2. SYNOPSIS

Sponsor/company Orion Corporation Orion Pharma	**Individual study table referring to a specific part of the dossier** **Volume:** **Page**	(for National Competent Authority use only)
Finished product: Not applicable		
Active ingredient: Dexmedetomidine		

Study code: 3005012

Study title: A prospective, multi-centre, randomised, double-blind comparison of intravenous dexmedetomidine with propofol for continuous sedation of ventilated patients in intensive care unit

Investigators and study centres:

This study was conducted in 7 countries (35 study centres): Finland (8), Germany (11), Switzerland (1), the United Kingdom (5), Belgium (3), the Netherlands (4) and Russia (3).

The coordinating investigator was Professor Esko Ruokonen, Kuopio University Hospital, ICU, Kuopio, Finland.

Development phase: III	**Study period:** 9 Jun 2007 - 3 Mar 2010 (first subject first visit - last subject last contact)

Objectives:

Primary objective: The study had hierarchical co-primary objectives to demonstrate that:

- Firstly: dexmedetomidine is at least as effective as sedation with propofol and daily sedation stops, in maintaining a target depth of sedation in ventilated patients in intensive care unit (ICU)
- Secondly: use of dexmedetomidine, compared with sedation with propofol and daily sedation stops, reduces the duration of mechanical ventilation in ventilated patients in ICU

Secondary objectives: The secondary objectives of this study were:

- To show that dexmedetomidine improves rousability, communication of pain and cooperation compared with propofol using nurse's assessment of subject communication
- To show that dexmedetomidine shortens length of ICU stay compared with propofol
- To evaluate the safety of dexmedetomidine compared to propofol

Methodology:

This was a phase III, multi-centre, prospective, randomised, double-blind, double-dummy, active comparator study. The study consisted of 3 periods: screening, double-dummy treatment and follow-up period.

All patients admitted to ICU were pre-screened according to inclusion and exclusion criteria prior to informed consent using available clinical data.

Informed consent, screening and randomisation procedures were completed ≤ 72 hours from the time of admission to ICU and ≤ 48 hours from starting continuous sedation. Eligible study subjects requiring light to moderate sedation (Richmond Agitation-Sedation Scale [RASS] = 0 to -3) were randomised to either continue on propofol or switch to dexmedetomidine. The patients should not have received any other continuously or regularly administered sedative agent than propofol infusion within the previous 12 hours prior to randomisation except for opioid analgesics.

Study treatments were titrated to achieve a target sedation range determined on a daily basis. Rescue treatment (midazolam boli) was given if needed to achieve the target depth of sedation. Continued need for sedation was assessed at a daily sedation stop, conducted at the same time each day. First sedation stop was 12-36 hours from randomisation, depending on the time of day the study subject was randomised. Weaning from the mechanical

ventilation was attempted during the daily sedation stops, using a spontaneous breathing trial (t-piece or low level pressure support/continuous positive airway pressure [CPAP]), unless clinically contraindicated. Following the withdrawal of sedation, the study subjects were monitored for 48 hours and contacted by telephone 31 and 45 days after randomisation.

Sample size:

Planned: 500 subjects (250 dexmedetomidine and 250 propofol); 15-20 subjects per centre

Analysed (randomised): 500 subjects (251 dexmedetomidine and 249 propofol); 1-71 subjects per centre

Diagnosis and main criteria for inclusion

Main criteria for inclusion

- Age ≥ 18 years
- Clinical need for sedation of an initially intubated (or tracheotomised) and ventilated (with inspiratory assistance) patient
- Prescribed light to moderate sedation (target RASS = 0 to -3) using propofol infusion
- Randomisation ≤ 72 hours from ICU admission and ≤ 48 hours of commencing continuous sedation in the ICU
- Expected requirement for sedation ≥ 24 hours from time of randomisation
- Written informed consent obtained according to local regulations before starting any study procedures other than pre-screening

Main criteria for exclusion

- Acute severe intracranial or spinal neurological disorder due to vascular causes, infection, intracranial expansion or injury
- Uncompensated acute circulatory failure at time of randomisation (severe hypotension with mean arterial pressure [MAP] < 55 mmHg despite volume and pressors)
- Severe bradycardia (heart rate [HR] < 50 beats/min)
- Atrioventricular (AV)-conduction block II-III (unless pacemaker installed)
- Severe hepatic impairment (bilirubin > 101 µmol/l)
- Need for muscle relaxation at the time of randomisation (could only be used for intubation and initial stabilisation)
- 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 anaesthesia or surgery (other injuries added by the 1st Amended protocol, 16 Nov 2007)
- Use of centrally acting alpha-2 agonists or antagonists (e.g. clonidine, titzanidine, apraclonidine and brimonidine) within 24 hours prior to randomisation (time limit added by the 1st Amended protocol, 16 Nov 2007)
- 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

