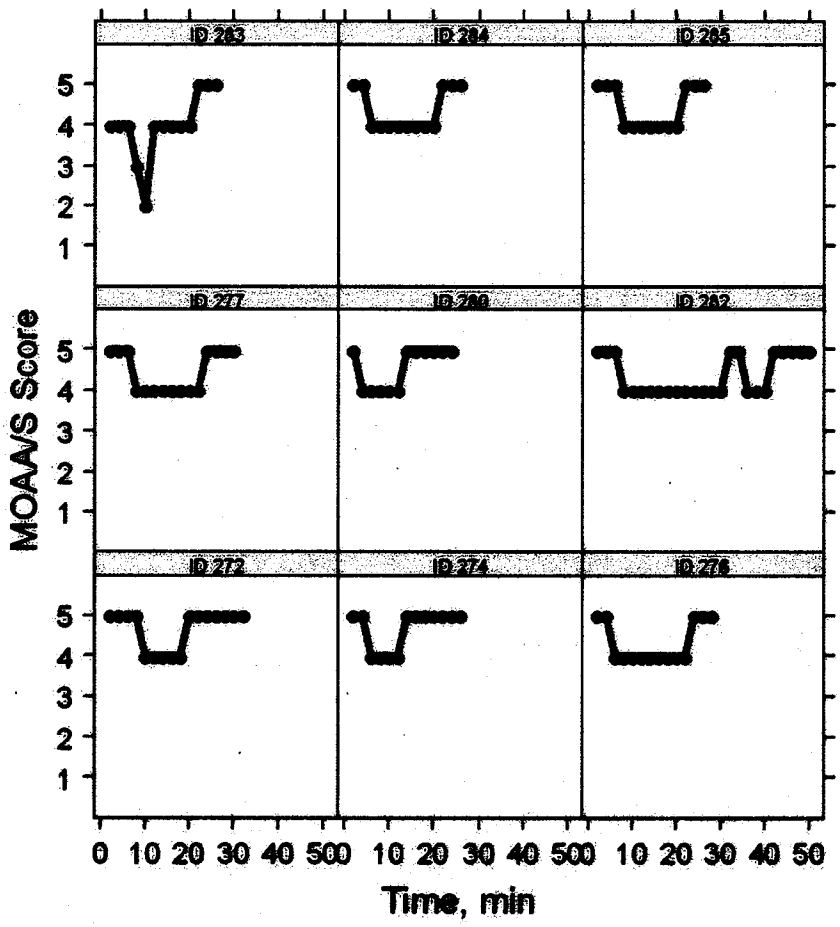
PK-PD of Fospropofol-Propofol

Figure 17 shows the time course of MOAA/S scores in Study 3000-0522 in 9 representative patients.

Figure 17. Time course of MOAA/S scores in 9 representative patients in Study 3000-0522 (The MOAA/S scores have 5 levels: 0, 1, 2, 3, 4, 5).



The time course of the proportion of patients with various MOAA/S scores is shown in Figure 18 below.

Figure 18. Time course of proportion of patients with MOAA/S scores of 0, 2, 3, 4 or 5 in Study 3000-0522.

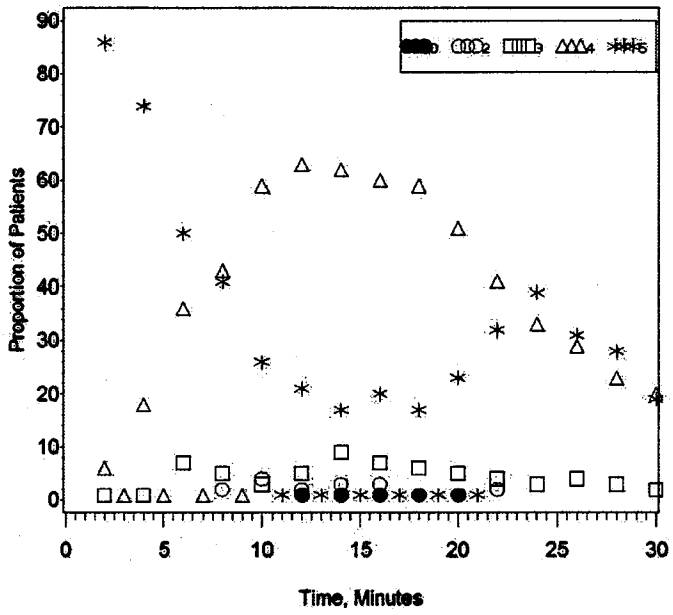


Figure 19 shows the goodness of fit for the fospropofol-propofol-MOAA/S PK/PD model. The model fits the data adequately. The estimates of the parameters are shown in Table 6 below.

Table 6. Estimated PK/PD parameters using Model 403 (Source: Table 27, on Page 90 from Sponsor's Report (pr-aqua-02-02.pdf).

Parameter	NONMEM notation	Population Estimate	Relative SE (%)	95% CI	Comment
K_{E0}(1/min)	θ_1	0.127	6.46	0.111 - 0.143	$t_{1/2,KE0}$=5.5 (4.8 – 6.2) min
E_{MAX}	θ_2	81.2	10.4	64.7 - 97.7	
B_1	θ_3	-50	6.67	-56.5 - -43.4	
$B_2 - B_1$	θ_4	3.33	20.9	1.97 - 4.7	
$B_3 - B_2$	θ_5	3.5	10.4	2.78 - 4.21	
$B_4 - B_3$	θ_6	8.6	3.29	8.05 - 9.15	
EC_{50} (mcg/mL)	θ_7	50.6	24.8	29.1 - 84	
ω^2_{KE0}	$\Omega(1,1)$	0.263	23.2	0.143 - 0.382	CV=51.3%
ω^2_{EMAX}	$\Omega(2,2)$	0.232	24.3	0.121 - 0.342	CV=48.1%
$R_{EMAX,B1}$ ω_{EMAX} ω_{B1}	$\Omega(2,3)$	0.191	24.7	0.0987 - 0.283	$R_{EMAX,B1}$=0.953
ω^2_{B1}	$\Omega(3,3)$	0.173	24.2	0.0911 - 0.256	CV=41.6%

Figure 19. Goodness of Fit for Fospropofol-Propofol-MOAA/S PK/PD model. The observed data are shown in symbols (black dot). The expected scores (based on model) are shown in red lines while the likely maximum score (based on the model) is shown in green line.

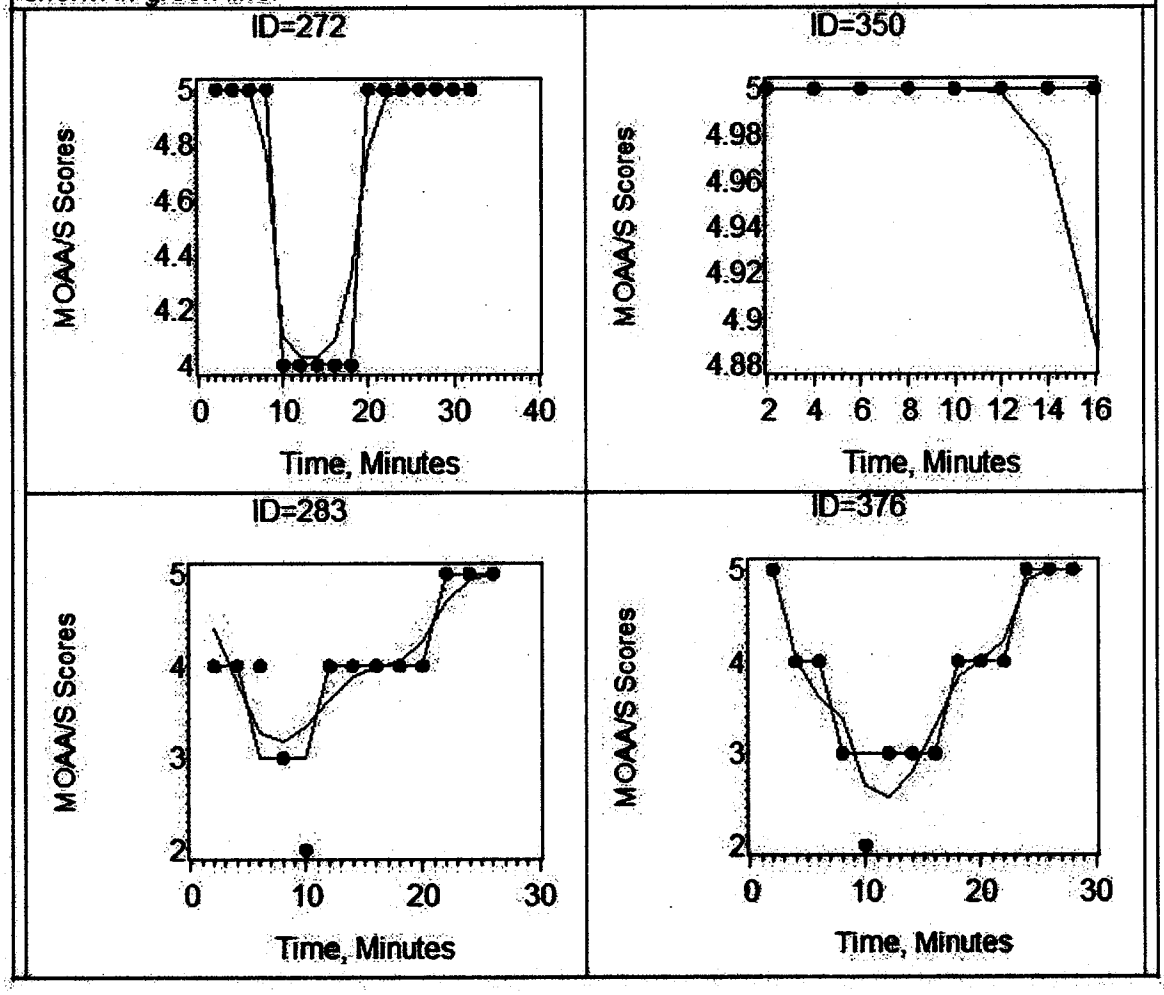
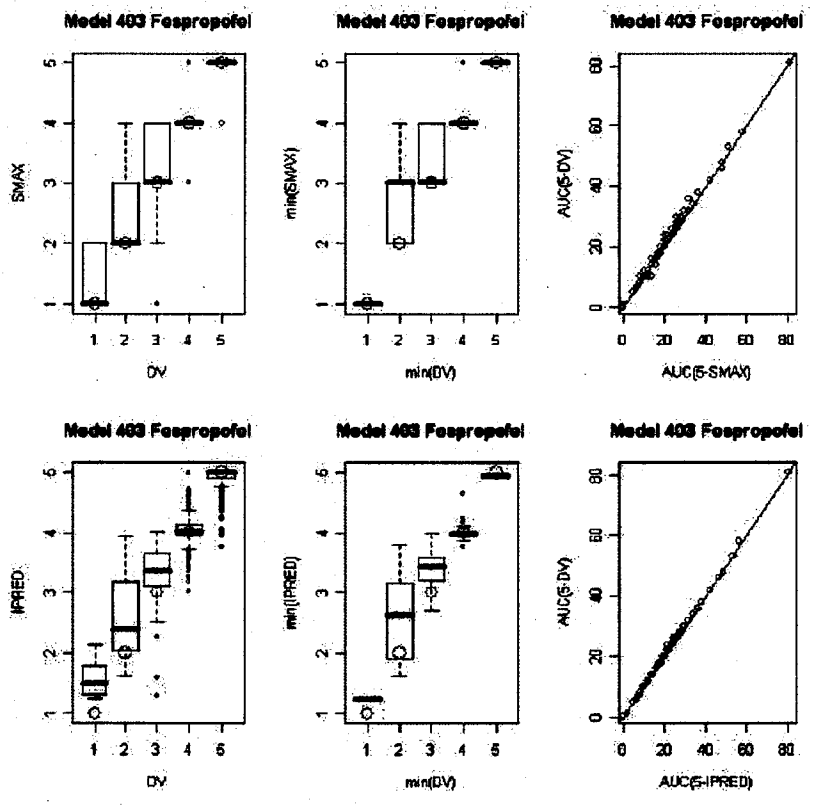


Figure 20 below shows the diagnostic plots of Fospropofol-Propofol-MOAA/S model. The model describes the data adequately.

Figure 20. Diagnostic Plots of Fospropofol-Sedation Model 403.
First Column: Individual Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores with maximum predicted probability (SMAX, upper plot) and expected individual MOAA/S scores (IPRED, lower plot) are plotted versus observed MOAA/S scores using box and whisker plots. Second Column: Minimum (within each patient) individual MOAA/S scores with maximum predicted probability (SMAX, upper plot) and minimum expected individual MOAA/S scores (IPRED, lower plot) are plotted versus observed minimums of MOAA/S scores using box and whisker plots. Median values of expected scores are designated by black lines in the centers of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles. Large circles corresponding to the identity line are provided for the reference. Third Column: Individual AUCs of the observed effect (AUC5-MOAA/S are plotted versus AUCs of the effect with maximum probability (AUC5-SMAX, upper plot) and AUCs of the expected effect (AUC5-IPRED, lower plot). A unit line is provided for the reference.



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PK/PD of Fospropofol

The model as described in the section 'PK/PD of Fospropofol-Propofol' was used to fit the relationship between fospropofol and MOAA/S scores obtained from studies 3000-0207, 3000-0415, 3000-0520, 3000-0522, 3000-0523, and 3000-0524. The model developed in the previous section indicated that the link between fospropofol concentrations and MOAA/S scores was better statistically when compared to the link between propofol and MOAA/S scores.

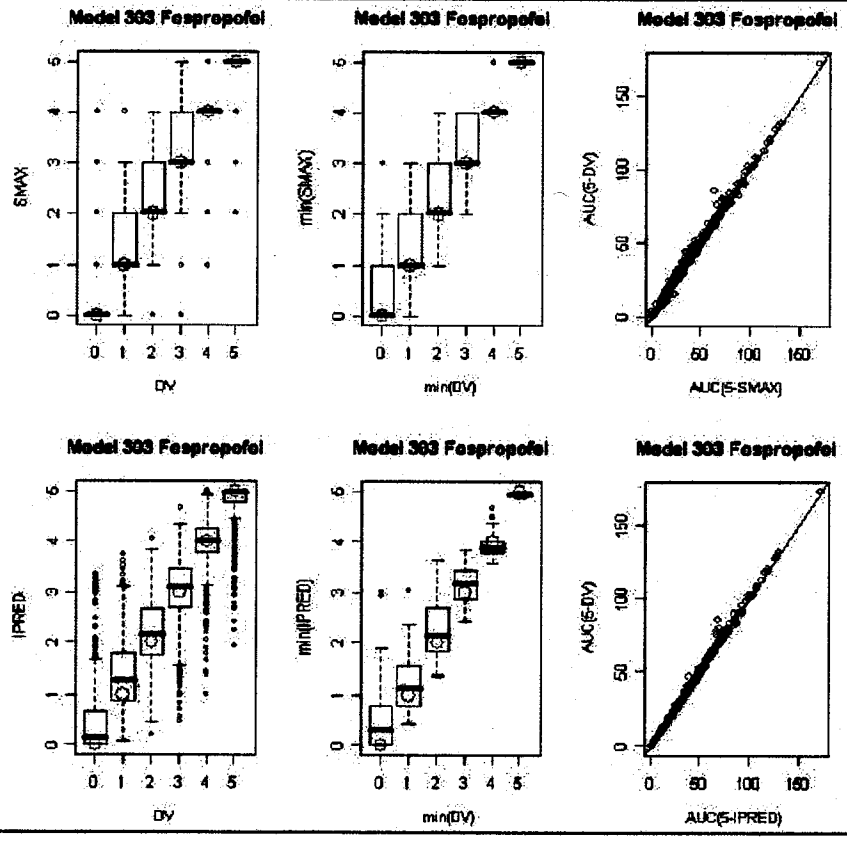
The parameter estimates are shown in Table 7 below.

Table 7. Summary of PK/PD parameters using Model 303. (Source: Table 30, on Page 93 from Sponsor's Report (pr-aqua-02-02.pdf).

Parameter	NONMEM notation	Population Estimate	Comment
K_{E0} (1/min)	θ_1	0.164	$t_{1/2,KE0}$=4.2 min
E_{MAX}	θ_2	56.2	
B_0	θ_3	-31.5	
B_1-B_0	θ_4	2.2	
B_2-B_1	θ_5	2.12	
B_3-B_2	θ_6	2.25	
B_4-B_3	θ_7	4.48	
EC_{50} (mcg/mL)	θ_8	71.7	
ω^2_{KE0}	$\Omega(1,1)$	0.268	CV=51.7%
ω^2_{EMAX}	$\Omega(2,2)$	0.227	CV=47.6%
$R_{EMAX,B0}\omega_{EMAX}\omega_{B0}$	$\Omega(2,3)$	0.163	$R_{EMAX,B0}$=0.901
ω^2_{B0}	$\Omega(3,3)$	0.145	CV=38.0%

The diagnostic plots are shown in Figure 21. The model describes the data adequately.

Figure 21. Diagnostic Plots of Fospropofol-Sedation Model 303. First Column: Individual Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores with maximum predicted probability (SMAX, upper plot) and expected individual MOAA/S scores (IPRED, lower plot) are plotted versus observed MOAA/S scores using box and whisker plots. Second Column: Minimum (within each patient) individual MOAA/S scores with maximum predicted probability (SMAX, upper plot) and minimum expected individual MOAA/S scores (IPRED, lower plot) are plotted versus observed minimums of MOAA/S scores using box and whisker plots. Median values of expected scores are designated by black lines in the centers of the boxes. Boxes indicate the inter-quartile range (IQR). Whiskers represent 1.5*IQR. Outliers are marked outside of the whiskers by circles. Large open circles corresponding to the identity line are provided for the reference.
Third Column: Individual AUCs of the observed effect (AUC5-MOAA/S are plotted versus AUCs of the effect with maximum probability (AUC5-SMAX, upper plot) and AUCs of the expected effect (AUC5-IPRED, lower plot). A unit line is provided for the reference.



Fospropofol-Sedation Population PK-PD Analysis of Colonoscopy and Bronchoscopy Studies Combined

The data included 8051 MOAA/S values from 471 patients who took part in the colonoscopy studies (3000-0207, 3000-0415, 3000-0520, and 3000-0522), bronchoscopy Study 3000-0524 and received a therapeutic (5 mg/kg and higher) dose of fospropofol injection.

Due to difficulties in modeling the data using approach for colonoscopy studies alone, the sponsor chose a different model. In the new model, the scores were assumed to be continuous and not ordered. The estimates of the final model (Model 356) are shown in Table 8 below.

Table 8. Summary of PK/PD parameters using Model 356. (Source: Table 37, on Page 100 from Sponsor's Report (pr-aqua-02-02.pdf).

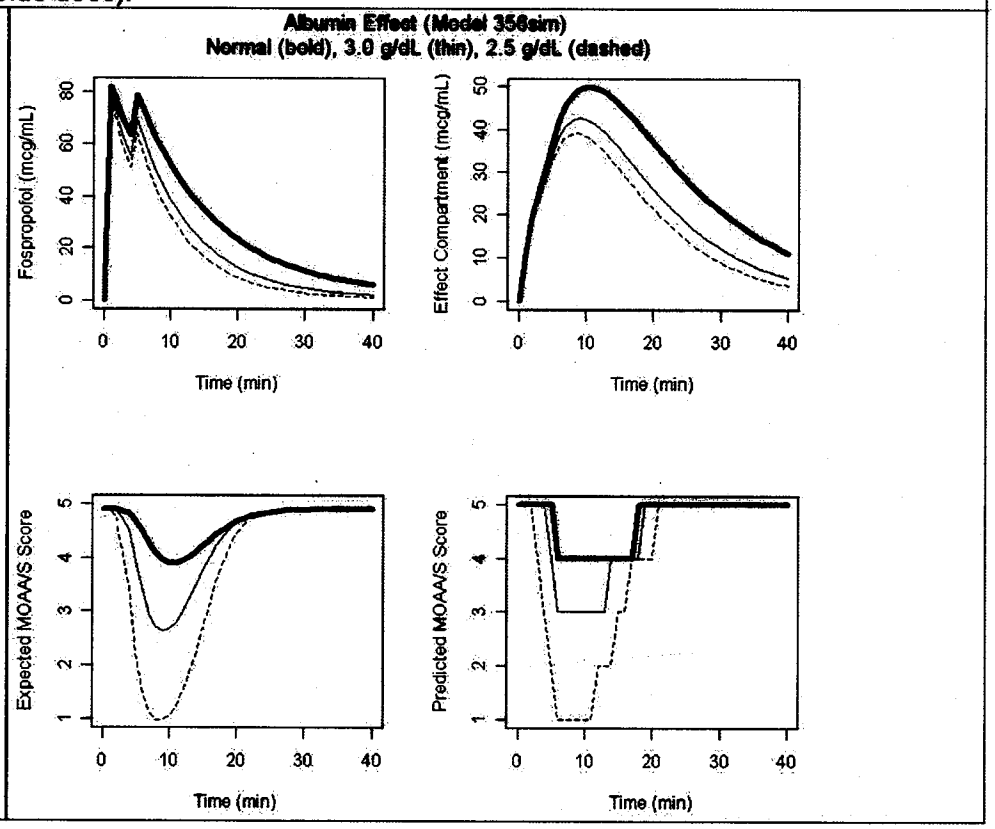
Parameter	NONMEM notation	Population Estimate	RSE (%)	95% CI	Comment
K_{E0} (1/min)	θ_1	0.133	3.13	0.125 - 0.142	$t_{1/2,KE0}$ = 5.2 (4.9 – 5.5) min
EFF_0	θ_2	0.602	3.86	0.557 - 0.648	
EC_{50} (mcg/mL)	θ_3	64.6	2.09	62 - 67.3	
γ	θ_4	5.65	5.36	5.06 - 6.25	
$EC_{50,AGE65}$	θ_5	0.813	3.19	0.762 - 0.864	
$EC_{50,Smoth}$	θ_6	0.898	4.51	0.819 - 0.978	
$EC_{50,ASAP3}$	θ_7	0.892	4.89	0.806 - 0.977	
$EC_{50,ASAP4}$	θ_8	0.828	9.9	0.667 - 0.989	
$EC_{50,CL}$	θ_9	-0.775	6.69	-0.977 - -0.573	
$EC_{50,ALB}$	θ_{10}	-0.438	29.9	-0.694 - -0.181	
$EC_{50,ALB=3.0}$	$3.0/3.8+\theta_{10}(1-3.0/3.8)$	0.697		0.643 - 0.751	
$EC_{50,ALB=2.5}$	$2.5/3.8+\theta_{10}(1-2.5/3.8)$	0.508		0.420 - 0.596	
ω^2_{KE0}	$\Omega(1,1)$	0.26	9.34	0.212 - 0.307	CV=50.9%
ω^2_{EFF0}	$\Omega(2,2)$	0.171	15.2	0.12 - 0.222	CV=41.4%
ω^2_{EC50}	$\Omega(2,3)$	0.0805	10.8	0.0634 - 0.0976	CV=28.4%
σ^2	$\Sigma(1,1)$	0.313	6.99	0.271 - 0.356	SD=0.56

Note the dependence of EC_{50} on random effect on albumin concentration and fospropofol clearance. The origin of these dependencies is not clear. The estimated the EC50 for patients ≥65 years of age to be 19% (95% CI: 14 – 24%). Direct (not model-based) comparison of the sedation results of the 6.5 mg/kg arm of study 3000-0522 confirmed the chosen dosing regimen: older patients who received a 25% reduced dose required the same number of supplemental doses and achieved, on average, the same sedation level as younger patients who received the full dose. No evidence of the gender effects on the PK-PD model parameters was found.

The PK-PD model predicted that the EC50 values for fospropofol decrease with decreasing plasma albumin concentrations. The estimated EC50 values for patients with albumin concentrations of 2.5 g/dL and 3.0 g/dL were 49% (95% CI 40-58%) and 30% (95% CI 25 - 36%) lower than for patients with albumin levels of 3.8 g/dL.

The prediction of the effect of albumin concentrations on the MOAA/S scores is shown in Figure 22 below.

Figure 22. Fospropofol concentration (**upper left**), effect compartment concentration (**upper right**), expected Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score (**ESC, lower left**) and rounded expected MOAA/S score (**ESC, lower right**) are plotted versus time (min), The bold solid lines illustrate model predictions for a typical patient with normal (> 3.8 g/dL) albumin level administered 6.5 mg/kg dose followed one supplemental dose (25% of the initial bolus dose). The solid lines illustrate model predictions for a typical patient with 3.0 g/dL albumin concentration administered 6.5 mg/kg dose followed one supplemental dose (25% of the initial bolus dose). The dashed lines illustrate model predictions for a typical patient with 2.5 g/dL albumin concentration administered 6.5 mg/kg dose followed one supplemental dose (25% of the initial bolus dose).



Although the PK-PD Model predicts that patients with low plasma albumin may reach MOAA/S scores of less than 2 if administered the full 6.5 mg/kg dose (PR-AQUA-02-02, Figure 107), data from the 3000-0522 and 3000-0524 studies indicate that sedation depth (as measured by the MOAA/S Scale) was not consistently influenced by albumin levels, even when examining results based on age, ASA status, and weight as shown in Figure 23.

Figure 23. Influence of albumin levels on EC50 for Studies 3000-0522 and 3000-0524 (data are mean and SD) using model 356, PR-AQUA-02-02).

