SYNOPSIS

Sponsor/company Orion Corporation Orion Pharma	**Individual study table referring to a specific part of the dossier**	(for National Competent Authority use only)
Finished product: NA	**Volume:**	
Active ingredient: Dexmedetomidine HCl	**Page**	

Study code: 3005011

Study title: A prospective, multi-centre, randomised, double-blind comparison of intravenous dexmedetomidine with propofol/midazolam for continuous sedation (24 hours to 14 days) of ventilated patients in intensive care unit

Investigators and study centres: The coordinating investigator was Professor Jukka Takala, University Hospital Bern, Bern, Switzerland. This study was conducted at 4 study centres, 3 in Finland and 1 in Switzerland.

Development phase: III	**Study period:** 18 Oct 2005–22 Jul 2006 (first randomisation - last contact)

Objectives:

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

- Firstly: dexmedetomidine is non-inferior to current best-practice sedation with propofol/midazolam and daily sedation stops, in maintaining a target depth of sedation in long-stay (> 24 hours sedation after randomisation) intensive care unit (ICU) patients
- Secondly: use of dexmedetomidine, compared with current best-practice sedation with propofol/midazolam and daily sedation stops, reduces the length of ICU stay in long-stay (> 24 hours sedation after randomisation) ICU patients.

Secondary objectives:

To explore the effects of dexmedetomidine compared with optimised standard care on:

- Nurse's assessment of subject communication
- Duration of mechanical ventilation, weaning time and ventilator-free days in ICU
- Length of total hospital stay
- Functional recovery during hospitalisation
- Need for rescue medication to maintain sedation

To describe the effects of dexmedetomidine compared with optimised standard care on:

- Frequency of delirium
- Frequency of organ failures and failure-free days
- Frequency of critical illness polyneuropathy (CIP)
- ICU- and in-hospital survival

To explore the potential differences between dexmedetomidine and optimised standard care in relation to:

- Costs of care in the ICU
- Total cost of hospitalisation
- To evaluate the range of blood levels seen with long-term treatment with dexmedetomidine

Methodology: This was a multi-centre, prospective, randomised, double-blind, double-dummy, active comparator study. The study consisted of 3 periods: screening, double-dummy treatment and the follow-up period. All patients admitted to ICU were pre-screened according to inclusion and exclusion criteria prior to

informed consent using standard of care data already available in the unit.

Screening procedures, randomisation and initiation of study treatment were to start ≤ 72 hours (According to the 2nd Amendment, dated 31 Dec 2005) from the time of admission to ICU. Eligible study subjects were randomised to either continue their current sedative agent (midazolam or propofol) or switch to dexmedetomidine. Study treatments were titrated to achieve an individually targeted sedation range. Rescue medication (propofol or midazolam bolus) could be 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 could be 12-36 hours from randomisation, depending on the time of day the study subject was randomised. The duration of study treatment was limited to a maximum of 14 days from randomisation.

Following the withdrawal of sedation, the study subjects were monitored for 48 hours and contacted by telephone 31 and 45 days after randomisation. The duration of the study per study subject was 45 days from randomisation.

Sample size: According to the original plan, the study was to recruit 90 patients as a pilot phase and continue recruiting up to 900 patients (450 in the dexmedetomidine and 450 in the current sedative agent [midazolam or propofol] group). However, only the pilot phase was conducted and the actual enrolment was 85 study subjects: 41 in the dexmedetomidine and 44 in the midazolam or propofol group. Due to slow recruitment rate, the pilot was terminated with 85 subjects recruited and, given the limitations of comparison with a combined standard of care group, the decision was made to close this study at the end of the pilot phase and plan instead to conduct 2 separate studies with single comparators of propofol and midazolam.

Diagnosis and main criteria for inclusion and exclusion:

Main criteria for inclusion:

- Age ≥ 18 years
- Clinical need for sedation and mechanical ventilation
- Receiving full intensive care life support
- Expected stay in ICU for ≥ 48 hours from admission
- Expected requirement for sedation ≥ 24 hours from time of randomisation
- Written informed consent obtained from the patient's representative (and an independent physician where appropriate) within 36 hours of starting sedation, but not more than 72 hours from the time of ICU admission (According to the 2nd Amendment, dated 31 Dec 2005)

Main criteria for exclusion:

- Acute severe 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 (Sequential Organ Failure Assessment [SOFA] score > 2, bilirubin > 101 µmol/l) (According to the 2nd Amendment, dated 31 Dec 2005)
- Positive pregnancy test or currently lactating
- Need for muscle relaxation at the time of randomisation (except for intubation and initial stabilization)
- Loss of hearing or vision, or any other condition that would significantly interfere with Richmond Agitation-Sedation Scale (RASS) assessment
- Use of α_2-agonists or antagonists at the time of randomisation

Investigational drug, dose and mode of administration: Dexmedetomidine was supplied in a 2 ml ampoule containing 200 µg (100 µg/ml) dexmedetomidine for dilution with 48 ml 0.9% sodium chloride (NaCl) injection (giving a solution containing 4 µg/ml). Dexmedetomidine dummy was a matching 2 ml ampoule containing 0.9% NaCl injection.

Dexmedetomidine was infused without a loading dose at an initial rate of 0.8 µg/kg/h for 1 hour. Thereafter, the infusion rate of dexmedetomidine was varied as needed between 0.25 and 1.4 µg/kg/h in order to maintain the target RASS score. The dosage steps were: 0.25, 0.5, 0.8, 1.1 and 1.4 µg/kg/h.

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

Comparative drug, dose and mode of administration:

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

Propofol was infused at an initial rate of 2.4 mg/kg/h for 1 hour. Thereafter, the infusion rate of propofol was varied as needed between 0.8 and 4 mg/kg/h in order to maintain the target RASS score. The dosage steps were: 0.8, 1.6, 2.4, 3.2 and 4.0 mg/kg/h.

Midazolam was supplied in a 5 ml ampoule containing 5 mg (1 mg/ml) of midazolam. Midazolam dummy was a matching 5 ml ampoule containing 0.9% NaCl injection.

Midazolam was given intravenously in boli of 1-2 mg (according to the weight of the patient), starting at 3 boli/h for 1 hour. Thereafter, the dose could be varied as needed between 1 bolus of 1-2 mg/h and a continuous infusion of 0.2 mg/kg/h, in order to maintain the target RASS score. The dosage steps were: 1 bolus/h of 1-2 mg, 2 boli/h of 1-2 mg, 3 boli/h of 1-2 mg, 4 boli/h of 1-2 mg and continuous infusion of 0.2 mg/kg/h.

Alternatively, midazolam treatment was initiated at randomisation as a continuous infusion. In this case, the starting dose was 0.12 mg/kg/h for 1 hour. Thereafter, the dose could be varied as needed between 0.04 mg/kg/h and 0.2 mg/kg/h, in order to maintain the target RASS score. The dosage steps for midazolam infusion were: 0.04, 0.08, 0.12, 0.16 and 0.20 mg/kg/h.

Variables and methods of assessments:

Primary efficacy variables:

- Depth of sedation using the RASS. The target RASS score (target depth of sedation) was determined for each study subject individually before the initiation of the study treatment and amended, if needed, at the daily sedation stop. RASS was also assessed 2 hourly during the treatment period, at the final sedation stop and 4 hourly during the follow-up period.
- Length of ICU stay (counted from ICU admission and from randomisation [According to the 2nd Amendment, dated 31 Dec 2005]) based on the treating clinician's decision that the study subject was medically fit for discharge, and the actual length of ICU stay.

Secondary efficacy variables included nurse's assessment of subject communication with visual analogue scales (VAS), duration of mechanical ventilation, weaning time and ventilator-free days in ICU, and length of total hospital stay based on the decision that the study subject was medically fit for discharge, actual total length of hospital stay, functional recovery during hospitalisation with a modification of the postoperative morbidity survey and need for rescue medication to maintain sedation.

Health economics variables included calculation of costs of care in ICU based on the cumulative Therapeutic Intervention Scoring System (TISS) points and other cost items recorded by nurses. Total costs of hospitalisations were calculated by adding up the cost of ICU and non-ICU days.

Pharmacokinetics included determination of the maximum concentration (C_{max}) of dexmedetomidine in blood samples drawn immediately before the daily sedation stops. The concentration data were used to evaluate the level of exposure to dexmedetomidine in long-term treatment, and to allow any necessary correlation with other safety findings. Dexmedetomidine concentrations in plasma were determined by liquid chromatography tandem mass spectrometry.

