Supplemental Material

Jakob SM, Ruokonen E, Grounds RM, et al; for the Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs. midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA*. 2012;307(11):1151-1160.

eAppendix

Complete list of exclusion criteria
Titration of study drugs
Prespecified endpoints
Safety monitoring
Imputation rules
Justification of non-inferiority boundary
Technique to estimate covariances
Length of stay
Adverse events
Occurrence rate of new infections and pneumonias

eResults

eFigure 1: Proportion of time at target sedation
eFigure 2a and 2b: Time to extubation
eFigure 3: Duration of mechanical ventilation, time to extubation, and length of intensive care unit (ICU) stay in the MIDEX and PRODEX trials

eTable 1: Stratification of patients based on mean RASS during the study drug infusion
eTable 2: Duration of mechanical ventilation
eTable 3: Time to extubation
eTable 4: Length of hospital stay
eTable 5: Length of mechanical ventilation, including observed data only
eTable 6: Time to extubation, including observed data only
eTable 7: Length of mechanical ventilation; patients who die during ventilation were censored at time of death
eTable 8: Time to extubation; patients who die while intubated were censored at time of death
eTable 9: Duration of mechanical ventilation, including survivors only
eTable 10: Reasons for restarting sedation
eTable 11: Between-group mean differences in changes from baseline serum glucose over time
eTable 12: Adverse events with incidence >2% in any treatment group, 45-day follow-up
eTable 13: Serious adverse events reported in >2% of patients in any treatment group
eTable14: Neurocognitive events that received concomitant treatment
eTable15: Incidence of neurocognitive disorders after randomization until 48-hour follow-up
eTable 16: Changes in serum cortisol concentrations

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix

Complete List of Exclusion Criteria

- Acute severe intracranial or spinal neurological disorder due to vascular causes, infection, intracranial expansion or injury.
- Uncompensated acute circulatory failure at time of randomization (severe hypotension with MAP < 55 mmHg despite volume and pressors).
- Severe bradycardia (HR < 50 beats/min).
- AV-conduction block II-III (unless pacemaker installed).
- Severe hepatic impairment (bilirubin > 101 μmol/l).
- Need for muscle relaxation at the time of randomization (could only be used for intubation and initial stabilization).
- Loss of hearing or vision, or any other condition which could significantly have interfered with the collection of study data.
- Burn injuries and other injuries requiring regular anesthesia or surgery.
- Use of centrally acting alpha-2 agonists or antagonists (e.g., clonidine, titzanidine, apraclonidine and brimonidine) within 24 hours prior to randomization.
- Known allergy to any of the study drugs or any excipients of the study drugs.
- Patients who had or were expected to have treatment withdrawn or withheld due to poor prognosis.
- Patients receiving sedation for therapeutic indications rather than to tolerate the ventilator (e.g. epilepsy).
- Patients unlikely to require continuous sedation during mechanical ventilation (e.g. Guillain-Barré syndrome).
- Patients who were unlikely to be weaned from mechanical ventilation; e.g. diseases/injuries primarily affecting the neuromuscular function of the respiratory apparatus such as clearly irreversible disease requiring prolonged ventilatory support (e.g., high spinal cord injury or advanced amyotrophic lateral sclerosis).
- Distal paraplegia.
- Positive pregnancy test or currently lactating.
- Received any investigational drug within the preceding 30 days.
- Concurrent participation in any other interventional study (any study in which patients were allocated to different treatment groups and/or non-routine diagnostic or monitoring procedures were performed).
- Previous participation in this study.
- Any other condition which, in the investigator's opinion, could make it detrimental for the participant to take part in the study.

Titration of Study Drugs

Both study drug (active and dummy) infusions were always altered simultaneously. If over-sedation occurred, the study drug could be temporarily discontinued. Patients who could not be adequately sedated with the maximum dose of study drug and rescue boli were withdrawn for lack of efficacy. The depth of sedation was assessed using the RASS score. The RASS score ranges from -5 to +4 as follows: -5- unarousable by physical stimulation; -4 deep sedation: no response to voice but movement or eye opening to physical stimulation; -3 moderate sedation: movement or eye opening to voice (no eye contact); -2 light sedation: briefly awakens with eye contact to voice (less than 10 seconds); -1 drowsy: not fully alert, sustained awakening to voice (eye opening/eye contact for at least 10 seconds); 0: alert and calm; +1: restless, anxious but movements not aggressive/vigorous; +2 agitated: frequent non-purposeful movement, fights ventilator; +3: very agitated, pulls or removes tubes or catheters, aggressive; +4 : combative: overtly combative, violent, immediate danger to the staff

Prespecified Endpoints

Additional pre-specified endpoints included length of hospital stay, time to extubation, need for rescue medication, and cost of care in the ICU based on cumulative therapeutic intervention scoring system (TISS) points.

Safety Monitoring

Midex and Prodex Studies Data Monitoring Committee

Name of member	**Address**
J. Bion (Chair)	Reader in Intensive Care Medicine University Department of Anaesthesia & Intensive Care Medicine N5 Queen Elizabeth Hospital Edgbaston Birmingham B15 2TH United Kingdom
E. Azoulay	Hôpital Saint-Louis 1 Avenue Claude-Vellefaux, 75010 Paris France
S. Rubertsson	Department of Surgical Sciences/Anesthesiology & Intensive Care Uppsala University Hospital 75185 Uppsala Sweden
R. Venn	Department of Anaesthesia Worthing Hospital Lyndhurst Road Worthing West Sussex BN11 2DH United Kingdom
R. Kay	rkstatistics St Giles View Main Street Great Longstone BAKEWELL Derbyshire, DE45 1TZ United Kingdom
Independent statistical support	T. Ramsden ICON UK Ltd 2 Globeside Globeside Business Park Marlow Buckinghamshire, SL7 1TB United Kingdom

DMC meetings:

Date	Purpose of meeting	Total patients evaluated
13/9/07	Preparation	0
11/1/08	Data review	59
29/4/08	Data review	144
4/7/08	Data review	203
17/11/08	Data review	366
25/3/09	Data review	570
10/10/09	Data review	910

Adverse events

Definition of adverse event (AE)

An AE was any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Thus, an AE could be an appearance or worsening of any undesirable sign or symptom, any worsening of the concomitant disease or onset of a new disease, compared with the previous observations or clinically significant adverse change in a laboratory variable or other diagnostic finding (e.g. ECG).

However, study participants required intensive care due to unstable function of one or several vital organs. Diverse and multiple clinical findings, symptoms and signs, and laboratory findings deviating from normal were expected to occur frequently, given the severity of their illness.

Expected minor fluctuations in the study participant's presenting illness did not represent an AE. Any clinically significant worsening in a study participant's condition based on clinical judgment, compared with the study participant's baseline status at the time of randomization, had to be recorded as an AE. This applied whether or not the worsening condition was considered to be due to the study participant's primary underlying illness, and whether or not it was considered to be related to study treatment. Clinically significant adverse changes in laboratory variables, vital signs or other diagnostic findings (e.g. ECG) had to also be recorded as AEs.

Definition of serious adverse event (SAE)

An SAE was any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event jeopardizing the study participant or requiring intervention to prevent serious outcome.

In this study, careful judgment was applied when reporting SAEs, since patients in ICU generally already had a life-threatening condition and their length of hospitalization could not be predicted with any certainty. Therefore, in the ICU setting, AEs could not readily be judged life-threatening or resulting in prolonged hospitalization. Similarly, any persistent disability did not necessarily indicate an SAE, if it was predictable from the study participant's clinical condition at the time of randomization. However, any newly-emergent condition that met the above definitions of an SAE was recorded as an SAE. In addition, the investigator made a best effort to identify any clinically significant worsening of the study participant's underlying condition that met the definitions of SAE. Survival and ICU stay were study endpoints that were additionally reviewed by the DMC.