AGE (years)	ASA	ALB (g/dL)	N	N doses	TDOS (mg)	MDOS (mg)	Mean MOAA/S	Minimum MOAA/S	EC_{50} (mcg/mL)	ALB (g/dL)	AGE (years)	WT (kg)
≥65	P1 or P2	Less than 3	4	2.8 (1.7)	570 (230)	400 (79)	4.2 (0.14)	3.2 (0.5)	33 (7.9)	2.8 (0.29)	73 (4.6)	89 (35)
≥65	P1 or P2	3-3.8	13	2.1 (1.1)	470 (170)	350 (81)	4.0 (0.68)	2.8 (1)	38 (11)	3.5 (0.13)	73 (3.3)	73 (15)
≥65	P1 or P2	Greater than 3.8	17	3.1 (1.5)	590 (180)	370 (59)	4.4 (0.36)	3.4 (1.1)	34 (18)	4.1 (0.29)	72 (3.7)	80 (17)
≥65	P3 or P4	Less than 3	4	1.2 (0.5)	300 (35)	280 (8.8)	3.5 (0.8)	2.2 (0.96)	22 (3.5)	2.6 (0.32)	72 (6.6)	52 (1.7)
≥65	P3 or P4	3-3.8	13	2.6 (1.4)	490 (130)	360 (74)	4.1 (0.37)	2.9 (1.1)	34 (11)	3.4 (0.17)	71 (3.2)	78 (15)
≥65	P3 or P4	Greater than 3.8	13	2.8 (1.7)	560 (190)	380 (66)	4.1 (0.42)	2.8 (1.3)	44 (13)	4.1 (0.25)	72 (3.6)	81 (20)
<65	P1 or P2	Less than 3	5	3.2 (1.9)	760 (250)	490 (80)	4.0 (0.39)	2.6 (1.1)	33 (18)	2.7 (0.23)	54 (12)	85 (30)
<65	P1 or P2	3-3.8	12	2.4 (1.0)	710 (170)	530 (62)	4.0 (0.6)	2.9 (1.2)	53 (19)	3.5 (0.2)	51 (9.5)	92 (28)
<65	P1 or P2	Greater than 3.8	13	3.3 (1.5)	810 (230)	510 (72)	4.4 (0.41)	3.6 (0.96)	69 (18)	4.2 (0.23)	50 (10)	85 (21)
<65	P3 or P4	Less than 3	8	3.2 (2.1)	620 (210)	410 (85)	3.9 (0.9)	2.4 (1.7)	23 (13)	2.6 (0.35)	53 (14)	75 (25)
<65	P3 or P4	3-3.8	14	2.9 (2.0)	650 (280)	440 (70)	4.0 (0.58)	2.9 (0.77)	41 (12)	3.4 (0.2)	57 (6)	77 (30)
<65	P3 or P4	Greater than 3.8	15	2.9 (2.1)	720 (210)	500 (77)	4.3 (0.54)	3.5 (1.1)	59 (15)	4.1 (0.22)	55 (7.6)	84 (25)

ALB: albumin, TDOS = Total dose (mg); MDOS = maximum dose (mg); MOAA/S = Modified Observer's Assessment of Alertness/Sedation; EC_{50} = concentration that induces 50% of maximum effect; ALB = Albumin; WT = weight
Source: 3000-0522 and 3000-0524, data run using Model 356, as defined in Report PR-AQUA-02-02

Although the sample size is different across various age, ASA groups, the lack a consistent albumin effect on MOAA/S scores would indicate that dose adjustment would not be needed for patients with different albumin levels.

Appendix-III

Body Weight based dosing algorithm

Sponsor evaluated using simulations the proposed dosing regimen vs alternate dosing regimen which does not have any weight boundaries (For example, 6.5 mg/kg in all patients). Four dosing regimens were tested by the sponsor:

1. 5.0 mg/kg with 60– 90 kg weight bounds
2. 6.5 mg/kg with 60 – 90 kg weight bounds
3. 6.0 mg/kg with 60 – 90 kg weight bounds
4. 6.5 mg/kg without weight bounds.

For dosing regimens with weight bounds, patients weighing less than 60 kg were administered the same dose as 60-kg patients, and patients weighing more than 90 kg were administered the same dose as 90-kg patients.

Predicted concentration-time course after the single bolus dose is illustrated in Figure 24. Gray circles show individual predictions for all patients administered therapeutic-level fospropofol injection dose. The bold solid and dashed lines show median and 95% CIs, respectively.

Imposing weight bounds slightly reduces the variability of the fospropofol exposure. Figure 25 compares medians of concentration-time distributions for patients in the lowest (green line), middle (bold line) and the highest (red line) 10% of weight and BMI distributions administered 6.5 mg/kg dose with and without weight bounds. Dosing regimen with weight bounds provides less variable exposure.

Figure 24. Simulations from Model 103: Fospropofol Concentration-Time Course for patients administered single bolus doses.
Points represent individual predictions of concentrations for patients included into the fosporpofol population PK analysis who were administered various single bolus doses. The solid and dashed lines illustrate the median, 2.5th and 97.5th percentiles of the concentration distributions at each time point.

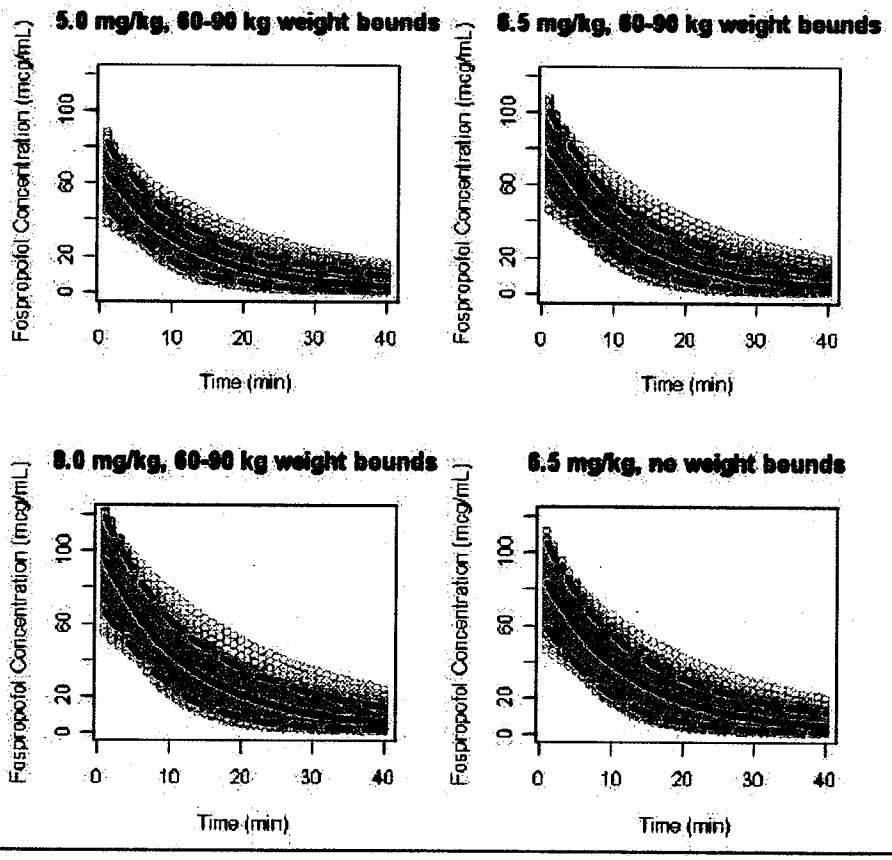
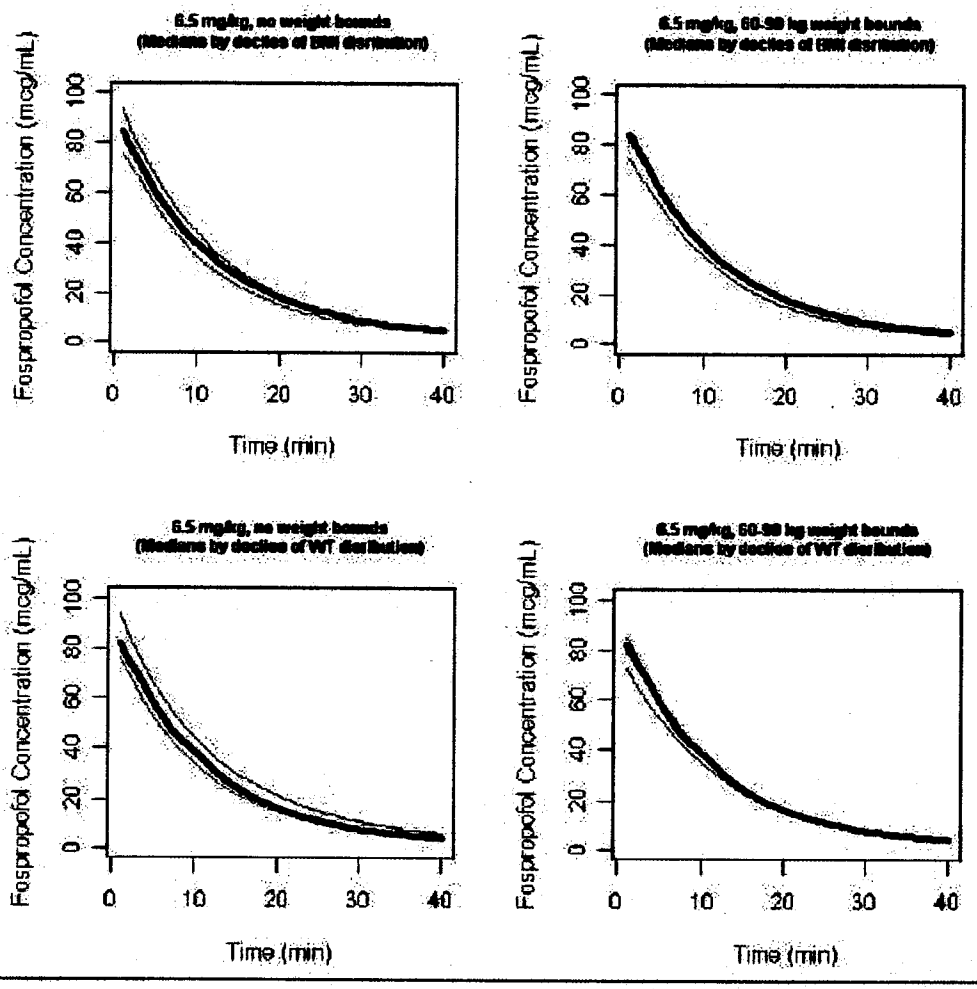


Figure 25. Comparisons of 6.5 mg/kg Dosing Regimens with and without Weight Bounds. The green, bold black and red lines correspond to the medians of the population predictions of fospropofol concentration in the lowest 10%, middle 10% and the highest 10% of BMI distributions (**the upper row**) and weight distribution (**the lower row**) plotted versus time after the dose (min)



4.3 Individual Study Synopses:

4.3.1 Mass Balance Study # 3000-0205 synopsis

b(4)

Title of Study: A Phase I, Open Label, Clinical Pharmacokinetic and Mass Balance Study of [^{14}C] AQUAVAN® Injection in Healthy Subjects
Investigator and Study Center: [redacted]
Publication (reference): None
Study Period: First subject enrolled: 31 July 2002 Last subject completed: 02 October 2002 — **Phase of Development:** I
Objectives: • To determine the pharmacokinetic (PK) profile of the radioactivity of [^{14}C] AQUAVAN® Injection after a single intravenous administration in healthy volunteers. • To determine the routes of elimination and mass balance following an administration of [^{14}C]AQUAVAN® Injection in healthy volunteers. • To assess the safety and tolerability of a single-dose administration of [^{14}C] AQUAVAN® Injection in healthy volunteers.
Methodology: This was an open-label, single-dose, pharmacokinetic, mass balance study of [^{14}C] AQUAVAN® Injection conducted in 8 healthy males. All 8 subjects received a single intravenous (i.v.) infusion of study drug over 10 minutes. Blood, plasma, urine, and feces samples were collected for determination of total radioactivity; plasma GPI 15715 and propofol concentrations were also determined. Blood samples were collected prior to dosing and 5, 10, 15, 40, and 70 minutes, and at 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose. For all subjects, the collection of blood samples was extended up to 168 hours post dose (7 days). Urine samples were collected at - 12 hours and 0 hours and at the following intervals: 0 to 4 hours; 4 to 8 hours; 8 to 12 hours; 12 to 24 hours; and every 24 hours until checking out of the clinic. Fecal samples were collected from check-in until dosing and at the following postdose intervals: 0 to 24 hours; and every 24 hours until checkout. Safety was assessed by the following: clinical laboratory testing, vital sign measurements, pulse oximetry results, physical and neurological examinations, visual assessments, electrocardiogram (ECG) results, Bispectral (BIS) Index assessments, concomitant medication recordings, and adverse event monitoring.

Number of Subjects (Planned and Analyzed):
A total of 8 healthy males were planned and enrolled. All 8 subjects completed all study procedures.

Diagnosis and Main Criteria for Inclusion:
Volunteers for this study were healthy males, 18 to 45 years of age, inclusive, who did not smoke for at least 1 year prior to start of study, and who signed an informed consent form.

Test Product, Dose and Mode of Administration, Lot Number:
[^{14}C] AQUAVAN® Injection was supplied by Guilford Pharmaceuticals Inc. as a sterile aqueous solution in 0.4% saline at a concentration of 20 mg/mL for intravenous injection. Each vial contained 20 mL of solution and 100 μCi of [^{14}C]-labeled GPI 15715. The [^{14}C] label was contained in the phenyl group of the GPI 15715 molecule. Lot No: 192I0702.

Duration of Treatment: This was a single-dose study with an approximate 7-day confinement in the clinic.

Reference Therapy, Dose and Mode of Administration, Batch Number: None

Criteria for Evaluation:
Bioanalytical:
Radioactivity levels (converted to GPI 15715 equivalents) were determined in blood, plasma, urine, and feces using a scintillation counter. GPI 15715 and propofol levels were determined in plasma using LC/MS/MS and LC/Fluorescence assay methods, respectively.
Pharmacokinetics:
Pharmacokinetic parameters for blood and plasma radioactivity (converted to GPI 15715 equivalents), and for plasma GPI 15715 and propofol concentrations were calculated for all 8 dosed subjects using noncompartmental methods of analysis in SAS (Version 8.02). The following PK parameters were determined: area under the plasma concentration-time curve from 0 hours to the time of the last quantifiable concentration (AUC_{0-t}), area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$), area under the plasma concentration-time curve from 0 hours to 24 hours (AUC_{0-24}), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), apparent terminal elimination half-life ($t_{1/2}$), apparent terminal elimination rate constant (k_{el}), total plasma clearance (CL), and terminal volume of distribution (Vz). Since the fraction of GPI 15715 converted to propofol is not known, propofol plasma clearance and volume of distribution values are reported as apparent values (CL/F and Vz/F, where F is the fraction of GPI 15715 converted to propofol). Amounts and cumulative amounts of radioactivity (CumAe), and fraction of dose excreted (%Fe) were evaluated in urine and feces.
Safety:
Safety evaluations consisted of physical and neurological examinations, a visual assessment, vital sign measurements, pulse oximetry measurements, ECG testing, clinical laboratory testing, BIS Index monitoring, recording of concomitant medications, and the monitoring of adverse events.

Statistical Methods:

Pharmacokinetics:

Radioactivity levels in blood, plasma, urine, and feces and plasma GPI 15715 and propofol levels and pharmacokinetic parameters were summarized using descriptive statistics. Subject 008 had a peak level much lower than the other subjects in the study and the PK parameters were summarized with and without this subject.

Safety:

All subjects who received study drug were included in the safety analysis. All data collected in the study were summarized using descriptive statistics. Adverse events, by subject, were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 5.0) and were summarized by dose and overall, by system organ class and preferred term.

SUMMARY OF RESULTS

Pharmacokinetics:

Arithmetic Mean (SD) of Pharmacokinetic Parameters for Blood and Plasma Radioactivity (in GPI 15715 Equivalents), and Plasma GPI 15715 and Propofol

Parameter	Blood Radioactivity (GPI 15715 equivalents)	Plasma Radioactivity (GPI 15715 equivalents)	GPI 15715	Propofol
AUC_{0-t} (μg•hr/mL)	41.9 (7.66)	80.8 (10.3)	16.7 (3.00)	0.740 (0.23)
$AUC_{0-\infty}$ (μg •hr/mL)	47.0 (8.01)	89.8 (11.8)	16.7 (3.00)	0.801 (0.241)
C_{max} (μg /mL)	23.1 (9.73)	37.8 (15.8)	46.4 (18.2)	0.378 (0.185)
$t_{1/2}$ (hr)	13.8 (4.75)	22.4 (6.93)	1.47 (0.20)	3.78 (0.71)
CL or CL/F (L/hr)	7.56 (1.53)	3.90 (0.500)	21.2 (3.78)	293 (102)
Vz or Vz/F (L)	142 (33.0)	123 (28.0)	44.6 (7.61)	1603 (638)

Based on ratios of AUC_{∞} values for radioactivity in plasma and plasma AUC_{∞} values for GPI 15715 and propofol, 21.4% and 1.7% of the total radioactivity in plasma was associated with unchanged GPI 15715 and propofol, respectively. The terminal elimination half-life for radioactivity in plasma and blood was much longer than for GPI 15715 and propofol as inactive metabolites of propofol are eliminated slower than propofol. GPI 15715 and propofol terminal half-life values (1.47 and 3.78 hours, respectively) were comparable to the previously observed values in healthy volunteer studies with similar doses of AQUAVAN® Injection. AUC values were also higher for blood and plasma radioactivity as compared with GPI 15715 and propofol, while the observed C_{max} was comparable between plasma radioactivity and GPI 15715. After adjusting for the hematocrit, the blood to plasma ratio was close to 1, indicating that radioactivity was equally distributed in plasma and erythrocytes.

An average of 71.3% of total radioactivity was recovered in urine in 8 days (192 hr) following a 400-mg dose of AQUAVAN® Injection containing 100 μCi of radioactivity. The majority of radioactivity (59%) was recovered in the first 24 hours, 65% of radioactivity was recovered in 48 hr period, and the rest of the radioactivity (6%) was recovered between 48 and 192 hours. Less than 1 percent (0.51%) of total amount of radioactivity was recovered in feces in 7 days. A total of 28% of the radioactivity was not recovered after 8 days.

Safety:

All 8 subjects experienced at least 1 treatment-emergent AE. The most commonly reported AEs were burning sensation not otherwise specified (NOS) and paresthesia (3 subjects, 37.5% each). All burning sensation and paresthesia AEs were considered by the Investigator to be mild in intensity and definitely related to study drug; all of these events resolved, most within 10 minutes, and no actions were required. Only mild sedation resulted from treatment with study drug, as indicated by the lowest mean BIS index values (84.6%; range 78% to 94%) that occurred 20 minutes after the start of infusion. There were no reports of hypoxia or apnea and no subject needed supplemental oxygen, mechanical ventilation, or respiratory assistance. No subjects experienced a serious adverse event, died, or discontinued from the study due to an adverse event. Mean results and change from baseline results for all vital signs parameters were not clinically significant. Results from clinical laboratory testing, ECG readings, pulse oximetry measurements, physical and neurological examinations, and visual assessments were unremarkable. At all time points, there were no clinically meaningful increases from baseline in either calcium or phosphorus. Moreover, no calcium-phosphorous product values exceeded the theoretical level of concern of more than 60 mg^2/dL^2.

CONCLUSIONS

Seventy-one percent of the total radioactivity from a 400-mg dose of AQUAVAN® Injection (containing 100 μCi of radioactivity) was recovered in the urine and less than 1% was recovered in the feces in 8 days; 28% of the radioactivity was not recovered. The majority of the radioactivity (65 %) was recovered in urine in the first 48 hours.

AQUAVAN® Injection, when administered as a 400-mg dose, was safe by all parameters measured (vital signs; physical examination, including visual assessments; clinical laboratory evaluations, particularly calcium phosphate product; neurological examinations; pulse oximetry; electrocardiograms; and measurements of Bispectral Index). As with previous studies of AQUAVAN® Injection, the most common AEs were burning sensations and paresthesias.

Table 1
Mean percent of radioactive dose as ^{14}C-GPI 15715 or metabolites of ^{14}C-GPI 15715 in urine after administration of a single oral dose of ^{14}C-GPI-15715 (400 mg, 100 µCi)

Peak	Retention Time (minutes)	Proposed Identification	Percent of Radioactive Dose: Collection Interval (Hours) 0-4	4-8	8-12	12-24	Total
M1	3.2	Unknown	0.25	0.09	ND	ND	0.27
M2	17.0	Quinol-4-sulfate	2.61	0.78	0.56	0.73	4.59
M3	17.9	Unknown	0.45	ND	ND	ND	0.45
M4	19.2	Quinol-1-glucuronide	5.37	2.48	1.36	1.90	11.1
M5	20.0	Unknown	0.21	0.14	0.06	ND	0.22
M6	21.6	Quinol-4-glucuronide	2.51	0.99	0.69	0.95	5.13
M7	22.5	Hydroxypropofol glucuronide No. 1	0.58	0.22	0.15	ND	0.81
M8	22.8	Hydroxypropofol glucuronide No. 1	0.25	0.11	0.15	ND	0.26
M9	25.1	Unknown	0.27	0.15	0.15	ND	0.32
M10	30.3	Propofol-glucuronide	18.0	8.80	3.97	3.96	34.8
		Total ^{14}C (% of Dose)	30.5	13.8	7.09	7.54	57.9
		Sample ^{14}C (% of Dose)	31.3	13.8	6.97	7.83	59.9

ND Not detected

Table 2
Percent of sample radioactivity as ^{14}C-GPI 15715 or metabolites of ^{14}C-GPI 15715 in pooled plasma after administration of a single oral dose of ^{14}C-GPI-15715 (400 mg, 100 µCi)

Peak	Retention Time (minutes)	Proposed Identification	Percent of Sample Radioactivity: Collection Time (Hours) 0.083	0.167	0.25	0.667	1.17	2	4	6
1	19.5	M4	ND	ND	ND	4.55	7.48	8.64	4.82	ND
2	21.5-22.0	M2	ND	ND	ND	6.36	3.24	2.33	ND	ND
3	26.5-28.0	GPI-15715	100	100	97.5	36.1	8.73	1.66	ND	ND
4	30.5-31.0	M10	ND	ND	2.43	49.1	72.6	79.4	88.6	97.1
5	33.5	M11	ND	ND	ND	3.94	6.98	7.97	6.63	2.90
		Total:	100	100	99.9	100	99.0	100	100	100

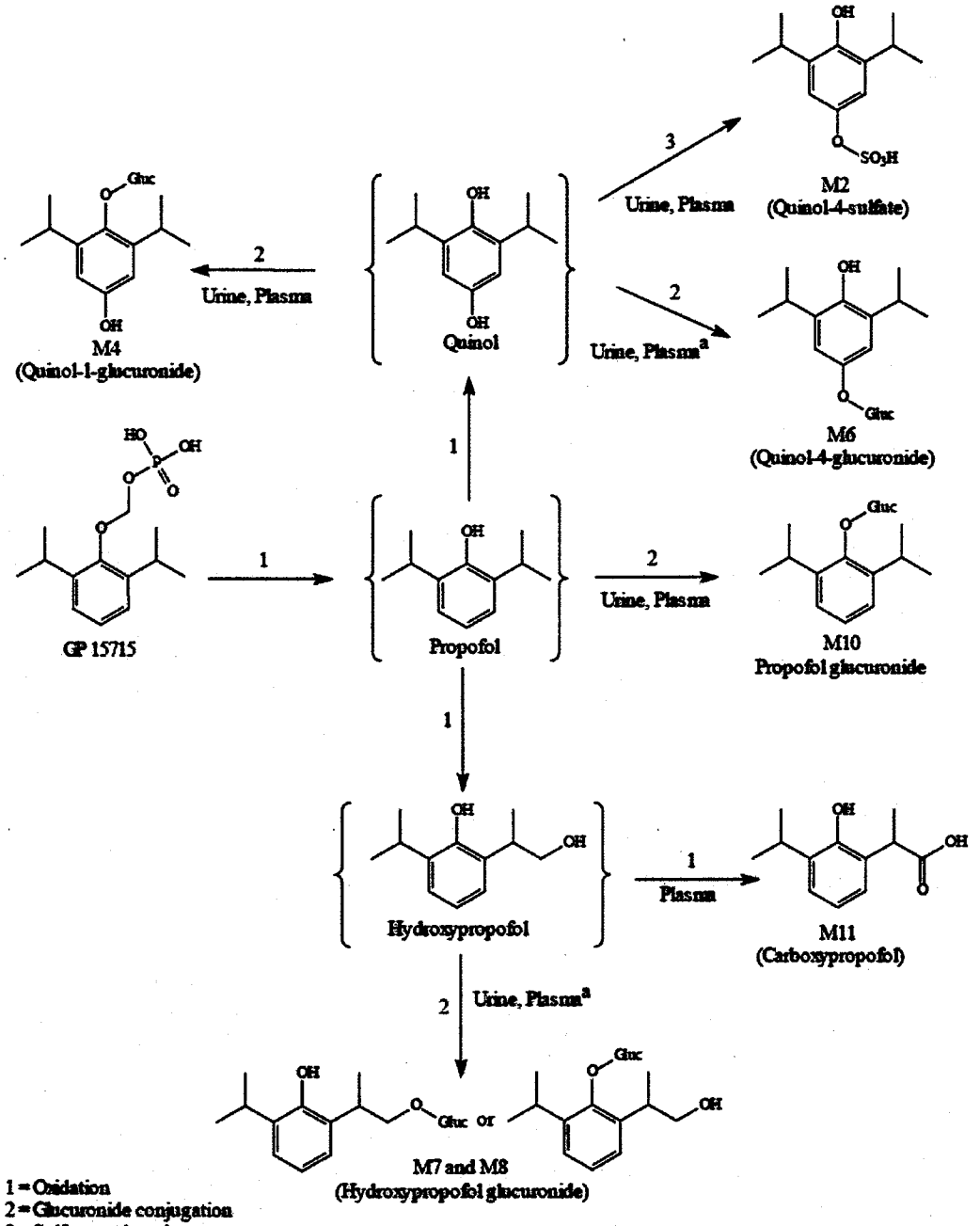
ND Not detected.

Table 3
Concentration of radioactivity as ^{14}C-GPI 15715 or metabolites of ^{14}C-GPI 15715 in pooled plasma after administration of a single oral dose of ^{14}C-GPI-15715 (400 mg, 100 µCi)

Peak	Retention Time (minutes)	Proposed Identification	Concentration (µg equivalents/mL): Collection Time (Hours) 0.083	0.167	0.25	0.667	1.17	2	4	6
1	19.5	M4	ND	ND	ND	0.545	0.625	0.528	0.187	ND
2	21.5-22.0	M2	ND	ND	ND	0.762	0.271	0.142	ND	ND
3	26.5-28.0	GPI-15715	21.0	39.5	30.8	4.32	0.729	0.101	ND	ND
4	30.5-31.0	M10	ND	ND	0.767	5.88	6.06	4.85	3.44	2.41
5	33.5	M11	ND	ND	ND	0.472	0.583	0.487	0.258	0.0720
		Total	21.0	39.5	31.5	12.0	8.27	6.11	3.89	2.48
		Pool	31.7	59.1	45.8	17.1	11.0	8.02	5.50	2.97

ND Not detected.

Figure 1
Proposed biotransformation of GPI 15715 in humans



[a] M6 and M7 were detected in plasma by LC/MS but were not detected by radioactivity.

Propofol, quinol, and hydroxypropofol were not detected by LC/MS or radioactivity.
Structures are postulated intermediates.

4.3.2 In vitro protein binding of fospropofol and propofol

ABSTRACT

GPI 15715 is a prodrug of propofol. The objectives of this study were to determine, *in vitro*: 1) protein binding of [^{14}C]GPI 15715 in mouse, rat, rabbit, dog, monkey, and human plasma; 2) binding of [^{14}C]GPI 15715 to isolated human serum albumin (HSA) and α_1-acid glycoprotein (AAG); 3) protein binding interactions of GPI 15715 and propofol in human plasma; and 4) blood-to-plasma partitioning of [^{14}C]GPI 15715 in mouse, rat, rabbit, dog, monkey, and human.

