

Population PK/PD model of GPI 15715 and GPI 15715-derived propofol in sedation and comparison of PK/PD models for ordered categorical observations

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AQUAVAN® Injection (GPI 15715) is a novel sedative/hypnotic water-soluble propofol prodrug with PK and PD properties that significantly differ from propofol emulsion. AQUAVAN may provide mild to moderate (procedural) sedation for short (<2h) procedures. A Phase 2 study was performed to assess AQUAVAN for sedation during colonoscopy.

Study Design: This was an effect-controlled, adaptive dose-ranging trial in 164 patients with several dose levels of AQUAVAN to produce mild to moderate sedation (Modified Observer's Assessment of Alertness/Sedation score, 2 ≤ MOAA/S ≤ 4). All patients were pre-medicated with fentanyl citrate (fentanyl).

Dosing: There were several dosing groups with different initial and supplemental AQUAVAN and fentanyl doses.

Fentanyl: 0.5–1.5 µg/kg i.v., five minutes prior to the initial AQUAVAN dose. **AQUAVAN:** initial bolus of 7.5–12.5 mg/kg. Supplemental boluses of 1.5–5.0 mg/kg (up to 4 doses at intervals of 4–5 min, if needed for sedation). **Total AQUAVAN dose:** range 495–1680 mg, mean 961 mg, SD 235 mg.

Objectives: To develop a population PK model of AQUAVAN (GPI 15715) and hydrolyzed propofol in venous plasma, and PK/PD model for MOAA/S score.

Data: **PK:** 4 venous samples: at 1 and 9 minutes post initial AQUAVAN dose, when patient returns to MOAA/S = 5 (awake) and at discharge; **PD:** MOAA/S score recorded every minute starting at first fentanyl dose (t = -5 min) and until 2 consecutive MOAA/S scores of 5.

Covariates: **Demographics:** gender (43% males), weight (45–140 kg), age (20–85 years), race (121 Caucasian/18 Hispanic/15 Black/4 Other), body surface, lean body weight (LBW 37–81 kg), BMI; **Lab values:** creatinine clearance, albumin, ALP, ALT, AST, bilirubin; **Fentanyl:** total dose (11–200 mg), concentration at 1 and 9 minutes (0–1660 pg/mL); **AQUAVAN total dose** (495–1680 mg).

Database: **PK:** 158 patients, 282 doses, 597 GPI 15715 and 599 propofol plasma concentrations. **PK/PD:** 153 patients, 275 doses and 3421 MOAA/S observations.

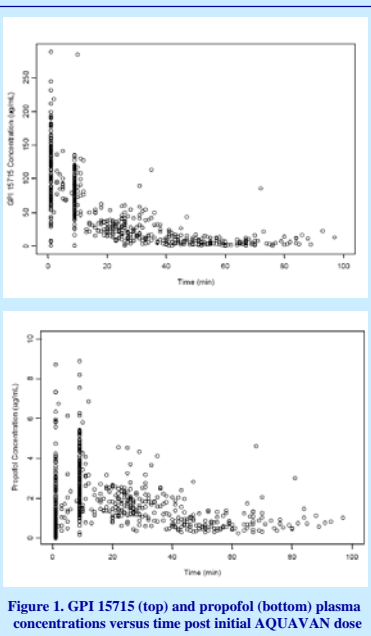


Figure 1. GPI 15715 (top) and propofol (bottom) plasma concentrations versus time post initial AQUAVAN dose