Death was generally presumed to occur as the outcome of an SAE. In cases where a study participant succumbed to the condition for which they were admitted to the ICU, there was a presumption of clinically significant worsening in the study participant's condition. It was therefore expected that death always resulted in an SAE report.

Other significant AEs

AEs that were clinically notable and not considered as SAEs were other significant AEs. These were identified by the investigator or the sponsor during or after the study. Withdrawal of study treatment due to an AE was always considered as other significant AE. Other examples that could be considered as other significant AEs were the following:

Diagnostic or therapeutic interventions, routine or pre-planned interventions or diagnostic procedures related to the study participant's underlying illness (e.g. tracheotomy in study participants requiring mechanical ventilation) were not AEs and were not to be recorded as such, whereas reduction of the dose of study treatment due to AE, significant additional concomitant treatment due to AE, marked hematological and other laboratory abnormalities, and treated hypertension episodes were to be recorded as other significant AEs.

Clinical safety assessments

Vital signs

Heart rate (HR) was measured by continuous ECG monitoring while it was still in place. Once continuous monitoring was no longer needed, HR was determined by palpation of the radial artery. Systolic, diastolic and mean arterial blood pressure (MAP) were measured by means of an arterial transducer when available, or else by automated sphygmomanometer. Recording of HR and blood pressure was avoided immediately after coughing, or nursing procedures.
MAP was recorded at screening and baseline. After starting study treatment, MAP was calculated within EDC system.
SpO2 was measured by pulse oximetry. Respiratory rate was measured for at least 30 seconds by clinical observation.
Weight was measured where possible, or estimated. In place of a measured weight at screening, the known weight could be used if it had been recorded within 3 months.
Any clinically relevant deviations in the vital signs were followed according to established clinical practice.

ECG and arrhythmias

Study participants in ICU had continuous ECG monitoring with alarms. Cardiac rhythm, including arrhythmias and AV blocks, was recorded daily. Any clinically significant abnormalities observed since the last report that were not present at baseline had to be reported as AEs. An ECG trace was printed for any occurrence of arrhythmia or AV block considered by the investigator to be clinically significant, wherever possible. The printout was forwarded to the sponsor for further analyses. A copy was taken and retained in the investigator's study file together with the study participant's worksheets.
A 12-lead ECG was recorded at specified times. A duplicate printout of the 12-lead ECG trace was provided to the study monitor. One printout was forwarded to the sponsor for central analysis and measurement of PR, QRS, QT and QTc intervals.
Any clinically relevant deviations in the ECG parameters were followed according to established clinical practice at the study center. Clinically significant changes in ECG parameters had to be reported as AEs. In addition, any changes indicative of myocardial ischemia were also reported as AEs. Diagnoses were reported when available. If the events were not related to a diagnosis, the individual events were reported separately.

Laboratory safety assessments

Blood samples for hematology and clinical chemistry analyses were collected from an arterial line, an antecubital vein, or a central or peripheral venous cannula, provided that sufficient blood was first discarded to avoid mixing with any infusate prior to collection of the samples. Because of the inevitable delay in obtaining results from the central laboratory, study samples were generally an addition to the daily standard care laboratory assessments of the study participant. Arterial blood gases were analyzed after extubation or stopping inspiratory assistance via tracheotomy, provided that an arterial cannula was still in place. FiO2 was recorded on the CRF.
A pregnancy test for all women of < 60 years of age was performed either with a proprietary "home" pregnancy test kit or by quantitative analysis of beta subunit of human chorionic gonadotropin (beta-HCG) concentration in blood or urine.

Other safety assessments

Concomitant treatment: concomitant treatments, including rescue treatment for sedation, were recorded. For treated hypertension episodes, the highest systolic blood pressure before initiating or during anti-hypertensive treatment was recorded. In addition, medication used to treat the hypertension was recorded. Blood pressure was recorded 2 hourly until stopping the anti-hypertensive treatment, at the end of the 48-hour follow-up period or ICU discharge, whichever came first. The treated hypertension had to be recorded as a significant AE and followed up accordingly unless it was a pre-existing condition for which the routine treatment was re-started.
Delirium: the presence of delirium was assessed based on the clinician's judgment, supplemented by the CAM-ICU procedure at the end of the 48-hour follow-up period (Ely EW et al., 2001) when sedation would no longer interfere with assessment. Positive CAM-ICU findings were only reported as AEs (i.e. delirium) if the investigator considered that clinically significant delirium was present. Delirium during the study treatment and/or 48-hour follow-up was analyzed by collecting AEs of delirium and related disorders under a single term. Episodes of anxiety or agitation requiring re-sedation at a sedation stop could in some cases reflect delirium and were therefore included in an analysis of cases of possible delirium.
Organ failures: organ failure was assessed using SOFA (Vincent JL et al., 1996). The individual scores were recorded, and the number of organ failures and total score for all organs were calculated. The function of several organs required laboratory assessments. Routine local laboratory values were used. If these were not available, results from central laboratory were used. For the purpose of this study, any laboratory test (study specific or part of the standard of care of the study participant) was considered normal until the first measurement fulfilling the criterion for organ dysfunction or failure for the respective organ. Similarly, a dysfunction or failure based on laboratory values was considered as being present, until the first subsequently normal values were observed.

Sensory and motor deficits: the presence of clinically relevant muscle weakness or sensory deficits was assessed using the Medical Research Council (MRC) scale (Medical Research Council 1976), peripheral tendon reflexes and pin-prick sensation testing.
Survival: time, date, location and main diagnosis for the cause of death were recorded. The main reason for death was classified by the investigator as described by Takala et al (Takala J et al., 1999).
Withdrawal syndrome: study participants were monitored during the 48-hour follow-up after withdrawal of sedation, to ensure that any signs of excessive sympathetic activity (such as agitation, sweating, tremor, palpitation, anxiety, nausea and headache) indicating a possible withdrawal syndrome were noted. Any such clinically significant symptoms were recorded on the assessment of withdrawal symptom CRF and investigators indicated whether in their opinion the study participant was experiencing a withdrawal syndrome. Withdrawal syndrome had to be reported as an AE. In addition, if the investigator considered that the participant was not experiencing the withdrawal syndrome, the separate symptoms were recorded as AEs unless they were part of any other reported AEs.

References

Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703–10.
Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996;22:707–10.
Medical Research Council. Aids to examination of the peripheral nervous system. Memorandum no. 45. London: Her Majesty's Stationary Office; 1976
Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med*. 1999;341:785-92.

Imputation rules

Imputation rules for the efficacy variables were used to account for missing data.

- Maintaining a target depth of sedation
    - If patient did not start study drug infusion, time on target was considered nil.
    - If RASS assessment was not performed or missing during the study drug infusion, value was not imputed but interpolated from preceding and consequent assessments. If the gap between the two RASS assessments was more than 7 hours or more than 30% of anticipated assessments were missing, participant was excluded from PP analysis set.
- Duration of mechanical ventilation
    - If end time of mechanical ventilation was missing, then time being medically fit for discharge from study hospital ICU was used.
    - If patient died while ventilated or participant was taken off ventilation for terminal care, duration of mechanical ventilation was considered to be 45 days (1080 hours)
    - Patients discharged from the ICU while still mechanically ventilated, or still ventilated at day 45, were censored at discharge or day 45, respectively
- Nurse's assessment of patient communication was defined as weighted average of each nursing shift. Missing dates and times of nursing shifts were imputed using middle date and time of the previous and the next assessment if available. In blind review of the data it appeared that more than 15% of the baseline data were not collected at site. There was no apparent systematic pattern and missing data were considered missing at random. Missing baseline was modeled using other baseline characteristics (baseline RASS and baseline SOFA CNS score) that were potentially related to lack of baseline assessment. Model was based on blinded PRODEX and MIDEX database and multiple imputation methodology. Multiple imputation procedure was used to replace each missing value with a set of plausible values that represent the uncertainty about the right value to impute. These multiple imputed data sets were then analyzed by using standard procedures for complete data and

combining the results from these analyses. Total of 100 random imputations were made using SAS® PROC MI MCMC method.

