SECTION 1.0 MATERIALS USED IN REVIEW

Table 1 MATERIALS UTILIZED IN REVIEW

ITEM	DATE	MATERIAL
Volumes 1,2,3	18 December 1998	Introductory Information Proposed Labeling Application Summary
Volumes 63-725	18 December 1998	Clinical Data Case Report Forms
Amendment	5 April 1999	Additional Information
Amendment	24 May 1999	Additional Information

SECTION 2.0 BACKGROUND

SECTION 2.1 INDICATION

Dexmedetomidine is an intravenous alpha-2 adrenoreceptor agonist indicated for sedation and analgesia in an Intensive Care Unit setting.

SECTION 2.2 RELATED NDA'S AND IND'S

All clinical studies were conducted ———— . No previous NDAs are applicable.

SECTION 2.3 PROPOSED DIRECTIONS FOR USE

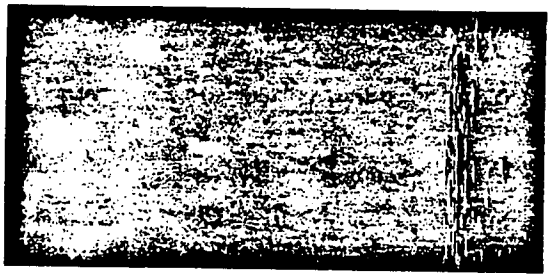
Dexmedetomidine is proposed for adults 18 years and older in an Intensive Care Setting who require sedation or potentiation of analgesia for up to 24 hours. The drug will be administered intravenously. Dosing is initiated with a loading dose of 1 µg/kg over 10 minutes followed by a maintenance dose of 0.2-0.7 µg/kg/hour; dosing is adjusted to achieve the desired level of sedation. The total daily dose will not exceed 20 µg/kg with a daily steady state plasma concentration exposure of less than 3.0 ng/ml.

SECTION 2.4. FOREIGN MARKETING

Dexmedetomidine is not marketed anywhere in the world.

SECTION 3.0 CHEMISTRY

[redacted]



Sponsor states the solution should be stored at room temperature (59 to 86 degree F).

SECTION 4.0 ANIMAL PHARMACOLOGY/TOXICOLOGY

The following is a summary of the pharmacology/toxicology provided by the sponsor:

"Alpha-2 adrenoceptor agonists have been in clinical use since the mid 1960s with the introduction of clonidine, the archetypal alpha-2 adrenoceptor agonist. Although clonidine has been used as an antihypertensive drug, it is also used as an adjunctive sedative in the intensive care setting.

Alpha-2 adrenoceptor activation is known to result in a variety of responses from several organs and tissues. A prominent effect is reduction in sympathetic nervous activity. Activation of presynaptic alpha-2 adrenoceptors located in sympathetic nerve endings inhibits the release of the neurotransmitter noradrenaline. Activation of postsynaptic alpha-2 adrenoceptors in the CNS leads to inhibition of sympathetic activity, causing decreases in blood pressure and heart rate, sedation, and relief of anxiety. Activation of alpha-2 adrenoceptors at the spinal cord results in analgesia. Peripheral alpha-2 adrenoceptors in blood vessels mediate vascular smooth muscle contraction.

Alpha-2 adrenoceptors agonists can decrease stress induced ACTH release and hence cortisol synthesis by a direct effect on the brain. Alpha-2 adrenergic agonists can inhibit insulin release by actions on pancreatic islet cells and have been shown to stimulate

growth hormone. Subcutaneous administration of Dexmedetomidine increased blood glucose, decreased insulin secretion, and inhibited lipolysis. Alpha-2 adrenoceptor agonists decrease circulating norepinephrine and epinephrine by central and peripheral mechanisms.

Dexmedetomidine is a specific alpha-2 adrenoceptor agonist as shown by both receptor binding and functional studies. Dexmedetomidine has very low affinity for alpha-1 adrenoceptors (1300 times less than for alpha-2 adrenoceptors in the rat membrane model) and negligible affinity for other receptors, including beta adrenergic, muscarinic, dopamine, serotonin, mu- and delta opiate, GABA, and benzodiazepine receptors. Dexmedetomidine is a lipophilic compound which is rapidly and extensively distributed to tissues and rapidly eliminated.

Dexmedetomidine is an alpha-2 sedative in various animal species including the rat, dog, rabbit, and mouse producing dose dependent sedation/hypnosis when administered either intracerebroventricularly, subcutaneously, intraperitoneally, or intravenously. The sedative effect is biphasic: lower (10-300 μg/kg) doses cause maximal sedation and higher doses (≥ 1000 μg/kg) result in a reversal of the Dexmedetomidine sedative effect. The reversal of the sedative effect seen at higher doses of Dexmedetomidine is hypothesized to be due to the activation of alpha-1 adrenoceptors by Dexmedetomidine, as the reversal could also be blocked by the alpha-1 antagonist prazosin. At low doses (< 3 μg/kg) Dexmedetomidine is anxiolytic in mice and rats. It acts synergistically with midazolam, diazepam, or fentanyl to induce sedation/hypnosis and has potent volatile anesthetic sparing properties which are mediated via central alpha-2 adrenoceptors.

Dexmedetomidine administered both spinally and peripherally to rats, dogs, mice monkeys, and sheep produces dose dependent analgesia which is more potent than that caused by clonidine, ST-91, xylazine, epinephrine, or norepinephrine. The analgesia effect in animals lasts 1 to 8 hours depending on the route of administration. The analgesic effects of Dexmedetomidine are mediated by alpha-2 adrenoceptors.

Lower doses of Dexmedetomidine cause reduction in blood pressure and heart rate through a central effect whereas higher doses of Dexmedetomidine result in peripheral alpha-1 adrenoceptor activation and resultant higher blood pressure. The initial hypertensive effect of Dexmedetomidine seen with IV bolus injections is reduced with a slower rate of infusion. At doses causing increases in mean arterial pressure, Dexmedetomidine reduces heart rate and cardiac output in a dose dependent manner. Dexmedetomidine has no direct depressant effect on the myocardium except at a very high supra-clinical concentration. Through its sympatholytic action, Dexmedetomidine depresses cardiac function and contractility; the effect on cardiac function and contractility are dose dependent.

Dexmedetomidine produces no significant effect on respiratory function except for mild respiratory depression at high supra-clinical doses.

Other effects of Dexmedetomidine in animals include reduced seizure thresholds, modulation of body temperature, and induction of hypothermia. Dexmedetomidine acts in an additive manner with opioids in producing analgesia and counteracts opioid induced muscle rigidity.

Animal deaths have been reported only after the administration of doses of Dexmedetomidine exceeding the LD50. All adverse effects are extensions of alpha-2 adrenergic activity."

SECTION 5.0 SUMMARY OF HUMAN PHARMOKINETICS

The pharmacokinetic and pharmacodynamic profiles of Dexmedetomidine were based on data from 14 studies. The sponsor has summarized the human pharmacokinetic and bioavailability data as follows:

"Dexmedetomidine is extensively metabolized in humans. In a radiolabeled Dexmedetomidine study, there was virtually no penetration of radioactivity into the cellular fraction. The major circulating metabolites are the N-glucuronides of Dexmedetomidine. Other minor metabolites include the carboxy (COOH), N-methylated (N-meth), the glucuronide conjugate of hydroxylated Dexmedetomidine, and additional unidentified minor metabolites.

The pharmacokinetics of Dexmedetomidine are biphasic with rapid distribution ($t\ ½\ \alpha \cong 6$ min) and a mean terminal half life of approximately 2.0 to 2.5 hours. Following the loading infusion, venous plasma concentrations rise rapidly. Due to the rapid distribution pharmacokinetics, concentrations drop quickly when the loading infusion stops, after which the combined effects of the loading and maintenance infusions hold plasma concentrations stable until the infusion is terminated. Dexmedetomidine is almost exclusively eliminated by metabolism; 95% of a radioactive dose is excreted as conjugates in the urine, and the remainder in the feces.

The following were measured PK parameters in healthy human subjects:

Table 2 Dexmedetomidine Pharmacokinetic Parameters

Parameter	Mean Value (±SD)
Cmax (ng Eq/g)	3.12 ± 0.27
T ½ (h)	2.85 ±1.1
AUC (ng-h/g)	3.49 ±0.68
Clearance (L/hour)	42.6 ±7.1
Volume of distribution (L)	143.9 ±15.5

Modified Sponsor's Table 3 Vol 8/10-1-69

Dexmedetomidine is 93.7% bound to plasma proteins. There is no difference in binding due to gender, and it does not differ in normal subjects or subjects with mild, moderate, or severe renal impairment. Subjects with hepatic impairment have protein binding that is 82-88% of the protein binding of normal subjects depending on the severity of the impairment.

Mean arterial pressure, systolic blood pressure, and diastolic blood pressure showed a biphasic response with initial decreases at the lowest concentrations, followed by a return to baseline and increases over the mean baseline level when the plasma concentration of Dexmedetomidine was greater than 3.2 ng/ml. The mean heart rate decreased progressively until the mean plasma concentration of Dexmedetomidine was 3.2-5.1 ng/ml; at this concentration heart rate reached a plateau and did not decline further. Cardiac output decreased approximately 20-30% at Dexmedetomidine plasma concentrations of 2-4 ng/ml in most subjects. At concentrations above 4 ng/ml, no further decrease in cardiac output was observed. There was no evidence of respiratory depression.

Special Populations:

Renal Failure: During a 2 day study period, six severely renally impaired subjects (creatinine clearance < 3 ml/min) received a single 10 minute intravenous infusion of Dexmedetomidine 0.6 µg/kg; they were compared to healthy subjects. Pharmacokinetics, sedation, heart rate, blood pressure, oxygen saturation, respiratory rate, and safety were assessed. Blood and urine samples were collected for assay of Dexmedetomidine and Dexmedetomidine metabolites. The collection of the samples occurred prior to dosing, during the infusion, and at protocol specified time points up to 24 hours post-dosing. There were no statistically significant differences between the two groups for any of the pharmacokinetic parameters. There were no clinically relevant differences between healthy subjects and renally impaired subjects. The renal subjects were slightly more sedated than control subjects.

Hepatic Impairment: During a 3 day study, 18 subjects with hepatic impairment received a single 10 minute intravenous infusion of Dexmedetomidine 0.6µg/kg; they were compared to healthy subjects. The objective of the study was to evaluate the effect of various degrees of hepatic impairment on the pharmacokinetics of Dexmedetomidine. In addition, sedation, heart rate, blood pressure, oxygen saturation, respiratory rate, and safety were assessed. The hepatic subjects contained groups with mild, moderate, and severe hepatic failure. Dexmedetomidine clearance values for subjects with mild, moderate, and severe hepatic impairment were only 74%, 64%, and 53%, respectively of those observed in the normal healthy subjects. Subjects with hepatic impairment appeared to have no clinically relevant different effects on hemodynamic or respiratory parameters. Sedation may have been greater in the hepatically impaired group. Therefore, the dose of Dexmedetomidine may need to be reduced in subjects with hepatic impairment.

Drug Interaction: 6 studies in humans were performed to evaluate possible interactions between Dexmedetomidine and other drugs. 5 of these studies involved pharmacokinetic

analysis. The agents studies were isoflurane, midazolam, alfentanil, propofol, rocuronium, and esmolol (no PK analyses were performed with esmolol). Except for alfentanil, no pharmacokinetic interactions were observed. PK effects by Dexmedetomidine on alfentanil were observed along with enhancement of alfentanil's analgesic effects.