Investigational product, dose and mode of administration, batch numbers:

Dexmedetomidine was supplied in a 2 ml ampoule containing 200 µg (100 µg/ml) dexmedetomidine (as a base) for dilution with 48 ml 0.9% sodium chloride injection (giving a solution containing 4 µg/ml).

Placebo for dexmedetomidine was a matching 2 ml ampoule containing 0.9% sodium chloride injection.

Dexmedetomidine was infused at the numeric dose level that best matched that of the pre-randomisation dose of propofol not exceeding the dose-level 3 (i.e. 0.7 µg/kg/h) for 1 hour. A lower starting dose could be used for subjects who were considered particularly frail. After the first hour, the infusion rate of dexmedetomidine was titrated stepwise (± 1 dose level) as needed between 0.2 and a maximum of 1.4 µg/kg/h in order to maintain the target RASS range. Allowable dose levels were 0.2, 0.45, 0.7, 0.95, 1.2, 1.4 µg/kg/ h. The study treatments were administered and titrated in parallel.

Batch numbers: 1084373, 1176153 and 1251742 (dexmedetomidine); 1083086, 1177900 and 1267865 (placebo for dexmedetomidine)

Duration of treatment:

Treatment was intended to continue for a minimum of 24 hours and no longer than 14 days.

Reference product, dose and mode of administration, batch numbers:

Propofol was supplied in a50 ml vial containing 2% weight/volume (1 g; 20 mg/ml) of propofol. Placebo for propofol was a non-matching 50 ml vial containing 0.9% sodium chloride injection.

Propofol was infused with the dose that was nearest to the pre-randomisation dose of propofol not exceeding the dose level 3 (i.e. 1.6 mg/kg/h) for 1 hour. A lower starting dose could be used for subjects who were considered particularly frail. After the first hour, the infusion rate of propofol was titrated stepwise (± 1 dose level) as needed between 0.3 and a maximum of 4.0 mg/kg/h, in order to maintain the target RASS range. Allowable dose levels were: 0.3, 0.8, 1.6, 2.4, 3.2, 4.0 mg/kg/h. The study treatments were administered and titrated in parallel.

Batch numbers: 6343A182, 6443A182, 6503A181, 7054A182, 7233A181, 7344A182, 8115A181 and 8422A183 (propofol); 1092632, 1169333, 1216280 and 1281645 (placebo for propofol)

Rescue treatment:

The first-line rescue treatment was midazolam (e.g. bolus of 1-2 mg), which could be given, if the study subject's sedative requirements were not met using the study treatment.

Variables and methods of assessments:

Primary efficacy variables:

- Maintaining target depth of sedation using the RASS. The target RASS range (target depth of sedation) was 0 to -3 for a patient included in the study. The target could be amended during the study treatment, if clinically required. RASS score was assessed approximately 2 hourly during the treatment period and during the 48-hour follow-up period. In addition, RASS score was assessed each time rescue treatment was given to maintain the target sedation level.
- Duration of mechanical ventilation

Secondary efficacy variables:

- Nurse's assessment of subject communication with visual analogue scales (VAS)
- Length of ICU stay

Additional efficacy and health economics variables:

- Ventilation free days in ICU
- Time to extubation
- Length of hospital stay
- Use of rescue treatment
- Cost of care in ICU based on the cumulative therapeutic intervention scoring system (TISS) points
- Total costs of hospitalisations by adding up the cost of ICU and other ward days

Pharmacokinetic variables:

- Steady-state concentration of dexmedetomidine and its H-3 metabolite concentrations in blood. Dexmedetomidine and its H-3 metabolite concentrations in plasma were determined using high performance liquid chromatographic method with tandem mass spectrometric detection.

