous propofol

Propofol is administered intravenously via a conventional infusion pump channel and intravenous tubing at a starting dose of 10–25 µg/kg/min or the pre-randomised dose in patients already receiving propofol for SOC sedation. Propofol is then titrated according to clinical assessment of sedation depth based on RASS score assessment in recommended increments of 5 –10 µg/kg/min every 5–10 min up to a maximum dose of 66 µg/kg/min to reach the RASS score target. Boluses of propofol can be administered in doses of 0.3–0.5 mg/kg to rapidly deepen sedation when clinically indicated.

Spontaneous awakening trials and the wake-up test

Sedation may be interrupted for clinical purposes, such as neurological examinations and/or daily spontaneous awakening trials (SATs), in accordance with SOC. Prior to the end of treatment (EOT), the time to wake-up is measured for all patients guided by a safety screen as delineated in online supplemental appendix B unless prohibited by patient safety considerations in the judgement of the clinical team or investigator. The wake-up test starts when the study drug is stopped and continues until one of four scenarios occurs: RASS≥0 is confirmed by blinded assessment, 4 hours pass after EOT, re-sedation is clinically indicated (eg, due to cardiorespiratory distress), or occurrence of a new-onset neurological deficit or detection of an intracranial event.

During SAT or the wake-up test, medications intended to reduce autonomic stress (eg, agitation), such as antipsychotics, analgesics or α2-adrenergic agonists (eg, dexmedetomidine), are permitted in patients who do not otherwise tolerate awakening. If the patient is deemed to require re-sedation after awakening, the study drug is restarted, and bolus doses of the assigned study drug may be given.

Spontaneous breathing tests and extubation

Daily paired SAT and spontaneous breathing trial (SBT) are considered elements of SOC as described, and extubation is to be performed per the SOC.

End of treatment

Cessation of the study drug is considered EOT when one of three scenarios are met:

1. Study drug is stopped for extubation,
2. 48±6 hours of study drug treatment, or
3. Study drug discontinuation based on investigator judgement (ie, when continued treatment is not in the patient's best interest).

Concomitant care

ABCDEF bundle

Care of patients in the ICU is managed as per the SOC guided by the widely adopted ABCDEF bundle, which has been shown to improve patient outcomes proportional to the compliance of bundle element delivery.[20 43] The **a**ssessment and monitoring of pain is accomplished via the validated CPOT scale.[42] Assessment of **b**oth

awakening and breathing with paired SAT and SBT is conducted daily when clinically appropriate, guided by a safety screen delineated in online supplemental appendix B. The **c**hoice of analgesic and sedative approaches is informed by continual clinical assessment and efforts to decrease unnecessary exposure to relevant agents. **D**elirium monitoring and management is aimed at maximising non-pharmacological strategies for its prevention and treatment. Strategies that promote **e**arly mobility and exercise are associated with reduced delirium and other favourable clinical outcomes. **F**amily engagement is the final component of the ABCDEF bundle, in recognition of the key role that family members and/or surrogate decision makers play in decision-making, treatment planning and support for the patient.

Treatment of pain

Treatment of pain throughout the trial follows the SOC and may include opioids, including infusions, or other non-opioid analgesic medications (eg, acetaminophen, non-steroidal anti-inflammatories). Decisions about analgesic approaches are at the discretion of the clinical team and investigator but should be guided by CPOT assessments. To minimise the potential adverse effects of opioids, it is recommended to use the lowest possible doses to achieve adequate analgesic and comfort.

Rescue sedation and treatment failure

Sedative requirements, whenever possible, are met using the assigned study drug, including active titration and/or bolus dosing up to two times per hour. Rescue sedation, in the context of the trial, is defined as the need for sedative agents other than the assigned study drug to address acute agitation despite adequate analgesia. If the assigned study drug is insufficient to alleviate inadequate sedation despite administration at the maximum dose, adequate analgesia and optimised clinical care (eg, ventilator settings that promote synchrony, positioning to promote comfort), permitted second line rescue sedative approaches include a dexmedetomidine infusion (for no more than 3 hours in a 24-hour period) and/or midazolam bolus doses (no more than three doses in 24 hours). When the assigned study drug and second line rescue sedative maximum doses are exceeded, the patient is considered to have failed treatment, the assigned study drug is stopped and sedation reverts back to the SOC. Full details about rescue sedation and treatment failure are delineated in online supplemental appendix C.

Prohibited and restricted medications

Medications used for the purpose of sedation or paralysis other than the assigned study and rescue drugs are prohibited during the treatment period. Examples of such medications include: barbiturates, chloral hydrate, chlorpromazine, clonidine, gamma-hydroxybutyrate and ketamine. Additionally, paralytics or neuromuscular blocking medications for >4 hours during the treatment period are prohibited as these preclude the ability to maintain the target RASS sedation range of −1 to −4. If prohibited medications are required for patient safety during the treatment period, the patient meets criteria for early study drug discontinuation and transition to SOC. Other sedative and paralytic medications are restricted except in specific circumstances including but not limited to propofol outside of its assignment as a study drug and specific types of procedural sedation in the ICU, benzodiazepines outside of midazolam as a rescue sedative per the protocol, α2-adrenergic agonists outside of dexmedetomidine as a rescue sedative or as part of SAT and wake-up testing, antipsychotics apart from those prescribed prior to ICU admission or as part of SAT and wake-up testing, and neuromuscular blocking drugs outside of application for ≤4 hours for procedures. Full details about prohibited and restricted medications are delineated in online supplemental appendix D.

Sedation for diagnostic or therapeutic procedures in the ICU

The assigned study drug is the primary modality by which to accomplish adequate procedural sedation in the ICU in addition to the treatment of pain, as applicable, per the SOC. Patients assigned to isoflurane requiring airway procedures (eg, bronchoscopy and endotracheal tube suctioning) may receive propofol in either bolus doses of 1–2 mg/kg or as an infusion up to 66 µg/kg/min.

Sedation for diagnostic or therapeutic procedures outside of the ICU

For purposes of this trial, administration of the assigned study drug is confined to the ICU during the treatment period. When sedation outside of the ICU is required (eg, for transfers to operating room or imaging) SOC sedation at the discretion of the clinical team will be administered.

Primary, secondary and exploratory outcomes

Primary outcome

The primary outcome is the percentage of time sedation depth is maintained within the prescribed RASS target range of −1 to −4, in the absence of rescue sedation, through the end of study drug treatment. This parameter will be derived for each patient, as follows:

% adequate sedation=(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: (a) blinded RASS is outside the target range (ie, less than −4 or greater than −1), (b) rescue sedation is needed, that is, RASS target is not achieved, despite use of study drug or (c) 'treatment failure', where 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.

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. Such omitted blinded RASS assessments due to SOC procedures in or outside the ICU are not considered protocol deviations and are not counted as failure time.

The detail of the analysis and the description of the estimand and missing data handling will be provided in the Statistical Analysis Plan (SAP) finalised prior to database lock.

Secondary and exploratory outcomes

Four key secondary outcomes will be evaluated. First, the change in mean fentanyl-equivalent opioid dose during the study drug treatment period compared with the mean opioid dose during the 60 min prior to randomisation. Second, the time from cessation of study drug treatment to RASS≥0 (up to 4 hours) as ascertained by the wake-up test. Third, delirium and delirium severity as assessed by the Confusion Assessment Method for the Intensive Care Unit-7 (CAM-ICU-7)[44] at 60±10 min after EOT in patients clinically appropriate for CAM-ICU-7 assessment, as discussed subsequently. Fourth, the proportion of ventilator parameter observations indicating spontaneous breathing during the study drug treatment period.

