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 Propofol for sedation compared to the majority of the placebo patients who required > 50mg of Propofol for sedation.

Table 24 Total Dose Categories of Propofol During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent-to-Treat Patients (N)	198	203	<0.001
0 mg	47(24%)	122(60%)	
> 0mg to 4 mg	30(15%)	43(21%)	
> 4 mg	121(61%)	38(19%)	
Evaluable Patients (N)	191	200	<0.001
0 mg	46(24%)	120(60%)	
>0 mg to 4 mg	30(16%)	42(21%)	
> 4 mg	115(60%)	38(19%)	

a: p-value from chi-square
Modified Sponsor's Table 8.2b Vol 8/10-86-74

SECONDARY EFFICACY ENDPOINTS

Total Dose of Propofol During Study Drug Administration

In both the Intent to Treat and the Evaluable patient analyses, Dexmedetomidine treated patients required statistically significantly less Propofol for sedation during study drug administration compared to placebo treated patients:

Table 25 Summary of Total Dose of Propofol (mg/hour) During Study Drug Administration

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	198	203	
Mean ± SEM	39.11±4.13	5.33±1.24	0.0001
Evaluable Patients (N)	191	200	
Mean ± SEM	38.43	5.41±1.26	0.0001

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3a Vol 8/10-86-75

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

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	198	203	
Mean ± SEM	0.89±0.07	0.43±0.05	0.0001
Evaluable Patients (N)	191	200	
Mean ± SEM	0.88±0.07	0.43±0.05	0.0001

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3b Vol 8/10-86-76

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. However, inspection of center level data confirm that the centers differ in magnitude of effect, not direction.

In both the Intent to Treat and the Evaluable patient analyses, Dexmedetomidine treated patients who received no Propofol during intubation required statistically significant less morphine during study drug administration compared to placebo treated patients who received no Propofol during intubation:

Table 27 Summary of Total Dose of Morphine (mg/hour) During Study Drug Administration for Patients Who Received No Propofol During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	47	122	
Mean ± SEM	0.41±0.07	0.25±0.04	0.0414
Evaluable Patients (N)	46	120	
Mean ± SEM	0.42±0.07	0.25±0.04	0.0387

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3c Vol 8/10-86-77

In both the Intent to Treat and the Evaluable patient analyses, there was no statistically significant difference in morphine use during study drug administration between Dexmedetomidine treated patients who received up to 50 mg of Propofol during intubation and placebo treated patients who received up to 50 mg of Propofol during intubation:

Table 28 Summary of Total Dose of Morphine (mg/hour) During Study Drug Administration for Patients Who Received Up to 50 mg of Propofol During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value[a]
Intent to Treat Patients (N)	30	43	
Mean ± SEM	0.73±0.14	0.54±0.12	0.2990
Evaluable Patients (N)	30	42	
Mean ± SEM	0.73±0.14	0.55±0.12	0.3359

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3d Vol 8/10-86-77

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:

3. During the first 6.5 hours of study drug administration. A statistically significant center effect was detected for the total dose of morphine in both the ITT and Evaluable patient analyses. However inspection of center level data confirm that the centers differ in magnitude of effect, not direction
4. From 6.5 hours after the start of study drug administration to the end of study drug administration. There was no center effect for this group.

Table 29 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)	198	203	
Mean ± SEM	8.46±0.64	4.09±0.47	<0.0001
Evaluable Patients (N)	191	200	
Mean ± SEM	8.3±0.65	4.15±0.48	<0.0001

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3e Vol 8/10-86-78

Table 30 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)	194	195	
Mean ± SEM	0.55±0.07	0.16±0.03	<0.0001
Evaluable Patients (N)	187	192	
Mean ± SEM	0.56±0.07	0.16±0.03	<0.0001

a: p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.3f Vol 8/10-86-79

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 3.1 ± 0.04 (SEM) vs 3.4 ± 0.05 (SEM) for the Dexmedetomidine treated patients. Sponsor states these differences are not clinically important.

A statistically significant center effect was observed for the Ramsay sedation scores during study drug administration in both the Intent to Treat and Evaluable patient analyses. However inspection of center level data confirm that the centers differ in magnitude of effect, not direction.

Anxiety

In both the Intent to Treat and Evaluable patient analyses, there were no statistically significant differences between treatments in the number of patients who reached a Ramsay score of 1 during study drug administration.

The percentage of Ramsay assessments equal to 1 was also computed for each patient and summarized by treatment group. Both the Intent to Treat and Evaluable patient analyses showed statistically significant differences ($p \leq 0.009$) between the treatment groups, with 7% of the assessments among placebo patients reaching a score of 1 compared to only 4% of the assessments among Dexmedetomidine patients indicating 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 42% 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, also indicating less anxiety among Dexmedetomidine treated patients.

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, 385 minutes; Dexmedetomidine, 395 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, 360 minutes; Dexmedetomidine 365 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, 430 minutes; Dexmedetomidine 432 minutes) and evaluable patient (placebo, 434 minutes; Dexmedetomidine 430 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, 398 minutes; Dexmedetomidine 404 minutes) and the evaluable patient (placebo, 400 minutes; Dexmedetomidine 403 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, 15 minutes; Dexmedetomidine 15 minutes) and evaluable patient (placebo 15minutes; Dexmedetomidine 15 minutes) analyses.

Nurses' and Patients' Assessment

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 31: 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=176 1.9±0.06	N=170 1.9±0.07	N=180 1.5±0.04	N=177 1.5±0.04
Tolerance of Endo Tube/ Ventilator[b]	N=175 1.5±0.04	N=169 1.5±0.04	N=180 1.3±0.03	N=177 1.3±0.03
Ease of Communication with Patient[c]	N=176 2.4±0.08	N=170 2.4±0.08	N=179 2.1±0.07	N=176 2.1±0.07
Ease of Management of the Patient[d]	N=175 1.6±.05	N=169 1.5±0.05	N=179 1.2±0.03	N=175 1.3±0.03
Patient Management Index p-value[e]: ITT: <0.001 Eval: <0.001	N=174 7.3±0.18	N=168 7.3±0.19	N=177 6.1±0.12	N=174 6.1±0.12

Modified Sponsor's Table 8.4a Vol 8/10-86-84

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.

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 (70%) rated their overall experience as "better than expected" compared to placebo treated patients (60%). 187 placebo treated patients vs 190 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 Propofol 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 Propofol for sedation compared to the majority of the placebo patients who required >50 mg of Propofol 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 Propofol 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. There were no significant differences between treatments in the number of patients who reached a Ramsay score of 1 during study drug administration, although the percent of assessments reaching a score of 1 was significantly greater in the placebo group than in the Dexmedetomidine group during study drug administration, 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 indicated that Dexmedetomidine treated patients were more comfortable during ICU sedation and had less memory of pain, discomfort from the breathing tube, people, and noise than placebo treated patients. A higher percentage of Dexmedetomidine treated patients rated their overall experience as better than expected and that they would have the same sedative treatment in future compared to placebo patients.

SECTION 7.2.2.6 REVIEWER'S EFFICACY DISCUSSION

As noted 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 Propofol 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 8.0 SAFETY ANALYSIS

SECTION 8.1 EXPOSURE

[*REVIEWER NOTE: THE FOLLOWING INFORMATION IS NOT AVAILABLE AT THE TIME OF THIS REVIEW. SPONSOR HAS AGREED TO SUPPLY THE NECESSARY INFORMATION; SUCH INFORMATION WILL BE REVIEWED AS AN ADDENDUM TO THE APPLICATION:*

- *Information delineating all the various doses of Dexmedetomidine administered to all subjects/patients*
- *Time periods the various doses were administered to all subjects/patients*
- *Tabulations that compare all deaths, all serious adverse experiences, and all premature discontinuations after exposure to Dexmedetomidine, active control, and placebo.*
- *Case Report Forms for the discontinuations noted in the 120 Day Safety Update*]

Sponsor claims Dexmedetomidine has been evaluated in 83 studies in which over 3303 subjects/patients received Dexmedetomidine. The agent has been given by various modes of administration including rapid or continuous intravenous infusion to normal subjects, to subjects with impaired renal and hepatic function, and to patients undergoing cardiac, abdominal, peripheral vascular, head and neck, and knee surgery. Patients' ages ranged from 17 to 88 years.

Table 32 Exposed Patients (All Abbott, Orion, and Japanese data)

	Perioperative and ICU Sedation Clinical Program								Phase II/III Clinical Program ICU Sedation (Pivotal)
	Phase I Studies					Phase II/III Studies			
	Continuous Infusion	Rapid Infusions	IM	Trans-Dermal	Oral	Continuous Infusion	Rapid Infusion	IM	Continuous Infusion
Number of Studies (Includes Crossover Studies)	13	18	5	3	1	23	13	14	3
Number of Crossover Studies	2	4	2	2	1	0	0	1	0
Dex Exposed Subjects/ Patients	184	233	54	37	12	1686	429	690	576
Placebo Exposed Subjects/ Patients	101	44	26	N/A	N/A	1004	165	314	379
Comparator	12	5	12	N/A	N/A	N/A	96	286	N/A
TOTAL: Dexmedetomidine Exposed Subjects/Patients: 3325									
TOTAL: Placebo Exposed Subjects/Patients: 1654									
TOTAL: Comparator Exposed Subjects/Patients: 411									

Modified Sponsor's Table Amendment Date May 21, 1999
IM = Intramuscular
Crossover Studies: Subjects may have been counted in more than one treatment group

SECTION 8.2 DEMOGRAPHICS:

APPEARS THIS WAY
ON ORIGINAL

Table 33 All Treated Subjects in Phase I Studies

	All Treated Dexmedetomidine N=285	Placebo N=97	Alfentanil N=12
Gender			
Male	182(64%)	69(71%)	8(67%)
Female	103(36%)	28(28%)	4(33%)
Age (Years)			
18-35	157(55%)	82(85%)	12(100%)
36-55	92(32%)	15(15%)	0
56-65	16(6%)	0	0
>65	20(7%)	0	0
Mean	36.7	28.2	24.6
Minimum	18	18	21
Maximum	82	45	31
Ethnic Origin			
Caucasian	212(74%)	75(77%)	4(33%)
Black	32(11%)	8(8%)	4(33%)
Asian	6(2%)	4(4%)	2(17%)
Hispanic	30(11%)	5(5%)	1(8%)
Other	5(2%)	5(5%)	1(8%)

Sponsor's Table 13 ISS Vol 8/10-239-47

Table 34 All Treated Patients in Phase II/III Continuous Infusion Studies
Abbott Sponsored Trials; Excludes Orion and Japanese Data

	All Treated Dexmedetomidine N=1337	Placebo N=817
Gender		
Male	934(70%)	555(68%)
Female	403(30%)	262(32%)
Age (Years)		
18-35	55(4%)	34(4%)
36-55	345(26%)	196(24%)
56-65	409(31%)	212(26%)
>65	528(39%)	375(46%)
Mean	60.6	61.9
Minimum	17[a]	17
Maximum	88	87
Ethnic Origin		
Caucasian	1194(89%)	751(92%)
Black	91(7%)	38(5%)
Asian	11(<1%)	7(<1%)
Hispanic	31(2%)	17(2%)
Other	10(<1%)	3(<1%)
Missing	0	1(<1%)

Modified Sponsor's Table 14 ISS Vol 8/10 -239-48

a: Study W97-246 had 2 patients who were 17 year of age; these patients are Summarized in the 18-35 age group.

