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: 3005013

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

Investigators and study centres:

This study was conducted in 9 countries (43 study centres): France (11), the Netherlands (9), Belgium (4), Norway (4), Estonia (4), Switzerland (3), Finland (2), Germany (3) and the United Kingdom (3). All except 1 centre in the Netherlands randomised subjects.
The coordinating investigator was Professor Stephan Jakob, University Hospital Bern, Bern, Switzerland.

Development phase: III	**Study period:** 28 Jun 2007 - 7 Oct 2009 (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 midazolam 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 midazolam 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 midazolam using nurse's assessment of subject communication
- To show that dexmedetomidine shortens length of ICU stay compared with midazolam
- To evaluate the safety of dexmedetomidine compared to midazolam

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 midazolam or switch to dexmedetomidine. The patients should not have received any other continuously or regularly administered sedative agent than midazolam 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 (propofol 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 midazolam); 15-20 subjects per centre

Analysed (randomised): 500 subjects (249 dexmedetomidine and 251 midazolam); 1-61 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 midazolam 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 midazolam 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 and 1177900 (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:

Midazolam was supplied in a 5 ml ampoule containing 5 mg (1 mg/ml) of midazolam. Placebo for midazolam was a matching 5 ml ampoule containing 0.9% sodium chloride injection. In Estonia and France, an alternative midazolam formulation was supplied in a 10 ml ampoule containing 50 mg (5 mg/ml) of midazolam (Amendment 2, 14 Mar 2008). Placebo for the alternative midazolam product was a matching 10 ml ampoule containing 0.9% sodium chloride injection.

Midazolam was infused with the dose that was nearest to the pre-randomisation dose of midazolam not exceeding the dose level 3 (i.e. 0.09 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 midazolam was titrated stepwise (± 1 dose level) as needed between 0.03 and a maximum of 0.2 mg/kg/h, in order to maintain the target RASS range. Allowable dose levels were 0.03, 0.06, 0.09, 0.12, 0.17 and 0.20 mg/kg/h. The study treatments were administered and titrated in parallel.

Batch numbers: 623060, 644058 and 709056 (midazolam, 5 ml); 1170950 (placebo for midazolam, 5 ml); 732068 and 814058 (midazolam, 10 ml); 1251542 (placebo for midazolam, 10 ml)

Rescue treatment:

The first-line rescue treatment was propofol (e.g. bolus of 20-40 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 midazolam in maintaining a target depth of sedation with daily sedation stops. Second co-primary objective was to evaluate superiority of dexmedetomidine compared with midazolam, 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 propofol 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 midazolam 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 study period. The time to being free from mechanical ventilation was compared between treatment groups by Kaplan-Meier curves and the Cox's proportional-hazards regression model with effect for treatment and stratified by country. During data analysis and after opening the treatment code, it was noticed that the proportionality of hazards assumption was violated. Therefore, the Gehan-Wilcoxon test, equivalent to the Wilcoxon test proposed in the SAP and which more accurately described the data, was also applied and is reported as the primary test in line with the principles laid down in the SAP. The Cox's proportional-hazards model is presented as a secondary analysis.

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, using the same principle as for duration of mechanical ventilation.
- 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 (249 subjects) or continue to receive midazolam (251 subjects). 2 subjects in the dexmedetomidine and 3 subjects in the midazolam group discontinued the study, all due to loss to follow-up. 58 (23.5%) and 49 (19.6%) subjects in the dexmedetomidine and midazolam groups, respectively, discontinued study treatment prematurely. More subjects discontinued study treatment prematurely due to lack of efficacy in the dexmedetomidine group (23 subjects) than in the midazolam group (10 subjects). The other reasons (more than 1 reason could be selected) for premature study treatment discontinuation were AE in 23 vs. 19 subjects, protocol deviation in 2 vs. 2 subjects and reason 'other' in 16 vs. 21 subjects in the dexmedetomidine and midazolam groups, respectively.