Additional secondary outcomes comparing the effects of isoflurane versus propofol on time to extubation, days alive and free of mechanical ventilation (through study day 30), days alive and free of the ICU (through study day 30), delirium and coma free days (until 7 days after EOT), mortality (at 30 days, 3 months and 6 months after randomisation), and use of restraints will be examined. Safety outcomes, exploratory outcomes and exploratory long-term outcomes are delineated in online supplemental appendix E.

Observations and measures, data collection and data management

Observations and measures

A listing of key observations and measures and their associated time points during the trial are delineated in online supplemental table and reviewed subsequently.

RASS and CPOT

RASS is used for the assessment of agitation and sedation throughout the trial, and CPOT is used to evaluate the adequacy of analgesia. Unblinded RASS and CPOT assessments are conducted within 30 min prior to study drug administration, serving as a baseline. For the primary endpoint, blinded RASS assessments begin 2 hours after initiation of the study drug and continue every 2 hours until EOT. A supplemental blinded RASS assessment also occurs within 15 min of EOT to establish a baseline value for the wake-up test. Blinded assessors are instructed to observe the patient for at least 30–60 s, score the lightest RASS observed, and use a shoulder shake (and not a sternal rub) if required to discriminate between a score of −4 and −5. Blinded pain assessment using the CPOT occurs every 2 hours until the EOT. Blinded RASS and CPOT assessment determinations are shared with bedside clinical staff after documentation. SOC assessments of agitation and pain by clinical staff to titrate medications are performed in addition to the blinded study assessments.

The extent to which blinded RASS and CPOT assessments reflect the overall depth of sedation may be confounded by clinically appropriate intentional deepening of sedation, lightening of sedation or the need for neuromuscular blocking agents. To that end, the protocol provides criteria for resumption of blinded RASS and CPOT assessments when these interventions are administered (see online supplemental appendix F).

Confusion Assessment Method for the Intensive Care Unit-7

Cognitive recovery at 60±10 min after EOT is evaluated by a blinded assessor using the CAM-ICU-7. This blinded assessor also ascertains the RASS at this time point as the evaluation could be confounded by deeper level of sedation. Patients already re-sedated under the auspices of the SOC are excluded, as well as patients with an RASS of −4 or −5. CAM-ICU-7 is assessed at least daily during the treatment period and through 7 days after EOT or until hospital discharge, whichever comes first.

Physical and neurocognitive function and outcomes

Activities of daily living and cognition at baseline are measured by the Katz Index of Independence in Activity of Daily Living,[45] Pfeffer functional activities questionnaire[46] and Informant Questionnaire on Cognitive Decline in the Elderly Short Form.[47] Long-term psychological and cognitive outcome assessments are conducted by blinded neuropsychology professionals over telephone at 3 months (±4 weeks) and 6 months (±4 weeks) using a comprehensive battery of instruments.

Other parameters

Patient characteristics, concomitant medications (eg, analgesics, sedatives, vasopressors), organ function assessed by Sequential Organ Failure Assessment (SOFA) score, ventilator parameters, laboratory findings (including arterial blood gas analysis), major ICU interventions, other clinical complications, length of stay, disposition and mortality are all assessed at specified intervals throughout the study period.

Data collection and management

Sites record data using an electronic case report form (eCRF), which is verified against source documentation by clinical research associates and reviewed during regularly occurring on-site and remote monitoring visits. Validation

checks programmed within the eCRF, as well as supplemental validation performed via review of the downloaded data, is applied to the data to ensure accuracy, consistency and reliability. Audits may be performed at individual sites to ensure data validity. Research staff at sites receive relevant training to support adherence to data collection and management protocols. The eCRF is used to facilitate automatic data validation alongside regular review and ad hoc checks of the entered data. Any known or suspected errors are referred to the relevant site for resolution. All corrections or changes made to any trial data are appropriately tracked in an audit trail in compliance with Title 21 of the Code of Federal Regulations Part 11.

Education and training, study withdrawal, adherence and monitoring

Education and training

Site research staff are trained to support successful protocol implementation, associated study procedures, and data collection and management. Given that inhaled isoflurane for routine sedation during mechanical ventilation in the ICU has been previously unavailable in the USA, a set of complete written, summary and audiovisual educational tools have been developed for the training of physician, nurse and respiratory therapy clinical staff, as well as investigational pharmacy. These educational efforts include multidisciplinary training in the setup, use, maintenance and discontinuation of the Sedaconda ACD-S and related equipment and other relevant protocol elements. Sites are additionally supported by dedicated educational staff.

Early study drug discontinuation and/or withdrawal

In certain instances, investigators may determine that continued study drug treatment is not in the best interest of the patient, warranting early study drug discontinuation. Similarly, clinical or other circumstances may warrant withdrawal from the trial. Criteria for early study drug discontinuation and study withdrawal are delineated in online supplemental appendix G.

Adherence

Investigators are charged with ensuring protocol adherence, and clinical research associates regularly monitor all participating centres to verify adherence. The principal investigators hold regular investigator meetings with the Sponsor to discuss trial updates and monitor trial progress, aid in the monitoring of adherence, provide feedback about quality and safety-related matters, review any site-specific issues and discuss adverse events.

Monitoring

At EOT, vital signs, laboratory assessments, adverse events and the time of extubation (among other variables summarised in online supplemental table are monitored for 24 hours. Patients are then monitored daily for 7 days for adverse events, relevant medications, RASS, CAM-ICU-7 and SOFA score. Additional assessments occur at day 30 (+5) days, including major ICU interventions, adverse events and outcomes. Exploratory long-term outcomes are assessed with phone calls in a consecutive subset of patients still alive at 3 months (±4 weeks) and 6 months (±4 weeks).

An independent data safety monitoring board (DSMB) monitors the safety of trial patients for both INSPiRE-ICU1 and the parallel INSPiRE-ICU2 trial. The DSMB is comprised of four members with appropriate expertise who are independent of the Sponsor. The DSMB reviews all relevant safety data, including adverse events, severe adverse events, serious adverse events and suspected unexpected serious adverse reactions. Adverse events of special interest for this trial are delineated in online supplemental appendix H. DSMB meetings are planned after approximately 25% of randomised patients in the two studies have completed the 30-day follow-up period and again when 50% and 75% of patients have completed 30-day follow-up. Stopping criteria are delineated in online supplemental appendix I. All DSMB recommendations apply to both INSPiRE-ICU1 and INSPiRE-ICU2 given the similarity of the studies.

Protocol amendments

The protocol details described herein are based on INSPiRE-ICU protocol Version 7, dated 6 October 2023. The timing of this protocol publication was informed by prior protocol amendments and a desire for the published protocol to most closely reflect and align with the eventual trial results published.

INSPiRE-ICU1 protocol Version 3 (dated 9 February 2022) was the first under which patients were enrolled, with Versions 1 and 2 having been revised in response to US FDA and IRB reviews.

Compared with Version 3, revisions to protocol Version 4 (dated 31 March 2022) included: expanded exclusion criteria for patients with contraindications to propofol or isoflurane, updated the approach to concomitant medication collection through day 30 for consistency, clarified the timing of day 30 study procedures and revised an original plan to monitor ABCDEF bundle compliance to instead focus on emphasis of ABCDEF compliance.