Stability of [^{14}C]GPI 15715 (50 μg/mL) in buffer and whole blood and plasma from each species was determined following incubation at 37°C for various time periods ranging from 0 to 240 minutes. Analysis of samples by high-performance liquid chromatography (HPLC) with radiochemical detection indicated that the radioactivity was associated with [^{14}C]GPI 15715 and [^{14}C]propofol (if present). The fraction of radioactivity in the form of GPI 15715 and propofol in buffer, whole blood, and plasma after incubation at 37°C for various time periods did not appear to change significantly in samples from mouse, rat, dog, and human. In rabbit and monkey blood, [^{14}C]GPI 15715 decreased by approximately 86% and 82%, respectively, after incubation for 240 minutes, with a corresponding increase in [^{14}C]propofol. In rabbit and monkey plasma, decrease of radioactivity associated with [^{14}C]GPI 15715 was approximately 5 to 10% after incubation for 15 minutes. These data demonstrate that [^{14}C]GPI 15715 is relatively stable in blood and plasma from mouse, rat, dog, and human, but is converted to [^{14}C]propofol in both blood and plasma from rabbit and monkey.

The *in vitro* binding of [^{14}C]GPI 15715 to plasma proteins was assessed by ultrafiltration at six concentrations (0.01, 0.5, 5, 50, 100, and 500 μg/mL). [^{14}C]GPI 15715-derived radioactivity was highly bound to plasma proteins in all species in a concentration dependent manner. Over the concentration range of 0.5 to 100 μg/mL (0.5 to 80 μg/mL in humans), plasma protein binding was relatively constant and averaged approximately 93% (mouse), 97% (rat), 91% (rabbit), 95% (dog), 96% (monkey), and 97-98% (3 individual humans). At 500 μg/mL, mean protein binding was 60.9% (mouse), 86.3% (rat), 83.1% (rabbit), 64.7% (dog), 87.9% (monkey), and 83.1 to 90.1% (3 individual humans). These results at 500 μg/mL were significantly lower than those at lower concentrations, and suggest saturation of protein binding sites at this high concentration.

[^{14}C]GPI 15715 was highly bound to HSA, but minimally bound to AAG. Over a concentration range of 0.01 to 100 μg GPI 15715/mL, protein binding for HSA and AAG was approximately 98% and <10%, respectively. At 500 μg GPI 15715/mL, binding to HSA decreased to 93.8%, suggesting saturation of binding to HSA.

The potential for protein binding interactions between GPI 15715 and propofol was assessed in human plasma from three separate individuals *in vitro*. Propofol, over a concentration range of 0.05 to 5.0 μg/mL, had minimal effects on the protein binding of GPI 15715. Similarly, GPI 15715 at concentrations up to 200 μg/mL did not affect the protein binding of propofol.

Table 5. Percent of Unbound and Bound [^{14}C]GPI 15715 at Various Concentrations in Human Plasma

Concentration (µg/mL)	Percent of Radioactivity				Standard Deviation
	Unbound		Bound		
	Individual	Mean	Individual	Mean	
		Human M94948			
0.01	7.4	6.2	92.6	93.9	NA
	4.9		95.1		
0.5	2.6	2.7	97.4	97.3	0.2
	2.9		97.1		
	2.7		97.3		
5	2.6	3.3	97.4	96.7	0.9
	3.0		97.0		
	4.4		95.6		
50	2.8	2.8	97.2	97.2	0.1
	2.8		97.2		
	2.9		97.1		
80	3.6	3.6	96.4	96.4	0.1
	3.7		96.3		
	3.6		96.4		
500	16.9	16.9	83.1	83.1	0.3
	17.2		82.8		
	16.6		83.4		
		Human M94949			
0.01	2.8	2.7	97.2	97.3	NA
	2.6		97.4		
0.5	2.5	2.5	97.5	97.5	0.1
	2.5		97.5		
	2.4		97.6		
5	2.7	2.7	97.3	97.3	0.1
	2.7		97.3		
	2.6		97.4		
50	2.5	2.5	97.5	97.5	0.1
	2.4		97.6		
	2.5		97.5		
80	2.6	2.3	97.4	97.7	0.6
	2.7		97.3		
	1.6		98.4		
500	11.1	10.9	88.9	89.1	0.3
	11.0		89.0		
	10.5		89.5		
		Human M94951			
0.01	22.7	12.4	77.3	87.6	9.0
	6.0		94.0		
	8.5		91.5		
0.5	2.4	2.3	97.6	97.7	0.1
	2.4		97.6		
	2.2		97.8		
5	2.4	2.4	97.6	97.6	0.1
	2.3		97.7		
	2.5		97.5		
50	2.5	2.5	97.5	97.5	0.1
	2.4		97.6		
	2.5		97.5		
80	2.8	2.9	97.2	97.1	0.2
	2.8		97.2		
	3.1		96.9		
500	10.5	9.9	89.5	90.1	0.5
	9.5		90.5		
	9.8		90.2		

NA Not applicable.

Note: At a concentration of 0.01 µg [^{14}C]GPI 15715/mL, the amount of radioactivity present in the ultrafiltrate was low (less than 100 dpm) due to which the accuracy in assessment of protein binding was low.

Table 6. Percent of [^{14}C]GPI 15715 Unbound and Bound to Human Serum Albumin (HSA) and Human α_1-Acid Glycoprotein (AAG) at Various Concentrations

Concentration (µg/mL)	Percent of Radioactivity				Standard Deviation
	Unbound		Bound		
	Individual	Mean	Individual	Mean	
		HSA (45 mg/mL)			
0.01	2.8	2.7	97.2	97.3	0.5
	3.1		96.9		
	2.1		97.9		
0.5	1.8	1.8	98.2	98.2	0.1
	1.8		98.2		
	1.7		98.3		
5	1.7	1.7	98.3	98.3	0.1
	1.8		98.2		
	1.7		98.3		
50	2.0	2.0	98.0	98.0	0.0
	2.0		98.0		
	1.9		98.1		
100	1.8	1.8	98.2	98.2	0.1
	1.9		98.1		
	1.7		98.3		
500	6.2	6.2	93.8	93.8	0.1
	6.3		93.7		
	6.1		93.9		
		AAG (0.7 mg/mL)			
0.01	92.1	92.8	7.9	7.2	2.3
	90.9		9.1		
	95.4		4.6		
0.5	94.0	93.3	6.0	6.7	0.6
	92.8		7.2		
	93.2		6.8		
5	92.2	91.9	7.8	8.1	0.7
	91.1		8.9		
	92.4		7.6		
50	94.7	94.7	5.3	5.3	0.2
	94.9		5.1		
	94.5		5.5		
100	92.9	92.8	7.1	7.2	0.4
	92.3		7.7		
	93.2		6.8		
500	94.3	94.8	5.7	5.2	0.5
	95.0		5.0		
	95.2		4.8		

Table 9. Percentage of Unbound and Bound [^{14}C]GPI 15715 (50 μg/mL) in the presence of Propofol at Various Concentrations in Human Plasma

Concentration Propofol (μg/mL)	Percentage of Radioactivity				Standard Deviation
	Unbound		Bound		
	Individual	Mean	Individual	Mean	
		Human M97454			
0.05	3.2	3.2	96.8	96.8	0.1
	3.3		96.7		
	3.2		96.8		
0.5	3.2	3.1	96.8	96.9	0.1
	3.0		97.0		
	3.2		96.8		
5	3.3	3.2	96.7	96.8	0.1
	3.2		96.8		
	3.2		96.8		
Control	2.8	2.8	97.2	97.2	0.0
	2.8		97.2		
	2.8		97.2		
		Human M97455			
0.05	3.3	3.3	96.7	96.8	0.1
	3.1		96.9		
	3.2		96.8		
0.5	3.2	3.2	96.8	96.8	0.1
	3.2		96.8		
	3.3		96.7		
5	3.1	3.2	96.9	96.8	0.1
	3.3		96.7		
	3.1		96.9		
Control	2.8	2.8	97.2	97.2	0.1
	2.8		97.2		
	2.7		97.3		
		Human M97456			
0.05	3.0	2.9	97.0	97.1	0.1
	2.8		97.2		
	2.9		97.1		
0.5	2.9	2.8	97.1	97.2	0.2
	2.6		97.4		
	2.9		97.1		
5	2.8	3.0	97.2	97.0	0.3
	3.3		96.7		
	2.9		97.1		
Control	2.4	2.4	97.6	97.6	0.1
	2.4		97.6		
	2.5		97.8		

Table 10. Percentage of Unbound and Bound [^{14}C]GPI 15715 (500 µg/mL) in the presence of Propofol at Various Concentrations in Human Plasma

Concentration Propofol (µg/mL)	Percentage of Radioactivity				Standard Deviation
	Unbound		Bound		
	Individual	Mean	Individual	Mean	
		Human M97454			
0.05	14.8	14.5	85.2	85.5	0.3
	14.3		85.7		
	14.5		85.5		
0.5	14.5	14.4	85.5	85.6	NA
	14.3		85.7		
5	14.6	14.4	85.4	85.6	0.2
	14.2		85.8		
	14.5		85.5		
Control	13.2	13.1	86.8	86.9	0.1
	13.0		87.0		
	13.1		86.9		
		Human M97455			
0.05	13.8	13.8	86.2	86.2	0.0
	13.8		86.2		
	13.8		86.2		
0.5	15.9	15.4	84.1	84.6	NA
	14.9		85.1		
5	14.3	14.3	85.7	85.7	0.1
	14.4		85.6		
	14.3		85.7		
Control	12.3	12.5	87.7	87.5	0.4
	12.3		87.7		
	13.0		87.0		
		Human M97456			
0.05	13.2	13.2	86.8	86.8	0.1
	13.1		86.9		
	13.3		86.7		
0.5	16.0	13.9	84.0	86.1	1.9
	12.5		87.5		
	13.2		86.8		
5	13.1	13.3	86.9	86.7	0.2
	13.3		86.7		
	13.4		86.6		
Control	11.8	11.8	88.2	88.2	0.0
	11.8		88.2		
	11.8		88.2		

NA Not applicable.

Table 11. Percentage of Unbound and Bound [^{14}C]Propofol (0.5 μg/mL) in the presence of GPI 15715 at Various Concentrations in Human Plasma

Concentration GPI 15715 (μg/mL)	Percentage of Radioactivity				Standard Deviation
	Unbound		Bound		
	Individual	Mean	Individual	Mean	
		Human M99856			
0.5	1.2	1.3	98.8	98.7	0.2
	1.5		98.5		
	1.2		98.8		
10	1.8	1.4	98.2	98.6	0.4
	1.3		98.7		
	1.0		99.0		
200	2.1	1.8	97.9	98.2	0.3
	1.8		98.2		
	1.5		98.5		
Control	1.8	1.7	98.2	98.3	0.1
	1.7		98.3		
	1.8		98.2		
		Human M99857			
0.5	0.9	1.2	99.1	98.8	0.3
	1.6		98.4		
	1.2		98.8		
10	1.5	1.2	98.5	98.8	0.2
	1.2		98.8		
	1.0		99.0		
200	1.2	1.2	98.8	98.8	0.3
	1.4		98.6		
	0.9		99.1		
Control	1.5	1.5	98.5	98.5	0.2
	1.7		98.3		
	1.4		98.6		
		Human M99858			
0.5	1.1	1.1	98.9	98.9	0.1
	1.1		98.9		
	1.0		99.0		
10	1.1	1.3	98.9	98.7	0.3
	1.2		98.8		
	1.7		98.3		
200	1.2	1.4	98.8	98.6	0.3
	1.7		98.3		
	1.4		98.6		
Control	2.1	1.7	97.9	98.3	0.4
	1.4		98.6		
	1.6		98.4		

Table 12. Percentage of Unbound and Bound [^{14}C]Propofol (5 μg/mL) in the presence of GPI 15715 at Various Concentrations in Human Plasma

Concentration GPI 15715 (μg/mL)	Percentage of Radioactivity				Standard Deviation
	Unbound		Bound		
	Individual	Mean	Individual	Mean	
			Human M99856		
0.5	1.6	1.3	98.4	98.7	0.2
	1.3		98.7		
	1.2		98.8		
10	1.6	1.5	98.4	98.5	0.1
	1.3		98.7		
	1.5		98.5		
200	1.8	1.7	98.2	98.3	0.1
	1.6		98.4		
	1.6		98.4		
Control	1.6	1.5	98.4	98.5	0.2
	1.5		98.5		
	1.2		98.8		
			Human M99857		
0.5	2.1	2.5	97.9	97.5	0.4
	2.4		97.6		
	2.9		97.1		
10	2.3	2.6	97.7	97.4	0.2
	2.6		97.4		
	2.8		97.2		
200	2.5	2.7	97.5	97.3	0.4
	2.5		97.5		
	3.1		96.9		
Control	1.8	2.4	98.2	97.6	0.6
	2.5		97.5		
	3.1		96.9		
			Human M99858		
0.5	1.1	1.3	98.9	98.7	0.2
	1.3		98.7		
	1.5		98.5		
10	1.4	1.7	98.6	98.3	0.3
	1.9		98.1		
	1.7		98.3		
200	2.3	2.3	97.7	97.7	0.1
	2.1		97.9		
	2.4		97.6		
Control	2.2	1.9	97.8	98.1	0.3
	1.9		98.1		
	1.6		98.4		

Table 14. The Blood-to-Plasma Partitioning of [^{14}C]GPI 15715 (50 µg/mL) at Various Incubation Times in Human Blood

Species	Incubation Time (Minutes)	Blood-to-Plasma Concentration Ratio			Percentage Associated with Cellular Components[a]		
		Individual		Mean	Individual		Mean
Human 1	0	0.482	0.487	0.485	0.0	0.0	0.0
Hct = 0.47	15	0.498	0.493	0.496	0.0	0.0	0.0
	30	0.478	0.453	0.466	0.0	0.0	0.0
	60	0.492	0.499	0.496	0.0	0.0	0.0
	120	0.491	0.493	0.492	0.0	0.0	0.0
	240	0.522	0.502	0.512	0.0	0.0	0.0
	Overall			0.491			
	Overall SD			0.016			
Human 2	0	0.520	0.531	0.526	0.0	0.0	0.0
Hct = 0.44	15	0.527	0.530	0.529	0.0	0.0	0.0
	30	0.511	0.523	0.517	0.0	0.0	0.0
	60	0.530	0.517	0.524	0.0	0.0	0.0
	120	0.531	0.554	0.543	0.0	0.0	0.0
	240	0.542	0.535	0.539	0.0	0.0	0.0
	Overall			0.529			
	Overall SD			0.011			
Human 3	0	0.493	0.495	0.494	0.0	0.0	0.0
Hct = 0.47	15	0.478	0.505	0.492	0.0	0.0	0.0
	30	0.495	0.523	0.509	0.0	0.0	0.0
	60	0.487	0.493	0.490	0.0	0.0	0.0
	120	0.495	0.501	0.498	0.0	0.0	0.0
	240	0.522	0.475	0.499	0.0	0.0	0.0
	Overall			0.497			
	Overall SD			0.015			

Hct Hematocrit
SD Standard deviation.
a Values ≤0% have been reported as zero.

Table 16. The Blood-to-Plasma Partitioning of [^{14}C]GPI 15715 at Various Concentrations in Human Blood

Species	Concentration (µg/mL)	Blood-to-Plasma Concentration Ratio			Percentage Associated with Cellular Components[a]		
		Individual		Mean	Individual		Mean
Human 1	0.05	0.395	0.423	0.409	0.0	0.0	0.0
Hct = 0.49	0.5	0.514	0.480	0.497	0.8	0.0	0.4
	5	0.558	0.542	0.550	8.6	5.9	7.3
	50	0.516	0.521	0.519	1.2	2.1	1.7
	100	0.494	0.505	0.500	0.0	0.0	0.0
	500	0.517	0.519	0.518	1.3	1.7	1.5
	Overall			0.499			
	Overall SD			0.047			
Human 2	0.05	0.473	0.473	0.473	0.0	0.0	0.0
Hct = 0.45	0.5	0.543	0.565	0.554	0.0	2.7	1.4
	5	0.566	0.552	0.559	2.8	0.4	1.6
	50	0.538	0.552	0.545	0.0	0.3	0.2
	100	0.535	0.536	0.536	0.0	0.0	0.0
	500	0.557	0.552	0.555	1.2	0.4	0.8
	Overall			0.537			
	Overall SD			0.032			
Human 3	0.05	0.455	0.502	0.479	0.0	0.0	0.0
Hct = 0.49	0.5	0.503	0.498	0.501	0.0	0.0	0.0
	5	0.491	0.492	0.492	0.0	0.0	0.0
	50	0.505	0.496	0.501	0.0	0.0	0.0
	100	0.505	0.502	0.504	0.0	0.0	0.0
	500	0.539	0.472	0.506	5.3	0.0	2.7
	Overall			0.497			
	Overall SD			0.020			

Hct Hematocrit
SD Standard deviation.
a Values ≤0% have been reported as zero.
Note: At a concentration of 0.05 µg/mL, the amount of radioactivity present in the aliquot of blood analyzed was very low (approximately 100 dpm) due to which the accuracy of measurement for blood-to-plasma partitioning at this concentration was low.

4.3.3 Influence of Time and Temperature on Metabolism of Fospropofol (GPI 15715) by alkaline phosphatase

GPI 15715 is a prodrug of propofol and in the presence of alkaline phosphatase it is metabolized to propofol and formaldehyde.

Two studies were conducted to evaluate the role of alkaline phosphatase in metabolism of GPI 15715. The first study investigated the course of metabolism of GPI 15715 in the presence of alkaline phosphatase over 30 min at physiological temperature (37°C). Three different concentrations (1, 10 and 50 µM) of GPI 15715 were incubated at 37°C in the presence of a constant amount of enzyme (0.5 units/mL). Samples were obtained at time zero and after start of the reaction at 5, 10, 15, 20, and 30 minutes. The progress of reaction was monitored by analyzing the samples for GPI 15715 by LC/MS/MS assay.

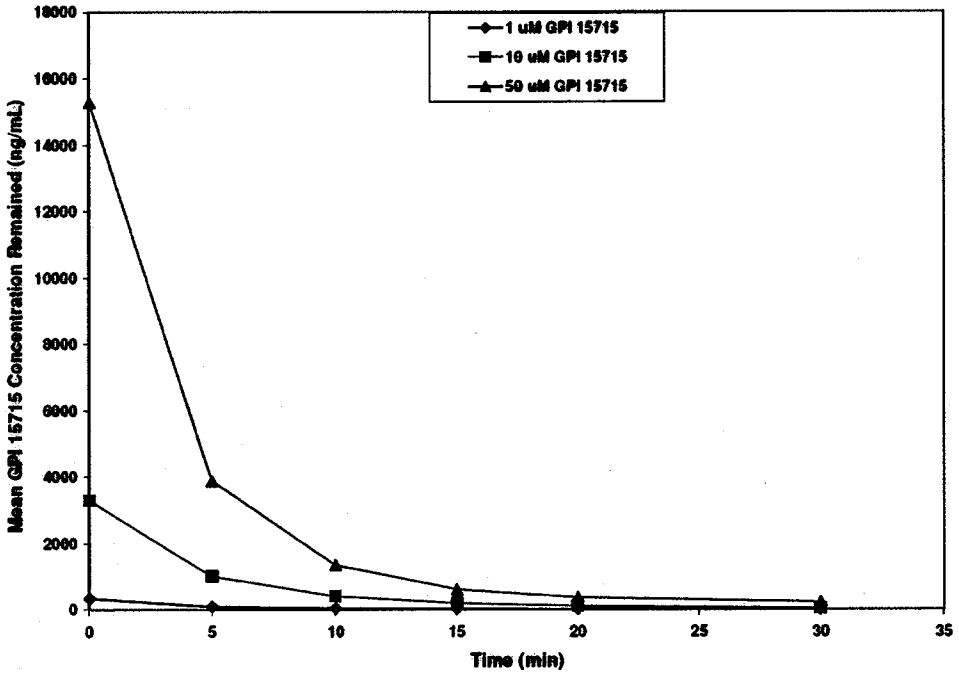
The second study was conducted in which the stoichiometry of GPI 15715 and its metabolites, propofol and formaldehyde, were investigated following incubation with alkaline phosphatase. The study consisted of GPI 15715 (approximately 2.5 µM) incubation at 37, 35, 33, 31, and 28°C in the presence and absence of alkaline phosphatase (0.5 units/mL). Reactions were sampled at time zero and after 5 minutes. Enzyme activity was measured after each reaction using a diagnostic kit specific for alkaline phosphatase. Samples collected were analyzed for GPI 15715 by LC/MS/MS method, propofol by HPLC/FL method, and formaldehyde by HPLC/UV method.

In the time course study, the GPI 15715 was rapidly metabolized over time and the rate of metabolism was approximately constant and independent of initial substrate concentration in all three incubation mixtures. Approximately 2/3 of the initial amount of GPI 15715 was degraded in 5 minutes from the start of incubation and the metabolism of GPI 15715 was almost complete within 20-30 minutes. Across the concentration range (1, 10 and 50 µM), the total percent of GPI 15715 metabolism at 5, 10, 15, 20 and 30 min ranged between 69.3-74.6%, 86.5-91.2%, 93.5-96.1%, 97.0-97.7%, and 98.5-98.8%, respectively.

In the second study, alkaline phosphatase activity decreased with reduction in incubation temperatures and its ability to metabolize GPI 15715 was reduced. Alkaline phosphatase activity fell from 3863 µmole of GPI 15751 hydrolyzed/min/mg protein at 37°C, to 2889 µmole of GPI 15751 hydrolyzed/min/mg protein at 28°C. Similar to the time course study it was observed that at 37°C, GPI 15715 rapidly metabolized to approximately 80% of the initial GPI 15715 by alkaline phosphatase after incubation for 5 minutes. At 28°C, only 60% of the GPI 15715 was metabolized after 5 minutes. Similarly, the amount of propofol and formaldehyde generated after 5 minutes decreased as the incubation temperature decreased.

The stochiometry of the reaction indicates that GPI 15715 is metabolized to propofol and formaldehyde and no further alkaline phosphatase mediated metabolism of propofol or formaldehyde occurs.

Figure 1: Metabolism of GPI 15715 by Alkaline Phosphatase at 37°C over 30 minutes (Study #1) (Linear: Upper Panel, Semi log: Lower Panel)



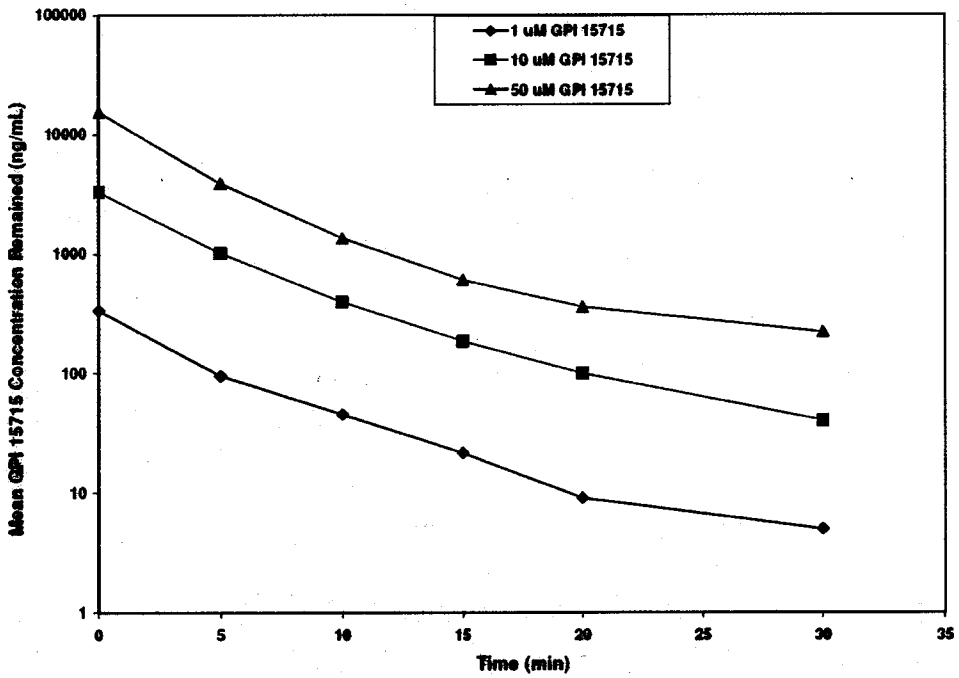


Figure 2: Reaction Time VS. Percent GPI 15715 Metabolized (Study #1)

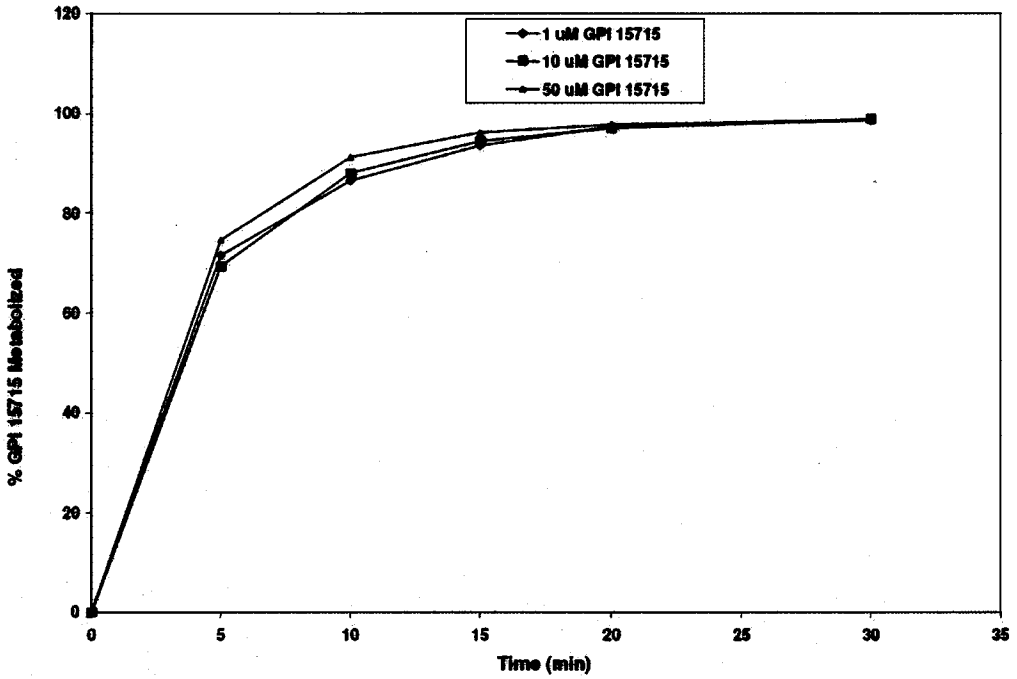


Figure 3: Metabolism of GPI 15715 by Alkaline Phosphatase at Various Incubation Temperatures (Study #2)