- Length of study ICU stay was defined as time from randomization to being medically fit for discharge or transfer from the study ICU. If participants were re-admitted to study ICU within 48 hours of initial discharge then the time to subsequent successful discharge was used instead.
    - If time of being medically fit for discharge was missing then actual ICU discharge time was used
    - If patient died during ICU stay or was discharged for terminal care, duration of ICU stay was considered to be 45 days (1080 hours)
    - If patient was re-admitted to study ICU within 48 hours of initial discharge then the time to subsequent successful discharge was used
- Time to extubation was defined as time from randomization until endotracheal tube was removed (or alternatively stopping inspiratory support in tracheotomized participants).
    - If extubation time was missing then end of mechanical ventilation was used.
    - If patient died while intubated or was extubated for terminal care, duration of intubation was considered to be 45 days (1080 hours)
    - Patients discharged from the ICU while intubated, or still intubated at day 45, were censored at discharge or day 45, respectively
- Length of study hospital stay was defined as time from randomization to actual discharge.
    - If actual hospital discharge date was missing or patient died during hospital stay, patient was considered hospitalized for 45 days.
    - Patients still hospitalized at 45 days were censored at day 45.

Justification of non-inferiority boundary

The main arguments for setting the boundary of non-inferiority at 15% were clinical relevance, expected variability in sedation, and statistical robustness. In routine clinical practice, sedation is commonly assessed at approximately 2 hr intervals; a 15% difference (equal to 3.6 hrs in 24 hrs and roughly the time span of two routine assessments of sedation) is therefore likely to be detectable and relevant for clinical use.

At the time the studies were designed, the only previous trial that used a similar sedation endpoint (time in target range of sedation without using rescue medication) and a non-inferiority design was our pilot study (reference 16). In that study, we used a non-inferiority boundary of 10%. For the current studies the number of centers was markedly higher than in the pilot study. An increase in variability in all relevant variables was very likely—specifically, the RASS scoring has poorest reproducibility at RASS levels of -3 to -2 (Sessler et al., Am J Respir Crit Care Med 2002, 166: 1338-1344). This was considered as a further argument for the 15% non-inferiority boundary.

Statistical robustness: the patients were anticipated to be in the target range of RASS -3 to 0 64% of the time they were receiving standard sedative treatment. Further, a common standard deviation of 31% was expected. As the estimated standard deviation was approximately twice the size of the non-inferiority margin, the possibility of dexmedetomidine being inferior to midazolam or propofol, but still meeting the non-inferiority criteria, was considered almost impossible.

Technique to estimate covariances

Primary data were analyzed in original scale using the SAS PROC MIXED procedure with fixed effects for treatment and country. The model estimated least square means, corresponding standard errors and covariance matrix for treatment responses. The ratio estimate was derived as ratio of the two least square means (lsDEX/lsSOC) and the variance was estimated using Taylor series expansion as Ratio^2 * ((seDEX^2 / lsDEX^2) + (seSOC^2 / lsSOC^2) – (2*COV(DEX,SOC) / (DEX*SOC))) (Lindsey J. K. (1996), Parametric Statistical Inference, Oxford Science Publications). Precision of the estimates was confirmed using Bootstrap simulations.

Length of stay

Length of ICU stay from ICU admission*

Length of ICU stay from admission to medically fit for discharge was similar between the groups [MIDEX: dexmedetomidine 239 hrs (141- 852 hrs) vs. midazolam 285 hrs (171-664 hrs) (Gehan-Wilcoxon p = 0.274); PRODEX: dexmedetomidine 190 hrs (117-511 hrs) vs. propofol 220 hrs (120-546 hrs) (Cox's proportional hazards test p = 0.346)].

Length of hospital stay*.

The median duration of study hospital stay in MIDEX was 35 days (14-45 days) for dexmedetomidine and 27 days (17-45 days) for midazolam (Cox's proportional hazards test p = 0.370). In PRODEX it was 25 days (13-45 days) for dexmedetomidine and 28 days (14-45 days) for propofol (Cox's proportional hazards test p =0.760).

Adverse events

In MIDEX, hypotension was recorded in 51 (20.6%) dexmedetomidine patients vs. 29 (11.6%) midazolam patients (p=0.007). Bradycardia was reported in 35 (14.2%) dexmedetomidine patients and in 13 (5.2%) midazolam patients (p<0.001). In PRODEX, the AEs hypotension and bradycardia were reported at similar rates. First-degree AV block in MIDEX was observed in three patients in each group, and in PRODEX, in 9 (3.7%) dexmedetomidine and 2 (0.8%) propofol patients (p=0.036). There were no differences between dexmedetomidine and standard care in infectious AEs. Critical illness polyneuropathy was more common in patients receiving propofol than in those receiving dexmedetomidine (11 patients vs. 2 patients, respectively; p=0.021).

Occurrence rate of new infections and pneumonias

We evaluated the occurrence rate of new infections and pneumonias based on the reported adverse events. We have taken all reported AEs consistent with an infection. We have separately looked at new pneumonias AEs.

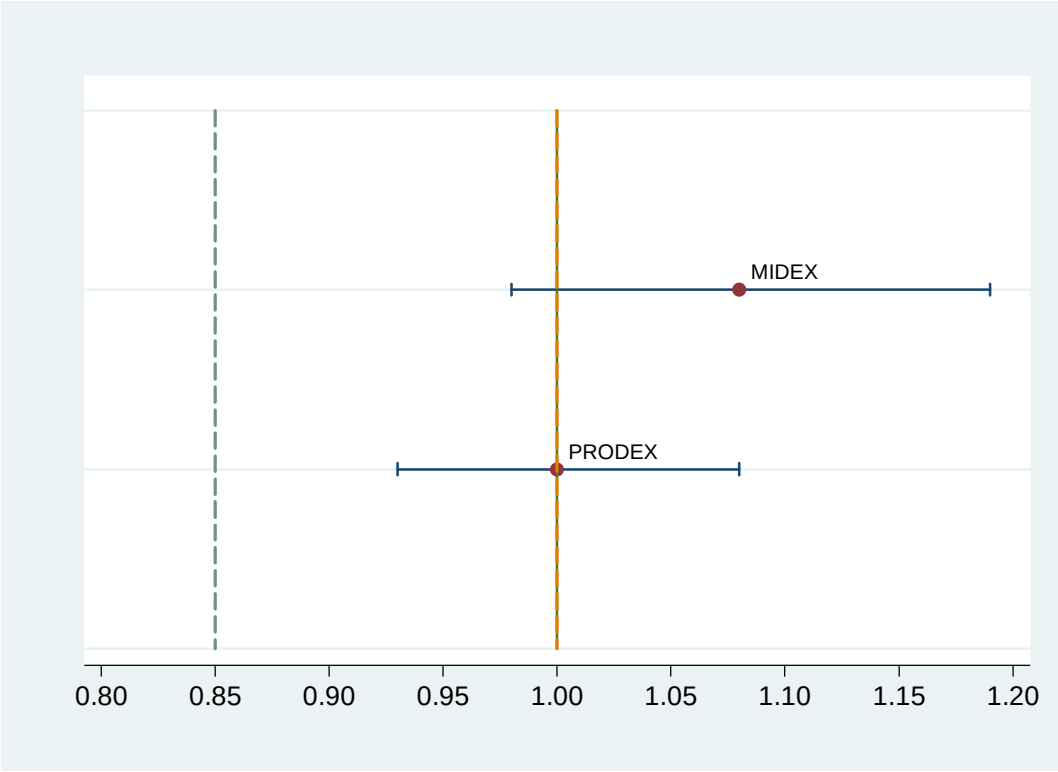
In the MIDEX study, new infections were reported as follows:
Dexmedetomidine: 91; midazolam: 98
New pneumonias:
Dexmedetomidine:17; midazolam: 18

