

10.1.3 Protocol 3000-524 A dose-controlled study in bronchoscopy 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 flexible bronchoscopy

Indication: minimal-to-moderate sedation

Objectives:

1. demonstrate that Fospropofol is effective in providing minimal-to-moderate sedation
2. demonstrate clinical benefit of Fospropofol to patients
3. Evaluate safety of Fospropofol

Study Design:

Patients are to be administered 50 mcg of fentanyl intravenously before beginning the procedure and before administering sedation. One additional dose of 25 mcg of fentanyl may be administered after an interval of 10 minutes if the patient appears to be in pain.

Randomized, double-blinded, dose-control with patients assigned 1:1 to one of two initial sedation doses of Fospropofol: either 2 mg/kg (range 120 mg to 180 mg) or 6.5 mg/kg (range 390 to 585 mg). The initial dose of fospropofol is to be administered 5 minutes after administration of the initial dose of fentanyl.

The initial dose of Fospropofol and up to two additional supplemental doses may be administered at four minute intervals to achieve an OAA/S score of not more than 4/5. The supplemental doses of Fospropofol are 0.5 mg/kg (range 30-45 mg) for the patients treated with an initial dose of 2 mg/kg and 1.63 mg/kg (range 97.5-146 mg) for patients treated with an initial dose of 6.5 mg/kg.

Patients classified as ASA 3 are to receive a 25% reduction in dose at the discretion of the investigator. Patients classified as ASA 4 are required to receive a 25% dose reduction.

Patients who do not achieve an OAA/S \leq 4 after receiving the maximum number of supplementary Fospropofol doses are to be considered a sedation failure and may receive the institutional standard of care alternative sedation to complete the procedure.

Population: 250 patients, randomized 1:1 to 2.0 or 6.5 mg/kg initial dose

Key Entry Criteria

Inclusion

- Patients over the age of 18 undergoing elective flexible bronchoscopy
- Females having a highly effective method of birth control
- Patients classified as ASA 1 through 4

Exclusion

- Complex airway defined by a Mallampati Classification of 4 or a thyromental distance of 4 cm or less, or other subjective criteria identifying a difficult to manage airway.
- Patient is not NPO

The primary endpoint: Sedation success rate defined as a patient having three consecutive modified OAA/S scores LE 4 after administration of sedation medication and completing the procedure without requiring the use of alternative sedative medication and without requiring manual or mechanical ventilation. The modified OAA/S is to be documented at 2-minute intervals.

Secondary endpoints:

1. Proportion of patients with success as defined in the primary efficacy endpoint
2. Proportion of patients with procedure interruptions due to inadequate sedation
3. Proportion of patients willing to be treated again with the same sedative agent
4. Proportion of patients with time-to-sedation \leq 5 minutes.

Key tertiary endpoints: Investigators satisfaction rating, patient's rating at time of discharge including recall of the procedure.

Safety Evaluations:

- Nature, frequency and indication of airway assistance
- Frequency of sedation related adverse events including apnea for 30 sec, hypoxemia (O₂ sat < 90 for >30 sec), bradycardia (hr of < 50 requiring intervention) and hypotension (systolic BP < 90 requiring intervention)
- Frequency of all adverse events (AEs) and serious adverse events (SAEs)
- Percent of treatment time that the patient demonstrates purposeful movement
- Laboratory parameters (hematology, chemistry, electrolytes including phosphorus, urinalysis, urine pregnancy test) and vital signs (monitored and documented at 2 minute intervals, continuously monitored EKG)
- Concomitant medications

Pharmacokinetic Assessments:

Pharmacokinetic samples for determination of fospropofol disodium and propofol plasma concentrations are to be obtained at 5 time points during the day of procedure in the first 65 patients and all patients who are:

- ASA 3 or 4
- Aged 65 years or older
- Have a screening albumin < 2.8
- Have a screening bilirubin > 3 mg/dl
- Have a calculated screening creatinine clearance \leq 50 mL/min

Amendment: March 6, 2006

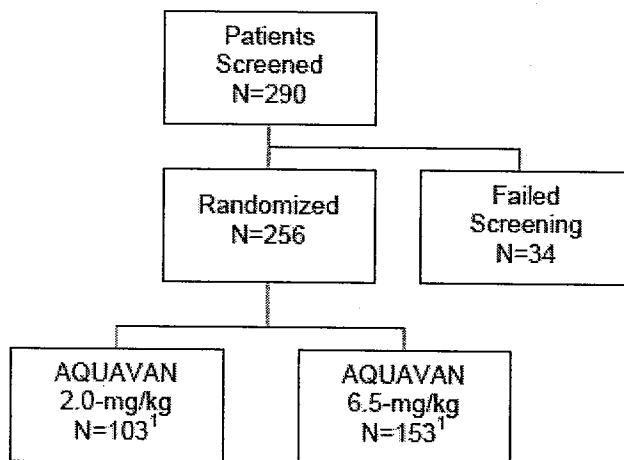
- Sedation Initiation phase study sedative medication administration was limited to bolus dose and 3 supplemental doses before assessment of sedation failure.
- The number of patients targeted for pharmacokinetic (PK) sampling was expanded from 65 to 75 patients. The occurrence of the healthy population sampling was changed from the first 75 patients enrolled in the study, to the sampling beginning after the first 50 patients are enrolled in the study. The PK sampling schedule was unchanged for all patients meeting the ASA, age, hepatically or renally impaired parameters.

Conduct of the Study

Disposition of Patients

Twenty-four study centers participated in this study.

Figure 10.3.1-1: Patient Disposition Flowchart



¹ One patient in the fospropofol 2.0-mg/kg group and 3 patients in the 6.5-mg/kg group did not receive study drug

From Sponsor's study report, Figure 1, page 59.

Thirty-four of 290 patients screened were screening failures and were not randomized. Of the 34 screen failures, 11 patients withdrew consent, 7 were ineligible because they did not meet inclusion or exclusion criteria, 5 were not randomized at the discretion of the Investigator, and 1

patient experienced an AE. The remaining 10 patients were screen failures for a variety of reasons (i.e., anesthesiologist uncomfortable administering study medication due to medical history, data not in computer prior to randomization, pharmacist unavailable, patient did not show up, lost to follow-up, patient on concomitant medication requiring delay in procedure, sponsor closed enrollment, unable to randomize patient in system, unable to obtain blood from patient, and unblinded pharmacist unavailable).

Table 10.3.1-1: Disposition of Patients

	AQUAVAN 2.0-mg/kg	AQUAVAN 6.5-mg/kg	Overall
Number and Percent (%) of Patients			
Patients randomized	103	153	256
Patients discontinued from the study prior to study drug administration ¹	1 (1.0)	3 (2.0)	4 (1.6)
Patients discontinued from the study after study drug administration	0	0	0

¹ Reasons for discontinuation were procedure canceled due to abnormal laboratory test results in the 2.0-mg/kg group; and patient not dosed, invalid consent, and bronchoscopy cancellation due to symptom resolution in the 6.5-mg/kg group.

From Sponsor's study report, Table 10, page 60.

Protocol Violations/Deviations

Table 10.3.1-2 Major Protocol Deviations (mITT Population)

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	AQUAVAN 2.0-mg/kg N=102	AQUAVAN 6.5-mg/kg N=150	Overall N=252
Number and Percent (%) of Patients			
Patients with ≥ 1 major protocol deviation	6 (5.9)	11 (7.3)	17 (6.7)
ICF-related compliance	1 (1.0)	1 (0.7)	2 (0.8)
SAE reporting violation	0	1 (0.7)	1 (0.4)
Study drug dosing compliance, eg incorrect dose or timing	4 (3.9)	8 (5.3)	12 (4.8)
Other treatment/procedure compliance	1 (1.0)	3 (2.0)	4 (1.6)
Deviations having a potential effect on interpretation of study results – patients excluded from per protocol population			
Subtotal ¹	5 (4.9)	9 (6.0)	14 (5.6)
Study drug dosing compliance, eg incorrect dose or timing	4 (3.9)	8 (5.3)	12 (4.8)
Other treatment/procedure compliance	1 (1.0)	2 (1.3)	3 (1.2)

ICF= Informed consent form; SAE= Serious adverse event

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 per protocol population.

Some patients are counted in more than 1 protocol deviation category.

From Sponsor's study report, Table 11, page 61.

Seventeen of the 252 patients (6.7%) who were randomized and received study drug had 1 or more major protocol deviations. Protocol deviations that could have had a potential effect on interpretation of study results were reported for 12 patients (4.8%) who had deviations in study drug dosing compliance (e.g., incorrect dose or timing) and for 3 patients (1.2%) who had deviations in other treatment or procedure compliance (1 patient had deviations in both categories). The 'other' treatment or procedure compliance deviations were as follows: patient not pretreated with fentanyl, patient received 75 mcg of pretreatment fentanyl, and site discontinued all study-related assessments after patient was declared a sedation failure

Efficacy Findings Reported by the Sponsor

Populations

For this study, 3 efficacy analysis populations (mITT, pP, and pP2) and 1 safety population (described below) were used.

The mITT population included all randomized patients who received at least 1 dose of fospropofol and had at least 1 postdose clinical assessment. Patients were analyzed according to the treatment group to which they were randomized. All results noted in the following synopsis of the Sponsor's study report are findings in the mITT population unless otherwise noted.

The pP population was defined as all randomized patients who received at least 1 dose of fospropofol, had at least 1 postdose clinical assessment (including AE evaluation), did not have their procedure terminated due to Investigator’s decision for non-study drug related findings, and did not incur major protocol deviations that had a potentially significant impact on the analysis or interpretation of the study results. Patients were analyzed according to the initial dose of study sedative medication they first received.

The pP2 population was defined as all patients in the mITT population who did not receive alternative sedative medication. Patients were analyzed according to the treatment group to which they were randomized.

Table 10.1.3-2 Study Populations Analyzed for Efficacy

	AQUAVAN	AQUAVAN	Overall
	2.0-mg/kg	6.5-mg/kg	
Number of Patients			
Patients randomized	103	153	256
mITT population	102	150	252
pP population	96	140	236
pP2 population	42	138	180

A total of 16 patients were excluded from the pP population due to major protocol deviations, to premature discontinuation of the procedure, or to non-study drug related finding. A total of 72 patients were excluded from the pP2 population due to administration of alternative sedative medications.

Demographics

- Age

Overall, the mean age of patients in the mITT population was 60.5 years. One hundred three of 252 patients (40.9%) were ≥ 65 years of age and 37 of those patients were ≥ 75 years of age (14.7% of the overall population).

- ASA Classification

Altogether, the fospropofol 6.5-mg/kg group had a larger percentage of patients with an ASA status of P3 (40.7%) than the fospropofol 2.0-mg/kg group (30.4%). Fifteen patients (6.0%) had an ASA status of P4. The dose of study drug was also reduced, at the discretion of the Investigator, for 13 of the 92 patients with an ASA status of P3.

- Gender

55.6% of the patients were male

- Race

84.9% of the patients were white

- Weight

Slightly more than half of the patients were in the mid-weight range (60 to <90 kg). The remaining patients were split, with 18.3% weighing <60 kg and 29.4% weighing ≥90 kg.

- Medical History

There were minimal differences between treatment groups in medical or surgical history at screening. Overall, the patient population had medical histories that included respiratory, thoracic, and mediastinal disorders (87.7%); surgical and medical procedures (86.5%); gastrointestinal disorders (60.7%); musculoskeletal and connective tissue disorders (55.2%); vascular disorders (55.2%); metabolism and nutrition disorders (54.8%); and infections and infestations (52.4%).

Primary Efficacy Endpoint

The primary efficacy endpoint for this study was Sedation Success, defined as a patient having (i) 3 consecutive Modified OAA/S scores of ≤ 4 after administration of sedative medication AND (ii) completing the procedure (iii) without requiring the use of alternative sedative medication AND (iv) without requiring manual or mechanical ventilation.

Table 10.1.3-3 Sedation Success: Sponsor's Analysis of Primary Efficacy Endpoint

	Sedation Success n/N (%)	95% Exact CI ¹ of Sedation Success Rate (%)	Comparison of AQUAVAN Groups
AQUAVAN 2.0-mg/kg (N=102)	28/102 (27.5)	(19.1, 37.2)	
AQUAVAN 6.5-mg/kg (N=150)	133/150 (88.7)	(82.5, 93.3)	
Difference in Sedation Success Rates (%)			61.2
95% CI of Difference (%)			(51.2, 71.3)
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, page 68.

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%) (p<0.001).

Secondary Efficacy Endpoints

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

- Treatment Success Rate

Treatment Success was defined as a patient (i) completing the procedure (ii) without requiring

alternative sedative medications AND (iii) without requiring manual or mechanical ventilation. The Treatment Success rate was higher in the fospropofol 6.5-mg/kg group (91%) compared with the fospropofol 2.0-mg/kg group (41%)

- Proportion of Patients willing to be treated again with the same study sedative medication
The proportion of patients willing to be treated again with the same study sedative medication was higher in the fospropofol 6.5-mg/kg group (95%) compared with the fospropofol 2.0-mg/kg group (78%).

- Proportion of patients who did not recall being awake during the procedure
The proportion of patients who did not recall being awake during the procedure was higher in the fospropofol 6.5-mg/kg group (83%) compared with the fospropofol 2.0-mg/kg group (55%).

Tertiary Efficacy Endpoints

- Proportion of Patients Requiring Supplemental Analgesic Medication
The proportion of patients requiring supplemental analgesic medication was lower for the fospropofol 6.5-mg/kg group (17%) than for the fospropofol 2.0-mg/kg group (37%) in the mITT population.

- Investigator Rating of Satisfaction
Physicians were queried at both the end of the Sedation Initiation Phase and at the End of Procedure regarding their level of satisfaction with the study medication administered. The highest level of physician satisfaction was reported for the fospropofol 6.5-mg/kg group as compared with the fospropofol 2.0-mg/kg group, on average. The End of Sedation Initiation Phase mean satisfaction was 8.0 versus 3.9, for the 6.5-mg/kg and 2.0-mg/kg groups, respectively, and the End of Procedure mean satisfaction was 8.3 versus 5.0, respectively.

- Patient Rating of Experience
When patients were queried about their overall satisfaction with the entire procedure and with their overall comfort level, higher mean scores were achieved in the fospropofol 6.5-mg/kg group (mean of 9.5 and 9.4, respectively) compared with the fospropofol 2.0-mg/kg group (mean of 8.7 and 8.5, respectively). The median scores for the 2 treatment groups were identical for both overall satisfaction and overall comfort level (10.0).

- Number of Supplemental Doses of Study Sedative Medication Administered

Sedation Period	AQUAVAN 2.0-mg/kg N=102	AQUAVAN 6.5-mg/kg N=150
	Number and Percent (%) of Patients	
Total		
0	2 (2.0)	38 (25.3)
1	5 (4.9)	46 (30.7)
2	13 (12.7)	25 (16.7)
3	69 (67.6)	23 (15.3)
4	9 (8.8)	6 (4.0)
5	2 (2.0)	5 (3.3)
>5	2 (2.0)	7 (4.7)
Mean	2.9	1.7
Standard deviation	0.9	1.6
Median	3.0	1.0
Initiation		
Mean	2.4	0.9
Standard deviation	0.9	1.0
Maintenance		
N ¹	48	141
Mean	1.0	0.9
Standard deviation	1.3	1.3

Note: All doses of study medication except initial bolus dose are counted as supplemental doses.

¹ The number of patients who did not receive alternative sedative medication during the Initiation Phase

Fewer patients receiving the 6.5 mg/kg initial bolus dose of Fospropofol, compared to the 2.0 mg/kg dose, required a supplemental dose of Fospropofol. Among patients who did require supplemental doses of Fospropofol the number of doses was small in the group initially treated with 6.5 mg/kg than in the group treated with 2.0 mg/kg.

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

This test was intended to assess acute memory recall. The learning retention scores were similar for both the 6.5 mg/kg treatment group (94.6%) and the 2.0 mg/kg treatment group (93.5%) during screening. The learning retention scores were also similar in the recovery period for the 6.5 mg/kg and 2.0 mg/kg groups (64.2% and 63.6% respectively) in the mITT population.

Other Endpoints

- Time to Sedation and Time to Procedural Milestones from the First Dose of Study Sedative Medication

Times from first dose of study medication to the following flexible bronchoscopy procedural milestones were measured: to sedation, to start of the procedure, to end of the procedure, to Fully Alert, and to Ready for Discharge.

Table 10.1.3-4 Time (minutes) to Sedation (mITT Population)

	AQUAVAN 2.0-mg/kg N=102	AQUAVAN 6.5-mg/kg N=150
n ¹	90	146
Mean	14.5	5.7
Standard deviation	6.5	4.2
Median	18.0	4.0
Min, max	0, 30	2, 22

¹ n= the number of patients who reached sedation

Note: Time to sedation was defined in the protocol as the time from first dose of study medication to the first of 2 consecutive Modified OAA/S scores \leq 4. A time to sedation of 0 indicates the patient was at a Modified OAA/S score \leq 4 at the time of study medication administration.

From Sponsor's study report, Table 25, page 83.