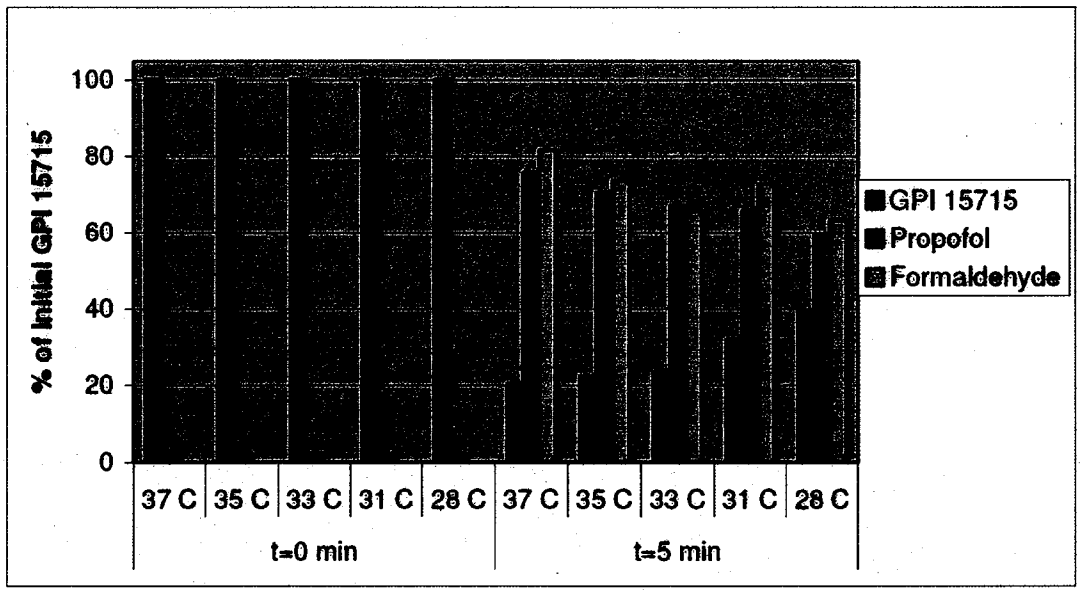


Figure 4: Alkaline Phosphatase Activity at Various Incubation Temperatures Measured [redacted] (Study #2) b(4)

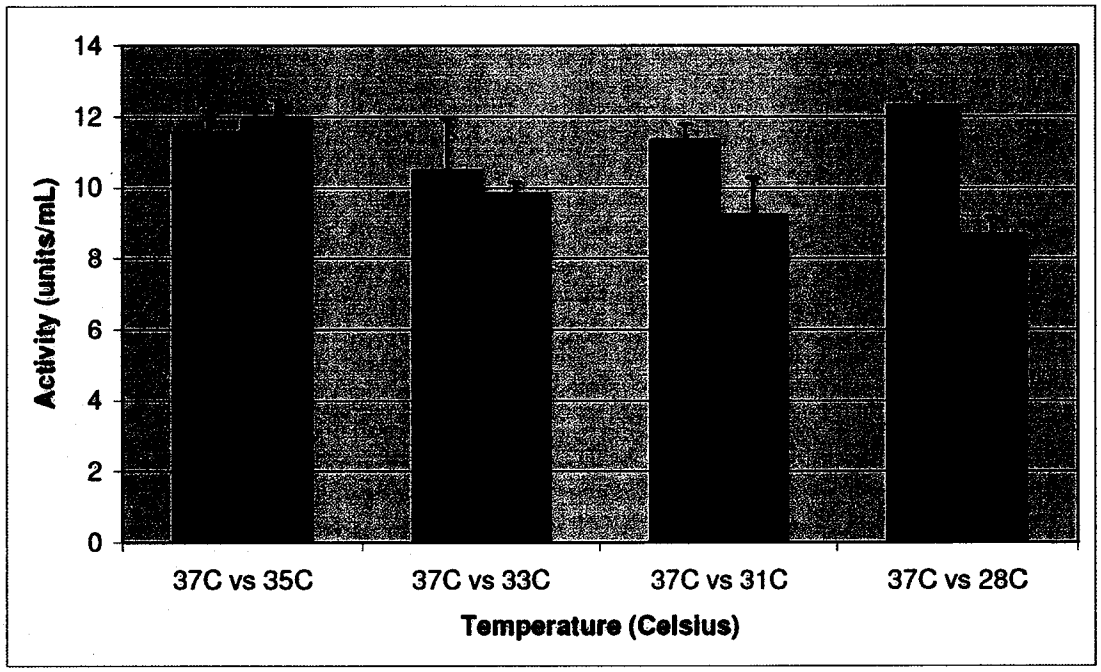
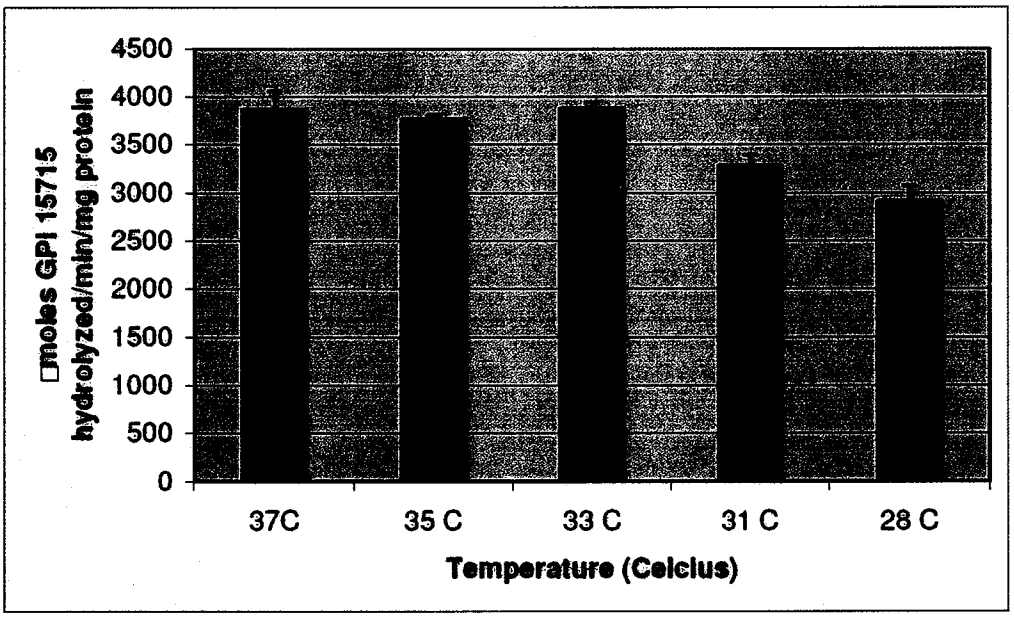


Figure 5: Alkaline Phosphatase Activity at Various Incubation Temperatures Measured by Hydrolysis of GPI 15715 (Study #2)



4.3.4 Metabolic stability of fospropofol (GPI 15715) in liver microsomes

The metabolic stability of GPI 15715 in Mouse, Rat, Dog, and Human microsomes has been investigated over a 2-hour time course at an initial concentration of 100 μM. Aliquots were taken at 0.00, 2.00, 5.00, 15.0, 30.0, 60.0, 90.0, and 120 minutes post drug administration. Analysis of the samples generated was then performed using an established LC-MS/MS assay.

The metabolic stability of GPI 15715 in mouse, rat, dog, and human microsomes over a 2-hour period was 72.8%, 52.2%, 19.2%, and 65.9%, respectively, using NADPH as a co-factor. The rates of metabolism in incubations without NADPH were similar to those with NADPH. Since the metabolism of GPI 15715 was independent of NADPH, it is unlikely that significant CYP450-based metabolism occurred in this test system. Metabolism may have been due to alkaline phosphatase in these studies.

Table 1. Metabolic Stability of 100 μM of GPI 15715 in Mouse Microsomes.

time (min)	concentration (μg/mL) NADPH	without NADPH
0	16.9	17.3
2	16.0	17.1
5	16.5	17.0
15	16.1	16.2
30	15.8	15.2
60	14.4	14.3
90	13.1	12.0
120	12.3	10.2

Table 2. Metabolic Stability of 100 μM of GPI 15715 in Rat Microsomes.

time (min)	concentration (μg/mL) NADPH	without NADPH
0	15.2	15.2
2	14.7	15.1
5	14.8	15.0
15	13.6	15.1
30	12.2	14.3
60	10.7	12.4
90	9.53	10.7
120	7.93	9.06

Table 3. Metabolic Stability of 100 μM of GPI 15715 in Dog Microsomes.

time (min)	concentration (μg/mL) NADPH	without NADPH
0	13.5	11.0
2	11.6	10.9
5	14.2	10.7
15	8.48	10.1
30	8.01	9.96
60	6.50	5.02
90	4.17	3.92
120	2.59	2.57

Table 4. Metabolic Stability of 100 μM of GPI 15715 in Human Microsomes.

time (min)	concentration (μg/mL) NADPH	without NADPH
0	12.2	12.6
2	13.7	11.9
5	13.8	12.4
15	13.8	12.0
30	12.3	9.64
60	8.60	8.24
90	10.2	7.39
120	8.04	6.90

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Figure 1. Metabolic Stability of GPI 15715 in Mouse Microsomes

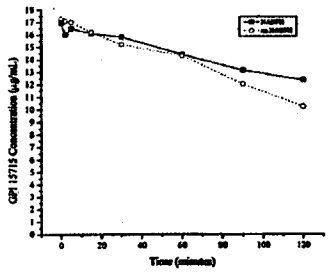


Figure 2. Metabolic Stability of GPI 15715 in Rat Microsomes

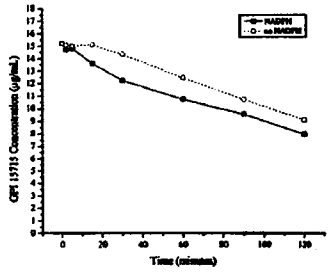


Figure 3. Metabolic Stability of GPI 15715 in Dog microsomes

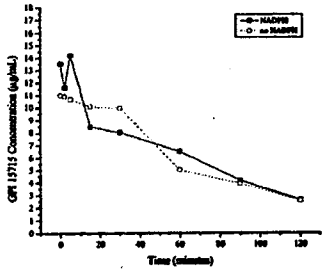
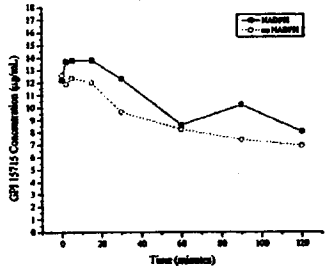


Figure 4. Metabolic Stability of GPI 15715 in Human Microsomes



4.3.5 Study # 3000-0001 Synopsis

See Analytical section 2.6 regarding propofol assay issue.

b(4)

Title of Study: Phase I Open Label, Single-Dose, Dose Escalation, Safety and Tolerability, Pharmacokinetic/Pharmacodynamic Study of GPI 15715 in Healthy Volunteers	
Investigator and Study Center: [redacted]	
Publication (reference): Fechner, J., Ihmsen, H., Hatterscheid, D., Schiessl, C., Vornov, J. Burak, E., Schwilden, H., Schüttler, J. Pharmacokinetics and Clinical Pharmacodynamics of the New Propofol Prodrug GPI 15715 in Volunteers, Anesthesiology, 2003, 99, 303-313.	
Study Period: 09 January 2001 (First volunteer enrolled) 29 January 2001 (Last volunteer completed Part 1) 15 March 2001 (Last volunteer completed Part 2)	**Phase of Development**: I
Objectives: • To evaluate the safety and tolerability of escalating doses of GPI 15715 up to a pharmacologically relevant dose • To compare the pharmacokinetic/pharmacodynamic properties of propofol derived from GPI 15715 to that derived from DISOPRIVAN® Injectable Emulsion	
Methodology: This was a non-IND, open-label, 2-part, single-center study conducted in healthy 18- to 45-year-old male volunteers. In Part 1, one group of 9 volunteers, 3 per dose group, received doses of 290 mg (Group 1), 580 mg (Group 2), or 1160 mg (Group 3) of GPI 15715. Each dose was administered by constant rate intravenous (i.v.) infusion over 10 minutes. Progression to the next dose group was dependent upon safety and tolerability results. Selection of the next dose level was dependent on the number of volunteers attaining loss of response to verbal command. The first dose group received the lowest dose of 290 mg of GPI 15715 as planned. As none of the volunteers in this group reached the endpoint, the dose was escalated by 100% to 580 mg as specified in the protocol. In the second group, 1 of 3 volunteers reached the endpoint, so the dose was again escalated to the maximum dose of 1160 mg for the final group in which all 3 volunteers lost response to verbal command. No adjustments for safety reasons were needed. Pharmacokinetic (PK) modeling was performed to relate the dose infused to plasma concentrations to provide parameters for the targeted infusion of Part 2. In Part 2, 9 volunteers were dosed in a crossover fashion. Each volunteer received DISOPRIVAN® Injectable Emulsion administered by continuous i.v. infusion over 60 minutes. The infusion rate was computer controlled to target (1) a plasma propofol concentration of 5 µg/mL to be attained by 20 minutes, (2) constant plasma propofol concentrations of 3 µg/mL for the next 20 minutes, and (3) constant plasma propofol concentrations of 1.5 µg/mL for the last 20 minutes of infusion. After a washout period of approximately 2 weeks, each of the 9 volunteers received an i.v. infusion of GPI 15715 targeting the pattern of plasma propofol concentrations described above. The total dose of GPI 15715 administered was planned to be less than 2700 mg. The actual doses in the dose escalation and crossover parts of the study are shown below.	

Part 1 – Dose Escalation*				Part 2 – Crossover †			
	GPI 15715				DISOPRIVAN®		GPI 15715
Volunteers (N=9)	**Group 1 (N=3)**	**Group 2 (N=3)**	**Group 3 (N=3)**	**Volunteers (N=9)**	**Dose 1**	~ 2-week washout	**Dose 2**
Planned Dose (mg/10 min)	290	580	1160	**Planned Dose** (mg/60 min)	400		< 2700
Actual Dose (mg/10 min) Mean (SD)	289.6 (4.6)	577.8 (7.9)	1137.2 (46.4)	**Actual Dose** (mg/60 min) Mean (SD)	505.0 (37.6)		2387.9 (65.2)

* 10-minute infusion
† 60-minute infusion

Serial plasma samples were collected prior to, during, and following each infusion for up to 360 minutes after start of the infusion, at checkout (24 hours) for determination of plasma GPI 15715 (following GPI 15715 administration), propofol, and formate concentrations.

The following procedures and evaluations were used for each study drug administration during Parts 1 and 2. The clinical assessment of drug effect onset (clinical sedation) was loss of the volunteer's ability to respond to a loud verbal command. Once the ability was regained (recovery phase), the volunteer was evaluated based on the Observer's Assessment of Alertness/Sedation (OAA/S) scale. Electroencephalogram (EEG) was recorded continuously and sampled at intervals specified by the protocol. Safety evaluations consisted of continuous monitoring of vital signs (systemic blood pressure and pulse) with recording of values for electrocardiogram (ECG), and pulse oximetry prior to, during and following infusions. Body temperature was measured pre- and post-treatment. An arterial blood sample was collected approximately 10 minutes after the start of the infusion to analyze for blood gases and electrolytes. Clinical signs were monitored continuously for the occurrence of adverse events (AEs). Clinical laboratory tests (serum chemistry, hematology, and urinalysis) and physical and neurological examinations were performed pre- and post-treatment. Each volunteer was confined to the clinic overnight and discharged on the morning following the day of study medication administration. Volunteers returned to the clinic for a follow-up visit approximately 3 days following drug administration for a physical and neurological examination, vital signs and body temperature measurements, and adverse event and concomitant medication review.

Number of Volunteers (Planned and Analyzed):
A total of 18 healthy volunteers (9 volunteers each in Part 1 and 2) were enrolled in this study. All 9 volunteers completed all scheduled dosing and study procedures in Part 1; 6 of the 9 volunteers from Part 1 also participated in Part 2. Three additional volunteers were recruited to provide a total of 9 volunteers for Part 2. Therefore, a total of 12 healthy volunteers were recruited for this study.

Diagnosis and Main Criteria for Inclusion:
Volunteers for this study were healthy Caucasian males 19 to 35 years of age, who had not smoked for at least 6 months prior to start of study, and signed the informed consent form.

Test Product, Dose and Mode of Administration, Batch Number:
GPI 15715 was supplied as a sterile aqueous solution in 0.4% sodium chloride at a concentration of 20 mg/mL. Each vial contained 20 mL of solution (Batch No: 1214-07).
Dosing - Part 1: GPI 15715 doses for the 3 dose groups were as follows:
Group 1: 290 mg (actual, mean ± SD: 289.6 ± 4.6)
Group 2: 580 mg (actual, mean ± SD: 577.8 ± 7.9)

Group 3: 1160 mg (actual, mean ± SD: 1137.2 ± 46.4) Each GPI 15715 dose was administered by i.v. infusion over 10 minutes. Dosing - Part 2: Actual individual doses of GPI 15715 ranged from 2271.7 mg to 2453.7 mg with a mean of 2387.9 ± 65.23 mg. GPI 15715 was administered by i.v. infusion over 60 minutes.
Reference Therapy, Dose and Mode of Administration, Batch Number: Propofol was supplied as DISOPRIVAN® Injectable Emulsion (1%). DISOPRIVAN® Injectable Emulsion contains 10 mg/mL of propofol (Batch No: not recorded). The average dose of propofol administered as DISOPRIVAN® Injectable Emulsion by i.v. infusion was 505.0 ± 37.6 mg.
Duration of Treatment: Part 1: One 10-minute i.v. infusion of GPI 15715 was administered to each volunteer. Part 2: Each volunteer received each of the 2 treatments as i.v. infusions over 60 minutes in the following order: (1) DISOPRIVAN® Injectable Emulsion; (2) GPI 15715. Treatments were separated by a washout period of approximately 2 weeks. For the 6 volunteers participating in both Parts 1 and 2, treatments of GPI 15715 in Part 1 and DISOPRIVAN® Injectable Emulsion in Part 2 were separated by approximately 2 weeks.
Criteria for Evaluation: Pharmacokinetics: In Parts 1 and 2, GPI 15715 and propofol, plasma concentration-time data were analyzed by non-compartmental methods to estimate the following pharmacokinetic (PK) parameters: area under the plasma concentration-time curve from time of dosing to the last measured concentration (AUC_{0-t}), area under the concentration versus time curve from the time of dosing to infinity (AUC_{0-inf}), maximum plasma concentration (C_{max}), time to attain C_{max} (T_{max}), terminal half-life ($T_{½}$), clearance (CL), and volume of distribution (V_z) (apparent values for propofol from GPI 15715). Since there was no consistent change in the concentration of plasma formate over time, only AUC_{0-t} and C_{max} were obtained. After the completion of the dose escalation in Part 1, PK modeling was performed to establish the relationship between the infusion rate of GPI 15715 and the plasma concentrations of propofol produced from GPI 15715. The information from this modeling was used to develop the infusion paradigm for GPI 15715 administration in Part 2. The dosing rate used for DISOPRIVAN® Injectable Emulsion was derived from a previously established PK model linking the observed plasma concentrations of propofol to the dose infused and the rate of infusion (Anesthesiology 2000, 93(6); 1557-1560). Pharmacodynamics: The pharmacodynamic (PD) effect of the study drug was determined from continuous EEG recordings and response to verbal command used in conjunction with the OAA/S scale. Safety: Safety was evaluated based on AEs, vital signs, body temperature, pulse oximetry, physical and neurological examinations, 12-lead ECG and clinical laboratory tests (including arterial blood gases and electrolytes).

Guidelines for Stopping Dose Escalation or Terminating Dosing – Part 1: Safety and tolerability, based on review of adverse events, clinical laboratory information, and physical/neurological assessments were the determining factors for stopping escalation.

The Investigator planned to stop escalation if any of the following occurred:

(a) Any laboratory result outside the range of normal was judged by the Investigator as clinically relevant.

(b) Any clinically significant adverse event was judged by the Investigator as probably or definitely related to study medication.

(c) Any change from baseline in the physical/neurological examination findings was judged by the Investigator as clinically significant.

If, in the Investigator's opinion, none of the criteria were met, dose escalation was continued. If, in the Investigator's opinion, the risk of continuing administration was unacceptable, the study was terminated.

Criteria for Dose Escalation – Part 1: The number of volunteers per dose group attaining clinical sedation at the previous dose level was the determining factor for selection of the next dose level:

If clinical sedation occurred in 0 or 1 of 3 volunteers, the dose was increased by 100%.

If clinical sedation occurred in 2 of 3 volunteers, the dose was increased by 50%.

If clinical sedation occurred in 3 of 3 volunteers, the dose was decreased by 25%.

Statistical Methods:

Pharmacokinetics: All pharmacokinetic data were listed according to dose, volunteer, and time. Descriptive statistics were used to summarize pharmacokinetic parameters. Although no formal statistical analysis was planned, an exploratory analysis of variance (ANOVA) was carried out for plasma formate concentrations in Part 2.

Pharmacodynamics: Similar to pharmacokinetics, all data collected were listed by dose, volunteer, and time and were summarized using descriptive statistics, as appropriate.

Safety: All volunteers who received at least 1 dose of study medication were included in safety evaluations. All data collected in the study were listed by dose, volunteer, and time, and were summarized using descriptive statistics. Adverse events were listed by volunteer, summarized by dose and overall for body systems and preferred terms; however, different dictionaries were used for Part 1 (COSTART, Version 5) and Part 2 (MedDRA, Version 3.3).

SUMMARY OF RESULTS

Pharmacodynamics – Part 1: In the 290-mg dose group of GPI 15715, none of the volunteers was sedated. In the 580-mg dose group of GPI 15715, only 1 of the volunteers was sedated, losing the ability to respond to a loud verbal command at the 12-minute timepoint. The highest tested dose of 1160 mg GPI 15715 caused sedation in all 3 volunteers: loss of response to verbal command at 7 minutes after the start of infusion in 2 volunteers and after 11 minutes in the third. The duration of the sedation was 11 to 33 minutes. The recovery time from sedation (an OAA/S score of 1) to full alertness (OAA/S score of 5) varied from 13-100 minutes. The EEG response was consistent with the lack of sedation in the 290-mg dose group.

Pharmacodynamics – Part 2: Clinical sedation (no response to a loud verbal command) was achieved at similar timepoints following both treatments: mean 9.6, range 6-14 minutes for GPI 15715 and mean 13.1, range 10-18 minutes for DISOPRIVAN® Injectable Emulsion. The duration of effect was almost twice as long in volunteers receiving GPI 15715 infusions (mean 60.3, range 40-80 minutes) compared with volunteers receiving DISOPRIVAN® Injectable Emulsion (mean 31.7 minutes, range 4-47 minutes).

The mean recovery time following the GPI 15715 treatment was longer (mean 57.4, range 12-72 minutes) than for DISOPRIVAN® Injectable Emulsion treatment (mean 37.2, range 11-98 minutes). EEG frequencies during GPI 15715 and DISOPRIVAN® Injectable Emulsion treatment periods corresponded to the volunteers' level of sedation.

Pharmacokinetics – Part 1:

The pharmacokinetic parameters of GPI 15175, propofol, and formate following administration of doses of 290 mg, 580 mg, 1160 mg of GPI 15715 to 3 volunteers per dose group are summarized in the following table:

Summary of Pharmacokinetics of GPI 15715, Propofol, and Formate following a 10-Minute I.V. Infusion of GPI 15715 in Part 1

GPI 15715 Dose	290 mg (n=3)			580 mg (n=3)			1160 mg (n=3)		
	Mean	SD	CV (%)	Mean	SD	CV (%)	Mean	SD	CV (%)
GPI 15715									
C_{max} (µg/mL)	34.2	10.2	29.8	71.6	3.02	4.2	133	12.2	9.2
T_{max}(min)	11.3	1.2	10.2	10	0	0	10	0	0
AUC_{0-t} (µg·min/mL)	617	211	34.2	1072	31.1	2.9	2223	450	20.2
AUC_{0-inf} (µg·min/mL)	618	212	34.3	1074	30.7	2.9	2229	453	20.3
Formate									
C_{max} (µg/mL)	34.8	12.7	36.5	31.9	4.9	15.4	33.5	2.0	6.0
AUC_{0-t} (µg·min/mL)	31058	8727	28.1	33156	3532	10.7	33830	3941	11.6
Mean (SD) [Range] Predose level (µg/mL)	24.3 (8.0) [15-36]								
Mean Postdose level† (µg/mL)	24.6	9.3 15-49*		21.6 15-36*	5.1		20.9 15-30*	3.0	

* Range

† Postdose level is a summary of all concentration time points after dosing began.

Following administration of the 3 different doses of GPI 15715 (290 mg, 580 mg, 1160 mg) to 3 volunteers per group, exposure to GPI 15715 and propofol, in terms of the mean AUC_{0-inf} and C_{max},

PK of propofol from this study were not reliable (see analytical assay 2.6 section)

4.3.6 Study # 3000-0102 Synopsis

See Analytical section 2.6 regarding propofol assay issue.

Title of Study: Phase 1, Open Label Study of Induction and Maintenance of Sedation, Safety and Tolerability, Pharmacokinetics/Pharmacodynamic of GPI 15715 in Healthy Volunteers
Investigator and Study Center: [redacted] b(4)
Publication (reference): None
Study Period: **Phase of Development**: 1 First subject enrolled: 09 July 2001 Last subject completed: 06 August 2001
Objectives: • To evaluate the safety and tolerability of intravenous infusion of GPI 15715 at doses targeted to induce and maintain sedation. • To evaluate potential dosing paradigm for clinical sedation. • To determine the pharmacokinetic/pharmacodynamic properties of propofol derived from GPI 15715 during constant-rate infusion.
Methodology: This was an open-label, nonrandomized, single-center study conducted in healthy 18- to 55-year-old male and female volunteers. Twelve volunteers (6 males and 6 females) received GPI 15715 by infusion for a total of 2 hours. Rather than using a strict constant-rate infusion as stated in the objectives, a computer-controlled pump was used to administer GPI 15715 to achieve the targeted plasma propofol concentration of 1.8 µg/mL as rapidly as possible and to maintain this plasma concentration for 1 hour. The level of sedation was predicted to be mild to moderate, ie, associated with a score of 3 or 2, respectively based on the Modified Observer's Assessment of Alertness/Sedation (OAA/S) scale. Dosing was adjusted by increasing the rate of infusion to achieve a higher target plasma propofol concentration after 1 hour if the subject's Modified OAA/S score was not 2 or 3. The infusion was then continued for an additional hour whether adjusted for clinical sedation or not. Dosing adjustments increased the target plasma propofol concentration to 3.0 µg/mL if the subject was alert (Modified OAA/S score of 5) or to 2.4 µg/mL if the subject attained a Modified OAA/S score of 4 after a 1-hour infusion. Dose adjustments for the second hour were made for 9 of the 12 enrolled subjects. Target plasma concentrations during the second hour and total doses applied during the 2-hour infusion of GPI 15715 are shown below.

