CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-244

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 870)** **Tracking/Action Sheet for Formal/Informal Consults**

From: Srikanth C. Nallani, Ph.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 11/18/2008	IND No.: Serial No.:	NDA No. 22-244 BZ-000 **Class 1 Resubmission**	DATE OF DOCUMENT	10/13/2008
NAME OF DRUG **| LUCEDRA (Fospropofol) Injection |**	PRIORITY CONSIDERATION **Standard**		Date of Informal/Formal Consult:	10/13/2008

NAME OF THE SPONSOR: **| MGI Pharma |**

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☒ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK-PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2-Pre-NDA CMC/Pharmacometrics Others)	☐ OTHER *(SPECIFY BELOW)*: | |
☐ PHASE IV RELATED		

REVIEW ACTION

☒ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: | |	☐ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others	meeting/Telecon, see meeting minutes	☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)	dated: | |	| |

REVIEW COMMENT(S)

☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☒ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

LUCEDRA (fospropofol disodium) Injection is an intravenous sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures. MGI Pharma's original NDA dated 9/26/2007 was not approved (7/22/2007) due to lack of adequate information to support the proposal that providers can safely manage sedation of patients with fospropofol. In response, on 10/13/2008 MGI submitted a Class 1 resubmission with a revised proposal to use LUCEDRA for monitored anesthesia care for sedation in adult patients undergoing diagnosite or therapeutic procedures. This submission does not contain any new clinical pharmacology information. Please see the original NDA clinical pharmacology review dated 6/23/2008 for the labeling recommendations pertinent to clinical pharmacology discipline. |

SIGNATURE OF REVIEWER: Srikanth C. Nallani Ph.D.	Date 11-18-2008
SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.	Date 11-18-2008
CC.: HFD # | |: TL: | |	**Project Manager:** **Date**

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

/s/

Srikanth Nallani
11/18/2008 01:13:54 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/18/2008 01:40:24 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-244	Submission Date(s): 09/26/2007
Proposed Brand Name	To be decided between "Lusedra" [redacted]
Generic Name	Fospropofol disodium injection
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Pharmacometrics Reviewer	Venkatesh Atul Bhattaram, Ph.D.
Pharmacometrics Team Leader	Joga Gobburu, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Rheumatology Products
Sponsor	Eisai Pharmaceuticals Inc.
Relevant IND(s)	62,860
Submission Type; Code	New Molecular Entity, 1S
Formulation; Strength(s)	Injection; 35 mg/mL
Indication	Procedural sedation
Proposed Dosage Regimen	In adults aged 18 to <65 years who are healthy or have mild systemic disease (ASA P1 or P2), the standard dosing regimen of Fospropofol is an initial IV bolus of 6.5 mg/kg followed by supplemental dosages of 1.6 mg/kg IV (25 % of initial dosage). Adults ≥65 years of age or those with severe systemic disease (ASA P3 or P4) should receive initial and supplemental intravenous dosages of 75 % of the standard dosing regimen.

b(4)

Table of Contents

1 Executive Summary 3
1.1 Recommendation 3
1.2 Phase IV Commitments 3
1.3 Summary of Clinical Pharmacology Findings 3
2 QBR 13
2.1 General Attributes 13
2.2 General Clinical Pharmacology 13
2.3 Intrinsic Factors 32
2.4 Extrinsic Factors 37
2.5 General Biopharmaceutics 42
2.6 Analytical 43
3 Labeling 48
4 Appendix 55

4.1 Proposed labeling 55
4.2 Pharmacometrics Review by Dr. Atul V. Bhattaram 67
4.3 Individual Study Synopses: 111
4.3.1 Mass Balance Study # 3000-0205 synopsis 111
4.3.2 In vitro protein binding of fospropofol and propofol 117
4.3.3 Influence of Time and Temperature on Metabolism of Fospropofol (GPI 15715) by alkaline phosphatase 126
4.3.4 Metabolic stability of fospropofol (GPI 15715) in liver microsomes 130
4.3.5 Study # 3000-0001 Synopsis 132
4.3.6 Study # 3000-0102 Synopsis 137
4.3.7 Study 3000-0103 Synopsis 141
4.3.8 Study 3000-0206 Synopsis 149
4.3.9 Study 3000-0308 Synopsis 155
4.3.10 Study 3000-0414 Synopsis 158
4.3.11 Study 3000-0401 Synopsis 165
4.3.12 Study 3000-0402 Synopsis 169
4.3.13 Study 3000-0521 Synopsis 173
4.3.14 Study 3000-0625 Synopsis 180
4.3.15 Study 3000-0207 Synopsis 186
4.3.16 Study 3000-0415 Synopsis 189
4.3.17 Study 3000-0520 Synopsis 195
4.3.18 Study 3000-0522 Synopsis 204
4.3.19 Study 3000-0523 Synopsis 211
4.3.20 Study 3000-0524 Synopsis 216
4.3.21 Filing Memo 224

1 Executive Summary

1.1 Recommendation

The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective provided that (1) the sponsor commits to conduct the studies identified in section 1.2 below as a post marketing requirement and (2) a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

- [redacted] b(4)
-

Preferred tools for assessing drug interaction potential of a new molecular entity with regard to CYP enzyme inhibition and induction are indicated in the Draft guidance for **Industry, Drug Interaction Studies — Study Design**, Data Analysis, and Implications for Dosing and Labeling (http://www.fda.gov/cder/guidance/6695dft.htm).

1.3 Summary of Clinical Pharmacology Findings

Background: MGI Pharma, now acquired by Eisai Pharmaceuticals Inc, submitted a 505(b)(1) application on 09/26/2007 seeking approval of Fospropofol injection for sedation in adult patients undergoing diagnostic or therapeutic procedures [redacted] The sponsor proposed brand **names "Lucedra" [redacted] after the initially proposed brand name "Aquavan" was** rejected. Hence, some parts of the review might refer to **the drug product as "Aquavan" or "Fospropofol" or "Fospropofol disodium"** interchangeably. Fospropofol disodium is a water-soluble, phosphono-O-methyl prodrug form of propofol. b(4)

Clinical Pharmacology Data: Sponsor carried out nine Phase 1 studies, five Phase 2 studies, and three Phase 3 studies in which the pharmacokinetics (PK) and pharmacodynamics (PD) of fospropofol and propofol following fospropofol disodium injection were characterized.

A fospropofol-propofol PK-PD relationship was determined by correlating depth of sedation, as determined by Modified Obser**ver's Assessment of Alertness/Sedation** (OAA/S) score to fospropofol and propofol plasma concentrations in patients receiving colonoscopy and bronchoscopy (PR-AQUA-02-02). Study protocols 3000-0207, 3000-0415, 3000-0520, and 3000-0522, and 3000-0524, contributed PD data that were correlated with plasma fospropofol concentrations in the fospropofol population PK-PD analysis.

1. Exposure (Dose)-Response of Efficacy:

The Exposure-Response of Fospropofol is discussed in reference to the following:

a) *Efficacy in clinical trials, and*

b) *Cardiac QT intervals in the Cardiovascular Report*

The dose-response relationship between fospropofol dose and sedation success was explored in dose finding study 3000-0520, clinical efficacy studies in patients undergoing colonoscopy (3000-522) and bronchoscopy (3000-524). Population PK and PD analysis of data from Phase 2 and Phase 3 studies was performed and reported in PR-AQUA-02-02.

For the primary endpoint, the number and proportion of patients who met the criteria for Sedation Success were calculated by treatment group in Phase 3 clinical studies 3000-0522 and 3000-0524. Sedation Success was a composite endpoint that included both efficacy and safety parameters. It measured the ability of the drug to effectively sedate patients, in a manner that did not require advanced airway maneuvers, including manual (bag valve mask) or mechanical ventilation. Specifically, the endpoint was defined as a patient meeting all of the following criteria:

(1) Having 3 consecutive MOAA/S scores of ≤ 4 after administration of sedative medication,

(2) Completing the procedure,

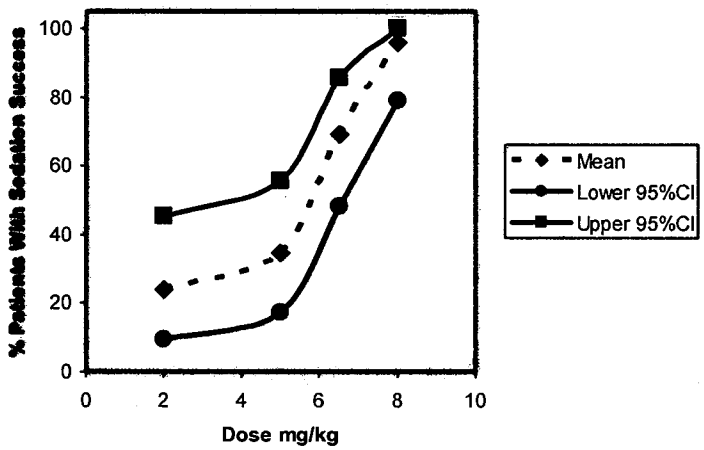
(3) Without requiring the use of alternative sedative medication (such as midazolam) and,

(4) Without requiring manual or mechanical ventilation.

a) Efficacy in Clinical Trials:

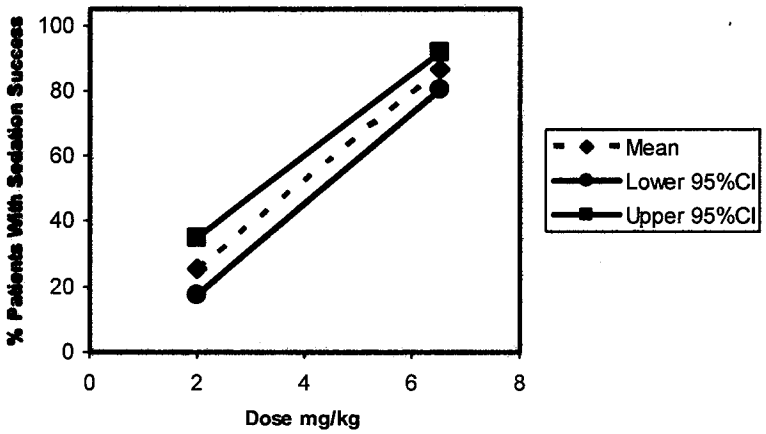
Dose-response in Study # 3000-520:

Patients undergoing colonoscopy were randomized to one of the following 5 groups (n~25 per group) in a 1:1:1:1:1 ratio including 4 dose levels of fospropofol disodium (8.0 mg/kg, 6.5 mg/kg, 5.0 mg/kg, 2.0 mg/kg) and midazolam 0.02 mg/kg. As shown in the figure below, six of 25 patients (24.0%) in the 2-mg/kg Fospropofol group, 9 of 26 (34.6%) in the 5-mg/kg group, 18 of 26 (69.2%) in the 6.5-mg/kg group, and 23 of 24 (95.8%) in the 8-mg/kg group achieved Sedation Success.



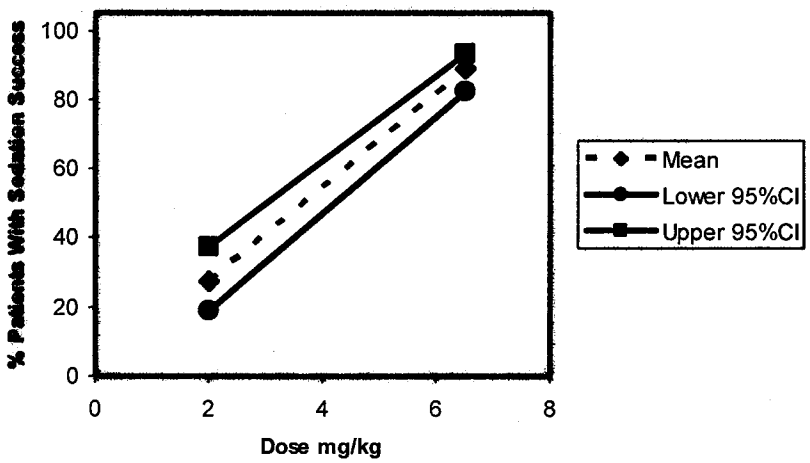
Dose-Response in Study # 3000-522:

Patients in study 3000-0522 were randomized to one of the following 3 groups in a 3:2:1 ratio: fospropofol disodium 6.5 mg/kg; fospropofol disodium 2.0 mg/kg; and midazolam 0.02 mg/kg, respectively. Sedation Success Rate was significantly higher in the Fospropofol 6.5 mg/kg group (86.7%) compared with the Fospropofol 2.0 mg/kg group (25.5%). Sedation Success was achieved in 69.2% of the patients treated with midazolam.



Dose-Response in Study # 3000-524:

Patients in study 3000-0524 were randomized to one of the following 2 groups in a 3:2 ratio: fospropofol disodium 6.5 mg/kg (n=150) and 2.0 mg/kg (n=102), respectively. The Sedation Success rate was significantly higher in the AQUAVAN 6.5-mg/kg group (88.7%) compared with the AQUAVAN 2.0-mg/kg group (27.5%).



b) Fospropofol exposure in reference to Cardiac QT intervals in the Cardiovascular Report (See QT-IRT review dated 1/22/2008 by Dr. Christine Garnett)

In a randomized, open-label, positive- and placebo-controlled crossover study (# 625), 68 healthy subjects were administered single IV bolus dose of Fospropofol 6 mg/kg, Fospropofol 18 mg/kg (3-times the recommended dose), placebo and a single oral dose of 400 mg moxifloxacin. At the anticipated clinical dose of 6 mg/kg, no significant effect on the QTcF was detected. Following the 18 mg/kg dose, the largest upper bound of the two-sided 90% CI for the **ΔΔ**QTcF at the 12-minute timepoint was greater than 10 ms which is identified as the threshold for regulatory concern in the ICH E14 guideline. Mean peak fospropofol and propofol derived from fospropofol plasma concentrations for the 18 mg/kg dose were approximately 3.6-fold higher than the peak concentrations following a 6 mg/kg dose. The overall findings are summarized in the following table.

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

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

***CI is adjusted with 11 post-baseline time points**

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

The Fospropofol doses evaluated in this study are acceptable. There are no known intrinsic or extrinsic factors that can increase exposure to fospropofol and propofol derived from fospropofol greater than what was observed following the supratherapeutic dose (Clinical Pharmacology Table, section 6.1). The sponsor states the expected high clinical exposure scenario is when a subject with low body weight receives the wrong dose (*e.g.*, a full vial of 1050 mg fospropofol) of Fospropofol.

2. Pharmacokinetics of Fospropofol:

Upon intravenous bolus administration, fospropofol plasma concentrations decrease in a biphasic manner with an initial decline followed by a relatively slower terminal phase ($t_{1/2}$ of 0.8 hours). Fospropofol remains preferentially in the extracellular component of blood (blood-to-plasma ratio ~ 0.5) and is highly bound (97 -98%) to plasma proteins at clinically observed concentrations (0.01 – 10 µg/mL). Fospropofol and propofol have a volume of distribution of about 0.39 and 5.3 L/kg, respectively. Upon administration of ^{14}C-fospropofol in Long Evans rats, significant amounts of radioactivity were found in the brain, the purported site of action. This indicates that the fospropofol-derived moieties cross the blood-brain barrier and the active moiety is thought to be propofol. Fospropofol is metabolized by alkaline phosphatase into propofol, formaldehyde and phosphate. In vitro studies indicate that more than 66% of fospropofol disappears within 5 minutes of incubation with alkaline phosphatase at 37°C. The peak plasma

concentrations of propofol are noted around 8 minutes following fospropofol administration (See Figure 1). Fospropofol and propofol have a short elimination half life of about 0.8 and 2 hrs, respectively. Mass balance study conducted in humans after oral administration of ^{14}C-fospropfol revealed that 65% of radioactivity is recovered in urine by 48 hours. While fospropofol and propofol were undetectable in urine, propofol-glucuronide was detected as the major metabolite along with two minor metabolites characterized as hydroxypropofol-glucuronides No.1 and No.2. The major metabolite, propofol-glucuronide appears to persist in plasma longer than fospropofol or propofol. In **the IV bolus dose range of 6 – 18 mg**/kg, dose-proportional increase in AUC of fospropofol was noted, although increase in C_{max} and AUC of propofol was slightly more than dose-proportional (See table below).

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

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

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

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

3. Pharmacokinetics and Pharmacodynamics of Fospropofol and Propofol

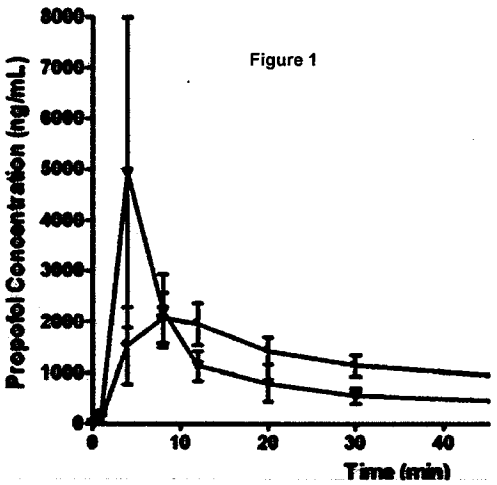


Figure 1 presents the mean propofol concentration over time profile upto 45 minutes following administration of Diprivan 50 mg/min (red inverted triangles and line) and Fospropofol disodium 10 mg/kg (blue circles and line).

The pharmacokinetics and pharmacodynamics of Fospropofol disodium (10 mg/kg bolus) and Diprivan (50 mg/min infusion) were compared in healthy volunteers in Study # 625.

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

Fospropofol PK profile is not indicated in this figure. Propofol plasma concentration profiles were different for the 2 treatments. Following administration of a single IV bolus dose of fospropofol, the median T_{max} for propofol was reached at a slightly later time than it was following Diprivan administration by infusion. Following fospropofol dosing, the mean propofol C_{max} was lower and mean $AUC_{0\text{-}inf}$ was higher than following Diprivan treatment without molar equivalent dose or bodyweight normalization. Following administration of an IV infusion of Diprivan 50 mg/min, plasma concentrations of propofol reached C_{max} at a median T_{max} of 4.0 minutes. The propofol concentration increased rapidly, and then declined after the infusion was stopped.

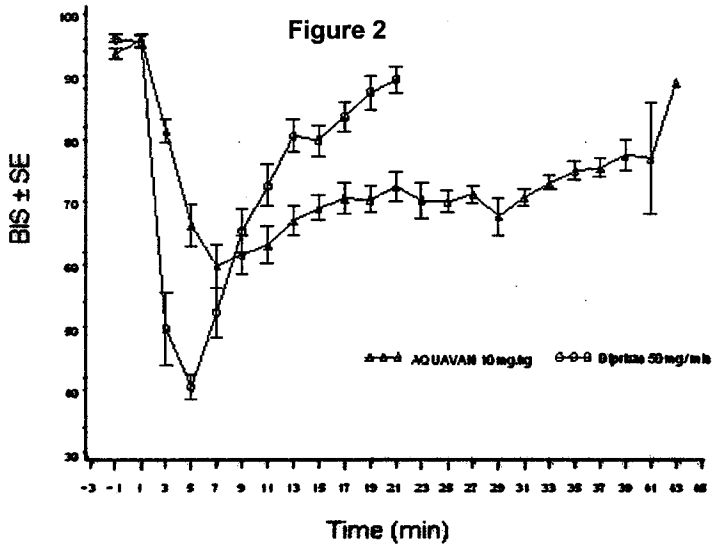


Figure 2 presents the mean BIS scores over time (±standard error [SE]) for the Fospropofol disodium 10 mg/kg (Green Open triangles and line) and Diprivan 50 mg/min (Red Open Circles and line) treatment groups from first dose of study medication to the last time point recorded (45 minutes).

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

Figure 3

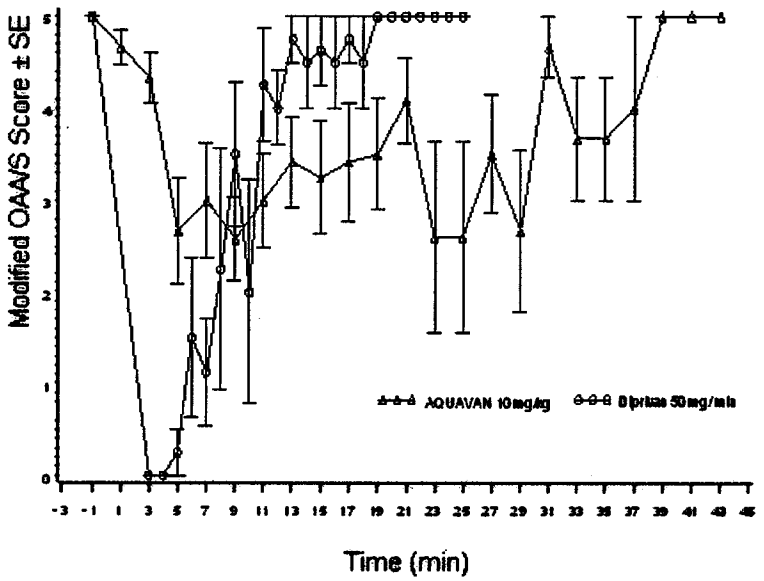


Figure 3 represents the mean changes in MOAA/S scores versus time after Fospropofol disodium 10 mg/kg (Green Open triangles and line) and Diprivan 50 mg/min (Red Open circles and line). MOAA/S scores reached a lower value and recovered faster in subjects after Diprivan treatment than after fospropofol administration. After fospropofol treatment, subjects spent a longer period of time at MOAA/S scores of 2 to 4 than they did following treatment with Diprivan.

4. Effect of prognostic factors on PK-PD of fospropofol and propofol

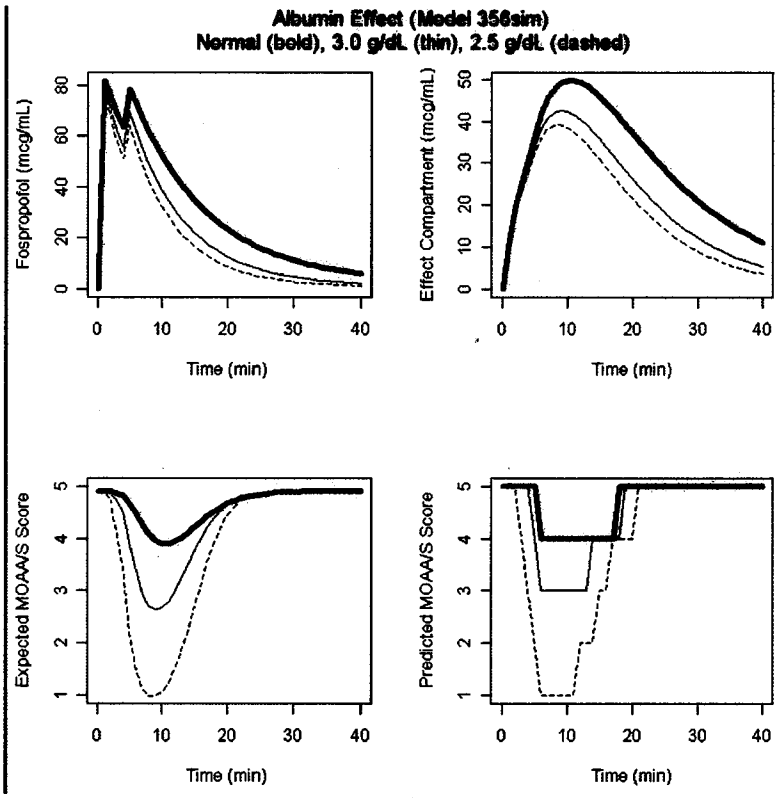
Pharmacokinetic analysis of fospropofol and propofol suggested dependence of clearance on total body weight. After compensating for the effect of body weight factors such as Age, Race, Albumin concentration, alkaline phosphatase concentrations, and renal impairment did not influence the pharmacokinetics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

Effect of albumin concentration on pharmacodynamics: The sponsor analyzed the relationship between fospropofol concentrations and effects on Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) using PK/PD models. For more details of the analysis please refer to the pharmacometrics review.

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 below.

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, 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.

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)	75 (4.6)	89 (35)
≥65	P1 or P2	3-3.8	15	2.1 (1.1)	470 (170)	350 (61)	4.0 (0.61)	2.8 (1)	36 (11)	3.5 (0.13)	73 (5.3)	73 (15)
≥65	P1 or P2	Greater than 3.8	27	3.1 (1.5)	590 (180)	370 (59)	4.4 (0.36)	3.4 (1.1)	54 (18)	4.1 (0.29)	72 (5.7)	80 (17)
≥65	P3 or P4	Less than 3	4	1.2 (0.5)	300 (33)	280 (8.8)	3.5 (0.8)	2.2 (0.96)	22 (3.3)	2.6 (0.32)	72 (6.6)	52 (8.7)
≥65	P3 or P4	3-3.8	15	2.6 (1.4)	490 (150)	360 (74)	4.1 (0.37)	2.9 (1.1)	34 (11)	3.4 (0.17)	71 (5.2)	76 (12)
≥65	P3 or P4	Greater than 3.8	15	2.8 (1.7)	560 (190)	380 (64)	4.1 (0.42)	2.6 (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 (86)	4.0 (0.39)	2.6 (1.1)	35 (18)	2.7 (0.25)	54 (12)	85 (30)
< 65	P1 or P2	3-3.8	22	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	83	3.3 (1.5)	810 (230)	510 (72)	4.4 (0.41)	3.6 (0.96)	69 (18)	4.2 (0.25)	50 (10)	85 (21)
< 65	P3 or P4	Less than 3	8	3.2 (2.1)	620 (210)	410 (83)	3.9 (0.9)	2.4 (1.7)	23 (15)	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 (0.34)	3.5 (1.1)	59 (15)	4.1 (0.22)	55 (7.6)	86 (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.

Hepatic impairment: Sponsor included 7 subjects with hepatic impairment in study # 3000-523 where blood samples were collected for PK analysis. Because of incomplete records on prothrombin time, the number of patients with mild/moderate/severe hepatic impairment is not clear.

As such fospropofol is metabolized by alkaline phosphatases that are ubiquitously present in various organs of the body apart from liver and hence its disposition is not expected to be affected by liver impairment. Propofol, on the other hand, is extensively metabolized by glucuronidation and oxidation possibly by hepatic involvement. The limited information on propofol clearance data from individual patients with hepatic impairment is not adequate to arrive at a recommendation for dose adjustment in patients with hepatic impairment. Hence, it is acceptable to **indicate that "AQUAVAN has not been** adequately studied in patients with hepatic **insufficiency". However, caution should be** exercised when using Fospropofol in patients with hepatic impairment.

