22 September 2011
EMA/789509/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dexdor

dexmedetomidine

Procedure No.: EMEA/H/C/002268

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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List of abbreviations

5 HT	5-hydroxytryptamine
AE	Adverse Event
ASMF	Active Substance Master File
AUC	area under the concentration time curve
AV	Atrioventricular
BIS	bispectral index
CABG	Coronary Artery Bypass Grafting
CAM-ICU	Delirium and confusion assessment method adapted for ICU
cAMP	cyclic 3', 5'adenosine monophosphate
CFFT	Critical Flicker Fusion Treshold
Cmax	Maximum plasma concentration level
CNS	Central Nervous System
CO	Cardiac Output
CV	Cardiovascular
CYP	cytochrome P450
DBT	Double blind treatment
dP/dT	first derivative of left ventricular pressure
EC50	half maximal effective concentration
ECG	electrocardiogram
ED_{50}	dose producing 50% of the maximum effect
EMA	European Medicines Agency
GCP	Good Clinical Practice
Gdex	dexmedetomidine N-glucuronide metabolites
GLP	Good Laboratory Practice
GS	gas chromatography
H-1	O-glucuronide of hydroxylated N-methyl dexmedetomidine
H-3	oxidised metabolite of dexmedetomidine
hERG	human ether-à-go-go related gene
HPLC	High-performance liquid chromatography
HR	Heart Rate
IC_{50}	half maximal inhibitory concentration
ICU	Intensive Care Unit
IP	Intraperitoneal
IT	Intratechal
ITT	Intent to Treat
IV	Intravenous
K_i	dissociation constant
LLD	Lowest lethal dose
MAH	marketing authorisation holder
MAP	Mean Arterial Pressure
MS	mass spectrometry
NA	Noradrenaline
NOAEL	No Observed Adverse Effect Level
NONMEM	using nonlinear mixed effects modeling methodology
PBT	Persistence, bioaccumulation and toxicity
PD	Pharmacodynamics
PEC_{SW}	Predicted Environmental Concentration in the Surface Water
P-gp	P-glycoprotein
PK	Pharmacokinetics
PP	Per Protocol
RASS	Richmond Agitation Sedation Scale
RM	Repeated Measure
RR	Respiratory Rate
RSS	Ramsay Sedation Scale
SAE	Serious Adverse Event
SAP II	Simplified Acute Physiology Score II
SC	subcutaneous
SD	Standard Deviation

SmPC	Summary of product characteristics
SOFA	Sequential Organ Failure Assessment
Sp02	Sturation of peripheral oxygen
$T_{1/2}$	Eimination half life (biological half-life)
T_{max}	time to reach maximum concentration following drug administration
VAS	Visual Analogue Scale
Vss	Volume of distribution at steady state

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Orion Corporation submitted on 29 September 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Dexdor, through the centralised procedure under Article 3 (2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 December 2005. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication: Dexdor is indicated for patients requiring light to moderate sedation in intensive care during or after intubation. Dexdor is indicated in adults aged over 18 years.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 October 2000. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Dexmedetomidine has been given a Marketing Authorisation in Poland on 19 December 2001. This marketing authorisation was subsequently withdrawn in April 2011.

Dexmedetomidine has also been given Marketing Authorisations in several countries outside EEA since 1999.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Ian Hudson**

Co-Rapporteur: **Tomas Salmonson**

- The application was received by the EMA on 29 September 2010.
- Procedure was agreed upon by CHMP on 18 December 2005.
- The procedure started on 20 October 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 January 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 January 2011.
- During the meeting on 14-17 February 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 February 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 April 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 3 June 2011.
- During the CHMP meeting on 20-23 June 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 30 June 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the list of outstanding issues to all CHMP members on 7 July 2011.
- During the meeting on 18-21 July 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Dexdor on 21 July 2011.

2. Scientific discussion

2.1. Introduction

The intensive care unit (ICU) population consists of heterogeneous patients, including for instance, post-operative, post-traumatic or medically disabled patients, patients under either controlled or spontaneous ventilation, patients with various underlying diseases such as cardiac, renal or hepatic insufficiency. Patients requiring intensive care commonly need sedation. The mode of sedation thus varies according to the settings and the type of patient.

In these patients, sedation has several objectives, e.g. improving patient comfort with pain relief and relief of anxiety, treating agitation, guaranteeing its efficiency, optimising mechanical ventilation condition, facilitating uncomfortable short-term diagnostic or therapeutic procedures, and decreasing the neuroendocrine response to stress.

Many different pharmacological agents and combinations of agents are employed in intensive care patients to produce sedation and analgesia and to reduce anxiety. These are benzodiazepines (e.g. midazolam) because of their anxiolytic, sedative, myorelaxant, and amnestic properties, general anaesthetics (e.g. propofol) because of their sedative property, opioids because of their analgesic and to a lesser extent sedative properties. Sedative protocols commonly include benzodiazepines or propofol combined with an opioid agent.

Dexmedetomidine acts as a selective alpha-2 receptor agonist with a broad range of pharmacological properties. The sedative effects are claimed to be mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem. Dexmedetomidine has shown some analgesic and anaesthetic/analgesic-sparing effects.

In 1998, an application for a Marketing Authorisation for dexmedetomidine was submitted to the European Medicine Agency (EMA) for use in an intensive care setting as an alpha-2 sedative with analgesic properties. Major objections regarding the claimed indication, the clinical relevance of the sparing effect, the absence of comparison to reference therapy, the cardiovascular safety were raised. Subsequently the application was withdrawn.

A scientific advice for dexmedetomidine was received from the CHMP on 19 October 2000 pertaining to clinical aspects of the dossier.

In September 2010, the applicant submitted to the EMA a complete new Marketing Authorisation based on a full documentation dossier for dexmedetomidine (Dexdor) through the centralised procedure, according to article 8(3) of Directive 2001/83/EC, as a "known active substance". At the time of this submission, dexmedetomidine was authorised as 100 µg /ml concentrate for solution for infusion in Poland under the name of Precedex. The authorised indication was sedation of previously intubated and artificially ventilated patients hospitalised in intensive care units (ICU). Precedex should be administered as a continuous infusion for no longer than 24 hours. This marketing authorisation was subsequently withdrawn in April 2011.

The new application has been completed by additional data including 3 comparator-controlled studies (**3005011, 3005012, 3005013**) and a further phase IV study comparing dexmedetomidine to midazolam (**2001-001**).

The following indication is initially applied for: Dexdor is indicated for patients requiring light to moderate sedation in intensive care during or after intubation. Dexdor is indicated in adults aged over 18 years.

The final recommended indication by the CHMP is: for sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3).

Dexdor is presented as 100 µg /ml concentrate for solution for infusion. The recommended dose is an initial infusion rate of 0.7 µg /kg/h which may then be adjusted stepwise within the dose range 0.2 to 1.4 µg /kg/h in order to achieve the desired level of sedation.

2.2. Quality aspects

2.2.1. Introduction

Dexdor is a concentrate for solution for infusion and contains 118 µg /ml of dexmedetomidine hydrochloride equivalent to 100 micrograms/ml of dexmedetomidine. Three presentations of the finished product are available: 200 µg/2 ml ampoules, 400 µg/4 ml and 1000 µg/10 ml single-use vials. The container closure system for 2 ml nominal fill volume is type I colourless glass ampoules. The other containers (4 ml and 10 ml nominal fill volumes) are type I colourless glass vials with two alternative fluoropolymer coated bromobutyl rubber stoppers (omniflex plus and ETFE), sealed with aluminium seals and polypropylene flip-off caps.

The other ingredients of this medicine are water for injections and sodium chloride.

Dexdor must be administered only as a diluted intravenous infusion using a controlled infusion device. Compatible admixture fluids and administration devices/bags have been investigated and use-times and storage conditions for diluted solutions for infusion have been established.

Dexdor can be diluted in glucose 50 mg/ml (5%), Ringers, mannitol 200 mg/ml (20%) or sodium chloride 9 mg/ml (0.9%) solution for injection to achieve the required concentration of 4 micrograms/ml prior to administration. Dexdor has been shown to be compatible when administered with the following intravenous fluids and medicinal products: Lactated Ringers, 5% glucose solution, sodium chloride 9 mg/ml (0.9%) solution for injection, mannitol 200 mg/ml (20%), thiopental sodium, etomidate, vecuronium bromide, pancuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, rocuronium bromide, glycopyrrolate bromide, phenylephrine HCl, atropine sulphate, dopamine, noradrenaline, dobutamine, midazolam, morphine sulphate, fentanyl citrate, and a plasma-substitute.

2.2.2. Active Substance

The chemical names of dexmedetomidine are 1H-imidazole, 4-[1-(2,3-dimethylphenyl)ethyl]-, (S)-, hydrochloride, or (+)-4-[(S)-α,2,3-trimethylbenzyl]-imidazole hydrochloride, corresponding to the molecular formula $C_{13}H_{16}N_2$.HCl. The structure of this active substance is described in figure 1.

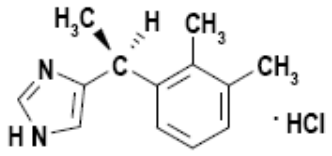


Figure 1: Dexmedetomidine hydrochloride

It appears as an almost white, or white, crystalline powder that is freely soluble in water, chloroform, ethanol and methanol; slightly soluble in acetonitrile and practically soluble in ethe. Dexmedetomidine has one chiral centre and is therefore optically active. During the synthesis only one (S)-enantiomer is manufactured and used in the manufacture of the finished product. There are two recognised

polymorphic forms of dexmedetomidine: anhydrous (form A) and monohydrate (form B). Form A is consistently obtained during synthesis and is used in the manufacture of the finished product.

2.2.2.1. *Manufacture*

The Active Substance Master File (ASMF) procedure was followed for the active substance. The manufacturing process of dexmedetomidine is a three step synthesis followed by purification (filtration and crystallisation). A full description of the synthetic route was provided in the restricted part of the ASMF. Adequate controls of critical steps and intermediates are in place to ensure the quality of the active substance, and adequate specifications for starting materials, reagents, and solvents have been provided. The purified active substance is packed in white polyethylene containers that are sealed within aluminium laminate bags. Statements from the Qualified Persons of the finished product manufacturers confirming that the manufacturing of the active substance is performed in compliance with current EU GMP or ICH Q7A were provided. The chemical structure of the active substance has been confirmed by spectroscopy (IR, 1H-NMR, 13C-NMR, UV and MS). In addition the molecular weight was determined by elemental analysis and the absolute configuration and crystal structure was determined by X-ray diffraction.

2.2.2.2. *Specification*

The active substance specification as tested by the finished product manufacturer includes tests for appearance (visual), identification (IR, chlorides and HPLC), loss on drying (Ph.Eur.), sulphated ash (Ph.Eur.), heavy metals (Ph.Eur.), pH, colour of solution (Ph.Eur.), clarity of solution (Ph.Eur.), optical purity (Ph.Eur.), impurities (HPLC), residual solvents (GC), assay (HPLC) and microbiological purity (Ph.Eur.). A detailed description for all analytical methods was provided. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH guidelines. In general, the analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data have been provided and show compliance with the predefined active substance specification.

2.2.2.3. *Stability*

The stability results from long-term (25°C/60%RH) for 6 production scale batches and accelerated studies (40°C/75%RH) for five production scale batches were completed according to ICH guidelines demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: appearance (visual), loss on drying, assay (HPLC), impurities (HPLC) and optical purity (HPLC), employing the test methods applied as used for release of the active substance. It can be concluded that the proposed re-test is justified based on the stability results when the active substance is stored in the original packaging material.

2.2.3. Finished Medicinal Product

2.2.3.1. *Pharmaceutical Development*

All information regarding the choice of the drug substance characteristics and the excipients are sufficiently justified. The excipients selected for this formulation are commonly used in pharmaceutical formulations and are described in the European Pharmacopeia. The main objective was to develop a stable, sterile, aqueous solution of dexmedetomidine hydrocloride for intravenous administration. Since it is freely soluble in water at room temperature, it was possible to develop a final formulation of a homogenous solution at the proposed concentration (100 µg/ml). Terminal sterilisation of the finished

product was considered and studied during drug development. The vials are sealed with coated butyl rubber stoppers. Since the product is intended for single use only, no preservative system has been considered. The manufacturing process employed is simple and has not changed significantly during product development.

2.2.3.2. *Manufacture of the product*

This Manufacturing process consists of the following steps: mixing and dissolution of ingredients, filtration, filing, terminal sterilization, inspection of ampoules/vials, assembly process (labeling and packaging).The critical steps of this particular manufacturing process have been identified and optimised during drug development.

Satisfactory process validation data have been provided for the major steps of the manufacturing process. The batch analysis results show that the medicinal product can be manufactured reproducibly according to the agreed finished product.

2.2.3.3. *Product specification*

The product specification is standard for concentrate for solution for infusion and contains tests with suitable limits for colour of solution (Ph.Eur), clarity of solution (Ph.Eur), particulate matter (Ph.Eur), extractable volume (Ph.Eur), pH (Ph.Eur), identification of dexmedetomidine (HPLC, UV), assay (HPLC), optical purity, impurities (HPLC), assay of sodium chloride, test for sterility (Ph.Eur) and bacterial endotoxins (Ph.Eur). Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. All analytical procedures that were used for testing the finished product were properly described and satisfactorily validated in accordance with the relevant ICH guidelines. The batch analysis data for 5 production scale batches confirm that the concentrate for solution for infusion can be manufactured reproducibly according to the agreed finished product specifications.

2.2.3.4. *Stability of the product*

Stability studies under ICH long-term and accelerated conditions (i.e. 25°C/60% RH and 40°C/75% RH) have been carried out for pilot and production batches covering all three proposed presentations (200 µg/2 ml, 400 µg/4 ml and 1000 µg/10 ml).

The results of the following tests were submitted: appearance (colour and clarity of solution), impurities, assay, pH, microbiological purity (Ph.Eur) and optical purity. The analytical methods used for the stability studies are identical with the methods proposed for routine testing of the finished product. During the stability studies the product did not show any significant change in its quality. All the results remained well within the specification limits during all the stability studies.

A Photostability testing program was conducted in accordance with the recommendations of ICH guideline Q1B. The results were found to meet the specifications and the finished product does not require any special light protection.

The stability of Dexmedetomidine 100 µg/ml concentrate for solution for infusion has been evaluated on repeated freezing and thawing. The freeze-thaw study of Dexmedetomidine 100 µg/ml concentrate for solution for infusion was carried out by storing 2 ml ampoules in a freezer at approximately -20 °C at least for 24 hours. Freezing and thawing was carried out four times. All results complied with the specification confirming that repeated freezing and thawing does not have an impact on the quality and stability of the finished product.

During the development work the stability and compatibility studies of the diluted solutions of Dexmedetomidine 100 µg/ml concentrate for solution for infusion in different infusion solutions have been investigated. Stability of the drug product after dilution in 0.9 % sodium chloride infusion solution to concentration 4 µg/ml has been demonstrated for 48 hours. Drug product has also been studied to be stable in dilutions with 5 % glucose (dextrose), 0.9 % sodium chloride solution, ringers solution and 20 % mannitol as the concentration of 1 and 50 µg/ml for 24 hours.

The stability of the diluted solutions of Dexmedetomidine 100 µg/ml concentrate for solution for infusion has been repeated at the end of shelf life in different infusion solutions in syringes after storage of 24 hours at ambient room temperature and at 2 to 8ºC. All results complied with the specification confirming that the dilution does not have an impact on the quality and stability of the finished product. Furthermore, the results demonstrate that the diluted finished product is stable for 24 hours. In accordance with this study Dexmedetomidine 100 µg/ml concentrate for solution for infusion is compatible with sodium chloride, glucose, Ringer-acetate and mannitol infusion solutions as a concentration 4 µg/ml for 24 hours at ambient room temperature and at 2 to 8ºC.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

2.2.4.1. *Quality Development*

The pharmaceutical development of the formulation, the manufacturing process, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated for production scale batches of each presentation at the proposed manufacturing site.

The routine specifications and tests methods proposed for the finished product will adequately control the quality of the finished product. Analytical methods were well described and validated in agreement with relevant guidelines.

Batch analyses were presented and the results showed that the finished product meets the specifications proposed.

The container-closure system was found to be suitable to ensure the quality of the finished product as shown by the stability data.

The conditions used in the stability studies comply with the ICH stability guideline. The control tests and specifications for finished were adequately established.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the medicinal product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, all quality issues have been resolved.

2.3. Non-clinical aspects

All main safety pharmacology and pivotal toxicology studies were performed according to Good Laboratory Practices (GLP), as stated by the applicant.

2.3.1. Introduction

Dexmedetomidine has been evaluated in a series of in vitro and in vivo studies to characterise its mechanism of action and sedative, anaesthetic-sparing, analgesic, anxiolytic effects. Effects on noradrenaline release and intracellular signalling were also studied. In vivo secondary pharmacodynamic studies were also performed to investigate the effects on cardiovascular function (e.g on blood pressure/flow, heart rate, vascular resistance/contractility), cerebral vascular system and nerve cells.

Dexmedetomidine is the dextro-enantiomer of medetomidine, a compound marketed as sedative/analgesic for veterinary use in several countries in the European Union.

2.3.2. Pharmacology

2.3.2.1. *Primary pharmacodynamic studies*

Dexmedetomidine has shown to be a potent and selective α2-adrenoceptor agonist. It is not selective for any specific α2-adrenoceptor subtype and has very low affinity for α1 adrenoceptors with a α2/α1 ratio of 1300/1. Similar pharmacological profiles for dexmedetomidine and the racemate, medetomidine were observed; however, the levo-rotatory enantiomer was shown to be pharmacologically inactive.

The principal human metabolites, H3 (imidazole oxidation product) and G-Dex (mixture of two N-glucuronide isomers) were >183 and >745-fold less potent at the α2-adrenoceptors, respectively and were not considered to have a significant contribution to the pharmacological effects of the compound.

In rats, dexmedetomidine caused a concentration–dependent inhibition of noradrenaline release (EC_{50}:4 nM) in locus coeruleus cells. At dose $\geq$30 μg/kg, it caused a dose-dependent decrease in the levels of the principal noradrenaline metabolite and increased the levels of noradrenaline. Inhibition of noradrenaline turnover was observed at low doses (30 μg/kg) with a maximal effects at 100 and 300 μg/kg. Dexmedetomidine also reduced the turnover of 5-hydroxytryptamine (5-HT) and dopamine at $\geq$30 μg/kg and $\geq$100 μg/kg, respectively. The sympathoinhibitory effect of dexmedetomidine was also observed in dogs at 0.25-20 μg/kg resulting in a significant, dose-dependent decrease in the plasma levels of noradrenaline and/or adrenaline.

Dexmedetomidine has also shown to inhibit adenylate cyclase (possibly via activation of the G_i protein) causing a decrease in the levels of cAMP. Studies also suggested inwardly-rectifying activation of potassium channels causing hyperpolarisation of the cell membrane and subsequent inhibition of neuronal cell firing rate. In addition, there is also evidence to suggest that dexmedetomidine causes a decrease in intracellular calcium via inhibition of N-type calcium channels, which in turn inhibits neurotransmitter release.

Similarly to all α2-adrenoceptor agonists, dexmedetomidine has sedative, analgesic and anxiolytic activity, the latter only being apparent at sub-sedative doses. Dexmedetomidine has been shown to produce dose dependent sedative and hypnotic effects in rats, dogs and in a variety of other species. These effects are likely to be mediated by α2-adrenoceptors located in the locus coeruleus. After chronic subcutaneous administration (1-10 μg/kg/h for 7 days), desensitization to the sedative and

hypnotic/anaesthetic effects were observed in rats, although tolerance did not appear to develop for the sympatholytic or anaesthetic-sparing effects in clinical settting. Dexmedetomidine has also anxiolytic activity in the rat. The analgesic and antinociceptive effects, both after systemic and intrathecal administration, have been shown in a number of species. These effects are likely to be mediated by the activation of both pre- and postsynaptic α2-adrenoceptors that have a central as well as a spinal component.

2.3.2.2. *Secondary pharmacodynamic studies*

The cardiovascular effects of dexmedetomidine have been extensively studied in a variety of species, in both the conscious and anaesthetised states. Intravenous (iv) administration of dexmedetomidine can be expected to produce transient hypertension and coronary vasoconstriction (peripheral post-synaptic effects), which will be dependent of the dose and rate of delivery, followed by hypotension and bradycardia (central and peripheral pre-synaptic sympatholytic effects and increased vagal tone). Depressed cardiac function was also characterised by an increase in left ventricular end diastolic pressure that have been observed in dogs after iv dexmedetomidine (2.5 and 5 µg/kg). In general, no adverse effects were observed on cardiac function as cardiac oxygen demand was reduced as a result of the reduced heart rate, contractility and cardiac output. It should be noted however, that the depressive effects on contractility might be deleterious in heart failure or left ventricular dysfunction. In some studies, anti-steal (reversal of abnormal myocardial blood flow) and anti-ischemic effects of dextemetomidine were also suggested.

Other secondary effects have been identified. In dogs, reduced cerebral blood flow was observed after concomitant administration of a number of anaesthetics. In rabbits and rats, some neuroprotective effects were observed and thought to be mediated via the α_{2A}-receptors.

Dexmedetomidine was also shown to inhibit in vitro human platelet adenylate cyclase via α_{2A}-receptors and effects on platelet (human) aggregation have been noted at 3 µM. Dexmedetomidine did not cause a full aggregatory response alone and is considered to act as partial agonist.

In rats, intraperitoneally administered dexmedetomidine (10-300 µg/kg) increased growth hormone and prolactin release and these effects appear to be mediated via the α_2-receptor.

In dogs, no effect was observed on cortisol response after chronic administration dexmedetomidine (50 µg/kg/day) as a 6-hour infusion. A slightly lower response was seen at higher dose (100 µg/kg/day).

Dexmedetomidine (0.1 and 0.3 mg/kg) caused a significant reduction in insulin secretion, an increase in plasma glucose, but had no effect on the serum levels of free fatty acids.

In mouse and rat models of sepsis, dexmedetomidine (40 µg/kg i.p. and 2.5-10 µg/kg i.v., respectively) was suggested to improve survival and attenuate the plasma levels of inflammatory mediators.

2.3.2.3. *Safety pharmacology programme*

Central nervous system

In rats, dexmedetomidine has shown anticonvulsant activity against kainic acid-induced and amygdala kindled seizures at 3-5 µg/kg s.c., bupivacaine and levobupivacaine-induced seizures at 3.6 µg/kg/h i.v. and cocaine induced seizures at 20 µg/kg/h followed by 1 µg/kg/h i.v. Intraperitoneal administration of up to 300 µg/kg, had no effect on pentylenetetrazol-induced convulsions in mice; however, high intravenous doses (100 and 500 µg/kg) reduced the pentylenetetrazol-induced seizure threshold in rats.

In rhesus monkeys, dexmedetomidine (0.25 and 1 μg/kg/infusion) demonstrated high rates of self-administration that were comparable to pentazocine (125 and 250 μg/kg/infusion). In rats, cessation of repeated-intravenous administration of dexmedetomidine (hourly injections of 8 and 16 μg/kg for 3-7 days) was associated with reduced weight gain and behavioural withdrawal signs (including hyperreactivity and piloerection); however, the degree of physical dependence was substantially less than that observed with morphine. Dexmedetomidine caused a dose-dependent decrease in body temperature in both rats and dogs. In dogs, cessation of a 7-day dexmedetomidine infusion (10 μg/kg/h s.c.) was also associated with tachycardia.

Cardiovascular system

Dexmedetomidine and its primary metabolites (H-3, G-Dex-1 and G-Dex-2) inhibited the hERG channel current at high concentrations in human embryonic kidney cells (IC_{50} values $\geq$ 10-30 μM) No significant binding/affinity to L-Ca^{2+}, $K_{ATP}{}^{+}$, voltage gated K^{+} or Na^{+} and chloride channels were observed with dexmedetomidine and its H-3 metabolite (1 μM).

No effects on cardiac conduction were observed in dogs and rabbits at 0.01 μM and 0.03-3 μM, respectively. At higher doses (0.1 and 1 μM), a small dose-dependent increase in action potential was observed in dog Purkinje fibres. At higher supra-therapeutic concentration of 10 μM, a decrease in action potential duration was noted that was associated with a decrease in the maximal rate of depolarisation. Early or delayed afterdepolarisations were not observed. In anaesthetised guinea pigs, cumulative intravenous infusion of dexmedetomidine at 9, 27 and 90 μg/kg/h at 20 min intervals did not induce any effects on the duration of ventricular repolarisation. In dogs, a number of studies were performed suggesting that observed QT prolongations were caused by hypothermia rather than torsadogenic effect.

Respiratory system

Respiratory depressive effects were observed in a number of studied species. In rats, dexmedetomidine decreased minute ventilation and respiratory frequency after i.p administration of 250 μg/kg followed by 0.5 μg/kg/h i.v. In dogs, respiratory rate was reduced at iv dose of $\leq$ 2.5 μg/kg while a dose dependent increase in respiratory depression was observed at 10- 100 μg/kg. Moderate respiratory depression has also been noted in conscious rabbits and monkeys following intravenous and subcutaneous administration at $\geq$ 80 μg/kg and $\geq$ 3 μg/kg, respectively. In sheep and goats, dexmedetomidine significantly increased respiratory resistance and induced arterial hypoxia and pulmonary oedema, particularly after rapid bolus administration (2 μg/kg). Significant increase in respiratory resistance was also observed.

