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Statistical Review and Evaluation

NDA 21-038
Drug name: [redacted] :detomidine hydrochloride)
Applicant: Abbott Labs, Inc.
Drug class: 1S
Indication: ICU sedation through infusion

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1. Introduction

Dexmedetomidine is a potent and highly selective alpha2-adrenoreceptor agonist. Dexmedetomidine is suggested to have a broad range of properties that include sedation and analgesia with arousability and cooperation, hemodynamic stability, less anxiety, and no respiratory depression. This NDA, submitted by Abbott Labs, Inc., is intended for obtaining an approval of marketing [redacted] (dexmedetomidine hydrochloride) for an indication of sedation through IV infusion in intensive care unit (ICU) patients.

To evaluate the safety and efficacy of dexmedetomidine, the sponsor conducted two well-controlled, phase III clinical studies, W97-245 and W97-246, both of which were multi-center, randomized, placebo-controlled and double-blind. They had a very similar design and differed only in the rescue medication for sedation allowed during the procedure. This statistical review is to focus on the efficacy evaluation of these two studies. The M.O.'s safety evaluation did not suggest any safety concerns requiring statistical evaluation.

Section 2 of this review briefly describes the study designs of the two clinical trials. The primary and secondary efficacy analyses are to be discussed in Section 3. The subgroup analyses can be found in Section 4, followed by the sections of Discussion and Conclusions.

2. Studies W97-245/W97-246

As stated previously, the two studies shared a common study design and the only difference was the rescue medication for sedation allowed during the study procedure. They both consisted of two parts. Part I was an open-label study with up to 4 patients per center. It was intended to allow investigators to become more familiar with the study treatment regimen before entering the Part II of the study that was double-blind and placebo-controlled.

Therefore, only patients from Part II in both studies will be included in the efficacy evaluation. The design of the two studies (Part II) is outlined in Table 2.1.

Table 2.1 Study Design of W97-245 (Part II) and W97-246 (Part II)

	W97-245 (Part II)	W97-246 (Part II)
Overall Design	Randomized, double-blind, double-dummy, multi-center	
Study Drug	Dexmedetomidine	
Dosing	Loading dose – 6.0 mcg/kg/h for 10 min. Maintenance - 0.4 mcg/kg/h (may be adjusted between 0.2-0.7)	
Comparator	Placebo with rescue medication	
Medication for Pain	Morphine	
Patient Population	Intensive care units (ICU)	
Primary Efficacy Endpoints	Total dose of and number of patients requiring rescue medication (midazolam for W97-245 and propofol for W97-246)	
Secondary Efficacy Endpoints	The total dose of morphine by time period; Ramsay sedation score; Time to extubation and weaning duration; etc.	
Rescue Medication for Sedation	Midazolam	Propofol
Sample Size	353 (178/175*)	401 (203/198*)
No. of Center	33 (10 countries)	36 (11 countries)

* Assigned to the dexmedetomidine treated and placebo groups, respectively.

In both studies, the sedation action was assessed based on a 6-point Ramsay score:

6 = asleep, no response;
5 = asleep, sluggish response to light glabellar tap loud auditory stimulus
4 = asleep but with brisk response to light glabellar tap or loud auditory stimulus
3 = patient responds to commands
2 = patient cooperative, oriented, and tranquil
1 = patient anxious, agitated, or restless

Within one hour after patient's arrival in the ICU, the study drug (dexmedetomidine) was administered as a two-stage infusion consisting of a 10-minute loading dose of 6.0 mcg/kg/h, followed by a maintenance infusion at a rate of 0.4 mcg/kg/h. The maintenance infusion rate then could be adjusted in increments of 0.1 mcg/kg/h or higher but maintained in the range of 0.2 to 0.7 mcg/kg/h to achieve and maintain a Ramsay sedation score of ≥ 3. Following extubation, the infusion rate could be adjusted to achieve a Ramsay sedation score of ≥ 2.

The only rescue medication for sedation allowed during the loading dose period was midazolam for Study W97-245 or propofol for Study W97-246. Investigators could give patients other appropriate rescue medication during the maintenance infusion period only if the study drug infusion rate reached a maximum 0.7 mcg/kg/h and patients had received 3 boluses of midazolam or propofol within 2 hours. Morphine was the only pain medication allowed.