Age: The influence of age on the pharmacokinetics of Dexmedetomidine in healthy subjects was evaluated by administration of 0.6 µg/kg Dexmedetomidine given as a 10 minute intravenous infusion. Subjects were studied up to 24 hours following infusion. Age groupings varied from 18 years to > 65 years. Dexmedetomidine pharmacokinetics were not different between young, middle aged, and elderly subjects nor between male and female subjects when differences in body weight were accounted for. Therefore the same Dexmedetomidine infusion is expected to produce the same Dexmedetomidine profile, and the elimination characteristics are expected to be the same irrespective of age or gender."

SECTION 6.0 DESCRIPTION OF CLINICAL DATA SOURCES

SECTION 6.1 DEVELOPMENT

Sponsor presents the following information on development of Dexmedetomidine:

"Farmos Group, Finland began research involving alpha-2 adrenoceptor agonists and antagonists in the late 1970s. One of the first agents was detomidine which has a higher affinity for the alpha-2 adrenoceptor than clonidine. Detomidine was developed for use as a sedative/analgesic in horses and cattle and it was first registered for marketing in Finland in 1983. Medetomidine, a more specific and selective alpha-2 adrenoceptor agonist than clonidine, was launched in 1987 in Finland and the Scandinavian countries for use as a veterinary sedative/analgesic in dogs and cats; it was approved for use in animals in the US in 1997. The sedative and anesthetic pharmacological activity of medetomidine resides predominantly in the dextro enantiomer, Dexmedetomidine, which was first synthesized by Farmos group in 1986.

Clinical work in the US began with the submission of an Investigational New Drug Application in 1989. Clinical investigation included many potential applications of Dexmedetomidine from preoperative through postoperative periods. In 1990 Farmos merged with Orion Corp. [redacted] ge form of Dexmedetomidine for clinical use to Abbott Laboratories in 1994."

SECTION 6.2 OVERVIEW OF CLINICAL STUDIES

[redacted] conducted a total of 56 clinical trials in which a total of 1527 subjects/patients were exposed to Dexmedetomidine. The [redacted] studies evaluated the use of Dexmedetomidine in the perioperative setting and utilized various modes of administration including rapid IV infusion, continuous IV infusion, and IM injection. Transdermal and oral administration of Dexmedetomidine were also studied in a limited capacity.

Abbott Laboratories initiated its own clinical program to evaluate Dexmedetomidine in the perioperative setting using IV infusion administration. A total of 21 studies (13 Phase I and 8 Phase II/III) have been completed in the US, Canada,, and Europe in support of the perioperative program, during which a total of 230 subjects were dosed and 767 patients received Dexmedetomidine. 13 of the 21 studies were Phase I trials assessing the pharmacokinetic/pharmacodynamic properties of Dexmedetomidine, the safety profile, the potential for drug interactions, and its use in special populations. The remaining 8 studies were Phase II/III trials evaluating the use of Dexmedetomidine as an anesthetic adjunct in patients undergoing major surgery and electroconvulsive therapy. The effect on minimum alveolar concentration of an inhalation anesthetic was also studied. 4 studies were conducted in Europe and Canada by Abbot Labs to evaluate Dexmedetomidine's potential as a sedative and analgesic agent for patients in the intensive care setting. A total of 631 subjects/patients were dosed/treated with Dexmedetomidine in these studies.

SECTION 6.3 DEMOGRAPHICS

See Section 8.2

SECTION 6.4 EXTENT OF EXPOSURE

See Section 8.1

SECTION 7.0 EFFICACY FINDINGS

SECTION 7.1 OVERVIEW OF CLINICAL EFFICACY STUDIES:

The Sponsor identified two Phase III studies that were conducted in support of this NDA application: W97-245 and W97-246. Sponsor also identified one Phase II study supporting the application, W97-249. Study W97-249 randomized 12 patients in one center and was not reviewed for findings of efficacy.

SECTION 7.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY

SECTION 7.2.1 STUDY W97-245

SECTION 7.2.1.1 PROTOCOL REVIEW SUMMARY

TITLE: A Phase III, Multi-Center, Randomized, Placebo-Controlled, Double-Blind Study Evaluating the Safety and Efficacy of Dexmedetomidine When Compared to Placebo, With Midazolam, in ICU Sedation in Post-Operative Patients

OBJECTIVES:

Primary: The primary objective of this two-part, Phase III study was to evaluate the efficacy and safety of Dexmedetomidine in patients requiring ventilation, sedation, and intensive care following surgery. Dexmedetomidine was to be administered as clinically indicated according to Ramsay sedation scores [see Appendix 1 for description of Ramsay sedation score]; the goal was to achieve Ramsay scores of ≥ 3, as clinically indicated. The primary efficacy variable for this study was the total dose (mg) of midazolam required in addition to the study drug to achieve adequate sedation (as clinically determined by the Ramsay sedation scale) during intubation.

Secondary: Secondary variables included total dose of midazolam (mg) administered during study drug infusion, use of morphine for pain, as assessed by total dose used with Dexmedetomidine as compared to placebo; use of paracetamol for pain after extubation, as assessed by total dose used with Dexmedetomidine as compared to placebo, and time to extubation, as measured by time to arrival in ICU until time to extubation.

STUDY DESIGN:
This was a two part study in postoperative patients requiring a minimum of 6 hours ventilation and sedation in ICU. Part I was open-label to allow the investigator to become more familiar with the observed clinical effects of Dexmedetomidine prior to starting the double-blind portion of the study. Part II was double blind, randomized, and placebo-controlled.

Patients were to be screened within 7 days prior to receiving study drug. Screening was to include a complete medical history and physical examination, laboratory assessments, and 12-lead electrocardiogram. Study drug administration was to be initiated as soon as possible after arrival in the ICU but not later than 1 hour after admission to the ICU. If

possible, study drug was to be started prior to the patient's awakening in the ICU or requiring any other medication for sedation. If a patient required sedation post-surgery and prior to the start of study drug, midazolam (1-mg bolus) could be given as required. Study drug infusion was to be continued for 6 hours post extubation. The investigator could have continued the infusion at his/her discretion for a maximum of 24 hours. Patients were to be observed for a 24-hour period after the end of the study drug infusion.

Part I of the study was to include up to 4 patients per site. Patients were to be administered a loading dose of 6.0 mcg/kg/h of Dexmedetomidine over a 10 minute period, followed by a maintenance infusion of 0.4 mcg/kg/h. Following the initial maintenance infusion, the rate was to be adjusted if clinically necessary, in increments of 0.1 mcg/kg/h or higher. The infusion rate was to be maintained between a range of 0.2 to 0.7 mcg/kg/h to achieve and maintain a Ramsay sedation score of 3 or higher (as clinically appropriate for the patient's needs). Following extubation, the infusion rate could have been adjusted to achieve a Ramsay sedation score of 2 and above (as clinically appropriate).

In Part II of the study (double blind, randomized, placebo controlled), approximately 300 patients were to be randomized to one of two treatment groups: Dexmedetomidine or placebo with additional doses of midazolam for sedation administered as clinically indicated. Patients were administered a two stage infusion consisting of a 10 minute loading dose of 6.0 mcg/kg/h of Dexmedetomidine or placebo followed by a maintenance infusion of 0.4 mcg/kg/h. Following the initial maintenance infusion, the rate could be adjusted in increments of 0.1 mcg/kg/h or higher, and was to be maintained in the range of 0.2 to 0.7 mcg/kg/h as clinically deemed necessary to achieve and maintain a Ramsay sedation score of 3 or higher as clinically appropriate. Following extubation, the infusion rate was to be adjusted to achieve a Ramsay sedation score of 2 or above as clinically appropriate.

INCLUSION CRITERIA:
To be included in the study, patients were to have satisfied all of the following inclusion criteria:

- Signed and dated the Informed Consent after the study had been fully explained or had a legally acceptable representative sign and date the Informed Consent.
- Required sedation for ventilation and intensive care for a minimum of 6 hours following surgery
- Male or female, age 18 and over (in Austria, age 19 or older)
- If female and of child bearing potential, was not pregnant (confirmed by negative pregnancy test) and not lactating.

EXCLUSION CRITERIA:
Patients were not eligible for the study if they met any of the following criteria:

- Had serious central nervous system trauma.
- Had undergone or required intracranial surgery during current hospitalization.

- Required the use of neuromuscular blocking agents during the study period, except for the insertion of the endotracheal tube.
- Required epidural or spinal analgesia during the ICU stay.
- In whom opiates or benzodiazepines were contraindicated or had known or suspected serious allergy to any medication that might have been administered during the course of the study.
- Was grossly obese (estimated body weight was greater than 50% above ideal body weight)
- Was currently hospitalized for drug overdose
- In whom alpha-2 antagonists or alpha-2 agonists were contraindicated
- Was currently being treated or had been treated within the last 30 days with alpha-2 agonists or antagonists
- Had participated in a trial with any experimental drug within 30 days prior to admission to the ICU
- Was terminally ill, whose life duration expectancy was no more than or around 24 hours.
- Was considered unable to undergo any procedure required by the protocol
- Had demonstrated tolerance to standard sedating medications
- Had previously received Dexmedetomidine
- Had unstable or uncontrolled diabetes
- Had excessive bleeding which was likely to require resurgery
- Had received midazolam for maintenance of anesthesia
- Has clinically significant arrhythmia or any other cardiac condition or factor which, in the investigator's opinion, might have increased the risk to the patient or precluded obtaining satisfactory data.

REMOVAL OF PATIENTS FROM THERAPY ASSESSMENT:
A patient was to be withdrawn from the study immediately if any of the following occurred:

- Due to an adverse event, the investigator decided that discontinuation was in the patient's best interest.
- The patient requested withdrawal from the study.
- Patients requiring reoperation
- A change occurred in the patient's status such that exclusion criteria became part of the patient profile.

Patients who withdrew from the study were not to be replaced. Those patients withdrawn from the study due to an adverse event were to have all events documented and followed to a satisfactory resolution. Patients who were withdrawn from the study for any reason during study drug administration were required to have all final evaluation procedures completed.

DOSING SCHEDULE:
Dexmedetomidine or placebo was to be administered as a two-stage infusion: a 10 minute loading dose followed by a maintenance infusion using standard syringe pump

and IV administration sets. Study drug was never to be administered directly into the pulmonary artery. Study drug was to be initiated as soon as possible after arrival in the ICU but no later than 1 hour after admission to ICU. If possible, study drug was to be started prior to the patient's awakening in ICU or requiring any other medication for sedation. If a patient required sedation post surgery and prior to start of study drug, additional doses of midazolam for sedation could have been given as required. Drug administration consisted of a 10 minute loading dose of 6.0 mcg/kg/h followed by a maintenance infusion of 0.4 mcg/kg/h. The 6 mcg/kg/h loading dose was chosen to achieve a Dexmedetomidine plasma concentration of approximately 1.5 ng/mg as a result of experience gained in Phase I studies and resultant PK modeling. Clinical effects of sedation should have been observed within 15 minutes of the start of the study drug. The infusion rate could have been adjusted in increments of 0.1 mcg/kg/h or higher, and should have been maintained in the range of 0.2-0.7 mcg/kg/h as clinically deemed necessary to achieve and maintain a Ramsay sedation score of at least 3 as clinically appropriate. Following extubation, the infusion rate could have been adjusted to achieve a Ramsay sedation score of 2 and above as clinically appropriate.

