5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

A detailed review was conducted by Dr. Srikanth Nallani. His findings, outlined here are based upon

- Three in vitro studies assessing protein binding and metabolism by alkaline phosphatase and CYP enzymes
- Nine Phase 1 PK, PK-PD studies in healthy subjects
  - Main contribution to PK data is from
    - Relative bioavailability study # 3000-625
    - QTc study # 3000-0521

- Three Phase 2 safety, efficacy and PK studies in patients
  - drug interaction, dose-ranging, elderly

- Three Phase 3 efficacy, safety and PK studies
  - 3000-522: Colonoscopy trial
  - 3000-523: Minor surgical procedures
  - 3000-524: Bronchoscopy trial

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

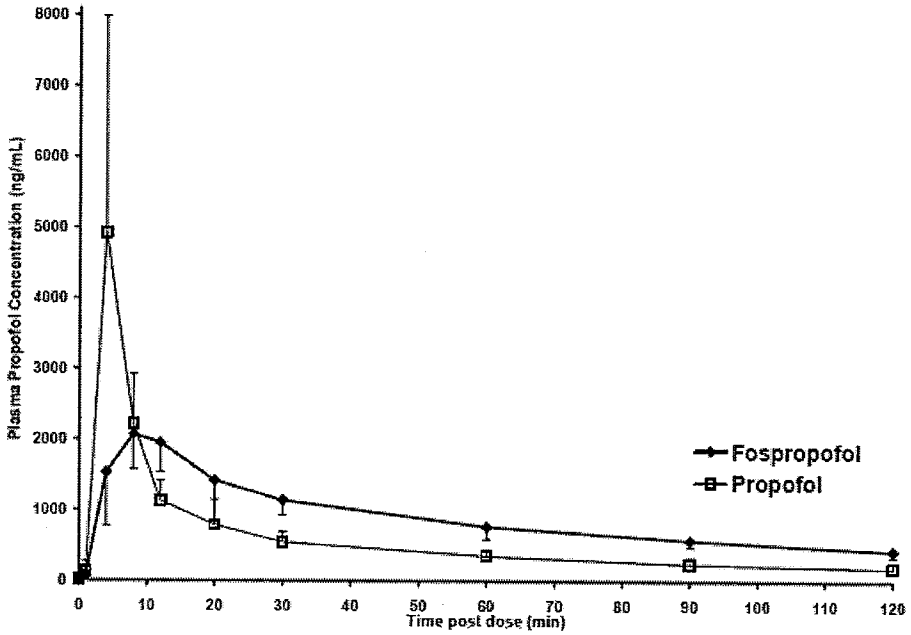
Pharmacokinetic analysis of fospropofol and propofol suggested dependence of clearance on total body weight. After compensating for the effect of body weight factors such as age, race, albumin concentration, alkaline phosphatase concentrations, and renal impairment did not influence the pharmacokinetics of fospropofol and propofol.

Only seven subjects with hepatic impairment were evaluated (Study 3000-523) where blood samples were also collected for PK analysis. The severity of hepatic impairment in these patients was not fully characterized using Child-Pugh criteria because the patients' prothrombin time data not reported. Fospropofol is metabolized by alkaline phosphatases that are ubiquitously present in various organs of the body apart from liver so disposition of fospropofol is not expected to be affected by liver impairment. However, propofol is extensively metabolized by glucuronidation and oxidation and may depend on hepatic involvement. The information on propofol clearance from patients with hepatic impairment is limited at this time. Therefore, the label for fospropofol should be comparable to the label for propofol and indicate that fospropofol should be used with caution in patients with hepatic insufficiency.

5.2 Pharmacodynamics

The pharmacokinetic/pharmacodynamic (PK/PD) profile of propofol derived from both fospropofol and propofol were compared in a cross-over study of 12 healthy subjects (Study 3000-0625). Subjects received approximately equipotent doses of fospropofol and propofol based on a processed electroencephalogram Bispectral Index (BIS). In the first treatment period, subjects received a 10 mg/kg bolus IV dose of fospropofol disodium injection. In the second treatment period, after a 7-day washout interval, each subject received a 50-mg/min infusion of propofol injectable emulsion targeted to produce the same peak BIS effect that was observed in that subject after administration of 10-mg/kg fospropofol disodium injection. On a molar basis, subjects received a mean dose of 2.102 mmoles of propofol from a bolus injection of fospropofol; and 0.906 mmoles of propofol following an infusion of propofol. Administration of propofol resulted in a rapid and dramatic rise and subsequent drop in plasma propofol concentrations; whereas, administration of fospropofol produced a gradual increase in plasma propofol concentration to therapeutic levels and a subsequent gradual decrease resulting in a lower C_{max} and later T_{max} than propofol.

Figure 5.2-1 Plasma Propofol Concentration after Administration of 10 mg/kg Bolus of Fospropofol and an Infusion of Propofol that Yielded Similar Bispectral Index Scores in Healthy Volunteers



From Sponsor's Clinical Overview of Biopharmaceutics 2.5.2 page 10 and Study 3000-0625

In the setting of propofol as the only anesthetic, healthy patients and normal body temperatures, bispectral index is expected to provide a reasonably reliable estimate of sedation depth. (Measuring Depth of Anesthesia by Donald R. Stanski and Steven L. Shafer (Chapter 31) in Anesthesia 6th Edition; Ronald D. Miller Editor. 2004

Figure 5.2-2 Bispectral Index after Administration of 10 mg/kg of Fospropofol and an Infusion of Diprivan (propofol)

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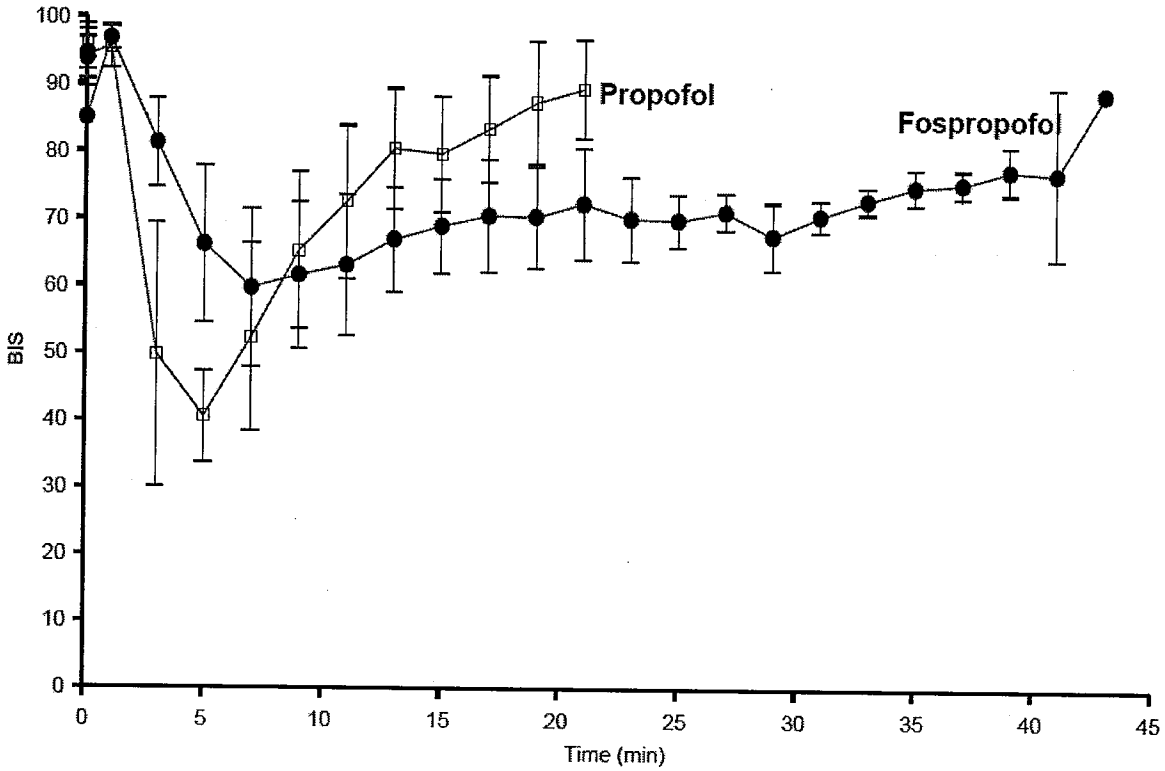


From Sponsor's Clinical Overview of Biopharmaceutics 2.5.2 page 10 and Study 3000-0625

A BIS value near 100 indicates that the subject was alert, and a BIS value of 0 indicated an isoelectric EEG or the absence of cortical activity under the electrodes (frontal lobes). The propofol dose derived from fospropofol disodium injection treatment (dose corrected for molecular weight=5.36 mg/kg) was higher compared with the propofol dose from treatment with propofol injectable emulsion (50 mg/minute infused for 2.06 to 4.60 minutes, total mean ± SD dose of 2.30 ± 0.39 mg/kg).

A fospropofol-propofol PK-PD relationship was also determined by correlating depth of sedation, as determined by Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score to fospropofol and propofol plasma concentrations in patients receiving colonoscopy and bronchoscopy. These findings were evaluated in Section 6 of this review.

The data sets for the fospropofol-propofol population PK-PD analyses included 2340 fospropofol concentration values from 665 patients and 1499 propofol concentrations from 399 patients. The data set for the fospropofol–sedation population PK/PD analysis included 8051 MOAA/S values from 471 patients who took part in the colonoscopy studies (3000-0207, 3000-0415, 3000-0520, and 3000-0522), bronchoscopy study 3000-0524, and received a therapeutic (5 mg/kg and higher) dose of fospropofol injection. In addition, population PK parameters in patients were compared to PK parameters from a study of healthy subjects (3000-0521) to evaluate similarities and differences in patients versus healthy subjects.

The influences of covariates in patients such as demographic characteristics (age, race, gender, weight, height), lab values at baseline (albumin, ALP, total bilirubin, and serum creatinine), and health status (ASA status of P3 or P4) of fospropofol and propofol PK and PD were included in the population PK-PD analyses. The effects of gender were also analyzed in the PK parameter analyses for study 3000-0521 (healthy subjects). The principal findings were:

- No difference in fospropofol PK between patients and in healthy subjects was observed.
- In the study population, gender was strongly correlated with body size measurements.
- After accounting for body weight, no gender-dependent effects on fospropofol or propofol PK were evident.
- No influence of fentanyl dose or exposure on fospropofol and propofol PK was detected.
- No influences of race (black and hispanic versus white) and age on fospropofol and propofol PK were detected.
- No influences of alkaline phosphatase concentration, total bilirubin concentration, and calculated normalized creatinine clearance on fospropofol and propofol PK were detected.

5.3 Exposure-Response Relationships

The exposure-response of fospropofol was reviewed in reference to the following:

- Efficacy findings from dose-ranging Study 3000-0520 in colonoscopy patients, dose-controlled Study 3000-0522 in colonoscopy patients and dose-controlled Study 3000-0524 in bronchoscopy patients
- Electrocardiographic QTc interval changes associated with fospropofol in Study 3000-0521

Dose-response: Efficacy
The dose-response relationship between fospropofol dose and sedation success was explored in dose-finding study 3000-0520, clinical efficacy studies in patients undergoing colonoscopy (3000-0522) and bronchoscopy (3000-0524). A population PK and PD analysis of data from Phase 2 and Phase 3 studies was also performed.

The dose-response findings for the controlled studies 3000-05020, -0522 and -0524 are summarized here and reviewed in detail in Section 6 below. The pharmacodynamic assessment was sedation success defined as a composite of three consecutive sedation scores indicating reduced alertness (Modified Observer Alertness Assessment Score ≤ 4), and completion of the

diagnostic procedure without the use of an alternative sedation product or manual or mechanical ventilation.

Dose-response in Study 3000-0520 conducted in colonoscopy patients

Patients were randomized to one of the following 5 groups (n~25 per group) in a 1:1:1:1:1 ratio including 4 dose levels of fospropofol disodium (8.0 mg/kg, 6.5 mg/kg, 5.0 mg/kg, 2.0 mg/kg) and midazolam 0.02 mg/kg. Six of 25 patients (24%) in the 2-mg/kg fospropofol group, 9 of 26 (35%) in the 5-mg/kg group, 18 of 26 (69%) in the 6.5-mg/kg group, and 23 of 24 (96%) in the 8-mg/kg group achieved Sedation Success.

Dose-response in Study 3000-0522 conducted in colonoscopy patients

Patients in study 3000-0522 were randomized to one of the following 3 groups in a 3:2:1 ratio: fospropofol disodium 6.5 mg/kg; fospropofol disodium 2.0 mg/kg; and midazolam 0.02 mg/kg, respectively. Sedation Success Rate was significantly higher in the fospropofol 6.5 mg/kg group (87%) compared with the fospropofol 2.0 mg/kg group (26%). Sedation Success was achieved in 69% of the patients treated with midazolam.

Dose-response in Study 3000-0524 conducted in bronchoscopy patients

Patients in study 3000-0524 were randomized to one of the following 2 groups in a 3:2 ratio: fospropofol disodium 6.5 mg/kg (n=150) and 2.0 mg/kg (n=102), respectively. The Sedation Success rate was significantly higher in the fospropofol 6.5-mg/kg group (89%) compared with the fospropofol 2.0-mg/kg group (28%).

Dr. Nallani's review also indicated that geriatric patients exhibited increased sedation fospropofol than patients who are younger than 65 years of age despite a reduction dose by 25% in clinical studies.

Dose-response: Effect of Fospropofol on the QTc Interval

In a randomized, open-label, positive- and placebo-controlled crossover study 3000-0521, 68 healthy subjects were administered single IV bolus dose of fospropofol 6 mg/kg, fospropofol 18 mg/kg (3-times the recommended dose), placebo and a single oral dose of 400 mg moxifloxacin. At the anticipated clinical dose of 6 mg/kg, no significant effect on the QTcF (Qt interval corrected for heart rate (RR) interval using $QT/RR^{1/3}$, Fridericia technique) was detected. Following the 18 mg/kg dose, the largest upper bound of the two-sided 90% CI for the $\Delta\Delta$QTcF (change in treatment – change in placebo) at the 12-minute time point was greater than 10 ms which is identified as the threshold for regulatory concern in the ICH E14 guideline. However, this exposure would not be expected clinically unless a subject weighing 60 kg or less received a full vial containing 1050 mg fospropofol.

Mean peak fospropofol and propofol derived from fospropofol plasma concentrations for the 18 mg/kg dose were approximately 3.6-fold higher than the peak concentrations following a 6 mg/kg dose. The overall findings are summarized in the following table.

Table 5.3-1 Dose-Response of Fospropofol on Mean QTc with 90% Confidence Intervals

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

*CI is adjusted with 11 post-baseline time points

Table is from Consultant's Review by Dr. Christine Garnett of the Interdisciplinary Review Team for QT Studies

The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms indicating that the study was adequately designed and conducted to detect an effect on the QT interval.

The fospropofol doses evaluated in this study are acceptable. There are no known intrinsic or extrinsic factors that can increase exposure to fospropofol and propofol derived from fospropofol greater than what was observed following the supratherapeutic dose. Therefore, when used as directed by the labeled dosing, fospropofol is not expected to cause clinically significant QT prolongation.

The Interdivisional Review Team for QT Studies recommended that the Sponsor consider reanalyze their data according to ICH E14 Guidelines. This recommendation was communicated to the Sponsor by Allison Meyer, the project manager of this submission. In addition, the Interdivisional Review Team suggested labeling changes to Section 12.2 Pharmacodynamics of the package insert which are included in the Line-by-Line Labeling Review 10.2 of this Review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Sedation for Procedures

The proposed indication is sedation in adult patients undergoing diagnostic or therapeutic procedures. The types of medical procedures that typically require sedation for adult patients are often associated with discomfort because they are invasive. Therefore it is common to administer an analgesic concomitantly with a sedation product that reduces awareness and recall of the unpleasant aspects of the procedure. However, some adult patients require a sedation product just to reduce anxiety. For example, patients who have symptoms of claustrophobia when being evaluated in a whole body scanner may require anxiolysis.

6.1.1 Methods

The Sponsor conducted three randomized, blinded and controlled clinical studies that enabled an evaluation of efficacy of the proposed dosing regimen of fospropofol. The patient population in these studies underwent elective bronchoscopy or colonoscopy. Study 3000-0520 was a dose-ranging study of four different loading and supplementary dosing regimens of fospropofol and a midazolam arm, using labeled dosing, as a safety comparator. In this Study, only 26 patients were evaluated at the proposed dosing. The findings from -0520 were used as a foundation for a larger dose-controlled study -0522, which compared low-dose to a high-dose of fospropofol in colonoscopy patients. In Study -0522, 158 patients who were administered the proposed dosing were compared to 102 patients who were administered the lower dose. A midazolam arm using labeled dosing was also included in Study -0522 as a safety comparator. Study -0524 in bronchoscopy patients was similar in size and design to -0522 in that the same fospropofol dosing comparison used in -0522 was also used in -0524. In this study, 150 bronchoscopy patients were administered the proposed dosing and 102 patients were administered the lower dose. In all studies, patients were administered a dose of intravenous fentanyl prior to fospropofol and before beginning the procedure.

Supplemental doses of fentanyl were allowed to be administered for analgesia, but the total dose of fentanyl was small. Patients having bronchscopy were also administered topical lidocaine to the airways. The analgesic regimens used were limited in cumulative dose and rate of administration so that they were not expected to exert a clinically measurable sedation effect.

6.1.2 General Discussion of Endpoints

The primary endpoint is the same for all three efficacy studies. It is a composite endpoint composed of three consecutive scores on a sedation scale indicating depressed consciousness (Modified Observer's Assessment of Alertness/Sedation Scale {MOAA/S Scale} of ≤ 4), completion of the procedure without the use of an alternative sedation product and without the use of manual or mechanical ventilation. The MOAA/S scale has six levels (scores 0-5). A

score of 0 denotes non-responsive and 5 denotes fully alert. The MOAA/S score of ≤ 4 corresponds to a range of patient responsiveness ranging from the capacity to t o respond to verbal and minimal tactile stimulation to incapacity to respond to pain.

The Division emphasized to the Sponsor during product development that demonstration that fospropofol caused depression of consciousness was not sufficient to establish efficacy. Therefore secondary endpoints were intended to permit a further evaluation of clinical benefit to the patient. Secondary endpoints for all three efficacy studies were similar. In the large efficacy studies -0522 and -0524 the secondary endpoints included the proportion of patients who required supplemental analgesic medication, who did not recall being awake and who were willing to be treated by the same sedation medication again. Investigator and patient satisfaction were evaluated using questionnaires. Treatment success was evaluated as the composite of completion of the procedure without requiring alternative sedation medication or manual or mechanical ventilation. The patients' short-term memory was also assessed in the recovery period (Hopkins Verbal Learning Test-Revised™ (HVLT-R™).

6.1.3 Study Design

Studies -0520, -0522, and -0524 were randomized, blinded and controlled. Study -0520 was designed to provide a dose-ranging comparison and the larger studies utilized a dose-control design.

The protocols stipulated that 50 mcg of fentanyl be given 5 minutes prior to administration of the study sedation drug. Next the patients were administered an initial bolus of fospropofol intravenously. The proposed dose, 6.5 mg/kg was administered to one treatment arm and 2.0 mg/kg were administered to the control arm. In Study -0522, another arm, included as a safety comparator, received 0.02mg of intravenous midazolam, the labeled dose for sedation. The level of sedation was scored using the MOAA/S scale and the procedure begun. Up to three supplemental doses of sedation study drug were allowed to be administered at four minute intervals if patients required additional sedation to begin the procedure. During the procedure supplemental doses of the sedation drug were permitted at intervals not less that 4 minutes and only if the patient was able to respond purposefully with a "thumb's up sign to the investigator's request. Supplemental doses of sedation product were 25% of the initial bolus for patient's receiving fospropofol and 1.0 mg for patient in the midazolam arm. Patients with serious concomitant comorbidities who were categorized as ASA 4 had their sedation dose reduced by 25%. Patients with less serious comorbidities classified as ASA 3 were allowed to have their sedation dose reduced by 25% at the discretion of the investigator. Patients weighing < 60 kg were dosed with fospropofol as though they weighed 60 kg. Also, patients weighing > 90 kg were dosed as though they weighed 90 kg. The dosing bounds imposed by body weight were based upon kinetic studies of the clearance and volume of distribution for fospropofol. Supplemental fentanyl was permitted in doses of 25 mcg at intervals of at least 10 minutes for signs of pain at the discretion of the investigator. The conduct of sedation was identical for the bronchoscopy Study -0524 except the airways were anesthetized with up to 4.5 mg/kg or 300 mg (whichever is lower) of topical lidocaine.

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

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

In the Sedation Initiation Phase, an initial dose and up to 4 supplemental doses of fospropofol/saline or midazolam were administered to reach minimal-to-moderate sedation (Modified OAA/S score ≤4). Midazolam supplements were administered every 2 minutes while active fospropofol supplements were administered only every 4 minutes. In order to maintain blinding, the fospropofol arms received a corresponding volume of sterile saline at 2 minutes and at 6 minutes. Supplemental boluses could have been administered in the Initiation Phase at 25% of the initial dose (fospropofol treatment arms) and at 1 mg/dose (midazolam arm). When the patient reached Modified OAA/S score ≤4, the Investigator was to start the procedure.

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

The depth of sedation was assessed using the MOAA/S scale at two minute intervals. Secondary endpoint assessment was performed on arrival in the recovery room and prior to discharge.