Other systems

In mice, dexmedetomidine (1-100 μg/kg/s.c) caused a transient (<3 hours) dose-dependent reduction in intestinal motility. In rats, inhibition of gastrointestinal transit (ED_{50} value: 40 μg/kg) and gastric emptying (slightly) was observed after i.p administration.

In rats, dexmedetomidine (10 and 30 μg/kg/s.c) caused diuresis, naturesis and kaliuresis. These effects are thought to be partly mediated via reduced arginine vasopressin-stimulated water and sodium transport.

Dexmedetomidine (3 μg/kg s.c.), when administered as a bolus alone or bolus dose plus infusion also reduced renal impairment in rat models of renal ischaemia and reperfusion. These effects appear to be mediated via preservation of blood flow within the outer medulla.

2.3.2.4. *Pharmacodynamic drug interactions*

Dexmedetomidine acts synergistically when given in combination with midazolam, diazepam and fentanyl. In rats and dogs, it enhanced the anxiolytic, sedative and hypnotic effects of benzodiazepines and the antinociceptive effects of opioids. It reduced the anaesthetic requirements by up to 90%. In guinea pigs, it prolonged the spinal anaesthesia induced by levobupivacaine and enhanced the local anaesthetic action of lidocaine.

In dogs, dexmedetomidine (10-50 μg/kg p.o or 10 μg/kg i.v) counteracted the increased heart rate, rate of increase of left ventricular pressure at 50 mmHg ($dP/dt_{50)}$, rate-pressure product and/or cardiac output caused by ketamine and attenuated the decrease in mean arterial blood pressure caused by halothane and isofluorane. In addition, dexmedetomidine prevented the increased heart rate and blood pressure observed during emergence from enfluorane anaesthesia with enfluorane and the loss of baroceptor reflex that occurs with halothane anaesthesia.

In several species (rats, cats and dogs), anti-cholinergics such as atropine and glycopyrrolate inhibited the reduced heart rate observed with dexmedetomidine and also increased the myocardial oxygen consumption and the severity and duration of hypertension. Dexmedetomidine had no effect on the neuromuscular blocking actions of pancuronium, vecuronium or suxamethonium in rats.

Effects of calcium channel blockers on dexmedetomidine were noted. Isradipine attenuated dexmedetomidine-induced (0.1-10 μg/kg i.v.) decrease in heart rate/cardiac output and increase in blood pressure without any effect on the decreased plasma levels of adrenaline and noradrenaline. Nifedipine normalised all dexmedetomidine-induced (20 μg/kg i.v.) haemodynamic changes observed during isoflurane anaesthesia, without decreasing its anaesthetic sparing activity. Nifedipine also enhanced the dexmedetomidine-induced (300 mg/kg) hypnosis, anaesthesia and diuresis.

In ethanol-fed rats, dexmedetomidine (10 mg/kg s.c.) has shown to relieve withdrawal reactions (rigidity, tremor, irritability) and prevent overactivity and degeneration of catecholaminergic neurons.

2.3.3. Pharmacokinetics

The pharmacokinetics and metabolism of dexmedetomidine were predominantly investigated in rats and dogs following different routes of administration (subcutaneous, intravenous, intramuscular, intrathecal and epidural). Additional studied species were also referred to (e.g rabbits, cats and sheeps).

Dexmedetomidine was readily absorbed following subcutaneous or intramuscular administration in rats and dogs. Cmax was reached within less than an hour and the half-life of elimination was up to approximately 2 hours after single administration. In these species, the pharmacokinetics was non-linear with C_{max} and AUC increasing with the dose in a supra-proportional manner. No evidence of accumulation was observed upon repeated-dosing.

The radioactive drug was rapidly and widely distributed over the body. The apparent volume of distribution ranged from 0.8-2.16 L/kg in the studied species. Tissue concentrations were higher than plasma in the liver, adrenal glands, kidneys, lungs, intestine, stomach, pancreas and eyes. Some binding to melanin was evidenced in eyes. Radioactivity in plasma and most tissues had decreased substantially within 72 hours with the exception of adrenals. Low binding to red blood cells was observed. Dexmedetomidine-related radioactivity crossed the placenta barrier in pregnant rats, with highest fetal levels in blood, liver and kidneys. Foetal levels of dexmedetomidine were similar to maternal plasma levels. It was also excreted into the milk of lactating rats and the plasma/milk ratios were less than 1 at all time points. The plasma protein binding was 88% in rats, 95% in mice, 93% in dogs, 90% in cats and about 85% in monkeys.

Biotransformation plays a major role in the elimination of dexmedetomidine with <1% excreted unchanged. Carboxy metabolite, hydroxy metabolite, its corresponding glucuronide and sulphate conjugates as well as unidentified metabolites were detected in rats and dogs plasma. The main metabolite was the 3-hydroxyderivative. This metabolite is present in human and is not pharmacologically active. The patterns of plasma and urinary metabolites were very similar in rats and dogs and different from humans. Elimination seemed to be relatively rapid with half lives ranging from 0.6 in dogs to 2.6 hours in humans, the urine being the major route of excretion. In rats, total excretion of radiolabelled material was 93% of the dose in 72 hours and the majority was excreted during the first 24 hours (52-74% in urine and 14-27% in faeces).

2.3.4. Toxicology

The studies were conducted with dexmedetomidine hydrochloride and were performed predominantly in rats and dogs, using different routes of administration (intravenous: i.v, subcutaneous: s.c, intramuscular: i.m and intrathecal: i.t). In addition, studies were performed in the mice, guinea pigs and rabbits. The toxicity profiles of the 4 major (human) metabolites and the impurity, levomedetomidine, were also investigated.

2.3.4.1. *Single dose toxicity*

Acute toxicity studies were performed in mice, rats and dogs using subcutaneous or intravenous routes. The lowest lethal dose (LLD) for acute toxicity of dexmetomidine in mice was 5 mg/kg for males and 10 mg/kg for females using the intravenous route and 20 mg/kg or greater (for females only) using the subcutaneous route. . The LLD for acute toxicity in rats was 5 mg/kg for both routes of administration for females and 5 mg/kg and 10 mg/kg for males for intravenous and subcutaneous routes, respectively. The main findings were dose dependent clinical signs consistent with the pharmacology of dexmedetomidine including sedation, piloerection, exophthalmos, tachypnoea, clonic convulsion, salivation, muscle twitching, decreased body temperature and tremors. The cause of death in rats (doses of >5 mg/kg) and dogs (doses of 2 mg/kg) were related to congestive heart failure, hyperpyrexia or gastrointestinal atony.

2.3.4.2. *Repeat dose toxicity*

Repeated-dose toxicity studies of up to 4 weeks were performed in rats and dogs by i.v., s.c. and i.m. , i.t. routes of administration. Dose ranges tested in these studies were 20-500 µg/kg/day (rats, s.c. and i.m.), 10-1250 µg/kg/day (rat, i.v.) and 10-250 µg/kg/day (dogs, i.m. and i.v.), 2-80 µg/kg/day (dogs, i.t.). Dose-related sedation and piloerection were seen at all doses in both species. Rats also presented exophthalmos, while dogs showed signs of sporadic muscle twitches and irregular respiration rate. Atrioventricular block were also observed in dogs and considered to be related to the pharmacological profile of dexmedetomidine. The corneal keratitis/opacity observed in both species were considered to be due to a reduction in the tear film and the blink reflex during sedation.

In lungs of rats, the presence of hemosiderin-laden macrophages was observed after chronic administration using different routes and were reversible over time. After iv bolus administration, changes in the levels of alkaline phosphatase and other hepatic enzymes, were noted in both species and liver weight and hepatocytes changes (i.e eosinophilic intracytoplasmic inclusions) were also observed in rats and dogs, respectively. These laboratory and histological changes were not observed using iv 6 hour infusion.

In addition, a juvenile animal study was performed in dogs using a 6 hour infusion/day. No deaths occurred and no changes in body weight or food consumption were observed. A sedative effect was

noted at all dose levels and the depth of sedation increased with dose. Induction and reversal of sedation occurred rapidly following the onset and termination of dexmedetomidine infusion, respectively. Decreased body temperature was noted during infusion at all doses, Decreased heart rate was observed during infusion for all dose groups, which was accompanied by a prolonged QT interval; both effects resolved within 1-2 hours after the completion of daily dosing.

2.3.4.3. *Genotoxicity*

The mutagenicity and clastogenicity of dexmedetomidine was evaluated using the standard battery of in vitro and in vivo tests: Ames test, DNA repair test, gene mutation assay in mouse lymphoma cells, mouse micronucleus test. All of these studies had negative results.

2.3.4.4. *Carcinogenicity*

No carcinogenicity studies were performed.

2.3.4.5. *Reproduction Toxicity*

The effect of dexmedetomidine on fertility and early embryonic development was assessed in male and female rats and in female rabbits using s.c or i.v administration. Dexmedetomidine had no effect on male or female fertility at all tested doses up to 54 µg/kg/s.c. Maternal and foetal toxicity (including embryo-foetal deaths) were observed in most studies with the exception of the teratogenicity study performed in rabbits. In rats, 200 µg/kg/day/s.c caused an increase in embryofetal death and reduced the fetal body weight. This was associated with clear maternal toxicity. Reduced fetal body weight also was noted in rats at dose 18 µg/kg/day/s.c and was accompanied with delayed ossification at dose 54 µg/kg/day/s.c.

2.3.4.6. *Toxicokinetic data*

Toxicokinetic data on dexmedetomidine and metabolites were collected from pharmacokinetic or toxicology studies previously described. In rats and dogs, kinetics were non-linear, with C_{max} and AUC increasing with dose in a supra proportional manner. No evidence of accumulation was observed upon repeated-dosing.

2.3.4.7. *Local Tolerance*

Dexmedetomidine has shown some haemolytic potential and local arterial/intramuscular irritancy. Perivascular fibrosis was also noted at the injections sites in previous described toxicology studies performed in rats and dogs.

2.3.4.8. *Other toxicity studies*

Dexmedetomidine did not absord light at ≥ 290 nm. No specific photoxicity study has been performed. It did not cause any sign of anaphylaxis and/or hypersensitivity in guinea pigs. Other findings related to dependence have been previously described in the safety pharmacology studies.

The toxicity profiles of a number of metabolites were studied and did not show any relevant findings. Although levometedomidine was found pharmacologically inactive, similar toxicity profile has been observed as compared to dexmedetomidine.

2.3.5. Ecotoxicity/environmental risk assessment

The results are summarised in Table 1.

Table 1 Summary of main study results

Substance (INN/Invented Name): dexmedetomidine/dexmedetomidine hydrochloride			
CAS-number : CAS-145108-58-3 (hydrochloride salt)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		2.89	Potential PBT : No
Phase I Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ refined (e.g. prevalence, literature)	0.00012738	µg/L	> 0.01 threshold : No

Dexmedetomidine PEC surfacewater value is below the action limit of 0.01 µg/L. and is not a PBT substance as log Kow does not exceed 4.5.Therefore dexmedetomidine is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The pharmacological studies adequately characterised the properties and principal effects of dexmedetomidine as well as potential harmful effects on vital organ systems. Receptor binding and functional studies in several in vitro and in vivo models demonstrated that dexmedetomidine acts as a potent and selective α2 adrenoceptor agonist. Sedative, analgesic and hypnotic effects were demonstrated in animals. Sedation and hypnotic effects were dose-dependent and enhanced by benzodiazepines and opioids. Anxiolytic effect appeared at sub sedative doses. Tolerance to the sedative and hypnotic effects was evidenced. The cardiovascular effects depend on the dose; with lower infusion rates the central effects dominate leading to decrease in heart rate and blood pressure. With higher doses, peripheral vasoconstriction prevailed leading to an increase in systemic vascular resistance and blood pressure, while bradycardia is further emphasised.

The safety pharmacology identified mainly drug dependence and cardiac effects as possible targets for dexmedetomidine regarding potential adverse effects in man. Warnings related to abuse potential and withdrawal reactions and effect on seizures have been added in the SmPC to address the issue on drug dependence. Cardiovascular risk is also further discussed under the clinical safety 2.6. Respiratory depressive effects were observed in a number of studied species. The significant findings related to glucose metabolism were considered clinically manageable and not observed in clinical setting.

The results of pharmacokinetic studies in animals showed: rapid absorption; extensive tissue distribution (crossed the blood brain and placenta barriers), high protein binding and rapid elimination. Dexmedetomidine drug related material is excreted both in urine and faeces and notably in milk. However, while the patterns of plasma and urinary metabolites were very similar in rats and dogs, it substantially differs from the human pattern. On this basis, extrapolation from animal data to man was considered limited.

However, further investigation on the potential for drug interactions with drug products that either inhibit or induce the levels of CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19 and on whether dexmedetomidine is a substrate or an inhibitor of the P-glycoprotein transport pathway was required. This is discussed under the clinical pharmacokinetics 2.4.2.

The majority of the findings in the repeated dose toxicity studies were related to the pharmacological activity of dexmedetomidine. Liver and cornea were identified as additional target organs in animals. In

these studies, the plasma concentrations observed at the No-Observe Adverse Effect Levels (NOAELs) in rats and dogs were higher (1.9 to 7.8 fold) than the proposed clinical plasma concentration of 2.5 ng/ml. Considering the intended clinical use, these safety margins were considered at an acceptable level.
In addition, a juvenile animal toxicity study was performed in dogs using a 6 hour infusion/day and show similar findings than those observed in adults.

There was no evidence of genotoxicity in a standard package of tests.

No carcinogenicity studies were performed and this can be considered acceptable in view of the proposed and anticipated maximum duration of treatment (14 days).

Dexmedetomidine had no effect on male or female fertility and no teratogenic effects were observed in animals. However, maternal and foetal toxicity (including embryo-foetal deaths) were noted. As a result, dexmedetomidine should not be used during pregnancy unless clearly necessary. The potential effect of dexmedetomidine on foetal heart rate was discussed. There is currently no evidence to suggest such effect with dexmedetomidine.

Appropriate recommendations concerning pregnancy, lactation and breastfeeding are included in the SmPC.

An ERA according to CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, June 2006) was submitted. The physiochemical properties of dexmedetomidine are: Molecular mass: 236.7 and freely soluble in water. Based its intended ICU use and maximum treatment duration of 14 days, the predicted environmental concentration in surface water was 0.00012738 µg/L (< 0.01 µg/L). No Phase II studies were performed. However, basis for the refined of Fpen and Log D determination were questioned by the CHMP prior to any conclusion on the persistent, bioaccumulative and toxic (PBT) properties of dexmedetomidine and its risk for the environment. Following clarifications provided by the applicant, the CHMP considered that a risk for the environment due to the intended use of dexmedetomidine in ICU patients is not expected.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of dexmedetomidine have been adequately documented and meet the requirements to support this application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Pharmacokinetic (PK) data were derived from phase I clinical pharmacology studies, that included 333 healthy subjects, 20 with hepatic impairment, 6 with renal impairment and 60 paediatric subjects. In addition, studies have been performed in order to investigate the potential for drug-drug interaction and included healthy subjects (midazolam: n=19; alfentanil:n=9; propofol:n=9; rocuronium: n=10;

isoflurane:n=9, esmolol:n=11/12). The pharmacokinetic/pharmacodynamic profile of dexmedetomidine was also investigated in some specific studies.

Concentrations of dexmedetomidine and its analysed metabolites were measured in plasma and urine using both GC/MS and HPLC-MS/MS methods in the PK studies. Dexmedetomidine and metabolites were also measured in faeces by radiolabel detection. Pharmacokinetic parameters were determined using non compartmental models. In addition, population PK analyses using nonlinear mixed effects modeling methodology (NONMEM) were also performed including data from patients at the highest infusion rate (1.4 µg/kg/h) and also following infusion rate duration exceeding 24 hours.

2.4.2.1. *Absorption*

No bioavailability, bioequivalence and food interaction studies were performed. This was considered acceptable by the CHMP considering the proposed formulation is a clear, colourless solution containing dexmedetomidine, sodium chloride and water for injection and is intended for intravenous infusion.

2.4.2.2. *Distribution*

Dexmedetomidine exhibits a rapid distribution phase with a central estimate of the distribution half-life of about 6 minutes. The mean estimate of the Vss is approximately 1.16 to to 2.16 l/kg (90 to 151 litres). Dexmedetomidine is highly bound (94%) to human plasma proteins including α1- acid glycoprotein and albumin, the latter being the major binding protein. No apparent concentration dependency or sex related differences were observed in the range of 0.85-85 ng/ml. Up to 1 % decrease in the protein binding for dexmedetomidine was noted with lidocaine, for the other substances (fentanyl, ketorolac, theophylline and digoxin), the decrease in protein binding was between 0.13-0.30 %. Displacement of other medicinal products (phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin) by dexmedetomidine was not observed. In a concentration range of 1-100 ng/ml, the total plasma protein bound fraction was 83 % the metabolite H-3. The free fraction of H-3 in plasma is observed to be three times higher than for dexmedetomidine.

2.4.2.3. *Elimination*

Dexmedetomidine is primarily eliminated by metabolism. Direct glucuronidation (main pathway), N-methylation and oxidation occurred. In a mass balance study, the majority of the radioactive dose was mainly recovered in urine (about 94%) with a dose identified for approximately 66%. Approximately 6 % of the radioactivity was not identified in plasma. Unchanged parent drug was not observed in urine and only trace amounts were noted in faeces. The radioactivity declined over a period of 9 days, traces were still present up to 24 days. The majority of the total radioactivity in plasma constituted of dexmedetomidine (14.7 %), G-Dex-1 (35 %), G-Dex-2 (6%), H-1 (21 %) and H-3 (10 %). In urine, the majority of the dose was excreted as G-Dex-1 and G-Dex-2 (20 % and 14 % respectively) and H-1 (15 %). Some secondary metabolites formed from another oxidative metabolite 3-OH were also observed in urine (G-OH and COOH), with 8 and 5 % respectively. Dexmedetomidine was not detected in urine and only trace amounts in faeces were observed. A large part of the dose in urine, 28 %, was not identified. In faeces, only trace amounts of the known metabolites were detected and with approximately 2 % of the dose unidentified.

After intravenous infusion, the mean estimate of the elimination t1/2 is approximately 1.9 to 2.5 hours (min 1.35 h and max 3.68 h) and total plasma clearance, the PK parameter interrelating i.v. infusion rate with steady-state plasma concentration, has mean estimated values of 0.46 to 0.73 l/h/kg (35.7 to 51.1 l/h). In healthy volunteers, the clearance values observed suggested that dexmedetomidine was a medium to high extraction ratio substance.

2.4.2.4. *Dose proportionality and time dependencies*

Although clearance appeared to be higher at 2.5 µg/kg/h, dose proportionality has been shown for dexmetomidine up to this dose covering thus the therapeutic dose range of interest, i;e 0.2-1.4 µg/kg/h. No convincing time dependency has been observed in dexmetomidine PK while high inter-individual variability has been noted: 57% to 63% for clearance and 60-68% for volume of distribution. This is suggested to be mainly due to the differences in the severity of the disease in ICU patients and is considered manageable given dexmetomidine is dosed to its effects and administered under close surveillance.

2.4.2.5. *Special populations*

Specific phases I studies evaluating renal and hepatic functions, paediatric population, effects of race and age were conducted. Other data related to age, gender and weight were derived from population PK analyses.

A specific study was conducted in subjects with stable severe renal impairment (creatinine clearance <30 ml/min) after a single 10-minute i.v. infusion of dexmedetomidine 0.6 µg/kg. The pharmacokinetics of dexmedetomidine in these subjects was not altered relative to healthy subjects (creatinine clearance >80 ml/min).

A specific study was conducted in subjects with mild, moderate and severe hepatic impairment based on Child-Pugh classification (sum Child Pugh scores of 5-6, 7-9 and 10-15) after a single 10-minute i.v. infusion of dexmedetomidine 0.6 µg/kg. Dexmedetomidine plasma protein binding is decreased in subjects with hepatic impairment compared with healthy subjects. The mean percentage of unbound dexmedetomidine in plasma ranged from 8.5% in healthy subjects to 17.9% in subjects with severe hepatic impairment. Subjects with varying degrees of hepatic impairment had decreased hepatic clearance of dexmedetomidine and prolonged plasma elimination $t_{1/2}$. The mean plasma clearance values of unbound dexmedetomidine for subjects with mild, moderate, and severe hepatic impairment were 59%, 51% and 32% of those observed in the normal healthy subjects, respectively. The mean $t_{1/2}$ for the subjects with mild, moderate or severe hepatic impairment was prolonged to 3.9, 5.4, and 7.4 hours, respectively.

Single and multiple dose studies were conducted in children and adolescent including 24 pediatric subjects (age 2.3-11.5 years of age) and 36 paediatric subjects (12 patients in the age range of 2 to <6 months, 17 patients in the age range 6 to <12 months and 7 patients in the range of 12 to 20 months), respectively. Dexmedetomidine half life appears similar to that seen in adults. In the age groups 2-20 months and 2-6 years, body weight-adjusted plasma clearance appeared higher (1.2 and 1.0 l/h/kg, respectively) but decreased in older children (0.8 l/h/kg) to be comparable to adults (0.5-0.6 l/h/kg).

A specific study was conducted to evaluate the effect of age after a single 10-minute i.v. infusion of dexmedetomidine 0.6 µg/kg and included 20 subjects >65 years. Nine subjects out of 20 were 74 years or older (up to 83 years). The Visual Analogue Scale (VAS) scores for sedation indicated a higher sensitivity in young subjects, and also females had a tendency to report higher level of sedation than males during the infusion and immediately after. Age did not appear to influence on the pharmacokinetics of dexmedetomidine.

Population pharmacokinetic analyses did not reveal any significant effect of age. In these analyses, there was a tendency to increased sedation in female subjects. Although variability was large, a relationship between weight and both clearance and volume of distribution of dexmetomidine was also noted.

Specific studies were conducted in Caucasian, South Korean and Japanese subjects to evaluate the effect of race. There were no significant differences observed between these populations after multiple dosing. The population PK analyses provided no further information with respect to race, since the major proportion of subjects in these analyses were Caucasians.

2.4.2.6. *Pharmacokinetic interaction studies*

In vitro studies suggested that the oxidative metabolism of dexmetomidine is mediated by several enzymes (CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19) with no apparent predominant pathways. Dexmetomidine has shown strongest properties for inhibition of CYP2D6, CYP3A4 and CYP2B6. Thus, interaction potential in vivo may exist between dexmedetomidine and substrates with dominant CYP2B6 metabolism. Inducing properties were also shown for dexmetomidine on CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4. Induction in vivo cannot be excluded although the clinical significance is unknown. Studied metabolites (H-1 analogue and H-3) appeared to inhibit CYP2B6 and CYP2C19 to a level suggesting a limited interaction potential in vivo. In addition, In vitro studies indicated that dexmetomidine was not regulated via the p-glycoprotein pathway.

The potential interactions were studied in humans for the following drugs: isoflurane, propofol, alfentanil, midazolam. Although no pharmacokinetic interactions were observed with these drugs, co-administration led to an enhancement of the pharmacodynamic effects.

Furthermore, a slight increase in the concentrations of rocuronium after administration of dexmedetomidine was initiated, likely due to steady state concentration of rocuronium that was not reached (t ½ between 66-80 minutes). The infusion rate was higher than the anticipated elimination rate, and a higher than targeted dexmedetomidine concentration was therefore observed.

Co-administration with esmolol suggested modest enhancement of hypotensive and bradycardic effects.

2.4.2.7. *Pharmacokinetics using human biomaterials*

See above.

2.4.3. Pharmacodynamics

2.4.3.1. *Mechanism of action*

Dexmedetomidine is a selective alpha-2 receptor agonist with a broad range of pharmacological properties. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. Unlike other sedative agents used in standard of care and acting as GABA receptor antagonists (e.g midazolam, propofol), its effects are claimed to be mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem conferring a mechanism of arousal and different form of sedation.

2.4.3.2. *Primary and Secondary pharmacology*

Pharmacodynamic effects of dexmedetomidine were studied on haemodynamic variables, respiratory system, gastrointestinal tract and endocrine systems. Sedative and analgesic effects were also investigated. Mechanistical studies covering the effects of dexmedetomidine on the function of the sympathetic nervous system were done to characterise pharmacological mechanisms underlying the observed pharmacodynamic effects of dexmedetomidine. Some of these studies were previously discussed in relation to the pharmacokinetic profile of dexmedetomidine.