In the PRODEX study, new infections were reported as follows:
Dexmedetomidine: 71; propofol: 70
New pneumonias:
Dexmedetomidine: 17; propofol: 14

eResults

eFigure 1

Proportion of time at target sedation. The estimated ratio (95% confidence interval) between dexmedetomidine/standard care in time at target sedation. The non-inferiority margin of 0.85 is shown with the dashed line.



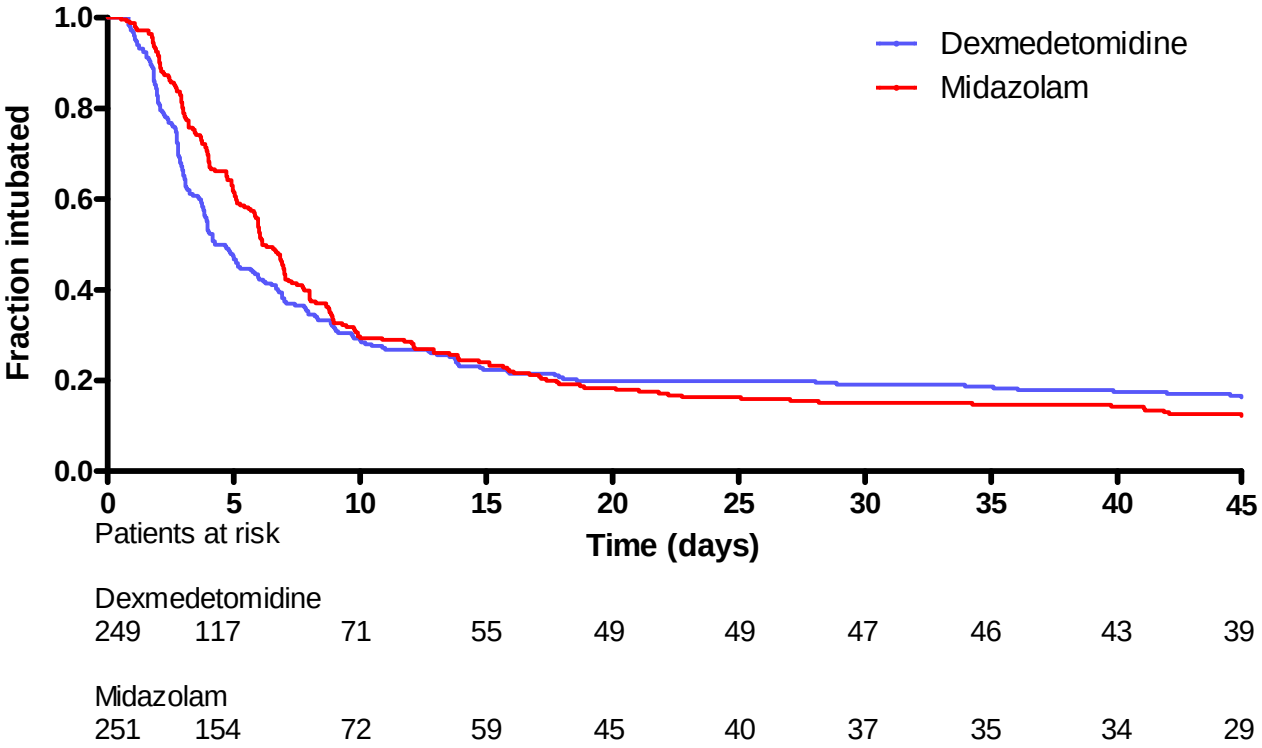
eFigure 2a and 2b

Time to extubation

The median time to extubation in MIDEX was 101 hrs (65-313 hrs) for dexmedetomidine and 147 hrs (81-325 hrs) for midazolam (Gehan-Wilcoxon p = 0.012) and in PRODEX 69 hrs (39-184 hrs) for dexmedetomidine and 93 hrs (45-286 hrs) for propofol (Gehan-Wilcoxon p = 0.041). If the proportionality assumption was violated, the Gehan-Wilcoxon test was used instead of Cox's proportional hazards.

