Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products

MEMORANDUM

DATE: April 11, 2008

FROM: Rigoberto Roca, M.D.
Deputy Director
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members, and Invited Guests
Anesthetic and Life Support Drugs Advisory Committee (ALSDAC)

RE: Overview of the May 7, 2008 ALSDAC Meeting to Discuss NDA 22-244 for fospropofol disodium injection for sedation in adult patients undergoing diagnostic or therapeutic procedures

Fospropofol disodium injection is a novel compound to be administered by bolus injection for the indication of procedural sedation. It is prodrug that is metabolized by circulating alkaline phophatase into propofol, phosphate and formate in a 1:1:1 ratio. The onset of peak pharmacodynamic effect is not immediate because the drug must be converted into propofol, which is the active metabolite.

During this meeting, representatives from the Agency and the applicant, MGI Pharma, Inc., will present:

- data from the clinical program for fospropofol;
- data on the chemistry and the clinical pharmacology of fospropofol, including information on pharmacokinetic/pharmacodynamic data; and
- data from the clinical trials performed to assess the safety and efficacy of fospropofol.

Following these presentations, you will be asked to assess these findings and to discuss the apparent risks and benefits of fospropofol. Specifically, we will ask the committee to address whether the applicant has presented adequate data to support the safety of the

administration of fospropofol by persons without training in the administration of general anesthesia. Factors that may be considered in this assessment would include the patient population, the procedures that were studied, and any differences between the way a product is administered in the setting of a clinical trial and how it would be administered in the setting of clinical practice.

We will also ask the committee to address whether the assessments of a patient's ability to respond purposefully to stimulation are useful in guiding supplemental dosing; and whether the available data is sufficient to administer fospropofol safely to geriatric patients, patient with serious cardiopulmonary comorbidity and to patients weighing less than 60 kg. In the event that the committee recommends approval of this application, we would like you also to consider whether there are any post-approval studies that should be required of the applicant.

The Division and the Agency are grateful to the members of the committee and our invited guests for taking time from your busy schedules to participate in this important meeting. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decision possible.

Briefing Document for the Anesthesia and Life Support Drug Advisory Committee Meeting

May 7, 2008

Fospropofol disodium
NDA 22-244

Department of Health & Human Services
Food & Drug Administration
Center for Drug Evaluation & Research
Division of Anesthesia, Analgesia and Rheumatology Products
Silver Spring, MD 20993

Table of Contents

Executive Summary

The purpose of this advisory committee meeting is to discuss the marketing application for fospropofol disodium (fospropofol), also known as GPI 15715, or Aquavan, a new molecular entity with sedative-hypnotic properties to be administered intravenously and proposed for the indication of sedation in adult patients undergoing diagnostic or therapeutic procedures.

Fospropofol was developed based on the hypothesis that the pharmacokinetic profile of this prodrug suggested that there would be a slow onset of sedation that would in turn reduce the likelihood of sudden and unexpected general anesthesia. Therapies that are available for this indication include a variety of sedation products that are presently marketed in the U.S. and in widespread use, including midazolam and diazepam, usually in conjunction with an opiate; propofol; ketamine; barbiturates, such as sodium thiopental or methohexital; and etomidate, an imidazole. In particular, the combination of midazolam and an opiate is currently used widely for the proposed indication, but has been associated with slow onset and recovery. Propofol is a popular alternative because of its rapid onset and recovery, but bolus injection of propofol is also characterized by high peak serum concentrations that may result in general anesthesia.

Fospropofol is metabolized by alkaline phosphatase into propofol, formaldehyde, and phosphate following intravenous (IV) administration. Plasma concentrations of propofol, the purported active moiety, peak by about eight minutes and eliminated with a $t_{1/2}$ of about 2 hours following fospropofol administration. Analysis of fospropofol and propofol pharmacokinetics suggested dependence of clearance on total body weight and hence support bodyweight based dosing.

The clinical development program for fospropofol was conducted in the United States (U.S.) and consisted of one dose-ranging study, two pivotal studies, and 18 supportive studies. The supportive studies included open-label studies; open-label, fixed-dose studies; prolonged treatment duration studies in intubated and mechanically ventilated patients; and clinical pharmacology studies in healthy subjects. A midazolam treatment group was included in the dose-ranging study and in one of the two pivotal studies as an assay sensitivity reference for measurements of sedation and clinical benefit that were chosen to assess the effectiveness of fospropofol (Modified OAA/S, described in Appendix 1, and patient and physician questionnaires, respectively).

A preliminary review of efficacy suggests that fospropofol is efficacious as a sedation product for procedures.

The primary safety database is comprised of all subjects enrolled in U.S. studies that received at least one dose fospropofol and includes 1611 unique subjects, of whom 1338 were patients and 273 were healthy volunteers. The cumulative dose of fospropofol that was studied ranged from < 450 mg/kg in 317 patients and 70 healthy volunteers to > 1200 mg/kg among 103 patients and 84 healthy volunteers. In addition, two studies were

conducted in healthy volunteers in the Netherlands (Studies 3100-0410 and 3100-0402, total n = 17).

Additional analyses were performed on 697 subjects enrolled in key pivotal and dose-ranging efficacy studies (Studies 3000-0520, 3000-0522, and 3000-0524), of whom 613 patients received fospropofol and 334 patients were administered fospropofol according to the proposed dosing guidelines. Relevant safety comparisons drawn from the pivotal trials were limited by the size of the dataset and the small overall number of adverse events (AEs).

Safety was assessed across treatment groups by assessing, clinical laboratory values, vital signs, ECG recordings, AEs, serious adverse events (SAEs), and the need for respiratory interventions. There were few clinically significant changes in laboratory values attributable to study drug. There were 10 deaths overall during the clinical development program, 9 of which occurred in subjects who received fospropofol. None were considered to be related to study drug. There were 10 cases reported where manual ventilation or mechanical ventilation was required, all in subjects who had received a dose of fospropofol. All but one of the cases requiring supportive ventilation occurred with early dosing regimens.

It should be noted that the Agency's assessment of this submission is ongoing, and the content of the briefing document reflects this reality. Our current assessment is not in substantial disagreement with the Applicant regarding the data or the findings contained in this application, although a final assessment has not been made.

We are interested in having the committee address whether the applicant has presented adequate data to support the safety of the administration of fospropofol by persons without training in the administration of general anesthesia. Factors that may be considered in this assessment would include the patient population, the procedures that were studied, and any differences between the way a product is administered in the setting of a clinical trial and how it would be administered in the setting of clinical practice.

We ask the Committee to consider the issues identified in its deliberations over the need for additional information about this product, including any potential safety concerns that may arise were the product to be approved and used in the general population.