Sedative Effects

Following a two-stage dexmedetomidine infusion continued for up to 24 h, after an initial loading dose, dexmedetomidine-treated subjects consistently exhibited greater average sedation than placebo-treated subjects. In one study, VAS sedation scores revealed no statistically significant difference between 0.6 ng/mL and 1.25 ng/mL dexmedetomidine groups. The percentage of time at Ramsay sedation scale (RSS) scores of 3, 4, or 5 revealed a dose-response among dexmedetomidine-treated subjects, with 0.6 ng/mL and 1.25 ng/mL groups exhibiting a longer duration of sedation than the 0.3 ng/mL group during the 12- and 24-hour infusions. Results on Critical Flicker Fusion Treshold (CFFT) suggested an arousal effect easily achieved with dexmetomidine as no differences were observed as compared to placebo. Overall, the rate of development of sedation (measured by the median time to a RSS score of 4 or higher within the first hour) was rapid during dexmedetomidine administration when the infusion was initiated with a rapid loading dose, ranging from a median of 15 minutes (0.6 ng/ml group) to 33 minutes (0.3 ng/ml group) after the start of the infusion. Sedation in the 1.25 ng/ml group developed at a slower rate than in 0.6 ng/ml group possibly due to the loading dose infused at a slower rate. The rate of onset of sedation in the absence of a loading dose has not been studied. The mean RSS score of 3 or higher was constantly rated starting from a dexmedetomidine plasma concentration range of 0.2 to 0.3 ng/ml. It also appears that a plateau in the level of sedation was achieved between 0.7 ng/ml and 1.25ng/ml target concentration for dexmedetomidine groups, corresponding to maintenance infusion rates between 0.337-0.7µg/kg/hr, and sedation did not increase further at higher dexmedetomidine concentration ranges. In another study including Japanese subjects, mean VAS sedation scores were statistically significantly greater than placebo at all targeted concentrations (ranging from 0.3-1.25 ng/ml) except 0.1 ng/ml. Only the 1.25 ng/ml concentration differed significantly from placebo, suggesting that treated subjects were easily arousable and able to complete the test. The four highest dose groups spent most of the treatment period with RSS score of 3, 4 or 5. No statistically significant differences were seen between active or placebo groups with regard to RSS scores of 6 (i.e. asleep) suggesting that patients although sedated, were not rendered unconscious with the active treatment.

Haemodynamic, cardiovascular effects

Several cases of bradycardia and sinus pauses have been reported after dexmedetomidine administration in healthy volunteers. The reported sinus pauses have lasted up to 30 seconds. Some of the reported sinus pauses have been associated with unconsciousness, convulsions, collapse and bradycardia, but all reported sinus pauses have resolved without sequelae.

A biphasic change on blood pressure has been observed with dexmedetomidine, with decreases at the low concentrations, followed by a return to baseline, and increases over the mean baseline level when the plasma concentration of dexmedetomidine was > 3.2 ng/ml. Heart Rate (HR) decreased until the actual mean plasma concentration of dexmedetomidine ranged from 3.2 to 5.1 ng/ml, after which HR reached a plateau.

Dexmedetomidine administration caused dose-related decreases in cardiac output (CO) of approximately 20% to 30% at dexmedetomidine plasma concentrations of 2 to 4 ng/ml, but at higher concentrations no further decrease in CO was observed. Decreases in CO have been associated with reduced hepatic elimination clearance of dexmedetomidine and decreased cerebral blood flow velocity. The safety of dexmedetomidine has not studied in patients requiring maintenance of normal cerebral blood flow.

Respiratory effects

Dexmedetomidine has caused a modest reduction in respiratory rate (RR) and/or ventilation in several clinical pharmacology studies, and in some cases supplementary oxygen has been administered to maintain blood oxygen saturation levels. There are also several reports of apnoea and abnormal breathing pattern associated with dexmedetomidine administrations, but no ventilatory support has been needed. However, results on respiratory effects are not consistent throughout all clinical pharmacology studies, e.g. low saturation of peripheral oxygen (SpO2) values observed after dexmedetomidine in some studies have been attributed to upper airway obstruction during sedation rather than to direct effects on respiratory system. Dexmedetomidine has potentiated the respiration depressant effect of alfentanil, when the drugs were given concomitantly,. Dexmedetomidine did not cause significant respiratory depression when compared to remifentanil in healthy volunteers, despite clearly deeper sedation (*Hsu Y et al., 2004*).

Analgesic effects

In human pharmacology, a decrease of pain perception has been generally observed with an increase of dexmedetomidine concentration ranging from 0.7-8.4 ng/ml.

In an interaction study with alfentanil, dexmedetomidine was analgesic at the target plasma concentrations of 0.3 and 0.6 ng/ml, which effect was additive with the analgesic action of alfentanil. In addition, dexmedetomidine has not shown to be as effective analgesic as some opioids (e.g fentanyl, remifentanil) reaching a maximal analgesic effect after an injected dose of 0.50 µg/kg. However, some literature data suggest that no analgesic effect is observed with dexmedetomidine as compared with placebo (*Angst MS et al., 2004*), others indicate that dexmedetomidine reduced consumption of other analgesic drugs postoperatively (*Cicek M et al., 2006*, *Gunes Y et al., 2008*).

Effect on Noradrenaline (NA)

In a study using dexmetomidine as a 0.375 µg/kg bolus over 1 minute, followed immediately by a 0.375 µg/kg/h infusion, the concentration of NA in plasma decreased to about 0.1-0.2 nmol/l in all 4 healthy subjects from a baseline concentration of 1.62±0.45 nmol/l. Maximal effects were noted about 2 hours after the beginning of the infusion. After termination of the infusion, NA levels gradually increased, although they were still below baseline 2 hours after termination of the infusion.

In another study using three different doses of dexmetomidine (0.10, 0.30 and 0.60 µg/kg), a dose-dependent decrease in NA concentrations was observed. After the highest dexmedetomidine dose (0.6 ug/kg), average peak drug concentrations were 1.068 ng/mL, which were associated with a decline in the NA concentrations from a baseline value of 0.11 ng/mL to 0.04 ng/mL at 0.25 hours postdosing. Effects at the 0.1 ug/kg dose level were minimal. NA levels returned to baseline values or higher 8 hours after dosing.

Endocrine and metabolic effects

After single dosing of dexmetomidine in 5 healthy males, significant and transient dose dependent increase in plasma human growth hormone (hGH) concentrations was seen but no significant alterations in cortisol plasma concentrations were noted after rapid dexmedetomidine injections (12.5-75 µg) when compared with placebo. No significant dexmedetomidine induced effects could be observed in plasma renine activity.

After rapid dexmedetomidine i.v. dosing (0.25-2.0 µg/kg), a significant and dose related increase (up to 26% increase from baseline) in arterial glucose concentrations has been measured after 10 minutes.

In the same study, dose dependent and persistent decreases in body temperature up to 0.74°C that were significant when compared with placebo (0.02°C) were noted.

Relationship between the infusion rate and the target plasma concentration/sedative effect

Further analyses from PK/PD studies were presented supporting a dose relationship for dexmedetomidine. Results are summarised in Table 2, Figures 2,3 and 4.

Study DEX95-007

Table 2

Table 4. Sedation scores and plasma concentration by infusion step, Study Dex-95-007

Step	Completing step (n)	Measured plasma concentration (ng/ml)	OAA/S composite /lowest of 4 assessments (median)[1]	VAS (mean)[2] mmHg
1	10	0.7	5	40.8
2	10	1.2	4	66.0
3	10	1.9	3	71.89
4	8	3.2	2	79.33
5	7	5.1	2	78.75
6	4	8.4	1	100
7	2	14.7	1	Not scored

[1] A low score indicates deeper sedation
[2] A high score indicates deeper sedation

Subjects were increasingly sedated by incremental rises in plasma dexmedetomidine concentration.

Figure 2

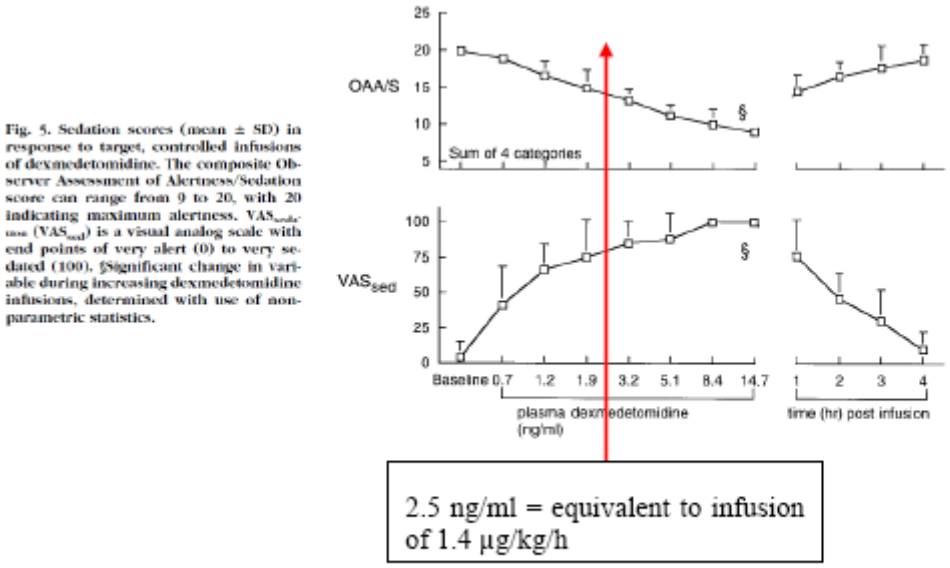


Fig. 5. Sedation scores (mean ± SD) in response to target, controlled infusions of dexmedetomidine. The composite Observer Assessment of Alertness/Sedation score can range from 9 to 20, with 20 indicating maximum alertness. $VAS_{sedation}$ (VAS_{sed}) is a visual analog scale with end points of very alert (0) to very sedated (100). §Significant change in variable during increasing dexmedetomidine infusions, determined with use of nonparametric statistics.

Figure 3. Sedation scores in response to plasma concentration of dexmedetomidine (from Ebert T et al., 2000)

A dose-response curve for VAS Sedation and for OAA/S is observed.

Figure 3

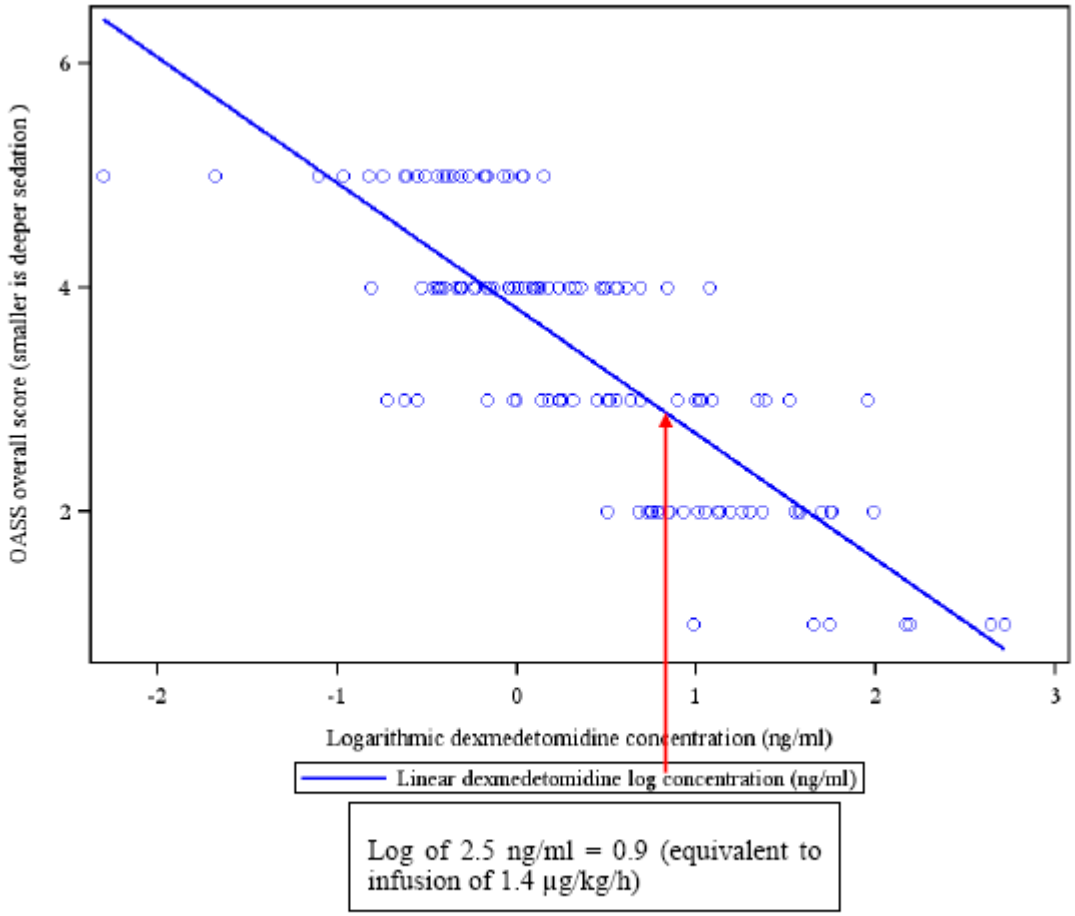
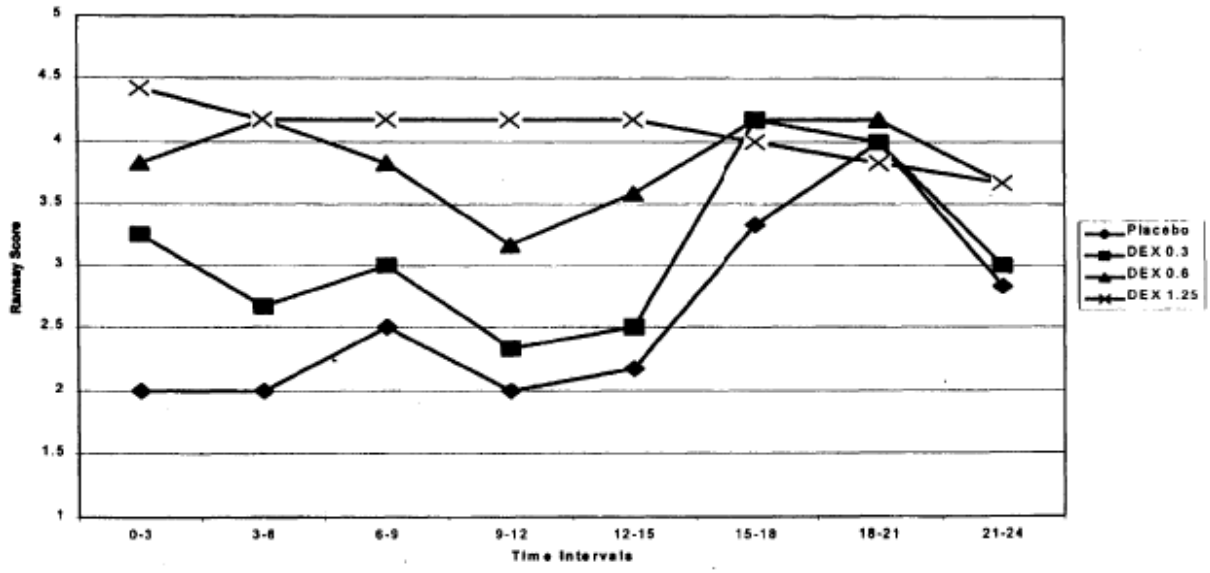


Figure 4. Correlation between OASS (sedation) and logarithmic dexmedetomidine concentration during treatment period, Dex-95-007

A dose-response over the range tested (note that Log10 of 2.5 ng is 0.4), which equates to an infusion of 1.4 µg/kg/h in the target population is also noted.

Study DEX95-028

Figure 4



An analysis of the median Ramsay scores at each time interval by target plasma concentration group revealed initial dose dependency with convergence due to diurnal placebo effects towards the end of the infusion, after 15 hours. There is a dose-response over the first 15 hours which does not indicate that a sedation plateau has been reached over this concentration range.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic profile (absorption, distribution, metabolism and elimination) of dexmedetomidine has been studied following short term IV administration in healthy volunteers and long term infusion in ICU population.

The pharmacokinetic profile dexmedetomidine in stable severe renal impaired subjects was not altered relative to healthy subjects (creatinine clearance >80 ml/min) and therefore no dose adjustment is required in case of renal impairment.

Changes in the pharmacokinetic profile of dexmedetomidine in patients with various degrees of hepatic impairment (Child-Pugh Class A, B, or C) were observed as compared to healthy subjects. Dexmedetomidine plasma protein binding is decreased in subjects with hepatic impairment.The mean percentage of unbound dexmedetomidine in plasma ranged from 8.5% in healthy subjects to 17.9% in subjects with severe hepatic impairment. Subjects had also decreased hepatic clearance of dexmedetomidine and prolonged plasma elimination $t_{1/2}$. On this basis, section 4.2 of the SmPC recommends that dexmedetomidine should be used with caution in patients with hepatic impairment and that a dose reduction may be considered in this population. At the CHMP request, a warning in section 4.4 of the SmPC was also added on severe hepatic impairment and possible excessive dosing that may lead to over sedation and increase risk of adverse reactions.

There are limited data in children and adolescents from 2 month to 17 years of age. Dexmedetomidine half life appears similar to that seen in adults. In the age groups 2-20 months and 2-6 years, body weight-adjusted plasma clearance appeared higher (1.2 and 1.0 l/h/kg, respectively) but decreased in older children (0.8 l/h/kg) to be comparable to adults (0.5-0.6 l/h/kg). At the CHMP request, this information has been reflected in the SmPC and a statement was also included to reflect that plasma clearance may be lower in children < 2 months due to immaturity. However, the safety and efficacy of dexmedetomidine in children and adolescents has not been established (see clinical safety 2.6.9).

Effect of age was specifically investigated and 20 subjects >65 years were studied. Nine subjects out of 20 were 74 years or older (up to 83 years). Age did not appear to influence on the pharmacokinetic profile of dexmedetomidine and therefore no dose adjustment is required in elderly population.

There were no significant PK differences between Caucasian South Korean and Japanese subjects. Additional population PK analyses did not provide further information as the majority of the subjects were Caucasians.

Population pharmacokinetic analyses did not reveal any significant effect of age. In these analyses, there was a tendency to increased sedation in female subjects. Although variability was large, a relationship between weight and both clearance and volume of distribution of dexmetomidine was also noted.
Interaction studies have only been performed in adults. Co-administration of dexmedetomidine with anaesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects. Specific studies have confirmed these effects with isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam have been observed. A modest enhancement of hypotensive and bradycardic effect was observed with esmolol. In vitro study suggests that interaction potential in vivo exists between dexmedetomidine and substrates with dominant CYP2B6 metabolism while induction in vivo cannot be excluded on CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4. This information has been considered relevant and reflected in the SmPC.

No relevant changes in the pharmacokinetic profile of rocuronium were noted when co-administered with dexmedetomidine.

Specific pharmacodynamic studies and literature data confirmed the effects of dexmedetomidine as typical of an alpha-2 adrenoceptor agonist in humans. The moderate sedative effects accompanied by analgesic properties are of benefits for its intended clinical use in the post surgical, intensive care setting. Dexmedetomidine can be considered relatively free from respiratory depressive effects in humans. Nevertheless, a plateau effect was observed between 0.7 ng/ml and 1.25ng/ml target concentration for dexmedetomidine, corresponding to maintenance infusion rates between 0.337-0.7µg/kg/hr, and sedation did not increase further at higher dexmedetomidine concentration ranges. On this basis, further analyses on the relationship between the infusion rate and the target plasma concentration/effect were provided to support the proposed dose range of 0.2-1.4 µg/kg/hr and were considered satisfactory (see Table 2, Figures 2,3 and 4).

In line with pre clinical findings, effects on haemodynamic, cardiovascular systems were observed. Following administration of dexmedetomidine, a dose dependent reduction in plasma noradrenaline level was also shown accompanied by significant reductions in cardiac output and mean arterial pressure. A number of warnings had been initially included in the SmPC regarding these effects. However, considering the clinical intended use in ICU setting, the CHMP was concerned about the haemodynamic changes observed with dexmedetomidine and the high risk population (e.g with cardiovascular conditions or requiring stable cerebral blood flow). Contraindications in patients with advanced heart block (grade 2 or 3) unless paced, uncontrolled hypotension and acute cerebrovascular conditions were subsequently added and reinforcement of the warnings were made. These changes were considered sufficient to ensure safe use of the product in the intended ICU setting.

On the basis of available literature data, the CHMP questioned the observed lack of effect on cortisol suppression in humans and required further discussion on this finding. This is reported under the clinical safety 2.6.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacological profile of dexmedetomidine in human studies has been adequately documented and meet the requirements to support this application.

2.5. Clinical efficacy

The following indication is initially applied for: Dexdor is indicated for patients requiring light to moderate sedation in intensive care during or after intubation. Dexdor is indicated in adults aged over 18 years.

The clinical development program to support the claimed indication consisted of early studies comparing dexmedetomidine with placebo (**W97-249, W98-274, J-DEX-99-001, W97-245 and W97-246**) and more recent studies comparing dexmedetomidine to either midazolam or propofol (**3005011, 3005012**) following the CHMP advice in October 2000. Midazolam and propofol account for 95% of sedative treatments in the ICU.

In addition, 3 open label studies (**1999-016, W99-314 and W99-302)** and a phase IV study (**2001-001)** were presented in the dossier (**1999-016, W99-314 and W99-302**) and their results are briefly summarised below.

2.5.1. Dose response study

There are no ICU studies that specifically evaluated the relationship between dose/concentration and sedative effect. In all studies, dexmedetomidine has been titrated to effect, i.e patients were not randomised to different dexmedetomidine doses or the effect of different doses were not systematically investigated for the same patient. This was considered acceptable by CHMP.

2.5.2. Main studies

2.5.2.1. *Placebo controlled studies*

The placebo controlled studies were designed as follows:

- **W97-249**: a Phase II, single centre, two part study (part I: open-label, part II randomised, placebo controlled, double-blind) with the primary objective of evaluating the safety, efficacy and titratability of dexmedetomidine versus placebo, with midazolam in post-operative coronary artery bypass grafting (CABG) patients requiring ventilation, sedation and intensive care. The study was conducted in the Netherlands.
- **W98-274**: a Phase II, multicentre, randomised, placebo controlled, double-blind study with the primary objective of evaluating the safety and efficacy of dexmedetomidine versus placebo, with midazolam, in post-operative patients requiring ventilation, sedation and intensive care following surgery. The study was conducted in Germany.
- **J-DEX-99-001**: a Phase III, multicentre, two part study (part I: open-label, part II randomised, placebo controlled, double-blind) with the primary objective of evaluating the safety, efficacy and titratability of dexmedetomidine versus placebo in post-operative ICU patients requiring intubation ventilation after cardiac and upper abdominal surgery. The study was conducted in Japan.
- **W97-245**: a Phase III, multicentre, two part study (part I: open-label, part II randomised, placebo controlled, double-blind) with the primary objective of evaluating the safety, efficacy and titratability of dexmedetomidine versus placebo, with midazolam, in ICU patients requiring intubation ventilation

following surgery. The study was conducted in Austria, Belgium, France, Germany, Greece, Italy, the Netherlands, Spain, the United Kingdom and Canada.
- **W97-246**: a Phase III, multicentre, two part study (part I: open-label, part II randomised, placebo controlled, double-blind) with the primary objective of evaluating the safety, efficacy and titratability of dexmedetomidine versus placebo, with propofol, in ICU patients requiring intubation ventilation following surgery. The study was conducted in in Austria, Belgium, France, Germany, Greece, Italy, the Netherlands, Spain, the United Kingdom and Canada.

The maximum duration of infusion was 30 or 72 hours for W97-249 and W98-274, respectively and 24 hours in all phase III studies.

2.5.2.1.1. Methods

Study participants

Main inclusion criteria

Males or females requiring ventilation for a minimum of 6 except for study W97-249 (8 hours), aged over 18 except for study J-DEX-99-001 (over 20 years) and sedation to a Ramsay score of ≥3 except for study W98-274 using a bispectral index (BIS) score of 60-70 (deep sleep) then 70-95 when weaning appeared imminent.

Main exclusion criteria

In study W97-249, these were CNS trauma or intracranial surgery, subjects requiring neuromuscular blocking agents or epidural/spinal anaesthesia or who were grossly obese. In all other placebo controlled studies, exclusion criteria mainly included: serious CNS trauma or intracranial surgery, unstable diabetes, severe hepatic failure, grossly obese, excessive bleeding likely to result in re-surgery and clinically significant arrhythmia or other important cardiac condition or factor.

Treatment

Placebo- controlled studies consisted of an open phase (part I) followed by a randomised double-blind placebo controlled phase (part II) apart from study W97-274. Dexmedetomidine administration was to begin within 1 hour of admission to ICU. In phase II and III studies, subjects were to receive dexmedetomidine 1µg/kg or 6 µg/kg/h loading dose over 10 minutes, respectively followed by an initial maintenance infusion of 0.2 µg/kg/h or 0.4 µg/kg/h. Thereafter, subjects were to be titrated between 0.2 and 0.7 µg/kg/h (in increments of 0.1 µg/kg/h) to maintain sedation: Ramsay score of ≥ 3 during intubation or 2 or higher after extubation; BIS score of 60-70 while intubated, a BIS score of 70-95 during weaning and a BIS score of 85-95 after extubation (W97-274). In part II, midazolam or propofol were used as rescue medication for sedation and morphine as treatment for pain.