Drug-Drug Interactions: Fospropofol is extensively metabolized by ubiquitously present alkaline phosphatases. Propofol appears to be directly glucuronidated as well as hydroxylated by unknown enzymes.

Studies have not been conducted to evaluate the potential for fospropofol or propofol to inhibit or induce major CYP enzymes. However, results from a clinical drug interaction study revealed no effect of pretreatment of fentanyl, midazolam, meperidine and morphine on the pharmacokinetics of fospropofol.

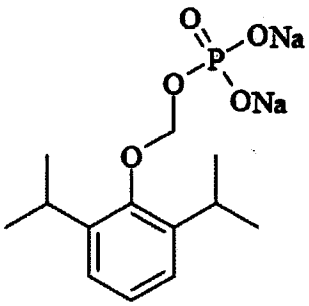
The information provided is not adequate to assess the potential for CYP inhibition or CYP induction by fospropofol or its major active metabolite propofol. Short term use proposed for the current indication and short half-life of the circulating moieties are noted. However, this issue will become relevant when the product use is proposed for longer duration use. Hence, the sponsor should conduct in vitro studies to evaluate the potential for major CYP inhibition or induction.

Overall, the clinical pharmacology submission is acceptable.

2 QBR

2.1 General Attributes

MGI Pharma submitted a 505(b)(1) application on 09/26/2007 seeking approval of Fospropofol injection for sedation in adult patients undergoing diagnostic or therapeutic procedures [redacted] The **sponsor proposed brand names "Lucedra" [redacted] after the initially proposed brand name "Aquavan" was rejected. Hence, s**ome parts of the review might refer to the **drug product as "Aquavan" or "Fospropofol" or "Fospropofol disodium"** interchangeably. b(4)



Fospropofol disodium (Mol. Wt. 332.24) is a water-soluble, phosphono-O-methyl prodrug form of propofol.

Chemical Name: 2,6-diisopropylphenoxymethyl phosphate, disodium salt

Unlike propofol which is highly lipophilic, fospropofol disodium is soluble in water [redacted] b(4)

Fospropofol disodium structure

Mechanism of Action: Fospropofol is metabolized by alkaline phosphatase into propofol, formaldehyde and phosphate. The exact mechanism of action leading to sedative-hypnotic actions of fospropofol or propofol is unknown.

Proposed dosage and route of administration: In adults aged 18 to <65 years who are healthy or have mild systemic disease (ASA P1 or P2), the standard dosing regimen of Fospropofol is an initial IV bolus of 6.5 mg/kg followed by supplemental dosages of 1.6 mg/kg IV (25 % of initial dosage).

Adults ≥65 years of age or those with severe systemic disease (ASA P3 or P4) should receive initial and supplemental intravenous dosages of 75 % of the standard dosing regimen.

2.2 General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies supporting the dosing regimen and other claims?

Clinical Pharmacology studies supporting dosing or other claims were designed to derive

1. Pharmacokinetics, ie., distribution, metabolism and excretion, of fospropofol and propofol was determined in healthy volunteers and patients undergoing procedural sedation.
    - Sponsor carried out nine Phase 1 studies, five Phase 2 studies, and three Phase 3 studies in which the pharmacokinetics (PK) and pharmacodynamics (PD) of

fospropofol and propofol following fospropofol disodium injection were characterized. Clinical studies, 3000-0207, 3000-0415, 3000-0520, 3000-0522, 3000-0523, and 3000-0524, contributed plasma fospropofol concentrations for the fospropofol-propofol population PK analysis. Studies 3000-0522, 3000-0523, and 3000-0524 contributed plasma propofol concentrations for the fospropofol-propofol population PK analysis. Study protocol 3000-0521 contributed healthy subject data used for comparison of PK model predictions for patients with observed PK data from healthy subjects. Subjects with hepatic and renal impairment were recruited in the open label safety study 3000-523 along with healthy patients for different diagnostic or therapeutic procedures.

2. Pharmacodynamics of fospropofol and propofol was determined in healthy volunteers and patients undergoing procedural sedation.

   - A fospropofol-propofol PK-PD relationship was determined by correlating **depth of sedation, as determined by Modified Observer's Assessment of** Alertness/Sedation (OAA/S) score to fospropofol and propofol plasma concentrations in patients receiving colonoscopy and bronchoscopy (PR-AQUA-02-02). Additionally, the PK-PD relationship between bispectral index (BIS), a PD measurement, and plasma concentrations of propofol in healthy subjects is included in PR-AQUA-02-01. Study protocol 3000-0522 contributed PD data that were correlated with plasma fospropofol concentrations and with plasma propofol concentrations in the fospropofol-propofol population PK-PD analysis. Study protocols 3000-0207, 3000-0415, 3000-0520, and 3000-0522, and 3000-0524, contributed PD data that were correlated with plasma fospropofol concentrations in the fospropofol population PK-PD analysis.

Clinical safety and efficacy of fospropofol was evaluated in three adequate and well-controlled Phase 2 and Phase 3 studies (Studies 3000-0520, 3000-0522, and 3000-0524) and a supportive Phase 3 study (3000-0523). Population PK and PD analysis of data from Phase 2 and Phase 3 studies was performed and reported in PR-AQUA-02-02.

Clinical/Clinical Pharmacology Studies are tabulated below:

Clinical Pharmacology/Clinical Studies

Healthy subject studies	
3000-0001	Phase 1 open label, single-dose, dose escalation, safety and tolerability, pharmacokinetic/pharmacodynamic study of GPI 15715 in healthy subjects
3000-0102	Phase 1, open label study of induction and maintenance of sedation, safety and tolerability, pharmacokinetics/pharmacodynamics of GPI 15715 in healthy subjects
3000-0103	Phase 1, open label, single-bolus dose, dose escalation, safety and tolerability, pharmacokinetic/pharmacodynamic study of AQUAVAN® injection in healthy subjects
3000-0205	Phase 1, open label, clinical pharmacokinetic and mass balance study of [^{14}C] AQUAVAN® injection in healthy subjects
3000-0206	Phase 1, open label, randomized safety, tolerability and pharmacokinetic/pharmacodynamic study of AQUAVAN® injection in healthy subjects
3000-0308	Phase 1, open label, safety and tolerability study of AQUAVAN® injection in healthy subjects premedicated with lidocaine HCl injection
3000-0414	A Phase 1 Randomized, Double-blind, Placebo-controlled, Parallel-design, Drug Interaction Study of AQUAVAN® Injection and Premedications in Healthy, Adult Subjects
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 subjects
3000-0625*	A Phase 1, open label, single dose, crossover pharmacokinetic-pharmacodynamic study of AQUAVAN® (fospropofol disodium) injection versus DIPRIVAN® injectable emulsion in healthy subjects
* Note: in these studies the propofol plasma concentrations were determined using the new, improved PK sample collection method.	
Studies in patients	
3000-0207	A Phase 2, two part study of AQUAVAN® injection in the presence of pre-medication in patients undergoing elective colonoscopy
3000-0415	A Phase 2, randomized, open-label study to assess the safety and efficacy of AQUAVAN® injection versus midazolam HCl for sedation in elderly patients undergoing colonoscopy procedures
3000-0520	A randomized, double-blind, dose-response study to assess the efficacy and safety of AQUAVAN® injection for procedural sedation in patients undergoing colonoscopy (Phase 2)
3000-0522*	A Phase 3, randomized, double-blind, dose-controlled study to assess the efficacy and safety of AQUAVAN® (fospropofol disodium) injection for sedation in patients undergoing colonoscopy
3000-0523*	A Phase 3 open-label, single arm study to assess the safety of AQUAVAN® (fospropofol disodium) injection for sedation in patients undergoing minor surgical procedures
3000-0524*	A Phase 3, randomized, double-blind, dose-controlled study to assess the efficacy and safety of AQUAVAN (fospropofol disodium) injection for sedation in patients undergoing flexible bronchoscopy
Studies in patients (prolonged infusion in mechanically ventilated patients)	
3000-0104	Phase 2, randomized study of AQUAVAN® injection in elective coronary artery surgery with comparison to Disoprivan® injectable emulsion
3000-0413	A Phase 2, randomized, open-label study to examine the safety and efficacy of AQUAVAN® injection for sedation of patients requiring intubation and mechanical ventilation in the intensive care unit setting
* Note: in these studies the propofol plasma concentrations were determined using the revised PK sample collection method. Disoprivan® injectable emulsion and Diprivan® injectable emulsion are brand names for propofol injectable emulsion.	

2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

For the primary endpoint, the number and proportion of patients who met the criteria for Sedation Success were calculated by treatment group in Phase 3 clinical studies 3000-0522 and 3000-0524. Sedation Success was a composite endpoint that included both efficacy and safety parameters. It measured the ability of the drug to effectively sedate

patients, in a manner that did not require advanced airway maneuvers, including manual (bag valve mask) or mechanical ventilation. Specifically, the endpoint was defined as a patient meeting all of the following criteria:

(1) Having 3 consecutive MOAA/S scores of ≤ 4 after administration of sedative medication,

(2) Completing the procedure,

(3) Without requiring the use of alternative sedative medication (such as midazolam) and,

(4) Without requiring manual or mechanical ventilation.

In a report by the American Society of Anesthesiologists (ASA) Task Force on sedation and analgesia by Non-anesthesiologists, the responsiveness of patients to commands during procedures performed with sedation/analgesia was recommended as a measure of level of consciousness (Anesthesiology 2002; 96: 1004-1017). The sponsor employed MOAA/S evaluation, described below, placed a grading score of 0 (nonresponsive) to 5 (alert) in the category of responsiveness.

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

3. Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Sponsor evaluated fospropofol and propofol levels in plasma from a variety of Clinical/Clinical Pharmacology Studies. Please refer to the Analytical Section below for details of validation for the methods employed in analyzing plasma levels of fospropofol and propofol.

4. Exposure-response

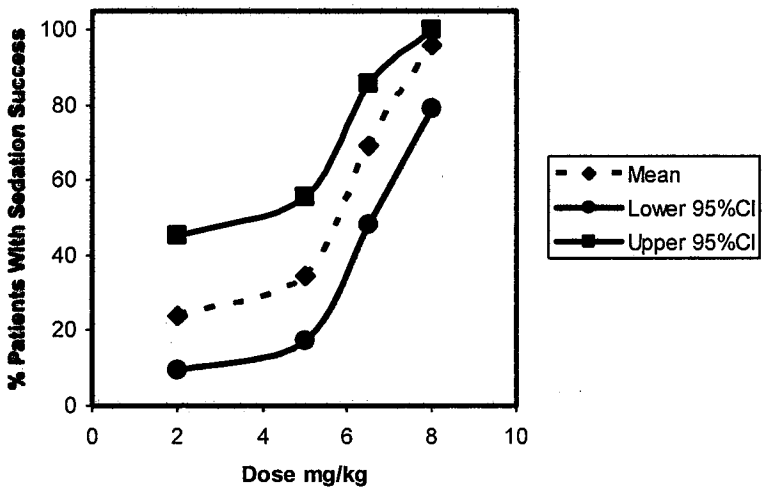
a) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Phase 1 clinical PK-PD studies indicated an association between plasma propofol concentration and sedation measured as MOAA/S scores. In Phase 3 studies, fospropofol dose-related sedation success, time to sedation, duration of sedation and time to ready for discharge were noted in patients undergoing colonoscopy or bronchoscopy.

Dose-Response: The dose response relationship between fospropofol dose and sedation success was explored in dose finding study 3000-0520, clinical efficacy studies in patients undergoing colonoscopy (3000-522) and bronchoscopy (3000-524).

Study # 3000-520: Patients undergoing colonoscopy were randomized to one of the following 5 groups (n~25 per group) in a 1:1:1:1:1 ratio including 4 dose levels of

fospropofol disodium (8.0 mg/kg, 6.5 mg/kg, 5.0 mg/kg, 2.0 mg/kg) and midazolam 0.02 mg/kg. As shown in the figure below, six of 25 patients (24.0%) in the 2-mg/kg Fospropofol group, 9 of 26 (34.6%) in the 5-mg/kg group, 18 of 26 (69.2%) in the 6.5-mg/kg group, and 23 of 24 (95.8%) in the 8-mg/kg group achieved Sedation Success.



Time to Sedation: Fospropofol produced dose-related decrease in time to sedation, defined as time from first dose of study medication to the first two consecutive MOAA/S scores ≤4. Median times to sedation were 12.0 minutes (range, 0-22) in the 2-mg/kg Fospropfol group, 12.0 minutes (range, 2-34) in the 5-mg/kg group, 6.0 minutes (range, 0-18) in the 6.5-mg/kg group, and 4.0 minutes (range, 0-12) in the 8-mg/kg group.

Time (minutes) to Sedation

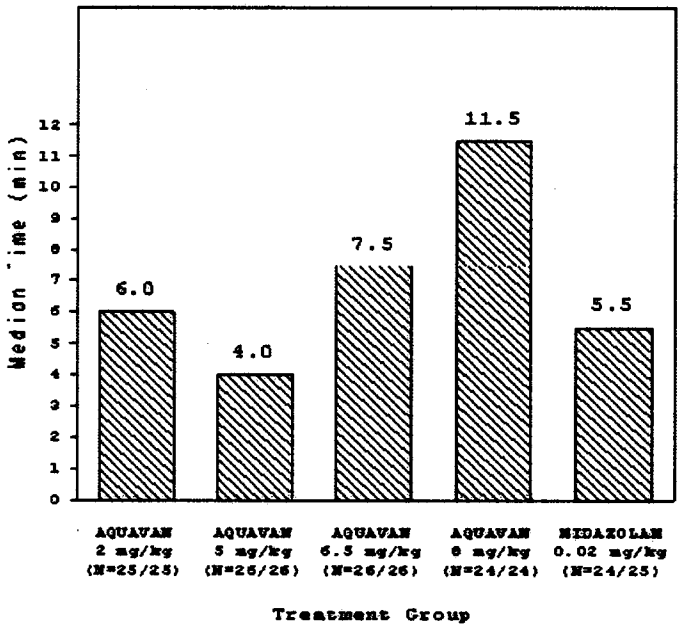
	AQUAVAN 2 mg/kg N=25	AQUAVAN 5 mg/kg N=26	AQUAVAN 6.5 mg/kg N=26	AQUAVAN 8 mg/kg N=24	Midazolam 0.02 mg/kg N=26
	Time (minutes) to Modified OAA/S Score of ≤4[1]				
N	23	23	24	24	25
Mean	12.4	11.0	6.5	4.7	5.0
Standard deviation	5.0	6.9	4.5	2.4	4.2
Median	12.0	12.0	6.0	4.0	4.0
Min, max	0, 22	2, 34	0, 18	0, 12	0, 16

[1] Time to sedation was defined in the protocol as the time from first dose of study medication to the first of 2 consecutive Modified OAA/S scores ≤4.

Duration of Sedation: The duration of sedation as assessed by the median percentages of time at MOAA/S scores of 2 to 4 from first dose of study medication to Fully Alert were higher in the 6.5-mg/kg and 8-mg/kg Fospropofol groups than in the 2-mg/kg and 5-mg/kg groups. The median percentages of time at MOAA/S scores of 2 to 4 were 50.0%, 58.6%, 72.7%, and 71.4% in the 2-, 5-, 6.5-, and 8-mg/kg Fospropofol groups, respectively.

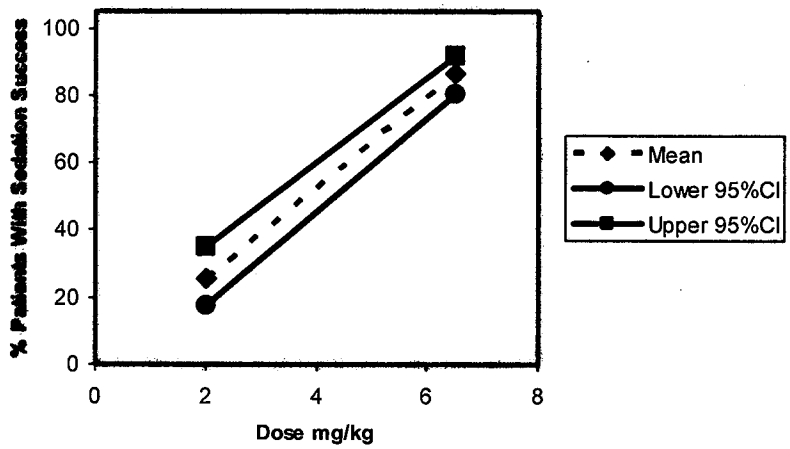
Time to Ready for Discharge after procedure: Dose-dependent increases in time to Ready for Discharge from the end of the procedure were observed across Fospropofol dosing groups with the exception of the 2 mg/kg Fospropofol group. The supplemental medications administered in the 2-mg/kg Fospropofol group could be the reason for this

group being an exception to the dose-response. Median times to Ready for Discharge from the end of the procedure were 6.0 minutes (range, 0-65), 4.0 minutes (range, 0-43), 7.5 minutes (range, 1-30), and 11.5 minutes (range, 1-61) in the 2-, 5-, 6.5-, and 8-mg/kg Fospropofol groups, respectively (See Figure below).



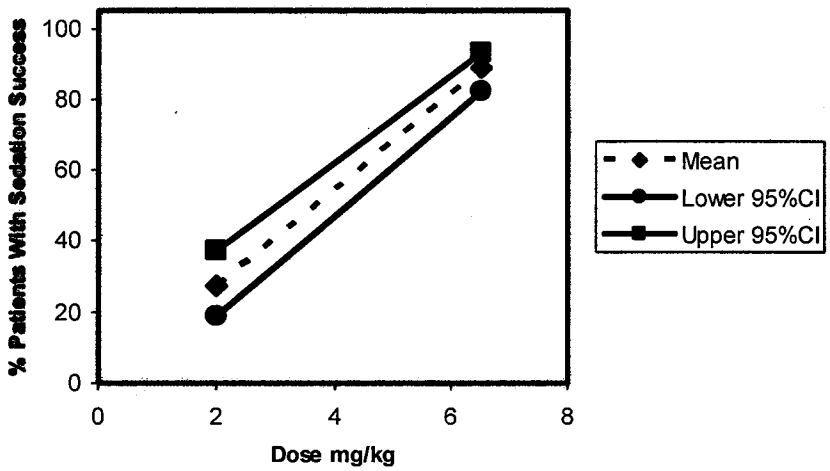
Dose Response in Study # 3000-522:

Patients in study 3000-0522 were randomized to one of the following 3 groups in a 3:2:1 ratio: fospropofol disodium 6.5 mg/kg; fospropofol disodium 2.0 mg/kg; and midazolam 0.02 mg/kg, respectively. Sedation Success Rate was significantly higher in the Fospropofol 6.5 mg/kg group (86.7%) compared with the Fospropofol 2.0 mg/kg group (25.5%). Sedation Success was achieved in 69.2% of the patients treated with midazolam.



Dose-Response in Study # 3000-524:

Patients in study 3000-0524 were randomized to one of the following 2 groups in a 3:2 ratio: fospropofol disodium 6.5 mg/kg (n=150) and 2.0 mg/kg (n=102), respectively. The Sedation Success rate was significantly higher in the AQUAVAN 6.5-mg/kg group (88.7%) compared with the AQUAVAN 2.0-mg/kg group (27.5%).



b) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Exposure-response relationship for safety has not been evaluated.

c) Does this drug prolong the QT or QTc interval? Does the thorough QT study report show that AQUAVAN does not cause QT prolongation?

There is dose-dependent lengthening of the QTcF interval following the administration of AQUAVAN.

In a randomized, open-label, positive- and placebo-controlled crossover study (# 625), 68 healthy subjects were administered single IV bolus dose of Fospropofol 6 mg/kg, Fospropofol 18 mg/kg (3-times the recommended dose), placebo and a single oral dose of 400 mg moxifloxacin. At the anticipated clinical dose of 6 mg/kg, no significant effect on the QTcF was detected. Following the 18 mg/kg dose, the largest upper bound of the two-sided 90% CI for the ΔΔQTcF at the 12-minute timepoint was greater than 10 ms which is identified as the threshold for regulatory concern in the ICH E14 guideline. Mean peak fospropofol and propofol derived from fospropofol plasma concentrations for the 18 mg/kg dose were approximately 3.6-fold higher than the peak concentrations following a 6 mg/kg dose. The overall findings are summarized in the following table. **FDA Analysis: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Fospropofol (Fospropofol 6 mg/kg and 18 mg/kg and the Largest Lower Bound for Moxifloxacin**

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

***CI is adjusted with 11 post-baseline time points**

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

The Fospropofol doses evaluated in this study are acceptable. There are no known intrinsic or extrinsic factors that can increase exposure to fospropofol and propofol derived from fospropofol greater than what was observed following the supratherapeutic dose (Clinical Pharmacology Table, section 6.1). The sponsor states the expected high clinical exposure scenario is when a subject with low body weight receives the wrong dose (*e.g.*, a full vial of 1050 mg fospropofol) of Fospropofol.

d) Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose and dosing regimen is consistent with the dose- and concentration-response noted in Phase 1/2 studies.

Concentration-Response of Fospropofol and Propofol

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

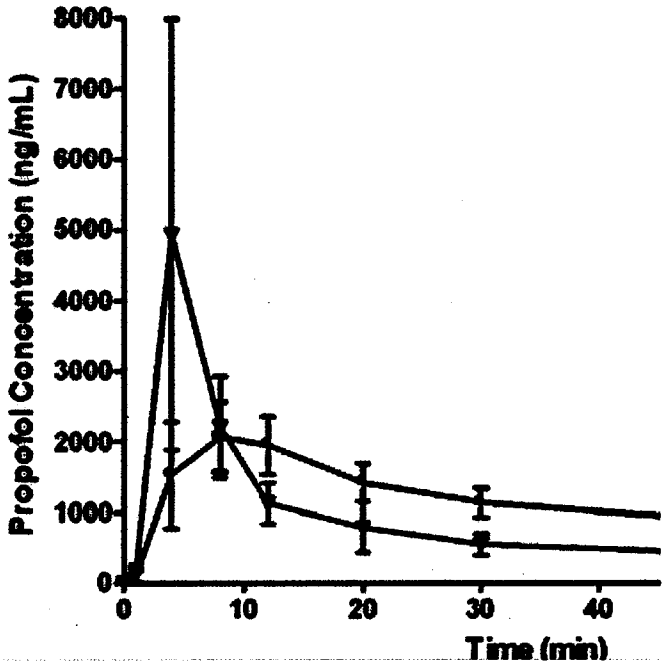


Figure above presents the mean propofol concentration over time profile upto 45 minutes following administration of Diprivan 50 mg/min (red inverted triangles and line) and Fospropofol disodium 10 mg/kg (blue circles and line). Fospropofol PK profile is not indicated in this figure. Propofol plasma concentration profiles were different for the 2 treatments. Following administration of a single IV bolus dose of fospropofol, the median T_{max} for propofol was reached at a slightly later time than it was following Diprivan administration by infusion. Following fospropofol dosing, the mean propofol C_{max} was lower and mean $AUC_{0\text{-}inf}$ was higher than following Diprivan treatment without molar equivalent dose or bodyweight normalization. Following administration of an IV infusion of Diprivan 50 mg/min, plasma concentrations of propofol reached C_{max} at a median T_{max} of 4.0 minutes. The propofol concentration increased rapidly, and then

Appears This Way
On Original

declined after the infusion was stopped.

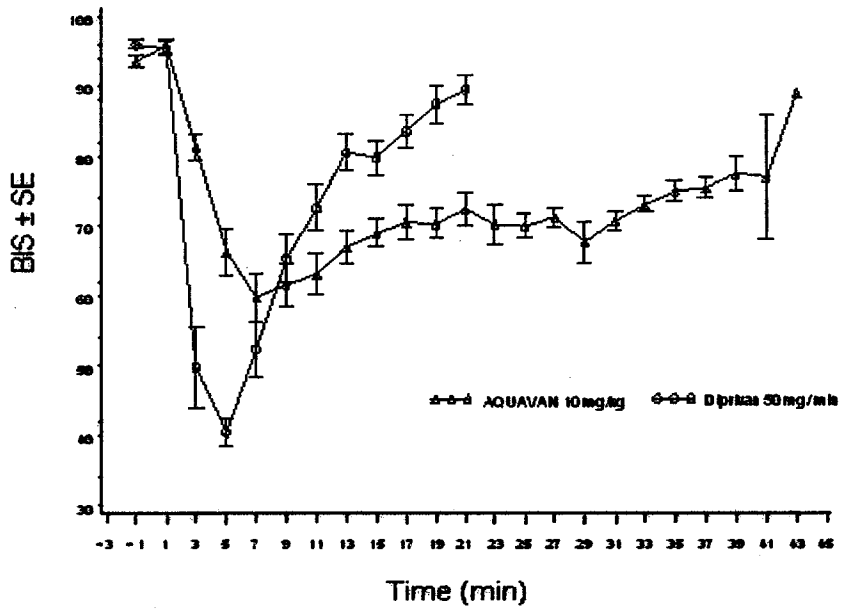


Figure above presents the mean BIS scores over time (±standard error [SE]) for the Fospropofol disodium 10 mg/kg (Green Open triangles and line) and Diprivan 50 mg/min (Red Open Circles and line) treatment groups from first dose of study medication to the last time point recorded (45 minutes). Subjects treated with Diprivan reached their lowest BIS scores at about 5 minutes (median) after drug administration and recovered (to a BIS of approximately 90) at about 21 minutes, when measurements were terminated. The dose of Diprivan was targeted to match the pharmacodynamic effect of a single dose of fospropofol 10 mg/kg. However, subjects treated with Diprivan went to a lower BIS score than those treated with fospropofol. Peak effect for fospropofol was reached at 7 minutes (median) following drug delivery. At 21 minutes after fospropofol administration BIS scores for the majority of subjects had not returned to ≥90. Recovery from sedation, as judged by BIS score, was slower after fospropofol disodium administration than after Diprivan infusion.