6.1.4 Efficacy Findings

For the efficacy endpoints, the primary analyses used the modified intent-to-treat (mITT) patient population, defined as all patients who were randomized, received at least one dose of study treatment and had at least one postdose clinical assessment. Six randomized patients were not included in the mITT population (2 in study #522; 4 in study #524). In all three studies, fospropofol at the proposed dosing achieved a statistical significance thereby demonstrating superiority over the lower-dose in primary efficacy endpoint.

Table 6.1.4-1 Efficacy Findings In The Primary Efficacy Endpoint

Procedure	Study	2 mg/kg (Total=229) n/N (%)	6.5 mg/kg (Total=334) n/N (%)	Fisher's Exact p-Value
colonoscopy	3000-0520	6/25 (24)	18/26 (69)	0.002
colonoscopy	3000-0522	26/102 (26)	137/158 (87)	< 0.001
bronchoscopy	3000-0524	28/102 (28)	133/150 (89)	< 0.001

Data were abstracted from the Sponsor's reports for Studies -0520, -0522 and -0524.

Trends in all secondary endpoints indicated an increased clinical benefit associated with the proposed dosing when compared with a lower dose of fospropofol.

Table 6.1.4-2 Success in Secondary Efficacy Endpoints was Dose Related (High-Dose (6.5 mg/kg) Versus Low-Dose (2.0 mg/kg) Fospropofol).

Secondary Endpoints:		Study -0520	Study -0522	Study -0524
Treatment Success Rate	n/N (%)	21/26 (81%) vs. 9/25 (36%)	139/158 (88%) vs. 29/102 (28%)	137/150 (91%) vs. 42/102 (41%)
% patients who required alternative sedative medication	n/N (%)	5/26 (19%) vs. 16/25 (64%)	19/158 (12%) vs. 29/102 (28%)	12/150 (8%) vs. 60/102 (59%)
% patients who did not recall being awake	n/N (%)	15/26 (58%) vs. 10/25 (40%)	83/158 (53%) vs. 45/102 (44%)	125/150 (83%) vs. 56/101 (55%)
% patients who required a supplemental analgesic	n/N (%)	14/26 (54%)vs. 19/25 (76%)	87/158 (55%) vs. 78/102 (76%)	25/150 (17%) vs. 38/102 (37%)
% of physicians satisfied at onset	n/N (%)	10/26 (38%) vs. 3/25 (12%)	61/158 (39%) vs. 4/102 (4%)	83/150 (55%) vs. 12/102 (12%)

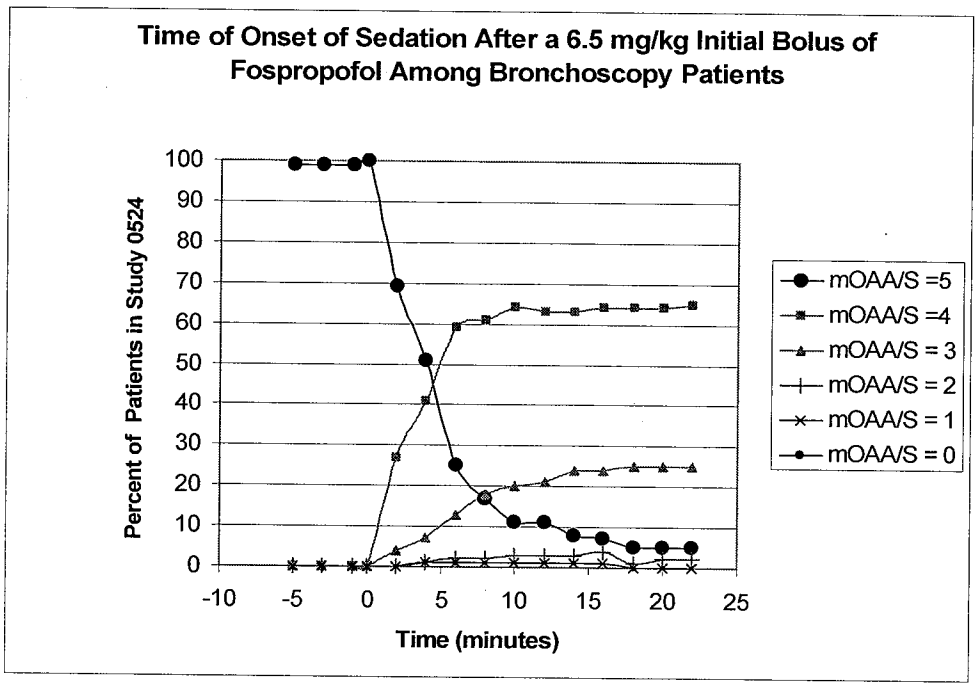
Secondary Endpoints:		Study -0520	Study -0522	Study -0524
% of physicians satisfied at end	n/N (%)	7/26 (27%) vs. 2/25 (8%)	82/158 (52%) vs. 15/102 (15%)	93/150 (62%) vs. 23/102 (23%)
Time to sedation onset (minutes)	Mean, Median (Range)	7, 6 (0,-18) vs. 12,12 (0-22)	9, 8 (2-28) vs. 17,18 (0-34)	6, 4 (2-22) vs. 14,18 (0- 30)
Time to fully alert (minutes)	Mean Median (Range)	8, 7(0-30) vs. 7,5 (0-29)	7, 5 (0-47) vs. 7, 3 (0-54)	8, 6 (0-61) vs. 9, 3 (0-114)

Data were abstracted from the Sponsor's reports for Studies -0520, -0522 and -0524.

The secondary efficacy findings from all three studies exhibited the same trend supporting improved efficacy among patients in the 6.5 mg/kg efficacy arm compared with patients in the 2.0 mg/kg efficacy arm. Each study indicated a dose-related trend toward a lower incidence of patients who required an alternative sedation medication or a supplemental analgesic. There was also a lower incidence of patients who were able to recall events during the procedure in the 6.5 mg/kg arm compared to the 2.0 mg/kg arm. A higher incidence of physicians reported satisfaction with the quality of sedation at the beginning and at the end of the procedure with the 6.5 mg/kg arm. There was also a slight trend toward faster onset of sedation with the higher dose of fospropofol and the recovery time for patients to achieve a fully alert sate was similar. In summary, these findings are all consistent with a dose-related clinical benefit of fospropofol.

The rate of onset of sedation data confirmed that fentanyl did not substantially contribute to observed efficacy in sedation. In the following figure, the percentage of bronchoscopy patients at each MOAA/S score is shown for various time points relative to the onset of sedation. The initial dose of fentanyl is administered at -5 minutes. Supplemental fentanyl was not allowed to be given until ten minutes after the first dose. Virtually all patients remained alert (MOAA/S score of 5) until fospropofol was administered at time 0 minutes. Thereafter, the percentage of patients who were alert fell rapidly so that by 10 minutes after the initial bolus of fospropofol, 90% of patients were no longer alert. This analysis indicates that sedation was associated with the initial dose of fospropofol, but not with the initial fentanyl dose.

Figure 6.1.4-1



Data were abstracted from the Sponsor's Electronic data tables.

6.1.5 Clinical Microbiology

Fospropofol is in aqueous solution and therefore is not expected to incur the same potential risks of bacterial growth as propofol in a lipid emulsion. Dr. John Metcalfe, Microbiologist Reviewer that there are no sterility concerns that affect approval of fospropofol.

6.1.6 Efficacy Conclusions

The data from replicated adequate and well-controlled studies indicate that fospropofol was efficacious for the proposed indication. Administration of the product resulted in a reduced level of responsiveness to stimulation, as evaluated on the MOAA/S scale. Colonoscopy and bronchoscopy are expected to be unpleasant procedures that typically require sedation in the U.S. population. Blinded assessments of fospropofol was associated with a statistically significant dose-related increase in the incidence of randomized patients who exhibited signs of sedation and were able to complete the scheduled procedure without requiring an alternative sedation product or techniques of positive pressure ventilation. Furthermore, additional subjective evidence indicated that other clinical benefits of sedation such as patient amnesia of the procedure and physician satisfaction were improved when higher doses of fospropofol were administered.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

A total of 1611 human subjects were exposed to fospropofol in 12 studies of patients and 9 studies of healthy volunteers during clinical development. The primary safety analysis is based upon findings from the three studies conducted to evaluate efficacy (-0520, -0522, and -0524) because they provide comparative dosing information to evaluate safety of the proposed dose of fospropofol. In colonoscopy Studies -0520 and -0522, a midazolam arm provided an additional safety comparison. Another study, -0523 utilized the proposed dosing of fospropofol, in an open-label, single-arm sedation study of various procedures other than colonoscopy or bronchoscopy. This reviewer pooled patient data from Study -0523 with data from randomized controlled studies where patient exposure was similar to further evaluate trends in adverse events observed in the controlled studies.

Earlier studies (3000-409, -0410, -0411, -0412, and 0415) utilizing a fixed weight-range based dosing regimen also provided useful safety information because the data provide insight about the potential risk if fospropofol were to be administered in higher doses than are recommended by the product labeling.

The findings of a thorough QTc study (3000-0521) conducted in healthy volunteers were reviewed by Dr. Christine Garnett from the Interdivisional Review Team for QT Studies. Her conclusions are also summarized in the general clinical review below.

7.1.1 Deaths

There were 10 deaths overall in clinical studies, 9 of which occurred in subjects who received fospropofol. None were considered to be related to study drug. Five of these patients participated in Study -0524 and received fospropofol sedation for bronchoscopy. The cause of and timing of death of the patients in Study -0524 are listed below.

Table 7.1.1-1 Patient Deaths in Bronchoscopy Study -0524

Patient Identifier	Underlying Condition	Cause of Death	Initial Dose of Fospropofol	Latency of AE Onset after Receiving Fospropofol (days)
3000-0524-544-0009	HIV/AIDS/TB/Cryptococal Meningitis	Anoxic encephalopathy	6.5 mg/kg	3
3000-0524-544-0003	Pneumonia/COPD/Lung Cancer	Respiratory arrest	2.0 mg/kg	9
3000-0524-	Lung Cancer	Septic Shock	2.0 mg/kg	17

Patient Identifier	Underlying Condition	Cause of Death	Initial Dose of Fospropofol	Latency of AE Onset after Receiving Fospropofol (days)
3000-0524-544-0009	HIV/AIDS/TB/Cryptococal Meningitis	Anoxic encephalopathy	6.5 mg/kg	3
3000-0524-544-0003	Pneumonia/COPD/Lung Cancer	Respiratory arrest	2.0 mg/kg	9
533-0008				
3000-0524-309-0006	Lung Cancer	Post-Obstructive Pneumonia	6.5 mg/kg	18
3000-0524-312-0003	Lung Cancer	Malignant lung neoplasm	6.5 mg/kg	18

Data from Sponsor's Study Report -0524, 14.4.1.1, pages 433-437

The remaining four patients were sedated with fospropofol for ventilator management in the intensive care unit in Study 3000-0413.

Table 7.1.1-2 Patient Deaths in Intensive Care Unit Study -0413

Patient Identifier	Underlying Condition	Cause of Death	Latency of AE Onset after Discontinuing Fospropofol (days)
3000-0413-431-002	COPD/Pneumonia	Acute Respiratory Failure	16
3000-0413-431-0042	Aspiration Pneumonia	Septic Shock	1
3000-0413-531-0016	Atrial Fibrillation/Staph. Aureus Bacteremia	Respiratory Failure	9
3000-0413-531-0080	Cerebrovascular Accident	Cardio-Respiratory Arrest	3

Data from Sponsor's Study Report -0413, 12.3.2.1, pages 76-78.

In each case, the onset of the adverse event that eventually resulted in the patient's death occurred well after the patient had recovered from sedation from fospropofol. This includes the episode of aspiration that resulted in pneumonia and septic shock. The cause of death was related to the patients' underlying serious disease rather than as a consequence of sedation.

7.1.2 Other Serious Adverse Events

In Studies 3000-0520, -0522 and -0524 the Sponsor reported 29/563 patients (5%) with serious adverse events. There was no clear dose relationship for SAEs overall with 14/229 (6%) cases occurring in the 2.0 mg/kg dosing arm and 15/334 (5%) cases in the 6.5 mg/kg dosing arm. The most prevalent SAE was an exacerbation of chronic obstructive disease (COPD) occurring in 3/229 patients (1%) in the 2.0 mg/kg arm and 3/334 patients (1%) in the 6.5 mg/kg dosing arm. Respiratory arrest and respiratory failure, taken collectively, occurred with the same incidence as COPD. There was no dose relationship to any reported SAE. The remaining reported SAEs are all single occurrences with the exception of malignant lung neoplasm and pneumonia. These SAEs were related to the patient's underlying chronic medical condition rather than as a consequence of acute administration of a sedation product.

Table 7.1.2-1 Reported Serious Adverse Events Other Than Death in Studies 3000-520, -0522, and -0524

Serious Adverse Event	Fospropofol 2.0 mg/kg (N =229) n (%)	Fospropofol 6.5 mg/kg (N =334) n (%)
Any SAE	14 (6.1)	15 (4.5)
Abdominal abscess	0	1 (0.3)
Abdominal sepsis	0	1 (0.3)
Acute respiratory failure	0	1 (0.3)
Anoxic encenphalopathy	0	1 (0.3)
Brain herniation	0	1 (0.3)
Brain oedema	0	1 (0.3)
Bronchitis acute	0	1 (0.3)
Bronchitis bacterial	1 (0.4)	1 (0.3)
Cardiac arrest	0	1 (0.3)
Cardiac failure congestive	1 (0.4)	0
cardiomyopathy	1 (0.4)	0
Cerebrovascular accident	1 (0.4)	0
Chronic obstructive pulmonary disease	3 (1.3)	3 (0.9)
Colon cancer	1 (0.4)	0
Coronary artery disease	0	1 (0.3)
Cystic fibrosis	1 (0.4)	0
Enterococcal bacteraemia	1 (0.4)	0
HIV test positive	1 (0.4)	0
Hypotension	1 (0.4)	0
Hypovolaemia	1 (0.4)	0
Intestinal perforation	0	1 (0.3)
Large intestine perforation	0	1 (0.3)
Larvngospasm	1 (0.4)	0
Lung infection pseudomonal	0	1 (0.3)
Lung neoplasm malignant	0	5 (1.5)
Lung squamous cell carcinoma stage unspecified	0	1 (0.3)
Non-small cell lung cancer	0	1 (0.3)
Pneumonia	1 (0.4)	3 (0.9)
Pneumonia pneumococcal	0	1 (0.3)
Pneumothorax	1 (0.4)	0
Respiratory arrest	1 (0.4)	0
Respiratory failure	2 (0.9)	3 (0.9)
Sepsis	0	1 (0.3)
Septic shock	1 (0.4)	0
Ventricular tachycardia	0	1 (0.3)

Data from Sponsor's Table 29, Summary of Clinical Safety 2.7.4, page 92

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Very few patients were discontinued from study participation because of an adverse event in Studies 3000-0520, -0522 and –524. The events that resulted in discontinuation were not serious.

7.1.3.2 Adverse events associated with dropouts

Table 7.1.3.2-1 Patient Dropouts Resulting From Adverse Events

Adverse Event	Fospropofol 2.0 mg/kg N = 229 n(%)	Fospropofol 6.5 mg/kg N = 334 n(%)
Any AE leading to discontinuation of Study Drug	0	2 (1)
Cough	0	1(<1)
Paraesthesia	0	1(<1)
Any AE leading to procedure Discontinuation	1 (< 1)	2(<1)
Cough	0	1(<1)
Hypotension	0	1(<1)
Pneumothorax	1 (<1)	0

From Sponsor's Table 29, Section 2.7.4, page 92

One patient experienced a paresthesia related to fospropofol during the onset of sedation that resulted in the patient's discontinuation. Another patient experienced hypotension during initiation of sedation with fospropofol that caused the procedure to be aborted. These events were related to fospropofol.

The coughing episode that lead to discontinuation of fospropofol and the procedure occurred during the maintenance period of sedation was related to the bronchoscopy procedure rather than to the study drug. A pneumothorax occurring in another patient was unrelated to fospropofol and resulted in discontinuation of the procedure.

7.1.4 Other Search Strategies

The MOAA/S scale was also used to evaluate safety because low scores (1 or 0) indicated that patients were minimally responsive or unresponsive to pain. Although patients who achieved these low scores may have met efficacy criteria, they were not intended because these conditions are believed to increase the risk of patients being unable to protect their airway and maintain adequate ventilation. The duration of time spent at these low sedation scores was also evaluated because the more time spent with an unprotected airway is expected to increase the risk to patients. This analysis was included in section Additional analyses and explorations, 7.1.5.6

even though a low score was not considered an adverse event without additional clinical deterioration.

A patient's ability to respond purposefully was a requirement for additional supplemental sedation to be administered in clinical studies. The relationship between purposeful responsiveness and adverse events such as hypoxia was explored to determine whether retention of purposeful responsiveness indicated that supplemental doses could be administered safely. This analysis was included in section Additional analyses and explorations, 7.1.5.6 even though an absence of purposeful responsiveness was not independently considered an adverse event.

All interventions to prevent loss of spontaneous ventilation and preserve oxygenation were evaluated in the clinical studies. A focus of this review is on the incidence of these interventions. Most of these interventions are simple to perform and do not require a high level of skill. However, in order for them to be effective, they must be instituted as result of a patient assessment that identifies an evolving risk early, before it becomes life-threatening. An end-consequence of inadequate ventilation is hypoxia, defined in the clinical protocols as hypoxemia and measured as hemoglobin desaturation on a peripheral oximeter as < 90% for more than 30 seconds. It is expected that minor interventions to maintain airway patency and preserve oxygenation in the clinical trials prevented life-threatening adverse events that would have resulted from sedation had the monitoring during the clinical trials been less vigilant.

List of Study Interventions to Maintain Airway Patency and Preserve Oxygenation

1. Mechanical Ventilation/Intubation
2. Manual Ventilation
3. Suction
4. Oral Airway
5. Nasal Trumpet
6. Chin Lift
7. Jaw Thrust
8. Face Mask
9. Tactile Stimulation
10. Verbal Stimulation
11. Patient Repositioning
12. Increase Oxygen Flow

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All clinical interventions made to improve spontaneous ventilation and oxygenation during sedation were captured on the CRF. This reviewer considers these interventions as evidence of a deteriorating clinical condition that would have resulted in an adverse event had the intervention not been performed. The incidence of airway interventions is found in Table 7.1.5.6-4.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The MedDRA system was used to categorize adverse events. Inspection of electronic data tables of adverse events by this reviewer indicated that verbatim statements were appropriately mapped into preferred terms and categorized correctly.

7.1.5.3 Incidence of common adverse events

Treatment-emergent AEs (TEAEs) were experienced by most patients in the blinded and controlled studies (3000-0520, -0522, and -0524), regardless of initial dose, 82% (187 of 229) in the 2.0 mg/kg group 88% (295 of 334) in the 6.5 mg/kg group. The most commonly reported TEAEs included: paresthesia (2.0 mg/kg: 52%; 6.5 mg/kg: 59%); procedural pain (2.0 mg/kg: 30%; 6.5 mg/kg: 30%); pruritus (2.0 mg/kg: 18%; 6.5 mg/kg: 15%); hypoxemia (2.0 mg/kg: 6%; 6.5 mg/kg: 9%); and hypotension (2.0 mg/kg: 2%; 6.5 mg/kg: 5%).

In this pooled analysis, only hypotension appeared to be dose dependent. The dose dependency of hypotension is more evident in the bronchoscopy data set, 2.0 mg/kg: 2%; 6.5 mg/kg: 8%, and may be driving the trend in the pooled dataset. No other TEAE, including paresthesia and pruritus, was to be dose dependent in the colonoscopy or bronchoscopy data sets.

The incidence of respiratory and airway interventions reported in the fixed weight-range based dosing studies (Studies 3000-409, -0410, -0411, -0412, -0415) was also considered when evaluating this adverse event because these data provide insight into the potential risk if the proposed dosing regimen for fospropofol were not to be followed strictly. In these studies, the frequency of all types of airway interventions among patients undergoing colonoscopy, bronchoscopy or other minor procedures was approximately 21%. Approximately 9% of the patients required an increase in delivered oxygen flow and approximately 2% were either manually or mechanically ventilated. Approximately twelve percent of the patients experienced hypoxia (peripheral oxygen saturation < 90%). Repositioning of the patient to manage ventilation was required approximately in 13% of the patients. The unacceptably high frequency of required airway management in these studies precipitated the dose-ranging study (3000-0520) and an individualized dosing regimen based upon patient weight for Studies -0522, and -0524.