Outcomes/endpoints

The primary efficacy variable was the amount of rescue medication used to maintain sedation. Sedation assessments (Ramsay or BIS scores) were made every 10 minutes for 30 minutes for 1 hour then hourly thereafter, prior to and 10 minutes after each rate change or administration of rescue medication and during recovery Pain was assessed by direct communication or by autonomic signs.
The primary efficacy variable was the amount of rescue propofol (J-DEX-99-001, W97-245) or midazolam (W97-246) used maintain the Ramsay score ≥ 3 or BIS score of 60-70 while intubated, a BIS score of 70-95 during weaning and a BIS score of 85-95 after extubation (W97-274).

2.5.2.1.2. Results

In study W97-249, twelve patients were enrolled in Part I; one prematurely discontinued due to circulatory collapse and subsequently died of multi organs failure, thus 11 subjects completed part I. Twelve new subjects enrolled and completed part II. In part I, all subjects remained successfully sedated through intubation and post extubation. The mean hourly RSS score was 3.9 (by AUC) and the mean (±SD) dose of dexmedetomidine was 5.4 (±1.58) µg/kg over mean duration of 13.8 (±1.48) h. One patient received midazolam 0.00057 mg/h as an infusion for additional sedation. In part II , the 6 dexmedetomidine patients required no additional midazolam (0.00 mg/kg/h) whereas 5 of the 6 placebo patients required midazolam (0.18 (±0.005) mg/kg/h); p = 0.010). The mean hourly RSS scores were similar (dexmedetomidine 3.5, placebo 3.4). The total dose of morphine used was higher in the placebo (0.008mg/kg/h) group than in the dexmedetomidine group (0.001 mg/kg/h); p = 0.040. Time to spontaneous breathing was similar.

In study W98-274, 30 subjects entered the randomised trial: 15 on dexmedetomidine and 15 on placebo. Patients were post-operative to cardiac surgery (53%), cancer (> 20% in each group) head and aneurysm requiring prosthesis (13%). Two patients in the placebo group were prematurely withdrawn : one could not be managed with BIS and one took a disallowed medication. There was a significant difference in the primary efficacy variable, amount of rescue propofol used, in favour of dexmedetomidine. During intubation the dexmedetomidine group required 0.87 mg/kg/h of propofol compared to the placebo group which required 1.52 mg/kg/h of propofol (p = 0.0058). During weaning the dexmedetomidine group required 0.17 mg/kg/h of propofol compared to the placebo group which required 0.62 mg/kg/h of propofol (p = 0.0003). Mean BIS scores were comparable during intubation (dexmedetomidine: 63, placebo: 66.6), weaning (dexmedetomidine: 67.8, placebo: 71.7) and extubation (dexmedetomidine: 89.0, placebo: 88.0), where the lower number indicates deeper sedation.During intubation the total dose of morphine required was not significantly lower for dexmedetomidine patients than for placebo patients during drug administration (dexmedetomidine 0.48 mg/h of morphine, placebo 0.76 mg of morphine, p=0.1741).

In study J-DEX-99-001, one hundred and thirteen subjects entered the randomised trial: 57 on dexmedetomidine and 56 on placebo were included. Patients were post-operative to cardiac surgery (> 85%) or abdominal surgery (> 14%). A total of 5 patients in the dexmedetomidine group and 3 patients in the placebo group were prematurely withdrawn. There was a significant difference in the primary efficacy variable; the results showed that 85.5% (47/55) of the patients in the dexmedetomidine treated group, compared with 37.5% (21/56) in the placebo treated group, did not require propofol rescue medication. There was a significant difference in the amount of rescue propofol used, in favour of dexmedetomidine; the dexmedetomidine group required 84.6 mg of propofol compared to the placebo group which required 330.5 mg of propofol during the intubation period (p = 0.0005) to maintain a RSS score ≥ 3. The RSS score was higher for dexmedetomidine than for placebo (dexmedetomidine 3.387, placebo 3.089, p = 0.032). Patients on dexmedetomidine (n=8) reached a RSS score of 1 (anxious, agitated or restless) on less occasions compared to placebo (n= 15); but this result did not achieve significance. The total dose of morphine required was lower for dexmedetomidine patients than for placebo patients during drug administration (dexmedetomidine 0.097 mg/h of morphine, placebo 0.225 mg of morphine, p = 0.012). There was a difference in time to the patient being ready for extubation both from admission to ICU (dexmedetomidine median 427 minutes, placebo median 395 minutes; p = 0.0317) and from start of study treatment (dexmedetomidine median 405 minutes, placebo median 376 minutes; p = 0.0319).

In study W97-245, 353 postoperative (cardiac surgery, laparotomy or head and neck surgery) subjects were randomised to receive dexmedetomidine (n = 178) or placebo (n = 175) in part II.

Dexmedetomidine-treated subjects required significantly less midazolam for sedation (RSS score ≥ 3) compared to placebo-treated subjects during the intubation period (mean dose of midazolam: 4.83 vs. 18.61 mg, p = 0.0011). During the study drug infusion period, dexmedetomidine-treated subjects required less midazolam for sedation (mean dose: 0.29 mg/h vs. 1.19 mg/h, p = 0.0001) and less morphine for pain (mean dose: 0.47 mg/h vs. 0.83 mg/h, p < 0.0001) than subjects in the placebo group.

In study W97-246, 403 postoperative (cardiac surgery, laparotomy or head and neck surgery) subjects were randomised to receive dexmedetomidine (n = 203) or placebo (n = 198) in part II. There was a significant difference in the primary efficacy variable; the results showed that patients in the dexmedetomidine treated group required significantly less propofol for sedation during intubation compared with the placebo treated group (mean dose of propofol 72.59 mg versus 504.69 mg, p<0.0001). Significantly less morphine was required in the dexmedetomidine group (0.43 mg/h vs 0.89 mg/h, p<0.0001).

2.5.2.2. *Active controlled studies*

The active controlled studies were designed as follows:

- **3005011:** A phase III, 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. The study was conducted in Finland and Switzerland.
- **3005012:** A phase III, multi-centre, randomised, double-blind comparison of intravenous dexmedetomidine with propofol for continuous sedation (24 hours to 14 days) of ventilated patients in intensive care unit. The study was conducted in Belgium, Finland, Germany, The Netherlands, Switzerland, Russia and the United Kingdom.
- **3005013:** A phase III, multi-centre, randomised, double-blind comparison of intravenous dexmedetomidine with midazolam for continuous sedation (24 hours to 14 days) of ventilated patients in intensive care unit. The study was conducted in Belgium, Estonia, Finland, France, Germany; The Netherlands, Norway; Switzerland and the United Kingdom.

According to protocol, study 3005011 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 groups). 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. Results of this study are briefly presented in this report.

The designs of 3005011 and 3005012 are presented in Figure 5 and 6. Similar design as study 3005012 has been used for study 3005013, except that propofol was replaced by midazolam.

Figure 5

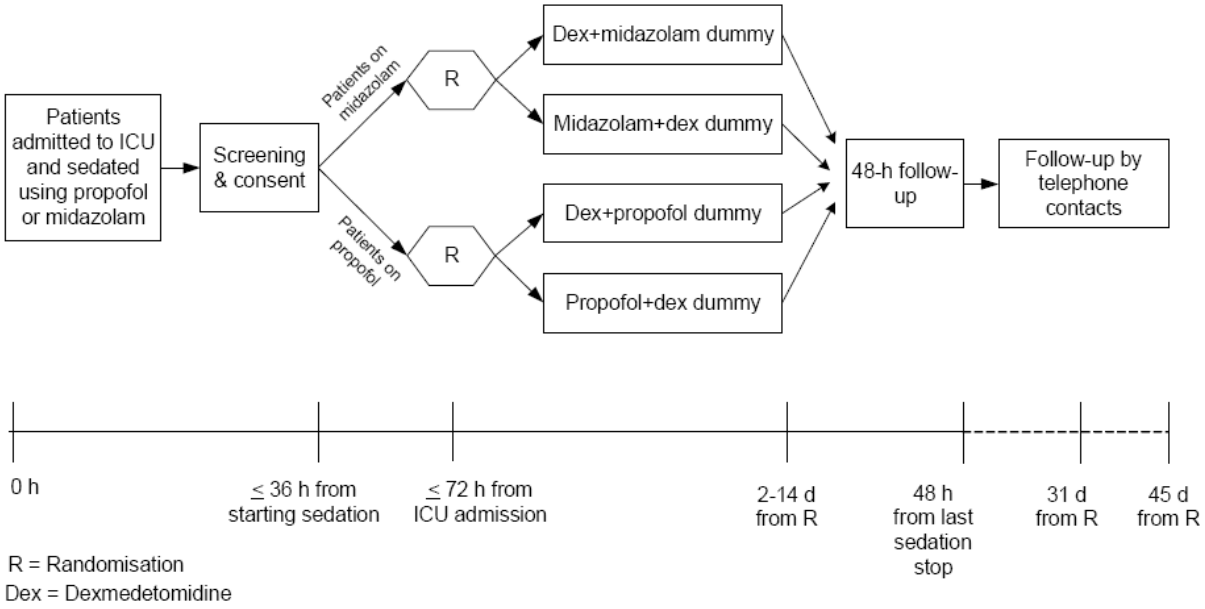
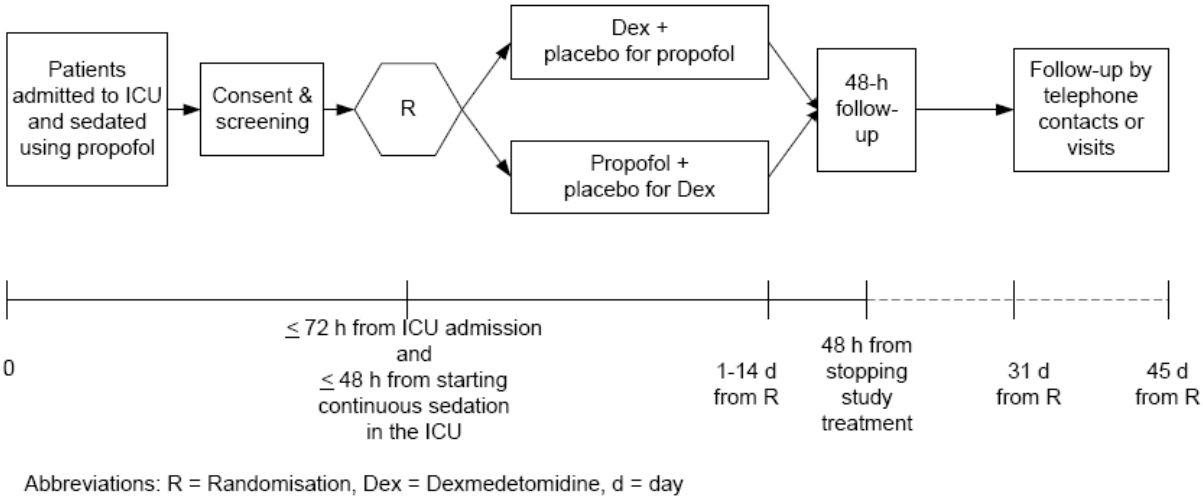


Figure 6



2.5.2.2.1. Methods

Study participants

Main inclusion criteria

These included subjects with age ≥ 18 years, requiring clinical need for sedation and mechanical ventilation, who were expected to stay in ICU for ≥ 48 hours from admission, requiring sedation ≥ 24 hours from time of randomisation, with written informed consent obtained from legal patient's representative.

In studies 3005012 and 3005013, subjects were prescribed light to moderate sedation (target RASS = 0 to -3) and were initially intubated (or tracheotomised) and ventilated (with inspiratory assistance).

Main exclusion criteria

These included subjects with 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 (HR < 50 beats/min); atrioventricular (AV) conduction block II-III (unless pacemaker installed); severe hepatic impairment (bilirubin > 101 µmol/L); requiring muscle relaxation at the time of randomisation (except for intubation and initial stabilization); with a loss of hearing or vision, or any other condition which would significantly interfere with RASS assessment; who have used α2-agonists or antagonists within 24 hours prior to randomisation; with positive pregnancy test or currently lactating; receiving any investigational drug within the preceding 30 days; with concurrent participation in any other interventional study (any study in which patients were allocated to different treatment groups and/or non-routine diagnostic or monitoring procedures were performed) or previous participation in the study.

In studies 3005012 and 3005013, additional exclusion criteria were subjects with burn injuries and other injuries requiring regular anaesthesia or surgery; who had or were expected to have treatment withdrawn or withheld due to poor prognosis; receiving sedation for therapeutic indications rather than to tolerate the ventilator (e.g. epilepsy); unlikely to require continuous sedation during mechanical ventilation (e.g. Guillain-Barré syndrome); 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); with distal paraplegia.

Treatments

Treatment duration was to be at least for 24 hours and was limited to a maximum of 14 days.

Dexmedetomidine was infused without a loading dose at an initial rate of 0.8 µg/kg/h for 1 hour. Previous sedative treatment was stopped simultaneously with the start of randomised sedative treatment. During the first hour of randomised treatment, no dosage adjustments were allowed. If necessary, rescue medication was given. Thereafter, the infusion rate of dexmedetomidine was varied as needed between 0.25 and a maximum of 1.4 µg/kg/h in order to maintain the target RASS score.

Dosage steps for dexmedetomidine were: 0.25, 0.5, 0.8, 1.1, 1.4 µg/kg/h for study 3005011 and 0.2, 0.45, 0.7,0.95, 1.2 and 1.4 µg/kg/h for studies 3005012 and 300513.

After an initial bolus the infusion rate of rescue medication was varied as needed: between 0.8 and 4 mg/kg/h for propofol and between 0.04 mg/kg/h and 0.2 mg/kg/h for midazolam in study 3005011; between 0.3 and 4 mg/kg/h for propofol in study 3005012 and between 0.03 mg/kg/h and 0.2 mg/kg/h for midazolam in study 3005013 Rescue medication was also counted as the use of any of opiates given for sedation and neuromuscular paralysis (this would lead to withdrawal).

In each treatment group, the dose of infusion used was the nearest to the pre-randomisation does of propofol or midazolam, not exceeding the dose level 3 in studies 3005012 and 3005013.

Dose levels for each study are presented in Tables 3 and 4.

Table 3. Dose levels for study 3005011

	Dexmedetomidine	Propofol	Midazolam
Dose level	**Infusion rate**	**Infusion rate**	**Infusion rate**
1	0.25 µg/kg/h	0.8 mg/kg/h	0.04 mg/kg/h
2	0.5 µg/kg/h	1.6 mg/kg/h	0.08 mg/kg/h
3	0.8 µg/kg/h	2.4 mg/kg/h	0.12 mg/kg/h
4	1.1 µg/kg/h	3.2 mg/kg/h	0.16 mg/kg/h
5	1.4 µg/kg/h	4.0 mg/kg/h	0.20 mg/kg/h

Table 4. Dose levels for studies 3005012 and 3005013

	Dexmedetomidine	Propofol	Midazolam
Dose level	**Infusion rate**	**Infusion rate**	**Infusion rate**
1	0.2 µg/kg/h	0.3 mg/kg/h	0.03 mg/kg/h
2	0.45 µg/kg/h	0.8 mg/kg/h	0.06 mg/kg/h
3	0.7 µg/kg/h	1.6 mg/kg/h	0.09 mg/kg/h
4	0.95 µg/kg/h	2.4 mg/kg/h	0.12 mg/kg/h
5	1.2 µg/kg/h	3.2 mg/kg/h	0.16 mg/kg/h
6	1.4 µg/kg/h	4.0 mg/kg/h	0.2 mg/kg/h

Main Objectives

All active controlled studies had hierarchical co-primary objectives.

3005011

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.

3005012 and 3005013

First co-primary objective was to evaluate non-inferiority of dexmedetomidine compared with first line rescue medication (propofol or midazolam) in maintaining a target depth of sedation with daily sedation stops. Second co-primary objective was to evaluate superiority of dexmedetomidine compared with first line rescue medication (propofol or 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.

Outcomes/endpoints

Co-Primary efficacy variables

In study 3005011: 1) maintenance of target depth of sedation in long-stay ICU patients defined as the proportion of time during sedative infusion with a Richmond Agitation Sedation (RASS) score within the individually-prescribed target range without any rescue medication); 2) length of ICU stay in long-stay ICU patients, defined as time from randomisation to 'medically fit for discharge' based on the treating clinician's decision that the study subject was medically fit for discharge

In studies 3005012 and 3005013: 1) maintenance of target depth of sedation in long-stay ICU patients defined as the proportion of time during sedative infusion with a RASS score within the individually-prescribed target range (0 to 3) without first line rescue medication; 2) Duration of mechanical ventilation defined as time (hours) from randomisation to being free from any kind of mechanical ventilation provided that is not re-instituted within 48 hours.

Secondary efficacy variables

In study 3005011 : nurse's assessment of subject communication; duration of mechanical ventilation defined as time from randomisation to being free from any kind of mechanical ventilatory support for 48 hours; weaning time defined as the time from decision to commence weaning to be being free from any ventilatory support; ventilator-free days in ICU defined as number of days during the ICU-stay without any mechanical ventilatory support, length of total hospital stay; actual length of stay (counted from admission and randomisation); time to 'medically fit for discharge' from hospital; functional recovery during hospitalization; need for rescue medication to maintain sedation.

In studies 3005012 and 3005013: nurse's assessment of subject communication, length of ICU stay in long-stay ICU patients, defined as time from randomisation to 'medically fit for discharge' based on the treating clinician's decision that the study subject was medically fit for discharge.

Other efficacy variables

Mainly, addition variables were related to ICU cost e.g based on Treatment Intervention Scoring System (TISS).

Sample size

In study 3005011: for the first co primary endpoint, the non inferiority margin was set to a difference of 10%. Based on assumptions, about 420 patients per group would provide 90% power at one-sided 0.025 significance level. For the second co primary endpoint, the sample size calculation was 450 patients per group, i.e 98% power to detect a difference in length of ICU stay at a two-sided 0.05 significance level. Therefore, 450 subjects per group (450 on dexmetomidine, 450 on midazolam or propofol) were planned for randomisation.

In study 3005012 and 3005013: for the first co primary endpoint, the non inferiority margin was set to a difference of 15%. Based on assumptions, about 225 patients per group would provide 90% power at one-sided 0.025 significance level; For the second co primary endpoint, the sample size calculation was 197 per group, i.e 90% power to detect a difference in proportion of subjects still mechanically ventilated. Therefore, 250 subjects per group (250 on dexmetomidine, 250 on midazolam or propofol) were planned for randomisation.

Randomisation

The random allocation of treatments to subject numbers was performed according to the design of the study by a two-step procedure. Firstly, the vials containing the study drugs were assigned a random package number using the randomly permuted blocks. A detailed description of the randomisation method, including the size of randomly permuted blocks used to balance the randomisation, is stored in the Department of Biostatistics and Data Management. Secondly, study subjects were randomised centrally, using an Interactive Voice Response System (IVRS), either to continue their current sedative agent or switch to dexmedetomidine in an equal allocation ratio 1:1. The package number was then assigned to the unique subject number allocated by the investigator.

Blinding (masking)

A double-dummy procedure was used to mask the identities of the study drugs. In order to maintain the blind for all study personnel involved in the care and assessment of study subjects, all stages of the preparation of all study drugs, including connection and disposal of syringes and infusion lines, were carried out in confidence only by nominated independent persons who were not involved in making study-related assessments (except for study 3005013). None of the persons directly involved in the conduct of the study were to have access to the treatment codes, with the exception of the investigator in case of an emergency. In such case, the unblinding of the treatment code for an individual study subject was possible via the IVRS.

Statistical methods

In all active controlled studies, the Per Protocol (PP) population was used as primary analysis and (ITT) population as secondary analysis for the first co-primary efficacy variable evaluating non inferiority. For the other efficacy variables, the ITT population was used as primary analysis and a sensitivity analysis was performed using PP population, according to study protocol. For the efficacy variables other than co-primary or secondary, the following statistical methods were used: 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) for survival data; descriptive statistics and applicable ANCOVA for continuous data, generalized linear models with appropriate distribution and link function (e.g Fisher's exact test or chi square's test) for count data or categorical data.

Missing values in the efficacy variables were replaced using the imputation method depending on the type of analysis performed. In studies 3005012 and 3005013, the following applied for co-primary efficacy missing values: If subject does not start study drug infusion, time on target is considered nil; If subject dies while on study drug, time of death is used as end of study drug infusion; If RASS target is not set at baseline, mild to moderate (RASS 0 to -3) is assumed. If RASS assessment is missing during the study drug infusion, value is not imputated but interpolated from preceding and consequent assessments. If gap between the two RASS assessments is more than 7 hours and more than 30% of anticipated assessments are missing, subject will be excluded from PP analysis set; if time of randomisation is missing, then the time of decision of entry will be used instead ; if end time of mechanical ventilation is missing then time being medically fit for discharge from study hospital ICU will be used.

3005011

For the first co-primary efficacy variable, comparison between the treatment groups was done using analysis of co-variance (ANCOVA) for the outcome variable. Non-inferiority of dexmedetomidine versus rescue medication (midazolam or propofol) was evaluated using 1-sided 97.5% confidence intervals (CIs) and less than 10% (non-inferiority criterion) difference between the treatment groups. For the second co-primary efficacy variable, comparison between the treatment groups was done using Kaplan-Meier method and Cox's proportional-hazards regression model. The hazard ratio between treatment groups was estimated together with corresponding 95% CI.

3005012 and 3005013

For the first co-primary efficacy variable, 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) and less than 15% (non-inferiority criterion) difference between the treatment groups. For the second co-primary efficacy variable, 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.

2.5.2.2.2. Results

2.5.2.2.2.1. Study 3005011

Around sixty-six % (27/41) of subjects received dexmedetomidine longer than 24 hours. The longest exposure to dexmedetomidine was 8 days 6 hours (198 hours). The longest exposure to midazolam bolus was 3 days 11 hours (83 hours), to midazolam infusion 4 days 9 hours (105 hours) and to propofol 10 days 16 hours (256 hours), respectively.

Maintenance of target depth of sedation

First co-primary efficacy results are presented in Table 5.

Table 5

Variable	N	Estimate[1]	SE	95 % CI	
				Lower	Upper
Dexmedetomidine	38	55.4%	4.79	48.9	65.0
Midazolam/Propofol	41	57.2%	4.89	47.4	66.9
Ratio		0.97		0.79[2]	1.15

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, although still failed to reach the pre-defined margin. 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).

Length of Stay in ICU

Second co-primary efficacy results are presented in Table 6.

Table 6

Variable, Time (day)	Dexmedetomidine (N=41)	Midazolam/Propofol (N=44)	P-value	Hazard ratio[1]	95% CI	
					Lower	Upper
Mean (SD)	7.3 (5.3)	7.8 (6.8)	0.453	0.834	0.519	1.340
Median	5.7	5.5				
Range	1.7-19.5	1.7-29.0				
n	38	42				

There were significant differences in favour of dexmedetomidine with regard to the secondary outcome measures of nurse's assessment of subject communication and the number of ventilator-free days in ICU. There were no differences between treatment groups with regard to any of the other secondary variables.

2.5.2.2.2.2. Studies 3005012 and 3005012

Participant flow

This is presented in Figures 7 and 8.