Appears This Way
On Original

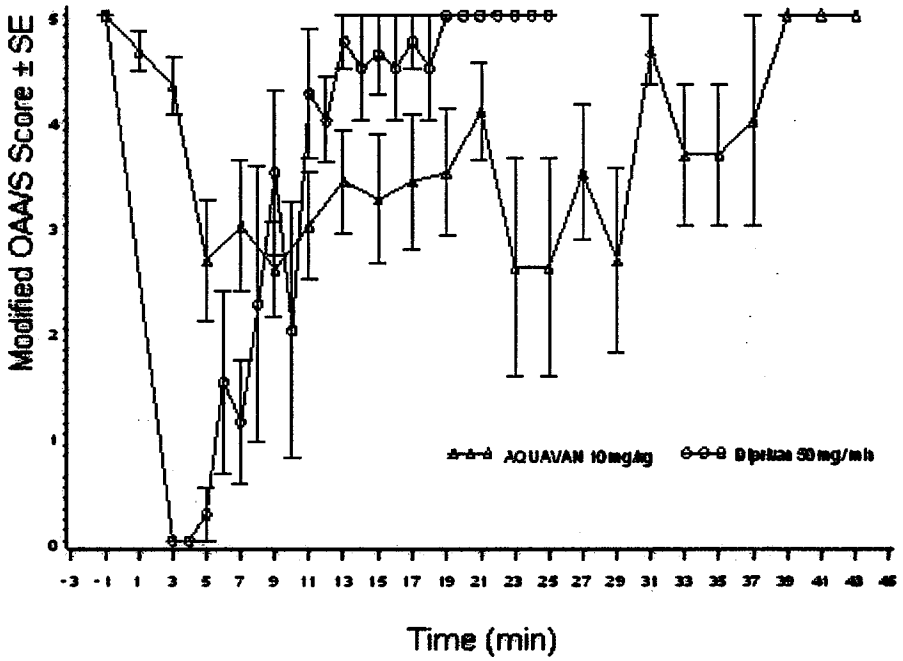


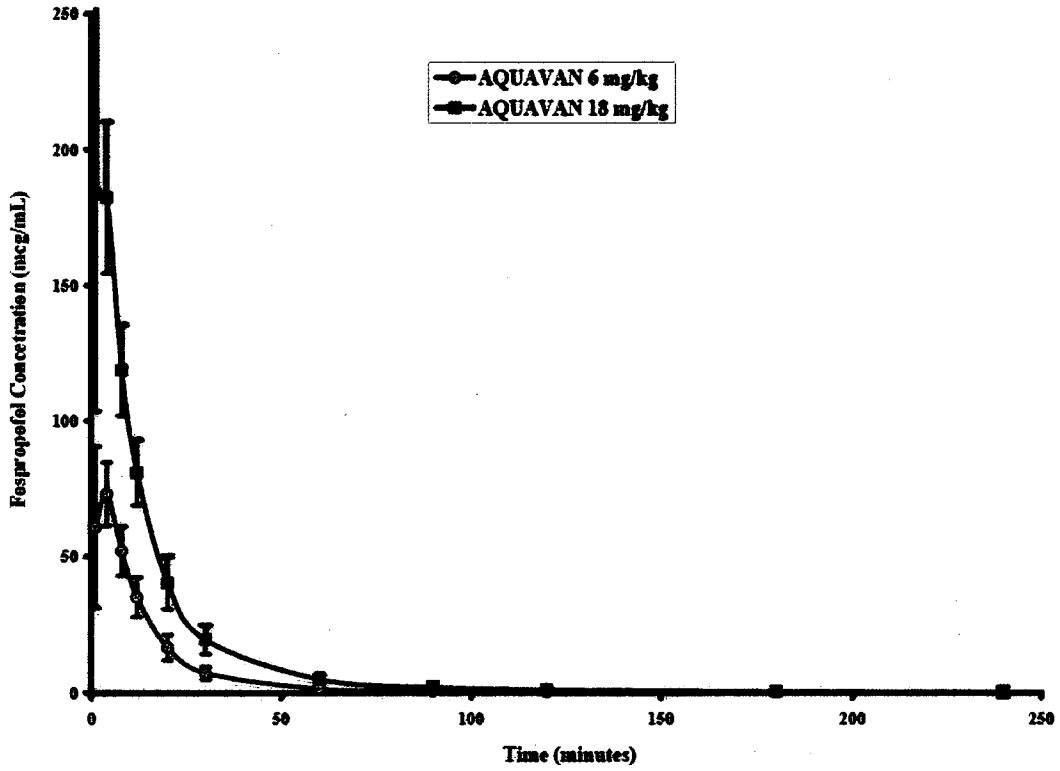
Figure above represents the mean changes in MOAA/S scores versus time after Fospropofol disodium 10 mg/kg (Green Open triangles and line) and Diprivan 50 mg/min (Red Open circles and line). MOAA/S scores reached a lower value and recovered faster in subjects after Diprivan treatment than after fospropofol administration. After fospropofol treatment, subjects spent a longer period of time at MOAA/S scores of 2 to 4 than they did following treatment with Diprivan.

5. What are the PK characteristics of the drug and its major metabolite?

a) What are the single dose and multiple dose PK parameters?

In clinical studies, fospropofol was administered as a single IV bolus dose followed by a supplemental IV bolus dose. The pharmacokinetic characteristics of fospropofol and the major metabolite propofol are described below:

Upon intravenous bolus administration, fospropofol plasma concentrations decrease in a biphasic manner with an initial decline followed by a relatively slower terminal phase ($t_{1/2}$ of 0.8 hours). Fospropofol is metabolized by alkaline phosphatase into propofol, formaldehyde and phosphate. In vitro studies indicate that more than 66% of fospropofol disappears within 5 minutes of incubation with alkaline phosphatase at 37°C. The peak plasma concentrations of propofol are noted around 8 minutes following fospropofol administration (See Figure below).



Appears This Way
On Original

Pharmacokinetic Parameters of Fospropofol in males and females (Study#3000-521)

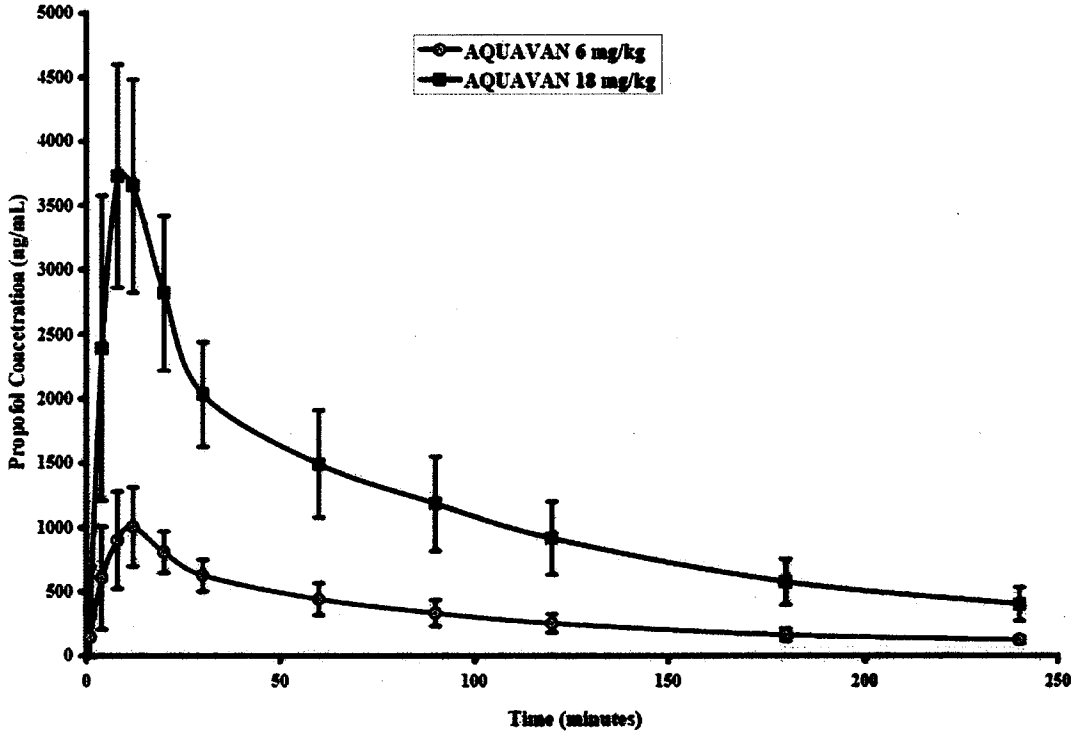
Parameter	Sex	n	AQUAVAN 6 mg/kg	n	AQUAVAN 18 mg/kg
T_{max} (min) Median (Min-Max)	Male and female combined	69	4.00 (1.00-8.00)	68	2.00 (1.00-6.00)
	Male	38	4.00 (1.00-8.00)	38	4.00 (1.00-4.00)
	Female	31	4.00 (1.00-8.00)	30	1.00 (1.00-6.00)
C_{max} (µg/mL) Mean (SD)	Male & Female Combined	69	78.7 (15.4)	68	211 (48.6))
	Male	38	78.1 (16.3)	38	202 (45.9)
	Female	31	79.3 (14.4)	30	223 (49.9)
$AUC_{0\text{-last}}$ (h•µg/mL) Mean (SD)	Male & Female Combined	69	19.2 (3.55)	68	50.1 (8.63)
	Male	38	18.3 (3.08)	38	48.8 (8.3)
	Female	31	20.3 (3.83)	30	51.7 (8.88)
$AUC_{0\text{-inf}}$ (h•µg/mL) Mean (SD)	Male & Female Combined	68	19.2 (3.59)	68	50.3 (8.4)
	Male	37	18.3 (3.10)	38	49.0 (8.39)
	Female	31	20.3 (3.85)	30	51.9 (8.93)
$t_{1/2}$ (h) Mean (SD)	Male & Female Combined	68	0.81 (0.08)	68	0.81 (0.09)
	Male	37	0.85 (0.07)	38	0.83 (0.10)
	Female	31	0.77 (0.08)	30	0.79 (0.09)
CL_p (L/h/kg) Mean (SD)	Male & Female Combined	68	0.280 (0.0528)	68	0.320 (0.0585)
	Male	37	0.293 (0.0533)	38	0.326 (0.058)
	Female	31	0.265 (0.0484)	30	0.310 (0.0577)
V_d (L/kg) Mean (SD)	Male & Female Combined	68	0.327 (0.0686)	68	0.374 (0.0724)
	Male	37	0.357 (0.0669)	38	0.388 (0.0725)
	Female	31	0.291 (0.0517)	30	0.352 (0.0671)

T_{max}=time to maximum plasma concentration; Min=minimum; Max=maximum; C_{max}=observed plasma drug concentration at T_{max}; AUC=area under the concentration versus time curve; $AUC_{0\text{-last}}$=AUC from the time of dosing to the last quantifiable concentration; $AUC_{0\text{-inf}}$=AUC from the time of dosing to infinity; $t_{1/2}$=terminal elimination half-life; CL_p=plasma clearance; V_d=volume of distribution; NA=not applicable

b) How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Pharmacokinetics of propofol, the major active metabolite, following administration of fospropofol were evaluated in healthy volunteers (Studies # 3000-521, # 3000-625) and patients (Studies # 3000-522, #3000-524) in separate studies. Population PK analysis revealed that PK of fospropofol and propofol were similar in healthy volunteers and patients.

Pharmacokinetics of propofol following administration of Fospropofol 6 mg/kg and Fospropofol 18 mg/kg in healthy volunteers are described below. Plasma concentrations of propofol reached Cmax at a median Tmax of 12 minutes for Fospropofol 6 mg/kg and 8 minutes for Fospropofol 18 mg/kg. Concentration profiles showed biphasic elimination with a mean $t_{1/2}$ of 2.06 hours for Fospropofol 6 mg/kg and 1.76 hours for Fospropofol 18 mg/kg. Mean Cmax values were 1.08 µg/mL and 3.90 µg/mL, and mean AUC0-inf **values were 1.70 h•µg/mL and 5.67 h•µg/mL**, for Fospropofol 6 mg/kg and 18 mg/kg, respectively.



PK parameters of propofol are tabulated below. The increase in propofol exposure was slightly more than dose proportional. A 3-fold increase in Fospropofol dose (from 6 to 18 mg/kg) led to a 3.6-fold increase in mean propofol Cmax and a 3.3-fold increase in mean propofol AUC 0-inf.

Pharmacokinetic Parameters of Propofol Following IV Fospropofol Administration

Parameter	Sex	n	AQUAVAN 6 mg/kg	n	AQUAVAN 18 mg/kg
T_{max} (min) Median (Min-Max)	Male and female combined	69	12.00. (4.00-60.00)	68	8.00 (4.00-60.00)
	Male	38	12.00. (4.00-60.00)	38	8.00 (4.00-20.00)
	Female	31	12.00. (4.00-33.00)	30	8.00 (8.00-60.00)
C_{max} (µg/mL) Mean (SD)	Male and female combined	69	1.08 (0.33)	68	3.90 (0.822)
	Male	38	1.14 (0.366)	38	4.06 (0.868)
	Female	31	1.01 (0.270)	30	3.69 (0.719)
$AUC_{0\text{-}last}$ (h•µg/mL) Mean (SD)	Male and female combined	69	1.33 (0.244)	68	4.63 (0.958)
	Male	38	1.38 (0.239)	38	4.93 (0.981)
	Female	31	1.27 (0.239)	30	4.25 (0.791)
$AUC_{0\text{-}inf}$ (h•µg/mL) Mean (SD)	Male and female combined	67	1.70 (0.290)	68	5.67 (1.28)
	Male	37	1.78 (0.266)	38	6.11 (1.34)
	Female	30	1.60 (0.290)	30	5.11 (0.963)
$t_{1/2}$ (h) Mean (SD)	Male and female combined	67	2.06 (0.77)	68	1.76 (0.54)
	Male	37	2.06 (0.51)	38	1.79 (0.51)
	Female	30	2.06 (1.02)	30	1.74 (0.58)
CL_p/F (L/h/kg) Mean (SD)	Male and female combined	67	1.95 (0.345)	68	1.79 (0.390)
	Male	37	1.85 (0.283)	38	1.65 (0.317)
	Female	30	2.08 (0.376)	30	1.96 (0.406)
V_d/F (L/kg) Mean (SD)	Male and female combined	67	5.76 (2.14)	68	4.46 (1.38)
	Male	37	5.50 (1.59)	38	4.19 (1.30)
	Female	30	6.07 (2.66)	30	4.80 (1.43)

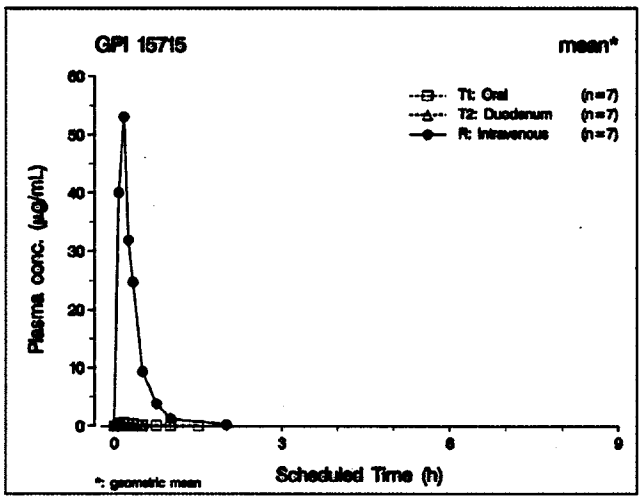
T_{max}=time to maximum plasma concentration; Min=minimum; Max=maximum; C_{max}=observed plasma drug concentration at T_{max}; AUC=area under the concentration versus time curve; $AUC_{0\text{-}last}$=AUC from the time of dosing to the last quantifiable concentration; $AUC_{0\text{-}inf}$=AUC from the time of dosing to infinity; $t_{1/2}$=terminal elimination half-life; CL_p/F=apparent plasma clearance; V_d/F= apparent volume of distribution; NA=not applicable

c) What are the characteristics of drug absorption?

Following oral administration of fospropofol plasma levels of fospropofol and propofol were detected and sedative effects were noted in healthy volunteers.

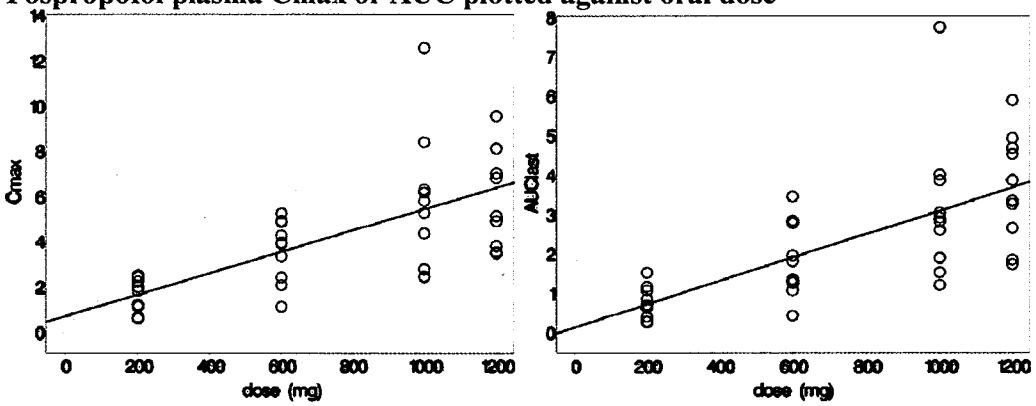
As such absorption of fospropofol is not relevant for the proposed intravenous dosing regimen. However, absolute bioavailability of fospropofol was evaluated following oral, duodenal or IV administration of 400 mg fospropofol (Study# 3100-0401). The mean absolute bioavailability (F) of fospropofol was 1% after oral administration and 0.1% after duodenal administration. The plasma propofol levels could not be estimated reliably due to problems with the analytical assay.

Mean fospropofol plasma concentration vs time profiles



In another study (#3100-402) pharmacokinetics of fospropofol following single ascending doses was evaluated in healthy volunteers. Dose-related increase in plasma fospropofol levels were noted in this study. Again, plasma levels of propofol could not be reliably estimated in this study due to problems with the analytical assay. However, significant sedative effects were felt by the subjects following oral and duodenal administration of fospropofol.

Fospropofol plasma Cmax or AUC plotted against oral dose



The implications of fospropofol oral absorption as it applies to abuse and misuse have been addressed by Dr. Patricia Beaston in the **controlled substances staff's assessment of fospropofol's abuse liability.**

d) What are the characteristics of drug distribution?

Fospropofol remains preferentially in the extracellular component of blood (blood-to-plasma ratio ~ 0.5) and is highly bound (97 -98%) to plasma proteins at clinically **observed concentrations (0.01 – 10 µg/mL).** Fospropofol and propofol have a volume of distribution of about 0.39 and 5.3 L/kg, respectively. Upon administration of ^{14}C-fospropofol in Long Evans rats, significant amounts of radioactivity were found in the brain, the purported site of action. This indicates that the fospropofol-derived moieties cross the blood-brain barrier and the active moiety is thought to be propofol.

The potential for protein binding interaction between fospropofol and propofol was assessed in human plasma collected from thr**ee separate individuals. Propofol (0.05 – 5** µg/mL) had minimal effects on protein bindi**ng of fospropofol. Fospropofol (0.01 – 200** µg/mL) did not affect the protein binding of propofol.

e) Does the mass balance study suggest renal or hepatic as the major route of elimination?

Fospropofol appears to be mainly eliminated by renal route followed by extensive metabolism.

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

Amount of Radioactivity Recovered in Urine and Feces in Fospropofol equivalents

Parameter	Urine		Feces	
	(N=8)	(N=7)*	(N=8)	(N=7)*
CumAe (mg)	246 (13.0)	247 (24.6)	1.76 (1.18)	1.77 (1.28)
%Fe †	71.3 (3.76)	71.7 (3.95)	0.51 (0.34)	0.51 (0.37)

%Fe = 100*CumAe/344.62

f) What are the characteristics of drug metabolism?

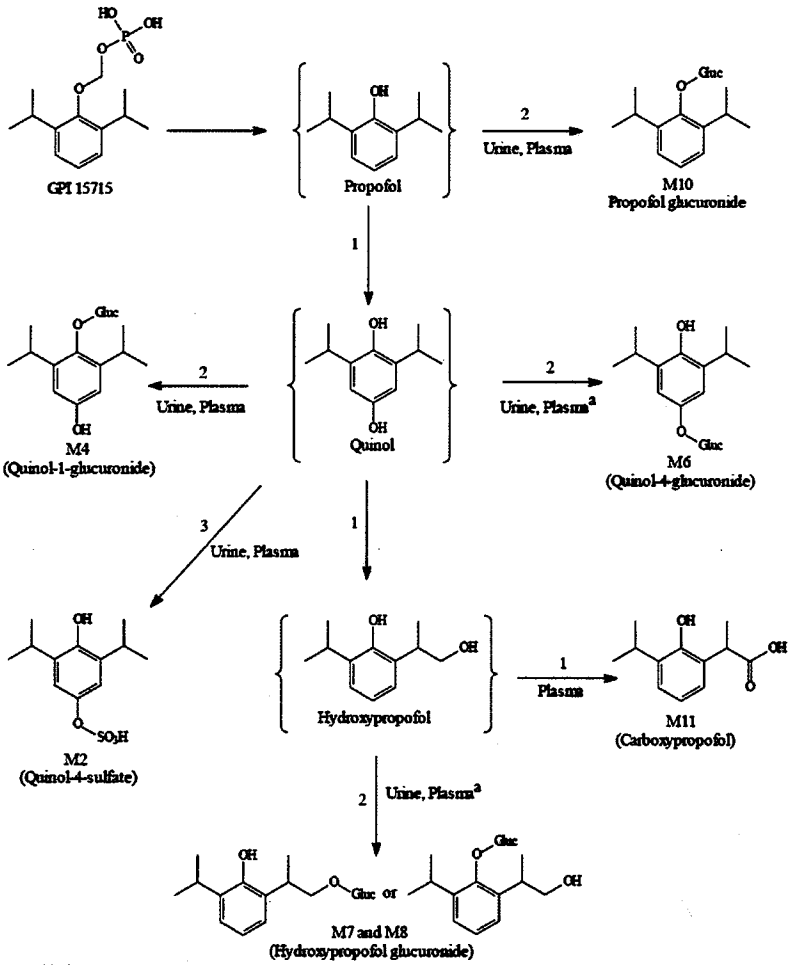
Fospropofol is metabolized by alkaline phosphatase into propofol, formaldehyde and phosphate. Propofol is further metabolized by glucuronidation.

In vitro studies indicate that more than 66% of fospropofol disappears within 5 minutes of incubation with alkaline phosphatase at 37°C. PK characteristics of propofol formed following administration of fospropofol are described in the above sections.

In study#3000-0205, eight healthy male subjects received a single i.v. infusion of 400 mg of [^{14}C] fospropofol disodium injection (100 µCi) over 10 minutes. Blood, plasma, urine, and feces samples were collected for determination of total radioactivity; plasma fospropofol and propofol concentrations.

The study demonstrated that, on the basis of ratios of AUC0-inf values for radioactivity in plasma to plasma $AUC_{0\text{-}inf}$ values for fospropofol, 21.4% of the total radioactivity in plasma was associated with unchanged fospropofol. An average of 71.3% of total radioactivity was recovered in urine in 8 days (192 hr). The majority of radioactivity (65%) was recovered in urine within 48 hours following dosing. Less than 1% of radioactivity was detected in feces.

Proposed biotransformation of fospropofol disodium in humans



1 = Oxidation
2 = Glucuronide conjugation
3 = Sulfate conjugation

[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.

^{14}C-fospropofol was detected in plasma but not urine. The major metabolite observed was propofol glucuronide (M10), and represented a mean value of 34.8% of the dose in

urine through 24 hours. Three other metabolites were observed at relatively low levels: quinol-4-sulfate (M2), quinol-1-glucuronide (M4), and quinol-4-glucuronide (M6), representing mean values of 4.59%, 11.1%, and 5.13% of the dose, respectively, in urine through 24 hours. Two other minor metabolites were detected: hydroxypropofol-glucuronide No. 1 (M7), and hydroxypropofol-glucuronide No. 2 (M8), representing mean values of 0.81% and 0.26% of the dose, respectively, in urine through 24 hours.

g) What are the characteristics of drug excretion?

Fospropofol and propofol have a short elimination half life of about 0.8 and 2 hrs, respectively. Mass balance study conducted in humans after oral administration of ^{14}C-fospropfol revealed that 65% of radioactivity is recovered in urine by 48 hours. While fospropofol and propofol were undetectable in urine, propofol-glucuronide was detected as the major metabolite along with two minor metabolites characterized as hydroxypropofol-glucuronides No.1 and No.2.

h) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Fospropofol pharmacokinetics is linear in ***the dose range of 6 – 18 mg/kg; propofol*** *pharmacokinetics is slightly nonlinear around 18 mg/kg dose compared to the 6 mg/kg dose.*

Fospropofol median T_{max} was observed at 4 minutes (range, 1 to 8 minutes) for subjects who received 6 mg/kg and at 2 minutes (range, 1 to 6 minutes) for those who received 18 mg/kg of fospropofol disodium injection. Mean fospropofol concentrations exhibited an approximate 2-fold decrease between 4 minutes and 12 minutes and an approximate 10-fold decrease between 4 minutes and 30 minutes following administration of single bolus doses of fospropofol disodium injection (see Table below). The initial decline was followed by a slower terminal phase with a mean $t_{1/2}$ of 0.81 hour.
Propofol median Tmax was 12 minutes for subjects who received 6 mg/kg and 8 minutes for subjects who received 18 mg/kg of fospropofol disodium injection (see Table below). Concentration profiles showed biphasic elimination with a mean t1/2 of 2.06 hours for subjects who received 6 mg/kg and 1.76 hours for subjects who received 18 mg/kg of fospropofol disodium injection.

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

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

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

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

i) How do the PK parameters change with time following chronic dosing?

Given the short duration of action need for the proposed indication, multiple dose PK studies in the conventional sense, i.e., up to steady state, were not conducted.

j) What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Low to moderate unexplained inter-individual variability was noted with estimates of 14.6% CV (2.9-23%), and 31.6% CV (27.7-47.3%) for central volume of distribution (V_1) and clearance (CL_F), respectively.

The population PK parameter estimates are presented in the table below. In particular, typical fospropofol volume was estimated as V1 = 4.41 L (4.23 - 4.56 L) and clearance as CL_F = 0.312 L/min (0.197 - 0.331 L/min).