7.1.5.4 Common adverse event tables

Table 7.1.5.4 Treatment-Emergent Adverse Events Occurring in at Least 2% of Patients by Organ Class, Preferred Term, and Initial Dose in Studies 3000-0520, -0522, and -0524

	Pooled studies		Colonoscopy studies		Bronchoscopy study	
	AQUAVAN		AQUAVAN		AQUAVAN	
System organ class[1] Preferred term[2]	2.0 mg/kg (N=229) n (%)	6.5 mg/kg (N=334) n (%)	2.0 mg/kg (N=127) n (%)	6.5 mg/kg (N=184) n (%)	2.0 mg/kg (N=102) n (%)	6.5 mg/kg (N=150) n (%)
Any TEAE	187 (81.7)	295 (88.3)	109 (85.8)	170 (92.4)	78 (76.5)	125 (83.3)
General disorders and administration site conditions	15 (6.6)	19 (5.7)	11 (8.7)	12 (6.5)	4 (3.9)	7 (4.7)
Inadequate analgesia	4 (1.7)	9 (2.7)	4 (3.1)	9 (4.9)	0	0
Injury, poisoning and procedural complications	70 (30.6)	102 (30.5)	57 (44.9)	83 (45.1)	13 (12.7)	19 (12.7)
Procedural pain	69 (30.1)	101 (30.2)	57 (44.9)	83 (45.1)	12 (11.8)	18 (12.0)
Nervous system disorders	125 (54. 6)	204 (61.1)	76 (59.8)	125 (67.9)	49 (48.0)	79 (52.7)
Paraesthesia	119 (52.0)	198 (59.3)	74 (58.3)	123 (66.8)	45 (44.1)	75 (50.0)
Respiratory, thoracic and mediastinal disorders	26 (11.4)	48 (14.4)	1 (0.8)	4 (2.2)	25 (24.5)	44 (29.3)
Hypoxia	14 (6.1)	29 (8.7)	0	3 (1.6)	14 (13.7)	26 (17.3)
Cough	4 (1.7)	13 (3.9)	0	0	4 (3.9)	13 (8.7)
Skin and subcutaneous tissue disorders	43 (18.8)	50 (15.0)	27 (21.3)	27 (14.7)	16 (15.7)	23 (15.3)
Pruritus	42 (18.3)	49 (14.7)	27 (21.3)	27 (14.7)	15 (14.7)	22 (14.7)
Vascular disorders	6 (2.6)	17 (5.1)	2 (1.6)	4 (2.2)	4 (3.9)	13 (8.7)
Hypotension	4 (1.7)	16 (4.8)	2 (1.6)	4 (2.2)	2 (2.0)	12 (8.0)

From Sponsor's Table 19, Summary of Clinical Safety 2.7.4, page 72.

7.1.5.5 Identifying common and drug-related adverse events

The high incidence of paresthesia and pain associated with injection of fospropofol is likely to be a direct consequence of exposure to the drug even though there is no dose-response relationship. Propofol, the active metabolite of fospropofol is also associated with these symptoms.

Pruritis occurred frequently, but is also without a dose-response relationship to fospropofol. Pruritis is not a common finding after subanesthetic doses of propofol.

Hypoxia was a dose-related finding and therefore likely caused by fospropofol, but was more common among bronchoscopy patients. Hypoventilation and hypoxia are also established risks of sedation with propofol.

Hypotension was also dose-related and is likely to have been caused by fospropofol because hypotension is associated with propofol.

Cough was reported among the bronchoscopy population. The high incidence of cough in this population was attributed to the presence of the bronchoscope in the airway.

Reports of inadequate analgesia were confined to colonoscopy studies, which are likely to be more painful than bronchoscopy because local anesthesia was used concomitantly only for bronchoscopy.

7.1.5.6 Additional analyses and explorations

In studies of fospropofol a MOAA/S level of 1 indicated that the patient only responded to painful stimulation and patients having a MOAA/S level of 0 were unarousable.

Patients who withdraw from a painful stimulus are not considered to exhibit a purposeful response. Patients who are unarousable even with pain are considered to be under general anesthesia.

The next table lists the incidence patients having a MOAA/S of 1 or zero and the range of time spent at these levels of sedation.

Table 7.1.5.6-1 Minimal Responsiveness and Unresponsiveness in Controlled Studies of Fospropofol (3000-0520, -0522, and -0524) at the Proposed Dosing (6.5 mg/kg)

Study	MOAA/S Score 0 or 1 N (%)	Time at Score 0 or 1
colonoscopy 3000-0520	1/26 (4%)	4 minutes
colonoscopy 3000-0522	6/158 (4%)	2 to 16 minutes

Study	MOAA/S Score 0 or 1 N (%)	Time at Score 0 or 1
bronchoscopy 3000-0524	24/150 (16%)	2 to 20 minutes

Overall incidence = 9%. Data were abstracted from Sponsor's electronic data tables.

Overall, approximately 4 percent of patients in studies of colonoscopy (0520 and 0522) achieved a sedation score of 0 or 1 during the conduct of sedation. Among the bronchoscopy patients in study 0524 the 16% of patients achieved a sedation score of 0 or 1. When these data were pooled the overall incidence of patients having a sedation score of 0 or 1 was 9%. The maximum duration of patient having a sedation score of 0 or 1 was 20 minutes.

However, none of the patients achieving these deep levels of sedation required rescue with a bag and mask or endotracheal tube. The nature of airway interventions among the most deeply sedated patients was similar to those required for patients who where more easily aroused.

The Sponsor compared the incidence of various adverse events associated with sedation to the sedation score measurement most closely associated in time with the adverse event. The most frequent event was hypoxia, defined here as a peripheral saturation of <90% for greater than 30 seconds.

Table 7.1.5.6-2 Hypoxia Occurred in Patients Who Were Responsive to Verbal Stimulation (3000-0520, -0522, and -0524) at the Proposed Dosing

	Pooled Studies 3000-0520, -0522, and -0524						
		Modified OAA/S Score at Time of SRAE					
	No. of events	**5 n (%)**	**4 n (%)**	**3 n (%)**	**2 n (%)**	**1 n (%)**	**0 n (%)**
Sedation AE requiring management	61	10 (16)	17 (28)	19 (31)	7 (12)	6 (10)	2 (3)
Apnea	1	0	1 (100)	0	0	0	0
Bradycardia	0	0	0	0	0	0	0
Hypotension	18	5 (28)	4 (22)	3 (17)	4 (22)	1 (6)	1 (6)
Hypoxia	**42**	**5 (12)**	**12 (29)**	**16 (38)**	**3 (7)**	**5 (12)**	**1 (2)**
Manual ventilation	3	0	0	2 (67)	0	1 (33)	0

Data were abstracted from Sponsor's electronic data tables.

The intended range of sedation with fospropofol in these studies was 4 to 2. It is particularly notable that the highest incidence of hypoxic events occurred when patients scored a "3", the middle range on the sedation scale. At this level, patients required that their name be called loudly and repeatedly before they would respond. Manual ventilation for two events was also required at this moderate level of sedation.

In the following table, the incidence of hypoxia is related to retention of purposeful responsiveness. This is informative because retention of purposeful responsiveness was required before supplemental sedation medication was administered. Therefore, in these clinical studies, investigators decided that administration of fospropofol was expected to be safe when patients were responding purposefully. In many cases, patients were able to produce a "thumbs up sign" or "wiggle toes" when investigators requested that the patient do so even in association with signs of hypoxia.

Table 7.1.5.6-3 Hypoxia Occurred in Patients Receiving the Proposed Dosing in Controlled Studies Who Were Able to Make a Purposeful Response to a Verbal Request

	Pooled Studies 3000-0520, -0522, and -0524		
Sedation-related Adverse Event	Number of Events	No Purposeful Response n (%)	Purposeful Response n (%)
Any SRAE requiring management	61	12 (19.7)	49 (80.3)
Apnea	1	0	1 (100)
Bradycardia	0	0	0
Hypotension	18	4 (22.2)	14 (77.8)
Hypoxia	**42**	**8 (19.0)**	**34 (81.0)**
Manual ventilation or intubation	Number of Events	No Purposeful Response n (%)	Purposeful Response n (%)
Manual ventilation	3	1 (33.3)	2 (66.7)

Data were abstracted from Sponsor's electronic data tables.

Therefore, retention of purposeful responses did not exclude an associated finding of hypoxia as indicated by peripheral desaturation < 90% on an oximeter.

The following table lists various types of airway maneuvers required to manage sedation with fospropofol in Studies -0520, 0522, -0524. Some patients received more than one intervention. The most common intervention was a dose-related increased flow of nasal oxygen, however mechanical interventions such as chin lift or suctioning were also required for some patients. Manual ventilation was needed in one patient.

Table 7.1.5.6-4 Incidence of Patients Requiring Airway Management in Controlled Studies 3000-0520, -0522, and -0524

	Pooled Studies		Colonoscopy Studies		Bronchoscopy Study	
	Dose of Fospropofol		Dose of Fospropofol		Dose of Fospropofol	
Type of Airway Management	2.0 mg/kg (N=229) n (%)	6.5 mg/kg (N=334) n (%)	2.0 mg/kg (N=127) n (%)	6.5 mg/kg (N=184) n (%)	2.0 mg/kg (N=102) n (%)	6.5 mg/kg (N=150) n (%)
Any airway management	15 (7)	35 (11)	1 (1)	3 (2)	14 (14)	32 (21)
Manual ventilation	0	1 (<1)	0	0	0	1 (1)
Suction	0	2 (1)	0	0	0	3 (2)
Chin lift	2 (1)	6 (2)	1 (1)	1 (1)	1 (1)	5 (3)
Jaw thrust	3 (1)	2 (1)	0	0	3 (3)	2 (1)
Face mask	1 (<1)	1 (<1)	0	0	1 (1)	1 (1)
Tactile stimulation	1 (<1)	4 (1)	0	0	1 (1)	4 (3)
Verbal stimulation	2 (1)	8 (2)	0	2 (1)	2 (2)	6 (4)
Patient repositioning	0	3 (1)	0	0	0	3 (2)
Increased oxygen flow	12 (5)	28 (8)	0	0	12 (12)	28 (19)

Data were abstracted from Sponsor's electronic data tables.

The incidence of hypoxia observed in these studies appeared to be primarily driven by the event rates in the bronchoscopy study -0524. Because the incidence of hypoxia was dose-related, it is likely to be related to fospropofol and cannot be entirely attributed to the presence of an instrument in the airway. In this study patients tended to be older and have more serious comobidities than in the colonoscopy studies.

Hypoxemia was the only treatment emergent and dose-related adverse event in fospropofol-treated patients that occurred at consistently different frequencies across age, weight, and ASA III/IV subgroups. Geriatric patients and patients categorized as ASA IV were expected to have a higher incidence of cardiopulmonary adverse events and therefore were prospectively assigned a 25% reduction in bolus and supplementary doses. Patients categorized as ASA III were administered this reduction in dosing at the investigator's discretion.

This reviewer's performed the following analysis of hypoxemia by subgroups from Studies -0520, -0522, and -0524:

Table 7.1.5.6-5: Dose-Related Hypoxia for the Geriatric Age Group

Initial Dose	2 mg/kg			6.5 mg/kg		
Age Group	18 to < 65 years N = 169	65 to < 75 years N = 60	> 75 years N = 19	18 to < 65 years N = 247	65 to < 75 years N = 87	> 75 years N = 25
Hypoxia n (%)	8 (5%)	3 (5%)	2 (11%)	14 (6%)	13 (15%)	6 (24%)

Data were abstracted from the Sponsor's Electronic Data Tables.

Table 7.1.5.6-6: Dose-Related Hypoxia for High ASA Categorization

Initial Dose	2 mg/kg		6.5 mg/kg	
ASA Category	All N = 229	III or IV N = 42	All N = 334	III or IV N = 74
Hypoxia n (%)	11 (5%)	5 (12%)	27 (8%)	12 (16%)

Data were abstracted from the Sponsor's Electronic Data Tables.

Table 7.1.5.6-7: Dose-Related Hypoxia for Weight < 60 kg

Initial Dose	2 mg/kg			6.5 mg/kg		
Weight Group	< 60 kg N = 35	60 to < 90 kg N = 123	>90 kg N = 71	< 60 kg N = 42	60 to < 90 kg N = 180	>90 kg N = 112
Hypoxia n (%)	2 (6%)	6 (5%)	3 (4%)	6 (14%)	12 (7%)	9 (8%)

Data were abstracted from the Sponsor's Electronic Data Tables.

In an effort to further elucidate whether a safety signal associated with geriatric age group, high ASA physical classification or body weight below 60 kg was present, data at the proposed dosing from the open label Safety study 0523 was pooled with the data at the same dosing from the blinded randomized and controlled studies 0520, 0522 and 0524. The population in safety study 0523 consisted of 123 patients undergoing a wider range of diagnostic and therapeutic procedures including TEE, upper endoscopy and hysteroscopy compared with patients having only colonoscopy or bronchoscopy in the controlled studies. The extent of exposure was similar in this analysis because the dosing was the same and the duration of procedure was similar.

Table 7.1.5.6-8 Incidence of Airway Assistance with the Proposed Dosing in Subpopulations

Age Group	18 to 65 yrs 24/346 (7%)	65 to 75 yrs 12/75 (16%)	>75 yrs 6/36 (16%)
ASA Category	I 4/109 (4%)	II 21/251 (8%)	III or IV 17/97 (18%)
Weight	< 60 kg 9/60 (15%)	60 to 90 kg 21/249 (8%)	>90 kg 12/148 (8%)

Data were abstracted from the Sponsor's electronic data tables for Studies -0520, -0522, -0523 and -0524.

In this analysis, the incidence of all airway interventions was compared by subpopulations of age, ASA classification and body weight. The trend in the incidence of hypoxia based upon small numbers of patients in the data from the blinded, randomized, controlled studies was also noted in the incidence of required airway assistance in pooled data that included patients having a broader range of procedures.

7.1.6 Less Common Adverse Events

Inspection of the Sponsor's electronic adverse event data tables by this reviewer focused on reported events that could have become serious.

Electrolyte abnormalities:
For example hypokalemia was selected because of the potential for this event to result in a malignant cardiac dysrhythmia. Seven patients in the Sponsor's database were reported to have low potassium or hypokalemia.

Because hypocalcemia may result in cardiac conduction abnormalities, reports of hypocalcemia or low calcium were identified. Three patients were reported to have an episode of hypocalcemia.

No case of malignant cardiac dysrhythmia was reported except for one case of nonsustained ventricular tachycardia in a healthy volunteer. No electrolyte abnormalities were reported in this patient.

Ocular abnormalities:
All reported ocular abnormalities were reviewed in detail because of formaldehyde, a metabolic by product of fospropofol is toxic to the optic nerve. Fifteen patients reported blurred vision, abnormal vision, eye pain or signs of inflammation such as redness, dryness or discharge.

These events appeared to originate superficially and were not associated with lasting changes to vision. It is notable that sedated patients occasionally develop irritation of the conjunctiva or cornea from local dehydration or inadvertent injury caused by health care providers or by patients rubbing their eyes during recovery.

Hepatic enzyme elevation:
Reported cases of hepatic enzyme abnormalities were reviewed in detail because hepatic insufficiency can present clinically well after patients have recovered from sedation and may not have been associated with the study drug by the investigator. Patients with elevations of hepatic enzymes such as LDH, ALT, and AST and elevation of bilirubin were identified. Eleven patients were reported to have elevations in hepatic enzymes or bilirubin. These events were attributed to underlying patient disease rather than to fospropofol. However, the etiology of

hepatic enzyme elevation could not be established with certainty. No patient developed symptoms of hepatic failure in clinical studies.

Tremor:
Reports of tremor were specifically reviewed because patients with hyperphosphatemia sometimes experience these symptoms. Five patients reported tremors or rigidity. One patient who experienced tremor also experienced an elevated phosphate level. The episode was self-limited without sequelae.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory testing was performed at screening and during recovery from sedation. Blood samples were drawn for hematology, serum chemistry, and electrolytes analysis as follows:

> **Hematology**: hemoglobin, hematocrit, red blood cell count, total white blood cell and full differential counts (neutrophils, lymphocytes, basophils, monocytes, eosinophils), platelet count
>
> **Serum Chemistry**: alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma glutamyl transferase, lactate dehydrogenase, total protein, albumin, bilirubin, serum creatinine, blood urea nitrogen, total carbon dioxide, glucose, creatine kinase, and lipids (including separate cholesterol and triglycerides)
>
> **Serum Electrolytes**: sodium, potassium, ionized calcium, total calcium, chloride and inorganic phosphorous, magnesium

Shifts from normal to abnormal (high or low), on the basis of standard values at the testing laboratory were analyzed for all patients participating in brief procedures, (3000-0524, 3000-0523, 3000-0522, 3000-0520, 3000-0415, 3000-0412, 3000-0411, 3000-0410, 3000-0409, and 3000-0207).

Clinical significant abnormalities as identified by the investigator were also analyzed. Laboratory data were grouped by study type for analysis: controlled, double-blind studies, open-label fixed weight-range based dose studies, intensive care unit studies, healthy subject studies as listed below.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Clinical significant abnormalities in laboratory values as identified by the investigator were analyzed in controlled, double-blind studies 3000-0520, -0522, and -0524.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Mean and median laboratory values were similar between screening, baseline and the recovery period in the controlled studies 3000-0520, -0522, and -0524. No dose-response relationships were reported.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 7.1.7.3.2 Shifts in Laboratory Parameters from Normal at Baseline to Above or Below the Normal Range in > 5% of Patients During Brief Procedures

	AQUAVAN-treated patients	
	N	n (%)
Chemistry		
Normal to low		
Calcium (ionized)	982	103 (11.4)
Albumin	1207	59 (5.8)
Cholesterol (high performance)	452	71 (16.2)
Potassium	1181	55 (5.9)
Total calcium	1259	62 (5.0)
Total protein	1222	98 (9.4)
Normal to high		
Glucose (high performance)	1120	106 (11.1)
Phosphate	1056	91 (9.0)
Hematology		
Normal to low		
Hemoglobin	1106	100 (11.0)
RBC	1005	104 (11.0)
Hematocrit	1180	54 (5.6)
Normal to high		
Neutrophil percentage	978	59 (6.4)

From Sponsor's Summary of Safety, Table 53, page 131. The Studies represented are 3000-0524, 3000-0523, 3000-0522, 3000-0520, 3000-0415, 3000-0412, 3000-0411, 3000-0410, 3000-0409,and 3000-0207.

The findings that were explored in more detail were calcium and phosphate abnormalities, because acute shifts in cholesterol and protein are of little clinical consequence. Hypokalemia, anemia, hyperglycemia and elevations of neutrophil percentage are common in invasive procedures because of adrenocortical responses and intravascular volume shifts so that drug effect cannot be separated from the stress response to a procedure. In these studies, these laboratory abnormalities were not persistent and therefore were not investigated further.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

Changed in laboratory values that were considered clinically significant by the investigator were separately analyzed.

1. Controlled studies: 3000-0520, 3000-0522, 3000-0524

   In the adequate and well-controlled double blind studies, the most frequently reported clinically significant changes from baseline laboratory test results for patients in the 2.0 and 6.5 mg/kg groups included: (1) phosphate levels in 1.0% (2 of 204), and 5.7% (18 of 315); (2) total calcium levels in 4.1% (9 of 218) and 2.7% (9 of 327); and (3) albumin levels in 3.2% (7 of 218) and 3.0% (10 of 330), respectively. With the exception of phosphate, the frequency of changes was similar in both fospropofol dose groups.

2. Open-label, fixed weight-ranged based dosing studies: 3000-0207, 3000-0409, 3000-0410, 3000-0411, 3000-0412, 3000-0415, 3000-0523

   In the open-label, supportive studies, the most frequently reported clinically significant changes from baseline laboratory test results for patients treated with fospropofol included phosphate levels in 12.3% (82 of 664) and total calcium levels in 2.1% (14 of 670) (Table 52).Clinically significant changes in midazolam treated patients included phosphate levels, 1.7% (2 of 120), and total calcium, 2.3% (3 of 129). Clinically significant changes in PTT values were noted in 6 patients in the open-label supportive studies. Maximum values ranged from 46 to 66 seconds, with no clinical sequelae.

3. Intensive care unit studies: 3000-0413, 3000-0104

   In prolonged treatment-duration (up to 12 hours) studies, the most frequently experienced clinically significant changes from baseline laboratory test results for patients treated with fospropofol included: hemoglobin (39.0%), hematocrit (37.5%), total calcium (34.1%) and phosphate (33.3%). The most frequently experienced clinically significant changes from baseline laboratory test results for patients treated with propofol injectable emulsion were: hemoglobin (44.4%), hematocrit (48.1%), total calcium (35.7%), and phosphate (53.6%). Other parameters that showed clinically significant changes in $\geq$25% of patients in the fospropofol and/or propofol injectable emulsion groups were AST, albumin, and folate.

4. Healthy subject studies: 3000-0001,3000-0102, 3000-0103, 3000-0205, 3000-0206, 3000-0308, 3000-0414, 3000-0521, 3000-0625

   In healthy subjects studies, clinically significant changes from baseline laboratory test results reported by $\leq$ 2% of subjects treated with fospropofol included: phosphate, 7.9% (21 of 265) and ionized calcium 3.8% (8 of 212).

7.1.7.5 Special assessments

Plasma phosphate and formate levels were specifically evaluated because metabolism of fospropofol yields free phosphate and formate.

Phosphate:
For the fospropofol dosage-titration regimen tested in the key studies (3000-0524, 3000-0522, and 3000-0520), increased plasma phosphate level was noted (6% of patients) especially when phosphate-containing bowel preparations had been used for colonoscopy. Therefore, the principal contribution to phosphate elevations in colonoscopy patients was most likely related to bowel preparation rather than fospropofol.

Formate:
Mean plasma formate concentrations following fospropofol dosing were similar to predose levels across several studies in patients and in healthy subjects. One patient (study 3000-0413: patient 3000-0413-507-0001) with hepatic and renal insufficiency who received fospropofol as an infusion over a prolonged period experienced an elevated plasma formate level at the end of the infusion (212 mcg/mL). The ophthalmologic examination of the optic nerve was unchanged from baseline. Therefore, formate release from fospropofol did not cause clinically measurable toxicity in these studies.