Summary of FDA Review of Clinical Efficacy & Safety

Efficacy

A dose-ranging study and two pivotal studies conducted by the applicant were particularly relevant to the efficacy evaluation of fospropofol. The endpoints and protocol methodology for each of these studies were similar. The total study enrollment was 697 subjects, of whom 613 received a dose of fospropofol. Earlier studies of clinical pharmacology and dosing were conducted to evaluate the doses of fospropfol selected for the Applicant's pivotal trials or to study special populations such as the elderly, patients with cardiac or pulmonary disorders, or subjects in the intensive care unit. Early studies were notable for a high incidence hypoxia and several cases of respiratory arrest. Subsequently, the findings of a new dose-ranging study lead to revised dosing regimen. The design of pivotal studies was also revised utilizing a dose control and additional assessments to evaluate the respiratory interventions required to administer fospropofol safely.

Endpoints:

The general objective was to determine whether administration of fospropofol resulted in a measurable sedative hypnotic effect and that this effect offered a benefit to patients.

The primary efficacy endpoint for the following studies was: Successful sedation defined as having 3 consecutive Modified OAS/S scores ≤ 4 and completing the procedure without requiring alternative sedative medications and without requiring manual or mechanical ventilation.

Secondary endpoints included patient and physician ratings of sedation adequacy, recall being awake during the procedure, administration of alternative sedation medication, analgesic supplementation, and assessments of recovery.

Sedation Methodology:

Fentanyl, 50 mcg IV, was administered as pretreatment and additional doses of 25 – 50 mcg were given if the patient experienced pain during the procedure at intervals of not less than ten minutes.

In order to titrate the sedation medication, the study protocols recognized 2 distinct phases of sedation: Sedation Initiation and Sedation Maintenance.

In the Sedation Initiation Phase, an initial dose and up to 4 supplemental doses of fospropofol/saline or midazolam were administered to reach minimal-to-moderate sedation (Modified OAA/S score ≤ 4). Midazolam supplements were administered every 2 minutes while active fospropofol supplements were administered only every 4 minutes. In order to maintain blinding, the fospropofol arms received a corresponding volume of sterile saline at 2 minutes and at 6 minutes. Supplemental boluses could have been administered in the Initiation Phase at 25% of the initial dose (fospropofol treatment

arms) and at 1 mg/dose (midazolam arm). When the patient reached Modified OAA/S score ≤4, the Investigator was to start the procedure.

In the Sedation Maintenance Phase, supplemental doses of sedative medication [25% of the initial bolus (fospropofol arms) or at 1 mg/dose (midazolam arm)] were permitted to be administered at intervals of ≥4 minutes, if a patient's Modified OAA/S score was ≥4 and the patient demonstrated purposeful movement.

Dose-Ranging Study 3000-520 A randomized, double-blind, dose-response study to assess the efficacy and safety of Aquavan Injection for procedural sedation in patients undergoing colonoscopy.

This study was conducted to develop new dose response information because earlier studies intended to evaluate fospropofol were discontinued because of an unacceptably high frequency of hypoxia and cases of respiratory arrest. In the current study, 127 patients were randomized into one of four fospropofol dosing arms or a midazolam arm as follows:

Dosing in Treatment Arms of Study 3000-520

Study Arm	Initial Bolus	Supplemental Doses
Fospropofol arm 1, n = 24	8 mg/kg	2.00 mg/kg
Fospropofol arm 2, n = 26	6.5 mg/kg	1.63 mg/kg
Fospropofol arm 3, n = 26	5 mg/kg	1.25 mg/kg
Fospropofol arm 4, n = 25	2 mg/kg	0.50 mg/kg
Midazolam arm, n = 26	0.02 mg/kg	1.0 mg

No patient was discontinued from the study prior to the administration of study drug. Two of 127 patients (one each in the 6.5 mg/kg and 8 mg/kg starting dose groups) were discontinued from the study after administration of study drug. The reported reason for discontinuation was "lost to follow-up" for both patients. One patient in the midazolam group did not complete the colonoscopy procedure because of patient discomfort.

Pivotal Study 3000-522 A Phase 3, Randomized, Double-Blind, Dose-Controlled Study To Assess The Efficacy And Safety Of Aquavan® (Fospropofol Disodium) Injection For Minimal-To-Moderate Sedation In Patients Undergoing Colonoscopy.

This study was conducted to evaluate the efficacy of fospropofol by comparing a higher-dose to a lower-dose regimen. The midazolam arm was not included to evaluate efficacy, but was intended to provide a comparator for fospropofol of an approved sedation product with its labeled dosing. A total of 314 patients were randomized with 102 patients to a 2.0 mg/kg starting dose of fospropofol, 160 patients randomized to a 6.5 mg/kg starting dose of fospropofol and 52 patients randomized to the midazolam arm.

Dosing in Treatment Arms of Study 3000-522

Treatment Group	Initial Bolus	Each Supplemental Dose
Fospropofol Dose 1:	2.0 mg/kg No less than 120 mg No more than 180 mg	0.5 mg/kg No less than 30 mg No more than 45 mg
Fospropofol Dose 2:	6.5 mg/kg No less than 390 mg No more than 585 mg	1.63 mg/kg No less than 97.5 mg No more than 146 mg
Midazolam:	0.02 mg/kg Not to exceed 2.5 mg	1.0 mg

No patients were discontinued after study drug administration.

Pivotal Study 3000-524 A Phase 3 randomized, double-blind, dose-controlled study to assess the efficacy and safety of Aquavan (fospropofol disodium) injection for minimal-to-moderate sedation in patients undergoing flexible bronchoscopy.

This was a study intended to evaluate the efficacy of fospropofol in a different population, comprised predominantly of patients with serious pulmonary disease who tended to be older and had more serious comorbid conditions than colonoscopy patients. It is similar in design and assessments to Study 3000-0522 except that a midazolam arm was not included. Topical lidocaine was also administered to anesthetize the airways.

Two hundred and fifty-six patients were randomized with 103 patients in the 2.0 mg/kg fospropofol starting dose arm and 153 patients in the 6.5 mg/kg fospropofol starting dose arm. No patients were discontinued after study drug administration.

Summary of Efficacy Findings**:**
Below is a summary table of evaluations of the primary efficacy endpoint from the pivotal efficacy trials 3000-520, -522, and -524.