- Time to Fully Alert and Ready for Discharge

Table 10.1.3-5 Time to Recovery from Sedation

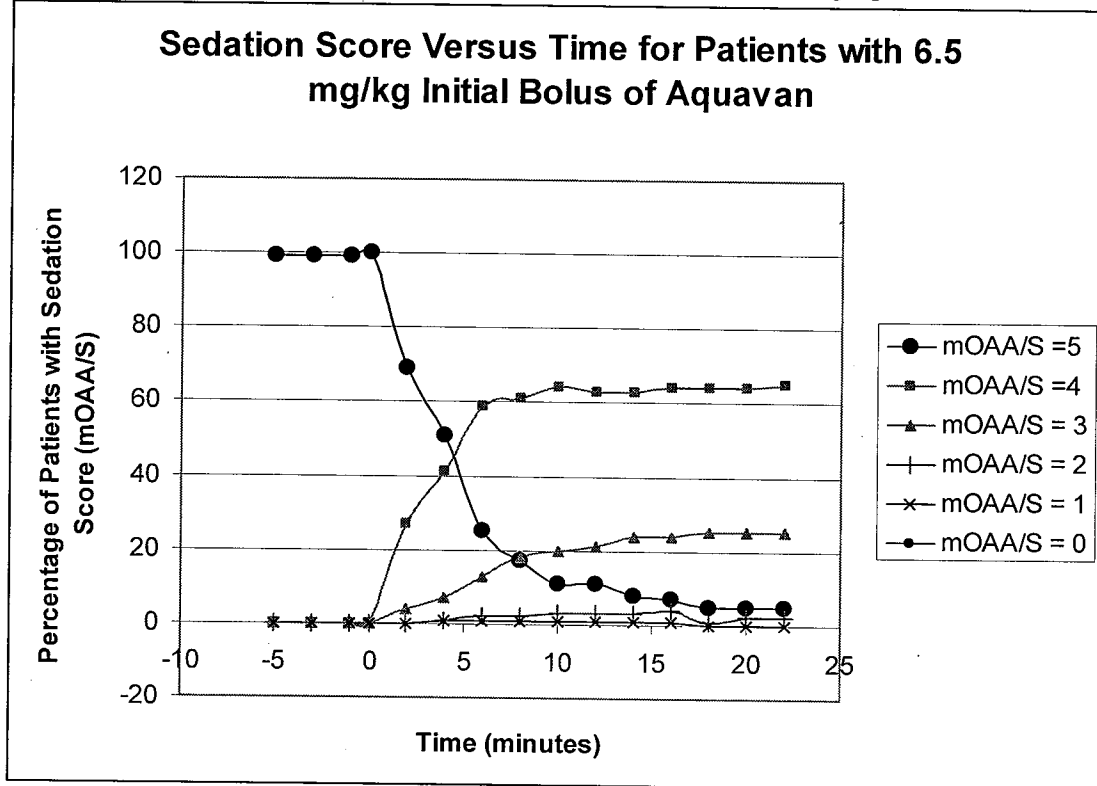
		AQUAVAN 2 mg/kg (N=102)	AQUAVAN 6.5 mg/kg (N=150)
TIME TO FULLY ALERT	N	100	148
	Mean	9.1	8.3
	SD	15.3	10.1
	Median	3.0	5.5
	Min	0	0
	Max	114	61
TIME TO READY FOR DISCHARGE	N	101	150
	Mean	14.1	12.1
	SD	19.7	12.3
	Median	8.0	8.5
	Min	0	0
	Max	124	66

From Sponsor's study report, Table 4.2, page 187.

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- Modified OAA/S Scores Over Time

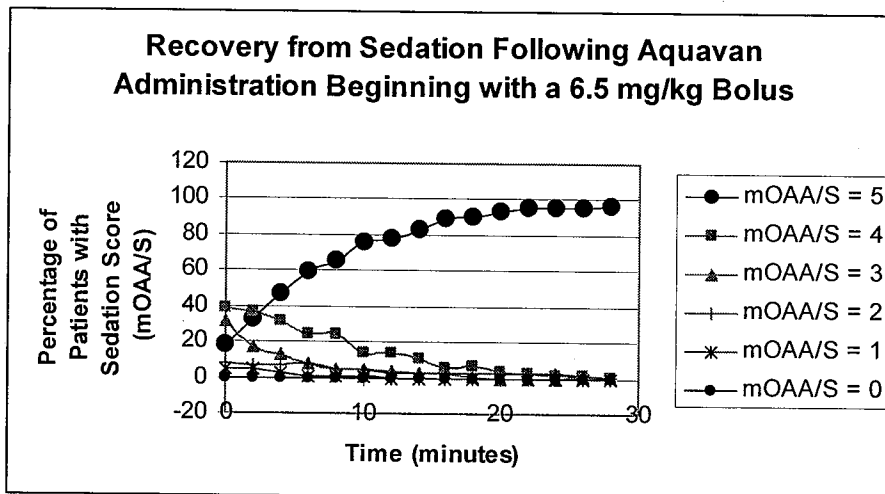
Figure 10.1.3-3 Time to Sedation with Fospropofol Following 6.5 mg/kg Initial Bolus



Data were abstracted from Sponsor's study report Table 4.3.4, pages 202-208 and compiled into graphical figure by this reviewer.

Figure 10.1.3-3 Time to Recovery from Fospropofol following 6.5 mg/kg Dose

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Data were abstracted from Sponsor's study report Table 4.3.4, pages 208-211 and compiled into graphical figure by this reviewer.

The median Modified OAA/S score immediately following the procedure was 4.0 in both treatment groups. The median of the average Modified OAA/S score during the procedure was 3.5 in the fospropofol 6.5-mg/kg group and 3.8 in the 2.0-mg/kg group.

- Duration and Percentage of Time When a Patient was at each MOAA/S score Between the First Dose of Study Medication and Fully Alert and During the Procedure

The mean duration of time that patients had Modified OAA/S scores of 2 to 4 from the first dose of study sedative medication to Fully Alert in the mITT population was 18.6 minutes (range: 0 to 64) in the fospropofol 6.5-mg/kg group and 18.5 minutes (range: 0 to 168) in the fospropofol 2.0-mg/kg group. The mean duration of time that patients had Modified OAA/S scores of 0 to 1 from the first dose of study sedative medication to Fully Alert was 1.0 minute in both treatment groups (range: 0 to 20 minutes for the fospropofol 6.5-mg/kg group and 0 to 52 minutes for the 2.0-mg/kg group).

The mean percentage of time that patients had Modified OAA/S scores of 2 to 4 from the first dose of study sedative medication to Fully Alert in the mITT population was 68.7% (range: 0 to 97.0%) in the fospropofol 6.5-mg/kg group and 48.1% (range: 0 to 97.2%) in the 2.0-mg/kg group. The mean percent of time that patients had Modified OAA/S scores of 0 to 1 from the first dose of study sedative medication to Fully Alert was 3.7% (range: 0 to 62.5%) in the fospropofol 6.5-mg/kg group and 1.5% (range: 0 to 51.0%) in the 2.0-mg/kg group.

- Duration of the Procedure

The mean duration of the procedure was 12 minutes (± 9 minutes SD) for the 2.0 mg/kg groups and 11 minutes (± 9 minutes SD).

Sponsor's Statistical Analysis

To address multiplicity issues, the Sponsor's hypothesis testing for the primary efficacy endpoint served as a gatekeeper. The hypotheses for the secondary efficacy endpoints were tested only after the primary analysis for the primary efficacy endpoint had yielded a statistically significant result at $\alpha=0.05$. The fixed sequence approach was used to control the family-wise error rate at 0.05 for the statistical tests for the secondary efficacy endpoints. The hypotheses for the secondary efficacy endpoints to be tested were hierarchically ordered and were tested in a predefined sequential order.

Primary Endpoint

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

Secondary Endpoints

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

Tertiary Endpoints

- The proportion of patients requiring supplemental analgesic medication was lower for the fospropofol 6.5-mg/kg group (16.7%) compared with the 2.0-mg/kg group (37.3%) in the mITT population, but the proportion was similar between groups in the pP2 population (14.5% and 16.7%, respectively).
- In the fospropofol 6.5-mg/kg group, 82.7% of the patients received only 1 dose of analgesic compared with 62.7% of the patients in 2.0-mg/kg group in the mITT population.
- A higher level of the physician satisfaction rating was reported for the fospropofol 6.5-mg/kg group as compared with the 2.0-mg/kg group both at the end of Sedation Initiation (mean of 8.0 versus 3.9) and at the End of Procedure (mean of 8.3 versus 5.0).
- Higher levels of overall patient satisfaction with the entire procedure and overall comfort level were achieved in the fospropofol 6.5-mg/kg group (mean of 9.5 and 9.4, respectively) compared with the 2.0-mg/kg group (mean of 8.7 and 8.5, respectively) in the mITT population.
- The procedure was initiated after ≤ 2 supplemental doses of fospropofol for 89.3% of

patients in the 6.5-mg/kg group and for 33.3% of patients in the 2.0-mg/kg group in the mITT population.

Safety Findings Reported by the Sponsor

Extent of Exposure

A total of 252 of the 256 randomized patients received at least 1 dose of fospropofol and were included in the safety population. One patient (430-0003) who was randomized to the Fospropofol 6.5-mg/kg group actually received Fospropofol 2.0 mg/kg. Based on the population definitions, this patient was included in the Fospropofol 2.0-mg/kg group for safety analyses.

There was a wide range in the doses of study drug administered. The mean total amount of fospropofol administered to patients during the combined Initiation and Maintenance Phases was 623.8 mg in the 6.5-mg/kg group (range: 280.0 to 1557.5 mg) and 224.1 mg in the 2.0-mg/kg group (range: 122.5 to 385.0 mg) in the safety population.

Table 10.1.3-X Total Dose of Fospropofol Received During Treatment Phase

	AQUAVAN 2.0-mg/kg N=103	AQUAVAN 6.5-mg/kg N=149	Overall N=252
Initiation Phase			
n	103	149	252
Mean	209.0	532.6	400.3
Standard deviation	54.7	167.3	207.7
Median	227.5	507.5	385.0
Min, max	87.5, 280.0	280.0, 997.5	87.5, 997.5
Maintenance Phase			
n	24	64	88
Mean	64.9	212.2	172.0
Standard deviation	44.2	161.1	153.9
Median	43.8	140.0	113.8
Min, max	17.5, 175.0	70.0, 700.0	17.5, 700.0
Total			
n	103	149	252
Mean	224.1	623.8	460.4
Standard deviation	56.0	241.0	272.6
Median	227.5	577.5	393.8
Min, max	122.5, 385.0	280.0, 1557.5	122.5, 1557.5

From Sponsor's study report Table 27, page 89.

Table 10.1.3-xx Exposure to Concomitantly Administered Fentanyl

	AQUAVAN 2.0-mg/kg N=103	AQUAVAN 6.5-mg/kg N=149	Overall N=252
Mean	80.6	57.0	66.7
Standard deviation	63.9	34.8	50.0
Median	50.0	50.0	50.0
Min, max	50.0, 400.0	0, 450.0	0, 450.0

From Sponsor's study report Table 28, page 90.

Overview of Adverse Events

Table 10.1.3- x Overview of Adverse Events

	AQUAVAN 2.0-mg/kg N=103	AQUAVAN 6.5-mg/kg N=149	Overall N=252
Number and Percent (%) of Patients			
Treatment-emergent AEs	79 (76.7)	124 (83.2)	203 (80.6)
Treatment-related AEs ¹	67 (65.0)	104 (69.8)	171 (67.9)
Adverse events leading to discontinuation of study medication	0	2 (1.3)	2 (0.8)
Adverse events leading to discontinuation of procedure	1 (1.0)	1 (0.7)	2 (0.8)
Adverse events leading to airway assistance	12 (11.7)	27 (18.1)	39 (15.5)
Adverse events leading to discontinuation from the study	0	0	0
Serious treatment-emergent AEs	13 (12.6)	15 (10.1)	28 (11.1)
Deaths	2 (1.9)	3 (2.0)	5 (2.0)

AE = adverse event

Note: The same patient may have been counted in more than 1 category. Adverse events were captured through 30 days following dosing with study medication.

¹ Treatment-related AEs refer to events that were considered definitely, probably, or possibly related to study drug as reported by the Investigator.

From Sponsor's study report Table 29, page 91.

Deaths

Three patients (2.0%) in the fospropofol 6.5-mg/kg group and 2 patients (1.9%) in the 2.0-mg/kg group died as a result of SAEs identified during the study. The SAEs that led to death were anoxic encephalopathy (544-0009), respiratory arrest (544-0003), malignant lung neoplasm (312-0003), septic shock (533-0008), and malignant lung neoplasm and pneumonia (309-0006). The deaths occurred 4, 11, 19, 22, and 23 days, respectively, after receiving study drug. None of the deaths were considered to be treatment-related by the Investigators or the Sponsor.

Other Serious Adverse Events

Fifteen patients (10.1%) in the Fospropofol 6.5-mg/kg group and 13 patients (12.6%) in the 2.0-mg/kg group experienced treatment-emergent SAEs (including the 5 patients who died). Treatment-emergent SAEs experienced by more than 1 patient were COPD (6 patients), respiratory failure and malignant lung neoplasm (5 patients each), pneumonia (4 patients), and

bacterial bronchitis (2 patients). Additional treatment-emergent SAEs that occurred in 1 patient each were cardiac arrest, brain herniation, brain edema, and sepsis; cardiomyopathy, congestive cardiac failure, and cerebrovascular accident; coronary artery disease; ventricular tachycardia; cystic fibrosis; intestinal perforation, large intestine perforation, abdominal abscess, and abdominal sepsis; acute bronchitis; enterococcal bacteremia and positive HIV test; pseudomonal lung infection; pneumococcal pneumonia and acute respiratory failure; hypovolemia and hypotension; squamous cell lung carcinoma; non-small cell lung cancer; laryngospasm; and pneumothorax.

The only SAEs that occurred with greater frequency in the Fospropofol 6.5-mg/kg group compared with the 2.0-mg/kg group were malignant lung neoplasm (5 patients versus 0 patients, respectively) and pneumonia (3 patients versus 1 patient). None of these SAEs were considered to be treatment-related. An additional patient experienced an SRAE of hypoxemia that was not classified as an SAE by the Investigator, but that MGI PHARMA considered to be serious and probably related to study drug. Five additional patients experienced SAEs prior to dosing with study medication.

Other significant adverse events

No TEAE led to discontinuation from the study.

One patient (533-0005; 6.5 mg/kg group) experienced an AE of severe coughing that led to discontinuation of both study drug and the procedure, 1 patient (309-0016; 2.0 mg/kg group) developed an SAE of pneumothorax (also an SAE) that led to discontinuation of the procedure, and 1 patient (321-0036; 6.5 mg/kg group) experienced an AE of severe paresthesia that led to discontinuation of study drug

10.1.4 Protocol 3000-0523 Open-label, uncontrolled safety study in a variety of procedures

Title: A Phase 3, open-Label, Single Arm Study to Assess the Safety of Fospropofol (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Minor Surgical Procedures

Objectives: To assess the safety of Fospropofol at the proposed dosing when used to provide minimal-to-moderate sedation in patients undergoing minor surgical procedures

Study Design: Open label, Single arm

Patients were to be pretreated with 50 mcg of intravenous fentanyl at five minutes before Fospropofol was to be administered. They are then to receive an initial bolus of 6.5 mg/kg Fospropofol and supplemented with 25% of the initial bolus dose as needed to achieve a MOAA/S score of ≤ 4 and to allow the investigator to begin the procedure. Patients who were ≥ 65 years of age or are classified as ASA P4 are to receive doses reduced by 25%. Patients

classified as ASA P3 may have doses reduced at the discretion of the Investigator. Up to five supplemental doses of Fospropofol were to be administered at intervals of > 4 minutes provided that the patient exhibited a MOAA/S score of > 4 and purposeful movement.

A person skilled in airway management (such as a respiratory therapist, a study nurse, or a clinician) and authorized by the facility in which the surgical/diagnostic procedure was performed was immediately available during the conduct of the study. Patients were placed on supplemental oxygen via nasal cannulae (4 L/min) during the study and connected to an electrocardiogram (ECG) monitor, pulse oximeter, and a blood pressure (BP) monitor prior to the administration of study medication.

Patient Population: approximately 125 patients having minor surgical procedures e.g. arthroscopy, arteriovenous [AV] shunt, bunionectomy, dilatation and curettage [D & C], esophagogastroduodenoscopy [EGD], lithotripsy, transesophageal echocardiography [TEE], and ureteroscopy) requiring sedation were to be studied.

Entry Criteria:

Inclusion:

1. Patient were to be able to understand, orally or in writing, and was able to consent and complete the required assessments and procedures.
2. Patient were to have a signed/dated informed consent form and HIPAA authorization after receiving a full explanation of the extent and nature of the study.
3. Patient were to be at least 18 years of age at the time of screening and was undergoing one of the specified minor surgical procedures.
4. If female, patient were to be surgically sterile, postmenopausal, or not pregnant or lactating and had been using an acceptable method of birth control for at least 1 month prior to dosing, with a negative urine pregnancy test result at screening and predose.
5. Patients were to have an ASA status of P1 to P4.

Exclusion:

1. Patients with a history of allergic reaction or hypersensitivity to any anesthetic agent, or opioid.
2. Patients who not meeting the nil per os (NPO) status per ASA guidelines or institution's guideline.
3. Patients having 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. Patients having an abnormal, clinically significant 3-lead ECG finding at Predosing period Day 0.
5. Patients participating in an investigational drug study within 1 month prior to study start.
6. Patients unwilling to adhere to pre- and postprocedural instructions.
7. Patients for whom the use of fentanyl citrate injection (fentanyl) would be contraindicated.

Safety Evaluations:

- Nature, frequency, and indication of airway assistance
 - Frequency of sedation-related adverse events (SRAEs; i.e., apnea, hypoxemia, bradycardia, or hypotension)
 - Nature, frequency, seriousness, severity, relationship to treatment, and outcome of all treatment-emergent adverse events (TEAEs)
 - Purposeful movement
 - Laboratory parameters, and vital signs
 - Concomitant medications
- Safety analyses were to include exposure to study drug.