Albumin:
Clinically notable changes in albumin levels from baseline were more common in bronchoscopy studies when compared with other studies. However, the changes in serum albumin had no medical consequences for the patients.

Liver function tests:
Clinically significant changes in ALT levels were reported more frequently in the minor procedure studies when compared with colonoscopy and bronchoscopy studies in the open-label, supportive studies. However, changes in bilirubin levels to clinically significant abnormal values were not observed in these studies. Although 11 fospropofol-treated patients in the minor procedures studies had clinically significant changes in ALT levels, only 4 patients had adverse events of ALT increase and 3 of these events were considered treatment-related.

In the open-label, fixed-dose studies, 4 patients (332-0031, 332-003, 332-013, and 374-0019) had AEs of hepatic enzyme increases (2 each at >8 to 11 mg/kg and >11 to 14 mg/kg fospropofol doses). Two of these patients (332-003 and 332-013) received combination hydrocodone drug for treatment of pain following the procedure.

One patient in the dose-titration studies had an elevated liver function tests (LFT) that increased further in recovery. The patient was on acetaminophen pre-procedure. Of the other patients with elevations, 1 was in study 3000-0207 and 2 were in study 3000-0410, and the remaining patients were in study 3000-0412. Only one of those patients had a peak value in recovery; the other patients had increases seen during the follow up laboratory tests that were generally collected 5

days later. In the dose-titration studies, follow up laboratory tests were consistently collected during this period of time.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The vital signs assessed were heart rate, systolic and diastolic blood pressure, respiratory rate and peripheral oxygen saturation measured on a pulse oximeter.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The blinded and controlled studies (3000-0520, -0522 and -0524) were used for drug-control comparisons.

7.1.8.3 Analyses and explorations of vital signs data

Hypoxia was identified on the basis of hypoxemia in peripheral oximetry measurements.

Table 7.1.8.3-1 Summary of Pulse Oximetry Results from Studies 3000-0520, -0522, and -0524

		Pooled studies		Colonoscopy studies		Bronchoscopy study	
Oxygen saturation level	Maximum duration of consecutive measures (min)	AQUAVAN 2.0 mg/kg (N=229) n (%)	AQUAVAN 6.5 mg/kg (N=334) n (%)	AQUAVAN 2.0 mg/kg (N=127) n (%)	AQUAVAN 6.5 mg/kg (N=184) n (%)	AQUAVAN 2.0 mg/kg (N=102) n (%)	AQUAVAN 6.5 mg/kg (N=150) n (%)
<90%	Total	18 (7.9)	33 (9.5)	4 (3.1)	6 (3.3)	14 (13.7)	27 (18.0)
	≤3	16 (7.0)	25 (7.5)	4 (3.1)	5 (2.7)	12 (11.8)	20 (13.3)
	3 to <6	1 (0.4)	6 (1.8)	0	1 (0.5)	1 (1.0)	5 (3.3)
	6 to <12	1 (0.4)	0	0	0	1 (1.0)	0
	≥12	0	2 (0.6)	0	0	0	2 (1.3)
<85%	Total	4 (1.7)	13 (3.9)	1 (0.8)	1 (0.5)	3 (2.9)	12 (8.0)
	≤3	4 (1.7)	12 (3.6)	1 (0.8)	1 (0.5)	3 (2.9)	11 (7.3)
	3 to <6	0	0	0	0	0	0
	6 to <12	0	0	0	0	0	0
	≥12	0	1 (0.3)	0	0	0	1 (0.7)
<80%	Total	1 (0.4)	5 (1.5)	1 (0.8)	1 (0.5)	0	4 (2.7)
	≤3	1 (0.4)	5 (1.5)	1 (0.8)	1 (0.5)	0	4 (2.7)
	3 to <6	0	0	0	0	0	0
	6 to <12	0	0	0	0	0	0
	≥12	0	0	0	0	0	0

From Sponsor's Summary of Safety, Table 57, page 142.

The incidence of hypoxemia was dose-related in colonoscopy and bronchoscopy studies. However, the bronchoscopy study -0524 was responsible for driving the trend when the studies were pooled. Relatively few patients developed hypoxemia with oximeter readings below 90%. However, it is important to recognize that because of the relationship of oxygen-hemoglobin

saturation to the partial pressure of oxygen in arterial blood, once the saturation declines below 90% patients are risk for a rapid and serious decline in oxygen delivery to vital organs.

The Sponsor analyzed mean changes and the range of excursion in blood pressure, heart rate and respiratory rate.

Table 7.1.8.3.1-2 Changes in Blood Pressure, Heart Rate and Respiration Rate in Colonoscopy Studies 3000-0520, -0522 and Bronchoscopy Study -0524

	Pooled studies		Colonoscopy studies		Bronchoscopy study	
	AQUAVAN 2.0 mg/kg	AQUAVAN 6.5 mg/kg	AQUAVAN 2.0 mg/kg	AQUAVAN 6.5 mg/kg	AQUAVAN 2.0 mg/kg	AQUAVAN 6.5 mg/kg
Change from baseline in systolic BP (mm Hg) to average during the procedure						
Mean (± standard deviation)	-6.6 (15.5)	-14.9 (16.0)	-10.2 (14.7)	-16.7 (15.3)	-2.0 (15.3)	-12.6 (16.6)
Min, max	-52, 35	-76, 33	-51, 24	-55, 26	-52, 35	-76, 33
Change from baseline in diastolic BP (mm Hg) to average during the procedure						
Mean (± standard deviation)	-2.7 (10.1)	-6.6 (10.8)	-4.6 (9.0)	-8.3 (8.9)	-0.3 (10.8)	-4.3 (12.5)
Min, max	-34, 53	-52, 34	-31, 15	-52, 20	-34, 53	-35, 34
Change from baseline in heart rate (bpm) to average during the procedure						
Mean (± standard deviation)	3.3 (10.8)	3.7 (9.9)	-1.5 (7.0)	-0.7 (7.3)	9.3 (11.7)	9.0 (10.2)
Min, max	-36, 50	-21, 38	-19, 17	-21, 21	-36, 50	-18, 38
Change from baseline in respiration rate (breaths per minute) to average during the procedure						
Mean (± standard deviation)	0.1 (3.5)	-0.3 (3.5)	-0.4 (3.1)	-0.4 (3.1)	0.8 (3.8)	-0.2 (3.9)
Min, max	-10, 11	-11, 15	-8, 10	-9, 15	-10, 11	-11, 12

From Sponsor's Summary of Safety, Table 55, page 138.

A high degree of variability was observed in blood pressure changes. For example, the minimum and maximum changes in systolic blood pressure observed for the 6.5 mg/kg dose were from a -52 mm Hg to 35 mm Hg. A decline of 50 mm is more likely to be clinically significant than an elevation of 35 mm, so analysis of outliers focused on cases of falling blood pressure. The decreases in systolic BP and diastolic BP appeared to be dose related with larger differences between dose groups occurring in bronchoscopy (2.0 mg/kg: -2.0 mm Hg; 6.5 mg/kg: -12.6 mm Hg) compared to colonoscopy patients (2.0 mg/kg: -10.2 mm Hg; 6.5 mg/kg: -16.7 mm Hg).

No dose-dependent changes in heart rate were observed.

No dose-dependent changes in respiration rates were observed

There were no dropouts in Studies 3000-0520, -0522, -0524 because of abnormalities in vitals signs.

7.1.8.4 Additional analyses and explorations

A comparison of the incidence of hypoxia and other sedation-related adverse events between fospropofol at the proposed dosing (6.5 mg/kg initial bolus) and midazolam at the labeled dosing (0.02 mg/kg) when used as a study arm in the colonoscopy studies was performed by this reviewer. The objective of this comparison was to identify whether a safety trend could differentiate sedation with midazolam from fospropofol in the same population.

Table 7.1.8.4-1 Safety Comparison of Fospropofol 6.5 mg/kg Treatment Arm to Midazolam 0.02 mg/kg Treatment Arm in Colonoscopy Studies 3000-0520 and -0522.

	Midazolam n = 78	Fospropofol n = 184
Hypoxemia Oxygen saturation < 90% by peripheral oximetry	0 (%)	6 (3%)
Systolic Hypotension 60 - 78 mm	5 (6 %)	9 (5%)
Bradycardia (Heart rate < 50 beats/minute)	3 (4%)	11 (6%)
Respiratory Rate 5 to 6 breaths/minute	3 (4%)	4 (2%)

Data were abstracted from the Sponsor's electronic data tables.

These results indicate a trend that hypoxia was more frequent with the proposed dosing of fospropofol than with labeled doses of midazolam.

All airway interventions performed in the controlled studies to prevent or ameliorate hypoventilation or hypoxia were documented in the CRF and analyzed by the Sponsor. This analysis provides an indicator of the incidence of hypoventilation even though tidal volume and therefore minute ventilation was measured. These data demonstrate a dose-related increase in the total number of interventions that was more apparent among bronchoscopy patients than in colonoscopy patients.

Table 7.1.8.4-2 Incidence of Airway Interventions in Controlled Studies 3000-0520, -0522 and -0524

	Pooled Studies		**Colonoscopy Studies**		**Bronchoscopy Study**	
	Dose of Fospropofol		**Dose of Fospropofol**		**Dose of Fospropofol**	
Type of Airway Management	**2.0 mg/kg (N=229) n (%)**	**6.5 mg/kg (N=334) n (%)**	**2.0 mg/kg (N=127) n (%)**	**6.5 mg/kg (N=184) n (%)**	**2.0 mg/kg (N=102) n (%)**	**6.5 mg/kg (N=150) n (%)**
Any airway management	15 (7)	35 (11)	1 (1)	3 (2)	14 (4)	32 (21)
Manual ventilation	0	1 (<1)	0	0	0	1 (1)
Suction	0	2 (1)	0	0	0	3 (2)
Chin lift	2 (1)	6 (2)	1 (1)	1 (1)	1 (1)	5 (3)
Jaw thrust	3 (1)	2 (1)	0	0	3 (3)	2 (1)

Face mask	1 (<1)	1 (<1)	0	0	1 (1)	1 (1)
Tactile stimulation	1 (<1)	4 (1)	0	0	1 (1)	4 (3)
Verbal stimulation	2 (1)	8 (2)	0	2 (1)	2 (2)	6 (4)
Patient repositioning	0	3 (1)	0	0	0	3 (2)
Increased oxygen flow	12 (5)	28 (8)	0	0	12 (12)	28 (19)

Adapted from Sponsor's Table 192, Summary of Clinical Safety, page 430

7.1.9 Electrocardiograms (ECGs)

A thorough QTc evaluation was conducted by the Sponsor in Study 3000-0521 following advice on the study design by consultants in the Interdivisional Review Team for QT Studies. A detailed review of the study report was completed by Dr. Christine Garnett of the Interdivisional Review Team for QT Studies for the NDA submission. This consultant's review is summarized below:

In this randomized, open-label, positive- and placebo-controlled crossover study, 68 healthy subjects were administered single IV bolus dose of fospropofol 6 mg/kg, fospropofol 18 mg/kg (3-times the recommended dose), placebo and a single oral dose of 400 mg moxifloxacin. At the anticipated clinical dose of 6 mg/kg, no significant effect on the QTcF was detected. Following the 18 mg/kg dose, the largest upper bound of the two-sided 90% CI for the ΔΔQTcF at the 12-minute time point was greater than 10 ms, which has been identified as the threshold for regulatory concern in the ICH E14 guideline. Mean peak fospropofol and propofol derived from fospropofol plasma concentrations for the 18 mg/kg dose were approximately 3.6-fold higher than the peak concentrations following a 6 mg/kg dose.

The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms indicating that the study was adequately designed and conducted to detect an effect on the QT interval.

The fospropofol doses evaluated in this study are acceptable. There are no known intrinsic or extrinsic factors that can increase exposure to fospropofol and propofol derived from fospropofol greater than what was observed following the supratherapeutic dose. The sponsor states the expected high clinical exposure scenario is when a subject with low body weight receives the wrong dose e.g., a full vial containing 1050 mg fospropofol.

Therefore, this study indicated that there is dose-dependent lengthening of the QTc interval using the Fredericia method of correction. However, to obtain a better precision of the effects of administering fospropofol on the QT interval, the Sponsor was advised to reanalyze the data using a individual corrected QT interval computed from the 24-hour Holter data obtained at baseline (Day -1 before each period). The effect of hysteresis between the RR-QT intervals should be assessed.

The Interdivisional Review Team for QT Studies has recommended the following labeling for fospropofol regarding changes to the QTc.

"The effect of fospropofol on the QTcF interval was measured in a crossover study in which healthy subjects (n=68) received the following treatments: 6 mg/kg IV fospropofol; 18 mg/kg IV fospropofol; moxifloxacin 400 mg P.O (positive control); and normal saline IV. After baseline and placebo adjustment, the maximum mean QTcF change was 2 ms (1-sided 95% Upper CI: 6 ms) for the 6 mg/kg dose and 8 ms (1-sided 95% Upper CI: 12 ms) for the 18 mg/kg dose. Used as a positive control, moxifloxacin had a maximum mean change in QTcF of 12 ms (1-sided 95% Lower CI: 6 ms)."

Therefore, fospropofol, when administered according to the proposed labeling is not anticipated to prolong the QTc and thereby increase the risk to patients of Torsaides de pointes.

7.1.10 Immunogenicity

No clinical studies of immunogenicity were performed because fospropofol is a nonbiologically derived product that is closely related to propofol, a product that is not immunogenically active.

7.1.11 Human Carcinogenicity

No clinical studies of human carcinogenicity were performed because fospropofol is intended for short exposures rather than for chronic use.

7.1.12 Special Safety Studies

There were no special safety studies.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No studies of withdrawal were performed. Instead the results of studies of propofol in the medical literature were summarized.

Pharmacokinetic bioavailability studies (3100-0401 and -0402) were reviewed by Dr. Patricia Beaston of the Controlled Substances Staff. Her review is summarized below:

The medical literature supported a conclusion that propofol demonstrated abuse potential, sometimes with fatal consequences when self-administered. One case specifically reported the development of dependence on propofol in a patient, who did not have a history of substance abuse, who received propofol for the treatment of tension headaches by an anesthesiologist. Propofol has also been an instrument of abuse during criminal activity.

Fospropofol has a less rapid onset of action than propofol, so dependent individuals may consider fospropofol safer for self-administration than propofol. Euphoria was reported as an adverse event in Studies 3100-0401 and -0402. Additionally, because fospropofol is orally bioavailable, it may be more convenient for misuse and abuse. Fospropofol is readily soluble in

water [redacted], and propofol is bioavailable after the ingestion of fospropofol. The combination of solubility and oral bioavailability with the sedative and amnestic properties makes fospropofol a drug of concern as it could be used to incapacitate victims of crime. b(4)

7.1.14 Human Reproduction and Pregnancy Data

No data was collected in patients to evaluate the effect of fospropofol on human reproduction of pregnancy. Patients who were pregnant were excluded from clinical studies.

7.1.15 Assessment of Effect on Growth

No data was collected in patients to evaluate the effect of fospropofol on human growth or development.

7.1.16 Overdose Experience

Open label, fixed-dose, supportive studies (3000-0409, -0410, -0411, -0412, and -0415) were notable for a higher incidence of hypoxemia (20%) than the controlled studies with the proposed dosing (8%). This difference is attributed to higher doses of fospropofol used in the fixed-dose studies. The incidence of hypotension in fixed-dose studies (5%) was comparable to the incidence observed in the controlled studies with the proposed dosing (5%).

7.1.17 Postmarketing Experience

Fospropofol has not been marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Healthy Volunteer Studies:

- Pharmacokinetic and Tolerability Studies:

  - Clinical pharmacokinetic and mass balance study: Study 3000-0205, N = 8
  - Tolerability, Pharmacokinetic and pharmacodynamic study: Study 3000-0206, N= 54
  - Bioavailability of fospropofol administered orally: Study 3100-0401, N = 7

- Ascending dose study of tolerability and pharmacokinetics of oral doses: Study 3100-0402, N = 10
- Tolerability study of fospropofol injection following premedication with intravenous lidocaine: Study 3000-0308, N = 10

➢ Pharmacodynamic and Pharmacokinetic Studies:

- Dose-escalation pharmacokinetic and pharmacodynamic study: Study 3000-0001, N = 12
- Induction and maintenance, pharmacokinetic and pharmacodynamic study: Study 3000-0102, N = 12
- Dose-escalation pharmacokinetic and pharmacodynamic study: Study 3000-0103, N = 36
- Parallel design, drug interaction study including premedications: Study 3000-0414, N = 60, n = 0 fospropofol
- Crossover pharmacokinetic and pharmacodynamic study of fospropofol versus Diprivan: Study 3000-0625, N = 12

Patient Studies:

➢ Blinded, Randomized, Controlled Studies of the Proposed Dosing:

- Dose-ranging study in colonoscopy patients: Study 3000-0520, N = 127, n = 121 fospropofol, n = 26 patients exposed to fospropofol at the proposed dosing
- Dose controlled study in colonoscopy patients: Study 3000-0522, N = 260 fospropofol, n = 158 exposures to the proposed dosing
- Dose controlled study in bronchoscopy patients: Study 3000-0524, N = 312 , n = 252 fospropofol, n = 150 exposures to the proposed dosing

➢ Supportive Safety Study with the Proposed Dosing: Study 3000-0523, Single-arm evaluation in patients having minor procedures N = 123

➢ Thorough QTc Study: Study 3000-0521, Positive and Negative-Controlled Crossover Study, N= 68

➢ Other Studies in Patients:

Study	Design	Number of Patients	
Study 3000-0104	Uncontrolled dose-finding sedation after cardiac surgery	8	
Study 3000-0207	Dose-finding Colonoscopy	164	
Study 3000-0409	Aquavan vs. Midazolam sedation for bronchoscopy	40	Stopped because of safety concerns in 3000-0410
Study 3000-0410	Aquavan vs. Midazolam sedation for colonoscopy	211	Stopped because of safety concerns
Study 3000-0411	Aquavan vs. Midazolam for percutaneous coronary procedures	6	Stopped because of respiratory arrest
Study 3000-0412	Aquavan vs. Midazolam sedation for minor surgical procedures	124	Stopped because of safety concerns in 3000-0410
Study 3000-0413	Infusion of Aquavan vs. Propofol in ICU, evaluate need for rescue sedation	52	
Study 3000-0415	Aquavan vs. Midazolam in geriatric patients undergoing colonoscopy	20	Stopped because of safety concerns in 3000-0410

Studies 3000-0409, -0410, -0411, -0412, and 0415 utilized a weight-range fixed dosing regimen. Studies 3000-0104 and -0413 were studies of fospropofol infusion in intensive care unit patients.

The dose-ranging Study 3000-0520 and the dose-controlled Studies 3000-0522 and -0524 are sufficient in size and design to enable an evaluation of safety and efficacy for a general population undergoing sedation for diagnostic and therapeutic procedures. The study of QTc prolongation (3000-0521) meets the ICH E14 criteria for thorough QT study. The remaining studies in patients provide additional safety information. Adequacy of the pharmacokinetic studies was reviewed in detail by the Biopharmacology Team. Drs. Srikanth Nallani and Suresh Doddapanini have indicated that they are acceptable for review.

7.2.1.2 Demographics

The following listings are of the distribution of patients by gender, race/ethnicity and age among patients administered the proposed dosing regimen (6.5 mg/kg initial bolus followed by 1.6 mg/kg boluses for maintenance).

Table 7.2.1.2-1 Distribution of Patients Exposed to the Proposed Dosing By Gender

Study	Males	Females
Dose-ranging colonoscopy Study 3000-0520	11	15
Dose-controlled colonoscopy Study 3000-0522	76	82
Dose-controlled bronchoscopy Study 3000-0524	86	64
Open-label minor procedures Study 3000-0523	56	67

Data was abstracted from the Sponsor's electronic safety tables.

The overall pooled distribution was similar between genders.

Table 7.2.1.2-2 Distribution of Patients Exposed to the Proposed Dosing By Ethnicity

Study	White	Black	Asian	Hispanic	Other
Dose-ranging colonoscopy Study 3000-0520	21	4	0	0	1
Dose-controlled colonoscopy Study 3000-0522	133	11	3	11	0
Dose-controlled bronchoscopy Study 3000-0524	130	16	1	3	0
Open-label minor procedures Study 3000-0523	109	9	1	3	1

Data was abstracted from the Sponsor's electronic safety tables.

The majority of patients studied were white. However, the clinical assessment and management of sedation is similar across ethnic groups. Among white patients, patients with red hair sometimes require lower doses of general anesthetics. A lower dose requirement of sedation medication has not been reported.

Table 7.2.1.2-3 Distribution of Patients Exposed to the Proposed Dosing By Age

Study	18 to < 65 years	65 to < 75 years	≥ 75 years
Dose-ranging colonoscopy Study 3000-0520	21	3	2

Dose-controlled colonoscopy Study 3000-0522	137	17	4
Dose-controlled bronchoscopy Study 3000-0524	89	42	19
Open-label minor procedures Study 3000-0523	99	13	11

Data was abstracted from the Sponsor's electronic safety tables.

Relatively fewer geriatric patients were studied than patients younger than age 65. However, the number of geriatric patients was expected to be sufficient to assess safety in this age group.