Figure 7 – Study 3005012

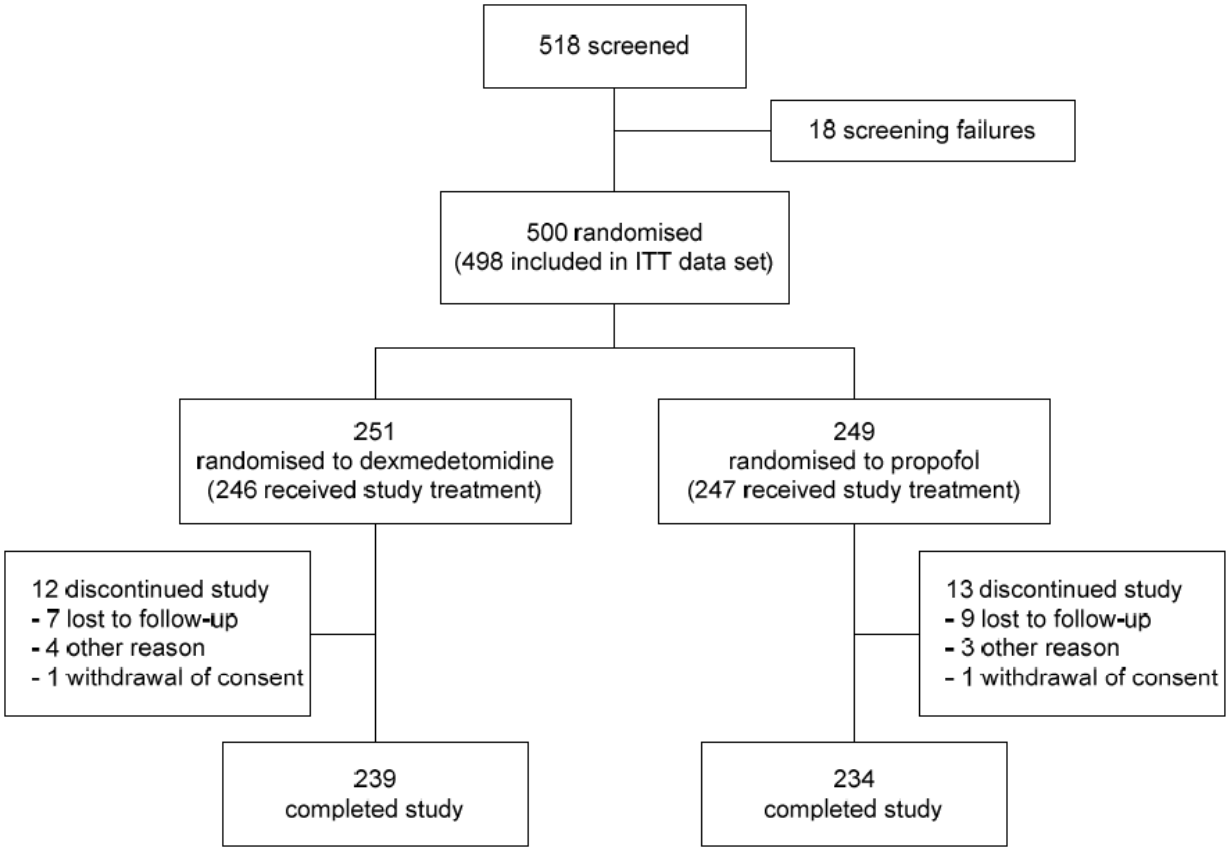
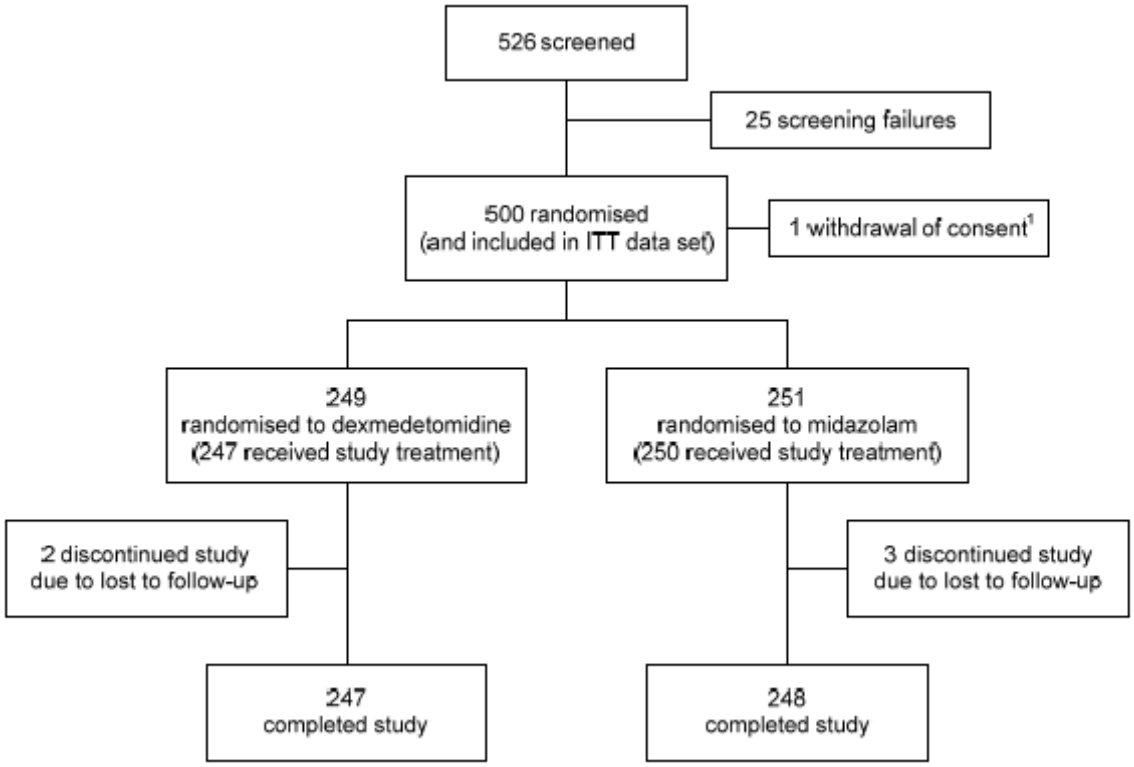


Figure 8 – Study 3005013



In addition, disposition of subjects and premature discontinuations of study treatments in both studies are presented in Table 7.

Table 7

Variable	Dexmedetomidine N = 251 (ITT) N = 246 (Safety)	Propofol N = 247 (ITT) N = 247 (Safety)	Dexmedetomidine N = 249 (ITT) N = 247 (Safety)	Midazolam N = 251 (ITT) N = 250 (Safety)
	Number (%) of subjects			
Randomised	251 (100)	249 (100)	249 (100)	251 (100)
Discontinued study	12 (4.8)	13 (5.3)	2 (0.8)	3 (1.2)
Completed study	239 (95.2)	234 (94.7)	247 (99.2)	248 (98.8)
Reason for discontinuation of study				
Lost to follow-up	7 (58.3)	9 (69.2)	2 (100)	3 (100)
Other reason	4 (33.3)	3 (23.1)	-	-
Withdrawal of consent	1 (8.3)	1 (7.7)	-	-
Started study treatment	246	247	247	250
Discontinued study treatment	66 (26.8)	58 (23.5)	58 (23.5)	49 (19.6)
Completed study treatment	180 (73.2)	189 (76.5)	189 (76.5)	201 (80.4)
Reason for discontinuation of study treatment				
Lack of efficacy	36 (54.5)	13 (22.4)	23 (39.7)	10 (20.4)
AE/SAE	29 (43.9)	28 (48.3)	23 (39.7)	19 (38.8)
Other reason	7 (10.6)	16 (27.6)	16 (27.6)	21 (42.9)
Protocol violation	1 (1.5)	3 (5.2)	2 (3.4)	2 (4.1)
Non-pharmacological intervention	1 (1.5)	4 (6.9)	-	-

Recruitment

Study periods were: from 9 Jun 2007 to 3 March 2010 for study 3005012 and from 28 June 2007 to 7 October 2009 for study 3005013.

Conduct of the study

In both studies, changes to protocol were made during the study and were related to study design, handling of data and conduct of exploratory pharmacogenetic analysis. In term of study design, existing exclusion criteria were modified and primary efficacy evaluation was also changed to allow the investigator to amend the subjects's target RASS from 0 to -3 to -4 or -5, if required for clinical reasons. Two sensitivity analyses handling the target RASS other than 0 to -3 were also added. These changes were not considered to affect the conduct of the study.

In boths studies, a number of major protocol deviations were identified in dexmedetomidine (3005012: 49; 3005013: 34) and active comparator groups (propofol: 57; midazolam: 32) which excluded some patients from the PP population.

Baseline data

These are presented in Table 8.

Table 8

		Dexmedeto-midine (N = 251)	**Propofol** (N = 247)	**Dexmedeto-midine** (N = 249)	**Midazolam** (N = 251)
Subject demographics (ITT)					
Gender, n (%)	Male	160 (63.7)	166 (67.2)	153 (61.4)	175 (69.7)
	Female	91 (36.3)	81 (32.8)	96 (38.6)	76 (30.3)
Age, years	Mean ± SD	61.8 ± 15.4	61.7 ± 15.7	63.0 ± 14.4	63.0 ± 13.9
	Range	18 - 94	20 - 88	19 - 97	19 - 88
Age categories, years, n (%)	18-45	38 (15.1)	41 (16.6)	31 (12.4)	27 (10.8)
	46-65	89 (35.5)	90 (36.4)	96 (38.6)	100 (39.8)
	66-75	72 (28.7)	66 (26.7)	70 (28.1)	73 (29.1)
	> 75	52 (20.7)	50 (20.2)	52 (20.9)	51 (20.3)
ICU admission characteristics (ITT)					
Clinical need for sedation	n (%)	239 (95.2)	240 (97.2)	234 (94.0)	244 (97.2)
Subjects initially intubated (or tracheotomised)	n (%)	228 (90.8)	227 (91.9)	226 (90.8)	231 (92.0)
Subjects initially ventilated (with inspiratory assistance)	n (%)	230 (91.6)	231 (93.5)	229 (92.0)	233 (92.8)
SAPS II score	Mean ± SD	46.6 ± 14.6	45.2 ± 15.2	47.3 ± 16.6	46.3 ± 16.5
Time category from ICU admission to randomisation, n (%)	0-6 h	19 (7.6)	27 (10.9)	18 (7.2)	11 (4.4)
	6-24 h	87 (34.7)	78 (31.6)	94 (37.8)	84 (33.5)
	>24 h	145 (57.8)	142 (57.5)	137 (55.0)	156 (62.2)
Reason for ICU admission (ITT)					
Main reason for admission to ICU, n (%)	Medical	137 (54.6)	143 (57.9)	182 (73.1)	171 (68.1)
	Surgical	92 (36.7)	77 (31.2)	55 (22.1)	58 (23.1)
	Trauma	22 (8.8)	27 (10.9)	12 (4.8)	22 (8.8)
ICU admission type, n (%)	Emergency	228 (90.8)	218 (88.3)	237 (95.2)	239 (95.2)
	Planned	23 (9.2)	29 (11.7)	12 (4.8)	12 (4.8)
Categorised primary diagnoses for ICU admission (ITT)					
Infections and infestations	n (%)	94 (37.5)	96 (38.9)	97 (39.0)	79 (31.5)
Sepsis	n (%)	60 (23.9)	58 (23.5)	86 (34.5)	77 (30.7)
Respiratory failure	n (%)	39 (15.5)	49 (19.8)	85 (34.1)	87 (34.7)
Other respiratory	n (%)	68 (27.1)	55 (22.3)	74 (29.7)	80 (31.9)
Cardiac and vascular	n (%)	53 (21.1)	57 (23.1)	53 (21.3)	61 (24.3)
Renal failure	n (%)	28 (11.2)	32 (13.0)	22 (8.8)	33 (13.1)
Other	n (%)	50 (19.9)	46 (18.6)	26 (10.4)	26 (10.4)

Numbers analysed

These are presented in Table 9.

Table 9

Data set	Dexmedetomidine (N = 251)	Propofol (N = 249)	Dexmedetomidine (N = 249)	Midazolam (N = 251)
	Number (%) of subjects			
ITT	251 (100)	247 (99.2)	249 (100)	251 (100)
PP	218 (86.9)	213 (86.2)	217 (87.1)	227 (90.4)

In addition, data from 5 dexmedetomidine-treated (resulting in 223 PP subjects) and 1 propofol-treated (resulting in 214 PP subjects) were included to the 1st co-primary endpoint analysis until the onset of non-compliance. Data from the 10 dexmedetomidine-treated (resulting in 227 PP subjects) and 6 midazolam-treated (resulting in 233 PP subjects) subjects were included in the 1st co-primary endpoint analysis until onset of non compliance. Percentages are based on numbers of subjects randomized

Outcomes and estimation

3005012

First co-primary efficacy results are presented in Tables 10, 11 and 12.

Table 10- PP set, Mean percentage of time at the target sedation level without use of rescue treatment

Variable	N	Estimate[1]	SE	95% CI	
				Lower	Upper
Dexmedetomidine	223	64.56	2.30	60.043	69.085
Propofol	214	64.66	2.41	59.925	69.402
Difference		-0.10	2.52	-5.050	4.851
Ratio		1.00		0.922[2]	1.075

Table 11

Table 14.2.1.1.1 Depth of sedation - proportion of patients maintaining target sedation level without use of rescue medication Per-Protocol

		Dexmedetomidine (N=223)	Propofol (N=214)	Total (N=437)
Variable				
Percentage of time at target	N	223	214	437
	Mean	62.29	62.20	62.24
	SD	27.45	25.84	26.64
	Min	0.0	0.0	0.0
	Median	65.24	66.35	66.04
	Max	100.0	100.0	100.0

Table 12 – ITT set, Mean percentage of time at the target sedation level without use of rescue treatment

Table 14.2.1.7.2 Statistical analysis of depth of sedation using ITT population (sensitivity D)
Intent-to-treat population

Parameter	Estimate*	Std.Error	P-value	95% Confidence Interval Lower	Upper
Dexmedetomidine	63.38	2.28	<.001	58.894	67.870
Propofol	65.60	2.36	<.001	60.961	70.247
DEXMEDETOMIDINE - PROPOFOL	-2.22	2.46	0.366	-7.047	2.603
RATIO: Dexmedetomidine / Propofol**	0.97	.	.	0.894	1.038
	.	.	.	.	.
COUNTRY	.	.	0.023	.	.

Second co-primary efficacy results are presented in Table 13 and figure 9.

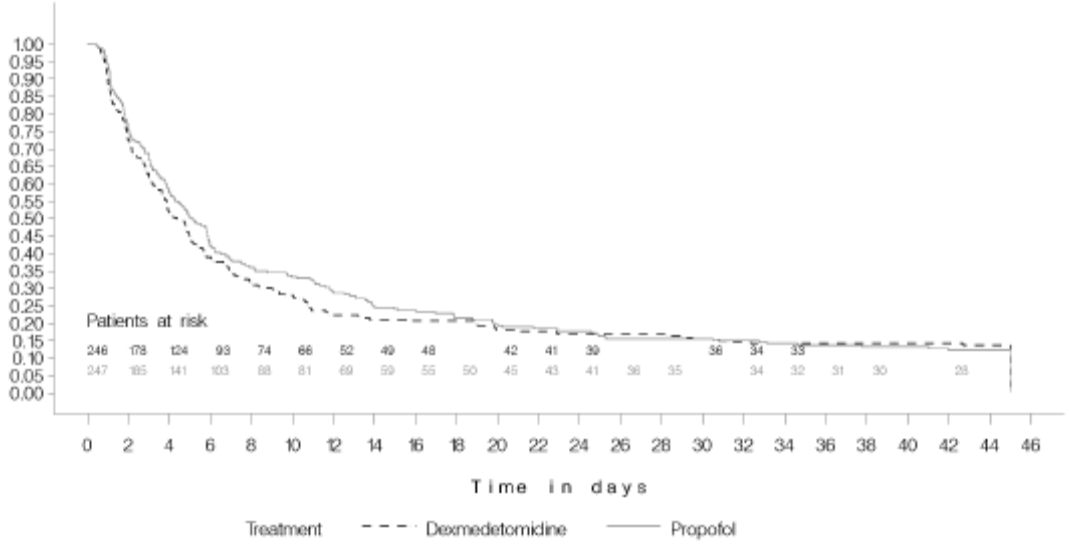
Table 13

Table 26. Duration of mechanical ventilation (ITT)

Time (hours)	Dexmedetomidine (N = 251)	Propofol (N = 247)	P-value	Hazard ratio or difference	95% CI Lower	Upper
Median	96.5	117.5				
Range	3-1080	10-1080				
n	242	240				
Statistical tests:						
Test for proportional hazards assumption (treatment by time interaction)			0.065			
Gehan-Wilcoxon			0.240			
Cox's proportional-hazards regression			0.492	0.936[1]	0.774	1.131
Median one-way test			0.295			
Hodges-Lehmann estimates for median difference (h)				7[2]	-3	25

[1] Cox's proportional-hazard method with effect for country. Hazard ratio < 1 favours dexmedetomidine
[2] Estimated median difference (propofol-dexmedetomidine) > 0 favours dexmedetomidine

Figure 9



Other results (including secondary efficacy) are presented in Tables 14 and 15

Table 14 Secondary efficacy results

	Mean and median		P-value	Difference or ratio	95% CI	
	DEX (N=251)	**PRO** (N=247)			**Lower**	**Upper**
Secondary variables (ITT)						
Nurse's total VAS scores, mean	51.3	40.1	<0.0012	11.2	6.4	15.9
Length of ICU stay, median (d)	6.8	7.7				
Cox's proportional-hazard model			0.535	0.941	0.778	1.139

Table Other efficacy results

	Mean and median		P-value	Difference or ratio	95% CI	
	DEX (N=251)	**PRO** (N=247)			**Lower**	**Upper**
Additional variables (ITT)						
Ventilator free days, median (d)	1.0	1.0	0.7563			
Time to extubation from randomisation, median (h)	69.0	93.0				
Gehan-Wilcoxon test*			0.041			
Cox's proportional-hazard regression			0.109			
Time to extubation from end of infusion, median (h)	4.0	7.0				
Cox's proportional-hazard regression			0.662	0.960	0.810	1.152
Length of hospital stay, median (d)	33.0	38.0				
Gehan-Wilcoxon*			0.750			

***** As the assumption for the proportionality of hazards was not valid, the statistically more appropriate Gehan-Wilcoxon test, which gives more weight to events of interest at early time points, was applied.

Around seventy- three % of subjects in the dexmedetomidine group and 64.4% of subjects in the propofol group used first-line rescue treatment (i.e. midazolam boli) for inadequate sedation during the study treatment period (Fisher's exact text, p = 0.054). The total number of doses of rescue treatment used was 2495 and 1986 doses in the dexmedetomidine and propofol groups, respectively. The distribution of the number of rescue treatment doses used per subject during the study treatment was statistically significant between the treatment groups (exponentiated Poisson estimate 1.67, 95% CI 1.64 to 1.69, p < 0.001), indicating that first-line rescue treatment was given more frequently for subjects in the dexmedetormidine group than in the propofol group. Duration of the infusion had to be at least 13 hours at a constant rate to reach steady-state concentration.

Both the mean total amount of rescue treatment (repeated measure (RM)-ANOVA, p < 0.001) and the average dose of rescue treatment (RM-ANOVA, p < 0.001) were higher in the dexmedetomidine group than in the propofol group over time.

Overall, 13.9% of subjects in the dexmedetomidine group 16.2% of subjects and in the propofol group used a second-line rescue treatment for inadequate sedation during study treatment period, with no significant (Fisher's exact text, p = 0.532) difference between the treatment groups. The most common second-line rescue treatment was fentanyl, which was used 218 times in 32 subjects in the dexmedetomidine group and 107 times in 34 subjects in the propofol group. The distribution of the number of second-line rescue doses used per subject during the study treatment was statistically significant between the treatment groups (exponentiated Poisson estimate 4.19, 95% CI 3.77 to 4.65, p < 0.001), indicating that second-line rescue treatment was given more frequently for subjects in the dexmedetomidine group than in the propofol group.

A comparable percentage of subjects used fentanyl during the study (78.5% dexmedetomidine vs. 80.6% propofol, Fisher's exact test, p = 0.580). Of all subjects (n = 498), the majority of subjects in both treatment groups received fentanyl for analgesia (78.1% dexmedetomidine vs. 80.2% propofol) and 15.5 and 15.4% of subjects in the dexmedetomidine and propofol groups, respectively, received fentanyl for sedation.

No statistically significant difference between the dexmedetomidine and propofol groups, respectively, was observed in the mean total amount of fentanyl (5.5 vs. 6.3 mg, p = 0.511) or the average dose of fentanyl (0.10 vs. 0.08 mg/h, p = 0.153).

The mean cumulative sum of TISS points was 28.6 points lower (354 vs. 382) in the dexmedetomidine-treated subjects than in the propofol-treated subjects from randomisation until day 45. The ICU costs were 1141.2 euros lower in the dexmedetomidine group than in the propofol group.

3005013

First co-primary efficacy results are presented in Tables 16 and 17.

Table 16- PP set, Mean percentage of time at the target sedation level without use of rescue treatment

Variable	N	Estimate[1]	SE	95% CI	
				Lower	Upper
Dexmedetomidine	227	60.74	2.74	55.351	66.119
Midazolam	233	56.56	2.71	51.234	61.896
Difference		4.17	2.85	-1.436	9.777
Ratio		1.07		0.971[2]	1.176

Table 17 – ITT set, Mean percentage of time at the target sedation level without use of rescue treatment

Table 14.2.1.7.2 Statistical analysis of depth of sedation using ITT population (sensitivity D)
Intent-to-treat population

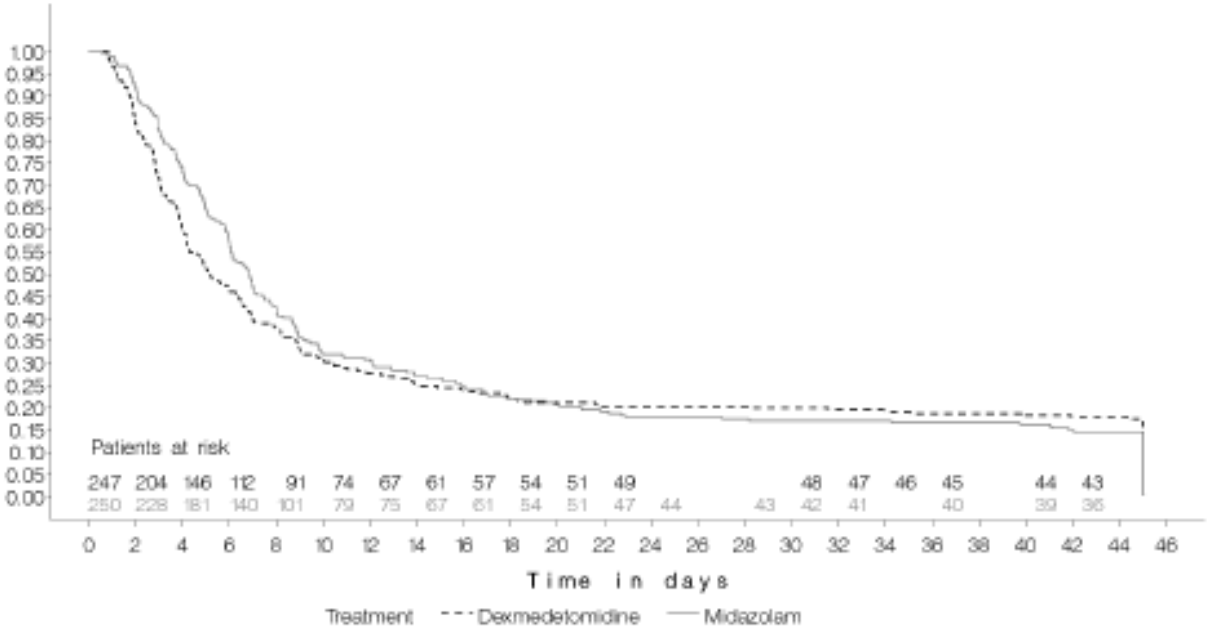
Parameter	Estimate*	Std.Error	P-value	95% Confidence Interval Lower	Upper
Dexmedetomidine	59.86	2.52	<.001	54.926	64.835
Midazolam	54.91	2.49	<.001	50.016	59.808
DEXMEDETOMIDINE - MIDAZOLAM	4.97	2.76	0.073	-0.459	10.397
RATIO: Dexmedetomidine / Midazolam**	1.09	.	.	0.987	1.194
	.	.	.	.	.
COUNTRY	.	.	<.001	.	.

Second co-primary efficacy results are presented in Table 18 and figure 10.

Table 18 Duration of mechanical ventilation (ITT)

Time (hours)	Dexmedetomidine (N= 249)	Midazolam (N= 251)	P-value	Hazard ratio or difference	95% CI	
					Lower	Upper
Median	123.0	164.0				
Range	20-1080	13-1080				
n	245	247				
Statistical tests:						
Test for proportional hazards assumption (treatment by time interaction)			0.001			
Gehan-Wilcoxon			0.033			
Cox's proportional-hazards regression			0.265	0.896[1]	0.738	1.087
Median one-way test			0.060			
Hodges-Lehmann estimates for median difference (h)				19[2]	0	42

Figure 10



Other results (including secondary efficacy) are presented in Tables 19 and 20

Table 19. Secondary efficacy results

	Mean and median		P-value	Difference or ratio	95% CI	
	DEX (N=249)	MDZ (N=251)			Lower	Upper
Secondary variables (ITT)						
Nurse's total VAS scores, mean	49.7	30.0	< 0.001	19.7	15.2	24.2
Length of ICU stay, median (d)	8.8	10.1				
Cox's proportional-hazard model			0.876	1.016	0.835	1.235

Table 20 Other efficacy results

	Mean and median		P-value	Difference or ratio	95% CI	
	DEX (N=249)	MDZ (N=251)			Lower	Upper
Additional variables (ITT)						
Ventilator free days, median (d)	1.0	1.0	0.924			

Time to extubation from randomisation, median (h)	101.0	147.0				
Gehan-Wilcoxon test*			0.012			
Time to extubation from end of infusion, median (h)	35.0	53.5				
Cox's proportional-hazard regression			0.156	0.875	0.727	1.053
Length of hospital stay, median (d)	42.0	38.0				
Cox's proportional-hazard regression			0.288	1.119	0.909	1.378

***** As the assumption for the proportionality of hazards was not valid, the statistically more appropriate Gehan-Wilcoxon test, which gives more weight to events of interest at early time points, was applied.