Pharmacokinetic evaluations:

Pharmacokinetic (PK) samples were collected at 5 time points on the day of the procedure for patients who met the American Society of Anesthesiologists (ASA) Physical Classification System status of ASA P3 or P4, were ≥ 65 years of age, or who had hepatic or renal insufficiency, as defined in the study protocol. These samples were analyzed for plasma fospropofol and propofol concentrations.

Amendment March 31, 2006

- The two distinct dosing Phases, Dosing Initiation and Dosing Maintenance, were combined and dosing will to be conducted under a single Sedation Phase which would encompass the bolus dose and any supplements that are required to initiate and to complete the procedure. The original design was implemented in order to evaluate the fospropofol dose required to initiate sedation and begin a procedure. The revised Sedation Phase was designed to more closely reflect the manner in which fospropofol was expected to be dosed in practice.
- The definition and measurement of Sedation Failure was removed as this study is not designed to assess the safety of fospropofol in a more realistic setting. As such, the protocol now recommends that alternative sedative medications not be administered until after administration of the bolus dose and 5 supplemental doses of fospropofol. At that point if the patient fails to become sedate or stay sedated for the procedure, they can receive alternative sedative medication.

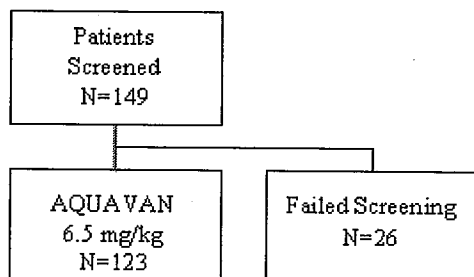
The following efficacy assessments were removed for the reasons mentioned above:

- The Psychometric Assessment – Hopkins Verbal Learning Test - Revised™.
- The Cognitive Assessment – Digit Symbol Substitution Test (DSST).
- Patient Anxiety Survey.
- Physician Satisfaction Survey at the End of the Procedure.
- Patient Satisfaction Survey After Ready for Discharge Criteria are Met.
- The Aldrete Discharge Criteria.
- The Assessment of Ready to Discharge.

Conduct of the Study:

Appendices

Disposition of Patients:



Summary of Safety Findings:

- The mean total dose of fospropofol administered during the procedure was 742.0 mg (range: 280.0 to 1592.5 mg).
- Serious treatment-emergent AEs were experienced by 4 patients. None of these SAEs were considered by the Sponsor to be related to the study drug. No deaths were reported in the study.
- No patient was discontinued from the study due to an AE.
- Treatment-emergent AEs were experienced in 90.2% of the patients, the majority mild to moderate and judged by the Sponsor to be treatment-related. The 3 most common TEAEs reported in patients were paresthesia (53.7%), procedural pain (50.4%), and pruritus (26.0%).
- Five patients (4.1%) experienced an SRAE (hypotension, bradycardia, or hypoxemia) on the day of the procedure. An SRAE of hypotension was reported in 4 patients and was considered to be related to the study drug in 3 of these patients. The events of hypotension occurred during the dosing and recovery periods of the procedure. Bradycardia was experienced by 1 patient concurrently with hypotension managed with atropine, and was considered unrelated to study drug. Hypoxemia (less than 1 minute) was reported in 1 patient, was managed with airway assistance (chin lift and verbal stimulation), and was considered to be definitely related to study drug. No patient experienced apnea on the day of the procedure.
- Seven of 123 patients (5.7%) received airway assistance, one of whom required airway assistance due to an SRAE of hypoxemia.
- The incidence of loss of purposeful movement was greater in patients ≥ 75 years of age (5 of 11 patients [45.5%]) compared with patients ≥ 65 to 74 years of age (4 of 13 patients [30.8%]) and patients 18 to 64 years of age (26 of 99 patient [26.3%]). Eight of these patients were unable to demonstrate purposeful movement on at least one timepoint in the preprocedural period and 10 in the post-procedural period.

10.1.5 Protocol 3000-0521 Controlled study of individually corrected QT interval

Study 3000-0521 is a thorough QTc study of healthy volunteers exposed to fospropofol. This protocol underwent a detailed review by the Interdisciplinary Review Team and suggestions were provided to the Sponsor who revised the protocol before beginning the study. A synopsis is listed below:

Title: Administration of fospropofol® Injection Compared with Placebo and a Positive Control in Healthy Volunteers

Objectives

- To determine the maximal effects of a single bolus dose of fospropofol® (fospropofol disodium) Injection (hereafter referred to as fospropofol) on the individually corrected QT interval (QTcI)
- To quantify the dose, concentration, and time relationships of fospropofol on the QT interval corrected for heart rate (QTc) at therapeutic and supratherapeutic doses
- To describe the pharmacokinetics of fospropofol and fospropofol-derived propofol in venous plasma

Study Description

Design

This was a single-center, randomized, 4-sequence, 4-treatment crossover study in which study drug administration was open label, but all electrocardiogram (ECG) data were evaluated by a central reader who was blinded with respect to subject, treatment, and time.

Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

Blinding

The study was open label. The sponsor's justification for not blinding study treatments, "This study was not blinded to treatment for safety reasons. Because fospropofol was administered at a supratherapeutic dose (18 mg/kg), which is known to produce deep levels of sedation in some subjects, it was necessary that appropriate personnel be available to manage potential sedation-related adverse events (SRAEs). Therefore, double blinding was not employed."

Treatment Regimen

Treatment Arms

The 4 treatments were as follows:

- (A) Placebo (normal saline) intravenous (I.V.)
- (B) Moxifloxacin 400 mg oral (P.O.)
- (C) fospropofol 6 mg/kg I.V. (but not <360 mg and not >540 mg)
- (D) fospropofol 18 mg/kg I.V. (but not <1080 mg and not >1620 mg)

Subjects were randomly assigned at Baseline prior to study drug administration in a ratio of 1:1:1:1 to one of the following 4 treatment sequences: ADBC (Treatment Sequence I), BACD (Treatment Sequence II), CBDA (Treatment Sequence III), or DCAB (Treatment Sequence IV).

Sponsor's Justification for Doses

"A dose of 6.0 mg/kg was chosen as the clinically-relevant efficacy dose for this study. The suprathreshold dose chosen, 18 mg/kg, is 3-fold higher than the clinically-relevant dose and is within the range for induction of general anesthesia, based on results of a previous volunteer study (study 3000-0103). Doses higher than 18 mg/kg produce longer periods of unconsciousness. The suprathreshold dose was chosen to balance the maximal pharmacologic effect with the safety of the subjects.

The pharmacokinetics of fospropofol support the use of a single I.V. bolus dose in this study. Both fospropofol and liberated propofol have short half-lives and will not accumulate with the proposed administration. The bolus dose provides the highest concentration of fospropofol and fospropofol-derived propofol for a given effect level."

ECG and PK Assessments

Table 1: Sampling Schedule

Study Day	-1	1	3-7
Intervention	No treatment (Baseline)	Single dose	No treatment (Washout)
12-Lead ECGs	Record ECGs ¹	Record ECGs ¹	None recorded
PK Samples for drug	None collected	Collected ²	None collected

¹ ECGs were obtained 1, 4, 8, 12, 20, 30, 60, 90, 120, 180, and 240 minutes after dosing

² Blood samples for PK were obtained at 1, 4, 8, 12, 20, 30, 60, and 90 minutes and 2, 3, and 4 hours after dosing. Samples were taken only for the fospropofol treatment periods.

Baseline

Four 12-lead ECGs were extracted from the flash card at each of 11 time points (1, 4, 8, 12, 20, 30, 60, and 90 minutes and 2, 3, and 4 hours) at 1-minute intervals at day -1. The average of the 4 ECGs at each time point was used as the baseline values.

ECG Collection

Electrocardiograms were obtained digitally using a _____ ECG

b(4)

continuous digital recorder at the specified time points. Four ECGs were recorded within 1 minute of each scheduled time point. The ECGs were stored on a flash card approximately every 10 seconds and were not available for review until the card was received by the central ECG laboratory and analyzed.

ECG's were read centrally by evaluators using a high-resolution manual on-screen caliper method with annotations for interval measurements. For all analyses, the 4 QT/QTc interval replicates for each subject were averaged at each extraction time point. The staff performing the analysis of ECGs was blinded to subject, treatment, and time. For the subjects' safety, standard digital 12-lead ECGs were performed to detect any immediate ECG effects at screening, 30 minutes before dosing, 1 hour after dosing, and at the follow-up visit.

The central lab performs quality control of interval duration measurements (IDMs) on a daily basis as follows: 5% of all normal ECG IDMs, all IDMs that are noted by the original cardiac safety specialist as being of poor quality, and all ECGs with IDMs that meet 'Outlier' criteria, which have been specified by the client. Two percent of the ECGs from each protocol will be randomly selected and placed in a QA environment for independent, blinded over read by technical quality assurance specialist.

Sponsor's Analysis:

Seventy subjects (38 males, 32 females) between 18-45 years of age, BMI between 18-30 kg/m², with a normal baseline ECG were randomly assigned to receive the study drug. A total of 68 subjects (97.1%) completed the study. Two subjects discontinued the study after administration of the study drug. An 18-year-old woman in Treatment Sequence III [CBDA] voluntarily withdrew from the study after dosing with moxifloxacin in Period 2, and the Investigator withdrew a 39-year-old woman in Treatment Sequence I [ADBC] because of the TEAE of ventricular extrasystoles exhibited upon telemetry assessment prior to dosing in Period 2.

Difference between fospropofol and Placebo in Maximum Time-Matched Change from Baseline in the QTcI (Primary Endpoint)

Parameter (unit) Statistic	AQUAVAN 6 mg/kg (n=69)	AQUAVAN 18 mg/kg (n=68)	Moxifloxacin 400 mg (n=69)
QTcI (ms)			
n	65	66	66
Mean (SD)	-3.1 (13.79)	1.9 (13.43)	6.5 (12.43)
Median	-4.0	2.5	6.0
Minimum, Maximum	-39, 34	-28, 33	-28, 32
90% CI	(-5.98, -0.27)	(-0.90, 4.62)	(3.90, 9.01)
QTcI=individually corrected QT interval; CI = confidence interval Source: Section 14.2, Table 14.2.2.2			

The summary findings were that the study was adequately designed, controlled and conducted to evaluate the effect of fospropofol on QTc. The data indicated that fospropofol did not cause a clinically significant increase in QTc.

10.1.6 Listing of Studies Discontinued Because of Safety Concerns

In Study 3000-410, A Phase III, randomized, open-label study to assess the safety and efficacy of fospropofol Injection versus midazolam HCl for sedation in patients undergoing colonoscopy. approximately 32% of patients exposed to fospropofol developed signs of hypoxia compared with 13% of patients in a midazolam comparator arm. This high incidence of hypoxia and adverse events reported in the initial stages of the following studies precipitated a change in the dosing regimen. Following analysis of findings from the new dose-ranging study 3000-0520, new phase 3 studies 3000-0522 and -0524 were conducted. Studies 3000-0520, -0522, and -0524 are the foundational efficacy studies in this submission. Study 3000-0523 also utilizes the same dosing regimen as the efficacy studies, but as a single arm study, can only provide additional safety information. The following studies were discontinued while in progress because of safety concerns:

- 3000-0409 A Phase III, randomized, open-label study to assess the safety and efficacy of fospropofol® Injection versus midazolam HCl for sedation in patients undergoing flexible bronchoscopy procedures
- 3000-0411 A Phase III, Randomized, Open-Label Study to Assess the Safety and Efficacy of fospropofol® Injection Versus Midazolam HCl for Sedation in Patients Undergoing Percutaneous Coronary (PC) Procedures
- 3000-0412 A Phase III, Randomized, Open-label Study to Assess the Safety and Efficacy of fospropofol® Injection Versus Midazolam HCl for Sedation in Patients Undergoing Minor Surgical Procedures

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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7/17/2008 05:04:18 PM
MEDICAL OFFICER

Rigoberto Roca
7/17/2008 06:26:35 PM
MEDICAL OFFICER

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: April 16, 2008

To: Bob Rappaport, M.D.
Director, Division of Anesthesia, Analgesia, and Rheumatology Products

Through: Michael Klein, Ph.D., Acting Director
Controlled Substance Staff (HFD-009)

Through: Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

From: Patricia Beaston, M.D., Ph.D., Medical Officer
Controlled Substance Staff (HFD-009)

Subject: Consult on NDA 22-244 (Fospropofol/Aquavan): Abuse liability and scheduling assessment
Indication: Sedation in adult patients undergoing diagnostic and therapeutic procedures b(4)

Formulation: 35 mg/ml (30 ml vial) for injection
Company: MGI Pharma

This memorandum provides a summary of comments taken from CSS consults dated March 11 and March 19 to be relayed to MGI Pharma.

The Controlled Substance Staff (CSS) has reviewed the Abuse Liability Assessment (Module 5.3.5.4) as well as supporting studies and data and does not agree with MGI Pharma's conclusion that fospropofol should not be scheduled under the CSA.

The data available demonstrate that fospropofol is soluble in water b(4)
_____ is orally bioavailable; and produces sedative and euphoric effects from enteral (either oral or duodenal) administration. Propofol, the active metabolite of fospropofol, produces sedative and euphoric effects; is misused and abused; and has been associated with the death of persons misusing or abusing it. Therefore, CSS has concluded that fospropofol has a higher abuse potential than that of propofol because fospropofol is orally bioavailable.

Additionally, the potential use of fospropofol in the context of criminal activity for the purpose of incapacitating a victim is of concern. Other orally active sedative agents such as GHB have been associated with criminal activity. In addition, if fospropofol is

ingested with alcohol a potentiation of the sedative and depressant effects of fospropofol is expected.

Fospropofol has a pharmacological profile similar to sedatives scheduled under the CSA; pentobarbital (Schedule II) and GHB (Schedule I). Thus, fospropofol, like pentobarbital, and GHB, has a high potential for abuse and its abuse may lead to severe psychological or physical dependence and should be placed under Schedule II of the CSA.

Therefore, CSS recommends that fospropofol be scheduled under the Controlled Substances Act (CSA). CSS reminds the Sponsor that Aquavan can not be marketed once approved until the scheduling action is complete. The scheduling process requires an eight-factor analysis and approval of the FDA Commissioner and HHS (Assistant Secretary for Health) prior to DEA notice of proposed rulemaking and final action.

The Sponsor should reevaluate all data available on fospropofol, taking into consideration the conclusions of the CSS, and accordingly submit a proposal for placing fospropofol under Schedule II of the CSA.

If the Sponsor proposes a different Schedule than Schedule II, the Sponsor will have to conduct studies to support their proposal. The following studies will be required:

1. Studies to characterize the binding profile of fospropofol should be repeated using validated experimental procedures.
2. Studies evaluating the bioavailability of fospropofol, oral and intravenous, should be repeated using only the liquid formulation (as to be marketed). Although fospropofol can be further metabolized to propofol *in vitro* use of sodium orthovanadate (an inhibitor of alkaline-phosphatase) in the studies examining the abuse liability of oral administration of fospropofol is not recommended because of the effects on the stability of propofol. The measurement of either fospropofol or propofol after the oral administration of fospropofol is sufficient to demonstrate oral bioavailability. An arm examining the oral bioavailability of propofol is recommended.

The protocol for these studies should include assessments for adverse events and drug effects, and evaluations for sedation.

3. Clinical studies examining the abuse potential oral fospropofol should be performed. In order to fully characterize the abuse potential of fospropofol, the drug should be compared to other CNS depressants that are controlled under the CSA as well as to propofol. Additionally, the effect of fospropofol in combination with ethanol should be examined as it may increase the abuse potential of fospropofol and might result in death.

4. CSS will be available to review the submitted eight factor analysis or protocols examining the abuse potential of intravenous and oral fospropofol and to discuss these issues with MGI Pharma.

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/s/

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4/16/2008 02:50:20 PM
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4/16/2008 03:30:41 PM
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REVIEW
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Review on NDA 22-244 (Fospropofol/Aquavan): Abuse liability and scheduling assessment

Indication: Sedation in adult patients undergoing diagnostic and therapeutic procedures

b(4)

Formulation: 35 mg/ml (30 ml vial) for injection

Company: MGI Pharma

Submission: NDA 22-224 is located in the EDR. The submission includes a section titled 'Abuse Liability Assessment' (found under Module 5.3.5.4)

This review provides recommendations to the Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170) regarding the abuse potential of fospropofol (Aquavan).

I. SUMMARY AND RECOMMENDATION

Fospropofol is a prodrug form of propofol and was developed as an intravenous sedative-hypnotic agent for the sedation in adult patients undergoing diagnostic and therapeutic procedures

MGI Pharma proposes that fospropofol not be controlled under the CSA, based mainly on the results from non-clinical studies, clinical trials and human abuse potential studies using propofol (which is not scheduled under the CSA) as support for their position.

b(4)

The pharmacokinetics and pharmacodynamics of propofol are such that administration by an anesthetist is required to monitor patient safety. MGI Pharma presents the case that the difference in pharmacokinetics between fospropofol and propofol improves the safety of sedation in procedures such as colonoscopy.

Propofol, although not scheduled under the CSA is an abused substance (see Section E.3. below). The same pharmacokinetic/pharmacodynamic issues that require monitoring of propofol anesthesia pose risk to individuals who misuse or abuse propofol and has resulted in death in many cases. Differences in the pharmacokinetics of fospropofol may decrease some of the safety issues associated with propofol use and possibly misuse. MGI Pharma asserts that these pharmacokinetic differences would further decrease the abuse potential of fospropofol compared to propofol however, the contrary may be true. Because the pharmacokinetic differences in t_{max} is a matter of minutes, not hours, and the duration is somewhat longer, fospropofol may have a greater abuse potential, especially if its use is perceived as safer than that of propofol. Additionally, despite issues with

sample preparation (discussed fully in the body of this consult) fospropofol was demonstrated to have oral bioavailability, which further increases its abuse potential.