7.2.1.3 Extent of exposure (dose/duration)

Fospropofol:

A total of 1611 subjects, of which 1338 were patients and 273 were healthy volunteers, received fospropofol during clinical development. Of the 1338 patients who received fospropofol, 750 (56.1%), 292 (21.8%), 250 (18.7%), and 46 (3.4%) were undergoing colonoscopy, bronchoscopy, minor procedures, or prolonged treatment duration (up to 12 hours), respectively.

Overall, 1047 (65.0%) of the 1611 subjects received fospropofol doses that exceeded 8mg/kg. Of the 1338 patients enrolled in the studies, 857 (64.1%) were administered fospropofol doses >8mg/kg.

For 750 patients under going colonoscopy, 130 (17.3%), 95 (12.7%), and 525 (70.0%) received fospropofol doses ≤5 mg/kg, >5-8mg/kg, and >8 mg/kg, respectively. The median duration of the colonoscopies was 11 minutes (range: 2 to 60).

For 292 patients undergoing bronchoscopy, 114 (39.0%), 74 (25.3%), and 104 (35.6%) received fospropofol doses ≤5 mg/kg, >5-8mg/kg, and >8 mg/kg, respectively. The median duration of bronchoscopies was 10 minutes (range: 1 to 62). A larger proportion of the patients in the bronchoscopy studies (64.4%) received doses ≤8 mg/kg than in the colonoscopy studies (30%). For 250 patients undergoing minor procedures, 6 (2.4%), 48 (19.2%), and 196 (78.4%) received fospropofol doses ≤5 mg/kg, >5-8mg/kg, and >8 mg/kg, respectively. The median duration of the minor procedures was 18 minutes (range: 2 to 110). The proportion of patients receiving ≤8.0 mg/kg was similar for minor procedures (21.6%) and colonoscopy (30%), but lower than for bronchoscopy (64.4%).

For 46 intubated and mechanically ventilated patients who received prolonged exposure to fospropofol (up to 12 hours), over half of the patients received fospropofol doses > 14 mg/kg. The median duration of the exposure was 389 minutes (range: 90 to 733). The mean (± standard deviation) total doses of fospropofol were 20.8 (20.0) mg/kg in study 3000-0413 and 59.4 (12.3) mg/kg in study 3000-0104.

More than 40% of the healthy subjects received fospropofol dose > 14 mg/kg. A similar proportion of patients received >700 mg and >8 mg/kg fospropofol doses for the colonoscopy (mg: 64.4%; mg/kg: 70%), bronchoscopy (mg: 25.7%; mg/kg: 35.6%), and minor procedures (mg: 74.8%, mg/kg: 78.4%) studies.

Protocol changes made during the fospropofol clinical development program to switch from fixed, weight-based dosing to the fospropofol dosage titration regimen (3000-0500 clinical series) led to a general reduction in patient exposure to fospropofol. For example, in the bronchoscopy studies, 81.3% of patients in study 3000-0524 compared to 30.0% in study 3000-0409 received a total fospropofol dose of 700 mg or less. In the colonoscopy studies, 62.0% of patients (3000-0520, 3000-0522) compared to 11.6% in (3000-0207, 3000-0410, 3000-0415) received a total fospropofol dose of 700 mg or less.

The switch from fixed, weight-based dosing to the fospropofol dosage titration regimen also reduced patient exposure on a mg/kg basis. For example, in the bronchoscopy studies, 71.4% of patients in study 3000-0524 compared to 20.0% in study 3000-0409 received a total fospropofol dose of 8.0 mg/kg or less. In the colonoscopy studies, 57% of patients (3000-0520, 3000-0522) compared to 4.9% in (3000-0207, 3000-0410, 3000-0415) received a total fospropofol dose of 8.0 mg/kg or less.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Other clinical studies were evaluated by the type of study for treatment emergent adverse events.

- Open label, fixed-dose, supportive studies (3000-0409, -0410, -0411, -0412, and -0415) were notable for a higher incidence of hypoxemia (30%) than the controlled studies with the proposed dosing (8%). This difference is attributed to higher doses of fospropofol used in the fixed-dose studies. The incidence of hypotension in fixed-dose studies (5%) was comparable to the incidence observed in the controlled studies with the proposed dosing (5%).

- Prolonged Treatment Duration Studies (3000-0413 and 3000-0104) exposed patients in the intensive care unit to continuous infusions of fospropofol for up to 12 hours. Treatment emergent adverse events that occurred in ≥10% of patients in the prolonged exposure studies were procedural pain, pleural effusion, hyperglycemia, constipation, atrial fibrillation, and nausea. Paresthesia (8.7%) and pruritus (6.5%) were also observed in fospropofol-treated patients. One fospropofol-treated patient had hypotension and none had hypoxemia. Most adverse events were experienced by patients at total doses (>14 mg/kg) higher than those received by patients undergoing brief therapeutic and diagnostic procedures receiving the standard initial dose of 6.5 mg/kg fospropofol.

- Clinical studies in healthy patients were evaluated for adverse events (3000-0001, -0102, -0103, -0205,-0206, -0308, -0414, -0521, and -0625). The only healthy volunteer studies to have SAEs or AEs leading to discontinuation were 1 subject each in the 3000-0414 and 3000-0521 studies. One subject (3000-0414-493-1050) in study 3000-0414 experienced an SAE diagnosed as paralysis and muscular weakness of psychogenic origin. In study 3000-0521, one subject (3000-0521-245-0120) was withdrawn by the Investigator for ventricular extrasystoles. However, the event was not considered to be related to the study drug. Common adverse events included paresthesia (75.8%); pruritus (21.6%); headache (7.7%); dry eye (6.2%); and dizziness (6.2%). These events were observed at lower frequencies in the studies of fospropofol in patients.

7.2.2.2 Postmarketing experience

Fospropofol is not marketed.

7.2.2.3 Literature

No manuscripts of clinical studies of fospropofol have been published.

7.2.3 Adequacy of Overall Clinical Experience

The clinical experience is expected to be generally representative of adult patients who are sedated for procedures in clinical practice. It was notable that all patients studied at the proposed dosing also received fentanyl as systemic analgesic before administration of fospropofol. The doses of fentanyl were small, but even in small doses concomitant fentanyl may increase the incidence of adverse events, especially respiratory depression and hypotension.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing included all airway interventions to support spontaneous ventilations and respiratory gas exchange. This level of detail is unique among sedation product applications that have been submitted to the Agency. It provided valuable information regarding the clinical reference skills necessary to administer fospropofol. Another assessment that was of unique value in these data was the frequent evaluation of patients' ability to respond purposefully during conduct of sedation. Purposeful responsiveness has been previously suggested by the American Society of Anesthesiology to demarcate depth of sedation and the associated risk (ASA Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia. Approved 1999; last amended 2004, www.ASAhq.org/publicationsAndServices/standards/20.pdf., Accessed May 1, 2008)

Other assessments, such as vital sign and laboratory measurements that are within the current scope of practice are expected to be generally adequate to assess safety of fospropofol sedation.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Fospropofol disodium is not a substrate for cytochrome P450 (CYP450) enzymes and does not induce these enzymes. Therefore, CYP450 metabolism mediated drug-drug interactions are unlikely to occur.

Fospropofol is metabolized by alkaline phosphatases to propofol, formaldehyde, and phosphate. Alkaline phosphatases are widely distributed in the body so that concomitant medications or disease states are not expected to change the rate of conversion of fospropofol to propofol.

Phosphate is a metabolite of fospropofol. The additional phosphate load from the recommended fospropofol dose is less than 2.5% of the phosphate load from the lowest recommended adult dose of phospho-soda oral saline laxative, a commonly prescribed colonoscopy bowel preparation.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The evaluation of sedation-related adverse events was facilitated by a more thorough documentation of airway interventions than has been previously conducted for new sedation product applications. In particular, impairment of spontaneous ventilation was the primary concern because the active metabolite of fospropofol is propofol, a drug with a narrow therapeutic index when used for sedation because it directly suppresses centrally mediated ventilatory drive. For fospropofol, every clinical intervention employed to improve ventilation, oxygenation or prevent airway obstruction was to be documented in the controlled studies (3000-0520, -0522 and -0524) and also in the open-label study of safety utilizing the proposed dosing (Study 3000-0523). The datasets provided enabled an adequate understanding of adverse events related to ventilation and the clinical interventions needed to manage these events.

Other adverse events associated with fospropofol were characterized appropriately in their clinical contexts and analyzed adequately.

7.2.8 Assessment of Quality and Completeness of Data

The overall quality of data was acceptable. There were few missing data elements and when abstracting data from the SAS datasets, this reviewer's quantitative analyses were consistent with the Sponsor's calculated information contained in their submission.

7.2.9 Additional Submissions, Including Safety Update

The 120-day safety update included three patients treated with fospropofol under protocol 3000-0523 that were not reported in the original NDA. There were no new deaths reported. Bleeding from an ateriovenous fisula one day after administration of fospropofol was reported as a new serious adverse event (patient 0523-560-0007), but this occurrence was not attributable to fospropofol. One patient (0523-560-0006) experienced mild hypotension on the day of fospropofol administration that was not captured in the original database. There were no additional cases of airway assistance reported. Laboratory findings and vital sign data were similar to the findings from the original database.

An analysis of patients having moderate to severe hepatic impairment based on Child Pugh criteria was also conducted in the 120-day safety update. No significant difference in adverse event profiles was observed in these patients compared with the overall study population. However, the total number of patients was small (n=8) and all criteria for hepatic insufficiency were not evaluated so that definite conclusions were not possible.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Administration of fospropofol was associated with a dose-related incidence of airway interventions described in Table 7.1.8.4-2. These interventions provide an insight into the frequency of impending hypoventilation in patients sedated with fospropofol. Furthermore, the majority of these interventions were to treat hypoxia, established by signs of hypoxemia by peripheral oximetry. Hypoxemia most likely resulted from hypoventilation, perhaps with an associated ventilation perfusion inequality; in this setting because an arteriovenous shunt or diffusion defect could not develop acutely. This means that hypoventilation in many instances was probably unrecognized until a patient's hemoglobin became significantly desaturated. It was not possible to assess hypoventilation directly because tidal volume was not measured to enable calculation of minute ventilation. Arterial sampling was also not performed to measure the partial pressure of carbon dioxide as a marker of minute ventilation. Even though a direct measure of ventilation was not available, the incidence of airway interventions is sufficient to establish a finding of respiratory insufficiency associated with fospropofol even when the respiratory insufficiency was preempted so that it did not rise to clinical significance.

Hypoxia, as indicated by peripheral hypoxemia was selected for additional study across age groups, ASA classifications and according to body size. The findings of this analysis are described in Section 7.4.2. In summary, geriatric age group, ASA classification of III or IV or body weight below 60 kg were associated with a dose-related increased incidence of hypoxia.

The incidence and duration of MOAA/S sedation scores of 0 or 1 were analyzed to provide insight into the degree of control over depth of sedation prescribers have when intending to maintain their patients' ability to respond purposefully while sedated during a procedure.

Approximately 4% of patients undergoing colonoscopy and 16% of patients undergoing bronchoscopy became more sedated than intended by achieving these low scores on the MOAA/S scale. The duration of undesired deep sedation lasted between 2 and 20 minutes, sufficient time for airway obstruction or aspiration to occur in patients who are not vigilantly monitored.

Hypotension was also reported as a dose-dependent adverse event in approximately 4% of patients at the proposed doses of fospropofol. In these cases, hypotension was managed by repositioning the patient and/or administration of additional intravenous crystalloid, without requiring a continuous infusion of an inotrope. Therefore, hypotension associated with fospropofol is expected to be managed in practice without a high level of clinical skill.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The incidence of adverse events was derived primarily from controlled Studies 3000-0520, -0522, and -0524 because these studies enabled a dose relationship to be described as evidence of causality. Adverse events where a dose relationship to incidence was observed were also evaluated for each study to determine whether the events were driven by comorbidities specific to the study sample population. For example, hypoxia was the most frequent adverse event that was readily attributable to administration of fospropofol because of a dose-relationship. The overwhelming majority of patients having hypoxia were reported among the bronchoscopy patients in Study -0524. These patients tended to be older and have more serious concomitant disease than the colonoscopy patients in Studies -0520 and -0522. Patients weighing less than 60 kg also had a higher incidence of hypoxia than patients over 60 kg. It is notable that dosing of fospropofol for patients weighing less than 60 kg was the same as for patients weighting 60 kg. The rationale for weight bounded dosing was founded on pharmacokinetic data obtained in healthy volunteers in early development.

In order to further establish whether a safety trend toward impaired respiratory gas exchange existed among geriatric patients, patients with serious comorbidities and among patients weighing less than 60 kg, an analysis of all airway interventions was performed. This reviewer interprets these interventions as an effort to preempt adverse events related to hypoventilation and therefore may be a more sensitive indicator than hypoxia for untoward safety trends associated with fospropofol. In order to broaden the database of patients with the identified putative vulnerabilities, safety data from single-arm open-label Study 3000-0523 of sedation conducted for a wide range of procedures was pooled with the findings from the controlled Studies 3000-0520, -0522, -0524. Patients in all these studies experienced the same degree of

exposure in terms of dose and duration so that the pooled data are expected to enhance sensitivity without reducing specificity of a safety signal.

7.4.1.2 Combining data

Pooled data was evaluated using the Sponsor's SAS compatible combined electronic dataset for safety and the associated data definition tables. These datasets are listed in the scs folder enclosed in the datasets folder in folder m5 of the Sponsor's electronic submission as follows:

Table 7.4.1.2-1 Electronic Datasets Used for Combined Data Analyses of Safety

Dataset Table of Contents			
Dataset Name	Description	Location	Keys
A_AE	Adverse Events	A_AE.XPT	STYTYPC, USUBJID, AESTDTC, AESTDTN, AETERM
A_CM	Concomitant Medication	A_CM.XPT	STYTYPC, USUBJID, CMDECOD, CMSTDTC
A_LB	Laboratory Test	A_LB.XPT	STYTYPC, USUBJID, LBCAT, LBTEST
A_RE	Purposeful Movement with MOASS	A_RE.XPT	STYTYP, USUBJID, REDTN
A_SL	Subject Level Information	A_SL.XPT	STYTYPC, USUBJID
A_SR	Airway Assistance	A_SR.XPT	STYTYPC, USUBJID, AIRWAY, SRSTDTC
A_SRAE	Sedation-relsted AE Requiring Intervention	A_SRAE.XPT	STYTYP, USUBJID, SRAE, ONSETDTN
A_VS	Vital Signs (Tabulate)	A_VS.XPT	STYTYP, USUBJID, VSTEST

From Sponsor's electronic submission of datasets.

Most analyses were conducted using the data from controlled studies 3000-0520, -0522 and -0524 because these studies enabled a dose-related comparison of incidence of adverse events. Safety data from controlled studies were also pooled with safety data from -0524 for analysis of hypoxia associated with patient subgroups because the exposure to fospropofol was the same and Study -0524 increased the number of patients in the subgroups of interest.

[redacted] the number of patient exposures to 6.5 mg/kg dosing from controlled studies was reduced by two patients compared to the number provided in the dataset A_SL because these two patients received 2 mg/kg. This discrepancy in exposure did not affect the incidence of adverse events when assessed to the nearest percentage point, so that the number of exposures used for the purpose of review was based upon the number of patients listed in the Sponsor's combined electronic dataset to facilitate a direct review of the Sponsor's Summary of safety. b(4)

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Dose-dependency was evaluated for all adverse events, and especially for sedation-related adverse events such as apnea, bradycardia, hypotension, and hypoxia.

7.4.2.2 Explorations for time dependency for adverse findings

The proposed indication of fospropofol is expected to expose patients for periods generally under thirty minutes, just as most patient were exposed in the controlled clinical trials. In this setting, it is difficult to establish a time dependency for adverse events. No relationship was observed between the number of doses administered or the total duration of exposure and incidences of adverse events.

In studies of intensive care unit patients (ICU), the duration of exposure ranged up to 12 hours. In this setting, it was possible to more fully evaluate metabolic abnormalities that may have resulted from fospropofol administration. For example, elevated plasma phosphate noted in the controlled colonoscopy study patients and attributed by the Sponsor to bowel preparation was also evaluated in the ICU patients. Plasma formate was also evaluated in the ICU patients along with serial ophthalmological examinations to detect possible signs of formate toxicity.

7.4.2.3 Explorations for drug-demographic interactions

The relationship of adverse events to patient age, gender and ethnicity was explored by the Sponsor. A dose-related increase in incidence of hypoxia was observed among the geriatric age group and patients having a body weight < 60 kg for patients in Studies 3000-0520, -0522, and -0524. This reviewer confirmed the Sponsor's findings and extended the analysis to include patients who required any form of airway assistance in the all studies utilizing the proposed dosing (Studies 3000-0520, -0522, -0523, and -0524). This analysis was presented in Section 7.1.5.6 of this review.

7.4.2.4 Explorations for drug-disease interactions

The relationship of ASA categorization to adverse events was explored. A dose dependent relationship was noted for airway interventions and to hypoxia. This analysis is presented in Section 7.1.5.6 of this review.

7.4.2.5 Explorations for drug-drug interactions

A feature of the blinded controlled studies that complicates safety evaluation of fospropofol is the concomitant administration of fentanyl to all patients. Fentanyl in low doses is an analgesic with a minimal sedation effect. However, patient response is variable and may be more pronounced in the geriatric age group. The possibility that concomitant fentanyl contributed to the adverse events, specifically hypoxia and ventilation abnormalities were evaluated by examination of the dose-response relationship.

Both fospropofol disodium and propofol are highly bound to plasma proteins (approximately 98 %). In an in vitro protein binding study there was no significant interaction between fospropofol up to 200 mcg/mL and propofol up to 5 mcg/mL plasma concentrations. The interaction of fospropofol disodium with other highly protein-bound drugs given concomitantly

was not studied. Fospropofol disodium is not a substrate for cytochrome P450 (CYP450) enzymes and does not induce these enzymes.

7.4.3 Causality Determination

The Sponsor identified four sedation-related adverse events (SRAE): apnea, bradycardia, hypotension and hypoxia. These events are expected to be caused by fospropofol, although concomitant medications such as fentanyl and comorbid conditions such as serious cardiopulmonary disease are expected to increase the likelihood of occurrence.

Adverse events related to respiratory insufficiencies that were not specifically identified as hypoxia or apnea were also suspected to have been caused by fospropofol. However, these cases occurred among bronchoscopy patients when the patient's history strongly suggested that patient disease was likely to have been the precipitating factor. The design of the controlled studies utilized a dose-control that facilitated evaluation of a dose-relationship to adverse events.

An increasing incidence of any adverse event associated with increasing fospropofol dose was considered to have been related to fospropofol. Other than hypoxia and hypotension, this relationship was not found in the controlled studies.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The Sponsor's proposed dosing regimen was efficacious for sedation of patients undergoing colonoscopy and bronchoscopy when concomitant analgesic medication was also administered. These procedures are sufficiently representative of diagnostic and therapeutic procedures for which sedation is used to satisfy the indication. Concomitantly administered analgesics are commonly required when patients are sedated for uncomfortable procedures because most sedation products have a hypnotic effect, but by themselves do not relieve pain or discomfort. Therefore the proposed dosing of fospropofol was acceptable from the standpoint of clinical efficacy for the proposed indication.

Fospropofol was also a safe product, under the conditions of the clinical studies. The dosing regimen proposed for labeling consisting of an initial dose (6.5 mg/kg) followed by small supplemental loading doses (1.6 mg/kg) is reasonable and supported by the clinical safety data for most patients. An earlier regiment utilizing fixed weight-range based dosing demonstrated that when the initial dose was high enough to enable a colonoscopy or other procedure to be completed without supplemental doses of fospropofol, the incidence of hypoxia was unacceptable. This dosing regimen was abandoned for the titration technique being proposed for labeling. A controlled dose-ranging study (3000-0520) in colonoscopy patients adequately demonstrated this dosing regimen achieved a balance between desired level of sedation and retention of respiratory function. The effect of variations in the interval between supplemental doses was not studied, however the prolonged duration of fospropofol indicates that reducing the interdosing interval will lead to drug accumulation.

No patients died or suffered a permanent injury as a result of fospropofol administration at the proposed dosing. However, evaluation of study safety data was notable for several features that must be carefully considered when attempting the study results to widespread clinical practice. First, the level of vigilance was very high in the clinical studies, especially in the controlled studies and in Study 3000-0523. In these studies, every single airway intervention was captured for later analysis. This means that the quality of spontaneous ventilation was rigorously monitored while patients were sedated. In an actual use setting, this level of vigilant monitoring may be difficult to achieve.

It is also notable that patients in geriatric age groups, or were classified as ASA III/IV or had a body weight below 60 kg had a higher incidence of hypoxia than the controlled study population as a whole. This increase in incidence occurred despite the 25% reduction in dosing for geriatric patients and for patients with comorbid conditions that resulted in an elevated ASA physical status classification. Therefore, it is possible that with a further decrease in dosing, a lower incidence of hypoxia could be achieved in these demographic groups. Further dose-ranging clinical studies are needed in these demographic groups to optimize safety.