Target plasma propofol concentration during the second hour of infusion* (μg/mL)	**1.8 (n=3)**	**2.4 (n=7)**	**3.0 (n=2)**
Total GPI 15715 dose administered over 2 hours (mg)			
Mean (SD)	2232.7 (546.1)	2564.9 (491.4)	2878.5 (505.7)
Minimum–Maximum	1602.3–2560.5	2147.7–3531.7	2520.9–3236.2

* During the first hour all subjects received GPI 15715 at rates targeting a plasma propofol concentration of 1.8 μg/mL

Serial plasma samples were collected prior to, during, and following GPI 15715 infusion for up to 240 minutes for arterial blood and for up to 1440 minutes for venous blood after start of the infusion for determination of plasma propofol, GPI 15715, and formate concentrations from GPI 15715 and estimates of pertinent pharmacokinetic (PK) parameters.

Clinical assessments of sedation were based on the subject's responsiveness scores based on the 6-point Modified OAA/S scale. Electroencephalogram (EEG), Bispectral (BIS) Index, electrocardiogram (ECG), pulse oximetry, and vital signs (systemic blood pressure and pulse) were recorded at baseline and monitored continuously during and following GPI 15715 infusion for up to 360 minutes (362 minutes for vital signs) after start of the infusion. A 12-lead ECG was performed prior to and at periodic intervals during and after the infusions. Arterial blood samples were collected during and after the infusion to analyze for blood gases, ionized calcium, and electrolytes. Body temperature was measured and physical/neurological examinations and clinical laboratory tests from venous blood samples (serum chemistry, electrolytes, hematology) and urinalysis conducted pre- and post treatment. Clinical signs were monitored continuously for the occurrence of adverse events (AEs). A total of 4 visits were scheduled: screening, study drug administration, and follow-up Visits 3 and 4. Each subject was confined to the anesthesiology laboratory for 4 hours following the last clinical sign of sedation prior to discharge from the clinic. Subjects returned to the clinic on the following day (Visit 3) and approximately 3 days following drug medication administration (Visit 4) for follow-up evaluations.

Number of Subjects (Planned and Analyzed):
A total of 12 healthy volunteers (6 male and 6 female subjects) were planned, enrolled, and completed all scheduled dosing and study procedures.

Diagnosis and Main Criteria for Inclusion: Volunteers for this study were healthy males and females 18 to 55 years of age, who had not smoked for at least 6 months prior to start of study, and who had signed the informed consent form.
Test Product, Dose and Mode of Administration, Batch Number: GPI 15715 was supplied by Guilford Pharmaceuticals as a sterile aqueous solution in 0.4% saline at a concentration of 20 mg/mL. Each vial contained 20 mL of solution (Batch No: 1214-07).
Duration of Treatment: 2-hour infusion
Reference Therapy, Dose and Mode of Administration, Batch Number: None
Criteria for Evaluation: Pharmacokinetics: Noncompartmental analysis of plasma (arterial and venous) GPI 15715, propofol, and formate concentration-time data were used in the determination of pharmacokinetic parameters using WinNonlin® Professional (Version 3.1). The following parameters were determined: area under the concentration-time curve from time of dosing to the last measured concentration (AUC_{0-t}), area under the concentration versus time curve from the time of dosing to infinity (AUC_{0-inf}), maximum plasma concentration (C_{max}), time to attain C_{max} (T_{max}), terminal rate constant (λ_z), elimination half-life ($t_{1/2}$.). For formate, mean pre-dose and post-dose levels, and percent of concentrations below quantification limit (%BLQ) were also assessed for all subjects together. The PK/PD relationships between plasma concentrations of propofol and/or GPI 15715 and measurements of clinical outcome, clinical chemistry, and physiological response were assessed, if possible. Pharmacodynamics: The pharmacodynamic (PD) effect of the study drug was determined from continuous EEG and BIS recordings and from clinical assessments of sedation using the Modified OAA/S scale. Safety: Safety was evaluated based on AEs, vital signs, body temperature, pulse oximetry, physical and neurological examinations, 12-lead ECG, clinical laboratory test results (hematology, serum chemistry, electrolytes from venous blood samples) including blood gases, ionized calcium, and electrolytes in arterial blood samples, and urinalysis.
Statistical Methods: Pharmacokinetics: Descriptive statistics (N, mean, standard deviation [SD], median, minimum, maximum, % coefficient of variation [CV] was used to summarize pharmacokinetic parameters. No formal statistical analysis was planned, but an analysis of variance (ANOVA) was performed for comparison of C_{max} and AUC in venous and arterial plasma samples.
Pharmacokinetics/Pharmacodynamics: Though planned in the protocol, the assessment of the PK/PD relationships between plasma concentrations of GPI 15715 and/or propofol and measurements of clinical outcome, clinical chemistry, and physiological measurements were not performed. Safety: All subjects who received study drug were included in safety evaluations. All data collected in the study were summarized using descriptive statistics. AEs (Medical Dictionary for Regulatory

Activities [MedDRA], Version 3.3) were listed by subject and were summarized by dose and overall for body systems and preferred terms.

Summary of Results

Pharmacodynamics: According to a prespecified criteria (Modified OAA/S score at minute 52), dose adjustments were made for 9 of the 12 subjects after the first hour of infusion: for 7 subjects and 2 subjects, the rate of infusion was increased to target plasma propofol concentration of 2.4 μg/mL and 3.0 μg/mL, respectively. After this adjustment, all subjects reached Modified OAA/S score of 3 or below. The induction in sedation was reflected by a reduction in the frequency of the EEG signal and reduction in the value of the BIS Index. Consistent with the variability in the Modified OAA/S scores during the first hour of the infusion, there were considerable variations in the reductions in the frequency of the EEG signal and the BIS Index across subjects. There were no apparent clinically meaningful differences in the median EEG frequency or BIS Index between males and females at baseline and during the first hour of infusion with GPI 15715.

Pharmacokinetics:

The results of the pharmacokinetic data analysis for all subjects, overall and by gender, for GPI 15715, propofol, and formate are presented below.

Summary of Pharmacokinetic Data Analysis for GPI 15715, Propofol, and Formate for All Subjects

Plasma	Analyte	Mean C_{max} [μg/mL] (SD)			Mean AUC_{0-t} §[μg·min/mL] (SD)			Mean AUC_{0-4} ^[μg·min/mL] (SD)
		Males (n=6)	Females (n=6)	Combined (N=12)	Males (n=6)	Females (n=6)	Combined (N=12)	Combined (N=12)
Arterial	GPI 15715	121 (16)	112 (16)	116 (16)	6918 (1071)	6644 (2195)	6781 (1653)	6781 (1653)
	Formate†	22.7 (NA)	23.1 (1.6)	23.0 (1.3)	4062 (NA)	3870 (138)	3918 (148)	3918 (148)
Venous**	GPI 15715	118 (20)	101 (16)	110 (19)	6981 (1046)	6206 (1792)	6628 (1412)	6592 (1394)
	Formate	23.9 (4.1)	23.5 (1.2)	23.7 (3.0)	22163 (2454)	22177 (1557)	22170 (1995)	4017 (341)

NA= Not applicable

† Males, n=1; Females, n=3; Combined, n=4

** Males, n=6; Females, n=5; Combined, n=11

§ Sampling interval was 5 – 240 min for arterial plasma, and 7-1440 min for venous plasma.

^ AUC from 0 to 4 hours (242 minutes for venous plasma), calculated for comparison of arterial and venous data.

4.3.7 Study 3000-0103 Synopsis

See Analytical section 2.6 regarding propofol assay issue.

Title of Study: Phase I, Open Label, Single-Bolus Dose, Dose Escalation, Safety, and Tolerability, Pharmacokinetic/Pharmacodynamic Study of AQUAVAN® Injection in Healthy Volunteers	
Investigator and Study Center: [redacted]	
Publication (reference): None	
Study Period: 10 December 2001 (first subject enrolled) 26 April 2002 (last subject completed)	**Phase of Development**: I
Objectives: • To evaluate the safety and tolerability of escalating bolus doses of AQUAVAN® Injection up to a dose producing maximal hypnotic effect as defined by electroencephalogram (EEG) assessment. • To compare the pharmacokinetic/pharmacodynamic properties of propofol when derived from AQUAVAN® Injection, delivered as a bolus, to that derived from DIPRIVAN® Injectable Emulsion.	
Methodology: This was an open-label, crossover, nonrandomized, single-center study conducted in 36 healthy males and females between the ages of 18 and 45 years. Eligible subjects were admitted to the supervised Phase 1 unit within the hospital approximately 2 hours prior to administration of AQUAVAN® Injection (hereafter, referred to as AQUAVAN) and resided in the clinic overnight as a safety precaution. Subjects were asked to return to the clinic approximately 3 days after dosing for a follow-up safety evaluation. After a washout period of 7 days, each subject returned to the clinic to receive a comparator dose of DIPRIVAN® Injectable Emulsion (hereafter, referred to as DIPRIVAN), targeted to produce the same peak EEG effect that had been observed after the AQUAVAN, as measured by the minimal Bispectral Index (BIS) value. The same procedures were followed for both the administration of AQUAVAN and DIPRIVAN.	
Three subjects of each gender were evaluated at each dose level of AQUAVAN. Dose escalation was dependent on attaining the maximal effect criterion, a burst suppression rate higher than 10 as shown on the BIS Monitor. Escalation in each gender was evaluated independently. After the completion of each dose group per gender, a preliminary assessment of the safety and tolerability profile was made, including a review of adverse events, vital signs measurements, clinical laboratory findings, and physical and neurological assessments. If mean arterial pressure fell below 40 in any subject for greater than 5 minutes, the escalation was stopped. After the complete review of each group, a decision on how to proceed was made according to the study schema and subject safety provided in the following dosing scheme.	

b(4)

Dose Escalation Scheme:

1. If the maximal effect criterion was reached in 0 of 3 subjects per gender, the dose was increased by 100%.
2. If the maximal effect criterion was reached in 1 of 3 subjects per gender, the dose was increased by 50%.
3. If the maximal effect criterion was reached in 2 of 3 subjects per gender, the dose was increased by 25%.

If the maximal effect criterion was reached in all 3 subjects per gender, the study was concluded. The maximum proposed dose of AQUAVAN was 2700 mg (30 mg/kg). If a laboratory phosphorous level at or above 12.4 mg/dL was observed in any subject after administration of AQUAVAN, the study was to be concluded.

The comparator dose of DIPRIVAN could not exceed the recommended maximal dose stated on the manufacturer's label (2.5 mg/kg). The dosing paradigm was completed with 6 AQUAVAN groups (5-, 10-, and 20-mg/kg groups followed the dose escalation scheme noted above, and 15- 25-, and 30-mg/kg groups were subsequently added to provide coverage up to the maximum proposed dose).

Serial arterial and venous plasma samples were collected prior to, during, and following AQUAVAN, or DIPRIVAN administration, for up to 8 hours for determination of plasma GPI 15715, propofol, and formate (venous only) concentrations and for estimates of pertinent pharmacokinetic parameters. An additional venous sample was taken at approximately 24 hours postdose. Urine was also collected to determine the extent of urinary excretion of GPI 15715 and propofol.

Safety was assessed by the monitoring of adverse events (AEs), vital signs, pulse oximetry, respiratory rate, end tidal CO_2 ($ETCO_2$), and electrocardiogram (ECG). Clinical laboratory tests, arterial blood gases, and body temperature were also performed and evaluated.

Each subject's BIS was measured as a quantitative measure of the pharmacodynamic (PD) response. Clinical measures included the subject's ability to respond to a loud verbal command (clinical rating of sedation level) and the Modified Observer's Assessment of Alertness Sedation (OAA/S) scale.

Number of Subjects (Planned and Analyzed): No formal sample size estimation was made for this study. Three males and 3 females in each group were considered sufficient for the objectives of this study. The dosing paradigm was completed with 6 AQUAVAN dose levels, for a total of 36 subjects (18 males and 18 females). Data from all 36 subjects were included in the safety, pharmacokinetic, and pharmacodynamic analyses.

Diagnosis and Main Criteria for Inclusion: Volunteers for this study were healthy males and females, 18 to 45 years of age, who had not smoked for at least 1 year prior to start of study, and who had signed the informed consent form.

Test Product, Dose and Mode of Administration, Batch Number:

AQUAVAN was supplied by Guilford Pharmaceuticals Inc. as a sterile aqueous solution in 0.4% saline (NaCl) at a concentration of 20 mg/mL. Each vial contained 20 mL of solution (Batch No: 1214-07).

AQUAVAN was administered manually, as quickly as possible. The duration of dosing was recorded.

Study Duration: Three to 4 days for each of 2 dose administrations separated by a washout period of approximately 7 days.

Reference Therapy, Dose and Mode of Administration, Batch Number: DIPRIVAN was supplied in its commercial form, and was administered as a rapid infusion at 50 mg/min via a standard infusion pump to produce a propofol effect equal to that produced by the preceding AQUAVAN bolus in that subject.

Criteria for Evaluation:

Pharmacokinetics: The following arterial and venous plasma pharmacokinetic parameters of GPI 15715 and propofol were determined for each dosing group using non-compartmental techniques: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, λ_z, CL, and Vd (CL/F and Vd/F for propofol from AQUAVAN), and $T_{1/2}$. In addition, due to differences in arterial and venous sampling times, partial AUC (over comparable time intervals) were computed for GPI 15715 and propofol from AQUAVAN for comparison of arterial and venous exposure. For formate in plasma, venous AUC_{0-t}, C_{max} and T_{max} were determined.

For urine, only cumulative fraction of GPI 15715 excreted could be estimated as a majority of urine samples showed no measurable levels. Bioanalytical assay for determination of propofol in urine could not be validated, therefore the analysis of propofol in urine was not performed.

Pharmacodynamics: The PD effect of the study drug was determined from continuous EEG and BIS recordings and from clinical assessments of sedation using the subject's ability to respond to a loud verbal command and the Modified OAA/S scale. Two minutes after subjects regained the ability to respond, the Modified OAA/S scale was implemented. For subjects who did not lose the ability to respond, the response to verbal command assessment was discontinued after 20 minutes and implementation of the Modified OAA/S scale began.

Safety: Safety was evaluated based on AEs, vital signs, body temperature, pulse oximetry, physical and neurological examinations, 12-lead ECG, and clinical laboratory test results (urinalysis; venous blood samples: hematology, serum chemistry, electrolytes; arterial blood samples: blood gases, calcium and phosphorus, and electrolytes).

Statistical Methods:

No formal statistical testing was planned. Pharmacodynamic and safety results were explored using descriptive statistics only. Although not planned, statistical comparisons (described below) were performed for pharmacokinetic results.

Pharmacokinetics: Plasma pharmacokinetic parameters of GPI 15715, propofol, and formate were summarized for each dosing group of the AQUAVAN and DIPRIVAN treatments. For formate, predose and postdose levels, and percent levels below quantification limit (%BLQ) were summarized across all subjects and time points for each dosing group of both treatments.

Dose proportionality of arterial and venous GPI 15715 and propofol C_{max} and AUC_{0-t} from AQUAVAN and arterial AUC_{0-t} from DIPRIVAN was evaluated by fitting a power model under the assumption of lognormal distribution of parameters, and obtaining 90% confidence intervals for the power parameter. Comparison of venous and arterial partial AUC for GPI 15715 and propofol was performed by ANOVA on log-transformed values. Ratios of arterial to venous parameters and their 90% confidence intervals were determined for each dosing group. Comparison of peak concentrations was not performed due to differences in sampling times; graphical comparisons of the overall concentration time curves were made. Formate C_{max} and AUC_{0-t} following AQUAVAN were compared with those following DIPRIVAN for the highest dosing group and all subjects combined by computing 90% confidence intervals for the means of the respective individual ratios under assumption of log-normal distribution of C_{max} and AUC_{0-t} parameters.

Pharmacodynamics: Bispectral Index results were summarized for the same subjects for each of the AQUAVAN and DIPRIVAN treatments. Burst suppression results were summarized for each time point

grouped by each dose level of AQUAVAN and by gender. Response to verbal command was summarized at each minute postdose for 20 minutes or until subjects lost the ability to respond. Responses were grouped by dose level and reported separately for AQUAVAN and DIPRIVAN. Response to verbal command was not summarized by gender. The frequency distribution for responsiveness scores from the Modified OAA/S scale is summarized by dose level of AQUAVAN.

Safety: All subjects who received study drug were included in the safety analysis. All data collected in the study were summarized using descriptive statistics. Adverse events (as categorized in the Medical Dictionary for Regulatory Activities [MedDRA] Version 5.0) were listed by subject and were summarized by dose and overall for system organ class and preferred terms.

SUMMARY OF RESULTS

Pharmacokinetics:

Pharmacokinetics of GPI 15715 and Propofol from AQUAVAN

Mean (SD) Arterial Pharmacokinetic Parameters of GPI 15715 and Propofol following Administration of AQUAVAN

Analyte	Dose (mg/kg)	C_{max} * [µg/mL]	AUC_{0-t} [µg•h/mL]	CL ** (L/h/kg)	Vd ** (L/kg)	$T_{1/2}$ (h)	T_{max} *,† (h)
Arterial GPI 15715	5	103 (8)	19.4 (4.2)	0.267 (0.057)	0.386 (0.104)	1.01 (0.24)	NA
	10	209 (17)	37.0 (4.2)	0.273 (0.032)	0.501 (0.139)	1.26 (0.26)	NA
	15	216 (40)	44.4 (10.0)	0.354 (0.090)	0.754 (0.214)	1.49 (0.30)	NA
	20	358 (41)	63.4 (11.8)	0.323 (0.049)	0.722 (0.245)	1.52 (0.32)	NA
	25	430 (55)	78.9 (11.2)	0.323 (0.051)	0.694 (0.143)	1.49 (0.16)	NA
	30	490 (42)	83.3 (9.5)	0.364 (0.040)	0.848 (0.157)	1.62 (0.26)	NA
Arterial Propofol (derived from GPI 15715)	5	0.615 (0.197)	0.480 (0.141)	5.864§ (0.974)	24.6§ (11.5)	2.84§ (0.91)	0.05 (0.03-0.17)
	10	1.55 (0.49)	1.15 (0.177)	4.37 (0.86)	20.5 (8.46)	3.40 (1.72)	0.07 (0.02-0.12)
	15	3.30 (1.08)	1.96 (0.345)	3.93 (0.62)	19.8 (7.17)	3.41 (0.69)	0.12 (0.07-0.12)
	20	4.87 (0.885)	2.81 (0.310)	3.51€ (0.298)	15.8€ (4.16)	3.09€ (0.75)	0.12 (0.07-0.17)
	25	5.28 (0.90)	3.84 (0.43)	3.33€ (0.427)	16.0€ (8.71)	3.39€ (2.11)	0.09 (0.07-0.17)
	30	8.24 (2.12)	5.37 (1.24)	2.85 (0.761)	19.4 (5.29)	4.89 (1.74)	0.09 (0.02-0.17)

* For GPI 15715, C_{max} was observed at the first sampling time (1 minute)

** For propofol, apparent value (CL/F or Vd/F) based on AQUAVAN dose adjusted for propofol molecular weight

† Median (range)

§ N=4

€ N=5

NA=Not applicable, since with bolus intravenous administration, T_{max} of GPI 15715 was observed at the first sampling time

Plasma concentrations of GPI 15715 rapidly declined after bolus administration. The initial rapid decline was followed by a slower terminal phase with half-life of 1.0 - 2.0 h. Propofol concentrations increased rapidly (median T_{max} of 3-7.2 and 9-12 min, in arterial and venous plasma, respectively). Rapid initial decrease after peak was followed by a slower terminal phase with half-life of 2.8 – 4.9 h. Mean systemic exposure (AUC_{0-t}) and peak concentrations (C_{max}) of GPI 15715 and propofol were similar between males and females. Exposure to GPI 15715 increased slightly less than dose proportionally (but statistically significant): for a 6-fold increase in dose, mean arterial C_{max} and AUC_{0-t} increased 4.8 and 4.3 times, respectively. Propofol exposure rose faster than dose: mean arterial C_{max} and AUC_{0-t} increased 13- and 11-fold, respectively. GPI 15715 arterial and venous concentration-time profiles were nearly identical. Propofol C_{max} and AUC_{0-t} were higher in arterial samples, with no significant differences in the partial AUC.

Pharmacokinetics of Propofol from DIPRIVAN: The average DIPRIVAN® doses (in the groups corresponding to AQUAVAN dose groups) ranged from 1.0 to 5.1 mg/kg. The infusion lasted from 0.9 to 9.4 minutes. Mean arterial AUC_{0-t} increased proportionally with dose (with the 90% confidence interval for the power parameter of the power model being (0.98 -1.25). Mean arterial C_{max} increased less than dose proportionally (2.3-fold), which should be expected for a drug with very high clearance administered as infusion. Venous exposure (both AUC_{0-t} and C_{max}) increased greater than dose proportionally, which could also be expected since the late first sampling time (5 min) missed C_{max} and larger portions of AUC_{0-t} at lower doses where infusions were shorter.

Arterial C_{max} and AUC_{0-t} were higher than the venous parameters, as expected based on the difference in the timing of the first sample.

Mean (SD) Arterial Pharmacokinetic Parameters of Propofol Following Administration of DIPRIVAN**

Analyte	DIPRIVAN® Dose* (mg/kg)	AQUAVAN Dose Group (mg/kg)	C_{max} † (μg/mL)	AUC_{0-t} (μg•h/mL)	CL (L/h/kg)	Vd (L/kg)	$T_{1/2}$ (h)
Arterial Propofol	1.01	5	7.24 (3.92)	0.507 (0.303)	2.39§ (0.12)	9.34§ (0.1.77)	2.73§ (0.66)
	1.33	10	8.32 (3.06)	0.648 (0.177)	1.93€ (0.29)	12.32€ (5.26)	4.44€ (1.73)
	2.37	15	11.9 (5.1)	1.27 (0.40)	1.89€ (0.53)	14.15€ (10.65)	4.73€ (2.81)
	2.85	20	14.1 (3.7)	1.42 (0.31)	1.84€ (0.16)	12.55€ (5.48)	4.64€ (1.63)
	4.03	25	16.5 (3.2)	2.136 (0.552)	1.82 (0.16)	7.89 (4.92)	3.02 (1.92)
	5.10	30	16.3€ (4.7)	2.92€ (0.69)	1.79† (0.21)	8.45† (3.96)	3.22† (1.353)

* DIPRIVAN average dose
**Total propofol including propofol aggregated in formulation (lipid emulsion)
§ N = 2, † N = 4, € N = 5

Comparison of Propofol Concentrations from DIPRIVAN and AQUAVAN: C_{max} of propofol delivered from DIPRIVAN was higher than those from AQUAVAN, with the ratio of C_{max} values of 12 –2, at the lowest to the highest dose groups. Decline of plasma concentrations was slower for propofol from AQUAVAN, and AUC values were higher in AQUAVAN treatment arms. Ratios of mean propofol AUC ranged between 1.8-1.0 from the lowest to the highest dose groups.

Formate Pharmacokinetics: Formate concentration-time profiles were relatively flat across all dose groups, regardless of the treatment arm. The C_{max} and AUC_{0-t} values for formate were similar for both male and female volunteers. There was no trend towards increasing formate exposure with increasing doses of DIPRIVAN or AQUAVAN: C_{max} and AUC_{0-t} were similar across all dose groups and treatments. A statistical comparison of Cmax and AUC_{0-t} showed no significant differences between the treatments. Mean post dose levels for all dose groups were also similar to the predose levels for both treatments.

GPI 15715 in Urine Following AQUAVAN: Following administration of AQUAVAN, out of 223 urinary samples analyzed for GPI 15715, only 10 samples (<5%) from 9 subjects showed measurable concentration. The majority (8 samples) of measurable concentrations were from the first collection time point (mainly 3 h) and from higher doses (25 and 30 mg/kg). The fraction of unchanged GPI 15715 excreted in urine was < 0.02%, indicating insignificant renal elimination of unchanged GPI 15715.

Pharmacodynamics: The maximal effect criterion of a burst suppression rate higher than 10 was not reached in any subject at the 5 mg/kg, 10 mg/kg, or 20 mg/kg dose of AQUAVAN. Increasing the dose to 25 mg/kg and then to 30 mg/kg induced a burst suppression rate of higher than 10 in 1 of 6 subjects in each dose group. The study maximal effect endpoint was therefore not reached. All subjects given AQUAVAN at 5 mg/kg and 10 mg/kg remained responsive to verbal command but experienced sedation as shown by BIS scores and by OAA/S scores. Higher doses of AQUAVAN caused loss of responsiveness to verbal command in 5 of 6 subjects (15 mg/kg) or 6 of 6 subjects (20 mg/kg, 25 mg/kg, 30 mg/kg). The time to loss of responsiveness showed a trend to dose relatedness for AQUAVAN and for DIPRIVAN. Time to recovery, as measured by the median time to attain alertness (a score of 5 on the Modified OAA/S scale), was dose dependent for both AQUAVAN and for DIPRIVAN. The median time to attain alertness (OAA/S score of 5) was longer for subjects receiving AQUAVAN at 15, 20, 25 or 30 mg/kg than for those receiving equivalent doses of DIPRIVAN (20, 45, 59.5, and 72 minutes, respectively for the AQUAVAN groups but only 9, <9.5, 20, and 26.5 minutes for the equivalent DIPRIVAN groups. The depth of sedation, measured objectively by BIS, was dose dependent for both AQUAVAN and DIPRIVAN, but the time to mean minimum BIS was not dose dependent for either drug. The mean time to minimum BIS was longer for AQUAVAN than DIPRIVAN at all doses (10 minutes versus 5 minutes)

Safety: Safety data were collected for all 36 subjects treated in this open-label study of bolus injections in healthy volunteers. No deaths or serious adverse events occurred during the study. There were no discontinuations due to adverse events. Across all dose levels of AQUAVAN, the most frequently reported events were nervous system disorders, which manifested primarily as paresthesias; all of which were considered potentially related to study drug.

Pharmacokinetic Conclusions

- Systemic exposure (C_{max} and AUC_{0-t}) to GPI 15715, propofol, and formate were similar between healthy male and female volunteers.
- GPI 15715 plasma concentrations increase slightly less than dose proportionally with increasing dose.