Protocol Version 5 (dated 30 May 2023) was developed but not submitted as FDA feedback was received on 31 May 2023, requiring further protocol review and revision. As such, no patients were enrolled under Version 5.

Compared with Version 4, revisions to protocol Version 6 (dated 22 June 2023) included: making specific assessments less frequent with wider time windows to enhance trial practicability, disallowing continuation of study drug after a failed extubation attempt to ensure validity of related endpoint measures, allowing more flexible isoflurane dosing and titration guided by clinical response, clarifying the approach to rescue sedation, clarifying circumstances in which blinded RASS and CPOT assessments are excluded, adding a blinded RASS assessment immediately prior to EOT, clarifying exclusion criterion #2 for re-intubated patients, and providing specific examples of severe neurological conditions constituting exclusions under criterion #3.

Compared with Version 6, revisions to protocol Version 7 (dated 6 October 2023 and described herein) included: clarifying that study assessments could be performed more frequently than specified in the protocol as clinically indicated, added meningitis as an additional example to exclusion criterion #3, defining study drug boluses as a rescue sedative and clarifying the analytic approach as outlined subsequently.

Data analysis

Categorical data will generally be summarised with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarised with descriptive statistics including n (number of non-missing values), mean and SD or median and IQR, minimum, and maximum. The SAP will be finalised before the database lock.

A fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the primary efficacy endpoint will be tested at the one-sided 0.025 level first (non-inferiority test), followed by testing the key secondary efficacy endpoints at the two-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 with mean opioid dose during the 60 min prior to randomisation.
2. Time from stop of study drug treatment to RASS 0, up to 4 hours.
3. Delirium by CAM-ICU-7 assessments 60 min (±10 min) after EOT in patients not re-sedated with benzodiazepine or propofol infusions.
4. Proportion of ventilator parameter observations with spontaneous breathing efforts during the study drug treatment period.

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

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)) as fixed effects.

The treatment comparisons will be estimated together with a one-sided 97.5% CI and p value for the hypothesis testing. Least squares mean for each treatment group will also be provided. The primary analysis will be performed on the intention to treat (ITT) Analysis Set. The hypothesis test for primary efficacy endpoint analysis is based on a one-sided significance level of 0.025. The primary efficacy endpoint will be summarised for the ITT Analysis Set by stratification factor. ANOVA model will be used to analyse the primary efficacy endpoint for each subgroup, which will include randomised treatment group as a fixed effect. Sensitivity and supplementary analyses will be specified in the SAP.

The analyses of the key secondary efficacy endpoints will be performed on the ITT Analysis Set (superiority analysis), unless otherwise specified. The hypothesis tests for the key secondary endpoint analyses are based on a two-sided significance level of 0.05.

No interim analysis of outcome data is planned for this trial. All safety analyses will be performed on the Safety Analysis Set. Patients will be analysed by the treatment received. Safety measures will be summarised descriptively. Qualitative variables will be summarised using counts and percentages by treatment group at each trial visit. A separate analysis and study report will be performed for the long-term outcomes (3 and 6 months) once all patients have performed the 6-month follow-up.

ETHICS AND DISSEMINATION

Ethical approvals were obtained from local IRB for each study site prior to patient recruitment. The trial protocol and appropriate documentation was reviewed and approved by the US FDA, as well as central (Advarra SSU00208265) and local IRBs (Cleveland Clinic IRB FWA 00005367, Tufts HS IRB 20221969, Houston Methodist IRB PRO00035247, Mayo Clinic IRB Mod22-001084-08, University of Chicago IRB21-1917-AM011 and Intermountain IRB 033175).

Continuing review processes occur as needed with final packet submission to be sent on trial completion. The trial is conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation guideline for Good Clinical Practice, and applicable local regulatory bodies. Written informed consent is obtained from the patient or patient's legally authorised representative (LAR) prior to the initiation of any study procedure. Final trial dataset will be available to investigators and provided within FDA submission. Datasets will be stored at Sedana Medical AB for at least 10 years following trial completion.

Trial results for publication will be submitted to peer-reviewed journals and the results will be presented at one or more scientific conferences with an expected timeframe for publication of 2025. The data will also be submitted to the FDA by Sedana Medical AB.

Protocol changes

ClinicalTrials.gov will be updated with any amendments to the protocol as per SPIRIT guidelines.

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Contributors CB contributed to trial design, protocol draft, review and editing of the manuscript. JWD, TDG and JK contributed to protocol development, writing and editing of the manuscript. SHH, FH and CSJ contributed to protocol draft and manuscript editing. IS, MF, PVS contributed to trial design, protocol development and funding acquisition. KS contributed to data collection and protocol design. CH contributed to trial design, protocol draft, biostatistical planning and editing of the manuscript. All authors revised the manuscript for important intellectual context and gave final approval for publication. Professional writer (MW) is employed for protocol editing. CB is the guarantor.

Competing interests CB, TDG, JK and CH have received consulting fees from Sedana Medical AB as members of their US Trials Steering Committee. JWD has received speaker honoraria from Sedana Medical AB. IS and MF and PVS are employed by Sedana Medical AB.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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Supplemental Materials

Contents

Standard Protocol Items for Randomized Trials (SPIRIT) 2013 Checklist

Section/item	Item No	Ms Pg	Description
Administrative information			
Title	1	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	5	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	1-27	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	23-24	Date and version identifier
Funding	4	2	Sources and types of financial, material, and other support
Roles and responsibilities	5a	1	Names, affiliations, and roles of protocol contributors
	5b	2	Name and contact information for the trial sponsor
	5c	2	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	2	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction			
Background and rationale	6a	6-8	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	8	Explanation for choice of comparators
Objectives	7	8	Specific objectives or hypotheses
Trial design	8	9	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes			
Study setting	9	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	9-10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	12-14	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	22	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	22	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

	11d	15-17	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	18-19	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	10,39	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	10	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	10	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions			
Allocation:			
Sequence generation	16a	11	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	11	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	11	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	11-12	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	11-12	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis			
Data collection methods	18a	21	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	21-22	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	21	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	24-25	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	25-26	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	25	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring			
Data monitoring	21a	23	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its

			charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	23	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	23	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	21	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination			
Research ethics approval	24	27	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	23-24	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	10	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b		Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	21	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	2	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	10	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30		Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	27	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	32	Authorship eligibility guidelines and any intended use of professional writers
	31c		Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices			
Informed consent materials	32		Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	S17	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

From: Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-7.

Appendix A: Calculation of Norepinephrine Equivalents

Norepinephrine equivalents for the purposes of trial exclusion criteria are calculated according the conversion factors outlined below.

Vasopressor	Range of ratios	Suggested ratio	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

Ratios are 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 dosed in ng/kg/min and must be converted to mcg/kg/min for calculations.

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

Appendix B: SAT/SBT and Wake-Up Test Safety Screen

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

Step 1: Spontaneous Awakening Trial (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);
- Neuromuscular blocking drugs: the patient is currently on a neuromuscular blocking drug infusion;
- Myocardial ischemia: documentation of myocardial ischemia in the last 24 hours;
- High intracranial pressure: there is evidence of elevated intracranial pressure (>20 mmHg); and
- Patient off the unit: effort should be made to attempt the safety screen when the patient returns to unit.