Safety variables:

- Adverse events (AEs)
- Vital signs: HR, systolic and diastolic blood pressure (SBP and DBP), MAP and oxygen saturation (SpO_2)
- Electrocardiography (ECG) and arrhythmias (12-lead ECG at specific timepoints and continuous ECG)
- Laboratory assessments (haematology, clinical chemistry and arterial blood gases)
- Concomitant treatments, including rescue medication for sedation
- Treated hypertension episodes
- Delirium with the confusion assessment method for the ICU (CAM-ICU) and AE preferred terms of delirium and related disorders according to an in-house search category
- Organ failures with the sequential organ failure assessment (SOFA)
- Sensory and motor deficits
- Survival
- Withdrawal syndrome

Evaluation and statistical methods:

A comparison against the standard of care sedatives was requested by the European Medicines Agency and a non-inferiority design was chosen. Centrally active alpha-2 adrenoceptor agonists are sedative and dexmedetomidine was confirmed superior as a sedative compared to placebo in 2 previous sedation studies conducted in postoperative ICU patients.

This study had hierarchical co-primary objectives. First co-primary objective was to evaluate non-inferiority of dexmedetomidine compared with propofol in maintaining a target depth of sedation with daily sedation stops. Second co-primary objective was to evaluate superiority of dexmedetomidine compared with propofol, in reducing the duration of mechanical ventilation. To follow hierarchy of the co-primary endpoints, superiority of mechanical ventilation was evaluated only if non-inferiority of maintaining a target depth of sedation was first shown.

A per-protocol (PP) population was used to evaluate the first co-primary objective, maintaining a target depth of sedation. The intention-to- treat (ITT) population was used in all other confirmatory statistical analyses. As a sensitivity analysis, PP population was used to evaluate the second co-primary objective, duration of mechanical ventilation.

Primary efficacy variables

The hierarchical co-primary objectives of the study were evaluated and analysed as follows:

1. Maintaining a target depth of sedation

   The first co-primary efficacy variable was defined as the proportion of time during study treatment with a RASS score within the initial target range (0 to -3) without first-line rescue medication. Use of midazolam boli was considered as the first-line rescue medication and the time from bolus to next RASS assessment was considered being off target despite the observed value. The comparison between the treatment groups was done using analysis of co-variance (ANCOVA) for the outcome variable with effect for treatment and country in the model. Non-inferiority of dexmedetomidine versus propofol was evaluated using 1-sided 97.5% confidence intervals (CIs). Less than 15% (non-inferiority criterion) difference between the treatment groups was considered acceptable from clinical and statistical standpoint.

2. Duration of mechanical ventilation

   The second co-primary efficacy variable was defined as time from randomisation to being free from any mechanical ventilatory support at least for 48 hours. If a subject died while ventilated the duration was assumed to last until 45 days, the end of the study period. The time to being free from mechanical ventilation

was compared between the treatment groups by Kaplan-Meier curves and the Cox's proportional-hazards regression model with effect for treatment and stratified by country. As the proportionality assumption was violated, the Gehan-Wilcoxon test was also applied according to the statistical analysis plan (SAP) and its amendment.

Secondary efficacy, pharmacokinetic and safety variables

- Variables with survival type of data were analysed by using the Kaplan-Meier curves and Cox's proportional-hazards regression model, unless the proportional hazards assumption was violated in which case Gehan-Wilcoxon test was used.
- Variables with continuous type of data were analysed using descriptive statistics and applicable AN(C)OVA model.
- Count data or categorical data over time were analysed using generalized linear models with appropriate distribution and link function.
- Incidences were compared between treatment groups using Fisher's exact test.

Summary-Conclusions

Subject disposition

500 subjects were randomised to either receive dexmedetomidine (251 subjects) or continue to receive propofol (249 subjects). 12 subjects in the dexmedetomidine and 13 subjects in the propofol group discontinued the study. The most common reason for the discontinuation of the study was loss to follow-up (7 dexmedetomidine vs. 9 propofol), followed by withdrawal of consent (1 in each group) and reason 'other' (4 dexmedetomidine vs. 3 propofol). 66 (26.8%) and 58 (23.5%) subjects in the dexmedetomidine and propofol groups, respectively, discontinued study treatment prematurely. More subjects discontinued study treatment prematurely due to lack of efficacy in the dexmedetomidine group (36 subjects) than in the propofol group (13 subjects). The other reasons (more than 1 reason could be selected) for the study treatment discontinuation were AEs in 29 vs. 28 subjects, protocol deviation in 1 vs. 3 subjects, non-pharmacological intervention in 1 vs. 4 subjects and reason 'other' in 7 vs. 16 subjects in the dexmedetomidine and propofol groups, respectively.