Summary Table of Efficacy

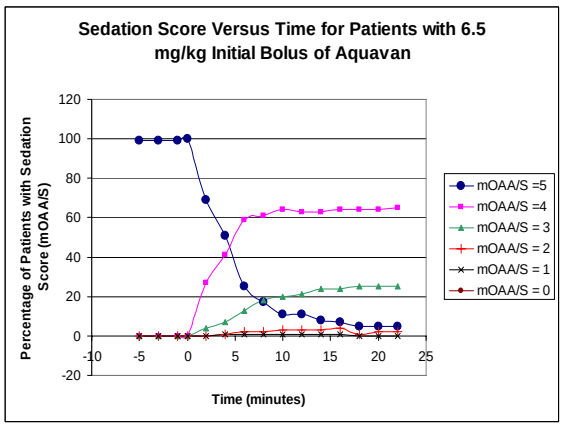
	Study Groups: Randomized Initial Bolus Dose						**Comparison**	
	Fospropofol					**Midazolam**	**Fospropofol** 6.5 mg/kg vs 2 mg/kg	
Procedure	Study	2 mg/kg (Total=229) n/N (%)	5 mg/kg (Total=26) n/N (%)	6.5 mg/kg (Total=334) n/N (%)	8 mg/kg (Total=24) n/N (%)	0.02 mg/kg (Total=78) n/N (%)	Difference in % and 95% CI	Fisher's Exact p-Value
		Sedation Success						
Colonoscopy	3000-0520	6/25 (24)	9/26 (35)	18/26 (69)	23/24 (96)	21/26 (81)	45 (21, 70)	0.002
	3000-0522	26/102 (26)	N/A	137/158 (87)	N/A	36/52 (69)	61(51, 71)	<0.001

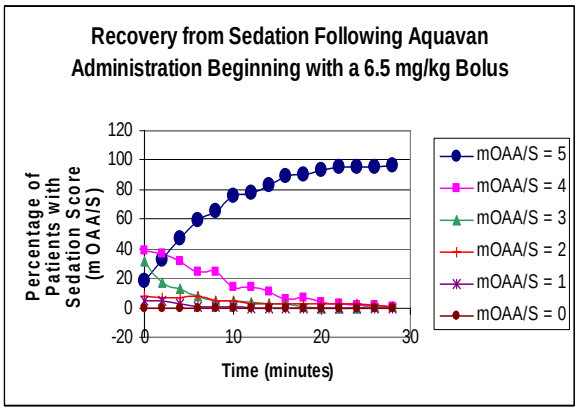
	Study Groups: Randomized Initial Bolus Dose						Comparison	
	Fospropofol					Midazolam	Fospropofol 6.5 mg/kg vs 2 mg/kg	
Procedure	Study	2 mg/kg (Total=229) n/N (%)	5 mg/kg (Total=26) n/N (%)	6.5 mg/kg (Total=334) n/N (%)	8 mg/kg (Total=24) n/N (%)	0.02 mg/kg (Total=78) n/N (%)	Difference in % and 95% CI	Fisher's Exact p-Value
		Sedation Success						
Bronchoscopy	3000-0524	28/102 (28)	N/A	133/150 (89)	N/A	N/A	61 (51, 71)	<0.001

The Applicant's primary and secondary efficacy analysis all demonstrated a significant treatment effect that favored fospropfol administered with an initial dose of 6.5 mg/kg and supplemental doses of 1.63 mg/kg compared with an initial dose of 2.0 mg/kg and supplemental doses of 0.5 mg/kg.

The timing of onset and recovery following fospropofol administration among is illustrated in the following figures.

Effect of Fospropofol Disodium Injection at the Proposed Dosing on the Modified Observer Assessment Sedation Score Among Patients Having Bronchoscopy





Safety

The safety review of the fospropfol NDA was still in progress at the time this briefing document was prepared. This summary of the findings to date is therefore provided and will be updated, if necessary, with an FDA clinical safety presentation during the Committee's meeting.

The safety data collected in the eleven studies conducted during the fospropfol clinical development program have been analyzed in a manner appropriate for the trial designs and for the safety assessments generally required for an NDA and specifically useful for an anesthetic product.

Pooled Data from the key dose-ranging and dose-controlled studies (3000-520, -522, -524): Data were pooled from the three trials in which the proposed dosing regimen for fospropfol was compared to alternative dosing. Safety endpoints included the nature, frequency, and indication of airway assistance. The percent of time that patients were able to demonstrate purposeful movement, vital signs, laboratory parameters, adverse events, and concomitant medications were also reported. These data allowed for an analysis of dose response, with particular interest on the proposed marketing doses of fospropfol: 6.5 mg/kg initial bolus followed by 1.63 mg/kg supplementary doses, with dosing extremes bounded for patients weighing $\geq$ 90 or $\leq$ 60 kg, reduced by 25% for geriatric patients (> 65 years) and for patients classified as ASA III or IV. A person skilled in airway management (such as a respiratory therapist, a study nurse, or a clinician) and authorized by the facility in which the procedure was performed was immediately available during the conduct of the study. All patients were placed on supplemental oxygen via nasal cannula (4 L/min), and placed on an electrocardiogram (ECG) monitor, pulse oximeter, and a blood pressure monitor prior to administration of study medication. In general, safety was assessed by the Applicant across trials by the reporting of adverse events (AEs), and assessment of changes from baseline in clinical laboratory values, vital signs, and electrocardiograms (ECGs).

Hypoxia, defined as a peripheral oxygen saturation of < 90% for > 30 seconds, occurred in 4% (13/334) of patients. Hypotension, defined as a systolic blood pressure < 90 mm Hg and requiring medical intervention, occurred in 5% (16/334) patients. Airway management particularly relevant to the maintenance of oxygenation and spontaneous ventilation were specifically assessed by the applicant.

Airway Management in Key Clinical Trials (3000-520, -0522, -0524)

	Pooled Studies		**Colonoscopy Studies**		**Bronchoscopy Study**	
	Dose of Fospropofol		**Dose of Fospropofol**		**Dose of Fospropofol**	
Type of Airway Management	**2.0 mg/kg (N=229) n (%)**	**6.5 mg/kg (N=334) n (%)**	**2.0 mg/kg (N=127) n (%)**	**6.5 mg/kg (N=184) n (%)**	**2.0 mg/kg (N=102) n (%)**	**6.5 mg/kg (N=150) n (%)**
Any airway management	15 (6.6)	35 (10.5)	1 (0.8)	3 (1.6)	14 (3.7)	32 (21.3)
Manual ventilation	0	1 (0.3)	0	0	0	1 (0.7)
Suction	0	2 (0.9)	0	0	0	3 (2.0)
Chin lift	2 (0.9)	6 (1.8)	1 (0.8)	1 (0.5)	1 (1.0)	5 (3.3)
Jaw thrust	3 (1.3)	2 (0.6)	0	0	3 (2.9)	2 (1.3)
Face mask	1 (0.4)	1 (0.3)	0	0	1 (1.0)	1 (0.7)
Tactile stimulation	1 (0.4)	4 (1.2)	0	0	1 (1.0)	4 (2.7)
Verbal stimulation	2 (0.9)	8 (2.4)	0	2 (1.1)	2 (2.0)	6 (4.0)
Patient repositioning	0	3 (0.9)	0	0	0	3 (2.0)
Increased oxygen flow	12 (5.2)	28 (8.4)	0	0	12 (11.8)	28 (18.7)

In the Applicant's analysis, sedation-related adverse events, including apnea, hypoxia, hypotension and bradycardia, occurred when patients were able to respond to verbal stimulation (OAA/S score 3).