If the patient does not pass the SAT 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.

If the patient passes the SAT safety screen, perform the SAT.

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. 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.

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.

If the patient fails the SAT, bedside staff should restart at the lowest possible infusion rate that is needed to achieve target RASS. Typically start at half of the most recent dose and titrate, as needed.

If the patient passes the SAT, then he/she exhibits either of the pass criteria and no failure criteria, and he/she advances to the spontaneous breathing trial (SBT) safety screen.

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 $\geq$ 2);
- Oxygen saturation <88%;
- Fraction of inspired oxygen (FiO_2) >50%;
- Positive end-expiratory pressure (PEEP) >7.5 cmH_2O;
- Myocardial ischemia: 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 the unit.

If the patient fails the SBT safety screen, bedside staff should try the safety screen again within 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: 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 $\leq$7.5 cmH_2O and pressure support of $\leq$7 cmH_2O. 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 fails the SBT, bedside staff should return the ventilatory support to the previous settings.

If the patient passes the SBT, defined as the patient exhibiting no failure criteria for 2 hours, at the end of the 2 hours the clinical team should consider extubation.

Appendix C: Per-Protocol Rescue Sedation

Inadequate sedation should first be addressed through titration of the study drug and treatment of pain, where applicable, per the standard of care. If sedation remains inadequate despite adequate analgesia, per-protocol rescue sedation is stepwise:

First-line rescue: bolus doses of the assigned study sedative drug	
Propofol: 0.3 to 0.5 mg/kg	A maximum of two bolus doses per hour are allowed before use of second-line sedatives
Isoflurane: 0.3 to 0.5 ml	
Second-line rescue: rescue sedatives when the study drug is insufficient	
Dexmedetomidine infusion: 0.15 to 0.7 mcg/kg/hour for up to 3 hours per 24 hour period; and/or	
Midazolam bolus: 0.5 to 5 mg per dose, up to 3 bolus doses per 24 hour period	
Treatment failure criteria	
Clinical need for dexmedetomidine infusion for >3 hours per 24 hours; and/or	
Clinical need for >3 midazolam bolus doses per 24 hours	

Patients meeting criteria for treatment failure should, as soon as possible, discontinue the assigned study drug and transition to medical care per the standard of care at the discretion of the treating physician.

Appendix D: Prohibited and Restricted Medications

Prohibited medications
Barbiturates
Chloral hydrate
Chlorpromazine
Clonidine
Gamma-hydroxybutyrate
Ketamine
Continued treatment with a neuromuscular blocking agent for >4 hours during the study drug treatment period
Restricted Medications
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
Benzodiazepines (i.e., midazolam): may only be used as rescue sedatives if study sedation is not sufficient
α2-adrenergic agonists (i.e., dexmedetomidine): may only be used as rescue sedatives if study sedation is not sufficient and during spontaneous awakening trials and the wake-up test
Antipsychotics (e.g., haloperidol, quetiapine, olanzapine, and chlorpromazine): should not be used during study sedation treatment period unless the patient has been on these medications before ICU admission, except during spontaneous awakening trials, and during the end of treatment wake-up test
Neuromuscular blocking agents: continuous infusions of neuromuscular blocking agents during the study drug sedation treatment period for >4 hours are not permitted. Shorter infusions of NMBA may be used as indicated for medical procedures.

Appendix E: Other secondary and exploratory outcomes

Other secondary outcomes
Time from end of treatment to extubation if the study drug is terminated for extubation
Days alive and free from mechanical ventilation through study day 30[1]
Days alive and free from the ICU through study day 30[2]
Delirium and coma free days from the start of the study drug until 7 days after end of treatment, as assessed by CAM-ICU-7 and RASS
Mortality rate at 30 days after randomization
Mortality rate 3 months after randomization
Mortality rate at 6 months after randomization
Proportion of patients receiving restraints during the study drug treatment period
Safety of isoflurane versus propofol
Frequency and type of Sedaconda ACD-S device deficiencies
Exploratory outcomes
Changes in isoflurane dose over time
Incidence of major ICU interventions through study day 30 or until ICU discharge: renal replacement therapy, extracorporeal life support, tracheostomy, and non-invasive ventilation
Level of care up to 30 days after randomization
End-tidal isoflurane concentration over time and relation to RASS
Oxygenation (PaO_2/FiO_2) in patients with ARDS/AHRF over time during the treatment period
Use of rescue sedatives, other sedatives, and antipsychotics from randomization to end of treatment
Change from baseline in highest daily vasoactive drug requirements during study drug treatment
Duration of mechanical ventilation
ICU length of stay
Change in minute ventilation every 8 hours during the study drug treatment period
Exploratory long-term outcomes
Number of factual memories, memories of feelings, or delusional memories, as assessed by the ICU Memory Tool, collected at 3 months follow-up
Activities of daily living, as assessed by the Katz ADL and Pfeffer FAQ, at 3 and 6 months post randomization
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
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
Quality of life at 3 and 6 months post-randomization, as assessed by WHODAS 2.0 and BPI

[1] For days alive and free from mechanical ventilation, only invasive ventilation is considered. Successful mechanical ventilator discontinuation is defined as being alive and free from mechanical ventilation for ≥ 48 hours following discontinuation. For example, if a patient was liberated from mechanical ventilation, and mechanical ventilation was initiated again within the next 48 hours, or the patient died within the next 48 hours, criteria would not be met for that that time (which is less than 48 hours) to count toward days alive and free from mechanical ventilation.

[2] Days alive and free from the ICU is defined similarly to the days alive and free from mechanical ventilation. Successful ICU discharge is defined as being alive and out of the ICU for ≥ 48 hours following discharge.

ACD-S, Anaesthetic Conserving Device - S; AHRF, acute hypoxemic respiratory failure; ARDS, acute respiratory distress syndrome; BPI, Brief Pain Inventory; CAM-ICU-7, Confusion Assessment Method Intensive Care Unit-7; FiO2, 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, arterial partial pressure of oxygen; Pfeffer FAQ, Pfeffer Functional Activities Questionnaire; PROMIS, Patient Reported Outcomes Measurement Information System; RASS, Richmond Agitation Sedation Scale; TICS, Telephone Interview for Cognitive Status; WAIS, Wechsler adult intelligence scale; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0; WMS, Wechsler memory scale

Appendix F: Exclusionary Periods for Blinded RASS and CPOT Assessments

Blinded Richmond Agitation Sedation Scale (RASS) and Critical Care Pain Observation Tool (CPOT) assessments will not be performed during or shortly after periods of intentional deepening of sedation for procedures, nor during a spontaneous awakening trial (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 (e.g., following bronchoscopy, prone-positioning, or wound dressing)
1 hour after resuming study sedation after a procedure outside the ICU (e.g., CT scan, endoscopy, surgery, etc.)
1 hour after an SAT
2 hours after a bolus of neuromuscular blocking agent
4 hours after the end of an infusion of neuromuscular blocking agent

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 neuromuscular blocking agent (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.