The ITT/safety analyses were performed in 249/247 subjects in the dexmedetomidine group and 251/250 subjects in the midazolam group. The PP analysis for the 1st co-primary variable included data from 227 subjects in the dexmedetomidine group and 233 subjects in the midazolam group. The PP analysis for the 2nd co-primary variable was performed as a sensitivity analysis in 217 and 227 subjects in the dexmedetomidine and midazolam groups, respectively.

Demography and other baseline characteristics:

Treatment groups were comparable for demographic characteristics. 65.6% of all subjects were male, 96.2% were Caucasian, and the mean age was 63.0 years (range: 19-97 years). Treatment groups were comparable also for other baseline characteristics, including SAPS II. Most subjects (70.6%) were admitted to ICU due to medical reasons and nearly all (95.2%) 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 60.7 (55.4 to 66.1)% for subjects on dexmedetomidine and 56.6 (51.2 to 61.9)% for subjects on midazolam. As the lower limit of the 2-sided 95% CI for the estimated ratio of dexmedetomidine vs. midazolam (0.97) was above the predefined non-inferiority margin (>0.85), dexmedetomidine was proven to be non-inferior to midazolam in maintaining a target depth of sedation. 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 41 hours shorter in the dexmedetomidine group (123.0 hours) than in the midazolam group (164.0 hours). The Kaplan-Meier curves showed that most events occurred during the first 16 days, and that the events occurred earlier in the dexmedetomidine group than in the midazolam group. After 16 days, the curves crossed, but no notable differences between groups were seen at later timepoints. The difference between groups was statistically significant with the Gehan-Wilcoxon test, which gives greater weight to early events, but not 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 midazolam. The adjusted mean (95% CI) for the total VAS score (a higher score represents a better outcome) was 49.7 (45.5 to 53.8) for dexmedetomidine and 30.0 (25.9 to 34.1) for midazolam ($p < 0.001$).

The median length of stay in the ICU from randomisation to medically fit for discharge or transfer was 1.3 days shorter in the dexmedetomidine group (8.8 days) than in the midazolam group (10.1 days). This difference was not statistically significant ($p = 0.269$).

Additional variables (ITT population)

The number of ventilator free days during ICU stay was small and did not differ between groups. The median number of ventilator free days was 1.0 in both groups, ranging from 0 to 43 days in the dexmedetomidine group and from 0 to 32 days in the midazolam group.

The median time to extubation was 46 hours shorter in the dexmedetomidine group (101.0 hours) than in the midazolam group (147.0 hours). This difference was statistically significant with the Gehan-Wilcoxon test ($p = 0.012$) but not with the Cox's proportional-hazards regression model ($p = 0.283$).

The length of stay in the hospital from randomisation to actual discharge did not differ ($p = 0.288$) between groups. Key efficacy findings are summarised in the following table.

Variable	DEX (N=249)	MDZ (N=251)	P-value	Difference or ratio	95% CI	
					Lower	Upper
Primary variables						
Time at target sedation level, mean (%) (PP)	60.74	56.56		1.07	0.971[1]	1.176
Duration of mechanical ventilation, median (hours) (ITT)	123.0	164.0				
Gehan-Wilcoxon test			0.033			
Cox's proportional-hazard regression			0.265	0.896	0.738	1.087
Secondary variables (ITT)						
Nurse's total VAS scores, mean	49.7	30.0	<0.001[2]	19.7	15.2	24.2
Length of ICU stay, median (days)	8.8	10.1				
Gehan-Wilcoxon test			0.269			
Cox's proportional-hazard regression			0.876	1.016	0.835	1.235
Additional variables (ITT)						
Ventilator-free days, median (days)	1.0	1.0	0.924[3]			
Time to extubation, median (hours)	101.0	147.0				
Gehan-Wilcoxon test			0.012			
Cox's proportional-hazard regression			0.283	0.900	0.742	1.091
Length of hospital stay, median (days)	42.0	38.0				
Cox's proportional-hazard regression			0.288	1.119	0.909	1.378

