- One patient experienced a myocardial infarction said to have unlikely causality.

PHASE III [redacted] IES

Deaths:
None

Serious Adverse Events:

- Patient experienced hypotension probably related to study drug; dyspnea/chest pain and pneumothorax with no stated relationship to study drug.
- Patient experienced cardiac arrest with a claimed possible relationship to study drug.
- Patient experienced diarrhea, tissue discharge, necrotic area on buttock, ischemic colitis, and vaginal fistula with claimed no relationship to study drug. Both the diarrhea and necrotic area on buttock were judged to be mild while the tissue discharge, ischemic colitis, and vaginal fistula were judged to be moderate.

SECTION 8.7 LABORATORY FINDINGS

SECTION 8.7.1 SERUM CHEMISTRY PARAMETERS

A summary of mean change from baseline to the last post baseline time point in hematology and chemistry parameters for patients in Phase II/III continuous infusion studies is presented in Table 41. Sponsor states the mean changes from baseline in hematology and chemistry values appear consistent with what would be expected in this post-surgical population. Statistically significant differences were noted between the randomized Dexmedetomidine treated patients and placebo treated patients for mean changes from baseline hematocrit, hemoglobin, and red blood cells. These changes are claimed by the sponsor to be small and not clinically important. This reviewer agrees that these hematology changes are small and not clinically insignificant.

Adverse events of hyperglycemia were reported by 2% of the patients in both the randomized Dexmedetomidine and placebo treatment groups but the mean change from baseline to the last post baseline time point in glucose values were statistically significantly higher in the randomized Dexmedetomidine patients than in the placebo patients. The changes were 1.5 mmol/L increase for randomized Dexmedetomidine patients and 1.0 mmol/L increase for placebo patients. [*Reviewer Note: Normal fasting glucose is 4.2-6.4 mmol/L or 75-115 mg/dL.*] Urine glucose was not collected in the Dexmedetomidine studies.

The mean changes from baseline to the last post baseline time point in liver chemistry parameters were similar between randomized Dexmedetomidine and placebo patients.

Table 41 Mean Change From Baseline to the Last Post Baseline Time Point in Hematology And Chemistry Parameters: All Treated Patients in Phase II/III Continuous Infusion Studies.

	All Treated Dexmedetomidine			Randomized Dexmedetomidine			Placebo		
	N	Base ±SD	Mean Change ±SD	N	Base ±SD	Mean Change ±SD	N	Base ±SD	Mean Change ±SD
Hematology Parameter									
Hematocrit, (1.0)	1046	0.4 ±0.07	0.0 ±0.07	915	0.4 ±0.07	-0.1* ± 0.07	641	0.4 ±0.07	0.0 ±0.07
Hemoglobin (g/L)	1077	121.5 ± 22.23	-16.1 ± 22.87	936	123.2 ± 22.04	-17.6* ± 23.13	673	121.3 ± 22.54	-16.6 ± 23.87
Platelets (X109/L)	947	227.0 ±92.94	-36.9 ± 58.36	832	230.4 ± 92.69	-39.2 58.83	579	226.1 ± 90.20	-36.7 ±60.63
RBC (x 10 "/L)	673	3.8 ±0.72	-0.3 ± 0.72	533	3.9 ±0.74	-0.3* ±0.75	469	3.8 ±0.72	-0.3 ±0.74
WBC (x109/L)	1075	8.1 ±3.56	3.4 ± 3.94	934	7.9 ±3.33	3.5 ±3.87	666	8.1 ± 3.28	3.4 ±3.79
Chemistry Parameter									
BUN/Urea (mmol/L)	1131	5.3 ±2.10	-0.1 ±2.55	976	5.3 ±2.12	-0.2 ±2.47	706	5.6 ± 2.58	-0.1 ± 2.59
Bicarbonate (mmol/L)	1091	23.9 ± 3.54	1.4 ±3.55	942	24.2 ± 3.56	1.3 ±3.60	685	23.6 ± 3.55	1.6 ± 3.63
Creatinine (umol/L)	1127	77.6 ±27.75	1.8 ±35.17	971	78.9 ±27.19	1.1 ±34.89	708	76.7 ±29.53	3.1 ±26.81
Glucose (mmol/L)	1094	7.0 ±2.70	1.3 ±4.52	946	6.9 ±2.62	1.5* ±4.25	688	7.2 ±2.78	1.0 ±3.42
LDH (U/L)	598	242.0 ± 135.52	56.0 ±197.27	598	242.0 ±13 5.52	56.0 ±197.27	358	234.7 ±150.82	57.7 ±177.44
Potassium (mmol/L)	1104	4.2 ± 0.46	-0.1 ±0.60	952	4.2 ±0.46	-0.1 ±0.59	696	4.2 ±0.45	-0.1 ±0.57
SGOT/ASAT (U/L)	1082	28.4 ± 43.70	8.9 ±61.30	933	26.7 ± 31.62	10.0 ±58.88	683	30.0 ± 82.47	6.4 ± 77.32
SGPT/ALAT (U/L)	1067	24.6 ± 37.52	4.4 ±74.93	918	24.4 ± 36.02	3.5 ±78.06	672	24.6 ± 46.89	3.8 ± 43.58
Total bilirubin (umol/L)	1056	11.3 ± 10.17	1.1 ±8.02	907	11.0 ± 10.39	1.6 ±7.92	665	12.2 ± 11.48	1.1 ± 10.04
Total protein (g/L)	1083	59.5 ± 13.3	-6.6 ±12.68	927	61.0 +13.05	-7.8 ±12.40	684	59.1 ±13.61	-5.6 ± 12.65