The ITT/safety analyses were performed in 251/246 subjects in the dexmedetomidine group and 247/247 subjects in the propofol group. The PP analysis for the 1st co-primary variable included data from 223 subjects in the dexmedetomidine group and 214 subjects in the propofol group. The PP analysis for the 2nd co-primary variable was performed as a sensitivity analysis in 218 and 213 subjects in the dexmedetomidine and propofol groups, respectively.

Demography and other baseline characteristics:

Treatment groups were comparable for demographic characteristics. 65.5% of all subjects were male, 98.6% were Caucasian, and the mean age was 61.7 years (range: 18-94 years). Treatment groups were comparable also for other baseline characteristics, including Simplified Acute Physiology Score (SAPS) II. Most subjects were admitted to ICU due to medical (56.2%) or surgical (33.9%) reasons, and nearly all (89.6%) for emergency care.

Efficacy results:

First co-primary variable – maintaining depth of sedation (PP population)

The adjusted mean (95% CI) percentage of the time at target sedation level without use of rescue treatment was 64.6 (60.0 to 69.1)% for subjects on dexmedetomidine and 64.7 (59.9 to 69.4)% for subjects on propofol. As the lower limit of the 2-sided 95% CI for the estimated ratio of dexmedetomidine vs. propofol (0.92) was above the predefined non-inferiority margin (>0.85), dexmedetomidine was proven to be non-inferior to propofol in maintaining a target depth of sedation. However, although more subjects in the dexmedetomidine group discontinued study treatment prematurely due to lack of efficacy, no notable difference between the treatments was observed in the rate of premature study treatment discontinuation for any cause.

Second co-primary variable - duration of mechanical ventilation (ITT population)

The median duration of mechanical ventilation was 21 hours shorter in the dexmedetomidine group (96.5 hours) than in the propofol group (117.5 hours). The Kaplan-Meier curves showed that most events occurred during the first 18 days, and that the events occurred earlier in the dexmedetomidine group than in the propofol group. After 18 days, the curves crossed, but no notable differences between groups were seen at later timepoints. The

difference between groups was not statistically significant either with the Gehan-Wilcoxon test, which gives greater weight to early events, or using the Cox's proportional hazards regression model, which accounts for all events equally throughout the 45-day period.

Secondary variables (ITT population)

The mean VAS scores for the nurse's assessment of subject communication demonstrated that the subjects on dexmedetomidine were significantly more arousable, cooperative and better able to communicate whether they had pain than those on propofol. The adjusted mean (95% CI) for the total VAS score (a higher score represents a better outcome) was 51.3 (46.9 to 55.7) for dexmedetomidine and 40.1 (35.7 to 44.6) for propofol ($p < 0.001$).

The length of stay in the ICU from randomisation to medically fit for discharge or transfer did not differ ($p = 0.535$) between groups.

Additional variables (ITT population)

The number of ventilator free days during ICU stay was small and did not differ ($p = 0.756$) between groups. The median number of ventilator free days was 1.0 in both groups, ranging from 0 to 35 days in the dexmedetomidine group and from 0 to 24 days in the propofol group.

The median time to extubation was 24 hours shorter in the dexmedetomidine group (69.0 hours) than in the propofol group (93.0 hours). This difference between groups was statistically significant with the Gehan-Wilcoxon test, which gives greater weight to early events, but not with the Cox's proportional hazards regression model, which accounts for all events equally throughout the 45-day period.

The length of stay in the hospital from randomisation to actual discharge did not differ ($p = 0.750$) between groups. Key efficacy findings are summarised in the following table.

Variable	DEX (N=251)	PRO (N=247)	P-value	Difference or ratio	95% CI	
					Lower	Upper
Primary variables						
Time at target sedation level, mean (%) (PP)	64.56	64.66		1.00	0.922[1]	1.075
Duration of mechanical ventilation, median (hours) (ITT)	96.5	117.5				
Gehan-Wilcoxon test			0.240			
Cox's proportional-hazard regression			0.492	0.936	0.774	1.131
Secondary variables (ITT)						
Nurse's total VAS scores, mean	51.3	40.1	<0.001[2]	11.2	6.4	15.9
Length of ICU stay, median (days)	6.8	7.7				
Cox's proportional-hazard regression			0.535	0.941	0.778	1.139
Additional variables (ITT)						
Ventilator free days, median (days)	1.0	1.0	0.756[3]			
Time to extubation, median (hours)	69.0	93.0				
Gehan-Wilcoxon test			0.041			
Cox's proportional-hazard regression			0.109	0.857	0.710	1.035
Length of hospital stay, median (days)	33.0	38.0				
Gehan-Wilcoxon test			0.750			
Cox's proportional-hazard regression			0.694	1.046	0.837	1.306