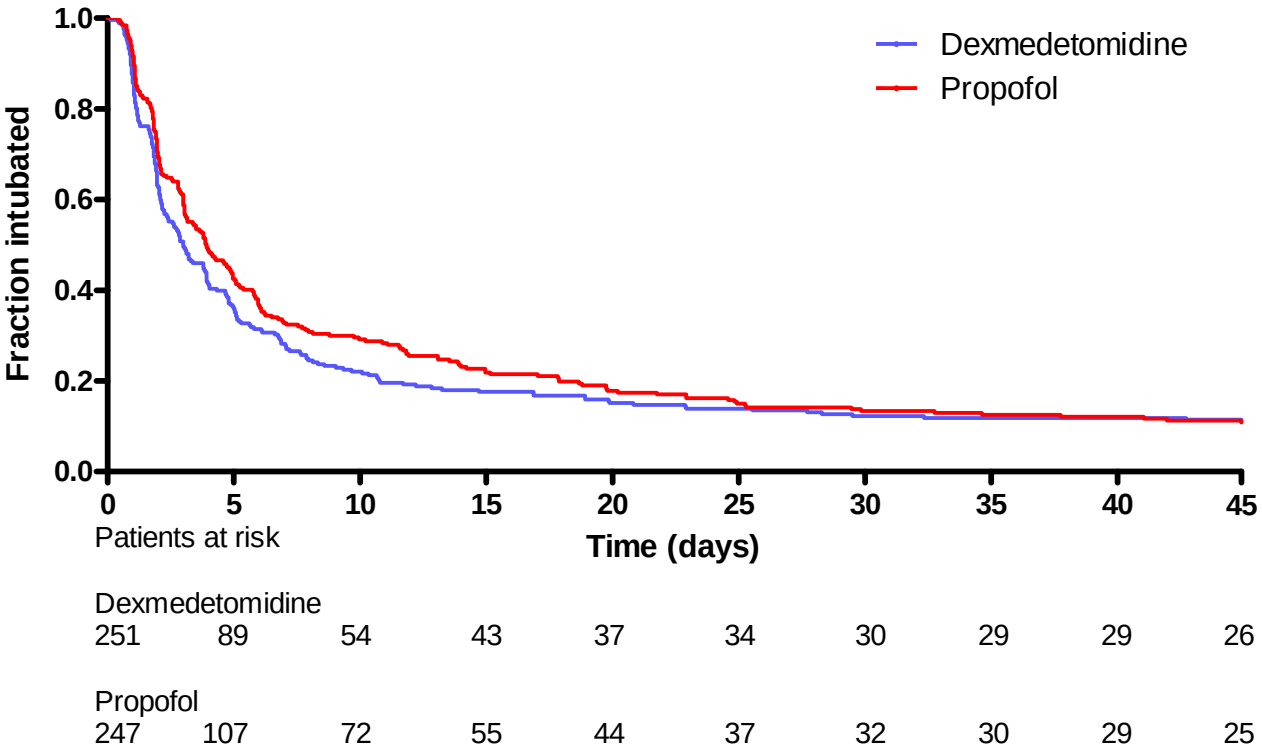
eFigure2a

Time to extubation: MIDEX study



eFigure2b

Time to extubation: PRODEX study

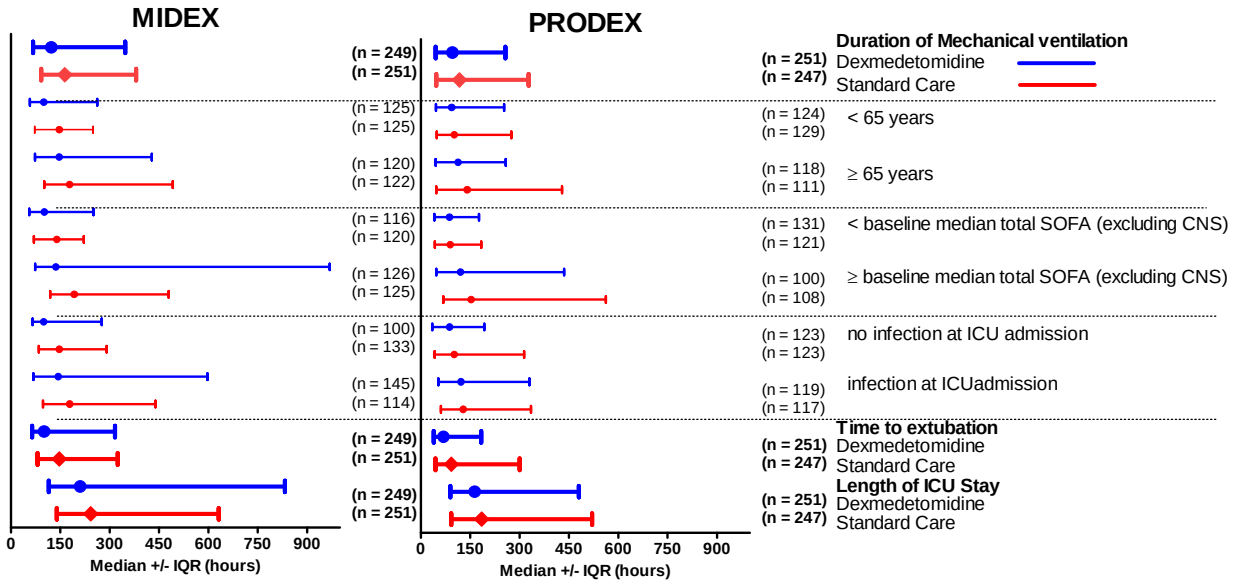


Patients at risk

Dexmedetomidine									
251	89	54	43	37	34	30	29	29	26
Propofol									
247	107	72	55	44	37	32	30	29	25

eFigure 3

Duration of mechanical ventilation, time to extubation, and length of intensive care unit (ICU) stay in the MIDEX and PRODEX trials. Duration of mechanical ventilation is also shown for clinically relevant subgroups. Standard care sedation was midazolam in the MIDEX study and propofol in the PRODEX study. Data are shown as median and interquartile range. SOFA= sequential organ failure assessment score; CNS=central nervous system



eTable 1

Stratification of patients based on mean RASS during the study drug infusion

Count of Participants in RASS strata (mean RASS during study drug)	-5 to -4	-3 to -2	-1 to 0	+1 to +2	Total
MIDEX	**11**	**202**	**277**	**7**	**497**
Dexmedetomidine	4	78	159	6	247
Midazolam	7	124	118	1	250
PRODEX	**3**	**193**	**291**	**6**	**493**
Dexmedetomidine		64	176	6	246
Propofol	3	129	115		247
Total	**14**	**395**	**568**	**13**	**990**

In the MIDEX study 2 patients randomized to dexmedetomidine and 1 randomized to midazolam and in the PRODEX study 5 patients randomized to dexmedetomidine never received the study drug and have been excluded from this table, i.e. this is the safety population.

eTable 2

Duration of mechanical ventilation. Frequency of observed, censored, and imputed data.

Duration of mechanical ventilation)	Study name		
Frequency Col Pct	MIDEX	PRODEX	Total
Observed data	405 81.00	411 82.53	816
Censored data	8 1.60	16 3.21	24
Imputed data	87 17.40	71 14.26	158
Total	500	498	998

eTable 3

Time to extubation. Frequency of observed, censored, and imputed data.

Time to extubation	Study name		
Frequency Col Pct	MIDEX	PRODEX	Total
Observed data	416 83.20	426 85.54	842
Censored data	7 1.40	6 1.20	13
Imputated data	77 15.40	66 13.25	143
Total	500	498	998

eTable 4

Length of hospital stay. Frequency of observed, censored, and imputed data.

Length of hospital stay	Study name		
Frequency **Col Pct**	**MIDEX**	**PRODEX**	**Total**
Observed data	305 61.00	340 68.27	645
Censored data	18 3.60	9 1.81	27
Imputated data	177 35.40	149 29.92	326
Total	500	498	998

eTables 5-9

In dexmedetomidine vs. midazolam, 17%, 15% and 35% of duration of mechanical ventilation, time to extubation and length of study hospital stay data were imputed; in dexmedetomidine vs. propofol, the percentages were 14%, 13%, and 30%, respectively. Imputation had no major impact on proportionality assumptions.

eTable 5

Length of mechanical ventilation, including observed data only (hours)**

	Treatment	N	Mean	Std Dev	Minimum	Maximum	Median	Lower Quartile	Upper Quartile
MIDEX*	Dexmedetomidine	194	148.0	161.2	20.0	1067.0	95.0	56.0	168.0
	Midazolam	211	193.7	181.7	13.0	1009.0	144.0	83.0	215.0
PRODEX[&]	Dexmedetomidine	203	132.8	158.6	3.0	1025.0	81.0	40.0	161.0
	Propofol	208	171.1	193.0	12.0	1007.0	97.0	44.5	203.5

*Dexmedetomidine vs. Midazolam, p<0.0001 (Gehan-Wilcoxon).
[&]Dexmedetomidine vs. Propofol, p=0.0266 (Gehan-Wilcoxon).

**If the proportionality assumption was violated, the Gehan-Wilcoxon test was used instead of Cox's proportional hazards

eTable 6

Time to extubation, including observed data only (hours)**

	Treatment	N	Mean	Std Dev	Minimum	Maximum	Median	Lower Quartile	Upper Quartile
MIDEX*	Dexmedetomidine	200	140.4	161.8	20.0	1067.0	89.5	50.0	166.0
	Midazolam	216	184.4	178.8	13.0	1009.0	140.0	73.0	211.5
PRODEX[&]	Dexmedetomidine	213	109.8	143.2	3.0	1025.0	54.0	28.0	122.0
	Propofol	213	153.6	189.8	12.0	1007.0	75.0	44.0	156.0

*Dexmedetomidine vs. Midazolam, p<0.0001 (Gehan-Wilcoxon).
[&]Dexmedetomidine vs. Propofol, p=0.0070 (Cox's proportional hazards)

**If the proportionality assumption was violated, the Gehan-Wilcoxon test was used instead of Cox's proportional hazards

eTable 7

Length of mechanical ventilation; patients who died during ventilation were censored at time of death (hours)**