The development program for fospropofol did not include evaluation of its abuse potential. Because of the differences in pharmacokinetics compared to propofol and because of its oral bioavailability the assumption that fospropofol has the same abuse potential as propofol and therefore should not be scheduled is not supported.

Conclusion: Propofol, although not currently scheduled, is abused not only by healthcare providers but also by others. Unfortunately, the majority of propofol abusers are detected only after they have died as a result of this abuse. The data submitted in NDA 22,244 are sufficient to suggest that fospropofol has sufficient bioavailability after oral administration to have an abuse potential greater than that of propofol. Therefore, the evaluation of the abuse potential of fospropofol can not totally rely on the data for propofol and additional assessments will be required to complete the evaluation.

Recommendation: CSS recommends studies to characterize the binding profile of fospropofol should be repeated using validated experimental procedures. CSS also recommends that clinical studies examining the abuse potential of both intravenous and oral fospropofol are required. Additionally, the effect of fospropofol in combination with ethanol should be examined as it may increase the abuse potential of fospropofol. It is recommended that the abuse potential studies include propofol as an active comparator.

The studies are directed at better characterizing the adverse event profile of fospropofol as would be related to its abuse potential. Although fospropofol can be further metabolized to propofol *in vitro* use of sodium orthovanadate (an inhibitor of alkaline-phosphatase) in the studies examining the abuse liability of oral administration of fospropofol is not recommended because of the effects on the stability of propofol. The measurement of either fospropofol or propofol after the oral administration of fospropofol is sufficient to demonstrate oral bioavailability.

The Controlled Substance Staff will be available to review and discuss protocols examining the abuse potential of intravenous and oral fospropofol.

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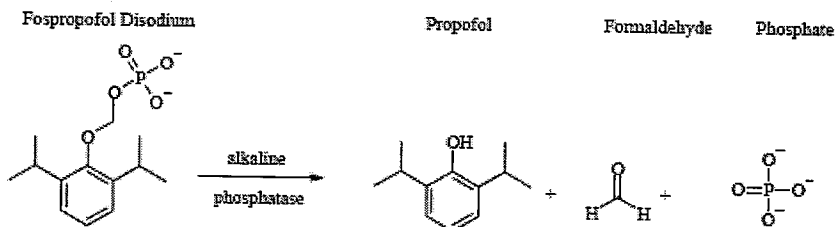
II. BACKGROUND

A. Drug Substance

Fospropofol is a prodrug that is metabolized by alkaline phosphatase enzymes to yield the active metabolite (propofol), phosphate, and formaldehyde in equimolar proportions (1.86 mg of fospropofol disodium in the molar equivalent of 1 mg propofol).

Fospropofol is soluble in water (~ 250 mg/ml); s

b(4)



The rationale for development of fospropofol is:

AQUAVAN was developed based on the hypothesis that the pharmacokinetic profile of a prodrug (lower C_{max} and later T_{max}) would provide an improvement in the side effect profile of propofol and allow intravenous bolus injection with minimal effects on the rapid times to sedation and awakening. Furthermore, AQUAVAN is provided as an aqueous solution rather than a lipid emulsion which reduces the risks of contamination and eliminates the concern of hyperlipidemia-related side effects. The clinical development program for AQUAVAN was undertaken to study the safety and efficacy of the prodrug of propofol, fospropofol disodium.

B. Proposed indication

Fospropofol was developed as an intravenous sedative-hypnotic agent for sedation in adult patients undergoing diagnostic and therapeutic procedures

b(4)

C. Regulatory History

Fospropofol is a prodrug for propofol. Propofol is an intravenous sedative-hypnotic agent for approved for sedation. Propofol is not scheduled under the Controlled Substances Act (CSA).

The CSS was not consulted during the developmental program for fospropofol or prior to filing the NDA.

b(4)

In submitting the NDA application, MGI Pharma agreed to not market the drug product, if the FDA determines that the drug should be scheduled under the CSA, until the DEA has issued a final schedule ruling. The CSS can not finish its evaluation of the abuse potential of fospropofol and make recommendations for scheduling, or not, until the deficiencies identified have been addressed.

D. Basic Science

1. Binding Profile for Fospropofol

The following table provides a summary of the binding profile of fospropofol (Study 1-1002929-0). This binding profile is reported to be similar to that of propofol (Study 1009415). For the reader's convenience, the results from the fospropofol study (in parenthesis) are incorporated into the table.

Results of In Vitro Radioligand Binding Assays for Fospropofol^a Compared to (Propofol)

Target	% Stimulation or Inhibition	Target	% Stimulation or Inhibition
Adenosine A ₁	2 (5)	Histamine H ₃	-16 (20)
Adenosine A _{2A}	-6 (12)	Insulin	-19 (1)
Adrenergic α ₁ , Non-selective	-12 (7)	Muscarinic M ₁	-6 (-6)
Adrenergic α ₂ , Non-selective	5 (-5)	Muscarinic M ₂	-9 (-6)
Adrenergic β ₁	25 (0)	Muscarinic M ₃	4 (-14)
Adrenergic β ₂	26 (42)	Neuropeptide Y ₂	-8 (3)
Angiotensin AT ₁	14 (7)	Nicotinic Acetylcholine, Central	-5 (14)
Bradykinin B ₂	-3 (-3)	Opiate δ	11 (-2)
Calcium Channel Type L	-2 (16)	Opiate κ	8 (8)
Dopamine D₁	-5 (-7)	Opiate μ	-9 (6)
Dopamine D_{2L}	0 (10)	Phorbol Ester	7 (12)
Estrogen ERα	4 (-10)	Progesterone	-1 (5)
GABA_A, Agonist Site	14 (-10)	Purinergic P2X	-4 (4)
GABA_A, Chloride Channel	6 (-9)	Serotonin 5-HT₁, Non-selective	32 (12)
Glucocorticoid	-19 (10)	Serotonin 5-HT₂	-17 (-5)
Glutamate, NMDA	0 (-7)	Sigma, Non-selective	26 (22)
Glutamate, Non-selective	9 (-4)	Sodium Channel, Site 2	1 (42)
Glutamate, Strychnine-sensitive	4 (0)	Tachykinin NK ₁	3 (11)
Histamine H ₁ , Central	21 (-5)	Testosterone	-5 (-8)

GABA= Gamma-Aminobutyric Acid; NMDA= N-Methyl-D-Aspartate; NK1= Neurokinin Receptor 1
^a positive response is ≥50% stimulation or inhibition

Negative values correspond to stimulation of binding or enzyme activity

(Adapted from Table from 2.6.2 Pharmacology Written Summary of NDA 22-244)

MGI concluded that fospropofol at 10 μM did not produce significant binding to any of the targets studied.

COMMENT: The primary site of propofol's action is considered to be through the GABA_A site¹². Therefore, the binding data do not appear to be reliable because the positive control in this assay, propofol, was not shown to have significant GABA_A binding. MGI states that this finding was unexpected and that the "most likely explanation for these results is that the specific sites used in the binding assays were not the pharmacologically relevant ones for these two drugs".

Because the quality of the binding studies is called in question, it is recommended that these studies (binding of fospropofol and propofol) are repeated. The binding profile of propofol is well described and as such, there is no question as to the action of the propofol that is released from the pro-drug, fospropofol. However, although the conversion of fospropofol to propofol is reportedly complete it is not immediate. Therefore, it is important to determine if fospropofol has a different binding potential/profile compared to propofol. MGI should characterize the binding profile of fospropofol using validated experimental procedures.

2. Animal Studies

No animal studies were performed to examine the reinforcing properties of fospropofol.

E. Clinical Studies

1. Evaluation of Adverse Events Related to Abuse Potential

Safety and efficacy data were reported from 21 studies; 12 studies in patients and 9 studies³ in healthy subjects. In all, 1611 patients and subjects were exposed to fospropofol. Two additional studies (discussed below) were performed to examine the bioavailability of fospropofol after oral administration.

The studies performed in the fospropofol development plan did not include prospective evaluations for adverse events associated for abuse liability nor were any evaluations for drug liking performed.

In the nine studies healthy subjects (N = 273) were given intravenous fospropofol. The most commonly reported adverse events were paraesthesia (75.8%), pruritus (21.6%), headache (7.7%), and dizziness (6.2%). Sedation was reported by 2.2%; and both euphoria and disorientation by 0.7%.

The adverse events from two studies (3100-0401 and 3100-0402) examining the oral bioavailability of fospropofol are not included in the adverse event data file. The adverse events from these two studies were provided in the individual study reports and are summarized in the following section.

¹ Campagna-Slater, V. and Weaver, D.F. (2007) Anaesthetic binding sites for etomidate and propofol on a GABA_A receptor model. *Neuroscience Letters* 418:28-33.

² Solt, K. and Forman, S.A. (2007) Correlating the clinical actions and molecular mechanisms of general anesthetics. *Current Opinion in Anaesthesiology* 20:300-306.

³ Studies 3000-0001, -0102, -0103, -0205, -0206, -0308, -0414, -0521, -0625

2. Oral Administration of Fospropofol

Bioavailability of Oral Fospropofol

Two studies (3100-0401 [N=7 subjects] and 3100-0402 [N=10 subjects]) were performed to assess the bioavailability of fospropofol after oral administration. The following table contains a summary of the subjects, design, doses of study drug for each study.

Studies Examining the Oral Bioavailability of Fospropofol

Study	Subjects	Design	Doses
3100-0401	N = 7 Male 21-45 years old	3-way crossover	fospropofol 400 mg (20 mg/ml) oral duodenum by gastroscopy intravenous (over 10 minutes) No placebo administration
3100-0402	N = 10 Male (6)/Female (4), 19-34 years old	double-blind, randomized, crossover, placebo-controlled, single ascending dose	fospropofol orally (capsule) 200 mg 600 mg 1000 mg 1200 mg placebo

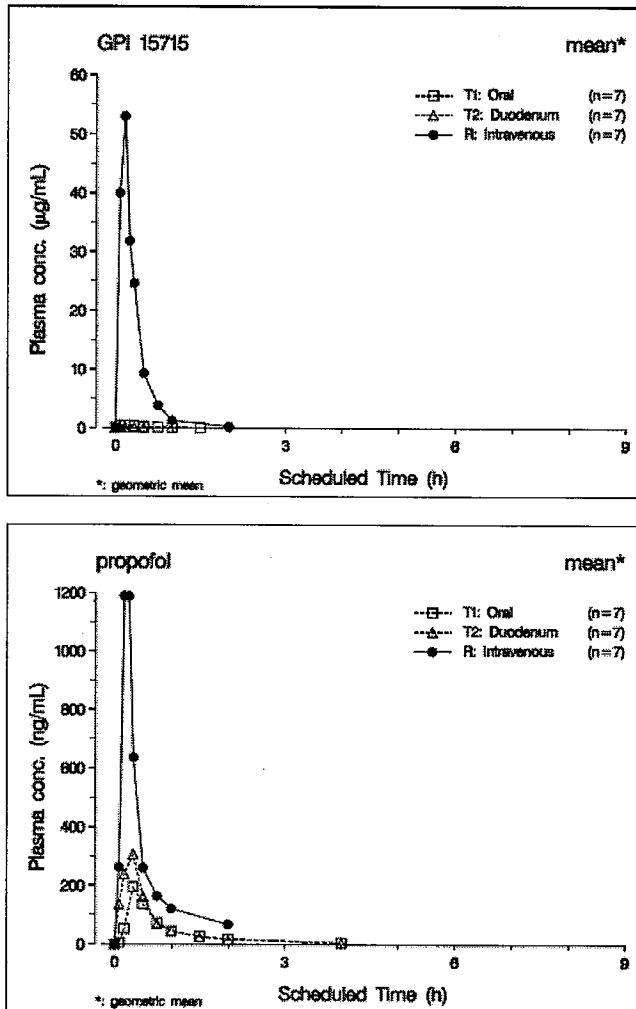
A methodological problem in both studies (3100-0401 and 3100-0402) prevented reliable measurement of propofol in the samples. In these studies sodium orthovanadate (SOV), an inhibitor of alkaline phosphatase, was added to each blood sample to prevent conversion of fospropofol to propofol in vitro. However, the SOV, added as a solid, did not dissolve uniformly and therefore the inhibition of alkaline phosphatase may have been incomplete. MGI Pharma argues that this problem did not affect the measurement of fospropofol and therefore reported fospropofol levels but not propofol levels. Further evaluation (Study DMPK06-085) of the assays for fospropofol and propofol revealed problems with the stability of propofol in stored samples, especially in hemolyzed samples.

Sample preparation and storage difficulties aside, the purpose of the oral studies was to examine the potential for oral absorption of fospropofol. The propofol levels reported in study 3100-0401 are from subjects who received fospropofol (oral, duodenal administration, intravenous); no subject in this study received propofol administration. Therefore, any level of fospropofol or propofol measured in the serum after oral or duodenal administration demonstrates the absorption of fospropofol or its metabolite propofol. The following figures show the plasma concentrations of fospropofol (GPI 15715⁴) and propofol for study 3100-0401.

⁴ In early studies, fospropofol is denoted as (GPI 15715). To avoid confusion, only the name fospropofol is used in this consult.

Plasma concentrations of fospropofol (GPI 15715) and propofol for study 3100-0401

Figure 2-3 Mean plasma concentration-time profiles (linear) for GPI 15715 and propofol



In Study 3100-0402 both fospropofol and propofol were detected after oral administration of fospropofol in capsule form. The mean values (\pm SD) of fospropofol and propofol were $6.63 \mu\text{g}$ ($\pm 2.37 \mu\text{g}$) and 589 ng ($\pm 298 \text{ ng}$), respectively, after administration of the 1200 mg dose. (No graphic representation available.) No discussion was found describing the dissolution properties of the capsule. Therefore, it would be difficult to compare exposures from fospropofol in solution (3100-0401) to fospropofol in capsule form (3100-0402).

COMMENT: Despite problems with the methodology, the ability to measure fospropofol and its metabolite propofol in the plasma demonstrates the absorption of fospropofol after oral administration, and more 'appealing' route of administration compared to intravenous use of propofol. An additional concern raised by the apparent

oral bioavailability of fospropofol/propofol is the potential for its combination with alcohol.

Adverse Events after Oral Administration of Fospropofol

The following table contains a summary of the number of subjects reporting adverse events related to abuse potential reported in Study 3100-0401 and Study 3100-0402.

Number of subjects reporting selected AEs from oral bioavailability studies	3100-0401 N = 7 (400 mg solution)			3100-0402 N = 10 (oral capsules)				
	oral	duodenal	I.V.	200 mg	600 mg	1000 mg	1200 mg	placebo
burning sensation			2		1	1	1	
disorientation			1					
dizziness	1		3		2			
euphoria	1	1	1		1		1	1
fatigue		2	2		2	1	1	
feeling abnormal			1					
feeling drunk			1					
feeling hot				1	3	3	4	
paraesthesia	1		5	3	5	5	2	
proctalgia	4		4		1			
sluggish speech/ speech disorder			6					
suprapubic pain		1						
somnolence		2	5	4	5	4	9	
visual disturbance			5					

Summarized from Study 3100-0401 Table 4-1 and Study 3100-0402 Table 16.2.4-1

Sedation was scored by the clinical staff (using the Modified OAA/S) during both studies. In Study 3100-0401, sedation was apparent (responding lethargically to spoken name) 43% of subjects receiving 400 mg fospropofol by duodenal administration and 57% of subjects receiving 400 mg fospropofol by intravenous administration. In study 3100-0402, sedation was apparent in 40% of the subjects receiving the 1200 mg capsule. Of note, the proposed formulation of 30 mg/ml will provide 1050 mg of fospropofol in solution.

COMMENT: Reports of paraesthesias and somnolence after oral administration are similar to those reported for intravenous administration of fospropofol. Furthermore, many of the paraesthesias, burning sensations, and reports of proctalgia or anal discomfort are similar to the ‘sexual sensations’ that have been reported with the use of anesthetics, including propofol⁵. Therefore, the concern that fospropofol may have sufficient bioavailability after oral administration is further supported by the adverse events and sedation reports from Studies 3100-0401 and 3100-0402.

⁵ Strickland, R.A. and Butterworth, J.F. (2007) Sexual Dreaming during Anesthesia. *Anesthesiology*: 106:1232-1236.

3. Studies for abuse potential:

No studies examining the abuse potential of fospropofol were reported in the NDA. Instead, the results of studies found in the literature using propofol were summarized.

Evidence for abuse potential – In a series of studies⁶ performed by Zacny et al. the authors concluded that propofol demonstrated abuse potential. The Abuse Liability Assessment contains summaries of these studies found in the literature.

Evidence of abuse or diversion – Although fospropofol is not marketed, propofol has been available in the U.S. since 1989. The Company presented case reports in their Abuse Liability Assessment cases of abuse of propofol; six of the 14 individuals described in the 12 case reports were found dead. The Company concludes that abuse of propofol is rare and mainly limited to health care professionals.

COMMENT: Propofol is not scheduled under the CSA, although there is evidence of abuse potential for propofol, as demonstrated by Zacny et al. Furthermore, the case reports of propofol abuse presented by the Company show that many of the cases of propofol abuse are only detected when the abuser has died. It is not unreasonable to assume that for each case of death there are additional cases of abuse that remain undetected. This contention is supported by a survey published by Wischmeyer et al.⁷ that found that of 126 academic anesthesiology training programs surveyed, 18% of the programs reported propofol diversion or abuse. In fact, of the 25 individuals reported to have abused propofol, 7 (28%) died from this abuse.