Safety variables included adverse events (AEs), laboratory assessments (haematology, clinical chemistry and arterial blood gases), vital signs (HR, blood pressure [BP], MAP and oxygen saturation), cardiac rhythm with electrocardiogram (ECG) (12-lead ECG at specific time points and continuous 2-lead ECG with alarms) and physical examination. Other safety variables included frequency of delirium with the confusion assessment method for the ICU (CAM-ICU), frequency of organ failures and failure-free days with the SOFA score, frequency of CIP recorded by trained observers, ICU, in-hospital and day 45 survival, and

withdrawal and rebound.

Evaluation and statistical methods:

The analyses were performed according to Statistical analysis plan. This study had hierarchical co-primary objectives. The first co-primary objective was to evaluate non-inferiority of dexmedetomidine compared with current sedative agent (midazolam/propofol) with daily sedation stops, in maintaining a target depth of sedation in long stay ICU patients without rescue medication. The second co-primary objective was to evaluate superiority of dexmedetomidine compared with the current sedative agent, reducing the length of ICU stay. To follow the hierarchy of co-primary endpoints, superiority was evaluated only if non-inferiority was shown.

A per-protocol (PP) population was used to evaluate the first co-primary objective depth of sedation. Intent-to-treat (ITT) population was used in all other confirmatory statistical analyses.

Primary efficacy variables

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

1. Depth of sedation in long-stay ICU patients

   The first of the co-primary efficacy variables was defined as the proportion of time during sedative infusion with a RASS score within the individually-prescribed target range without rescue medication. The comparison between the treatment groups was done using analysis of co-variance (ANCOVA) for the outcome variable. Non-inferiority of the dexmedetomidine vs. the current sedative agent was evaluated using one-sided 97.5% confidence interval (CI). Less than 10% (non-inferiority criteria) difference between the treatment groups was considered acceptable from the clinical standpoint. This means that non-inferiority was claimed when lower CI of the estimated ratio of the dexmedetomidine and the current sedative agent lied entirely above 90%.
2. The length of ICU stay in long-stay ICU patients was analysed hierarchically as follows (According to the 2nd Amendment, dated 31 Dec 2005):
   - I The length of ICU stay in long-stay ICU patients, defined as time from randomisation to "medically fit for discharge". It was calculated and compared between the treatment groups by applying the Kaplan-Meier method and Cox's proportional-hazards regression model. The hazard ratio between treatment groups was estimated together with corresponding 95% CI.
   - II The length of ICU stay in long-stay ICU patients, defined as time from ICU admission to "medically fit for discharge". It was calculated and compared between the treatment groups by applying the Kaplan-Meier method and Cox's proportional-hazards regression model. The hazard ratio between treatment groups was estimated together with corresponding 95% CI.

Secondary efficacy, health economic, pharmacokinetic and safety variables

- Variables with survival type of data were analysed applying the Kaplan-Meier method and Cox's proportional-hazards regression model.
- Variables with continuous type of data were analysed using descriptive statistics and applicable AN(C)OVA model, if feasible.
- Variables with ordered or categorical data were analysed using Fisher's exact test or chi square's test.

Summary/Conclusions:

Subject disposition: 95 subjects were screened, 85 of whom were randomized (ITT population) and either switched to receive dexmedetomidine (n=41), or continued to receive midazolam or propofol (n=44: midazolam [n=16] and propofol [n=28]). PP population comprised 92.9% of ITT population (n=79: dexmedetomidine [n=38] and midazolam/propofol [n=41]). The reasons for exclusion from PP population were treatment duration of less than 12 hours for 1 subject in the dexmedetomidine and 2 the in midazolam/propofol group and/or missing more than 30% of RASS assessments for 2 subjects in the dexmedetomidine group and 1 in the midazolam/propofol group.

83 subjects completed the study as planned. 2 subjects (1 in each group) discontinued the study due to loss to follow-up after the day 31 follow-up. 10 subjects (24.4%) in the dexmedetomidine and 7 (15.9%) in the midazolam/propofol group discontinued the study treatment; due to AE 3 subjects in the dexmedetomidine and 5 in the midazolam/propofol group; due to lack of efficacy 6 subjects in the dexmedetomidine and 1 in the midazolam/propofol group; due to protocol violation 1 subject in the midazolam/propofol group; and due to transfer to another hospital 1 subject in the dexmedetomidine group.

Demographic and baseline characteristics:

Treatment groups were comparable for demographic characteristics. 82.4% of all subjects were male, all were Caucasian, and age ranged from 18 to 83 years. Treatment groups were comparable for all relevant baseline characteristics.