Table 35 Demographic Characteristics: All Treated Patients in Phase II/III Continuous Infusion ICU Sedation Studies (Pivotal Studies)

	All Treated Dexmedetomidine N=576	Placebo N=379
Gender		
Male	425(74%)	271(72%)
Female	151(26%)	108(28%)
Age (Years)		
18-35	29(5%)	16(4%)
36-55	139(24%)	79(21%)
56-65	172(30%)	90(24%)
>65	236(41%)	194(51%)
Mean	60.8	63
Minimum	17	17
Maximum	88	87
Ethnic Origin		
Caucasian	561(97%)	375(>99
Black	4(<1%)	2(<1%)
Asian	7(1%)	0
Other	4(<1%)	1(<1%)
Missing	0	1(<1%)
Surgery Type		
Cardiac	214(54%)	206(54%)
Head and Neck	27(7%)	34(9%)
Laparotomy	95(24%)	87(23%)
Others	63(16%)	52(14%)
Country		
Austria	22(4%)	20(5%)
Belgium	35(6%)	14(4%)
Canada	29(5%)	13(3%)
France	98(17%)	62(16%)
Germany	94(16%)	69(18%)
Greece	33(6%)	22(6%)
Italy	22(4%)	15(4%)
Netherlands	77(13%)	54(14%)
Spain	70(12	37(10%)
Sweden	6(1%)	3(<1%)
UK	90(16%)	70(18%)

Modified Sponsor's Table 15 ISS Vol 8/10-239-49

SECTION 8.3 DEATHS

The following is a review of all deaths (N=12) that occurred in Abbott sponsored trials. There were no deaths in the Japanese trials. The Orion studies involved one death (N=1) but information on this subject is not provided by sponsor.

STUDY 95-002

Patient 1115

82 year old with cancer of the colon underwent a low anterior colon resection. Patient experienced intermittent low blood pressure. Two hours after being initiated, Dexmedetomidine was stopped. Two days later, patient experienced a cardiac arrest and died. Autopsy findings indicated severe ASHD.
Reviewer Comment: There is no apparent relation to study drug.

STUDY 95-004

Patient 000202

77 year old with history of diabetes, hypertension, hyperlipidemia, Class III CHF underwent 3 vessel coronary artery by-pass grafting. 2 days after extubation and discontinuation of Dexmedetomidine, patient developed pulmonary aspiration and expired. Patient appeared stable after discontinuation of Dexmedetomidine.
Reviewer Comment: There is no apparent relation to study drug.

Patient 0622

59 year old with coronary artery disease, hypertension, hypercholesterolemia, paroxysmal atrial fibrillation, gout, depression, and chronic renal insufficiency underwent coronary artery bypass. Post operatively patient developed acute renal failure. While on Dexmedetomidine infusion, patient was reasonably stable for post operative coronary artery bypass procedure. Date and exact cause of death are not clear but occurred a few days after study infusion was discontinued.
Reviewer Comment: From the supplied documentation, the death has no apparent relation to study drug.

STUDY 96-015

Patient 1004

72 year old with a history of abdominal aneurysm, hyperlipidemia, COPD, epilepsy, malaria, and cutaneous ulcer underwent an aorto-femoral by-pass procedure. 11 days after Dexmedetomidine was discontinued, patient developed retroperitoneal bleeding, septic shock and died.
Reviewer Comment: There is no apparent relation to study drug.

STUDY 96-021

Patient 0406

64 year old with history of myocardial infarction, angina, CHF, and two coronary artery by-pass procedures underwent total knee replacement. 4 days after discontinuation of Dexmedetomidine, patient experienced cardiac arrest and died. Patient appeared stable after discontinuation of Dexmedetomidine.
Reviewer Comment: There is no apparent relation to study drug.

STUDY W97-246

Patient XO202

78 year old with history of ischemic heart disease and renal failure underwent a repair of abdominal aortic aneurysm. 48 hours after discontinuation of Dexmedetomidine, patient experienced cardiac failure, renal failure and cardiac arrest. Patient appeared stable after discontinuation of Dexmedetomidine.
Reviewer Comment: There is no apparent relation to study drug.

Patient XO403

53 year old with severe kyphosis, hiatal hernia, and dyspnea with mild exertion, underwent instrumentation and repair of kyphosis. 5 days after discontinuation of Dexmedetomidine, patient developed bronchopneumonia; 11 days later the patient expired.
Reviewer Comment: There is no apparent relation to study drug.

Patient X4602

70 year old with insulin dependent diabetes, COPD, cachexia, and lung cancer underwent a pneumectomy. 12 days after Dexmedetomidine was discontinued, patient developed pneumonia, pulmonary edema and died.
Reviewer Comment: There is no apparent relation to study drug.

Patient 202

72 year old with esophageal cancer underwent a thoracic esophagectomy. 2 days after study drug was stopped, patient developed adult respiratory distress syndrome and possible pulmonary embolism. His liver enzymes were minimally elevated. Autopsy disclosed cirrhosis.
Reviewer Comment: There is no apparent relation to study drug.

Patient 7405

75 year old with abdominal aortic aneurysm, cirrhosis, effort dyspnea with respiratory failure, history of pneumonectomy underwent an abdominal aortic aneurysm repair and splenectomy. 3 days after patient completed the infusion protocol for Dexmedetomidine without incident, patient vomited, aspirated and sustained a cardiac arrest.
Reviewer Comment: There is no apparent relation to study drug.

Patient 10202

74 year old with ischemic cardiac disease, hypertension, diabetes secondary to steroid treatment, hypercholesterolemia, hyperuricemia, pulmonary fibrosis, underwent coronary artery bypass. Patient developed hypotension soon after institution of study drug. Hypotension continued intermittently during Dexmedetomidine infusion. Study drug was discontinued prematurely 9 hours after initiation. Following infusion, renal insufficiency occurred. Over the next 3 days, patient appeared stable. However 3 days after termination of Dexmedetomidine, patient developed an acute myocardial infarction and died.
Reviewer Comment: Relation of Dexmedetomidine to acute MI and death is not clear. While Dexmedetomidine is likely causal for the hypotension while it was being infused, patient appeared hemodynamically stable for 3 days until the occurrence of the MI. It appears doubtful the Dexmedetomidine was causal for the MI and death.

STUDY 97-249

Patient 109

Sponsor coded this patient as a Discontinuation. However, patient died 16 days after start of study drug. This is a 47 year old with a history of coronary artery disease, prior coronary artery surgery, hyperlipidemia, dyspnea on exertion, and obesity who underwent coronary artery by-pass surgery. Approximately 14 hours following initiation of Dexmedetomidine, patient developed circulatory collapse, hypotension, and acute myocardial infarction. At this time, Dexmedetomidine was discontinued and patient was returned to the Operating Room for apparent repair of incomplete coronary re-vascularization. Patient died as a result of multi-organ failure.
Reviewer Comment: The record is not clear as to the proximate cause of death: was the initial surgical repair insufficient as to cause a myocardial infarction and subsequent circulatory collapse or did Dexmedetomidine cause hypotension that resulted in an acute MI? This reviewer is of the opinion that the cause of death was the direct result of the surgical repair.

SECTION 8.4 DISCONTINUATIONS

The following is a review of all discontinuations (N=41) that occurred in Abbott sponsored trials. Sponsor reports no discontinuations in the Japanese trials. Fourteen

(N=14) discontinuations occurred in [redacted]-sponsored trials; sponsor states 3 of the case report forms involving these discontinuations are not available. In addition, sponsor says no patient data listings are available for any of the Orion discontinuations.

STUDY 95-002

Patient 0202

65 year old with cholangiocarcinoma, mild COPD, and angina underwent a biopsy of peritoneal implants and alcohol splanchnicectomy. Patient was discontinued because surgeon decided to extend surgical prep to the neck which necessitated removal of study required EKG leads. Patient received a minimal amount of agent.
Reviewer Comment: Discontinuation not related to study drug.

STUDY 95-004

Patient 0109

59 year old with coronary artery disease, insulin dependent diabetes, hyperlipidemia, hypertension and morbid obesity underwent 4 vessel coronary artery by-pass. Surgeon canceled study drug infusion 44 min prior to scheduled termination; at time of cancellation of infusion, patient was hypotensive with low O2 saturation and receiving inotropic support. Postoperatively, patient developed cerebrovascular accident.

Reviewer Comment: While there are many confounders associated with this subject, Dexmedetomidine maybe involved in the development of the hypotension.

Patient 212

68 year old with coronary artery disease, hypertension, cardiac arrhythmias, unstable angina underwent coronary artery by-pass grafting. Study drug was discontinued about 3 hours after initiation secondary to an aortic dissection. A long coronary artery by-pass time occurred. Liver function enzymes were mildly elevated the day after surgery.
Reviewer Comment: Discontinuation is not likely related to effects of the drug. Postoperative elevation of liver function enzymes is likely due to long by-pass time.

Patient 503

51 year old with a history of non insulin diabetes, symptomatic peripheral vascular disease, hypertension, history of hepatitis, history of myocardial infarction, and congestive heart failure underwent coronary artery bypass. Left ventricular ejection fraction was poor (31%) preoperatively. The patient should have been excluded from the study but was inadvertently included. Patient developed hypotension soon after start of study drug. Hypotension was persistent. Infusion began prior to the repair of coronary vessels.

Reviewer Comment: Dexmedetomidine appears responsible for the hypotension. It is possible however that the hypotension was primarily the result of the patient's very poor myocardial function.