A survey of reports in the AERS DataMart data base returned 5,497 cases associated with propofol use; with 1,690 of these cases categorized with outcome of “death” or “life-threatening”. The scope of this consult does not allow for individual review of all of the detected cases. Therefore, a more limited review was performed to identify cases which may suggest drug abuse, misuse, or diversion. To perform this search, the following categories were chosen under ‘Reaction’: toxicology and therapeutic drug monitoring (under investigations); suicidal and self-injurious behaviors (under psychiatric disorders); legal issues (under social circumstances); and drug and chemical abuse (under life style issues). This search returned 67 cases. After accounting for duplicate cases and cases in which propofol was used for anesthesia and or sedation, 25 cases were found to be associated with abuse or misuse. Eleven cases involved a healthcare provider, either physician or nurse, who abused propofol; nine cases were reports of death. One additional case involving a healthcare provider involved the use of propofol as part of a

⁶ Zacny JP, Lichtor JL, Coalson DW, Finn RS, Uitvlugt AM, Glostén B, et al. (1992) Subjective and psychomotor effects of subanesthetic doses of propofol in healthy volunteers. *Anesthesiology* 76(5):696-702.

Zacny JP, Lichtor JL, Thompson W, Apfelbaum JL. (1993) Propofol at a subanesthetic dose may have abuse potential in healthy volunteers. *Anesth Analg.* 77(3):544-552.

Zacny JP, Lichtor JL, Zaragoza JG, Coalson DW, Uitvlugt AM, Flemming DC, et al. (1993) Assessing the behavioral effects and abuse potential of propofol bolus injections in healthy volunteers. *Drug Alcohol Depend.* 32(1):45-57.

⁷ Wischmeyer PE, Johnson BR, Wilson JE, Dingmann C, Bachman HM, Roller E, Tran ZV, and Henthorn TK. (2007) A survey of propofol abuse in academic anesthesia programs. *Anesth Analg.* 105(4):1066-1071.

sexual assault on a patient. 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. After the physician declined to continue treatments the patient obtained and used propofol, 200 mg IV 10 to 15 times daily; the patient underwent a detoxification program. The source of the propofol was assumed to be illicit.

Although the Company submits that the difference in PK properties between fospropofol and propofol would further limit the potential for fospropofol abuse, the contrary may be true. The difference in onset of action and t_{max} between fospropofol and propofol is a matter of minutes not hours, and the $t_{1/2}$ of fospropofol is somewhat greater giving a longer experience. Therefore, because of its less rapid onset of action, individuals may consider fospropofol safer to abuse than propofol. Additionally, because fospropofol has oral bioavailability, thereby providing a convenient route for misuse and abuse, it may be attractive to individuals who avoid intravenous drug use. Furthermore, propofol has sedative and amnestic properties. Fospropofol is readily soluble in water ~~_____~~ ~~_____~~; 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, including date rape/sexual abuse and robbery.

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Comments to be relayed to MGI Pharma:

The Controlled Substance Staff (CSS) has reviewed the Abuse Liability Assessment (Module 5.3.5.4) and supporting studies and concluded that additional studies should be performed to complete the assessment of the abuse potential of fospropofol. CSS recommends that:

1. Studies to characterize the binding profile of fospropofol should be repeated using validated experimental procedures.
2. Clinical studies examining the abuse potential of both intravenous and oral fospropofol should be performed. Additionally, the effect of fospropofol in combination with ethanol should be examined as it may increase the abuse potential of fospropofol. It is recommended that the abuse potential studies include propofol as an active comparator.

The studies requested are directed at better characterizing the adverse event profile of fospropofol as would be related to its abuse potential. Although fospropofol can be further metabolized to propofol *in vitro* use of sodium orthovanadate (an inhibitor of alkaline-phosphatase) in the studies examining the abuse liability of oral administration of fospropofol is not recommended because of the effects on the stability of propofol. The measurement of either fospropofol or propofol after the oral administration of fospropofol is sufficient to demonstrate oral bioavailability.

3. In submitting the NDA application, MGI Pharma agreed to not market the drug product, if the FDA determines that the drug should be scheduled under the CSA, until the DEA has issued a final schedule ruling. The CSS can not finish its evaluation of the abuse potential of fospropofol and make recommendations for scheduling, or not, until the deficiencies identified have been addressed.
4. CSS will be available to review and discuss protocols examining the abuse potential of intravenous and oral fospropofol.

Date: March 19, 2008

Primary Reviewer: Patricia Beaston, M.D., Ph.D., Medical Officer
Controlled Substance Staff (HFD-009)

Concurred by: Michael Klein, Ph.D., Acting Director
Controlled Substance Staff (HFD-009)

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this page is the manifestation of the electronic signature.**

/s/

Patricia Beaston
3/19/2008 01:24:56 PM
MEDICAL OFFICER

Michael Klein
3/19/2008 01:37:49 PM
PHARMACOLOGIST
Acting Director - Controlled Substance Staff

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 11, 2008

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products
(HFD-170)

Through: Michael Klein, Ph.D., Acting Director
Controlled Substance Staff (HFD-009)

From: Silvia N. Calderon, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

Subject: NDA 22-244 (Fospropofol disodium/Aquavan). Abuse potential assessment.
Indication: Intravenous sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures and for sedation in adult patients
Dosage form and strengths: 1,050 mg/30 mL (35 mg/ml , 30 ml vial) for IV injection
Sponsor: MGI Pharma, Inc.
Submission: NDA 22-224 is located in the EDR. The submission includes a section titled 'Abuse Liability Assessment' (found under Module 5.3.5.4, Other Study Reports). This section can also be accessed through a link provided under the Risk Management Plans section which is found under Module 1-US-Regional section of the electronic document. Labeling is also found under Module 1- US-Regional

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This memorandum summarizes key findings related to the CSS abuse potential assessment of fospropofol in response to a consultation from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP, HFD-170).

BACKGROUND

Aquavan injection is an aqueous formulation of fospropofol disodium. Fospropofol disodium is a water-soluble, phosphono-O-methyl prodrug of propofol and is intended for use as an intravenous (i.v.) sedative-hypnotic agent.

Since 1989, propofol injectable emulsion (10mg/mL) has been marketed for human use under the brand name Diprivan (Astra-Zeneca). Two generic versions and two veterinary

versions, Rapinovel (Schering Plough) and Propoflo (Abott) were approved for marketing in 1999 and 2000, respectively. Propofol is also being studied for use as a component of veterinary euthanasia products. Propofol is not a controlled substance under the Controlled Substance Act (CSA). However, labeling of both the human products and the veterinary products include a *Drug Abuse and Dependence* section that acknowledges the existence of propofol abuse among health care professionals.

Regarding the abuse potential of propofol, since June 1996 to November 2001, the FDA received 26 reports associated with the abuse of propofol through the FDA's spontaneous adverse event reporting system (AERS). All 26 cases describe abuse of the drug by health care professionals. Five of twenty-six cases resulted in death. Therefore, health care professionals who have access to the drug and are trained to administer intravenous solutions seem to be particularly at risk of abusing propofol.

A recent survey published by Wischmeyer et al. (Wischmeyer PE, Johnson BR, Wilson JE, Dingmann C, Bachman HM, Roller E, Tran ZV, and Henthorn TK. A survey of propofol abuse in academic anesthesia programs. *Anesth Analg.* 2007; 105(4):1066-1071) found that of 126 academic anesthesiology training programs, 18% of the programs reported propofol diversion or abuse. Abuse of propofol is associated with high mortality rates. Out of the 25 individuals reported to have abused propofol, 7 (28%) died from this abuse.

CONCLUSIONS AND RECOMMENDATIONS

- 1- Fospropofol should be considered for control under the Controlled Substances Act (CSA). However the appropriate level of controls, dictated by the different Schedules in the CSA, will be determined by the complete and full assessment of the abuse potential of fospropofol in comparison to that of other drugs with similar pharmacological profiles that are controlled under the CSA.
- 2- Considering the hypnotic and sedative properties of fospropofol disodium and its oral availability, CSS concludes that fospropofol has a higher abuse potential than that of propofol. As such fospropofol needs to be marketed under the distribution controls provided by the CSA.
- 3- The information that has been submitted by the Sponsor indicates that fospropofol pharmacology has been compared with propofol and found similar. In addition, fospropofol offers the additional risk of greater oral bioavailability.
- 4- Actual abuse of propofol has been documented in the public domain. Data demonstrate that where propofol product is available, it is abused.
- 5- The risks associated with the potential abuse and misuse of fospropofol is of concern and the drug should not be introduced on the market until its abuse potential has been fully characterized.

6- In order to fully characterize the abuse potential of fospropofol, the drug needs to be compared with other CNS depressants that are controlled under the CSA, in addition to propofol. In addition, the Sponsor should characterize the abuse potential of oral versus intravenous fospropofol in the human abuse potential pharmacology studies.

7- The interaction of orally administered fospropofol with alcohol should also be characterized. A potentiation of the sedative and hypnotic effects of fospropofol is expected.

8- The potential use of fospropofol in the context of criminal activity for the purpose of incapacitating a victim is of concern. Other orally active sedative agents such as GHB have been associated with criminal activity. Therefore appropriate distribution controls should be in place to prevent this scenario.

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Appendix

- Pharmacodynamic effects of orally administered fospropofol.

Two studies (3100-0401 [N=7 subjects] and 3100-0402 [N=10 subjects]) were conducted in The Netherlands to assess the safety and tolerability of fospropofol disodium when administered orally or directly into the duodenum to healthy subjects. The pharmacodynamic effects of fospropofol were captured in both studies, although due to problems in sample collection pharmacokinetic data was found unreliable and not reported. In both studies, orally administered fospropofol displayed the expected adverse event profile of an orally active sedative drug.

In Study 3100-0401 the effects of 400 mg of fospropofol administered orally or directly into the duodenum by gastroscopy were compared to the effects of 400 mg of fospropofol administered i.v. The oral or duodenal administration of 400 mg of fospropofol disodium resulted in fewer treatment emergent adverse events, TEAEs, (6/7 subjects in each group reported 8 and 9 events, respectively) when compared with i.v. administration (7 subjects reported 56 events). This protocol used the Modified Observer's Assessment of Alertness and Sedation (OAA/S) scale to assess subjects' level of sedation. The lowest observed Modified OAA/S score during this study was 4 (responded lethargically to name spoken in normal tone). Three of 7 (43%) and 4 of 7 (57%) subjects in the duodenal and i.v. groups, respectively, had a Modified OAA/S score of 4 at some time following drug administration. All other subjects in those treatment groups and all subjects in the oral treatment group responded readily to their name spoken in normal tone (Modified OAA/S score of 5) at all times. The sedative effects lasted no more than 1.5 hours postdose.

In study 3100-0402 each subject (N=10) received 4 ascending oral doses of fospropofol disodium (200, 600, 1000 and 1200 mg) and one of placebo. The Modified Observer's Assessment of Alertness and Sedation (OAA/S) score was used to assess subjects' level of sedation, and the digit symbol substitution test (DSST) was used to assess psychomotor impairment. Oral administration of fospropofol disodium in capsules was safe and well tolerated in healthy volunteers at doses of up to 1200 mg, under the conditions of this study. There was pharmacodynamic evidence of drug effect, most prominently at the 2 highest doses (1000 mg and 1200 mg), reflected in the frequency and severity of somnolence reported as an AE. Corresponding changes were observed in Modified OAA/S scores and DSST changes from baseline. Euphoric mood was reported as a TEAE in 3 out of 10 subjects during this study (one subject in the placebo, one subject in the 600 mg group, and one subject in the 1200 mg group). At most time points $\geq 80\%$ of subjects in each of the treatment groups responded readily to their names spoken in a normal tone (Modified OAA/S scores of 5). However, at the 1.5-hour time point in the 1200 mg treatment group, four subjects (40 %) had a Modified OAA/S score of 4 (responded lethargically to their names spoken in a normal tone).

- *Abuse potential of fospropofol*

Under the *Drug Abuse and Dependence* section of the label the Sponsor states that "no formal studies of the abuse potential of AQUAVAN have been conducted. AQUAVAN has been associated with descriptions of euphoria in a small number of subjects who have received intravenous or oral dosing."

The Sponsor believes that the abuse potential of fospropofol is lower than that of propofol, because as a prodrug fospropofol shows a slower time to onset of active drug effect and reduced C_{max} , and speculates that this delay in onset of effect and more gradual rise to peak effect should serve to reduce the potential for abuse of fospropofol disodium relative to propofol. However this theory does not consider the fact that oral bioavailability of this new formulation offers a convenient route of abuse and that subjects who might not have abused propofol because it required intravenous injection might easily abuse Aquavan.

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/s/

Silvia Calderon
3/11/2008 03:48:09 PM
CHEMIST

Michael Klein
3/11/2008 03:54:11 PM
PHARMACOLOGIST
Acting Director - Controlled Substance Staff

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

IND or NDA	22244 N000
Brand Name	AQUAVAN®
Generic Name	Fospropofol disodium
Sponsor	MGI Pharma
Indication	Minimal-to-moderate sedation for brief diagnostic and therapeutic procedures
Dosage Form	Solution for injection
Drug Class	Anesthetic
Therapeutic Dose	Single dose of 6.5 mg/kg i.v.
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Single dose of 30 mg/kg
Application Submission Date	26 Sept 2007
Review Classification	Standard NDA
Date Consult Received	29 Oct 2007
Clinical Division	DAARP / HFD 170
PDUFA Date	27 Jul 2008

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

In this randomized, open-label, positive- and placebo-controlled crossover study, 68 healthy subjects were administered single IV bolus dose of AQUAVAN 6 mg/kg, AQUAVAN 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 $\Delta\Delta\text{QTcF}$ at the 12-minute timepoint was greater than 10 ms which is 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 overall findings are summarized in the following table.

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

Treatment	Time (min)	$\Delta\Delta\text{QTcF}$ (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

The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ 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 AQUAVAN 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 suprathreshold dose (Clinical Pharmacology Table, section 6.1). 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 of 1050 mg fospropofol) of AQUAVAN.

1.2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

1.2.1 Does AQUAVAN cause QT prolongation? Does the thorough QT study report show that AQUAVAN does not cause QT prolongation?

There is dose-dependent lengthening of the QTcF interval following the administration of AQUAVAN (refer to section 1.1 Overall Summary of Findings).

Any method of correcting the QT interval for heart rate using the preceding RR interval is potentially misleading for drugs that rapidly change heart rate. To obtain a better precision of the effects of administering AQUAVAN on the QT interval, the sponsor may want 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 interval should be assessed.

1.3 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- The sponsor's primary endpoint is QTcI which was computed using the 11 time points extracted from the continuous Holter monitor at baseline (Table 1). Based on visual inspection of the trends in individual's QTcI and RR intervals, the sponsor's individual correction method did not sufficiently correct for heart rate (Figure 5). AQUAVAN causes increase in heart rate immediately after dosing (Figure 6). The range of baseline heart rates from the 11 time points extracted from the Holter data was too narrow to compute an individual heart rate correction to account for the increase in heart rate with AQUAVAN administration (Figure 7). Therefore, the FDA's analysis was based on QTcF.
- The study was not blinded. The sponsor chose not to blind the treatments because at the suprathreshold dose (18 mg/kg), AQUAVAN produces deep levels of sedation and it was necessary that appropriate personnel be available to manage

potential sedation-related adverse events. We agree with the sponsor's rationale for not blinding treatments.

- The timing of ECGs to determine assay sensitivity was not optimal. After moxifloxacin administration, 11 ECGs were collected for 4 hours which coincide with T_{max} . We typically recommend collecting a full moxifloxacin profile since we also consider the time-course of QTc during our assessment of assay sensitivity.

2 PROPOSED LABEL

The sponsor states in the proposed label (12.2 Pharmacodynamics):

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Reviewer's Comments:

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The following recommendations are only our suggestions for labeling. We defer all final labeling decisions to the review divisions.

The effect of AQUAVAN on the QTcF interval was measured in a crossover study in which healthy subjects (n=68) received the following treatments: 6 mg/kg IV AQUAVAN; 18 mg/kg IV AQUAVAN; 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).

3 BACKGROUND

Fospropofol disodium is a water-soluble, phosphono-O-methyl (POM) prodrug form of propofol. AQUAVAN[®] (fospropofol disodium) Injection is an aqueous formulation of fospropofol disodium. AQUAVAN is being developed as an intravenous (i.v.) sedative-hypnotic agent for sedation in adult patients undergoing diagnostic and therapeutic procedures _____

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3.1 MARKET APPROVAL STATUS

Aquavan is currently not approved for marketing in the USA.

3.2 PRECLINICAL INFORMATION

The sponsor states in the nonclinical summary:

"The effects of fospropofol (as AQUAVAN) and propofol (as Diprivan) on the hERG ion current channel (IKr) in human embryonic kidney (HEK293) cells were

compared. A concentration of 3000 μM fospropofol inhibited hERG current by $7.0 \pm 0.9\%$ compared with the vehicle control at $0.1 \pm 0.3\%$. The IC_{50} for the inhibitory effect of fospropofol on hERG current was considered to be $>3000 \mu\text{M}$. Propofol at 300 μM inhibited hERG current by $38 \pm 0.3\%$ compared with the controls ($-2.5 \pm 0.3\%$). Because the emulsion was believed to be producing a significant current leak in most of the cells, the study was repeated with bulk propofol. Four concentrations of bulk propofol were tested for effect on hERG current: 30, 100, 200, and 300 μM . At these concentrations, hERG inhibition was $15.7 \pm 1.1\%$, $49.2 \pm 2.3\%$, $82.3 \pm 1.6\%$, and $92.6 \pm 1.5\%$, respectively, compared with $-0.1 \pm 0.1\%$ for the vehicle control. The IC_{50} for the inhibitory effect of propofol on hERG current was 92.8 μM . Terfenadine (60 nM) was the positive control in this assay, and it inhibited hERG current by $78.3 \pm 3.5\%$. It was concluded that fospropofol did not cause physiologically meaningful inhibition of hERG current in HEK293 cells up to and including 3000 μM . In contrast inhibition of K^+ conductance by bulk propofol was similar to that of the positive control. The IC_{50} of propofol could not be established because of interference from the lipid vehicle.