Efficacy results:

First co-primary endpoint - depth of sedation

In the PP population (n=79), the proportion of time at target sedation level without rescue medication was 55.4% in the dexmedetomidine and 57.2% in the propofol/midazolam group. The lower limit of the 95% CI for the estimated ratio of dexmedetomidine vs. midazolam/propofol (0.79) was not within the pre-defined non-inferiority margin (>0.90); therefore dexmedetomidine was not proven to be non-inferior to midazolam/propofol.

However, there was a statistically significant (p=0.057) interaction in treatment effect with regard to baseline target RASS score. In subjects requiring light to moderate sedation (target RASS score 0 to -3; n=63), the proportion of time at target sedation level without rescue medication was 67.6% in the dexmedetomidine and 63.7% in the midazolam/propofol group. The lower limit of the 95% CI for the estimated ratio (0.87) approached the pre-defined non-inferiority margin, indicating a trend towards dexmedetomidine being non-inferior compared to midazolam/propofol. In subjects requiring deep sedation (target RASS score -4; n=16), dexmedetomidine was less effective than midazolam/propofol (30.7% vs. 63.0%, p = 0.006).

Second co-primary endpoints:

Length of stay in the ICU from randomisation (or admission) to medically fit for discharge

In the ITT population (n=85), the median time from randomisation (admission) to medically fit for discharge was 5.7 (6.6) days in the dexmedetomidine group and 5.5 (6.7) days in the midazolam/propofol group, the differences between the treatment groups being not statistically significant (Cox proportional hazards model).

However, there was a statistically significant interaction (from randomisation: p=0.007; from admission: p=0.041) in treatment effect with regard to admission reason to ICU. The length of stay in the ICU from randomisation (admission) tended to be shorter in the dexmedetomidine group than in the midazolam/propofol group in subjects who were admitted to ICU due to a medical reason (from randomisation: hazard ratio 0.514, p=0.056; from admission: hazard ratio 0.490, p=0.040) and was statistically significantly shorter in the midazolam/propofol group than in the dexmedetomidine group in subjects who were admitted to ICU for post-operative/trauma care (from randomisation: hazard ratio 2.43, p=0.031; from admission: hazard ratio 2.28, p=0.044).

Secondary endpoints

Total scores on the VAS for nurse's assessment of subject communication demonstrated that subjects

receiving dexmedetomidine were statistically significantly more arousable, cooperative and better able to communicate their pain than subjects receiving midazolam/propofol, with mean (SD) overall VAS score of 30.6 (21.0) for dexmedetomidine compared to 47.5 (27.5) for midazolam/propofol ($p<0.001$).

The median duration of mechanical ventilation (77.2 vs. 96.9 hours) and median weaning time (59.4 vs. 78.0 hours) were numerically, but not statistically significantly, shorter in the dexmedetomidine than in the propofol/midazolam group. In subjects with light to moderate sedation (RASS 0 to -3), the duration of mechanical ventilation was statistically significantly different between the treatment groups ($p=0.027$), with a median duration of 70.2 hours in the dexmedetomidine group and 92.5 hours in the midazolam/propofol group. The median of ventilator free days was 1.0 day for both treatment groups, mean number of ventilator free days favouring dexmedetomidine (1.9 days vs. 1.4 days).

The median time to discharge from hospital from randomisation (admission) was 20.0 (22.0) days in the dexmedetomidine group and 19.0 (22.0) days in the midazolam/propofol group, the differences between the treatment groups being not statistically significant (Cox proportional hazards model).

Based on the functional recovery assessment, the majority of subjects (87.1%) had a residual dysfunction at the end of the 48-hour follow-up period. There were no clinically notable differences between the treatment groups in any dysfunction class.

The percentage of patients who needed rescue therapy (80.5% vs. 75.0%) and median time to use of rescue medication (8.6 vs. 5.9 hours) were similar between the dexmedetomidine and midazolam/propofol groups. Likewise, in the total doses of any rescue medications received, no statistically significant differences between the treatment groups were observed.

A tendency for dexmedetomidine to reduce the cost of care in the ICU was observed.

Pharmacokinetic results:

Dexmedetomidine seemed not to accumulate with the increasing infusion rate from 0.25 to 1.4 µg/kg/h.

Safety results:

Exposure

The mean total dose and median duration of dexmedetomidine infusion (n=41) were 0.82 µg/kg/h and 39.6 hours, of midazolam boli (n=8) 40.4 µg/kg/h and 24.4 hours, of midazolam infusion (n=12) 91.3 µg/kg/h and 26.6 hours, and of propofol infusion (n=28) 2193 µg/kg/h and 61.0 hours. It should be noted that 4 subjects were switched from bolus group to infusion in the midazolam group. 65.9% of subjects received dexmedetomidine longer than 24 hours.