Population PK parameter estimates

Parameter	NONMEM notation	Model 010			
		Population Estimate	Relative SE (%)	Bootstrap median (95% CI)	Relative SE (%)
V_1 (L)	θ_1	4.41	1.81	4.4(4.24 - 4.56)	1.76
CL_F (L/min)	θ_2	0.312	3.67	0.312(0.197 - 0.331)	2.03
K_{12} (1/min)	θ_3	0.0147	13.5	0.0147(0.0122 - 0.0397)	FIXED
K_{21} (1/min)	θ_4	0.0128	29.1	0.0131(0.00302 - 0.0215)	12.6
$V_{1,DOSE}$	θ_7	0.236	9	0.232(0.19 - 0.272)	8.85
$CL_{F,DOSE}$	θ_8	0.138	16.8	0.134(0.0757 - 0.185)	16.4
$V_{1,SMI}$	θ_9	-0.199	29.1	-0.196(-0.314 - -0.0827)	27.4
$CL_{F,ALB}$	θ_{10}	3.34	10.5	3.44(2.72 - 4.79)	10.3
$CL_{F,ALP}$	θ_{11}	0.117	34.4	0.124(0.046 - 0.208)	32.3
$CL_{F,BILI}$	θ_{12}	-0.0322	29.5	-0.0313(-0.0517 - -0.00638)	29.1
$CL_{F,CRCL}$	θ_{13}	-0.0738	75.7	-0.069(-0.166 - 0.0289)	54.1
$CL_{F,ASA}$	θ_{14}	1.21	3.53	1.21(1.13 - 1.34)	3.5
ω^2_V	$\Omega(1,1)$	0.0214	58.6	0.0221(0.000843 - 0.0529)	60.2
$R_{V,CL}\omega_V\omega_{CL}$	$\Omega(1,2)$	0.0187	53.9	0.0193(0.0036 - 0.0426)	53.8
ω^2_{CL}	$\Omega(2,2)$	0.0998	13.7	0.101(0.0767 - 0.223)	12.4
σ^2_{add}	θ_5	0.191	33.3	0.184(0.0422 - 0.354)	30.1
σ^2_{prop}	θ_6	0.111	9.16	0.109(0.091 - 0.131)	9.14
		Variability estimates (derived)			
CV_{V1}	$100\ \Omega(1,1)^{1/2}$ %	14.6%		14.9 (2.9 - 23)	
R_{CLV1}		0.405		0.418 (0.117 - 1)	
CV_{CL}	$100\ \Omega(2,2)^{1/2}$ %	31.6%		31.8 (27.7 - 47.3)	
$SD_{sigmaAdd}$	$\theta_5^{1/2}$	0.437		0.429 (0.205 - 0.595)	
$CV_{sigmaExp}$	$100\ \theta_6^{1/2}$	33.3%		33.0 (30.2 - 36.2)	

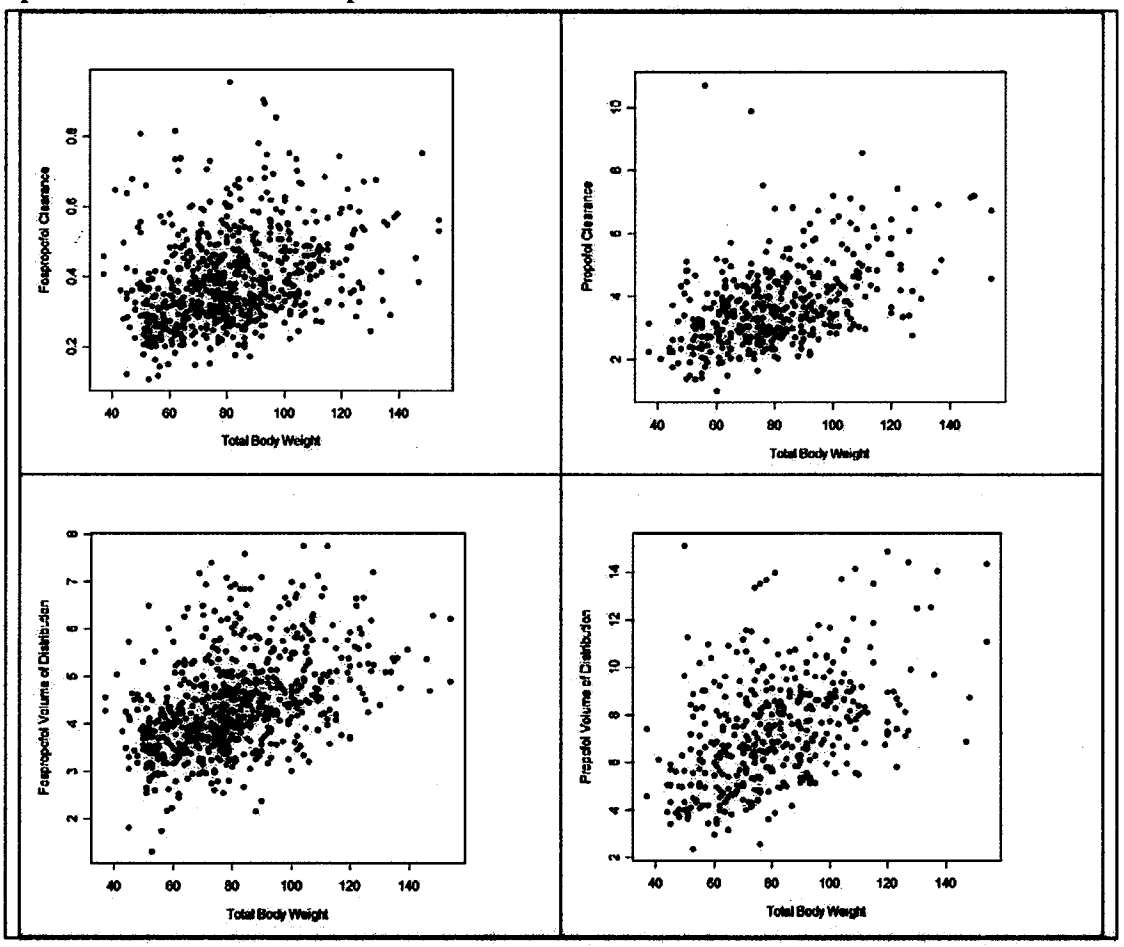
2.3 Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Significant impact of body weight on pharmacokinetics of fospropofol and propofol was noted. These findings support the weight based dosing algorithm proposed by the sponsor: The dosage of Fospropofol is limited by lower and upper weight bounds of 60 kg and 90 kg, respectively. Adults who weigh >90 kg should be dosed as if they are 90 kg; adults who weigh <60 kg should be dosed as if they are 60 kg.

The population pharmacokinetics of fospropofol was adequately described by a two-compartment model. Population pharmacokinetic analysis evaluated the effect of race, age, gender, body weight, albumin concentration, alkaline phosphatase concentration, renal impairment and hepatic impairment on the pharmacokinetics of fospropofol and propofol derived from fospropofol. None of the prognostic factors except body weight affected PK of fospropofol or propofol (See attached Pharmacometrics review). Allometric scaling adequately described the dependence of fospropofol population PK parameters on body size measures. Body weight (WT) was normalized to a reference weight of 70 kg. For both fospropofol and propofol central volume of distribution increased linearly with weight (WT/70), and clearance increased as $(WT/70)^{3/4}$ while rate constants decreased as $(WT/70)^{-1/4}$. After adjusting for body weight renal impairment and hepatic impairment did not significantly affect fospropofol pharmacokinetics.

Relationship between CL, V for fospropofol and propofol and total body weight in patients without extreme parameter values.



Pharmacokinetic-pharmacodynamic (PK-PD) analysis was conducted to evaluate the relationship between venous plasma concentrations of fospropofol and propofol, and **Modified Observer's Assessment of Al**ertness/Sedation (MOAA/S) score following administration of therapeutic bolus dose(s) of fospropofol injection. Effect of prognostic

factors such as age, race, gender, body weight, albumin concentration, alkaline phosphatase concentration was evaluated on sedative effects of propofol. The analysis indicated that older patients (age > 65 years) were more sensitive to fospropofol treatment. The changes to the effective concentration for fospropofol to produce 50% of maximal sedative effect (EC_{50}) were evaluated in the population PK-PD analysis. Decreases in EC_{50} with a decrease in albumin concentration for different strata of patients based on age, ASA status, and weight. However, Sedation depth (as measured by the **Modified Observer's Assessment of Alertness**/Sedation Scale) was not consistently influenced by albumin levels across these populations. Hence, dose adjustment is not recommended with respect to albumin concentrations.

2. **Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups (examples shown below)?**

a) elderly

Patients ≥ 65 years age should receive 25% lower dose at any given weight range compared to patients <65 years age.

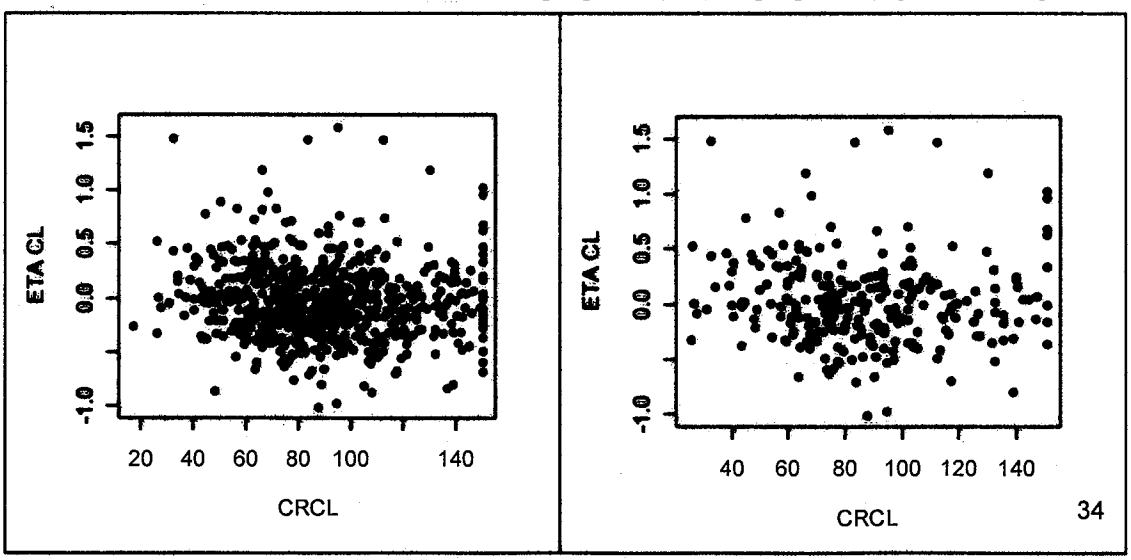
b) pediatric

The sponsor has not conducted any clinical studies in pediatric patients. The sponsor is requesting a deferral of clinical studies of fospropofol disodium in pediatric populations including neonates, infants, children, and adolescents.

c) renal impairment

Dose adjustment is not needed with respect to renal impairment.

A total of 7 renally impaired patients were included into population PK analysis. Five of these patients had normalized creatinine clearance between 10 and 30 mL/min/1.73m2. Two patients had normalized creatinine clearance less than 10 mL/min/1.73m2 . The data from these patients with renal impairment were merged along with other patients and the pharmacokinetic parameters were determined. Significant relationship was not noted between random effects on clearance of fospropofol (left) or propofol (right) with regard



to creatinine clearance (See Figure above).

d) hepatic impairment

Recommendation cannot be made with regard to dose adjustment in patients with hepatic impairment. Caution should be exercised when using fospropofol in patients with hepatic impairment.

Fospropofol data from seven patients (five patient data for propofol) with hepatic impairment were merged along with other patients and the pharmacokinetic parameters were determined. Five of these patients were present in the main data set of the **fospropofol – propofol population PK analysis** (population analysis report for MGI Study number PR-AQUA-02-02). Data for two additional patients with hepatic impairment became available after the main analysis was completed and NDA submitted to the FDA.

Demographic information for the seven patients is presented below.

ID	Usubjid	AGE (yrs)	WT (kg)	LBW (kg)	BMI (kg/m^2)	SEX	ASA	ALB (g/dL)	ALP (U/L)	CREA (mg/dL)	BILI (mg/dL)	CRCL ($mL/min/1.73m^2$)
230	5203650001	53	100	67.7	33	Male	P2	4.2	68	1.1	2.4	88.7
444	5235590002	59	80	62.1	25.2	Male	P3	2.8	134	1.0	2.1	78.6
450	5235650016	53	76	51	26.9	Female	P3	3.3	206	0.8	1.1	90.9
453	5235650023	60	50	38.1	20.8	Female	P3	2.5	203	0.6	5.9	92.8
612	5245440003	61	74	55.7	27.2	Male	P4	2.7	94	0.8	0.6	96.8
703	5235610001	53	84	65.4	25.1	Male	P3	2.7	149	0.6	1.8	141.9
704	5235650025	85	60	43.4	23.4	Female	P3	3.3	105	0.9	4.1	46.2

The hepatic impairment noted in these patients as per the Child-Pugh scores is indicated below. Prothrombin time was not collected in all patients and 1 point was assigned to each patient. With the adjustment one patient with mild, three with moderate and two patients with severe hepatic impairment are recorded.

Child-Pugh Scores for Patients with Hepatic Impairment (Score of 5-6 indicates mild, score of 7-9: moderate and a score of >9 indicates severe hepatic impairment)

	0520-365-0001	0524-544-0003	0523-547-0006[1]	0523-559-0002	0523-565-0016	0523-561-0001	0523-565-0023	0523-565-0025
Encephalopathy grade[2]	1	1	1	1	2	1	1	2
Ascites[2]	1	1	1	1	2	2	2	2
Serum bilirubin, mg/dL	1	1	1	2	1	2	3	3
Serum albumin, g/dL	1	3	3	3	2	3	3	2
Prothrombin time, sec prolonged[3]	1	1	1	1	1	1	1	1
Child-Pugh Score	5	7	7	8	8	9	10	10

[1] While this patient met the criteria for hepatic impairment, PK samples were not available for this patient, and the patient was not included in the PR-AQUA-02-03 analysis.
[2] Encephalopathy grade and ascites determined by medical history taken at baseline.
[3] Prothrombin time was not collected; all patients were assigned 1 point for this assessment.

Propofol data for one patient with hepatic impairment (Patient 0520-365-0001, ID=230) were not available and unreliable in another patient (0523-565-0023). The PK information for individuals

The individual clearance value for fospropofol noted for each patient with hepatic impairment

Patient No.	Child-Pugh Score	Child-Pugh Classification	CL_F[a] (L/min)	$t_{1/2}$ (min)	$AUC_{(0-\infty)}$[b] (mcg•hr/mL)
All Patients (N = 667)	-	-	0.4	53	19
5203650001	5	A (mild)	0.439	54.6	14.7
5235590002	8	B (moderate)	0.53	49	12.8
5235650016	8	B (moderate)	0.37	50.7	18.1
5245440003	7	B (moderate)	0.543	46.6	12.3
5235610001	9	B (moderate)	0.478	50.4	14.4
5235650023	10	C (severe)	0.433	45.6	16.8
5235650025	10	C (severe)	0.305	48.7	15.6

[a] Normalized CL_F, was computed as $CL_F/(WT/70)^{0.75}$

[b] Predicted AUC from time 0 to infinity after single bolus fospropofol dose of 6.5 mg/kg. Patients weighing less than 60kg (greater than 90 kg) were administered 390 mg (585 mg) dose. Dose for 65-years old and older patients was reduced by 25%.

Mean of fospropofol PK parameters in "all patients" was estimated by Population PK Model 120

The individual clearance value for fospropofol and propofol noted for each patient with hepatic impairment

Patient No.	Child-Pugh Score	Child-Pugh Classification	CL_P[a] (L/min)	$t_{1/2}$ (min)	$AUC_{(0-\infty)}$[b] (mcg•hr/mL)
All Patients	-	-	3.5	68	1.2
5203650001	5	A (mild)	NA	NA	NA
5235590002	8	B (moderate)	2.92	90.8	1.44
5235650016	8	B (moderate)	2.24	63.2	1.85
5245440003	7	B (moderate)	4.31	43.3	0.958
5235610001	9	B (moderate)	3.56	58.9	1.2
5235650023[c]	10	C (severe)	--	--	--
5235650025	10	C (severe)	1.64	89.1	1.79

[a] Normalized CL_F was computed as $CL_P/(WT/70)^{0.75}$

[b] Predicted AUC from time 0 to infinity after single bolus fospropofol dose of 6.5 mg/kg. Patients weighing less than 60kg (greater that 90 kg) were administered 390 mg (585 mg) dose. Dose for 65-years old and older patients was reduced by 25%.

[c] Excluded from propofol PK evaluation due to inconsistent and extremely low values

NA: propofol data was not available

Mean of propofol PK parameters in "all patients" was estimated by Population PK Model 120

As such fospropofol is metabolized by alkaline phosphatases that are ubiquitously present in various organs of the body apart from liver and hence its disposition is not expected to be affected by liver impairment. Propofol, on the other hand, is extensively metabolized by glucuronidation and oxidation possibly by hepatic involvement. The limited information on propofol clearance data from individual patients with hepatic impairment is not adequate to arrive at a recommendation for dose adjustment in patients with hepatic impairment. Hence, it is acceptable to **indicate that "AQUAVAN has not been** adequately studied in patients with hepatic **insufficiency". However, caution should be** exercised when using Fospropofol in patients with hepatic impairment.

e) what pregnancy and lactation use information is there in the application?

No clinical studies were conducted in pregnant and lactating women.

Clinical studies were not conducted in pregnant and lactating women with fospropofol. Reproduction studies have been performed in rats and rabbits at doses up to 3.5 and 5.4 times the anticipated cumulative human dose of fospropofol. Please refer to the Pharmacology toxicology review for the information on effects of fospropofol on fertility and fetus.

Fospropofol is not recommended for use in labor and delivery, including Cesarean section deliveries. Based on published information propofol is known to cross the placenta, and as with other sedative-hypnotic agents, the administration of Fospropofol may be associated with neonatal respiratory and cardiovascular depression (Gin T et. al. 1990, Anaseth. Intens. Care 18: 180-184, He Y et. al. 2002 Anesth. Analg. 94:1312-1314). Fospropofol is not recommended for use in nursing mothers because propofol has been reported to be excreted in human milk (Nitsun M et.al. 2006 Clin Pharm Ther. 79: 549-557).

2.4 Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Dosage adjustment is not required with respect to concomitantly administered drugs such as midazolam, fentanyl, morphine, and meperidine from a pharmacokinetic interaction perspective.

Effect of herbal products and smoking on pharmacokinetics and pharmacodynamics of fospropofol have not been evaluated. Food or alcohol is not expected to be coadministered with fospropofol and as such a change in the pharmacokinetics of fospropofol is not expected.

2. Drug-Drug Interactions

a) is there an in vitro basis to suspect in vivo drug-drug interactions?

There is no basis to suspect in vitro drug-drug interactions between fospropofol and coadministered drugs. The potential for drug interactions with propofol, the major and active metabolite, however, has not been addressed.

Fospropofol is extensively metabolized by ubiquitously present alkaline phosphatases. Propofol appears to be directly glucuronidated as well as hydroxylated by unknown enzymes.

b) is the drug a substrate of CYP enzymes?

Fospropofol is not a substrate of CYP enzymes. It is rapidly and extensively metabolized by alkaline phosphatase.

In vitro incubation of fospropofol in the absence of NADPH did not result in significant disappearance of the drug.

c) is the drug an inhibitor and/or an inducer of CYP enzymes?
Studies were not conducted to evaluate the effect of fospropofol on CYP inhibition or induction.

Sponsor clearly indicated in **the clinical pharmacology summary that "No induction or** inhibition of CYP450 enzymes were observed in vivo in nonclinical studies of fospropofol disodium (*in vitro* results of fospropofol interaction with CYP450 enzymes are summarized in Module 2.6.4). Upon examination of the information provided it was found inadequate to conclude the potential for fospropofol to induce or inhibit CYP enzymes. Briefly, following 14 day exposure of dogs (Study # 3000-15715-00-06G) to fospropofol or propofol, the samples of liver were analyzed for total protein and CYP450 content.

The information provided is not adequate to assess the potential for CYP inhibition or CYP induction by fospropofol or its major active metabolite propofol. Short term use proposed for the current indication and short half-life of the circulating moieties are noted. However, issue of drug interaction will be relevant when the product use is proposed for longer duration use. Hence, the sponsor should conduct in vitro studies to evaluate the potential for major CYP inhibition or induction.

d) is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?
Status of fospropofol as a substrate or inhibitor of P-gp has not been evaluated.

e) does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?
A number of medications are expected to be coadministered related to the procedure (bronchoscopy or colonoscopy). Pharmacokinetic changes in fospropofol are not expected when fospropofol is coadministered with midazolam, and opiate analgesics such as fentanyl, meperidine and morphine. Although a PK drug interaction between lidocaine and fospropofol has not been evaluated, the use of this combination in bronchoscopy patients has been studied.

PK drug interaction study between fospropofol and fentanyl, midazolam and meperidine: In clinical studies, an opioid premedication (fentanyl citrate 50 mcg IV) was administered prior to the initial dose of Fospropofol. Pharmacokinetic drug interaction between fospropofol when coadministered with midazolam and opiate analgesics such as fentanyl, morphine, and meperidine was evaluated in study #3000-414. Subjects randomized to morphine (0.1 mg/kg) received pretreatment 15 minutes prior to the initial bolus dose of Fospropofol (8 mg/kg). Subjects randomized to fentanyl (1 μg/kg), meperidine (0.75 mg/kg), or midazolam (0.01 mg/kg) received pretreatment 5 minutes prior to the initial bolus dose of Fospropofol (8 mg/kg). To ensure maintenance of the blind, subjects randomized to morphine received placebo 5 minutes prior to administration of Fospropofol and those randomized to fentanyl, meperidine, or midazolam received placebo 15 minutes prior to the initial bolus dose of Fospropofol. Subjects randomized to placebo received a placebo injection at both 5 and 15 minutes prior to initial AQUAVAN bolus administration. Supplemental doses (2 mg/kg) of

Fospropofol could have been administered to achieve the target sedation level (Modified OAA/S score ≤3).

Plasma concentrations of Fospropofol were generally similar in all treatment groups. The initial rapid decline was followed by a slower terminal phase with half-life of 0.44 to 0.52 hour, and this pattern was similar for all groups. Mean Cmax and $AUC_{0\text{-inf}}$ were similar for all treatment groups and ranged from 74.8 to 88.5 µg/mL and from 20.9 to 29.6 h·µg/mL, respectively. Mean weight normalized clearance (CLp) and mean weight normalized volume of distribution (V_d) were also similar for all groups, and ranged from 0.32 to 0.41 L/h/kg and from 0.22 to 0.31 L/kg, respectively. Although ANOVA comparison of $AUC_{0\text{-inf}}$ showed statistically significant difference (p=0.045) among treatment groups, pairwise comparisons between the placebo and all other premedication groups did not show a significant difference.

Mean (SD) Fospropofol Plasma Pharmacokinetic Parameters After AQUAVAN Treatment by Premedication Group

Parameter	Pre-Treatment Group				
	Morphine	Fentanyl	Meperidine	Midazolam	Placebo
n	12	12	12	11	12
T_{max}[£] (h)	0.07 (0.07-0.27)	0.07 (0.07-0.20)	0.07 (0.05-0.13)	0.07 (0.05-0.07)	0.07 (0.07-0.07)
$C_{4\ min}$ (µg/mL)	80.46 (18.06)	87.23 (12.41)	84.91 (16.83)	74.79 (15.59)	87.25 (15.67)
C_{max} (µg/mL)	84.40 (19.18)	88.48 (12.50)	86.11 (16.27)	74.79 (15.59)	87.25 (15.67)
$AUC_{0\text{-last}}$ (h·µg/mL)	29.19 (9.32)	28.61 (9.63)	24.40 (5.71)	20.66 (6.72)	23.28 (5.79)
$AUC_{0\text{-inf}}$ (h·µg/mL)	29.61 (9.44)	28.97 (9.84)	24.71 (5.83)	20.92 (6.81)	23.48 (5.85)
$t_{1/2}$ (h)	0.50 (0.1)	0.47 (0.06)	0.45 (0.09)	0.52 (0.21)	0.44 (0.08)
CL_p (L/h/kg)	0.36 (0.09)	0.32 (0.06)	0.35 (0.10)	0.41 (0.11)	0.38 (0.07)
V_d (L/kg)	0.25 (0.05)	0.22 (0.04)	0.22 (0.05)	0.31 (0.16)	0.24 (0.05)

T_{max}= Time to maximum plasma concentration; $C_{4\ min}$= Observed plasma drug concentration at 4 min; AUC= Area under the time-concentration curve; $AUC_{0\text{-last}}$= AUC from the time of dosing to the last quantifiable concentration; $AUC_{0\text{-inf}}$= AUC from the time of dosing to infinity; $t_{1/2}$= Terminal elimination half-life; CL_p= Plasma clearance; V_d= Volume of distribution.

The sponsor reported propofol pharmacokinetic data was not considered for review due to unreliable bioanalytical results. The study was not designed to identify effect of **fospropofol on coadministered drugs' pharmacoki**netics and as such plasma levels of concomitant medications were not assessed.

Use of fospropofol with lidocaine: Concomitant use of lidocaine with fospropofol has been studied in two different settings.

1. Most of the patients undergoing bronchoscopy in study # 3000-524 were administered lidocaine as a topical anesthetic for suppression of cough upon introduction of the flexible bronchoscope.

2. Paresthesias such as burning and tingling sensations were common adverse events with Fospropofol administration. A study (#3000-308) was conducted to determine the lowest dose levels of lidocaine that would reduce or eliminate the paresthesias associated with administration of Fospropofol.

Study#3000-0524 is a Phase 3, Randomized, Double-blind, Dose-controlled Study to Assess the Efficacy and Safety of Fospropofol Disodium Injection for Minimal-to-Moderate Sedation in patients undergoing flexible bronchoscopy. All patients were to receive lidocaine as a topical anesthetic for suppression of cough upon the introduction of the flexible bronchoscope. The recommended lidocaine dose for this study was ≤ 300 mg, or ≤ 4.5 mg/kg (whichever was less on a per patient basis), per procedure. Lidocaine was administered in most patients that underwent the procedure (see table below):

NUMBER OF PATIENTS WHO TOOK LIDOCAINE ON THE DAY OF PROCEDURE
SAFETY POPULATION

	AQUAVAN 2 mg/kg (N=103) n (%)	AQUAVAN 6.5 mg/kg (N=149) n (%)	All AQUAVAN (N=252) n (%)
Lidocaine was administered at <= 300mg or <= 4.5 mg/kg	78 (75.7)	116 (77.9)	194 (77.0)
Lidocaine was administered at > 300mg or > 4.5 mg/kg	22 (21.4)	24 (16.1)	46 (18.3)
Lidocaine was not administered	3 (2.9)	9 (6.0)	12 (4.8)

A number of other concomitant medications (Study # 3000-524, bronchoscopy trial) were administered as required for the procedure (See table below). Plasma levels of lidocaine or any other concomitant medications were not assessed as it was not an endpoint of this study.