Appendix G: Criteria for Early Study Drug Discontinuation and Study Withdrawal

Criteria for early study drug discontinuation
Treatment failure (i.e., clinical failure of the patient to be adequately sedated with the study drug)
New onset of coma due to structural brain disease (e.g., stroke, intracranial hemorrhage, cranial trauma, malignancy, anoxic brain injury, or cerebral edema)
Severe or serious adverse events: - Development of an adverse event of special interest that qualifies as a severe adverse event or serious adverse events at least possibly related to study drug, without a clear alternate explanation; - For any other severe adverse events, the decision on whether to continue with study drug will be made by the investigator and clinical team in accordance with whether continuation/reintroduction of study drug is in the best interest of the patient for the first severe adverse event; or - A second severe adverse event or any serious adverse event without a clear alternate explanation will lead to discontinuation of study treatment
Unresolved Sedaconda ACD-S device-related issues
Transition to comfort care
Death
Requirement of prohibited concomitant medication
Need for ECMO, $ECCO_2R$, HFOV, or HFPV
Any medical condition that indicates to the investigator that continued study drug treatment is not in the best interest of the patient
Withdrawal of consent to receive study drug
Criteria for study withdrawal
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 legally authorized representative, 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
Termination of the study by the Sponsor or the regulatory authority

ACD-S, Anaesthetic Conserving Device – S; $ECCO_2R$, extracorporeal CO2 removal; ECMO, extracorporeal membrane oxygenation; HFOV, high frequency oscillation ventilation; HFPV, high frequency percussive ventilation

Appendix H: Adverse Events of Special Interest

AESI	Severity			
	Mild	**Moderate**	**Severe**	**Serious**
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	$PaCO_2$ 10 to 15 mmHg above baseline on 2 consecutive blood gases at least 60 minutes apart, despite ventilator optimization.	$PaCO_2$ 16 to 20 mmHg above baseline on 2 consecutive blood gases at least 60 minutes apart, despite ventilator optimization.	$PaCO_2$ >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.
Malignant hyperthermia				Any episode of MH.[1]
Propofol-related infusion syndrome suspected by the investigator in a patient recently exposed to propofol				Any episode of PRIS.[2]
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 (e.g., 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.
Rhabdomyolysis independent of malignant hyperthermia	CK 10,000 to 20,000 units/L	CK >20,000 units/L with moderate renal failure graded as AKIN Stage 3.[3]	CK >20,000 units/L requiring dialysis.	Life-threatening consequences of rhabdomyolysis.

* Unless a different clinical target is selected by the clinical team prior to randomization.

[1] MH may be characterized by muscle rigidity; unexplained hypercapnia resistant to increasing minute ventilation; elevated CK or urine myoglobin suggesting rhabdomyolysis; acute hyperkalemia >6 mEq/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.

[2] PRIS may be characterized by the development of otherwise unexplained metabolic acidosis and cardiac dysfunction with at least one of the following: rhabdomyolysis, hypertriglyceridemia, or renal failure after initiation of propofol.

[3] 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.

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; $PaCO_2$, arterial partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; PRIS, propofol-related infusion syndrome; SBP, systolic blood pressure; SpO_2, peripheral capillary oxygen saturation; ULN, upper limit of normal.

Appendix I: Study Stopping Criteria

Criteria in the isoflurane group triggering an ad hoc data safety monitoring board meeting:

Occurrence of moderate or severe adverse events related to isoflurane or the device	**Events observed in the isoflurane group**
Serious adverse event – death	>1 patient
Serious adverse event	≥5 patients
Suspected unexpected serious adverse reaction	≥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

Definitions and grading of each AE of special interest are described in the preceding appendix.

If >5 reports of suspected unexpected serious adverse reactions concerning the same type of medical event (i.e., unlabeled events with a suspected relationship to treatment), there will be an ad hoc data safety monitoring board meeting.

Appendix J: Informed Consent Materials

Protocol: 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 No.:	SED003
Sponsor:	Sedana Medical AB, which is providing financial support and material for this study.
Principal Investigator: (Study Doctor)	[Insert Principal Investigator name and address]
24-hr. Telephone #:	[Insert 24-h phone number]
Address:	[Insert Site Location and address]

This form is for use in a research study that involves participants who may or may not have the capacity to take part in the study. In this document, "you" generally refers to the research participant. If you are being asked as the legally authorized representative (LAR) to permit the participant to take part in this research, "you" in the remainder of this consent form, refers to the research participant. During the course of the study, if the participant regains the capacity to consent, informed consent will be sought from the participant, and the participant will be offered the ability to leave the study if desired.

Why are you being asked to participate in this research study?

You are being invited to take part in a research study. Before agreeing, it is important that you read and understand why this research is being done and what it will involve for you. This form describes the purpose, procedures, benefits, risks, discomforts, and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time.

A member of the study staff will review this form with you and explain the study to you. Please read this form carefully and ask any questions you may have. You can discuss this information with your doctors, family, or anyone else you would like before making your choice.

What is the background and purpose of the study?

You are being asked to participate in this research study because you will likely be on a ventilator in the Intensive Care Unit (ICU) for more than 12 hours and require continuous sedation as part of your normal medical care. The ventilator is used to assist your breathing while sedation is used to keep you comfortable on the ventilator. Sedation can range from minimal sedation (drowsy and relaxed) to deep sedation (unconscious and not awakened by verbal stimulation).

Sedation is commonly achieved using medications such as propofol, dexmedetomidine, benzodiazepines, or opioids administered through an intravenous catheter (IV; a tube in your vein) into the bloodstream. These sedatives, given as part of your routine medical care, help to

maintain comfort and safety, but they can have side effects, including longer time to wake up, confusion, lower blood pressure and heart rate, and change in breathing pattern.

Another method to provide sedation involves breathing inhaled medications such as isoflurane through the ventilator. Isoflurane is commonly used to achieve deep sedation (anesthesia) during surgery, in the United States and around the world. It may allow faster wake-up, less need for pain medications, and earlier return to more normal breathing patterns when compared to IV sedation. Traditionally, isoflurane administration has required large, specialized equipment called an anesthesia machine, limiting its use to operating rooms. A small device, placed in the ventilator breathing circuit, was developed to permit administration of isoflurane without an anesthesia machine, enabling administration in the ICU environment. This adaptor, called the Sedaconda Anaesthetic Conserving Device - S (Sedaconda ACD-S) is approved for use in Europe, Australia, Canada, Japan, and other countries, and isoflurane via the Sedaconda ACD-S is routinely prescribed as sedation for ICU patients in these countries. Isoflurane delivered by the Sedaconda ACD-S is approved for ICU sedation in several European countries, including Germany and France, but is not currently approved in the United States. As such, the use of isoflurane for ICU sedation delivered by the Sedaconda ACD-S in this research study is considered investigational.

The purpose of this study is to compare the effects of inhaled isoflurane sedation delivered via the Sedaconda ACD-S with the standard of care IV sedative propofol.

Do you have to take part in the study?

Taking part in this research study is voluntary and entirely up to you. You will have to sign and date the consent page within this consent form to indicate you choose to take part. You may change your mind and withdraw without giving any reason, at any time. If you choose to not participate or you withdraw from the study, you will not lose any medical benefits to which you are entitled, and it will not have any effect on your future medical care. You may decide to stop taking part in the study at any time by notifying the study doctor in writing of your decision. If you have some unresolved health problems when you leave the study, the study doctor may, if you agree, need to collect information about your health until the problem resolves.

What are your other options should you decide not to take part in the study?

You do not need to take part in this study. If you do not participate, you will receive standard of care sedation as prescribed by your doctors.

How many people will be in the study and how long will you be in this study?

Approximately 300 participants will take part in this study at approximately 15 to 20 study hospitals in the United States. Approximately 15-25 patients will be enrolled at this site.