Gehan-Wilcoxon test was applied when the proportionality assumption for the Cox model was not met (p-value for the treatment by time interaction < 0.1). Cox's proportional-hazards regression model with effects for treatment and country; hazard ratio < 1 favours DEX

[1] ANCOVA with effects for treatment and country; lower CI of the ratio >0.85 shows that DEX is non-inferior to PRO

[2] ANCOVA with effects for treatment, country and baseline values

[3] Generalised linear model with log-link function and log of ICU length as an offset variable

DEX = dexmedetomidine; PRO = propofol

Rescue treatments:

72.5% of subjects in the dexmedetomidine group and 64.4% of subjects in the propofol group needed the first-line (i.e. midazolam boli) rescue treatment for inadequate sedation during the treatment period ($p = 0.054$). The total number of doses of the rescue treatment was 2495 and 1986 in the dexmedetomidine and propofol groups, respectively. The mean average dose (0.74 vs. 0.31 mg/h, $p < 0.001$) and the mean total dose (32.9 vs. 22.8 mg,

p = 0.024) of the first-line rescue treatment were higher in the dexmedetomidine group than in the propofol group. The first-line rescue treatment also started earlier in the dexmedetomidine group (median of 1.4 vs. 4.3 hours, p = 0.018).

No statistically significant (p = 0.532) difference in the percentage of subjects receiving the second-line rescue treatment (mostly fentanyl) (13.9 vs. 16.2%) was observed; however, the second-line rescue treatment was started earlier (median of 12.9 vs. 31.9 hours, p < 0.001) in the dexmedetomidine group than in the propofol group. The total use of fentanyl was similar in both groups during the study.

Health economic variables:

The mean (SD) cumulative sum of TISS points was 354.0 (342.1) points in the dexmedetomidine-treated subjects and 382.6 (332.6) points in the propofol-treated subjects, the difference being numerically lower (28.6 points) in the dexmedetomidine group. The ICU costs, as calculated using an estimate of 40 euros per TISS point, were 1141.2 euros lower per subject for dexmedetomidine group than for propofol.

Pharmacokinetic variables:

The steady-state dexmedetomidine concentrations (i.e. constant infusion rate of dexmedetomidine for at least 13 hours) were reached 268 times in 127 subjects, indicating that a proportion of these subjects received more than 1 dose level of dexmedetomidine (or the same dose level of dexmedetomidine more than once) for at least 13 hours. The mean steady-state concentration of dexmedetomidine increased approximately linearly with the increasing infusion rate although slightly less than proportionately. The mean H-3 metabolite concentration exceeded the mean dexmedetomidine concentration starting from day 2.

Safety results:

Exposure

The mean infusion rate of dexmedetomidine was 0.900 µg/kg/h (mean total dose 50.16 µg/kg) and the mean infusion rate of propofol was 1.911 mg/kg/h (mean total dose 145.65 mg/kg). The median duration of infusion (with sedation stops) was 43.2 hours in the dexmedetomidine group and 53.0 hours in the propofol group. Overall, 71.1% of dexmedetomidine and 81.0% of propofol subjects received study treatment longer than 24 hours. The longest exposure to study treatment was 13 days (318 hours) in both groups.

AEs during the study: from the start of study treatment to the last contact on day 45 (+5)

Nearly all subjects had at least 1 AE during the study: 89.0% of subjects in the dexmedetomidine group and 91.9% of subjects in the propofol group. The most common AEs were hypertension (21.1 vs. 15.0%), sinus tachycardia (19.5 vs. 11.3%), hypotension (13.0 vs. 13.4%), atrial fibrillation (12.2 vs. 14.2%), respiratory failure (12.2 vs. 13.8%), bradycardia (13.0 vs. 10.1%), pleural effusion (7.3 vs. 13.8%), agitation (7.7 vs. 11.7%) and anxiety (8.5 vs. 10.1%) in the dexmedetomidine and propofol groups, respectively.