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 MDZ

[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

Rescue treatments

A similar percentage of subjects in the dexmedetomidine group (43.8%) and midazolam group (45.4%) received the first-line (i.e. propofol boli) rescue treatment for inadequate sedation during the treatment period (p = 0.720). The total number of doses (1100 vs. 1008), the mean average total dose (5.00 vs. 3.59 mg/h, p = 0.173) and the mean total dose (360 vs. 299 mg, p = 0.317) of the first-line rescue treatment were similar in both groups. The median time to the first use (19.3 vs. 20.0 hours) was also similar (p = 0.741). No differences between groups were observed in the use of second-line rescue treatment (mostly fentanyl) during the study treatment period or in the total use of fentanyl during the study.

Health economics variables:

The mean (SD) cumulative sum of TISS points was 346.3 (295.9) points in the dexmedetomidine-treated subjects and 409.9 (328.0) points in the midazolam-treated subjects, the difference being numerically lower (63.6 points) in the dexmedetomidine group. The ICU costs, as calculated using an estimate of 40 euros per TISS point, were 2541.5 euros lower per subject for dexmedetomidine than for midazolam.

Pharmacokinetic variables:

The steady-state dexmedetomidine concentrations (i.e. constant infusion rate of dexmedetomidine for at least 13 hours) were reached 366 times in 161 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 linearly with the increasing infusion rate although slightly less than proportionately. The mean H-3 metabolite concentration seemed to increase when dexmedetomidine was given for longer periods, exceeding the mean dexmedetomidine concentration starting from day 4.

Safety results:

Exposure

The mean infusion rate of dexmedetomidine was 0.546 µg/kg/h (mean total dose 38.00 µg/kg) and the mean infusion rate of midazolam was 0.075 mg/kg/h (mean total dose 5.32 mg/kg). The median duration of infusion (with sedation stops) was similar in both groups: 46.0 hours in the dexmedetomidine group and 47.2 hours in the midazolam group. Overall, 72.1% of dexmedetomidine and 76.0% of midazolam subjects received study treatment for more than 24 hours. The longest exposure to dexmedetomidine was 13 days (308 hours) and to midazolam 14 days (327 hours).

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: 93.5% of subjects in the dexmedetomidine group and 90.8% of subjects in the midazolam group. The most common AEs were hypertension (21.5 vs. 20.8%), hypotension (20.6 vs. 11.6%), agitation (15.8 vs. 16.4%), bradycardia (14.2 vs. 5.2%), sinus tachycardia (13.8 vs. 21.6%), atrial fibrillation (13.4 vs. 16.8%) and delirium (7.7 vs. 10.0%) in the dexmedetomidine and midazolam groups, respectively.

A significantly higher percentage of subjects treated with dexmedetomidine than midazolam had hypotension (20.6 vs. 11.6%, p = 0.007), bradycardia (14.2 vs. 5.2%, p = 0.001), sepsis (7.7 vs. 3.2%, p = 0.030), hypoglycaemia (4.0 vs. 0.8%, p = 0.020) and shock haemorrhagic (2.0 vs. 0%, p = 0.030). Likewise, a significantly higher percentage of subjects treated with midazolam than dexmedetomidine had sinus tachycardia (21.6 vs. 13.8%, p = 0.025) and an increase in gamma-glutamyltransferase (GGT) (8.0 vs. 2.4%, p = 0.008).

The most common AE categories of special interest (grouped medical dictionary of regulatory activities [MedDRA] preferred terms) were supraventricular tachyarrhythmias (15.0 vs. 18.8%), sepsis (14.6 vs. 12.0%) and respiratory failure (14.2 vs. 10.4%) in the dexmedetomidine and midazolam groups, respectively. No statistically significant difference between groups was observed in the incidence of any AE category.

