Pharmacokinetics and pharmacodynamics of remimazolam for procedural sedation in children and adolescents

Presenting author: Michel M.R.F. Struys[1,7]

Co-authors: Pieter J. Colin[1], Keira Mason[2], RJ Ramamurthi[3], Kumar Belani[4], Lynn Bichajian[5], Valentin Curt[5], Jeroen V. Koomen[1], Thomas Stöhr[6], and Michel M.R.F. Struys[1,7]

[1] Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands., [2]Department of Anesthesiology, Boston Children's Hospital, Boston, Massachusetts., [3]Department of Anesthesiology, Stanford University Medical Center, Palo Alto, California., [4]Department of Anesthesiology, University of Minnesota, Minneapolis, Minnesota., [5]Department of Clinical Drug Development, Eagle Pharmaceuticals, Inc., Woodcliff Lake, New Jersey., [6]Department of Development and Regulatory Affairs, PAION AG, Aachen, Germany., [7]Department of Basic and Applied Medical Sciences, Ghent University, Ghent, Belgium

Background/Introduction: Remimazolam, a short-acting benzodiazepine is currently not approved for use in patients <18 years of age. As part of the pediatric study plan agreed with the U.S.-F.D.A. a clinical trial was initiated in 2021 to assess the efficacy and safety of IV remimazolam in inducing and maintaining appropriate sedation levels in pediatric patients undergoing diagnostic and/or therapeutic procedures. This study reports on an interim analysis of the pharmacokinetics and pharmacodynamics of remimazolam and a subsequent model-based optimization of the dosing regimen that was studied in the trial.

Methods: 31 patients ≥ 6 years and ≤ 18 years of age were included in the trial. Patients were stratified across 4 treatment arms: repeated bolus administration, continuous infusion and repeated bolus administration, repeated bolus + fentanyl co-administration or continuous infusion and repeated bolus + fentanyl co-administration. The University of Michigan Sedation (UMSS) scale was used to assess the level of sedation. Blood samples were drawn to measure remimazolam and CNS7054, the main metabolite of remimazolam. Population pharmacokinetic pharmacodynamic modelling was performed in NONMEM®. Optimization of the dosing regimen and power/sample size calculations were performed in R®.

Results: A joint population pharmacokinetic model was developed describing the concentration-time profile of remimazolam and CNS7054 in the absence or presence of fentanyl. Size-adjusted typical PK parameters were similar to PK parameters previously reported in adults. A proportional odds logistic regression PD model combined with a simplified Minto model, assuming an additive interaction between remimazolam and fentanyl, described the observed UMSS well. The steady-state exposure response relationship according to our model is shown in Figure 1. Clinical trial simulations confirmed that the dosing regimen which was tested in our trial was unlikely to lead to appropriate sedation in a large proportion of patients. An optimized dosing regimen consists of higher per kg remimazolam bolus doses (200 vs. 150 $\mu g.kg^{-1}$) and infusion rates (up to 80 instead of 20 $\mu g.kg^{-1}.min^{-1}$), an extended titration scheme for continuous infusion dosing (10 – 80 instead of 7.5 – 20 $\mu g.kg^{-1}.min^{-1}$), shorter inter-dose intervals for top-up bolus doses (at least 2 min gap vs. 3 min gap between bolus doses), removal of the

maximum dose cap which had been based on adult dosing and a more frequent fentanyl co-administration at higher (per kg) bolus doses (2 $\mu g.kg^{-1}$ vs. 1 $\mu g.kg^{-1}$). Finally, clinical trial simulations showed that a trial with 30 patients ≥3 years and <18 years receiving the optimized dosing regimen has a high probability of demonstrating that >70 % of patients achieve a UMSS ≥3 15 min after the first remimazolam bolus dose.

Conclusions: This study has shown that the pharmacokinetics of remimazolam are likely not different in children ≥6 years old and adults (after correcting for size differences) while the pharmacodynamics are perhaps different, although this difference may be in part (or wholly) due to investigators' deeper desired level of sedation in children compared to adults for procedural sedation. At the same time, the exposure response relationship shows that the currently studied dosing regimen is insufficient to meet the protocol specified primary endpoint. In order to effectively use remimazolam for procedural sedation in children ≥6 years it's dosing schedule has to be modified to allow for higher remimazolam exposures.