Study drug administration began within 1 hour of admission to the ICU and continued for 6 hours after extubation to a maximum of 24 hours total study drug infusion. Efficacy and safety measurements were taken at specified time points up to 24 hours after the start of the study drug infusion.

Both studies used the same inclusion/exclusion criteria. Patients had to satisfy all of the inclusion criteria in order to be included in the study:

- Signed and dated the Informed Consent after the study had been fully explained or had a legally acceptable representative (if acceptable by local law and acceptable to the IEC) 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 only, age 19 or older)
- If female and of child-bearing potential, was not pregnant (confirmed by negative pregnancy test) and not lactating

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

- Had serious central nervous system (CNS) 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 benzdiazepines were contraindicated or had known or suspected serious allergy to any medication that might have been administered during the course of the study

and some other medical conditions.

3. Primary and Secondary Efficacy Analyses

Study# W97-245: 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

This study consisted of 33 sites in total, including 6 in France, 5 in Belgium, 1 in Canada, 4 in Germany, 6 in Spain, 1 in Austria, 1 in Greece, 3 in Netherlands, 4 in UK, and 2 in Italy.

In Part II of the study, a total of 178 patients were randomized to receive dexmedetomidine and 175 to placebo. All of them received the assigned treatment, but 9 treated patients and 10 placebo patients were prematurely discontinued from the study.

The intent-to-treat (ITT) population included all of the randomized population, i.e., the 175 placebo patients and 178 dexmedetomidine treated patients. Of these, 6 placebo patients and 2 treated patients were identified by the sponsor as nonevaluable. The evaluable sub-population then consisted of 169 placebo and 176 treated patients. In the final report, the sponsor performed all efficacy analyses based on both the ITT population and the evaluable sub-population. The results were quite similar. In the remainder of the review, only the ITT analyses (analyses based on the ITT population) will be discussed.

Table 3.1 shows the demographic and baseline characteristics of the ITT population. The two treatment groups appeared to be quite similar with respect to the factors listed below. They were both mostly male, at a mean age of around 63 years, and mostly Caucasian.

Table 3.1 Demographic and Baseline Characteristic Parameter
Intent-to-Treat Population, Study W97-245 (Part II)

Characteristic Parameter	Placebo			Dexmedetomidine		
	Male	Female	Total	Male	Female	Total
Number of Patients	133	42	175	134	44	178
Age (yrs)						
Mean (S.D.)	63 (12)	65 (12)	64 (12)	62 (12)	65 (13)	62 (12)
Race						
Caucasian	131 (98%)	42 (100%)	173 (99%)	130 (97%)	42 (95%)	173 (97%)
Non-Caucasian	2 (2%)	0 (0%)	2 (2%)	4 (3%)	2 (5%)	6 (3%)
Weight (kg)						
Mean (S.D.)	77 (12)	67 (12)		78 (14)	63 (15)	
Height (cm)						
Mean (S.D.)	173 (7.2)	161 (6.5)		173 (7.3)	161 (7.2)	

Source: Table 11.2, Vol. 8/10-62-150.

The primary efficacy endpoint was the total dose of midazolam (mg) received as rescue medication for sedation during intubation. The continuous primary efficacy variable was analyzed using an ANOVA model including the treatment effect and center effect. A significant p value for treatment effect ($p < 0.05$) would imply that the two groups were different in terms of

the total dose of midazolam during intubation adjusting for the centers. In addition, the sponsor also compared the two groups based on the categorized total dose of midazolam during intubation: no use (0 mg), subtherapeutic dose (0–4 mg), and therapeutic dose (> 4 mg). A chi-square test was performed on the proportions of patients in the three categories.

As shown in Table 3.2, the treatment effect was statistically significant ($p = 0.0011$) in the ANOVA model. In other words, the dexmedetomidine treated group used significantly less amount of midazolam during intubation than the placebo group (4.8 mg for the treated group vs. 18.6 mg for the placebo group). The center effect was not significant in this ANOVA model.

