

## **Title: Simultaneous Population Pharmacokinetic-Pharmacodynamic Modeling of Fospropofol Injection (Propofol Prodrug) and Propofol Emulsion in Healthy Volunteers**

**Authors:** Leonid Gibiansky\* (1), Marc R. Gastonguay (2), and Ajit Shah (3)

**Institutions:** (1) QuantPharm LLC, North Potomac, MD, USA (the work was done when LG was at (2)); (2) Metrum Research Group LLC, Tariffville, CT, USA; (3) MGI Pharma, Inc., Bloomington, MN, USA

**Background:** Fospropofol disodium is a water-soluble prodrug of propofol being developed for sedation during brief diagnostic and therapeutic procedures. The pharmacokinetic and pharmacodynamic (PK-PD) profiles of propofol liberated following a bolus intravenous (IV) injection of fospropofol disodium are distinct from propofol injectable emulsion

**Objectives:** To develop (1) PK model of fospropofol and propofol concentrations in venous plasma samples following administration of a 10 mg/kg IV bolus dose of fospropofol or a 50 mg/min propofol infusion for over approximately 3-4 minutes, (2) PK-PD model of the relationship between plasma concentrations of propofol, and bispectral (BIS) index following administration of fospropofol or propofol; (3) PK-PD model of the relationship between venous plasma concentrations of propofol and sedation score (Modified Observer's Assessment of Alertness/Sedation score, MOAA/S) following the administration of fospropofol or propofol. The main goal of building these PK and PK-PD models was to compare the PK and PK-PD properties of propofol delivered from two different formulations.

**Methods:** This was an open-label, 2-period, crossover study of fospropofol versus propofol in 12 healthy volunteers (6 males, 6 females). Each subject received a single 10 mg/kg IV bolus dose of fospropofol in the first period, and the resulting maximal electroencephalogram (EEG) effect was recorded by the minimal BIS index. In the second period (after a 7-day washout), each subject received a 50 mg/min infusion of propofol with varied duration intended to produce the same maximal EEG effect as observed with a 10 mg/kg IV bolus of fospropofol. For PK evaluation, venous blood samples were obtained during both treatment periods at pre-dose and at 1, 4, 8, 12, 20, 30, 60, 90, 120, 180, and 240 minutes after drug administration. Samples were assayed for fospropofol by LC/MS/MS and for propofol (liberated from fospropofol or delivered by propofol emulsion) by HPLC with fluorescence detection. MOAA/S and BIS index were assessed approximately every two minutes from pre-dose to 20-40 minutes post dose when all subjects returned to the fully alert state. A crossover design permitted intra-subject comparison of propofol PK and PD properties as a function of its delivery system, fospropofol or propofol. The goal of the population PK modeling was to describe individual propofol concentrations during sedation and for subsequent PK-PD modeling; therefore, only PK data obtained up to 70 minutes post dose were included in the analysis. A PK model that simultaneously described both formulations was developed, and the effect of formulation on propofol clearance and volume was estimated. After the population PK model was established, individual PK parameters were used to predict propofol concentrations for the PK-PD analysis. Depth of sedation (MOAA/S) and BIS data were used to develop the population PK-PD models. The population PK and PK-PD analyses were conducted via nonlinear mixed-effects modeling with NONMEM software, Version V.

**Results:** The population PK of fospropofol and propofol liberated from fospropofol was described by a four-compartment linear model. The first two compartments of the model described fospropofol. A complete (100%) linear fospropofol-to-propofol metabolism was assumed. The population PK of propofol from either formulation was adequately described by the remaining two compartments of the combined model. Fospropofol and propofol models included body-size dependence via allometric scaling.

Typical fospropofol volume of distribution and clearance were estimated as  $V_F = 4.58$  L (3.79 - 4.81 L) and  $CL_F = 0.251$  L/min (0.185 - 0.414 L/min), respectively. Typical propofol volume and clearance were estimated as  $V_P = 24.6$  L (15.1 - 56.1 L) and  $CL_P = 2.01$  L/min (1.3 - 3.46 L/min), respectively. Variance parameter estimates were indicative of small to moderate unexplained inter-subject variability. Formulation effects on propofol clearance and volume were estimated to be 0.915 (0.417 - 1.18) and 1.02 (0.595 - 1.54), respectively: close to the null value of 1, but relatively imprecise. Independence of propofol PK parameters on formulation indicates almost complete metabolism of fospropofol to propofol.

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The direct sigmoid  $E_{MAX}$  model with random effects on  $EC_{50}$  and  $\gamma$  parameters and a formulation effect on  $EC_{50}$  adequately described dependence of the BIS index on propofol concentrations. The formulation effect was precisely estimated at 0.911 (95%CI 0.822 - 1.03) indicating no difference in the sedation effect between propofol formulations.  $E_{MAX}$  was estimated at 71.9 (95%CI 67.3 – 91.3) and  $EC_{50}$  was estimated at 2.11 mcg/mL (95% CI 1.84 - 2.90).

A proportional odds population PK-PD model with the effect proportional to propofol plasma concentration adequately described the ordered categorical MOAA/S data for both propofol formulations. No apparent formulation effect was observed. When included, the slope of the concentration-effect relationship was estimated to be 9% (95% CI -4 - 22%) higher for propofol than for fospropofol. Predictions of models with and without the formulation effect were very similar.

The comparative PK and PK-PD (BIS) results were different than reported earlier [1-3]. The differences could, most likely, be explained by the improvement in the propofol assay methodology in the current study.

**Conclusions:** The developed PK and PK-PD models adequately described fospropofol and propofol plasma concentrations, BIS index, and MOAA/S sedation data obtained within one hour following a fospropofol bolus (10 mg/kg) or infusion of propofol emulsion (over 3-4 minutes targeted to produce the same minimum BIS index as from 10 mg/kg fospropofol injection). Results indicated that:

- Propofol distribution and clearance were independent of the formulation indicating complete metabolism of fospropofol to propofol;
- Effect of propofol on sedation, as measured by the BIS index or MOAA/S sedation score, was independent of the formulation.

**References:**

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