Patient 612

45 year old with prior myocardial infarction, angina, multivalvular heart disease (but good left ventricular function), and hypercholesterolemia underwent coronary artery bypass. Study drug was infused for approximately 1.5 hours. Operation was uneventful until opening of pericardium when cardiac arrest occurred. Following revascularization, patient experienced a routine postoperative course. Dexmedetomidine was discontinued at time of cardiac arrest.
Reviewer Comment: There is no clear relationship of study drug to the cardiac arrest.

Patient 930

52 year old with coronary artery disease, insulin dependent diabetes, hypothyroidism, and hypercholesterolemia underwent coronary artery bypass. Study drug was stopped after 10 minutes because of need to awaken patient. Subject had a malformed airway making intubation impossible.
Reviewer Comment: Study drug was not responsible for premature discontinuation.

STUDY 96015

Patient 113

56 year old with Type II diabetes, hepatitis secondary to drug abuse, underwent an aorto-femoral by-pass. 8 hours after Dexmedetomidine was initiated, patient was awake, extubated and appeared hemodynamically stable. At this time, while Dexmedetomidine was infusing, patient experienced cardiac arrest. Study drug was discontinued and successful CPR was initiated.
Reviewer Comment: Relationship of study drug to the cardiac arrest is unknown but not likely related.

Patient 507

Incomplete records. Age, prior medical condition, surgery are unknown. Post-operatively, patient developed a heart rate of 35-40/bpm and consequently Dexmedetomidine was discontinued. Apparently Dexmedetomidine had been infusing for approximately 10 hours prior to bradycardia. Prior to discontinuation, bradycardia had not been an issue.
Reviewer Comment: Dexmedetomidine appears to be responsible for bradycardia.

Patient 1404

60 year old with aorto-iliac thrombosis, obesity, long smoking history, chronic diarrhea, insulin dependent diabetes, hyperthyroidism, dyspnea with mild exertion, history of pulmonary hypertension and acute pulmonary edema, arterial hypertension, cardiac insufficiency, prior myocardial infarction, manic-depression psychosis, and known carotid artery disease with history of stroke underwent aorto-bypass grafting. Significant hypotension developed 30 minutes after start of Dexmedetomidine infusion. Dexmedetomidine was terminated 5 hours after initiation because of accompanying hypotension.
Reviewer Comment: Dexmedetomidine may have been the cause of the hypotension. However the actual cause of hypotension in this patient with multiple medical problems undergoing surgery known to be commonly associated with low blood pressure is uncertain.

Patient 1412

55 year old with dyslipidemia, dyspnea on exertion, and peripheral vascular disease underwent an aorto-bypass graft. Dexmedetomidine was terminated after 11 hours of infusion because patient was returned to the operating room for thrombectomy. Prior to the return for surgery, patient appeared to be tolerating study drug well.
Reviewer Comment: The discontinuation does not appear related to study drug.

STUDY W97-245

Patient XO801

46 year old with coronary artery disease underwent coronary artery by-pass. Following surgery, Dexmedetomidine was infusing and patient appeared to be stable. Because of surgical site bleeding, patient was returned to the operating room and Dexmedetomidine was discontinued.
Reviewer Comment: Dexmedetomidine does not appear related to the discontinuation.

Patient XO802

72 year old with coronary artery disease and hypertension underwent aortic valve replacement along with coronary artery by-pass graft. Dexmedetomidine was infusing and patient appeared to be stable when surgical bleeding occurred and patient was returned to the OR. Dexmedetomidine was discontinued at this time.
Reviewer Comment: Dexmedetomidine does not appear related to the discontinuation.

Patient X2703

62 year old with sigmoid cancer underwent an abdominal-perineal resection. Dexmedetomidine was infused for about 11 hours during which time blood pressure progressively dropped from 128/55 to 89/49; the drop in BP was accompanied by oliguria. Soon after the discontinuation of Dexmedetomidine, the blood pressure returned to baseline.

Reviewer Comment: Dexmedetomidine appears to be a likely source of the hypotension.

Patient X2803

56 year old with hypertension, greater than a pack a day cigarette history for 25 years, diabetes mellitus, hypercholesterolemia, COPD, mammary carcinoma, post-operative hemiplegia 10 years prior to current procedure, and aorto-occlusive disease underwent an aorto-femoral bypass. Dexmedetomidine was infused for about 6 hours without any apparent ill effects. The infusion was discontinued after patient developed acute ischemia of the leg and underwent surgical thrombectomy. Subsequent to this second operation, patient developed paralysis of the peroneal nerve.
Reviewer Comment: Dexmedetomidine does not appear related to the discontinuation.

Patient X3701

64 year old with an abscessed aorto-bifemoral bypass, COPD and heavy smoking, acute renal failure, underwent an axillobifemoral bypass. 10 minutes after Dexmedetomidine was initiated, patient suffered a cardiac arrest probably due to acidosis and hyperkalemia. Blood pressure prior to and at time of arrest was normal. Dexmedetomidine was discontinued when cardiac arrest occurred.
Reviewer Comment: Dexmedetomidine does not appear related to the discontinuation.

Patient X4402

74 year old with coronary artery disease, transient ischemic cerebral attacks, prior carotid endarterectomy, chronic ischemia of the lower limbs, underwent coronary artery bypass grafting with implantation of pacemaker. Study drug was discontinued approximately 10 hours after start of infusion because of the development of a myocardial infarction. From a cardiovascular viewpoint, patient appeared hemodynamically stable at time of discontinuation.
Reviewer Comment: Dexmedetomidine does not appear related to the discontinuation.

Patient X4703

75 year old with 3 vessel coronary disease, hypertension, diabetes, and exertional dyspnea underwent a coronary artery bypass. In this open label study, Dexmedetomidine was infused for about 11 hours. During the infusion, patient was being weaned from the ventilator. The patient had persistent hypercarbia during the weaning process and was noted to be quite sedated. Morphine was also administered at this time. Decision was made to discontinue all sedatives. Hemodynamically, patient appeared stable.
Reviewer Comment: Dexmedetomidine appeared to be the cause or contributor to the oversedation and resultant hypercarbia.

Patient X4704

52 year old with angina, hypertension, hypercholesterolemia, and non insulin-diabetes underwent coronary artery by-pass. Patient had a functioning pacemaker postoperatively. Dexmedetomidine had been infusing for approximately 7 hours when an apparent pacemaker related arrhythmia occurred that resulted in hypotension. Investigators decided to discontinue Dexmedetomidine in this open label study.
Reviewer Comment: Dexmedetomidine does not appear related to the discontinuation.

Patient 201

69 year old with mitral stenosis, atrial fibrillation and dyspnea on exertion underwent a mitral valve replacement. Dexmedetomidine was infused for about 50 minutes when it was discontinued due to bradycardia rate of 45. Prior to infusion, heart rate was 60. Patient apparently was not responsive to pacemaker.
Reviewer Comment: Dexmedetomidine could have been a likely cause of the bradycardia.

Patient 206

30 year old with aortic valve endocarditis underwent an aortic valve replacement. Patient smoked ½ pack of cigarettes/day for 12 years. Study drug was discontinued after 7 hours because lung function was deteriorating and patient was fighting the ventilator. After Dexmedetomidine was discontinued, a neuromuscular blocking agent was administered.
Reviewer Comment: Dexmedetomidine does not appear related to the discontinuation.

Patient 605

72 year old with angina, history of myocardial infarction, and insulin dependent diabetes underwent coronary artery bypass graft. Study drug was discontinued after 19 hours of infusion because of development of episodes of bradycardia, supraventricular tachycardia, and hypotension.
Reviewer Comment: Dexmedetomidine may have been responsible for the events leading to its discontinuation.

Patient 902

78 year old with angina, peripheral vascular disease, carotid artery stenosis, and hypercholesterolemia underwent coronary artery bypass surgery. Study drug was infused for 45 minutes when it was discontinued because patient was returned to the operating room to repair a hole in one of the coronary artery grafts.
Reviewer Comment: Dexmedetomidine is not related to the discontinuation.

Patient 1206

73 year old with angina, hypertension, and multiple transient ischemic attacks underwent coronary artery bypass. Study drug was infused for about 3 hours when it was discontinued because of the development of heart block, hypotension, and acidosis.

Reviewer Comment: Dexmedetomidine may have been responsible for the events leading to its discontinuation.

Patient 1301

71 year old with 3 vessel coronary disease, angina, hypertension, hypercholesterolemia, and transient ischemic attacks underwent coronary artery bypass grafting. Study drug was discontinued after 2.5 hours because of bleeding that proved to be related to a leaking coronary graft.
Reviewer Comment: Dexmedetomidine is not related to the discontinuation.

Patient 6502

67 year old with hyperthyroidism, liver metastasis, colon cancer, underwent a partial resection of the liver. Study drug had infused for about 21 hours when it was discontinued prematurely because of mental confusion, agitation, and a positive Babinski on the left side. Patient appeared hemodynamically stable during drug infusion.
Reviewer Comment: Relationship of Dexmedetomidine to confusion and agitation is not clear. There are multiple confounding variables involved.

Patient 7503

64 year old with prior history of 2 myocardial infarctions, hypercholesterolemia, and abdominal aortic aneurysm underwent an aortic bi-femoral bypass. Dexmedetomidine was infused for 6 hours and appeared well tolerated. Study drug was terminated early because patient was returned to the operating room to correct bleeding related to the original surgery.
Reviewer Comment: Dexmedetomidine does not appear related to the early termination.

STUDY W97-246

Patient 0101

66 year old with unstable angina, 3 vessel coronary disease, hypertension, and hyperlipidemia underwent coronary artery by-pass grafting. Soon after starting study drug, patient experienced oxygen desaturation, pulmonary edema and mild hypotension. Dexmedetomidine was discontinued after 45 minutes of infusion time.
Reviewer Comment: It is likely some pulmonary edema was present prior to initiation of Dexmedetomidine. Study drug may have been causal for the mild hypotension.

Patient X0502

68 year old with a history of myocardial infarction and coronary artery disease underwent coronary artery by-pass surgery. Patient was stable post-operative; however because patient was over sedated, extubation could not be performed. Study drug was discontinued and patient was extubated 1.5 hours later.
Reviewer Comment: Dexmedetomidine appears responsible for the over-sedation.

Patient 13505

63 year old with rectal carcinoma, left ventricular hypertrophy and hypertension underwent an abdominoperineal resection. Patient was tolerating Dexmedetomidine which was started post-operatively. Patient developed surgery based bleeding and was returned to the operating room at which time Dexmedetomidine was discontinued. Dexmedetomidine was restarted 3 hours later upon completion of surgery.
Reviewer Comment: Dexmedetomidine does not appear related to the discontinuation.