The chi-square test based on the three categories also gave a significant p value ($p < 0.001$). It can be seen from Table 3.2 that, while a majority (61%) of the dexmedetomidine-treated patients required no midazolam for sedation during intubation, only a quarter (25%) of the placebo patients did so.

Table 3.2 Summary of Midazolam Use as Rescue Medication During Intubation Intent-to-Treat Population, Study W97-245 (Part II)

	Placebo (N = 175)	Dexmedetomidine (N = 178)	P-value
Mean total dose of midazolam (mg)	18.6	4.8	0.0011*
Standard error of the mean	4.0	1.4	
Categorized midazolam use			
# of patients used 0 mg	43 (25%)	108 (61%)	<0.001**
0 – 4 mg	34 (19%)	36 (20%)	
> 4 mg	98 (56%)	34 (19%)	

*P-value was obtained from an ANOVA model with treatment and center
**P-value was obtained from a chi-square test.
Source: Tables 11.9.1 & 11.9.2, Part II, Vol. 8/10-63R-279

The treatment effect was also assessed for a number of secondary efficacy endpoints, including

- The total dose of midazolam (mg) during study drug administration
- The total dose of morphine during study drug administration
- The total dose of morphine by time period
- Ramsay sedation score
- Ratio of Ramsay sedation score of 1 during study drug administration
- Time to extubation and weaning duration

etc.

ANOVA models were also used to analyze these secondary endpoints (except for the time to extubation and weaning duration variables, which were analyzed using the Kaplan-Meier curves and a log-rank test). Shown in Table 3.3 were the total dose of midazolam during study drug

administration (mg/h), total dose of morphine during study drug administration (mg/h), the Ramsay sedation score area under curve (AUC) during drug administration, and ratio of Ramsay sedation score of one during study drug administration.

The total dose of morphine was also stratified on two different periods of time: from the start of study drug infusion to 6.5 hours (mg) and from 6.5 hours to the end of study drug infusion (mg/h). These time periods were chosen because it was anticipated that most patients would require most intense analgesic for the first 6.5 hours and would be extubated shortly after the protocol-required 6 hours intubation period.

It should be noted that the Ramsay score itself was not necessarily a good efficacy endpoint simply because, for both groups, dose titration and rescue medication were used to maintain the patients at certain level of sedation indicated by the Ramsay. However, the ratio of Ramsay sedation score of 1 (patient anxious, agitated, or restless) during study drug administration was used to assess the effect on anxiety of dexmedetomidine. For a particular patient, a smaller ratio might imply a less frequency of being anxious through out the procedure. The ratio was computed for each patient as the number of Ramsay assessments equal to 1 divided by the total number of assessments.

Table 3.3 Summary for Secondary Efficacy Endpoints Intent-to-Treat Population, Study W97-245 (Part II)

	Placebo (N = 175)†	Dexmedetomidine (N=178)†	P-value* Treatment	P-value* Center
Total dose of midazolam during drug administration (mg/h)	1.19 (0.23)	0.29 (0.07)	0.0001	0.32
Total dose of morphine during drug administration (mg/h)	0.83 (0.07)	0.47 (0.06)	<0.0001	<0.0001
Total dose of morphine during (0, 6.5 hrs) (mg)	8.5 (0.79)	4.9 (0.56)	<0.0001	<0.0001
Total dose of morphine during (6.5, end) (mg/h)	0.42 (0.08)	0.24 (0.05)	0.042	<0.0001
Ramsay sedation score AUC during drug administration	3.3 (0.05)	3.6 (0.05)	<0.0001	<0.0001
Ratio of Ramsay sedation score of 1 during drug administration (%)	7 (0.8)	3 (0.5)	<0.0001	<0.0001

† Sizes varied slightly due to missing observations.

* P-value was obtained from an ANOVA model with treatment and center.

Source: Tables 8.3a, 8.3b, 8.3e, 8.3f, 8.3g, Vol. 8/10-62-76, and Table 11.15.5, Vol. 8/10-63R-335.

The p values for the treatment effect and the center effect in the ANOVA models are shown in Table 3.3. The treatment effect was statistically significant for all 6 variables. The center effect was also significant except for the total dose of midazolam during study drug administration.