The longest exposure to dexmedetomidine infusion was 8 days 6 hours (198 hours), to midazolam boli 3 days 11 hours (83 hours), to midazolam infusion 4 days 9 hours (105 hours) and to propofol infusion 10 days 16 hours (256 hours). Dose reduction due to an AE was reported for 3 dexmedetomidine subjects and 5 midazolam/propofol subjects. Study treatment was permanently discontinued due to an AE for 3 dexmedetomidine subjects and 5 midazolam/propofol subjects. Exposure to higher doses of dexmedetomidine (1.1 and 1.4 µg/kg/h) did not appear to be associated with an increase in SAEs.

AEs:

The overall incidence of AEs was similar in both groups:

AE category	Number (%) of subjects	
	Dexmedetomidine (N=41)	Midazolam/Propofol (N=44)
AE	41 (100%)	42 (95.5%)
Treatment-related AEs	27 (65.9%)	24 (54.5%)
SAEs	17 (41.5%)	18 (40.9%)
AEs leading to death	10 (24.4%)	7 (15.9%)
AEs leading to discontinuation of study drug	3 (7.3%)	5 (11.4%)

100% of subjects in the dexmedetomidine group reported 296 AEs and 95.5% of subjects in the midazolam/propofol group reported 275 AEs. The most frequently reported AEs (subject count) were

delirium (34.1%), confusional state (24.4%), hypotension (29.3%) and hypertension (26.8%) in the dexmedetomidine group and hypotension (36.4%) and delirium (22.7%) in the midazolam/propofol group. A statistically significantly greater proportion of subjects in the dexmedetomidine group compared to the midazolam/propofol group reported rebound effect (17.1% vs. 2.3%, p=0.020), confusional state (24.4% vs. 6.8%, p=0.025) and hypertension (26.8% vs. 4.5%, p=0.004).

65.9% of subjects in the dexmedetomidine group reported 55 treatment-related AEs (i.e. AEs that were considered to be causally related to the study treatment by the investigator) and 54.5% of subjects in the midazolam/propofol group reported 47 treatment-related AEs. The most frequently reported treatment-related AEs were hypotension (17.1% vs. 13.6%), delirium (14.6% vs. 11.4%), rebound effect (14.6% vs. 2.3%), bradycardia (12.2% vs. 4.5%) and drug withdrawal syndrome (7.3% vs. 2.3%) in the dexmedetomidine and midazolam/propofol groups, respectively.

41.5% of subjects in the dexmedetomidine group reported 41 SAEs and 40.9% of subjects in the midazolam/propofol group reported 47 SAEs. In the dexmedetomidine group bradycardia was reported as an SAE in 3 subjects compared to none in the midazolam/propofol group. Of the 3 bradycardia SAEs, 2 were considered to be treatment-related whilst 1 occurred 8 days after stopping the study treatment. Fewer subjects in the dexmedetomidine group compared to the midazolam group reported respiratory failure (4.9% vs. 11.4%), cardiac failure (0 vs. 4.5%) pneumonia (0 vs. 4.5%) and pulmonary oedema (0 vs. 4.5%).

An AE leading to permanent discontinuation of the study treatment was reported for 7.3% of subjects in the dexmedetomidine group and 11.4% of subjects in the midazolam/propofol group. Bradycardia was the reason for 2 subjects in the dexmedetomidine group for discontinuation of study treatment. 24.4% (n=10) of subjects in the dexmedetomidine group and 15.9% (n=7) of subjects in the midazolam/propofol group died between randomisation and day 45 follow up. In addition, 2 subjects died at screening before randomisation.

Laboratory findings

For blood glucose, repeated measures analysis of variance (RM-ANOVA, p=0.002) indicated a small but statistically significant between-group difference (dexmedetomidine 0.68 mmol/l greater than midazolam/propofol) in change from baseline. Lower serum cortisol values from day 4 onwards were observed in the dexmedetomidine group compared to the midazolam/propofol group, but this result was driven by a single outlier. Adrenal insufficiency was reported for 1 subject in the dexmedetomidine group, but was considered to be related to etomidate and not to study treatment. There were no other notable changes from baseline in any other laboratory variable between the treatment groups during the study.