Patient 13603

51 year old with history of angina pectoris, hypertension, cancer of the colon, hyperlipidemia, and Type II diabetes mellitus underwent coronary artery by-pass. Study drug was discontinued because patient was oversedated and not breathing adequately for extubation. This situation is confounded by the addition of a large dose of morphine prior to the discontinuation of Dexmedetomidine.
Reviewer Comment: Dexmedetomidine may have been the cause of oversedation in this patient.

Patient 13604

74 year old with a history of coronary artery disease, hypertension, hyperlipidemia, and depression underwent coronary artery by-pass. Post operatively, patient did not develop adequate spontaneous respirations until study drug was stopped.
Reviewer Comment: Dexmedetomidine was the likely cause of oversedation in this patient.

Patient X1803

78 year old with coronary artery disease, Type II diabetes, hyperlipidemia, and aortic stenosis underwent an aortic valve replacement and coronary artery by-pass. Dexmedetomidine was infused for about 14 hours in this open label study. It was discontinued because of the development 2nd Degree AV conduction disturbance, bigeminy, and resultant activation of external pacemaker. Other than the rhythm disturbance, patient appeared stable at the time of discontinuation.
Reviewer Comment: The cause of the arrhythmia is not clear. There are confounding factors. Dexmedetomidine may have been the cause or a contributor to the problem.

Patient X2701

75 year old with atrial fibrillation and transient ischemic attack underwent a repair of an abdominal aortic aneurysm. During the infusion of Dexmedetomidine, patient experienced mild hypotension that was probably due to re-warming from the operative hypothermia. Investigators decided to terminate study drug in this open label trial because of prolonged and repetitive apnea during the weaning process. Ramsay sedation scores were approximately 3.
Reviewer Comment: The Dexmedetomidine may have been a factor in the difficult weaning process but this is not a certainty.

Patient 5806

70 year old with coronary artery disease, history of myocardial infarction, hypercholesterolemia, hypertension, and seizures underwent coronary artery by-pass. Study drug was infused for less than 2 hours when it was discontinued because patient was returned to the operating room to treat surgery related bleeding.
Reviewer Comment: Premature discontinuation was not related to Dexmedetomidine.

Patient 6202

59 year old with bladder tumor, hypertension, and hyperuricemia, underwent cystectomy with ileal conduit. Study drug was discontinued 25 minutes after initiation after the development of concomitant septic shock, pulmonary edema and apparent pre-operative fluid overload.
Reviewer Comment: Premature discontinuation unlikely related to study drug because of the very short period of time from infusion of Dexmedetomidine to development of septic shock.

Patient 7106

76 year old with angina, hypercholesterolemia, and chronic obstructive pulmonary disease underwent coronary artery by-pass graft. Dexmedetomidine was terminated after 4 hours of infusion because of a return to the operating room to correct surgical bleeding.
Reviewer Comment: Premature discontinuation was not related to Dexmedetomidine.

Patient 7203

61 year old with aortic stenosis, left ventricular hypertrophy and asthma underwent an aortic valve replacement. Asthma symptoms were present prior to institution of cardiac by-pass and continued after initiation of Dexmedetomidine infusion. Study drug was continued for about 13 hours and was terminated prematurely in an attempt to eliminate sedation for facilitation of extubation. Early extubation was performed to control the asthma symptoms.
Reviewer Comment: Asthma symptoms were present prior to Dexmedetomidine infusion. It is possible but unlikely that Dexmedetomidine perpetuated the asthma symptoms.

Patient 8005

62 year old with lung cancer underwent a pulmonary lobectomy. Dexmedetomidine was terminated after a 10 minute infusion because patient was returned to the operating room to repair a laceration of the pulmonary vein.
Reviewer Comment: Premature discontinuation was not related to Dexmedetomidine.

Patient 2904

60 year old with prior myocardial infarction, Type I diabetes mellitus and hypercholesterolemia underwent coronary artery bypass grafting. Dexmedetomidine was discontinued after 7 hours when patient returned to the operating room because of bleeding. The cause of bleeding was found to be related to a loose coronary graft.
Reviewer Comment: Premature discontinuation was not related to Dexmedetomidine.

Patient 10101

71 year old with hypertension, intermittent claudication, Paget disease, bronchitis, and abdominal aortic aneurism underwent an aorto bifemoral by-pass. Dexmedetomidine was infused for about 4 hours when it was discontinued when patient returned to the operating room for embolectomy. Mild hypotension occurred during the infusion.
Reviewer Comment: Premature discontinuation was not related to Dexmedetomidine.

Patient 11601

72 year old with lung cancer, hypertension, peripheral arterial insufficiency, history of hepatitis, pulmonary fibrosis, and kidney stones underwent a pneumonectomy. Dexmedetomidine was prematurely terminated after 7 hours because of cardiac arrest which was ascribed to poor myocardial function and sensitivity to dopamine. During the infusion study drug appeared well tolerated except for mild hypotension.
Reviewer Comment: Relationship of discontinuation to study drug is not clear. Dexmedetomidine does not appear to be causal for the cardiac arrest.

THE FOLLOWING ARE REVIEWS OF CASE REPORT FORMS FROM ORION STUDIES. ACCORDING TO SPONSOR, PATIENT LISTINGS ARE NOT AVAILABLE:

Patient # 27: 41 year old underwent reduction mammoplasty. Study drug apparently discontinued due to bradycardia, rate 48.
Reviewer Comment: Premature discontinuation likely related to Dexmedetomidine

Patient 224: 71 year old with angina and psoriasis underwent coronary artery by-pass procedure. Study drug was discontinued because of post-operative hypotension and bradycardia that required frequent vasopressor support. Patient also developed perioperative myocardial infarction.

Reviewer Comment: Relationship of Dexmedetomidine to premature discontinuation is not clear. Dexmedetomidine could have been responsible for the hypotension and bradycardia. The cause of the myocardial infarction is unknown. All of the events occurring in this patient may be the result of Dexmedetomidine.

Patient 135: 62 year old smoker with a history of diabetes, myocardial infarction, and angina underwent coronary artery bypass surgery. Study drug was discontinued prematurely apparently as the result of post-operative bleeding which required return to the operating room for correction.
Reviewer Comment: Dexmedetomidine does not appear responsible for the discontinuation.

Patient 226: 67 year old smoker with history of coronary disease, COPD, history of cerebral contusion, mitral insufficiency, and unstable angina underwent coronary artery bypass. Study drug was discontinued postoperatively apparently because of hypotension.
Reviewer Comment: Dexmedetomidine may have caused or been a contributor to this patient's hypotension.

Patient 251: 59 year old with hyperlipidemia, coronary artery disease underwent coronary artery bypass. Dexmedetomidine was discontinued because patient required return to operating room to correct surgery related bleeding. Perioperative myocardial infarction also occurred.
Reviewer Comment: Surgical bleeding is not related to Dexmedetomidine. Perioperative MI also does not appear related to Dexmedetomidine as patient was relatively stable with respect to cardiovascular system.

Patient 106: 65 year old with history of myocardial infarction, and angina underwent coronary artery bypass procedure. Patient was discontinued prematurely because of a surgical complication requiring re-anastomosis of a distal graft.
Reviewer Comment: Dexmedetomidine is not responsible for the premature discontinuation.

Patient 111: 62 year old former smoker with angina underwent coronary artery bypass grafting. Intraoperatively, patient developed bronchial obstruction and cardiovascular instability requiring use of intraaortic balloon pump.
Reviewer Comment: Relationship of Dexmedetomidine to bronchial obstruction is not clear. It is possible that Dexmedetomidine caused bronchospasm as a result of sympathetic inhibition.

Patient 03-11: 46 year old underwent hysterectomy. Cause of premature discontinuation is not clear although CRF noted patient was experiencing pain and nausea at time of discontinuation.
Reviewer Comment: There is insufficient data to ascribe an etiology to the discontinuation of study drug. Patient appeared stable from the accounts in the record.

Patient 06-39: 38 year old healthy individual underwent surgery for gastric carcinoma.

The reason for the discontinuation is not stated but the patient experienced significant intraabdominal post-operative bleeding.
Reviewer Comment: If the postoperative bleeding is the reason for the discontinuation, then the discontinuation does not appear related to study drug.

Patient 06-89: 50 year old with history of supraventricular tachycardia underwent laparotomy for gastric carcinoma. The reason for the discontinuation is not stated but the patient apparently experienced a pneumothorax. Other than the pneumothorax, the patient appeared stable.
Reviewer Comment: If the pneumothorax is the reason for the discontinuation, then the discontinuation does not appear related to study drug.

Patient 06-12: This CRF contains very limited information. Patient was apparently healthy prior to study except for history of supraventricular tachycardia and elevated bilirubin from unknown cause. This appears to have been a skin patch application study. Patient was withdrawn because of allergic reaction manifesting as generalized urticaria.
Reviewer Comment: Dexmedetomidine appears capable of causing true allergic reactions.

SECTION 8.5 ALL ADVERSE EVENTS

PHASE I STUDIES (Abbott Sponsored Trials)

In the Phase I studies, 62% (176/285) of all Dexmedetomidine treated subjects and 57% (55/97) of all placebo treated subjects experienced at least one adverse event. The most frequently experienced adverse events among all Dexmedetomidine treated subjects were dry mouth (21%), headache (20%), somnolence (19%), and hypotension (16%). The most frequently experienced adverse events among placebo treated patients were headache (16%), nausea (9%), and hyperkinesia (8%). None of the alfentanil treated subjects experienced an adverse event.

