4.3.14 Study 3000-0625 Synopsis

Study Title: A Phase 1, Open Label, Single Dose, Crossover Pharmacokinetic/Pharmacodynamic Study of AQUAVAN® (Fospropofol Disodium) Injection Versus DIPRIVAN® In Healthy Volunteers
Investigator(s) and Study Center(s): This study was done at a single site [redacted]
Publication (reference): see Appendix 16.1.11
Studied Period: 07 September 2006 (first subject enrolled) to 30 September 2006 (last subject completed)
Phase of Development: 1
Objective: To compare descriptively the pharmacokinetic (PK)/pharmacodynamic (PD) profiles of propofol when liberated from AQUAVAN® (fospropofol disodium) Injection (hereafter referred to as AQUAVAN) with those of DIPRIVAN® (propofol) Injectable Emulsion (hereafter referred to as Diprivan) in healthy volunteers.
Methodology: This is an open-label, 2-period, single sequence, crossover PK/PD study of AQUAVAN versus Diprivan in 12 healthy volunteers (6 male, 6 female). Subjects were screened for enrollment up to 28 days prior to dosing. In the first period, volunteers received a 10 mg/kg bolus intravenous (i.v.) dose of AQUAVAN. The maximal electroencephalogram (EEG) effect reached in each volunteer was recorded, as measured by the minimal bispectral (BIS) Index. In the second period, after a 7-day washout period, each volunteer received a 50 mg/min infusion of Diprivan targeted to produce the same peak EEG effect that was observed in that volunteer after administration of AQUAVAN 10 mg/kg. The dose of Diprivan administered was not allowed to exceed the label recommendation. Assessment of depth of sedation (using Modified Observer's Assessment of Alertness and Sedation [OAA/S] scale and BIS index), evaluation of purposeful movement, and vital signs in all subjects were documented 1 minute prior to and 1 minute following study drug administration, and at 2 minute intervals thereafter until 20 minutes postdose or until the subject reached Fully Alert status, whichever was later. Twelve venous blood samples were collected for the determination of plasma concentrations of fospropofol and propofol following an i.v. bolus dose of 10 mg/kg of AQUAVAN in Period 1 and for determination of propofol following i.v. infusion (50 mg/min) of Diprivan in Period 2 at predose and at 1, 4, 8, 12, 20, 30, 60, and 90 minutes and 2, 3, and 4 hours after dosing.

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An anesthesiologist was present during both treatment periods for the safety of the subjects.
Number of Subjects (Planned and Analyzed): Twelve healthy subjects were planned (6 male and 6 female); 12 subjects were analyzed for safety; 12 subjects were included in the analyses of PK variables.
Diagnosis and Main Criteria for Inclusion: Volunteers were 18 to 45 years of age, inclusive, with a body mass index (BMI) of 18 to 30 kg/m^2, inclusive. Female volunteers were non-pregnant and non-lactating, had a negative serum or urine pregnancy test result prior to enrollment into the trial, and were using appropriate birth control during the duration of the trial.
Test Product, Dose and Mode of Administration, Lot Number: AQUAVAN was supplied as a sterile solution containing 35 mg/mL of fospropofol disodium ready for i.v. injection.. Each subject received a 10 mg/kg bolus dose (Lot No: 900015) intravenously (i.v.).
Duration of Treatment: There were two 2-day treatment periods in the study, separated by a washout period of 7 days. Each administration of study drug took less than one day.
Reference Therapy, Dose and Mode of Administration, Lot Number: The comparator, DIPRIVAN® (propofol) Injectable Emulsion, was supplied in its commercial form, and was administered as a 50 mg/min i.v. infusion, targeted to produce the same peak electroencephalogram (EEG) effect, as that measured by the minimal bispectral (BIS) index observed in that healthy volunteer after administration of AQUAVAN.
Criteria for Evaluation: **Pharmacokinetic variables:** • Area under the plasma concentration-time curve (AUC) from time of dosing to the last quantifiable concentration ($AUC_{0\text{-last}}$) • AUC from time of dosing to infinity ($AUC_{0\text{-inf}}$) • Observed maximum plasma concentration (C_{max}) • Time to achieve C_{max} (T_{max}) • Terminal-phase elimination half-life ($t_{1/2}$) • Total body clearance (CLp or CLp/F) • Apparent volume of distribution (V_d or V_d/F) **Pharmacodynamic (Exploratory) variables:** • Time to minimum BIS score and area above the curve • Time to minimum Modified OAA/S score and area above the curve **Safety:** • Nature, frequency, and indication of airway assistance • Frequency of sedation-related adverse events (SRAEs; ie, apnea, hypoxemia, bradycardia,

hypotension)

- Nature, frequency, seriousness, severity, relationship to treatment, and outcome of all treatment-emergent adverse events (TEAEs)
- Duration subjects do not demonstrate purposeful movement
- Laboratory parameters, saturation of hemoglobin with oxygen in peripheral blood (SpO_2) and vital signs

Statistical Methods:

Two analysis populations were defined in the Statistical Analysis Plan (SAP) for this study:

- The PK analysis population included all subjects who received either AQUAVAN or Diprivan and had at least one postdose PK parameter estimate
- The safety analysis population included all subjects who received at least 1 dose of study medication.

All endpoints were summarized by study drug. For continuous variables, data were summarized with mean, standard deviation (SD), median, and range. For categorical variables, data were tabulated with the number and proportion of subjects in each category.

Because this was a Phase 1 study of explorative nature, no formal hypothesis testing was planned. However, for descriptive purpose, 90% confidence intervals were constructed for the comparisons where appropriate.

Pharmacokinetic Variables:

Pharmacokinetic analyses were based on the PK analysis population. Pharmacokinetic variables ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, $t_{1/2}$, CLp, CLp/F, and V_d or V_d/F) were calculated using non-compartmental analysis, and summarized for each study drug. Descriptive comparisons were made between AQUAVAN and Diprivan treatments.

Pharmacodynamic (Exploratory) Variables:

Minimum BIS and minimum Modified OAA/S scores were summarized by treatment. Times to minimum BIS and to minimum Modified OAA/S scores were listed and summarized by study drug and area above the curve was calculated using trapezoidal calculations, listed by subject and summarized by study drug. Plasma propofol concentrations and BIS index values were described by the Emax model using NONMEM and results are presented in a separate report (3000-0625PKPD).

Safety:

The following safety analyses were based on the safety analysis population:

- The total dose of study medication was calculated by subject and summarized.
- All airway assistance was listed with subject information. The subject incidence was to be summarized and cross-tabulated by associated SRAE.

- The subject incidence of SRAEs (apnea, hypoxemia, bradycardia, and hypotension) was to be summarized and events listed with pertinent subject information.
- All adverse events (AEs) were summarized by preferred term and by preferred term within system and organ class according to the MedDRA dictionary (Version 9.1).
- For TEAEs, an incidence table was presented by maximum severity and relationship to study medication.
- All AEs, TEAEs resulting in study discontinuation, and serious TEAEs were listed with the pertinent subject information.
- The duration that subjects did not have purposeful movement was calculated for each subject and summarized for all subjects. The numbers and percent of subjects who demonstrated no purposeful movement at any timepoint and at 2 consecutive timepoints during the study were summarized.
- For laboratory data, all results outside of the normal range were flagged low or high and flagged values were assessed by the Investigator to establish their clinical significance. Baseline and change from baseline in continuous data from hematology and chemistry tests were summarized at each timepoint. Shifts from baseline laboratory values were tabulated. All abnormal laboratory data were listed by subject.
- Baseline vital signs and the changes from baseline on the day of drug administration were summarized. The number and proportion of subjects whose pulse oximetry values of <90%, <85% and <80% which occurred at any timepoint and at 2 consecutive timepoints were tabulated.
- All abnormal ECG changes were listed by subject with other pertinent information.
- The physical examinations during screening were summarized.

Summary of Results

Pharmacodynamic:

- Subjects treated with AQUAVAN reached a mean minimum BIS score of 54.0 (range: 40-69) at a mean of 8.2 (range: 5-17) minutes following study drug administration. Subjects treated with Diprivan reached a mean minimum BIS score of 37.7 (range: 25-51) at a mean of 4.7 (range: 3-7) minutes after the start of infusion.
- Mean areas above the BIS curve were 769.0 (range: 473-1365) and 591.6 (range: 332-752) following AQUAVAN and Diprivan administrations, respectively.
- The minimum BIS score and time to minimum BIS were not the same for AQUAVAN and Diprivan in this study.
- Subjects treated with AQUAVAN reached a minimum mean Modified OAA/S score of 1.3 (range: 0-3) in 7.2 (range: 1-15) minutes, while subjects treated with Diprivan reached a minimum mean Modified OAA/S score of 0 in 4.2 (range: 3-7) minutes.
- Mean areas above the Modified OAA/S score curve were 41.8 (range: 4-130) and

25.3 (range: 9-51) for AQUAVAN and Diprivan treatments, respectively.

- The minimum Modified OAA/S scores following AQUAVAN and Diprivan treatments were not the same, indicating that the sedative effect of Diprivan in the study was greater than that of AQUAVAN.
- While peak effect (measured by BIS index and Modified OAA/S score) following administration of AQUAVAN was not as great as it was for Diprivan, the duration of effect was longer.

Pharmacokinetic:

Following administration of fospropofol disodium, plasma concentrations of fospropofol rapidly declined after C_{max}. Mean fospropofol concentrations decreased approximately 1.5-fold between 4 minutes and 8 minutes and a 10-fold between 4 minutes and 30 minutes. The initial rapid decline was followed by a terminal phase with a mean $t_{1/2}$ of 0.84 hour. Median T_{max} for fospropofol was observed at 4 minutes (range: 1-6 minutes). Mean C_{max}, $AUC_{0\text{-inf}}$, total body clearance (CL_p) and volume of distribution (V_d) values for fospropofol were 114 µg/mL, 27.1 µg•h/mL, 0.326 L/h/kg, and 0.395 L/kg, respectively. Mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values were similar. The intersubject variability in PK parameters was low (parameter CV% ranged between 11.1-19.2%).

Following a single i.v. bolus dose of AQUAVAN, the propofol median T_{max} was reached at slightly later time (8 minutes, range: 4-13 minutes) than following Diprivan (4 minutes, range: 4-8 minutes). Following AQUAVAN administration, mean propofol C_{max} (2.20 µg/mL) was lower and mean $AUC_{0\text{-inf}}$ (3.07 µg•h/mL) was higher than following Diprivan administration (5.16 µg/mL and 1.72 µg•h/mL, respectively). The propofol dose derived from AQUAVAN treatment (dose-corrected for molecular weight=5.36 mg/kg) was higher than the propofol dose from Diprivan treatment (50 mg/minute infused for 2.06 to 4.60 minutes, total mean [SD] dose of 2.30 [±0.39] mg/kg) which explains the higher propofol exposure ($AUC_{0\text{-inf}}$) following AQUAVAN administration than after Diprivan infusion. AQUAVAN is a prodrug and requires metabolism by alkaline phosphatases in the body, resulting in a gradual increase in propofol concentrations and a relatively lower C_{max}, occurring at a later T_{max}. The intersubject variability in the C_{max} and AUC of propofol derived from AQUAVAN was lower (coefficient of variation [CV]=16.0 to 18.8%) than propofol delivered as Diprivan (CV=24.4 to 53.5%) .

The PK of propofol liberated from AQUAVAN is linear. Therefore, one can compare the C_{max} and AUC of propofol from the 2 treatments by dose-normalization to determine bioavailability (BA). The dose-normalized C_{max} ratio, as expected, was lower (20%) and completely outside of confidence interval (CI) limits (80 to 125%) and the $AUC_{0\text{-inf}}$ ratio was approximately 76% (partially outside of limits) following AQUAVAN treatment compared with those following administration of Diprivan. Apparent total body clearance (CL_p/F) for propofol was slightly higher following AQUAVAN treatment than total body clearance (CL_p) following administration of Diprivan, which suggests that the conversion of fospropofol to propofol was

almost complete. Mean $t_{1/2}$ values were similar (approximately 2 h) following both treatments. The mean apparent volume of distribution (V_d/F) for propofol following AQUAVAN administration was higher than the mean volume of distribution (V_d) following Diprivan treatment.

Safety:

- The mean total dose (SD) of AQUAVAN administered during this study was 698.6 (83.3) mg and the mean total dose (SD) of Diprivan administered was 161.6 (36.7) mg. When calculated as a molar propofol dose, the AQUAVAN bolus resulted in the delivery of a mean dose of 2.102 mmoles of propofol compared with 0.906 mmoles following the Diprivan infusion.
- No death occurred in the study, and no subject experienced a serious AE or was discontinued from the study because of an AE.
- There were no SRAEs reported during this study, although there were 3 subjects who required airway assistance (chin lift, jaw thrust, not associated with any AE) after receiving Diprivan.
- Treatment-emergent AEs were experienced by 100% of subjects treated with AQUAVAN. The most frequently reported events were paresthesia in 11 subjects (91.7%) and pruritus in 6 subjects (50.0%). All episodes of paresthesia and pruritus were mild, of short duration (≤4 min) and resolved without intervention.
- Treatment-emergent AEs were experienced by 25% of subjects after Diprivan administration. The most common TEAE reported was mild dizziness, in 16.7% of subjects.
- All TEAEs reported in this study were considered treatment-related, were mild in severity, and resolved before the end of the study.
- Subjects in the safety population were unable to demonstrate purposeful movement between first dose of study medication and Fully Alert for a mean duration (SD) of 8.5 (8.4) and 8.5 (2.6) minutes after AQUAVAN and Diprivan treatments, respectively.
- After AQUAVAN treatment, 83.3% of subjects were not able to show purposeful movement at one timepoint and 58.3% were without purposeful movement at more than one timepoint. All (100%) subjects treated with Diprivan lost purposeful movement and, for 83.3% of subjects, this loss continued through ≥2 timepoints.
- No subject had a pulse oximetry reading of <90%.

CONCLUSIONS

Pharmacodynamic Conclusion:

This study was designed to descriptively compare a fixed dose of AQUAVAN to an infusion of Diprivan that achieved similar peak EEG effect as measured by minimum BIS index. Since the effect was not well-matched, it is difficult to draw conclusions from comparing the effect profiles of the 2 drugs. Comparison of the PD curves (Modified OAA/S and BIS index over time) confirm qualitatively that, for a given molar dose of propofol administered, AQUAVAN was slightly slower to peak effect, achieved a lower peak effect, but provided a more sustained effect than propofol administered as Diprivan.

Pharmacokinetic Conclusions:

Fospropofol plasma concentration rapidly declined after peak plasma concentration with a short $t_{1/2}$ of less than an hour. Following administration of a single i.v. bolus dose of AQUAVAN, propofol median T_{max} was reached at slightly later time than following Diprivan infusion. Comparable values of propofol total body clearance following both treatments suggest that the conversion of fospropofol to propofol was almost complete. The $t_{1/2}$ values were similar (approximately 2 h) following both administrations. For fospropofol and propofol the intersubject variability in PK was lower based on % CV of PK parameters for AQUAVAN treatment compared with Diprivan treatment.

Safety Conclusion:

AQUAVAN was safe and well tolerated when administered to healthy subjects under the conditions described in this study.

4.3.15 Study 3000-0207 Synopsis

See Analytical section 2.6 regarding propofol assay issue

Title of Study: A Phase 2, Two Part Study of AQUAVAN® Injection in the Presence of Pre-Medication in Patients Undergoing Elective Colonoscopy. Part 1: An Open Label, Adaptive Dose Ranging, Randomized, Multi-Center, Pilot Study of AQUAVAN® Injection Following Pre-Medication with Fentanyl Citrate Injection	
Investigator(s) and Study Centers: Eight investigators in the United States (U.S.)	
Publication(s): None	
Study Period: 09 January 2003 (first patient enrolled) 30 October 2003 (data cut-off for Amendment 003) 26 February 2004 (last patient, last visit)	**Clinical Phase:** 2
Objective(s): • To determine the sedative dose/dose range and dosing paradigm of AQUAVAN® Injection following pretreatment with fentanyl citrate injection which consistently produces mild-to-moderate sedation. • To determine the safety, tolerability, and efficacy of pretreatment with fentanyl citrate injection in conjunction with AQUAVAN® Injection. • To determine the sedative dose/dose range and dosing paradigm of AQUAVAN® Injection following pretreatment with fentanyl citrate injection which produces mild-to-moderate sedation in a subset of elderly patients.	
Methodology: This was a Phase 2, randomized, open-label, multicenter, 2-part (Part 1A and Part 1B), adaptive dose-ranging study designed to determine an "optimal sedative dose" of AQUAVAN® Injection (hereafter, referred to as AQUAVAN), defined as one that consistently provided mild-to-moderate sedation (Modified Observer's Assessment of Alertness/Sedation [Modified OAA/S] of ≥2 and ≤4) in patients undergoing elective colonoscopy. Part 1 initially investigated the use of premedication with fentanyl citrate injection (hereafter, referred to as fentanyl), celecoxib, and an AQUAVAN priming dose as mitigants of the known paresthesias associated with AQUAVAN dosing. Neither celecoxib nor AQUAVAN priming appeared to change the paresthesias in a small number of patients; therefore, these pretreatments were removed from the protocol. Part 1 of the study was subdivided into Part 1A and Part 1B. Part 2 of the study was never initiated. Part 1A used a matrix-adaptive randomization scheme to evaluate 3 pretreatment doses (0.5, 1.0, or 1.5 µg/kg) of fentanyl followed by 7.5, 10.0, or 12.5 mg/kg bolus doses of AQUAVAN. Part 1B of this study was designed to evaluate a weight-based, fixed-dose regimen of AQUAVAN in conjunction with fentanyl.	
Number of Patients: The planned enrollment for Part 1 (A and B) of the study was up to 200 male and female patients undergoing elective colonoscopy with sedation; a subset of 50 patients >60 years and <85 years of age was permitted. A total of 100 patients who received study drug are included in the Part 1A analysis; an additional 64 patients who received study drug are included in the Part 1B analysis.	
Diagnosis and Key Criteria for Inclusion: Eligible patients must have had American Society of Anesthesiologists (ASA) Physical Classification System status of I or II, required an elective colonoscopy procedure that was anticipated to be performed in <60 minutes (ie, procedure was predicted to be uncomplicated), desired sedation for the colonoscopy procedure, and were considered by the Investigator to be physically capable of maintaining an adequate airway during mild-to-moderate sedation.	
Test Product, Dose, Mode of Administration, Batch No(s): AQUAVAN was provided as a sterile aqueous solution at concentrations of 20 mg/mL (Part 1A, CBL Lot 1214-10) or 35 mg/mL (Part 1B, [redacted] ot 176I0603) packaged in 20-mL glass vials suitable for i.v. administration. Dosage: 7.5, 10.0, or 12.5 mg/kg (bolus dose); up to 4 supplemental doses (range, 1.5 to 5.0 mg/kg per dose) of AQUAVAN, not to exceed 30 mg/kg. Pretreatment: fentanyl 0.5, 1.0, or 1.5 µg/kg, i.v.; supplemental doses were not to exceed 200 µg. Pretreatment: celecoxib [CELEBREX®] (original protocol only); a single oral dose of 400 mg (2, 200-mg capsules) with no more than 2 oz of water.	

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Reference Therapy, Dose, Mode of Administration, Batch No(s): Not applicable
Criteria for Evaluation: Efficacy: Clinical assessments of sedation were performed at regular intervals using the Modified OAA/S Scale, time to sedation, time to Fully Alert, time to Fully Recovered, and time to Ready for Discharge. The number of doses and amount of AQUAVAN were evaluated. Cognitive function was assessed using the Digit Symbol Substitution Test (DSST), and motor skills were assessed using the 5-Meter Heel-to-Toe Test. Patient discomfort levels were measured using a Verbal Rating Scale (VRS) and Visual Analog Scale (VAS). In addition, patient and physician surveys were evaluated. Safety: Safety was assessed based on the reporting of adverse events, continuous monitoring of vital signs, pulse oximetry, and electrocardiograms (ECGs), clinical laboratory tests, physical examination findings, and formate plasma concentration levels. Additional analyses were performed for hypoxia, apnea, and paresthesia.
Statistical Methods: No inferential statistical testing was planned or performed. All study results were presented by using descriptive statistics. Efficacy: Efficacy in Part 1A was analyzed for the All Treated population, and included all patients who received study medication, including those who received celecoxib, AQUAVAN priming dose (original protocol only), or alternate sedative medications. Efficacy in Part 1B was analyzed for the All Treated population, and included all patients who received study medication, including those who received alternate sedative medications. Safety: For both Parts 1A and 1B of the study, safety was assessed based on the reporting of adverse events, including adverse events of special interest (ie, apnea, hypoxemia, and paresthesia), vital signs, pulse oximetry and clinical laboratory tests, urinalysis, ECG measures, and physical examinations. Pharmacokinetics: Formate concentration levels were summarized.
Efficacy Results: AQUAVAN provided rapid and effective sedation in the dosing schemes evaluated with both adaptive dose-ranging (Part 1A) and weight-based, fixed-dose (Part 1B) schedules. Neither the use of priming doses of AQUAVAN, nor the use of celecoxib pretreatment substantively changed the perception of paresthesias in a small cohort of the subjects treated. Onset of the designated sedation (defined as first Modified OAA/S score ≤4) was rapid; the median time from initial bolus administration of AQUAVAN to achieve sedation was 2 minutes in both dosing schemes. Most patients required only a single injection of AQUAVAN to achieve this effect, and many required no supplementation for the procedure, with little difference between adaptive dose-ranging and weight-based, fixed-dose schedules. Variability of sedation effects in many measurements in the 910-mg dosing group (Part 1B) was noted in all aspects of the analysis, and may be related to distributions of weights inside that group. Recovery from the agent was also rapid, the overall median time from withdrawal of the colonoscope until the patient met the criteria for Fully Alert, Fully Recovered, and Ready for Discharge was 11.0, 20.0, and 37.0 minutes, respectively (Part 1A) and 12.0, 20.0, and 36.5 minutes, respectively (Part 1B). The patients regained baseline cognitive abilities within 30 minutes after the patient was Fully Alert. Satisfaction with the sedation as evaluated on the Satisfaction Survey was highly positive, as a large majority of both patients and physicians showed their satisfaction and reported they would use this sedative regimen again. Two patients each in Part 1A and Part 1B were Treatment Failures (ie, patient required rescue medication).

Safety: Overall, AQUAVAN administered to patients undergoing elective colonoscopy was well tolerated. All reports of paresthesia, apnea, hypoxia, and hypo/hypertension were considered by the Investigator to be related to study medication. No deaths or patient withdrawals due to adverse events were reported. There was one serious adverse event reported in Part 1A. One patient experienced a 3-minute episode of apnea following pretreatment with celecoxib, an initial dose of 10 mg/kg of AQUAVAN, and a subsequent dose of 100 µg of fentanyl.

Across all dose levels of AQUAVAN in both parts of the study, the most frequently reported events were paresthesias and hypoxia. In Part 1A, 84% of patients experienced paresthesias (ie, all MedDRA preferred terms potentially related to paresthesia). Most of the adverse events reported during the study were considered by the Investigator to be treatment-related and of mild to moderate intensity.

Forty-four (44%) patients in Part 1A exhibited hypoxia/hypoxemia, defined as an oxygen saturation measuring below 90%, compared with 7 (11%) patients who exhibited hypoxia/hopoxemia in Part 1B, which was defined as an oxygen saturation measuring below 90% and sustained for >20 seconds. However, due to the differing clinical conditions (ie, no supplemental oxygen in Part 1A) and definitions of hypoxia/hypoxemia (no specified duration of oxygen saturation <90% in Part 1A), comparison of hypoxemia rates should be viewed with caution. As would be expected for a sedative, the incidence of hypoxia/hypoxemia increased with increasing initial bolus doses of AQUAVAN. Primarily, the incidence of hypoxia/hypoxemia was related to the level of sedation, as there was also a relationship to the amount of fentanyl given to the patient.

In both parts of the study, apnea was defined as a lack of spontaneous breathing for >15 seconds. Six of the 7 patients in Part 1A who experienced apnea received either an initial bolus dose of ≥931 mg AQUAVAN and/or a total dose of AQUAVAN >1100 mg. Three patients experienced apnea in Part 1B of the study; 1 patient received an initial AQUAVAN bolus dose of 630 mg and 2 patients received an initial AQUAVAN bolus dose of 980 mg.

Most clinical laboratory test results remained unchanged from baseline. Approximately one-third of the 97 patients in Part 1A who had phosphate data at both predosing at 9 minutes after dosing had shifts from normal to high. There were no important changes in serum calcium; levels were normal at 24 hours.

The effect of AQUAVAN on blood pressure (systolic, diastolic, and mean arterial) and pulse rate was mild, transient (ie, values typically returned to near baseline levels by the time subjects were Fully Alert), and without sequelae. AQUAVAN appears to demonstrate a safety profile similar to that produced by available sedatives in this clinical use.

CONCLUSIONS:

AQUAVAN appears to be safe and effective in combination with i.v. doses of fentanyl for the induction and maintenance of sedation for colonoscopy procedures. AQUAVAN may be used in a per-kilogram dosing scheme, but appears to be equally safe and efficacious when used in a weight-based, fixed-dose scheme. AQUAVAN induces sedation within approximately 2 minutes, and maintains that sedation throughout an appropriate period without the need for supplemental dosing in most cases. The recovery times are fast, and most patients are Ready for Discharge within 40 minutes following the procedure.

The safety profile of AQUAVAN and fentanyl seen in this study is consistent with those described for mild-to-moderate sedation. Paresthesias, while very common, were of such mild intensity that patients' satisfaction scores were not substantively lowered by their occurrence. When appropriately defined and anticipated, hypoxemia and apneic episodes can be minimized and supported. Higher doses of fentanyl and AQUAVAN appear to be associated with these effects, and future dosing schemes should anticipate and avoid this interaction.

Future studies of mild-to-moderate sedation may use a weight-based, fixed-dose paradigm for AQUAVAN and fentanyl combination.

4.3.16 Study 3000-0415 Synopsis

See Analytical section 2.6 regarding propofol assay issue

Study Title: **A Phase II, Randomized, Open-Label Study to Assess the Safety and Efficacy of AQUAVAN® Injection Versus Midazolam HCl for Sedation in Elderly Patients Undergoing Colonoscopy Procedures**
Investigators and Study Centers: Multicenter (see Appendix 16.1.4)
Publication (reference): see Appendix 16.1.11
Studied Period: 22 February 2005 (first patient enrolled) 17 March 2005 (last patient completed)
Phase of Development: 2
Objectives: Primary Objective: • To evaluate that AQUAVAN® Injection was effective in providing adequate sedation in elderly patients undergoing colonoscopy. Secondary: • To assess the safety profile of AQUAVAN® Injection versus that of midazolam HCl in elderly patients. • To evaluate the recovery times after colonoscopy procedures in elderly patients receiving AQUAVAN® Injection with those receiving midazolam HCl. • To determine the pharmacokinetics of GPI 15715, propofol, and formate following administration of AQUAVAN® Injection in elderly patients undergoing colonoscopy.
Methodology: This was a randomized, open-label, multicenter study designed to assess the safety and efficacy of AQUAVAN® Injection (hereafter, referred to as AQUAVAN) versus midazolam hydrochloride (hereafter, referred to as midazolam) in producing sedation in elderly patients undergoing colonoscopy. Patients underwent screening assessments within 2 weeks of their scheduled colonoscopy. After completion of preprocedure sedation assessments, patients were randomly assigned to 1 of the 2 intravenous (i.v.) treatment groups at a 4:1 (AQUAVAN: midazolam) allocation ratio on the day of the scheduled procedure (Day 0) via an Interactive Voice Response System (IVRS). To ensure that a distribution of ages was obtained, enrollment was stratified into 2 equal-size groups by age (>65 to <72 years of age and ≥72 years of age). Randomization was stratified by site within each age group.

All study patients, irrespective of treatment group assignment, received fentanyl citrate injection (hereafter, referred to as fentanyl) as an analgesic pretreatment at a dose of 0.5 μg/kg. Supplemental doses of fentanyl, up to a total dose of 50 μg per patient, could be administered if the patient reported pain or if inadequate analgesia was present as demonstrated by increased heart rate and/or blood pressure in the presence of adequate sedation. At no time was fentanyl administered to increase sedation levels. AQUAVAN or midazolam was administered to induce a state of adequate sedation based on a validated measure, a Modified Observer's Assessment of Alertness and Sedation (OAA/S) score of ≤4. Supplemental doses were administered if necessary to increase depth or duration of sedation. Supplemental doses were not administered if the Modified OAA/S score was ≤2 or if there was no purposeful response to verbal or tactile stimulation. Patient and Investigator assessments were used to confirm that the depth of sedation met the goals of sedation, reduction of anxiety, and reduced awareness. Follow-up patient assessments were conducted in a telephone interview 24 hours following treatment and during a clinic visit 2 to 5 days following treatment.
Number of Patients (Planned and Analyzed): Approximately 100 patients were planned to be enrolled in this study at 16 study sites. Thirty-four patients were screened and 20 patients were actually enrolled and randomized. Data from 20 patients were included in the analysis of safety and efficacy. Screening and enrollment were stopped prior to completion of enrollment on 17 March 2005 and were officially terminated by Guilford Pharmaceuticals Inc. in a letter to Investigators dated 24 March 2005. Patient enrollment was stopped prior to completion in order to evaluate the dosing regimen.
Diagnosis and Main Criteria for Inclusion: Males and females over 65 years old who underwent colonoscopy; prior to procedure, patients were an American Society of Anesthesiologists (ASA) Physical Status Classification of I to III.
Test Product, Dose and Mode of Administration, Lot Number: AQUAVAN was administered by i.v. bolus. Initial bolus doses were 525 mg, 595 mg, or 735 mg based on weight, with supplemental doses of 105 mg. Lot number GAA002 was used in this study.
Duration of Treatment: The duration of the treatment was 1 day.

Reference Therapy, Dose and Mode of Administration, Lot Number:
Commercially available midazolam (Versed®, or generic equivalent) was administered by i.v. bolus. Initial bolus doses were 0.5, 0.75, or 1 mg, with supplemental doses of 0.25, 0.35, or 0.5 mg, based on weight.

Criteria for Evaluation:

Efficacy

Primary Efficacy Endpoint:

- Sedation Success was defined as a patient having 3 consecutive Modified OAA/S scores ≤4 and completing the procedure without requiring alternative sedative medications and without requiring manual or mechanical ventilation.

Secondary Efficacy Endpoints:

- Measures of recovery and cognitive functions by the blinded evaluator
- Measures of sedation adequacy
- Patient-reported outcome and Investigator's assessment
    - Patient's rating of experience after Fully Recovered
    - Patient's rating at telephone survey
    - Investigator's rating at the end of the procedure
    - Blinded evaluator's rating after Fully Recovered

Safety Endpoints:

- Nature, frequency, severity, relationship to treatment, and outcome of all treatment-emergent adverse events (TEAEs)
- Airway assistance and stimulation
- Sedation-related AEs (SRAEs)
- Laboratory parameters and vital signs
- Concomitant medications
- Alternative sedation/hypnotic medications

Statistical Methods:
Summary statistics were provided for all endpoints. For continuous variables, data were summarized with mean, standard deviation (SD), and median. For categorical variables, data were tabulated with number and proportion for each category.

Efficacy:
For the primary efficacy endpoint, Sedation Success, frequency count and proportion of patients who were sedated successfully were calculated. Summary descriptive statistics were presented for the Time to Fully Recovered. The analysis population for efficacy endpoints was the modified intent-to-treat (mITT) population.

Safety:
All patients who received study medication were included in the safety analysis. The incidences of AEs, sedation-related AEs, and airway assistances were calculated by treatment group. Changes from baseline in laboratory tests, vital signs and pulse oximetry, electrocardiograms (ECGs), and physical examination were summarized by treatment group and abnormal findings were listed with pertinent patient information.

Pharmacokinetics:
Formate concentrations were analyzed for patients who received AQUAVAN and were summarized by timepoint. Plasma concentrations of GPI 15715 and propofol were combined with data from other studies and analyzed separately.

Summary of Results

Efficacy:

- All 15 patients treated with AQUAVAN achieved Sedation Success.
- None of the 5 patients treated with midazolam achieved Sedation Success.
- A significantly higher percentage of patients achieved Sedation Success in the AQUAVAN group when compared with the midazolam group (100% versus 0%; $p<0.001$).
- The median time to sedation (first of 2 Modified OAA/S scores ≤ 4) was shorter in the AQUAVAN group (2.0 minutes) than in the midazolam group (12.0 minutes). Times to sedation of more than 5 minutes were observed in 1 patient in the AQUAVAN group (6 minutes) compared with all patients in the midazolam group (8 to 18 minutes).
- Patients in both treatment groups recovered rapidly. The median times to Fully Alert and to Fully Recovered from the end of the procedure were longer in AQUAVAN-treated patients (8 minutes and 10 minutes, respectively) compared with midazolam-treated patients (1 minute and 2 minutes, respectively).
- Patients in the AQUAVAN group were more deeply sedated for longer durations compared with patients in the midazolam group. All midazolam-treated patients had Modified OAA/S scores of 4 or 5 from initiation of study drug to Fully Alert. In the AQUAVAN group, Modified OAA/S scores of ≤ 3 were observed for a mean percent time of 54.1% and scores of ≤ 1 for a mean percent time of 16.1% from initiation of study drug to Fully Alert.

- The deeper level of sedation (evaluated using Modified OAA/S scale) in AQUAVAN-treated patients permitted faster times to procedure milestones when compared with midazolam-treated patients. For example, the median times from initiation of study drug treatment to splenic flexure and to end of procedure were 6 minutes and 16 minutes, respectively, in the AQUAVAN group compared with 16 minutes and 21 minutes, respectively, in the midazolam group.
- Fourteen out of 15 AQUAVAN-treated patients compared with only 1 of 5 midazolam-treated patients required a single bolus dose to achieve sedation. No AQUAVAN-treated patients required more than 2 doses of study medication. Two of the 5 midazolam-treated patients required 5 doses of study drug to achieve adequate sedation.
- A single bolus dose was sufficient to initiate and maintain adequate sedation throughout the procedure for 13 of 15 AQUAVAN-treated patients compared with 1 of 5 midazolam-treated patients.
- No additional doses of study drug were required to maintain sedation for 13 of 15 AQUAVAN-treated patients and for 3 of 5 midazolam-treated patients during the Procedure period. One patient required 2 additional doses and another patient required 4 additional doses of study drug to maintain sedation in the midazolam group.
- Regardless of treatment, all patients regained baseline cognitive abilities by discharge.
- No patient in the AQUAVAN group and 1 patient in the midazolam group had their procedure interrupted (3 interruptions) due to inadequate sedation.
- All patients in the AQUAVAN group felt they were adequately sedated. By comparison, in the midazolam group, only 1 of 5 patients felt that the level of sedation was adequate.
- Physicians likewise, although unblinded to the treatment administered, felt the majority of patients in AQUAVAN group (12 of 15 patients) and 1 of 5 patients in the midazolam group were adequately sedated.
- Physicians were satisfied with the time to sedation for 13 of 15 AQUAVAN-treated patients and for 1 of 5 midazolam-treated patients.
- Physicians reported that the level of sedation was considered too heavy for 2 of 15 patients in the AQUAVAN group and responses to instruction during the procedure were considered poor for 3 of the 15 patients.
- In the midazolam group, physicians reported that the level of sedation was considered too light in 4 out of the 5 patients and that the response to instructions during the procedure was adequate for all patients.

- The blinded evaluator's ratings at discharge were excellent or good for 13 of 15 AQUAVAN-treated patients and for all midazolam-treated patients.

Safety:

- Overall, AQUAVAN was well tolerated when administered to elderly patients undergoing colonoscopy. Ten of 15 patients in the AQUAVAN group and 3 of 5 patients in the midazolam group experienced TEAEs during the course of the study.
- No patient experienced a serious adverse event (SAE).
- There were no deaths and no patient withdrew due to AEs.
- The most frequently reported TEAEs in the AQUAVAN group were hypoxia events in 6 patients and paresthesia in 4 patients.
- All AEs were mild or moderate in intensity.
- Eight of 15 AQUAVAN-treated patients and 1 of 5 midazolam-treated patients experienced AEs that were considered by the Investigator to be treatment related.
- Sedation-related AEs hypoxemia/hypoxia or bradycardia were reported for 6 of 15 AQUAVAN-treated patients and 1 of 5 midazolam-treated patients. All SRAEs were mild in intensity.
- Six of 15 patients in the AQUAVAN group and 1 of 5 patients in the midazolam group experienced hypoxia SRAEs. Three of 15 patients in the AQUAVAN group and no patient in the midazolam group required airway assistance (increased oxygen flow) for the treatment of hypoxia. No patient required mechanical airway management or manual ventilation.
- Most clinical laboratory test results remained unchanged from baseline. Any observed changes were not clinically meaningful.
- Formate levels did not increase following AQUAVAN dosing.

OVERALL CONCLUSIONS

No conclusions were made because of the small size of the study, however, the following efficacy and safety observations were made:

- Overall, patients in the AQUAVAN group were adequately sedated.
- The time to onset of sedation was more rapid in the AQUAVAN group with 14 of 15 patients in the AQUAVAN treated group having a time to onset of sedation of less than 5 minutes.
- In a majority of patients treated with AQUAVAN, a single i.v. dose initiated and maintained an appropriate level of sedation for the entire colonoscopy procedure without the need for supplemental or maintenance dosing.
- Both patients and physicians were highly satisfied following treatment with AQUAVAN.

- There were no SAEs in this study.
- All TEAEs resolved without sequelae.
- Sedation-related side effects such as hypoxemia and bradycardia were minimal and managed without difficulty.
- There were no patients who required manual ventilation and/or intubation during the conduct of the trial.

Overall, AQUAVAN appears to be both safe and effective in combination with i.v. doses of fentanyl for the initiation and maintenance of sedation for colonoscopy in the elderly population.

4.3.17 Study 3000-0520 Synopsis

See Analytical section 2.6 regarding propofol assay issue

Study Title: A Randomized, Double-blind, Dose-response Study to Assess the Efficacy and Safety of AQUAVAN® Injection for Procedural Sedation in Patients Undergoing Colonoscopy
Investigators and Study Centers: Multicenter (see Appendix 16.1.4)
Publication (reference): see Appendix 16.1.11
Studied Period: 11 August 2005 (first patient enrolled) to 18 October 2005 (last patient completed)
Phase of Development: 2
Objectives: • To estimate the dose-response relationship in Sedation Success rate for patients who receive different initial bolus doses of AQUAVAN; • To estimate the dose-response relationship in patient's and Investigator's satisfaction; • To evaluate the dose-response relationship of the nature, frequency, seriousness, severity, relationship to treatment, and outcome of all treatment-emergent adverse events; • To estimate the dose-response relationship of the incidences of airway assistance; and • To estimate the dose-response relationship in the duration and percent time of patient's Modified OAA/S score=0 or 1.
Methodology: This was a randomized, double-blind, dose-response study designed to evaluate the dose-response relationship in the Sedation Success rate for 4 different initial bolus doses of AQUAVAN® Injection (fospropofol disodium, hereafter referred to as AQUAVAN) following pretreatment with an analgesic, fentanyl citrate injection (hereafter referred to as fentanyl), in patients undergoing a colonoscopy. A group of patients received midazolam hydrochloride (hereafter referred to as midazolam) as a safety reference therapy. Following completion of preprocedure assessments, patients were randomly assigned to 1 of 5 intravenous (i.v.) treatment groups, described below, at an equal allocation ratio on the day of the scheduled procedure. Randomization was stratified by age and American Society of Anesthesiologists (ASA) status Physical Status Classification system. All patients were placed on supplemental oxygen via nasal cannula (4 L/min), and connected to an electrocardiogram (ECG) monitor, a pulse oximeter, and a blood pressure monitor prior to administration of study medication. All patients received an injection of fentanyl for analgesia (50 µg) followed, after 5 minutes, by

the initial administration of sedative medication. In order to titrate the sedation medication, this protocol 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 AQUAVAN/saline or midazolam were administered to reach minimal-to-moderate sedation (Modified OAA/S score ≤4). The 5 study arms were dosed as follows: • AQUAVAN initial bolus dose 1: 8 mg/kg • AQUAVAN initial bolus dose 2: 6.5 mg/kg • AQUAVAN initial bolus dose 3: 5 mg/kg • AQUAVAN initial bolus dose 4: 2 mg/kg • Midazolam initial bolus dose: 0.02 mg/kg Midazolam supplements were administered every 2 minutes while active AQUAVAN supplements were administered only every 4 minutes. In order to maintain blinding, the AQUAVAN 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 (AQUAVAN treatment arms) and at 1 mg/dose (midazolam arm). When the patient reached Modified OAA/S score ≤4, the Investigator was to start the colonoscopy procedure. In the Sedation Maintenance Phase, supplemental doses of sedative medication [25% of the initial bolus (AQUAVAN arms) or at 1 mg/dose (midazolam arm)] may have been administered at intervals of ≥4 minutes, if a patient's Modified OAA/S score was ≥4 and the patient demonstrated purposeful movement. Laboratory samples were taken prior to and following the procedure. Vital signs, saturation of hemoglobin with oxygen in peripheral blood (SpO_2), and ECGs were followed from predosing through recovery. Assessments were made to evaluate the patients for levels of sedation, cognitive function, and recovery. Blood samples were collected for pharmacokinetic (PK) analysis.
Number of Patients (Planned and Analyzed): 125 patients were planned; 127 patients were analyzed for safety; 127 patients were analyzed for efficacy.
Diagnosis and Main Criteria for Inclusion: Patients were at least 18 years of age at the time of screening and met the ASA Physical Classification System status of P1 to P4. If female, patients were surgically sterile, postmenopausal, or not pregnant or lactating and had been using an acceptable method of birth control for at least 1 month prior to dosing, with a negative urine pregnancy test result at screening and predose.

Test Product, Dose and Mode of Administration, Lot Number:
AQUAVAN (Lot number GAA002) was administered intravenously. Initial boluses were: 8 mg/kg, 6.5 mg/kg, 5 mg, and 2 mg/kg. The median total dose of AQUAVAN used to initiate and complete the procedure for all AQUAVAN groups combined was 595.0 mg (range, 150.0-1277.5 mg).
All patients were pretreated with fentanyl (50 µg) for analgesia 5 minutes before their initial bolus of AQUAVAN. The median total dose of fentanyl used to complete the procedure for all AQUAVAN groups combined was 75.0 µg (range, 50.0-200.0 µg).

Duration of Treatment: The duration of treatment was 1 day.

Safety Reference Therapy, Dose, and Mode of Administration, Lot Number:
Commercially available midazolam (Versed®, or generic equivalent) was administered by i.v. bolus. The initial bolus was 0.02 mg/kg. The median total dose of midazolam used to initiate and complete the procedure was 2.4 mg (range, 0.87-6.22 mg).

Patients were pretreated with fentanyl (50 µg) for analgesia 5 minutes before their first dose of midazolam. The median total dose of fentanyl used to complete the procedure for the midazolam group was 75.0 µg (range, 50.0-100.0 µg).

Criteria for Evaluation:

Primary Efficacy Endpoint:

- Sedation Success was defined as a patient having 3 consecutive Modified OAA/S scores of ≤4 after administration of sedative medication and completing the procedure 1) without requiring the use of alternative sedative medication and 2) without requiring manual or mechanical ventilation.

Secondary Efficacy Endpoints:

- Measures of clinical benefit;
- Measures of recovery and cognitive functions; and
- Measures of sedation adequacy.

Safety Endpoints:

- Nature, frequency, and indication of airway assistance;
- Frequency of sedation-related adverse events (SRAEs: apnea, hypoxemia [hypoxia], bradycardia, hypotension);
- Nature, frequency, seriousness, severity, relationship to treatment, and outcome of all TEAEs;
- Percent of time that patients demonstrated purposeful movement;

- Laboratory parameters and vital signs; and
- Concomitant medications.

Statistical Methods:

For this study, 2 efficacy analysis populations (mITT and pP) and 1 safety population were used in planned analyses. The modified intent-to-treat (mITT) analysis population was defined as all randomized patients who received at least one dose of either AQUAVAN or midazolam and had at least 1 postdose clinical assessment. The pP population was defined as all patients from the mITT population who did not incur serious protocol violations and did not have their procedures terminated for non-study-drug related findings. The safety population was defined as all patients who were randomized and received at least one dose of either AQUAVAN or midazolam. Other analysis populations were evaluated where appropriate, and these other analysis populations are described in the text of this study report.

In general, for continuous variables, data were summarized with mean, standard deviation (SD), median, minimum, and maximum by treatment group. For categorical variables, data were tabulated with number and proportion for each category by treatment groups.

Since randomization was not stratified by site, the analyses of neither continuous nor categorical variables were adjusted for site variation. All confidence intervals and statistical comparisons were based on 2-sided test with an alpha of 0.05, unless specified otherwise.

Efficacy:

For efficacy endpoints, the primary analyses were based on the mITT population. The secondary analyses were based on the pP population. When the results of the 2 analyses did not support each other, further analyses were carried out to investigate the difference and an explanation was presented in the appropriate sections of this report. Otherwise, only the analysis results from mITT population are discussed.

- For the primary endpoint, the number and proportion of patients considered to be a Sedation Success were calculated by treatment group. An exact 95% confidence interval for the Sedation Success rate was calculated for each treatment group and a 95% confidence interval for the between-group difference provided. The pairwise p-values for the between-group differences were calculated using the Fisher's exact test.
- Measures of clinical benefit, recovery, and sedation adequacy were provided per treatment group using summary statistics.

Safety:

All safety analyses were based on the safety population.

- The total cumulative doses of study medication were summarized by treatment group.

- The patient and event incidences of airway assistance, both overall and by type were tabulated by treatment group. The patient incidence was presented by number and proportion of patients within each study group that required airway assistance. The event incidence was presented by number of airway management events recorded for each study group.
- Percent of time that patients demonstrate purposeful movement was calculated for each patient. Summary statistics were provided by study group.
- Treatment-emergent adverse events (TEAEs) were summarized by preferred term as well as by preferred term within system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) (version 7.1).
- The patient incidence of TEAEs was tabulated by treatment group, by severity, and by causal relationship to study medication.
- The following sedation related adverse events of concern were tabulated separately from all other adverse events: apnea, hypoxemia (or hypoxia), bradycardia, and hypotension.
- Shifts from baseline were tabulated by treatment group for laboratory values, vital signs, and ECG results. The baseline values and changes from baseline in laboratory values and vital sign measurements were summarized by treatment group. The numbers and proportions of patients experiencing the following values for vital signs were tabulated by treatment group: <90 mm Hg for systolic blood pressure; >120 mm Hg for diastolic blood pressure; ≤50 beats per minute (BPM) for heart rate; and <90%, <85%, and <80 % for SpO_2. Also, the numbers and proportions of patients experiencing the following values for percent change from baseline were tabulated by treatment group: any change of <20% or <30% for all vital signs; and, for blood pressure only, increases or decreases of ≥20% or ≥30%. All abnormal laboratory values, vital signs, and ECG results were presented in by-patient listings.
- All medications taken prior to, on and after the day of procedure as well as medications taken on or after the first dose of study sedative medication were summarized by treatment group respectively. The number and proportion of patients receiving rescue sedative medications during the study were tabulated by treatment group.

Summary of Results

Efficacy:

- A highly significant dose-dependent trend in Sedation Success rate was observed across AQUAVAN dosing groups in the mITT population ($p<0.001$ by Cochran-Armitage trend test). The frequencies of Sedation Success rates were 69.2% in the 6.5-mg/kg AQUAVAN group, and were 24.0%, 34.6%, and 95.8% in the 2-, 5-, and 8-mg/kg AQUAVAN groups, respectively.

- Pairwise comparisons (using Fisher's exact test) of Sedation Success rates showed statistically significant differences between the 8-mg/kg group and the 6.5-mg/kg group compared with the 2-mg/kg group ($p<0.001$ and $p=0.002$ for the 8-mg/kg and 6.5-mg/kg groups, respectively).
- Consistent with the Sedation Success results, highly significant dose-dependent increases in Treatment Success (an exploratory endpoint) were observed across AQUAVAN dosing groups ($p<0.001$). The Treatment Success rate was 80.8% in the 6.5-mg/kg AQUAVAN group, and ranged from 36.0% in the 2-mg/kg AQUAVAN group to 95.8% in the 8 mg/kg group.
- All patients (26 of 26 patients [100.0%]) in the 6.5-mg/kg AQUAVAN group reported an adequate level of sedation on the Patient Satisfaction Survey at Ready for Discharge. The percentages of patients who reported an adequate level of sedation ranged from 76.0% in the 2-mg/kg AQUAVAN group to 83.3% in the 8-mg/kg group.
- The patient's memory of being awake during the procedure was dose dependent across AQUAVAN treatment groups. In the 6.5-mg/kg AQUAVAN group, 42.3% of patients remembered being awake during the procedure. The percentages of patients who remembered being awake during the procedure decreased from 58.3% in the 2-mg/kg group to 33.3% in the 8-mg/kg group.
- Overall satisfaction with the entire procedure was rated as 9 to 10 (high) by more patients in the 6.5-mg/kg group (24 of 26 patients [92.3%]) than in the other treatment groups. Overall satisfaction scores of 9 to 10 (high) were reported by 79.2% of patients in the 8-mg/kg group, by 84.0% in the 5-mg/kg group, and by 72.0% in the 2-mg/kg group.
- Responses to the Physician Satisfaction Survey at End of Procedure demonstrated that sedation adequacy was dose-dependent across AQUAVAN dosing groups. Physicians reported adequate sedation for 80.8% of patients in the 6.5-mg/kg group, and reports of adequate sedation ranged from 32.0% of patients in the 2-mg/kg group to 83.3% in the 8-mg/kg group.
- The physician's overall satisfaction with the study medications administered increased with increasing dose levels of AQUAVAN. Mean overall satisfaction scores on a scale from 0 (low) to 10 (high) were 6.8 in the 6.5-mg/kg group, and ranged from 3.5 in the 2-mg/kg group to 7.7 in the 8-mg/kg group.
- The use of alternative sedative medications decreased across AQUAVAN dosing groups. The percentages of patients who received alternative sedative medication were 19.2% (5 of 26 patients) in the 6.5-mg/kg group, and ranged from 64.0% (16 of 25) in the 2-mg/kg group to 4.2% (1 of 24) in the 8-mg/kg group.
- The mean number of supplemental fentanyl doses received by patients decreased across AQUAVAN dosing groups. The mean number of supplemental fentanyl doses was

0.7 doses in the 6.5-mg/kg group, and ranged from a mean of 1.0 dose in the 2-mg/kg group to a mean of 0.5 doses in the 8-mg/kg group.

- Dose-dependent decreases in time to sedation were observed across AQUAVAN dosing groups. Median times to sedation were 6.0 minutes (range, 0-18) in the 6.5-mg/kg group, and ranged from 12.0 minutes (range, 0-22) in the 2-mg/kg AQUAVAN group to 4.0 minutes (range, 0-12) in the 8-mg/kg group.
- Increases in time to Ready for Discharge from the end of the procedure were observed across AQUAVAN dosing groups, with the exception of the 2-mg/kg AQUAVAN group. Median times to Ready for Discharge were 7.5 minutes (range, 1-30) in the 6.5-mg/kg group, and were 6.0 minutes (range, 0-65), 4.0 minutes (range, 0-43), and 11.5 minutes (range, 1-61) in the 2-, 5-, and 8-mg/kg groups, respectively.
- The median percentages of time at Modified OAA/S scores of 2 to 4 from first dose of study medication to Fully Alert were higher in the 6.5-mg/kg and 8-mg/kg AQUAVAN groups than in the 2-mg/kg and 5-mg/kg groups. The median percentages of time at Modified OAA/S scores of 2 to 4 were 50.0%, 58.6%, 72.7%, and 71.4% in the 2-, 5-, 6.5-, and 8-mg/kg AQUAVAN groups, respectively.
- During the Recovery Period, the mean percent retention on the Hopkins Verbal Learning Test-Revised™ (HVLT-R™) test was higher in the 6.5-mg/kg AQUAVAN group (99.3%) when compared to the 2-, 5-, and 8-mg/kg AQUAVAN groups (71.4%, 90.0%, and 75.5%, respectively).
- The percentages of patients who had times to sedation of ≤5 minutes showed a significant dose-dependent trend across AQUAVAN dose groups ($p<0.001$). The percentages of patients with times to sedation of ≤5 minutes were 38.5% in the 6.5-mg/kg AQUAVAN group, and ranged from 4.0% in the 2-mg/kg AQUAVAN group to 50.0% in the 8-mg/kg group.

Safety:

- No patient experienced a serious adverse event (SAE) or adverse event (AE) leading to discontinuation of study medication, and no patient died during the study.
- Treatment-emergent AEs were experienced by 81.5% patients in the 2-mg/kg AQUAVAN group, by 84.6% in the 5-mg/kg group, by 96.0% in the 6.5-mg/kg group, and by 73.9% in the 8-mg/kg group in the safety population. In the midazolam group, 61.5% patients experienced TEAEs.
- Treatment-related AEs were experienced by 61.4% patients in the AQUAVAN groups and by 7.7% in the midazolam group. The most common treatment-related AEs experienced by patients in the AQUAVAN groups were burning sensation (23.8%), genital burning sensation (17.8%), paresthesia (8.9%), and pruritus (7.9%).

- Most TEAEs were mild or moderate in severity. Severe treatment-related AEs of genital burning sensation or burning sensation were experienced by 2 patients in the 5-mg/kg group and by 2 patients in the 6.5-mg/kg group.
- Four patients had SRAEs during the study. In the 6.5-mg/kg group, 2 patients experienced SRAEs of hypoxia and 1 patient had a hypotension SRAE; and in the 5-mg/kg group, 1 patient experienced hypotension SRAEs. Of these 4 patients who had SRAEs, 1 patient from the 6.5-mg/kg group required airway assistance (verbal stimulation) for the treatment of hypoxia.
- Purposeful movement was demonstrated for slightly higher percentages of time from first dose of study medication to Fully Alert in the 6.5-mg/kg AQUAVAN group (95.5%) and in the midazolam group (96.7%) when compared with the other treatment groups (88.3%, 90.5%, and 75.5% in the 2-, 5-, and 8-mg/kg groups, respectively).
- Changes in blood pressure, SpO_2, and heart rate that resulted in AEs of hypotension, hypoxia, and bradycardia were experienced by 6 patients. However, these AEs satisfied the protocol-defined criteria for SRAEs in 4 patients only (ie, hypotension in 1 patient and bradycardia in another patient were not considered SRAEs).

CONCLUSION

Efficacy Conclusions:

- The primary endpoint, Sedation Success, showed a dose-dependency across AQUAVAN treatment groups with 6.5-mg/kg and 8-mg/kg giving the highest rates.
- The highest overall satisfactions scores were reported by patients in the 6.5-mg/kg group, and this group had the highest proportion of patients who reported a willingness to use the same sedative treatment again when compared to other AQUAVAN groups.
- Physicians showed a dose-response in their overall satisfaction with AQUAVAN treatment, with satisfaction scores increasing from 2- to 8-mg/kg. They did, however, express a greater willingness to use the 6.5-mg/kg dose than any other AQUAVAN dose in subsequent procedures.
- Patient's memory recall during the Recovery Period was highest in the 6.5-mg/kg treatment group, indicating a clear-headed recovery.
- Patients treated in the 6.5-mg/kg AQUAVAN group spent the largest percent of the procedure time at a level of minimal-to-moderate sedation.
- More patients in the 8-mg/kg group had Modified OAA/S scores of 0 or 1 (deep sedation) and were at these levels for longer periods of time than those in the 6.5-mg/kg group.
- Treatment with 6.5- and 8-mg/kg AQUAVAN resulted in the use of less rescue sedative medication during the colonoscopy procedure when compared to other AQUAVAN treatment groups.

- The 6.5-mg/kg and 8-mg/kg treatment groups were administered less supplemental opiate analgesia to complete their procedures when compared to other AQUAVAN treatment groups.

Safety Conclusions:

- AQUAVAN was safe and well tolerated. No patients died during this study and none were discontinued from participating in this study. Most treatment-emergent adverse events were of mild or moderate intensity.
- There were 4 severe TEAEs and 4 SRAEs during the study. The TEAEs resolved within 2 minutes without treatment. The 2 hypoxia SRAEs resolved quickly; one, following verbal stimulation and the other without treatment. The 2 hypotension events were resolved by concomitant treatment with saline.
- Patients in the 6.5-mg/kg treatment group displayed purposeful movement for the longest periods of time during their procedures when compared with all other AQUAVAN treatment groups.

Overall:

- Taken together, these data indicate that an initial dose of 6.5-mg/kg of AQUAVAN plus supplemental doses at 25% of the initial dose was the optimal treatment regimen to produce safe minimal-to-moderate sedation for colonoscopy in this study.

4.3.18 Study 3000-0522 Synopsis

Study Title:
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

Investigators and Study Centers: Multicenter (see Appendix 16.1.4)

Publication (reference): see Appendix 16.1.11

Studied Period:

20 March 2006 (first patient enrolled) to
01 August 2006 (last patient completed)

Phase of Development: 3

Objectives:

Primary Objective:

- To demonstrate that AQUAVAN* is effective in providing minimal-to-moderate sedation in patients undergoing colonoscopy.

Secondary Objectives:

- To demonstrate that sedation with the therapeutic dose of AQUAVAN provides a clinical benefit to the patient during minimal-to-moderate sedation; specifically, the following objectives will be demonstrated in hierarchical order:
  a. AQUAVAN enables the completion of the procedure without alternative sedative medications and mechanical airway management.
  b. AQUAVAN reduces the need for analgesic medications for the procedure.
  c. AQUAVAN minimizes the patient's memory recall of the procedure.
  d. AQUAVAN eases the patient's overall experience as measured by their willingness to be treated again.
- To evaluate the safety profile of the therapeutic dose of AQUAVAN.

*Because this was a dose-controlled study, the reference to AQUAVAN in the objectives refers to the 6.5-mg/kg AQUAVAN dose group.

Methodology: This was a Phase 3, randomized, double-blind, dose-controlled study designed to evaluate the efficacy and safety of AQUAVAN 6.5 mg/kg compared with a lower active-control dose of AQUAVAN 2.0 mg/kg, both following pretreatment with an analgesic, fentanyl, in patients who were undergoing elective colonoscopy. A group of patients received midazolam hydrochloride (hereafter referred to as midazolam) as a safety reference therapy.

Following completion of preprocedural assessments, patients were randomly assigned to 1 of 3 treatment groups in a 2:3:1 allocation ratio (AQUAVAN Dose 1: AQUAVAN Dose 2: Midazolam Dose) on the day of the scheduled procedure. Randomization was stratified by site. Treatment groups are defined below.

Treatment Group	Sedation Initiation Dose
AQUAVAN Dose 1:	2.0 mg/kg
AQUAVAN Dose 2:	6.5 mg/kg
Midazolam Dose:	0.02 mg/kg

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 colonoscopy 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 connected to an electrocardiogram (ECG) monitor, pulse oximeter, and a blood pressure monitor prior to administration of study medication. Five minutes prior to Sedation Initiation, fentanyl was administered at a dose of 50 μg. An initial bolus dose and up to 3 supplemental doses of AQUAVAN or midazolam were administered as needed to reach a Modified Observer's Assessment of Alertness/Sedation (OAA/S) score of ≤4 and to start the colonoscopy. Initial bolus dose ranges were defined as follows: 120 to 180 mg for the AQUAVAN 2.0-mg/kg group; 390 to 585 mg for the AQUAVAN 6.5-mg/kg group; and ≤2.5 mg for the midazolam group. Supplemental doses of AQUAVAN were 25% of the initial dose; with ranges of 30 to 45 mg each for the 2.0-mg/kg treatment group and 97.5 to 146 mg each for the 6.5-mg/kg treatment group. Supplemental doses of midazolam were each 1 mg. In the Sedation Maintenance Phase, supplemental doses of sedative medication may have been administered at intervals of ≥4 minutes, if a patient's Modified OAA/S score was ≥4 and the patient demonstrated purposeful movement.
Number of Patients (Planned and Analyzed): Approximately 300 patients were planned for enrollment. Of the 314 patients randomized, 312 patients received at least 1 dose of study drug and were analyzed for safety and efficacy.
Diagnosis and Main Criteria for Inclusion: Patients were at least 18 years of age at the time of screening and met the American Society of Anesthesiologists (ASA) Physical Classification System status of P1 to P4. If female, patients were surgically sterile, postmenopausal, or not pregnant or lactating; had been using an acceptable method of birth control for at least 1 month prior to dosing; and had a negative urine pregnancy test result at screening and predose.
Test Product, Dose and Mode of Administration, Lot Number: AQUAVAN (Lot number GAA002) was administered intravenously (i.v.). Initial boluses were 2.0 mg/kg and 6.5 mg/kg. All patients were pretreated with fentanyl (50 μg) for analgesia 5 minutes before their first dose of AQUAVAN.
Duration of Treatment: The duration of treatment was 1 day.
Safety Reference Therapy, Dose, and Mode of Administration, Lot Number: Commercially available midazolam (Versed® or generic equivalent) was administered by i.v. bolus. The initial bolus was 0.02 mg/kg. All patients were pretreated with fentanyl (50 μg) for analgesia 5 minutes before their first dose of midazolam.

Criteria for Evaluation:
Primary Efficacy Endpoint:

- Sedation Success rate – Sedation Success was defined as a patient having (i) 3 consecutive Modified OAA/S scores of ≤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.

Secondary Efficacy Endpoints:

- Treatment Success rate – Treatment Success was defined as a patient (i) completing the procedure (ii) without requiring alternative sedative medications AND (iii) without requiring manual or mechanical ventilation.
- Proportion of patients requiring supplemental analgesic medication
- Proportion of patients who do not recall being awake during the procedure
- Proportion of patients willing to be treated again with the same study sedative agent

Tertiary Efficacy Endpoints:

- Number of analgesic doses administered
- Investigator's rating of level of satisfaction with the study sedative medication at the end of the Sedation Initiation Phase and at the end of procedure
- Patient's rating of experience after Ready for Discharge (memory recall, level of satisfaction with the entire procedure, level of comfort)
- Number of supplemental doses of study sedative medication administered
- Retention score during the Recovery Period based on the Hopkins Verbal Learning Test-Revised™ (HVLT-R)

Safety Endpoints:

- Nature, frequency, and indication of airway assistance
- Frequency of sedation-related adverse events (SRAEs; ie, apnea, hypoxemia, bradycardia, or hypotension)
- Nature, frequency, seriousness, severity, relationship to treatment, and outcome of all treatment-emergent adverse events (TEAEs)
- Purposeful movement
- Laboratory parameters, vital signs, pulse oximetry, and ECG

Statistical Methods:
For this study, 3 efficacy analysis populations and 1 safety population were used in the planned analyses. The modified intent-to-treat (mITT) analysis population was defined as all randomized patients who received at least 1 dose of either AQUAVAN or midazolam and had at least 1 postdose clinical assessment. The per Protocol (pP) population was defined as all patients from the mITT population who did not incur protocol violations with the potential to significantly affect the study results and who did not have their procedures terminated for non–study-drug related findings. The pP2 population was defined as all patients in the mITT population who did not receive alternative sedative medications. The safety population was defined as all randomized patients who received at least 1 dose of either AQUAVAN or midazolam.

In general, for continuous variables, data were summarized with mean, standard deviation (SD), median, minimum, and maximum by treatment group. For categorical variables, data were tabulated with number and proportion for each category by treatment group.

Efficacy:

For the primary and secondary efficacy endpoints, primary analyses were based on the mITT population and secondary analyses were based on the pP population. Tertiary efficacy endpoints were analyzed using the mITT and/or the pP2 populations. Due to the confounding effect of the alternative sedative medications, endpoints of interest were analyzed using both the mITT and/or pP2 population. Summary statistics were provided for all endpoints. All hypothesis tests were based on the comparisons between AQUAVAN Dose 2 (6.5 mg/kg initial bolus) and AQUAVAN Dose 1 (2.0 mg/kg initial bolus) groups.

- For the primary endpoint, the number and proportion of patients considered to have achieved Sedation Success were calculated by treatment group. A 95% exact confidence interval (CI) for the sedation success rate was calculated for each treatment group. Statistical tests comparing Sedation Success rates between the 2 AQUAVAN treatment groups were performed using Fisher's exact test. A 95% CI for the between-group difference was provided. AQUAVAN was declared effective in providing minimal-to-moderate sedation in patients undergoing colonoscopy if the Fisher's exact test proved that the sedation success rate for the Dose 2 group was significantly higher than that for the Dose 1 group. A Cochran-Armitage permutation test, adjusted for site variation, was used as an exploratory analysis.
- The secondary efficacy endpoints were analyzed using the same statistical methods as those used for analysis of the primary efficacy endpoint (Sedation Success). Statistical tests for the secondary efficacy endpoints were performed if and only if the primary efficacy hypothesis was proved to be statistically significant at α=0.05 level. The statistical tests were performed in a pre-defined hierarchical order, ie, the testing proceeded only if all the endpoints in the top hierarchy proved to be statistically significant at an α=0.05 level.
- The tertiary efficacy endpoints were evaluated using summary statistics.

Safety:

All safety analyses were based on the safety population, and include the following analyses:

- The total cumulative doses of study medication were summarized by treatment group.
- The patient and event incidences of airway assistance, both overall and by type, were tabulated by treatment group. The patient incidence was presented by number and proportion of patients within each treatment group that required airway assistance. The event incidence was presented by number of airway management events recorded for each treatment group.
- The number and percentage of patients who did not have purposeful movement were tabulated by treatment group. The duration of time that patients did not have purposeful movement was presented by treatment group using summary statistics.
- Treatment-emergent AEs were summarized by preferred term as well as by preferred term within system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA, version 9.0). In all analyses of TEAEs, events with similar preferred, lower limit and verbatim terms were grouped to the terms "paresthesias" and "pruritus."
- The following SRAEs of concern were tabulated separately from all other adverse events (AEs): apnea, hypoxemia, bradycardia, and hypotension.
- Shifts from baseline were tabulated by treatment group for laboratory values. Baseline values and changes from baseline in vital sign measurements were summarized by treatment group. Also, the numbers and proportions of patients experiencing pulse oximetry saturation values of <90%, <85%, and <80% at any time point and at 2 consecutive time points were tabulated by treatment group. All abnormal laboratory values, ECG results, and physical examination findings were identified in patient data listings.
- All medications taken within 14 days prior to study start, on the day of the procedure, and from the day after the procedure until the last patient contact were summarized by treatment group.

- The number and proportion of patients receiving alternative sedative medications during the study were tabulated by treatment group.
- Ad hoc analyses were done of phosphorus levels. Screening values, baseline values, changes from screening to baseline, and changes from baseline to recovery were tabulated by treatment group and by phosphate or non-phosphate bowel preparation.

Summary of Results

Efficacy:

Primary Endpoint

- Sedation Success rate was significantly higher in the AQUAVAN 6.5-mg/kg group (86.7%) compared with the AQUAVAN 2.0-mg/kg group (25.5%) in the mITT population ($p<0.001$).

Secondary Endpoints

- Treatment Success rate was also significantly higher in the AQUAVAN 6.5-mg/kg group (88.0%) compared with the 2.0-mg/kg group (28.4%) in the mITT population ($p<0.001$).
- The proportion of patients requiring supplemental analgesic medication was significantly lower for the AQUAVAN 6.5-mg/kg group (55.1%) than the AQUAVAN 2.0-mg/kg group (76.5%) in the mITT population ($p=0.001$).
- No significant difference was observed in the proportion of patients who did not recall being awake during the procedure between the 2 AQUAVAN groups in the mITT population. For those patients who did not receive an alternative medication (pP2 population), a significantly higher percentage of patients in the AQUAVAN 6.5-mg/kg group (48.9%) did not recall being awake during the procedure than in the AQUAVAN 2.0-mg/kg group (0%) ($p<0.001$).
- The proportion of patients willing to be treated again with the same study medication was generally high and was similar between treatment groups (>90%) in the mITT population.

Tertiary Endpoints

- In the AQUAVAN 6.5-mg/kg group, 94.9% of the patients required ≤2 doses of analgesic compared with only 75.5% of the patients in the 2.0-mg/kg group who received ≤2 doses (mITT population).
- A higher level of the physician satisfaction rating was reported for the AQUAVAN 6.5-mg/kg group as compared with AQUAVAN 2.0-mg/kg, both at the end of Sedation Initiation (mean of 7.1 versus 3.3) and at the End of Procedure (mean of 7.7 versus 4.5). In each treatment group, physician satisfaction scores were higher at End of Procedure than at the end of the Sedation Initiation Phase (mITT population).
- Higher levels of overall patient satisfaction with the entire procedure and overall comfort level were achieved in the AQUAVAN 6.5-mg/kg group (mean of 9.4 and 9.1, respectively) compared with the AQUAVAN 2.0-mg/kg group (means of 9.1 and 8.7) for the mITT population.
- The colonoscopy procedure was initiated after ≤2 supplemental doses of AQUAVAN for 75.9% of patients in the 6.5-mg/kg group, but for only 11.8% of patients in the 2.0-mg/kg group (mITT population).
- During the Recovery Period, the mean retention percentage (using the HVLT-R) was higher in the AQUAVAN 6.5-mg/kg group (67.0%) than in the 2.0-mg/kg group (59.2%) in the mITT population.

Safety:

- The mean total dose (±SD) of study sedative used to initiate and complete the colonoscopy was 789.1 mg (±206.7) in the AQUAVAN 6.5-mg/kg group, 264.0 mg (±46.1) in the 2.0-mg/kg group, and 4.34 mg (±1.54) in the midazolam group.
- No deaths occurred in the study.
- No patient was discontinued from the study because of an AE.
- No AQUAVAN-treated patient experienced a treatment-emergent SAE. One patient treated with midazolam experienced an SAE (peritoneal hemorrhage and splenic hematoma) that was judged by the Investigator to be unrelated to study drug. One patient in the AQUAVAN 2.0-mg/kg group experienced an SAE (adenocarcinoma of the colon) that was not related to study medication.
- Two patients required airway assistance (verbal stimulation and chin lift). Only the hypoxemia managed with verbal stimulation was considered an SRAE.
- Two patients had AEs (hypotension [AQUAVAN 6.5 mg/kg], lower left quadrant abdominal tenderness [midazolam]) that led to discontinuation of the colonoscopy.
- Treatment-emergent AEs were experienced by 91.8%, 87.3%, and 59.6% of patients in the AQUAVAN 6.5-mg/kg group, the 2.0-mg/kg group, and the midazolam group, respectively, in the safety population.
- Treatment-related AEs were experienced by 78.5%, 75.5%, and 5.8% of patients in the AQUAVAN 6.5-mg/kg, the 2.0-mg/kg group, and the midazolam group, respectively, in the safety population.
- The most common TEAEs experienced by patients in the AQUAVAN groups combined were paresthesia (65.0%), procedural pain (53.8%), and pruritus (19.6%).
- The frequency of procedural pain was similar across all treatment groups (range: 52.5 to 59.6%). However, for the majority of patients in the AQUAVAN 6.5-mg/kg group who had an AE of procedural pain, the pain was of mild severity (29.1%), with 22.2% experiencing moderate pain and 2 patients (1.3%) with severe procedural pain. The majority of patients who experienced procedural pain following midazolam or AQUAVAN 2.0-mg/kg treatment had pain that was moderate in severity (40.4% and 30.4%, respectively).
- Most TEAEs were mild or moderate in severity. Five patients (4 AQUAVAN 6.5-mg/kg and 1 AQUAVAN 2.0-mg/kg) experienced AEs that were judged to be severe in intensity. The AEs (pruritus and paresthesia) in 2 of these 4 patients in the 6.5-mg/kg group were considered treatment-related. Severe procedural pain that was not considered treatment related was experienced by the other 2 patients in the AQUAVAN 6.5-mg/kg group.
- Six patients experienced SRAEs during the study (6.5-mg/kg: hypoxemia [1], hypotension [2]; 2.0-mg/kg: hypotension [2]; midazolam: hypotension [1]). The hypoxemia required airway assistance (verbal stimulation), while the hypotension was treated with i.v. sodium chloride in 4 patients and led to discontinuation of the colonoscopy in the other patient.
- Inability to demonstrate purposeful movement at any time point on the Day of Procedure was observed in 12.7%, 8.8%, and 1.9% of the patients in the AQUAVAN 6.5-mg/kg group, the 2.0-mg/kg group, and the midazolam group, respectively. The mean total duration of time that patients did not demonstrate purposeful movement was 1.1, 0.5, and 0.1 minutes in the 6.5-mg/kg group, the 2.0-mg/kg group, and the midazolam group, respectively. The maximum duration was 18.0, 12.0, and 7.0 minutes in the 6.5-mg/kg group, the 2.0-mg/kg group, and the midazolam group, respectively.
- The AQUAVAN 2.0-mg/kg group had the highest percentage of patients who received alternative sedative medication (71.6%) compared with the 6.5-mg/kg (12.0%) and midazolam (19.2%) groups.
- With the exception of phosphorus, the frequencies of patients who had shifts in laboratory chemistry test

results from the normal range at baseline to below or to above normal at recovery were generally the same across treatment groups. Seventy percent of patients who received a phosphate preparation to cleanse the bowel prior to the colonoscopy had an increase of ≥1.0 mg/dL in their serum phosphorus levels. On the other hand, only 5.8% of the patients who received a non-phosphate medication had similar increases in serum phosphorus levels. Similar frequencies for these changes were seen in all treatment groups. In comparing the magnitude of the changes in serum phosphorus levels during different periods of the study (Screening, Baseline, and Recovery), the largest changes were increases that occurred between Screening and Baseline. A similar pattern for these increases in serum phosphorus levels between Screening and Baseline was observed across all treatment groups.

- Fourteen patients (13 in the AQUAVAN 6.5-mg/kg group and 1 in the midazolam group) had a shift between baseline and recovery in phosphorus from normal to high. Nine of these 14 patients had used phosphate-containing preparations prior to the procedure. In 12 of the 14 patients who had a predose baseline blood sample collected, the serum phosphorus level was higher at baseline than at the screening visit. Eleven of these 12 patients received AQUAVAN 6.5-mg/kg and had a mean change from screening to predose (baseline) of 1.13 mg/dL (range: 0 to 2.4) while the mean change from predose to recovery was 0.52 mg/dL (range: 0.2 to 0.90). None of the increases in phosphorus levels observed after the administration of study drug were judged by the Investigator to be clinically significant.
- No patient had pulse oximetry readings of <90% for 2 consecutive time points. No patient had readings of <85% at any time.

CONCLUSIONS

Efficacy:

AQUAVAN 6.5-mg/kg as an initial bolus dose followed by supplemental doses at 25% of the initial dose was efficacious when used to induce and maintain minimal-to-moderate sedation in patients undergoing colonoscopy, when used under the conditions described in this study.

Safety:

AQUAVAN was safe when used under the conditions of this study. Sedation-related AEs occurred infrequently and resolved with minimal intervention (verbal stimulation or i.v. fluid administration). When the TEAEs of pruritus and paresthesias, which are characteristic of AQUAVAN, are removed from the analysis, the safety profile of 6.5-mg/kg AQUAVAN was similar to that of midazolam, delivered at 0.02 mg/kg.

Overall:

An initial bolus dose of AQUAVAN 6.5-mg/kg followed by supplemental doses at 25% of the initial dose is a safe and effective treatment regimen for minimal-to-moderate procedural sedation in patients undergoing colonoscopy.

4.3.19 Study 3000-0523 Synopsis

Study Title: A Phase 3, 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
Investigators and Study Centers: Multicenter (see Appendix 16.1.4)
Publication (reference): see Appendix 16.1.11
Studied Period: 22 June 2006 (first patient enrolled) to 01 March 2007 (last patient completed)
Phase of Development: Phase 3
Objective: To assess the safety profile of AQUAVAN when used to provide minimal-to-moderate sedation in patients undergoing minor surgical procedures.
Methodology: This was a phase 3, open-label, single arm study designed to evaluate the safety of AQUAVAN® 6.5 mg/kg following pretreatment with an analgesic, fentanyl, in patients who were undergoing minor surgical procedures that required sedation (arthroscopy, arteriovenous [AV] shunt, bunionectomy, dilatation and curettage [D & C], esophagogastroduodenoscopy [EGD], lithotripsy, transesophageal echocardiography [TEE], and ureteroscopy). 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 surgical/diagnostic procedure was performed was immediately available during the conduct of the study. Patients were placed on supplemental oxygen via nasal cannula (4 L/min) during the study and connected to an electrocardiogram (ECG) monitor, pulse oximeter, and a blood pressure (BP) monitor prior to the administration of study medication. Five minutes prior to the Sedation phase, fentanyl was administered at a dose of 50 μg. In the Sedation phase, an initial bolus dose followed by supplemental doses (of 25% the initial bolus dose) of AQUAVAN were administered as needed to reach a Modified Observer's Assessment of Alertness/Sedation (OAA/S) score of ≤ 4 and to allow the Investigator to start the procedure. Up to 5 supplemental doses of AQUAVAN were administered at intervals of ≥ 4 minutes, if a patient's Modified OAA/S score was ≥ 4 and the patient demonstrated purposeful movement. Safety assessments were made during the course of the study. Pharmacokinetic (PK) samples were collected at 5 time points on the day of the procedure for patients who met the

American Society of Anesthesiologists (ASA) Physical Classification System status of ASA P3 or P4, were ≥ 65 years of age, or who had hepatic or renal insufficiency, as defined in the study protocol. These samples were analyzed for plasma fospropofol and propofol concentrations.
Number of Patients (Planned and Analyzed): Approximately 125 patients were planned for enrollment. A total of 123 patients were enrolled and analyzed for safety.
Diagnosis and Main Criteria for Inclusion: Patients were at least 18 years of age at the time of screening and met the ASA status of P1 to P4. If female, patients were surgically sterile, postmenopausal, or not pregnant or lactating; had been using an acceptable method of birth control for at least 1 month prior to dosing; and had a negative urine pregnancy test result at screening and predose.
Test Product, Dose and Mode of Administration, Lot Number: AQUAVAN (Lot number 900015) was administered intravenously (i.v.). Initial bolus was 6.5 mg/kg. Patients who were ≥ 65 years of age or were classified as ASA P4 received doses that were reduced by 25%. Patients who were classified as ASA P3 may have received reduced doses at the discretion of the Investigator. Patients were to be pretreated with fentanyl (50 µg) 5 minutes before their first dose of AQUAVAN.
Duration of Treatment: The duration of treatment was 1 day.
Reference Therapy, Dose, and Mode of Administration, Lot Number: There was no reference therapy for this single arm study.
Criteria for Evaluation: Safety Endpoints: • Nature, frequency, and indication of airway assistance • Frequency of sedation-related adverse events (SRAEs; ie, apnea, hypoxemia, bradycardia, or hypotension) • Nature, frequency, seriousness, severity, relationship to treatment, and outcome of all treatment-emergent adverse events (TEAEs) • Purposeful movement • Laboratory parameters, and vital signs • Concomitant medications Safety analyses included exposure to study drug. Pharmacokinetic Endpoints: The pharmacokinetics of fospropofol and propofol will be presented in a separate report.

Statistical Methods:

The safety population was used in the planned analyses. The safety population was defined as all enrolled patients who received at least 1 dose of AQUAVAN.

In general, for continuous or ordinal variables, data were summarized with mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, data were tabulated with number and proportion for each category.

Safety:

All safety analyses were based on the safety population, and included the following analyses:

- The total cumulative doses of AQUAVAN was calculated for each patient and summarized. The total cumulative dose of analgesic drug (fentanyl in µg) was also summarized.
- The patient incidence and event incidences of airway assistance were summarized. The endpoint was also cross-tabulated by the associated SRAE. Airway assistance was listed by patient and patient incidence of airway assistance was summarized by subgroup (sex, age, ASA status, type of surgical procedure, weight, and race).
- The following SRAEs of concern were tabulated separately from all other adverse events (AEs): apnea, hypoxemia, bradycardia, and hypotension. Patient incidence of SRAEs was summarized and a listing of all SRAEs was provided. In addition, patient incidence was summarized by subgroup (sex, age, ASA status, type of surgical procedure, weight, and race).
- The total duration of time when patients did not have purposeful movement (between the first dose of study drug to Fully Alert) was summarized using descriptive statistics. The number and percent of patients who demonstrated no purposeful movement at any time on the day of the procedure, and over 2 consecutive time points on the day of the procedure, were also summarized overall and by subgroup.
- Treatment-emergent AEs were summarized by preferred term as well as by preferred term within system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 9.1). In all analyses of TEAEs, events with similar preferred, lower level and verbatim terms were grouped to the terms "paresthesias" and "pruritus."
- Shifts from baseline laboratory values were tabulated. Baseline values and changes from baseline laboratory values and vital sign measurements were summarized. The number and proportion of patients with pulse oximetry values of < 90%, < 85%, and < 80% at any time point and at 2 consecutive time points on the day of the procedure were tabulated.
- All abnormal laboratory values, ECG results, and physical examination findings were

identified in patient data listings.

- Patient incidence of the worst shift in overall 3-lead ECG from baseline to Fully Alert was summarized.
- Patient incidence of medications taken prior to, on, and after the day of the procedure was summarized.

Exploratory endpoints:

Tabular summaries were presented for the following exploratory endpoints as defined in the statistical analysis plan (SAP):

- The number and proportion of patients receiving alternative sedative medication
- The number of supplemental doses of study drug administered
- Patient incidence of Modified OAA/S scores over time
- Duration and percent of time patients were at each Modified OAA/S score from the first dose of study drug to Fully Alert
- Duration of the procedure

Summary of Results

Safety:

- The mean total dose of AQUAVAN administered during the procedure was 742.0 mg (range: 280.0 to 1592.5 mg).
- Serious treatment-emergent AEs were experienced by 4 patients. None of these SAEs were considered to be related to the study drug. No deaths were reported in the study.
- No patient was discontinued from the study due to an AE.
- Treatment-emergent AEs were experienced in 90.2% of the patients, the majority mild to moderate and judged to be treatment-related. The 3 most common TEAEs reported in patients were paresthesia (53.7%), procedural pain (50.4%), and pruritus (26.0%).
- Five patients (4.1%) experienced an SRAE (hypotension, bradycardia, or hypoxemia) on the day of the procedure. An SRAE of hypotension was reported in 4 patients and was considered to be related to the study drug in 3 of these patients. The events of hypotension occurred during the dosing and recovery periods of the procedure. Bradycardia was experienced by 1 patient concurrently with hypotension managed with atropine, and was considered unrelated to study drug. Hypoxemia (less than 1 minute) was reported in 1 patient, was managed with airway assistance (chin lift and verbal stimulation), and was considered to be definitely related to study drug. No patient experienced apnea on the day of the procedure.
- Seven of 123 patients (5.7%) received airway assistance, one of whom required airway assistance due to an SRAE of hypoxemia.
- The incidence of loss of purposeful movement was greater in patients $\geq$ 75 years of age

(5 of 11 patients [45.5%]) compared with patients ≥ 65 to 74 years of age (4 of 13 patients [30.8%]) and patients 18 to 64 years of age (26 of 99 patient [26.3%]). Eight of these patients were unable to demonstrate purposeful movement on at least one timepoint in the preprocedural period and 10 in the post-procedural period

Exploratory:

- Alternative sedative medication was administered in 6 of 123 patients (4.9%). There did not appear to be any association between the type of surgical procedure and the incidence of alternative sedative medication administered.
- A mean of 2.4 supplemental doses of study sedative medication was administered to initiate and complete the various procedures.
- Mean duration of time that patients had Modified OAA/S scores 2 to 4 from the first dose of study sedative medication to Fully Alert was 25.1 minutes, and was less than 1 minute at deeper levels of sedation (Modified OAA/S scores 0 to 1).
- Median duration of the minor surgical procedures was 17.0 minutes, ranging from 2 minutes to 110 minutes. Seventy-five percent (75%) of the procedures were completed in 26.0 minutes or less.

CONCLUSIONS

The dosing regimen of an initial bolus of AQUAVAN 6.5 mg/kg followed by supplemental doses of 1.63 mg/kg had an acceptable and manageable safety profile when used to provide sedation for brief diagnostic, therapeutic, and surgical procedures under the conditions described in this study. The loss of purposeful movement prior to procedure initiation in 8 of 123 patients (6.5%) and after procedure completion in 10 of 123 patients (8.1%) and the occurrence of hypotensive events after procedure completion underscore the need to monitor patients from first administration of AQUAVAN until discharge criteria are met.

4.3.20 Study 3000-0524 Synopsis

Study Title:
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

Investigators and Study Centers: Multicenter (see Appendix 16.1.4)

Publication (reference): see Appendix 16.1.11

Studied Period:
18 April 2006 (first patient enrolled) to
09 February 2007 (last patient completed)

Phase of Development: Phase 3

Objectives:

Primary Objective:

- To demonstrate that AQUAVAN* is effective in providing sedation in patients undergoing flexible bronchoscopy.

Secondary Objectives:

- To demonstrate that sedation with AQUAVAN* provides a clinical benefit to the patient during sedation. Specifically, the following objectives were to be demonstrated in hierarchical order:
    a. AQUAVAN enables the completion of the procedure without alternative sedative medications and mechanical airway management.
    b. AQUAVAN eases the patient's overall experience as measured by their willingness to be treated again.
    c. AQUAVAN minimizes the patient's memory recall for the procedure.
- To evaluate the safety profile of the therapeutic dose of AQUAVAN.

*Because this was a dose-controlled study, the reference to AQUAVAN in the objectives refers to the initial high dose AQUAVAN group.

Methodology: This was a phase 3, randomized, double-blind, dose-controlled study designed to evaluate the efficacy and safety of AQUAVAN 6.5-mg/kg compared with a lower active control dose of AQUAVAN 2.0-mg/kg, both following pretreatment with an analgesic, fentanyl, in patients who were undergoing flexible bronchoscopy.

Following completion of preprocedural assessments, patients were randomly assigned to 1 of 2 treatment groups in a 2:3 allocation ratio (AQUAVAN Dose 1:AQUAVAN Dose 2) on the day of the scheduled procedure. Randomization was stratified by site.

Treatment groups are defined below.

Treatment Group	Sedation Initiation Dose
AQUAVAN Dose 1:	2.0-mg/kg
AQUAVAN Dose 2:	6.5-mg/kg

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 flexible bronchoscopy was performed was immediately available during the conduct of the study. All patients were placed on supplemental oxygen via nasal cannula (4 L/min) during the study. Patients were connected to an electrocardiogram (ECG) monitor, pulse oximeter, and a blood pressure (BP) monitor prior to administration of study medication.

Five minutes prior to Sedation Initiation, fentanyl was administered at a dose of 50 μg. In the Sedation Initiation Phase, an initial bolus dose and up to 3 supplemental doses of AQUAVAN were administered as needed to reach a Modified Observer's Assessment of Alertness/Sedation (OAA/S) score of ≤ 4 and to allow the Investigator to start the flexible bronchoscopy. In the Sedation Maintenance Phase, up to 4 sedation maintenance doses of AQUAVAN were administered at intervals of ≥ 4 minutes, if a patient's Modified OAA/S score was ≥ 4 and the patient demonstrated purposeful movement.

Number of Patients (Planned and Analyzed):
Approximately 250 patients were planned for enrollment. Of the 256 patients randomized, 252 patients received at least 1 dose of study medication and were analyzed for safety and efficacy.

Diagnosis and Main Criteria for Inclusion:

Patients were at least 18 years of age at the time of screening and met the American Society of Anesthesiologists (ASA) Physical Classification System status of P1 to P4. If female, patients were surgically sterile, postmenopausal, or not pregnant or lactating; had been using an acceptable method of birth control for at least 1 month prior to dosing; and had a negative urine pregnancy test result at screening and predose.

Test Product, Dose and Mode of Administration, Lot Number:
AQUAVAN (Lot number GAA002) was administered intravenously (i.v.). Initial boluses were 2.0 mg/kg or 6.5 mg/kg. Patients who were ≥ 65 years of age or were classified as ASA P4 received doses that were reduced by 25% from the randomized dose. Patients who were classified as ASA P3 may have received reduced doses at the discretion of the Investigator.

Patients were to be pretreated with fentanyl (50 μg) 5 minutes before their first dose of AQUAVAN and lidocaine was to be administered as a topical anesthetic for suppression of cough upon introduction of the flexible bronchoscope.

Duration of Treatment: The duration of treatment was 1 day.

Criteria for Evaluation:
Primary Efficacy Endpoint:

- Sedation Success rate, where Sedation Success was defined as a patient having (i) 3 consecutive Modified OAA/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.

Secondary Efficacy Endpoints:

- Treatment success rate–Treatment success was defined as a patient (i) completing the procedure (ii) without requiring alternative sedative medications AND (iii) without requiring manual or mechanical ventilation.
- Proportion of patients willing to be treated again with the same study sedative agent
- Proportion of patients who do not recall being awake during the procedure

Tertiary Efficacy Endpoints:

- Proportion of patients requiring supplemental analgesic medication
- Investigator's rating of level of satisfaction with the study sedative medication at the end of the Sedation Initiation Phase and at the end of the procedure
- Patient's rating of experience after Ready for Discharge (remembrance of the insertion and removal of the bronchoscope, level of satisfaction with the entire procedure, level of comfort)
- Number of supplemental doses of study sedative medication administered
- Retention score during the Recovery period based on the Hopkins Verbal Learning Test-Revised™ (HVLT-R™)

Safety Endpoints:

- Nature, frequency, and indication of airway assistance
- Frequency of sedation-related adverse events (SRAEs; ie, apnea, hypoxemia, bradycardia, or hypotension)

- Nature, frequency, seriousness, severity, relationship to treatment, and outcome of all treatment-emergent adverse events (TEAEs)
- Purposeful movement
- Laboratory parameters, vital signs, pulse oximetry, and ECG
- Concomitant medications
- Alternative sedative medications

Statistical Methods:

For this study, 3 efficacy analysis populations (mITT, pP, and pP2) and 1 safety population were used in planned analyses. The modified intent-to-treat (mITT) analysis population was defined as all randomized patients who received at least 1 dose of AQUAVAN and had at least 1 postdose clinical assessment. The per Protocol (pP) population was defined as all patients in the mITT population who did not incur major protocol deviations that had the potential to significantly impact the analysis or interpretation of the study results and who did not have their procedure terminated for non–study-drug related findings. The pP2 population was defined as all patients in the mITT population who did not receive alternative sedative medication. The safety population was defined as all randomized patients who received at least 1 dose of AQUAVAN.

In general, for continuous or ordinal variables, data were summarized with mean, standard deviation (SD), median, minimum, and maximum by treatment group. For categorical variables, data were tabulated with number and proportion for each category by treatment groups.

All confidence intervals and statistical comparisons were based on 2-sided tests with α=0.05.

Efficacy:

The primary and secondary efficacy endpoints were analyzed using the mITT population. Additional analyses were performed using the pP and/or pP2 populations. The tertiary efficacy endpoints were analyzed using the mITT and/or pP2 populations. Summary statistics were provided for all endpoints.

- For the primary endpoint, the number and proportion of patients considered to be a Sedation Success were calculated by treatment group. A 95% exact confidence interval (CI) for the Sedation Success rate was calculated for each treatment group. Statistical tests comparing Sedation Success rates between AQUAVAN Dose 2 (Sedation Initiation dose of 6.5-mg/kg) and AQUAVAN Dose 1 (Sedation Initiation dose of 2.0-mg/kg) were performed using Fisher's exact test. A 95% CI for the between-group difference was provided. AQUAVAN was declared effective in providing sedation in patients undergoing flexible bronchoscopy if the Fisher's exact test proved that the Sedation Success rate for the Dose 2 group was significantly higher than that for the Dose 1 group.

- The secondary efficacy endpoints were analyzed using the same statistical methods as those used for analysis of the primary efficacy endpoint (Sedation Success). Statistical tests for the secondary efficacy endpoints were performed if and only if the primary efficacy hypothesis was proved to be statistically significant at α=0.05 level. The statistical tests were performed in a predefined hierarchical order, ie, the testing proceeded only if all the endpoints in the top hierarchy proved to be statistically significant at an α=0.05 level.
- The tertiary efficacy endpoints were evaluated using summary statistics.

Safety:

All safety analyses were based on the safety population, and include the following analyses:

- The total cumulative doses of study medication were summarized by treatment group.
- The patient and event incidences of airway assistance, both overall and by type, were tabulated by treatment group. Airway assistance events were also cross-tabulated by the associated SRAEs.
- The following SRAEs were tabulated separately from all other AEs: apnea, hypoxemia, bradycardia, and hypotension.
- The number and percentage of patients who did not have purposeful movement were tabulated by treatment group. The duration of time that patients did not have purposeful movement was presented by treatment group using summary statistics.
- Treatment-emergent AEs were summarized by preferred term as well as by preferred term within system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA) (version 9.1). The patient incidence of TEAEs was tabulated by treatment group, by severity, and by causal relationship to study medication. In all analyses of TEAEs, events with similar preferred terms, lower limit terms, and verbatim terms were grouped to the terms "paresthesia" or "pruritus."
- Shifts from Baseline laboratory values were tabulated by treatment group. Baseline values and changes from Baseline in vital sign measurements were summarized by treatment group. Also, the numbers and proportions of patients experiencing the following changes from Baseline in pulse oximetry values were tabulated by treatment group as <90%, <85%, and <80% saturation at any time point and at 2 consecutive time points. All abnormal laboratory values, ECG results, and physical examination findings were identified in patient data listings.
- All concomitant medications taken prior to, on, and after the day of the procedure were summarized by treatment group.
- The number and proportion of patients receiving alternative sedative medications during the study were tabulated by treatment group.

Summary of Results
Efficacy:
Primary Endpoint

- Sedation Success rate was significantly higher in the AQUAVAN 6.5-mg/kg group (88.7%) compared with the AQUAVAN 2.0-mg/kg group (27.5%) in the mITT population ($p<0.001$).

Secondary Endpoints

- Treatment Success rate was significantly higher in the AQUAVAN 6.5-mg/kg group (91.3%) compared with the 2.0-mg/kg group (41.2%) in the mITT population ($p<0.001$).
- The proportion of patients willing to be treated again with the same study medication was significantly higher in the AQUAVAN 6.5-mg/kg group (94.6%) compared with the 2.0-mg/kg group (78.2%) in the mITT population ($p<0.001$).
- The proportion of patients who did not recall being awake during the procedure was significantly higher in the AQUAVAN 6.5-mg/kg group (83.3%) compared with the 2.0-mg/kg group (55.4%) in the mITT population ($p<0.001$).

Tertiary Endpoints

- The proportion of patients requiring supplemental analgesic medication was lower for the AQUAVAN 6.5-mg/kg group (16.7%) compared with the 2.0-mg/kg group (37.3%) in the mITT population, but the proportion was similar between groups in the pP2 population (14.5% and 16.7%, respectively).
- A higher level of the physician satisfaction rating was reported for the AQUAVAN 6.5-mg/kg group compared with the 2.0-mg/kg group both at the end of Sedation Initiation (mean of 8.0 versus 3.9) and at the End of Procedure (mean of 8.3 versus 5.0) in the mITT population.
- Higher levels of overall patient satisfaction with the entire procedure and overall comfort level were achieved in the AQUAVAN 6.5-mg/kg group (mean of 9.5 and 9.4, respectively) compared with the 2.0-mg/kg group (mean of 8.7 and 8.5, respectively) in the mITT population.
- The procedure was initiated after ≤ 2 supplemental doses of AQUAVAN for 89.3% of patients in the 6.5-mg/kg group and for 33.3% of patients in the 2.0-mg/kg group in the mITT population.
- During the Recovery Period, the mean retention percentage (using the HVLT-R™) was

similar in the AQUAVAN 6.5-mg/kg and 2.0-mg/kg groups (64.2% and 63.6%, respectively) in the mITT population.

Safety:

- The mean total dose (±SD) of AQUAVAN used during the bronchoscopy was 623.8 mg (±241.0) in the 6.5-mg/kg group and 224.1 mg (±56.0) in the 2.0-mg/kg group.
- Three patients (2.0%) in the AQUAVAN 6.5-mg/kg group and 2 patients (1.9%) in the 2.0-mg/kg group died as a result of SAEs identified during the study. The deaths occurred 4, 11, 19, 22, and 23 days after receiving study drug. None of the deaths were considered to be related to study drug.
- Serious treatment-emergent AEs were experienced by 15 patients (10.1%) in the AQUAVAN 6.5-mg/kg group and 13 patients (12.6%) in the 2.0-mg/kg group within 30 days of study drug administration. None of these SAEs were considered to be related to study drug. An additional patient in the 6.5-mg/kg group experienced an SRAE of hypoxemia requiring manual ventilation that was not classified as an SAE by the Investigator, but that MGI PHARMA considered to be serious and probably related to study drug.
- No patient was discontinued from the study due to an AE.
- In the AQUAVAN 6.5-mg/kg group, 1 patient experienced an AE that led to discontinuation of both study drug and the procedure and another patient experienced an AE that led to discontinuation of study drug. In the 2.0-mg/kg group, 1 patient discontinued the procedure due to an AE.
- Treatment-emergent AEs were experienced by 83.2% of patients in the AQUAVAN 6.5-mg/kg group and by 76.7% of patients in the 2.0-mg/kg group. Treatment-emergent AEs that occurred with the greatest frequency overall were paresthesia (47.6%), hypoxemia (15.9%), pruritus (14.7%), and procedural pain (11.9%).
- Treatment-emergent AEs that occurred in a higher percentage of patients in the AQUAVAN 6.5 mg/kg group compared with the 2.0 mg/kg group included paresthesia (49.7 % versus 44.7%, respectively), hypoxemia (17.4% versus 13.6%), cough (8.7% versus 3.9%), hypotension (8.1% versus 1.9%), and malignant lung neoplasm (3.4% versus 0%).
- Treatment-related AEs were experienced by 69.8% of patients in the AQUAVAN 6.5-mg/kg and by 65.0% of patients in the 2.0-mg/kg group. The treatment-related TEAEs that occurred with the greatest frequency overall were paresthesia (47.6%), pruritus (14.7%), hypoxemia (9.9%), and hypotension (4.4%).
- Most TEAEs were mild or moderate in severity. Severe TEAEs were experienced by 22 patients (14.8%) in the AQUAVAN 6.5-mg/kg group and 13 patients (12.6%) in the

AQUAVAN 2.0-mg/kg group. Severe AEs that were also considered treatment related were paresthesia (5 patients in the 6.5 mg/kg group and 1 patient in the 2.0-mg/kg group), pruritus (1 patient in each group), and hypoxemia (2 patients in the 6.5-mg/kg group).

- Sedation-related AEs were experienced by 30 patients (20.1%) in the AQUAVAN 6.5-mg/kg group; including 1 patient with apnea, 8 patients with hypotension, and 23 patients with hypoxemia (1 patient experienced all 3 events). Hypoxemia was experienced by 13 patients in the 2.0-mg/kg group and no patients in the 2.0-mg/kg group experienced apnea or hypotension.
- Airway assistance was required by 32 patients (21.5%) in the AQUAVAN 6.5-mg/kg group and by 14 patients (13.6%) in the 2.0-mg/kg group. Increased oxygen flow due to hypoxemia was the most frequently required airway assistance (20 patients in the 6.5-mg/kg group and 11 patients in the 2.0-mg/kg group). No patients required mechanical ventilation and 1 patient (6.5-mg/kg group) required manual ventilation.
- Inability to demonstrate purposeful movement at some time point on the Day of Procedure was observed in 29.5% of patients in the AQUAVAN 6.5-mg/kg group and in 13.6% of patients in the 2.0-mg/kg group. The mean total duration of time that patients did not demonstrate purposeful movement was 2.6 minutes in the 6.5-mg/kg group and 1.4 minutes in the 2.0-mg/kg group. The maximum duration was 58.0 minutes in the 6.5-mg/kg group and 52.0 minutes in the 2.0-mg/kg group.
- Alternative sedative medication was required by a lower percentage of patients in the AQUAVAN 6.5-mg/kg group (8.0%) compared with the 2.0-mg/kg group (58.8%).
- The frequencies of patients who had shifts in laboratory chemistry test results from the normal range at Baseline to below or to above normal at Recovery were similar in the 2 treatment groups. The means of the largest increases and decreases from Baseline vital signs on the Day of Procedure were also similar in the 2 treatment groups.
- Pulse oximetry values <80% were observed in 4 patients in the AQUAVAN 6.5-mg/kg group, including 1 patient who had values <80% for 2 consecutive two-minute time points. Pulse oximetry values <85% were observed in 13 patients in the AQUAVAN 6.5-mg/kg group, including 5 patients who had values <85% for 2 consecutive time points. Pulse oximetry values <85% were observed in 3 patients in the 2.0-mg/kg group.

CONCLUSIONS

Efficacy Conclusion:

An initial bolus dose of AQUAVAN 6.5 mg/kg followed by supplemental doses at 25% of the initial dose was efficacious when used to induce and maintain minimal-to-moderate sedation in patients undergoing a bronchoscopy, when used under the conditions described in this study.

Safety Conclusion:

AQUAVAN had an acceptable and manageable safety profile when used under the conditions described in this study. Adverse events related to treatment with AQUAVAN were generally mild or moderate in severity and resolved with minimal intervention.

Overall:

An initial bolus dose of AQUAVAN 6.5 mg/kg followed by supplemental doses at 25% of the initial dose is an effective treatment regimen with a manageable safety profile for sedation in patients undergoing a bronchoscopy.

4.3.21 Filing Memo

Office of Clinical Pharmacology ***New Drug Application Filing and Review Form***			
General Information About the Submission			
	Information		Information
NDA Number	22-244	Brand Name	Aquavan
OCP Division	2	Generic Name	Fos-propofol
Medical Division	Anesthesia, Analgesia and Rheumatology Products	Drug Class	Sedative
OCP Reviewer	Srikanth C. Nallani, Ph.D.	Indication(s)	[redacted] b(4)
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	IV injection
		Dosing Regimen	Initial dose of 6.5 mg/kg followed by 1.6 mg/kg
Date of Submission	9/26/2007	Route of Administration	Intravenous Bolus
Estimated Due Date of OCP Review	6/9/2008	Sponsor	MGI Pharma/ Eisai Pharmaceuticals Inc.
PDUFA Due Date	6/26/2008	Priority Classification	Standard
Division Due Date	6/11/2008		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**	**1**	**1**	**Plasma samples have hemolysis-related assay problem (AP)**
Isozyme characterization:	**X**	**2**	**2**	**Metabolic stability & Influence of alkaline phosphatase on aquavan metabolism**
Blood/plasma ratio:	**X**	**1**	**1**	
Plasma protein binding:	**X**	**1**	**1**	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	8	8	
multiple dose:				

Patients-				
single dose:		7	7	
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	1	1	
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X	1	1	
renal impairment:	X	1	1	As part of Phase 2/3 study
hepatic impairment:	X	1	1	As part of Phase 2/3 study
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	3	3	
Phase 3 clinical trial:	X	2	2	
Population Analyses -				
Data rich:				
Data sparse:	X			
2II. Biopharmaceutics				
Absolute bioavailability:	**X**	**1**	**1**	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other Clin Pharm Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			

Total Number of Studies		**18**	**18**	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. It is indicated in the submission that after being liberated from fospropofol disodium, propofol undergoes further biotransformation as described by others (Simons, 1988, Gray, 1992). It is also mentioned that fospropofol does not induce or inhibit CYP enzymes based on results from a 14-day IV infusion toxicity study (3000-15715-00-06G) in dogs. Provide information about the specific metabolic pathways (e.g., CYP or non-CYP) of propofol clearance. Provide information on the potential for fospropofol and propofol to induce or inhibit major CYP enzymes. If this information is provided within the submission indicate the location of the information. Preferred tools for assessing drug interaction potential with regard to CYP enzyme inhibition and induction are indicated in the Draft guidance for Industry, Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling (http://www.fda.gov/cder/guidance/6695dft.htm).		
QBR questions (key issues to be considered)	**What are the intrinsic factors that influence the following ? Disposition of fospropofol and propofol; and Sensitivity of sedative effects of the drug(s) in different surgery populations.**			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Srikanth Nallani
6/23/2008 12:40:13 PM
BIOPHARMACEUTICS

Atul Bhattaram
6/23/2008 01:50:10 PM
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