	Treatment	N	Mean	Std Dev	Minimum	Maximum	Median	Lower Quartile	Upper Quartile
MIDEX*	Dexmedetomidine	209	186.8	237.9	20.0	1080.0	100.0	62.0	199.0
	Midazolam	217	211.7	217.9	13.0	1080.0	144.0	84.0	227.0
PRODEX[&]	Dexmedetomidine	220	176.6	245.9	3.0	1080.0	91.0	42.5	179.5
	Propofol	214	174.2	200.6	10.0	1080.0	98.5	45.0	211.0

*Dexmedetomidine vs. Midazolam p=0.0088 (Gehan-Wilcoxon)
[&]Dexmedetomidine vs. Propofol p= 0.2193 (Gehan-Wilcoxon)

**If the proportionality assumption was violated, the Gehan-Wilcoxon test was used instead of Cox's proportional hazards

eTable 8

Time to extubation; patients who died while intubated were censored at time of death (hours)**

	Treatment	N	Mean	Std Dev	Minimum	Maximum	Median	Lower Quartile	Upper Quartile
MIDEX*	Dexmedetomidine	212	169.7	222.6	20.0	1080.0	91.5	53.5	187.5
	Midazolam	222	202.5	215.4	13.0	1080.0	142.0	74.0	214.0
PRODEX[&]	Dexmedetomidine	227	140.5	214.0	3.0	1080.0	62.0	29.0	136.0
	Propofol	220	159.0	198.8	10.0	1080.0	76.0	43.5	166.5

*Dexmedetomidine vs. Midazolam p=0.0026 (Gehan-Wilcoxon)
[&]Dexmedetomidine vs. Propofol p=0.0347 (Gehan-Wilcoxon)

**If the proportionality assumption was violated, the Gehan-Wilcoxon test was used instead of Cox's proportional hazards

eTable 9

Duration of mechanical ventilation, including survivors only (hours)**

	Treatment	N	Mean	Std Dev	Minimum	Maximum	Median	Lower Quartile	Upper Quartile
MIDEX*	Dexmedetomidine	176	193.6	254.8	20.0	1080.0	99.5	61.5	198.0
	Midazolam	194	214.8	227.1	13.0	1080.0	144.0	76.0	235.0
PRODEX[&]	Dexmedetomidine	199	180.8	253.8	10.0	1080.0	87.0	43.0	189.0
	Propofol	193	177.9	208.5	12.0	1080.0	100.0	44.0	196.0

*Dexmedetomidine vs. Midazolam p=0.0033 (Gehan-Wilcoxon)
[&]Dexmedetomidine vs. Propofol p=0.4088 (Gehan-Wilcoxon)

**If the proportionality assumption was violated, the Gehan-Wilcoxon test was used instead of Cox's proportional hazards

eTable 10

Reasons for restarting sedation

	MIDEX			PRODEX		
	DEX (n = 249) n (%)	MDZ (n = 251) n (%)	P value	DEX (n = 251) n (%)	PRO (n = 247) n (%)	P value
Agitation						
Participants	72	91	0.086	53	65	0.206
Events[1]	123 (35.1)	209 (46.6)	0.042	84 (33.2)	118 (26.9)	0.160
Anxiety						
Participants	38	29	0.239	25	29	0.566
Events	67 (19.1)	59 (13.1)	0.126	41 (16.2)	46 (10.5)	0.131
CV Instability						
Participants	29	22	0.304	21	23	0.754
Events	51 (14.6)	40 (8.9)	0.071	37 (14.6)	35 (8.0)	0.126
Poor tolerance ET tube						
Participants	67	75	0.488	50	67	0.072
Events	143 (40.9)	158 (35.2)	0.309	66 (26.1)	131 (29.8)	0.298
Poor tolerance MV						
Participants	60	73	0.225	34	60	0.003
Events	129 (36.9)	161 (35.9)	0.868	51 (20.2)	118 (26.9)	0.185
Weaning from MV not successful						
Participants	41	39	0.808	37	54	0.048
Events	77 (22)	82 (18.3)	0.535	46 (18.2)	95 (21.6)	0.701
Other						
Events	35 (10.0)	57 (12.7)		78 (30.8)	104 (23.7)	

[1]Calculated based on proportion of events in each category

eTable 11

Between-group mean differences in changes from baseline serum glucose over time

	Change from baseline in serum glucose (mmol/l)					
Visit	Dex-propofol comparison			Dex-midazolam comparison		
	Mean	CI	p value	Mean	CI	p value
Day 2	0.22	-0.15, 0.59	0.238	0.36	-0.24, 0.95	0.241
Day 4	0.28	-0.25, 0.81	0.306	-0.23	-0.73, 0.28	0.378
Day 6	0.30	-0.53, 1.14	0.473	0.11	-0.59, 0.81	0.748
Day 9	0.27	-1.33, 1.88	0.730	0.29	-1.13, 1.71	0.680
Day 14	0.71	-2.50, 3.91	0.624	0.67	-1.51, 2.85	0.521
48h follow-up	-0.20	-0.62, 0.22	0.357	-0.19	-0.67, 0.28	0.425
Overall treatment effect	0.21	-0.11, 0.53	0.191	0.12	-0.27, 0.50	0.558
	DEX	PRO	p value	DEX	MDZ	p value
	N (%)	N (%)		N (%)	N (%)	
Patients with value > 10 mmol/l at any time	65 (26.6)	58 (23.6)	0.466	97 (39.3)	101 (40.6)	0.784
Hyperglycemia as an AE	2 (0.8)	-		5 (2.0)	5 (2.0)	1.00
Hypoglycemia as an AE	3 (1.2)	3 (1.2)		10 (4.0)	2 (0.8)	0.020

eTable 12

Adverse events with incidence >2% in any treatment group, 45-day follow-up

Preferred term	Midex							Prodex						
	Dexmedetomidine (N = 247)			Midazolam (N = 250)				Dexmedetomidine (N = 246)			Propofol (N = 247)			
	N	(%)	events	N	(%)	events	P value	N	(%)	events	N	(%)	events	P value
Hypertension	53	(21.5)	70	52	(20.8)	74	0.913	52	(21.1)	62	37	(15.0)	40	0.08
Sinus tachycardia	34	(13.8)	46	54	(21.6)	89	0.025	48	(19.5)	85	28	(11.3)	46	0.013
Hypotension	51	(20.6)	58	29	(11.6)	51	0.007	32	(13.0)	38	33	(13.4)	41	
Atrial fibrillation	33	(13.4)	42	42	(16.8)	68	0.317	30	(12.2)	38	35	(14.2)	45	0.595
Agitation	39	(15.8)	44	41	(16.4)	44	0.903	19	(7.7)	20	29	(11.7)	33	0.171
Bradycardia	35	(14.2)	47	13	(5.2)	16	< 0.001	32	(13.0)	51	25	(10.1)	33	0.328
Respiratory failure	16	(6.5)	19	15	(6.0)	17	0.855	30	(12.2)	31	34	(13.8)	39	0.688
Pleural effusion	16	(6.5)	21	17	(6.8)	20		18	(7.3)	20	34	(13.8)	37	0.027
Pneumonia	24	(9.7)	25	15	(6.0)	15	0.136	22	(8.9)	22	23	(9.3)	24	
Anxiety	20	(8.1)	22	15	(6.0)	16	0.385	21	(8.5)	21	25	(10.1)	25	0.643
Delirium	19	(7.7)	22	25	(10.0)	25	0.431	12	(4.9)	12	24	(9.7)	26	0.056
Diarrhea	13	(5.3)	14	14	(5.6)	15		14	(5.7)	14	19	(7.7)	19	0.472
Pyrexia	16	(6.5)	20	20	(8.0)	30	0.604	13	(5.3)	16	9	(3.6)	10	0.394
Multiorgan failure	11	(4.5)	11	17	(6.8)	17	0.331	12	(4.9)	13	17	(6.9)	17	0.444
GGT increased	6	(2.4)	7	20	(8.0)	21	0.008	10	(4.1)	12	14	(5.7)	14	0.531
Sepsis	19	(7.7)	20	8	(3.2)	8	0.03	12	(4.9)	12	10	(4.0)	10	0.67
Septic shock	17	(6.9)	17	18	(7.2)	19		6	(2.4)	6	8	(3.2)	8	0.787
Nausea	9	(3.6)	10	4	(1.6)	7	0.172	18	(7.3)	19	12	(4.9)	13	0.265
Anemia	11	(4.5)	11	13	(5.2)	13	0.835	13	(5.3)	15	6	(2.4)	6	0.108
Supraventricular tachycardia	11	(4.5)	15	6	(2.4)	7	0.227	10	(4.1)	17	12	(4.9)	14	0.828
Withdrawal syndrome	17	(6.9)	17	8	(3.2)	8	0.067	4	(1.6)	4	7	(2.8)	7	0.544
Hypokalemia	12	(4.9)	15	10	(4.0)	11	0.669	7	(2.8)	7	7	(2.8)	7	
Vomiting	11	(4.5)	11	9	(3.6)	10	0.655	10	(4.1)	12	5	(2.0)	5	0.203
Acute respiratory distress syndrome	10	(4.0)	10	4	(1.6)	4	0.112	8	(3.3)	8	13	(5.3)	13	0.373
Renal failure	6	(2.4)	6	5	(2.0)	6	0.771	9	(3.7)	9	15	(6.1)	16	0.295
Confusional state	11	(4.5)	14	12	(4.8)	13		4	(1.6)	4	7	(2.8)	7	0.544
Decubitus ulcer	7	(2.8)	8	6	(2.4)	7	0.787	8	(3.3)	9	8	(3.2)	9	
Pneumothorax	10	(4.0)	11	7	(2.8)	8	0.471	3	(1.2)	3	7	(2.8)	9	0.339
Endotracheal intubation complication	9	(3.6)	9	6	(2.4)	6	0.445	5	(2.0)	6	7	(2.8)	8	0.772
Cardiac arrest	8	(3.2)	8	7	(2.8)	7	0.8	7	(2.8)	8	5	(2.0)	5	0.576
Constipation	3	(1.2)	3	9	(3.6)	11	0.141	9	(3.7)	9	4	(1.6)	4	0.173
Hypoxia	7	(2.8)	7	8	(3.2)	8		2	(0.8)	2	7	(2.8)	8	0.176
Ventricular tachycardia	2	(0.8)	2	4	(1.6)	4		8	(3.3)	8	8	(3.2)	9	
Oxygen saturation decreased	2	(0.8)	2	3	(1.2)	8		6	(2.4)	6	11	(4.5)	11	0.324
Urinary tract infection	6	(2.4)	6	10	(4.0)	10	0.447	2	(0.8)	3	4	(1.6)	4	
Hemoglobin decreased	2	(0.8)	2	3	(1.2)	3		10	(4.1)	11	6	(2.4)	6	0.324
Acute renal failure	5	(2.0)	5	4	(1.6)	4	0.75	8	(3.3)	8	4	(1.6)	4	0.26
Pulmonary edema	8	(3.2)	8	4	(1.6)	4	0.259	4	(1.6)	4	5	(2.0)	5	
Cardiac failure	7	(2.8)	7	5	(2.0)	6	0.574	2	(0.8)	2	7	(2.8)	8	0.176
Acute respiratory failure	10	(4.0)	11	4	(1.6)	4	0.112	2	(0.8)	3	4	(1.6)	5	
Hepatic enzyme increased	1	(0.4)	1	2	(0.8)	2		10	(4.1)	10	7	(2.8)	7	0.472
Insomnia	3	(1.2)	3	4	(1.6)	4		7	(2.8)	7	6	(2.4)	6	0.787
Impaired gastric emptying	7	(2.8)	7	7	(2.8)	7	1	2	(0.8)	2	4	(1.6)	4	
Restlessness	4	(1.6)	6	7	(2.8)	11	0.544	1	(0.4)	1	8	(3.2)	8	0.037
Hypoglycemia	10	(4.0)	12	2	(0.8)	4	0.02	3	(1.2)	3	3	(1.2)	3	
Atelectasis	3	(1.2)	4	5	(2.0)	5		5	(2.0)	5	5	(2.0)	6	
AV block 1st degree	3	(1.2)	3	3	(1.2)	3		9	(3.7)	9	2	(0.8)	2	0.036
Bronchitis	7	(2.8)	7	8	(3.2)	8		0			2	(0.8)	2	
Hypernatremia	6	(2.4)	6	4	(1.6)	7	0.543	3	(1.2)	3	4	(1.6)	4	
Gastrointestinal hemorrhage	4	(1.6)	4	6	(2.4)	6	0.751	5	(2.0)	5	2	(0.8)	2	0.285
Peritonitis	8	(3.2)	8	4	(1.6)	5	0.259	4	(1.6)	4	0			
Depression	3	(1.2)	3	3	(1.2)	3		6	(2.4)	6	4	(1.6)	4	0.544
Sedation	3	(1.2)	4	11	(4.4)	12	0.054	0			2	(0.8)	2	
Thrombocytopenia	6	(2.4)	6	4	(1.6)	4	0.543	2	(0.8)	2	3	(1.2)	3	

eTable 12 continued

Preferred term	Midex							Prodex						
	Dexmedetomidine (N = 247)			Midazolam (N = 250)				Dexmedetomidine (N = 246)			Propofol (N = 247)			
	N	(%)	events	N	(%)	events	P value	N	(%)	events	N	(%)	events	P value
CIP	0			2	(0.8)	2		2	(0.8)	2	11	(4.5)	11	0.021
Myocardial ischemia	4	(1.6)	4	2	(0.8)	2		5	(2.0)	5	3	(1.2)	3	0.504
Blood potassium decreased	1	(0.4)	1	2	(0.8)	2		7	(2.8)	8	4	(1.6)	4	0.382
Hyperkalemia	8	(3.2)	10	4	(1.6)	4	0.259	0			1	(0.4)	1	
Headache	3	(1.2)	3	3	(1.2)	3		5	(2.0)	5	2	(0.8)	2	0.285
Wound infection	2	(0.8)	2	3	(1.2)	3		3	(1.2)	3	5	(2.0)	5	0.724
Hyperthermia	8	(3.2)	8	2	(0.8)	2	0.062	2	(0.8)	2	0			
Hyperglycemia	5	(2.0)	5	5	(2.0)	5		2	(0.8)	2	0			
Acute pulmonary edema	7	(2.8)	7	5	(2.0)	5	0.574	0			0			
Alanine aminotransferase increased	0			2	(0.8)	2		6	(2.4)	6	4	(1.6)	4	0.544
Circulatory collapse	5	(2.0)	5	2	(0.8)	2	0.283	2	(0.8)	2	3	(1.2)	3	
Tachyarrhythmia	0			1	(0.4)	2		5	(2.0)	7	6	(2.4)	8	
Drug ineffective	3	(1.2)	3	0				8	(3.3)	8	0			0.004
Abdominal pain upper	1	(0.4)	1	2	(0.8)	2		5	(2.0)	5	3	(1.2)	3	0.504
Bronchopneumonia	5	(2.0)	7	6	(2.4)	6		0			0			
Ventricular extrasystoles	5	(2.0)	5	1	(0.4)	1	0.121	1	(0.4)	1	3	(1.2)	3	
C-reactive protein increased	1	(0.4)	1	0				3	(1.2)	3	6	(2.4)	6	0.504
Abdominal abscess	6	(2.4)	6	2	(0.8)	2	0.174	1	(0.4)	1	0			
Subcutaneous emphysema	5	(2.0)	5	2	(0.8)	2	0.283	1	(0.4)	1	1	(0.4)	1	
Blood triglycerides increased	0			1	(0.4)	1		2	(0.8)	2	6	(2.4)	6	0.285
Shock	5	(2.0)	5	2	(0.8)	2	0.283	0			1	(0.4)	1	
Extubation	5	(2.0)	5	1	(0.4)	1	0.121	1	(0.4)	1	0			
Palpitations	0			0				5	(2.0)	5	2	(0.8)	2	0.285
Hypercapnia	5	(2.0)	6	1	(0.4)	1	0.121	0			0			
Hemorrhagic shock	5	(2.0)	5	0			0.03	0			1	(0.4)	1	