Hypoxia Occurred In Patients Who Were Responsive To Verbal Stimulation

	Pooled Studies						
Modified OAA/S Score at Time of SRAE	**Number of events**	**5 n (%)**	**4 n (%)**	**3 n (%)**	**2 n (%)**	**1 n (%)**	**0 n (%)**
Any SRAE requiring management	61	10 (16.4)	17 (27.9)	19 (31.1)	7 (11.5)	6 (9.8)	2 (3.3)
Apnea	1	0	1 (100)	0	0	0	0
Bradycardia	0	0	0	0	0	0	0
Hypotension	18	5 (27.8)	4 (22.2)	3 (16.7)	4 (22.2)	1 (5.6)	1 (5.6)
Hypoxia	42	5 (11.9)	12 (28.6)	16 (38.1)	3 (7.1)	5 (11.9)	1 (2.4)

Manual ventilation or intubation	**Number of events**	**5 n (%)**	**4 n (%)**	**3 n (%)**	**2 n (%)**	**1 n (%)**	**0 n (%)**
Manual ventilation	3	0	0	2 (66.7)	0	1 (33.3)	0

Furthermore, in the setting of hypoxia, the patient's response was frequently categorized as purposeful, as evidenced by a thumb's up sign when they were stimulated by the investigator.

Retention of Purposeful Responsiveness Did Not Reduce the Frequency of Hypoxia

	Pooled Studies		
Sedation-related adverse event	**Number of Events**	**No Purposeful Response n (%)**	**Purposeful Response n (%)**
Any SRAE requiring management	61	12 (19.7)	49 (8.3)
Apnea	1	0	1 (100)
Bradycardia	0	0	0
Hypotension	18	4 (22.2)	14 (77.8)
Hypoxia	42	8 (19.0)	34 (81.0)

Manual ventilation or intubation	**Number of Events**	**No Purposeful Response n (%)**	**Purposeful Response n (%)**
Any airway management	3	1 (33.3)	2 (66.7)
Manual ventilation	3	1 (33.3)	2 (66.7)

In addition to the routine analyses of adverse events and events specifically related to cardiac and respiratory effects associated with sedation, the Applicant focused special attention on geriatric patients and patients classified as ASA III or IV, because these patients were expected to have a higher incidence of cardiopulmonary adverse events and therefore were prospectively assigned a 25% reduction in bolus and supplementary doses. Hypoxemia was the only TEAE in fospropofol-treated patients that occurred at consistently different frequencies across age, weight, and ASA III/IV subgroups.

- Age: The frequency of hypoxemia increased with increasing age (18 to <65: 6.1%; ≥65: 16.1%, ≥ 75: 28.0%) and, as for the pooled key study population, this was a dose-related event.

- ASA Classification: The frequency of hypoxemia was higher in ASA III/IV patients (17.6%) compared to the total population (8.7%), a finding that was dose-related.

- Weight: The frequency of hypoxemia was higher in patients weighing <60 kg (14.3%) compared to patients who weighed ≥60 kg (≥60 kg to 90kg: 7.8% or >90 kg: 8.0%), and this was a dose-related event in the <60 kg group.

Review of the data thus far has not produced evidence that contradicts the Applicant's finding of relative safety for the proposed marketing doses of fospropfol. In particular, the nature and frequency of adverse events, including respiratory adverse events were limited under the conditions that the studies were conducted.

Safety data from an uncontrolled study of the proposed dosing among patients undergoing a variety of procedures:

Study 3000-0523: Open-Label, Single Arm Study to Assess the Safety of AQUAVAN® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Minor Surgical Procedures

This study consisted of 123 patients undergoing a variety of diagnostic, therapeutic or surgical procedures with the proposed dosing regimen. The procedures included arthroscopy(22, 18%), bunionectomy (18, 15%), esophagogastroduodenoscopy (27, 22%) hysteroscopy (21, 17%), lithotripsy (8, 7%), transesophogeal echocardiography (13, 11%) uteroscopy (10, 8%) , dilation and curettage (3, 2%) and arteriovenous shunt placement (1, 1%). The adverse event profile was similar to the key clinical studies (3000-520, -522 and -524) with airway management required in 5 (4%) of the patients. No patient required manual or mechanical ventilation during sedation. Three patients (2%) experienced ventricular extrasystoles during sedation and one patient experienced hypotension requiring treatment with ephedrine.

Safety data from a thorough QTc study conducted in healthy volunteers:
Study 3000-0521: A Single-Site, Randomized, 4-Sequence, 4-Treatment Crossover Study of a Single Administration of Fospropofol Injection Compared with Placebo and a Positive Control in Healthy Volunteers

There was no clinically significant QTc prolongation with doses as high as 18 mg/kg.

Respiratory safety data from early studies in patients administered a fixed weight-range-based dosing regimen (Studies 3000-409, -0410, -0411, -0412, -0415:

The frequency of all recorded airway interventions in early studies of patients undergoing colonoscopy, bronchoscopy or other minor procedures was approximately 21%. Approximately 9% of the patients required an increase in delivered oxygen flow and approximately 2% were either manually or mechanically ventilated. Approximately twelve percent of the patients experienced hypoxia (peripheral oxygen saturation < 90%). Repositioning of the patient to manage ventilation was required approximately in 13% of the patients. The unacceptably high frequency of required airway management in these studies precipitated a new dose-ranging study (3000-0520) and an individualized dosing regimen based upon patient weight.

Analysis of possible increases in phosphate and formate levels in patients exposed to fospropfol disodium.

For the fospropofol dosage-titration regimen tested in the key studies (3000-0524, 3000-0522, and 3000-0520), increased plasma phosphate level was noted (6% of patients) especially when phosphate-containing bowel preparations had been used for colonoscopy. Mean plasma formate concentrations following fospropofol dosing were similar to predose levels across several studies in patients and in healthy subjects. In patients in the ICU exposed to fospropofol for up to 12 hours (Study 3000-0413), the ophthalmologic examination of the optic nerve was unchanged from baseline.