Medications Taken on the Day of Procedure in ≥ 3 Patients (Safety Population)

	AQUAVAN 2.0-mg/kg N=103	AQUAVAN 6.5-mg/kg N=149	Overall N=252
	Number and Percent (%) of Patients		
Patients with ≥ 1 medication	103 (100.0)	149 (100.0)	252 (100.0)
Lidocaine[1]	99 (96.1)	139 (93.3)	238 (94.4)
Oxymetazoline	21 (20.4)	28 (18.8)	49 (19.4)
Atropine	14 (13.6)	20 (13.4)	34 (13.5)
Salbutamol	13 (12.6)	18 (12.1)	31 (12.3)
Cetacaine	13 (12.6)	16 (10.7)	29 (11.5)
Normosol	11 (10.7)	18 (12.1)	29 (11.5)
Sodium chloride	12 (11.7)	17 (11.4)	29 (11.5)
Xylocaine/epinephrine	10 (9.7)	9 (6.0)	19 (7.5)
Benzocaine	8 (7.8)	9 (6.0)	17 (6.7)
Dextrose/sodium chloride injection	4 (3.9)	10 (6.7)	14 (5.6)
Glucose injection	6 (5.8)	7 (4.7)	13 (5.2)
Phenylephrine HCl	5 (4.9)	7 (4.7)	12 (4.8)
Paracetamol	4 (3.9)	5 (3.4)	9 (3.6)
Acetylcysteine	2 (1.9)	3 (2.0)	5 (2.0)
Acetylsalicylic acid	1 (1.0)	3 (2.0)	4 (1.6)
Levosalbutamol	0	4 (2.7)	4 (1.6)
Promethazine	1 (1.0)	3 (2.0)	4 (1.6)
Combivent	2 (1.9)	1 (0.7)	3 (1.2)
Enoxaparin	0	3 (2.0)	3 (1.2)
Methylprednisolone	2 (1.9)	1 (0.7)	3 (1.2)
Prednisone	1 (1.0)	2 (1.3)	3 (1.2)
Vancomycin	2 (1.9)	1 (0.7)	3 (1.2)

[1] Lidocaine and Lidocaine HCL are combined as "Lidocaine"
Note: The same patient may have been counted in more than 1 category.
Note: Oxygen, fentanyl, and alternative sedative medications are not included in this table.

Study 3000-0308 was conducted to evaluate safety of a single bolus dose of 12.5 mg/kg Fospropofol following premedication with lidocaine HCl injection. The first cohort of 5 subjects received pretreatment with 50 mg lidocaine followed by 12.5 mg/kg Fospropofol 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. The first cohort **of 5 subjects (Subjects 001 – 005) received** Fospropofol at the 35-mg/mL concentration, the second cohort of 5 subjects (Subjects **006 – 010) received Fospropofol 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. A 3 lead ECG was used to continuously monitor subjects during the study. Any 3-lead ECGs that are reported as abnormal were to be printed and retained in the study records and a 12-lead ECG was performed as soon as possible following this abnormal finding. QT prolongation related adverse events were not reported in this study.

f) are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

None

g) **is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?**

None

2.5 General Biopharmaceutics

Fospropofol disodium injection is prepared in saline at a concentration of 20 mg/mL for intravenous use. Two different Fospropofol disodium formulations were administered (35-mg/mL and 20-mg/mL formulations) in different clinical studies (see table below). Considering the intravenous use, the bioavailability of fospropofol is not expected to be different between the different strengths/formulations used in the clinical studies.

Formulation	Lot #	Study#	Phase
Fospropofol disodium as a sterile aqueous solution in 0.4% saline at a concentration of 20 mg/mL for intravenous (i.v.) injection. Each vial contained 20 mL of solution.	1214-07	3000-0001	1
		3000-0102	1
		3000-0103	1
	1214-10	3000-0104	2
		3000-0206	1
[^{14}C] Fospropofol disodium as a sterile aqueous solution in 0.4% saline at a concentration of 20 mg/mL for i.v. injection. Each vial contained 20 mL of solution and 100 µCi of [^{14}C]-labeled fospropofol. The [^{14}C] label was contained in the phenyl group of the fospropofol molecule.	192I702	3000-0205	1
Fospropofol disodium as a sterile aqueous solution in 0.4% saline at 20 mg/mL, suitable for i.v. administration. Each vial contained 20 mL of solution.	1214-10	3000-0207 1a	2
		3000-0308[2]	1
Fospropofol disodium as a sterile aqueous solution in 0.4% saline at 35 mg/mL, suitable for i.v. administration. Each vial contained 20 mL of solution	176I0603	3000-0207 1b	2
		3000-0308[2]	1
Fospropofol disodium as a sterile aqueous solution at concentration of 35 mg/mL, suitable for i.v. administration. Formulation included contains monothioglycerol (MTG; 0.25%) and tromethamine (TRIS; 0.12%). Each vial contained 30 mL of solution.	GAA002	3000-0409	3
		3000-0410	3
		3000-0411	3
		3000-0412	3
		3000-0414	1
		3000-0415	2
		3000-0520[3]	2
		3000-0521	1
		3000-0522[3]	3
		3000-0524[3]	3
		3000-0413	2
Fospropofol disodium was supplied as a sterile solution containing 35 mg/mL of fospropofol disodium ready for i.v. injection. Formulation includes contains monothioglycerol (MTG; 0.25%) and tromethamine (TRIS; 0.12%). Each vial contained 30 mL of solution.	900015	3000-0523[4]	3
		3000-0625	1

2.6 Analytical

Analytical methods for determining fospropofol, propofol, and formate concentrations in plasma were developed and validated for linearity, accuracy, precision, specificity and limits of quantitation and detection (see tables below). The analytical methods were found to have satisfactory precision and accuracy for measuring fospropofol and formate concentrations in plasma samples from clinical studies.

Fospropofol Analytical Assay

Fospropofol concentrations in human plasma and urine were determined by a method utilizing separation by high performance liquid chromatography (HPLC) and detection by a tandem mass spectroscopy (MS/MS) system. The fospropofol assay methods in plasma and urine were validated for linearity, accuracy, precision, specificity and limits of quantitation. A [redacted] was used as the internal standard. High and low assay ranges were validated to cover the wide range of fospropofol concentrations observed in clinical samples. Fospropofol was quantified by peak area ratio to its internal standard. Fospropofol and [redacted] (internal standard) were extracted from plasma and urine using [redacted]. Samples were then analyzed by MS/MS detection using a selective reaction monitoring mode (for fospropofol m/z= 287.1→79.1, for [redacted], and for [redacted]. The performance characteristics for the method validations and performance evaluation of assay method in each study are summarized in the Table below. Plasma fospropofol assays in study 3000-0207 were conducted at [redacted] Plasma fospropofol assays in studies 3000-0520, 3000-0522, 3000-0523 and 3000-0524 were conducted at [redacted]. Plasma fospropofol assays in study 3000-0521 were conducted at [redacted]

b(4)

Appears This Way
On Original

Summary of the LC/MS/MS Assay Performance Characteristics for Fospropofol (GPI 15715)

3000-0207	A Phase 2, Two-part Study of AQUAVAN® Injection in the Presence of Pre-medication in Patients Undergoing Elective Colonoscopy	AA04445-UGT (LMS-S-6945-03) (M.val.: 000628/OXS)	[redacted]	Plasma	5 to 1000	5	QC-A 107 QC-B 101 QC-C 98.6	QC-A 6.8 QC-B 6.1 QC-C 5.4	-	416 @ -20°C	-
NA	LC/MS/MS Assay Validation Of GPI 15715 In Human Plasma (Low Assay Range)	48-0401	[redacted]	Plasma	5 to 1000	5	QC-A 100 QC-B 105 QC-C 101	QC-A 11.2 QC-B 7.2 QC-C 7.4	139 Days @ -20°C and @ -70°C	-	10
NA	LC/MS/MS Assay Validation Of GPI 15715 In Human Plasma (High Assay Range)	48-0522	[redacted]	Plasma	500 to 100, 000	500	QC-A 95.3 QC-B 103 QC-C 96.1	QC-A 8.4 QC-B 5.4 QC-C 9.2	346 Days @ -70°C	-	100
3000-0409†	A Phase 3, Randomized, Open-Label Study to Assess the Safety and Efficacy of AQUAVAN® Injection Versus Midazolam HCL for Sedation in Patients Undergoing Flexible Bronchoscopy Procedures	48-0515 (M.Val: 48-0401 and 48-0522)	[redacted]	Plasma	5 to 1000 & 500 to 100,000	5	QC-A[ε] 102, 101 QC-B[ε] 99.0, 97.5 QC-C[ε] 98.9, 105	QC-A[ε] 18.3, 9.0 QC-B[ε] 5.8, 8.5 QC-C[ε] 7.3, 5.7	-	304 @ -20°C	-
3000-0410†	A Phase 3, Randomized, Open-Label Study to Assess the Safety and Efficacy of AQUAVAN® Injection Versus Midazolam HCL for Sedation in Patients Undergoing Colonoscopy Procedures	48-0515 (M.Val: 48-0401 and 48-0522)	[redacted]	Plasma	5 to 1000 & 500 to 100,000	5	QC-A[ε] 102, 101 QC-B[ε] 99.0, 97.5 QC-C[ε] 98.9, 105	QC-A[ε] 18.3, 9.0 QC-B[ε] 5.8, 8.5 QC-C[ε] 7.3, 5.7	-	304 @ -20°C	-
3000-0411†	A Phase 3, Randomized, Open-Label Study to Assess The Safety And Efficacy of AQUAVAN® Injection Versus Midazolam HCL for Sedation in Patients Undergoing Percutaneous Coronary (PC) Procedures	48-0515 (M.Val: 48-0401 and 48-0522)	[redacted]	Plasma	5 to 1000 & 500 to 100,000	5	QC-A[ε] 102, 101 QC-B[ε] 99.0, 97.5 QC-C[ε] 98.9, 105	QC-A[ε] 18.3, 9.0 QC-B[ε] 5.8, 8.5 QC-C[ε] 7.3, 5.7	-	304 @ -20°C	-

b(4)

Summary of the LC/MS/MS Assay Performance Characteristics for Fospropofol (GPI 15715) continued

Study #	Study Title	Project ID (Method ID)	Analytical Lab	Sample Matrix	Assay Range (ng/mL)	LLOQ (ng/mL)	Accuracy (%)	Precision (%)	Stability (Days)	Duration of Sample Storage (Days)	DF
3000-0415†	A Phase 2, Randomized, Open-Label Study to Assess the Safety and Efficacy of AQUAVAN® Injection Versus Midazolam HCL for Sedation in Elderly Patients Undergoing Colonoscopy Procedures	48-0515 (M.Val: 48-0401 and 48-0522)	[redacted]	Plasma	5 to 1000 & 500 to 100,000	5	QC-A[ε] 102, 101 QC-B[ε] 99.0, 97.5 QC-C[ε] 98.9, 105	QC-A[ε] 18.3, 9.0 QC-B[ε] 5.8, 8.5 QC-C[ε] 7.3, 5.7	-	304 @ -20°C	-
3000-0413	A Phase 2, Randomized, Open-Label Study to Examine the Safety and Efficacy of AQUAVAN® Injection for Sedation of Patients Requiring Intubation and Mechanical Ventilation in the Intensive Care Unit Setting	48-0516A (M.Val: 48-0401 and 48-0522)	[redacted]	Plasma	5 to 1000 & 500 to 100,000	5	QC-A[ε] 96.0, 81.3 QC-B[ε] 94.7, 103 QC-C[ε] 95.5, 90.9	QC-A[ε] 2.9, 12.1 QC-B[ε] 5.5, 2.4 QC-C[ε] 3.5, 4.9	-	212 @ -70°C	-
3000-0414	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Drug Interaction Study Of AQUAVAN® Injection And Premedications In Healthy, Adult Subjects	48-0517A (M.Val: 48-0401 and 48-0522))	[redacted]	Plasma	5 to 1000	5	QC-A[ε] 87.1, 92.8 QC-B[ε] 98.8, 102 QC-C[ε] 98.6, 99.1	QC-A[ε] 23.7, 11.5 QC-B[ε] 6.7, 7.1 QC-C[ε] 4.5, 10.4	-	90 @ -20°C	-

b(4)

3000-0520	A Randomized, Double-Blind, Dose-Response Study To Assess The Efficacy And Safety of AQUAVAN® Injection For Procedural Sedation In Patients Undergoing Colonoscopy	48-0525B (M.Val: 48-0401 and 48-0522)	[redacted]	Plasma	5 to 1000 & 500 to 100,000	5	QC-A[¶] 99.1, 97.2 QC-B[¶] 102, 99.5 QC-C[¶] 99.9, 104	QC-A[¶] 20.4, 11.0 QC-B[¶] 7.1, 8.9 QC-C[¶] 4.1, 5.7	-	88 @ -70°C	-
NA	Quantitation of GPI 15715 in Human Plasma via HPLC with MS/MS Detection (Low Assay Range Validation)	LCMS 378		Plasma	5 to 1000	5	QC-A 99.8 QC-B 96.0 QC-C 102	QC-A 7.8 QC-B 3.2 QC-C 4.0	92 @ -70°C	-	-
NA	Quantitation of GPI 15715 in Human Plasma via HPLC with MS/MS Detection (High Assay Range Validation)	LCMS 378.1		Plasma	500 to 100 000	500	QC-A 95.8 QC-B 96.4 QC-C 99.0	QC-A 10.2 QC-B 5.2 QC-C 3.2	78 @ -70°C	-	-
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	BLP & BLP2 (M.Val: LCMS 378 and LCMS 378.1)		Plasma	5 to 1000 & 500 to 100,000	5.0	QC-A[¶] 102, 101 QC-B[¶] 102, 99.9 QC-C[¶] 103, 103	QC-A[¶] 7.1, 10.5 QC-B[¶] 4.7, 5.4 QC-C[¶] 3.5, 4.0	88 @ -70°C	-	-
3000-0522	A Phase 3, Randomized, Double-blind, Dose-controlled Study to Assess the Efficacy And Safety Of AQUAVAN® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Colonoscopy	68-0608A (M.Val: 48-0522)		Plasma	500 to 100,000	500	QC-A 101 QC-B 101 QC-C 100	QC-A 25.9 QC-B 4.2 QC-C 8.1	151 @ -70°C	-	-
3000-0523	A Phase 3, Open-Label, Single Arm Study to Assess the Safety Of AQUAVAN® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Minor Surgical Procedures	68-0609A (M.Val: 48-0522)		Plasma	500 to 100,000	500	QC-A 92.0 QC-B 104 QC-C 109	QC-A 9.6 QC-B 9.1 QC-C 6.4	165 @ -70°C	-	-
3000-0524	A Phase 3, Randomized, Double-Blind, Dose-Controlled Study to Assess The Efficacy And Safety of AQUAVAN® (Fospropofol Disodium) Injection for Minimal-to-Moderate Sedation in Patients Undergoing Flexible Bronchoscopy	68-0610A (M.Val: 48-0522)		Plasma	500 to 100,000	500	QC-A 99.3 QC-B 106 QC-C 107	QC-A 9.2 QC-B 10.3 QC-C 9.6	-	317 @ -70°C	-

Summary of the LC/MS/MS Assay Performance Characteristics for Fospropofol (GPI 15715) continued

Study #	Study Title	Project ID (Method ID)	Analytical Lab	Sample Matrix	Assay Range (ng/mL)	LLOQ (ng/mL)	Accuracy (%)	Precision (%)	Stability (Days)	Duration of Sample Storage (Days)	DF
3000-0625	A Phase 1, Open-Label, Single-Dose, Crossover Pharmacokinetic/ Pharmacodynamic Study of AQUAVAN® (Fospropofol Disodium) Injection Versus DIPRIVAN® Injectable Emulsion in Healthy Volunteers	68-0622A (M.Val: 48-0401 and 48-0522)	[redacted]	Plasma	5 to 1000 & 500 to 100,000	5	QC-A[¶] 93.3, 110 QC-B[¶] 105, 103 QC-C[¶] 104, 104	QC-A[¶] 5.6, 0.4 QC-B[¶] 4.1, 0.0 QC-C[¶] 5.1, 4.4	-	19 @ -70°C	-

DF= dilution factor; LC= Liquid chromatography; MS= Mass spectroscopy
NA=Not applicable; LLOQ=Lower limit of quantitation; QC-A=Low quality control sample, QC-B = Middle quality control sample and QC-C=High quality control sample
NOTE: All Plasma samples had sodium heparin added.
MGI*=Sponsor MGI PHARMA Inc., Non GLP Lab
[†]Samples from studies were combined for analysis
[§]Accuracy and precision from samples analysis from two separate batches
[¶]Accuracy and precision from low and high assays
[‡]No PK assessment performed

Propofol Analytical Assay

Propofol concentrations in human plasma were determined by an HPLC method with fluorescence detection at excitation and emission wavelengths of 276 nm and 310 nm, respectively. The propofol assay method in plasma was validated for linearity, accuracy, precision, specificity, and limits of quantitation and detection. Propofol and [redacted] (internal standard) were extracted from plasma by [redacted] and injected into an HPLC with fluorescence detection. Propofol was quantitated by peak height ratio to its internal standard. The performance characteristics for the method validations and performance evaluation of assay method in each study that is reported are summarized in the attachment. Plasma propofol assays in study 3000-0207 were conducted at [redacted] Plasma propofol assays in studies 3000-0520, 3000-0522, 3000-0523 and 3000-0524 were conducted at [redacted] Plasma propofol assays in study 3000-0521 were conducted at [redacted]

b(4)

However, during the drug development program, it was discovered that factors associated with plasma sample processing had affected measurement of propofol concentration. As a result, data related to propofol concentrations from earlier studies (identified in table below) were not considered reliable for quantitative assessment of propofol PK. Sponsor did not take into account the Propofol PK data from these studies for the population PK analysis (see table below).

Summary of the HPLC/fluorescence Assay Performance Characteristics for Propofol (*Clinical Studies with Propofol Data not Reported*) continued

Study #	Study Title	Project ID (Method ID)	Analytical Lab	Sample Matrix	Assay Range (ng/mL)	LLOQ (ng/mL)	Accuracy (%)	Precision (%)	Stability (Days)	Duration of Sample Storage (Days)	DF
3000-0207	A Phase 2, Two-Part Study of AQUAVAN® Injection in the Presence of Pre-medication in Patients Undergoing Elective Colonoscopy	AA04445-UGT (LC-S-6947-03)	[redacted]	Plasma	5 to 2000	5	QC-A 98.0 QC-B 99.3 QC-C 102	QC-A 9.4 QC-B 3.0 QC-C 2.9	-	274 @ -20°C	10
NA	HPLC/Fluorescence Assay Validation of Propofol in Human Plasma	48-0504	[redacted]	Plasma	5 to 2500	5	QC-A 112 QC-B 95.9 QC-C 101	QC-A 4.0 QC-B 5.3 QC-C 5.1	117 @ -20°C	-	5 & 10
3000-0409[†]	A Phase III, Randomized, Open-Label Study To Assess The Safety And Efficacy Of AQUAVAN® Injection Versus Midazolam HCL For Sedation In Patients Undergoing Flexible Bronchoscopy Procedures	48-0515 (M.val: 48-0504)	[redacted]	Plasma	5 to 2500	5	QC-A 103 QC-B 88.4 QC-C 101	QC-A 9.1 QC-B 6.2 QC-C 4.8	-	304 @ -20°C	10
3000-0410[†]	A Phase 3, Randomized, Open-Label Study to Assess the Safety and Efficacy Of AQUAVAN® Injection Versus Midazolam HCL For Sedation In Patients Undergoing Colonoscopy Procedures	48-0515 (M.val: 48-0504)	[redacted]	Plasma	5 to 2500	5	QC-A 103 QC-B 88.4 QC-C 101	QC-A 9.1 QC-B 6.2 QC-C 4.8	-	304 @ -20°C	10
3000-0411[†]	A Phase 3, Randomized, Open-Label Study to Assess the Safety and Efficacy Of AQUAVAN® Injection versus Midazolam HCL For Sedation In Patients Undergoing Percutaneous Coronary (PC) Procedures	48-0515 (M.val: 48-0504)	[redacted]	Plasma	5 to 2500	5	QC-A 103 QC-B 88.4 QC-C 101	QC-A 9.1 QC-B 6.2 QC-C 4.8	-	304 @ -20°C	10
3000-0415[†]	A Phase 2, Randomized, Open-Label Study to Assess the Safety And Efficacy of AQUAVAN® Injection versus Midazolam HCL for Sedation in Elderly Patients Undergoing Colonoscopy Procedures	48-0515 (M.val: 48-0504)	[redacted]	Plasma	5 to 2500	5	QC-A 103 QC-B 88.4 QC-C 101	QC-A 9.1 QC-B 6.2 QC-C 4.8	-	304 @ -20°C	10
3000-0413	A Phase 2, Randomized, Open-Label Study to Examine the Safety and Efficacy of AQUAVAN® Injection for Sedation of patients Requiring Intubation and mechanical ventilation in the intensive care unit setting	48-0516B (M.val: 48-0526)	[redacted]	Plasma	10 to 5000	5	QC-A 102 QC-B 99.1 QC-C 101	QC-A 2.1 QC-B 2.3 QC-C 2.6	-	283 @ -70 °C	-
3000-0414	A Phase I, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Drug Interaction Study Of AQUAVAN® Injection And Premedications In Healthy, Adult Subjects	48-0517B (M.val: 48-0526)	[redacted]	Plasma	10 to 5000	10	QC-A 105 QC-B 91.9 QC-C 98.2	QC-A 5.5 QC-B 5.2 QC-C 5.3	-	131 @ -20 & -70 °C	-
3000-0520	A Randomized, Double-Blind, Dose-Response Study To Assess The Efficacy And Safety of AQUAVAN® Injection For Procedural Sedation In Patients Undergoing Colonoscopy	48-0525A (M.val: 48-0526)	[redacted]	Plasma	10 to 5000	10	QC-A 95.7 QC-B 99.1 QC-C 99.0	QC-A 2.9 QC-B 2.1 QC-C 2.1	-	97 @ -70 °C	-

DF= dilution factor; HPLC= High performance liquid chromatography
NA=Not applicable; LLOQ=Lower limit of quantitation; QC-A=Low quality control sample, QC-B = Middle quality control sample and QC-C=High quality control sample
NOTE: Plasma samples had sodium heparin added
[D] Method could not be validated and was not used for any analysis.
[†] Accuracy and precision from samples analysis from 2 separate batches
[‡] Samples from studies were combined for analysis
[§] No PK assessment performed

Formate Analytical Assay

Formate concentrations in human plasma were determined by gas chromatography (GC) using a MS detection method. The formate assay method in plasma was validated for linearity, accuracy, precision, specificity, and limits of quantitation and detection. A calibration standard (in water), plasma sample, or quality control sample in plasma was mixed with [redacted] (internal standard) and concentrated sulfuric acid in a vial. The vial was tightly capped, mixed, and incubated at 37°C for 30 minutes, followed by injection of an aliquot of vapors from the headspace of the vial into the GC/MS. Formate was quantified by peak area ratio to its internal standard. The performance characteristics for the method validations and performance evaluation of assay method in each study are summarized in the table below. Formate concentrations were not measured in every clinical study; blood samples were collected for determination of formate concentrations in only the studies described in this table.