eTable 13

Serious adverse events reported in >2% of patients in any treatment group

	Midex			Prodex		
Preferred Term	Dexmedetomidine (N=247) n (%) events	Midazolam (N=250) n (%) events	p value	Dexmedetomidine (N=246) n (%) events	Propofol (N=247) n (%) events	p value
Respiratory failure	14 (5.7) 15	12 (4.8) 12	0.692	24 (9.8) 25	23 (9.3) 25	0.879
Multi-organ failure	11 (4.5) 11	17 (6.8) 17	0.331	12 (4.9) 13	17 (6.9) 17	0.444
Pneumonia	11 (4.5) 11	4 (1.6) 4	0.071	12 (4.9) 12	9 (3.6) 9	0.514
Sepsis	13 (5.3) 14	5 (2.0) 5	0.058	7 (2.8) 7	7 (2.8) 7	1.000
Cardiac arrest	8 (3.2) 8	6 (2.4) 6	0.600	7 (2.8) 8	5 (2.0) 5	0.576
Septic shock	15 (6.1) 15	11 (4.4) 12	0.427	6 (2.4) 6	6 (2.4) 6	1.000
Acute respiratory distress syndrome	8 (3.2) 8	3 (1.2) 3	0.140	6 (2.4) 6	7 (2.8) 7	1.000
Hypoxia	6 (2.4) 6	7 (2.8) 7	1.000	2 (0.8) 2	4 (1.6) 4	
Hypotension	3 (1.2) 3	3 (1.2) 3		8 (3.3) 8	4 (1.6) 4	0.260
Acute respiratory failure	7 (2.8) 7	4 (1.6) 4	0.380	2 (0.8) 3	4 (1.6) 5	
Renal failure	3 (1.2) 3	3 (1.2) 3		4 (1.6) 4	6 (2.4) 6	0.751
Cardiac failure	5 (2.0) 6	4 (1.6) 5	0.750	0	5 (2.0) 5	0.061
Renal failure acute	5 (2.0) 5	2 (0.8) 2	0.283	4 (1.6) 4	2 (0.8) 2	
Peritonitis	5 (2.0) 5	3 (1.2) 3	0.502	4 (1.6) 4	0	
Gastrointestinal hemorrhage	2 (0.8) 2	5 (2.0) 5		3 (1.2) 3	2 (0.8) 2	
Acute pulmonary edema	7 (2.8) 7	1 (0.4) 1	0.037	0	0	
Critical illness polyneuropathy	0	1 (0.4) 1		1 (0.4) 1	5 (2.0) 5	0.216

eTable 14

Neurocognitive events that received concomitant treatment

System Organ Class Preferred Term	Dexmedetomidine (N=247) Participants n (%)	 Events n	Midazolam (N=250) Participants n (%)	 Events n	Dexmedetomidine (N=246) Participants n (%)	 Events n	Propofol (N=247) Participants n (%)	 Events n
Delirium (IHSC)*								
Total	63 (25.5)	85	56 (22.4)	72	37 (15.0)	43	61 (24.7)	70
AGITATION	33 (13.4)	33	29 (11.6)	31	15 (6.1)	16	24 (9.7)	25
ANXIETY	18 (7.3)	19	8 (3.2)	8	15 (6.1)	15	18 (7.3)	18
DELIRIUM	18 (7.3)	19	17 (6.8)	17	6 (2.4)	6	16 (6.5)	16
Fisher's Exact test	p = 0.462				p = 0.009			

***** delirium (IHSC) refers to a search of adverse events including one of the following terms:

Abnormal behavior	Delirium febrile	Irritability
Affect lability	Delirium tremens	Mental disorder
Aggression	Delusion	Mental impairment
Agitation	Depressed level of consciousness	Mental status changes
Altered state of consciousness	Depression	Metabolic disorder
Amnesia	Disorientation	Mood altered
Anesthetic complication neurological	Disturbance in attention	Neurological examination abnormal
Anger	Disturbance in social behavior	Psychomotor hyperactivity
Anterograde amnesia	Dysarthria	Restlessness
Anxiety	Emotional disorder	Retrograde amnesia
Apathy	Emotional distress	Screaming
Aphasia	Euphoric mood	Sleep disorder
Brain injury	Fear	Somnolence
Cognitive disorder	Hallucination	Speech disorder
Confusion postoperative	Hallucination, auditory	Thinking abnormal
Confusional state	Hallucination, visual	Judgment impaired
Consciousness fluctuating	Hypokinesia	Lack of spontaneous speech
Decreased activity	Illusion	Memory impairment
Delirium	Incoherent	

eTable 15

Incidence of neurocognitive disorders after randomization until 48-hour follow-up

	Midex							Prodex						
	Dexmedetomidine			Midazolam				Dexmedetomidine			Propofol			
	N	(%)	Events	N	(%)	Events	P value	N	(%)	Events	N	(%)	Events	P value
Neurocognitive AEs to end of 48-hour follow-up														
Total	71	(28.7)	104	67	(26.8)	87	0.689	45	(18.3)	55	71	(28.7)	85	0.008
Agitation	37	(15.0)	39	36	(14.4)	38		18	(7.3)	19	28	(11.3)	32	
Anxiety	19	(7.7)	21	10	(4.0)	10		20	(8.1)	20	20	(8.1)	20	
Delirium	19	(7.7)	20	19	(7.6)	19		7	(2.8)	7	17	(6.9)	18	
Neurocognitive AEs requiring concomitant treatment														
Total	63	(25.5)	85	56	(22.4)	72	0.462	37	(15.0)	43	61	(24.7)	70	0.009
CAM-ICU assessment at 48- hour follow-up														
Positive	28	(11.9)		33	(13.9)		0.393	22	(9.6)		31	(13.7)		0.231
Negative	138	(58.7)		123	(51.7)			148	(64.9)		139	(61.5)		
Unassessable	69	29.4		82	34.5			58	(25.4)		56	(24.8)		

eTable 16

Changes in serum cortisol concentrations

Serum total cortisol concentrations at baseline and changes from baseline during the study are shown for the dexmedetomidine patients from both studies combined and for patients receiving propofol (PRODEX study) and midazolam (MIDEX study)

Mean cortisol changes from baseline, studies PRODEX and MIDEX

	Patients (n)	Baseline cortisol (nmol/L)	Mean cortisol change from baseline (nmol/L)					
			Day 2	Day 4	Day 6	Day 9	Day 14	48 h follow-up after stopping study drug
Dexmedetomidine	476	888.9	-23.4	-102.0	-383.0	-702.6	-377.3	-138.3
Propofol	232	783.7	25.7	-121.1	-174.5	-370.2	-827.4	-113.8
Midazolam	246	1047.0	4.4	-165.4	-181.8	-367.2	-516.5	-267.6