The percentage of subjects using first-line rescue treatment (i.e. propofol boli) for inadequate sedation during the study treatment period was similar in the dexmedetomidine and midazolam groups (43.8 vs. 45.4%; Fisher's exact text, p = 0.720). The total number of doses of rescue treatment used was also similar: 1100 doses in the dexmedetomidine vs. 1008 doses in the midazolam group. The distribution of the number of rescue treatment doses used per subject during the study treatment was statistically significant different between the treatment groups (exponentiated Poisson estimate 0.90, 95% CI 0.88 to 0.92, p < 0.001), indicating that more subjects received rescue treatment more frequently in the midazolam group than in the dexmedetomidine group. However, the numbers of subjects receiving rescue treatment in the higher frequency categories (> 100 times and > 200 times) were small in both treatment groups, with no notable differences between the groups. Hypothetically, the 2 subjects in the midazolam group using > 200 rescue treatment doses compared with none in the dexmedetomidine group can have skewed the results.

Similar time to reach steady state concentration than previous study 3005012 was observed i.e duration of the infusion had to be at least 13 hours at a constant rate to reach steady-state concentration.

No statistically significant differences between the treatment groups were observed over time with regard the total amount (RM-ANOVA, p = 0.213) or the average daily dose (RM-ANOVA, p = 0.221) of the first-line rescue treatment.

Overall, 5.6% of subjects in the dexmedetomidine group and 4.8% of subjects in the midazolam group used a second-line rescue treatment for inadequate sedation during study treatment, with no significant (Fisher's exact text, p = 0.692) difference between the treatment groups. The most common second-line rescue treatment was fentanyl, which was used 23 times in 6 subjects in the dexmedetomidine group and 31 times in 9 subjects in the midazolam group. The distribution of the number of second-line rescue doses used per subject during the study treatment was similar between the treatment groups (exponentiated Poisson estimate 1.04, 95% CI 0.81 to 1.32, p = 0.779).

A comparable percentage of subjects used fentanyl (77.9% dexmedetomidine vs. 82.9% midazolam, Fisher's exact test, p = 0.177) (Table 14.2.3.9). Of all subjects (n = 500), the majority of subjects in both treatment groups received fentanyl for analgesia (77.5% dexmedetomidine vs. 81.7% midazolam) and 3.2 and 4.4% of subjects in the dexmedetomidine and midazolam groups, respectively, received fentanyl for sedation.

No statistically significant difference between the dexmedetomidine and midazolam groups, respectively, was observed in the mean total amount of fentanyl (10.6 vs. 15.8 mg, p = 0.590) or the mean average dose of fentanyl (0.3 vs. 0.6 mg/h, p = 0.570).

The mean cumulative sum of TISS points was 63.6 points lower (346 vs. 409) in the dexmedetomidine-treated subjects than in the midazolam-treated subjects from randomisation until day 45. The ICU costs were 2541.5 euros lower in the dexmedetomidine-treated subjects than in the midazolam-treated subjects.

2.5.2.3. *Ancillary analyses*

In responses to CHMP request, the applicant provided post-hoc analyses on co-primary endpoints, accounting for subjects prematurely withdrawn for the non inferiority analysis, and using time to extubation for the second co-primary analysis. In addition, further analysis was conducted to clarify the increased use of rescue medication in the dexmedetomidine group as compared to propofol in study 3005012.

First co-primary analysis: non inferiority versus standard of care (SOC)

Subjects prematurely withdrawn for any reason were additionally assumed after withdrawal to be out of range and to remain out of range until extubation (or end of inspiratory assist if tracheostomy inserted), death or the end of the study (45 days). A further post hoc sensitivity analysis was performed where the extubation was assumed to be at insertion of tracheostomy (i.e. removal of the endotracheal tube) for those subjects receiving a tracheostomy (Onset), rather than at removal of inspiratory assist. Results are presented in Table 21.

Table 21

Study	Population	PW imputed[1]	Tracheostomy[2]	DEX %	SOC[3] %	Ratio	Lower CI	Upper CI
3005012	PP	All PW	EoIA	54.50	54.24	1.00	0.895	1.114
3005012	ITT	All PW	EoIA	53.89	55.76	0.97	0.867	1.066
3005012	PP	All PW	Onset	55.68	55.77	1.00	0.894	1.102
3005012	ITT	All PW	Onset	55.11	57.44	0.96	0.865	1.054
3005013	PP	All PW	EoIA	54.66	49.62	1.10	0.969	1.234
3005013	ITT	All PW	EoIA	53.16	47.73	1.11	0.980	1.247
3005013	PP	All PW	Onset	56.77	51.51	1.10	0.976	1.228
3005013	ITT	All PW	Onset	55.02	49.27	1.12	0.988	1.245

[1] PW imputed; all premature withdrawals are included

[2] Tracheostomy; the protocol definition for extubation was removal of inspiratory assist where a tracheostomy was inserted (EoIA); a *post hoc* sensitivity analysis was performed where the extubation was assumed to be at insertion of tracheostomy (Onset)

[3] SOC = standard of care, for 3005012 this is propofol, for 3005013 this is midazolam

PP = per-protocol; ITT = intention-to-treat; CI = confidence interval

Second co-primary analysis: duration of mechanical ventilation

Post-hoc analysis of the mechanical ventilation was performed censoring at 14 days (longest infusion of investigational treatment) or death confirmed the benefits of dexmedetomidine. See Table 22.

Table 22

Table 8. *Post-hoc* analysis of duration of mechanical ventilation and time to extubation to 14 days or until death

Variable	Study	DEX median (IQR)	SOC[1] median (IQR)	Ratio	Lower CI	Upper CI	Cox's	Gehan-Wilcoxon
Duration of mechanical ventilation	3005012	72 (36-134)	83 (42-142)	0.87	0.710	1.067	0.183	0.194
	3005013	93 (53-156)	122 (73-172)	0.81	0.661	1.001	0.051	0.007
	Pooled	83 (45-143)	102 (50-164)	0.85	0.736	0.983	0.028	0.006
Time to extubation	3005012	51 (28-114)	69 (41-119)	0.79	0.650	0.969	0.023	0.032
	3005013	78 (48-144)	119 (70-169)	0.80	0.651	0.977	0.029	0.002
	Pooled	68 (43-122)	91 (48-147)	0.80	0.695	0.923	0.002	0.000

[1]SOC = standard of care, for 3005012 this is propofol, for 3005013 this is midazolam

Increased use of rescue medication compared to propofol (study 3005012)

When subjects who are withdrawn for lack of efficacy are removed from the analysis, the difference in use of rescue medication is markedly diminished. The number of subjects requiring rescue sedation (midazolam) was 121 on dexmedetomidine and 122 on propofol for those subjects not withdrawn for lack of efficacy (Table 23). The frequency distribution appeared similar between the treatment groups (Table 24). The total amount of (mean) rescue used was 26.3 mg in the dexmedetomidine group and 22.1 mg in the propofol group (Table 25). It appears that the excess use of rescue medication in the dexmedetomidine group is mainly associated with subjects who subsequently are withdrawn for lack of efficacy.

Table 23

Table 3. Number of subjects receiving any rescue sedation, in subjects not withdrawn for Lack of Efficacy; study 3005012

Variable		Dexmedetomidine (N=251) n (%)	Propofol (N=247) n (%)	Total (N=498) n (%)
First line rescue used	NO	64 (34.6)	67 (35.4)	131 (35.0)
	YES	121 (65.4)	122 (64.6)	243 (65.0)
	Fisher's Exact test	p = 0.914		

Tables 24, 25

Table 4. Number of doses of rescue sedation use in subjects not withdrawn for Lack of Efficacy; study 3005012

Variable		Dexmedetomidine (N=251) n (%)	Propofol (N=247) n (%)	Total (N=498) n (%)
Number of times rescue used	none	64 (34.6)	67 (35.4)	131 (35.0)
	<= 5	54 (29.2)	59 (31.2)	113 (30.2)
	<= 10	25 (13.5)	16 (8.5)	41 (11.0)
	<= 20	18 (9.7)	21 (11.1)	39 (10.4)
	<= 50	21 (11.4)	22 (11.6)	43 (11.5)
	<= 100	3 (1.6)	4 (2.1)	7 (1.9)

Table 5. Total amount of rescue medication used in subjects not withdrawn for lack of efficacy; study 3005012

Variable		Dexmedetomidine (N=251) n (%)	Propofol (N=247) n (%)	Total (N=498) n (%)
Total amount of rescue medication (midazolam) (mg)	N	121	122	243
	Mean	26.3	22.14	24.21
	SD	44.4	30.61	38.09
	Min	1	1	1
	Median	12	14	12.5
	Max	377.5	245	377.5
	ANOVA	p = 0.322		

This finding, that the excess use of rescue medication is associated with the subjects prematurely withdrawn for lack of efficacy, is in line with the finding that the dexmedetomidine subjects withdrawn for lack of efficacy performed less effectively in the sedation analysis prior to withdrawal. In conclusion, a large majority of subjects who were successfully managed on dexmedetomidine did not require more rescue sedation than did subjects receiving propofol.

2.5.2.4. *Summary of main studies*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26. Summary of Efficacy for trial 3005012

Title: A prospective, multi-centre, randomised, double-blind comparison of intravenous dexmedetomidine with propofol for continuous sedation of ventilated patients in intensive care unit			
Study identifier	3005012		
Design	Phase III, Multicenter, Prospective, Randomized, Double-Blind, Double-Dummy, Active Comparator controlled		
	Duration of main phase:		24 hours – 14 days (depending on the need of sedation; following the withdrawal of sedation, the study subjects were monitored for 48 hours and contacted by telephone 31 and 45 days after randomization.)
	Duration of Run-in phase: Duration of Extension phase:		Not applicable Not applicable
Hypothesis	Non-inferiority		
Treatments groups	Dexmedetomidine (+ placebo for Propofol)		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 Richmond Agitation-Sedation score (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. Number of randomized patients: 251
	Propofol (+ placebo for Dexmedetomidine)		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. Number of randomised patients: 249
Endpoints and definitions	Co-primary endpoint	Maintaining a target depth of sedation	Proportion of time during study treatment with a RASS 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.
	Co-primary endpoint	Duration of mechanical ventilation	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.

Database lock	not available in the dossier		
Results and Analysis			
Analysis description	**Primary Analysis of the co-primary endpoints**		
Analysis population	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 to evaluate the second co-primary endpoint, duration of mechanical ventilation.		
Descriptive statistics and estimate variability	Treatment group	Dexmedetomidine	Propofol
	Number of subjects - PP	223	214
	Maintaining a target depth of sedation (PP) Adjusted Mean	64.6%	64.7%
	95% CI	60.0%;69.1%	59.9%; 69.4%
	Number of subjects - ITT	251	247
	Duration of mechanical ventilation in hrs (ITT) Median	96.5	117.5
Effect estimate per comparison	Maintaining a target depth of sedation	Comparison groups	Dexdor vs Propofol
		Ratio DEX/Propofol	1.00
		95% CI	0.922*;1.075 (LL of the 95%CI > 0.85 non-inferiority margin)
	Duration of mechanical ventilation	Comparison groups	Dexdor vs Propofol
		Gehan-Wilcoxon test** P-value	0.24
		Cox´s proportional-hazard regression P-value	0.492
		Cox´s proportional-hazard regression Hazard ratio***	0.936
		Cox´s proportional-hazard regression 95% CI for Hazard ratio	0.774; 1.131
Notes	*ANCOVA with effects for treatment and country; lower CI of the ratio >0.85 shows that DEX is non-inferior to Propofol **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		

Table 27.Summary of Efficacy for trial 3005013

Title: A prospective, multi-centre, randomised, double-blind comparison of intravenous dexmedetomidine with midazolam for continuous sedation of ventilated patients in intensive care unit			
Study identifier	3005013		
Design	Phase III, Multicenter, Prospective, Randomized, Double-Blind, Double-Dummy, Active Comparator controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 hours – 14 days (depending on the need of sedation; following the withdrawal of sedation, the study subjects were monitored for 48 hours and contacted by telephone 31 and 45 days after randomization.) Not applicable Not applicable
Hypothesis	Non-inferiority		
Treatments groups	Dexmedetomidine (+ placebo for Midazolam)		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. Number of randomized patients: 249
	Midazolam (+ placebo for Dexmedetomidine)		Midazolam was infused with the dose that was nearest to the pre-randomisation dose of propofol 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 0.2 mg/kg/h. Number of randomised patients: 251
Endpoints and definitions	Co-primary endpoint	Maintaining a target depth of sedation	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 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.
	Co-primary endpoint	Duration of mechanical ventilation	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.
Database lock	not available in the dossier		

Results and Analysis			
Analysis description	**Primary Analysis of the co-primary endpoints**		
Analysis population	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 to evaluate the second co-primary endpoint, duration of mechanical ventilation.		
Descriptive statistics and estimate variability	Treatment group	Dexmedetomidine	Midazolam
	Number of subjects - PP	227	233
	Maintaining a target depth of sedation (PP) Adjusted Mean	60.7%	56.6%
	95% CI	55.4%;66.1%	51.2%; 61.9%
	Number of subjects - ITT	249	251
	Duration of mechanical ventilation in hrs (ITT) Median	123.0	164.0
Effect estimate per comparison	Maintaining a target depth of sedation	Comparison groups	Dexdor vs Midazolam
		Ratio DEX/Midazolam	1.07
		95% CI	0.971*;1.176 (LL of the 95%CI > 0.85 non-inferiority margin)
	Duration of mechanical ventilation	Comparison groups	Dexdor vs Midazolam
		Gehan-Wilcoxon test** P-value	0.033
		Cox´s proportional-hazard regression P-value	0.265
		Cox´s proportional-hazard regression Hazard ratio***	0.896
		Cox´s proportional-hazard regression 95% CI for Hazard ratio	0.738; 1.087
Notes	*ANCOVA with effects for treatment and country; lower CI of the ratio >0.85 shows that DEX is non-inferior to Propofol **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		

2.5.2.5. *Analysis performed across trials (pooled analyses and meta-analysis)*

Data from studies 3005011, 3005012 and 3005013 were pooled for analyses of efficacy endpoints, specifically for subgroup analyses by gender, age, ICU admission reason, simplified acute physiology score II (SAP II), pre admission length of stay, and to investigate the effect of alcohol or chemical addiction, Sequential Organ Failure Assessment (SOFA) CV score, SOFA renal score.

There was no treatment by age (>75 years) interaction for the sedation or outcome measures,. Median values did not show major differences in therapeutic effect by age, with the exception of mechanical ventilation. The median time to extubation is lower for dexmedetomidine in the >75 year-old group but the medians are similar for mechanical ventilation; this observation was not significant for treatment by interaction (p = 0.151).

There was no treatment by ICU admission reason interaction for the sedation or outcome measures. Median values did not show major differences in therapeutic effect by admission reason, with the exception of trauma patients, who did not show a benefit in mechanical ventilation or ICU length of stay, rather a reverse, this is likely to be artefact as the trauma group is small compared to the medical and surgical groups. The same is true of length of hospital stay for which the interaction approached significance (p = 0.107).

There was no treatment by SAPS II interaction for the sedation or outcome measures, except hospital stay (p = 0.066), for which the medians were unremarkable. The cut-off for SAPS II was the median value, 46. Median values suggested higher SAPS II score was associated with higher medians for mechanical ventilation, length of stay and time to extubation compared to lower SAPS II scores and the effect of dexmedetomidine may have been better where there is a high SAPS II score.

There was no treatment by pre-admission length of stay interaction for the sedation or outcome measures, except for length of hospital stay (p = 0.086); this appears due to reversal of effect between the admission groups and is highly unlikely to be a real effect. Median values did not show major differences in therapeutic effect of dexmedetomidine by reason of pre-admission length of stay (except for aforementioned length of hospital stay). The cut-off for pre-admission length of stay was the median value, 30 hours.

There was no treatment by alcohol or chemical addiction interaction for the outcome measures , except sedation corrected for additional (rescue) sedative and nurses VAS. Sedation (p = 0.037) and nurses VAS (p = 0.041) showed an interaction, dexmedetomidine and addiction result to lower response than dexmedetomidine without addiction (suggestive of extra use of rescue sedation in the alcohol or chemically addicted group). The reduction in mechanical ventilation and time to extubation is, if anything, more pronounced on dexmedetomidine in the group with alcohol or chemical addiction.

There was no treatment by baseline SOFA CV score interaction for the sedation or outcome measures , except for mechanical ventilation (p = 0.067); median differences showed mechanical ventilation was shortened on dexmedetomidine compared to standard of care in both SOFA groups. Median values did not show major differences in therapeutic effect of dexmedetomidine by reason of baseline high SOFA CV score.

There was no treatment by baseline SOFA renal score interaction for the sedation or outcome measures, except for hospital length of stay (p = 0.078), which was unremarkable in the medians. Median values does not show major differences in therapeutic effect of dexmedetomidine by reason of baseline high SOFA renal score, if anything dexmedetomidine had a more pronounced effect for sedation, mechanical ventilation, time to extubation and ICU length of stay in subjects with high SOFA renal score at baseline.

2.5.2.6. *Clinical studies in special populations*

See clinical pharmacology studies.

2.5.2.7. *Supportive studies*

These consisted of 3 open label studies (**1999-016, W99-314 and W99-302)** and a phase IV study (**2001-001)** that were designed as follows:

- **1999-016:** A phase II, randomised, multicentre, open-label, comparator study evaluating the safety and effectiveness of dexmedetomidine compared to IV midazolam in ICU patients requiring greater than twenty four hours of continuous sedation.
- **W99-314:** A phase IIIb, multi-centre, open-label, randomised study comparing the safety and efficacy of dexmedetomidine to propofol based standard of care, for ICU sedation following coronary artery bypass graft (CABG) surgery.
- **W99-302:** A phase IIIb, multicentre, open-label, randomised study comparing the safety and efficacy of dexmedetomidine to Propofol based standard of care for ICU sedation following CABG surgery.
- **2001-001:** a phase IV, randomized, double-blind, multicentre, comparator study evaluating the safety and efficacy of dexmedetomidine compared to iv midazolam in ICU subjects requiring greater than twenty-four hours of continuous sedation.

Their results are summarised below.

2.5.2.7.1. Study 1999-016

Fourteen subjects received dexmedetomidine and 13 received midazolam. There were 10 premature discontinuations on dexmedetomidine (5 AEs including 2 subjects with hypotension, 3 protocol errors including the subject who did not receive drug and 2 subjects who could not be sedated in this dose range) and one subject on midazolam who could not be sedated.

There was no statistically significant difference in the primary efficacy variable, (percentage of time in a Ramsay range of 2-4); dexmedetomidine 71.7% (mean), 83.1% (median), midazolam 77.2% (mean) 86.6% (median). Similar results were noted in a subgroup analysis of subjects receiving > 24h sedation: dexmedetomidine 84.6% (mean), 87.8% (median); midazolam 77.2% (mean) 86.6% (median). Bolus use of midazolam was similar between groups, hourly rate of morphine was similar, no evidence of reduced effect for dexmedetomidine over time and for the data available there was a trend to faster ICU discharge post extubation on dexmedetomidine (1 day) compared to midazolam (3 days).

2.5.2.7.2. Study W99-314

Eighty three subjects entered the open-label randomised trial (32 in South Africa and 51 in Taiwan). In South Africa 16 received dexmedetomidine and 16 received propofol standard of care . In Taiwan 26 received dexmedetomidine and 25 received propofol standard of care. A total of 1 subject in the dexmedetomidine group and 1 subject in the propofol group were prematurely withdrawn.

Mean RSS scores were similar for the dexmedetomidine (4.39) and propofol (4.49) standard of care groups in South Africa, p=0.730, and similar for the dexmedetomidine (3.65) and propofol (3.68) standard of care groups in Taiwan, p = 0.855.

Subjects requiring morphine in South Africa were dexmedetomidine 25.0%, propofol 68.8% (p=0.014) during mechanical ventilation. Subjects requiring morphine in Taiwan were dexmedetomidine 23.1%, propofol 44.0% (p=0.051) during mechanical ventilation.

The amount of morphine used was reduced; 0.0035 mg/kg/h on dexmedetomidine and 0.0072 mg/kg/h on propofol standard of care up until extubation (p=0.090) in South Africa. The amount of morphine used was reduced; 0.0025 mg/kg/h on dexmedetomidine and 0.0046 mg/kg/h on propofol standard of care up until extubation (p=0.075) in Taiwan.

In South Africa, there was a statistical difference in time to weaning and time to extubation, the dexmedetomidine patients were ready for weaning at 193 minutes compared to 315 minutes for Propofol (p=0.012) the dexmedetomidine patients were extubated at 316 minutes compared to 415 minutes for propofol (p= 0.011). Time to weaning and extubation was similar in Taiwan.

Mean total length of ICU stay was comparable as was patient satisfaction and nursing assessment.

2.5.2.7.3. Study W99-302

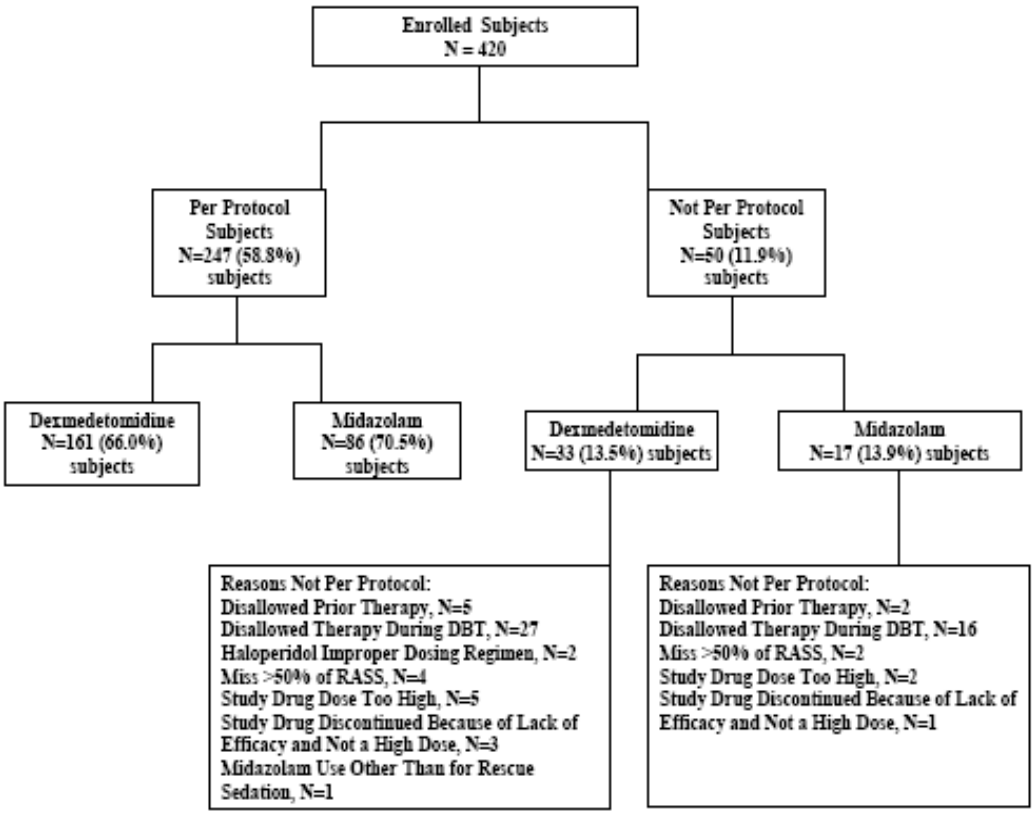
Three hundred and eight subjects entered the open-label randomised trial; 153 randomised to and 148 received dexmedetomidine and 155 randomised to and 147 received propofol standard of care. A total of 14 patients in the dexmedetomidine group and 6 patients in the propofol group were prematurely withdrawn.

Mean RSS scores were similar for the dexmedetomidine (4.5) and propofol (4.7) standard of care groups p=0.259. 11% of the dexmedetomidine group required additional propofol to maintain the Ramsay scores while mechanically ventilated. The median time from stopping the drug to extubation was longer on propofol (145 min) compared to dexmedetomidine (0 min) due to the requirement to stop propofol prior to extubation to allow recovery of the patient's respiratory function. Subjects not requiring morphine were dexmedetomidine 72%, propofol 37% (p<0.001) during mechanical ventilation; dexmedetomidine 69%, propofol 24% (p<0.001) during the 6 hours after extubation and dexmedetomidine 50%, propofol 12% (p<0.001) from start of study drug to 6 hours after extubation. The amount of morphine used was reduced; 0.16 mg/h on dexmedetomidine and 0.61 mg/h on propofol standard of care up until extubation (p=0.0003). There was no statistical difference in time to weaning or time to extubation. Mean total length of ICU stay was comparable.

2.5.2.7.4. 2001-001

Participant flow is presented in Figure 11.

Figure 11



A total of 224 (61%) subjects completed study drug infusion, and of these, 144 (59%) subjects in the dexmedetomidine group and 55 (45%) subjects in the midazolam group were extubated or were ready for extubation, and 10 (4%) subjects in the dexmedetomidine group and 15 (12%) subjects in the midazolam group no longer required sedation.