Summary of the GC/MS Assay Performance Characteristics for Formate

Study #	Study Title	Project ID (Method ID)	Analytical Lab	Sample Matrix	Assay Range (µg/mL)	LLOQ (µg/mL)	Accuracy (%)	Precision (%)	Stability (Days)	Duration of Sample Storage (Days)	DF
3000-0413	A Phase 2, Randomized, Open-Label Study to Examine the Safety and Efficacy of AQUAVAN® Injection for Sedation of Patients Requiring Intubation and Mechanical Ventilation in the Intensive Care Unit Setting	[redacted]S05-046 (M. val.: [redacted]S05-045)	[redacted]	Plasma	15 to 150	15	QC-A 101 QC-B 103 QC-C 104	QC-A 8.3 QC-B 4.6 QC-C 5.4	-	326 @ -70° C	
3000-0415	A Phase 2, Randomized, Open-Label Study to Assess the Safety and Efficacy of AQUAVAN® Injection Versus Midazolam HCL for Sedation in Elderly Patients Undergoing Colonoscopy Procedures	[redacted]S05-047 (M. val.: [redacted]S05-045)		Plasma	15 to 150	15	QC-A 114 QC-B 107 QC-C 108	QC-A NC QC-B NC QC-C NC	-	162 @ -70° C	

DF= dilution factor; GC= Gas chromatography; MS= Mass spectroscopy
NA=Not applicable; NC = not calculated; LLOQ=Lower limit of quantitation; QC-A=Low quality control sample, QC-B = Middle quality control sample and QC-C=High quality control sample

19 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 10

4.2 Pharmacometrics Review by Dr. Atul V. Bhattaram

Office of Clinical Pharmacology

NDA	22244
Drug	Aquavan® (Fospropofol)
Indication	AQUAVAN® is an intravenous sedative-hypnotic agent indicated for sedation in adult patients undergoing diagnostic or therapeutic procedures. [redacted]
Pharmacometrics Reviewer	Venkatesh Atul Bhattaram, Ph.D
Pharmacometrics Team Leader	Joga Gobburu, Ph.D
Clinical Pharmacology Reviewer	Srikanth Nallani, Ph.D
Clinical Pharmacology Team Leader	Suresh Doddapaneni, Ph.D

b(4)

TABLE OF CONTENTS

Introduction 71
Recommendations 71
Comments to Medical Officer 71
Regulatory Issues 72
Appendix-I 77
  Dose Finding 77
Appendix-II 81
  Pharmacokinetic-Pharmacodynamic (PK/PD) Modeling 81
  Introduction 81
  Data 81
  Methodology 82
  Results 84
Appendix-III 108
  Body Weight based dosing algorithm 108

LIST OF FIGURES

Figure 1. Relationship between race, age, alkaline phosphatase, albumin clearance and random effects of clearance, volume of distribution (after adjustment for body weight) for fospropofol....73
Figure 2. Relationship between race, age, alkaline phosphatase, albumin clearance and random effects of clearance, volume of distribution (after adjustment for body weight) for propofol....74
Figure 3. 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)....75
Figure 4. 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)....76
Figure 5. Dose reponse relationship in Study 3000-0520....79
Figure 6. Sedation Success in Studies 3000-0522, Colonoscopy and 3000-0524, Bronchoscopy....80
Figure 7. Time course of fospropofol and propofol concentrations after intravenous administration of fospropofol....84
Figure 8. Diagnostic plots for model 010 (Fospropofol PK Model) (A) Observed versus individual predicted plasma concentrations, (B) Observed versus population predicted plasma concentrations, (C) Weighted residuals versus time, (D) Weighted residuals versus population predicted plasma concentrations....86
Figure 9: Fospropofol-Propofol population PK model....88
Figure 10. Relationship between CL, V for fospropofol and propofol and total body weight....89
Figure 11. Relationship between CL, V for fospropofol and propofol and total body weight in patients without extreme parameter values. A clear relationship between clearance, volume of distribution and tota bodyweight can be seen in comparison to Figure 10....90
Figure 12. Relationship between race, age, alkaline phosphatase, albumin clearance and random effects of clearance, volume of distribution (after adjustment for body weight) for fospropofol....91
Figure 13. Relationship between race, age, alkaline phosphatase, albumin clearance and random effects of clearance, volume of distribution (after adjustment for body weight) for propofol....92
Figure 14. Basic Goodness-of-fit Plots of Fospropofol – Propofol Model 103: Fospropofol Fit First column: Observed fosprepofol concentration (mcg/mL) are plotted

versus population (upper plot) and individual (lower plot) predictions of fospropofol concentrations (mcg/mL). Unit lines are provided a reference. 93
Figure 15. Basic Goodness-of-fit Plots of Fospropofol – Propofol Model 103: Propofol Fit First column: Observed fospropofol concentration (mcg/mL) are plotted versus population (upper plot) and individual (lower plot) predictions of fospropofol concentrations (mcg/mL). Unit lines are provided a reference. 94
Figure 16. Relationship between random effects of clearance of (Left) Fospropofol (Right) Propofol versus creatinine clearance 96
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) 99
Figure 18. Time course of proportion of patients with MOAA/S scores of 0, 2, 3, 4 or 5 in Study 3000-0522. 100
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. 101
Figure 20. Diagnostic Plots of Fospropofol-Sedation Model 403. 102
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. 104
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) 106
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). 107
Figure 24. Simulations from Model 103: Fospropofol Concentration-Time Course for patients administered single bolus doses. 109
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)..... 110

LIST OF TABLES

Table 1. Fospropofol dosing regimen in Phase 3 pivotal studies. 78
Table 2. List of dose groups, number of patients and observations in studies utilized for PK and PK/PD modeling. 81
Table 3. Estimated structural and stochastic parameter values for fospropofol using Model 010 (Source: Table 16 on Page 76 from Sponsor's Report (pr-aqua-02-02.pdf).87
Table 4. Estimated structural and stochastic parameter values for Fospropofol and Propofol using Model 103 (Source: Table 17 on Page 76 from Sponsor's Report (pr-aqua-02-02.pdf)..... 95
Table 5. Influence of prognostic factors on the pharmacokinetics of fospropofol and propofol. 97
Table 6. Estimated PK/PD parameters using Model 403 (Source: Table 27, on Page 90 from Sponsor's Report (pr-aqua-02-02.pdf). 100
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). 103
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). 105

Introduction

Fospropofol injection (fospropofol disodium) is a water-soluble prodrug of propofol developed for minimal-to-moderate sedation during brief diagnostic and therapeutic procedures. The pharmacologically active compound is not fospropofol, but propofol, its metabolite.

Recommendations

The Pharmacometrics group in Office of Clinical Pharmacology has reviewed the submitted information and edited the label to reflect the findings based on population PK and PK/PD analysis.

Comments to Medical Officer

None

Appears This Way
On Original

Regulatory Issues

In the current submission, the sponsor conducted extensive population pharmacokinetics (PK) and pharmacokinetic-pharmacodynamic (PK/PD) analysis of data collected from several studies as shown in Appendix-I. The review will focus on addressing the two labeling statements as discussed below:

Labeling Claim 1 (Section 12.3, Pharmacokinetics, Elimination): Population pharmacokinetic analysis indicated no influence of race, age, and alkaline phosphatase concentrations on the pharmacokinetics of fospropofol and propofol derived from fospropofol.

Pharmacokinetic analysis showed dependence of body weight on clearance and volume of distribution of fospropofol and propofol. After accounting for the affect of body weight on PK parameters of fospropofol and propofol, Figure 1 and Figure 2 in Appendix-II shows that there is no relationship between random effects (between patients; ETA for CL, V of fospropofol and propofol) and prognostic factors such as race, age and alkaline phosphatase after adjustment for body weight. Hence the pharmacokinetics of fospropofol and propofol would not be dependent on race, age and alkaline concentrations.

Appears This Way
On Original

Figure 1. Relationship between race, age, alkaline phosphatase, albumin clearance and random effects of clearance, volume of distribution (after adjustment for body weight) for fospropofol.

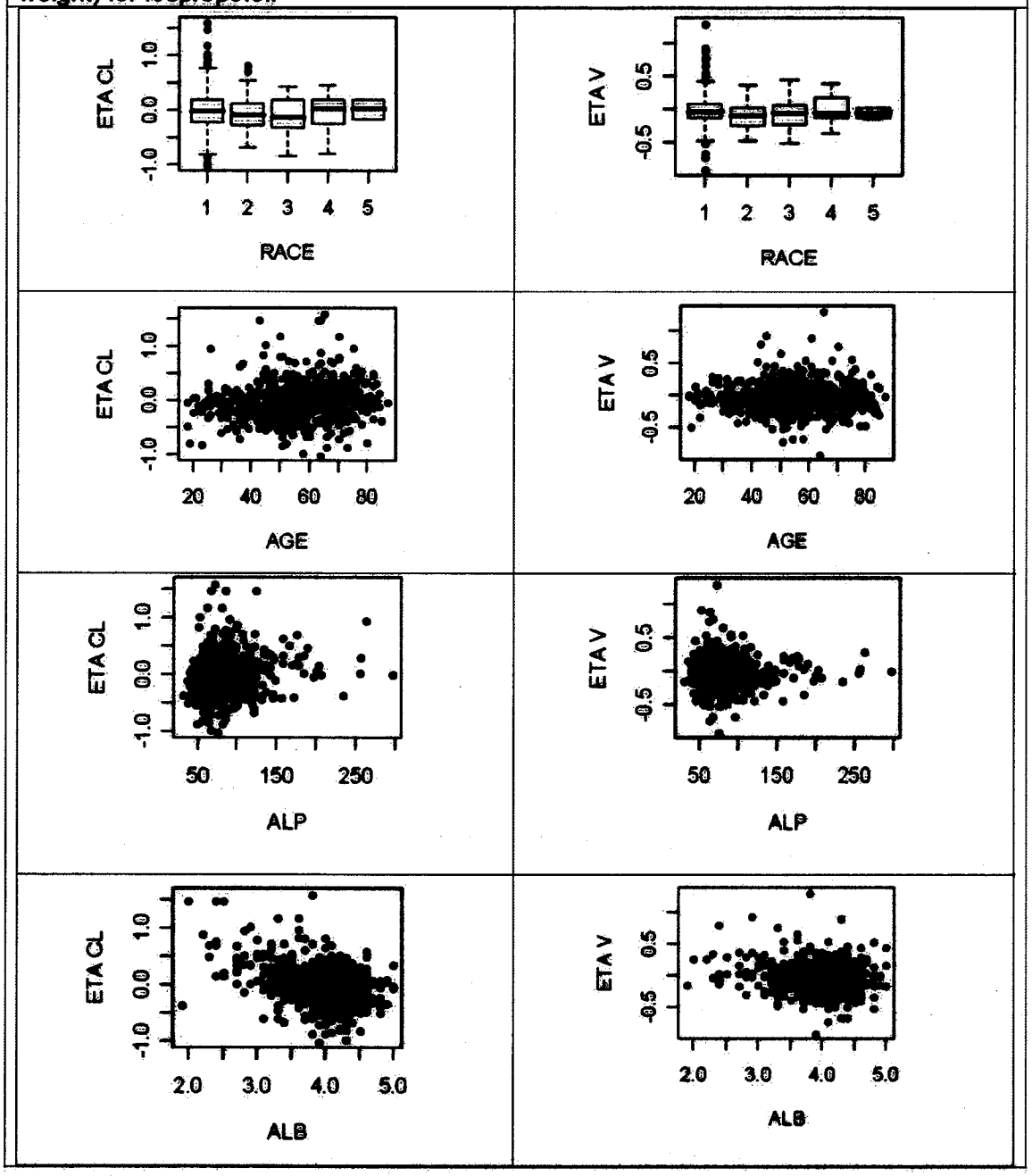
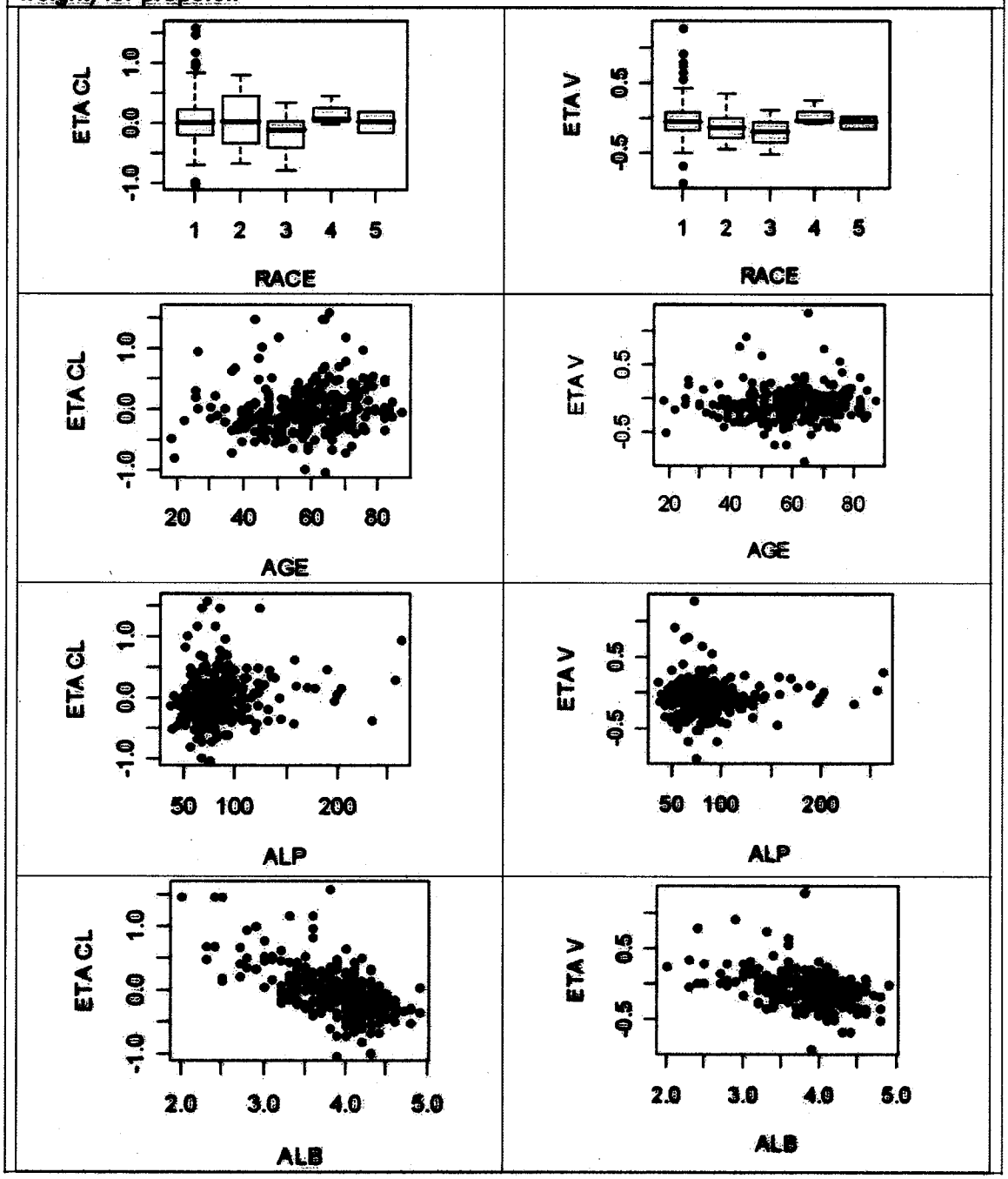


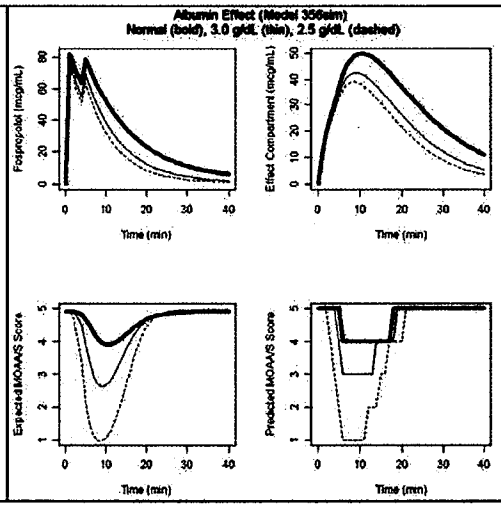
Figure 2. Relationship between race, age, alkaline phosphatase, albumin clearance and random effects of clearance, volume of distribution (after adjustment for body weight) for propofol.



Issue 2 (Section 12.3, Pharmacokinetics, Distribution): In Population PK/PD studies, the EC50 for fospropofol decreases with a decrease in albumin concentration for different strata of patients based on age, ASA status, and weight. Sedation depth (as measured by the Modified Observer's Assessment of Alertness/Sedation Scale) was not consistently influenced by albumin levels across these populations.

The sponsor analyzed the relationship between fospropofol concentrations and effects on Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) using PK/PD models. For more details of the analysis please refer to Appendix-II.
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 3 below.

Figure 3. 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 4.

Figure 4. 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} (ng/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)	75 (4.6)	83 (35)
≥65	P1 or P2	3-3.8	15	2.1 (1.1)	470 (170)	350 (81)	4.0 (0.61)	2.8 (1)	36 (11)	3.5 (0.13)	75 (7.3)	75 (13)
≥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 (16)	4.1 (0.29)	72 (5.7)	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 (3.3)	2.6 (0.32)	72 (6.0)	52 (1.7)
≥65	P3 or P4	3-3.8	15	2.6 (1.9)	490 (150)	360 (74)	4.1 (0.37)	2.9 (1.1)	34 (11)	3.4 (0.17)	71 (5.2)	76 (12)
≥65	P3 or P4	Greater than 3.8	15	2.8 (1.7)	560 (190)	380 (64)	4.1 (0.42)	2.6 (1.3)	44 (13)	4.1 (0.23)	72 (3.6)	81 (20)
<65	P1 or P2	Less than 3	5	3.2 (1.9)	760 (230)	490 (80)	4.0 (0.59)	2.6 (1.1)	35 (16)	2.7 (0.23)	54 (1.2)	83 (30)
<65	P1 or P2	3-3.8	22	2.4 (1.0)	710 (170)	530 (62)	4.0 (0.6)	2.9 (1.2)	53 (19)	3.5 (0.3)	51 (0.5)	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 (1.0)	85 (21)
<65	P3 or P4	Less than 3	8	3.2 (2.1)	820 (210)	410 (83)	3.9 (0.9)	2.4 (1.7)	23 (15)	2.6 (0.33)	53 (1.9)	75 (23)
<65	P3 or P4	3-3.8	14	2.9 (2.0)	850 (280)	440 (70)	4.0 (0.38)	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)	750 (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.

Reviewer's Comments

Appendix-I

Dose Finding

Sponsor conducted several dose finding studies in healthy subjects and patients with the aim of achieving predictable sedation and minimizing the likelihood of reaching deep levels of sedation. Studies conducted in the initial clinical development used a relatively high, fixed dose regimen in which the same dose, in milligrams (mg) was administered to all patients who fell within a broad weight range and the data showed that a single IV dose of between 10 and 12.5 mg/kg sedated the majority of patients (study 3000-0207). However, results of subsequent series of studies (3000-0409, 3000-0410, 3000-0411, 3000-0412, 3000-0415) indicated that this regimen led several patients to inappropriate levels of sedation. This observation led to the development of a revised dose titration (based on bodyweight, age, health status etc) regimen that would sedate the majority of patients while minimizing the number of patients reaching deep sedation.

The updated dosing regimen was used to evaluated the effectiveness of fospropofol in 3 controlled studies.
Study 3000-0520: Dose ranging study in patients undergoing colonoscopy.
Study 3000-0522: Pivotal study in patients undergoing colonoscopy.
Study 3000-0524: Pivotal study in patients undergoing flexible bronchoscopy.

Patients in study 3000-0520 were randomized to one of the following 5 groups in a 1:1:1:1:1 ratio including 4 dose levels of fospropofol disodium (8.0 mg/kg, 6.5 mg/kg, 5.0 mg/kg, 2.0 mg/kg) and midazolam 0.02 mg/kg. Patients in study 3000-0522 were randomized to one of the following 3 groups in a 3:2:1 ratio: fospropofol disodium 6.5 mg/kg; fospropofol disodium 2.0 mg/kg; and midazolam 0.02 mg/kg, respectively. Patients in study 3000-0524 were randomized to one of the following 2 groups in a 3:2 ratio: fospropofol disodium 6.5 mg/kg and 2.0 mg/kg, respectively
All patients in studies 3000-0520, 3000-0522, 3000-0523, and 3000-0524 received supplemental oxygen, nasally (4 L/min), throughout the dosing period and until the patient met the criteria for ready for discharge. All patients in studies 3000-0520, 3000-0522, 3000-0523, and 3000-0524, received fentanyl at an initial dose of 50 mcg as analgesic pretreatment 5 minutes prior to administration of the initial dose of study sedative medication. If the patient was experiencing pain during the procedure, 1 additional dose of 25 mcg of fentanyl was allowed per protocol. At least 10 minutes were to have elapsed between the initial fentanyl dose and the single additional fentanyl dose allowed per protocol. Sites were instructed that if additional analgesic medication was required, only fentanyl 0.5 mcg/kg (not to exceed 50 mcg) was to be administered.

The dosing regimen in Phase-III studies is shown in Table 1 below.

Table 1. Fospropofol dosing regimen in Phase 3 pivotal studies.

	Sedation Initiation[1]		Sedation Maintenance
Dosing Group[2]	Initial Bolus[3]	Supplemental Dose[3,4]	Dose
Fospropofol disodium 2.0 mg/kg	2.0 mg/kg No less than 120 mg. No more than 180 mg.	0.5 mg/kg No less than 30 mg. No more than 45 mg.	0.5 mg/kg No less than 30 mg. No more than 45 mg
Fospropofol disodium 6.5 mg/kg	6.5 mg/kg No less than 390 mg. No more than 585 mg.	1.6 mg/kg No less than 97.5 mg. No more than 146 mg.	1.6 mg/kg No less than 97.5 mg. No more than 146 mg.
Midazolam[5]	0.02 mg/kg Not to exceed 2.5 mg.	1.0 mg	1.0 mg

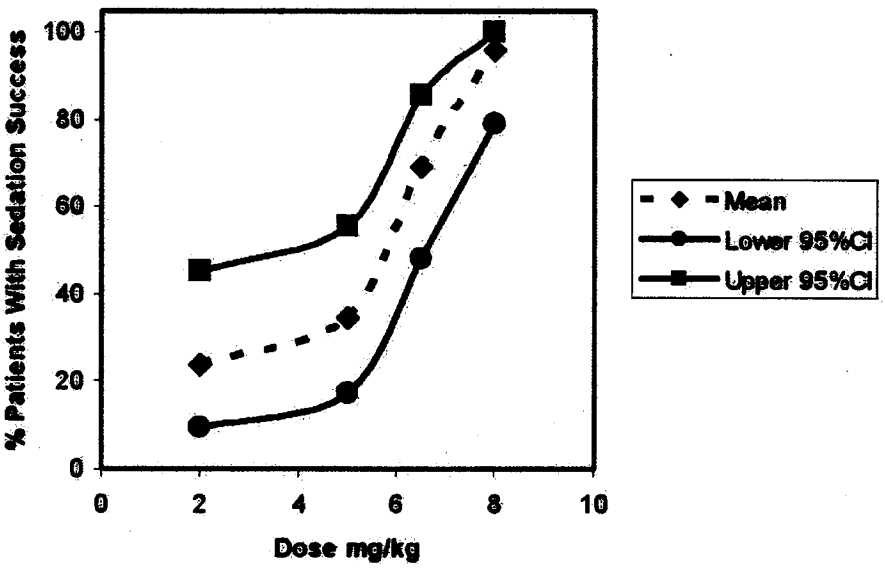
[1] Initial dose of study sedative administered 5 minutes after fentanyl administration
[2] The lower and upper dosing limits were based on a weight boundary of <60 kg or >90 kg.
[3] Patients who were ≥ 65 years of age or ASA P4 (or P3 at the discretion of the Investigator) received doses that were 75% of the proposed standar dose.
[4] In the Sedation Initiation phase, supplemental doses were administered only as required to reach a Modified OAA/S score of ≤4 and to start the procedure.
[5] Midazolam was included only in the 3000-0522 study.
Source: Study 3000-0522, Protocol, Section 6, page 420

The primary efficacy endpoint, Sedation Success, was a composite endpoint that included both efficacy and safety parameters. It measured the ability of the drug to effectively sedate patients, in a manner that did not require advanced airway maneuvers, including manual (bag valve mask) or mechanical ventilation. Specifically, the endpoint was defined as a patient meeting all of the following criteria:
(1) having 3 consecutive MOAA/S scores of ≤4 after administration of sedative medication,
(2) completing the procedure,
(3) without requiring the use of alternative sedative medication (such as midazolam) and,
(4) without requiring manual or mechanical ventilation.

For the primary endpoint, the number and proportion of patients who met the criteria for Sedation Success were calculated by treatment group.

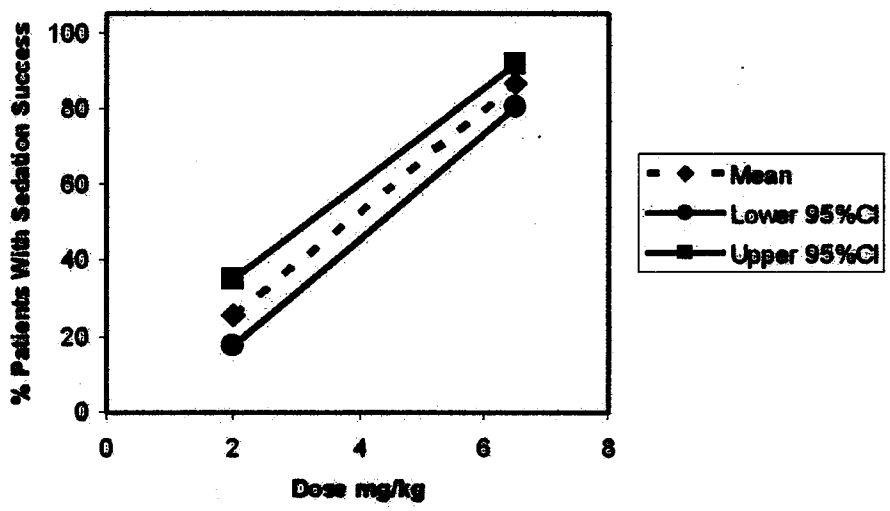
The dose response relationship from Study 3000-05200 is shown in Figure 5. The effectiveness of 2 and 6.5 mg/kg dose was tested in pivotal trials. The results of the pivotal trials are shown in Figure 6.

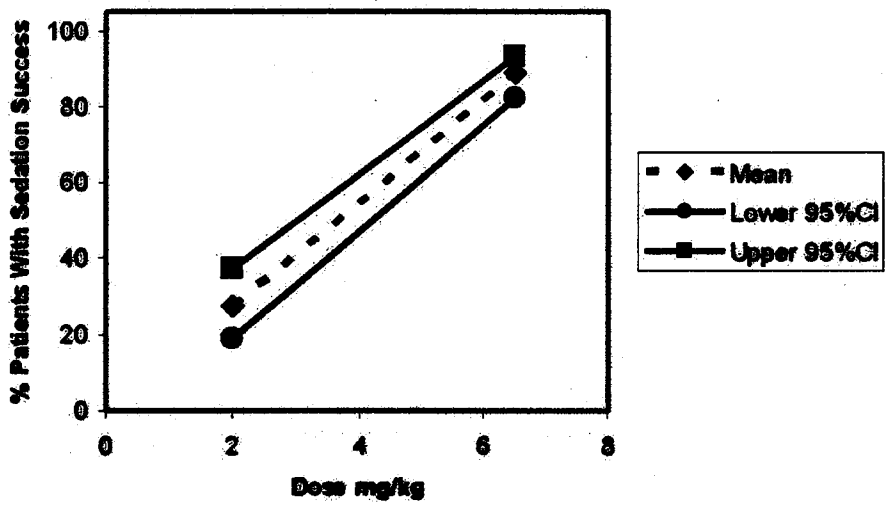
Figure 5. Dose reponse relationship in Study 3000-0520.



Appears This Way
On Original

Figure 6. Sedation Success in Studies 3000-0522, Colonoscopy and 3000-0524, Bronchoscopy.





Appendix-II

Pharmacokinetic-Pharmacodynamic (PK/PD) Modeling

Introduction

The objectives of this population analysis were to investigate the following population models:

- A pharmacokinetic (PK) model of fospropofol in venous plasma concentrations following administration of an initial bolus dose and up to several supplemental doses of fospropofol injection
- A PK model of fospropofol and propofol in venous plasma concentrations following administration of an initial bolus dose and up to several supplemental doses of fospropofol injection
- A pharmacokinetic-pharmacodynamic (PK-PD) model of the relationship between venous plasma concentrations of fospropofol and propofol, and Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score following administration of therapeutic bolus dose(s) of fospropofol injection
- A PK-PD model of the relationship between venous plasma concentrations of fospropofol and MOAA/S score following administration of therapeutic bolus dose(s) of fospropofol injection.

