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Original Contribution

Population pharmacokinetic/pharmacodynamic modeling for remimazolam in the induction and maintenance of general anesthesia in healthy subjects and in surgical subjects

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ABSTRACT

Study objective: To evaluate factors affecting variability in response to remimazolam in general anesthesia.
Design: Plasma concentration-time data from 11 Phase 1–3 clinical trials were pooled for the population pharmacokinetic (popPK) analysis and concentration-bispectral index (BIS) data were pooled from 8 trials for popPK-PD analysis. A 3-compartment model with allometric exponents on clearance and volume described remimazolam concentrations over time. An effect compartment model with an inhibitory sigmoid Emax model was fit to the concentration-BIS data. Simulations were performed to assess sedation in general anesthesia and post-surgical sedation in healthy and sensitive populations.
Setting: General anesthesia and post-surgical sedation.
Patients: 689 subjects included in popPK and 604 subjects included in popPK-PD. Most subjects (> 85%) were ASA Class 1 or 2, with the remaining subjects being ASA Class 3.
Interventions: Serial plasma concentrations and BIS scores.
Measurements: Standard intra-operative monitoring.
Main Results: PopPK model included an effect of extracorporeal circulation, ASA class, and sex on PK and a time-dependent clearance (~30% lower at 24 h) that was not related to cumulative dose. Co-administered remifentanil had a synergistic decrease in BIS with remimazolam. Remimazolam IC50 increased with cumulative dose. Onset was faster in overweight subjects and slower in Asian subjects. If using a weight-based regimen, simulations showed that remimazolam 6 mg/kg/h until loss of consciousness followed by 1 mg/kg/h during general anesthesia and 0.25 mg/kg/h for post-surgical sedation for up to 24 h is optimal, regardless of ASA class or sensitivity of subjects.
Conclusions: If using a weight-based regimen, results illustrated an appropriate regimen of remimazolam for general anesthesia and post-surgical sedation in general and sensitive populations, although lower doses can be considered in elderly patients with a significant disease burden or in ASA Class 3 patients. The time-dependent change in clearance is not clinically relevant for up to 24 h.

1. Introduction

Remimazolam is an ultra-short acting benzodiazepine being investigated for induction and maintenance of general anesthesia in Japan and Europe and for procedural sedation in the United States and European. Five Phase 1 studies [1–4] and 4 Phase 2–3 studies were conducted for the general anesthesia indication [1,5–7].

Population pharmacokinetic (popPK) models were previously

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developed for remimazolam using data from up to 4 different studies, but given their limited scope, these models did not fully describe the factors affecting the variability in remimazolam PK and PK-PD in general anesthesia. Initially, remimazolam popPK was described using physiologic recirculation [4] assuming metabolism by carboxylesterase (CES) 1 to form an inactive metabolite CNS-7054 occurred in lungs, which was subsequently discredited because in vitro data showed that carboxylesterases are 41-fold higher in the liver than in the lung [8]. Additionally, previous population pharmacokinetic-pharmacodynamic (popPK-PD) models were developed with bispectral index (BIS) data in healthy subjects not receiving an opioid (data on file), limiting its use in general anesthesia where opioids are administered resulting in known synergistic potentiation of benzodiazepine-induced sedation [9].

Subsequently, data from 49 Japanese patients in the intensive care unit (ICU) showed that 7 subjects treated longer than 24 h had higher than expected concentrations of remimazolam for samples collected > 24 h after the initiation of remimazolam dosing [10].

These high concentrations were not related to remimazolam-induced CES-1 inhibition based on an in vitro bioreactor study [11]. Instead, they are more likely related to a time-related change in clearance (CL) in ICU patients that is unlikely to be dependent on remimazolam concentration or dose based on currently available data.

Present analyses use PK-PD data from all available studies to evaluate covariates affecting variability in the PK-PD of remimazolam, to describe the PK-PD of remimazolam in the presence and absence of remifentanil, to predict the level of sedation in patients receiving remimazolam regimens for up to 24 h in the surgical and post-surgical setting and to evaluate whether the high concentrations > 24 h after remimazolam initiation are related to cumulative dose or a time-related change in CL. The goal of the model was to develop a conservative worst-case scenario for the use of remimazolam in general anesthesia and post-surgical sedation for up to 24 h by including data from general anesthesia patients receiving remimazolam for < 10 h and ICU patients receiving remimazolam for up to 4.5 days.

2. Methods

2.1. Study design

Table A.1 summarizes the studies included in the popPK and popPK-PD analyses. Concentration-time data from 11 Phase 1–3 studies were pooled for popPK analysis and concentration-BIS data from 8 studies were pooled for popPK-PD analysis. Studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practice, across Japan, the US, and the EU. All studies were approved by Ethics Committees (Table A.1, along with principal investigators' names, clinical-trial-registry numbers and registration dates) and written informed consent was obtained prior to study procedures.

For general anesthesia studies (ONO-2745-03 [1], ONO-2745-05 [5], ONO-2745-06 [7], and CNS7056–010 [6]), remimazolam doses of 0.1 to 30 mg/kg/h were administered intravenously (IV) for induction; following loss of consciousness, subjects received a remimazolam 1 mg/kg/h (range: 0.5 to 3 mg/kg/h) for maintenance, and infusion rates were adjusted to maintain adequate sedation (BIS between 40 and 60). Remifentanil 0.01 to 1 μg/kg/min was administered for analgesia. For the ICU study (ONO-2745-04 [10]), remimazolam was administered for induction at 0.10, 0.25, or 0.50 mg/kg/h and for maintenance at doses up to 2.0 mg/kg/h.

One study (ONO-2745-02) in healthy subjects had an IV infusion of 1 mg/kg/h remimazolam for 1 h [1]. For 3 other healthy subject studies (ONO-2745-01 [1], ONO-2745-IVU007 [2], and CNS7056–001 [4]) and procedural sedation studies (CNS7056–002 [3] and CNS7056–004 [12]), IV bolus remimazolam doses of 0.1–0.5 mg/kg or 5–8 mg were administered with or without subsequent supplemental bolus doses.

Three studies collected only arterial samples [1,4], 5 studies collected only venous samples [1,3,5,7,12], and 3 studies had both arterial and venous sampling [1,4]. Simultaneous venous-arterial samples were collected within 5, 15, and 45 min of initiation of remimazolam dosing in one study [1] and between 1 and 4 h post-dose in all 3 studies.

In general anesthesia studies, sedation was assessed using the continuously-monitored BIS score and infusion rate was adjusted to maintain a BIS score between 40 and 60.

2.2. PopPK model

A PopPK model was developed as described in Appendix B. The development of the model is summarized in Table B.1. The base popPK model was a 3-compartment model with allometric exponents of 0.75 on CL terms and 1 on volume terms (to allow for predictions in pediatrics), with inter-individual variability (IIV) added as a full omega block on all parameters. Box-Cox transformation [13] of ETAs on CL and volume of the central compartment (V1) were used along with separate additive models describing residual error for venous and arterial concentrations on the log scale.

Covariates were added to the popPK model using four steps (Table A.2) with significant covariates added based on the change in objective function value (OFV; $p < .001$), theoretical rationale for effect, lack of bias of goodness-of-fit plots, precision of estimates, magnitude of effect, and reduction in residual variability.

The following prespecified covariates were evaluated:

- Age, presence of obesity, sex, American Society of Anesthesiologists (ASA) class, and extracorporeal circulation (EC) on CL and volume parameters;
- Cumulative dose and duration of remimazolam infusion on CL;
- Concomitant medications that have been shown to inhibit CES-1 in vitro, on CL (only if > 20 subjects):
  - o Simvastatin, lovastatin, rosiglitazone, glibenclamide, or pioglitazone;
  - o Fatty acids, nitredipine, felodepine, or diltiazem;
- Time-related effect on CL by three methods using:
  - o Available acute phase reactants (white blood cell count, platelet count, and albumin);
  - o A linear time-related change in CL; and
  - o A sigmoidal shaped time-related change in CL (Eq. (1)):

$$\boldsymbol{CL_{ij}} = \boldsymbol{BASECL_i} \times \left(1 - IMAX\_CL_i \times \frac{\boldsymbol{Time_{i,j}^{Hill}}}{\boldsymbol{IT50_i^{Hill}} + \boldsymbol{Time_{i,j}^{Hill}}}\right) \quad (1)$$

where $IMAX\_CL_i$ is the maximum percentage decrease of CL in the i^{th} subject, $IT50_i$ is the time at which 50% of the maximal decrease in CL is observed in the i^{th} subject, $Hill$ is the Hill coefficient describing the shape of the relationship, $BASECL_i$ is the baseline CL in the i^{th} subject, at time 0, $CL_{i,j}$ is the CL value in the i^{th} subject at j^{th} time, and $Time_{i,j}$ is the j^{th} time in the i^{th} subject.

2.3. PopPK-PD analysis

A PopPK-PD model was developed as described in Appendix C, with the steps in the model development described in Table C.2. Sequential PK-PD modeling was used where the population parameter estimates were fixed from the final popPK model and parameters for the popPK-PD model were estimated using the combined PK-PD dataset.

The remimazolam popPK-PD model utilized an effect compartment with an inhibitory sigmoid Emax model (Eq. (2)):

$$\boldsymbol{BIS_{ij}} = \boldsymbol{BLBIS_i} - IMAX\_BIS_i \times \frac{\boldsymbol{CE_{i,j}^{Hill}}}{\boldsymbol{IC50_i^{Hill}} + \boldsymbol{CE_{i,j}^{Hill}}} \quad (2)$$

where $IMAX\_BIS_i$ is the maximum drop in BIS in the i^{th} patient, $IC50_i$ is the concentration at which 50% of the maximal drop in BIS is observed

in the i^{th} patient, $BLBIS_i$ is the baseline BIS score in the i^{th} patient, $BIS_{i,j}$ is the j^{th} BIS score in the i^{th} subject, and $CE_{i,j}$ is the j^{th} concentration in the effect compartment in the i^{th} subject. Effect compartment concentrations were driven by a first-order rate constant (keo). IIV was added to BLBIS as additive and on IC50 and keo as proportional error models, and an additive residual error model was used.

The following pre-specified covariates were evaluated: synergistic effects of opioids on remimazolam's IC50 and IMAX_BIS; demographic (e.g., age, weight, sex, ASA class) effects on BLBIS, IC50, and keo; cumulative dose and duration of surgery on IC50; and acute inflammation (e.g., WBC count, platelet count, and albumin) on IC50 and on BLBIS.

Concomitant opioid dose or concentration was considered the most important covariate to evaluate on remimazolam's IC50 because of the well-established synergistic relationship between opioids and benzodiazepines [9,14,15]. Since remifentanil concentrations were not collected, the effect of remifentanil infusion rate on remimazolam's IC50 was tested (Fig. C. 1) [9].

2.4. Simulations

Simulations for 1000 virtual subjects were conducted using R v.3.3.1 to evaluate sedation levels achieved based on dosing regimens of remimazolam in general anesthesia and post-surgical sedation settings for typical subjects and for more sensitive general anesthesia populations (e.g., ASA class 3 subjects with a time-related change in CL) (Fig. 1).

Plasma concentrations and BIS scores were predicted using the established popPK-PD model over 24 h for the treatment scenarios listed in Table 1 and illustrated in Fig. 1. Scenarios #1a and #1b simulated standard remimazolam dosing regimen in general anesthesia in patient populations with ASA class 1/2 or 3, respectively. Scenarios #2 and #3 simulated remimazolam dosing regimens in a more sensitive population with ASA class 3, where the simulation of PK starts at 24 h to allow the subject to experience the time-related decreased CL prior to dosing with remimazolam; in this case, times started at 24 h for predictions of concentrations and times started at time 0 for predictions of BIS score. There was no change in dose for Scenario #2 and there was a reduced dose for Scenario #3. In all scenarios, remifentanil 0.2 μg/kg/min was administered during surgery (for 6 h) and 0.05 μg/kg/min was administered for post-surgical sedation (up to 24 h).

Simulated BIS scores were collected every 15 s during the first 3 min, every 15 min over 1 h, and then every 30 min for ≤6 h, and every 1 h for 6–24 h. Sedation levels over time were categorized as: "Adequate" (BIS ≥ 40 to ≤60); "Deeper than needed" (BIS > 20 to < 40); "Too deep" (BIS ≤ 20); and "Shallow" (BIS > 60) during general anesthesia and as "Adequate" (sedation = BIS score ≥ 60 and ≤ 80); "Deeper than needed" (sedation = BIS score > 20 and < 60); "Too deep" (sedation = BIS score ≤ 20); and "Shallow" (sedation = BIS score > 80) for post-surgical sedation (7 to 24 h post-dose).

3. Results

3.1. PopPK

3.1.1. Demographics

There were 4448 observations from 689 subjects included in the analysis. The demographics and other covariates are summarized in Table A.1. Subjects included 61% males and 39% females, who were mostly Asian, with 19% White, and 9% Black or other. Fifty percent of subjects were ASA class 1, while 36% of subjects were ASA class 2, and 14% were ASA class 3.

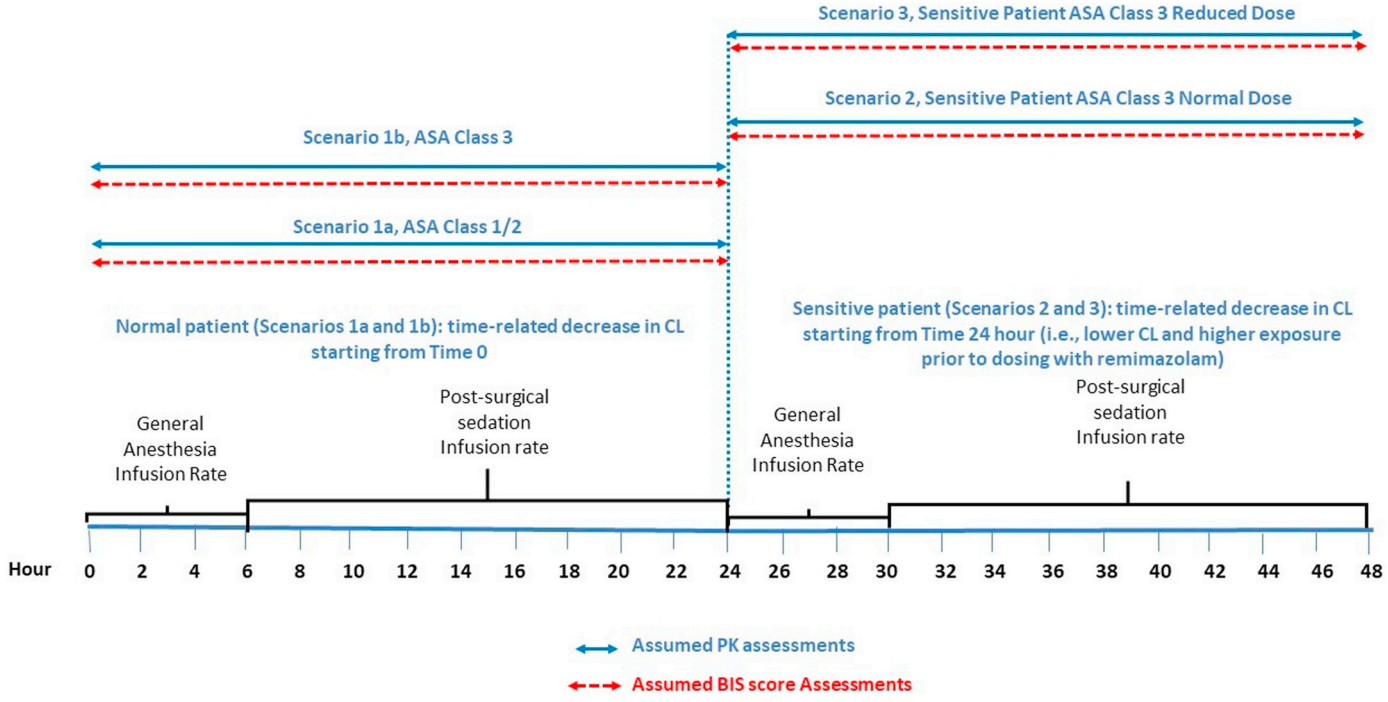


Fig. 1. Illustration of Methods Used in Simulations to Predict BIS Score After Remimazolam Administration in Normal Patients and in Sensitive Patients
Legend: Scenario 1a and 1b are healthy subjects with ASA Class 1/2 or 3, respectively, receiving the normal dose of remimazolam. The PopPK and PK-PD models were used to simulate concentrations and BIS scores over time, without any modifications. Scenario 2 and 3 are ASA Class 3 subjects representing a "sensitive" subject with time-dependent reduced CL prior to receiving a normal dose or a reduced dose of remimazolam. The PopPK model was used to simulated concentrations over time assuming that the subject would start out with higher concentrations (e.g., those that would be expected if he/she had received remimazolam for 24 h). These concentrations were then input into the PK-PD model to predict the BIS scores over time. Blue solid line represents the times of PK assessments that were assumed; Red dashed line represents the times of BIS scores that were assumed; black dashed line represents the shift in time to 24 h for PK assessments in sensitive subjects. The dashed blue line with arrow represents how the PK assessments are linked to the BIS score for sensitive subjects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Simulation conditions for remimazolam co-administered with remifentanil in general anesthesia.

Scenario[a,b]	ASA class	Start time (hr)	Induction dose (Time)	Operating room maintenance dose (Duration)	Post-surgical sedation dose (Duration)
#1a	1/2	0 h	6 mg/kg/h (3 min)	1 mg/kg/h (5 h, 57 min)	0.25 mg/kg/h (18 h)
#1b	3	0 h	6 mg/kg/h (3 min)	1 mg/kg/h (5 h, 57 min)	0.25 mg/kg/h (18 h)
#2	3	PK: 24 h PD: 0 h	6 mg/kg/h (3 min)	1 mg/kg/h (5 h, 57 min)	0.25 mg/kg/h (18 h)
#3	3	PK: 24 h PD: 0 h	6 mg/kg/h (3 min)	0.5 mg/kg/h (5 h, 57 min)	0.125 mg/kg/h (18 h)

ASA = American Society of Anesthesiologists.
[a] Simulation settings also include the following: 1:1 ratio of male:female; 3:1 ratio of Asian to Non-Asian subjects; weight and BMI were simulated assuming bivariate normal distribution with a correlation, with parameters estimated from observed popPK/PD NONMEM dataset;
[b] Co-administered remifentanil infusion rate is at 0.2 μg/kg/min while in the operation room (0–6 h), and at 0.05 μg/kg/min during post-surgical sedation.

3.1.2. Model development

There were multiple unsuccessful attempts to fit a combined arterial-venous model which resulted in non-physiologically plausible parameter estimates. The difficulty to model the data was due to the small number of simultaneous samples ($n = 1$) during the first 5 min after drug administration, when differences between arterial and venous concentrations are most prominent. Ultimately, an empiric 3-compartment base model was used to meet the objectives of the present analysis, with both arterial and venous samples in the same compartment but with separate residual variabilities estimated for each matrix.

The effect of age, sex, ASA class, and EC on CL and V1 were tested (Steps 4–7 of Table B.1). ASA class 3 affected V1 and V2; EC affected CL and V1; and sex affected CL. There was no effect of age on CL or V1. After testing these standard covariate effects on CL and V1, a cumulative dose or time-related change in CL were evaluated to account for the elevated concentrations after 24 h of administration in 7 ICU subjects. There was no apparent relationship between conditional weighted residuals (CWRES) and cumulative dose. The relationship was tested statistically using a linear model with all data and the data available prior to 24 h only. For both of these models, there was no statistically significant relationship and the slope was miniscule. A time-related change in CL was then tested. A linear effect utilizing data from erythromycin CL in surgical subjects [16] was attempted, but overcorrected for the effect of time on CL, where observations show that a plateau should be reached (Supplementary Appendix B, Fig. B.2). Therefore, a sigmoid Emax model was chosen to describe the decrease in CL over time (Step 9 of Table B.1).

3.1.3. Final model

The final popPK model was a 3-compartment model with allometric exponents of 0.75 on CL terms and 1 on volume terms, with an effect of ASA class 3 on V1 and V2, an effect of sex on CL, an effect of EC on CL and V1, and a time-related change in CL described using an inhibitory sigmoid Emax model. The parameter estimates are given in Table 2 with goodness-of-fit plots presented in Supplementary Appendix B, Fig. B.3 and B.4. All parameters were estimated with good precision. The IIV was low for CL, intermediate for V2 and V3, and high for Q2, Q3, and V1. V1 was 56% lower and V2 was 22% higher in ASA class 3 subjects than in ASA class 1 or 2 subjects. When subjects were on EC, V1 increased by 507% and CL increased by 35%. CL is 11% higher in females than in males. The time to reach 50% of CL (IT50) occurred around 31 h, but with high IIV, as expected based on the small number of subjects with late concentrations.

The model was used to predict the change in CL over time, which showed that remimazolam CL is 25% lower at ~22 h in males and in females.

3.1.4. Model performance

The primary PK parameters were all nearly identical between NONMEM estimates and bootstrap results (Table 2). VPCs stratified by study showed good consistency between observed and predicted data (Supplementary Appendix B, Fig. B.5).

Table 2
NONMEM estimates and bootstrap estimates for the final popPK model.

Description	NONMEM Estimate (%RSE)	Bootstrap Median (95% CI)
CL (L/h/70 kg)	61.6 (1.56%)	61.6 (59.3,64.4)
V1 (L/70 kg)	2.92 (6.27%)	2.95 (2.58,3.52)
Q2 (L/h/70 kg)	22.9 (5.90%)	24 (19.6,31.3)
V2 (L/70 kg)	19.1 (3.01%)	19.5 (18.0,21.9)
Q3 (L/h/70 kg)	69.6 (4.54%)	69.6 (61.9,80.3)
V3 (L/70 kg)	9.81 (4.49%)	9.59 (8.54,10.8)
Effect of ASA class 3 on V1 (%)	−0.56 (12.8%)	−0.52 (−0.98,0.24)
Effect of ASA class 3 on V2 (%)	0.22 (48.9%)	0.23 (−0.17,0.84)
Effect of EC on CL (%)	0.35 (8.07%)	0.29 (−1,0.51)
Effect of EC on V1 (%)	5.07 (18.3%)	5.41 (−1,17)
Effect of Female on CL (%)	0.11 (18.1%)	0.11 (0.08,0.17)
Time-dependent change in CL - IMAX_CL	0.94 (0.77%)	0.95 (0.82,0.98)
Time-dependent change in CL - IT50 (hours)	31.5 (16.2%)	37.0 (21.5,67.4)
Time-dependent change in CL - Hill coefficient	2.75 (6.69%)	2.81 (1.75,8.43)
Box-Cox transformation parameter for CL IIV	−0.53 (16.6%)	−0.32 (−1.12,0)
Box-Cox transformation parameter for V IIV	0.59 (11.8%)	0.58 (0.37,0.85)
IIV of CL (%)	24.5 (0.83%)	24 (21,27)
IIV of V1 (%)	87.0 (5.50%)	88 (75,100)
IIV of Q2 (%)	74.0 (4.9%)	66 (47,85)
IIV of V2 (%)	40.0 (2.49%)	40 (33,47)
IIV of Q3 (%)	70.0 (3.10%)	65 (48,87)
IIV of V3 (%)	45.0 (2.31%)	45 (39,53)
IIV of IT50 (%)	82.0 (8.70%)	98 (37,127)
Unexplained Error (Venous) (%)	33.0 (0.71%)	33 (28,37)
Unexplained Error (Arterial) (%)	17.0 (0.61%)	16 (11,19)

ASA = American Society of Anesthesiologists; CI = confidence interval; CL = clearance; EC = extracorporeal circulation; IIV = inter-individual variability; IMAX_CL = maximum percentage decrease of CL; IT50 = time at which 50% of the maximal decrease in CL is observed; NONMEM = nonlinear mixed effects modeling; RSE = relative standard error; V1 = volume of the central compartment.

3.2. PopPK-PD

3.2.1. Demographics

The final dataset included 24,612 observations from 604 subjects. Demographics and other covariates are summarized in Table A.1. Subjects included 59% males and 41% females, who were mostly Asian, with 8% White, and 10% Black or other; most subjects had a normal BMI, but 29% had a BMI between 25 and 30 kg/m^2 and 2% had a BMI > 30 kg/m^2. All subjects from general anesthesia studies received

remifentanil. Subjects from healthy volunteer studies did not receive any opioids.

3.2.2. Model development

The most important covariate evaluated was co-administered remifentanil, where potentiation of sedation was apparent (i.e., there is a more pronounced remimazolam-related drop in BIS when remifentanil is present).

During model development, IMAX_BIS could not be estimated in the presence or absence of opioids since the protocols were designed to keep BIS between 40 and 60 and the model would estimate an IMAX_BIS of 40 based on that data (Steps 2–3 of Table C.2). Since the goal of the analysis was to have a conservative PK-PD model where simulations would allow a BIS score to be < 20 (an indication of too deep sedation) if concentrations were elevated, a model that estimated Emax of 40 would not meet this goal since there would be no increased sedation with increasing doses of remimazolam. Therefore, the IMAX_BIS was fixed to 73.3, an IMAX_BIS value reported for an early healthy volunteer study (ONO-2745-02) with 1 mg/kg/h remimazolam infusion for 1 h where BIS scores were < 40 (data on file); using this value allowed the BIS score to theoretically drop below 20. Sensitivity analyses were conducted to evaluate the effects of the IMAX_BIS (fixed at 50, 70, or 90) on parameter estimates and showed that fixing IMAX_BIS to 73.3 was appropriate (Step 5 of Table C.2).

There was a strong relationship between CWRES and cumulative dose of remimazolam, which was similar between CWRES and time (Supplementary Appendix C, Fig. C.3.a). When the effect of cumulative dose on remimazolam IC50 was incorporated into the model, these relationships both disappeared (Supplementary Appendix C, Fig. C.3.b). There were no effects of age or ASA class on IC50. Asian race was associated with a slower keo and BMI > 25 m^2 was associated with a faster keo.

3.2.3. Final popPK-PD model

The final popPK-PD model had an effect compartment with an inhibitory sigmoid Emax model, where the largest effect was a synergistic effect of remifentanil on remimazolam's PD (Fig. 2). There was an effect of cumulative dose on IC50, and of BMI > 25 kg/m^2 and Asian race on keo. Parameters are given in Table 3 with goodness-of-fit plots given in Supplementary Appendix C, Figs. C.4 and C.5. The model describes the data well, with the only bias illustrated at the lower BIS scores, where the population predictions are lower than observed, as expected given that IMAX_BIS was fixed to 73.3. All parameters were estimated with adequate precision. The IIV on baseline BIS score is low relative to the baseline BIS score, the IIV on keo is large relative to the estimate of keo, and the IIV on the IC50 of remimazolam is moderate.

The keo was 17% faster in obese and overweight subjects than in those with a BMI ≤25 kg/m^2 and 48% slower in Asians than in non-Asians. IC50 increased by 31.2% for every cumulative 1 mg/kg remimazolam dose.

3.2.4. Model performance

PD parameters were all nearly identical between NONMEM estimates and bootstrap results, except for the betaEmax, (Supplementary Appendix C, Fig. C.1.) which had wide confidence intervals from the bootstrap method (Table 3). The agreement between predicted and observed BIS scores over time was good to excellent as illustrated in the representative VPC plot stratified by study in Supplementary Appendix C, Fig. C.6.

3.3. Simulations

Simulated probabilities of subjects achieving sedation benchmarks over time during general anesthesia and post-surgical sedation are summarized in Fig. 3. During general anesthesia, most simulated subjects in Scenarios #1a and #1b (ASA 1/2 vs 3) achieved "adequate" sedation and a maximum of ~25% achieved "deeper than needed" sedation between 0 and 2 h of infusion. Scenario #2 (population with presumed time-related reduced CL and dosed with standard remimazolam) resulted in ~50% achieving "adequate" sedation and a maximum of ~50% of subjects reaching "deeper than needed sedation" between 0 and 6 h of infusion.

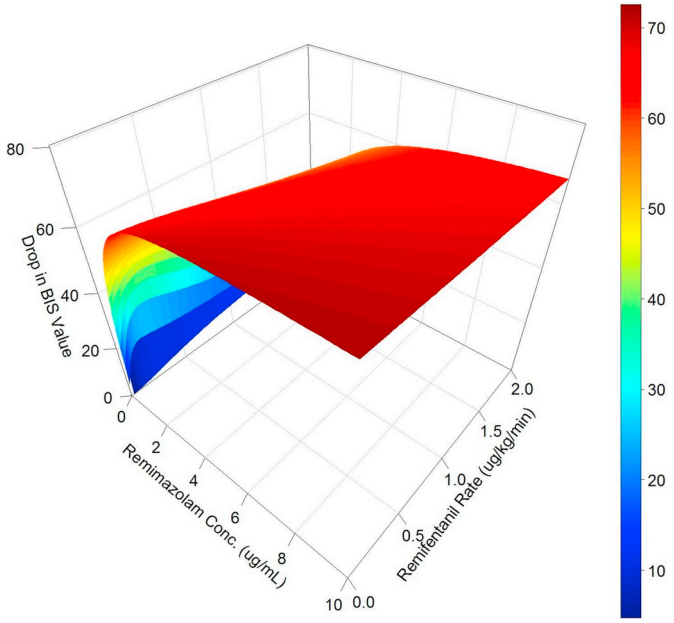


Fig. 2. Illustration of the Synergistic Effect of Remifentanil on Remimazolam. Legend: The colors change from red (which represents the largest drop in BIS score) to blue (which represents the smallest drop in BIS score). The drop in BIS gets larger with increasing remimazolam concentrations in the absence of remifentanil, but this effect becomes more and more pronounced as the remifentnyl infusion rate increases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Scenario #3 (population with time-related reduced CL and dosed with a lower dose of remimazolam) resulted in ~60% achieving "adequate" sedation and a maximum of ~25% of subjects reaching "deeper than needed" sedation between 0 and 6 h of infusion, but the proportion of subjects with "shallow" sedation increased (from ~5% to ~15%) compared to Scenario #2. For all simulation scenarios during general anesthesia, a negligible number of patients reached BIS ≤20 (< 1%).

During post-surgical sedation (> 6 h), most simulated subjects in Scenario #1a and #1b (ASA 1/2 vs 3; > 90%) achieved "adequate" to "shallow" sedation, while < 10% achieved "deeper than needed" sedation. For Scenario #2 (population with time-related reduced CL and dosed with standard remimazolam), ~70% of subjects achieved "adequate" or "shallow" sedation, while ~30% had "deeper than needed" sedation. For Scenario #3 (population with time-related reduced CL and dosed with a lower dose of remimazolam), the proportion of subjects with "shallow" sedation increased (from ~30% to ~35%) and the proportion with "deeper than needed" sedation decreased (from ~30% to ~25%) when compared to Scenario #2. For all simulation scenarios during post-surgical operation, a negligible proportion of subjects (< 1%) reached BIS ≤20.

4. Discussion

"Fit-for-purpose" models were developed to describe the popPK-PD of remimazolam in surgical subjects and to predict sedation in subjects receiving remimazolam (with remifentanil) for up to 24 h in surgical and post-surgical settings. Data from ICU patients were included to produce a conservative worst-case scenario in general anesthesia, given that there were no general anesthesia subjects receiving remimazolam

Table 3
NONMEM estimates and bootstrap estimates for the final popPK-PD model.

Description	NONMEM Estimate (%RSE)	Bootstrap Median (95% CI)
keo (rate constant for effect compartment) (1/h)	8.08 (5.0%)	8.30 (6.78,10.4)
Baseline BIS Score	95.2 (0.4%)	95.1 (93.9, 96.0)
IC50 of remimazolam (μg/mL)	0.52 (2.4%)	0.53 (0.484, 0.603)
IC50 of remifentanil (μg/kg/min)	0.758 (2.7%)	0.774 (0.587, 0.980)
betaU, for synergistic effect on IC50	2.05 (2.5%)	2.11 (1.03, 2.53)
Hill coefficient	1.58 (0.7%)	1.57 (1.36, 1.67)
IMAX_BIS for remimazolam	73.3 FIX	73.3 FIX
IMAX_BIS for remifentanil	12.7 (7.5%)	12.3 (0.554, 19.3)
betaEmax, for synergistic effect on IMAX_BIS	11.3 (21.6%)	8.13 (0.634, 75.9)
Box-Cox transformation parameter for keo IIV	0.374 (9.7%)	0.363 (0.266, 0.494)
Effect of cumulative dose on IC50 of remimazolam	0.312 (1.6%)	0.304 (0.246, 0.373)
Coefficient for effect of BMI > 25 on keo	1.17 (3.9%)	1.16 (1.02, 1.34)
Coefficient for effect of Asian Race on keo	0.520 (4.8%)	0.522 (0.413, 0.660)
IIV of IC50 of remimazolam (%)	42.5 (6.0%)	45.3 (39.4, 51.1)
IIV of keo (±)	3.1 (13.7%)	3.08 (2.55, 3.78)
IIV of Baseline BIS score (±)	5.0 (7.6%)	5.01 (3.24, 5.79)
Unexplained Error on BIS Score (±)	6.7 (0.2%)	6.67 (6.45, 6.89)

BIS = bispectral index; BMI = body mass index; CI = confidence interval; IC50 = concentration (remimazolam) or rate of infusion (remifentanil) at which 50% of the maximal drop in BIS is observed; IIV = inter-individual variability; IMAX_BIS = maximum drop in BIS; keo = first-order rate constant; RSE = relative standard error.

for > 10 h, yet subjects may receive up to 24 h of remimazolam in post-surgical sedation. Very few covariates explained variability in remimazolam's PK, yet there was change in CL that was not related to cumulative remimazolam dose, but was related to time. While changes in CL are significant for remimazolam and are consistent with reports in ICU subjects receiving midazolam for 4 days (CL decreased to 1/8th of normal) [17], the remimazolam CL is only 25% lower at ~22 h after initiation of remimazolam dosing. BIS scores were most affected by the synergistic effect of remifentanil on remimazolam's IC50, and cumulative dose, which is consistent with acute tolerance development, as reported for benzodiazepines [18,19]. Simulations showed that the proportion of subjects achieving sedation benchmarks throughout general anesthesia and post-surgical sedation for < 24 h did not differ by ASA class; and more sensitive subjects may experience “deeper than needed” sedation, but the proportion of patients that are “too deep” (BIS < 20) is negligible. These simulations confirmed the appropriate weight-based dose of remimazolam and demonstrated that high plasma concentrations in ICU patients won't lead to excessive sedation in surgical patients treated for ≤24 h. Even more important is that in clinical practice the level of anesthesia would be titrated to effect while the current simulation needed to assume a constant maintenance infusion rate.

The covariates explaining variability in remimazolam's PK included sex, ASA class, and EC. There was no effect of age on the PK of remimazolam. Remimazolam CL was 11% higher in females than in males, consistent with a 3–5 min faster time to extubation in females [20]. V1 was 56% lower and V2 was 22% higher in ASA class 3 subjects than in ASA class 1–2 subjects, which may be because some medically complex patients may have changes in heart rate and cardiac output. EC increased V1 by 507% (an expected finding given the large volume of fluids administered) and may lead to the need for additional bolus doses. The 35% decrease in CL with EC is not clinically relevant.

There were no effects of telmisartan or simvastatin (drugs that inhibit CES-1 in vitro [21,22]) or dexamethasone (inhibition of CES-1 based on clinical study [23]) on remimazolam CL. The time-related change in CL is best described by an IT50 of 31.5 h after remimazolam initiation, but with high IIV based on the small subject numbers with late concentrations. The decrease in CL was steeper with remimazolam than with erythromycin, a CYP3A4 inhibitor and P-gp substrate, after surgery [16]. Importantly, the popPK model is a conservative “fit-for-purpose” model to evaluate the *worst-case* if there were changes in CL over the first 24 h in general anesthesia.

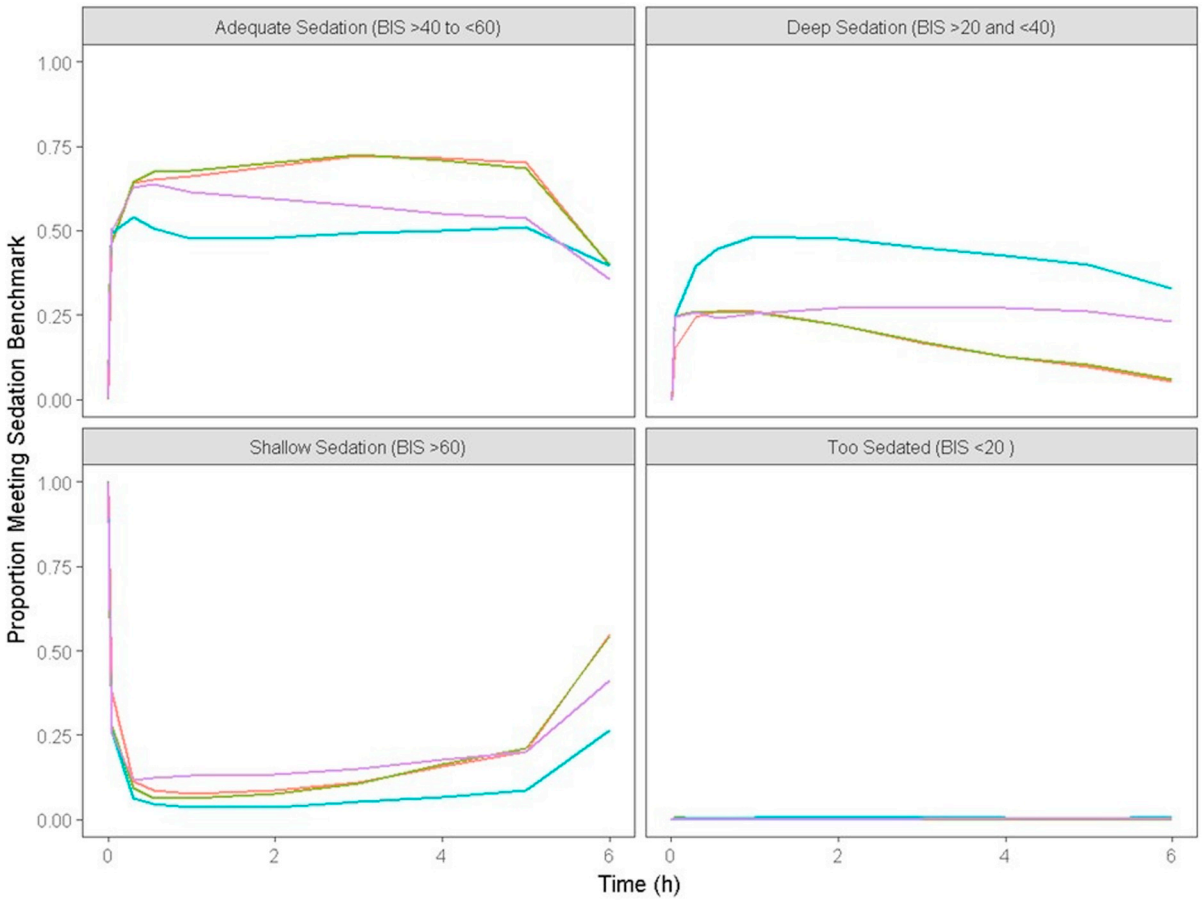
The popPK-PD model identified that keo is slightly faster in overweight and obese subjects than in subjects with BMIs < 25 kg/m^2. While there is not a direct correlation between BIS score and loss of consciousness, the findings from the present PopPK-PD model using BIS score were consistent with the 20-s faster time to loss of consciousness (using more standard criteria) in obese subjects [20]. The keo was 50% lower in Asians, suggesting that the onset is slower in Asians than in non-Asians. There was no effect of age on IC50. The most clinically relevant covariate was the effect of remifentanil on remimazolam's IC50, which was consistent with the well-known synergistic effect between benzodiazepines and opioids [14,15]. The present data had tightly-controlled remifentanil infusion rates and represents situations for the majority of surgeries, but not for surgeries where painful stimuli may be more severe.

As for other benzodiazepines [18,19], acute tolerance development (i.e., decreasing sedation with time in the presence of constant concentrations resulting in an increasing IC50 with increasing time) with remimazolam was apparent; however, the magnitude of tolerance development based on changes in IC50 was not consistent with clinical data where the infusion rate remained constant at 1 mg/kg/h and did not increase over time (data on file). Ignoring tolerance development would result in a more conservative, yet biased model (Supplementary Appendix C, Fig. C.3), that is not consistent with known effects of benzodiazepines. Therefore, the effects of cumulative dose on IC50 were included ensuring that any changes in BIS scores over time would be described appropriately in this “fit for purpose” model.

The popPK model is limited by the inability to develop a physiologic model describing arterial-venous differences because of the lack of early simultaneous arterial-venous samples (n = 1 subject at 5 min). The arterial-venous differences were handled as different residual errors, which were substantially lower for arterial than for venous blood.

The main limitation of the popPK-PD model was the inability to estimate the true IMAX_BIS because the studies were designed to maintain BIS scores between 40 and 60 with infusion rate adjustments based on sedation and the protocol guidance was well followed. If IMAX_BIS was estimated (~40) during model development, BIS scores would generally be no lower than ~45 (Baseline BIS-IMAX_BIS-2xSD of residual error), even with 10-fold higher concentrations. Fixing IMAX_BIS to 73.3, the estimate of IMAX_BIS from an earlier healthy subject study of remimazolam (data on file), more conservatively allowed BIS to theoretically drop to 12, resulting in “too deep” sedation (BIS < 20). This value was chosen for the purpose of investigation of

a



b

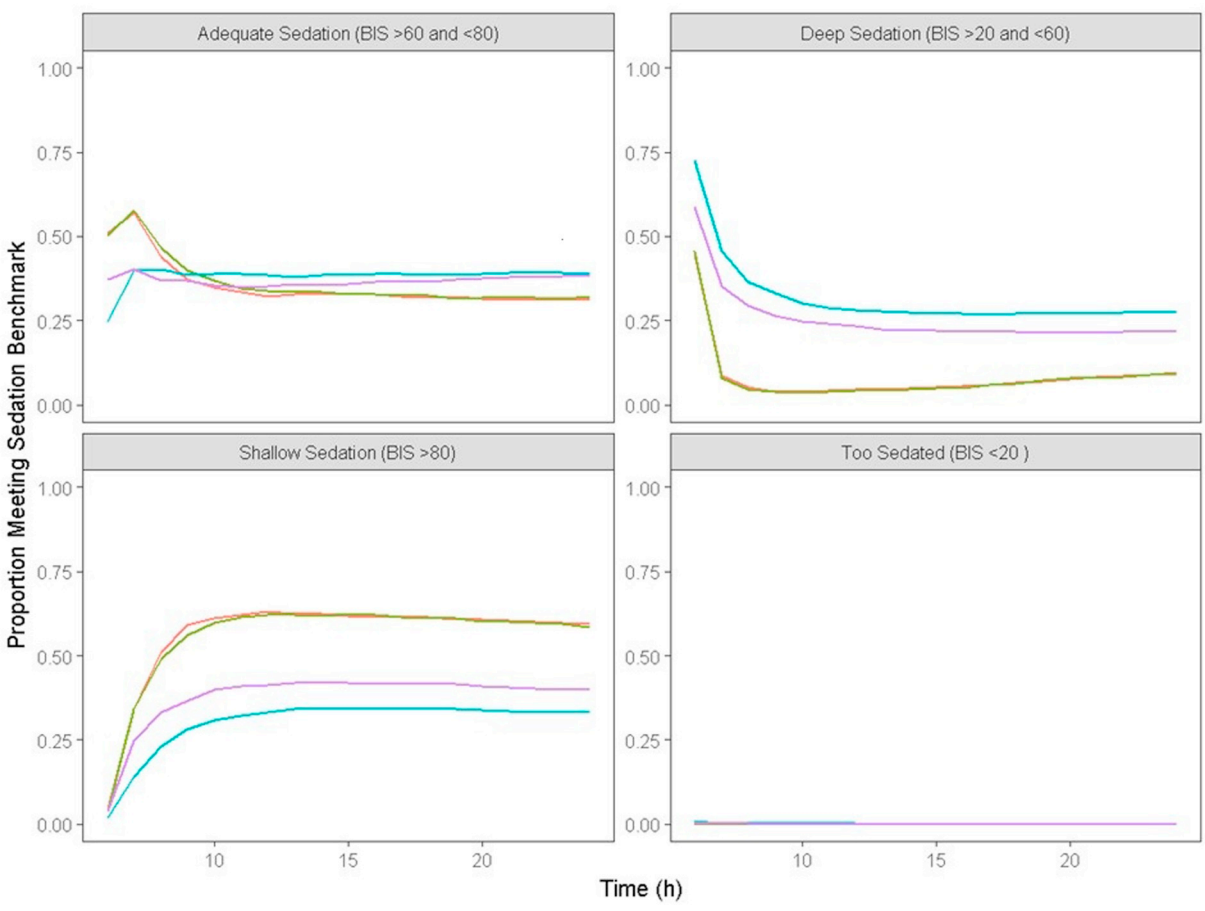


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Fig. 3. Simulated proportion of patients achieving sedation benchmarks in general anesthesia (panel a) and during post-surgical sedation (panel b) for different dosing scenarios.
Legend: For panel a of general anesthesia (from 0.5 to 6 h post-dose). "Adequate" sedation represents a BIS score ≥ 40 and ≤ 60; "Deeper than needed" sedation represents a BIS score > 20 and < 40; "Too deep" sedation represents a BIS score ≤ 20; "Shallow" Sedation represents aBIS score > 60.
For panel b of post-surgical sedation (> 6 to 24 h post-dose). "Adequate" sedation represents a BIS score ≥ 60 and ≤ 80; Deeper than needed" sedation represents a BIS score > 20 and < 60; "Too deep" sedation represents a BIS score ≤ 20; "Shallow" Sedation represents a BIS score > 80.
Red line = Scenario 1a (ASA 1 and 2); Green line = Scenario 1b (ASA 3); Blue line = Scenario 2 (ASA 3; population with time-dependent reduced CL and dosed with standard remimazolam); Purple line = Scenario 3 (ASA 3, population with time-dependent reduced CL and dosed with reduced remimazolam). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the effects of the high remimazolam concentration in a "fit for purpose" worst-case scenario.

A limitation of both the popPK and the PopPK-PD analyses is that the majority of patients (~72%) of subjects were Asian, with ~19% White/Caucasians and ~ 9% Black/African Americans. No one covariate explained variability in the PK of remimazolam and over 100 subjects were White/Caucasians suggests that the findings are relevant to Asians and White/Caucasians. There were ~ 60 Black/African Americans, which is a reasonable number of subjects, but the lack of any changes in the PK of remimazolam in Black/African Americans cannot be ruled out.

The objectives of the simulations were to describe sedation in the surgical and post-surgical setting up to 24 h, not the ICU setting. The simulations accounted for sensitive subjects assuming time-related reduced CL and ASA class 3 as outlined in Fig. 1. For sensitive subjects, concentrations started at 24 h to allow the subject to experience the time-related decreased CL prior to dosing with remimazolam; in this case (Simulations Scenarios #2 and #3), times started at time 0 for predictions of BIS score. A standard dose was given for Scenario #2 and reduced doses were given in Scenario #3. These simulations show that 6 mg/kg/h until loss of consciousness followed by 1 mg/kg/h are appropriate for induction and maintenance of general anesthesia and 0.25 mg/kg/h is appropriate for post-surgical sedation (when less sedation is required) for up to 24 h to maintain subjects in "adequate" to "deeper than needed" sedation in both settings, regardless of whether they are ASA class 1/2 or ASA class 3, with or without time-related reduced CL. However, lower remimazolam doses can be considered for some medically complex, elderly, or ASA class 3 patients, as for other anesthetics.

One limitation of the simulations is the fact that they use BIS as the endpoint and may not account for the appearance of Suppression Ratio, quantifying the percentage of suppression during burst suppression pattern. The suppression ratio was not recorded as part of these studies, so the effect of this on the simulations is unknown.

Thus, the "fit-for-purpose" popPK-PD model of remimazolam was established to describe the PK-PD of remimazolam along with co-administered remifentanil and was used for evaluating dosing regimens in general anesthesia and post-surgical sedation for up to 24 h. While this analysis showed the adequacy of weight-dependent dosing, a currently ongoing phase III trial for general anesthesia in Europe (NCT03661489) explores the possibility of weight-independent dosing.

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Declaration of competing interest

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