A higher percentage of subjects had related AEs in the dexmedetomidine group (40.9%) than in the midazolam group (23.6%). Of the most common related AEs, hypotension (9.3 vs. 0.4%) and bradycardia (8.5 vs. 2.4%) were reported more frequently in the dexmedetomidine group than in the midazolam 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 48-hour follow-up periods

During the treatment period, hypotension and bradycardia were experienced by more subjects in the dexmedetomidine group than in the midazolam group and sinus tachycardia by more subjects in the midazolam group than in the dexmedetomidine group. Hypertension as well as agitation and atrial fibrillation occurred at a similar frequency in both groups.

During the 48-hour follow-up period, no notable differences between groups were observed in the frequency of any AE. The most common AEs (≥ 5% in either group) are summarised in the following table.

Preferred term	Dexmedetomidine (N = 247)		Midazolam (N = 250)	
	Subjects n (%)	Events n	Subjects n (%)	Events n
During the study treatment period				
Hypotension	40 (16.2)	46	17 (6.8)	19
Hypertension	34 (13.8)	43	26 (10.4)	30
Bradycardia	32 (13.0)	41	8 (3.2)	10
Agitation	24 (9.7)	26	16 (6.4)	16
Sinus tachycardia	19 (7.7)	23	36 (14.4)	53
Atrial fibrillation	16 (6.5)	17	27 (10.8)	35
Pyrexia	8 (3.2)	8	14 (5.6)	18
During the 48-hour follow-up period after stopping study treatment				
Hypertension	21 (8.5)	22	22 (8.8)	26
Sinus tachycardia	18 (7.3)	21	25 (10.0)	28
Withdrawal syndrome	15 (6.1)	15	6 (2.4)	6
Agitation	10 (4.0)	10	18 (7.2)	18
Atrial fibrillation	7 (2.8)	9	15 (6.0)	18

123 subjects died between the start of study treatment and the last contact on day 45 (+5). The death rate was numerically higher in the dexmedetomidine group (27.9%, 69/247) than in the midazolam group (21.6%, 54/250) (see analysis of survival below). Only 4 subjects in each group died on the same day as the study treatment was stopped. In both groups, the most common categorised causes of death were refractory respiratory failure, septic shock or uncontrolled infection, and multiple organ failure.

A similar percentage of subjects had SAEs in both groups: 47.0% of subjects in the dexmedetomidine group and 42.4% of subjects in the midazolam group, although the total number of SAEs was higher on dexmedetomidine than on midazolam (311 vs. 246 events, respectively). A significantly higher percentage of subjects treated with dexmedetomidine than midazolam experienced acute pulmonary oedema (2.8 vs. 0.4%, p = 0.037). Sepsis (5.3 vs. 2.0%, p = 0.058) and pneumonia (4.5 vs. 1.6%, p = 0.071) were also reported by more subjects in the dexmedetomidine group than in the midazolam group, but these differences were not statistically significant. Most of these SAEs started after the 48-hour follow-up period in both groups and none was considered related to study treatment by the investigator. No single related SAE was reported in more than 2 subjects in either group.

A higher percentage of subjects in the dexmedetomidine group (15.4%) than in the midazolam group (10.8%) had at least 1 AE that led to discontinuation of study treatment. Similarly, a higher percentage of subjects in the dexmedetomidine (7.3%) than in the midazolam group (0.8%) had at least 1 AE that led to dosage reduction of study treatment. The most common AEs leading to study treatment discontinuation were agitation (1.6 vs. 2.4%) and sedation (oversedation by reported AE terms) (0.4 vs. 1.6%) and the most common AEs leading to dose reduction were hypotension (4.5 vs. 0.4%) and bradycardia (2.8 vs. 0%) in the dexmedetomidine and midazolam groups, respectively.