Data

Table 2 lists the dose groups, number of patients and observations in studies utilized for the PK and PK/PD modeling. The data collected was adequate to develop PK/PD models.

Table 2. List of dose groups, number of patients and observations in studies utilized for PK and PK/PD modeling.
3000-0207: A phase 2, two-part study of AQUAVAN ® Injection in the presence of premedication in patients undergoing elective colonoscopy. Part 1: Open Label, Adaptive Dose Ranging, Randomized, Multi-Center, Pilot Study of AQUAVAN® Injection Following Pre-Medication with Fentanyl Citrate Injection; 3000-0415: A phase 2, randomized, open-label study to assess the safety and efficacy of AQUAVAN® Injection versus Midazolam HCL for sedation in elderly patients undergoing colonoscopy procedures; 3000-0520: A randomized, double-blind, dose-response study to assess the efficacy and safety of AQUAVAN® Injection for procedural sedation in patients undergoing colonoscopy 3000-0521: A single-site, randomized, 4-sequence, 4-treatment crossover study of a single administration of AQUAVAN® Injection compared with placebo and positive control in healthy volunteers.

3000-0522: A phase 3, randomized, double-blind, dose-controlled study to assess the efficacy and safety of AQUAVAN® (fospropofol disodium) injection for minimal- to moderate sedation in patients undergoing colonoscopy.

3000-0523: A phase 3 open-label, single arm study to assess the safety of AQUAVAN® (fospropofol disodium) injection for minimal-to-moderate sedation in patients undergoing minor surgical procedures.

3000-0524: A phase 3, randomized, double-blind, dose-controlled study to assess the efficacy and safety of AQUAVAN® (fospropofol disodium) injection for minimal-tomoderate sedation in patients undergoing flexible bronchoscopy.

Specifically, study protocols 3000-0207, 3000-0415, 3000-0520, 3000-0522, 3000-0523, and 3000-0524 contributed fospropofol data for fospropofol and combined fospropofol-propofol population PK analysis. Study protocols 3000-0522, 3000-0523, and 3000-0524 contributed propofol data for combined fospropofol-propofol population PK analysis. Study protocol 3000-0522 contributed data for fospropofol-propofol-sedation population PK-PD analysis. Study protocols 3000-0207, 3000-0415, 3000-0520, 3000-0522 and 3000-0524 contributed data for fospropofol-sedation population PK-PD analysis. Study protocol 3000-0521 contributed healthy volunteers data used for comparison of PK model predictions for patients with observed healthy volunteers PK data.

Methodology

The sequence of model development methodology by the sponsor is described below:

- Development of fospropofol population PK model.
- Development of the combined fospropofol–propofol population PK model.
- Development of fospropofol-propofol PK/PD model using data from Study 3000-522 (Colonoscopy). The individual PK parameters from fospropofol-propofol PK model were used to predict the concentrations of fospropofol and propofol. The PD effect of fospropofol was described by the model that depicted the probabilities of being at or below each sedation (MOAA/S) level. Logits of these probabilities were presented as a sum of the effect and the baseline values. Effect was related (by linear or EMAX function) to the propofol or fospropofol concentration in the effect compartment.

$$EFF=E_{MAX}*CE/(EC_{50}+CE);$$
$$A_i = B_i + EFF, \quad i=0,4$$
$$C_i = exp(A_i), \quad i=0,4$$
$$P_i = C_i/(1+C_i), \quad i=0,4$$

Probability of a particular MOAA/S score:

$$PR_5 = (1 - P_4),\ PR_4 = (P_4-P_3)$$
$$PR_3 = (P_3-P_2),\ PR_2 = (P_2-P_1)$$
$$PR_1 = (P_1-P_0),\ PR_0 = P_0$$

Expected score:

$$ESC = 5\,PR_5+4\,PR_4+3\,PR_3+2\,PR_2+PR_1$$

- Development of fospropofol PK-PD model using data from studies 3000-0207, 3000-0415, 3000-0520, 3000-0522, 3000-0523, and 3000-0524. The PD model details are as described above for fospropofol-propofol. Patients from sub-therapeutic 2 mg/kg dosing groups were excluded from the population PK-PD analysis.
- After the PK-PD model for colonoscopy procedure was developed, data from bronchoscopy Study 3000-0524 were added. The combined model was re-estimated; influence of the procedure (colonoscopy versus bronchoscopy) on the parameters of the model was investigated.

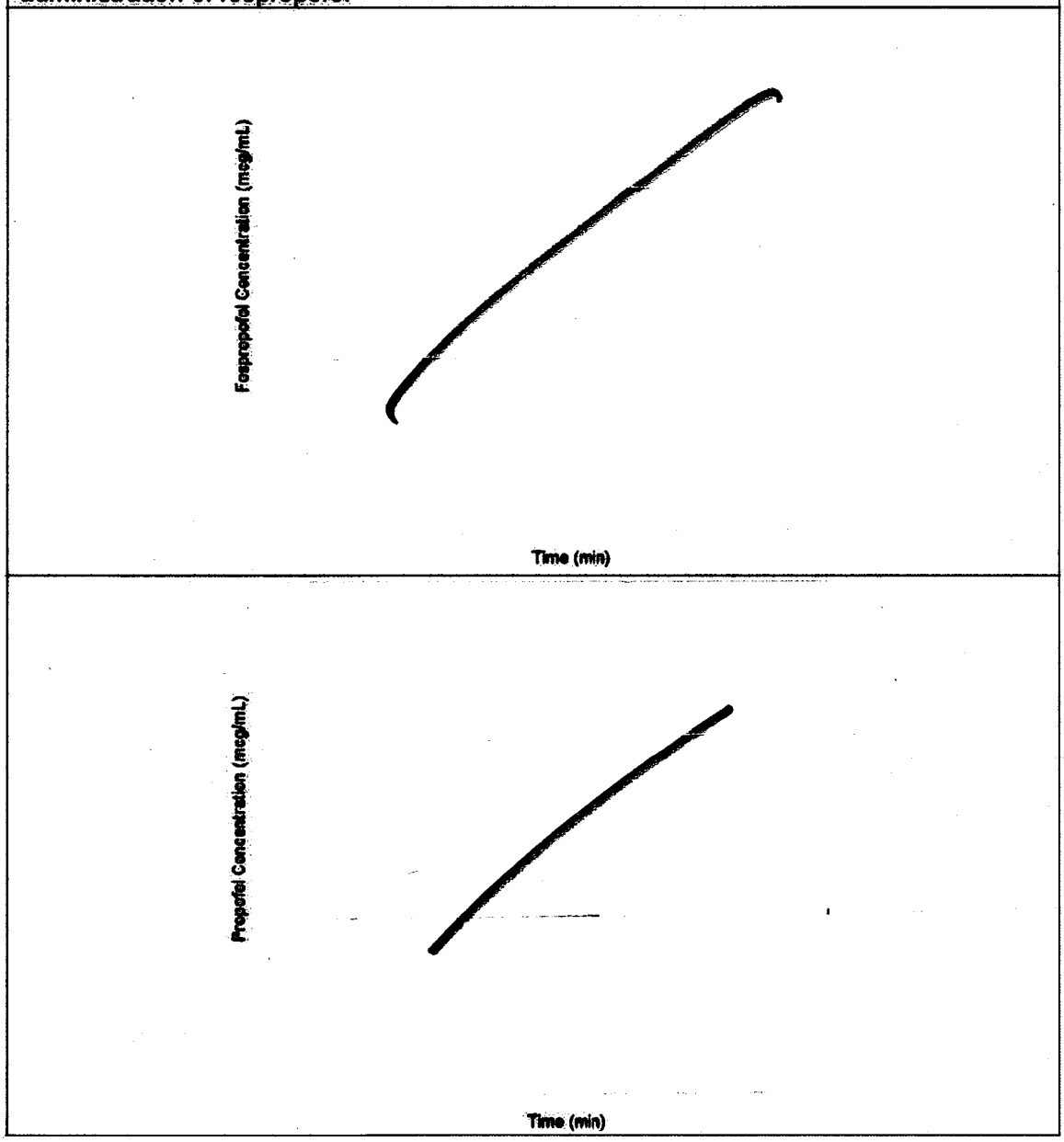
Model selection was guided by various goodness-of-fit criteria, including diagnostic plots, convergence with at least three significant digits, plausibility of parameter estimates, precision of parameter estimates, correlation between model parameter estimation errors, and the Akaike information criterion (AIC) given the minimum objective function value and number of estimated parameters. Final model parameter estimates were reported with a measure of estimation uncertainty including the asymptotic standard errors (obtained from the NONMEM $COVARIANCE step) and non-parametric bootstrap 95% confidence intervals (CI).

A covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented for this population PK analysis. First, pre-defined covariate parameter relationships were identified based on scientific interest, mechanistic plausibility or prior knowledge, and a full model was constructed with care to avoid correlation or collinearity in predictors. Model parameters were estimated, and assessment of any remaining trends was conducted by graphical inspection of all covariate effects. Inferences about clinical relevance of parameters were based on the parameter estimates of the full model and measures of estimation precision. Individual PK parameters were also estimated and summarized by groups of interest. A bootstrap procedure was used to estimate the uncertainty of the parameter estimates, and predictive check methods assessed the performance of the final models and parameters.

Results

Figure 7 shows the time course of fospropofol and propofol concentrations after intravenous administration of fospropofol.

Figure 7. Time course of fospropofol and propofol concentrations after intravenous administration of fospropofol



b(4)

b(4)

PK of Fospropofol

The basemodel for fospropofol included

(A) Allometric scaling of the population parameters

- V1 was scaled weight-proportionally;
- CL/F was scaled as weight in ¾ power
- Rate constants K12 and K21 were scaled as weight in -¼

(B) Assumption that fospropofol clearance and volume, relative to the 6.5 mg/kg dose, increases with per-kilogram dose (Based on diagnostic plots of the model indicated dependence of the random effects on V1 and CLF on the sedation dose: patients who received sub-therapeutic doses of fospropofol injection (2 mg/kg) had, on average, smaller values of both V1 and CLF.

The full Model 010 was constructed by inclusion of all covariates of interest. Specifically, Model 010 included

- Power-dependence of the fospropofol central volume on BMI (Body Mass Index).
- Linear dependencies of fospropofol clearance on laboratory values (Albumin: ALB, Alkaline Phosphatase: ALP, Bilirubin: BILI) and normalized creatinine clearance. Dependence of fospropofol clearance on albumin concentration was linear up the lower bound of the normal range (3.8 g/dL) and then was flat.

Overall, the model provided adequate fit of the data as shown in Figure 8. The estimates of the parameters are shown in Table 3.

Figure 8. Diagnostic plots for model 010 (Fospropofol PK Model) (A) Observed versus individual predicted plasma concentrations, (B) Observed versus population predicted plasma concentrations, (C) Weighted residuals versus time, (D) Weighted residuals versus population predicted plasma concentrations.

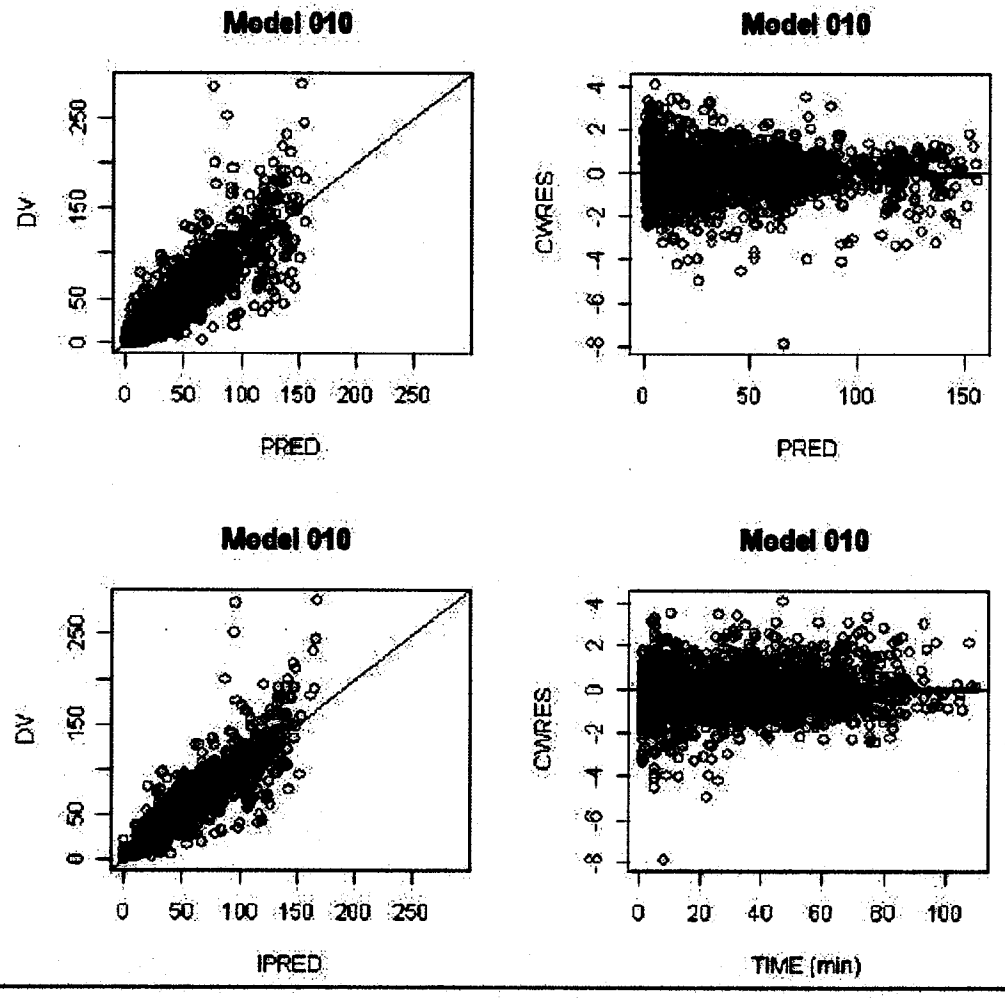


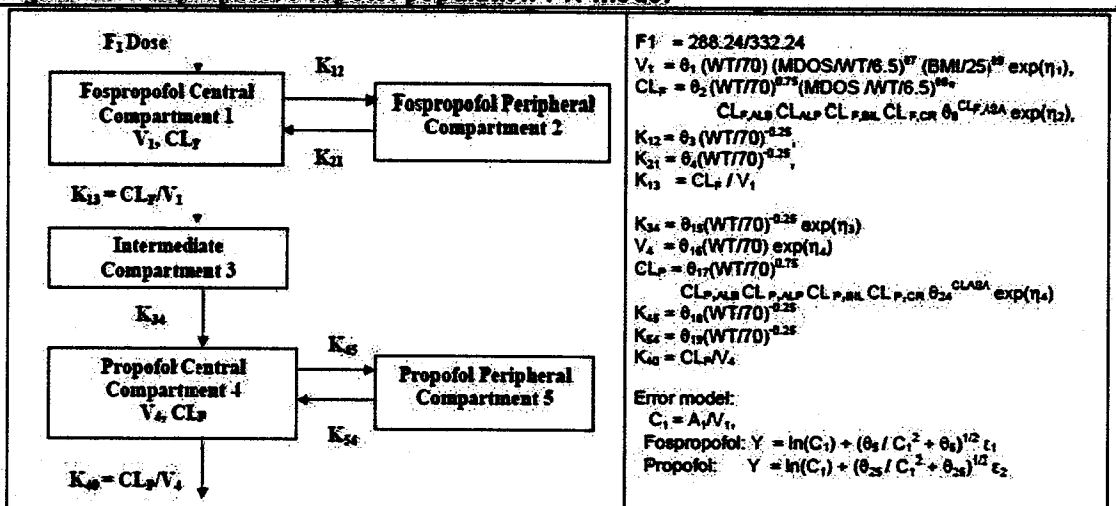
Table 3. Estimated structural and stochastic parameter values for fospropofol using Model 010 (Source: Table 16 on Page 76 from Sponsor's Report (pr-aqua-02-02.pdf).

Parameter	NONMEM notation	Model 010		
		Population Estimate	Relative SE (%)	Bootstrap median (95% CI)
V_1 (L)	θ_1	4.41	1.81	4.4(4.24 - 4.56)
CL_F (L/min)	θ_2	0.312	3.67	0.312(0.197 - 0.331)
K_{12} (1/min)	θ_3	0.0147	13.5	0.0147(0.0122 - 0.0397)
K_{21} (1/min)	θ_4	0.0128	29.1	0.0131(0.00302 - 0.0215)
$V_{1,DOSE}$	θ_7	0.236	9	0.232(0.19 - 0.272)
$CL_{F,DOSE}$	θ_8	0.138	16.8	0.134(0.0757 - 0.185)
$V_{1,BMI}$	θ_9	-0.199	29.1	-0.196(-0.314 - -0.0827)
$CL_{F,ALB}$	θ_{10}	3.34	10.5	3.44(2.72 - 4.79)
$CL_{F,ALP}$	θ_{11}	0.117	34.4	0.124(0.046 - 0.208)
$CL_{F,BILI}$	θ_{12}	-0.0322	29.5	-0.0313(-0.0517 - -0.00638)
$CL_{F,CRCL}$	θ_{13}	-0.0738	75.7	-0.069(-0.166 - 0.0289)
$CL_{F,ASA}$	θ_{14}	1.21	3.53	1.21(1.13 - 1.34)
ω^2_V	$\Omega(1,1)$	0.0214	58.6	0.0221(0.000843 - 0.0529)
$R_{V,CL}\omega_V\omega_{CL}$	$\Omega(1,2)$	0.0187	53.9	0.0193(0.0036 - 0.0426)
ω^2_{CL}	$\Omega(2,2)$	0.0998	13.7	0.101(0.0767 - 0.223)
σ^2_{add}	θ_5	0.191	33.3	0.184(0.0422 - 0.354)
σ^2_{prop}	θ_6	0.111	9.16	0.109(0.091 - 0.131)
			Variability estimates (derived)	
CV_{V1}	100 $\Omega(1,1)^{1/2}$ %	14.6%		14.9 (2.9 - 23)
R_{CLV1}		0.405		0.418 (0.117 - 1)
CV_{CL}	100 $\Omega(2,2)^{1/2}$ %	31.6%		31.8 (27.7 - 47.3)
$SD_{sigmaAdd}$	$\theta_5^{1/2}$	0.437		0.429 (0.205 - 0.595)
$CV_{sigmaExp}$	100 $\theta_6^{1/2}$	33.3%		33.0 (30.2 - 36.2)

PK of Fospropofol-Propofol

A combined PK model for both Fospropofol and Propofol was developed. The model is shown in Figure 9 below.

Figure 9: Fospropofol-Propofol population PK model



The relationship between body weight and clearance, volume of distribution for fospropofol and propofol following fospropofol administration is shown in Figure 10. The model included allometric scaling for the PK parameters. Figure 12 and Figure 13 shows the individual random effects estimates for clearance and volume of distribution of fospropofol and propofol versus race, age, alkaline phosphatase, and albumin. There is no relationship between individual random effects estimates and race, alkaline phosphatase and age indicating that these factors do not influence PK. The effect of albumin on PK of fospropofol can be clearly seen and hence was included as a prognostic factor in the final model.

Figure 10. Relationship between CL, V for fospropofol and propofol and total body weight.

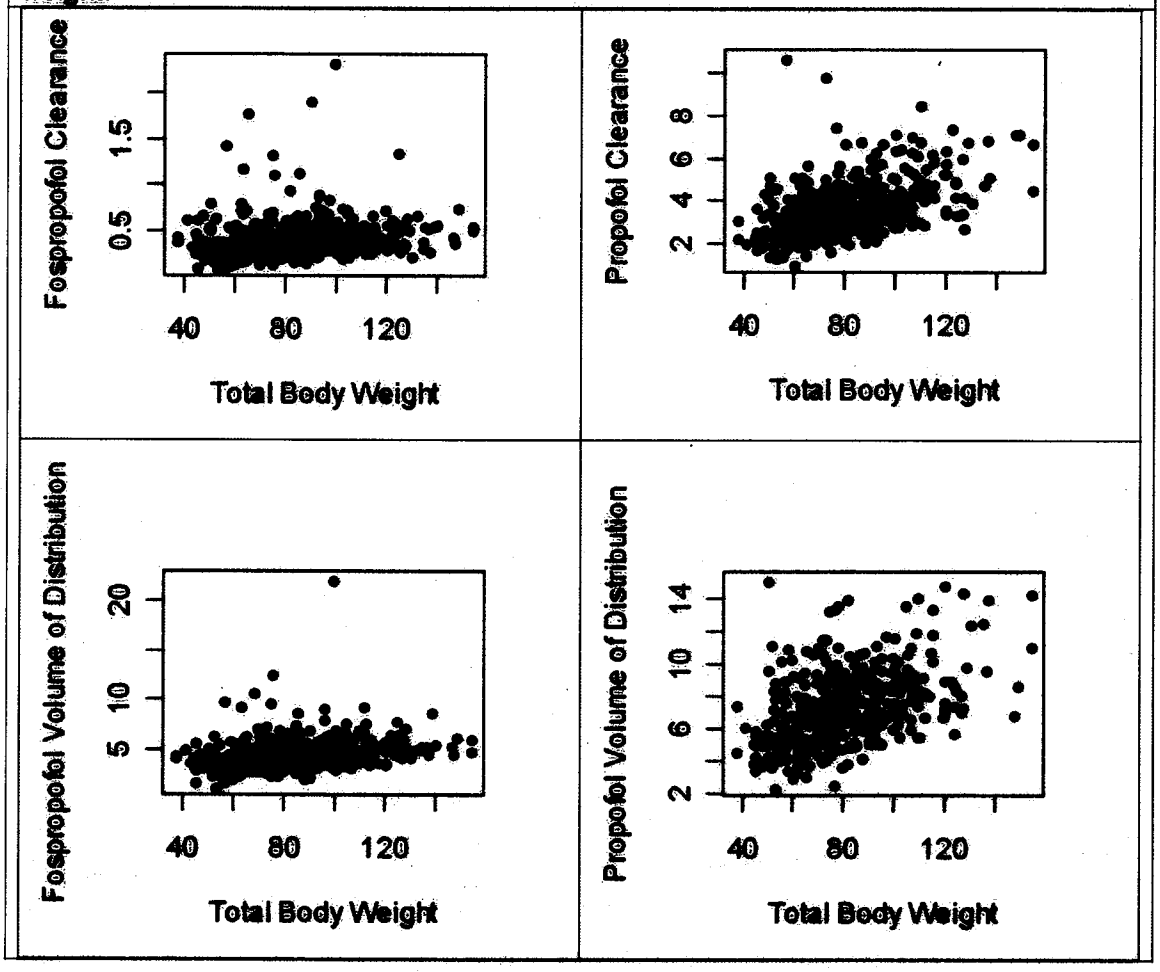


Figure 11. Relationship between CL, V for fospropofol and propofol and total body weight in patients without extreme parameter values. A clear relationship between clearance, volume of distribution and tota bodyweight can be seen in comparison to Figure 10.

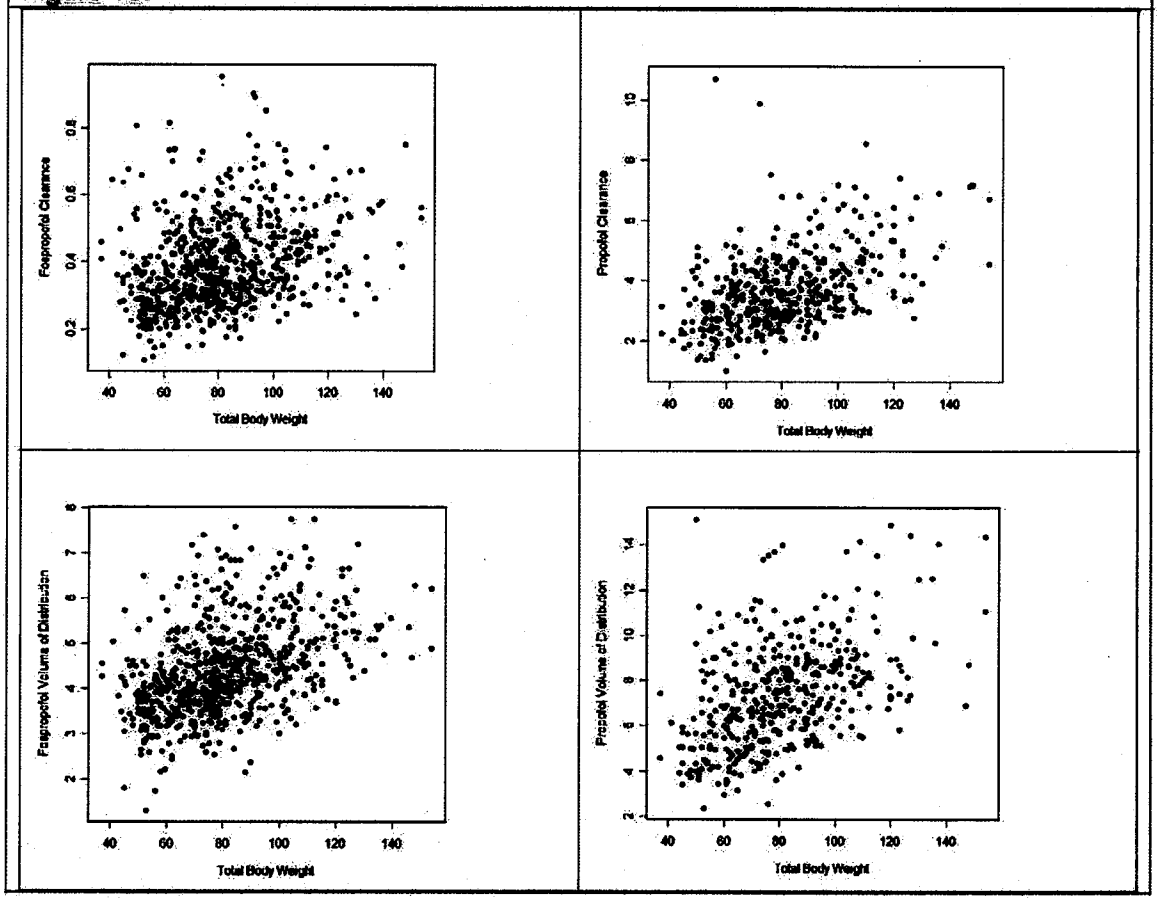


Figure 12. Relationship between race, age, alkaline phosphatase, albumin clearance and random effects of clearance, volume of distribution (after adjustment for body weight) for fospropofol.