A statistically significantly higher percentage of subjects treated with dexmedetomidine than propofol had sinus tachycardia (19.5 vs. 11.3%, p = 0.013), AV block 1st degree (3.7 vs. 0.8%, p = 0.036) and drug ineffective (3.3 vs. 0%, p = 0.004). Likewise, a statistically significantly higher percentage of subjects treated with propofol than dexmedetomidine had pleural effusion (7.3 vs. 13.8%, p = 0.027), restlessness (0.4 vs. 3.2%, p = 0.037) and critical illness polyneuropathy (CIP) (0.8 vs. 4.5%, p = 0.021). In addition, hypertension tended to occur in a higher percentage (21.1 vs. 15.0%, p = 0.080) and delirium in a lower percentage (4.9 vs. 9.7%, p = 0.056) of subjects in the dexmedetomidine group than in the propofol group.

No statistically significant differences between groups were observed in the frequency of any AE category of special interest (consisting of grouped medical dictionary of regulatory activities [MedDRA] preferred terms). The most common AE categories of special interest were respiratory failure (16.7 vs. 20.6%, p = 0.298), supraventricular tachyarrhythmias (13.0 vs. 16.2%, p = 0.372) and sepsis (10.2 vs. 8.5%, p = 0.540) in the dexmedetomidine and propofol groups, respectively.

Related AEs were reported in 30.9 and 27.1% of subjects in the dexmedetomidine and propofol groups, respectively. The most common related AE was bradycardia, which occurred in 7.7% of subjects in the dexmedetomidine group compared with 3.2% of subjects in the propofol group.

No unexpected differences between groups were observed when AEs were analysed by severity, dose levels of study treatment, onset time, duration of study treatment, age or gender.

AEs during the study treatment and the 48-hour follow-up period

During the treatment period, no notable differences between groups were observed in the frequency of bradycardia, sinus tachycardia, hypotension or hypertension. Atrial fibrillation and pleural effusion occurred in a higher percentage of subjects in the propofol group than in the dexmedetomidine group.

During the 48-hour follow-up period, hypertension and sinus tachycardia were common in the dexmedetomidine group than in the propofol group and agitation was more common in the propofol group than in the dexmedetomidine group. The most common AEs (≥ 5% in either group) are summarised in the following table.

Preferred term	Dexmedetomidine (N = 246)		Propofol (N = 247)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
During the study treatment period				
Bradycardia	28 (11.4)	41	20 (8.1)	26
Sinus tachycardia	21 (8.5)	39	16 (6.5)	25
Hypotension	19 (7.7)	22	22 (8.9)	28
Hypertension	17 (6.9)	20	16 (6.5)	16
Atrial fibrillation	12 (4.9)	12	25 (10.1)	28
Pleural effusion	5 (2.0)	5	19 (7.7)	20
During the 48-hour follow-up period after stopping study treatment				
Hypertension	31 (12.6)	34	19 (7.7)	20
Sinus tachycardia	27 (11.0)	32	14 (5.7)	15
Anxiety	14 (5.7)	14	11 (4.5)	11
Agitation	7 (2.8)	7	19 (7.7)	20

92 subjects died between the start of study treatment and the last contact on day 45 (+5). A similar percentage of subjects died in the dexmedetomidine (17.9%, 44/246) and propofol (19.4%, 48/247) groups (see analysis of survival below). Only 4 subjects in the dexmedetomidine and 6 subjects in the propofol group died on the same day as the study treatment was stopped. In both groups, the most common categorised cause of death was multi-organ failure (28.6% dexmedetomidine vs. 29.2% propofol).

A similar percentage of subjects had SAEs in both groups: 43.9% of subjects in the dexmedetomidine group and 45.3% of subjects in the propofol group. The total number of SAEs was also similar: 257 events in the dexmedetomidine group and 245 events in the propofol group. No statistically significant differences between groups were observed for any SAE. The most common SAEs were respiratory failure (9.8 vs. 9.3%, p = 0.879), multi-organ failure (4.9 vs. 6.9%, 0.444) and pneumonia (4.9 vs. 3.6%, 0.514) in the dexmedetomidine and propofol groups, respectively.

A similar percentage of subjects had at least 1 AE that led to discontinuation of study treatment in the dexmedetomidine (17.5%) and propofol (13.4%) groups. Similarly, a similar percentage of subjects in the dexmedetomidine (2.0%) and the propofol group (2.8%) had at least 1 AE that led to dosage reduction of study treatment. The most common AEs leading to study treatment discontinuation were bradycardia (2.4% dexmedetomidine vs. 0.4% propofol) and drug ineffective (2.0 vs. 0%) and the most common AE leading to dose reduction was hypotension (1.2% in each group, p > 0.999).