Summary:
Adverse clinical consequences of hypoxia and or hypoventilation associated with administration of fospropofol at the doses proposed for labeling were generally minimized or avoided by timely preemptive interventions in the clinical studies. A person skilled in airway management was immediately available during these studies. The committee is to consider is how effectively safety in the context of these clinical trials may be extrapolated to the general clinical population likely to be exposed if the product were to be marketed. The committee will also be asked to evaluate whether the person administering fospropofol for sedation should be trained in general anesthesia or whether having an expert in airway management immediately available for assistance is sufficient for patient safety.

Retention of purposeful responsiveness by patients being sedated has been suggested as a clinical marker to identify the boundary between depths of sedation. It is understood that the depth of sedation can not always be precisely controlled by dosing, but is subject to various factors, including inter-patient variability and concomitant surgical stimulation. While it is recognized that depth of sedation is assessed subjectively, the committee should consider whether the new data collected in the clinical trials of fospropofol suggests that retention of purposeful responsiveness is a reliable indicator of depth of sedation that can be used to guide decisions regarding supplementary dosing.

Finally, a higher frequency of respiratory adverse events was present among the patients undergoing bronchoscopy than colonoscopy. This may be a consequence of the fact that the bronchoscopy patients constituted an older population, often with more serious concomitant disease. Also, adverse events were reported more frequently among patients weighing less than 60 kg than the general population. The committee will be asked to consider whether the data submitted is sufficient to inform the dosing recommendations for geriatric patients, patients with cardiopulmonary co-morbidity, and for adult patients weighing less than 60 kg.

Summary of Preliminary Statistical Analyses

Conclusions and Recommendations

This application requests consideration of one dose of Aquavan (6.5 mg/kg) for the indication of sedation in adult patients undergoing diagnostic or therapeutic procedures. The applicant conducted a dose response study and two confirmatory controlled clinical studies to support the efficacy of Aquavan for use in sedation in adult patients undergoing diagnostic or therapeutic procedures. In all three studies, the results for the Aquavan 6.5 mg/kg dose group demonstrated efficacy as measured by the higher proportion of patients meeting the sedation success criteria. The efficacy of Aquavan 6.5 mg/kg was also evident for secondary endpoints evaluating treatment success, patients' memory of being awake during the procedure, physician satisfaction with the level of sedation, and time to being fully alert after the procedure.

Brief Overview of Clinical Studies

This application includes data from three prospectively planned, controlled, randomized, double-blind clinical studies. A Phase 2 dose response study (Study #520) in patients undergoing colonoscopy included five treatment arms: four doses of Aquavan (2, 5, 6.5, and 8 mg/kg) and a midazolam arm. Based on this study, the 6.5 mg/kg dose was selected as the effective dose for the confirmatory trials and the 2 mg/kg dose was selected as a lower dose active comparator. The Phase 3 study in colonoscopy patients (Study #522) included three treatment arms: Aquavan 2 mg/kg, Aquavan 6.5 mg/kg, and midazolam. In each of these studies, the midazolam arm was included for general information and was not planned or intended for efficacy comparisons. The Phase 3 study in patients undergoing a flexible bronchoscopy (Study #524) included the same two Aquavan doses but did not include a midazolam arm.

In all three studies, the primary endpoint was defined as the sedation success rate. Success required that four criteria be met: (i) 3 consecutive Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) scores ≤ 4 after administration of sedative medication and (ii) completing the procedure (iii) without requiring the use of alternative sedative medication and (iv) without requiring manual or mechanical ventilation. The MOAA/S scale has six levels (scores 0-5). A score of 0 denotes non-responsive and 5 denotes fully alert. Important secondary endpoints included treatment success, patients' memory of being awake during the procedure, physician satisfaction with the level of sedation, and time to fully alert after the procedure.

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized, received at least one dose of study treatment and had at least one postdose clinical assessment. Only 6 randomized patients were not included in the mITT population (2 in study #522; 4 in study #524).

Support for efficacy was tested by the pairwise comparison of the Aquavan 6.5 mg/kg group to the Aquavan 2.0 mg/kg group. Fisher's Exact test was used for the primary efficacy endpoint.

Findings

In all three studies, the 6.5 mg/kg dose was statistically significantly better than the 2 mg/kg dose for the sedation success rate. Success rates in the Aquavan 6.5 mg/kg groups ranged from 69% to 89%, compared to 24% to 28% in the Aquavan 2 mg/kg groups. Additional secondary endpoints also supported efficacy for the 6.5 mg/kg dose. The results are presented in Tables 1-3 for studies 520, 522, and 524 respectively, and provide sufficient information to conclude Aquavan 6.5 mg/kg is efficacious for this indication.

Table 1: Study 520 (Phase 2; Colonoscopy) Efficacy Analysis Results

		Aquavan 6.5 mg/kg n=26	Aquavan 2.0 mg/kg n=25
Primary Endpoint: Sedation Success Rate	n/N % Difference p-value	18/26 69% 45% p<0.001	6/25 24%
Secondary Endpoints:			
Treatment Success Rate	n/N %	21/26 81%	9/25 36%
Proportion of patients who required alternative sedative medication	n/N %	5/26 19%	16/25 64%
Proportion of patients who did not recall being awake	n/N %	15/26 58%	10/25 40%
Proportion of patients who required supplemental analgesic medication	n/N %	14/26 54%	19/25 76%
Proportion of physicians who rated high overall satisfaction at sedation initiation	n/N %	10/26 38%	3/25 12%
Proportion of physicians who rated high overall satisfaction at end of procedure	n/N %	7/26 27%	2/25 8%
Time to sedation (minutes)	Mean Median Range	7 6 0, 18	12 12 0, 22
Time to fully alert (minutes)	Mean Median Range	8 7 0, 30	7 5 0, 29

Source: Clinical Study Report 3000-0520

Table 2: Study 522 (Phase 3; Colonoscopy) Efficacy Analysis Results

		Aquavan 6.5 mg/kg N=158	Aquavan 2.0 mg/kg N=102
Primary Endpoint: Sedation Success Rate	n/N % Difference p-value	137/158 87% 61% p < 0.001	26/102 25%
Secondary Endpoints:			
Treatment Success Rate	n/N %	139/158 88%	29/102 28%
Proportion of patients who required alternative sedative medication	n/N %	19/158 12%	73/102 72%
Proportion of patients who did not recall being awake	n/N %	83/158 53%	45/102 44%
Proportion of patients who required supplemental analgesic medication	n/N %	87/158 55%	78/102 76%
Proportion of physicians who rated high overall satisfaction at sedation initiation	n/N %	61/158 39%	4/102 4%
Proportion of physicians who rated high overall satisfaction at end of procedure	n/N %	82/158 52%	15/102 15%
Time to sedation (minutes)	Mean Median Range	9 8 2, 28	17 18 0, 34
Time to fully alert (minutes)	Mean Median Range	7 5 0, 47	7 3 0, 54