Vital signs and ECG

Dexmedetomidine predictably reduced HR. The mean decrease in HR from baseline during the study treatment period was 14.1 bpm greater in the dexmedetomidine group compared to the midazolam/propofol group (RM-ANOVA, p<0.0001). After discontinuation of the study treatment, the mean HR returned to the baseline level in the dexmedetomidine group, indicating recovery of HR.

After initial mild decreases, increases from baseline in systolic and diastolic BP were observed in both treatment groups after start of study treatment. The mean increases in systolic and diastolic BP from baseline during the study treatment period were 7.0 mmHg and 3.4 mmHg, respectively, greater in the dexmedetomidine group compared to the midazolam/propofol group (RM-ANOVA, p<0.0001).

A small (1.3%) but statistically significant (RM-ANOVA, p<0.0001) difference between the treatment groups in oxygen saturation from baseline was observed, favouring dexmedetomidine. Dexmedetomidine appeared to have no effect on ventricular repolarisation, as suggested by an unchanged QTc (Fridericia) interval. 1 subject on dexmedetomidine progressed from AV block I to AV block III with associated bradycardia.

SOFA

At day 2, a greater proportion of subjects in the dexmedetomidine group had a SOFA cardiovascular score >1 compared to the midazolam/propofol group (77.5% vs. 56.1%, p=0.024), indicating that the subjects on dexmedetomidine received more vasopressors/inotrope support during the first 24 hours of study treatment. No clinically relevant changes between the treatment groups were observed in any other organ system.

Delirium

The frequency of delirium was statistically significantly higher in the dexmedetomidine group compared to

the midazolam/propofol group (43.9% vs. 25.0%, p=0.035), when delirium was analysed by the combined endpoint of CAM-ICU and AEs of delirium and confusional state. However, more CAM-ICU assessments were performed in the dexmedetomidine group, perhaps because of greater rousability, and no statistically significant difference between the treatment groups was observed when positive CAM-ICU results were expressed as a percentage of assessments completed. CAM-ICU appeared to be unreliable for the assessment of sedated patients in this study.

CIP and MRC score

1 subject in each treatment group was diagnosed as having CIP at the end of treatment. Similar proportion of subjects had symmetrical muscle weakness (MRC score ≤ 2) in any muscle group at the end of treatment in the dexmedetomidine and midazolam/propofol groups (18.2% vs. 19.4%).

ICU and in-hospital survival

During the stay in the ICU, 3 subjects in the dexmedetomidine and 2 subjects in the midazolam/propofol group died, with median times of 7.0 vs. 2.5 days to death. During the stay in the hospital, 10 subjects in the dexmedetomidine and 7 subjects in the midazolam/propofol group died, with median times of 15.0 and 13.0 days to death. There were no statistically significant differences between the treatment groups in either variable.

Haemodynamic rebound and withdrawal syndrome

A statistically significantly greater proportion of subjects in the dexmedetomidine group were assessed as meeting the pre-defined criteria for haemodynamic rebound compared to the midazolam/propofol group (20.0% vs. 2.4%, p=0.011). However, this was mainly attributable to recovery of HR. No notable difference between the dexmedetomidine and midazolam/propofol groups was observed in the percentage of subjects who met the pre-defined criteria for withdrawal syndrome (10.5% vs. 7.3%).

Conclusions: The results of this pilot study indicated that dexmedetomidine has the potential to be an effective sedative, comparable to midazolam/propofol in its ability to maintain targeted light to moderate sedation (RASS 0 to -3) in ventilated patients requiring sedation for more than 24 hours. Although the predefined statistical non-inferiority margin was not met, the proportion of subjects maintained at the target level of sedation (RASS 0 to -3) was similar in the dexmedetomidine and midazolam/propofol-treated subjects. Dexmedetomidine achieved this level of sedation whilst improving subjects' rousability and ability to communicate better than midazolam/propofol, and a trend towards a shorter time on mechanical ventilation was observed. Dexmedetomidine appeared to be well tolerated when given for more than 24 hours and at doses up to 1.4 µg/kg/h. The mean concentration at steady state (C_{ss}) increased linearly with the increasing infusion rate. The results of the pilot study therefore support further evaluation of dexmedetomidine for this indication in a larger study. However, given the limitations of comparison with a combined standard of care group, the decision was made to close this study at the end of the pilot phase and plan instead to conduct 2 separate studies with single comparators of propofol and midazolam.

Date of report: 30 Apr 2007