During study drug administration, rescue medication was limited to midazolam for sedation and morphine for pain as required. After extubation, paracetamol use was to be permitted as clinically indicated. During the 10 minute loading dose 1 mg bolus dose of midazolam was allowed if necessary. The maintenance dose of Dexmedetomidine or placebo was to be adjusted prior to any administration of additional midazolam. Study drug infusion was to be continued for 6 hours post extubation. The investigator may have continued the infusion at his/her discretion for a total of 24 hours total drug infusion.

In the ICU, midazolam for sedation was to be administered following an increase in study drug infusion. Prior to the administration of midazolam, patients were to be assessed for sedation using the Ramsay sedation scale. The Ramsay assessment was to be performed prior to and 10 minutes after every rate change in study drug administration or administration of any midazolam. Pain was assessed either by direct communication with the patient or by autonomic signs (sweating, tachycardia, hypertension). Sponsor recommended that initial doses of midazolam be administered as a bolus in doses of 0.02 mg/kg. If, in addition to increasing the infusion rate of study drug, the patient received 3 boluses of midazolam within any 2 hour (during study drug infusion), further midazolam, if necessary, may have been administered at a continuous infusion rate of 0.01-0.02 mg/kg/h. Morphine may have been administered for pain in increments of 2-mg IV boluses. Prior to the administration of morphine, the patient was to be assessed for pain.

Standard ICU monitoring protocols were to be employed. All patients were to be ventilated to maintain PaC02 and Pa02 tensions as determined by the investigator. Minimum ventilatory support was to be utilized. Patients were to be weaned from the ventilator and extubated only if the investigator deemed it appropriate and after meeting the following criteria:

- Patient was awake or arousable, neurologically intact, cooperative, and comfortable.

- Patient had an FiO2 value ≤ 0.4, PEEP < 5 cm H20, and pressure support ≤ 10cm H2O.
- Patient had the following lung mechanics: minute ventilation expired > 4 L/min but < 15 L/min, tidal volume > 5 ml/kg and spontaneous respiratory rate <25/min.

The following drugs were not to be allowed during study drug infusion:

- Sedating agents other than midazolam; analgesic agents other than morphine (after extubation, use of paracetamol was permitted as clinically indicated).
- Neuromuscular blocking agents except for the insertion of the endotracheal tube.
- Epidural or spinal analgesic agents.
- Any drugs contraindicated with the use of Dexmedetomidine, midazolam, or morphine.
- Alpha-2 agonist/antagonist.

SECTION 7.2.1.2 STATISTICAL ANALYSIS

Only patients from the randomized, double-blind, placebo-controlled part of the study (Part II) were to be included in the efficacy analyses. A patient was required to satisfy the following evaluability criteria in order to be included in the evaluable subset:

- The patient received study drug for at least 6 hours, unless the patient was prematurely discontinued by the investigator due to an adverse event.
- The patient received none of the following medications during study drug administration: sedating agents other than midazolam, analgesic agents other than morphine or paracetamol, neuromuscular blocking agents except for insertion of the endotracheal tube, epidural or spinal analgesic/anesthetic agents, any drugs contraindicated with the use of midazolam, Dexmedetomidine, or morphine, or other prohibited medications
- The patient received only morphine or paracetamol for pain management.
- The patient was intubated for at least 6 hours.

A patient was included in the intent-to-treat subset if he or she was randomized and required intensive care and sedation following surgery. Patients in Part I and II of the study were included in the safety subset if he/she received any study drug.

EFFICACY ANALYSES:
The primary efficacy analysis was based on the intent-to-treat subset of patients. A second set of efficacy analyses was completed on the evaluable subset.

Primary Efficacy Analysis

The primary efficacy variable in this study was the total dose (mg) of midazolam during intubation received as rescue medication for sedation during the period of study drug administration. The total dose was summarized by the number of patients in the following three total dose categories: no midazolam (0 mg); a subtherapeutic dose over time (>0 mg

to 4 mg); and a therapeutic dose (>4 mg). Differences in the distributions of the proportion of patients in each category between the dexmedetomidine treatment group and the placebo treatment group were tested with a chi-square statistic. Center differences were also explored. The total dose was also summarized by N, mean, standard error of the mean (SEM), minimum, median, and maximum. The treatment groups were compared using an analysis of variance (ANOVA) with treatment, center and treatment-by-center interaction included in the model.

[Reviewer Note: The final primary efficacy analysis submitted in this application is different from the sponsor's proposal in the original protocol. None of the amendments to this study reflect the analysis that was performed. At a meeting with the sponsor at the conclusion of the Phase II studies, Dr. Thomas Permutt (the reviewing statistician) suggested that the capability of Dexmedetomidine to provide sedation would be more convincingly demonstrated by an analysis of how many patients needed any rescue medication rather than by measuring the amount of rescue medication utilized by both placebo and Dexmedetomidine patient groups. Consequently, the sponsor was encouraged to incorporate calculations of the number of patients receiving any amount of midazolam in the primary efficacy analysis.]

Secondary Efficacy Analyses

The following are secondary efficacy variables in the study:

- Total dose of midazolam during study drug administration:

  The total dose of midazolam (mg) administered during study drug infusion was calculated. The total dose was divided by the length of infusion to determine the total dosing rate during infusion and was expressed as mg/h. The length of infusion was defined as the difference between the time of the start of study drug and the end of study drug infusion. The total dosing rate was summarized by N, mean, SEM, median, minimum, and maximum. The treatment groups were compared using an ANOVA with treatment, center, and treatment-by-center interaction included in the model.

- The total dose of morphine during study drug administration:

  Analysis of total dose of morphine during study drug administration was run on three populations of patients. The first population consisted of patients who did not receive any midazolam during intubation. The second population consisted of patients with a subtherapeutic total dose over time of midazolam during intubation of > 0 — 4 mg. All patients were included in the third population.

- The total dose of morphine by time period (first 6.5 hours of study drug infusion; 6.5 hours after the start to the end of study drug infusion):

It was anticipated that this was the time period of most intense analgesic requirements.
Additionally, it was expected most patients would be extubated within 6.5 hours, thus the selection of the time period. The total dose (mg) of morphine during study drug administration was divided by the length of time between the start of study drug infusion and the end of study drug infusion and was expressed in mg/h. Total dose of morphine was also calculated from the start of study drug infusion to 6.5 hours after the start of study drug infusion and from 6.5 hours after the start of study drug to the end of study drug infusion. The total dose was summarized by descriptive statistics (mean, SEM, median, minimum, and maximum). The treatment groups were compared using an ANOVA with treatment, center and treatment-by-center interaction included in the model.

- Ramsay sedation score

For each patient, the average of the Ramsay scores was calculated using the trapezoidal rule for the area under the curve (AUC). The AUC Ramsay score was to be divided by the length of the study drug administration period. This AUC Ramsay variable for dexmedetomidine was compared to placebo using an ANOVA and was summarized by N, mean, SEM, median, minimum, and maximum. In addition, the AUC Ramsay score was calculated for each 1-hour interval during the study drug administration. One-hour AUC Ramsay scores were summarized by N, mean, SEM, median, minimum, and maximum. The mean hourly Ramsay was plotted by treatment group. Variability of AUC scores was displayed using error bars.

The number of patients having at least one Ramsay score of 1 (anxious, agitated, restless) during study drug infusion was summarized by counts and percents. Treatment groups were compared using a chi-square test.

The percentage of Ramsay assessments equal to 1 was computed for each patient and was summarized by descriptive statistics. The percentage is the number of assessments that equal 1 over the total number of Ramsay assessments for each patient. An ANOVA with treatment, center, and treatment-by-center interaction included in the model was used to compare the mean ratio between treatment groups.

- Time to extubation and weaning duration:

The time to extubation was defined as the difference between ICU arrival and the time when the patient was deemed ready for extubation. A second analysis of the time to extubation was performed using the difference between start of study drug and the time when the patient was deemed ready for extubation.

Weaning duration was defined as the difference between initiation of weaning from the ventilator and readiness for extubation. If weaning had not been initiated within 24 hours after start of study drug, the patient was to be dropped from the analysis. In all cases, a patient was considered censored if the patient was not deemed ready for

extubation 24 hours after the start of study drug infusion or if the patient discontinued prior to extubation.

Time to extubation and weaning duration were summarized by N, mean, SEM, median, minimum, and maximum. Treatment differences for time to extubation and weaning duration were displayed using Kaplan-Meier survival curves and analyzed with the log-rank analysis procedure. In addition, the duration of time from the arrival to the ICU and extubation and the duration of time from the start of study drug to extubation were summarized by N, mean, standard deviation (SD), median, minimum, and maximum.

- Nurse assessment:
  Nurse assessments were summarized (N, mean, SEM, median, minimum, and maximum) for any nursing shift that covered intubation (starting or ending during intubation). If multiple assessments were performed for a patient during intubation, the mean score was summarized.

  A patient management index was calculated as the sum score per patient. The patient management index was summarized by descriptive statistics. The Cochran-Mantel-Haenszel statistic was used to test for differences between the treatments and adjust for center differences.

- Study Drug Exposure:

  The total dose (mcg/kg) of dexmedetomidine received was summarized by descriptive statistics (N, mean, SEM, median, minimum, and maximum). Total dose was the sum of the loading and maintenance doses. Total maintenance dose (mcg/kg) was the sum of the dose at each rate change. The formula for calculating the loading and maintenance dose was as follows:

$$\frac{\text{Duration at rate (h)} * \text{infusion pump rate (ml/h)} * \text{concentration (mcg/mL)}}{\text{Weight at screening physical exam (kg)}}$$

  The infusate concentration of dexmedetomidine was to be 4 mcg/mL.
  The number of rate change adjustments per patient was summarized by descriptive statistics (N, mean, SD, median, minimum, and maximum) for each treatment group. The duration of study drug infusion (h) was summarized by N, mean, SD, median, minimum, and maximum for each treatment group.

PLANNED SAMPLE SIZE

The target enrollment (300 patients, 150 patients per treatment group) for Part II of this study allowed a detection of significant differences in rescue medication for sedation at the 0.05 (two-tailed) level with 80% power. This sample size estimation was based on the following assumptions:

- Midazolam usage over 24 hours would be 1.0 mg/kg for the placebo group and 0.30 mg/kg for the dexmedetomidine group;
- The effect size was 0.35;
- Ninety percent of the patients enrolled would be evaluable.

SECTION 7.2.1.3 PROTOCOL AMENDMENTS

Three amendments were made to the original protocol.

Amendment One (06 March 1998):

- Corrected typographical errors.

- Clarified that the results of the Phase II study were preliminary.

- Clarified that the primary efficacy variable was to be assessed during the time the patient was intubated and clarified the secondary variables.

- Extended the study drug infusion to 6 hours after extubation in order to be consistent with the previous Phase II study design and allowed the investigator to continue study drug infusion up to a maximum of 24 hours.

- Clarified the initial maintenance dose from 0.2 mcg/kg/h to 0.4 mcg/kg/h.

- Identified the appropriate target Ramsay sedation score during intubation (≥3) and postextubation (≥2) and allowed the use of paracetamol for pain post-extubation.