Fospropofol (300, 1000, and 3000 μM) did not prolong the action potential duration (APD) at any concentration in isolated Purkinje fibers from canine ventricles. Shortening of the APD_{60} and APD_{90} (APD for 60% and 90% repolarization, respectively) was observed at the concentrations tested.

In conscious dogs, fospropofol disodium was administered in bolus dosages of 20 to 41 mg/kg followed by infusions at 45 to 150 mg/kg/h for up to 18 min (median=15 min). Infusion dosages were adjusted throughout the first 3 sessions to establish a level of sedation that would elicit burst suppression or a "sedation" pattern on the EEG. There was a decrease in MAP of approximately 40-60% below baseline. HR changes were variable. While ECG's were recorded, no data on effects on QT interval or other parameters are reported."

3.3 PREVIOUS CLINICAL EXPERIENCE

The sponsor states in the summary of clinical safety:

"A total of 1,611 subjects received AQUAVAN during the clinical development program. Of these individuals, 273 were healthy subjects and 1,338 were patients undergoing procedures. The majority of these studies have been in patients undergoing screening colonoscopy. The most common treatment-related AEs in AQUAVAN-treated patients and healthy subjects were events of paresthesia and pruritus. These events occurred in the majority of individuals, were generally mild to moderate in intensity, self limited, and lasted only a few minutes. Adverse events due to sedation/pharmacological class included hypoxemia, bradycardia, apnea, and hypotension

Ten patients (5 in study 3000-0413 and 5 in study 3000-0524) died during the protocol-defined observation period (from the time of study drug administration to 30 days after the last study visit). In study 3000-0413 (phase II study in patients requiring intubation and mechanical ventilation), 4 patients in the AQUAVAN infusion only group and 1 patient in the propofol injectable emulsion group died as a result of SAEs identified during the study. The SAEs that led to death of the patient in the AQUAVAN infusion only group were acute respiratory failure, septic shock, respiratory failure, and cardio-respiratory arrest. The deaths occurred 16, 1, 9, and 3 days, respectively, after receiving study drug. The SAEs in the patient

receiving propofol injectable emulsion were gastrointestinal hemorrhage and respiratory distress and occurred 31 days after receiving study drug. In study 3000-0524 (phase III trial in patients undergoing flexible bronchoscopy), three patients in the AQUAVAN 6.5-mg/kg group and 2 patients (2.0%) in the 2.0-mg/kg group died as a result of SAEs identified during the study. The SAEs that led to death were anoxic encephalopathy, respiratory arrest, malignant lung neoplasm, septic shock and malignant lung neoplasm with pneumonia. The deaths occurred 4, 11, 19, 22, and 23 days, respectively, after receiving study drug.

A total of 6 patients experienced SAEs that were considered probably or possibly related to AQUAVAN. Of these, four patients had SAEs that were considered to be sedation-related and required airway management. A SAE of non-sustained (estimated 10 second run) ventricular tachycardia in the prolonged duration study (3000-0413) was considered possibly related to study drug. The patient narrative suggests the likely contributing factors of hypomagnesemia and hypokalemia. One healthy volunteer experienced 'psychogenic paralysis'."

Reviewers comment: QT abnormalities/ventricular arrhythmias are not reported in the death narratives.

3.4 Clinical Pharmacology

Appendix 6.1 summarizes the key features of AQUAVAN's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted one TQT study report.

4.2 TQT STUDY

4.2.1 Title

A Single-Site, Randomized, 4-Sequence, 4-Treatment Crossover Study of a Single Administration of AQUAVAN® Injection Compared with Placebo and a Positive Control in Healthy Volunteers

4.2.2 Protocol Number

3000-0521

4.2.3 Study Dates

19 September 2005 (first subject enrolled) to 10 December 2005 (last subject completed)

4.2.4 Objectives

- To determine the maximal effects of a single bolus dose of AQUAVAN® (fospropofol disodium) Injection (hereafter referred to as AQUAVAN) on the individually corrected QT interval (QTcI)
- To quantify the dose, concentration, and time relationships of AQUAVAN on the QT interval corrected for heart rate (QTc) at therapeutic and supratherapeutic doses

- To describe the pharmacokinetics of AQUAVAN and AQUAVAN-derived propofol in venous plasma

4.2.5 Study Description

4.2.5.1 Design

This was a single-center, randomized, 4-sequence, 4-treatment crossover study in which study drug administration was open label, but all electrocardiogram (ECG) data were evaluated by a central reader who was blinded with respect to subject, treatment, and time.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The study was open label. The sponsor's justification for not blinding study treatments, "This study was not blinded to treatment for safety reasons. Because AQUAVAN was administered at a suprathreshold dose (18 mg/kg), which is known to produce deep levels of sedation in some subjects, it was necessary that appropriate personnel be available to manage potential sedation-related adverse events (SRAEs). Therefore, double blinding was not employed."

Reviewer's Comments: The sponsor's rationale for not blinding this study due to safety issues is reasonable..

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

The 4 treatments were as follows:

- (A) Placebo (normal saline) intravenous (i.v.)
- (B) Moxifloxacin 400 mg oral (p.o.)
- (C) AQUAVAN 6 mg/kg i.v. (but not <360 mg and not >540 mg)
- (D) AQUAVAN 18 mg/kg i.v. (but not <1080 mg and not >1620 mg)

Subjects were randomly assigned at Baseline prior to study drug administration in a ratio of 1:1:1:1 to one of the following 4 treatment sequences: ADBC (Treatment Sequence I), BACD (Treatment Sequence II), CBDA (Treatment Sequence III), or DCAB (Treatment Sequence IV).

4.2.6.2 Sponsor's Justification for Doses

"A dose of 6.0 mg/kg was chosen as the clinically-relevant efficacy dose for this study. The suprathreshold dose chosen, 18 mg/kg, is 3-fold higher than the clinically-relevant dose and is within the range for induction of general anesthesia, based on results of a previous volunteer study (study 3000-0103). Doses higher than 18 mg/kg produce longer periods of unconsciousness. The suprathreshold dose was chosen to balance the maximal pharmacologic effect with the safety of the subjects.

The pharmacokinetics of AQUAVAN support the use of a single i.v. bolus dose in this study. Both fospropofol and liberated propofol have short half-lives and will not accumulate with the proposed administration. The bolus dose provides the highest concentration of fospropofol and fospropofol-derived propofol for a given effect level.”

Reviewer’s Comments: The choice of 18 mg/kg is reasonable. Also a single i.v. bolus dose is acceptable given the short half-life of fospropofol and propofol.

4.2.6.3 Instructions with Regard to Meals

Reviewer’s Comments: The timing of dosing relative to meals was not described. This is not important since AQUAVAN is administered by IV infusion.

4.2.6.4 ECG and PK Assessments

Table 1: Sampling Schedule

Study Day	-1	1	3-7
Intervention	No treatment (Baseline)	Single dose	No treatment (Washout)
12-Lead ECGs	Record ECGs ¹	Record ECGs ¹	None recorded
PK Samples for drug	None collected	Collected ²	None collected

¹ECGs were obtained 1, 4, 8, 12, 20, 30, 60, 90, 120, 180, and 240 minutes after dosing

²Blood samples for PK were obtained at 1, 4, 8, 12, 20, 30, 60, and 90 minutes and 2, 3, and 4 hours after dosing. Samples were taken only for the AQUAVAN treatment periods.

4.2.6.5 Baseline

Four 12-lead ECGs were extracted from the flash card at each of 11 time points (1, 4, 8, 12, 20, 30, 60, and 90 minutes and 2, 3, and 4 hours) at 1-minute intervals at day -1. The average of the 4 ECGs at each time point was used as the baseline values.

4.2.7 ECG Collection

Electrocardiograms were obtained digitally using a _____ . ECG continuous digital recorder at the specified time points. Four ECGs were recorded within 1 minute of each scheduled time point. The ECGs were stored on a flash card approximately every 10 seconds and were not available for review until the card was received by the central ECG laboratory and analyzed.

ECG’s were read centrally by evaluators using a high-resolution manual on-screen caliper method with annotations for interval measurements, For all analyses, the 4 QT/QTc interval replicates for each subject were averaged at each extraction time point. The staff performing the analysis of ECGs was blinded to subject, treatment, and time.

b(4)

For the subjects' safety, standard digital 12-lead ECGs were performed to detect any immediate ECG effects at screening, 30 minutes before dosing, 1 hour after dosing, and at the follow-up visit.

The central lab performs quality control of interval duration measurements (IDMs) on a daily basis as follows: 5% of all normal ECG IDMs, all IDMs that are noted by the original cardiac safety specialist as being of poor quality, and all ECGs with IDMs that meet 'Outlier' criteria, which have been specified by the client. Two percent of the ECGs from each protocol will be randomly selected and placed in a QA environment for independent, blinded over read by technical quality assurance specialist.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Seventy subjects (38 males, 32 females) between 18-45 years of age, BMI between 18-30 kg/m², with a normal baseline ECG were randomly assigned to receive the study drug. A total of 68 subjects (97.1%) completed the study. Two subjects discontinued the study after administration of the study drug. An 18-year-old woman in Treatment Sequence III [CBDA] voluntarily withdrew from the study after dosing with moxifloxacin in Period 2, and the Investigator withdrew a 39-year-old woman in Treatment Sequence I [ADBC] because of the TEAE of ventricular extrasystoles exhibited upon telemetry assessment prior to dosing in Period 2.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the mean difference between AQUAVAN and placebo in the maximum time-matched change from baseline in QTcI, where $QTcI = QT/(RR)^\beta$. RR is an RR interval (seconds) measured along the QT interval (ms) in the ECG, exponent β is estimated from the linear regression model $\log(QT) = \alpha + \beta \cdot \log(RR)$ using baseline observations for each subject and period.

The primary analysis was the maximum time-matched change from baseline in QTcI. The sponsor's results from the Study Report are reported in Table 2.

Table 2: Difference between AQUAVAN and Placebo in Maximum Time-Matched Change from Baseline in the QTcI (Primary Endpoint)

Parameter (unit) Statistic	AQUAVAN 6 mg/kg (n=69)	AQUAVAN 18 mg/kg (n=68)	Moxifloxacin 400 mg (n=69)
QTcI (ms)			
n	65	66	66
Mean (SD)	-3.1 (13.79)	1.9 (13.43)	6.5 (12.43)
Median	-4.0	2.5	6.0
Minimum, Maximum	-39, 34	-28, 33	-28, 32
90% CI	(-5.98, -0.27)	(-0.90, 4.62)	(3.90, 9.01)
QTcI=individually corrected QT interval; CI = confidence interval			
Source: Section 14.2, Table 14.2.2.2			

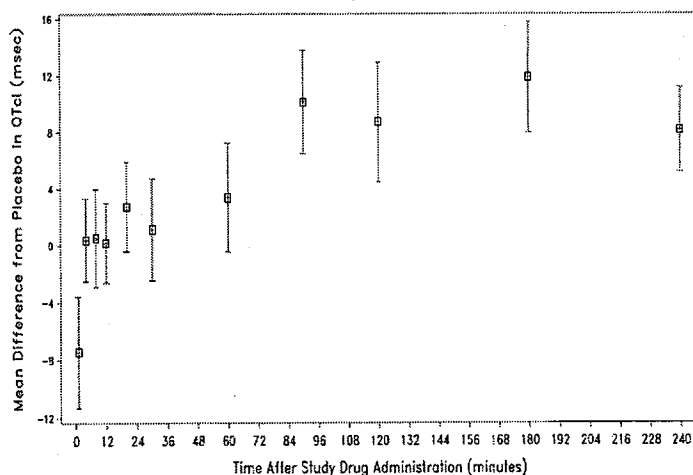
Sponsor's Table 9 on page 49 of Clinical Study Report: 3000-0521

Reviewer's Comments:

1. *The sponsor's primary analysis is not the analysis described in the ICH E14 guideline. The FDA statistical reviewer reanalyzed the sponsor's ECG data using the preferred analysis (see Statistical Assessments, section 5.1).*
2. *Based on visual inspection of the trends in individual's QTcI and RR intervals, the sponsor's individual correction method did not sufficiently correct for heart rate (Figure 5). AQUAVAN causes increase in heart rate immediately after dosing (Figure 6). The range of baseline heart rates was too narrow to compute an individual heart rate correction to account for the heart rate changes with AQUAVAN (Figure 7). Therefore, the FDA's analysis was based on QTcF (see Statistical Assessments, section 5.1).*

The assay sensitivity analysis for QTcI measurement was conducted using the positive control (moxifloxacin) compared to placebo. The largest lower bound of the 2-sided 90% CI for the mean difference in time-matched change from baseline was 6.47 ms (Figure 2).

Figure 1. Moxifloxacin: Means and 90% CIs for the Difference From Placebo in Change From Baseline in the QTcI Interval at Each Extraction Time Point



Sponsor's Figures 9 on pages 63 of Clinical Study Report: 3000-0521

Reviewer's Comments: The statistical reviewer used QTcF for the assessment of assay sensitivity (see Statistical Assessments, section 5.1).

4.2.8.2.2 Categorical Analysis

Categorical analysis was used to summarize QTcI >450, >480 and >500 ms, and absolute changes from baseline > 30 and > 60 ms. No subject observed a QTcI >480 ms or a change from baseline QTcI > 60 ms.

4.2.8.2.3 Additional Analyses

The sponsor also performed analyses based on the endpoints QTcB, QTcF, and QTcS (corrected for heart rate by Study wise formula) and subgroup analysis by gender.

Reviewer's comments: The sponsor's analysis of QTcF showed that at 12 minutes post-dosing the maximum mean change in $\Delta\Delta QTcF$ was 8 ms with an upper two-sided 90% confidence bound of 12 ms (Sponsor's Table 14.2.3.1, page 159 of the report).

4.2.8.3 Safety Analysis

No deaths or SAEs were experienced during the study. There were no reports of sedation-related adverse events (SRAEs) or of any need for airway assistance during this study. As mentioned earlier, the Investigator withdrew a 39-year-old woman in Treatment Sequence I [ADBC] because of the TEAE of ventricular extrasystoles exhibited upon telemetry assessment prior to dosing in Period 2.

Treatment-emergent AEs (TEAEs) were experienced by 97.1% of subjects in both the AQUAVAN 6 mg/kg group and the AQUAVAN 18 mg/kg group. In contrast, 11.6% of subjects in the moxifloxacin group and 2.9% of subjects in the placebo group experienced TEAEs. No subject experienced a severe TEAE during the study, and the majority of TEAEs were mild. Two TEAEs of moderate severity occurred; hypersensitivity (following moxifloxacin) and vomiting (following AQUAVAN 18 mg/kg) were each experienced by 1 subject. The most common treatment-related TEAEs experienced by subjects in the AQUAVAN treatment groups were burning sensation (71.0% in the 6 mg/kg group and 77.9% in the 18 mg/kg group), paresthesia (24.6% in the 6 mg/kg group and 13.2% in the 18 mg/kg group), and dry eye (25.0% in the 18 mg/kg group).

Mean systolic and diastolic blood pressure measurements in the AQUAVAN treatment groups began to decrease from Baseline between 2 and 4 minutes after dosing and remained below Baseline at all remaining time points. Similar trends were not observed in the moxifloxacin and placebo groups. The greatest mean decreases from Baseline in systolic blood pressure (-26.0 mm Hg at 82 minutes after dosing) and diastolic blood pressure (-19.0 mm Hg at 76 minutes after dosing) were observed in the AQUAVAN 18 mg/kg group.

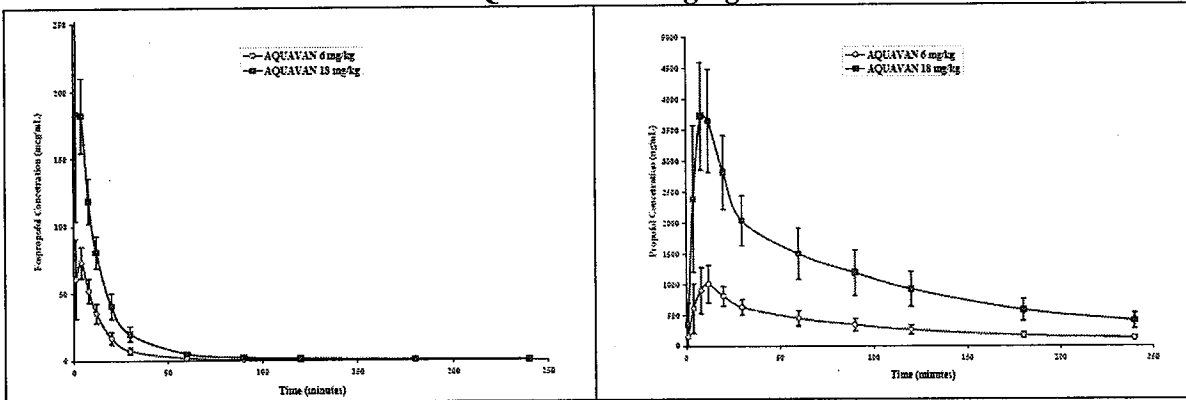
4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

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.