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N = number of patients; base = baseline; SD = standard deviation; RBC = red blood cells; WBC = white blood cells;
BUN = blood urea nitrogen; LDH= lactate dehydrogenase; SGOT/ASAT = serum glutamic oxaloacetic transaminase/aspartate transaminase; SGPT/ALAT = serum glutamic-pyruvic transaminase/alanine transaminase

* Statistically significant difference (Shaded Areas) between randomized dexmedetomidine patients and placebo patients, $p \leq 0.05$.

SECTION 8.7.2 VITAL SIGNS AND ELECTOCARDIOGRAMS

Phase I Studies

One of the Phase I studies was designed to determine the highest safe plasma concentrations of Dexmedetomidine. Continuous monitoring of subjects EKGs was performed. The Dexmedetomidine plasma concentrations achieved were greater than those expected based on PK parameters in use. A total of 7 subjects in the study had significant abnormalities on post-baseline EKGs; all had received Dexmedetomidine. 5 subjects had sinus bradycardia; one also had nonsustained junctional rhythm. One subject had Mobitz Type I second degree heart block which resolved spontaneously one minute after onset. Another subject had intermittent premature atrial contractions with variable first degree AV block.

The EKG disorders occurred primarily at the plasma concentrations > 1.2 ng/ml. Sponsor speculates the probable mechanism of action was enhanced vagal nerve reflex activity without opposing sympathetic activity. Evaluation was confounded by use of phenylephrine which was used to determine baroreceptor sensitivity. Known adverse effects of phenylephrine administration include bradycardia and heart block. In this study involving EKGs, subjects were able to tolerate Dexmedetomidine plasma concentrations exceeding the anticipated therapeutic range by as much as 13 times.

Phase II/III Studies

Several of the perioperative studies collected vital sign data using a said novel monitoring system. Sponsor claims that as a result of validation concerns about the system and the inability to synchronize the data with an actual event or time of treatment, the data collected by this system could not be appropriately analyzed or interpreted. The vital sign data collected in the Phase II/III ICU sedation studies used traditional techniques to assure the reliability of the data. Because of the validation concerns, sponsor is only presenting vital sign data from the continuous infusion ICU sedation studies in the Integrated Summary of Safety.

Analyses of vital signs in the continuous infusion ICU sedation studies included systolic and diastolic blood pressure, heart rate, central venous pressure, respiratory rate, oxygen saturation, and cardiac output.

Systolic Blood Pressure (SBP):
Mean baseline SBP was 126 mmHg in the randomized Dexmedetomidine group and 126 mmHg in the placebo group and was maintained within the normal range for both groups during the entire period of observation. After initial increases during the first 10 minutes, rapid moderate decreases (about 15 mmHg) occurred within the next 10 minutes in the randomized Dexmedetomidine group after which decreases occurred more gradually until 12-13 hours. After 15 hours, the time at which most patients completed study drug infusion, SBP slowly increased. In the placebo group, increases occurred during the first hour, after which there were decreases until 5 hours. Mean change from baseline in SBP during study drug infusion showed statistically significant differences between the treatment groups from 20 minutes through the 21 hour time point; variability between treatment and placebo groups was the same. After the 12-15 hour time point, SBP tended

to return to baseline with increases in the Dexmedetomidine group and decreases in the placebo group.