See Analytical Section 2.6 regarding Propofol assay issues.

- Propofol plasma concentrations following AQUAVAN increase greater than dose proportionally with increasing dose.
- Observed peak concentrations of GPI 15715 and propofol (from both treatments) were higher in arterial than in the venous plasma. In the case of GPI 15715 and propofol delivered from DIPRIVAN, this can be attributed to the differences in arterial and venous sampling schedules.
- Arterial and venous exposures (AUC) of GPI 15715 and propofol delivered from AQUAVAN were similar.
- Peak concentrations of propofol delivered from AQUAVAN were 2 – 12 times lower than from equipotent doses of DIPRIVAN even though the peak pharmacodynamic effect was the same. This effect can partially be explained by the "trapping" of propofol in the lipid emulsion and preventing its distribution from plasma into tissues following treatment with DIPRIVAN.
- Propofol exposure (AUC) from AQUAVAN was 1.0 – 1.8 times higher than the exposure from the corresponding dose groups of DIPRIVAN.
- Formate exposure from AQUAVAN and DIPRIVAN were similar. Administration of AQUAVAN did not lead to an increase in formate plasma concentrations over endogenous levels.
- The fraction of unchanged GPI 15715 excreted in urine was <0.02%, indicating insignificant renal elimination of unchanged GPI 15715.

Pharmacodynamic Conclusions

- Subjects treated with 5 mg/kg or 10 mg/kg AQUAVAN did not lose responsiveness to verbal command. The time to nonresponsiveness was dose dependent.
- Subjects receiving AQUAVAN remained sedated longer than subjects receiving the equivalent dose of DIPRIVAN. The time taken to become fully alert was longer for AQUAVAN treated subjects and the time to alertness was dependent on the dose of propofol for both drugs.
- There were no consistent clinically relevant differences in burst suppression rate, BIS Index, response rate, or Modified OAA/S scores between males and females.

Safety Conclusions

- Overall, AQUAVAN and DIPRIVAN administered to healthy volunteers as a bolus were well tolerated. No unexpected clinically significant findings or adverse trends in ECGs, clinical laboratory parameters from venous blood, body temperature, or neurological and physical examinations during the study were noted.
- No serious adverse events occurred during the study and no withdrawals due to adverse events were reported.
- The number of AEs reported after AQUAVAN administration was twice the number of AEs reported after the administration of DIPRIVAN.
- Across all dose levels of AQUAVAN, the most frequently reported events were nervous system disorders, which manifested primarily as paresthesias; all of which were considered potentially related to study drug.
- With the exception of paresthesias (occurring only in AQUAVAN groups) and injection site pain

(occurring only in DIPRIVAN groups), there did not appear to be a clinically relevant difference in the type of adverse events among subjects who received different doses of either treatment.

- The effects of propofol delivered from AQUAVAN on blood pressure (including mean arterial pressure) and pulse rate were mild, transient (ie, values typically returned to near baseline levels by the time subjects were fully alert), and without sequelae. The decrease in systolic and diastolic blood pressure coincided with the time most subjects were fully sedated. There were no effects on body temperature. Mild and transient decreases in pulse rate and pulse oximetry were observed. These effects of AQUAVAN are similar to those seen at doses of DIPRIVAN that produce comparable pharmacodynamic effects
- Arterial blood gas and electrolyte values outside the normal range were noted for all subjects; however, none was considered by the Investigator to be clinically significant.
- There was no increase in formate exposure in AQUAVAN treated subjects compared with DIPRIVAN
- Mean triglyceride values were notably higher 10 minutes postdose among subjects who received higher doses of DIPRIVAN (equivalent to AQUAVAN doses of 20 mg/kg, 25 mg/kg, and 30 mg/kg) These mean increases were not noted after AQUAVAN administration, and in all probability were related to the oil-in-water emulsion formulation of DIPRIVAN.

4.3.8 Study 3000-0206 Synopsis

See Analytical section 2.6 regarding propofol assay issue.

Title of Study: Phase 1 Open Label, Randomized, Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Study of AQUAVAN® Injection in Healthy Volunteers	
Investigator and Study Center: [redacted]	
Publication (reference): None	
Study Period: First subject enrolled: 10 May 2002 Last subject completed: 01 August 2002	**Phase of Development**: 1

Objectives:

- To evaluate and compare the safety and tolerability of a 400-mg dose of AQUAVAN® Injection (AQUAVAN) administered under the following conditions:
  - A. 400-mg bolus injection
  - B. 200-mg/min infusion over 2 minutes
  - C. 40-mg/min infusion over 10 minutes
  - D. 30-mg/min infusion over 5 minutes, followed by a 250-mg bolus injection
  - E. 50-mg bolus injection, wait 5 minutes, followed by a 350-mg bolus injection
  - F. 0.10 mg of fentanyl, wait 5 minutes, followed by 400-mg bolus AQUAVAN
  - G. 0.10 mg of fentanyl, wait 5 minutes, followed by 400-mg AQUAVAN administered as 200-mg/min infusion over 2 minutes
  - H. 0.10 mg of fentanyl, wait 5 minutes, followed by 400-mg AQUAVAN administered as 40-mg/min infusion over 10 minutes
  - I. 75 mg meperidine, wait 5 minutes, followed by 400-mg bolus AQUAVAN
- To determine the pharmacokinetic and pharmacodynamic profile of a 400-mg dose of AQUAVAN administered as a bolus injection and at various rates of administration as listed in the first objective.

Methodology:

This was an open-label, single-center, pharmacokinetic, pharmacodynamic, and safety study conducted in healthy males 18 to 45 years of age.

Number of Subjects (Planned and Analyzed):

A total of 54 healthy males (6 per dosing regimen) were planned, enrolled, and completed all scheduled dosing and study procedures. Data from all 54 subjects were included in the safety, pharmacokinetic, and pharmacodynamic analyses.

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Diagnosis and Main Criteria for Inclusion:

Healthy males between the ages of 18 and 45 years; nonsmoker for at least 1 year prior to study start; and in good health as determined by medical history, physical examination, and clinical laboratory tests.

Test Product, Dose and Mode of Administration, Batch Number:

All drugs were administered intravenously.

AQUAVAN was supplied by Guilford Pharmaceuticals as a sterile aqueous solution in 0.4% saline at a concentration of 20 mg/mL. Each vial contained 20 mL of solution. Lot No: 1214-10.

Fentanyl® Citrate Injection was supplied in 2-mL ampoules (50 μg/mL). Lot No: 88-102-DK, obtained commercially.

Meperidine (Demerol®) was supplied in 20-mL vials (100 mg/mL). Lot No: 874453A, obtained commercially

Duration of Treatment: Subjects checked into the clinic the night before study drug administration and were released 24 hours following dosing. Subjects were asked to return approximately 3 days following their study drug administration for a follow-up safety evaluation.

Reference Therapy, Dose and Mode of Administration, Batch Number: None.

Criteria for Evaluation:

Pharmacokinetics: The following pharmacokinetic parameters were determined for GPI 15715 and propofol from plasma concentration-time data: area under the concentration-time curve from time of dosing to the last measured concentration ($AUC_{0\text{-last}}$), area under the concentration-time curve from the time of dosing to infinity ($AUC_{0\text{-inf}}$), maximum plasma concentration (C_{max}), time to attain C_{max} (t_{max}), terminal elimination rate constant (λ_z), elimination half-life ($t_{1/2}$), plasma clearance (CL_p), and volume of distribution (V_d). For propofol, plasma clearance and volume of distribution are apparent values (CL/F and Vz/F, where F is the fraction of GPI 15715 converted to propofol). For formate, baseline-corrected and uncorrected C_{max}, $AUC_{0\text{-last}}$ and uncorrected t_{max} were calculated as well as pre- and postdose levels and percent of concentrations below quantification limit (%BLQ) across all subjects and time points

Pharmacodynamics: Pharmacodynamic variables were the Bispectral Index (BIS), the Modified Observer's Assessment of Alertness/Sedation Scale (Modified OAA/S) Scale, and the Visual Analog Scale (VAS).

Safety: Safety was evaluated based on adverse event reporting; vital sign measurements; pulse oximetry; physical, neurological, and visual examinations; 3-lead and 12-lead electrocardiogram (ECGs); and clinical laboratory testing (hematology, serum chemistry, and urinalysis), including blood gases, ionized calcium, and electrolytes in arterial blood samples.

Statistical Methods:

Pharmacokinetics: Pharmacokinetic parameters were calculated using non-compartmental analysis in SAS (Version 8.02). Descriptive statistics (n, mean, median, standard deviation, minimum, maximum, and geometric mean) were tabulated for plasma concentrations at each time point and for calculated pharmacokinetic parameters.

Pharmacodynamics: Results for BIS scores were summarized for all subjects by dosing regimen and time point. The number and percentage of subjects with results from the Modified OAA/S scale were tabulated by time point. Results from the discomfort and sensation VAS scales were summarized for all subjects at 110 minutes postdose using descriptive statistics. No correlations between plasma concentrations and pharmacodynamic parameters were calculated.

Safety: All subjects who received study drug were included in the safety analyses. All data collected in the

study were summarized using descriptive statistics. Adverse events (coded using Medical Dictionary for Regulatory Activities [MedDRA], Version 3.3) were listed by subject and were summarized by dose and overall for body systems and preferred terms. Results for vital signs; body temperature; respiratory rate; pulse oximetry; laboratory testing; ECGs; VAS; and physical, neurological, and visual examinations were tabulated and presented using descriptive statistics.

SUMMARY OF RESULTS

A total of 54 subjects participated in the study; one subject did not complete the study per-protocol as he did not complete the follow-up visit.

Pharmacokinetics:

Mean (SD) GPI 15715 Pharmacokinetic Parameters

Dosing Scheme	Regimen	N	$AUC_{0\text{-}inf}$ (µg•hr/mL)	$AUC_{0\text{-}last}$ (µg•hr/mL)	C_{max} (µg/mL)	CL_p (L/hr)	Vd (L)	$t_{1/2}$ (hr)
Bolus Injection	A	6	15.6 (4.0)	15.6 (4.0)	110 (16)	23.4 (6.1)	28.1 (8.2)	0.87 (0.27)
	F	6	21.3 (3.3)	21.3 (3.3)	106 (25)	16.5 (2.8)	24.3 (4.3)	1.02 (0.14)
	I	6	23.2 (9.0)	23.2 (9.0)	140 (103)	17.0 (6.8)	25.0 (12.9)	0.99 (0.14)
	I*	5	20.5 (7)	20.4 (7)	100 (29)	18.5 (6)	27.8 (12)	1.02 (0.13)
2-minute infusion	B	6	17.0 (2.3)	17.0 (2.3)	105 (20)	20.6 (2.8)	30.5 (5.3)	1.03 (0.10)
	G	6	19.4 (5.4)	19.4 (5.4)	94.2 (19.9)	19.0 (5.1)	26.8 (8.7)	0.97 (0.09)
10-minute infusion	C	6	16.8 (3.1)	16.8 (3.1)	67.9 (7.1)	21.0 (3.2)	28.0 (5.0)	0.93 (0.09)
	H	6	16.0 (2.8)	16.0 (2.8)	60.2 (9.5)	22.1 (3.9)	31.3 (6.0)	0.98 (0.04)
5-minute infusion + bolus injection	D	6	12.2 (1.2)	12.2 (1.2)	66.9 (9.9)	28.5 (2.6)	37.8 (5.7)	0.92 (0.13)
Small bolus + large bolus	E	6	13.6 (4.8)	13.5 (4.8)	70.2 (12.5)	28.1 (9.4)	35.2 (8.0)	0.90 (0.14)

* Values without outlier, Subject 067

Dosing regimens:

A = 400-mg bolus dose of AQUAVAN

B = 200-mg/min infusion of AQUAVAN over 2 minutes

C = 40-mg/min infusion of AQUAVAN over 10 minutes

D = 30-mg/min infusion of AQUAVAN over 5 minutes, then a 250-mg bolus dose of AQUAVAN

E = 50-mg bolus dose of AQUAVAN, wait 5 minutes, then a 350-mg bolus dose of AQUAVAN

F = 0.10 mg fentanyl, wait 5 minutes, then 400-mg bolus dose of AQUAVAN

G = 0.10 mg fentanyl, wait 5 minutes, then 400-mg AQUAVAN administered as 200 mg/min infusion over 2 minutes

H = 0.10 mg fentanyl, wait 5 minutes, then 400-mg AQUAVAN administered as 40 mg/min infusion over 10 minutes

I = 75 mg meperidine, wait 5 minutes, then AQUAVAN administered as a 400-mg bolus injection

Mean terminal half-life of GPI 15715 was similar (close to 1 hour) for all dosing regimens, for AQUAVAN administered alone as well as in combination with fentanyl or meperidine. As expected, C_{max} was similar for

the bolus and the 2-minute infusion of AQUAVAN, and were lower for longer infusions or 2 injections. Mean AUC values were similar for bolus and infusion regimens (Regimens s A, B, C), and were slightly lower for treatments with 2 bolus doses or infusion + bolus injections (Regimens D, E). Consequently, clearance and volume and distribution were slightly higher for these treatments (Regimens D, E). Pretreatment with fentanyl or meperidine did not the alter pharmacokinetic parameters of GPI 15715.

Mean (SD) Propofol Pharmacokinetic Parameters

Dosing Scheme	Regimen	N	$AUC_{0\text{-}inf}$ (µg*hr/mL)	$AUC_{0\text{-}last}$ (µg*hr/mL)	C_{max} (µg/mL)	T_{max}* (hr)	CL/F (L/hr)	Vz/F (L)	$t_{1/2}$ (hr)
Bolus Injection	A	6	0.447 (0.069)	0.404 (0.074)	0.488 (0.129)	0.117 (0.067 – 0.167)	490 (72)	1237 (215)	1.76 (0.21)
	F	6	0.465 (0.070)	0.427 (0.068)	0.538 (0.101)	0.200 (0.150 – 0.200)	470 (68)	1283 (270)	1.88 (0.28)
	I	6	0.458 (0.060)	0.434 (0.061)	0.464 (0.055)	0.250 (0.150 – 0.250)	475 (63)	1196 (246)	1.75 (0.31)
2-minute infusion	B†	5	0.497 (0.103)	0.468 (0.101)	0.683 (0.349)	0.067 (0.033 – 0.167)	448 (94)	1087 (365)	1.66 (0.27)
	G	6	0.521 (0.159)	0.481 (0.159)	0.580 (0.256)	0.200 (0.200 – 0.200)	436 (96)	1179 (341)	1.85 (0.20)
10-minute infusion	C	6	0.494 (0.051)	0.460 (0.056)	0.513 (0.130)	0.209 (0.167 – 0.250)	439 (44)	1172 (240)	1.84 (0.26)
	H	6	0.483 (0.085)	0.445 (0.091)	0.477 (0.139)	0.290 (0.250 – 0.330)	456 (80)	1207 (340)	1.81 (0.23)
5-minute infusion + bolus injection	D	6	0.379 (0.081)	0.350 (0.077)	0.506 (0.153)	0.167 (0.117 – 0.250)	585 (109)	1553 (398)	1.84 (0.32)
Small bolus + large bolus	E	6	0.460 (0.061)	0.431 (0.061)	0.692 (0.285)	0.167 (0.167 – 0.167)	475 (69)	1177 (181)	1.73 (0.28)

* Median and range are presented.
† Values without Subject 016 (erroneous values because of inappropriate handling of samples)
Dosing regimens:
A = 400-mg bolus dose of AQUAVAN
B = 200-mg/min infusion of AQUAVAN over 2 minutes
C = 40-mg/min infusion of AQUAVAN over 10 minutes
D = 30-mg/min infusion of AQUAVAN over 5 minutes, then a 250-mg bolus dose of AQUAVAN
E = 50-mg bolus dose of AQUAVAN, wait 5 minutes, then a 350-mg bolus dose of AQUAVAN
F = 0.10 mg fentanyl, wait 5 minutes, then 400-mg bolus dose of AQUAVAN
G = 0.10 mg fentanyl, wait 5 minutes, then 400-mg AQUAVAN administered as 200 mg/min infusion over 2 minutes
H = 0.10 mg fentanyl, wait 5 minutes, then 400-mg AQUAVAN administered as 40 mg/min infusion over 10 minutes
I = 75 mg meperidine, wait 5 minutes, then AQUAVAN administered as a 400-mg bolus injection

Mean terminal half-life of propofol was similar (1.7-1.9 hour) for all dosing regimens, for AQUAVAN administered alone as well as in combination with fentanyl or meperidine. All other pharmacokinetic parameters were comparable for all dosing regimens (except T_{max}). Pretreatment with fentanyl or meperidine did not alter pharmacokinetic parameters of propofol.

Formate:

Pharmacokinetic parameters of formate were similar for all dosing regimens. The tables below present the ranges of $AUC_{0\text{-last}}$ and C_{max} across all dosing regimens, and a summary of all pre- and postdose formate levels.

Mean (SD) Formate Pharmacokinetic Parameters

	$AUC_{0\text{-last}}$ (µg*hr/mL)	Baseline-corrected $AUC_{0\text{-last}}$ (µg*hr/mL)	C_{max} (µg/mL)	Baseline-corrected C_{max} (µg/mL)
Mean	72.4 - 102	-21.8 – 36.5	24.3 – 34.0	-1.27 – 16.5
SD	6.3 - 33	15 – 42	3.5 – 8.6	5.9 – 14.6

Summary of all Pre- and Postdose Formate Concentration Levels

	PREDOSE	POSTDOSE
Mean (µg/mL)	18.2	18.8
Range	15-33	15-44
SD	4.9	5.7
N	54	540
%BLQ	52	54

There was no increase of mean formate postdose concentrations compared with the predose levels.

Pharmacodynamics:

As the doses in this study were expected to be subtherapeutic, pharmacodynamic assessments, including BIS Index, the Modified OAA/S Scale, and the VAS were conducted for increased measures of safety.

After 2 minutes, the only dosing regimen that exhibited a notable decrease in mean BIS Index occurred after receiving the bolus dose of AQUAVAN. Because most subjects did not reach sedation levels, had 2 consecutive ratings of 5 (alert) for the Modified OAA/S early in the evaluation period; thus the assessment

was discontinued. Pretreatment with fentanyl had no effect on the BIS scores, regardless of dosing regimen. For the VAS, subjects who received pretreatment with fentanyl and either a bolus dose or a 10-minute infusion of AQUAVAN experienced the least amount of discomfort. Overall, sensation ratings were comparable across dosing regimens, with the highest sensation rating in those subjects who received pretreatment with meperidine.

Safety:

No serious adverse events were reported during this study and no subject discontinued due to an adverse event. Overall, adverse events were comparable across dosing regimens. A total of 53 (98.1%) subjects experienced 139 treatment-emergent adverse events. Of these 139 events, 126 (90.6%) were considered potentially related to study drug. The highest incidence of treatment-emergent adverse events occurred in the nervous system, and manifested as paresthesia and burning sensation. These events were noted in all dosing regimens. The majority of events were mild in intensity. No severe events were reported

No adverse trends in clinical laboratory findings were noted. Fluctuations in laboratory results were those expected in a healthy population. For most subjects, venous hematology, serum chemistry, and electrolyte laboratory values remained unchanged throughout the evaluation period. There were no clinically meaningful changes in calcium or phosphorus. There were no clinically significant treatment-emergent changes in vital sign measurements, pulse oximetry, ECG results, or physical and neurological examination findings.

CONCLUSIONS

The findings indicate that a 400-mg dose of AQUAVAN, administered as one of several different dosing regimens (bolus, infusion, and bolus combined with infusion) and pretreatments (fentanyl or meperidine) was safe and tolerable. Although the dose was expected to be nonsedating, 3 subjects who received the bolus dose had Modified OAA/S scores of 4, indicating that they were not fully alert.

Neither fentanyl nor meperidine appeared to potentiate the sedative effects or change the safety profile of AQUAVAN. They did appear to lessen the subjective measures of discomfort, based on their VAS scores. However, in the analysis of adverse events, the incidence of events was comparable across regimens, indicating that pretreatment with fentanyl and meperidine had little effect on the tolerability of AQUAVAN administration. Given the small number of subjects in each dosing regimen, no definitive conclusions can be reached regarding the effect of these opioids on the tolerability of AQUAVAN.

Based on the overall safety findings of this study, it may be appropriate to examine the combination of fentanyl and AQUAVAN in a larger study.

4.3.9 Study 3000-0308 Synopsis

See Analytical section 2.6 regarding propofol assay issue.

Title of Study: A Phase 1, Open Label, Safety and Tolerability Study of AQUAVAN® Injection in Healthy Volunteers Pre-Medicated with Lidocaine HCl Injection	
Investigator(s) and Study Centers: One Investigator in the United States (U.S.) enrolled 10 subjects into the study.	
Publication(s): None	
Study Period: 04 Aug. 2003 (first subject enrolled) 04 Sep. 2003 (last subject completed)	**Clinical Phase:** 1
Objective(s): **Primary** • To determine whether systemic pretreatment with lidocaine HCl injection will reduce or eliminate the paresthesias associated with administration of AQUAVAN® Injection. • To assess the safety profile of pretreatment with lidocaine HCl injection followed by a bolus of AQUAVAN® Injection. **Secondary** • To evaluate the level of, and time to, sedation of a single dose of AQUAVAN® Injection following pretreatment with lidocaine HCl injection. • To evaluate the time to return to baseline alertness of a single dose of AQUAVAN® Injection following pretreatment with lidocaine HCl injection.	
Methodology: This Phase 1, open-label, single-center, nonrandomized, de-escalation study was designed to evaluate a single bolus dose of 12.5 mg/kg AQUAVAN® Injection (hereafter, referred to as AQUAVAN) following premedication with lidocaine HCl injection (hereafter, referred to as lidocaine) to determine the lowest of 4 dose levels of lidocaine that would reduce or eliminate the burning and tingling sensations, usually in the genital or anal regions and collectively termed "paresthesias", associated with administration of AQUAVAN. In the absence of mitigation of paresthesia at the 35-mg/mL concentration, AQUAVAN was administered at the 20-mg/mL concentration following premedication with lidocaine to assess if a link existed between the concentration of AQUAVAN and the occurrence of paresthesia. The first cohort of 5 subjects received pretreatment with 50 mg lidocaine followed by 12.5 mg/kg AQUAVAN at the 35-mg/mL concentration. If the paresthesias were successfully mitigated at this dose combination, additional cohorts of 5 subjects each were tested at decreasing doses of lidocaine (ie, 40 mg, 30 mg, 20 mg) until either the lowest dose of lidocaine had been administered or a dose was tested that did not mitigate paresthesias, at which point the study was to be completed. If, following the initial dosing of 50 mg lidocaine and 12.5 mg/kg AQUAVAN at the 35-mg/mL concentration, the paresthesias were not successfully mitigated; a second cohort of 5 subjects was to be treated with 50 mg lidocaine followed by 12.5 mg/kg AQUAVAN at the 20-mg/mL concentration. If this combination was not successful in mitigating paresthesia, the study was to be completed. If this combination was successful in mitigating paresthesias, the same de-escalation pattern of lidocaine dosing was to be implemented.	
Number of Subjects: The planned enrollment for this study was up to 25 male and female subjects; 10 subjects (8 females; 2 males) were enrolled in the study.	
Diagnosis and Key Criteria for Inclusion: Eligible subjects must have been ≥18 years and ≤50 years of age, in general good health, without significant medical illness, as determined by medical history, physical examination, ECG, and clinical laboratory testing.	
Test Product, Dose, Mode of Administration, Batch No(s).: AQUAVAN is formulated as a sterile aqueous solution of GPI 15715 at concentrations of 20 and 35 mg/mL, suitable for intravenous (i.v.) administration. Each vial contained 20 mL of solution (Batch Numbers: 1214-10 for the 20-mg/mL concentration and [redacted] 176I0603 for the 35-mg/mL concentration). Dosage: 12.5 mg/kg (bolus dose) Pretreatment: Lidocaine was supplied by the site and administered intravenously. Dosage: 20, 30, 40, and 50 mg	

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Duration of Treatment: The duration of the treatment was 1 day; subjects received a single pretreatment dose of lidocaine followed by a 12.5-mg/kg bolus dose of AQUAVAN.
Reference Therapy, Dose, Mode of Administration, Batch No(s): Not applicable
Criteria for Evaluation: Pharmacodynamics: Clinical assessments of sedation were performed at regular intervals using the Modified OAA/S Scale. Motor skills were assessed using the 5-Meter Heel-to-Toe assessment. Subject discomfort levels were measured using a Verbal Rating Scale (VRS) and Visual Analog Scale (VAS). Safety: Safety was assessed based on the reporting of adverse events, continuous monitoring of vital signs, pulse oximetry, ECGs, clinical laboratory tests, visual assessment, physical examination findings, and any changes in formate levels.
Statistical Methods: No formal statistical testing was planned or done. All study results were explored using descriptive statistics only. Pharmacodynamics: Pharmacodynamics (PD) were analyzed for all subjects who received study medication (n = 10; All Treated Subjects). The PD effect of the study drug was determined from clinical assessments of sedation using the subject's ability to respond to a loud verbal command and the Modified OAA/S scale. Modified OAA/S results were summarized for each level. Safety: All subjects receiving study medication (n = 10; All Treated Subjects) were included in the analysis of adverse events, clinical laboratory test results, vital signs, pulse oximetry, ECGs, and physical and visual examinations. Adverse events (as categorized in the Medical Dictionary for Regulatory Activities [MedDRA], Version 5.0) were listed by subject and were summarized by body system and preferred term.
RESULTS: **Subject Disposition:** This report summarizes PD and safety data for 10 subjects, all of whom received a single pretreatment dose of 50 mg lidocaine followed by a bolus dose of 12.5 mg/kg AQUAVAN. The first cohort of 5 subjects (Subjects 001 – 005) received AQUAVAN at the 35-mg/mL concentration, the second cohort of 5 subjects (Subjects 006 – 010) received AQUAVAN at the 20-mg/mL concentration. Paresthesia or paresthesia-related adverse events were reported for all 10 subjects; therefore, per the protocol, no further cohorts were dosed.
Pharmacodynamics: All subjects were sedated. Overall, the median time to sedation was 1.0 minute following the administration of AQUAVAN. Subjects recovered from sedation and were alert in approximately 30 minutes (median time from first sedation to Fully Alert was 31.0 minutes). Eight of the 10 subjects reached a Modified OAA/S score of 0 (did not respond to painful trapezius squeeze). There was considerable variability in the depth and duration of sedation among subjects. On a scale of 0 to 10 (with 10 = the most intense discomfort), VRS scores ranged from 0 to 10 (median, 7.5), and VAS scores ranged from 0.2 to 6.6 (median, 4.15). In general, no clinically meaningful differences were noted between the AQUAVAN formulations.