As mentioned earlier, the time-to-event measurements were compared between the two groups using Kaplan-Meier curves and a log-rank test. A pooled analysis (Studies W97-245/W97-246 data combined) for these variables may be found at the end of this section.

Study# W97-246: 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

This study consisted of 36 sites in total, including 7 in France, 1 in Belgium, 5 in Canada, 5 in Germany, 5 in Spain, 1 in Austria, 4 in Greece, 2 in Netherlands, 4 in UK, 1 in Italy, and 1 in Sweden.

In Part II of the study, a total of 203 patients were randomized to receive dexmedetomidine and 198 to placebo. All of them received the assigned treatment, but 14 dexmedetomidine treated patients and 8 placebo patients were prematurely discontinued from the study.

The intent-to-treat (ITT) population included all of the randomized population, i.e., the 198 placebo patients and 203 treated patients. Of these, 7 placebo patients and 3 treated patients were identified by the sponsor as nonevaluable. The evaluable sub-population then consisted of 191 placebo and 200 treated patients. In the final report, the sponsor performed all efficacy analyses based on both the ITT population and the evaluable sub-population. The results were quite similar. Only the ITT analyses (analyses based on the ITT population) will be discussed in the following.

Table 3.4 shows the demographic and baseline characteristics of the ITT population. The two treatment groups appeared to be quite similar with respect to the factors listed below. They were both mostly male, at a mean age of around 63 years old, and mostly Caucasian.

Table 3.4 Demographic and Baseline Characteristic Parameter
Intent-to-Treat Population, Study W97-246 (Part II)

Characteristic Parameter	Placebo			Dexmedetomidine		
	Male	Female	Total	Male	Female	Total
Number of Patients	134	64	198	141	62	203
Age (yrs)						
Mean (S.D.)	62 (11)	63 (17)	63 (13)	62 (12)	65 (13)	62 (12)
Range						
Race						
Caucasian	133 (>99%)	64 (100%)	197 (>99%)	138 (98%)	61 (98%)	199 (98%)
Non-Caucasian	1 (<1%)	0 (0%)	1 (1<%)	3 (2%)	1 (2%)	4 (2%)
Weight (kg)						
Mean (S.D.)	77 (12)	64 (12)		77 (12)	64 (11)	
Height (cm)						
Mean (S.D.)	172 (7.2)	161 (5.7)		172 (15)	160 (7.2)	

Source: Table 11.2, Vol. 8/10-86-150.

The primary efficacy endpoint was the total dose of propofol (mg) received as rescue medication for sedation during intubation. The continuous primary efficacy variable was analyzed using an ANOVA model including the treatment effect and center effect. A significant p value for treatment effect ($p < 0.05$) would imply that the two groups were different in terms of the total dose of propofol during intubation adjusting for the centers. In addition, the sponsor also compared the two groups based on the categorized total dose of propofol during intubation: no use (0 mg), subtherapeutic dose (0–50 mg), and therapeutic dose (> 50 mg). A chi-square test was performed on the proportions of patients in the three categories.

As shown in Table 3.5, the treatment effect was statistically significant ($p < 0.0001$) in the ANOVA model. In other words, the dexmedetomidine treated group used significantly less amount of propofol during intubation than the placebo group (73 mg for the treated group vs. 513 mg for the placebo group).

There was a significant center effect in the ANOVA model. A visual inspection on the data showed that patients from different countries tended to require different amount of sedative and pain medicine regardless of placebo or treated groups. In other words, the treatment effect differed only in magnitude, not in directions, across the centers.

The chi-square test based on the three categories also gave a significant p value ($p < 0.001$). It can be seen from Table 3.5 that, while a majority (60%) of the dexmedetomidine-treated patients required no propofol for sedation during intubation, only about a quarter (24%) of the placebo patients did so.