Clinical laboratory findings

As expected in this patient population, there were many clinically relevant individual abnormal laboratory findings. When analysed using the predefined thresholds considered clinically relevant, increases of troponin I >0.5 µg/l from baseline were recorded in 33 subjects in the dexmedetomidine group vs. 17 subjects in the propofol group (p = 0.025); 16 vs. 10 subjects of whom, respectively, had normal baseline values. Few increases in either group were attributed to AEs. Most increases in both groups reached maximum value at day 2. The median maximum change from baseline in subjects with troponin abnormalities did not differ between groups but more dexmedetomidine subjects appeared to have troponin increases of >2 µg/l. Cortisol values ≤ 100 nmol/l were observed in 4.1% of subjects in the dexmedetomidine group and 7.9% of subjects in the propofol group (p = 0.087). The mean values of gamma-glutamyltransferase (GGT) increased from baseline statistically significantly

more in the propofol group than in the dexmedetomidine group and a higher percentage of propofol subjects had GGT ≥ 3 times the upper limit of normal (42.3% propofol vs. 29.5% dexmedetomidine, p = 0.004). The mean cholesterol and triglycerides concentrations increased from baseline statistically significantly more in the propofol group than in the dexmedetomidine group; however, all observed changes were relatively small. There were also statistically significant differences between groups in mean changes from baseline in platelets, haemoglobin, haematocrit and red blood cells; however, all observed changes were relatively small.

Vital signs

HR decreased more in the dexmedetomidine group than in the propofol group after the start of study treatment. The mean difference between dexmedetomidine and propofol in change from baseline was -5.9 bpm (95% CI -7.7 to -4.1, p < 0.0001) over time during the treatment period. After the discontinuation of the study treatment, HR remained relatively unchanged in the propofol group whereas in the dexmedetomidine group there was an initial increase that gradually decreased toward baseline level.

After the start of study treatment, MAP increased from baseline in the dexmedetomidine group during the first 10 hours while it remained relatively unchanged in the propofol group, with the maximum mean difference between groups being 5.7 mmHg at 8 hours. MAP increased in both groups approximately up to the 52-hour timepoint. Thereafter, no notable differences between groups were observed during the remainder of the treatment period. The mean (95% CI) overall difference between dexmedetomidine and propofol in change from baseline was 3.4 (2.0 to 4.9) mmHg (p < 0.0001) during the study treatment period.

At the discontinuation of study treatment, MAP was lower in the dexmedetomidine group than in the propofol group. After the discontinuation of study treatment, MAP increased gradually to the levels of propofol over the 24 hours in the dexmedetomidine group while it remained relatively unchanged in the propofol group. The mean (SE) difference between dexmedetomidine and propofol in change from baseline was 2.7 (2.1) mmHg (p = 0.206) at the 24-hour timepoint and 2.2 (2.4) mmHg (p = 0.361) at the 48 hour-hour timepoint.

For SBP and DBP, respectively, the mean overall difference between dexmedetomidine and propofol in change from baseline was 3.8 mmHg (95% CI 1.5 to 6.1, p = 0.0016) and 3.2 mmHg (95% CI 1.9 to 4.4, p < 0.0001) over time during the treatment period.

The mean changes from baseline in SpO_2 were similar in both groups throughout the treatment period (mean difference of 0.06%, p = 0.720) and at the 48-hour follow-up (mean difference of -0.08%, p = 0.847).

Treated hypertension episodes

A similar percentage of subjects received treatment for hypertension in both groups during the study: 22.0% in the dexmedetomidine and 20.2% in the propofol group. Of these, 29.6 vs. 46.0% of subjects had a pre-existing condition and 42.1 vs. 40.4% of episodes started during the treatment period in the dexmedetomidine and propofol groups, respectively. The mean duration of the hypertension episodes was 4.6 hours shorter in the dexmedetomidine group than in the propofol group (38.0 vs. 42.6 hours).

Cardiovascular AEs (grouped MedDRA terms)

During the treatment period, no statistically significant differences between the treatment groups were observed in the incidence of any cardiovascular AE category (i.e. grouped AEs of bradycardia, hypotension, hypertension and tachycardia) or in the incidence of any treated cardiovascular AE category.