8.2 Drug-Drug Interactions

Table 8.2-1 Extent of Fentanyl Exposure by Population and Study – Total Fentanyl Dose (mcg) Received

Population/ Procedure	Study	Median duration (minutes) of procedure (min, max)	Total fentanyl dose (µg) 0-<50 n (%)	50-<100 n (%)	100-<150 n (%)	≥150 n (%)
Colonoscopy	3000-0207 (N=164)	10 (2, 50)	25 (15.2)	82 (50.0)	46 (28.0)	11 (6.7)
	3000-0410 (N=210)	11 (2, 54)	5 (2.4)	111 (52.9)	81 (38.6)	13 (6.2)
	3000-0415 (N=15)	14 (5, 28)	12 (80.0)	3 (20.0)	0 (0.0)	0 (0.0)
	3000-0520 (N=101)	12 (3, 32)	0 (0.0)	76 (75.2)	20 (19.8)	5 (5.0)
	3000-0522 (N=260)	11 (4, 60)	0 (0.0)	195 (75.0)	52 (20.0)	13 (5.0)
	Total (N=750)	11 (2, 60)	42 (5.6)	467 (62.3)	199 (26.5)	42 (5.6)
Bronchoscopy	3000-0409 (N=40)	10 (3, 34)	11 (27.5)	22 (55.0)	7 (17.5)	0 (0.0)
	3000-0524 (N=252)	10 (1, 62)	2 (0.8)	219 (86.9)	18 (7.1)	13 (5.2)
	Total (N=292)	10 (1, 62)	13 (4.5)	241 (82.5)	25 (8.6)	13 (4.5)
Minor procedures	3000-0411 (N=6)	26 (13, 41)	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)
	3000-0412 (N=121)	18 (2, 102)	3 (2.5)	37 (30.6)	67 (55.4)	14 (11.6)
	3000-0523 (N=123)	17 (2, 110)	2 (1.6)	116 (94.3)	5 (4.1)	0 (0.0)
	Total (N=250)	18 (2, 110)	7 (2.8)	155 (62.0)	73 (29.2)	15 (6.0)
Grand Total	Overall (N=1292)	11 (1, 110)	62 (4.8)	863 (66.8)	297 (23.0)	70 (5.4)

Source data: Module 5.3.5.3,Table 74

From Sponsor's Summary of Safety, 2.7.4, Table 10, page 55.

8.3 Special Populations

The special patient populations that were analyzed as separate subsets included geriatric patients, patients classified as ASA III or IV, patients with body weight < 60 kg, and patients with renal insufficiency and patients with hepatic insufficiency. Many of these patients were in more than one of these subsets because older patients tended to be debilitated and have more serious comorbid conditions.

Table 8.3-1 The Incidence Of Dose Related Hypoxia Was Associated With The Geriatric Age Group

Initial Dose	2 mg/kg			6.5 mg/kg		
Age Group	18 to < 65 years N = 169	65 to < 75 years N = 60	> 75 years N = 19	18 to < 65 years N = 247	65 to < 75 years N = 87	> 75 years N = 25

Initial Dose	2 mg/kg			6.5 mg/kg		
Incidence of Hypoxia n (%)	8 (5%)	3 (5%)	2 (11%)	14 (6%)	13 (15%)	6 (24%)

Data were abstracted from the Sponsor's electronic data set from Studies -0520, -0522, and-0524.

Table 8.3-2 The Incidence of Dose-Related Hypoxia Was Associated with High ASA Categorization

Initial Dose	2 mg/kg		6.5 mg/kg	
ASA Category	All N = 229	III or IV N = 42	All N = 334	III or IV N = 74
Incidence of Hypoxia n (%)	11 (5%)	5 (12%)	27 (8%)	12 (16%)

Data were abstracted from the Sponsor's electronic data set from Studies -0520, and - 0522, and-0524.

Table 8.3-3 The Incidence of Dose-Related Hypoxia Was Associated with Patient Weight < 60 Kg

Initial Dose	2 mg/kg			6.5 mg/kg		
Age Group	< 60 kg N = 35	60 to < 90 kg N = 123	>90 kg N = 71	< 60 kg N = 42	60 to < 90 kg N = 180	>90 kg N = 112
Incidence of Hypoxia n (%)	2 (6%)	6 (5%)	3 (4%)	6 (14%)	12 (7%)	9 (8%)

Data were abstracted from the Sponsor's electronic data set from Studies -0520, -0522, and-0524.

Patients having low body weight and experiencing hypoxia also tended to be in the geriatric age group and be classified as ASA III or IV.

Patients were considered to have moderate to severe renal insufficiency if their calculated screening creatinine clearance values were ≤50 mL/min. Only one patient with hepatic insufficiency was enrolled. Insufficient hepatic function was defined by a screening serum albumin levels were <2.8 g/dL or screening total bilirubin levels were >3 mg/dL.

Table 8.3-2 Patients Categorized as ASA III/IV and Patients Having Renal Insufficiency

	Pooled studies			
	AQUAVAN 2.0 mg/kg		AQUAVAN 6.5 mg/kg	
Sedation-related adverse event	ASA P3/P4 (N=42) n (%)	Renal insufficiency (N=10) n (%)	ASA P3/P4 (N=74) n (%)	Renal insufficiency (N=19) n (%)
Any SRAE requiring management [1]	5 (11.9)	1 (10.0)	15 (20.3)	3 (15.8)
Apnea	0	0	0	0
Bradycardia	0	0	0	0
Hypotension	0	0	3 (4.1)	1 (5.3)
Hypoxia	5 (11.9)	1 (10.0)	12 (16.2)	3 (15.8)
Manual ventilation or intubation [2]				
Manual ventilation	0	0	1 (1.4)	0

From Sponsor's Summary of Clinical Safety, Table 48, Pg 120. ASA P3 = ASA III, ASA P4 = ASA = IV.

These findings suggest that dose-related hypoxia is associated with debilitated conditions found in geriatric populations.

8.4 Pediatrics

A pediatric deferral was requested with this submission. A pediatric deferral should be granted for patients below three years of age pending neurotoxicological studies in developing animals as recommended by the Pharmacology/toxicology review team.

8.5 Advisory Committee Meeting

A Scientific Advisory Meeting to evaluate the data from clinical studies of fospropofol was held on May 7, 2008. The committee was asked to address the following questions:

1. Do the clinical trial data support the adequacy of using purposeful responsiveness as a clinical sign to make appropriate and safe decisions regarding supplemental dosing of fospropofol disodium?

If not, which other clinical responses should be incorporated in this assessment?

- The majority of the committee indicated that purposeful responsiveness was not sufficient to indicate that supplemental doses may be safely administered. Several committee members suggested that expired carbon dioxide monitoring may be a more sensitive indicator of impending respiratory insufficiency.

2. Adverse events, particularly respiratory adverse events, were observed at a greater frequency among geriatric patients, patients categorized as ASA III or IV, and patients weighing less than 60 kg.

Are additional data needed for these patient populations in order to provide appropriate dosing guidelines for these subpopulations? Please vote "yes" or "no."

If additional data are needed, what studies do you recommend?

- The majority of the committee suggested that additional data were needed to improve safety in these populations.

3. Do the data from clinical trials indicate that fospropofol disodium sedation can be safely managed by health care providers without training in general anesthesia? Please vote "yes" or "no."

If you voted "no," what types of studies would best provide this data?

- The majority of the committee indicated that fospropofol should be administered by health care providers with training in general anesthesia. Several committee members suggested that it may be possible to train non-anesthesiologists in sedation within anesthesia residency training programs.

4. The committee was asked whether fospropofol may be approved.

- The majority of the committee indicated that fospropofol should be approved.

8.6 Literature Review

There are no published clinical manuscripts of clinical studies of fospropofol.

8.7 Postmarketing Risk Management Plan

The Sponsor concluded that non-interventional observational studies (e.g. registries) would not provide meaningful data. Instead, the Sponsor proposes to regularly analyze spontaneous reports, literature searches and reports from the Drug Abuse Warning Network database provided by the Substance Abuse and Mental Health Services Administration and National Forensic Laboratory Information System sponsored by the Drug Enforcement Administration.

The Sponsor further proposes to monitor and periodically review Adverse Drug Reactions including Sedation Related Adverse Events.

This reviewer proposes that additional steps be incorporated into post-marketing risk management activity. The Sponsor should:

- Provide clinical training in the population to be treated by nonanesthesiologist care teams by an anesthesia professional

- Require supervised administration of fospropofol by a non-anesthesiologist care team to 100 patients after initial training and demonstration of sedation management skills before sale of fospropofol to nonanesthesia professionals.

- Provide follow-up evaluation and reporting of adverse events by treatment site after an interval of unsupervised use. The occurrence of a prespecified number of serious adverse events at a commercial site should terminate sales to the treatment site.

- Anticipate scheduling of fospropofol

- Institute a monitoring program for abuse and diversion.

8.8 Other Relevant Materials

None.

9 OVERALL ASSESSMENT

9.1 Conclusions

The data contained in this submission indicate that fospropofol is efficacious as a sedative for diagnostic and therapeutic procedures and that sedation with fospropofol is beneficial to patients. Furthermore, fospropofol can be administered safely when patients are appropriately monitored by vigilant healthcare providers who are able to adequately screen patients, recognize early signs of respiratory insufficiency, preempt evolution of hypoventilation to hypoxia and rescue patients from inadvertent general anesthesia. The Sponsor did not provide an adequate mechanism to inform prescribers how the product may be used safely through labeling and/or a risk evaluation and mitigation strategy.

9.2 Recommendation on Regulatory Action

Fospropofol should be not approved unless the label is revised to include warnings comparable to the propofol label or additional safety measures are developed to evaluate and mitigate risk in the actual setting of use.

9.3 Recommendation on Postmarketing Actions.

9.3.1 Risk Management Activity

Fospropofol should be a scheduled drug product because of its oral bioavailability and potential for abuse.

A clear audit trail is needed for distribution of fospropofol because its potential for abuse may lead to significant diversion.

9.3.2 Required Phase 4 Commitments

A development program for sedation of pediatric patients is required under the Pediatric Equity Research Act unless the Sponsor provides evidence that the risk would outweigh the benefit.

Additional dose-ranging studies should be conducted in geriatric patients, patients with serious comorbidities such as cardiopulmonary conditions that place them in categorizes ASA III or IV and in healthy patients with a body weight below 60 kg.

9.3.3 Other Phase 4 Requests

No other post marketing requests are being proposed.

9.4 Labeling Review

The Sponsor's proposed label will need to be revised in the following Sections:

[redacted]

b(4)

[redacted]

[redacted]

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 2

10 APPENDICES

10.1 Review of Individual Study Reports

Efficacy Trials

10.1.1 Protocol 3000-0520: A dose-ranging study in colonoscopy patients

Title: "A randomized, double-blind, dose-response study to assess the efficacy and safety of Fospropofol Injection for procedural sedation in patients undergoing colonoscopy."

Objectives:

1. To estimate the dose response relationship in sedation success rate for patients who receive different initial bolus doses of Fospropofol.
2. To estimate the dose-response relationship in patients' and Investigators' satisfaction.
3. To evaluate the dose-response relationship of the nature, frequency, seriousness, severity, relationship to treatment and outcome of all treatment-emergent adverse events.
4. To estimate the dose-response relationship of the incidences of need for airway intervention.
5. To estimate the dose-response relationship of duration of the percentage of time that patient's Modified OAA/S = 0 or 1.

Study Design: randomized, double-blind, dose-response

Population: N= 125; 25 patients per arm at up to 25 sites. Patients are to be at least 18 years of age and undergoing elective colonoscopy.

Study Schematic:

Study Flow Diagram

Visit 1	Visit 2				Visit 3	Visit 4
Screening	Colonoscopy Procedure Day				Follow Up	
	Pre-dosing	Dosing	Procedure	Recovery	Telephone	Site Visit

	Time from admission to immediately *prior* to administration of fentanyl citrate pretreatment	Time from fentanyl citrate administration to start of colonoscopy	Time from endoscope insertion to time endoscope withdrawn	Time from end of procedure until the patient is Ready for Discharge	Follow-up and Patient Survey	Follow-up
Day: -14 to 0	Day 0				Day 1	Day 2 to 5

Fentanyl Dosing

Fentanyl, 50 mcg I.V., is to be administered as a pretreatment; additional doses of 25 mcg may be given if the patient experiences pain during the procedure.

Fospropofol Dosing

Study Arm	Initial Bolus	Supplemental Doses
fospropofol Arm 1*	8 mg/kg No less than 480 mg No more than 720 mg	2.00 mg/kg No less than 120 mg No more than 180 mg
fospropofol Arm 2*	6.5 mg/kg No less than 390 mg No more than 585 mg	1.63 mg/kg No less than 97.5 mg No more than 146 mg
fospropofol Arm 3*	5 mg/kg No less than 300 mg No more than 450 mg	1.25 mg/kg No less than 75 mg No more than 112.5 mg
AQUAV AN Arm 4*	2 mg/kg No less than 120 mg No more than 180 mg	0.50 mg/kg No less than 30 mg No more than 45 mg
Midazolam Arm 5	0.02 mg/kg Not to exceed 2.5 mg	1.0 mg

*Round all fospropofol doses (initial and supplemental) down to the next 0.5 mL. Patients who are over 65 years of age or who have a score of ASA III or IV will receive initial and supplemental doses which are reduced by 25% from the randomized dose.

Supplemental doses of either midazolam or Fospropofol are to be given to reach a Modified OAA/S score of ≤ 4. At least 4 minutes must elapse between administration of each supplemental dose of Fospropofol, but midazolam may be administered every 2 minutes; therefore, patients in the Fospropofol arms are to receive injections of saline equal to corresponding volumes of midazolam between doses of active drug to maintain the blinding of

the study.

Timing of Doses: Sedation Initiation Phase

Relative Time (min)	Fentanyl Dosing Scheme (All Patients)	Fospropofol Dosing Scheme		Midazolam Dosing Scheme
		Fospropofol	Saline	
-5	x			
0		x		x
2			x	x
4		x		x
6			x	x
8		x		x

Inclusion Criteria:

1. Patient provides a signed/dated Informed Consent and HIPAA Authorization after receiving a full explanation of the extent and nature of the study.
2. Patients are males or females at least 18 years of age at the time of screening.
3. If female, patient must be surgically sterile, post-menopausal or non-pregnant and non-lactating and using an acceptable method of birth control for at least one (1) month prior to dosing, with a negative urine pregnancy test result at screening and pre-dosing periods.
4. Patient meets the American Society of Anesthesiologists Physical Classification system status of I-IV.

Exclusion Criteria:

1. Patient has a history of allergic reaction or hypersensitivity to any anesthetic agent, narcotic, or benzodiazepine
2. Patient does not meet NPO status per ASA guidelines or institution's guidelines.
3. Patient has a Mallampati Score of 4 or a score of 3 and a thyromental distance of 4 cm or less or any other indication of difficult airway per investigator.
4. Patient has participated in an investigational drug study within 1 month of beginning current study.
5. Patient is unwilling to follow instructions of protocol
6. Fentanyl is contraindicated.
7. Midazolam HCL is contraindicated.

Pharmacokinetic Assessments:

Plasma concentrations of GPI 15715 and propofol are to be obtained at:

- 5 minutes ± 2 minutes after the initial sedative medication bolus administration
- 12 minutes ± 3 minutes after the initial sedative medication bolus administration

- at the time of achieving Fully Alert status
- at 40 minutes ± 15 minutes after achieving Fully Alert or Fully Recovered which ever is later (but prior to discharge).

Schedule:

	Visit 1	**Visit 2**				**Visit 3**	**Visit 4**
	Day -14 to -0	**Day 0**				**Day 1**	**Day 2-5**
Procedure	**Screening**	**Predosing (Baseline)**	**Dosing**	**Procedure**	**Recovery**	**Phone**	**Follow-Up**
Informed Consent/HIPPAA Authorization	X						
Medical History	X	X					
Sedation History	X						
Physical Examination	X	X					X
Weight and Height	X						
Weight		X					
ASA Status	X	X					
Vital Signs: Blood Pressure, Heart Rate, Respiratory Rate	X	X(1)	X(1)	X(1)	X(1)		X
ECG — 3-lead		X	X(2)	X(2)	X(2)		
Modified OAA/S Scale		X(3)	X(3)	X(3)	X(3)		
BIS		X(4)	X(4)	X(4)	X(4)		
Clinical Laboratory Testing (Venous)	X	X			X		X

	Visit 1	**Visit 2**				**Visit 3**	**Visit 4**
	Day -14 to -0	**Day 0**				**Day 1**	**Day 2-5**
Procedure	**Screening**	**Predosing (Baseline)**	**Dosing**	**Procedure**	**Recovery**	**Phone**	**Follow-Up**
Urinalysis	X	X			X		X
PK Samples			X(5)	X(5)	X(5)		
Urine Pregnancy Test	X	X					
Pulse Oximetry (02 saturation)		X	X(1)	X(1)	X(1)		
Satisfaction Survey and Assessment of Anxiety and Cooperation - Physician				X(6)	X(6)		
Satisfaction Survey — Patient					X(7)		
Cognitive Testing (DSST)	X(8)	X			X(8)		
Assessments for Fully Alert					X(9)		
Assessments for Fully Recovered					X(10)		
Concomitant Medications	X	X	X	X	X	X	X
Adverse Event Reporting		X	X	X	X	X	X
Patient Satisfaction Survey — Telephone Follow-up Assessment						X	

1. To be monitored immediately prior to fentanyl and documented at 2-minute intervals until the patient is Fully Recovered.

2. To be monitored continuously per standard of care. Any abnormal change from pre-dosing period will be documented.
3. To be monitored and documented by the evaluator starting at 1 minute prior to Analgesic Pretreatment, 1 minute following Analgesic Pretreatment, and documented at 2-minute intervals until Fully Alert Status is reached.
4. To be recorded 5 minutes poor to Analgesic Pretreatment, monitored continuously and recorded 1 minute prior to Sedation Initiation, and documented every 2 minutes until the patient is Fully Recovered.
5. To be drawn for all patients.
6. To be completed by the Investigator after administration of sedative medication (prior to initiating the procedure) and upon completion of procedure.
7. To be completed by the patient once Fully Recovered.
8. Practice DSST performed at Screening. on Day 0, during Recovery, to be performed at 15, 30, and 60 minutes after the end of the procedure and at discharge.
9. To be performed at 2-minute intervals from the termination of the procedure until the patient meets the criteria for Fully Alert status.
10. To be performed at 2-minute intervals from the time the patient is Fully Alert until the patient meets the criteria for Fully Recovered status.

Definition of Recovery Levels

Fully Alert	Two consecutive Modified OAS/S scores of 5, measured 2 minutes apart
Fully Recovered	On or after Fully Alert AND Systolic blood pressure >= 90 mmHg or within 20% of predosing value AND Heart rate >= 50 bpm or within 20% of predosing value AND Oxygen saturation > 85% breathing room air AND Ability to stand without instability or assistance*
Ready for Discharge	On or after Fully Recovered AND Able to ambulate* And ADSST score equal to or higher than DSST pre-dosing (baseline) score

* If a patient is unable to stand without instability or assistance at the pre-dosing (baseline) period, this assignment is not to be considered for the Fully Recovered criterion.
** If a patient is unable to ambulate at the predosing (baseline) period, this assessment is to

not be considered for the Ready for Discharge criterion.

Safety Assessments

Laboratory testing:

- Hematology: CBC with platelet and differential white blood count
- Serum Chemistry: Alk Phos., AST, ALT, GGT, LDH, TP, Alb, Bili, CPK, BUN, CO2, Glu, Lipid profile
- Serum Electrolytes: Na, K, Ca (ionized), total Ca, Cl, Phos. Mg
- Urinalysis: Protein, glucose, blood, leukocytes, pH, microscopic analysis prn
- Urine Pregnancy Test: screening and pre-dosing only

Pulse oximetry:
Recorded every 2 minutes beginning 6 minutes prior to Analgesic Pretreatment until patient is Fully Recovered.

Blood pressure, heart rate and respiratory rate:
Recorded in the supine position every 2 minutes beginning 6 minutes prior to Analgesic Pretreatment until patient is Fully Recovered.

Electrocardiography:
A 3-lead EKG will be recorded and screened for abnormalities at predosing, dosing initiation, throughout the procedure and until the patient is determined to be Fully Alert.

Sedation Assessments

Bispectral Index

BIS scores are to be recorded 5 minutes prior to Analgesic Pretreatment, 1 minute prior to Sedation Initiation, and at 2 minute intervals until the patient is Fully Recovered.

Modified Observer Alertness Assessment Sedation Scale (Modified OAAS/S)

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

Digit Symbol Substitution Test (DSST)

The DSST (part of the Wechsler Adult Intelligence Scale test battery) is to be used to rate the patient's capabilities prior to and following administration of sedative drugs. Patients are to recall pairings of digits and symbols over a specified period of time (90 seconds).

Satisfaction surveys:

The sponsor includes patient and physician satisfaction surveys intended to evaluate the quality of the sedation regimen. The questions in each survey differ slightly, however, there are areas of similarity.

- Both questionnaires use:

A 10 point overall satisfaction scale with the study medications

Categorical scales to rate the:

1. Adequacy of sedation, (yes, or no), (too heavy, just right, too light)
2. Degree of discomfort associated with
   a. The administration of sedation medication, (none, mild, moderate, severe)
   b. The mechanical aspects of the colonoscopy,(none, mild, moderate, severe)

A question posed to the patient and physician is whether they would consider using the same sedatives again. (yes or no)

- Differences between the patient and physician questionnaires:

Patient Satisfaction Survey Day of Colonoscopy Procedure

1. Recall of scope insertion, (yes or no)?
2. Recall of scope removal, (yes or no)?
3. Recall of being awake during the procedure (yes, no, partially)?

Patient Satisfaction Survey Telephone Follow-Up Visit Assessment (Day 1 after procedure)

1. Degree of mental impairment following the procedure (none, mild, moderate, severe)?
2. Degree of physical impairment following the procedure (none, mild, moderate, severe)?
3. Hours slept since the procedure?
4. Hours routinely slept at night?