Table 3.5 Summary of Propofol Use as Rescue Medication During Intubation Intent-to-Treat Population, Study W97-246 (Part II)			
	Placebo (N = 198)	Dexmedetomidine (N = 203)	P-value
Mean total dose of propofol (mg)	513	72	<0.0001*
Standard error of the mean	55.6	17.5	
Categorized propofol use			
# of patients used 0 mg	47 (24%)	122 (60%)	<0.001**
0 – 50 mg	30 (15%)	43 (21%)	
>50 mg	121 (61%)	38 (19%)	

*P-value was obtained from an ANOVA model with treatment and center
**P-value was obtained from a chi-square test.
Source: Tables 11.9.1 & 11.9.2, Part II, Vol. 8/10-88-188

The treatment effect was also assessed for a number of secondary efficacy endpoints, including

- The total dose of propofol (mg) during study drug administration
- The total dose of morphine during study drug administration
- The total dose of morphine by time period
- Ramsay sedation score
- Ratio of Ramsay sedation score of 1 during study drug administration
- Time to extubation and weaning duration

etc.

ANOVA models were also used to analyze these secondary endpoints (except for the time to extubation and weaning duration variables, which were analyzed using Kaplan-Meier curves and a log-rank test). Shown in Table 3.6 were the total dose of propofol during study drug administration (mg/h), total dose of morphine during study drug administration (mg/h), Ramsay sedation score area under curve (AUC) during study drug administration, and ratio of Ramsay sedation score of 1 during study drug administration.

The total dose of morphine was also stratified on two time periods: from the start of study drug infusion to 6.5 hours (mg) and from 6.5 hours to the end of study drug infusion (mg/h). These time periods were chosen because it was anticipated that most patients would require most intense analgesic for the first 6.5 hours and would be extubated shortly after the protocol-required 6 hours intubation period.

The ratio of Ramsay sedation score of 1 (patient anxious, agitated, or restless) during study drug administration was used to assess the effect on anxiety of dexmedetomidine. The ratio was computed for each patient as the number of Ramsay assessments equal to 1 divided by total number of assessments. An ANOVA model was used to analyze the ratios.

The p values for the treatment effect and the center effect in the ANOVA models are shown in Table 3.6. The treatment effect was statistically significant for all 6 variables. The center effect was also significant except for the total dose of morphine during (6.5 hours, end).

Table 3.6 Summary for Secondary Efficacy Endpoints Intent-to-Treat Population, Study W97-246 (Part II)

	Placebo (N = 198)†	Dexmedetomidine (N=203)†	P-value Treatment	P-value Center
Total dose of propofol during drug administration (mg/h)	39 (4.1)	5.3 (1.2)	<0.0001	<0.0001
Total dose of morphine during drug administration (mg/h)	0.89 (0.07)	0.43 (0.05)	<0.0001	<0.0001
Total dose of morphine during (0, 6.5 hrs) (mg)	8.5 (0.64)	4.1 (0.47)	<0.0001	<0.0001
Total dose of morphine during (6.5, end) (mg/h)	0.55 (0.07)	0.16 (0.03)	<0.0001	0.18
Ramsay sedation score AUC during drug administration	3.1 (0.04)	3.4 (0.04)	<0.0001	<0.0001
Ratio of Ramsay sedation score of 1 during drug administration (%)	7 (0.7)	4 (0.5)	0.0008	<0.0001

† Sizes varied slightly due to missing observations.
* P-value was obtained from an ANOVA model with treatment and center.
Source: Tables 8.3a, 8.3b, 8.3e, 8.3f, 8.3g, Vol. 8/10-86-75, and Table 11.15.5, Vol. 8/10-88-241.

Time to Extubation and Weaning (Pooled Analysis)

As part of the secondary efficacy analyses, the two treatment groups were also compared on several key time-to-event variables. In Table 3.7, the times to readiness for extubation from three different time points were analyzed using a log-rank test. Studies W97-245 and W97-246 were pooled together in this analysis to increase the power for detecting any significant differences between the two groups.

It is shown in Table 3.7 that the lengths of these time periods were quite comparable between the two groups and no statistically significant difference was observed. Same analysis on data from individual study yielded similar results.

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. There were 25 placebo patients and 23 treated patients considered as censored for the first two

variables in Table 3.7, and 5 placebo patients and 6 treated patients censored for the third variable (weaning duration). No unbalanced censoring was observed for the two groups in the two studies.