Randomized Dexmedetomidine patients with hypotension showed a mean decrease in SBP of 20 to 25 mmHg during the first 20 minutes. SBP in the randomized Dexmedetomidine group with hypotension remained lower than the randomized Dexmedetomidine group without hypotension until 17-hours, after which they were similar.

Diastolic Blood Pressure (DBP)

Baseline DBP was 64 mmHg in the placebo group and 65 in the randomized Dexmedetomidine group. In the randomized Dexmedetomidine group, after initial increases the first 10 minutes, DBP returned to baseline followed by gradual decreases to 12-13 hours and slight increases thereafter. In the placebo group, DBP remained increased for 2 hours before returning to baseline. At all times after the initial 10 minute evaluation, mean DBP was lower for the randomized Dexmedetomidine patients than for placebo patients. Analyses of mean change from baseline in DBP during study drug infusion showed statistically significant differences between the treatment groups at several time points. The most pronounced difference was at 12 hours after start of infusion with a difference of about 8 mmHg. Although statistically significant, the difference in variability between treated and placebo groups was clinically insignificant. Actual DBP was similar in the 2 groups by 24 to 27 hours.

Heart Rate

Baseline heart rate was 81 in the placebo group and 80 in the randomized Dexmedetomidine group. For the Dexmedetomidine treated group, heart rate decreased about 5 beats per minutes about 10 minutes after drug initiation. For both groups, mean rate remained within the normal range throughout the entire range of observation.

Central Venous Pressure (CVP)

Baseline CVP was 8 mmHg in the placebo group and 7 mmHg in the randomized Dexmedetomidine group. Mean change from baseline in CVP during study drug infusion showed small statistically significant differences between treatment groups from 1-12 hours, the differences were not clinically significant. Mean CVP for randomized Dexmedetomidine patients with hypotension was clinically insignificantly higher than in Dexmedetomidine patients without hypotension.

Respiratory Rate (RR)

Respiratory Rate was similar between treatment groups.

Oxygen Saturation

All patients received oxygen while being ventilated and remained in the normal range. After extubation oxygen saturation decreased slightly within both treatment groups but remained within the normal range. Oxygen saturation was similar between placebo and Dexmedetomidine treatment groups.

Cardiac Output

Few patients had cardiac output measurements collected during the study. Among those that did, the pattern of changes was similar between placebo and Dexmedetomidine treatment groups.

SECTION 8.8 ADVERSE EVENTS AND PRECLINICAL STUDIES

In 28 day repeated dosing nonclinical toxicology studies, the primary Dexmedetomidine related effects were sedation, slightly reduced body weight, exophthalmos, piloerection, gait changes, muscle twitching, irregular respiration, glucosuria. *[Discussion with pharmacology reviewer Dr. Geyer discloses no concomitant elevations of blood glucose in the animals with glucosuria. However other animals in other studies did show significant hyperglycemia although the urine for glucose was not analyzed.]*Changes in hepatic weight, some hepatic serum enzymes, and pulmonary hemosiderin deposits were also observed at the highest doses studied. In the clinical studies, the most frequently reported adverse events were likely extensions of the pharmacological effects of alpha2 agonists, including hypotension, hypertension, and bradycardia.

A dose related increase in the incidence of corneal keratitis and opacities was also reported in the preclinical studies. Sponsor states these last ophthalmological findings were due to the pharmacological effect of Dexmedetomidine decreasing lacrimal secretions and blinking during sedation. *[This reviewer agrees with this assessment.]* A total of 8 patients in the Phase II/III continuous infusion studies reported vision disorders, including 5 reports of abnormal vision, one report of conjunctivitis, one report of diplopia, and one report of photopsia. The abnormal vision reports were primarily described as blurred vision. The one report of conjunctivitis was related to a corneal abrasion. Each of these events resolved without intervention.

SECTION 8.9 DOSE-RESPONSE DATA

Sponsor states that one of the Phase I studies (Dexmedetomidine-95-007) demonstrated that subjects were able to tolerate Dexmedetomidine plasma concentrations exceeding the anticipated therapeutic range of 1.2 ng/ml; maximum individual Dexmedetomidine concentrations in this study ranged from 2.123 ng/ml to 16.100 ng/ml. A summary of the

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