- Clarified how to manage the syringe labeling.

- Removed the need to use 60 mL syringes and updated stability data on dexmedetomidine.

- Removed the need to provide drug preparation envelopes as study drug was fully blinded.

- Corrections to reflect actual drug label.

- Required patients at Austrian sites to be at least 19 years of age.

- Clarified the time frame for the number of midazolam boluses and changed infusion rate to reflect the standard of practice for the use of midazolam in ICU sedation.

- Allowed the use of paracetamol after extubation.

- Noted that the protocol only provided guidelines for the weaning/extubation of patients.

- Added analyses of midazolam use during intubation and paracetamol use post-extubation.

- Included amendment #1 in the investigator agreement.

- Updated the study schematic to reflect the body of the protocol.

- Updated the list of Affiliate Medical/Scientific Directors.

- Clarified the time frame for the number of boluses and updated the standard of practice for the use of midazolam in ICU sedation.

Amendment Two (11 March 1998), Site Specific: UK, Greece, Finland, and Sweden

- Allowed for the legally acceptable representative of the patient to give consent for the patient to be enrolled in the study.

Amendment Three (01 October 1998):

- Changed personnel on the signature page.

- Removed weight and time from the primary efficacy variable (total dose of midazolam required in addition to study drug to achieve adequate sedation during intubation).

- Changed the primary efficacy variable to be based on the intent-to-treat patient subset, in order to increase the generalizability of the results.

- Removed weight from efficacy variable (total dose of morphine, total dose of paracetamol).

Included Amendment #3 in the Investigator Agreement.

Changes to the Planned Analyses

As outlined in the statistical analysis plan, certain efficacy variables were to have center-by-treatment interaction analyses performed; however, several centers had no patients or only one patient per treatment group. Therefore, visual inspection of parameters across centers was performed to determine if the treatment effect was consistent across centers.

Additionally, the AUC Ramsay score was to be divided by the duration of the study drug administration time period. Instead, the AUC Ramsay scores were divided by the time period over which Ramsay scores were collected.

Temperature was not summarized due to differences in the collection methods as well as the infrequency of the collections.

The statistical analysis plan outlined an ANOVA with treatment, center, and treatment-by-center interaction included in the model to compare the number of patients having at least one Ramsay score of 1. Instead, treatment groups were compared using a chi-square test.

SECTION 7.2.1.4 STUDY CONDUCT

DISPOSITION / DISTRIBUTION:

A total of 86 patients were enrolled in Part I of the study. One patient did not receive study medication; therefore, a total of 85 patients were treated with Dexmedetomidine. In Part II of the study, a total of 178 patients were randomized to Dexmedetomidine and 175 were randomized to placebo; all of these patients received their assigned treatment. A total of 9 patients in the Dexmedetomidine treatment group and 10 patients in the placebo treatment group were prematurely discontinued from the study.

Table 3 Summary of Patient Disposition

	Part I	Part II	
	Dexmedetomidine	Dexmedetomidine	Placebo
All Randomized	86	178	175
Randomized, Not Treated	1	0	0
All Treated Patients	85 (100%)	178 (100%)	175 (100%)
Discontinued Patients	8 (9%)	9[a] (5%)	10 (6%)
Completed Dosing[b]	77 (91%)	169 (95%)	165 (94%)

Modified Sponsor's Table 6.1a Vol 8/10-62-67
a: For description of discontinuations, refer to Safety Analysis, Study W97-245
b: This is not evaluable set.

A total of 175 patients received placebo and 178 patients received Dexmedetomidine in Part II of the study and comprise the Intent-to-Treat dataset. Of these, 6 placebo patients and 2 Dexmedetomidine patients did not meet the evaluability criteria specified in the protocol and were excluded from the " evaluable patient" dataset.

Table 4 Reasons for Non-evaluability, Part II of Study

	Placebo	Dexmedetomidine
Intent-to Treat Patients (All Treated)	175	178
Non-Evaluable patients	6	2
Evaluable Patients	169	176
Reasons for Non-Evaluability (Patient Numbers)[a]		
Insufficient Study drug therapy	1001,4104	1806
Insufficient Intubation	1001,11705	1806
Received disallowed medication	1303,6004, 7601	6106

a: Patients could have had more than one reason for nonevaluability
Modified Sponsor's Table 8.1a Vol 8/10-62-73

PROTOCOL VIOLATIONS:

One patient in Part I of the study violated an exclusion criterion which stated that the patient was not to receive midazolam for maintenance of anesthesia; however the sponsor approved entry of this patient into the study. Additionally, one Dexmedetomidine patient in Part II of the study violated an exclusion criterion which stated that the patient was not to be grossly obese.

Numerous protocol deviations were identified during the study; most were associated with the timing of assessments or missed assessments. Additional deviations of interest included 4 Dexmedetomidine patients who received overdoses of study drug; 5 Dexmedetomidine patients (3 in Part I and 2 in Part II) and 2 placebo patients who received study medication for greater than 24 hours (overall range from 24.05 to 29.08 hours); and 73 Dexmedetomidine patients (14 Part I and 59 Part II) and 39 placebo patients who received study drug infusions less than the 0.2 mcg/kg/h dose stated in the protocol. The primary reasons for decreasing the study drug infusion below 0.2 mcg/kg/h or even intermittently stopping the infusion included the occurrence of hypotension, oversedation, hypoventilation, and preparation for extubation. Additionally, at some centers patients were enrolled out of numeric sequence.

DEMOGRAPHICS

Part I

Table 5 Summary of Patient Demographics, Study Part I

Parameter	Dexmedetomidine		
	Male	Female	Total
Number of patients	66	19	85
Ethnic Origin n (%)			
Asian	1(2%)	0	1(1%)
Caucasian	64(97%)	19(100%)	83(%)98
Other	1(2%)	0	1(1%)
Age (mean ± SD)	59 ± 11.31	66 ± 11.18	61 ± 11.52

Modified Sponsor's Table 6.3a Vol 8/10-62-69

Mean age among patients in Part I of the study was 61 years. The majority of the patients were male (78%) and of Caucasian (98%) ethnic origin. Among patients who had smoking status and alcohol use data reported at baseline, most were non-users or ex-users of tobacco (82%) and most consumed alcohol (66%). None of the patients in Part I of the study was of childbearing potential.

Part II

Table 6 Summary of Patient Demographics, Study Part II

Parameter	Placebo			Dexmedetomidine		
	Male	Female	Total	Male	Female	Total
Number of patients	133	42	175	134	44	178
Ethnic Origin						
Asian	0	0	0	3(2%)	1(2%)	4(2%)
Black	2(2%)	0	2(%)	1(<1%)	1(2%)	2(1%)
Caucasian	131(98%)	42(100%	173(99%)	130(97%	42(95%)	172(97%
Age (mean ± SD)	63±11.9	65±12.2	64.12	62.11.7	65.12.5	62.12

Modified Sponsor's Table 6.3b Vol 8/10-62-70

Mean age among patients in Part II of the study was comparable between the treatment groups (placebo: 64 years; Dexmedetomidine 62 years). The majority of the patients in both treatment groups were male (≥ 75%) and of Caucasian (≥ 97%) ethnic origin. Within both treatment groups, the majority of the patients were non-users or ex-users of tobacco (≥ 82%) and most consumed alcohol (≥58%).

The types of surgical procedures performed on patients in Part II of the study were comparable between the treatment groups. The majority of the patients had cardiac surgery performed (≥ 60%), followed by laparotomy (≥15%) and head and neck surgery (≥8%); 11% of the patients in the placebo group and 12% of the patients in the Dexmedetomidine group had other surgical procedures performed.

A total of 12 females (6 placebo and 6 Dexmedetomidine) in Part II of the study were of childbearing potential. Pregnancy tests were all negative. 120 patients (69 placebo and 51 Dexmedetomidine) in Part II of the study had clinically significant abnormal ECG at baseline, but none were excluded from study participation because of these abnormalities.

SECTION 7.2.1.5 SPONSOR'S EFFICACY RESULTS

Table 7 Exposure
Mean (± SD) Total Dexmedetomidine Dose and Total Duration of Infusion During the Entire Study Drug-Infusion Period, All Treated Patients, Study Part II

	Placebo Mean±SD	Dexmedetomidine Mean ± SD
During Entire Study Drug Infusion Period	N=175	N=178
Mean total dose (mcg/kg)	N/A	7.0 ± 2.95
Mean total duration of infusion (hours)	15.7 ± 4.84	16.6 ± 5.0
Prior to Extubation	N=163	N=171
Mean total dose (mcg/kg)	N/A	5.2 ± 2.33
Mean total duration of infusion (hours)	9.6 ± 4.51	10.2 ± 4.7
After Extubation	N=163	N=171
Mean total dose (mcg/kg)	N/A	1.8 ± 1.61
Mean total duration of infusion (hours)	6.2 ± 2.29	6.6 ± 2.79

Modified Sponsor's Table 9.1a Vol 8/10-62-87

PRIMARY EFFICACY VARIABLES:

In both the Intent-to-Treat and the evaluable patient analyses, Dexmedetomidine treated patients required statistically significantly less midazolam for sedation during intubation compared to placebo-treated patients:

I. Total Dose of Midazolam (mg) During Intubation:

Table 8 Total Dose of Midazolam (mg) During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	175	178	
Mean ± SEM	18.61±4.02	4.83±1.43	0.0011
Evaluable Patients (N)	169	176	
Mean ± SEM	18.46±4.14	4.56±1.42	0.0014

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.2a Vol 8/10-62-74

Sponsor states that no statistically significant center effect was detected for the total dose of midazolam during intubation in either the Intent-to-Treat or evaluable patient analyses.

II. Number of Patients Receiving Midazolam:

The total dose of midazolam used during intubation was also analyzed according to the number of patients who received no midazolam (0 mg), the number of patients who received a subtherapeutic dose over time (>0 mg to 4 mg) of midazolam, and the number of patients who received a therapeutic dose (> 4 mg) of midazolam. Statistically significant differences were observed between the treatment groups in both the Intent-to-Treat and evaluable patient analyses, with the majority of the Dexmedetomidine treated patients requiring no midazolam for sedation compared to the majority of the placebo patients who required > 4 mg of midazolam for sedation.

Table 9 Total Dose Categories of Midazolam During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent-to-Treat Patients (N)	175	178	<0.001
0 mg	43(25%)	108(61%)	
>0mg to 4 mg	34(19%)	36(20%)	
>4 mg	98(56%)	34(19%)	
Evaluable Patients (N)	169	176	<0.001
0 mg	43(25%)	107(61%)	
>0 mg to 4 mg	32(19%)	36(20%)	
> 4 mg	94(56%)	33(19%)	

a: p-value from chi-square
Modified Sponsor's Table 8.2b Vol 8/10-62-75

SECONDARY EFFICACY ENDPOINTS

I. Total Dose of Midazolam During Study Drug Administration

In both the Intent-to-Treat and the evaluable patient analyses, Dexmedetomidine treated patients required statistically significantly less midazolam for sedation during study drug administration compared to placebo treated patients. No statistically significant center effect was detected for the total dose of midazolam during study drug administration in either the Intent-to-Treat or evaluable patient analyses.