Table 3.7 Summary for Time-to-Event Secondary Efficacy Endpoints Intent-to-Treat Population, Studies W97-24/W97-246 (Part II) Pooled

		Placebo (N=359)	Dexmedetomidine (N=370)	P-value**
Time to readiness for extubation,				
from ICU arrival (min.)	Mean	516 ± 32	572 ± 74	
	Median*	385	398	0.78
from start of study drug administration (min.)	Mean	489 ± 32	543 ± 74	
	Median*	360	370	0.81
from initiation of weaning from the ventilator (weaning duration) (min)	Mean	86 ± 18	65 ± 19	
	Median*	15	15	0.74

* Kaplan-Meier estimates.

** P-value was obtained from a log-rank test.

Source: Tables 29 & 30, Vol. 8/10-238-61.

4. Subgroup Analyses

The sponsor conducted subgroup analyses on the primary efficacy endpoint, total dose of midazolam (W97-245) or propofol (W97-246) during intubation. The patient population was stratified by age, gender, race, country, and type of surgery.

By Age

The subgroup analysis was done on four age groups: 18-35 years; 36-55 years; 56-65 years; and >65 years. Table 4.1 shows the p values from both ANOVA models and chi-square tests. The results were mostly consistent with those of the overall analysis.

Table 4.1 Subgroup Analyses by Age for Rescue Medication During Intubation (mg) Intent-to-Treat Population (Studies W97-245/W97-246, Part II)

Age	Study # (Rescue Medication)	Placebo	Dexmedetomidine	P-value*	Chi-square Test on Categrorized Dose†
18-35 Years	W97-245 (Midazolam)	N=6 35 ± 11	N=4 14 ± 8.0	-	-
	W97-246 (Propofol)	N=10 605 ± 170	N=13 314 ± 167	0.031	0.31
36-55 Years	W97-245 (Midazolam)	N=36 13 ± 2.5	N=43 12 ± 5.7	0.71	0.0001
	W97-246 (Propofol)	N=41 907 ± 196	N=47 66 ± 37	0.002	<0.0001
56-65 Years	W97-245 (Midazolam)	N=32 22 ± 7.0	N=45 1.8 ± 0.5	0.005	<0.0001
	W97-246 (Propofol)	N=58 485 ± 86	N=66 79 ± 29	0.0004	<0.0001
>65 Years	W97-245 (Midazolam)	N=101 18 ± 6.5	N=86 2.4 ± 0.5	0.028	<0.0001
	W97-246 (Propofol)	N=89 340 ± 52	N=77 28 ± 9.6	<0.0001	<0.0001

* P-value was obtained from an ANOVA model with treatment and center

† Categorized dose was 0, 0-50, and >50 mg for midazolam and 0, 0-4, and >4 mg for propofol.

\- Test was not performed because there were less than 5 patients in the treatment group.

Source: Tables 6 & 7, Vol. 8/10-238-26.

By Gender

The only non-significant p value (p = 0.14) was observed for the midazolam use in the female patients (Study W97-245), which had relatively small sample sizes (42 vs. 44 in the two groups, respectively). But the corresponding chi-square test was significant (p = 0.004).

Table 4.2 Subgroup Analyses by Gender for Rescue Medication During Intubation (mg) Intent-to-Treat Population (Studies W97-245/W97-246, Part II)

Gender	Study # (Rescue Medication)	Placebo	Dexmedetomidine	P-value*	Chi-square Test on Categrorized Dose†
Male	W97-245 (Midazolam)	N=133 16 ± 2.2	N=134 5.2 ± 1.9	0.0004	<0.0001
	W97-246 (Propofol)	N=134 547 ± 77	N=141 71 ± 21	<0.0001	<0.0001
Female	W97-245 (Midazolam)	N=42 27 ± 15	N=44 3.7 ± 1.4	0.14	.0.004
	W97-246 (Propofol)	N=64 443 ± 62	N=62 73 ± 31	<0.0001	<0.0001

* P-value was obtained from an ANOVA model with treatment and center
† Categorized dose was 0, 0-50, and >50 mg for midazolam and 0, 0-4, and >4 mg for propofol.
Source: Tables 8 & 9, Vol. 8/10-238-29.

By Race

There were not enough non-Caucasian patients to make meaningful comparisons. The results in the Caucasian patients were consistent with those of the overall analysis.