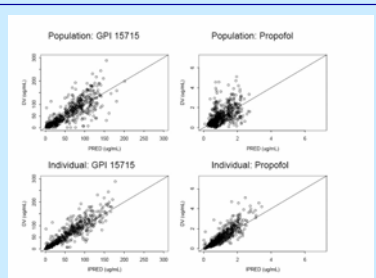
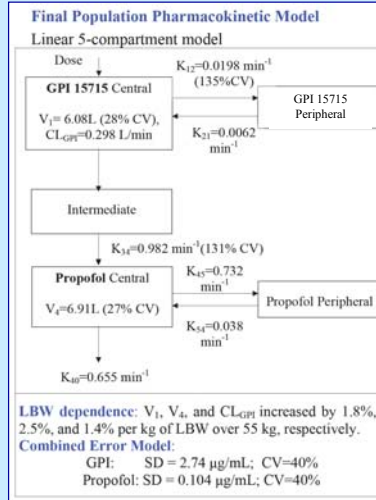
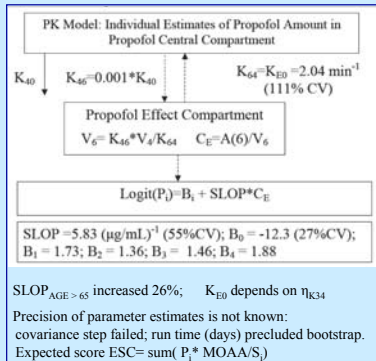


Figure 2. Predicted versus observed for PK model

Predictive check simulations: simulate 500 trials, compute propofol mean and 9-minute concentrations, find quartiles and 95th percentiles, compare observed and simulated values for these statistics. **Results:** good agreement with the observed data, slight under-estimation of GPI 15715 and propofol concentrations and over-estimation of the GPI 15715 variability.

Probabilistic Population Model for MOAA/S Score

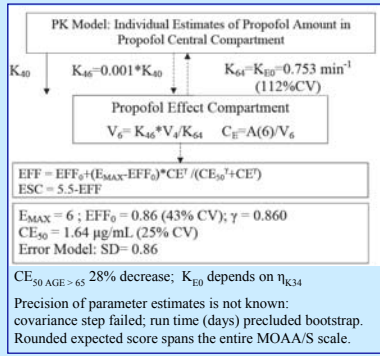
Proportional odds model: logit of probability of MOAA/S being at level i ($i=0,1,...,5$) is linear function of propofol concentration in the effect compartment



Expected score $ESC = \sum(P_i * MOAA/S_i)$

Continuous Population Model for MOAA/S score

Expected score (ESC) is a Hill function of propofol effect-site concentration



Rounded expected score spans the entire MOAA/S scale.

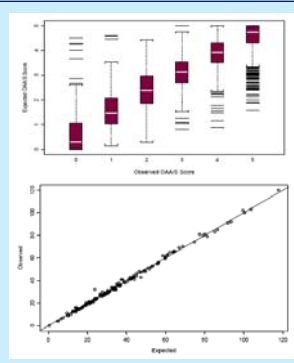


Figure 3. Expected versus observed MOAA/S score (top) and Area Under Effect (bottom, AUE=sum(5-MOAA/S))

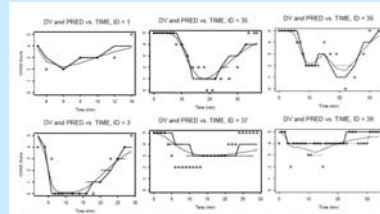


Figure 4. Individual predictions for 6 typical patients. Smooth solid: expected score, Solid: score with maximal probability, Dashed: rounded expected score, Circles: observed. Plots were similar for probabilistic and continuous models

Influence of Age on MOAA/S

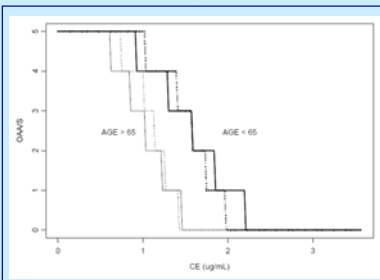


Figure 5. Expected MOAA/S score (ESC) versus effect-compartment concentration for probabilistic (solid) and continuous (dash) models.