A slightly higher incidence of subjects in the midazolam group (52 [43%] subjects) than subjects in the dexmedetomidine group (90 [37%] subjects) prematurely discontinued study drug infusion; however, this difference between the treatment groups was not statistically significant (p=0.3070). The most common reasons for study drug discontinuation were the occurrence of AEs (dexmedetomidine group: 36 [15%] subjects, midazolam group: 14 [12%] subjects), lack of efficacy (dexmedetomidine group: 20 [8%] subjects, midazolam group: 18 [15%] subjects), and investigator's reason/decision (dexmedetomidine group: 10 [4%] subjects, midazolam group: 10 [8%] subjects). One subject in the midazolam group (109/16) was discontinued because of oversedation. This subject was treated with flumazenil and the blind on this subject was broken following discontinuation of study drug during the 48 hour follow-up period. There was no serious adverse event reported for this discontinuation.

Baseline data for the dexmedetomidine and midazolam groups of the ITT population were similar. The mean ages were 61.6 and 63.8 years for the dexmedetomidine and midazolam groups, respectively. The mean weights were 91.33 and 87.42 kg for the dexmedetomidine and midazolam groups, respectively. The majority of subjects were Caucasian men < 65 years of age with a Child-Pugh score of either A (5 to 6) or B (7 to 9). The mean Acute Physiology And Chronic Health Evaluation (APACHE II) scores were 19.4 and 18.3 for the dexmedetomidine and midazolam groups, respectively. The time from ICU admission to start of study drug was not different between treatment groups with 29% of the total subjects ≤ 24 hours and 24% of the total subjects > 72 hours.

The primary efficacy variable of this study was the percentage of time subjects were adequately sedated within the target RASS range of -2 to +1 during the double blind treatment period (DBT). Dexmedetomidine and midazolam were both effective at adequately sedating subjects requiring sedation for greater than 24 hours, maintaining subjects within the target RASS range for 80.8% and 81.0% of the time on double-blind treatment (p=0.9493), respectively.

There was also a similar profile in the percentage of subjects who had a RASS score greater than +1, less than -2, or were adequately sedated during DBT without study drug discontinuation or interruption. Midazolam was significantly better at maintaining subjects within the target RASS range during the first 24 hours, 80.6% in the midazolam group and 74.1% in the dexmedetomidine group. However with continued longer sedation, dexmedetomidine was numerically greater for the time between 48 and 264 hours, and significantly greater for 3 of those 9 time segments.

Time to extubation was significantly longer for the midazolam group (median time: 138.4 hours) than the dexmedetomidine group (median time: 93.8 hours) (p=0.0162). Dexmedetomidine shortened the median time to extubation by 44 hours.

Baseline delirium and confusion assessment method adapted for ICU (CAM-ICU) prior to randomization was similar between treatment groups; 54.4% for midazolam and 56.2% for dexmedetomidine (p=0.8066). The comparison of the number and percentage of subjects who had delirium at the daily assessment showed that a higher percentage of midazolam-treated subjects (75.7%) than dexmedetomidine-treated subject (54.6%) had delirium at the daily assessment at any time during the DBT (p=0.0004). For subjects with delirium at baseline, 69.7% of dexmedetomidine subjects and 94.6% of midazolam subjects had delirium during the double blind treatment (DBT) period (p=0.0001). For subjects without delirium at baseline, 33.3% of dexmedetomidine subjects and 55.3% of midazolam subjects had delirium during the DBT (p=0.0397). There was a consistently greater than 20% treatment effect between dexmedetomidine and midazolam in the incidence of delirium.

Midazolam-treated subjects experienced more delirium days than dexmedetomidine-treated subjects overall (mean days: 3.3 and 1.9 days, respectively; p<0.0001), during the DBT (mean days: 2.7 and 1.4 days, respectively; p<0.0001), and in the follow-up period (mean days: 0.7 and 0.5 days, respectively; p=0.0401). Dexmedetomidine-treated subjects experienced more delirium-free days than midazolam-treated subjects overall (mean days: 4.3 and 3.2 days, respectively; p=0.0050), during the DBT (mean days: 2.8 and 1.9 days, respectively; p=0.0018), and in the follow-up period (1.8 and 1.5 days, respectively; p=0.1269). Dexmedetomidine-treated subjects reached a delirium-free day sooner (3.1 days) than midazolam-treated subjects (7.8 days) during the DBT and 48 hour follow-up (p<0.0001).Therefore, at equivalent levels of sedation (RASS -2 to +1) dexmedetomidine causes less delirium than midazolam as well as reduces the incidence of pre-existing delirium in mechanically ventilated subjects in the ICU.

The incidence of fentanyl use and the doses of fentanyl used for any reason and for pain relief were not significantly different between the treatment groups during DBT (p>0.2778).

Midazolam rescue sedation was significantly higher in the dexmedetomidine group compared with the midazolam group. A higher percentage of dexmedetomidine-treated subjects (65.5%) than midazolam treated subjects (53.4%) received open-label midazolam for rescue sedation during DBT (p=0.0460); and a higher mean dosage of midazolam (0.203 mg/kg) was administered to dexmedetomidine-treated subjects than midazolam treated subjects (0.138 mg/kg) during DBT (p=0.0503).

The overall total nursing assessment score was significantly higher for the dexmedetomidine group (mean score: 22.0) than for the midazolam group (mean score 19.9; p=0.0145), representing a more favourable overall score for dexmedetomidine compared with midazolam. Mean separate communication and cooperation scores were significantly different between the treatment groups (p = 0.0064 and p = 0.0191, respectively); however, the mean overall tolerance of ventilator score was not significantly different between the treatment groups (p = 0.2391). These data indicate that nurses caring for critically-ill patients on ventilators were more satisfied with dexmedetomidine sedation than midazolam.

2.5.3. Discussion on clinical efficacy

Early Studies

In early studies comparing dexmedetomidine with placebo and using the RSS score to measure sedation level, the population studied was post-surgery patients and composed mostly of post-cardiac surgery patients. The study drug administration was limited to 24-30 hours. The treatment was preventive in intubated patients. Dexmedetomidine, in comparison to placebo, demonstrated a sparing effect of sedative drugs used i.e midazolam or propofol. The mean dose of midazolam during intubation was 4.8 mg for dexmedetomidine and 18.6 mg for placebo (p=0.0011). The mean dose of propofol during intubation was 72 mg for dexmedetomidine and 513 for placebo (p<0.0001). The RSS score was statistically higher in the dexmedetomidine groups. The dexmedetomidine treated patients required on average less than half of the amount of morphine given to the placebo-controlled patients. The mean total dose of morphine by ITT analysis was 0.9 and 0.4 mg/h for the placebo (n=373) and dexmedetomidine (n=381) groups respectively (p<0.001). Results were consistent in all phase III placebo controlled studies.

In a phase II study (W98-274) using the BIS score to measure the sedation level, the population studied was differently composed with less post-surgery patients to cardiac surgery (53%). Other surgery relates to cancer (>20% in each group), head and aneurysm requiring prosthesis (13%). The maximum duration of infusion was 72 hours. During intubation the dexmedetomidine group required 0.87 mg/kg/h of propofol compared to the placebo group which required 1.52 mg/kg/h of propofol (p = 0.0058). During weaning the dexmedetomidine group required 0.17 mg/kg/h of propofol compared to the placebo group which required 0.62 mg/kg/h of propofol (p = 0.0003). Mean BIS scores were comparable during intubation (dexmedetomidine: 63, placebo: 66.6), weaning (dexmedetomidine : 67.8, placebo: 71.7) and extubation (dexmedetomidine: 89.0, placebo: 88.0), where the lower number indicates deeper sedation. During intubation the total dose of morphine required was not significantly lower for dexmedetomidine patients than for placebo patients during drug administration (dexmedetomidine 0.48 mg/h of morphine, placebo 0.76 mg of morphine, p=0.1741).

The above results provided positive findings regarding the efficacy of dexmedetomidine as a sedative agent. However, the CHMP considered that in these trials, the population studied, the duration of the treatment and the study design (lack of active comparator, scales used to measure sedation) did not allow to draw a definite conclusion concerning the use of dexmedetomidine in the current ICU setting. In a subsequent phase III study (3005011) using midazolam and propofol as active comparators (considered as standard of care) and RASS as scale to measure sedation level, dexmedetomidine was not proven to be clinically non-inferior to midazolam/propofol. The lower limit of the 95% CI for the estimated between-group ratio (0.79) was not within the pre-defined non-inferiority margin (> 0.90). Dexmedetomidine was less effective where a greater level of sedation (RASS -4) was required whereas

no difference between midazolam and propofol was found in this regard. Furthermore, no statistically significant differences between the treatment groups were observed in the length of stay in the ICU from randomisation. However, the CHMP noted that this study was early terminated and included only a total 85 patients and therefore was not conclusive on the efficacy of dexmedetomidine.

Pivotal Studies

With respect to the 2 additional phase III studies using both active comparators (midazolam for study 3005013 and propofol for study 3005012) and conducted line with the CHMP advice received in October 2000, efficacy results did not appear consistent:

Study 3005012 (with propofol)

In study 3005012, treatment groups were balanced with respect to gender, age, weight and ethnic origin. In the ITT population (n=498), 326 (65.5%) were male. The mean age of the subjects was 61.7 years, ranging between 18 and 94 years. The majority of subjects (98.6%) were Caucasian, 0.6% were Black, 0.4% were Asian and 0.4% were of other origin. The treatment groups were balanced with respect to clinical need of sedation, SAPS II and median time from ICU admission to randomisation: The treatment groups were also balanced with respect to main reason for admission to ICU (medical, surgical or trauma) and type of ICU admission (emergency or planned): No statistically significant differences between the treatment groups were observed in the categorised primary diagnoses for admission to ICU.

The mean percentage of time at target sedation without use of rescue treatment were 64.6% versus 64.7% for dexmedetomidine and propofol groups, respectively, confirming non inferiority for the first co-primary endpoint. Both PP and ITT population showed consistent results, however; ITT results were less convincing than the PP (ratio: 0.97 versus 1.00), although the confidence interval (CI) was still above the non-inferiority margin of 0.85. For the second co-primary endpoint, the duration of mechanical ventilation did not differ statistically significantly between treatment groups using different tests (Gehan Wilcoxon : p=0.240; Cox HR:0.49, 0.77-1.13). From a statistical perspective, the hierarchical approach used for the co-primary endpoints can be considered sufficient to make the study positive.

However, the chosen non inferiority margin of 15%, higher than the previous early terminated pilot study (3005011) set up as 10% of difference was questioned by the CHMP. The CHMP also noted that patients were excluded if they were likely to require deep sedation i.e. a RASS > -3, suggesting a possible enrichment of the population, given the findings of study 3005011. Furthermore, the CHMP was concerned that patients randomised to dexmedetomidine spent on average a substantially shorter time at target (33.51 versus 47.12 , ie 14 hours less) suggesting that patients on dexmedetomidine were discontinuing study treatment earlier than those on propofol for related treatment reasons. The number of discontinuations because of lack of efficacy further supported this finding. Therefore a post hoc analysis excluding the total duration of infusion to avoid masking the difference in % time at target , e.g using the total time for sedation instead was recommended. In this study, the use of rescue drugs was also significantly higher compared to propofol (e.g 72.5% versus 64.4% for first line rescue medication).

Study 3005013 (with midazolam)

In study 3005013, the treatment groups were balanced with respect to gender, age, weight and ethnic origin. In the ITT population (n=500), 328 (65.6%) were male. The mean age of the subjects was 63 years, ranging between 19 and 97 years. The majority of subjects (96.2%) were Caucasian, 1.4% were Hispanic, 1.0% were Black, 0.4% were Asian and 1.0% were of other origin.The treatment groups were balanced with respect to the clinical need of sedation, SAPS II and median time from ICU admission to randomisation. The treatment groups were balanced with respect to main reason for admission to ICU (medical, surgical or trauma) and type of ICU admission (emergency or planned). The majority of subjects (70.6%) were admitted to ICU due to medical reasons and most subjects (95.2%) needed emergency care. No statistically significant differences between the treatment groups were observed in the categorised primary diagnoses for admission to ICU.

The mean percentage of time at the target sedation level without use of rescue treatment was 60.7% and 56.6% for dexmedetomidine and midazolam groups, respectively confirming non inferiority for the first co-primary endpoint. As the lower limit of the 95% CI for the estimated ratio between the treatment groups (0.97) was above the predefined non-inferiority margin (> 0.85), dexmedetomidine was proven clinically non-inferior to midazolam. Both PP and ITT population showed consistent results with a better trend in the PP population (ratio: 1.09 versus 1.07) supporting the primary analysis. Although duration of infusion was shorter as observed in the previous study 3005012, longer time at target was observed for dexmedetomidine group as compared with midazolam group (37.75 versus 37.07) supporting non inferiority results. However, the number of discontinuations because of lack of efficacy required further analyses prior any final conclusions are made.

The median duration of mechanical ventilation (i.e., time to being free from mechanical ventilation that was not re-instituted within 48 hours) was 41 hours shorter in the dexmedetomidine group (123 hours) than in the midazolam group (164 hours) in the ITT population. The pre-specified primary analysis was Cox's proportional hazards did not show statistical significance (Cox HR: 0.896, 0.738-1.087) while the Gehan-Wilcoxon test (which gives more weight to early events) did achieve statistical significance (p=0.033), suggesting a positive trend for the second co-primary endpoint.

Supportive studies

Results from open label and phase IV studies were supportive of the efficacy of dexmedetomidine in the clinical intended use. However, it should be noted that the level of sedation used as endpoint for the Phase IV study was only at 2.

Overall discussion

Overall, the CHMP requested further analyses to support the robustness of the results for the non inferiority (given potential lack of efficacy) and efficacy on mechanical ventilation versus standard of care. The clinical relevance of a few hours shorter ventilation compared to midazolam should also be further discussed prior any final conclusions are made. For both studies, additional data on patient disposition regarding the presence or absence of an analgesic epidural (in the post-surgical patients) and that of a tracheostomy were also requested. The CHMP noted that none of the pivotal studies investigated the use of dexmedetomidine as an 'induction agent' for the initiation of sedation. All of the patients studied were already sedated and ventilated at the time of randomisation. Furthermore, as a sedative rather than an anaesthetic agent, dexmedetomidine is unlikely to be suitable for intubation

and this scenario was not studied either. The CHMP therefore recommended the applicant to re consider the indication initially applied for, based on the robustness of the efficacy data. Furthermore, the CHMP noted that the use of a loading dose was not studied in phase III studies and recommended to remove it from the proposed dosing recommendation.

In responses to CHMP request, the applicant provided post-hoc analyses on co-primary endpoints, accounting for subjects prematurely withdrawn for the non inferiority analysis, and using time to extubation for the second co-primary analysis (see ancillary analyses 2.5.2.3).

On the basis of these analyses, the applicant made the following conclusions:

- The lower confidence intervals of the dexmedetomidine: ratios for standard treatment (propofol and midazolam) are > 0.85 in each analysis, thus establishing non-inferiority. The ratios of dexmedetomidine / propofol or midazolam range from 0.96 to 1.12 indicating close similarity.
- Considering tracheostomy patients to be extubated at insertion of the tracheostomy rather than at removal of inspiratory assist made very small differences in either direction in these analyses.
- The pooled data showed dexmedetomidine to be significantly better than standard sedation in reducing the duration of mechanical ventilation by both Cox's test (p=0.028) and Gehan Wilcoxon test (p=0.006). The combined reduction in mechanical ventilation time is 0.8 days (dexmedetomidine 83h; standard of care 102h). Dexmedetomidine was significantly better in the combined analysis than standard sedation in reducing the time to extubation by both Cox's test (p=0.002) and Gehan Wilcoxon test (p<0.001). The combined reduction in time to extubation is 0.96 days (dexmedetomidine 68h; standard of care 91h). Individually, studies 3005012 and 3005013 showed significant reductions in time to extubation by Cox's test (p=0.023 and p=0.029 respectively) and by Gehan Wilcoxon test (p=0.032 and p=0.002 respectively). Study 3005013 showed that dexmedetomidine reduced the duration of mechanical ventilation compared midazolam by Gehan Wilcoxon test (p=0.007) and approached significance by Cox's test (p=0.051).

Although, in the design of the phase III studies, there is an inherent methodological bias unfavouring dexmedetomidine in that patients who are already established on a sedative at an efficacious dose are likely to enter a period of "instability" when being switched to an alternative sedative, the CHMP noted that the majority of the patients who were successfully managed on dexmedetomidine did not require more rescue sedation than subjects receiving propofol, achieving a stable sedation.

The CHMP noted that the applicant proposed to revise the indication as follows:

"Dexdor is indicated for the light to moderate sedation of adult ICU patients. Light to moderate sedation means a sedation level not deeper than arousal in response to verbal stimulation (RASS 0 to -3)."

In addition, the applicant proposed to clearly inform the prescribers via the SmPC about the risk of insufficient sedation that was increased in patients who were difficult to sedate with standard care immediately prior to switching. In line with the CHMP recommendation, the applicant also amended the SmPC information to reflect that the use of a loading dose is not recommended as it can be associated with increased adverse reactions.

Having considered above, the CHMP was of the opinion that the applicant provided sufficient evidence to conclude on the efficacy of dexmedetomidine as a sedative agent and that appropriate information has been included in the SmPC to ensure effective use of dexmedetomidine in the intended clinical use.

On this basis, the CHMP recommended the following indication:

"For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3)."

The applicant agreed with the above recommended CHMP indication.

2.5.4. Conclusions on the clinical efficacy

The CHMP concluded that the efficacy in maintaining sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3)" was demonstrated in adult ICU patients in the proposed dosing regimen for Dexdor (dexmedetomidine).

2.6. Clinical safety

The safety database contains 106 clinical studies conducted in over 30 countries in Europe, North and South America, the Middle East, Africa, and the Far East. Studies conducted in Australia, New Zealand and Japan are also included. This comprised of 18 intensive care unit (ICU) studies, 45 non-ICU studies and 43 phase I studies that include 19 pharmacokinetic (PK) studies, 15 pharmacodynamic (PD) studies and 9 other studies conducted in healthy volunteers. Over 7500 subjects who received any injectable study drug, dexmedetomidine, placebo, or comparator (midazolam or propofol) are evaluated, in addition to those in studies where data was not pooled for safety analysis. In total: 2103, 2230 and 432 subjects in pooled data received dexmedetomidine at various doses and durations in the ICU, non-ICU and in the volunteer studies, respectively. In addition, there are over 1 million exposures to Dexmedetomidine, based on sales, mainly in the US since 1999.

2.6.1. Patient exposure

Data are presented in Tables 28, 29 and 30.

Table 28

Study grouping	Treatment group			
	All Dex	Randomised DEX	Placebo	Active comparator
All ICU studies	2103	1879	394	864
Comparator-controlled double blind	778	778	-	663
Placebo-controlled double blind	591	402	394	-
Comparator-controlled open	204	204	-	201
Non-comparator-controlled open	530	495	-	-
Non-ICU	2230	2166	1079	408
Continuous infusion procedural	324	320	113	-
Continuous infusion non-procedural	923	888	533	-
Single bolus i.v./i.m.	983	958	433	408
Healthy volunteers	432	432	141	26
Total subjects exposed	4765	4477	1614	1298

In the comparator-controlled double-blind ICU studies a dose up to 1.4 µg/kg/h was permitted for up to 14 days in Studies 3005011, 3005012 and 3005013 or 30 days in Study 2001-001. Most other ICU studies were conducted with a maximum dose level of 0.7 µg/kg/h for not more than 24 hours. Dosing schedules in the non- ICU studies were varied, some subjects receiving a single bolus of dexmedetomidine and others receiving a continuous infusion, sometimes over many hours. Infusions in the non-ICU studies were commonly based on target plasma concentrations (mostly between 0.2 – 0.6 ng/ml) so actual doses were variable. However for comparison mean dexmedetomidine concentration on day 2 of treatment in study 3005012 was 1.9 ng/ml.

Table 29

	ICU Studies		Non-ICU studies
	All DEX (N = 2103)	Randomised DEX (N = 1879)	All DEX (N = 2230)
Variable	n (%)		
Total cumulative dose (µg/kg)			
Mean	25.2	25.6	1.9
Median	7.6	7.8	2.0
Max	783	490	13
Dose per hour (µg/kg/h)			
Mean	0.6	0.6	0.9
Median	0.5	0.5	0.6
Max	6	6	16
Dose per hour category, n (%)			
≤ 0.7 µg/kg/h	1519 (72.2)	1326 (70.6)	597 (26.8)
> 0.7-1.1 µg/kg/h	370 (17.6)	352 (18.7)	132 (5.9)
> 1.1 µg/kg/h	201 (9.6)	190 (10.1)	275 (12.3)
Unknown	13 (0.6)	11 (0.6)	1226 (55.0)

Most subjects received dexmedetomidine for < 24 hours, including a significant proportion of subjects in the comparator-controlled double-blind ICU studies. 112 subjects received dexmedetomidine for longer than 5 days and only 22 subjects for longer than 10 days. Very few subjects required continuous sedation for longer than the 14 days permitted in the 3005012 and 3005013 studies and in

Study 2001-001 the longest exposure to dexmedetomidine was 15.6 days. In non-ICU studies almost all continuous infusions were shorter than 24 hours.

Table 30

	ICU Studies		Non-ICU studies
	All DEX (N = 2103)	Randomised DEX (N = 1879)	All DEX (N = 2230)
Variable		n (%)	
> 5 days	90 (4.3)	84 (4.5)	-
> 10 days	22 (1.0)	20 (1.1)	-
Unknown	8 (0.4)	8 (0.4)	924 (41.4)
Total subject days	2944	2709	300.7
Total subject days by dose			
≤ 0.7 µg/kg/h	1538.6	1375.5	194.4
> 0.7-1.1 µg/kg/h	801.0	779.9	10.4
> 1.1 µg/kg/h	611.7	552.3	12.9
Unknown	2.8	2.1	83.1

2.6.2. Adverse events

Tables 31 and 32 detail the number of subjects in all of the ICU studies (both placebo and comparator controlled) who experienced an adverse event and those AE with an incidence of >2% and statistically significantly greater than the comparator:

Table 31

	All DEX (N = 2103)	Randomised DEX (N = 1879)	MDZ (N = 401)	PRO (N = 463)	PBO (N = 394)
Category			n (%)		
Number of subjects who had an AE	1609 (76.5)	1447 (77.0)	377 (94.0)	374 (80.8)	268 (68.0)
Number of AEs	7001	6453	2438	1712	717
Number of subjects who had treatment related AEs	771 (36.7)	667 (35.5)	104 (25.9)	94 (20.3)	107 (27.2)
Number of treatment related AEs	1397	1213	194	137	192
Number of subjects who had moderate or severe AEs	1202 (57.2)	1086 (57.8)	290 (72.3)	292 (63.1)	189 (48.0)
Number of moderate or severe AEs	3644	3349	1281	1000	427
Number of subjects who had SAEs	515 (24.5)	480 (25.5)	176 (43.9)	151 (32.6)	48 (12.2)
Number of SAEs	1107	1012	357	320	96
Number of subjects who had treatment related SAEs	63 (3.0)	57 (3.0)	4 (1.0)	8 (1.7)	6 (1.5)
Number of treatment related SAEs	113	97	5	9	10
Death on prior to study treatment start	4 (0.2)				
Death on treatment	22 (1.0)	17 (0.9)	7 (1.7)	1 (0.2)	
Death on treatment or short term follow-up period	45 (2.1)	39 (2.1)	20 (5.0)	9 (1.9)	2 (0.5)
Death on long term follow-up period	176 (8.4)	165 (8.8)	77 (19.2)	42 (9.1)	6 (1.5)
AEs leading to discontinuation of study treatment	172 (8.2)	155 (8.2)	35 (8.7)	39 (8.4)	14 (3.6)
Number of subjects who had an AE prior to treatment	186 (8.8)	152 (8.1)	32 (8.0)	44 (9.5)	68 (17.3)
Number of AEs prior to treatment	260	208	45	61	87

Table 32

Comparator-controlled double-blind ICU studies				Placebo-controlled double-blind ICU studies		
	DEX N = 778%	MDZ N = 388%	PRO N = 275%		DEX N = 402%	PBO N = 394%
Preferred term	%			Preferred term	%	
Bradycardia	23.7	11.9[2]	9.8[2]	Hypotension	27.4	11.2[2]
Hypotension	21.7	17.3	13.8[1]	Bradycardia	5.2	2.5[1]
Tachycardia	14.9	17.3	1.1[2]	Dry mouth	3.2	1.0[1]
Diastolic hypotension	13.8	13.9	0[2]	Blood pressure increased	2.5	0.3[1]
Systolic hypertension	11.7	14.9	0[2]	Tachycardia	2.2	4.3[1]
Atrial fibrillation	8.2	11.1	12.4[1]	Thirst	2.0	0.3[1]
Anxiety	7.2	3.9[1]	8.7	Pneumothorax	0.2	2.0[1]
Hypokalaemia	6.6	6.7	2.2[1]			
Nausea	5.7	2.3[1]	4.0			
Diastolic hypertension	5.1	5.7	0[2]			
Constipation	4.0	5.2	1.5[1]			
Hypoglycaemia	3.6	3.4	1.1[1]			
Hyperglycaemia	3.3	1.8	0[2]			
Pleural effusion	3.1	3.9	10.5[2]			
Renal failure	2.2	1.0	5.1[1]			
GGT increased	1.9	4.9[1]	4.7[1]			
Generalised oedema	0.9	2.3[1]	0			
Hypomagnesaemia	0.8	2.6[1]	0.4			
Sedation	0.4	3.1[2]	0.4			
Blood triglycerides increased	0.3	0.3	2.2[1]			

PBO = placebo, GGT = gamma-glutamyl transferase
[1] $p < 0.05$ compared to DEX
[2] $p < 0.001$ compared to DEX

2.6.3. Serious adverse event/deaths/other significant events

The overall mortality rate in the ICU studies was similar for dexmedetomidine and propofol but higher in the midazolam treatment group. See Table 33.