Table 10 Summary of Total Dose of Midazolam (mg/hour) During Study Drug Administration

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	175	178	
Mean ± SEM	1.19±0.23	0.29±0.07	0.0001
Evaluable Patients (N)	169	176	
Mean ± SEM	1.17±0.24	0.27±0.07	0.0002

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3a Vol 8/10-62-76

II. Total dose of Morphine During Study Drug Administration

In both the Intent-to-Treat and the evaluable patient analyses, Dexmedetomidine treated patients required statistically significantly less morphine for pain during study drug administration compared to placebo treated patients.

Table 11 Summary of Total Dose of Morphine (mg/hour) During Study Drug Administration

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	175	178	
Mean ± SEM	0.83±0.07	0.47±0.06	0.0001
Evaluable Patients (N)	169	176	
Mean ± SEM	0.83±0.07	0.46±0.06	0.0001

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3b Vol 8/10-62-77

Statistically significant center effects were detected for the total dose of morphine during study drug administration in both the Intent-to-Treat and evaluable patient analyses. These significant differences were associated with the low amount of morphine use among both Dexmedetomidine and placebo treated patients at the four sites located in Belgium compared with the other sites and the high amount of morphine use among both Dexmedetomidine and placebo treated patients at the three sites located in Germany compared with the other sites. The remaining sites consistently demonstrated that

Dexmedetomidine treated patients required less morphine during study drug administration compared to placebo treated patients.

In both the Intent-to-Treat and the evaluable patient analyses, no statistically significant difference was noted between the two treatment groups for the total dose of morphine required during study drug administration for those patients who received no midazolam during intubation:

Table 12 Summary of Total Dose of Morphine (mg/hour) During Study Drug Administration for Patients Who Received No Midazolam During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	43	108	
Mean ± SEM	0.20±0.04	0.20±0.05	0.9827
Evaluable Patients (N)	43	107	
Mean ± SEM	0.20±0.04	0.20±0.05	0.9989

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3c Vol 8/10-62-78

In both the Intent-to-Treat and the evaluable patient analyses, Dexmedetomidine treated patients who received up to 4 mg of midazolam during intubation required statistically significantly less morphine during study drug administration compared to placebo treated patients who received up to 4 mg of midazolam during intubation:

Table 13 Summary of Total Dose of Morphine (mg/hour) During Study Drug Administration for Patients Who Received >0 mg and ≤ 4mg of Midazolam During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	34	36	
Mean ± SEM	0.85±0.13	0.53±0.07	0.0275
Evaluable Patients (N)	32	36	
Mean ± SEM	0.85±0.13	0.53±0.07	0.0287

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3d Vol 8/10-62-78

III. Total Dose of Morphine by Time Period

In both the Intent-to-Treat and the evaluable patient analyses, Dexmedetomidine treated patients (as compared to placebo treated patients) required statistically significantly less morphine for pain:

1. During the first 6.5 hours of study drug administration.
2. From 6.5 hours after the start of study drug administration to the end of study drug administration.

Table 14 Summary of Total Dose of Morphine (mg) During First 6.5 Hours of Study Drug Administration

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	175	178	
Mean ± SEM	8.51±0.79	4.88±0.56	<0.0001
Evaluable Patients (N)	169	176	
Mean ± SEM	8.5±0.81	4.78±0.55	<0.0001

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3e Vol 8/10-62-79

Table 15 Summary of Total Dose of Morphine (mg/hr) From 6.5 Hours After the Start of Study Drug Administration to the End of Study Drug Administration

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	N=169	N=173	
Mean ± SEM	0.42±0.08	0.24±0.05	0.0419
Evaluable Patients (N)	N=165	N=172	
Mean ± SEM	0.43±0.08	0.24±.05	0.0361

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3f Vol 8/10-62-80

Statistically significant center effects were detected for the total dose of morphine during the first 6.5 hours of study drug administration in both the Intent-to-Treat and Evaluable patient analysis. These statistically significant center effects were also noted for the total dose of morphine from 6.5 hours after the start of study drug administration to the end of study drug administration in both the Intent-to-Treat and evaluable patient analyses. Both of these significant differences were associated with the low amount of morphine use among both Dexmedetomidine and placebo treated patients at the 4 sites located in Belgium compared with the other sites and the high amount of morphine use among both Dexmedetomidine and placebo treated patients at the 3 sites located in Germany compared with the other sites. The remaining sites consistently demonstrated that Dexmedetomidine treated patients required less morphine during the first 6.5 hours of

study drug administration compared to placebo treated patients. The remaining sites also demonstrated that Dexmedetomidine treated patients required less morphine from 6.5 hours after the start of study drug administration to the end of study drug administration compared to placebo treated patients.

IV. Ramsay Sedation Score

In both the Intent-to-Treat and evaluable patient analyses, the mean Ramsay sedation score during study drug administration was statistically significantly higher for Dexmedetomidine treated patients compared to placebo treated patients. The Ramsay sedation scores for both groups fell within the protocol defined range of ≥3. The Ramsay sedation score for the placebo treated group was mean 3.3 ± 0.05 (SEM) vs 3.6 ± 0.05 (SEM) for the Dexmedetomidine treated patients. Sponsor states these differences are not clinically important.

Statistically significant center effects were detected for the Ramsay sedation scores during study drug administration in both the Intent-to-Treat and evaluable patient analyses. These significant differences were associated with the low Ramsay sedation scores among both Dexmedetomidine and placebo treated patients at sites located in Spain, France, Italy, and Austria compared with the other sites and the high Ramsay sedation scores among both Dexmedetomidine and placebo treated patients at sites located in the UK, Germany, and the Netherlands compared with the other sites. The remaining sites consistently demonstrated that mean Ramsay sedation scores were higher for Dexmedetomidine treated patients compared to placebo treated patients.

V. Anxiety

In both the Intent-to-Treat and evaluable patient analyses, there were statistically significant differences between treatments in the number of patients who reached a Ramsay score of 1 during study drug administration, with more placebo treated patients reaching a Ramsay score of 1 (48%) compared with Dexmedetomidine treated patients (36%). The percentage of Ramsay assessments equal to a ratio of a Ramsay sedation score of 1 was computed for each patient and was summarized by treatment group. The ratio is the proportion of assessments that equal 1, divided by the total number of Ramsay assessments for each patient. Both the Intent-to-Treat and evaluable patient analyses showed statistically significant differences ($p<0.001$) between the treatment groups. Examination of the mean percentages indicates that the average placebo patient reached a Ramsay score of 1 on 7% of the occasions the patient was assessed compared to the average Dexmedetomidine patient who reached a score of 1 on 3% of the assessments. Sponsor believes this finding may indicate less anxiety among Dexmedetomidine treated patients.

A statistically significant center effect was observed for the ratio analysis. The mean percentage per center ranged from 0% to 11.5% with the sites consistently demonstrating

that placebo treated patients had more Ramsay sedation assessments that reached a score of 1 compared to Dexmedetomidine treated patients.

VI. Time to Extubation and Weaning

Using Kaplan-Meier estimates and the log-rank test, no statistically significant differences were observed between the treatment groups (placebo, 390 minutes; Dexmedetomidine, 420 minutes) for the median time between ICU arrival and readiness for extubation in both the Intent-to-Treat and evaluable patient analyses. Additionally, no statistically significant differences were observed between the treatment groups (placebo, 362 minutes; Dexmedetomidine 405 minutes) for the median time between the start of study drug and readiness for extubation in both the Intent-to-Treat and evaluable patient analyses.

The median time from ICU arrival to actual extubation was similar between the two treatment groups in both the Intent-to-Treat (placebo, 525 minutes; Dexmedetomidine 547 minutes) and evaluable patient (placebo, 523 minutes; Dexmedetomidine 551 minutes) analyses. Likewise, the median time from the start of study drug to actual extubation was similar between the two treatment groups in both the Intent-to-Treat (placebo, 480 minutes; Dexmedetomidine 525 minutes) and the evaluable patient (placebo, 480 minutes; Dexmedetomidine 530 minutes) analyses.

Using Kaplan-Meier estimates and the log-rank test, no statistically significant differences were observed between the treatment groups for the median duration of weaning in both the Intent-to-Treat (placebo, 23 minutes; Dexmedetomidine 15 minutes) and evaluable patient (placebo 20 minutes; Dexmedetomidine 15 minutes) analyses.

VII. Nurses' and Patients' Assessment

Nurses:
Nurses assessed their impressions of the patient's overall sedation and tolerance of the ICU, tolerance of the endotracheal tube/ventilator, ease of communication with the patient, and the ease of patient management. Scores from each of these assessments were summed to arrive at a composite score defined as the "Patient Management Index." In both the Intent-to-Treat and evaluable patient analyses, a statistically significant difference was observed between the treatment groups for the patient management index. Dexmedetomidine treated patients demonstrated a lower patient management index score compared with placebo treated patients, with lower scores corresponding to the ease with which patients tolerated sedation, the ICU, and the endotracheal tube/ventilator, as well as the ease with which the nurse was able to communicate with the patient and care for the patient.

Table 16 Summary of Nursing Assessments and Patient Management Index

	Placebo Mean ± SEM		Dexmedetomidine Mean ± SEM	
	ITT	Evaluable	ITT	Evaluable
Overall Sedation and Tolerance of the ICU[a]	N=139 1.8±0.07	N=135 1.8±0.07	N=149 1.5±0.05	N=149 1.5±0.05
Tolerance of Endo Tube/ Ventilator[b]	N=139 1.5±0.05	N=135 1.5±0.05	N=148 1.3±0.03	N=148 1.3±0.03
Ease of Communication with Patient[c]	N=139 2.6±0.09	N=135 2.5±0.09	N=149 2.6±0.08	N=149 2.6±0.08
Ease of Management of the Patient[d]	N=139 1.5±0.05	N=135 1.5±0.05	N=149 1.4±0.05	N=149 1.4±0.05
Patient Management Index p-value[e]: ITT: 0.024 Eval: 0.046	N=139 7.4±0.21	N=135 7.3±0.20	N=148 6.8±0.16	N=148 6.8±0.16

Modified Sponsor's Table 8.4a Vol 8/10-62-85

a: 1=very easy, 2=easy, 3=moderate, 4=difficult

b: 1=good, 2=moderate, 3=poor

c: 1=very easy, 2=easy, 3=moderate, 4=difficult, 5=not possible

d: 1=good, 2=moderate, 3=poor

e: p-value from Cochran-Mantel-Haennszel row mean score statistic adjusted for center differences

Sponsor claims that these results indicate that patients were arousable, cooperative, and had less anxiety than placebo treated patients.

VIII. Patient Satisfaction Survey

Patients were surveyed with respect to their experience as a participant in the study. Among the Part II patients who completed the survey, responses were generally similar between Dexmedetomidine and placebo treated patients in rating their present experience compared to prior sedation experience, their overall comfort during ICU sedation, their remembrance of pain, discomfort from the breathing tube, people and noise, and whether or not they would have the same sedative treatment in the future. A higher percentage of Dexmedetomidine treated patients (61%) rated their overall experience as "better than expected" compared to placebo treated patients (52%). 164 placebo treated patients vs 170 of the Dexmedetomidine treated patients completed the survey.

SPONSOR'S SUMMARY OF EFFICACY:

The Intent-to-Treat and evaluable patient analyses of the primary efficacy endpoint demonstrated that Dexmedetomidine treated patients required statistically significantly

less midazolam for sedation during intubation compared to placebo treated patients. Statistically significant differences were observed between the treatment groups in both the Intent-to-Treat and evaluable patient analyses, with the majority of the Dexmedetomidine treated patients requiring no midazolam for sedation compared to the majority of the placebo patients who required >4 mg of midazolam for sedation.