Back-Stage Estimation (BSE) Method (Kjellsson MC, Jönsson S, Karlsson MO. AAPS J. 2004; 6 (3): article 19) was applied to the probabilistic model, but showed unstable convergence. Starting from 40th iteration it was modified to allow ≤ 10% change in parameters from i^{th} iteration to $i+1^{th}$. This improved convergence. After 60 iterations no significant improvement in parameters was noticed.

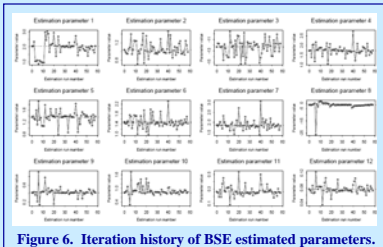


Figure 6. Iteration history of BSE estimated parameters.

Individual Predictions and Predictive Check Simulations: Sedation Levels Comparison

Observed	Probabilistic Model				Continuous Model				
	IPRED	Simulation	Fixed PK	Simulated PK	IPRED	Simulation	Fixed PK	Simulated PK	
P	E	P	E	P	E	P	E	P	
% patients with MOAA/S ≤ 1	56	53	53	50	51	48	50	50	44
% patients with MOAA/S = 3	95	86	92	71	75	68	71	92	72
% patients with MOAA/S = 4	99	97	99	83	88	81	86	99	91
% with MOAA/S ≤ 1 for < 5min	35	33	29	44	41	43	40	33	40
% with MOAA/S = 4 for < 5min	98	96	98	79	84	76	82	97	87
Mean time to MOAA/S < 1 (min)	7.5	6.4	6.1	4.8	4.8	4.5	4.6	6.7	5.7
Mean time to MOAA/S < 4 (min)	3.0	4.3	3.8	3.8	3.6	3.8	3.5	3.7	3.1
Mean duration MOAA/S < 1 (min)	9	8	9	15	14	15	15	8	12
Mean duration MOAA/S = 4 (min)	20	20	23	21	22	20	22	23	23
% of time in MOAA/S = 5	14	16	12	16	13	16	14	13	12
% of time in MOAA/S = 4	62	63	72	48	55	46	54	70	61
% of time in MOAA/S = 1	24	20	15	37	31	38	32	18	27

P: MOAA/S=score with maximum probability; E: MOAA/S=expected score

Summary of PK Results

- GPI 15715 and propofol central volumes, and GPI 15715 clearance increased by 1.8%, 2.5%, and 1.4% per kg of LBW, respectively.
- GPI 15715 C_{max} (end of the injection) ~1/LBW.
- Propofol C_{max} (4–5 minutes post-dose) ~1/LBW^{0.45}.
- There was no fentanyl effect on GPI 15715 or propofol PK.
- Gender and body weight (WT) were strongly correlated. There was no gender effect after accounting for LBW effect.
- The effect of age was not significant (10% of patients were older than 65 years of age).

Summary of PK/PD Results

- Probabilistic and continuous models adequately described the observed data with generally similar results.
 - Older patients (≥ 65 years) were more sensitive to propofol. They were sedated to the same level as younger patients at approximately 33% (probabilistic model) and 25% (continuous model) lower propofol effect-site concentrations.
 - At fentanyl doses used in the study, fentanyl effect on sedation was very small. Only 7 (5%) patients had MOAA/S score below 5 by the time of AQUAVAN dosing (5 min). PK/PD models were not able to distinguish fentanyl effect from the propofol effect.
 - No gender effect was detected.
- Conclusions:**
- A linear PK model adequately described the data.
 - LBW was the best predictor of propofol concentrations. Strictly weight-proportional dosing may overdose overweight individuals. Mg/kg dosing with an upper dose boundary or fixed-dose (mg) in the ranges of weights may be preferable.
 - Age did not affect PK, but increased the PD effect. A reduction in dose of about 25% is indicated for patients over 65 years of age.
 - Fentanyl did not affect PK or PD.
 - Continuous and probabilistic PD models adequately described the data and the covariate effects.