The study sedation period will be up to 54 hours and only as long as sedation is required. After 54 hours, the treating doctor will decide whether to continue or stop sedation. If sedation is continued, you will receive standard of care sedation as prescribed by your doctors. You will be monitored for up to 7 days or until you are discharged from the hospital, whichever happens first. After 1 month, data regarding your hospital course will be collected from your medical records. The study team may give you or your representative a call if additional information regarding your hospital course is needed. At approximately 3 and 6 months after end of study treatment, members of the study team from Vanderbilt University will call or videocall you to ask about your ability to think clearly, your quality of life, and your mobility and function. They will ask you questions about what you remember from your time in the ICU.

What will happen if you decide to be in this research study?

There are 3 stages to this study: Screening, Study Treatment Period, and Follow-Up.

Screening

If you agree to participate in this study, study staff will check to see if there is any reason you should not be in the study. Study staff will review and collect information about your medical history, surgical history, present health and any medications that you are currently taking. We will ask you or your family questions about your ability to think clearly, quality of life, and mobility and function. These questions will take about 5-10 minutes, and you or your family will not have to answer any questions that make you or them feel uncomfortable. A blood sample will be taken to determine baseline safety assessments. For females who could become pregnant, a pregnancy test will be taken if not previously done during your hospital stay. The study team will ask for your contact information (phone numbers, email, and address) so that we can reach you after you leave the hospital to ask about your recovery.

Study Treatment Period

You will be randomized (like a flip of a coin) to determine which study treatment you receive: inhaled isoflurane (administered via the Sedaconda ACD-S device) or propofol (administered via IV infusion) for sedation. You will have a 60% chance to receive isoflurane and a 40% chance to receive propofol.

The bedside clinical nurse, study doctor, and study staff will know the study treatment and the doses that you are given. If the study medication (either isoflurane or propofol) you receive does not have the desired effect, you may receive other approved standard of care medications to achieve the sedation level prescribed by the clinical team. The appropriate level of sedation to be targeted will be determined by your treating physician and clinical team, not study staff.

In case of procedures outside the ICU, study drug must be stopped. If you return to the ICU before 42 hours from starting the study drug treatment, the study drug treatment can be resumed. If you return to ICU later than 42 hours from start of study drug treatment, you should transition to standard of care sedation and medical care at the discretion of the treating physician.

Because this is a research study, the study treatment will be given to you only during the study sedation period and not after the study is over. You will not receive isoflurane for ICU sedation after the study period, but your doctors can choose to prescribe propofol or another routinely used sedative provided through the hospital after the study sedation period.

Propofol: If you are assigned to receive propofol, then propofol will be given through an IV directly into your vein.

Isoflurane: If you are assigned to receive isoflurane, then isoflurane will be administered via the Sedaconda ACD-S device, which connects between the ventilator and the breathing tube.

Monitoring: While you are sedated with study medication, study staff will closely monitor you, your overall health, and your ongoing medical care, including medications that you are receiving. Study staff will frequently evaluate your sedation level, comfort, breathing pattern, and assess for any confusion. Your sedation tubing may be covered to ensure these assessments are not influenced by knowledge of which study medication you are receiving.

Physical Examinations: physical examination including an evaluation of your general appearance and your vital signs will be measured (body temperature, oxygen saturation, heart rate and blood pressure).

Blood samples: Blood samples will be collected and analyzed by the hospital clinical laboratory for safety monitoring. When able, these samples will be drawn from your existing lines to minimize discomfort. The total amount of blood taken will be

approximately 60 mL (4 tablespoons). For comparison, a standard blood donation at a blood collection center is about 475 mL of blood (about 96 teaspoons/2 cups).

Study treatment duration: The study sedation period will last for up to 54 hours and only as long as sedation is required. After this time, the treating doctor will decide whether to continue or stop sedation. If sedation is continued, you will receive standard of care sedation as prescribed by your doctors. If you are ready to come off the ventilator before end of the study sedation period, study medication will be stopped, and the breathing tube will be removed. You will not be kept on a ventilator any longer than your treating doctors think is medically necessary.

Follow-Up

After the study medication stops, the study team will monitor how fast you wake up, assess your comfort level, evaluate for confusion, and review your overall health and hospital course. These assessments will occur while you are in the hospital. You will not be kept in the hospital any longer than your treating doctors think is medically necessary.
At approximately 1 month after the study treatment, our site study team may call you or your representative to ask about any medications you may be taking and your current health status if the study team cannot find this information in your medical records.

Our site team and the study team from Vanderbilt University will need contact information for multiple contacts to help ensure that their efforts to contact you will be successful. The study team will request contact information (such as cell number, home number, work number, address, email) from you and additional contacts of your choosing. Any contact information you or your family choose to share with us will remain confidential and will be stored in a password protected database.

There are no outpatient (clinic) appointments associated with this study.

At approximately 3 and 6 months after end of study treatment, study team members from Vanderbilt University will call or videocall you to ask about your ability to think clearly, quality of life, mobility, and function, and what you remember from your time in the ICU. This phone/ video call should take about 1 hour.

What are the potential benefits of participating in this study?

You may or may not benefit as a result of your participation in this study. With either study treatment, additional close monitoring from the study team may help ensure sedation is carefully adjusted to within the range prescribed by the treating physician. Isoflurane may decrease the need for opioids (pain medications) while on the ventilator. Participants receiving isoflurane may wake up faster once sedation is stopped. Results from this study may benefit others in the future and help us identify best options for sedation in patients on the ventilator in the ICU.

What are the risks or side effects of participating in this study?

All treatments have risks and may cause side effects. These may happen to you from the study treatment. These effects could be mild or serious. In some cases, these effects might be long lasting or permanent, and might be life-threatening. It is possible some risks may not be known at this time.

The study medications will only be given while you are in the ICU and on continuous monitoring, and you will be closely observed for side effects throughout the study. The study doctor or study staff may give you treatment to help reduce any side effects or stop the study treatment early. The side effects that are most likely to happen to you if you take part in this study are noted below.

Risks of Propofol given Intravenously:

Propofol has been shown to be safe and effective for ICU sedation in well controlled clinical trials and was approved for the sedation of ICU patients on the ventilator in 1993. Propofol for ICU sedation is considered part of the standard of care in the United States and around the world. The dose and administration of propofol used in this study follows FDA-approved dosing instructions.

Common side effects of propofol (which occur in more than 1 in 10 patients) include a decrease in blood pressure, heart rate, or breathing effort. Discomfort, itching, or a rash at the IV site may occur occasionally.

Rare but potentially serious side effects of propofol (which occur in far less than 1 in 100 patients) include:

- Allergic reactions
- Abnormal heart rhythm
- Pancreatitis (inflammation of the pancreas, which can cause pain and nausea)
- Propofol infusion syndrome: a rare but life-threatening condition characterized by too much acid in the blood, high potassium, muscle breakdown, and/or heart, kidney, and liver failure. This rare event is most commonly reported at higher doses and longer durations than will be used in this study.

Risks of Isoflurane given Inhaled with the Sedaconda ACD-S:

Isoflurane has been shown to be safe and effective for deep sedation (anesthesia) during surgery and is routinely used for that purpose in the United States and around the world. Isoflurane administered via the Sedaconda ACD-S is approved for sedation of ventilator-dependent ICU patients in Europe but not yet in the United States. The dose of isoflurane administered for ICU sedation is generally lower than required during surgery, and so dose-dependent side effects may be less common and less severe.