Table 4.3 Subgroup Analyses by Race for Rescue Medication During Intubation (mg) Intent-to-Treat Population (Studies W97-245/W97-246, Part II)

Race	Study # (Rescue Medication)	Placebo	Dexmedetomidine	P-value*	Chi-square Test on Categrorized Dose†
Caucasian	W97-245 (Midazolam)	N=173 17.5 ± 3.9	N=172 4.8 ± 1.5	0.002	<0.0001
	W97-246 (Propofol)	N=197 516 ± 56	N=199 73 ± 18	<0.0001	<0.0001
Others	W97-245 (Midazolam)	N=2 114 ± 104	N=6 5.0 ± 2.6	-	-
	W97-246 (Propofol)	N=1 0.0 ± 0.0	N=4 12.5 ± 7.5	-	-

* P-value was obtained from an ANOVA model with treatment and center
† Categorized dose was 0, 0-50, and >50 mg for midazolam and 0, 0-4, and >4 mg for propofol.
- Test was not performed because there were less than 5 patients in the treatment group.
Source: Tables 10 & 11, Vol. 8/10-238-32.

By Country

Centers from two countries showed some departure from the overall trends. The five centers (a total of 43 patients) from Germany in Study W97-245 had less than 5% of patients in both groups (1 patient in each group) requiring 0 mg of midazolam during intubation, while other countries typically had more than 50% of the treated patients doing so. The single center (20 patients) from Austria in Study W97-246 observed a similar amount of propofol use for the placebo and the dexmedetomidine groups (50.1 mg vs. 51.2 mg, respectively).

Other countries were mostly consistent with the overall results.

Table 4.4 Subgroup Analyses by Country for Rescue Medication During Intubation (mg) Intent-to-Treat Population (Studies W97-245/W97-246, Part II)

Country	Study # (Rescue Drug)	Placebo	Dexmedetomidine	P-value*	Chi-square Test on Categrorized Dose†
Austria (1 Center)	W97-245 (Midazolam)	N=10 5.4 ± 2.8	N=10 1.4 ± 0.6	0.18	0.43
	W97-246 (Propofol)	N=10 50 ± 4.2	N=10 51 ± 5.2	0.86	0.64
Germany (5 Centers)	W97-245 (Midazolam)	N=21 31 ± 5.1	N=22 20 ± 9.5	0.33	0.11
	W97-246 (Propofol)	N=48 846 ± 99	N=49 101 ± 36	<0.0001	<0.0001

* P-value was obtained from an ANOVA model with treatment and center
† Categorized dose was 0, 0-50, and >50 mg for midazolam and 0, 0-4, and >4 mg for propofol.
Source: Tables 12 & 13, Vol. 8/10-238-35.

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By Surgery Type

Surgery type was classified as cardiac, head and neck, laparotomy, and other. For propofol use in Study W97-246, the treated group beat the placebo group in every surgery type with a significant p value. However, for midazolam use in Study W97-245, only cardiac and "other" surgeries had significant p values. The head and neck surgery showed a reverse outcome, i.e., the treated group on average actually used more midazolam for sedation during intubation than the placebo group (19 mg vs. 16 mg, respectively), although the difference was not statistically significant.

Table 4.5 Subgroup Analyses by Surgery Type for Rescue Medication During Intubation (mg) Intent-to-Treat Population (Studies W97-245/W97-246, Part II)					
Surgery Type	Study # (Rescue Drug)	Placebo	Dexmedetomidine	P-value*	Chi-square Test on Categrorized Dose†
Cardiac	W97-245 (Midazolam)	N=110 17.2 ± 6.0	N=106 2.0 ± 0.4	0.013	<0.0001
	W97-246 (Propofol)	N=90 440 ± 93	N=90 42 ± 20	<0.0001	<0.0001
Head and Neck	W97-245 (Midazolam)	N=19 16 ± 3.7	N=15 19 ± 14	0.96	0.36
	W97-246 (Propofol)	N=15 411 ± 208	N=12 171 ± 141	0.052	0.08
Laparotomy	W97-245 (Midazolam)	N=26 14.2 ± 3.4	N=36 6.7 ± 3.6	0.11	0.0002
	W97-246 (Propofol)	N=61 630 ± 83	N=59 79 ± 29	<0.0001	<0.0001
Other	W97-245 (Midazolam)	N=20 35 ± 11	N=21 5.9 ± 2.9	0.03	0.002
	W97-246 (Propofol)	N=32 545 ± 125	N=42 95 ± 45	<0.0001	0.002