Source: Clinical Study Report 3000-0522

Table 3: Study 524 (Phase 3; Flexible Bronchoscopy) Efficacy Analysis Results

		Aquavan 6.5 mg/kg n=150	Aquavan 2.0 mg/kg n=102
Primary Endpoint: Sedation Success Rate	n/N % Difference p-value	133/150 89% 61% p<0.001	28/102 27%
Secondary Endpoints:			
Treatment Success Rate	n/N %	137/150 91%	42/102 41%
Proportion of patients who required alternative sedative medication	n/N %	12/150 8%	60/102 59%
Proportion of patients who did not recall being awake	n/N %	125/150 83%	56/101 55%
Proportion of patients who required supplemental analgesic medication	n/N %	25/150 17%	38/102 37%
Proportion of physicians who rated high overall satisfaction at sedation initiation	n/N %	83/150 55%	12/102 112%
Proportion of physicians who rated high overall satisfaction at end pf procedure	n/N %	93/150 62%	23/102 23%
Time to sedation (minutes)	Mean Median Range	6 4 2, 22	14 18 0, 30
Time to fully alert (minutes)	Mean Median Range	8 6 0, 61	9 3 0, 114

Source: Clinical Study Report 3000-0524

Table 4 provides additional descriptive information on the number of patients in the three efficacy studies who had Modified OAA/S scores of 1 or 0 at any time after the first dose of study medication. A score of 1 denotes "Responds only after painful trapezius squeeze" and a score of 0 denotes "Did not respond to painful trapezius squeeze." Sedation in the 2-4 range (responds to name or mild prodding/shaking) was preferred during the procedures in the clinical studies. The results for the midazolam arm in each study are included for descriptive purposes only. The studies were not designed for any comparisons of Aquavan treatment groups to the midazolam groups.

Table 4: Patients Who had MOAA/S Scores of 0 or 1

		Aquavan 6.5 mg/kg	Aquavan 2.0 mg/kg	Midazolam 0.02 mg/kg
Study #520	n/N %	1/26 4%	2/25 8%	1/26 4%
Study #522	n/N %	6/158 4%	1/102 1%	0/52 0%
Study #524	n/N %	24/150 16%	8/102 8%	NA

Source: SAS datasets

Clinical Pharmacology Summary

Fospropofol disodium injection is an aqueous formulation intended for intravenous (IV) administration. Fospropofol disodium (Mol. Wt. 332.24) is a water-soluble, phosphono-O-methyl prodrug form of propofol (Mol. Wt. 178.27).

Pharmacokinetics of Fospropofol and Propofol

Upon intravenous bolus administration, fospropofol plasma concentrations decrease in a biphasic manner with an initial decline followed by a relatively slower terminal phase ($t_{1/2}$ of 0.8 hours). Fospropofol remains preferentially in the extracellular component of blood (blood-to-plasma ratio ~ 0.5) and is highly bound (97 -98%) to plasma proteins at clinically observed concentrations (0.01 – 10 μg/mL). Fospropofol and propofol have a volume of distribution of about 0.39 and 5.3 L/kg, respectively. Upon administration of ^{14}C-fospropofol in Long Evans rats, significant amounts of radioactivity were found in the brain, the purported site of action. This indicates that the fospropofol-derived moieties cross the blood-brain barrier and the active moiety is thought to be propofol. Fospropofol is metabolized by alkaline phosphatase into propofol, formaldehyde and phosphate. In vitro studies indicate that more than 66% of fospropofol disappears within 5 minutes of incubation with alkaline phosphatase at 37^{o}C. The peak plasma concentrations of propofol are noted around 8 minutes following fospropofol administration (See Figure 1). Fospropofol and propofol have a short elimination half life of about 0.8 and 2 hrs, respectively. Mass balance study conducted in humans after oral administration of ^{14}C-fospropfol revealed that 65% of radioactivity is recovered in urine by 48 hours. While fospropofol and propofol were undetectable in urine, propofol-glucuronide was detected as the major metabolite along with two minor metabolites characterized as hydroxypropofol-glucuronides No.1 and No.2. The major metabolite, propofol-glucuronide appears to persist in plasma longer than fospropofol or propofol. In the IV bolus dose range of 6 – 18 mg/kg, dose-proportional increase in AUC of fospropofol was noted, although increase in C_{max} and AUC of propofol was slightly more than dose-proportional (See table below).

Mean (standard deviation) Pharmacokinetic Parameters in Healthy Subjects (Studies 3000-0625 and 3000-0521)

Study number	C_{max} (μg/mL)	T_{max}[1] (min)	$t_{1/2}$ (h)	AUC_{0-Inf} (μg.h/mL)	CL_p (L/h/kg)	V_d (L/kg)
Fospropofol						
AQUAVAN 6 mg/kg						
3000-0521 N =68	78.7 (15.4)	4.0 (1.0 – 8.0)	0.81 (0.08)	19.2 (3.59)	0.280 (0.0528)	0.327 (0.0686)
AQUAVAN 10 mg/kg						
3000-0625 N =12	114 (17.5)	4.0 (1.0 – 6.0)	0.84 (0.09)	27.1 (3.90)	0.326 (0.0491)	0.395 (0.0759)
AQUAVAN 18 mg/kg						
3000-0521 N =68	211 (48.6)	2.0 (1.0 – 6.0)	0.81 (0.09)	50.3 (8.4)	0.320 (0.0585)	0.374 (0.0724)
Propofol						
AQUAVAN 6 mg/kg						
3000-0521 N =68	1.08 (0.33)	12.0 (4.0 – 60.0)	2.06 (0.77)	1.70 (0.290)	1.95 (0.345)	5.76 (2.14)
AQUAVAN 10 mg/kg						
3000-0625 N =12	2.20 (0.413)	8.0 (4.0 – 13.0)	2.09 (0.62)	3.07 (0.490)	1.79 (0.313)	5.29 (1.49)
AQUAVAN 18 mg/kg						
3000-0521 N =68	3.90 (0.822)	8.0 (4.0 – 60.0)	1.76 (0.54)	5.67 (1.28)	1.79 (0.390)	4.46 (1.38)

Note: C_{max}=maximal concentration; AUC=area under the concentration-time curve; T_{max}=time to Cmax; $t_{1/2}$=elimination half-life; For propofol CL_p and V_d are CL_p/F and V_d/F

[1] Tmax data are median (minimum, maximum)