Clinical laboratory findings

As expected in this patient population, there were many clinically relevant individual abnormal laboratory findings. With the exception of GGT values, there were no consistent changes in the laboratory findings suggestive of an association to study drug administration. When analysed using the predefined thresholds considered clinically relevant, a higher percentage of subjects had GGT ≥ 3 times t the upper limit of normal in the

midazolam group (46.2%) than in the dexmedetomidine group (36.8%) during the treatment period (p = 0.037). The mean GGT values increased from baseline more in the midazolam group than in the dexmedetomidine group. This difference between dexmedetomidine and midazolam was not statistically significant over time during the treatment period (-9.0 U/l, 95% CI -20.1 to 2.1, p = 0.113) but was significant at the 48-hour follow-up timepoint (-41.6 U/l, p = 0.019).

Vital signs

HR decreased more in the dexmedetomidine group than in the midazolam group after the start of study treatment. The mean difference between dexmedetomidine and midazolam in change from baseline was -8.4 bpm (95% CI -10.3 to -6.5, p < 0.0001) over time during the treatment period. After the discontinuation of study treatment, HR remained relatively unchanged in the midazolam group whereas in the dexmedetomidine group there was an initial increase that gradually decreased toward baseline level.

After a slight decrease (-1.3 mmHg at 30 minutes) from baseline in the dexmedetomidine group, MAP gradually increased in both groups during the treatment period. MAP increased slightly less in the dexmedetomidine group than in the midazolam group. The mean difference between dexmedetomidine and midazolam in change from baseline was -1.5 mmHg (95% CI -2.9 to -0.06, p = 0.041) over time during the treatment period. After the discontinuation of study treatment, MAP continued to increase compared to values at baseline in both groups approximately until 22-24 hours. The mean (SE) difference between dexmedetomidine and midazolam in change from baseline was 1.5 (2.0) mmHg (p = 0.451) at 24 hours and -1.2 (2.3) mmHg (p = 0.609) at 48 hours.

For SBP and DBP, respectively, the mean overall difference between dexmedetomidine and midazolam in change from baseline was -2.7 mmHg (95% CI -5.0 to -0.40, p = 0.022) and -0.86 mmHg (95% CI -2.1 to 0.36, p = 0.167) over time during the treatment period.

Mean changes from baseline in SpO_2 were similar in both groups throughout the treatment period (mean difference of 0.11%, p = 0.494) and at the 48-hour follow-up (mean difference of -0.35%, p = 0.409).

Treated hypertension episodes

A similar percentage of subjects received treatment for hypertension in both groups during the study: 22.3% in the dexmedetomidine and 24.8% in the midazolam group. Of these, 40.0 vs. 37.1% of subjects had a pre-existing condition and 53.3 vs. 54.1% of episodes started during the treatment period in the dexmedetomidine and midazolam groups, respectively. The mean duration of the hypertension episodes was 10.4 hours shorter in the dexmedetomidine group than in the midazolam group (32.9 vs. 43.3 hours).

Cardiovascular AEs (grouped MedDRA terms)

During the treatment period, a significantly higher percentage of subjects treated with dexmedetomidine than midazolam had bradycardia (17.0 vs. 4.8%, p < 0.001) and hypotension AEs (21.1 vs. 11.2%, p = 0.003), whereas a significantly (p = 0.001) higher percentage of subjects treated with midazolam (30.0%) than dexmedetomidine (17.4%) had tachycardia AEs. No difference between groups was observed in the incidence of hypertension AEs (14.2% dexmedetomidine vs. 13.2% midazolam, p = 0.795). A similar pattern was observed for the treated cardiovascular AEs.

ECG variables

The mean PR interval value increased from baseline slightly more (5.9 ms, 95% CI 2.8 to 9.1, p = 0.0002) in the dexmedetomidine group than in the midazolam group. In keeping with the effects of dexmedetomidine on heart rate, the RR and QT intervals were prolonged. With the Bazett correction, no statistical significant difference between groups was observed for the mean change in QTcB from baseline (-2.0 ms, 95% CI -6.5 to 2.5, p = 0.382). With the Fridericia correction, the difference between dexmedetomidine and midazolam was significant (5.9 ms, 95% CI 1.3 to 10.5, p = 0.013).