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Figure 2. Mean Concentration-Time Profiles for Fospropofol (left panel) and Propofol (right panel) Following Administration of AQUAVAN 6 mg/kg and AQUAVAN 18 mg/kg



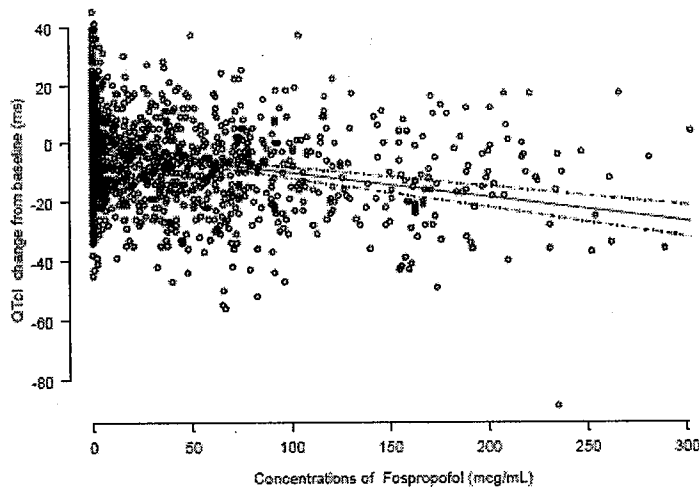
Sponsor's Figures 10 and 11, pages 65 and 68 of Clinical Study Report 3000-0521

4.2.8.4.2 Exposure-Response Analysis

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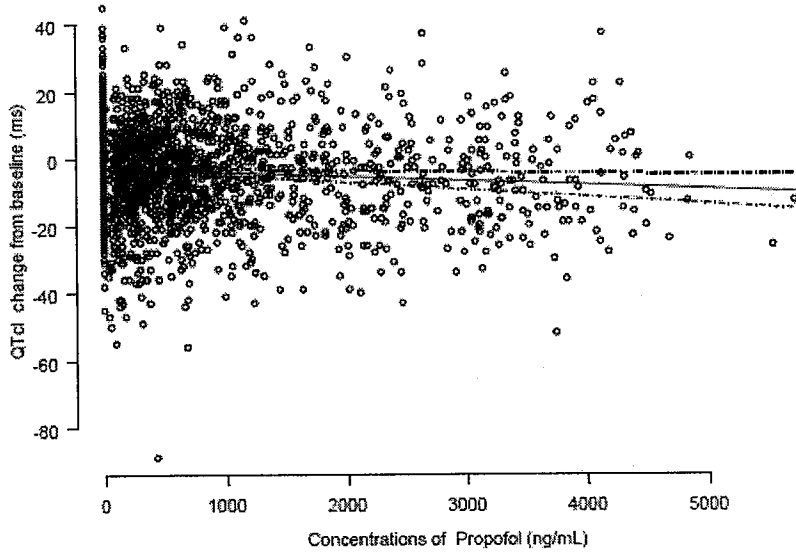
The exploratory analysis of relationships between fospropofol and propofol plasma concentrations and the QTcI interval was performed using the linear mixed-effects models of time-matched change from baseline in QTcI interval versus fospropofol or propofol plasma concentrations. Slopes of the relationships were negative for both compounds.

Figure 3. Relationship between Fospropofol Concentrations and Δ QTcI



Sponsor's Figure 6, page 55 of Clinical Study Report 3000-0521

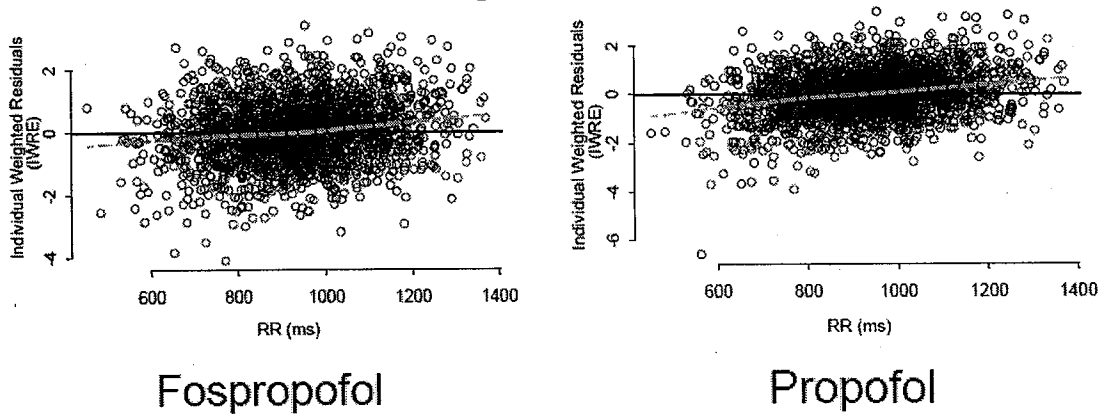
Figure 4. Relationship between Propofol Concentrations and Δ QTcI



Sponsor's Figure 7, page 56 of Clinical Study Report 3000-0521

The positive trend on the plot of weighted residuals versus RR (Figure 4) indicates that individual correction has not completely eliminated the dependence of QTcI interval on heart rate, and this effect may be responsible for the negative slope of the relationships.

Figure 4. Diagnostic Plots for Models of Relationships of Time-Matched Change in QTcI Interval from Baseline with Drug Concentrations: Individual-Weighted Residuals versus RR



Sponsor's Figure 8, page 56 of Clinical Study Report 3000-0521

Reviewer's Comments: Refer to Clinical Pharmacology Assessment (section 5.2.2) for exposure-response analysis using QTcF. Based on our analysis of the heart rate correction method, QTcI is biased and should not be used.

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

The data was submitted electronically and was located on \\fdswa013\qt-studies\Studies\N22244\sas\qt.xpt. The ECG analysis included all subjects who received any dose of the study drug and had digital ECG data collected before dosing and at 1 or more time points after dosing. Two subjects who did not complete the study were excluded from the primary analysis and sensitivity analysis. For all analyses, the 4 QTcF interval replicates were averaged at each extraction time point. All the data were used in the categorical analysis.

Table 3 summarizes the mean difference of QTcF using the observed data at each extraction time point for subjects who had observations in both placebo and AQUAVAN treatment groups.

Table 3: Summary of Time-Matched, Placebo-Adjusted, Mean Change from Baseline in QTcF

Treatment	Time (min)	ΔQTcF			Placebo			N	Diff	ΔΔQTcF (SD)	90% CI
		N	Mean	(SD)	N	Mean	(SD)				
AQUAVAN 6 mg	1	67	-5.68	(12.52)	66	-2.26	(12.71)	65	-3.4	(16.70)	(-6.85, 0.06)
	4	67	-1.65	(10.90)	66	-0.97	(10.97)	65	-0.97	(14.93)	(-4.06, 2.12)
	8	67	0.96	(10.30)	65	-0.35	(11.86)	64	0.89	(18.11)	(-2.89, 4.67)
	12	67	0.3	(12.16)	66	-2.06	(12.99)	65	2.22	(18.98)	(-1.71, 6.15)
	20	67	-1	(9.91)	66	-2.56	(11.21)	65	1.3	(15.77)	(-1.96, 4.57)
	30	67	-1.18	(11.59)	66	-1.88	(11.26)	65	0.45	(17.71)	(-3.22, 4.12)
	60	66	-2.13	(10.99)	66	0	(11.60)	64	-2.5	(16.51)	(-5.95, 0.94)
	90	64	-1.29	(11.04)	66	-1.16	(11.73)	62	-0.59	(16.89)	(-4.18, 2.99)
	120	64	-0.05	(10.64)	64	-1.11	(11.52)	61	1.23	(16.63)	(-2.32, 4.79)
	180	65	-1.25	(10.12)	64	-0.76	(11.61)	62	0.6	(15.96)	(-2.79, 3.98)
	240	65	-2.71	(11.31)	65	1.82	(10.00)	63	-4.12	(14.80)	(-7.23, -1.01)
AQUAVAN 18 mg	1	67	0.09	(13.16)	65	-2.02	(12.65)	65	2.25	(19.16)	(-1.72, 6.21)
	4	67	2.92	(12.72)	65	-0.85	(11.01)	65	3.97	(18.31)	(0.18, 7.76)
	8	66	5.61	(13.58)	64	-0.08	(11.75)	63	5.74	(19.52)	(1.63, 9.85)
	12	66	6.09	(10.90)	65	-2.14	(13.08)	64	8.32	(18.28)	(4.51, 12.13)
	20	66	6.08	(10.91)	65	-2.36	(11.18)	64	8.66	(14.16)	(5.71, 11.62)
	30	66	3.04	(11.90)	65	-1.78	(11.32)	64	4.88	(16.82)	(1.37, 8.39)
	60	68	-1.13	(13.04)	66	0	(11.60)	66	-1.42	(16.65)	(-4.84, 2.00)
	90	67	1.57	(11.85)	66	-1.16	(11.73)	65	2.52	(15.52)	(-0.69, 5.73)
	120	68	-0.64	(12.54)	65	-0.71	(11.88)	65	-0.13	(18.20)	(-3.89, 3.64)
	180	68	0.28	(12.54)	65	-0.87	(11.55)	65	1.3	(18.05)	(-2.44, 5.03)
	240	66	3.03	(9.32)	64	2.18	(10.31)	64	0.85	(12.56)	(-1.77, 3.47)

Table 4 summarizes the results of the baseline corrected mean difference of moxifloxacin and placebo, as well as the 2-sided 90% CI. Without multiple time point adjustment, the largest lower bound is 6.33 ms at 180 minute. After adjusted for 11 post-baseline time points, the largest lower bound is 5.70 ms at the same time.

Table 4: Time-Matched, Placebo-Adjusted, Mean Change from Baseline QTcF

Time (Minute)	Moxifloxacin			Placebo			Diff		90% CI	Adjusted 90% CI*
	N	Mean	(SD)	N	Mean	(SD)	N	(M - P)		
1	67	-9.6	(14.09)	66	-2.26	(12.71)	65	-7.09	(-13.4, -0.78)	(-14.1, -0.09)
4	67	-1	(11.18)	66	-0.97	(10.97)	65	-0.03	(-4.39, 4.32)	(-4.86, 4.80)
8	67	-0.98	(11.65)	65	-0.35	(11.86)	65	-0.37	(-5.64, 4.89)	(-6.22, 5.47)
12	66	-3	(9.96)	66	-2.06	(12.99)	64	-0.53	(-4.93, 3.87)	(-5.41, 4.36)
20	66	-0.79	(10.36)	66	-2.56	(11.21)	64	2.45	(-2.44, 7.35)	(-2.98, 7.88)
30	66	-0.64	(13.06)	66	-1.88	(11.26)	64	2.11	(-3.74, 7.96)	(-4.38, 8.60)
60	65	5.72	(12.29)	66	0	(11.60)	63	6.07	(0.47, 11.66)	(-0.14, 12.28)
90	66	8.49	(10.55)	66	-1.16	(11.73)	64	10.05	(4.40, 15.70)	(3.78, 16.32)
120	66	7.89	(11.32)	65	-0.71	(11.88)	63	9.23	(3.47, 15.00)	(2.84, 15.63)
180	66	11.75	(12.81)	65	-0.87	(11.55)	63	12.16	(6.33, 17.98)	(5.70, 18.62)
240	66	10.23	(9.68)	66	2.09	(10.17)	64	8.26	(4.10, 12.42)	(3.65, 12.87)

*CIs are adjusted with 11 post-baseline time points

Diff (M - P): Moxifloxacin-Placebo

Table 5 summarized the categorical analysis for QTcF using all ECG data. No subject had QTcF > 480 ms, QTcF > 500 ms, Δ QTcF > 60 ms. For the group of QTcF > 450 ms, 8 subjects (12%) in placebo, 12 subjects (17%) in moxifloxacin, 8 subjects (12%) in the 6 mg/kg AQUAVAN, and 7 subjects (10%) in the 18 mg/kg AQUAVAN. For the group of $30 \text{ ms} \leq \Delta$ QTcF < 60 ms, 6 subjects (9%) in placebo, 13 subjects (19%) in moxifloxacin, 9 subjects (13%) in the 6 mg/kg AQUAVAN, and 15 subjects (22%) in the 18 mg/kg AQUAVAN.

Table 5. Categorical Analysis

Category	Treatment	Subject		
		# of Subj	of Subj	% of Subj
QTcF > 450 ms	Placebo	8	69	11.59%
	Moxifloxacin	12	69	17.39%
	AQUAVAN 6 mg	8	69	11.59%
	AQUAVAN 18 m	7	68	10.29%
$30 \leq \Delta$ QTcF < 60 ms	Placebo	6	67	8.96%
	Moxifloxacin	13	69	18.84%
	AQUAVAN 6 mg	9	68	13.23%
	AQUAVAN 18 m	15	68	22.06%

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

5.2.1 Evaluation of HR Correction Method

The sponsor's exposure-response analysis indicated that individual correction method for deriving QTcI was not optimal. The reviewer analyzed the data using QTcF and QTcI to understand the differences in the two correction methods.

Figure 5 shows the relationship between QTcF, QTcB and QTcI at baseline versus RR. Based on visual inspection of the trends in QTcF vs RR and QTcI vs RR, it appears that

QTcF is a better correction method than QTcI. Figure 6 shows that increase in heart rate are observed initially after dosing in Aquavan 6 mg/kg and 18 mg/kg dose groups. The reason for the increase in heart rate is not known. Figure 7 shows that the ranges of RR and QT data are different during pre-dose (Day-1) and on the days of treatment (Day 1). This could influence the estimation of individual correction factor.

Figure 5: Relationship between QT, corrected QT interval (QTcF, QTcI, QTcB) versus RR

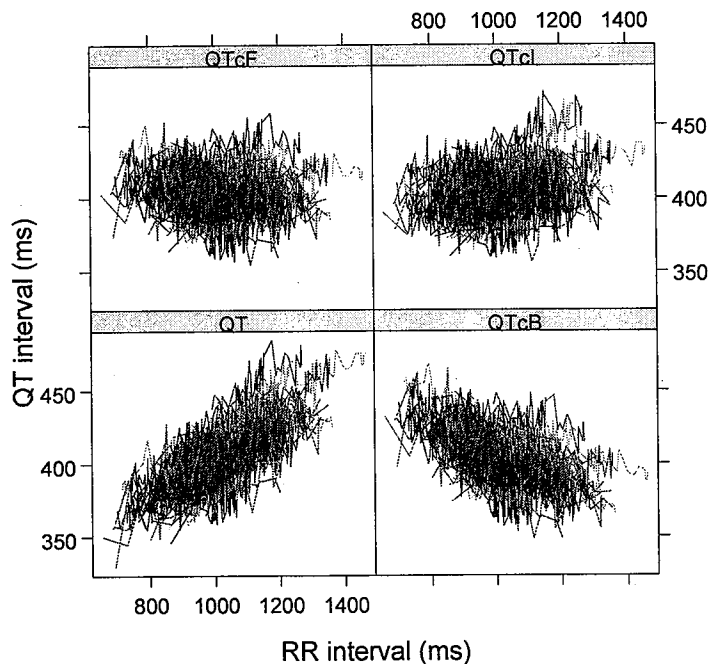


Figure 6: Time Course of Mean Change from Baseline in HR by Treatment Group

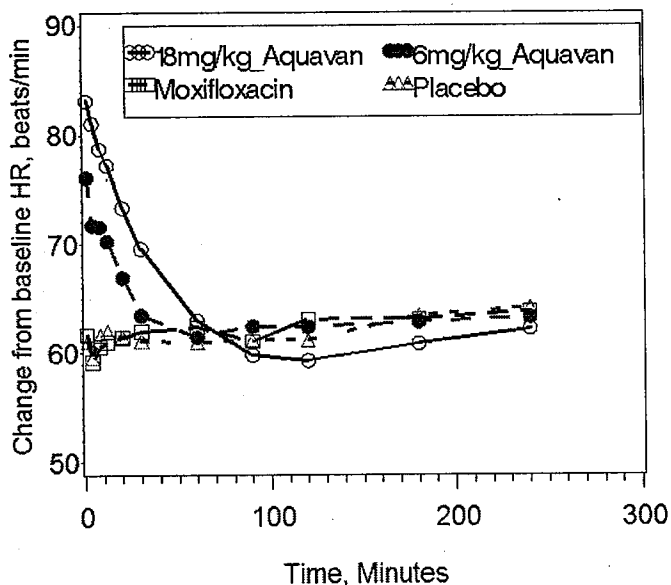
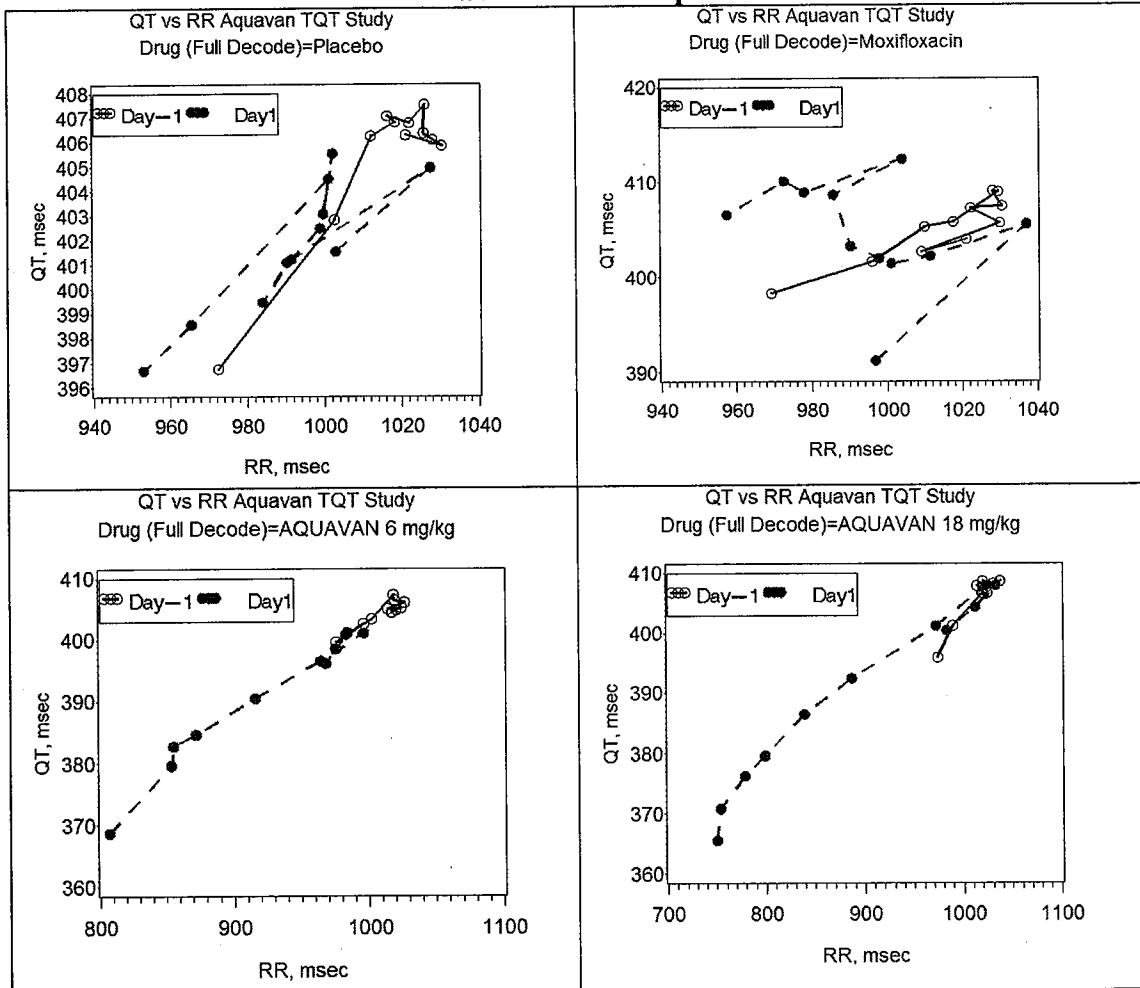