Table 36 Summary of Treatment Emergent Adverse Events Experienced by ≥ 2% of All Dexmedetomidine Subjects in Phase I Studies (Abbott Sponsored Trials)

Adverse Event	All Treated Dexmedetomidine (N=285)	Placebo (N=97)
Subjects with at least one treatment-emergent adverse event	175(61%)	48(49%)
Mouth dry	59(21%)	6(6%)
Somnolence	55 (19%)	4(4%)
Headache	49(17%)	15 (15%)
Hypotension	45(16%)	4(4%)
Nausea	20(7%)	9(9%)
Hypoxia	18(6%.)	1 (1%)
Dizziness	16(6%)	3 (3%)
Bradycardia	13 (5%)	0
Muscle contractions involuntary	13 (5%)	0
Pallor	10(4%)	6(6%)
Apnea	10(4%)	2(2%)
Stupor	9(3%)	1 (1%)
Hyperkinesia	8(3%)	8(8%)
Pain	8(3%)	1 (1%)
Pharyngitis	8(3%)	2(2%)
Paresthesia	8(3%)	0
Xerophthalmia	8(3%)	1 (1%)
Fatigue	7(2%)	1 (1%)
Hallucination	7(2%)	0
Vomiting	6(2%)	4(4%)
Agitation	6(2%)	4(4%)
Pruritus	6(2%)	4(4%)
Rhinitis	6(2%)	1 (1%)
Back pain	6(2%)	1 (1%)
Vision abnormal	5 (2%)	3 (3%)
Abdominal pain	5 (2%)	1 (1%)
Conjunctivitis	5 (2%)	0

Modified Sponsor's Table 16 ISS Vol 8/10-239-52

PHASE II/III STUDIES (Abbott Sponsored Trials)

In the Phase II/III continuous infusion studies, 66% (886/1337) of all Dexmedetomidine treated patients experienced at least one adverse event. The most frequently experienced adverse events among all Dexmedetomidine treated patients included hypotension (31%), hypertension (14%), and nausea (13%). The Dexmedetomidine randomized patients had a statistically significantly higher incidence of hypotension (30% vs 16%) and bradycardia (7% vs 3%). Placebo treated patients had a significantly higher incidence of tachycardia than the randomized Dexmedetomidine treated patients (8% vs 5%).

Table 37 Summary of Treatment Emergent Adverse Events Experienced by ≥ 2% of All Dexmedetomidine Subjects in Phase II/III Continuous Infusion Studies (Abbott Sponsored Trials)

Adverse Event	All Treated Dexmedetomidine (N=1337)	Randomized Dexmedetomidine (N= 1148)	Placebo (N=817)
Patients with at least one treatment-emergent adverse Event	814(61%)	695(61%)	477(58%)
Hypotension	392(29%)	343(30%)*	131(16%)
Hypertension	178(13%)	155(14%)	135(17%)
Nausea	162(12%)	146(13%)	105(13%)
Bradycardia	95(7%)	79(7%)*	25(3%)
Tachycardia	65(5%)	60(5%)*	62(8%)
Fever	61(5%)	56(5%)	42(5%)
Hypoxia	58(4%)	54(5%)	36(4%)
Anemia	52(4%)	44(4%)	24(3%)
Vomiting	48(4%)	41(4%)	43 (5%)
Hemorrhage NOS	36(3%)	3113%)	22 (3%)
Pain	34(3%)	25(2%)	19(2%)
Rigors	33 (2%)	30(3%)	27(3%)
Atrial fibrillation	33 (2%)	27(2%)	19(2%)
Mouth dry	30(2%)	17(1%)	4(<1%)
Agitation	30(2%)	28(2%)	27(3%)

Modified Sponsor's Table 18 Vol 8/10-239-59
NOS = not otherwise specified

* Statistically significant difference ($p \leq 0.05$) between randomized Dexmedetomidine patients and placebo patients. P-value from Chi-square test.

SECTION 8.6 SERIOUS ADVERSE EVENTS

SECTION 8.6.1 SERIOUS ADVERSE EVENTS FOR ABBOTT SPONSORED STUDIES (NON JAPANESE)

The following two tables (Table 38 and Table 39) present the number of serious adverse events reported in the safety database for the Phase II/III continuous infusion studies and the Phase II/III continuous infusion ICU sedation studies for the Abbott sponsored studies (exclusive of Japan). The total listing of all Serious Adverse Events reported for subjects/patient includes events reported from the time informed consent is signed to at least 30 days after participation in the Abbott sponsored trials (exclusive of Japan).

Table 38 Serious Adverse Events and Death: Phase II/III Infusion Studies
Abbott Sponsored Trials (Non Japanese)

	All Treated Dex (N=1337)			Dexmedetomidine						Placebo (N=817)		
				Open-label (N=189)			Randomized (N= 1148)					
Body System Preferred Term			TOTAL			TOTAL			TOTAL			TOTAL
Application Site Disorders			1 (<1%)			0			1 (<1%)			0
Injection Site Inflammation			1 (<1%)			0			1 (<1%)			0
Body As A Whole - General Disorders			14(1%)			2(1%)			12(1%)			11 (1%)
Abdomen Enlarged			1 (<1%)			0			1 <1%)			0
Anaphylactoid Reaction			1 (<1%)			0			1 (<1%)			0
Chest Pain			2 (<1%)			0			2			1 <1%)
Death			0			0			0			1 (<1%)
Fatigue			0			0			0			2 (<1%)
Fever			4 (<1%)			0			4 (<1%)			1 (<1%)
Hypovolemia			1 (<1%)			0			1 (<1%)			0
Light Anesthesia			0			0			f)			1 (<1%)
Mediastinitis			1 (<1%)			1(<1%)			0			2 (<1%)
Multiple Organ Failure			1 (<1%)			1 (<1%)			0			1 (<1%)
Necrosis Ischemic			2 (<1%)			0			2 (<1%)			1 (<1%)
Other			1 (<1%)			0			1 (<1%)			0
Pain			2 (<1%)			0			2 (<1%)			1 (<1%)
Sudden Death			0			0			0			2 (<1%)
Cardiovascular Disorders, General			29(2%)			6(3%)			23(2%)			20(2%)
Aneurysm			0			0			0			1 (<1%)
Cardiac Failure			0			0			0			1 (<1%)
Cardiac Failure Left			0			0			0			1 (<1%)
Circulatory Failure			3 (<1%)			1 (<1%)			2 (<1%)			1 (<1%)
ECG Abnormal Specific			2 (<1%)			1 <1%			1 (<1%)			<1%)
Heart Disorder			2 (<1%)			1 (<1%)			1 (<1%)			0
Hypertension			3 (<1%)			0			3 (<1%)			2 (<1%)

Dex = dexmedetomidine; ECG = electrocardiogram; AV = atrioventricular; BUN blood urea. nitrogen; NOS = not otherwise specified; NPN = nonprotein nitrogen; LDH = lactate dehydrogenase; RES = reticuloendothelial system;

Modified Sponsor's Table 35, ISS 8/10-106

Table 38 Serious Adverse Events and Death: Phase II/III Infusion Studies Continued
Abbott Sponsored Trials (Non Japanese)

	All Treated Dexmedetomidine (N= 1337)			Dexmedetomidine Open Label (N=189)			Dexmedetomidine Randomized (N= 1148)			Placebo (N=817)		
Body System Preferred Term			TOTAL			TOTAL			TOTAL			TOTAL
Cardiovascular Disorders, General Continued												
Hypertension Pulmonary			1 (<1%)			1 (<1%)			0			0
Hypotension			18(1%)			2 (1%)			16(1%)			13(2%)
Central & Peripheral Nervous System Disorders			7 (<1%)			2(1%)			5 (<1%)			9(1%)
Aphasia			1 (<1%)			0			1 (<1%)			2 (<1%)
Coma			0			0			0			1 (<1%)
Coordination Abnormal			0			0			0			1 (<1%)
Dizziness			0			0			0			2 (<1%)
Hemiparesis			0			0			0			1 (<1%)
Neuralgia			1 (<1%)			0			1 (<1%)			0
Neuritis			1 (<1%)			0			1 (<1%)			1 (<1%)
Neuropathy			1 (<1%)			1 (<1%)			0			0
Paresthesia			0			0			0			1 (<1%)
Paralysis			2 (<1%)			0			2 (<1%)			0
Paresis			0			0			0			1 (<1%)
Speech Disorder			0			0			0			1 (<1%)
Stupor			2 (<1%)			1 (<1%)			1 (<1%)			0
Fetal Disorders			1 (<1%)			0			1 (<1%)			0
Respiratory Tract Malformation			1 (<1%)			0			1 (<1%)			0
Gastrointestinal System Disorders			19 (<1%)			2(1%)			17(1%)			11 (1 %)
Colitis			0			0			0			1 (<1%)
Diarrhea			1 (<1%)			0			1 (<1%)			1 (<1%)
Clostridium Difficile			0			0			0			1 (<1%)
Duodenal Ulcer Perforated			1 (<1%)			0			1 (<1%)			0
Gastrointestinal Disorders NOS			0			0			1 (<1%)			0

Dex = dexmedetomidine; ECG = electrocardiogram; AV = atrioventricular; BUN blood urea. nitrogen; NOS = not otherwise specified; NPN = nonprotein nitrogen; LDH = lactate dehydrogenase; RES = reticuloendothelial system;

Table 38 Serious Adverse Events and Death: Phase II/III Infusion Studies Continued
Abbott Sponsored Trials (Non Japanese)

	All Treated Dexmedetomidine (N= 1337)			Dexmedetomidine Open label (N=189)			Dexmedetomidine Randomized (N= 1148)			Placebo (N=817)		
Body System Preferred Term			TOTAL			TOTAL			TOTAL			TOTAL
Gastrointestinal System Disorders (cont'd)												
GI Hemorrhage			0			0			0			2 (<1%)
Hematemesis			1 (<1%)			0			1 (<1%)			0
Hemorrhage Intraabdominal			1 (<1%)			1 <1%			0			2 (<1%)
Hemorrhage Rectum			2 (<1%)			0			2 (<1%)			0
Ileus			2 (<1%)			0			2 (<1%)			0
Ileus Paralytic			0			0			0			1 (<1%)
Intestinal Ischemia			0			0			0			2 (<1%)
Intestinal Obstruction			1 (<1%)			0			1 (<1%)			0
Intestinal Perforation			1 (<1%)			0			1 (<1)			1 (<1%)
Nausea			4 (<1%)			0			4 (<1%)			1 (<1%)
Esophagitis			1 (<1%)			0			1 (<1%)			0
Peptic Ulcer Aggravated			1 (<1%)			0			1 (<1%)			0
Peptic Ulcer Perforated			1 (<1%)			1 (<1%)			0			0
Peritonitis			2 (<1%)			1 (<1%)			1 (<1%)			2 (<1%)
Tongue Disorder			1 (<1%)			0			1 (<1%)			0
Vomiting			4 (<1%)			0			4 (<1%)			1 (<1%)
Heart Rate And Rhythm Disorders			33(2%)			6(3%)			27(2%)			13(2%)
Arrhythmia			2 (<1%)			0			2 (<1%)			1 (<1%)
Arrhythmia Ventricular			1 (<1%)			0			1 <1%)			0
AV Block			0			0			0			1 (<1%)
AV Block Complete			1 (<1%)			0			1 (<1%)			0
Bradycardia			7 (<1%)			1 (<1%)			6 (<1%)			1 (<1%)
Cardiac Arrest			13(<1%)			3(2%)			10 (<1%)			4 (<1%)
Fibrillation Atrial			10 (<1%)			2(1%)			8 (<1%)			2 (<1%)
Fibrillation Ventricular			1 (<1%)			0			1 (<1%)			1 (<1%.)

