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