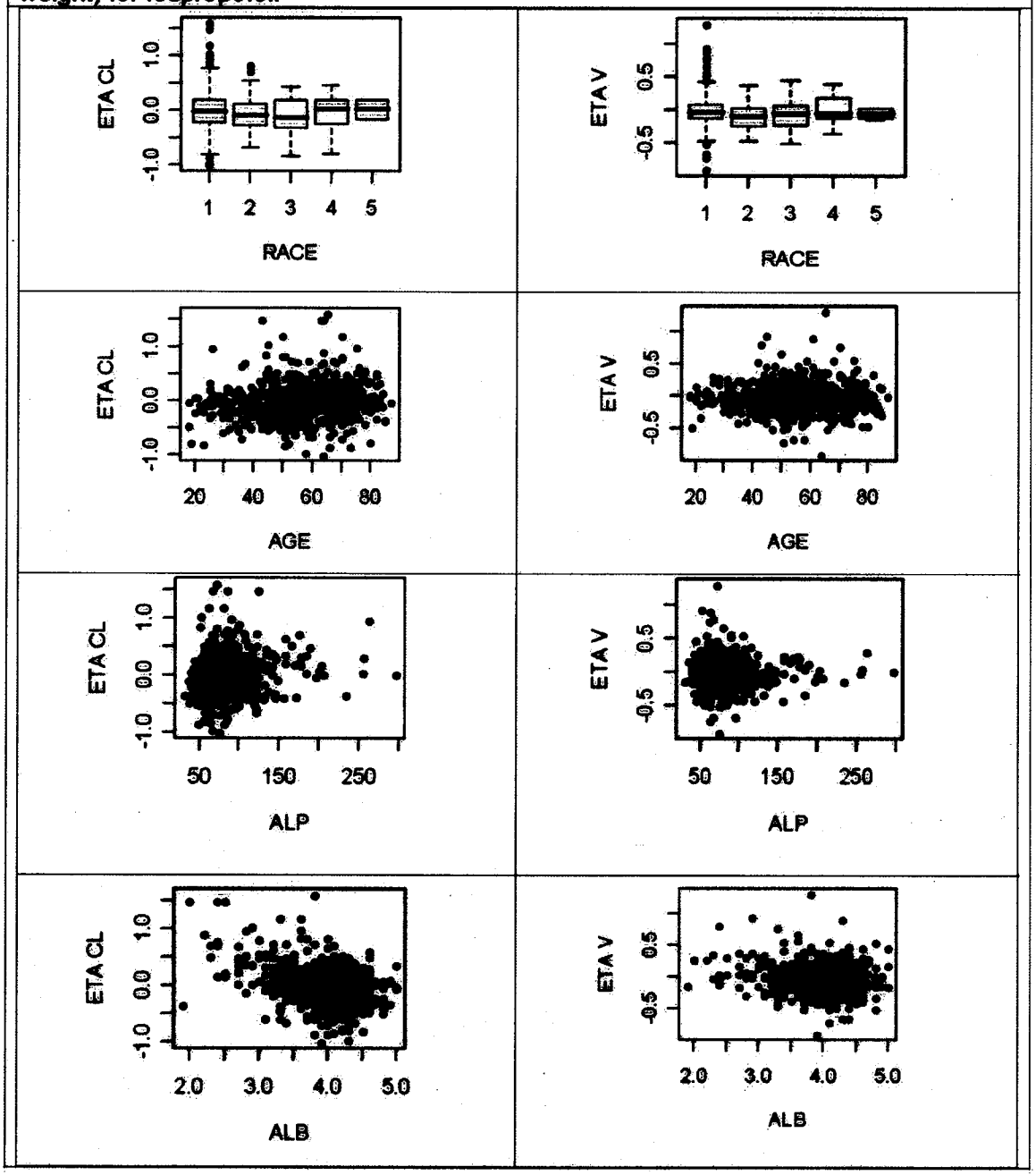


Figure 13. Relationship between race, age, alkaline phosphatase, albumin clearance and random effects of clearance, volume of distribution (after adjustment for body weight) for propofol.

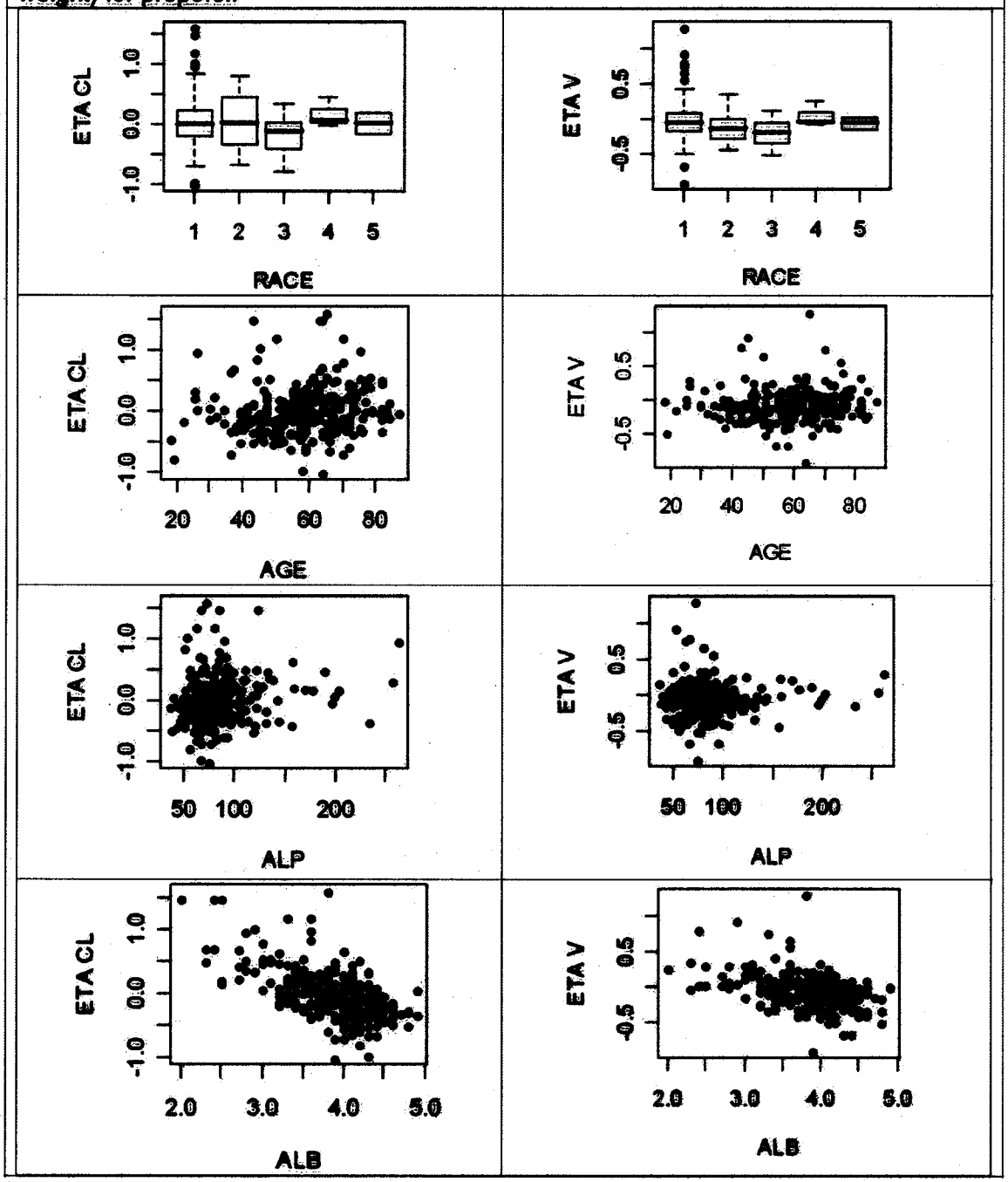


Figure 14 shows the goodness of fit plots for fospropofol and propofol for the PK model incorporating only body weight effects on PK parameters.

Figure 14. Basic Goodness-of-fit Plots of Fospropofol – Propofol Model 103. Fospropofol Fit First column: Observed fospropofol concentration (mcg/mL) are plotted versus population (upper plot) and individual (lower plot) predictions of fospropofol concentrations (mcg/mL). Unit lines are provided a reference.
Second column: Conditional weighted residuals (CWRES) are plotted versus population predictions of fospropofol concentrations (mcg/mL) (upper plot) and time (min) (lower plot). Solid line at y=0 are included as a reference. The bold red lines are lowess (local regression smoother) trend lines.

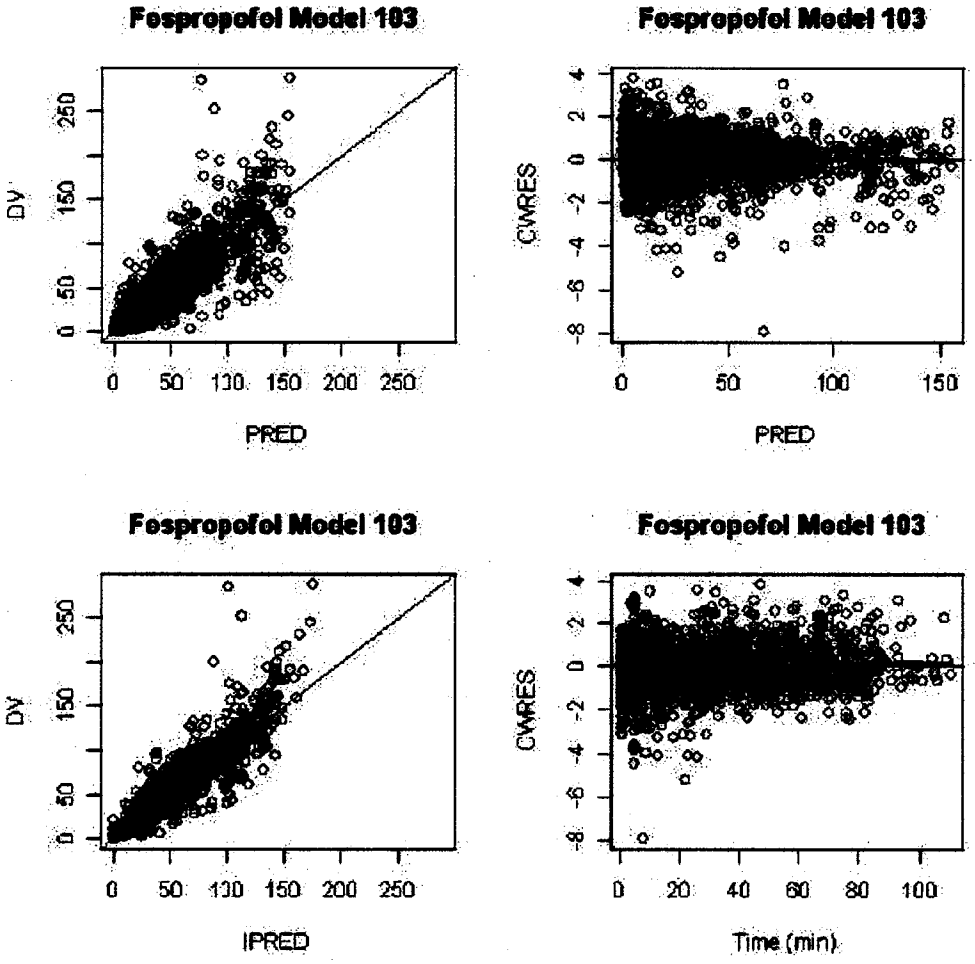
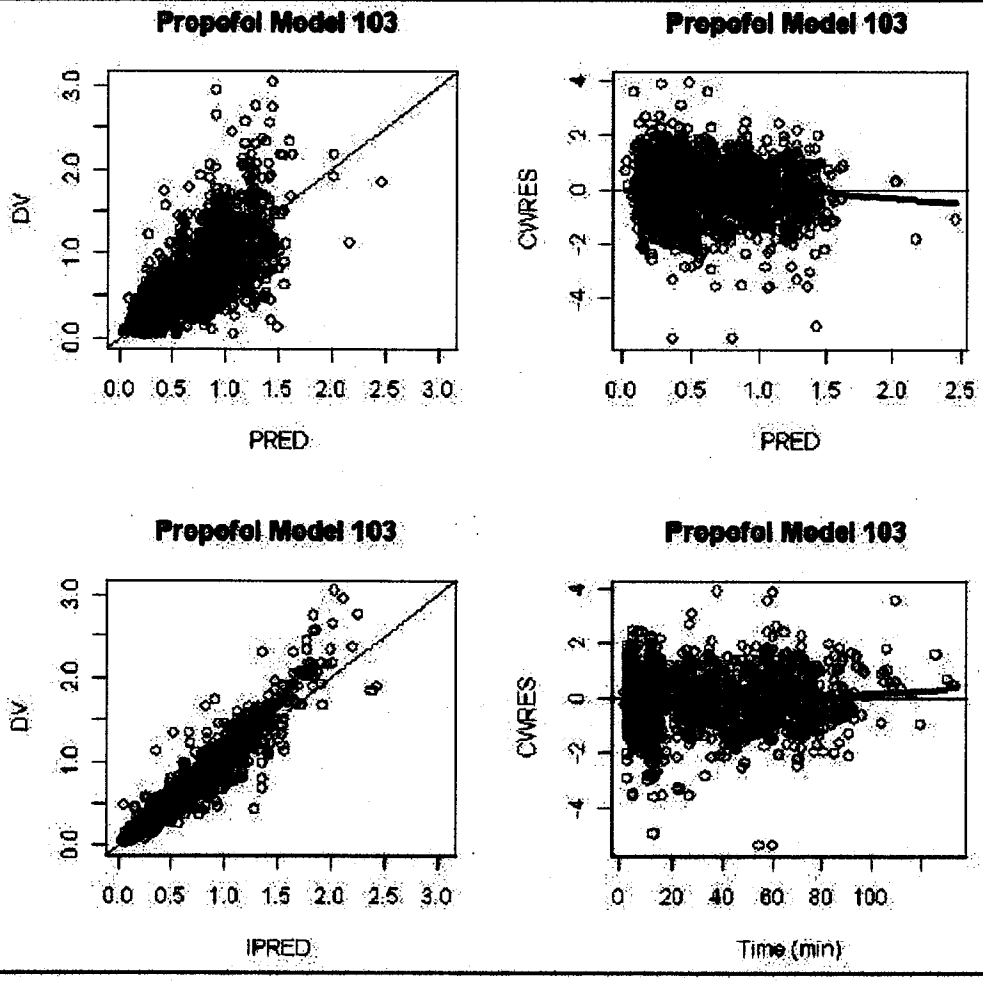


Figure 15. Basic Goodness-of-fit Plots of Fospropofol – Propofol Model 103: Propofol Fit
First column: Observed fospropofol concentration (mcg/mL) are plotted versus population (upper plot) and individual (lower plot) predictions of fospropofol concentrations (mcg/mL). Unit lines are provided a reference.
Second column: Conditional weighted residuals (CWRES) are plotted versus population predictions of fospropofol concentrations (mcg/mL) (upper plot) and time (min) (lower plot). Solid line at y=0 are included as a reference. The bold red lines are lowess (local regression smoother) trend lines.



The estimated structural and stochastic parameter values for the PK model is shown in Table 4 below.

Table 4. Estimated structural and stochastic parameter values for Fospropofol and Propofol using Model 103 (Source: Table 17 on Page 76 from Sponsor's Report (pr-aqua-02-02.pdf).

Parameter	NONMEM notation	Population Estimate	Relative SE (%)	95% CI	Comment
V_1 (L)	θ_1	4.43	2.06	4.25 - 4.61	
CL_F (L/min)	θ_2	0.321	2.84	0.304 - 0.339	
K_{12} (1/min)	θ_3	0.0128	7.99	0.0108 - 0.0149	
K_{21} (1/min)	θ_4	0.0164	23.9	0.00871 - 0.0241	
$V_{1,DOSE}$	θ_7	0.237	9.57	0.192 - 0.281	
$CL_{F,DOSE}$	θ_6	0.14	15.7	0.097 - 0.183	
$V_{1,BMI}$	θ_9	-0.227	28.7	-0.354 - -0.0992	
$CL_{F,ALB}$	θ_{10}	3.17	8.74	2.62 - 3.71	
$CL_{F,ALP}$	θ_{11}	0.126	31.2	0.0489 - 0.203	
$CL_{F,BILI}$	θ_{12}	-0.0341	47.1	-0.0656 – (-0.00262)	
$CL_{F,CRCL}$	θ_{13}	-0.0538	93.6	-0.153 - 0.0449	
$CL_{F,ASA}$	θ_{14}	1.22	3.88	1.12 - 1.31	
K_{34} (1/min)	θ_{15}	0.422	13.8	0.308 - 0.536	
V_4 (L)	θ_{16}	21.4	15.2	15.1 - 27.8	
CL_F (L/min)	θ_{17}	3.06	5.75	2.72 - 3.41	
K_{40} (1/min)	θ_{18}	0.414	15.8	0.286 - 0.542	
K_{34} (1/min)	θ_{19}	0.0437	7.38	0.0374 - 0.05	
$CL_{P,ALB}$	θ_{20}	2.05	13.3	1.52 - 2.59	
$CL_{P,ALP}$	θ_{21}	0.0041	1050	-0.0801 - 0.0883	
$CL_{P,BILI}$	θ_{22}	-0.074	25.1	-0.111 – (-0.0376)	
$CL_{P,CRCL}$	θ_{23}	0.156	47.2	0.0117 - 0.3	
$CL_{P,ASA}$	θ_{24}	1.12	5.03	1.01 - 1.23	
ω^2_V	$\Omega(1,1)$	0.0456	14.7	0.0324 - 0.0587	CV=21.3%
$R_{V,CL}\omega_V\omega_{CL}$	$\Omega(1,2)$	0.0253	17.8	0.0165 - 0.0341	R=0.38
ω^2_{CL}	$\Omega(2,2)$	0.0973	6.93	0.0841 - 0.11	CV=31.2%
ω^2_{K34}	$\Omega(3,3)$	1.28	16.8	0.862 - 1.71	CV=113%
ω^2_{V4}	$\Omega(4,4)$	0.05	9.92	0.0403 - 0.0598	CV=22.4%
$\sigma^2_{F,add}$	θ_5	0.161	12.2	0.122 - 0.199	SD=0.40 mcg/mL
$\sigma^2_{F,exp}$	θ_8	0.105	2.68	0.0995 - 0.111	CV=32.4%
$\sigma^2_{P,add}$	θ_{25}	0.00137	19.2	0.0009 - 0.0019	SD=0.037 mcg/mL
$\sigma^2_{P,exp}$	θ_{26}	0.0561	4.48	0.0512 - 0.061	CV=23.7%

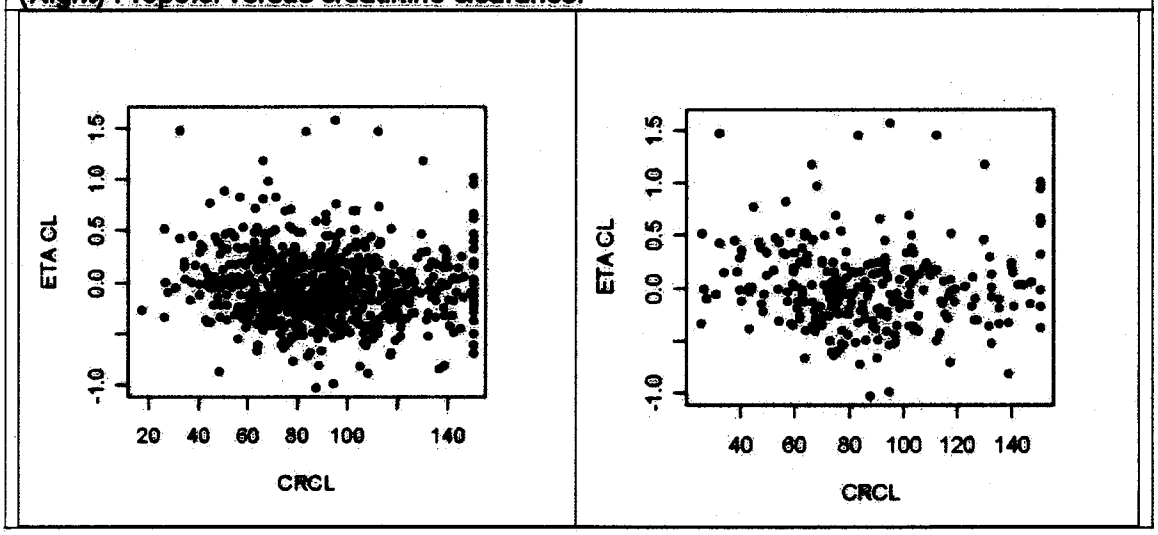
Sponsor also evaluated the effect of renal and hepatic impairment on the pharmacokinetics of fospropofol and propofol.

Study Report PR-AQUA-02-03: Population Pharmacokinetic-Pharmacodynamic Modeling of Fospropofol Injection in Patients: Evaluation in Hepatically Impaired Patients. The data from 7 patients with hepatic impairment were merged along with other patients and the pharmacokinetic parameters were determined. The pharmacokinetic analysis in patients with hepatic impairment did not include classification of patients as per Child-Pugh scores. The sponsor should conduct a study in patients with hepatic impairment to provide clear information in the drug label.

Study Report PR-AQUA-02-04: Population Pharmacokinetic-Pharmacodynamic Modeling of Fospropofol Injection in Patients: Evaluation in Renally Impaired Patients. A total of 7 patients were included into this additional analysis. Five of these patients had normalized creatinine clearance between 10 and 30 mL/min/1.73m^2. Two patients had normalized creatinine clearance less than 10 mL/min/1.73m^2. The data from these patienst with renal impairment were merged along with other patients and the pharmacokinetic parameters were determined.

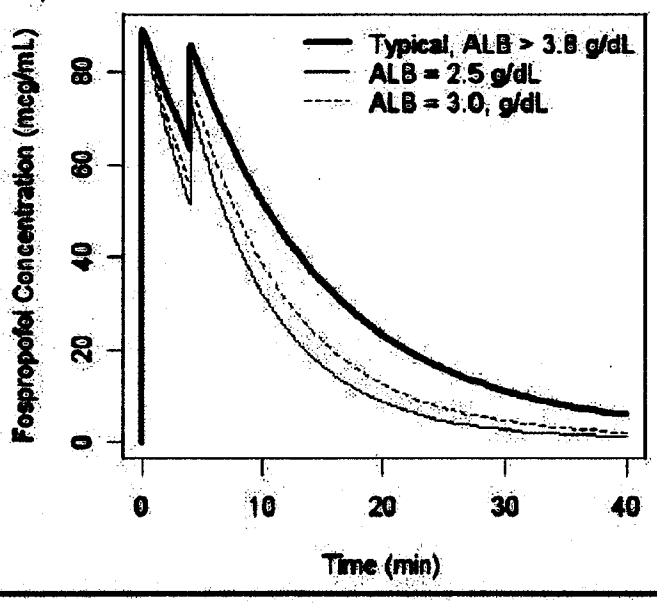
Figure 16 shows that the clearance of fospropofol, propofol are not influenced by renal function. This is also supported by the fact that fospropofol is metabolized to propofol and propofol subsequently undergoes conjugation. The conjugated metabolites are eliminated via renal pathway.

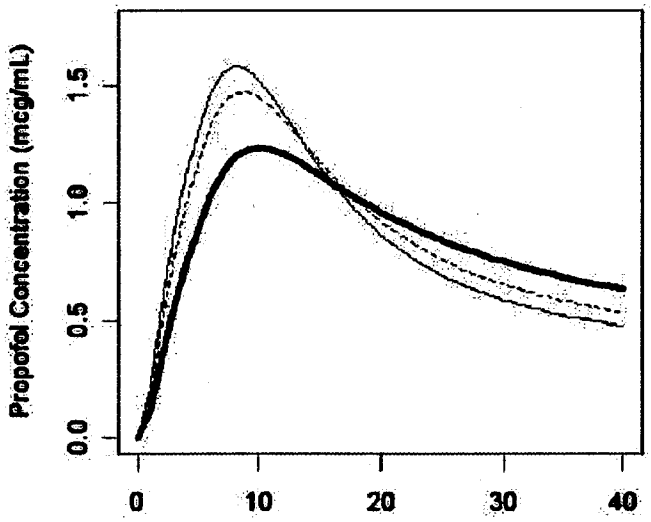
Figure 16. Relationship between random effects of clearance of (Left) Fospropofol (Right) Propofol versus creatinine clearance.



The influence of the prognostic factors such as age, renal function etc on the pharmacokinetics of fospropofol and propofol is summarized in Table 5.

Table 5. Influence of prognostic factors on the pharmacokinetics of fospropofol and propofol.

Prognostic Factor	Impact on PK
Body Weight	Significant impact on PK of Fospropofol and Propofol. These findings support the weight based dosing algorithm: *The dosage of AQUAVAN is limited by lower and upper weight bounds of 60 kg and 90 kg, respectively. Adults who weigh >90 kg should be dosed as if they are 90 kg; adults who weigh <60 kg should be dosed as if they are 60 kg.*
Gender	No effect on PK.
Fentanyl	No effect on PK.
Race	No effect on PK.
Age	No effect on PK.
Albumin	Significant impact on PK of Fospropofol and Propofol. 

	 Population predictions of fospropofol and propofol concentrations after administration of a 6.5 mg/kg initial bolus dose followed by a supplemental dose (25% of the initial bolus dose). The bold solid line illustrates model predictions for patients with normal albumin level (3.8 g/dL or higher). The thin solid line and the dashed lie are the model predictions for patients with albumin concentration of 2.5 and 3.0 g/dL, respectively. Patients with low albumin concentration have higher fospropofol clearance and faster fospropofol to propofol metabolism resulting in initial increase in propofol concentrations. However, they also have faster propofol clearances resulting in faster decrease of propofol concentration when compare to patients with normal albumin level. No dose adjustments are being proposed.
Renal Function	No effect on PK.