Safety: Overall, 12.5 mg/kg AQUAVAN, administered to healthy volunteers as a bolus dose, at concentrations of 35 mg/mL and 20 mg/mL following pretreatment with 50 mg lidocaine, was well tolerated. There were no serious adverse events, deaths, or subject withdrawals due to adverse events.

All 10 subjects reported adverse events. The most frequently reported events were Nervous System Disorders, which manifested primarily as paresthesias, and were experienced by 8 of the 10 subjects (4 with each AQUAVAN concentration).

Three subjects experienced hypoxia, defined as any oxygen saturation falling below 90%; the events were brief (≤30 seconds) and required minimal intervention (jaw thrust, sternal rub, and verbal stimulation) to resolve. Since nasal oxygen was not used in this study, it was not unexpected that hypoxic effect would be more pronounced under sedation. There were no reports of apnea (lack of spontaneous breathing for >15 seconds).

All adverse events that occurred during or following administration of AQUAVAN were considered by the Investigator to be treatment-related, including all reports of paresthesia and hypoxia.

Most adverse events reported during the study were mild; no severe adverse events were reported. All reports of paresthesia and hypoxia were considered by the Investigator to be mild.

All adverse events resolved spontaneously, with the exception of 4 events of hypoxia (3 subjects, as described above), and one event of headache that resolved following 1 dose (500 mg) of acetaminophen.

No unexpected clinically significant findings or adverse trends in ECGs or clinical laboratory parameters were noted, with the exception of 2 subjects who had moderate elevations in CK results at Follow-up. Although the Investigator noted the elevations in CK and follow-up levels obtained, these elevations were not reported as adverse events.

The effect of AQUAVAN on blood pressure was mild, transient, and without clinical sequelae. The decrease in blood pressure coincided with the time most subjects were fully sedated, and typically returned to near baseline levels by the time the subjects were Fully Alert. The effect of treatment on heart rate and pulse oximetry were mild and transient and followed similar trends. No unexpected clinically significant findings or adverse trends in ECGs, clinical laboratory parameters, and physical examinations during the study were noted.

There was no evidence of ocular toxicity associated with AQUAVAN; there were no changes from baseline in levels of formate.

Conclusions:

The use of AQUAVAN Injection and lidocaine was generally safe, with only mild, transient side effects noted. However, pretreatment with 50 mg lidocaine HCl injection does not mitigate the paresthesias associated with administration of either formulation of AQUAVAN.

A single 12.5-mg/kg dose of AQUAVAN provides rapid and deep sedation in volunteers that lasts for approximately 30 minutes. This is consistent with the intended development of AQUAVAN into brief procedural sedation. All volunteers were more deeply sedated than patients undergoing procedures using similar doses. The lack of procedural pain or stimulation may have allowed a more pronounced effect, or the combination of AQUAVAN and lidocaine may have produced additive CNS effects. No material differences between the 35-mg/mL and 20-mg/mL formulations of AQUAVAN were noted in either the efficacy or safety profiles of these small groups.

4.3.10 Study 3000-0414 Synopsis

See Analytical section 2.6 regarding propofol assay issue.

Study Title: A Phase 1 Randomized, Double-blind, Placebo-controlled, Parallel-design, Drug Interaction Study of AQUAVAN® Injection and Premedications in Healthy, Adult Subjects
Investigator(s) and Study Center(s): [redacted] b(4)
Publication (reference): None
Studied Period: 10 May 2005 (first subject enrolled) to 26 July 2005 (last subject completed)
Phase of Development: 1
Objectives: • To estimate the adjustment in the cumulative dose of AQUAVAN® Injection required to achieve targeted sedative effect when preceded by typical medications used for procedural sedation. • To evaluate the safety and tolerability of AQUAVAN® Injection at sedative doses when given in combination with different premedications. • To evaluate the pharmacodynamics of AQUAVAN® Injection at sedative doses when given in combination with different premedications. • To evaluate the pharmacokinetics of AQUAVAN® Injection at sedative doses when given in combination with different premedications.
Methodology: This study was a randomized, double-blind, placebo-controlled, single-center, parallel-design study conducted in healthy males and females aged 18 to 45 years, inclusive. The study was designed to estimate the adjustment in the cumulative dose of AQUAVAN® Injection (hereafter, referred to as AQUAVAN) required to achieve targeted sedative effect when preceded by typical medications used for minimal-to-moderate (procedural) sedation. The safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) were also evaluated. Following completion of eligibility confirmation, subjects were randomly assigned to receive 1 of 5 blinded pretreatments: fentanyl citrate (hereafter, referred to as fentanyl), meperidine hydrochloride (hereafter, referred to as meperidine), midazolam hydrochloride (hereafter, referred to as midazolam), morphine sulfate (hereafter referred to as morphine), or placebo. Pretreatment was followed by a single bolus

injection of AQUAVAN, and if needed, up to 4 supplemental doses of AQUAVAN. To account for the time required for the pretreatment effect, active pretreatment was administered 15 minutes prior to the initial AQUAVAN bolus for morphine and 5 minutes prior to AQUAVAN administration for fentanyl, meperidine, and midazolam. To ensure maintenance of the blind, subjects randomized to morphine received placebo 5 minutes prior to initial AQUAVAN bolus and those randomized to fentanyl, meperidine, or midazolam received placebo 15 minutes prior to receiving AQUAVAN. Subjects randomized to placebo received a placebo injection at both 5 and 15 minutes prior to AQUAVAN administration. All pretreatments were prepared as identical volumes. Following the administration of the initial bolus dose of AQUAVAN, sedation levels were assessed with the Modified Observer's Assessment of Alertness/Sedation (OAA/S) scale. Supplemental doses, if needed, were administered to each subject at 4-minute intervals until the target level of sedation, a Modified OAA/S score of ≤3, was reached.
Number of Subjects (Planned and Analyzed): Sixty subjects (12 per treatment group) at a single investigative site were planned and were enrolled; data for all 60 subjects were analyzed for safety and were included in the analyses of PD and PK variables.
Diagnosis and Main Criteria for Inclusion: Eligible subjects were between the ages of 18 and 45 years, inclusive, and had a body mass index (BMI) of 18 to 30 kg/m^2, inclusive.
Test Product, Dose and Mode of Administration, Lot Number: AQUAVAN was administered by intravenous (i.v.) bolus. The initial bolus dose was 8 mg/kg with supplemental doses of 2 mg/kg. Lot number GAA002 was used in this study. Pretreatments: All pretreatments were administered i.v. and were supplied by the site. Fentanyl: 1µg/kg Meperidine: 0.75 mg/kg Midazolam: 0.01 mg/kg Morphine: 0.1 mg/kg Placebo: saline
Duration of Treatment: Single (1 day) treatment period.

Reference Therapy, Dose and Mode of Administration, Lot Number:
Not applicable.

Criteria for Evaluation:

Primary Endpoint:

- The cumulative dose of AQUAVAN required to achieve the targeted level of sedation (Modified OAA/S score of ≤3) as a measure of dose alteration produced by premedication.

Pharmacodynamics:

- Duration and percent of time when a subject's Modified OAA/S score was at each level between the first dose of study medication and Fully Alert (ie, 3 consecutive Modified OAA/S scores of 5).
- Time to targeted sedation, defined as the time from the first dose of AQUAVAN to the first of 2 consecutive Modified OAA/S scores of 3 or less.
- The Bispectral (BIS) Index was used as a quantitative assessment of electroencephalogram (EEG) effect for exploratory analysis.

Pharmacokinetics:

The following venous plasma pharmacokinetic parameters of GPI 15715 (fospropofol disodium) and propofol were determined for each treatment group using non-compartmental techniques:

- Area under the plasma time-concentration curve (AUC) from the time of initial dosing to the last quantifiable concentration ($AUC_{0\text{-last}}$);
- AUC from time of the initial dose to infinity ($AUC_{0\text{-inf}}$);
- Observed concentration at 4 minutes (C_{4min});
- Observed maximum plasma concentration (C_{max});
- Time to achieve C_{max} (T_{max});
- Terminal elimination half-life ($t_{1/2}$);
- Plasma clearance (CL_p) and volume of distribution (V_d) for GPI 15715; and
- Apparent clearance (CL_p/F) and apparent volume of distribution (V_d/F) for propofol.

Safety:

- Nature, frequency, seriousness, severity, relationship to treatment, and outcome of all treatment-emergent adverse events (TEAEs)
- Sedation-related adverse events (SRAEs)
- Laboratory parameters, vital signs, pulse oximetry, and electrocardiograms (ECGs)

Statistical Methods

Populations: Three populations were defined:

- The pP population was used in the analysis of the primary endpoint and PD endpoints.
- The mITT population was used for the exploratory endpoint and for the summary of extent of exposure.
- The safety population was used in the analyses of disposition, demographics, baseline characteristics, and all safety data.

Statistical Analyses: In general, all endpoints were summarized by treatment group. For continuous variables, data were summarized with mean, standard deviation (SD), median, and range. For categorical variables, data were tabulated with the number and proportion of subjects in each category. For the primary endpoint, pairwise 95% confidence intervals were calculated and presented following analysis of variance (ANOVA) with a model containing the term treatment. The number and percent of subjects with supplemental doses were compared between treatment groups using the Cochran-Mantel Haenszel (CMH) test.

Safety Endpoints:

- All treatment-emergent adverse events (TEAEs, including sedation-related adverse events, [SRAEs]) were summarized by treatment group and by system organ class (SOC) and preferred term. AEs were also summarized by relationship and maximum severity. Listings were presented for all AEs and SAEs.
- For continuous laboratory data (chemistry, hematology, and serum electrolyte parameters), summary statistics for the observed value and change from baseline were presented by premedication and by timepoint. For all laboratory results, shift tables from check-in to follow-up were presented by premedication.
- The lowest observed values after the first administration of AQUAVAN were categorized (<90%, <85%, and <80%) and tabulated by premedication, for oxygen saturation.
- For end tidal carbon dioxide ($ETCO_2$), the highest observed value after the first administration of AQUAVAN was summarized by premedication.
- For vital signs, the highest and the lowest observed values after the first administration of AQUAVAN were separately summarized by premedication.
- For ECG results, the highest observed value and the maximum change from baseline after the first administration of AQUAVAN were summarized for QT, QTcB, QTcF, QRS, PP, and RR by premedication. For QT, QTcB and QTcF, the maximum categorized value (>450, >480, or >500 msec) and maximum change from baseline (>5, >10, >30, >60 msec) were tabulated by premedication. The

changes from baseline in ECG parameters were summarized at 1, 7, and 60 minutes after first dose of AQUAVAN. Abnormal ECG results were identified in a data listing.

Pharmacokinetic Endpoints:

- Plasma concentrations and PK parameters of GPI 15715 and propofol were summarized by treatment groups.
- Log-transformed PK parameters (C_{4min}, AUC_{0-inf}, and CL_p or CL_p/F) were compared across treatment groups using ANOVA at 5% significance level. For parameters that showed an overall statistically significant difference among treatment groups, pairwise comparisons were performed between placebo premedication and other premedication groups by two-sided t-tests at 5% significance level without multiplicity adjustment.

Summary of Results

Primary endpoint and pharmacodynamics:

- The mean cumulative dose of AQUAVAN required to achieve a Modified OAA/S score of ≤3 was 9.8 mg/kg in the placebo group (no premedication) and ranged from 9.3 mg/kg to 11.5 mg/kg in the active premedication groups. Subjects who received no premedication (placebo group) and subjects who received active premedication required generally similar mean cumulative doses of AQUAVAN to reach a Modified OAA/S score of ≤3. The median cumulative dose of AQUAVAN (10.0 mg/kg) was identical in all groups.
- Comparisons among placebo and active premedication groups showed no overall statistically significant effect of premedication on the cumulative dose of AQUAVAN (p=0.099 for overall effect of premedication).
- Results of the time at each Modified OAA/S score from first dose of AQUAVAN to Fully Alert varied across placebo and active premedication groups. The total mean percent time at a Modified OAA/S score of ≤3 was 47.7% in the placebo group and 52.9% in all groups combined.
  Numerically, patients pretreated with meperidine spent the largest percentage of time at levels of deep sedation (below a Modified OAA/S score of 3), when compared to other pretreatment groups, while patients treated with morphine spent the least.
- The median time to targeted sedation was 6.0 minutes across all placebo and active premedication groups. The use of premedication or the type of premedication had no significant effect on time to targeted sedation in this study.

Pharmacokinetic:

GPI 15715:

- Plasma concentrations and PK parameters of GPI 15715 were similar in all treatment groups.
- Plasma concentrations rapidly declined after initial AQUAVAN administration and, by 30 minutes after last dose, were 8 times lower than at 4 minutes following the initial dose; by 60 minutes after last dose elimination was almost complete. The mean terminal half-life ($t_{1/2}$) in all treatment groups was 0.44 to 0.52 hours.
- For the majority of subjects, C_{max} was observed at the first measured timepoint (4 min). Overall comparisons of parameters C_{4min} and CL_p, using ANOVA, indicated that there were no significant differences across the treatment groups (p=0.19 and 0.20, respectively).
- $AUC_{0\text{-}inf}$ showed a statistically significant difference overall (p=0.045) across the treatment groups, however, pair-wise comparisons between the placebo and all other pretreatment groups showed no significant differences (p>0.05, range=0.09 to 0.66).

Propofol:

- Plasma concentrations and PK parameters of propofol were variable within and across the treatment groups. Since subjects received different numbers of doses of AQUAVAN during the first 16 minutes after initial bolus, some variation was expected.
- Concentrations at 4 minutes after initial AQUAVAN dose reached 49% to 75% of peak propofol concentrations.
- Median T_{max} was 0.13 to 0.27 hour.
- Concentration profiles showed biphasic elimination with a mean $t_{1/2}$ of 0.90 to 1.57 hours, similar to that seen in previous studies.
- Overall comparison of log-transformed PK parameters, C_{4min}, $AUC_{0\text{-}inf}$ and CL_p/F between the treatment groups using ANOVA did not show any significant differences (p=0.08, 0.49, and 0.77, respectively).

Safety:

- Overall, treatment with AQUAVAN after placebo or active premedication was well tolerated in this study of healthy, adult subjects.
- Fifty-seven of 60 (95.0%) subjects had TEAEs that were considered possibly or probably related to AQUAVAN treatment.
- No subject died during the study. One subject in the placebo group experienced a treatment-related SAE of mental disorder (psychogenic paralysis). This event was considered possibly related to AQUAVAN.

- No subject experienced an AE leading to discontinuation from the study.
- The most frequently experienced treatment-related AEs were burning sensation in 28 of 60 (46.7%) subjects; paresthesia in 9 subjects (15.0%); genital pruritus in 10 subjects (16.7%); and dizziness in 7 subjects (11.7%). There were no substantial differences in the frequencies of common treatment-related AEs across placebo and active premedication groups.
- Most AEs were mild in severity. Forty-nine of 60 (81.7%) subjects experienced mild AEs and only 7 (11.7%) subjects had moderate AEs. One subject experienced a severe AE (mental disorder, psychogenic paralysis) that was also an SAE.
- Four subjects experienced treatment-related SRAEs of apnea during the study (1 each in the fentanyl and morphine groups and 2 in the meperidine group). Two of these events were moderate in severity, and 2 events were mild.
- There were no clinically significant laboratory test results, vital signs, or pulse oximetry results during this study.
- End-tidal CO_2 levels, a measure of the adequacy of respiration, after AQUAVAN dosing were lowest in the placebo premedication group. The mean highest value after AQUAVAN dosing was 45.9 mm Hg in placebo-premedicated subjects, and the mean highest value was >50 mm Hg only in the fentanyl and meperidine premedications groups.
- Analyses of changes from baseline in ECG parameters over time demonstrated that treatment with AQUAVAN resulted in transient shortening of uncorrected QT intervals and RR intervals. Because the decrease in RR was greater than the decrease in uncorrected QT interval, there was transient lengthening of corrected QT intervals when standard formulas were used to calculate QT corrections (QTcB and QTcF). The changes in QT and RR were most apparent at 1 minute after first dose of AQUAVAN, and these parameters had returned to baseline values by 60 minutes. The type of premedication had no clear effect on AQUAVAN-induced changes in QT or RR intervals.
- Two subjects (placebo and fentanyl premedication groups) had clinically significant shifts from baseline in QTc interval. These events were considered treatment-related AEs (prolonged QTc interval) and were mild in severity.

CONCLUSIONS

- Comparisons among placebo and active premedication groups showed no overall statistically significant effect of premedication on the cumulative dose of AQUAVAN required to achieve the targeted sedation level of ≤3 on the Modified OAA/S scale. Overall, treatment with AQUAVAN after placebo or active premedication was well tolerated in this study of healthy adult subjects.
- There were no substantial differences in the frequencies of common treatment-related AEs across placebo and active premedication groups.
- Study results indicate that the use of premedication or the type of premedication had no substantial effect on the time to targeted sedation or depth of sedation induced by AQUAVAN.
- No clinically relevant differences in pharmacokinetics of GPI 15715 and propofol were observed when AQUAVAN was given alone (placebo pretreatment) or co-administered with morphine, fentanyl, meperidine, or midazolam premedication.

4.3.11 Study 3000-0401 Synopsis

See Analytical section 2.6 regarding propofol assay issue

Title of Study: Study on the absolute bioavailability of GPI 15715, administered orally, directly into the duodenum and intravenously in healthy male volunteers (Protocol number 3100-0401)	
Investigator(s) and Study Centers: [redacted]	
Publication(s): None	
Study Period: 21 July 2004 (first screening) – 16 August 2004 (last follow-up)	**Clinical Phase:** 1
Objective(s): **Primary Objective:** To study the absolute bioavailability of GPI 15715 (hereafter referred to as fospropofol disodium) and liberated propofol, when fospropofol disodium is administered orally and directly into the duodenum compared with intravenous administration **Secondary Objective:** To study the tolerability and safety of fospropofol disodium, when administered orally, directly into the duodenum, and intravenously	
Methodology: This was a single center, 3-way crossover study with 7 subjects. Subjects stayed in the clinical unit for 3 consecutive periods of 3 days each, with a 3-day washout between periods. For 6 subjects, the order of the administration routes was as follows: period 1 oral, period 2 duodenal, and period 3 intravenous (i.v.). For 1 subject the order of the administration routes was the following: period 1 duodenal, period 2 i.v, and period 3 oral.	
Number of Subjects: Seven healthy male subjects were enrolled in the study. Data from all 7 subjects were used for both pharmacokinetic and safety evaluations.	
Diagnosis and Key Criteria for Inclusion: Healthy male volunteers; between 18 and 45 years of age, inclusive; with a body mass index between 18 and 28 kg/m^2.	
Test Product, Dose, Mode of Administration, Batch No: Fospropofol disodium was supplied by Guilford Pharmaceuticals Inc (now MGI PHARMA, INC.) as a sterile aqueous solution at a concentration of 20 mg/mL. Each vial contained 20 mL of solution, suitable for i.v. injection. Batch number: 312I1002 Test treatment 1 (T1): single dose of 400 mg (20 mL solution) fospropofol disodium administered orally Test treatment 2 (T2): single dose of 400 mg (20 mL solution) fospropofol disodium administered directly into the duodenum by gastroscopy Reference treatment (R): A single dose of 400 mg of fospropofol disodium (20 mg/mL sterile aqueous solution) was administered intravenously over 10 minutes	
Duration of Treatment: Subjects spent 3 consecutive days per treatment period in the clinical unit. Three-day washout periods followed each testing regimen. Each period of drug administration lasted less than one day.	
Reference Therapy, Dose, Mode of Administration, Batch No: Name: Fospropofol disodium (GPI 15715) Active substance: Fospropofol disodium (GPI 15715)	

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Strength: 20 mg/mL

Dosage form: sterile aqueous solution

Lot number: 312I1002

Reference treatment (R): A single dose of 400 mg of GPI 15715 in a 20 mg/mL sterile aqueous solution was administered intravenously over 10 minutes.

Criteria for Evaluation:

Pharmacokinetics: The following pharmacokinetic parameters were determined for fospropofol and propofol from plasma:

- AUC_{last} (concentration-time data: area under the concentration-time curve from time of dosing to the last measured concentration)
- $AUC_{0\text{-}inf}$ (area under the concentration-time curve from the time of dosing to infinity)
- AUC_{extra} (percentage estimated part of the calculation of AUC_{inf})
- C_{max} (maximum plasma concentration)
- t_{max} (time to attain C_{max})
- $t_{1/2}$ (elimination half-life)

Levels of fospropofol and propofol were to be determined in plasma following each test treatment, and absolute bioavailability (F) was calculated for each individual subject as the ratio of AUC_{inf} resulting from oral or duodenum administration to AUC_{inf} following i.v. administration.

Safety: Safety was evaluated based on adverse events, defined according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 6.1), vital signs, electrocardiogram (ECG), Modified Observer's Assessment of Alertness/Sedation (OAA/S) score, clinical laboratory tests, and physical examination.

Statistical Methods:

Data from all subjects (N=7) who received treatment were analyzed for pharmacokinetics and safety.

Pharmacokinetic parameters: Analysis of variance was performed on log-transformed AUC_{inf}, AUC_{last}, and C_{max}; descriptive statistics are presented for other pharmacokinetic parameters. Treatment groups were compared by determining the ratios of oral(T1)/i.v (R) and intraduodenal (T2)/i.v (R) for the following parameters: C_{max}, AUC_{last}, and AUC_{inf} .

Point estimates of the ratios of the means and the 90% and 95% confidence intervals for the C_{max}, AUC_{last}, and AUC_{inf} for fospropofol obtained from ANOVA were determined.

Safety parameters: All subjects who received study drug were included in the safety analysis. All data collected in the study (adverse events [AEs], vital signs, ECG-parameters, laboratory parameters, physical parameters, Modified OAA/S score.) were summarized using descriptive statistics. In addition, AEs were listed by subject and were summarized by dose and overall for system organ class and preferred terms.

RESULTS:

Pharmacokinetics:

MGI PHARMA discovered an assay problem in the measurement of propofol plasma concentrations after this study was conducted. Sodium orthovanadate (SOV), an inhibitor of alkaline phosphatase, was added to each collected blood sample during clinical studies to prevent further conversion of fospropofol to

propofol. It was determined that the added solid SOV may not have been completely dissolved in each sample during the blood sample collection procedure, resulting in variable concentrations of dissolved SOV in samples. As a result, the inhibition of alkaline phosphatase in harvested plasma may not have been complete or consistent from sample to sample. The presence of inconsistent SOV in plasma samples adversely affected the sample stability and propofol recoveries in the [redacted] used for sample preparation. Further, it was discovered that SOV causes hemolysis, which affects the propofol stability. Because of these methodology problems, the propofol PK data were considered unreliable. It was determined through stability studies that the inconsistent SOV concentrations and hemolysis did not affect fospropofol measurements; the degradation of fospropofol was less than 15%, ie within the accepted bioanalytical assay variability. PK data for fospropofol are considered reliable. Data and PK parameters from PK analyses of fospropofol and propofol are included in the tables and listings appended to the report, but only fospropofol data is reported in this synopsis.

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The results indicate that the absolute bioavailability of the prodrug fospropofol after oral and duodenal administration was very low (1% for oral and 0.1% for duodenal administration). The administration route had no effect on the median values for t_{max} (0.17 hours for all methods of delivery). The geometric mean values for $t_{1/2}$ of fospropofol were similar following all methods of delivery (0.32, 0.34, and 0.33 h for oral, intraduodenal, and i.v., respectively). Inter-individual variability in plasma concentrations for the non-i.v. administration routes for fospropofol was as expected, considering the small number of subjects in this study.

Propofol was detectable in plasma samples from all 3 treatment groups.

Safety:

Seventy-three treatment emergent adverse events (TEAEs) were reported in 7 of 7 subjects (100%). Seventy of the reported TEAEs were considered to be possibly or probably related to study drug. The most frequently reported TEAEs were somnolence (11 events in 7/7 subjects [100%]), paresthesia (10 events in 6/7 subjects [86%]), speech disorder (6 events in 6/7 subjects [86%]), and burning sensation (6 events in 3/7 subjects [43%]). Two subjects (29%), one in the oral group and one in the i.v. group, reported one AE each of euphoria. Both events were mild, considered related to study medication and resolved after 17 and 34 minutes, respectively.

There was a marked difference in the number of treatment-related TEAEs reported among the different routes of administration. When fospropofol disodium was administered i.v., 7 of 7 (100%) subjects reported 56 treatment-related TEAEs. When fospropofol disodium was administered either orally or intraduodenally, 6 of 7 (86%) subjects in each group reported 8 and 9 treatment-related TEAEs, respectively. No severe or serious AEs were reported during this study. There was no death or study discontinuation because of an AE. All but one TEAE (rash, which resolved without treatment) resolved without sequelae within 1 hour of dosing. The Investigator considered all TEAEs mild.

The Modified Observer's Assessment of Alertness and Sedation (OAA/S) scale was used 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. All subjects had Modified OAA/S scores of 5 by 1.5 hours postdose. No clinically-relevant abnormalities were found with regard to clinical laboratory results, vital signs, ECG, or physical examination.

CONCLUSIONS:

Pharmacokinetic Conclusions:

- Due to problems with the analysis of propofol, propofol PK data are not considered reliable and are not reported here. However, propofol was detectable in plasma samples following all 3 methods of fospropofol disodium delivery.
- The mean absolute bioavailability (F) of fospropofol was 1% after oral administration and 0.1% after duodenal administration.
- The t_{max} and $t_{1/2}$ for fospropofol were similar after i.v., oral and intraduodenal administrations.

Safety Conclusions:

- There were no deaths or serious adverse events during this study and no subjects discontinued from the study due to an AE.
- Seventy-three TEAEs, were reported by 7 subjects; 70/73 events were considered to be possibly or probably related to the study drug.
- The most frequently reported TEAEs were somnolence (11 events in 7/7 subjects [100%]), paresthesia (10 events in 6/7 subjects [86%]), speech disorder (6 events in 6/7 subjects [86%]), and burning sensation (6 events in 3/7 subjects [43%]).
- The Investigator considered all of the reported TEAEs to be mild. Most of the TEAEs were of short duration and all but one (rash on the forehead experienced by Subject 001 in the intraduodenal dosing period) had resolved without sequelae within 1 hour after dosing. Long-term follow-up indicated that the rash resolved without intervention.
- Oral and duodenal administrations of fospropofol disodium resulted in fewer treatment-related TEAEs (6/7 subjects in each group reported 8 and 9 events, respectively) when compared with i.v. administration (7 subjects reported 56 events).
- Duodenal and i.v. administrations of fospropofol disodium resulted in reports of transient mild sedation, as measured by the Modified OAA/S score. Three of 7 (43%) and 4 of 7 (57%) subjects in the duodenal and i.v. groups, respectively, had a minimum Modified OAA/S score of 4 at some time following drug administration. All other subjects in those groups remained at Modified OAA/S scores of 5 (alert at all times). No subjects in the oral treatment group recorded a Modified OAA/S score of less than 5.
- A singe dose of 400 mg fospropofol disodium administered orally, duodenally, and i.v. was safe and well tolerated by healthy male volunteers under the conditions of this study.