Dex = dexmedetomidine; ECG = electrocardiogram; AV = atrioventricular; BUN blood urea. nitrogen; NOS = not otherwise specified; NPN = nonprotein nitrogen; LDH = lactate dehydrogenase; RES = reticuloendothelial system;

Table 38 Serious Adverse Events and Death: Phase II/III Infusion Studies Continued
Abbott Sponsored Trials (Non Japanese)

	All Treated Dexmedetomidine (N= 1337)			Dexmedetomidine						Placebo (N=817)		
				Open label (N=189)			Randomized (N= 1148)					
Body System Preferred Term			TOTAL			TOTAL			TOTAL			TOTAL
Heart Rate And Rhythm Disorders (cont'd)												
Heart Block			1 (<1%)			0			1 (<1%)			0
Sinus Arrest			1 (<1%)			0			1 (<1%)			0
Tachycardia			3 (<1%)			1 (<1%)			2 (<1%)			1 (<1%)
Tachycardia. Supraventricular			1 (<1%)			1 (<1%)			0			0
Tachycardia. Ventricular			0			0			0			3 (<1%)
Liver And Biliary System Disorders			2 (<1%)			1 (<1%)			1 (<1%)			1 (<1%)
Cholecystitis			0			0			0			1 (<1%)
Hepatic Enzymes Increased			1 (<1%)			1 (<1%)			0			0
Hepatic Function Abnormal			1 (<1%)			0			1 (<1%)			0
Metabolic And Nutritional Disorders			5 (<1%)			3(2%)			2 (<1%)			5 (<1%)
Acidosis			2 (<1%)			1 (<1%)			1 (<1%)			1 (<1%)
Acidosis Lactic			1 (<1%)			1 (<1%)			0			0
BUN Increased			1 (<1%)			1 (<1%)			0			1 (<1%)
Creatine Phosphokinase Increased			1 (<1%)			0			1 (<1%)			1 (<1%)
Hyperkalemia			1 (<1%)			1 <1%			0			0
LDH Increased			0			0			0			1 (<1%)
NPN Increased			1 (<1%)			1 (<1%)			0			1 (1%)
Weight Decrease			0			0			0			1 (<1%)
Musculoskeletal System Disorders			2 (<1%)			0			2 (<1%)			1 (<1%)
Muscle Weakness			2 (<1%)			0			2 (<1%)			1 (<1%)

Dex = dexmedetomidine; ECG = electrocardiogram; AV = atrioventricular; BUN blood urea. nitrogen; NOS = not otherwise specified; NPN = nonprotein nitrogen; LDH = lactate dehydrogenase; RES = reticuloendothelial system;

Table 38 Serious Adverse Events and Death: Phase II/III Infusion Studies Continued
Abbott Sponsored Trials (Non Japanese)

	All Treated Dex (N= 1337)			Dexmedetomidine						Placebo (N=817)		
				Open label (N =189)			Randomized (N= 1148)					
Body System Preferred Term			TOTAL			TOTAL			TOTAL			TOTAL
Myo Endo Pericardial & Valve Disorders			12 (<1%)			3(2%)			9 (<1%)			11 (1%)
Angina Pectoris			2 (<1%)			0			2 (<1%)			1 (<1%)
Cardiac Tamponade			1 (<1%)			0			1 (<1%)			2 (<1%)
Myocardial Infarction			5 (<1%)			2(1%)			3 (<1%)			5 (<1%)
Myocardial Ischemia.			2 (<1%)			0			2 (<1%)			2 (<1%)
Pericardial Effusion			2 (<1%)			1 (<1%)			1 (<1%)			1 (<1%)
Neoplasm			2 (<1%)			0			2 (<1%)			2 (<1%)
Carcinoma			0			0			0			1 (<1%)
Colon Carcinoma			1 (<1%)			0			1 (<1%)			0
Gastric Carcinoma			1 (<1%)			0			1 (<1%)			0
Pulmonary Carcinoma			0			0			0			1 (<1%)
Platelet, Bleeding & Clotting Disorders			26(2%)			3(2%)			23(2%)			21(3%)
Coagulation Disorder			1 (<1%)			0			1 (<1%)			2 (<1%)
Embolism Cerebral			1(<1%)			0			1 (<1%)			0
Embolism Pulmonary			1 (<1%)			0			1 (<1%)			1 (<1%)
Hematoma			1 (<1%)			0			1 (<1%)			1 (<1%)
Hemorrhage NOS			14 (1%)			1 (<1%)			13(1%)			15(2%)
Prothrombin Decreased			0			0			0			1 (<1%)
Thrombocytopenia			2 (<1%)			1 (<1%)			1 <1%)			0
Thromboembolism			1 (<1%)			0			1 (<1%)			0
Thrombosis			4 (<1%)			1 (<1%)			3 (<1%)			0
Thrombosis Arterial			2 (<1%)			0			2 (<1%)			1 <1%
Thrombosis Arterial Leg			1 (<1%)			0			1 (<1%)			2 (<1%)
Psychiatric Disorders			6 (<1%)			1 (<1%)			5 (<1%)			8 (<1%)
Aggressive Reaction			0			0			0			1 (<1%)
Agitation			1 (<1%)			0			1 (<1%)			3 (<1%)

Dex = dexmedetomidine; ECG = electrocardiogram; AV = atrioventricular; BUN blood urea. nitrogen; NOS = not otherwise specified; NPN = nonprotein nitrogen; LDH = lactate dehydrogenase; RES = reticuloendothelial system;

Table 38 Serious Adverse Events and Death: Phase II/III Infusion Studies Continued
Abbott Sponsored Trials (Non Japanese)

	All Treated Dex (N= 1337)			Dexmedetomidine						Placebo (N=817)		
				Open label (N= 189)			Randomized		(N= 1148)			
Body System Preferred Term			TOTAL			TOTAL	CTDB	SAGE	TOTAL			TOTAL
Psychiatric Disorders Continued												
Confusion			4 (<1%)			1 (<1%)			3 (<1%)			5(<1%)
Delirium			1 (<1%)			0			1 (<1%)			1(<1%)
Somnolence			1 (<1%)			0			1 (<1%)			1(<1%)
Reproductive Disorders, Male			1 (<1%)			1 (<1%)			0			1(<1%)
Orchitis			1 (<1%)			1 (<1%)			0			0
Prostatic Disorder			0			0			0			1(<1%)
Resistance Mechanism Disorders			23(2%)			4(2%)			19(2%)			12(1%)
Abscess			2 (<1%)			0			2 (<1%)			0
Healing Impaired			2 (<1%)			0			2 (<1%)			1(<1%)
Infection			9 (<1%)			1 <1%			8 (<1%)			5(<1%)
Infection Bacterial			2 (<1%)			0			2 (<1%)			2(<1%)
Infection Fungal			1 (<1%)			1 (<1%)			0			0
Sepsis			6 (<1%)			2(1%)			4 (<1%)			6 (<1%)
Respiratory System Disorders			36(3%)			9(5%)			27(2%)			29(4%)
Adult Respiratory Stress Syndrome			3 (<1%)			1 (<1%)			2 (<1%)			2(<1%)
Aspiration			1 (<1%)			0			1 (<1%)			0
Atelectasis			3 (<1%)			1 (<1%)			2 (<1%)			1(<1%)
Bronchitis			0			0			0			1(<1%)
Bronchospasm			0			0			0			1(<1%)
Coughing			2 (<1%)			0			2 (<1%)			0
Dyspnea			3 (<1%)			0			3 (<1%)			3(<1%)
Hemothorax			1 (<1%)			0			1 (<1%)			0
Hypercapnia			0			0			0			1(<1%)
Hypoventilation			0			0			0			2 (<1%)
Hypoxia			12 (<1%)			3(2%)			9 (<1%)			9(1%)

Dex = dexmedetomidine; ECG = electrocardiogram; AV = atrioventricular; BUN blood urea. nitrogen; NOS = not otherwise specified; NPN = nonprotein nitrogen; LDH = lactate dehydrogenase; RES = reticuloendothelial system;

Table 38 Serious Adverse Events and Death: Phase II/III Infusion Studies Continued
Abbott Sponsored Trials (Non Japanese)

	All Treated Dex (N=1337)			Dexmedetomidine						Placebo (N=817)		
				Open label (N=189)			Randomized (N=1148)					
Body System Preferred Term			TOTAL			TOTAL			TOTAL	CTDB	SAGE	TOTAL
Respiratory System Disorders (cont'd)												
Pleural Effusion			4 (<1%)			1 (<1%)			3 (<1%)			3 (<1%)
Pneumonia			7 (<1%)			3(2%)			4 (<1%)			2 (<1%)
Pneumothorax			1 (<1%)			0			1 (<1%)			0
Pulmonary Edema			7 (<1%)			3(2%)			1 (<1%)			3 (<1%)
Respiratory Depression			0			0			0			2 (<1%)
Respiratory Disorder			4 (<1%)			1 (<1%)			3 (<1%)			2 (<1%)
Respiratory Insufficiency			8 (<1%)			2(1%)			6 (<1%)			4 (<1%)
Sinusitis			1 (<1%)			0			1 (<1%)			0
Upper Respiratory Tract Infection			1 (<1%)			1 (<1%)			0			0
Secondary Terms			14 (1%)			4(2%)			9 (<1%)			8 (<1%)
Medication Error			4 (<1%)			1 (<1%)			3 (<1%)			0
Surgical Intervention			5 (<1%)			1 (<1%)			4 (<1%)			5 (<1%)
Surgical Site Reaction			5 (<1%)			2 (1%)			2 (<1%)			2 (<1%)
Surgical Skin Tear			0			0			0			1 (<1%)
Skin And Appendages Disorders			2 (<1%)			0			2 (<1%)			0
Bullous Eruption			1 (<1%)			0			1 (<1%)			0
Rash			0			0			1 (<1%)			0
Urticata			1 (<1%)			0			1 (<1%)			0
Urinary System Disorders			11 (<1%)			2(1%)			9 (<1%)			10(1%)
Anuria			1 (<1%)			0			1 (<1%)			1 (<1%)
Oliguria			2 (<1%)			0			2 (<1%)			2 (<1%)
Renal Failure Acute			4 (<1%)			2(1%)			2 (<1%)			5 (<1%)