ECG variables

The mean PR interval value increased from baseline slightly more (6.5 ms, 95% CI 3.5 to 9.4, p < 0.0001) in the dexmedetomidine group than in the propofol group. In keeping with the effects of dexmedetomidine on HR, the RR and QT intervals were prolonged. However, no statistical significant differences between groups were observed in the difference between groups in QTcB or QTcF over time during the treatment period or at the 48-hour follow-up. No notable differences in the percentages of subjects with the QTcB or QTcF interval of >500 ms or with the QTcB or QTcF interval increases of >60 ms from baseline were observed between groups. In the propofol group, 1 episode of Torsades de Pointes occurred 2 days after the start of the study treatment.

Delirium

Analysis of delirium and related AEs (grouped MedDRA preferred terms) showed that a significantly (p = 0.008) higher percentage of subjects developed delirium-like events in the propofol group (28.7%) than in the

dexmedetomidine group (18.3%) during the treatment and/or the 48-hour follow-up period. With respect to onset time, delirium developed more frequently in the propofol group (17.0%) than in the dexmedetomidine group (9.3%) during the 48-hour follow-up period. No notable differences between groups were observed during the treatment period (6.5% propofol vs. 5.3% dexmedetomidine) or during the sedation stops (6.1% vs. 4.1%). Concomitant treatments for delirium-like events were given more frequently to propofol subjects than to dexmedetomidine subjects (24.7 vs. 15.0%, p = 0.009).

At the end of the 48-hour follow-up period, a positive/negative CAM-ICU finding was observed in 22/148 and 31/139 of subjects in the dexmedetomidine and propofol groups, respectively, with no statistically significant (p = 0.231) difference between groups. CAM-ICU was not assessable in 58 subjects in the dexmedetomidine and 56 subjects in the propofol group.

Organ failures – SOFA

The mean total SOFA scores slightly decreased in both groups during the treatment and 48-hour follow-up periods, with no clinically relevant differences between groups. No consistent differences between groups were observed in the number or percentages of subjects with SOFA score > 1 for any organ system. Overall, 16.7% of subjects in the dexmedetomidine group and 14.1% of subjects in the propofol group had at least 1 organ failure free day (day on which no organ system had a SOFA score > 1).

Sensory and motor deficits - Medical Research Council (MRC) scale

No statistically significant differences between the treatment groups were observed in any motor or sensor deficit at day 7, at day 14 or at the 48-hour follow-up.

Survival

Subjects who died within 45 days of randomisation (n = 90) were included in the analysis of survival. A similar percentage of subjects died in the dexmedetomidine (17.1%, 42/246) and propofol (19.4%, 48/247) groups. The median time to death was 14 days in the dexmedetomidine group and 13 days in the propofol group, with no statistically significant difference between groups (Cox's proportional hazard ratio 0.88, 95% CI 0.58 to 1.33, p = 0.548). Likewise, there were no statistically significant differences between groups in time to death during the stay in the ICU (p = 0.872) or during the stay in the hospital (p = 0.518).

Withdrawal syndrome

The incidence of signs of sympathetic activation indicating withdrawal syndrome was similar in both groups (2.0% in each group, p > 0.999) during the 48-hour follow-up period.

Conclusions:

Dexmedetomidine at doses of 0.2 to 1.4 µg/kg/h, together with sedation stops and spontaneous breathing trials, was non-inferior to propofol in maintaining targeted light to moderate sedation (RASS 0 to -3) in ventilated subjects requiring sedation for more than 24 hours. However, although the withdrawals from study treatment for any cause were comparable between groups, more dexmedetomidine-treated subjects were withdrawn due to lack of efficacy. The duration of mechanical ventilation did not differ statistically significantly between groups, but the time to extubation was significantly shorter in the dexmedetomidine group. Dexmedetomidine also improved patients' rousability, cooperativeness and ability to communicate pain. The length of ICU stay did not differ significantly between groups.

Dexmedetomidine was well tolerated and no new safety concerns were observed. The cardiovascular disorders, including bradycardia and hypotension, were comparable between groups. The incidence of delirium was lower in the dexmedetomidine group than in the propofol group after completion of study treatment during the 48-hour follow-up period.

Overall, dexmedetomidine was an effective sedative in intubated and mechanically ventilated subjects in the ICU setting for greater than 24 hours, with some evidence of clinical benefit and a comparable safety profile compared to propofol.

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