4.3.12 Study 3000-0402 Synopsis

See Analytical section 2.6 regarding propofol assay issue

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Title of Study: A Single Ascending Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of Oral Doses of GPI 15715 in Healthy Volunteers (Protocol 3100-0402)	
Investigator(s) and Study Centers: [redacted]	
Publication(s): None	
Study Period: First Patient Enrolled: 25 Nov 2004 Last patient completed: 11 Jan 2005	Clinical Phase: 1
Objectives: **Primary Objective:** To study the safety and tolerability of single ascending doses of fospropofol disodium (GPI 15715), when administered orally to healthy volunteers **Secondary Objective:** To study the pharmacokinetics (PK) of single ascending doses of fospropofol disodium, when administered orally to healthy volunteers	
Methodology: This was a single center, double-blind, randomized, crossover, placebo-controlled, single ascending dose study in 10 healthy subjects. Each subject received 4 ascending oral doses of fospropofol disodium (200, 600, 1000 and 1200 mg) and one of placebo. Placebo was administered randomly, in one of 5 periods. Subjects stayed in the clinical research unit for 3 days per treatment for 5 consecutive treatments. Between treatments, there were wash-out periods of at least 6 days during which interim safety evaluations were made to determine assess the safety of the subsequent higher doses. The most recent version of the study protocol (Amendment 2) is provided in Section 16.1.1. Earlier versions of the protocol are on file with the Sponsor and are available upon request. A sample Case Report Form is in Section 16.1.2. The Approving EC and a sample Informed Consent Form is in 16.1.3. Section 16.1.4 lists the Principle Investigator and presents his CV. The signature of the Sponsor's Medical monitor is in Section 16.1.5.	
Number of Subjects: 10 healthy volunteers were enrolled in the study (6 males and 4 females), 10 were included in the PK analyses and 10 were included in the safety analyses. Subject demographics and other details are displayed in listings in Section 16.2	
Diagnosis and Key Criteria for Inclusion: Subjects were healthy men and women between the ages of 18 and 45 years, inclusive, with a body mass index of between 18 to 28 kg/m^2, inclusive. If female, volunteer was surgically sterile, post-menopausal or non-pregnant, using an acceptable method of birth control for at least one month prior to dosing, with a negative urine pregnancy test at screening and predose before each dosing period.	

Test Product, Dose, Mode of Administration, Batch No:

Active compound: fospropofol disodium (GPI 15715)

Strength: 200 mg

Dosage form: oral capsule

Lot number: GPI-009, supplied by Guilford Pharmaceuticals (now MGI PHARMA, INC.)

Duration of Treatment: Four dose levels of fospropofol disodium and a placebo were administered over 5 treatment days. While volunteers remained in the clinical research unit for 3 days for each treatment period, each treatment lasted less than one day. A washout period of 6 days separated each treatment period.

Safety Reference Therapy, Dose, Mode of Administration, Batch No: Visually identical oral placebo capsules, manufactured by [redacted] were included as a safety control.

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Criteria for Evaluation:

Pharmacokinetics: The primary pharmacokinetic (PK) endpoints in this study were the concentrations of fospropofol and propofol in plasma. The following parameters were determined:

- C_{max} (maximum plasma concentration)
- t_{max} (time to attain C_{max})
- k_{el} (elimination rate constant)
- $t_{1/2}$ (elimination half-life)
- AUC_{last} (concentration-time data: area under the concentration-time curve from time of dosing to the last measured concentration)
- $AUC_{0\text{-}inf}$ (area under the concentration-time curve from the time of dosing to infinity)
- AUC_{extra} (percentage estimated part of the calculation of AUC_{inf})

Safety: Evaluations used to assess safety and tolerability were: the recorded adverse events (AEs), vital signs, electrocardiogram (ECG), Modified Observer's Assessment of Alertness and Sedation (OAA/S) score, bispectral (BIS) index monitoring, psychomotor testing (digit symbol substitution test [DSST]), Visual Analog Score (VAS) score, clinical laboratory parameters, and physical examinations.

Statistical Methods: The study Statistical Analysis Plan is provided in Section 16.1.9.

Pharmacokinetic parameters:

Pharmacokinetic parameters for fospropofol and propofol were to be summarized using descriptive statistics including, mean (except for t_{max}), SD, median, min and max (by gender and for males and females combined). Individual plasma concentrations were to be listed and summarized using descriptive statistics for fospropofol and propofol. Additionally, the dose proportionality was to be assessed for propofol C_{max} and AUC using a mixed-effects power model.

Safety parameters:

Summary tables of treatment emergent AEs were presented by system organ class and Medical dictionary for Regulatory Activities (MedDRA, version 7.0) preferred terms by frequency, by treatment, by intensity,

and by relationship to study drug.

Individual results are listed and summary tables presented by treatment for:

- Clinical lab data, vital signs, and ECG parameters (absolute change and shift from baseline)
- Modified OAA/S (frequency by timepoint)
- BIS scores (mean over time)
- Psychomotor testing (DSST), VAS, and physical examination (change from baseline)

RESULTS:

Pharmacokinetics:
MGI PHARMA discovered an assay problem in the measurement of propofol plasma concentrations after this study was conducted. Sodium orthovanadate (SOV), an inhibitor of alkaline phosphatase, was added to each collected blood sample during clinical studies to prevent further conversion of fospropofol to propofol. It was determined that the added solid SOV may not have been completely dissolved in each sample during the blood sample collection procedure, resulting in variable concentrations of dissolved SOV in samples. As a result, the inhibition of alkaline phosphatase in harvested plasma may not have been complete or consistent from sample to sample. The presence of inconsistent SOV in plasma samples adversely affected the sample stability and propofol recoveries in the [redacted] used for sample preparation. Further, it was discovered that SOV causes hemolysis, which affects the propofol stability. Because of these methodology problems, the propofol PK data were considered unreliable. It was determined through stability studies that the inconsistent SOV concentrations and hemolysis did not affect fospropofol measurements; the degradation of fospropofol was less than 15%, i.e. within the accepted bioanalytical assay variability, therefor PK data for fospropofol are considered reliable. Propofol was detectable in plasma samples from all treatment groups.

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Bioanalytical report generated to document the findings of the study are in Section 16.5 for informational purposes only.

Because this is a safety report only, pharmacokinetic data will not be reported in this synopsis.

Safety: All subject safety data are displayed in Summary Tables in Section 14 and in Listings in Section 16.2.

- No subject died during this study. No subject experienced a serious AE and no subject discontinued from the study for any reason.
- All subjects (10 of 10 [100%]) experienced treatment-related, treatment-emergent AEs (TEAEs). The patient incidence of TEAEs by treatment was: 40%, 80%, 90%, 80%, and 90% for placebo, 200 mg, 600 mg, 1000 mg, and 1200 mg, respectively.
- All subjects (10 of 10 [100%]) experienced somnolence, the most frequently reported AE during the study. Somnolence was reported in 0%, 40%, 50%, 40%, and 80% of subjects in the placebo, 200 mg, 600 mg, 1000 mg, and 1200 mg groups, respectively. Following somnolence in rate of occurrence were paresthesia (60%), nausea (50%), and phlebitis superficial (50%).
- Most of the TEAEs were mild or moderate in severity and resolved without intervention. Two

subjects (1 in the 1000 mg treatment group and 1 in the 1200 mg group) experienced somnolence that was considered severe by the Investigator. Only 1 TEAE (erythema in the placebo group, considered not related to study drug) required treatment and resolved before the end of the study.

- Euphoric mood was reported as a TEAE in 3 subjects during this study; 1 each in the placebo, 600 mg, and 1200 mg groups.
- There were no changes in laboratory values, vital signs, ECGs, or physical examinations that were considered clinically relevant by the Investigator during this study.
- At most time points ≥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, 40% of subjects had a Modified OAA/S score of 4 (responded lethargically to their names spoken in a normal tone). The lowest Modified OAA/S scores (score of 3; responded only after name was called loudly and/or repeatedly) were recorded by the same subject (Subject 003, following treatment with 1000 mg), at 1 and 1 ½ hours after treatment with fospropofol disodium.
- The maximal DSST changes from baseline for all fospropofol disodium treatment groups were recorded at the 1-hour time point. At 1 hour post-treatment, mean changes were 6, -5, -11, and -13 for the 200 mg, 600 mg, 1000 mg, and 1200 mg groups, respectively.
- Mean BIS scores were ≥90% at all time points for all subjects following all treatments. Ranges were 67-98%, 80-98%, 71-98%, 70-98%, and 70-98% for the placebo, 200 mg, 600 mg, 1000 mg, and 1200 mg groups, respectively.

CONCLUSIONS:

- 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. BIS scores were not sensitive to these clinically observed changes.
- Euphoria was seldom reported (3 out of 50 administrations, 1/10 placebo and 2/40 fospropofol disodium administrations). There was no apparent association between this AE and dosing level in the active treatments.

4.3.13 Study 3000-0521 Synopsis

Also see TQT study review by Dr. Christine Garnett.

Study Title:

3000-0521: 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

Investigator and Study Center: [redacted]

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Publication (reference): see Appendix 16.1.11

Studied Period:

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

Phase of Development: 1

Objectives:

(1) 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)

(2) To quantify the dose, concentration, and time relationships of AQUAVAN on the QT interval corrected for heart rate (QTc) at therapeutic and supratherapeutic doses

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

Methodology: 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.

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)

A total of 70 healthy male and female subjects between the ages of 18 and 45 years, inclusive, were planned for enrollment in the study. 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).

Because a supratherapeutic dose (18 mg/kg) of AQUAVAN was administered, at which deep levels of sedation were expected, the administration of the drug was open label, and a board-certified anesthesiologist was immediately available during administration of the AQUAVAN doses throughout the study to monitor subject safety. The safety and tolerability of AQUAVAN was assessed by vital sign measurements, 12-lead ECG assessments, and saturation of hemoglobin with oxygen in peripheral blood as measured by pulse oximetry, treatment-emergent AEs (TEAEs), physical examination findings, and clinical laboratory evaluations.

Moxifloxacin was used as a positive control to confirm the assay sensitivity of this study with an expected time-averaged mean change from Baseline placebo-corrected QTc result of 5 to 10 ms.

Electrocardiograms were obtained digitally using a [redacted] ECG continuous digital recorder. 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. Electrocardiograms

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recorded at the protocol-specified time points were read centrally by blinded evaluators using a high-resolution manual on-screen caliper method with annotations.

During the Baseline Period (Day –1 for each Treatment Period) 4 ECGs were recorded at each of 11 time points at the same clock times and under similar conditions as during the Treatment Period. The purpose of these measurements was the construction of an individualized correction of the QT interval. Thus, 44 ECGs per subject were recorded during each Baseline Period for construction of the individual correction curve for that particular subject for that particular administration. If 44 ECG measurements from the Baseline could not adequately construct an individual QT correction, additional baseline ECGs were to be retrospectively retrieved from the [redacted] flash card to provide an accurate individual QT correction. However, only the original 44 ECGs at Baseline were used to establish the baseline ECG interval values. During each Treatment Period, four 12-lead ECGs recorded within 1 minute of each scheduled time point were downloaded to the [redacted] flash card at 11 time points (1, 4, 8, 12, 20, 30, 60, and 90 minutes and 2, 3, and 4 hours) after administration of the study drug for a total of 44 ECGs per subject for each treatment. For subject safety, standard digital 12-lead ECGs were recorded at specified times to detect any immediate ECG effects.

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Blood samples were collected for the determination of plasma concentrations of fospropofol and propofol during both AQUAVAN Treatment Periods at 1, 4, 8, 12, 20, 30, 60, and 90 minutes and 2, 3, and 4 hours after dosing.

Subjects underwent Screening between 2 and 21 days before the initial dosing. For the first and each of 3 subsequent administrations, identical procedures were followed for the Baseline and Treatment Periods. A Washout Period of ≥3 days but ≤7 days followed each of the first 3 treatments. After the fourth Treatment Period, all subjects underwent a final evaluation.

Number of Subjects (Planned and Analyzed):

A total of 70 subjects were planned; 70 subjects were included in the ECG, efficacy, and safety analyses; and 69 subjects were included in the pharmacokinetic analyses.

Diagnosis and Main Criteria for Inclusion:

Male subjects and nonpregnant and nonlactating female subjects aged 18 through 45 who were free of any clinical disease or condition that could interfere with the study evaluation and who were willing and able to provide written informed consent enrolled in this study.

Test Product, Dose and Mode of Administration, Lot Number: AQUAVAN 6 mg/kg and 18 mg/kg for i.v. administration, lot number GAA002.

Duration of Treatment: Subjects received 1 single dose of placebo, moxifloxacin, AQUAVAN 6 mg/kg, and AQUAVAN 18 mg/kg (<1 day treatment period for each treatment) separated by ≥3 days but ≤7 days.

Reference Therapy, Dose and Mode of Administration, Lot Number: Normal saline for i.v. administration, (no lot number); moxifloxacin 400 mg p.o. (provided as 400-mg Avelox® tablets), lot number 5400JXH.

Criteria for Evaluation:

Primary Endpoint:

- Maximum time-matched change from Baseline in the QTcI interval

Secondary Endpoints:

- Time-matched change from Baseline in the QTcI interval at each extraction time point
- Time-matched change from Baseline in the QTcI interval at time of maximum plasma concentration (T_{max}) for fospropofol and propofol
- Time-averaged change from Baseline in the QTcI interval

Pharmacokinetic endpoints:

The following parameters were assessed based on fospropofol and propofol plasma concentrations: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, $t_{1/2}$, CLp or CLp/F, λ_z and Vd or Vd/F.

Safety Endpoints:

- QT prolongation-related adverse events (AEs)
- All other TEAEs
- Laboratory parameters, vital signs, and pulse oximetry measurements

Efficacy Endpoints:

- Minimum Modified Observer's Assessment of Alertness/Sedation (OAA/S) score
- Minimum Bispectral Index (BIS) score

Statistical Methods:

Three populations were defined for analyses in this study: safety, ECG, and pharmacokinetic populations. The safety population included all subjects who were randomly assigned to receive treatment and received any dose of the study drug. Subjects in this population were used for all demographic and safety summaries, including the safety 12-lead ECG results. The ECG population 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. Subjects in this population were used for all digital ECG summaries and analyses. The pharmacokinetic population included all subjects who received any study drug and had sufficient plasma concentration data to facilitate calculation of the pharmacokinetic parameters. Subjects in this population were used for all pharmacokinetic summaries and analyses.

The QT intervals were individually corrected by RR interval using the formula $QTcI = QT/(RR)^{\beta}$, where β is estimated from the model $\log(QT)=\alpha + \beta \cdot \log(RR)$ using baseline observations for each subject and period. For sensitivity analysis, the lengths of the QT intervals were also corrected using Fridericia's formula (QTcF), Bazett's formula (QTcB), and the Studywise QT correction (QTcS).

In general, continuous data were summarized using descriptive statistics: number, mean, standard deviation, median, minimum, and maximum. For QT/QTc variables, 90% confidence intervals (CIs) were derived. Categorical data were summarized by presenting the number (frequency) and percentage of subjects in each category. Unless stated otherwise, all summary tables present descriptive statistics and/or frequency by treatment. All statistical summaries and listings were created using SAS® System, Version 8.2.

For all analyses, the 4 QTcI interval replicates were averaged at each extraction time point. For the primary endpoint, the mean difference between the AQUAVAN therapeutic dose (6 mg/kg) and placebo in time-matched change from Baseline at each of the extraction time points was calculated by determining the difference between the measurement in the Treatment Period and the measurement in the Baseline Period at the corresponding extraction time point. The maximum of the time-matched changes from Baseline in the QTcI interval was calculated for each subject by period. The mean difference between these values after administration of the AQUAVAN therapeutic dose and placebo was calculated with 2-sided 90% CIs. The potential of AQUAVAN to affect the QT/QTc was declared not inferior to the effect of placebo on the QT/QTc if the upper limit of the 90% CI was below the noninferiority margin of 10 ms. The time from the study drug administration to reach the maximum time-matched change from Baseline was summarized by treatment group.

For analysis of the secondary endpoints, the mean differences between the AQUAVAN therapeutic dose and placebo in time-matched change from baseline QTcI interval at each extraction time point and at T_{max} for fospropofol and propofol were assessed by 2-sided 90% CIs. Also, the time-averaged change from Baseline was calculated by averaging all time-matched changes from Baseline. The mean difference between the AQUAVAN therapeutic dose and placebo in time-averaged change from baseline

QTcI interval was calculated with 2-sided 90% CIs.

In addition, the AQUAVAN supratherapeutic dose was compared with placebo using the same methods as described for the comparison of placebo and the therapeutic dose of AQUAVAN.

The treatment-by-gender interaction was analyzed for QT/QTc using a mixed-effect model. If the conclusions from this mixed model were different from the conclusions derived from analyses of the primary and secondary endpoints, each fixed effect in the mixed model was to be explored and final conclusions were to be based on this exploratory analysis.

The relationships between fospropofol and propofol concentrations and QTcI interval were evaluated using linear mixed-effects models of time-matched change from Baseline in QTcI interval. Ninety percent CIs were constructed by simulation using estimates from the models.

For the analysis of sensitivity to the correction method, analysis of QTcB, QTcF, and QTcS intervals were performed the same way as for primary, secondary, exploratory, categorical, and assay sensitivity analyses.

Natural log-transformed AUC and C_{max} were analyzed using a linear mixed-effect model for assessment of dose proportionality of fospropofol and propofol, where the model included sequence, period, and treatment as fixed effects and subject as a random effect. Ninety percent CIs were constructed around the mean ratios of dose-normalized pharmacokinetic parameters (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$) for AQUAVAN 18 mg/kg to AQUAVAN 6 mg/kg.

Pharmacokinetic parameters (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$) of female subjects were compared with male subjects. Natural log-transformed AUC and C_{max} were analyzed using a linear mixed-effect model for assessment of gender differences in fospropofol and propofol, where the model included sex as a fixed effect and subject as a random effect. Ninety percent CIs were constructed around the mean ratios of dose-normalized pharmacokinetic parameters (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$) for female to male subjects following AQUAVAN treatments of 6 mg/kg and 18 mg/kg.

Efficacy endpoints were summarized descriptively for each treatment, and safety endpoints were analyzed by subject-incidence shift tables.

Safety:

Safety assessments included vital sign measurements, saturation of hemoglobin with oxygen in peripheral blood as measured by pulse oximetry, 12-lead ECG assessments, physical examination findings, TEAEs, and clinical laboratory evaluations (hematology, serum chemistry, serum electrolytes, and urinalysis).

Pharmacokinetic Results:

Fospropofol:

- Following administration of single i.v. bolus doses of AQUAVAN, mean fospropofol concentrations exhibited an approximate 2-fold decrease between 4 minutes and 12 minutes and a 10-fold decrease between 4 minutes and 30 minutes. The initial rapid decline was followed by a slower terminal phase with a mean $t_{1/2}$ of 0.81 hour. This pattern was similar for both AQUAVAN treatments.
- Median T_{max} was observed at 4 minutes (range of 1 to 8 minutes) for AQUAVAN 6 mg/kg, and at 2 minutes (range of 1 to 6 minutes) for AQUAVAN 18 mg/kg.
- Mean C_{max} values were 78.7 µg/mL and 211 µg/mL, and mean $AUC_{0\text{-}inf}$ values were 19.2 h•µg/mL and 50.3 h•µg/mL, for AQUAVAN 6 mg/kg and 18 mg/kg, respectively.
- Mean weight-normalized CL_p and V_d were similar for both AQUAVAN treatments (0.280 and 0.320 L/h/kg for CL_p, and 0.327 and 0.374 L/kg for V_d, for the 6 mg/kg and 18 mg/kg doses, respectively).
- A 3-fold increase in AQUAVAN dose (from 6 to 18 mg/kg) led to a 2.7-fold increase in mean fospropofol C_{max} and a 2.6-fold increase in mean fospropofol AUC. Mean dose-normalized parameters, C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$, were 11% to 13% lower for the 18 mg/kg dose. The 90% CIs for the mean ratios did not include 1, but all CIs were contained within the bioequivalence limits (of 0.8 to 1.25), indicating that the pharmacokinetics of fospropofol are clinically dose proportional.
- Mean dose-normalized parameters, C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ were 6% to 9% higher for the female subjects compared to the male subjects. The 90% CIs for the mean ratios did not include 1, but all CIs were contained within the bioequivalence limits (0.8 to 1.25), indicating that the pharmacokinetics of fospropofol show no gender differences.

Propofol:

- Following administration of single i.v. bolus doses of AQUAVAN, plasma concentrations of propofol reached C_{max} at a median T_{max} of 12 minutes for AQUAVAN 6 mg/kg and 8 minutes for AQUAVAN 18 mg/kg.
- Concentration time profiles showed biphasic elimination with a mean terminal $t_{1/2}$ of 2.06 hours for AQUAVAN 6 mg/kg and 1.76 hours for AQUAVAN 18 mg/kg.
- Mean C_{max} values were 1.08 µg/mL and 3.90 µg/mL, and mean $AUC_{0\text{-}inf}$ values were 1.70 h•µg/mL and 5.67 h•µg/mL, for AQUAVAN 6 mg/kg and 18 mg/kg, respectively.
- Mean weight-normalized CL_p/F and V_d/F were similar for both AQUAVAN treatments (1.95 and

1.79 L/h/kg for CL_p/F, and 5.76 and 4.46 L/kg for V_d/F, for the 6 mg/kg and 18 mg/kg doses, respectively).

- The increase in propofol exposure was slightly greater than dose proportional. A 3-fold increase in AQUAVAN dose (from 6 to 18 mg/kg) led to a 3.6-fold increase in mean propofol C_{max} and a 3.3-fold increase in mean propofol $AUC_{0\text{-}inf}$. The mean dose-normalized parameters of C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ were 10% ($AUC_{0\text{-}inf}$) to 24% (C_{max}) higher for the 18 mg/kg AQUAVAN dose. The 90% CIs for the mean ratios did not include 1, and while the CIs for the mean ratios of $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ were contained within the bioequivalence limits (0.8 to 1.25), the CI for the mean ratio of C_{max} (1.18–1.30) was just outside this limit.
- Mean dose-normalized parameters, C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$, were 10% to 14% lower for the female subjects compared to the male subjects. The 90% CIs for the mean ratios did not include 1, but all CIs were contained within the bioequivalence limits (0.8 to 1.25), indicating that the pharmacokinetics of propofol show no gender differences.

Efficacy Results:

- Minimum scores on the Modified OAA/S showed that the expected levels of minimal-to-moderate sedation were achieved at the AQUAVAN 6 mg/kg therapeutic dose level (median score of 5.0; range 0 to 5), and the deepest levels of sedation and hypnotic state were achieved at the AQUAVAN 18 mg/kg supratherapeutic dose level (median score of 0.0; range 0 to 2). The BIS Index confirmed the pharmacodynamic drug effect.

Safety Results:

- No deaths, SAEs, or QT prolongation-related AEs were experienced during the study, and no subject discontinued from the study because of an AE related to AQUAVAN.
- There were no reports of sedation-related adverse events (SRAEs) or of any need for airway assistance during this study.
- 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.
- Treatment-related 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, 10.1% of subjects in the moxifloxacin group and none of the subjects in the placebo group experienced treatment-related TEAEs.
- 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.
- No clinically significant clinical laboratory, pulse oximetry, physical examination, or safety ECG findings were observed.

Pharmacokinetic Conclusions:

- Mean fospropofol C_{max} values were 78.7 µg/mL and 211 µg/mL, and mean $AUC_{0\text{-}inf}$ values were 19.2 h•µg/mL and 50.3 h•µg/mL, following single i.v. bolus doses of AQUAVAN 6 mg/kg and 18 mg/kg, respectively. Intersubject variability was low for both the parameters (C_{max} and AUC) following single i.v. bolus doses of AQUAVAN 6 mg/kg and 18 mg/kg.
- Mean propofol C_{max} values were 1.08 µg/mL and 3.90 µg/mL, and mean $AUC_{0\text{-}inf}$ values were 1.70 h•µg/mL and 5.67 h•µg/mL, following single i.v. bolus doses of AQUAVAN 6 mg/kg and 18 mg/kg, respectively. Intersubject variability was low for both the parameters (C_{max} and AUC) following single i.v. bolus doses of AQUAVAN 6 mg/kg and 18 mg/kg.
- Exposure to fospropofol was dose proportional. While the mean ratios of dose-normalized C_{max} and $AUC_{0\text{-}inf}$ for the 6 mg/kg and 18 mg/kg doses were less than 1, the 90% CIs ([0.85-0.93] and [0.85-0.89], respectively) were within the limits of bioequivalence. These results indicate that the pharmacokinetics of fospropofol can be considered clinically dose proportional.
- The increase in propofol exposure was slightly greater than dose proportional. A 3-fold increase in AQUAVAN dose (from 6 to 18 mg/kg) led to a 3.6-fold increase in mean propofol C_{max} (90% CI for the mean ratio of [1.18-1.30]) and a 3.3-fold increase in mean propofol $AUC_{0\text{-}inf}$ (90% CI for the mean ratio of [1.05-1.14]). These results indicate that the pharmacokinetics of propofol derived from AQUAVAN can be considered clinically dose proportional.
- There were no gender differences in the pharmacokinetics of fospropofol and propofol derived from AQUAVAN.

Efficacy Conclusion:

- The expected levels of minimal to moderate sedation were achieved at the AQUAVAN 6 mg/kg therapeutic dose level, and the deepest levels of sedation and hypnotic state were achieved at the AQUAVAN 18 mg/kg supratherapeutic dose level. The BIS Index confirmed the pharmacodynamic drug effect.

Safety Conclusions:

- Although treatment-related AE's were observed in 97.1% of the patients treated with AQUAVAN, the events observed were not considered clinically important.
- AQUAVAN 6 mg/kg and 18 mg/kg appeared to be safe and well tolerated when compared with the administration of moxifloxacin or placebo.
- AQUAVAN at doses nearly 3-times the clinically-relevant dose resulted in no SRAEs and no need for airway assistance.

Pharmacokinetic Conclusion:

- Pharmacokinetics of fospropofol and propofol were clinically dose proportional.

Overall Conclusion:

- The results of this study indicate that single i.v. bolus doses of AQUAVAN 6 mg/kg or 18 mg/kg are not inferior to placebo with regard to prolongation of the QTcI interval.

Also see Thorough QT study review by Dr. Christine Garnett.