Dex = dexmedetomidine; ECG = electrocardiogram; AV = atrioventricular; BUN blood urea. nitrogen; NOS = not otherwise specified; NPN = nonprotein nitrogen; LDH = lactate dehydrogenase; RES = reticuloendothelial system;

Table 38 Serious Adverse Events and Death: Phase II/III Infusion Studies Continued
Abbott Sponsored Trials (Non Japanese)

	Dexmedetomidine									Placebo (N=817)		
	All Treated Dex (N=1337)			Open-label (N=189)			Randomized (N=1148)					
Body System Preferred Term			TOTAL			TOTAL			TOTAL			TOTAL
Urinary System Disorders (cont'd)												
Renal Function Abnormal			1 (<1%)			0			1 (<1%)			1 (<1%)
Renal Infarction			1 (<1%)			0			1 (<1%)			0
Strangury			1 (<1%)			0			1 (<1%)			0
Urinary Retention			1 (<1%)			0			1 (<1%)			0
Urinary Tract Infection			0			0			0			1 (<1%)
Vascular (Extracardiac) Disorders			13 (<1%)			1(<1%)			12(1%)			9(1%)
Cerebral Hemorrhage			1 (<1%)			0			1 (<1%)			1 (<1%)
Cerebrovascular Disorder			4 (<1%)			0			4 (<1%)			3 (<1%)
Peripheral Ischemia			6 (<1%)			1 (<1%)			5 (<1%)			4 (<1%)
Phlebitis			1 (<1%)			0			1 (<1%)			0
Transient Ischemic Attack			1 (<1%)			0			1 (<1%)			0
Vision Disorders			1 (<1%)			0			1 (<1%)			0
Diplopia			1 (<1%)			0			1 (<1%)			0
White Cell And RES Disorders			1 (<1%)			0			1 (<1%)			0
Leukocytosis			1 (<1%)			0			1 (<1%)			0

Dex = dexmedetomidine; ECG = electrocardiogram; AV = atrioventricular; BUN blood urea. nitrogen; NOS = not otherwise specified; NPN = nonprotein nitrogen; LDH = lactate dehydrogenase; RES = reticuloendothelial system;

Table 39 Serious Adverse Events and Death: Phase II/III Infusion ICU Studies
Abbott Sponsored Trials (Non Japanese)

	All Treated Dex (N=576)	Dexmedetomidine					Placebo (N=379)		
		Open-label (N= 189)			Randomized (N=387)				
Body System Preferred Term	TOTAL			TOTAL			TOTAL		TOTAL
Body As A Whole - General Disorders	5(<1%)			2(1%)			3(<1%)		7(2%)
Chest Pain	0			0			0		1 (<1%)
Fatigue	0			0			0		1 (<1%)
Fever	0			0			0		1 (<1%)
Death	1 (<1%)			1(<1%)			0		0
Light Anesthesia	0			0			0		1 (<1%)
Mediastinitis	1 (<1%)			1(<1%)			0		2 (<1%)
Multiple Organ Failure	1 (<1%)			1(<1%)			0		1 (<1%)
Necrosis Ischemic	2(<1%)			0			2(<1%)		1(<1%)
Other	1(<1%)			0			1 (<1%)		0
Pain	0			0			0		1(<1%)
Cardiovascular Disorders, General	18(3%)			6(3%)			12(3%)		9(2%)
Aneurysm	0			0			0		1 (<1%)
Circulatory Failure	3(<1%)			1(<1%)			2(<1%)		1 (<1%)
ECG Abnormal Specific	1(<1%)			1 (<1%)			0		0
Heart Disorder	2 (<1%)			1(<1%)			1(<1%)		0
Hypertension	1 (<1%)			0			1(<1%)		1 (<1%)
Hypertension Pulmonary	1(<1%)			1 (<1%)			0		0
Hypotension	11(2%)			2(1%)			9(2%)		6(2%)
Central & Peripheral Nervous System Disorders	4 (<1%)			2(1%)			2(<1%)		5(1%)
Aphasia	0			0			0		1(<1%)
Coordination Abnormal	0			0			0		1 (<1%)
Hemiparesis	0			0			0		1 (<1%)

ICU = intensive care unit; Dex dexmedetomidine; ECG electrocardiogram; ; NOS not otherwise specified; NPN nonprotein nitrogen;
BUN: blood urea nitrogen;

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Table 39 Serious Adverse Events and Death: Phase II/III Infusion ICU Studies Continued
Abbott Sponsored Trials (Non Japanese)

	All Treated Dex (N=576)			Dexmedetomidine						Placebo (N=379)		
				Open-label (N=189)			Randomized (N=387)					
BODY SYSTEM Preferred Term			TOTAL			TOTAL			TOTAL			TOTAL
Central & Peripheral Nervous System Disorders Continued												
Neuralgia			1 (<1%)			0			1 (<1%)			0
Neuritis			1 (<1%)			0			1 (<1%)			1 (<1%)
Neuropathy			1 (<1%)			1(<1%)			0			0
Paresthesia			0			0			0			1 (<1%)
Paralysis			1 (<1%)			0			1 (<1%)			0
Paresis			0			0			0			1(<1)
Speech Disorder			0			0			0			1 (<1%)
Stupor			1 (<1%)			1(<1%)			0			0
Gastrointestinal System Disorders			8(1%)						6(2%)			4(1%)
Duodenal Ulcer Perforated			1(<1%)			0			1 (<1%)			0
Hematemesis			1 (<1%)			0			1 (<1%)			0
Hemorrhage Intraabdominal			1(<1%)			1(<1%)			0			1 (<1%)
Intestinal Ischemia			0			0			0			2 (<1%)
Intestinal Perforation			0			0			0			1 (<1%)
Nausea			3(<1%)			0			1 (<1%)			0
Peptic Ulcer Perforated			1 (<1%)			1 (<1%)			0			0
Peritonitis			2(<1%)			1 (<1%)			1 (<1%)			2(<1)
Tongue Disorder			1(<1%)			0			1 (<1%)			0
Vomiting			1(<1%)			0			1 (<1%)			0

ICU = intensive care unit; Dex dexmedetomidine; ECG electrocardiogram; ; NOS not otherwise specified; NPN nonprotein nitrogen;
BUN: blood urea nitrogen;

Table 39 Serious Adverse Events and Death: Phase II/III Infusion ICU Studies Continued
Abbott Sponsored Trials (Non Japanese)

	All Treated Dex (N=576)	Dexmedetomidine			Placebo (N=379)
		Open-label (N=189)	Randomized (N=387)		
BODY SYSTEM Preferred Term	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL
Heart Rate And Rhythm Disorders	15(3%)	6(3%)	9(2%)	5(1%)
Arrhythmia	1 (<1%)	0	1 (<1%)	1 (<1%)
Arrhythmia Ventricular	1 (<1%)	0	1 (<1%)	0
Bradycardia	4 (<1%)	1 (<1%)	3 (<1%)	0
Cardiac Arrest	6(1%)	3(2%)	3 (<1%)	1 (<1%)
Fibrillation Atrial.	4(<1%)	2(<1%)	2 (<1%)	0
Fibrillation Ventricular	1 (<1%)	0	1 (<1%)	1(<1%)
Heart Block	1(<1%)	0	1(<1%)	0
Tachycardia	2(<1%)	1 (<1%)	1 (<1%)	0
Tachycardia Supraventricular	1 (<1%)	1(<1%)	0	0
Tachycardia Ventricular	0	0	0	1 (<1%)
Liver And Biliary System Disorders	2(<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Cholecystitis	0	0	0	1 (<1%)
Hepatic Enzymes Increased	1 (<1%)	1 (<1%)	0	0
Hepatic Function Abnormal	1(<1%)	0	1 (<1%)	0
Metabolic And Nutritional Disorders	4(<1%)	3(2%)	1(<1%)	2 (<1%)
Acidosis	2 (<1%)	1 (<1%)	1 (<1%)	0
Acidosis Lactic	1 (<1%)	1 (<1%)	0	0
BUN Increased	1 (<1%)	1 (<1%)	0	1 (<1%)
Creatine Phosphokinase Increased	0	0	0	1 (<1%)
Hyperkalemia	1(<1%)	1(<1%)	0	0
NPN Increased	1 (<1%)	1 (<1%)	0	1(<1%

ICU = intensive care unit; Dex dexmedetomidine; ECG electrocardiogram; ; NOS not otherwise specified; NPN nonprotein nitrogen;
BUN: blood urea nitrogen;

Table 39 Serious Adverse Events and Death: Phase II/III Infusion ICU Studies Continued
Abbott Sponsored Trials (Non Japanese)

	All Treated Dex (N=576)			Dexmedetomidine						Placebo (N=379)		
				Open-label (N=189)			Randomized (N=387)					
BODY SYSTEM Preferred Term			TOTAL			TOTAL			TOTAL			TOTAL
Musculoskeletal System Disorders			0			0			0			1 (<1%)
Muscle Weakness			0			0			0			1 (<1%)
Myo Endo Pericardial & Valve Disorders			6(1%)			3(2%)			3(<1%)			3 (<1%)
Angina Pectoris			0			0			0			1 (<1%)
Cardiac Tamponade			0			0			0			1 (<1%)
Myocardial Infarction			4 (<1%)			0			2(<1%)			0
Myocardial Ischemia			1 (<1%)			0			1 (<1%)			0
Pericardial Effusion			1 (<1%)			1 <1%			0			1 (<1%)
Neoplasm			0			0			0			1 (<1%)
Carcinoma			0			0			0			1 (<1%)
Platelet, Bleeding & Clotting Disorders			11(2%)			3(2%)			8(2%)			1 (3%)
Coagulation Disorder			0			0			0			1 (<1%)
Hematoma			1 (<1%)			0			1(<1%)			1 (<1%)
Hemorrhage NOS			7(1%)			1(<1%)			6(2%)			10(3%)
Thrombocytopenia			1 (<1%)			1(<1%)			0			0
Thromboembolism			1(<1%)			0			1(<1%)			0
Thrombosis			1(<1%)			1(<1%)			0			0
Psychiatric Disorders			2(<1%)			1(<1%)			1(<1%)			7(2%)
Aggressive Reaction			0			0			0			1 (<1%)
Agitation			0			0			0			3 (<1%)
Confusion			2(<1%)			1 (<1%)			1(<1%)			4(1%)
Delirium			0			0			0			1(<1%)
Somnolence			0			0			0			1 (<1%)