Figure 7: Relationship Between HR and RR on Day -1 (baseline) and Day 1 by Treatment Group



5.2.2 Exposure-Response Analysis

Figure 8 shows the mean and 90%CI for the corrected QT interval (QTcF or QTcI) at each time point (0-4 h) for AQUAVAN 6 mg/kg, AQUAVAN 18 mg/kg and moxifloxacin groups. Clear differences can be seen in mean changes and the 90% CI due to correction methods. There is a dose-dependent increase in $\Delta\Delta\text{QTcF}$ following the administration of AQUAVAN.

Figure 8: Relationship between change from $\Delta\Delta\text{QTcF}$ and QTcI versus time for AQUAVAN 6 mg/kg, AQUAVAN 18 mg/kg and Moxifloxacin.

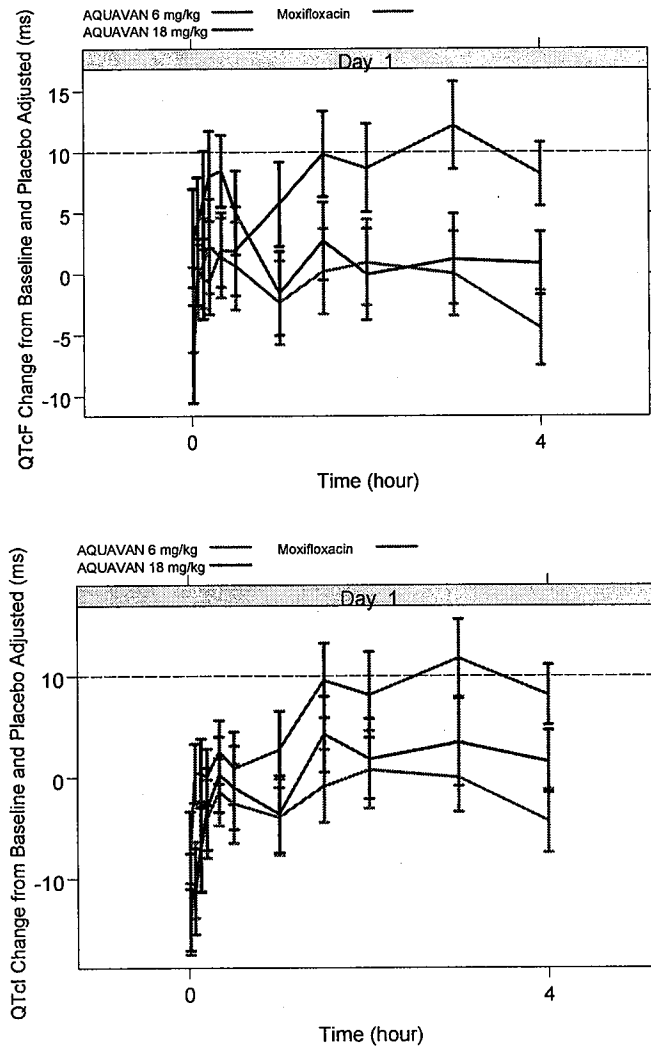
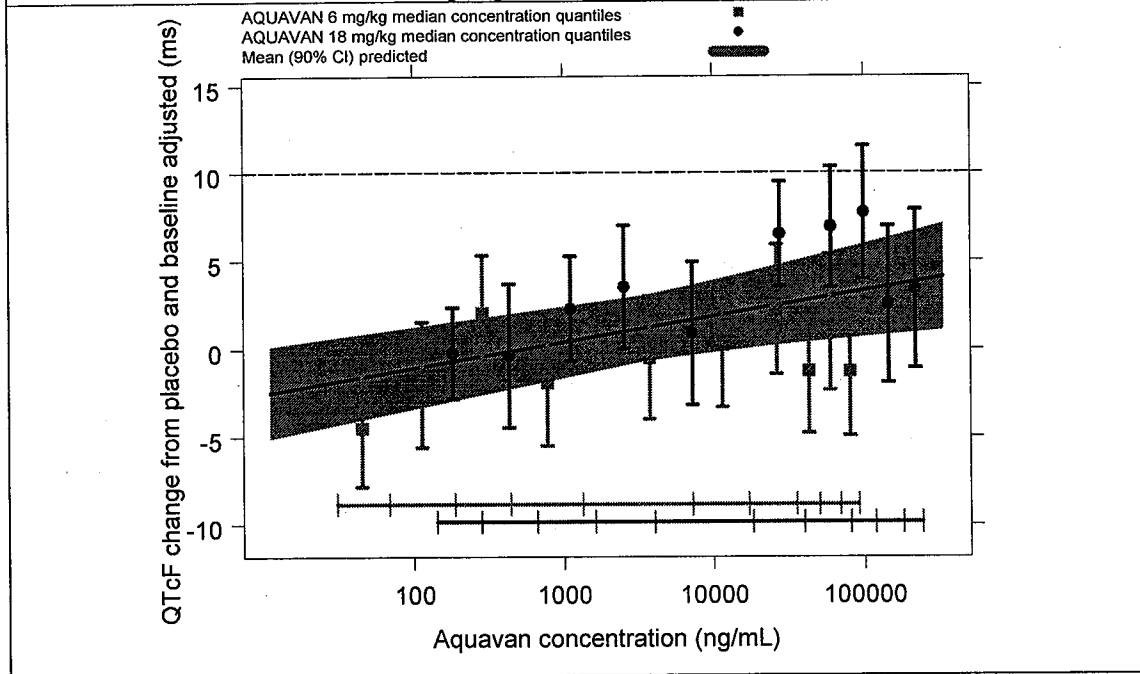


Figure 9 shows the relationship between logarithm plasma concentrations of fospropofol and $\Delta\Delta\text{QTcF}$. There is a general trend for the QTcF to increase with increasing concentrations of fospropofol. There is, however, model misspecification because the observed values fall outside of the 90% confidence interval for the predictions.

Figure 9: Relationship between logarithm plasma concentrations of fospropofol and $\Delta\Delta\text{QTcF}$



5.3 CLINICAL ASSESSMENTS

None of the clinical events identified as of particular importance in ICH E14 (i.e. death, serious ventricular arrhythmia, syncope and seizure) were observed in this study.

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6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Include maximum proposed clinical dosing regimen. 6.5 mg/kg with supplemental doses of 1.6 mg/kg, as needed.	
Maximum tolerated dose	Include if studied or NOAEL dose A single dose of 30 mg/kg (this was the maximum dose tested).	
Principal adverse events	Include most common adverse events; dose limiting adverse events Transient paresthesia and pruritus are the most common adverse reactions to AQUAVAN. Toxicities are not dose-limiting for AQUAVAN, however, as with any sedative-hypnotic agent, depressed levels of consciousness associated with hypoxemia, hypotension and loss of purposeful movement and/or spontaneous respiration may occur.	
Maximum dose tested	Single Dose	Specify dose 30 mg/kg
	Multiple Dose	Specify dosing interval and duration 8 mg/kg followed by 2 mg/kg for three additional doses given every four minutes.
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C _{max} and AUC Exposure data from 30 mg/kg is not available. Exposure data from 18 mg/kg is as follows: Mean (%CV) Fospropofol C _{max} (mcg/mL) = 211 (23.0%) AUC (mcg.h/mL) = 50.3 (16.7%) Propofol C _{max} (mcg/mL) = 3.90 (21.1%) AUC (mcg.h/mL) = 5.67 (22.6%)
	Multiple Dose	Mean (%CV) C _{max} and AUC Not Determined.

<p>Range of linear PK</p>	<p>Specify dosing regimen</p> <p>Linear PK was observed at doses from 6 mg/kg to 18 mg/kg administered as a single IV bolus dose. Population PK analysis demonstrated linear PK for both the proposed standard and modified dosing regimen as detailed below.</p> <p>Dosing regimen:</p> <ul style="list-style-type: none"> • The standard dosing regimen for AQUAVAN is an initial IV bolus dose of 6.5 mg/kg followed by supplemental dosages of 1.6 mg/kg IV (25 % of the initial dose) as needed. • A modified dosing regimen for AQUAVAN is an initial IV bolus dose at 75% of the standard regimen. A modified dosing regimen is recommended for patients who are ≥65 years of age or who have severe systemic disease (ASA P3 or P4). • The dosage of AQUAVAN is limited by lower and upper weight bounds of 60 kg and 90 kg, respectively. Adults who weigh >90 kg should be dosed as if they are 90 kg; adults who weigh <60 kg should be dosed as if they are 60 kg. • Supplemental doses of AQUAVAN should be administered only when patients can demonstrate purposeful movement in response to verbal or light tactile stimulation and no more frequently than every four minutes. 	
<p>Accumulation at steady state</p>	<p>Mean (%CV); specify dosing regimen</p> <p>At the proposed dosing regimen of 6.5 mg/kg IV bolus followed by three supplemental 1.6 mg/kg IV doses, no accumulation of fospropofol occurs. The accumulation of propofol based on the C_{max} is 1.5-fold.</p>	
<p>Metabolites</p>	<p>Include listing of all metabolites and activity</p> <p>Propofol, formaldehyde, and phosphate. Propofol is the principal active moiety.</p>	
<p>Absorption</p>	<p>Absolute/Relative Bioavailability</p>	<p>Mean (%CV)</p> <p>Not applicable as dosed by IV route.</p>
	<p>T_{max}</p>	<ul style="list-style-type: none"> • Median (range) for parent 4 (1-8) minutes • Median (range) for metabolite (propofol) 12 (4-60) minutes

Distribution	Vd/F or Vd	Mean (%CV) Fospropofol: 0.327 (21.0) L/kg Propofol: 5.76 (37.1%) L/kg
	% bound	Range: Fospropofol: 97- 98% Propofol: 98.1 – 98.4%
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated <p>Metabolism is the primary route of elimination for both fospropofol and propofol with 71% of dose recovered in urine.</p> <ul style="list-style-type: none"> • Other routes <p>Not applicable.</p>
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent 0.81 (9.9%) h • Mean (%CV) for metabolite (propofol) 2.06 (37.4%) h
	CL/F or CL	<p>Mean (%CV) for parent 0.280 (18.9%) L/h/kg</p> <p>Mean (%CV) for metabolite (propofol) 1.95 (17.7%) L/h/kg</p>
Intrinsic Factors	Age	<p>Specify: mean changes in C_{max} and AUC</p> <p>Patients ≥65 yrs old received a 25% reduction in fospropofol dose (4.88 mg/kg). This resulted in a mean AUC that was 29% lower for both fospropofol and propofol relative to patients <65 yrs old who received a full dose (6.5 mg/kg dose).</p> <p>Clearance and volume of distribution of both fospropofol and propofol were not altered due to age.</p>

Extrinsic Factors	Drug interactions	<p>Include listing of studied DDI studies with mean changes in Cmax and AUC</p> <p>Patients received AQUAVAN alone or together with one of the drugs listed below. Fospropofol parameters (% change relative to receiving AQUAVAN alone) were as follows:</p> <table border="1"> <thead> <tr> <th></th> <th>% change in Cmax</th> <th>% change in AUC</th> </tr> </thead> <tbody> <tr> <td>Fentanyl pretreatment</td> <td>1.4 %</td> <td>23.3 %</td> </tr> <tr> <td>Meperidine pretreatment</td> <td>-1.3 %</td> <td>5.2 %</td> </tr> <tr> <td>Midazolam pretreatment</td> <td>-14.3 %</td> <td>-10.9 %</td> </tr> <tr> <td>Morphine pretreatment</td> <td>-3.3 %</td> <td>26.1 %</td> </tr> </tbody> </table>		% change in Cmax	% change in AUC	Fentanyl pretreatment	1.4 %	23.3 %	Meperidine pretreatment	-1.3 %	5.2 %	Midazolam pretreatment	-14.3 %	-10.9 %	Morphine pretreatment	-3.3 %	26.1 %
		% change in Cmax	% change in AUC														
Fentanyl pretreatment	1.4 %	23.3 %															
Meperidine pretreatment	-1.3 %	5.2 %															
Midazolam pretreatment	-14.3 %	-10.9 %															
Morphine pretreatment	-3.3 %	26.1 %															
Food Effects	<p>Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)</p> <p>Not applicable for IV route of administration.</p>																
Expected High Clinical Exposure Scenario	<p>Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</p> <p>In the worst case scenario of a small adult (40 kg) accidentally receiving a supra-therapeutic dose from administration of a full vial (1050 mg fospropofol equivalent to 26.25 mg/kg) in a single IV bolus, the patient might experience sedation related adverse events such as hypotension, hypoxemia, loss of purposeful movement and/or spontaneous respiratory effort.</p> <p>For a 40 kg person with 1050 mg dose (26.25 mg/kg): Fospropofol AUC=59.2 mcg.h/mL Propofol AUC=3.61 mcg.h/mL</p> <p>These exposures have been seen after supra-therapeutic doses.</p>																

6.2 TABLE OF STUDY ASSESSMENTS

	Screening	Completed for each of the 4 Treatment Periods			Follow-up Visit
		Baseline Period	Treatment Period	Washout Period	
Timing	-21 to -2 days before first drug administration	Day before each drug administration	Day of each drug administration	≥3 and ≤7 days between each Treatment Period	3 to 7 days after last drug administration
Obtain informed consent/HIPAA authorization	X				
Drugs of abuse and serology status defined	X				
Serum/urine pregnancy test	X	X			
Prior/concomitant medication assessment	X	X	X		X
Medical history	X	X			
Physical examination	X	X			X
Safety digital ECGs*	X		X		X
Routine vital signs†	X	X	X		X
Saturation of hemoglobin with oxygen in peripheral blood		X	X		
Efficacy measurements‡			X		
Oral temperature measured	X	X	X		X
Weight	X				X
Digital 12-lead ECG capture		X	X		
Clinical laboratory tests	X	X			X
Randomization		X			
Pharmacokinetic blood samples (AQUAVAN only)§			X		
Adverse event assessment		X	X		X

* Two safety ECGs were completed during the Treatment Period (30 minutes before and 1 hour after dosing).

† Blood pressure and heart rate were collected at Screening, at Baseline (Day -2), within 30 minutes before dosing, at 15, 10, 6, 4, and 2 minutes before dosing, every 2 minutes after dosing for ≥30 minutes and until subjects are deemed Fully Alert, then every 15 minutes until 4 hours after dosing. Respiratory rate was collected at Screening, at Baseline (Day -2), within 30 minutes before dosing, every 2 minutes after dosing for ≥20 minutes and until subjects were deemed Fully Alert, every 15 minutes until 4 hours after dosing, and at the Follow-up Visit.

‡ Measurements included Modified Observer's Assessment of Alertness/Sedation and Bispectral Index.

§ Blood samples for plasma pharmacokinetic analysis of fospropofol and propofol and for exploratory analysis of their correlation with QT/QTc were collected during both AQUAVAN Treatment Periods at 1, 4, 8, 12, 20, 30, 60, and 90 minutes and 2, 3, and 4 hours after dosing.

HIPAA=Health Insurance Portability and Accountability Act, ECG=electrocardiogram

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