Pharmacokinetics and Pharmacodynamics of Fospropofol and Propofol

The pharmacokinetics and pharmacodynamics of Fospropofol disodium (10 mg/kg bolus) and Diprivan (50 mg/min infusion) were compared in healthy volunteers in Study # 625. In the first period, subjects received a 10 mg/kg bolus IV dose of fospropofol disodium injection. The pharmacodynamic endpoints for the level of sedation were the bispectral (BIS) Index (see Figure 2) and Modified Observer's Assessment of Alertness/Sedation (MOAA/S) (see Figure 3). A BIS value near 100 indicates that the subject was awake, and a BIS value of 0 indicated isoelectric EEG or the absence of brain activity. MOAA/S evaluation placed a grading score of 0 (nonresponsive) to 5 (alert) in the category of responsiveness. In the second period, after a 7-day washout period, each subject received a 50-mg/min infusion of propofol injectable emulsion targeted to produce the same peak EEG effect that was observed in that subject after administration of 10-mg/kg fospropofol disodium injection. The propofol dose derived from fospropofol disodium injection treatment (dose corrected for molecular weight=5.36 mg/kg) was higher compared with the propofol dose from treatment with propofol injectable emulsion (50 mg/minute infused for 2.06 to 4.60 minutes, total mean ± SD dose of 2.30 ± 0.39 mg/kg). The results are discussed in figures 1 to 3.

Figure 1

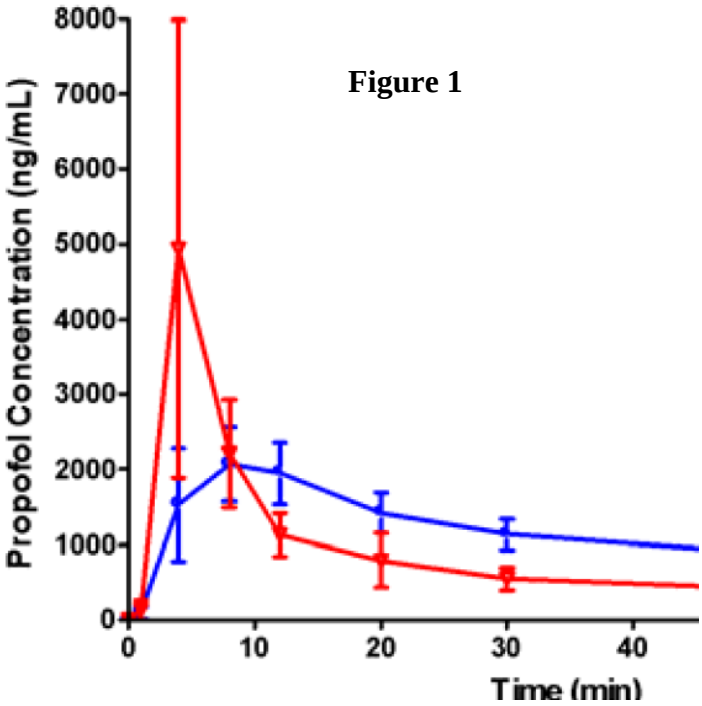


Figure 1 presents the mean propofol concentration over time profile upto 45 minutes following administration of Diprivan 50 mg/min (red inverted triangles and line) and Fospropofol disodium 10 mg/kg (blue circles and line).

Fospropofol PK profile is not indicated in this figure. Propofol plasma concentration profiles were different for the 2 treatments. Following administration of a single IV bolus dose of fospropofol, the median T_{max} for propofol was reached at a slightly later time than it was following Diprivan administration by infusion. Following fospropofol dosing, the

mean propofol C_{max} was lower and mean $AUC_{0\text{-}inf}$ was higher than following Diprivan treatment without molar equivalent dose or bodyweight normalization. Following administration of an IV infusion of Diprivan 50 mg/min, plasma concentrations of propofol reached C_{max} at a median T_{max} of 4.0 minutes. The propofol concentration increased rapidly, and then declined after the infusion was stopped.

Figure 2

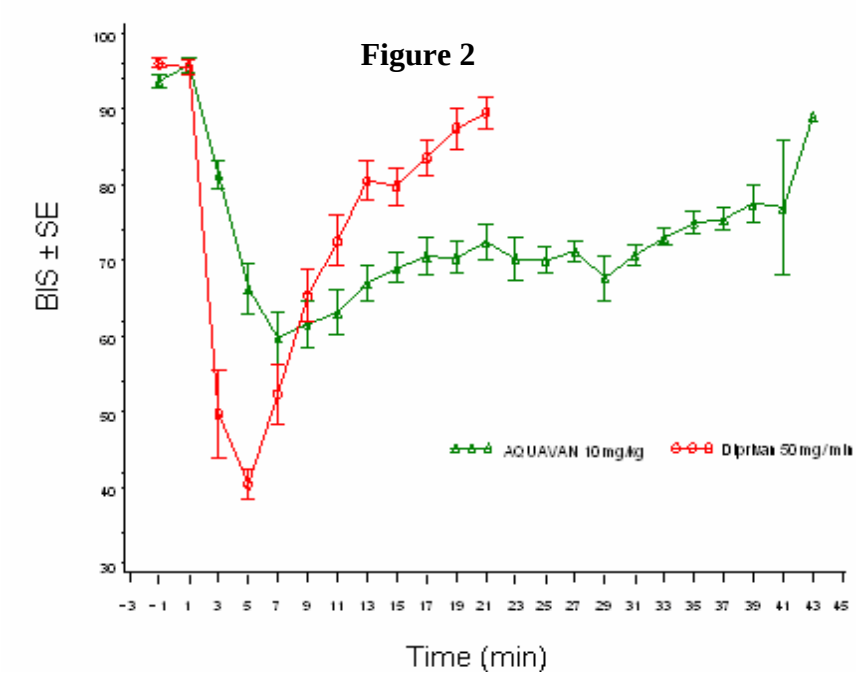


Figure 2 presents the mean BIS scores over time (±standard error [SE]) for the Fospropofol disodium 10 mg/kg (Green Open triangles and line) and Diprivan 50 mg/min (Red Open Circles and line) treatment groups from first dose of study medication to the last time point recorded (45 minutes).

Subjects treated with Diprivan reached their lowest BIS scores at about 5 minutes (median) after drug administration and recovered (to a BIS of approximately 90) at about 21 minutes, when measurements were terminated. The dose of Diprivan was targeted to match the pharmacodynamic effect of a single dose of fospropofol 10 mg/kg. However, subjects treated with Diprivan went to a lower BIS score than those treated with fospropofol. Peak effect for fospropofol was reached at 7 minutes (median) following drug delivery. At 21 minutes after fospropofol administration BIS scores for the majority of subjects had not returned to ≥90. Recovery from sedation, as judged by BIS score, was slower after fospropofol disodium administration than after Diprivan infusion.

Figure 3

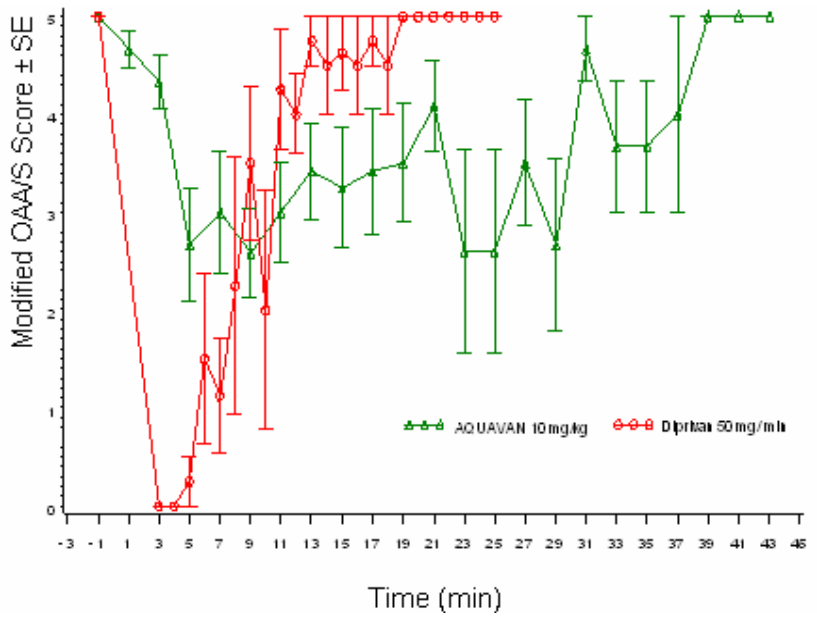


Figure 3 represents the mean changes in MOAA/S scores versus time after Fospropofol disodium 10 mg/kg (Green Open triangles and line) and Diprivan 50 mg/min (Red Open circles and line).

MOAA/S scores reached a lower value and recovered faster in subjects after Diprivan treatment than after fospropofol administration. After fospropofol treatment, subjects spent a longer period of time at MOAA/S scores of 2 to 4 than they did following treatment with Diprivan.

Effect of prognostic factors on PK of fospropofol, propofol

Pharmacokinetic analysis of fospropofol and propofol suggested dependence of clearance on total body weight. Age, Race and Alkaline phosphatase concentrations did not influence the pharmacokinetics of fospropofol and propofol.

Effect of Fospropofol on QT prolongation

In a randomized, open-label, positive- and placebo-controlled crossover study, 68 healthy subjects were administered single IV bolus dose of fospropofol disodium 6 mg/kg, Fospropofol disodium 18 mg/kg (3-times the recommended dose), placebo and a single oral dose of 400 mg moxifloxacin. At the anticipated clinical dose of 6 mg/kg, no significant effect on the QTcF was detected.

Following the 18 mg/kg dose, the largest upper bound of the two-sided 90% CI for the ΔΔQTcF at the 12-minute time point was greater than 10 ms which is identified as the threshold for regulatory concern in the ICH E14 guideline.

The overall findings are summarized in the following table.

FDA Analysis: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for AQUAVAN (AQUAVAN 6 mg/kg and 18 mg/kg and the Largest Lower Bound for Moxifloxacin

Treatment	Time (min)	ΔΔQTcF (ms)	90% CI (ms)
AQUAVAN 6 mg	12	2.2	-1.7, 6.2
AQUAVAN 18 mg	12	8.3	4.5, 12.1
Moxifloxacin	180	12.2	5.7, 18.0*

*CI is adjusted with 11 post-baseline time points

Points for Discussion

- In the ASA Practice Guidelines for Sedation and Analgesia by Non-Anesthesiologists, retention of purposeful responsiveness is used to demarcate levels of sedation and their associated risk. These guidelines suggest that practitioners should be able to safely manage patients who become more deeply sedated than intended and are therefore at risk for airway complications. Do the clinical trial data support that retention of purposeful responsiveness is a reliable indicator of depth of sedation so as to allow practitioners to make appropriate and safe decisions regarding supplemental dosing of fospropofol disodium?

- Adverse events, particularly respiratory adverse events were observed with higher frequency among geriatric patients, patients with cardiopulmonary morbidities and/or patients having a low body weight. Are additional data needed for these patient populations in order to provide appropriate dosing guidelines?

- Do these data suggest that fospropofol disodium sedation can be safely managed by health care providers without training in general anesthesia?

Appendix 1

Modified Observer Sedation Scale (Modified OAA/S)

Responsiveness	Score
Responds readily to name spoken in a normal tone	5 (Alert)
Lethargic response to name spoken in a normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after a painful trapezius squeeze	1
Does not respond to a painful trapezius squeeze	0

References

1. American College of Gastroenterology, American Gastroenterological Association and American Society of Gastrointestinal Endoscopy Consensus on Recommendations for Sedation During Endoscopic Procedures. **<www.gastro.org/wmspage.cfm?parm1=371>**

2. ASA Practice Guidelines for Sedation and Analgesia by Nonanesthesiologists. Approved 2001. **<www.ASAhq.org/publicationsAndServices/sedation1017.pdf>**.

3. ASA Position on Monitored Anesthesia Care. Approved 1986; last amended 2003. **<www.ASAhq.org/publicationsAndServices/standards/23.pdf>**.

4. ASA Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia. Approved 1999; last amended 2004. **<www.ASAhq.org/publicationsAndServices/standards/20.pdf>**.

5. ASA Statement on Safe Use of Propofol. Approved 2004. **<www.ASAhq.org/publicationsAndServices/standards/37.pdf>**.

6. Green SM, Krauss B. Propofol in emergency medicine: Pushing the sedation frontier. *Ann Emerg Med*. 2003; 42:792-797.

7. Heuss LT, Schnieper P, Drewe J, et al. Risk stratification and safe administration of propofol by registered nurses supervised by the gastroenterologist: A prospective observational study of more than 2000 cases. *Gastrointest Endosc.* 2003; 57:664-671.

8. Rex DK, Overley C, Kinser K, et al. Safety of propofol administered by registered nurses with gastroenterologist supervision in 2000 endoscopic cases. *Am J Gastroenterol.* 2002; 97:1159-1163.

9. Walker JA, McIntyre RD, Schleinitz PF, et al. Nurse-administered propofol sedation without anesthesia specialists in 9152 endoscopic cases in an ambulatory surgery center. *Am J Gastroenterol*. 2003; 98:1744-1750.

10. Yagiela JA. Making patients safe and comfortable for a lifetime of dentistry: Frontiers in office-based sedation. *J Dent Educ*. 2001; 65: 1348-1356.