Table 33

	All DEX N = 2103	Randomised DEX N = 1879	MDZ N = 401	PRO N = 463	PBO N = 394
Study period	N (%)				
During study treatment	22 (1.0)	17 (0.9)	7 (1.7)	1 (0.2)	0 (0.0)
Short term follow-up period[1]	23 (1.1)	22 (1.2)	13 (3.2)	8 (1.7)	2 (0.5)
Long term follow-up period[2]	176 (8.4)	165 (8.8)	77 (19.2)	42 (9.1)	6 (1.5)
Total deaths	221 (10.5)	204 (10.9)	97 (24.2)	51 (11.0)	8 (2.0)

A total of 1880 serious adverse events (SAEs) were reported in a total of 890 subjects in the ICU sedation population, of which 1107 SAEs were in 515 dexmedetomidine treated, 357 SAEs were in 176 midazolam treated, 320 SAEs were in 151 propofol treated and 96 SAEs in 48 placebo treated subjects. The majority of SAEs (1403/1880 SAEs in 642/890 subjects) were reported in the comparator controlled, double-blind ICU studies, consistent with a population that was more severily ill than those in the non-ICU and PK/PD populations, as reflected in the mortality rates and baseline SAPS of this patient population.

The most commonly reported treatment emergent SAEs in the integrated ICU population with dexmedetomidine were hypotension, respiratory failure, bradycardia, multi-organ failure, acute respiratory distress syndrome, septic shock and sepsis. The majority of SAEs occurred in < 1% of dexmedetomidine treated subjects and involved relatively few subjects. See Table 34.

Table 34

	All DEX (N = 2103)	Randomised DEX (N = 1879)
Preferred term	Subjects n (%)/Events n	
Hypotension	37 (1.8) 38	32 (1.7) 33
Respiratory failure	20 (1.0) 21	19 (1.0) 20
Bradycardia	18 (0.9) 20	16 (0.9) 18
Multi-organ failure	14 (0.7) 15	10 (0.5) 10
Septic shock	13 (0.6) 13	13 (0.7) 13
Acute respiratory distress syndrome	13 (0.6) 13	12 (0.6) 12
Sepsis	13 (0.6) 13	12 (0.6) 12
Pneumonia	13 (0.6) 13	11 (0.6) 11
Cardiac arrest	11 (0.5) 12	9 (0.5) 10
Haemorrhage	9 (0.4) 9	9 (0.5) 9

In the comparator controlled studies, SAEs were seen to have comparable incidence across treatment groups. See Table 35.

Table 35

	Randomised DEX (N = 778)	Midazolam (N = 388)	Propofol (N = 275)
Preferred term	Subjects n (%)/Events n		
Respiratory failure	16 (2.1) 17	9 (2.3) 9	7 (2.5) 7
Septic shock	11 (1.4) 11	10 (2.6) 11	2 (0.7) 2
Sepsis	11 (1.4) 11	4 (1.0) 4	2 (0.7) 2
Bradycardia	10 (1.3) 12		2 (0.7) 2
Acute respiratory distress syndrome	10 (1.3) 10	5 (1.3) 5	2 (0.7) 2
Hypotension	10 (1.3) 10	2 (0.5) 2	3 (1.1) 3
Pneumonia	10 (1.3) 10	3 (0.8) 3	
Multi-organ failure	9 (1.2) 9	4 (1.0) 4	5 (1.8) 5
Cardiac arrest	5 (0.6) 5	2 (0.5) 2	1 (0.4) 1
Drug ineffective	5 (0.6) 5		
Renal failure	5 (0.6) 5	1 (0.3) 1	3 (1.1) 3
Endotracheal intubation complication	4 (0.5) 4		3 (1.1) 3
Hypoxia	4 (0.5) 4	4 (1.0) 4	1 (0.4) 1
Peritonitis	4 (0.5) 4		
Renal failure acute	4 (0.5) 4	1 (0.3) 1	
Agitation	3 (0.4) 4		
Acute myocardial infarction	3 (0.4) 3		
Acute lung injury	3 (0.4) 3		
Acute respiratory failure	3 (0.4) 3		1 (0.4) 1
Atrial fibrillation	3 (0.4) 3	2 (0.5) 2	2 (0.7) 2
Myocardial infarction	3 (0.4) 3	1 (0.3) 1	1 (0.4) 1
Pneumothorax	3 (0.4) 3	5 (1.3) 5	1 (0.4) 2
Respiratory distress	3 (0.4) 3	3 (0.8) 3	
Ventricular tachycardia	3 (0.4) 3		1 (0.4) 1

2.6.4. Laboratory findings

Laboratory abnormalities are very common in ICU patients. There were no large or notable differences between the study treatments in the comparator-controlled double-blind ICU studies.

2.6.5. Safety in special populations

Intrinsic Factors

There was a slight tendency for female subjects to have more bradycardia, hypotension and hyperglycaemia on dexmedetomidine compared to males, despite that clearance of dexmedetomidine was comparable to males when corrected for weight. The number of black subjects was low and so results may be significantly affected by case-mix but these subjects seemed to have a higher incidence of bradycardia and hyperglycaemia on dexmedetomidine. Subjects with cardiovascular disease, diabetes and neurological disorders appeared to be at higher risk for cardiovascular adverse events during sedation with dexmedetomidine but this difference was common to other sedatives (especially midazolam) and did not identify any group with higher susceptibility to dexmedetomidine effects. Severity of illness judged by SAPS II score did not predict any increase in adverse events on dexmedetomidine.

No studies on the use of dexmedetomidine in pregnancy or lactation have been performed and there are no exposures to pregnant or lactating women in the available studies.

Extrinsic Factors

The ICU studies were primarily conducted in Northern Europe or the USA. In those territories ICU practices are relatively consistent and that is expected to be the case also in general in Southern Europe. There may be less frequent use of sedation stops in Southern European states and this could be expected to lead to more over-sedation and less agitation with standard of care but it is not known whether such differences would also exist during dexmedetomidine treatment. The pattern of adverse effects during clinical studies of dexmedetomidine in Japan does not appear substantially different from the European experience.

The standardised environment in the ICU somewhat reduces the possible impact of social factors such as culture and education. The major ICU studies did not collect data on these issues or on factors such as diet, alcohol use, smoking or drug abuse and therefore these cannot be tested adequately on the available database. However such substances are not continued in an ICU environment (except occasionally administration of nicotine to prevent withdrawal) and subjects in the submitted studies were not generally included until a point when high drug or alcohol levels at hospital admission could be expected to have diminished considerably.

2.6.6. Safety related to drug-drug interactions and other interactions

See clinical pharmacology studies.

2.6.7. Discontinuation due to adverse events

Data are presented in Table 36.

Table 36. Significant AEs leading to drug discontinuation in the comparator-controlled double-blind ICU studies

	All DEX N = 778	**MDZ N = 388**	**PRO N = 275**
	Subjects n (%)/Events n		
Bradycardia	18 (2.3) 18	1 (0.3) 1	1 (0.4) 1
Agitation	17 (2.2) 17	7 (1.8) 7	2 (0.7) 2
Hypotension	12 (1.5) 13	1 (0.3) 1	3 (1.1) 3
Drug ineffective	11 (1.4) 11	0	0
Drug effect decreased	4 (0.5) 4	0	1 (0.4) 1
Sedation	1 (0.1) 1	6 (1.5) 6	0

2.6.8. Post marketing experience

On the basis of more than 1.5 million patient treatment days with dexmedetomidine worldwide, the number of individual case reports received in this period is 978, and they included altogether 1497 adverse reactions, 731 of which were serious and 766 of which were non-serious. The most commonly reported events were hypotension included in 358 reports (MedDRA PTs hypotension, blood pressure decreased, and blood pressure systolic decreased combined) and bradycardia included in 221 reports (PTs bradycardia, sinus bradycardia and heart rate decreased combined). Hypertension is included in 65 reports (PTs hypertension, blood pressure increased, and blood pressure systolic increased combined) and aspartate aminotransferase increased in 58, alanine aminotransferase increased in 34, blood bilirubin increased in 33 and hepatic function abnormal in 29 reports.

The most commonly reported adverse reactions arising from the spontaneous reports are in line with the clinical study AE data and no new safety signals have been identified from these post-marketing data.

2.6.9. Discussion on clinical safety

Patients treated in an ICU have typically substantial instability in several organ systems. Signs and symptoms that could be classified as AEs are very common among ICU patients and to identify AEs related to a certain drug requires large study populations if not obviously linked to a certain drug. The exposure to dexmedetomidine both in clinical studies and when used in daily clinical settings can be considered large. In clinical studies, 4765 subjects, whereof 2103 < were ICU patients, have been exposed to dexmedetomidine. The estimated post-marketing exposure included more than 1 million patients. The safety database for dexmedetomidine is however limited regarding patients who required a duration of infusion longer than 24 hours and also those who experienced upper dose range >0.7 µg/kg/h and representing approximately half of the total exposure. No studies on the use of dexmedetomidine in pregnancy or lactation have been performed and there are no exposures to pregnant or lactating women in the available studies. Considering the reproductivity seen in animal studies, dexmedetomidine should not be used during pregnancy unless clearly necessary.

The overall safety profile of dexmedetomidine has been found to be rather consistent and most reported AEs can be associated to its agonist effects on alpha-2 adrenoceptors, mainly cardiovascular related AEs.

Cardiovascular events were most prominent with hypotension, hypertension and bradycardia being the most commonly reported AEs on dexmedetomidine. These AEs were reported with statistically significantly greater incidence in dexmedetomidine group as compared to propofol and midazolam groups. However no clear dose relationship has been established.

Dexmedetomidine had an overall neutral effect on mortality. Most deaths occurred well after the treatment period, were considered not related and reflected the common causes of death in critically ill patients in the ICU being refractory respiratory failure, multiple organ failure and septic shock or uncontrolled infection. In particular, cardiovascular deaths were not increased on dexmedetomidine. Mortality in postsurgical patients and those in studies outside the ICU was very low with no apparent difference between treatment groups.

In the comparator controlled studies, SAEs were seen to have comparable incidence across treatment groups. The most common treatment emergent SAEs reported were respiratory failure, septic shock, sepsis, bradycardia, acute respiratory distress syndrome and hypotension. These are all common conditions that would be expected of a general ICU patient population with predominance of medical patients. The most common reasons for discontinuing study drug or reducing the dose were bradycardia, agitation and hypotension. Insufficient effect of dexmedetomidine was among the more common reasons for discontinuation and was previously discussed under clinical efficacy aspects.

Due to its pharmacological activity, dexmedetomidine also reduced HR resulting in more AEs of bradycardia as well as prolonged PR and QT interval on the 12-lead electrocardiogram (ECG). Four % of dexmedetomidine patients had bradycardia sufficiently severe to require treatment (normally anticholinergics) in studies 3005012 and 3005013. Additional cases of hypotension on dexmedetomidine reflected central sympatholysis. The pharmacological effect on glucose (reduction of insulin secretion leading to hyperglycaemia) was most likely masked by close glycaemic control in ICU patients and therefore both hypo/hyperglycaemia were commonly reported.

Hallucinations were reported in more patients receiving dexmedetomidine than propofol and midazolam, particularly in the ICU, although this was still uncommon. Hallucinations were not observed in the non-ICU studies. Hallucinations are known to be common in critically ill patients regardless of the method of sedation.

Overall, the safety profile of dexmedetomidine is considered well known and manageable in the intended clinical use. Dexmedetomidine is for hospital use only and should be administered by healthcare professionals skilled in the management of patients requiring intensive care. The CHMP however was concerned about literature data suggesting off label use of dexmedetomidine, particularly in the paediatric population and recommended the conduct of a drug utilisation study to address this issue. In addition to previous SmPC recommendations related to cardiovascular safety of dexmedetomidine, the CHMP also requested to include a warning related to risk of hypothermic bradycardia in neonates and information on higher incidence of cortisol suppression in dexmedetomidine as compared to midazolam and propofol observed in clinical studies.

2.6.10. Conclusions on the clinical safety

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics. Appropriate measures including an additional pharmacovigilance activity (see 2.7) has been put in place to ensure safe and effective use of the product in the recommended indication.

2.7. Pharmacovigilance

2.7.1. Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.7.2. Risk Management Plan

The applicant submitted a risk management plan

Table 37. Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risks		
Bradycardia	Routine pharmacovigilance,	Routine risk minimisation (Bradycardia is identified in the proposed SPC in Section 4.4 Special warnings and precaution for use, Section 4.5 Interaction with other medicinal products and other forms of interaction and Section 4.8 Undesirable effects. The SPC may be updated if new patterns develop during ongoing review)
Hypotension	Routine pharmacovigilance,	Routine risk minimisation

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		(Hypotension is identified in the proposed SPC in Section 4.4 Special warnings and precaution for use, Section 4.5 Interaction with other medicinal products and other forms of interaction and Section 4.8 Undesirable effects, and uncontrolled hypotension is included in section 4.3 Contraindications. The SPC may be updated if new patterns develop during ongoing review)
Hypertension	Routine pharmacovigilance	Routine risk minimisation (Hypertension is identified in the proposed SPC in Section 4.4 Special warnings and precaution for use and Section 4.8 Undesirable effects. The SPCmay be updated if new patterns develop during ongoing review) may be updated if new patterns develop during ongoing review)
Hyperglycaemia	Routine pharmacovigilance	Routine risk minimisation (Hyperglycaemia is identified in the proposed SPC in Section 4.8 Undesirable effects. The SPC may be updated if new patterns develop during ongoing review)
Withdrawal symptom	Routine pharmacovigilance,	Routine risk minimisation (Withdrawal syndrome is identified in the proposed SPC in Section 4.4 Special warnings and precaution for use and Section 4.8 Undesirable effects. The SPC may be updated if new patterns develop during ongoing review)
Important potential risks		
Hypoglycaemia	Routine pharmacovigilance Close monitoring with specified follow-up queries for each ICSR. Detailed review in PSURs.	Routine risk minimisation (Hypoglycaemia is identified in the proposed SPC in Section 4.8 Undesirable effects. The SPC may be updated if new patterns develop during ongoing review)
Atrioventricular block	Routine pharmacovigilance Close monitoring with specified follow-up queries for each ICSR. Detailed review in PSURs.	Routine risk minimisation (Atrioventricular block is identified in the proposed SPC in Sections 4.3 Contraindications and 4.8 Undesirable effects. The SPC may be updated if new patterns

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		develop during ongoing review)
Ischaemic heart disease	Routine pharmacovigilance Close monitoring with specified follow-up queries for each ICSR. Detailed review in PSURs.	Routine risk minimisation (The proposed SPC states that all patients should have continuous cardiac monitoring during Dexdor infusion. Myocardial ischaemia is described in Section 4.4. Special warnings and precautions for use and myocardial ischeamia or infarction in Section 4.8 Undesirable effects in the proposed SPC for Dexdor. The SPC may be updated if new patterns develop during ongoing review)
Cortisol suppression	Routine pharmacovigilance Close monitoring with specified follow-up queries for each ICSR. Detailed review in PSURs.	Routine risk minimisation (Cortisol suppression is identified in the proposed SPC in Section 5.1 Pharmacodynamic properties. The SPC may be updated if new patterns develop during ongoing review).
Convulsions	Routine pharmacovigilance Close monitoring with specified follow-up queries for each ICSR. Detailed review in PSURs.	Re-assessment of the need for risk minimisation measures (e.g. updating the SPC) will be conducted should specific new evidence regarding the risk be revealed from the routine pharmacovigilance practices.
Hypothermia	Routine pharmacovigilance Close monitoring with specified follow-up queries for each ICSR. Detailed review in PSURs.	Re-assessment of the need for risk minimisation measures (e.g. updating the SPC) will be conducted should specific new evidence regarding the risk be revealed from the routine pharmacovigilance practices.
Respiratory depression	Routine pharmacovigilance Close monitoring with specified follow-up queries for each ICSR. Detailed review in PSURs.	Re-assessment of the need for risk minimisation measures (e.g. updating the SPC) will be conducted should specific new evidence regarding the risk be revealed from the routine pharmacovigilance practices.
Tachypnoeic potential	Routine pharmacovigilance Close monitoring with specified follow-up queries for each ICSR. Detailed review in PSURs.	Re-assessment of the need for risk minimisation measures (e.g. updating the SPC) will be conducted should specific new evidence regarding the risk be revealed from the routine pharmacovigilance practices.
Overdose	Routine pharmacovigilance	Routine risk minimization

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	Close monitoring with specified follow-up queries for each ICSR. Detailed review in PSURs.	(Overdose is discussed in the proposed SPC in section 4.9. Guidances on the proper administration of dexmedetomidine and preparation of the infusion solution are given in section 4.2 Posology and method of administration and section 6.6 Special precautions for disposal and other handling of the proposed SPC, respectively.)
Misuse	Routine pharmacovigilance Close monitoring with specified follow-up queries for each ICSR. Detailed review in PSURs	Routine risk minimization (Dexdor is for hospital use only, and it is administered by healthcare professionals skilled in the management of patients in intensive care ensuring the proper detection and treatment of the identified and potential risks and reducing the possibility of misuse.)
Off label use	Routine pharmacovigilance Close monitoring with specified follow-up queries for each ICSR. Detailed review in PSURs Drug utilisation study to evaluate off label use (specifically paediatric use)	Routine risk minimization (Dexdor is indicated for sedation of adult ICU patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to RASS 0 to -3)). Dexdor should be administered by healthcare professionals skilled in the management of patients requiring intensive care. All patients should have continuous cardiac monitoring during Dexdor infusion or respiration should be monitored in non intubated patients
Missing information		
Pregnancy	Routine pharmacovigilance Detailed review in PSURs	Routine risk minimization (Pregnancy is discussed in proposed SPC in section 4.6 Fertility, Pregnancy and Lactation The SPC may be updated if new patterns develop during ongoing review)

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Drug utilisation study to evaluate the off-label use of Dexdor	Study protocol: within 3 months after EC decision Study initiation date: approximately 12 months after EC decision

No additional risk minimisation activities were required beyond those included in the product information.

2.8. Significance / Non-Conformity of paediatric studies

Not applicable

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

There has been a shift in ICU practice in recent years away from an absolute requirement for deep sedation and it is increasingly recognised that lighter levels of sedation with a resultant reduced period of time on a ventilator is desirable. Dexmedetomidine appears to offer a level of sedation comparable to an equivalent dose of midazolam and therefore may have some desirable qualities for patients requiring light to moderate sedation.

In study 3005013, the mean percentage of time at the target sedation level without use of rescue treatment was 60.7% and 56.6% for dexmedetomidine and midazolam groups, respectively confirming non inferiority for the first co-primary endpoint. As the lower limit of the 95% CI for the estimated ratio between the treatment groups (0.97) was above the predefined non-inferiority margin (> 0.85), dexmedetomidine was proven clinically non-inferior to midazolam. Both PP and ITT population showed consistent results with a better trend in the PP population (ratio: 1.09 versus 1.07) supporting the primary analysis. Although duration of infusion was shorter as observed in the previous study 3005012, longer time at target was observed for dexmedetomidine group as compared with midazolam group (37.75 versus 37.07) supporting non inferiority results. The median duration of mechanical ventilation (i.e., time to being free from mechanical ventilation that was not re-instituted within 48 hours) was 41 hours shorter in the dexmedetomidine group (123 hours) than in the midazolam group (164 hours) in the ITT population.

In study 3005012, the mean percentage of time at target sedation without use of rescue treatment were 64.6% versus 64.7% for dexmedetomidine and propofol groups, respectively, confirming non inferiority for the first co-primary endpoint. Both PP d ITT population showed consistent results. However; ITT results were less convincing than the PP (ratio: 0.97 versus 1.00), although the CI was still above the non-inferiority margin of 0.85.

The pooled data of phase III studies showed dexmedetomidine to be significantly better than standard sedation in reducing the duration of mechanical ventilation by both Cox's test (p=0.028) and Gehan Wilcoxon test (p=0.006). The combined reduction in mechanical ventilation time was 0.8 days (dexmedetomidine 83h; standard of care 102h). Dexmedetomidine was significantly better in the combined analysis than standard sedation in reducing the time to extubation by both Cox's test (p=0.002) and Gehan Wilcoxon test (p<0.001). The combined reduction in time to extubation was 0.96 days (dexmedetomidine 68h; standard of care 91h). Individually, studies 3005012 and 3005013 showed significant reductions in time to extubation by Cox's test (p=0.023 and p=0.029 respectively) and by Gehan Wilcoxon test (p=0.032 and p=0.002 respectively).

Uncertainty in the knowledge about the beneficial effects.

There are ICU patients for whom dexmedetomidine will not be able to provide a sufficient level of sedation. Furthermore, there are clinical ICU situations that may not be suitable for the use of dexmedetomidine considering its cardiovascular adverse effects and that no clear dose response has been established, dexmedetomidine is being administered to effect. These uncertainties have been considered manageable via routine pharmacovigilance and adequate labelling.

In study 3005012, the CHMP was concerned that patients randomised to dexmedetomidine spent on average a substantially shorter time at target (33.51 versus 47.12, ie 14 hours less) suggesting that patients on dexmedetomidine were discontinuing study treatment earlier than those on propofol for reasons related treatment. The number of discontinuations because of lack of efficacy further supported this finding. This uncertainty was addressed by adequate post-hoc analyses. Although, in the design of phase III studies, there is an inherent methodological bias unfavouring dexmedetomidine in that patients who are already established on a sedative at an efficacious dose are likely to enter a period of "instability" when being switched to an alternative sedative, the CHMP noted that in study 3005012, the majority of the patients who were successfully managed on dexmedetomidine did not require more rescue sedation than subjects receiving propofol , achieving a stable sedation.

In study 3005012, for the second co-primary endpoint, the duration of mechanical ventilation did not differ statistically significantly between treatment groups using different tests (Gehan Wilcoxon : p=0.240; Cox HR:0.49, 0.77-1.13). However, from a statistical perspective, the hierarchical approach used for the co-primary endpoints can be considered sufficient to make the study positive.

Literature suggested off label use of dexmedetomidine, particularly in the paediatric population while there are limited paediatric data. A drug utilisation study to address the issue of off label use has been included as part of the risk management plan.

Risks

Unfavourable effects

Maternal and foetal toxicity (including embryo-foetal deaths) in animal studies were noted.

Dexmedetomidine is a specific alpha-2 adrenoceptor agonist and its safety profile can be considered well known (e.g. bradycardia, hypotension, reduced cardiac output) and supported by more than ten years of post-marketing experience. No new safety signals have been identified from the clinical studies and post-marketing data.

Excessive dosing in patients with severe hepatic impairment may lead to over sedation and increase risk of adverse reactions. Dexmedetomidine should be used with caution in patients with hepatic impairment and that a dose reduction may be considered in this population.

Uncertainty in the knowledge about the unfavourable effects

It should be noted that the proposed posology is different to that approved elsewhere in the world and this should be considered when interpreting the global post-marketing safety data. Therefore, the safety database for dexmedetomidine is limited regarding patients who required a duration of infusion longer than 24 hours and also those who experienced upper dose range >0.7 µg/kg/h.

No studies on the use of dexmedetomidine in pregnancy or lactation have been performed and there are no exposures to pregnant or lactating women in the available studies. Considering the pre-clinical data, dexmedetomidine should not be used during pregnancy unless clearly necessary.

No clear dose relationship has been established regarding the adverse events profile of dexmedetomidine.

Benefit Risk Balance

Importance of favourable and unfavourable effects

Non inferiority versus midazolam and propofol as a standard of care has been established. Dexmedetomidine is of particular benefit as an additional alternative to achieve desirable sedation level not greater than -3 according to the RASS, in ICU patients considering the current clinical practice. Dexmedetomidine also allows further flexibility in the ICU setting for patients who do not require deep sedation and has shown additional advantage in reducing the time for extubation as compared to standard of care. In addition, the safety profile of dexmedetomidine is considered well known based on its extensive clinical and post-marketing exposure and is manageable via routine pharmacovigilance and adequate Labelling. The product is intended for hospital use and should be administered by healthcare professionals skilled in the management of patients requiring intensive care.

Benefit-risk balance

Having considered the benefits of dexmedetomidine as a sedative agent over the potential and identified risks, the CHMP concluded that the benefit risk balance for dexmedetomidine is positive for the following indication:

For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3).

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Dexdor (dexmedetomidine) *"For sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3)."* is favourable and therefore recommends the granting of the marketing authorisation.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable