

ARTICLE

Population Pharmacokinetics of Remimazolam in Procedural Sedation With Nonhomogeneously Mixed Arterial and Venous Concentrations

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Remimazolam is an ultra-short acting benzodiazepine under development for procedural sedation and general anesthesia. Population pharmacokinetic analysis (PopPK) was conducted for remimazolam with arterial and venous samples previously, but results were limited by arterial-venous concentration differences and inaccurate central volume of distribution (V1) estimates. A new model was developed to describe covariate effects after accounting for arterial-venous differences. Arterial and venous plasma concentration-time data from 11 clinical trials were pooled for PopPK. Data from two constant-rate infusion studies were used to account for venous-to-arterial (VtoA) ratio within residual error and to accurately estimate V1. V1 and VtoA ratio from the pilot model were applied to the full dataset, where the optimal fixed/random effects and covariates were assessed. VtoA ratio was described using a maximum effect (E_{max}) model during infusion and as a constant postdose. V1 was estimated as 4.83 L for a 70 kg subject and interindividual variability (IIV) on V1 could only be estimated in studies with early concentrations. IIV on clearance was low (22.9%). Covariates included effects of sex on clearance (women 10% > men), and race on clearance and steady-state volume of distribution (African Americans 16% < other races). Arterial-venous concentration differences were best described using an E_{max} model during infusion with a constant ratio after infusion, resulting in low residual error (20.7%). There are no clinically relevant dose adjustments needed for any covariates based on pharmacokinetic differences.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Although the population pharmacokinetics of remimazolam were described previously, models were limited by the high interindividual variability (IIV) in central volume of distribution (V1) and the lack of ability to account for differences in arterial-venous concentrations.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ How can we describe V1 and venous-arterial differences with limited data, and what factors affect remimazolam pharmacokinetics (PKs) in procedural sedation?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✓ The venous-arterial differences can be described using a venous to arterial ratio on residual error. IIV on V1 should only be estimated in those with early samples after dosing. IIV is very low for remimazolam clearance. Sex-related and race-related effects on PK were small and not clinically relevant.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ This model describes a novel alternative to complex physiologic models attempting to describe venous-arterial differences when there is sparse data.

Remimazolam is an ultra-short acting benzodiazepine being investigated for procedural sedation and induction and maintenance of general anesthesia. Remimazolam is an ester-based drug that is rapidly hydrolyzed by carboxylesterase 1 (CES-1) in the liver to an inactive metabolite, CNS7054. Unlike midazolam, remimazolam appears to offer a rapid and predictable onset and offset, due to its rapid distribution and elimination. This is critical for procedural sedation indication where patients undergoing uncomfortable medical procedures of limited duration (e.g.,

colonoscopy and bronchoscopy) that generally require sedation and/or analgesia in order to minimize their discomfort and aid in procedure performance.

There are previously reported population pharmacokinetic (PopPK) analyses of remimazolam. Initially, PopPK utilized a physiologic recirculation model¹; these models assumed that a significant portion of the metabolism occurred in the lungs, and later *in vitro* data suggested that the rate of metabolism by CES-1 in the lungs is much slower than in the liver.² The most recent PopPK and population pharmacokinetic/

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pharmacodynamic (PopPK/PD³) analysis pooled data across studies in healthy volunteers,^{1,4,5} surgical patients,^{4,6–8} procedural sedation patients,^{9,10} and patients in the intensive care unit.¹¹ There was high interindividual variability (IIV, 87%) in the volume of the central compartment (V1) likely due to the imprecise calculation of V1 after i.v. bolus dose administration and inadequate modeling of venous-to-arterial (VtoA) differences due to the limited subjects ($N = 8$) with early simultaneous venous-arterial concentrations (i.e., 1 sample < 5 minutes of administration). The estimation of V1 is more accurate when determined after an infusion and is important for remimazolam PopPK due to its critical role in predicting the maximal plasma concentration (C_{max}) as well as the maximal pharmacodynamic (PD) effect.

The early VtoA differences are associated with nonhomogenous intravascular mixing, as well as the imbalanced rapid elimination for venous and arterial concentrations arising from circulation through tissues. Nonhomogenous mixing is related to cardiac output^{12,13} and dispersion,¹³ but difficult to model when there is sparse data and inadequate early simultaneous samples. Weiss¹³ reported that intravascular mixing can occur within 1 minute after bolus dosing in a non-eliminated system, but the rapid elimination of remimazolam complicates the timing of nonhomogenous mixing.

Since conduct of the previous PopPK, additional data from 20 healthy volunteers receiving an infusion with intensive, early arterial pharmacokinetic (PK) sampling (CNS7056-017¹⁴) was available. Data from 28 subjects from study ONO-2745-02⁴ and CNS7056-017¹⁴ who also received an infusion could be used to allow a better estimate of V1.

The current PopPK was conducted to more accurately estimate V1 and to account for VtoA differences using a novel empirical-based approach. Patient covariates that explain variability in the PKs of remimazolam in the procedural sedation indication were also evaluated.

METHODS

Study design

Concentration-time data from 11 phase I–III studies described in **Table S1** were pooled for PopPK. Studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practice, across Japan, the United States, and the European Union. All studies were approved by ethics committees (**Table S1**; along with clinical-trial-registry numbers and registration dates) and written informed consent was obtained prior to study procedures. These studies included:

- Five phase I studies in healthy volunteers (ONO-2745-01,⁴ ONO-2745-02,⁴ ONO-2745-IVU007,⁵ CNS7056-001,¹ and CNS7056-017¹⁴);
- Two phase II studies in procedural sedation (CNS7056-004,¹⁰ CNS7056-002⁹);
- Three phase III studies in procedural sedation (CNS7056-006,¹⁵ CNS7056-008,¹⁶ and CNS7056-015¹⁷);
- One phase II study in both young and elderly patients undergoing induction and maintenance of anesthesia for general surgery (ONO-2745-03⁴). This study was

only included to enable the full evaluation of age as a covariate on remimazolam PKs.

Plasma concentration-time data were available from 359 subjects receiving remimazolam with at least one quantifiable concentration. There were:

- One hundred twenty-six healthy volunteers, 193 procedural sedation patients, and 40 patients undergoing induction and maintenance of anesthesia for surgery who received i.v. bolus dosing or infusions of remimazolam;
- Three thousand six hundred forty-two plasma samples (2,168 arterial and 1,474 venous samples; **Figure 1**).

For procedural sedation studies, subjects received an initial dose of 5–8 mg as a 1-minute infusion of remimazolam with 2 mg, 2.5 mg, or 3 mg top up doses, depending on the study.^{9,15–17}

One study (ONO-2745-02⁴) in healthy subjects had an i.v. infusion of 1 mg/kg/hour remimazolam for up to 1 hour. For a second study (CNS7056-017) in healthy subjects,¹⁴ remimazolam infusions of 5 mg/minute for 5 minutes were followed by 3 mg/minute for 15 minutes and then 1 mg/minute for 15 minutes (85 mg total). For three other healthy subject studies (ONO-2745-01,⁴ ONO-2745-IVU007,⁵ and CNS7056-001¹), i.v. bolus remimazolam doses of 0.01–0.5 mg/kg were administered.

For a general anesthesia study (ONO-2745-03⁴), remimazolam infusions of 4–30 mg/kg/hour were administered i.v. for induction followed by 1 mg/kg/hour for maintenance of anesthesia. The dose was adjusted to maintain a bispectral index score of 40–60.

Two studies collected only arterial samples,^{5,11} five studies collected only venous samples,^{4,9,10,15–17} and three studies had both arterial and venous sampling.^{1,4} Simultaneous venous-arterial samples were collected within 5, 15, and 45 minutes of initiation of remimazolam administration in one study⁴ and between 1 and 4 hours postdose in all three studies.

General modeling methods

NONMEM version 7.3 (ICON Development Solutions, Ellicott City, MD) was used to develop the model using First Order Conditional Estimation with Interaction. All graphical analyses were performed using R version 3.0.2 (or higher) and Xpose version 4.5.3; bootstrapping and visual predictive checks (VPCs) were conducted using Perl-speaks-NONMEM program version 4.4.0.

Model development

The base structural model included three compartments to describe remimazolam concentrations over time. Even though there is no relationship between body weight and remimazolam PK parameters,¹ the effect of body weight on all clearance (CL) and volume (V) of distribution parameters was included using Eq. 1, to allow potential predictions in pediatric subjects:

$$TVP = A * WT^b \quad (1)$$

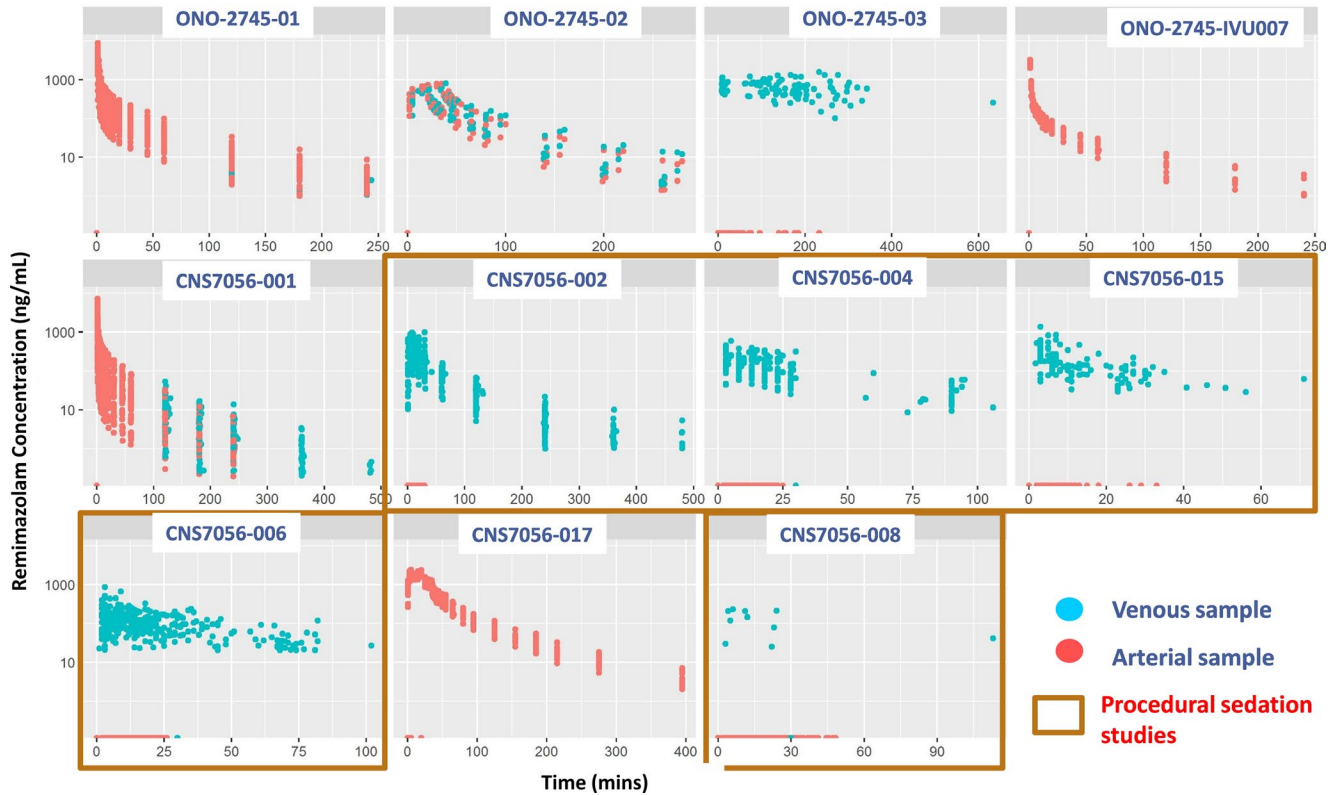


Figure 1 Plasma remimazolam concentration (ng/mL) vs. time (minutes) data by study. Red represents arterial observations and green represents venous observations. Procedural sedation studies are outlined by orange boxes.

where TVP represents the typical value of a PK parameter in a subject with a specific weight (WT); A is the allometric coefficient representing the typical value of the parameter for a subject with unit body weight (in kg) and b represents the allometric exponent (fixed to 0.75 for CL and intercompartmental clearances, Q2 and Q3, and 1.0 for V1 and volumes of the peripheral compartments (V2 and V3)).

IIV was to be estimated for CL, V1, V2, V3, and Q3 according to the following relationship (Eq. 2):

$$P_i = \text{TVP} * e^{\eta_i} \quad (2)$$

where P_i is the estimated parameter for subject i , TVP is the typical population value of the parameter, and η_i are individual-specific interindividual random effects for individual i , and assumed to be normally distributed according to $\eta \sim N(0, \omega^2)$.

Residual error on concentrations were modeled using a proportional error model that was multiplied by a VtoA ratio to account for the arterial-venous differences, given the low number of simultaneous venous-arterial samples during the first 5 minutes after remimazolam administration.

VtoA ratio. Physiologically based modeling to account for arterial-venous differences where venous and arterial samples was attempted, but was unsuccessful. Additionally, a literature-based approach using the VtoA ratios for midazolam¹⁸ from concentration after bolus administration was considered, but did not describe observed ratios

(**Figure 2**), where the ratios of remimazolam could be more than 1 while the midazolam ratios were less than 1 postdose.

Ultimately, the observed venous-arterial ratios in studies ONO-2745-02,⁴ CNS7056-001,¹ and ONO-2745-01⁴ calculated from paired arterial/venous samples were evaluated (**Figure 2**) and an empirical mathematical model (Eq. 3) during infusion and after infusion/bolus dose was used for VtoA ratio relationship included as part of the residual error (Eq. 4).

$$\text{VtoARatio} = \frac{R_{\max} * \text{TSLC}}{\text{TSLC} + T_{50}} (\text{During Infusion}); \quad (3)$$

$$\text{VtoARatio} = \text{Rcons} (\text{After Dose})$$

$$Y_{\text{obs},ij} = Y_{\text{pred},ij} * (1 + \varepsilon_{ij}) * \text{VtoA Ratio} \quad (4)$$

where R_{\max} is the maximum ratio (fixed to 1 based on observed data), TSLC is the time since the start of infusion/bolus dose, and T_{50} is the time to reach 50% of the maximum ratio; the VtoA ratio postinfusion was estimated as a constant (Rcons) based on observed data (**Figure 2**); VtoA ratio was set to 1 for arterial samples; $Y_{\text{obs},ij}$ denotes the observed concentration for the i^{th} individual at the j^{th} time; $Y_{\text{pred},ij}$ denotes the subject-specific predicted concentration for the i^{th} individual at the j^{th} time, ε_{ij} denotes the residual error (as a proportional error random effect having zero mean and variance, σ^2). Sensitivity analyses

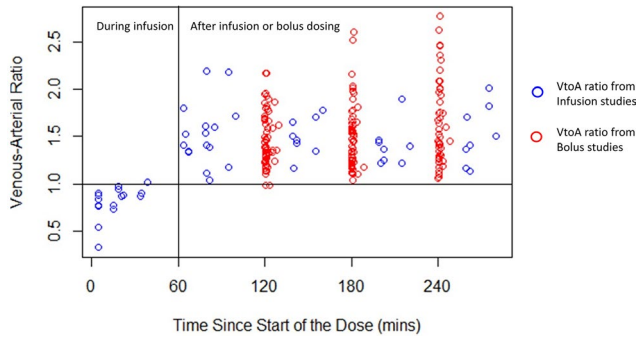


Figure 2 Plots of observed venous to arterial ratio vs. time since the start of dosing (minutes). Open circles represent observed venous to arterial (VtoA) ratios calculated from paired venous and arterial samples of the same individual from i.v. bolus studies ONO-2745-01 and CNS7056-001 (bolus dose, red color), and from infusion study ONO-2745-02 (infusion, blue color). In ONO-2745-01 and CNS-7056-001, simultaneous venous-arterial samples were collected at 2, 3, and 4 hours after bolus dose administration. In ONO-2745-02, simultaneous venous-arterial samples were collected between 5 and 35 minutes from the beginning of the infusion, immediately before the end of infusion (1 mg/kg/hour for 1 hour) (around 60 minutes since the start of administration), between 20 and 45 minutes, and 1, 2, 3, and 4 hours after the end of the 1-hour infusion (about 80–300 minutes since the start of administration).

were conducted to evaluate assumptions related to bolus dosing.

Pilot vs. full dataset modeling. General steps taken included evaluation of a pilot model with data from just the two studies with remimazolam infusions in healthy subjects (CNS7056-017¹⁴ and ONO-2745-02⁴) to estimate V1 and to estimate the VtoA ratio as a component of the residual error. Then, the full dataset was used with V1 and VtoA ratio fixed to values estimated for the pilot model.

Once the pilot dataset was applied to the full dataset, the optimal number of parameters with IIV were evaluated. Because patients in procedural sedation studies (CNS7056-002,¹⁰ CNS7056-004,⁹ CNS7056-006,¹⁵ CNS7056-008,¹⁶ and CNS7056-015¹⁷) and the general anesthesia study (ONO-2745-03⁴) generally had their first concentration > 2 minutes after a bolus dose or change in infusion rate, the IIV on V1 could not be estimated (shrinkage toward the mean) as V1 is highly dependent on early concentrations. Therefore, those subjects without early concentrations were assumed to have the typical value for V1 with no IIV, whereas IIV was estimated on V1 for those subjects with early sampling (CNS7056-001,¹ CNS7056-017,¹⁴ ONO-2745-01,⁴ ONO-2745-02,⁴ and ONO-2745-IVU007⁵). The base model for the full dataset had an OMEGA block for CL, Q3, and V3, and a diagonal OMEGA for V1 and V2. IIV on Q2 was not supported because of high shrinkage and removing it did not affect the objective function value (OFV) or goodness-of-fit plots.

Addition of covariates to PopPK Model. Using the full dataset, only minimal prespecified covariates were to be added to describe the effects of covariates on

remimazolam plasma concentrations based on biological plausibility. Forward addition of each parameter(s) was made using a change in OFV of least 6.635 ($P \leq 0.01$, with 1 degree of freedom) for inclusion. The decision to include a covariate was not to be based solely on the change in the OFV. In addition, goodness-of-fit plots, the precision of estimates, biological plausibility, and the magnitude of IIV and residual variability were considered, with the goal to describe a conservative model with adequate precision for simulation.

If two or more covariate effects were highly correlated ($r^2 > 0.7$; e.g., age, creatinine clearance, estimated glomerular filtration rate, and American Society of Anesthesiology classification (ASA class)), then the model with the largest change in the OFV, the largest slope, and/or the more physiologically or clinically relevant covariate was to be included in the full model and other correlated covariates were not to be included in the full model.

Each categorical covariate was to be added as described in Eq. 5:

$$\text{Parameter}_j = \text{THETA}(1) \times \text{SLP}_k^{\text{COVARIATE}_k} \quad (5)$$

where the k^{th} covariate has an indicator variable (0,1) and SLP_k is estimated as the fractional change in the j^{th} parameter associated with the k^{th} covariate. The relationships between continuous covariates and PK parameters were added using a power model (Eq. 6):

$$\text{Parameter}_j = \text{THETA}(1) * \text{COVARIATE}_k^{\text{SLP}2k} \quad (6)$$

where the $\text{SLP}2_k$ is the power exponent for the k^{th} covariate, respectively, in the j^{th} parameter. The k^{th} covariate was centered at the median value. Other models were considered, if needed to improve goodness of fit.

The evaluation of the effect of concomitant medications that inhibit CES-1 enzyme and, therefore, may influence CL was limited by the small number of subjects ($n = 22$) receiving any one of these concomitant medications. Therefore, this effect was evaluated as 0 = none vs. 1 = all (lovastatin, simvastatin, clopidogrel, or telmisartan) together.

Backward elimination was conducted where multiple models were run (i.e., full model minus each covariate effect eliminated individually) in steps. Each step eliminated all covariates that did not increase the OFV by at least 10.828 ($P \leq 0.001$, with 1 degree of freedom). A new, full model was run and each covariate was once again tested for elimination; this process was rerun until there were no nonstatistically significant increases in the OFV.

Sensitivity analysis

The following sensitivity analyses were done to evaluate assumptions made during the modeling process:

1. The effect of a constant VtoA ratio (with values fixed to pilot model) after dose: The VtoA ratio used assumes that the ratio is constant after dose (whether the infusion lasts 1 minute as a bolus or 1 hour as an infusion, and this assumption may not be

correct after a bolus dose given the lack of homogeneity of mixing, but is limited by the lack of simultaneous venous-arterial data early after a bolus dose. To evaluate the sensitivity to this assumption, a VtoA ratio model (where there was only a maximum effect (E_{max}) model with a maximum miotic response (R_{max}) and a maximum ratio (T_{50}), based on the time since initiation of the dose, not end of infusion) was applied to the final model.

2. Elimination of venous concentrations < 1 minute after the start of infusion in study ONO-2745-03: Because there is not homogeneity of mixing and there were no data to evaluate the VtoA ratio at these timepoints, either from the literature or from remimazolam, these values were excluded. The final model was rerun with these values included to evaluate its influence.
3. Outliers: The model was rerun with the outliers with conditional weighted residuals > 5 included to evaluate the influence of outliers.

Model performance

After model development, model performance was assessed using VPCs and nonparametric bootstrapping, stratified by study. For VPCs, simulations ($n = 1000$) of the final model and final model parameters were conducted and the observed data were compared with model-predicted median and 95% prediction interval over time. Nonparametric bootstrapping was conducted ($n = 250$, due to feasibility of run time). Each bootstrapped dataset was fit to the final model and the median and 95% confidence intervals of parameter estimates were calculated.

RESULTS

Demographics

There were 3,642 observations from 359 subjects included in analysis. Demographics and other covariates are summarized in **Table 1**. Subjects included 63% men and 37% women, who were mostly white (51.3%) with 22.8% African Americans and 25.3% Asians. Eighteen percent of subjects were obese (body mass index (BMI) > 30 kg/m²). Sixty-five percent of subjects were ASA class 1, 24% of subjects were ASA class 2, 6.4% were ASA class 3, and 4.2% were ASA class 4. Forty-seven percent of subjects had mild renal impairment and 5.9% of subjects had moderate renal impairment, using estimated glomerular filtration rate.

Model development

Pilot model. Parameter estimates from the best model for the pilot dataset are given in **Table S2**, with goodness-of-fit plots included in **Figure S1**. R_{max} during an infusion was 1, the ratio at 50% of T_{50} was 1.63 minutes, and the constant ratio after an infusion was 1.28. The V_1 was estimated as 4.83 L for a 70 kg subject.

Base model for the full dataset. Parameters from the pilot model were applied to the full dataset. V_1 was fixed to 4.83 L, R_{max} was fixed to 1, T_{50} was fixed to 1.63 minutes, and the constant VtoA ratio was fixed to 1.28 (as estimated in the pilot model).

Initially, some models were run to confirm whether V_1 and the VtoA ratio should be fixed or estimated. The V_1 was estimated as 2.17 L, with better goodness-of-fit plots than when V_1 is fixed to 4.83 L (**Figure S2**). However, because a V_1 of 2.17 L is biologically implausible (less than plasma volume) and having a more biologically plausible V_1 value was prespecified as more important (hence, the need for pilot studies with data from infusions only), the V_1 was fixed to the estimate from the pilot model and not estimated.

Two issues were identified when applying IIVs to all CL/V parameters: (i) the IIV on V_1 was high (with resulting unphysiologically high/low V_1 estimates in some subjects) and (ii) the shrinkage was high on all ETAs. The following changes improved the model fit:

- IIV on V_1 could not really be estimated from studies with no early blood samples. Therefore, the V_1 from subjects in all procedural sedation studies and ONO-2745-03⁴ was fixed to the typical value of V_1 . For all other studies, V_1 in subjects was estimated as V_1 with IIV;
- An ETA on Q2 (slower or deeper compartment) was not needed;
- A partial OMEGA block structure with an OMEGA block on CL, Q3, and V3 and then diagonal OMEGAs on V_1 and V_2 was the most appropriate structural model.

The parameters for the full base model are given in **Table S2**.

Addition of covariates to PopPK model. The following covariates were identified as statistically significant after forward addition: a very small (< 10%) effect of sex on CL; a very small (< 10%) effect of race (African Americans vs. whites and Asians) on CL; a very small (< 10%) effect of race on volume of distribution at steady state (V_{ss}); and an effect of BMI on V_{ss} using a linear model, relative to a BMI = 25.

Backward elimination led to the following covariate effects: an effect of race and sex on CL and an effect of race on V_{ss} . The BMI effect was found to be not significant after backward elimination.

Final PopPK model of remimazolam. The final parameters are summarized in **Table 2**, with goodness-of-fit plots presented overall in **Figure 3**. There is some bias at higher concentrations in healthy volunteer studies that is expected given that V_1 was fixed to the value from the infusion pilot model because concentrations during these early times are artifactual given the lack of homogeneous mixing. All parameters were estimated with good precision. The IIV was low for CL and V_2 , intermediate for V_1 and V_3 , and high for Q3.

Sensitivity analyses

First, the assumption that the VtoA ratio is constant after dose (whether the infusion lasts 1 minute or 1 hour) was tested with a different VtoA ratio model (where there was only an E_{max} model with an R_{max} and a T_{50} , based on the time since initiation of the dose, not end of infusion) was

Table 1 Demographics of subjects included in PopPK analysis

Characteristic ^a	Statistic	CNS001	CNS002	CNS004	CNS006	CNS008	CNS015	CNS017	ONO01	ONO02	ONO03	ONO07	All subjects
Age, years	N	54	45	28	85	4	31	20	35	8	40	9	359
	Mean (SD)	35.2 (9.91)	38.3 (12.2)	53.4 (10.0)	54.7 (10.2)	79.2 (1.71)	63.1 (8.65)	25.0 (4.27)	34.9 (15.4)	25.9 (5.25)	53.2 (16.6)	48.2 (7.40)	46.1 (16.2)
BMI, kg/m ²	N	54	45	28	85	4	31	20	35	8	40	9	359
	Mean (SD)	25.7 (2.05)	26.2 (2.34)	27.2 (3.31)	28.5 (4.69)	25.8 (6.47)	30.9 (8.28)	23.9 (1.80)	21.6 (1.49)	21.2 (1.44)	23.0 (4.01)	31.1 (4.68)	26.2 (4.90)
CrCL, mL/minute	N	54	45	28	85	4	31	20	35	8	40	9	359
	Mean (SD)	103 (22.2)	122 (28.7)	101 (24.3)	105 (29.2)	51.2 (13.7)	94.3 (44.6)	132 (18.7)	124 (27.1)	121 (13.4)	88.4 (32.9)	109 (33.7)	107 (31.8)
eGFR, mL/minute/1.73 m ²	N	54	45	28	85	4	31	20	35	8	40	9	359
	Mean (SD)	85.4 (17.6)	101 (22.8)	81.8 (16.8)	83.6 (15.9)	61.5 (5.27)	72.2 (24.9)	99.5 (13.5)	119 (20.9)	114 (16.0)	99.0 (25.8)	74.5 (13.3)	91.3 (23.7)
Weight, kg	N	54	45	28	85	4	31	20	35	8	40	9	359
	Mean (SD)	78.4 (7.72)	76.8 (9.42)	77.5 (11.8)	82.6 (18.4)	65.5 (20.3)	91.0 (28.1)	77.2 (9.62)	64.5 (6.63)	62.9 (6.34)	56.1 (10.0)	89.8 (18.4)	76.1 (17.5)
Sex: M/F	N	42/12	23/22	14/14	48/37	1/3	17/14	20/0	35/0	8/0	11/29	7/2	226/133
Race: White/Black/Asian/ Other	N	13/38/2/1	22/23/0/0	27/0/0/1	65/14/6/0	4/0/0/0	25/6/0/0	20/0/0/0	0/0/35/0	0/0/8/0	0/0/40/0	8/1/0/0	184/82/91/2
ASA: 1/2/3/4	N	54/0/0/0	45/0/0/0	14/12/2/0	30/50/5/0	0/4/0/0	0/0/16/15	20/0/0/0	35/0/0/0	8/0/0/0	19/21/0/0	9/0/0/0	234/87/23/15
On a chronic medication that inhibits CES1 (N/Y)	N	54/0	45/0	25/3	77/8	4/0	20/11	20/0	35/0	8/0	38/2	9/0	335/24
AGE Category: ≥65 (years)	N (%)	0 (0%)	2 (4.44%)	3 (10.7%)	15 (17.6%)	4 (100%)	13 (41.9%)	0 (0%)	5 (14.3%)	0 (0%)	10 (25.0%)	0 (0%)	52 (14.5%)
EGRF category: normal (≥90 mL/ minute/1.73 m ²)/ Mild (≥60 to < 90 mL/ minute/1.73 m ²)/ Moderate (≥30 to < 60 mL/ minute/1.73 m ²)/ Severe (< 30 mL/ minute/1.73 m ²)	N (%)	16/37/1/0	31/12/2/0	5/21/2/0	25/58/2/0	0/3/1/0	7/12/11/1	16/4/0/0	32/3/0/0	8/0/0/0	26/11/2/1	1/8/0/0	167/169/21/2

BMI, body mass index; CrCL, creatinine clearance; PopPK, population pharmacokinetic.
^aStudy numbers are abbreviated where ONO is short for ONO-2745- and CNS is short for CNS7056-; and ONO07 is short for ONOIVU007.

Table 2 NONMEM estimates and bootstrap estimates for the final PopPK model

Description	NONMEM estimate (%RSE)	Bootstrap median (%RSE) [95% CI]
CL L/minute/70 kg ^a	1.18 (2%)	1.17 (1.7%) [1.14, 1.21]
V1 L/70 kg ^a	4.83 Fixed	4.83 Fixed
Q2 L/minute/70 kg ^a	0.284 (2.7%)	0.279 (4.7%) [0.258, 0.309]
V2 L/70 kg ^a	18.7 (2.8%)	18.5 (3.4%) [17.3, 19.9]
Q3 L/minute/70 kg ^a	1.92 (6%)	1.90 (4.8%) [1.74, 2.12]
V3 L/70 kg ^a	18 (5.3%)	17.9 (3.3%) [16.5, 19.1]
R _{max} ^x max venous:arterial ratio ^b	1 Fixed	1 Fixed
T ₅₀ , minutes ^c	1.63 Fixed	1.63 Fixed
Ratio2, venous:arterial ratio after infusion ^d	1.28 Fixed	1.28 Fixed
Sex effect on CL, female:male ratio	1.1 (2.5%)	1.10 (2.7%) [1.04, 1.16]
Race, African Americans vs. Asians and whites, effect on CL	0.87 (2.9%)	0.867 (3.2%) [0.817, 0.932]
Race, African Americans vs. Asians and whites, effect on V _{ss}	0.839 (2.1%)	0.840 (3.8%) [0.787, 0.922]
CL IIV	22.9 (5%)	23.0 (10.9%) [20.6, 25.3]
CL/Q3 correlation	0.51 (9.4%)	0.524 (20.3%) [0.418, 0.578]
Q3 IIV	92.9 (4.8%)	94.5 (16.2%) [83.0, 112]
CL/V3 correlation	0.55 (8%)	0.569 (15.3%) [0.500, 0.612]
Q3/V3 correlation	0.9 (1.9%)	0.900 (12.1%) [0.882, 0.902]
V3 IIV	74.1 (5.2%)	73.9 (8.8%) [69.7, 79.9]
V1 IIV	61.7 (11.1%)	61.6 (9.5%) [55.2, 67.6]
V2 IIV	24.8 (6.4%)	24.9 (18.2%) [20.2, 29.5]
Residual error	20.7 (0.7%)	20.7 (5.7%) [19.5, 21.8]

CI, confidence interval; CL, clearance; IIV, interindividual variability; PopPK, population pharmacokinetic; R_{max}^x, maximum ratio; RSE, relative standard error; T₅₀, time to reach 50% of the maximum ratio; V1, volume of distribution; VSS, volume of distribution at steady state.

^aClearance and volume parameters are based on a 70 kg subject.

^bMaximum venous:arterial ratio, fixed to 1 based on the data.

^cT₅₀ is the venous:arterial ratio at 50% of R_{max}^x.

^dVenous:arterial ratio after the infusion ends.

applied to the final model. This sensitivity analysis resulted in substantial increases in residual error (20.7% to 26.6%) and in IIV parameters of CL, Q3, V3, and V2, suggesting that it was an inferior model (**Table S3**).

Second, exclusion of concentrations between 0.06 and < 1 minute following initiation of the infusion from 8 subjects in ONO-2745-03 was tested. Addition of these samples from these eight subjects led to substantial increases in residual variability (20.7% to 23%) and in IIV of CL, Q3, V3, and V2 (**Table S3**). Thus, the inclusion of the 0.06 and < 1-minute samples cannot be modeled appropriately because of the lack of simultaneous venous-arterial concentrations at those times.

Last, the impact of 12 outliers identified during model development were tested using the final model. Including the outliers led to substantial increases in residual variability (20.7–24.9%) and in IIVs of CL, Q3, V3, and V2 (**Table S3**).

Model performance

Primary PK parameters were all nearly identical between NONMEM estimates and bootstrap results (**Table 2**). VPCs showed good consistency between observed and predicted data (**Figure 4**). The final model NONMEM code is presented in **Figure S3**.

DISCUSSION

The PKs of remimazolam are well-characterized after up to 1-hour infusions in studies ONO-2745-02⁴ and CNS7056-017.¹⁴ In this case, V1 (0.07 L/kg) was similar to plasma volume, IIV on CL was low (13.6%), IIV on all other parameters was 20–28.5%, and residual error was 10.9%. When applying this model to the full dataset (which included data from 11 studies, 8 of which had bolus dosing), the IIV and residual error increased substantially as expected, but the CL was similar between models. Using this model allowed the characterization of variability in the PKs of remimazolam in procedural sedation, covariates that may affect that variability, and the estimation of PK parameters from individual subjects with sparse sampling to allow development of a PopPK/PD model (which will be reported in a separate paper).

After adding data from subjects receiving remimazolam as a bolus dose, V1 (if estimated) becomes > 50% lower than the pilot model estimate (estimated from subjects receiving an infusion of remimazolam) and IIV on V1 increased from 28.5% to > 120%. Thus, samples from bolus dose significantly biased V1 due to nonhomogenous mixing. In addition, the increase in IIV was partially due to the fact that samples were not collected during the first few minutes after bolus administration in the procedural sedation phase II and III studies, with some patients having extremely low predicted values of V1 and some having extremely high predicted values of V1. Therefore, V1 was fixed to the value from the pilot model and IIV was only estimated in those subjects that had early sampling. The final model ended up with an IIV on V1 that was 61.7%, which was lower than the value (87%) previously reported for remimazolam in general anesthesia,³ but still relatively high and consistent with some inability to estimate the true V1.

There was a tradeoff made between fixing V1 to a biologically plausible value vs. estimating V1, which is less than plasma volume and not biologically plausible (4.83 vs. 2.17 L, respectively). Although estimating V1 does result in better goodness-of-fit plots at higher concentrations that occur early after administration of remimazolam, the high concentrations where there are deviations between predicted and observed (when V1 is fixed) are also at doses that were > 500× higher (up to 0.3–0.5 mg/kg) than the clinical doses of remimazolam used in procedural sedation. In addition, using estimates of V1 for predictions could lead to predictions of initial concentrations that represent a local concentration (specific to the site of collection) prior to mixing and not a true C_{max} that can be interpreted. Last, the current PopPK model was developed with the intent to conduct a PK/PD model (i.e., to fix the predicted PK parameters from individual subjects to be used as input into the PopPK/

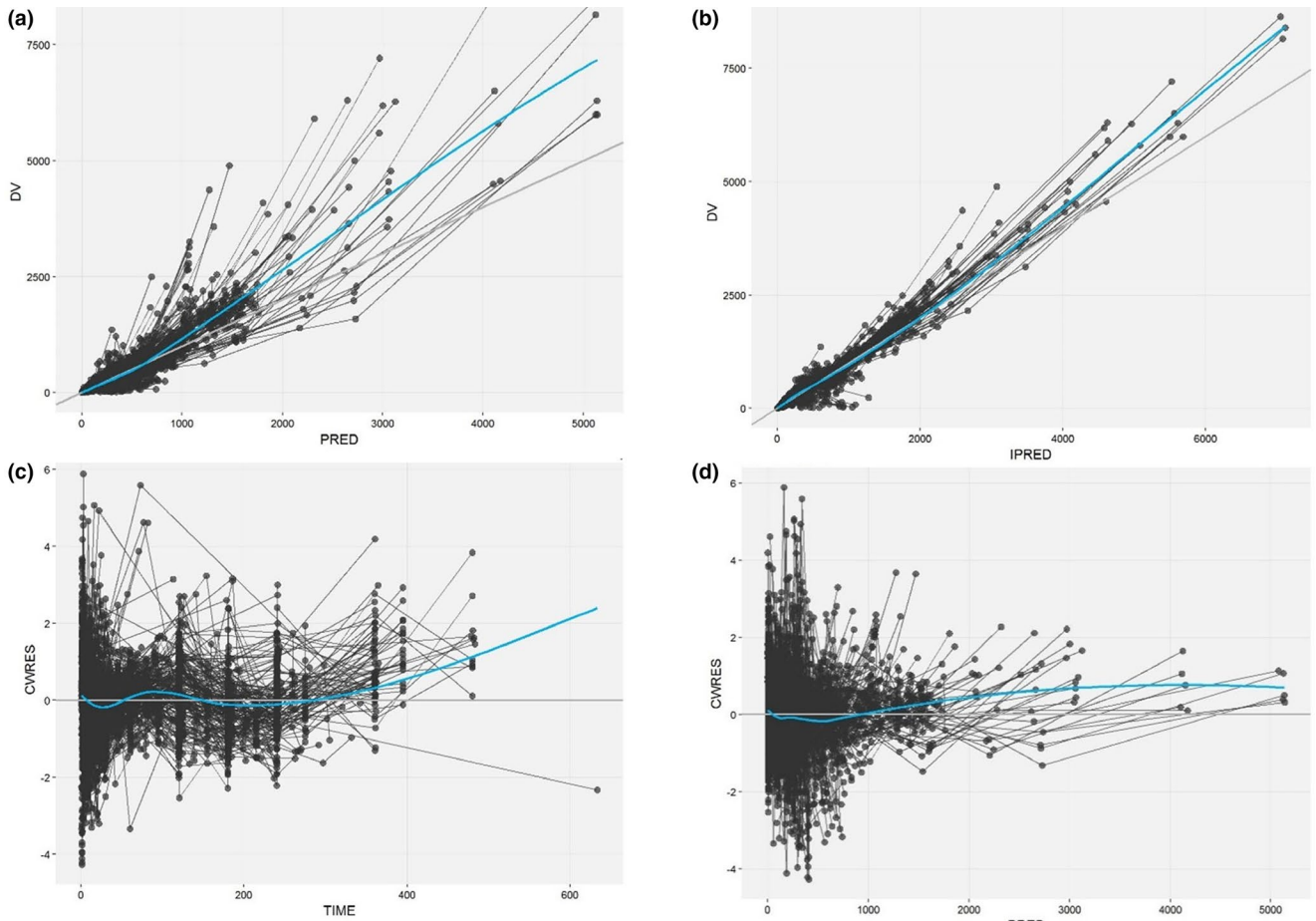


Figure 3 Goodness-of-fit plots for the final model. Observed (DV) vs. population predicted (PRED) (a), DV vs. individual predicted (IPRED) (b), conditional weighted residuals (CWRES) vs. time (c) and CWRES vs. PRED (d). Solid circles and lines represent observed data from individual subjects; the grey line represents the line of no trend (unity or $y = 0$ line); the blue line represents a local regression (LOESS) curve.

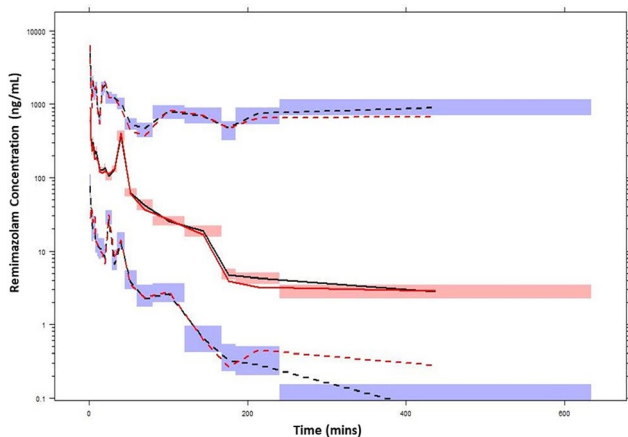


Figure 4 Visual predictive check of concentration (ng/mL) vs. time (minutes). Black lines indicate 2.5%, 50%, and 97.5% of observations; red lines indicate 2.5%, 50%, and 97.5% of simulations; shaded areas indicate 95% confidence intervals of 2.5%, 50%, and 97.5% of simulated data.

PD model). Therefore, all data input into the PopPK/PD model have the concentrations represented as biologically plausible (but not necessarily observed) arterial concentrations. Evaluation of the conditional weighted residuals vs. predicted plots suggests predicting concentrations in the range of doses for procedural sedation should not be affected.

In addition to issues on estimation of V_1 , the existence of profound arterio-venous concentration differences occurs, particularly early after dosing, given that there is not homogenous mixing in the blood stream.¹² There was also an unexpectedly high V_{toA} ratio at late time points (e.g., > 1 hour after initiation of treatment) that does not have a biologically plausible rationale. This difference between arterial vs. venous concentrations were attempted using a semi-physiologic model by Wiltshire,¹ but were limited by the low number of simultaneous arterial and venous concentrations early after administration and the assumptions about lung metabolism, which have since been shown to be invalid. For the PopPK model in general anesthesia,³

differences between arterial and venous concentrations were modeled by assuming different residual errors.

The present model applied a VtoA ratio to the residual error term and showed that the VtoA ratio was best described using an E_{\max} model during infusion with a constant ratio after infusion. The sensitivity analysis with one uniform E_{\max} model (i.e., no constant after end of infusion or bolus) resulted in an inferior model, where there were substantial increases in residual error (20.7–26.6%) and in IIV parameters of CL, Q3, V3, and V2, suggesting that it was an inferior model (even though it may be more biologically plausible). Assuming that there is a constant VtoA ratio after a short infusion or bolus is not ideal, misspecification is accounted in the residual error (which is relatively low at 20.7%). Importantly, use of this ratio allowed the combination of arterial and venous data without a physiologic model in the nonideal clinical setting where frequent simultaneous venous and arterial samples cannot be collected.

Importantly, the model characterized the variability in the PK of remimazolam. There is very low IIV in the remimazolam CL, with very small differences (< 16%) in CL related to sex and in CL and Vss related to race that are not clinically relevant. Thus, there are no dose adjustments needed for any covariates based on PK differences.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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