ICU = intensive care unit; Dex dexmedetomidine; ECG electrocardiogram; ; NOS not otherwise specified; NPN nonprotein nitrogen;
BUN: blood urea nitrogen;

Table 39 Serious Adverse Events and Death: Phase II/III Infusion ICU Studies Continued
Abbott Sponsored Trials (Non Japanese)

	All Treated Dex (N=576)	Dexmedetomidine Open-label (N=189)	Dexmedetomidine Randomized (N=387)	Placebo (N=379)
BODY SYSTEM Preferred Term	TOTAL	TOTAL	TOTAL	TOTAL
Reproductive Disorders, Male	1 (<1%)	1 (<1%)	0	0
Orchitis	1 (<1%)	1 (<1%)	0	0
Resistance Mechanism Disorders	7(1%)	4(2%)	3(<1%)	8(2%)
Abscess	1 (<1%)	0	1 (<1%)	0
Infection	2 (<1%)	1 (<1%)	1(<1%)	3(<1%)
Infection Bacterial	0	0	0	2 (<1%)
Infection Fungal	1 (<1%)	1 (<1%)	0	0
Sepsis	3(<1%)	2(1%)	1 (<1%)	5(1%)
Respiratory System Disorders	18(3%)	9(5%)	9(2%)	15(4%)
Adult Respiratory Stress Syndrome	3(<1%)	1 (<1%)	2(<1%)	2(<1%)
Atelectasis	3(<1%)	1 (<1%)	2(<1%)	1(<1%)
Bronchitis	0	0	0	1(<1%)
Bronchospasm	0	0	0	1 (<1%)
Dyspnea	0	0	0	1 (<1%)
Hemothorax	1 (<1%)	0	1 (<1%)	0
Hypercapnia	0	0	0	1 (<1%)
Hypoventilation	0	0	0	1 (<1%)
Hypoxia	4 (<1%)	3 2%	1 (<1%)	5(1%)
Pleural Effusion	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Pneumonia	5 (<1%)	3(2%)	2 (<1%)	0
Pulmonary Edema	6(1%)	3(2%)	2 (<1%)	2 (<1%)
Respiratory Depression	0	0	0	1 (<1%)
Respiratory Disorder	3 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
Respiratory Insufficiency	3 (<1%)	2(1%)	1 (<1%)	0
Upper Respiratory Tract Infection	1 (<1%)	1 (<1%)	0	0

ICU = intensive care unit; Dex dexmedetomidine; ECG electrocardiogram; ; NOS not otherwise specified; NPN nonprotein nitrogen;
BUN: blood urea nitrogen;

Table 39 Serious Adverse Events and Death: Phase II/III Infusion ICU Studies Continued
Abbott Sponsored Trials (Non Japanese)

	All Treated Dex (N=576)	Dexmedetomidine Open-label (N=189)	Dexmedetomidine Randomized (N=387)	Placebo (N=379)
BODY SYSTEM Preferred Term	TOTAL	TOTAL	TOTAL	TOTAL
Secondary Terms	12(2%)	4(2%)	8(2%)	7(2%)
Medication Error	4(<1%)	1 (<1%)	3 (<1%)	0
Surgical Intervention	4 (<1%)	1 (<1%)	3 (<1%)	4(1%)
Surgical Site Reaction	4(<1%)	2 (1%)	2 (<1%)	2(1%)
Surgical Skin Tear	0	0	0	1 (<1%)
Urinary System Disorders	5(<1%)	2(1%)	3 (<1%)	8(2%)
Anuria	1 (<1%)	0	1 (<1%)	1 (<1%)
Oliguria	1 (<1%)	0	1 (<1%)	1(<1%)
Renal Failure Acute	3(<1%)	2(1%)	1 (<1%)	4(1%)
Renal Function Abnormal	0	0	0	1 (<1%)
Urinary Tract Infection	0	0	0	1 (<1%)
Vascular (Extracardiac) Disorders	2(<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Cerebral Hemorrhage	1(<1%)	0	1(<1%)	1 (<1%)
Peripheral Ischemia	1 (<1%)	1(<1%)	0	0
Vision Disorders	1 (<1%)	0	1(<1%)	0
Diplopia	1(<1%)	0	1 (<1%)	0

ICU = intensive care unit; Dex dexmedetomidine; ECG electrocardiogram; ; NOS not otherwise specified; NPN nonprotein nitrogen; BUN: blood urea nitrogen;

SECTION 8.6.2 SERIOUS ADVERSE EVENTS FOR ABBOTT SPONSORED STUDIES (JAPANESE)

Two studies of Dexmedetomidine were conducted by Abbott Laboratories in Japan. One study was a Phase I trial to evaluate the pharmacokinetic and safety profile of Dexmedetomidine in healthy Japanese male adult volunteers. The second study was a Phase II trial to evaluate the safety and dose response correlation in the variations in the circulatory pattern during the perioperative period in patients undergoing a surgical procedure under inhalation anesthesia.

Sponsor states in the Phase I trial Dexmedetomidine was infused IV for 10 minutes at doses of 0.1, 0.3, and 0.6 mcg/kg to 9 healthy Japanese male adult volunteers. One subject experienced bradycardia, hypotension, AV rhythm, ventricular extrasystole, and nausea during administration of Dexmedetomidine 0.6 mcg/kg that resolved after IV injection of atropine. In the Phase II trial, Dexmedetomidine was infused IV for 5 minutes at doses of 0.2, 0.4, 0.6 and 0.8 mcg/kg to 139 Japanese patients undergoing surgical procedures under inhalation anesthesia. No serious adverse events were reported during the conduct of this study. No deaths were reported during the conduct of either of the Japanese studies.

Case Report Forms and Data Listings have been requested by the Agency on the Japanese trials. [*Reviewer Note: It appears 148 subjects were exposed to Dexmedetomidine in Japan*].

SECTION 8.6.3 SERIOUS ADVERSE EVENTS IN NON ABBOTT SPONSORED STUDIES

A total of 56 studies (19 Phase I, 26 Phase II, and 11 Phase III) of Dexmedetomidine were conducted by [redacted]. A total of 174 subjects were dosed with Dexmedetomidine in the Phase I trials using rapid IV injection, continuous IV infusion, intramuscular injection, or transdermal or oral administration. A total of 778 patients were treated with Dexmedetomidine in the Phase II trials using rapid IV injection, continuous IV infusion, or intramuscular injection. A total of 575 patients were treated with Dexmedetomidine in the Phase III trials using continuous IV or IM injection. The numbers of subjects/patients dosed/treated in the Phase I, II, and III studies conducted by [redacted] are presented by Table 40.

Table 40 [redacted] Deaths, Serious Adverse Events, and Premature Discontinuations Due to Adverse Events Experienced by Dexmedetomidine Treated Subjects/Patients

	Deaths	Serious Adverse Events	Premature Discontinuations
Phase I	0	2	2
Phase II	1	22	12
Phase III	0	3	0

Patient/subject may be counted in more than one column

Data Listings are not available for any of the [redacted] ubjects/patients exposed to Dexmedetomidine. The Case Report Form is not available for the death in the [redacted] study.

PHASE I [redacted]

Deaths:
None

Serious Adverse Events:

- Subject experienced sinus arrest 2h after discontinuation of Dexmedetomidine; the event was considered related to study drug and resolved after administration of glycopyrrolate and ephedrine.
- Subject experienced severe fainted during cannulation prior to study drug administration; the event resolved within 2 minutes after administration of 100% oxygen.

Premature Discontinuations:

- Subject was D/C due to a mild allergic reaction (nausea, fever, urticaria) within 48 h after removal of the 15 cm^2 transdermal Dexmedetomidine patch; the event was considered related to study drug and patient recovered without medical intervention.
- Subject was D/C before receiving any study drug due to a serious adverse event (fainting).

PHASE II [redacted]

Deaths:

- Patient died from bleeding considered unrelated to study drug administration.

Serious Adverse Events:

- Patient had gram negative rod sepsis which was treated with antibiotics.
- Patient with bilateral pitting edema treated with diuretics
- Patient had acute pancreatitis with rapid ventricular response which required electric cardioversion
- Patient experienced nausea, dizziness and headache which was felt to be possibly causal. Patient recovered on second post op day.

- Patient experienced sinus arrest and recovered spontaneously.
- Patient experienced bradycardia and was treated with atropine and oxygen and patient recovered.
- Patient experienced bradycardia which resolved spontaneously.
- Patient experienced ventricular fibrillation and hypotension said possibly related to study drug
- Patient experienced myocardial ischemia and bradycardia said not related to study drug.
- Patient experienced a MI which was claimed unlikely related to study drug.
- Patient had postoperative bleeding which was claimed unlikely related to study drug. The patient recovered after surgical hemostasis was performed within 12 hour of the initial surgery.
- Patient suffered cardiac arrest of 20 seconds after having received 260 mcg of Dexmedetomidine IM. Patient recovered within 5 minutes after cardiac massage, atropine and oxygen.
- Patient experienced ST segment elevation felt to have a causality of none.
- Patient experienced arrhythmia said to have a causality of unlikely.
- Patient experienced bronchial obstruction, low systemic blood pressure, high pulmonary blood pressure, and ST segment depression, all of which were felt to have a causality of unlikely.
- Patient experienced elevated CK-MB and angina, both of which were felt to have a causality of unlikely.
- Patient experienced bleeding which was felt to have an unlikely causality.
- Patient experienced bleeding which was felt to have a causality of none.
- Patient experienced atrial fibrillation which was felt to have a causality of none.
- Patient experienced dyspnea which was felt to have a causality of none.
- Patient experienced bleeding and a myocardial infarction which were both said to have an unlikely causality.
- Patient experienced atrial fibrillation which was felt to have no causality.

Premature Discontinuations:

- Patient underwent an emergency femoral popliteal bypass within 24 h of the first operation (aorto-femoral bypass). The study drug was D/C immediately prior to second surgery.
- Patient was D/C from the dose finding stage due to an excessive increase of systolic and diastolic blood pressure after the loading dose of Dexmedetomidine. The maintenance infusion was stopped 1 minute after its initiation.
- Patient D/C due to sudden hypoxia
- Patient D/C due to intra abdominal bleeding and was considered of unlikely relationship to study drug.
- Patient was excluded due to a migraine attack prior to receiving study drug in part 2.
- Patient experienced a sinus pause during intubation and was treated with atropine and was excluded from the study.
- 5 patients were discontinued early due to serious adverse events and are mentioned in the Serious Adverse Events category.