Both QTcB and QTcF intervals >500 ms were observed in a higher percentage of subjects treated with dexmedetomidine (13.6 and 6.6%, respectively) than midazolam (11.0 and 4.1%, respectively). However, a similar imbalance was present already at screening and at baseline. QTcB and QTcF increases >60 ms were observed in 7.3 and 12.9% of subjects in the dexmedetomidine group and 5.9% and 9.7% of subjects in the midazolam group, respectively. No consistent differences between groups were observed for any ECG variable at the 48-hour follow-up timepoint.

No episodes of Torsade de Pointes were identified using continuous cardiac monitoring. However, 1 subject in the dexmedetomidine group experienced Torsade de Pointes on 3 separate occasions: 22, 29 and 41 days after the end of study treatment.

Delirium

Analysis of delirium and related disorder AEs (grouped MedDRA preferred terms) showed no differences between the dexmedetomidine and midazolam groups in the percentage of subjects who developed delirium during the treatment and/or the 48-hour follow-up period. No notable differences between groups were observed during the treatment period, during the sedation stops or during the 48-hour follow-up period in the incidence of these events or in the incidence of treated events.

A positive/negative CAM-ICU finding was observed in 28/138 and 33/123 of subjects in the dexmedetomidine and midazolam groups, respectively, with no statistically significant (p = 0.393) difference between groups. CAM-ICU was not assessable in 69 dexmedetomidine subjects compared to 82 midazolam subjects.

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 a SOFA score > 1 for respiratory, CNS, renal, coagulation or liver organ systems. Small but statistically significant differences between groups were observed for cardiovascular organ system during the treatment period. On day 2, a higher percentage of subjects had cardiovascular SOFA score > 1 in the dexmedetomidine group (70.7%, 147/208) than in the midazolam group (59.7%, 126/211) (p = 0.024). The percentage of subjects with organ failure free days (days on which no organ system had a SOFA score > 1) was similar in both groups (21.7% dexmedetomidine vs. 18.2% midazolam).

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

During the sedation stops at days 7 and 14, the incidence of motor and sensory deficits was low and did not differ between groups. At the 48-hour follow-up, muscle weakness was observed more frequently (p = 0.031) in the midazolam group (7.1%) than in the dexmedetomidine group (2.6%). No differences between groups were observed for decreased tendon reflexes (12.6% dexmedetomidine vs. 11.8% midazolam, p = 0.888) or abnormalities of skin sensation (1.7% vs. 2.5%, p = 0.752).

Survival

Subjects who died within 45 days of randomisation (n = 118) were included in the analysis of survival. A higher percentage of subjects died in the dexmedetomidine group (26.7%, 66/247) than in the midazolam group (20.8%, 52/250) and the median time to death was shorter in the dexmedetomidine group (12.0 days) than in the midazolam group (14.5 days). However, the Cox's proportional-hazards regression model revealed no statistically significant difference between groups (hazard ratio 1.36, 95% CI 0.95 to 1.95, p = 0.094). Likewise, there was no statistically significant difference between groups in time to death during the stay in the ICU (p = 0.107) or during the stay in the hospital (p = 0.088).

Post-hoc comparisons based on baseline characteristics and post-randomisation events were made to determine a biological explanation to the imbalance in death rate. These comparisons did not reveal any systematic differences between groups among subjects who died and those who did not.

Withdrawal syndrome

The incidence of signs of sympathetic activation indicating withdrawal syndrome during the 48-hour follow-up period did not differ significantly between the dexmedetomidine and midazolam groups (6.9 vs. 3.6%, p = 0.111).

Conclusion:

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

not differ significantly between groups.

As expected, the most common AEs on dexmedetomidine were hypotension and bradycardia during the study treatment period. Mortality over 45 days was numerically higher in the dexmedetomidine group than in the midazolam group, but the treatment difference was not statistically significant and no explanation of this difference could be determined. No other new safety concerns were observed.

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 compared to midazolam, and safety findings were largely as expected from previous studies.

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