Statistically significant differences were also demonstrated between the treatment groups in secondary efficacy variables for both the Intent-to-Treat and evaluable patient analyses. Dexmedetomidine treated patients required less midazolam for sedation during the entire study drug administration period, less morphine for pain during study drug administration, less morphine during the first 6.5 hours of study drug administration, and less morphine from 6.5 hours after the start of study to the end of study drug administration.

Ramsay sedation scores were significantly higher among Dexmedetomidine treated patients compared to placebo treated patients. Dexmedetomidine treated patients achieved a higher level of sedation during the first hour of study drug administration compared to placebo treated patients. Dexmedetomidine treated patients had a statistically significantly lower percentage of Ramsay assessments that reached a score of 1 compared to placebo treated patients, indicating less anxiety among Dexmedetomidine treated patients.

No statistically significant differences were observed between the treatment groups in the analyses of time to extubation and weaning. This outcome may have been influenced by the design of the study, which required a minimum of 6 hours intubation.

Dexmedetomidine treated patients demonstrated a statistically significantly lower patient management index score compared with placebo treated patients, with lower scores corresponding to the ease with which patients tolerated sedation, the ICU, and the endotracheal tube/ventilator, as well as the ease with which the nurse was able to communicate with the patient and care for the patient. Results indicate that Dexmedetomidine treated patients were arousable and cooperative, and had less anxiety than placebo treated patients.

Patient satisfaction survey responses were generally similar; however, a higher percentage of Dexmedetomidine treated patients (61%) rated their overall experience as "better than expected" compared to placebo treated patients (52%).

SECTION 7.2.1.6 REVIEWER'S EFFICACY DISCUSSION

As noted previously in the Primary Efficacy Analysis Section, the final primary efficacy analysis submitted in this application is different from what the sponsor proposed in the original protocol. None of the amendments to this study reflect the analysis that was

performed. At a meeting with the sponsor at the conclusion of the Phase Two studies, Dr. Thomas Permutt (the reviewing statistician) suggested that the capability of Dexmedetomidine to provide sedation would be more convincingly demonstrated by an analysis of how many patients needed any rescue medication rather than by measuring the amount of rescue medication utilized by both placebo and Dexmedetomidine patient groups. Consequently, the sponsor was encouraged to incorporate calculations of the number of patients receiving any amount of midazolam in the primary efficacy analysis. The sponsor followed the Agency's recommendations and performed the calculations prior to unwrapping the study blind.

This reviewer agrees that Dexmedetomidine provides significantly greater sedation than placebo. This pivotal study demonstrates that Dexmedetomidine is independently capable of providing sedation in intubated patients in an intensive care setting.

With respect to analgesia, the study measured the total milligrams of morphine required by the Dexmedetomidine group versus placebo group. There was no evaluation of the number of individuals in either group who required any morphine. Consequently, while the study did show the total amount of morphine administered to the Dexmedetomidine group was less than the total amount of morphine given to the placebo group for pain; no conclusion can be made that Dexmedetomidine is independently capable of providing analgesia. This study did convincingly demonstrate that Dexmedetomidine is capable of potentiating morphine.

In the secondary efficacy analysis, sponsor states that Dexmedetomidine treated patients had less anxiety as compared to the placebo treated patients. This claim is based on Dexmedetomidine patients scoring a statistically significantly lower percentage of Ramsay assessments that reached a score of 1 as compared to placebo treated patients. This reviewer agrees the Dexmedetomidine treated patients exhibited less outward display of anxiety, agitation or restlessness. However, patients can be dysphoric but appear calm. An example of this situation is with the drug droperidol. When given without additional sedative/hypnotic agents, patients sometimes reply that they "feel terrible" although by outward appearances they appear calm. Since the Ramsay observation scale is not a valid objective measure of anxiety, no claim can be made that Dexmedetomidine treated patients had less anxiety than placebo treated patients.

Another claim in the secondary efficacy analysis is based on the patient management index. Sponsor states the results of this score indicate the Dexmedetomidine treated patients were more arousable and more cooperative and had less anxiety than the placebo treated patients. The subjective factors that the index measured were 1) Overall sedation and tolerance of the ICU 2) Tolerance of Endotracheal tube/ventilator 3) Ease of communication with the patient and 4) Ease of management of the patient. No validation has been provided to substantiate the claim that the Patient Management Index is a measure of arousability, co-operation or anxiety. In addition, while the difference between placebo and Dexmedetomidine groups in the patient management index was statistically significant, the observed values were so small as to be clinically meaningless.

SECTION 7.2.2 STUDY W97-246

SECTION 7.2.2.1 : PROTOCOL REVIEW SUMMARY:

TITLE: A Phase III, Multi-Center, Randomized, Placebo-Controlled, Double-Blind Study Evaluating the Safety and Efficacy of Dexmedetomidine When Compared to Placebo, With Propofol, in ICU Sedation in Post-Operative Patients

OBJECTIVES:

Primary: The primary objective of this two-part, Phase III study was to evaluate the efficacy and safety of Dexmedetomidine in patients requiring ventilation, sedation, and intensive care following surgery. Dexmedetomidine was to be administered as clinically indicated according to Ramsay sedation scores [see Appendix 1 for description of Ramsay sedation score]; the goal was to achieve Ramsay scores of ≥ 3, as clinically indicated. The primary efficacy variable for this study was the total dose (mg) of Propofol required in addition to the study drug to achieve adequate sedation (as clinically determined by the Ramsay sedation scale) during intubation.

Secondary: Secondary variables included total dose of Propofol (mg) administered during study drug infusion, use of morphine for pain, as assessed by total dose used with Dexmedetomidine as compared to placebo; use of paracetamol for pain after extubation, as assessed by total dose used with Dexmedetomidine as compared to placebo, and time to extubation, as measured by time to arrival in ICU until time to extubation.

STUDY DESIGN:
This was a two part study in postoperative patients requiring a minimum of 6 hours ventilation and sedation in ICU. Part I was open-label to allow the investigator to become more familiar with the observed clinical effects of Dexmedetomidine prior to starting the double-blind portion of the study. Part II was double blind, randomized, and placebo-controlled.

Patients were to be screened within 7 days prior to receiving study drug. Screening was to include a complete medical history and physical examination, laboratory assessments, and 12-lead electrocardiogram. Study drug administration was to be initiated as soon as possible after arrival in the ICU but not later than 1 hour after admission to the ICU. If possible, study drug was to be started prior to the patient's awakening in the ICU or

requiring any other medication for sedation. If a patient required sedation post-surgery and prior to the start of study drug, Propofol (0.2 mg/kg bolus) could be given as required.

Study drug infusion was to be continued for 6 hours post extubation. The investigator could have continued the infusion at his/her discretion for a maximum of 24 hours. Patients were to be observed for a 24-hour period after the end of the study drug infusion.

Part I of the study was to include up to 4 patients per site. Patients were to be administered a loading dose of 6.0 mcg/kg/h of Dexmedetomidine over a 10 minute period, followed by a maintenance infusion of 0.4 mcg/kg/h. Following the initial maintenance infusion, the rate was to be adjusted if clinically necessary, in increments of 0.1 mcg/kg/h or higher. The infusion rate was to be maintained between a range of 0.2 to 0.7 mcg/kg/h to achieve and maintain a Ramsay sedation score of 3 or higher (as clinically appropriate for the patient's needs). Following extubation, the infusion rate could have been adjusted to achieve a Ramsay sedation score of 2 and above (as clinically appropriate).

In Part II of the study (double blind, randomized, placebo controlled), approximately 300 patients were to be randomized to one of two treatment groups: Dexmedetomidine or placebo with additional doses of Propofol for sedation administered as clinically indicated. Patients were administered a two stage infusion consisting of a 10 minute loading dose of 6.0 mcg/kg/h of Dexmedetomidine or placebo followed by a maintenance infusion of 0.4 mcg/kg/h. Following the initial maintenance infusion, the rate could be adjusted in increments of 0.1 mcg/kg/h or higher, and was to be maintained in the range of 0.2 to 0.7 mcg/kg/h as clinically deemed necessary to achieve and maintain a Ramsay sedation score of 3 or higher as clinically appropriate. Following extubation, the infusion rate was to be adjusted to achieve a Ramsay sedation score of 2 or above as clinically appropriate.

INCLUSION CRITERIA:
To be included in the study, patients were to have satisfied all of the following inclusion criteria:

- Signed and dated the Informed Consent after the study had been fully explained or had a legally acceptable representative sign and date the Informed Consent.
- Required sedation for ventilation and intensive care for a minimum of 6 hours following surgery
- Male or female, age 18 and over (in Austria, age 19 or older)
- If female and of child bearing potential, was not pregnant (confirmed by negative pregnancy test) and not lactating.

EXCLUSION CRITERIA:
Patients were not eligible for the study if they met any of the following criteria:

- Had serious central nervous system trauma.

- Had undergone or required intracranial surgery during current hospitalization.
- Required the use of neuromuscular blocking agents during the study period, except for the insertion of the endotracheal tube.
- Required epidural or spinal analgesia during the ICU stay.
- In whom opiates or Propofol were contraindicated or had known or suspected serious allergy to any medication that might have been administered during the course of the study.
- Was grossly obese (estimated body weight was greater than 50% above ideal body weight)
- Was currently hospitalized for drug overdose
- In whom alpha-2 antagonists or alpha-2 agonists were contraindicated
- Was currently being treated or had been treated within the last 30 days with alpha-2 agonists or antagonists
- Had participated in a trial with any experimental drug within 30 days prior to admission to the ICU
- Was terminally ill, whose life duration expectancy was no more than or around 24 hours.
- Was considered unable to undergo any procedure required by the protocol
- Had demonstrated tolerance to standard sedating medications
- Had previously received Dexmedetomidine
- Had unstable or uncontrolled diabetes
- Had excessive bleeding which was likely to require resurgery
- Has clinically significant arrhythmia or any other cardiac condition or factor which, in the investigator's opinion, might have increased the risk to the patient or precluded obtaining satisfactory data.

REMOVAL OF PATIENTS FROM THERAPY ASSESSMENT:

A patient was to be withdrawn from the study immediately if any of the following occurred:

- Due to an adverse event, the investigator decided that discontinuation was in the patient's best interest.
- The patient requested withdrawal from the study.
- Patients requiring reoperation
- A change occurred in the patient's status such that exclusion criteria became part of the patient profile.

Patients who withdrew from the study were not to be replaced. Those patients withdrawn from the study due to an adverse event were to have all events documented and followed to a satisfactory resolution. Patients who were withdrawn from the study for any reason during study drug administration were required to have all final evaluation procedures completed.

DOSING SCHEDULE:

Dexmedetomidine or placebo were to be administered as a two-stage infusion: a 10 minute loading dose followed by a maintenance infusion using standard syringe pump and IV administration sets. Study drug was never to be administered directly into the pulmonary artery. Study drug was to be initiated as soon as possible after arrival in the ICU but no later than 1 hour after admission to ICU. If possible, study drug was to be started prior to the patient's awakening in ICU or requiring any other medication for sedation. If a patient required sedation post surgery and prior to start of study drug, additional doses of Propofol for sedation could have been given as required. Drug administration consisted of a 10 minute loading dose of 6.0 mcg/kg/h followed by a maintenance infusion of 0.4 mcg/kg/h. The 6 mcg/kg/h loading dose was chosen to achieve a Dexmedetomidine plasma concentration of approximately 1.5 ng/mg as a result of experience gained in Phase I studies and resultant PK modeling. Clinical effects of sedation should have been observed within 15 minutes of the start of the study drug. The infusion rate could have been adjusted in increments of 0.1 mcg/kg/h or higher, and should have been maintained in the range of 0.2-0.7 mcg/kg/h as clinically deemed necessary to achieve and maintain a Ramsay sedation score of at least 3 as clinically appropriate. Following extubation, the infusion rate could have been adjusted to achieve a Ramsay sedation score of 2 and above as clinically appropriate.

During study drug administration, rescue medication was limited to Propofol for sedation and morphine for pain as required. After extubation, paracetamol use was to be permitted as clinically indicated. During the 10 minute loading dose, additional medication was to be avoided if possible. The maintenance dose of Dexmedetomidine or placebo was to be adjusted prior to any administration of additional Propofol. Study drug infusion was to be continued for 6 hours post extubation. The investigator may have continued the infusion at his/her discretion for a total of 24 hours total drug infusion.

In the ICU, Propofol for sedation was to be administered following an increase in study drug infusion. Prior to the administration of Propofol, patients were to be assessed for sedation using the Ramsay sedation scale. The Ramsay assessment was to be performed prior to and 10 minutes after every rate change in study drug administration or administration of any Propofol. Pain was assessed either by direct communication with the patient or by autonomic signs (sweating, tachycardia, hypertension). Sponsor recommended that initial doses of Propofol be administered as a bolus in doses of 0.2 mg/kg. If, in addition to increasing the infusion rate of study drug, the patient received 3 boluses of Propofol within any 2 hour (during study drug infusion), further Propofol, if necessary, may have been administered at a continuous infusion rate of 0.5- 4 mg/kg/h. Morphine may have been administered for pain in increments of 2-mg IV boluses. Prior to the administration of morphine, the patient was to be assessed for pain.

Standard ICU monitoring protocols were to be employed. All patients were to be ventilated to maintain PaC02 and Pa02 tensions as determined by the investigator. Minimum ventilatory support was to be utilized. Patients were to be weaned from the ventilator and extubated only if the investigator deemed it appropriate and after meeting the following criteria:

- Patient was awake or arousable, neurologically intact, cooperative, and comfortable.
- Patient had an FiO2 value ≤ 0.4, PEEP < 5 cm H20, and pressure support ≤ 10cm H2O.
- Patient had the following lung mechanics: minute ventilation expired > 4 L/min but < 15 L/min, tidal volume > 5 ml/kg and spontaneous respiratory rate <25/min.

The following drugs were not to be allowed during study drug infusion:

- Sedating agents other than Propofol; analgesic agents other than morphine (after extubation, use of paracetamol was permitted as clinically indicated). No other analgesics were to be permitted.
- Neuromuscular blocking agents except for the insertion of the endotracheal tube.
- Epidural or spinal analgesic agents.
- Any drugs contraindicated with the use of Dexmedetomidine, Propofol , or morphine.
- Alpha-2 agonist/antagonist.

SECTION 7.2.2.2 STATISTICAL ANALYSIS

Only patients from the randomized, double-blind, placebo-controlled part of the study (Part II) were to be included in the efficacy analyses. A patient was required to satisfy the following evaluability criteria in order to be included in the evaluable subset:

- The patient received study drug for at least 6 hours, unless the patient was prematurely discontinued by the investigator due to an adverse event.
- The patient received none of the following medications during study drug administration: sedating agents other than Propofol, analgesic agents other than morphine or paracetamol, neuromuscular blocking agents except for insertion of the endotracheal tube, epidural or spinal analgesic/anesthetic agents, any drugs contraindicated with the use of Propofol, Dexmedetomidine, or morphine, or other prohibited medications
- The patient received only morphine or paracetamol for pain management.
- The patient was intubated for at least 6 hours.

A patient was included in the intent-to-treat subset if he or she was randomized and required intensive care and sedation following surgery. Patients in Part I and II of the study were included in the safety subset if he/she received any study drug.

EFFICACY ANALYSES:

The primary efficacy analysis was based on the intent-to-treat subset of patients. A second set of efficacy analyses was completed on the evaluable subset.

Primary Efficacy Analysis

The primary efficacy variable in this study was the total dose (mg) of Propofol during intubation received as rescue medication for sedation during the period of study drug

administration. The total dose was summarized by the number of patients in the following three total dose categories: no Propofol (0 mg); a subtherapeutic dose over time (>0 mg to 50 mg); and a therapeutic dose (>50 mg). Differences in the distributions of the proportion of patients in each category between the dexmedetomidine treatment group and the placebo treatment group were tested with a chi-square statistic. Center differences were also explored. The total dose was also summarized by N, mean, standard error of the mean (SEM), minimum, median, and maximum. The treatment groups were compared using an analysis of variance (ANOVA) with treatment, center and treatment-by-center interaction included in the model.

[Reviewer Note: The final primary efficacy analysis submitted in this application is different from the sponsor's proposal in the original protocol. None of the amendments to this study reflect the performed analysis. At a meeting with the sponsor at the conclusion of the Phase II studies, Dr. Thomas Permutt (the reviewing statistician) suggested that the capability of Dexmedetomidine to provide sedation would be more convincingly demonstrated by an analysis of how many patients needed any rescue medication rather than by measuring the amount of rescue medication utilized by both placebo and Dexmedetomidine patient groups. Consequently, the sponsor was encouraged to incorporate calculations of the number of patients receiving any amount of Propofol in the primary efficacy analysis.]

Secondary Efficacy Analyses

The following are secondary efficacy variables in the study:

- Total dose of Propofol during study drug administration:

  The total dose of Propofol (mg) administered during study drug infusion was calculated. The total dose was divided by the length of infusion to determine the total dosing rate during infusion and was expressed as mg/h. The length of infusion was defined as the difference between the time of the start of study drug and the end of study drug infusion. The total dosing rate was summarized by N, mean, SEM, median, minimum, and maximum. The treatment groups were compared using an ANOVA with treatment, center, and treatment-by-center interaction included in the model.

- The total dose of morphine during study drug administration:

  Analysis of total dose of morphine during study drug administration was run on three populations of patients. The first population consisted of patients who did not receive any Propofol during intubation. The second population consisted of patients with a subtherapeutic total dose over time of Propofol during intubation of > 0 — 50 mg. All patients were included in the third population.

- The total dose of morphine by time period (first 6.5 hours of study drug infusion; 6.5 hours after the start to the end of study drug infusion):

It was anticipated that this was the time period of most intense analgesic requirements. Additionally, it was expected most patients would be extubated within 6.5 hours, thus the selection of the time period. The total dose (mg) of morphine during study drug administration was divided by the length of time between the start of study drug infusion and the end of study drug infusion and was expressed in mg/h. Total dose of morphine was also calculated from the start of study drug infusion to 6.5 hours after the start of study drug infusion and from 6.5 hours after the start of study drug to the end of study drug infusion. The total dose was summarized by descriptive statistics (mean, SEM, median, minimum, and maximum). The treatment groups were compared using an ANOVA with treatment, center and treatment-by-center interaction included in the model.

- Ramsay sedation score

For each patient, the average of the Ramsay scores was calculated using the trapezoidal rule for the area under the curve (AUC). The AUC Ramsay score was to be divided by the length of the study drug administration period. This AUC Ramsay variable for dexmedetomidine was compared to placebo using an ANOVA and was summarized by N, mean, SEM, median, minimum, and maximum. In addition, the AUC Ramsay score was calculated for each 1-hour interval during the study drug administration. One-hour AUC Ramsay scores were summarized by N, mean, SEM, median, minimum, and maximum. The mean hourly Ramsay was plotted by treatment group. Variability of AUC scores was displayed using error bars.

The number of patients having at least one Ramsay score of 1 (anxious, agitated, restless) during study drug infusion was summarized by counts and percents. Treatment groups were compared using a chi-square test.

The percentage of Ramsay assessments equal to 1 was computed for each patient and was summarized by descriptive statistics. An ANOVA with treatment, center, and treatment-by-center interaction included in the model was used to compare the mean ratio between treatment groups.

- Time to extubation and weaning duration:

The time to extubation was defined as the difference between ICU arrival and the time when the patient was deemed ready for extubation. A second analysis of the time to extubation was performed using the difference between start of study drug and the time when the patient was deemed ready for extubation.

Weaning duration was defined as the difference between initiation of weaning from the ventilator and readiness for extubation. If weaning had not been initiated within 24 hours after start of study drug, the patient was to be dropped from the analysis. In all cases, a patient was considered censored if the patient was not deemed ready for extubation 24 hours after the start of study drug infusion or if the patient discontinued

prior to extubation.

Time to extubation and weaning duration were summarized by N, mean, SEM, median, minimum, and maximum. Treatment differences for time to extubation and weaning duration were displayed using Kaplan-Meier survival curves and analyzed with the log-rank analysis procedure. In addition, the duration of time from the arrival to the ICU and extubation and the duration of time from the start of study drug to extubation were summarized by N, mean, standard deviation (SD), median, minimum, and maximum.

- Nurse assessment:
  Nurse assessments were summarized (N, mean, SEM, median, minimum, and maximum) for any nursing shift that covered intubation (starting or ending during intubation). If multiple assessments were performed for a patient during intubation, the mean score was summarized.

A patient management index was calculated as the sum score per patient. The patient management index was summarized by descriptive statistics. The Cochran-Mantel-Haenszel statistic was used to test for differences between the treatments and adjust for center differences.

- Study Drug Exposure:

  The total dose (mcg/kg) of dexmedetomidine received was summarized by descriptive statistics (N, mean, SEM, median, minimum, and maximum). Total dose was the sum of the loading and maintenance doses. Total maintenance dose (mcg/kg) was the sum of the dose at each rate change. The formula for calculating the loading and maintenance dose was as follows:

$$\frac{\text{Duration at rate (h)*infusion pump rate (ml/h)*concentration (mcg/mL)}}{\text{Weight at screening physical exam (kg)}}$$

The infusate concentration of dexmedetomidine was to be 4 mcg/mL.
The number of rate change adjustments per patient was summarized by descriptive statistics (N, mean, SD, median, minimum, and maximum) for each treatment group. The duration of study drug infusion (h) was summarized by N, mean, SD, median, minimum, and maximum for each treatment group.

PLANNED SAMPLE SIZE

The target enrollment (300 patients, 150 patients per treatment group) for Part II of this study allowed a detection of significant differences in rescue medication for sedation at the 0.05 (two-tailed) level with 80% power. This sample size estimation was based on the following assumptions:

- Propofol usage over 24 hours would be 70 mg/kg for the placebo group and 0.30 mg/kg for the dexmedetomidine group;

- The effect size was 0.35;
- Ninety percent of the patients enrolled would be evaluable.

SECTION 7.2.2.3 PROTOCOL AMENDMENTS

Three amendments were made to the original protocol.

Amendment One (06 March 1998):

- Corrected typographical errors.

- Clarified that the results of the Phase II study were preliminary.

- Clarified that the primary efficacy variable was to be assessed during the time the patient was intubated and clarified the secondary variables.