Common side effects of isoflurane (which occur in more than 1 in 10 patients) include a decrease in blood pressure, heart rate, or breathing effort. Nausea may occur occasionally.

Rare but potentially serious side effects of isoflurane (which occur in far less than 1 in 100 patients) include:

- Allergic reactions
- Abnormal heart rhythm
- Increased liver enzymes which may be a sign of liver dysfunction

Very rare but potentially serious side effect of isoflurane (which occurs in far less than 1 in 10,000 patients) include:

- Malignant hyperthermia (high body temperature, rigid muscles, rapid heart rate)

One event of further increased pressure in the brain was observed in an adult participant with elevated pressure in the brain being treated with Sedaconda/Isoflurane.

Preliminary results from a Sedaconda/Isoflurane study in children identified one participant who developed confusion, one participant who had lower blood pressure, and one participant with increased pressure in the brain who had further increased pressure in the brain.

Common side effects of using the Sedaconda ACD-S device include a slight increase in the amount of carbon dioxide in the blood. Rare potential side effects of the Sedaconda ACD-S include a decrease in the amount of sedation received over time or increase in breathing circuit resistance if the device becomes clogged by moisture or sputum.

Risks from Other Study Procedures:

- **Blood Samples:** Possible adverse effects from drawing blood include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
- **Video/ Telephone Assessments**: The follow-up telephone assessments of your thinking, quality of life, and physical function could be emotionally uncomfortable. If this occurs, you may choose to end the phone/video call at any time and are not required to answer any questions you do not want to answer.

Other Unknown Risks:

Since the use of Isoflurane administered via the Sedaconda ACD-S is an investigational study treatment, there may be other risks that are unknown. All medications have the potential risk of an allergic reaction, which if not treated promptly, could become life-threatening. Symptoms of an allergic reaction could be trouble breathing, or swelling of the face, mouth, lips, gums, tongue, or neck. Other symptoms of an allergic reaction may include rash, hives, or blisters. In the event of an allergic reaction, you will be treated promptly by the staff in the ICU. You will not be allowed to participate if you have a known allergy to propofol or if you or a family member has had a severe reaction to anesthesia (such as malignant hyperthermia).

It is important that you tell the study doctor about any adverse changes in your health as soon as they occur, whether or not you think they are caused by the study treatment.

Risk of Loss of Privacy:

Every reasonable step will be taken to protect your privacy and confidentiality. Participation in any research study, including this one, may involve a risk of loss of privacy, and absolute confidentiality cannot be guaranteed. To minimize this risk, we will assign codes instead of using names and personal information. All information collected on paper will be kept in a secure location. Information collected on computer will be password protected and stored on a secure network. Staff at the study site will handle your personal information very carefully. We are required to make sure that people not involved with the study do not have access to your records. When results of the research are published or discussed at conferences, no information will be included that would reveal your identity.

Birth Control and Pregnancy-related Risks?

The effect of the study treatment in an unborn baby, a breast fed child, the female egg or on sperm is unknown. Therefore, you cannot participate in this study if you are pregnant or breast-feeding. If you are found to be pregnant during the 7 day follow-up after end of study treatment, the study staff will collect information about the pregnancy, its outcome, and the health of the child after birth.

What happens if there is new information?

Sometimes during the course of a research study, new information becomes available about the study treatment. The study doctor will inform you in a timely manner about any new important

information that is discovered while you are in the study and discuss with you if you want to continue in the study. If this occurs, you may be asked to sign and date an updated consent form to confirm you agree to continue in the research study.

The study doctor may remove you from the study at any time without your consent if:

- Your study doctor does not consider it to be in your best interest to continue.
- Your study doctor has received new information about the safety or effectiveness of the study treatment that would cause you to no longer be able to participate.
- You cannot tolerate the study treatment.
- The study is stopped by the study site, the Sponsor, or regulatory authorities
- For administrative reasons

What happens if you are injured during the study?

If you are hurt or suffer other physical injury as a direct result of taking part in the study, the Sponsor will pay for the reasonable costs of medical treatment in accordance with applicable laws. The study site will treat your injury right away. The Sponsor has insurance to cover such costs, and will make these payments where the adverse effect or other physical injury resulted from:

- A medicine being tested or administered as part of the study, or
- Any test or procedure you received as part of the study.

The Sponsor will only pay for the medical costs that are not covered by your insurance or other programs. If you have medical insurance, check with your insurance company that taking part in this study will not affect your policy. There are no plans for the Sponsor to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for the Sponsor or study site to give you money for the injury. By signing and dating this document, you will not lose any of your legal rights or release anyone involved in the research from responsibility for mistakes.

What are the costs to you of taking part in the study?

There are no costs for you if you take part in this study. You will receive the study treatment at no charge, and you will not be charged for any study-related procedures. You are still responsible for paying for the usual care you would normally receive for the treatment of your illness. You, your insurance company, or some other third-party payer must pay for all other medicines and hospital costs.

Will you be paid to be in this study?

If you are enrolled and randomized into the study, you will receive a $50.00 check for completing the 3-month follow-up phone assessment and a $50.00 check for completing the 6-month follow-up phone assessment. Vanderbilt University is responsible for providing these payments to you. Your reimbursement checks should arrive in about 6-8 weeks after each follow up phone/video call. We may use your Social Security Number, name, and address in order to process your compensation for taking part in this study.

How will your privacy be protected?

Confidentiality

Once this consent form is signed and dated, you will be assigned a study code. During the study, the study doctor and study staff will collect information about you, including demographics, health data, and results of study procedures. Your records and study data (information) will not include

your name or personal identity but will identify you with a study code. This code can only be tracked back to you via a code key that is held by authorized study personnel at the site. Although procedures are in place to protect your privacy, absolute confidentiality cannot be guaranteed.

Authorization to Use and Disclose Protected Health Information

Access to your health information is required for this study. If you choose to take part in this study, you are giving us permission to use the protected health information and information collected during research that can identify you. The health information that we may collect and use for this research includes your past, present, and future physical or mental health and condition, and results of lab tests, examinations, or procedures. Information needed for this research may be obtained from any hospital, doctor, or other healthcare provider involved in your care. The research information that is shared with people outside of [site/hospital name], with the exception of research team members from Vanderbilt University who will be performing the follow-up phone/video calls, will not include your name, address, telephone number, or other direct identifiers unless disclosure of the information is required by law, or you have authorized the disclosure. Study personnel are required by law to protect your health information.

By signing and dating this document, you authorize [site/hospital name] to use and/or disclose (release) your health information for this research. Those who receive your health information may not be required by federal privacy laws to protect it and may share your information with others without your permission, if allowed by laws governing them. Your authorization to use and share your health information does not have an expiration (ending) date. You may change your mind and revoke (take back) this consent and authorization at any time and for any reason. To revoke this consent and authorization, you must contact the study physician identified on the first page of this document. If you revoke your consent and authorization, you will not be allowed to continue taking part in the research. Also, even if you revoke this consent and authorization, the Researchers and the Sponsor may continue to use and disclose the information they have already collected.