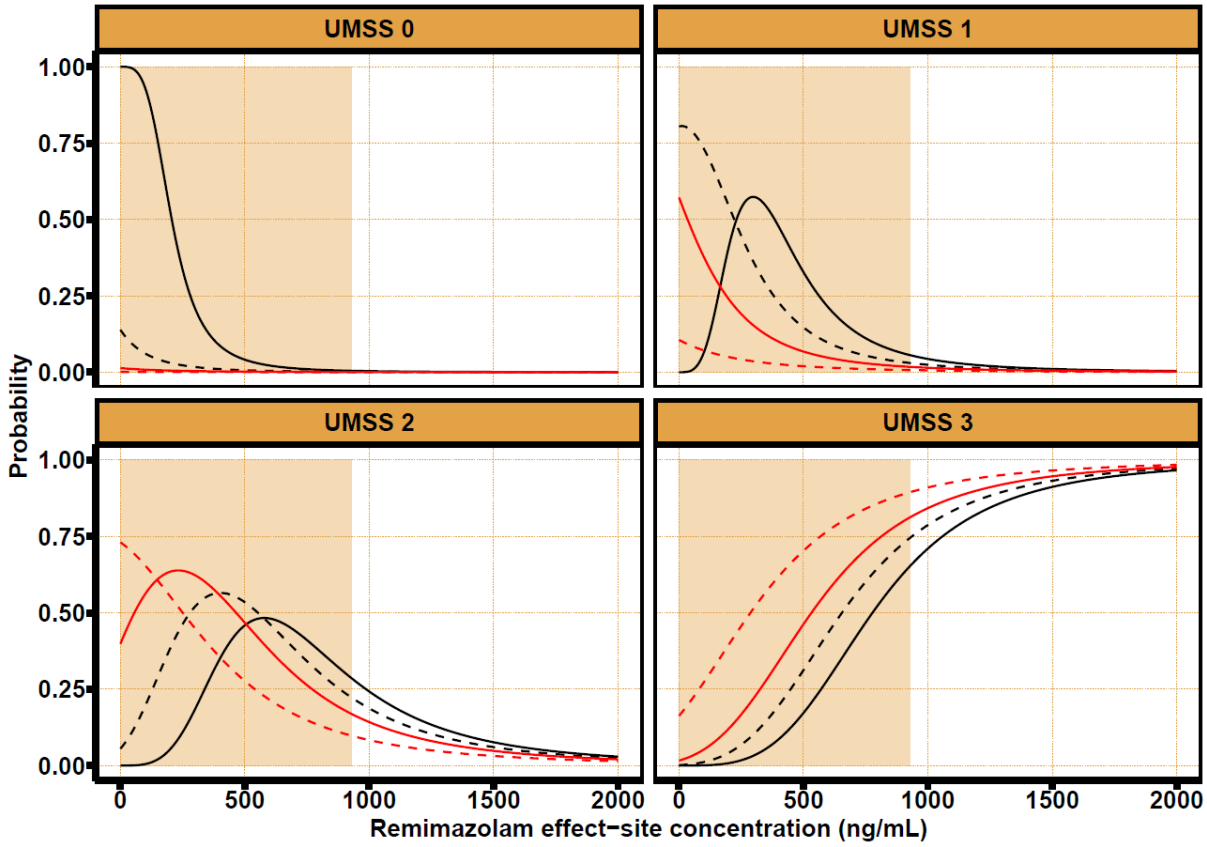

Figure 1. Steady-state pharmacodynamic interaction between fentanyl and remimazolam. *The predicted probability for UMSS = k with k ∈{0, 1, 2, 3} for different combinations remimazolam – fentanyl according to our final pharmacodynamic model. The remimazolam effect-site concentration driving the pharmacodynamic effect is depicted on the x-axis. The background fentanyl regimens, expressed as predicted effect-site concentrations, are depicted by different line types: no fentanyl co-administration (solid black line), 1 ng.mL-1 (dashed black line), 2 ng.mL-1 (solid red line) and 4 ng.mL-1 (dashed red line). The range of predicted remimazolam effect-site concentrations from this study are denoted by the orange shaded area.*