* P-value was obtained from an ANOVA model with treatment and center
† Categorized dose was 0, 0-50, and >50 mg for midazolam and 0, 0-4, and >4 mg for propofol.
- Test was not performed because there were less than 5 patients in the treatment group.
Source: Tables 14 & 15, Vol. 8/10-238-41.

5. Discussion

It appeared that both Studies W97-245 and W97-246 were adequate and well-controlled, aiming for the evaluation of the safety and efficacy of dexmedetomidine indicated for ICU sedation. It appeared that the sponsor chose appropriate efficacy endpoints and performed adequate analyses.

In the primary efficacy analyses, the results consistently showed that the dexmedetomidine treated patients required significantly less midazolam/propofol for sedation rescue than the placebo patients. In Study W97-245, the treated group on average used approximately 1/4 of the amount of midazolam used by the placebo group for sedation rescue during intubation (4.8 mg for treated group and 18.6 mg for the placebo group). In Study W97-246, the treated group on average used approximately 1/7 of the amount of propofol used by the placebo group for sedation rescue during intubation (72 mg for treated group and 513 mg for the placebo group).

Also, around 60% of dexmedetomidine treated patients required no midazolam/propofol for sedation rescue, but approximately the same percent of placebo patients required a therapeutic

dose of midazolam/propofol (>4 mg or >50 mg, respectively) for sedation rescue during intubation.

Therefore, the sedative property of dexmedetomidine looked quite convincing by such sharp contrasts.

The analgesic property of dexmedetomidine was also confirmed in these two trials. The morphine requirements for pain from the treated group were typically around ½ of those from the placebo group and all comparisons for treatment effect were statistically significant.

Center effect was statistically significant in most of the ANOVA models. It was found that patients from different countries tended to require different amount of sedative and pain medicine regardless of placebo or treated groups.

In sponsor's final statistical reports, one major departure from the protocols was the exclusion of the treatment by center interaction term from the ANOVA model. The sponsor argued that this was because several planned centers had no patients or very few patients recruited. Through visual inspection, it was found that, in most cases, the treatment effect differed only in magnitude, not in directions, across the centers.

In fact, I believe that the model without the treatment by center interaction term is not only easier to interpret but also more meaningful in many cases. Especially, this model should be used when the main purpose for such multi-center design is to recruit enough patients from many small study centers, rather than to explore the difference in treatment effect across the centers.

Subgroup analyses by age (18-35 years; 36-55 years; 56-65 years; and >65 years), gender (male and female), race (Caucasian and non-Caucasian), country (11 countries), and surgery type (cardiac, head and neck, laparotomy, and other) mostly confirmed the above findings.

There were a few exceptions from the subgroup analyses, however. From the five centers (a total of 43 patients) from Germany in Study W97-245, only 1 (5%) patient in the treated group required 0 mg of midazolam during intubation, while typically more than 50% of the treated patients did so in other centers. Also, from the single center (20 patients) from Austria in Study W97-246, similar amounts of propofol during intubation were required by the placebo and the dexmedetomidine treated groups (50.1 mg vs. 51.2 mg, respectively). Finally, for head and neck surgeries (34 patients) in W97-245, the two treatment groups used similar amount of midazolam during intubation (16 mg and 19 mg for the placebo and treated groups, respectively).

However, these exceptions should not influence the overall conclusions.

Lastly, there seemed to be no difference between the two treatment groups on time to extubation and weaning duration in the two trials.

6. Conclusions

This reviewer concludes that the sponsor has provided sufficient statistical evidence from two adequate and well-controlled studies in ICU settings that patients treated with dexmedetomidine require less medication (midazolam/propofol) for sedation rescue and less morphine for pain rescue than patients treated with placebo.

/S/ — 9/7/99

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