- Extended the study drug infusion to 6 hours after extubation in order to be consistent with the previous Phase II study design and allowed the investigator to continue study drug infusion up to a maximum of 24 hours.

- Identified the appropriate target Ramsay sedation score during intubation (≥3) and postextubation (≥2) and allowed the use of paracetamol for pain post-extubation.

- Clarified how to manage the syringe labeling.

- Removed the need to use 60 mL syringes and updated stability data on dexmedetomidine.

- Removed the need to provide drug preparation envelopes as study drug was fully blinded.

- Corrections to reflect actual drug label.

- Required patients at Austrian sites to be at least 19 years of age.

- Allowed the use of paracetamol after extubation.

- Noted that the protocol only provided guidelines for the weaning/extubation of patients.

- Clarified contraindicated medications.

- Added analyses of Propofol use during intubation and paracetamol use post-extubation.

- Included amendment #1 in the investigator agreement.

- Updated the study schematic to reflect the body of the protocol.

- Updated the list of Affiliate Medical/Scientific Directors.

- Clarified the time frame for the number of boluses and updated the standard of practice for the use of Propofol in ICU sedation.

Amendment Two (11 March 1998), Site Specific: UK, Greece, Finland, and Sweden

- Allowed for the legally acceptable representative of the patient to give consent for the patient to be enrolled in the study.

- Amended the Investigator Agreement to reflect the incorporation of Amendment 2.

Amendment Three (1 October 1998):

- Reflected a change in Abbott personnel

- Removed weight and time from the primary and secondary efficacy variable

- Changed the primary efficacy variable to be based on the intent-to-treat patient subset.

- Included Amendment #3 in the Investigator Agreement.

Changes to the Planned Analyses

As outlined in the statistical analysis plan, certain efficacy variables were to have center-by-treatment interaction analyses performed; however, several centers had no patients or only one patient per treatment group. Therefore, visual inspection of parameters across centers was performed to determine if the treatment effect was consistent across centers.

Additionally, the AUC Ramsay score was to be divided by the duration of the study drug administration time period. Instead, the AUC Ramsay scores were divided by the time period over which Ramsay scores were collected.

The incidence of Ramsay score of 1 was analyzed using a chi-square test instead of the categorical ANOVA stated in the statistical analysis plan.

Temperature was not summarized due to differences in the collection methods as well as the infrequency of the collections.

SECTION 7.2.2.4 STUDY CONDUCT

DISPOSITION / DISTRIBUTION:

A total of 93 patients were enrolled in Part I of the study. One patient did not receive study medication; therefore, a total of 92 patients were treated with Dexmedetomidine. In Part II of the study, a total of 203 patients were randomized to Dexmedetomidine and 198 were randomized to placebo; all of these patients received their assigned treatment. A total of 14 patients in the Dexmedetomidine treatment group and 8 patients in the placebo treatment group were prematurely discontinued from the study.

Table 17 Summary of Patient Disposition

	Part I	Part II	
	Dexmedetomidine	Dexmedetomidine	Placebo
All Randomized	93	203	198
Randomized, Not Treated	1	0	0
All Treated Patients	92(100%)	203(100%)	198(100%)
Discontinued Patients	3(3%)	14[a](7%)	8(4%)
Completed Dosing[b]	89(97%)	189(93%)	190(96%)

Modified Sponsor's Table 6.1a Vol 8/10-86-66
a: For description of discontinuations, refer to Safety Analysis, Study W97-246
b: This is not evaluable set.

A total of 198 patients received placebo and 203 patients received Dexmedetomidine in Part II of the study and comprise the Intent to Treat data set. Of these 7 placebo patients and 3 Dexmedetomidine patients did not meet the evaluability criteria specified in the protocol and were excluded from the Evaluable patient data set.

Table 18 Reasons for Non-evaluability, Part II of Study

	Placebo	Dexmedetomidine
Intent to Treat Patients (All Treated)	198	203
Non-Evaluable patients	7	3
Evaluable Patients	191	200
Reasons for Non-Evaluability (Patient Numbers)		
Insufficient Intubation	1	N/A
Received disallowed medication	5	3
Enrolled twice	1	N/A

Modified Sponsor's Table 8.1a Vol 8/10-86-73

PROTOCOL VIOLATIONS:

Table 19 Protocol Deviations (Violations of Inclusion/Exclusion Criteria)

NUMBER OF PATIENTS	VIOLATION
2	Younger than 18 years
1	Original patient in Part I
2	Received alpha-2 agonists/antagonists in 30 days prior to current study
1	Patient with excessive bleeding likely to need re-operation

Numerous protocol deviations were identified during the study; most were associated with the timing of assessments or missed assessments. Additional deviations of interest included 5 Dexmedetomidine patients (2 in Part I and 3 in Part II) and 2 placebo patients who received study medication for greater than 24 hours (overall range from 24.02 to 25.33 hours); and 39 Dexmedetomidine patients (16Part I and 23 Part II) and 2 placebo patients who received study drug infusions less than the 0.2 mcg/kg/h dose stated in the protocol. The primary reasons for decreasing the study drug infusion below 0.2 mcg/kg/h or even intermittently stopping the infusion included the occurrence of hypotension and oversedation. One placebo patient had the study blind broken due to the occurrence of a serious adverse event of hypotension.

DEMOGRAPHICS

Part I

Table 20 Summary of Patient Demographics, Study Part I

Parameter	Dexmedetomidine		
	Male	Female	Total
Number of patients	70	22	92
Ethnic Origin n (%)			
Black	1(1%)	0	1(1%)
Caucasian	68(97%)	22(100%)	90(98%)
Other	1(1%)	0	1(1%)
Age (mean ± SD)	60±13.49	52.9±17.56	58.3±14.78

Modified Sponsor's Table 6.3a Vol 8/10-86-69

The mean age among patients in Part I of the study was 58 years. The majority of the patients were male (76%) and of Caucasian (98%) ethnic origin. Among patients who had smoking status and alcohol use data reported at baseline, most were non-users or ex-users of tobacco (86%) and a little more than half of the patients did not consume alcohol (52%). 8 females were of child bearing potential.

Part II

Table 19 Protocol Deviations (Violations of Inclusion/Exclusion Criteria)

NUMBER OF PATIENTS	VIOLATION
2	Younger than 18 years
1	Original patient in Part I
2	Received alpha-2 agonists/antagonists in 30 days prior to current study
1	Patient with excessive bleeding likely to need re-operation

Numerous protocol deviations were identified during the study; most were associated with the timing of assessments or missed assessments. Additional deviations of interest included 5 Dexmedetomidine patients (2 in Part I and 3 in Part II) and 2 placebo patients who received study medication for greater than 24 hours (overall range from 24.02 to 25.33 hours); and 39 Dexmedetomidine patients (16Part I and 23 Part II) and 2 placebo patients who received study drug infusions less than the 0.2 mcg/kg/h dose stated in the protocol. The primary reasons for decreasing the study drug infusion below 0.2 mcg/kg/h or even intermittently stopping the infusion included the occurrence of hypotension and oversedation. One placebo patient had the study blind broken due to the occurrence of a serious adverse event of hypotension.

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The mean age among patients in Part I of the study was 58 years. The majority of the patients were male (76%) and of Caucasian (98%) ethnic origin. Among patients who had smoking status and alcohol use data reported at baseline, most were non-users or ex-users of tobacco (86%) and a little more than half of the patients did not consume alcohol (52%). 8 females were of child bearing potential.

Part II

Table 21 Summary of Patient Demographics, Study Part II

Parameter	Placebo			Dexmedetomidine		
	Male	Female	Total	Male	Female	Total
Number of patients	134	64	198	141	62	203
Ethnic Origin						
Asian	0	0	0	1(<1%)	0	1(<1%)
Black	0	0	0	1(<1%)	0	1(<1%)
Caucasian	133(>99%)	64(100%)	197(>99%)	138(98%)	61(98%)	199(98
Other	1(<1%)	0	1(<1%)	1(<1%)	1(2%)	2(<1%)
Age (mean ± SD)	62±11.27	63±16.52	63±13.16	61±11.5	60±17.5	60±13.

Modified Sponsor's Table 6.3b Vol 8/10-86-69

Mean age among patients in Part II of the study was comparable between treatment groups (placebo 63 years; Dexmedetomidine 60 years). The majority of patients in both treatment groups were male (≥ 68%) and of Caucasian (> 98%) ethnic origin. Within both treatment groups, the majority of the patients were non-users or ex-users of tobacco (≥ 66%); more than half of the patients in the placebo group (56%) consumed alcohol while more than half of the patients in the Dexmedetomidine group did not.

The types of surgical procedures performed on patients in Part II of the study were comparable between the treatment groups. The majority of the patients had cardiac surgery performed (≥ 44%), followed by laparotomy (≥ 29%) and head and neck surgery (≥ 6%); 16% of the patients in the placebo group and 21% of the patients in the Dexmedetomidine group had other surgical procedures performed.

A total of 26 females (12 placebo, 14 Dexmedetomidine) in Part II of the study were of childbearing potential. Pregnancy tests were negative at baseline. 218 patients (106 placebo and 112 Dexmedetomidine) in Part II of the study had abnormal EKGs at baseline, but none were excluded from study participation because of these abnormalities.

SECTION 7.2.2.5. SPONSOR'S EFFICACY RESULTS

Table 22 Exposure

Mean (± SD) Total Dexmedetomidine Dose and Total Duration of Infusion During the Entire Study Drug Infusion Period, All Treated Patients, Study Part II

	Placebo Mean±SD	Dexmedetomidine Mean ± SD
During Entire Study Drug Infusion Period	N=198	N=203
Mean total dose (mcg/kg)	N/A	7.1 ± 2.81
Mean total duration of infusion (hours)	14.9 ± 3.95	14.7 ± 4.51
Prior to Extubation	N=195	N=198
Mean total dose (mcg/kg)	N/A	4.8± 1.93
Mean total duration of infusion (hours)	8.1 ± 3.63	8.3 ± 3.77
After Extubation	N=195	N=198
Mean total dose (mcg/kg)	N/A	2.5 ± 1.64
Mean total duration of infusion (hours)	6.8 ± 2.73	6.7 ± 2.65

Modified Sponsor's Table 9.1a Vol 8/10-86-86

PRIMARY EFFICACY VARIABLES:

In both the Intent-to-Treat and the evaluable patient analyses, Dexmedetomidine treated patients required statistically significantly less Propofol for sedation during intubation compared to placebo-treated patients:

Total Dose of Propofol During Intubation:

Table 23 Total Dose of Propofol (mg) During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	N=198	N=203	
Mean ± SEM	513±55.58	71.58±17.51	<0.0001
Evaluable Patients (N)	N=191	N=200	
Mean ± SEM	504.69±56.4	72.59±17.76	<0.0001

a: p-value from ANOVA

SEM = Standard Error of Mean

Modified Sponsor's Table 8.2a Vol 8/10-86-73

A statistically significant center effect was detected for the total dose of propofol during intubation in both the Intent to Treat and Evaluable patient analyses; however, sponsor states inspection of center level data confirm that the centers differ in magnitude of effect, not direction.

The total dose of Propofol used during intubation was also analyzed according to the number of patients who received no Propofol (0 mg), the number of patients who received a subtherapeutic dose over time (> 0 mg to 50 mg of Propofol), and the number of patients who received a therapeutic dose over time > 50mg of Propofol. Statistically