5. Consider being treated with these sedatives again (yes or no)?
6. Return to normal activities after discharge (<2 hours, 2 to 6 hours, 6 to 12 hours, >12 hours)?

Proposed Analysis Plan

Efficacy

- Primary Efficacy Endpoint: Successful sedation is defined as having 3 consecutive Modified OAS/S scores ≤ 4 and completing the procedure without requiring alternative sedative medications.
- Secondary Efficacy Endpoints:
  1. Patient's rating of experience after Fully Recovered (levels of sedation and comfort, amnesia, and willing to be treated again with the medication)
  2. Investigator's rating at the end of procedure (level of sedation, patient's comfort, anxiety, and ability to move following instructions, willing to use the medication again)
  3. Percent of patients requiring alternative sedative medication
  4. Number of doses/amount of fentanyl administered
  5. Number of doses of study sedative medication administered
  6. Time to sedation, start of procedure, reach splenic flexure, hepatic flexure, cecum, and end of procedure, and Fully Recovered from the first dose of study sedative medication.
  7. Percent of patients requiring repositioning
  8. Percent of patients whose procedures are interrupted de to inadequate sedation

- Sedation Failure: If MOAA/S ≤ 4 is not achieved following the initial bolus dose and up to 4 supplemental doses of Fospropofol/saline or midazolam injection, the case is considered a sedation failure and alternative medication is administered per the site's standard of care. Propofol is not to be used as alternative sedation. If supplemental doses of sedation fail to keep the patient at an adequate level of sedation, alternative medication may be used. Sedation failure is to be documented in the CRF with the alternative medication used as rescue.

Safety

- Nature, frequency and indication of airway assistance
- Frequency of sedation-related adverse events (apnea, bradycardia, hypoxia, hypotension)
- Nature, frequency, seriousness, severity, relationship to treatment, and outcome of all treatment-emergent adverse events
- Percent of time that patients demonstrate purposeful movement
- Laboratory parameters and vital signs
- Concomitant medications

Statistics

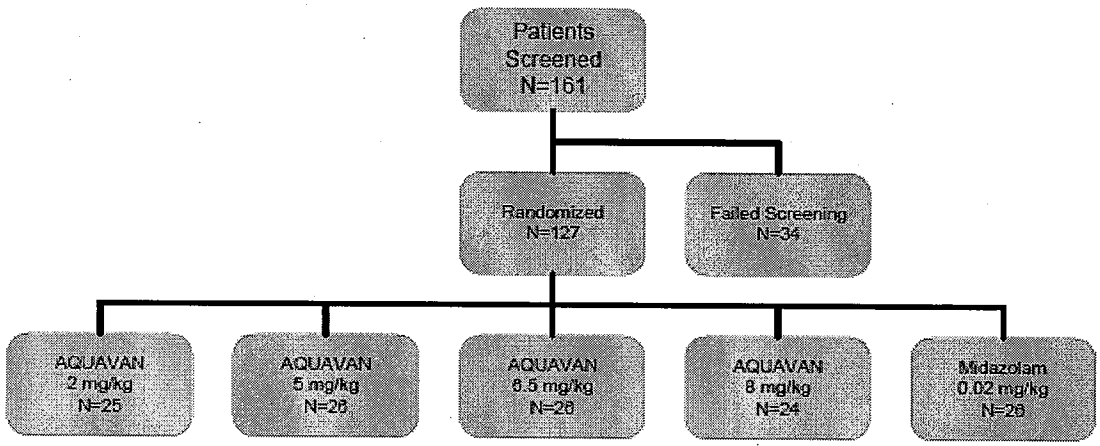
Sample size: Approximately 125 patients from 25 sites are to be enrolled. About 25 patients will we treated in each of the 5 study groups (Fospropofol bolus dose 2, 5, 6.5 and 8 mg/kg and midazolam 0.02 mg/kg) The sample size was determined by (1) feasibility to gain clinical experience (2) ability to differentiate sedation success rate by dose, (3) integrate PK/PD data with findings from other studies for modeling purposes.

Interim analysis: None

Efficacy analysis: The number and proportion of patients considered to be a sedation success will be calculated by treatment group. A 95% confidence interval for the sedation success rate will be calculated for each treatment group and for the between group differences. Pair-wise p-values for the between group difference will be calculated using the Fisher's exact test. The hypothesis that there is a dose-related trend in sedation success with Fospropofol will be tested using the Cochran-Armitage Test of the ITT population (all patients who receive Fospropofol or midazolam and have at least 1 post-dose clinical assessment. There is to be no imputation of missing data. Summary descriptive statistics will be collected on efficacy endpoints including the total amount of study medication for each patient and the total dose of fentanyl.

Conduct of the Study:

Disposition of Patients



From Sponsor's Study Report, Figure 1, page 55.

	AQUAVAN 2 mg/kg	AQUAVAN 5 mg/kg	AQUAVAN 6.5 mg/kg	AQUAVAN 8 mg/kg	Midazolam 0.02 mg/kg	All
	Number and Percent (%) of Patients					
Patients randomized	25	26	26	24	26	127
Patients discontinued prior to study drug administration	0	0	0	0	0	0
Patients discontinued after study drug administration	0	0	1 (3.8)	1 (4.2)	0	2 (1.6)
Lost to follow-up	0	0	1 (3.8)	1 (4.2)	0	2 (1.6)

From Sponsor's Study Report Table 9, Page 56.

No patient was discontinued from the study prior to the administration of study drug. Two of 127 patients (1.6%) (Patients 459-0002 and 504-0008) were discontinued from the study after administration of study drug. The reported reason for discontinuation was "lost to follow-up" for both patients. One patient in the midazolam group (patient 348-0002) did not complete the colonoscopy procedure because of patient discomfort.

Protocol Violations/ Deviations

	AQUAVAN 2 mg/kg (N=25)	AQUAVAN 5 mg/kg (N=26)	AQUAVAN 6.5 mg/kg (N=26)	AQUAVAN 8 mg/kg (N=24)	Midazolam 0.02 mg/kg (N=26)	All (N=127)
	Number and Percent (%) of Patients					
Patients with ≥1 major protocol deviation	5 (20.0)	5 (19.2)	10(38.5)	6 (25.0)	8 (30.8)	34(26.8)
ICF-related compliance	1 (4.0)	0	2 (7.7)	2 (8.3)	2 (7.7)	7 (5.5)
Deviations having a potential effect on interpretation of study results - excluded from pP population						
Subtotal[1]	5 (20.0)	5 (19.2)	8(30.8)	6 (25.0)	7 (26.9)	31(24.4)
Study drug given ≥4 minutes apart during Initiation Phase instead of every 2 minutes	2 (8.0)	5 (19.2)	5(19.2)	2 (8.3)	3(11.5)	17(13.4)
No record of study drug preparation by the pharmacist	2 (8.0)	2 (7.7)	2 (7.7)	4 (16.7)	2 (7.7)	12 (9.4)
Initial bolus dose of study drug differed by ≥25% from protocol-defined dose	2[2] (8.0)	1 (3.8)	2(7.7)	1 (4.2)	3[3] (11.5)	9[4] (7.1)
Treatment unblinded at the patient, Investigator, site monitor, or sponsor level	0	1 (3.8)	0	1 (4.2)	0	2 (1.6)
Supplemental dose of study drug given when patient had Modified OAA/S ≤3 and no purposeful movement	0	0	0	0	1 (3.8)	1 (0.8)

[1] Subtotal is the total number of patients with deviations that had a potential effect on interpretation of study results. These patients were excluded from the pP population.

[2] Both of these incidents were determined to be transcription errors and not deviations. Memos to file were generated.

[3] One of these incidents was determined to be a transcription error and not a deviation. A memo to file was generated.

[4] Three of these incidents were determined to be transcription errors and not deviations. Memos to file were generated.

From Sponsor's study report Table 10, page 57.

10.1.2 Protocol 3000-0522: A dose-controlled study in colonoscopy patients

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

Objectives:
Primary Objective: To demonstrate that fospropofol* is effective in providing minimal-to-moderate sedation in patients undergoing colonoscopy.
Secondary Objectives

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

Reference to fospropofol in the objectives refers to the high initial dose fospropofol group.

Study Design: Randomized, double-blind, two arm, dose-controlled study of initial dose of Fospropofol following pretreatment with fentanyl and with a midazolam arm for safety comparisons

Following completion of preprocedure assessments, patients are to be randomly assigned to 1 of 3 treatment groups at a 2:3:1 (fospropofol Dose 1: fospropofol Dose 2: Midazolam) allocation ratio on the day of the scheduled procedure. Treatment groups are defined below. Randomization will be stratified by site.

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

Patients who are ≥65 years of age or who are classified as ASA P4 were to receive initial and supplemental doses that were reduced by 25% from the randomized dose. Patients classified as ASA P3 were allowed to receive initial and supplemental doses reduced by 25% if the

Investigator deemed it necessary. The reduced dose syringes were to have been prepared as equal volumes. In the Sedation Phase, supplemental doses* were to have been administered only as required to reach the Modified OAA/S scale score of < 4 and to allow the Investigator to start the procedure.

The following table provides the timing of Sedation Initiation phase dose administration.

Timing of Doses in the Sedation Initiation Phase Doses for all Patients

Relative Time (min)	Fentanyl Dosing Scheme (all patients)	AQUAVAN Dosing Scheme	Midazolam Dosing Scheme
-5	X		
0		X	X
4		X*	X*
8		X*	X*
12		X*	X*
16	**Patient's Modified OAA/S scale score not ≤4 OR not able to start the procedure? Sedation failure; may administer alternative sedative medication**		

Sedation Maintenance Phase Drug Dosage
The Sedation Maintenance phase began when the procedure had started and continued until the end of the colonoscopy. Supplemental blinded doses of sedative medication prepared for the Sedation Maintenance phase were to be available and administered if the patient has a Modified OAA/S scale score of ≥4 and demonstrated purposeful movement. At least 4 minutes were to have elapsed from the last Sedation Initiation phase dose administration before the first and subsequent administration of a Sedation Maintenance phase dose.

Sedation Maintenance phase doses are shown in the following table. In order to maintain the blind, syringes were to be prepared as equal. If the Sedation Maintenance doses fail to keep the patient at a Modified OAA/S scale score of ≤4, an alternative sedative medication (See Section 5.7) was allowed to be administered per the site's standard of care. The patient was then to be considered a sedation failure. It was recommended that the Investigator administer at least 4 sedation maintenance doses of the study sedative medication before choosing an alternative sedative medication.

Patients who are ≥65 years of age or who are classified as ASA P4 were to receive Sedation Maintenance doses that reduced by 25% from the randomized dose. Patients who were classified as ASA P3 were allowed to receive Sedation Maintenance doses reduced by 25% if the Investigator deemed it necessary. The reduced dose syringes were to have been prepared as equal volumes. Only one additional dose of 25 mcg of fentanyl was to have been administered and only if the patient was experiencing pain during the procedure. At least 10 minutes was to elapse between initial fentanyl dose and the single additional fentanyl dose allowed per protocol. Prior to and after fentanyl administration, the venous catheter was to be flushed with 2-mL of sterile saline solution. If the patient continued to experience pain during the procedure following the administration of the single fentanyl dose allowed per protocol, additional doses of fentanyl were

allowed to be administered. At least 10 minutes were to elapse between each subsequent administration of fentanyl. If additional analgesic medication is required, only fentanyl at a dose of 0.5 mcg/kg (not to exceed 50 mcg) was to be administered.

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 to have been immediately available during the conduct of the study. All patients were to be placed on supplemental oxygen via nasal cannulae (4 L/min), and an electrocardiogram (ECG) monitor, pulse oximeter, and blood pressure monitor were to have been attached prior to administration of study medication.

Blinding Procedures
All MGI PHARMA and site personnel, except the study pharmacist or designee preparing the study medications and the administrator of the randomization system, and personnel at were to be blinded to study treatments. The pharmacist or designee was to provide the appropriately labeled, blinded syringes to the Investigator. To facilitate dose preparations, the fospropofol dose volumes were to be provided (1) by weight group ranged in increments of 2 kg and (2) rounded to the nearest 0.5 mL.

Population: Approximately 300 patients at least 18 years old undergoing elective colonoscopy randomized at approximately 30 sites.

Entry Criteria:

Inclusion:
1. Patient was to be able to understand, either orally or in writing, and to be able to consent and complete the required assessments and procedures.
2. Patient was to provide signed/dated Informed Consent and Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization after receiving a full explanation of the extent and nature of the study.
3. Patient was to be at least 18 years of age at the time of screening.
4. If female, patient was to be surgically sterile, postmenopausal, or not pregnant or lactating and was have 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.
5. Patient was to meet American Society of Anesthesiologists (ASA) Physical Classification System status of P1 to P4.

Exclusion:
1. Patient had a history of allergic reaction or hypersensitivity to any anesthetic agent, opioid, or benzodiazepine.
2. Patient did not meet nils per os (NPO) status per ASA guidelines or institution's guideline.
3. Patient had a Mallampati Classification Score of 4; OR a Mallampati Classification Score of 3 AND a thyromental distance $\leq$4 cm, or for any other reason had a difficult

airway, in the opinion of the Investigator.
4. Patient had an abnormal, clinically significant 3-lead ECG finding at predosing period Day 0.
5. Patient had participated in an investigational drug study within 1 month prior to study start.
6. Patient was unwilling to adhere to pre- and postprocedural instructions.
7. Patient for whom the use of fentanyl citrate injection (fentanyl) was contraindicated.
8. Patient for whom the use of midazolam HCL (midazolam) was contraindicated.

Primary Endpoint:

Sedation Success rate—Sedation Success is defined as a patient having (i) 3 consecutive Modified OAA/S scale 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 Endpoint:

• Treatment Success rate – Treatment Success is 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 medication.

Tertiary 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 Evaluations:
• Nature, frequency, and indication of airway assistance.
• Frequency of sedation-related adverse events (apnea, hypoxemia, bradycardia, hypotension).
• Nature, frequency, seriousness, severity, relationship to treatment, and outcome of all treatment-emergent adverse events.
• Purposeful movement.
• Laboratory parameters and vital signs.

Pharmacokinetic Assessments:

Pharmacokinetic samples for determination of fospropofol disodium and propofol plasma concentrations will be obtained at 5 time points during the procedure day. Samples will be collected from all patients satisfying one or more of the following criteria:

- ASA P3 or P4 status;
- Elderly patients (aged ≥65 years);
- Screening serum albumin <2.8 g/dL;
- Screening total bilirubin >3 mg/dL;
- Calculated screening creatinine clearance ≤50 mL/min.

Samples will also be collected from all of the last 150 patients enrolled.

Samples will be drawn during the following timeframes:

- Sample 1 during Predosing period
- Sample 2 at 5 minutes ± 2 minutes after the initial sedative medication bolus administration,
- Sample 3 at 12 minutes ± 3 minutes after the initial sedative medication bolus administration,
- Sample 4 at the 3rd MOAA/S scale score of 5 when Fully Alert status is established or within 5 minutes after that time, and
- Sample 5 at 40 minutes ± 15 minutes after achieving status of Fully Alert or at Ready for Discharge which ever is later.

Amendment:

- Changes were made to refine secondary and tertiary endpoints in an effort to demonstrate a clear clinical benefit of sedation in the Phase 3 program.
- Sedation Initiation phase study sedative medication timing altered to occur every 4 minutes rather than every 2 minutes to more closely adhere to the midazolam HCl package insert instructions.
- Administration limited to bolus dose and 2 supplemental doses before assessment of sedation failure.
- Sedation Maintenance phase supplemental administration of study sedative medication altered to be an unlimited number of administrations depending on the length of the procedure.
- Pharmacokinetic (PK) sampling schedule is being changed from the first 150 patients enrolled in the study, to the last 150 patients enrolled in the study.
- The PK sampling schedule is unchanged for all patients meeting the ASA, age, or criteria for hepatic or renal impairment.
- Global change throughout the document where applicable: 'Modified OAA/S score' changed to 'Modified OAA/S scale score'.
- The Appendices have been renumbered throughout the document as a result of the deletion of the DSST Appendix.

- The protocol is also being revised to correct administrative changes such as typographical and/or grammatical errors.

Amendment February 20, 2006

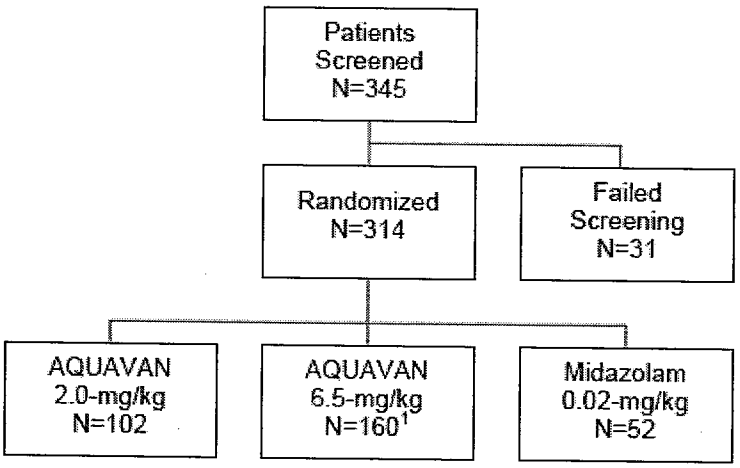
- Sedation Initiation phase study sedative medication timing was altered to occur every 4 minutes rather than every 2 minutes to more closely adhere to the midazolam HCl package insert instructions. The administration limited to bolus dose and 2 supplemental doses before assessment of sedation failure.

- The Sedation Maintenance phase supplemental administration of study sedative medication was altered to be an unlimited number of administrations depending on the length of the procedure.

- Pharmacokinetic (PK) sampling schedule is being changed from the first 150 patients enrolled in the study, to the last 150 patients enrolled in the study. The PK sampling schedule is unchanged for all patients meeting the ASA, age, hepatically or renally impaired parameters.

Conduct of the Study

Disposition of Patients



[1] Two patients randomized to the AQUAVAN 6.5-mg/kg group did not receive study drug

From Sponsor's study report, Figure 1, page 55.

Thirty-one of 345 screened patients were screening failures and were not randomized. Of the 31 screen failures, 15 patients withdrew consent, 4 were not randomized at the discretion of

the Investigator, 3 exceeded the 14-day screening window, 2 were ineligible because they did not meet inclusion or exclusion criteria, and 2 patients were not randomized because the targeted number of patients had been enrolled in the study. The remaining 5 patients were screen failures for a variety of reasons (i.e., abnormal chemistry panel, abnormal laboratory values, colonoscopy fee denied by insurance company, insurance not accepted, and patient canceled the appointment).

	AQUAVAN 2.0-mg/kg	AQUAVAN 6.5-mg/kg	Midazolam 0.02-mg/kg	All
	Number and Percent (%) of Patients			
Patients randomized	102	160	52	314
Patients discontinued prior to study drug administration	0	2 (1.3)	0	2 (0.6)
Adverse Event	0	1 (0.6)	0	1 (0.3)
Other	0	1 (0.6)	0	1 (0.3)
Patients discontinued after study drug administration	0	0	0	0

From Sponsor's study report, Table 10, Page 56.

Protocol Violations/Deviations

	AQUAVAN 2.0-mg/kg (N=102)	AQUAVAN 6.5-mg/kg (N=158)	Midazolam 0.02-mg/kg (N=52)	All (N=312)
	Number and Percent (%) of Patients			
Patients with ≥1 major protocol deviation	4 (3.9)	10 (6.3)	4 (7.7)	18 (5.8)
ICF-related compliance	1 (1.0)	4 (2.5)	0	5 (1.6)
SAE reporting violation[1]	1 (1.0)	0	0	1 (0.3)
Treatment unblinded at the patient, Investigator, site monitor, or sponsor level	1 (1.0)	0	0	1 (0.3)
Study drug dosing compliance, e.g. incorrect dose or timing	3 (2.9)	5 (3.2)	2 (3.8)	10 (3.2)
Other treatment/procedure compliance[2]	1 (1.0)	1 (0.6)	2 (3.8)	4 (1.3)
Deviations having a potential effect on interpretation of study results – patients excluded from pP population				
Subtotal[3]	3 (2.9)[4]	5 (3.2)	0	8 (2.6)[4]
Treatment unblinded at the patient, Investigator, site monitor, or sponsor level	1 (1.0)	0	0	1 (0.3)
Study drug dosing compliance, e.g. incorrect dose or timing	3 (2.9)	5 (3.2)	0	8 (2.6)
Other treatment/procedure compliance	1 (1.0)	0	0	1 (0.3)

ICF= Informed consent form; SAE= Serious adverse event; pP= Per protocol

1 This SAE was a procedural finding of adenocarcinoma of the colon which was not reported within the 24-hour timeframe required by the protocol.

2 Other treatment/procedure compliance deviations in this study concerned initial dosing of fentanyl (outside window or wrong dose given)

3 Subtotal is the total number of patients with deviations that had a potential effect on interpretation of study results. These patients were excluded from the pP population.

4 One of these patients (368-0001) had 3 major protocol deviations and was excluded from the pP population

From Sponsor's Study Report, Table 11, page 57.

Dosing errors occurred in approximately 3% of each of the Fospropofol treatment arms, but did not occur in the midazolam arm.