Data will be stored, processed, and compiled by the Sponsor both manually and electronically. Your collected information will be used and disclosed only in accordance with the law. Your identity will not be shared in any reports or publications resulting from this study. Your information will be identified only by your study code when sent to the Sponsor. Your study information may be disclosed to and used by:

- The study doctor and study staff
- The Critical Illness, Brain Dysfunction, and Survivorship Center at Vanderbilt University, who will be conducting the follow-up phone/video calls
- Sedana Medical AB, the study Sponsor paying for this research study
- Medpace, the contract research organization facilitating the study on behalf of Sponsor
- Authorized representatives and contractors of the Sponsor or Medpace
- U.S. Food and Drug Administration (FDA)
- Other agencies in the U.S. and other countries that have the authority to review study records
- Ethics committees overseeing the study, including Advarra Institutional Review Board (IRB)
- Any successors to any of these organizations.

They are committed to protecting your privacy. As the research staff at the study site, we are required to make sure that people not involved with this study cannot see your research and

medical information. We will keep your research files in a safe place and will handle your personal information very carefully.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can you contact about this study?

If you have any questions or concerns about the research or your rights as a participant, an injury, or are unwell, please contact the study doctor at the telephone number listed on the first page of this document.

All research studies are reviewed by an independent group of people called the IRB to help protect the rights of research participants. This study has been reviewed and approved by the IRB. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, you should write to [IRB name and address], or call [IRB phone number].

STATEMENT OF CONSENT AND HIPAA AUTHORIZATION TO PARTICIPATE IN THE INSPIRE STUDY

I have read or had explained to me the information in this consent form. I believe that I understand this information. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. By signing and dating this consent, I am stating that I want to join this study and authorize the use and disclosure of my health information to conduct this study. I do not give up any of my legal rights by signing this consent form. I will receive a copy of this signed and dated consent form.

_____	_____	_____
Research Participant: Print Name	*Research Participant: Signature*	*Date & Time*

– OR –

[ ] Study participant lacks capacity to consent. Consent given by LAR below.

LEGALLY AUTHORIZED REPRESENTATIVE

If consent was provided by a legally authorized representative (LAR), complete below.

You are being asked as the legally authorized representative (LAR) to permit the participant to take part in the research. By signing below, you indicate you agree that the person named above can take part in this study.

_____	_____
LAR: Print Name	*LAR Relationship to Participant*

Boncyk C, *et al. BMJ Open* 2024; 14:e086946. doi: 10.1136/bmjopen-2024-086946

_____ _____

LAR: Signature *Date & Time*

STUDY STAFF OBTAINING CONSENT

_____ _____ _____

Study Staff: Print Name *Study Staff: Signature* *Date & Time*

WITNESS SIGNATURE FOR PARTICIPANTS WHO CANNOT READ

The study participant has indicated that he/she is unable to read. The consent document has been read to the participant by study staff, discussed with the participant by study staff, and the participant has been given an opportunity to ask questions of the study staff.

_____ _____ _____

Impartial Witness: *Print Name Impartial Witness: Signature* *Date & Time*

Supplementary Table: Summary of Key Observations and Measures

	Screening Period			Treatment Period					Follow-up Period		
									Post-Treatment Monitoring	Follow-up contact	
	Screening/Randomisation		Baseline								
Hour, Day, or Month (± Window)	**Initial Screening D -30 to Randomisation**	**Complete Screening -24h to Randomisation**	**Randomisation to Initiation of Study Drug (up to 6 hours)**	**Q2h (±0.5h)**	**Q4h (±0.5h)**	**Q8h (±2h)**	**Daily**	**End of treatment / Up to 48h (±6h)**	**Until 24h After End of Treatment**	**Until D7 After End of Treatment (±2D)**	**D30 (±5D)**
Laboratory assessments[1]		X					X		X[2]		
Physical function and outcomes[3]	X										
Cognitive function and outcomes[4]	X										
Ventilator parameters[5]			X			X[6]					
Blood gases[7]			X			X[6]					
Organ function (SOFA)[8]			X				X			X	
Vital signs[9]			X[10]			X[6]			X		
RASS			X[10]	X[11]			X[12]	X[11]		X[12]	
CPOT			X[10]	X[11]							
Isoflurane end-tidal concentration measurement[13]					X						
CAM-ICU-7[14]							X[12]	X[14]		X[12]	
Wake-up test[15]								X			
Major ICU interventions[16]											X
Time of extubation[17]									X		
Duration of mechanical ventilation											X
Level of care											X
Mortality											X

[1] Includes clinical chemistry, lipid profile, hematology, coagulation, and blood gas analysis if an arterial line is available. Screening/baseline clinical laboratory tests, other than those pertaining to trial eligibility, are collected at any time during the complete screening (-24 hours to 0 hour) or post-randomisation (0 hour to +6 hours) periods prior to initiation of study drug treatment.

[2] Assessment is performed once during post-treatment monitoring period, if the patient is still in the ICU. Analyses performed per standard of care with an 18-to-48-hour window after end of treatment can be used.

[3] Physical outcomes assess activities of daily living by the Katz ADL and Pfeffer FAQ.

[4] Cognitive baseline is assessed by the IQCODE. Long-term outcomes are 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.

[5] 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.

[6] These assessments are performed more frequently when clinically indicated (patients are observed continuously or more frequently than every 8 hours in clinical practice).
[7] Only applicable when an arterial line is available.
[8] Organ function is assessed by SOFA once daily at baseline, during the study drug treatment period, the 24-hour post-treatment period, and until 7 days after end of treatment.
[9] Vital signs include systolic, diastolic, and mean arterial blood pressure, heart rate, SpO_2 (measured by pulse oximetry; is not assessed while patients are on ventilator support, as it is captured as a ventilator parameter), respiratory rate (not recorded as part of vital sign assessments while patient is on ventilator support, as it is captured in the ventilator parameter records as observed breathing rate), and body temperature.
[10] Unblinded baseline assessment for RASS and CPOT is performed within 30 minutes prior to initiation of study drug administration. Vital signs are performed within 60 minutes prior to initiation of study drug administration.
[11] Assessment is performed in a blinded manner by a blinded assessor.
[12] CAM-ICU-7 and RASS is performed daily (at a minimum) during the study drug treatment period and until 7 days after end of treatment or until hospital discharge, whichever comes first. However, more frequent assessments are performed when clinically indicated. RASS is assessed first. If RASS is ≥-3, CAM-ICU-7 is assessed. If RASS is -4 or -5, CAM-ICU-7 is not assessed.
[13] A separate gas monitor is readily available during the study drug treatment period for measurement of end-tidal isoflurane concentrations. Only applicable for isoflurane treated patients.
[14] CAM-ICU-7 is assessed 60 (±10) minutes after end of treatment in all patients by a blinded assessor. CAM-ICU-7 is not required for patients reaching end of treatment 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 end of treatment.
[15] Wake-up test is assessed through blinded RASS assessments.
[16] Major ICU interventions through study Day 30 or until ICU discharge, whichever comes first, include the following: renal replacement therapy, extracorporeal life support, tracheostomy, non-invasive ventilation, and re-admission to the ICU.
[17] Collected for patients who are extubated on study drug only.

ABG, arterial blood gas; 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; $EtCO_2$, end-tidal carbon dioxide; 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; 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; SOFA, sequential organ failure assessment; SpO_2, peripheral capillary oxygen saturation; TICS, Telephone Interview for Cognitive Status; W, week(s); WAIS, Wechsler Adult Intelligence Scale; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0; WMS, Wechsler Memory Scale