Efficacy Findings

Populations

Efficacy endpoints were analyzed by using both the mITT and the pP populations. Additional summaries of efficacy data were presented using the pP2 population, which excluded from the mITT population patients who received alternative sedative medications. The pP2 population, therefore, represented those patients who were treated only with their originally assigned study sedative, and allowed for analysis without the confounding mixed effects of multiple sedative medications.

	AQUAVAN 2.0-mg/kg	AQUAVAN 6.5-mg/kg	Midazolam 0.02-mg/kg	All
	Number of Patients			
Patients randomized	102	160	52	314
mITT population[1]	102	158	52	312
pP population	99	153	51	302
pP2 population	29	139	42	210
Safety population	102	158	52	312

Two patients randomized for the 6.5 mg/kg fospropofol group did not receive study drug. All patients who received study medication were treated with the medication to which they were randomized.
From Sponsor's Study Report Table 13, page 61.

Demographics

- Age

Overall, the mean age of patients in the mITT population was 53 years. Forty-five of 312 patients (14%) were ≥ 65 years of age and 6 of those patients were ≥ 75 years of age (2 % of the overall population).

- ASA Classification

The majority (96%) of the patients had an ASA status P1 or P2. Twelve patients (4%) had an ASA status of P3. No patients with an ASA status P4 were enrolled. Based on age (≥65 years) or ASA status (P4), the initial and maintenance doses were to be reduced by 25% from the standard dose. The dose of study drug for ASA status P3 was also allowed to be reduced at the discretion of the Investigator. Overall, 45 patients (14.4%) received reduced doses of study medication.

- Gender

Overall, 50.0% of the patients were male.

- Race

Overall, 79% of the patients were white and 12% were black. Approximately 8% were Hispanic/Latino and 7% were Asian.

- Weight

Slightly more than half of the patients (55%) were in the mid-weight range (60 to <90 kg). Most of the remaining patients were in the high weight category of ≥ 90 kg (36%), and 8% weighed <60 kg.

- Medical History

There were minimal differences among treatment groups in medical or surgical history at baseline.

Primary Efficacy Endpoint

Table10.1.2-3 Sedation Success: Sponsor's Analysis of Primary Efficacy Endpoint

	Sedation Success n/N (%)	95% CI[1] of Sedation Success Rate (%)	Comparison of AQUAVAN Groups
AQUAVAN 2.0-mg/kg (N=102)	26/102 (25.5)	(17.4, 35.1)	
AQUAVAN 6.5-mg/kg (N=158)	137/158 (86.7)	(80.4, 91.6)	
Midazolam 0.02-mg/kg (N=52)	36/52 (69.2)	(54.9, 81.3)	
Difference in Sedation Success Rates (%)			61.2
95% CI of Difference (%)			(51.2, 71.2)
p-value[2]			<0.001

1 The 95% confidence interval (CI) is an exact computation.
2 Fisher's exact test.

From Sponsor's Study Report Table 16, Section 11.4.1.1 on pg 65 of Sponsor's Study Report

Secondary Efficacy Endpoints

These endpoints were intended to enable an evaluation of clinical benefit of sedation by Fospropofol when the product was used during colonoscopy.

- Treatment Success Rate

Table 10.1.2-4 Treatment Success

	Treatment Success n/N (%)	95% CI[1] of Treatment Success Rate (%)	Comparison of AQUAVAN Groups
AQUAVAN 2.0-mg/kg (N=102)	29/102 (28.4)	(19.9, 38.2)	
AQUAVAN 6.5-mg/kg (N=158)	139/158 (88.0)	(81.9, 92.6)	
Midazolam 0.02-mg/kg (N=52)	41/52 (78.8)	(65.3, 88.9)	
Difference in Treatment Success Rates (%)			59.5
95% CI of Difference (%)			(49.4, 69.7)
p-value[2]			<0.001

From Sponsor's Study Report, Table 17, Section 11.4.1.2 pg 66

- Proportion of Patients requiring Supplemental Analgesic Medication

Table 10.1.2-5 Patients Requiring Supplemental Analgesia Medication

	Patients Requiring Supplemental Analgesic Medication n/N (%)	95% CI[1] for the Proportion (%)	Comparison of AQUAVAN Groups
AQUAVAN 2.0-mg/kg (N=102)	78/102 (76.5)	(67.0, 84.3)	
AQUAVAN 6.5-mg/kg (N=158)	87/158 (55.1)	(47.0, 63.0)	
Midazolam 0.02-mg/kg (N=52)	33/52 (63.5)	(49.0, 76.4)	
Difference in Proportions (%)			-21.4
95% CI of Difference (%)			(-32.7, -10.1)
p-value[2]			0.001

From Sponsor's Study Report, Table 18, Section 11.4.1,2 pg 67

- Proportion of Patients willing to be treated again with the same study sedative medication

Table 10.1.2-6 Patients Willing to Be Treated Again With the Same Study Medication

	Patients Willing to be Treated Again n/N (%)	95% CI[1] for the Proportion (%)	Comparison of AQUAVAN Groups
AQUAVAN 2.0-mg/kg (N=102)	93/102 (91.2)	(83.9, 95.9)	
AQUAVAN 6.5-mg/kg (N=158)	151/158 (95.6)	(91.1, 98.2)	
Midazolam 0.02-mg/kg (N=52)	48/52 (92.3)	(81.5, 97.9)	
Difference in Proportions (%)			4.4
95% CI of Difference (%)			(-2.0, 10.8)
p-value[2]			0.188

From Sponsor's Study Report, Table 21, Section 11.4.1.2 page 69

- Proportion of patients who did not recall being awake during the procedure

Table 10.1.2-7 Patients Who Recall Being Awake During Procedure

	Patients Who Did Not Recall Being Awake n/N (%)	95% CI[1] for the Proportion (%)	Comparison of AQUAVAN Groups
AQUAVAN 2.0-mg/kg (N=102)	45/102 (44.1)	(34.3, 54.3)	
AQUAVAN 6.5-mg/kg (N=158)	83/158 (52.5)	(44.4, 60.5)	
Midazolam 0.02-mg/kg (N=52)	23/52 (44.2)	(30.5, 58.7)	
Difference in Proportions (%)			8.4
95% CI of Difference (%)			(-4.0, 20.8)
p-value[2]			0.205

From Sponsor's Study Report Table 19, Section 11.4.1.2 pg 68

Tertiary Efficacy Endpoints

- Number of Supplemental Doses of Study Medication Administered by Study Period

Table 10.1.2-8 Number of Supplemental Doses of Study Medication

Sedation Period	AQUAVAN 2.0-mg/kg (N=102)	AQUAVAN 6.5-mg/kg (N=158)	Midazolam 0.02 mg/kg (N=52)
Total			
Mean	3.2	2.3	2.8
Standard Deviation	1.0	1.4	1.4
Initiation			
Mean	2.8	1.6	1.7
Standard Deviation	0.7	1.1	1.1
Maintenance			
N[2]	32	143	43
Mean	1.3	0.8	1.4
Standard Deviation	1.3	0.9	1.3

From Sponsor's Study Report, Table 25, Section 11.4.1.3, page 73

- Investigator Rating of Satisfaction

Table 10.1.2-9 Physician's Rating of Satisfaction with Sedation

	AQUAVAN 2.0-mg/kg N=102	AQUAVAN 6.5-mg/kg N=158	Midazolam 0.02-mg/kg N=52
	Number and Percent (%) of Patients		
End of Sedation Initiation Phase - Overall satisfaction with the study medication administered			
1-5	74 (72.5)	37 (23.4)	24 (46.2)
6-8	24 (23.5)	60 (38.0)	18 (34.6)
9-10	4 (3.9)	61 (38.6)	10 (19.2)
Mean	3.3	7.1	5.6
Standard deviation	2.9	2.7	3.0
Median	2.0	8.0	6.0
Min, max	1, 10	1, 10	1, 10
End of Procedure - Overall satisfaction with the study medication administered			
1-5	60 (58.8)	26 (16.5)	20 (38.5)
6-8	27 (26.5)	50 (31.6)	19 (36.5)
9-10	15 (14.7)	82 (51.9)	13 (25.0)
Mean	4.5	7.7	6.1
Standard deviation	3.3	2.6	3.0
Median	4.0	9.0	7.0
Min, max	1, 10	1, 10	1, 10

From Table 23, Sponsor's Study Report Section 11.4.1.3 pg 71.

- Patient Rating of Experience

Table 10.1.2-10 Patient's Overall Rating of Experience

Appears This Way
On Original

	AQUAVAN 2.0-mg/kg N=102	AQUAVAN 6.5-mg/kg N=158	Midazolam 0.02-mg/kg N=52
	Number and Percent (%) of Patients		
Do you remember the scope being inserted?			
Yes	46 (45.1)	50 (31.6)	20 (38.5)
No	56 (54.9)	108 (68.4)	32 (61.5)
Do you remember being awake during the procedure?			
Yes	57 (55.9)	75 (47.5)	29 (55.8)
No	45 (44.1)	83 (52.5)	23 (44.2)
Do you remember having the scope removed?			
Yes	38 (37.3)	45 (28.5)	14 (26.9)
No	64 (62.7)	113 (71.5)	38 (73.1)
If you undergo a colonoscopy in the future, would you agree to use this sedative medication again?			
Yes	93 (91.2)	151 (95.6)	48 (92.3)
No	9 (8.8)	7 (4.4)	4 (7.7)
Overall satisfaction with the entire procedure[1]			
1-5	4 (3.9)	3 (1.9)	3 (5.8)
6-8	21 (20.6)	24 (15.2)	8 (15.4)
9-10	77 (75.5)	131 (82.9)	41 (78.8)
Mean	9.1	9.4	9.1
Standard deviation	1.6	1.1	2.0
Median	10.0	10.0	10.0
Min, max	1, 10	4, 10	1, 10
Overall comfort level during the procedure[2]			
1-5	9 (8.8)	8 (5.1)	3 (5.8)
6-8	23 (22.5)	27 (17.1)	9 (17.3)
9-10	70 (68.6)	123 (77.8)	40 (76.9)
Mean	8.7	9.1	8.9
Standard deviation	2.0	1.5	1.9
Median	10.0	10.0	10.0
Min, max	1, 10	3, 10	1, 10

[1] Scale for overall satisfaction was numbered 1 (dissatisfied) through 10 (highly satisfied).
[2] Scale for overall comfort was numbered 1 (least comfortable) through 10 (most comfortable)

From Sponsor's Table 24, Study Report Section 11.4.1.3 pg 72

Appears This Way
On Original

- Number of Supplemental Doses of Analgesic Medication Administered

Table 10.1.2-10 Number of Supplemental Doses of Medication Administered

Number of Doses	AQUAVAN 2.0-mg/kg N=102	AQUAVAN 6.5-mg/kg N=158	Midazolam 0.02-mg/kg N=52
	Number and Percent (%) of Patients		
1	24 (23.5)	71 (44.9)	19 (36.5)
2	53 (52.0)	79 (50.0)	29 (55.8)
3	22 (21.6)	8 (5.1)	4 (7.7)
4	1 (1.0)	0	0
5	1 (1.0)	0	0
>5	1 (1.0)	0	0
Mean	2.1	1.6	1.7
Standard deviation	0.9	0.6	0.6
Median	2.0	2.0	2.0

From Table 22 of Sponsor's Study Report, Section 11.4.1.3 pg 70

- Retention Score During the Recovery Period, Based on the HVLT-R

Table 10.1.2.2-11 Retention Score During Recovery Period

RETENTION SCORE DURING THE RECOVERY PERIOD, BASED ON THE HVLT-R

The HVLT-R is a brief assessment of verbal learning and memory (recognition and recall). Table 26 presents the mean percent retention from baseline to recovery by treatment group in the mITT population.

Table 26. Retention Score (%) from HVLT-R™ at Screening and Recovery (mITT Population)

Period Parameter	AQUAVAN 2.0-mg/kg N=102	AQUAVAN 6.5-mg/kg N=158	Midazolam 0.02-mg/kg N=52[1]
Screening			
Mean	94.8	93.4	90.0
Standard Deviation	18.7	20.8	15.0
Median	100.0	100.0	88.9
Min, max	38, 167	38, 250	60, 120
Recovery Period			
Mean	59.2	67.0	41.0
Standard Deviation	36.3	33.2	32.0
Median	60.0	70.0	42.9
Min, max	0, 160	0, 133	0, 125

[1] N=51 for Recovery Period
Retention score calculated as total correct responses for Trial 4 divided by maximum correct responses between Trials 2 and 3 times 100%, range 0-infinity

From Sponsor's Table 26, Study Report Section 11.4.1.3 pg 74

Safety Findings Reported by the Sponsor

Extent of Exposure

- Total Amount of Study Medication Administered

Table 10.1.2-12 Total Sedation Medication Administered (mg)

	AQUAVAN 2.0-mg/kg N=102	AQUAVAN 6.5-mg/kg N=158	All AQUAVAN Groups N=260	Midazolam 0.02-mg/kg N=52
Initiation Phase				
n	102	158	260	52
Mean	249.3	704.3	525.8	3.20
Standard deviation	36.9	178.1	263.3	1.20
Median	245.0	717.5	542.5	3.13
Min, max	140.0, 350.0	297.5, 1277.5	140.0, 1277.5	1.0, 5.5
Maintenance Phase				
n	21	75	96	31
Mean	71.7	178.5	155.1	1.92
Standard deviation	39.1	89.2	92.2	1.02
Median	70.0	140.0	140.0	2.00
Min, max	35.0, 175.0	70.0, 490.0	35.0, 490.0	0.7, 5.0
Total				
n	102	158	260	52
Mean	264.0	789.1	583.1	4.34
Standard deviation	46.1	206.7	304.5	1.54
Median	262.5	778.8	577.5	4.30
Min, max	140.0, 420.0	297.5, 1277.5	140.0, 1277.5	1.6, 9.6

From Sponsor's Table 29 Study Report Section 12 pg 81

- Total Exposure to Fentanyl

Table 10.1.2-13 Total Amount of Fentanyl (mcg) Administered

	AQUAVAN 2.0-mg/kg N=102	AQUAVAN 6.5-mg/kg N=158	All AQUAVAN Groups N=260	Midazolam 0.02-mg/kg N=52
Mean	89.7	66.6	75.7	72.6
Standard deviation	36.6	17.8	29.0	23.4
Median	75.0	75.0	75.0	75.0
Min, max	50.0, 250.0	50.0, 150.0	50.0, 250.0	50.0, 150.0

From Sponsor's Table 30, Study Report Section 12.1 pg 82

Overview of Adverse Events

Table 10.1.2-14 Serious Adverse Events

	AQUAVAN 2.0-mg/kg N=102	AQUAVAN 6.5-mg/kg N=158	All AQUAVAN Groups N=260	Midazolam 0.02-mg/kg N=52
	Number and Percent (%) of Patients			
Treatment-emergent AEs	89 (87.3)	145 (91.8)	234 (90.0)	31 (59.6)
Treatment-related AEs	77 (75.5)	124 (78.5)	201 (77.3)	3 (5.8)
Adverse events leading to discontinuation of procedure	0	1 (0.6)	1 (0.4)	1 (1.9)
Adverse events leading to discontinuation of study medication	0	0	0	0
Adverse events leading to concomitant medication	58 (56.9)	82 (51.9)	140 (53.8)	30 (57.7)
Adverse events leading to airway assistance	0	1 (0.6)	1 (0.4)	0
Adverse events leading to discontinuation from the study[1]	0	0	0	0
SAEs[2]	1 (1.0)	0	1 (0.4)	1 (1.9)
Deaths	0	0	0	0

Note: The same patient may have been counted in more than 1 category.
[1] Patient 520-0002 (AQUAVAN 6.5-mg/kg) was discontinued from the study due to AEs (facial rash, pruritus, and warmth) that occurred prior to dosing; therefore, this patient was not included in the safety population.
[2] Patient 267-0013 (AQUAVAN 2.0-mg/kg) had an SAE of adenocarcinoma of the colon and patient 518-0029 (midazolam) had a peritoneal hemorrhage and subcapsular splenic hematoma. Neither SAE was related to study medication and both patients were included in all analysis populations.

From Sponsor's Table 31, Study Report Section 12.2.1 pg 83

Vital Signs

- Maximum Change in Vital Signs on the Day of the Procedure

Table 10.1.2-15 Maximum Change in Blood Pressure, Heart Rate, Respiration Rate and Pulse Oximetry

	AQUAVAN 2.0-mg/kg N=102	AQUAVAN 6.5-mg/kg N=158	All AQUAVAN Groups N=260	Midazolam 0.02-mg/kg N=52
Vital sign[1]				
Systolic blood pressure (mm Hg)				
Largest increase, mean (SD)	14.7 (13.0)	12.5 (12.7)	13.4 (12.8)	12.0 (12.4)
Largest decrease, mean (SD)	-29.1 (19.9)	-32.6 (18.7)	-31.2 (19.2)	-28.1 (18.8)
Range (min, max)	(-109, 74)	(-89, 72)	(-109, 74)	(-102, 52)
Diastolic blood pressure (mm Hg)				
Largest increase, mean (SD)	13.3 (9.7)	11.0 (10.0)	11.9 (9.9)	10.8 (11.8)
Largest decrease, mean (SD)	-18.7 (12.5)	-21.4 (11.5)	-20.3 (12.0)	-18.4 (10.3)
Range (min, max)	(-68, 44)	(-63, 43)	(-68, 44)	(-59, 66)
Mean arterial pressure (mm Hg)				
Largest increase, mean (SD)	11.0 (9.0)	9.4 (8.9)	10.0 (9.0)	9.0 (10.2)
Largest decrease, mean (SD)	-20.3 (13.6)	-23.3 (12.0)	-22.1 (12.7)	-19.3 (11.7)
Range (min, max)	(-82, 39)	(-62, 39)	(-82, 39)	(-73, 47)
Heart rate (beats per minute)				
Largest increase, mean (SD)	10.1 (10.1)	11.8 (10.4)	11.2 (10.3)	11.4 (12.0)
Largest decrease, mean (SD)	-10.6 (8.3)	-9.0 (8.0)	-9.6 (8.2)	-8.7 (6.6)
Range (min, max)	(-46, 55)	(-50, 81)	(-50, 81)	(-31, 67)
Respiration rate (breaths per min)				
Largest increase, mean (SD)	4.6 (6.1)	3.9 (5.2)	4.2 (5.5)	4.1 (5.7)
Largest decrease, mean (SD)	-3.7 (3.2)	-3.9 (3.6)	-3.8 (3.4)	-4.1 (5.3)
Range (min, max)	(-13, 41)	(-25, 35)	(-25, 41)	(-35, 33)
Pulse oximetry (%)				
Largest increase, mean (SD)	0.7 (1.5)	0.7 (1.3)	0.7 (1.4)	1.0 (2.1)
Largest decrease, mean (SD)	-2.6 (2.6)	-2.9 (2.5)	-2.7 (2.6)	-2.5 (2.3)
Range (min, max)	(-13, 10)	(-12, 8)	(-13, 10)	(-9, 10)

[1] Baseline is the last observation prior to fentanyl administration.

From Table 43 Sponsor's Study Report Section 15.5 pg 104

Laboratory

With the exception of phosphorus, the frequencies of patients who had shifts in laboratory chemistry test results from the normal range to below or to above normal were generally similar across treatment groups. Shifts from normal to low occurred in a higher percentage of patients in the midazolam group compared with the combined fospropofol groups for hematocrit (15.6% versus 6.2%), hemoglobin (20.5% versus 11.1%), platelets (10.3% versus 4.7%), and white blood cells (14.3% versus 6.5%).

Safety Conclusions

1. The mean total dose (±SD) of study sedative used to initiate and complete the colonoscopy was 789.1 mg (±206.7) in the fospropofol 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.

2. No deaths occurred in the study.

3. No patient was discontinued from the study because of an AE.

4. No fospropofol-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 fospropofol 2.0-mg/kg group experienced an SAE (adenocarcinoma of the colon) that was not related to study medication.

5. Two patients required airway assistance (verbal stimulation and chin lift). Only the hypoxemia managed with verbal stimulation was considered an SRAE.

6. Two patients had AEs (hypotension [fospropofol 6.5 mg/kg], lower left quadrant abdominal tenderness [midazolam]) that led to discontinuation of the colonoscopy.

7. Treatment-emergent AEs were experienced by 91.8%, 87.3%, and 59.6% of patients in the fospropofol 6.5-mg/kg group, the 2.0-mg/kg group, and the midazolam group, respectively, in the safety population.

8. Treatment-related AEs were experienced by 78.5%, 75.5%, and 5.8% of patients in the fospropofol 6.5-mg/kg, the 2.0-mg/kg group, and the midazolam group, respectively, in the safety population.

9. The most common TEAEs experienced by patients in the fospropofol groups combined were paresthesia (65.0%), procedural pain (53.8%), and pruritus (19.6%).

10. 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 fospropofol 6.5-mg/kg group who had an AE of procedural pain, the pain was of mild severity, 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 fospropofol 2.0-mg/kg treatment had pain that was moderate in severity (40.4% and 30.4%, respectively).

11. Most TEAEs were mild or moderate in severity. Five patients (4 fospropofol 6.5-mg/kg and 1 fospropofol 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 fospropofol 6.5-mg/kg group.

12. 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.

13. 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 fospropofol 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.

14. The fospropofol 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.

15. 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 $\geq$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.

16. Fourteen patients (13 in the fospropofol 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 fospropofol 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.

17.No patient had pulse oximetry readings of <90% for 2 consecutive time points. No patient had readings of <85% at any time.