ANESTHESIOLOGY

Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male Volunteers

Part I. Pharmacokinetics and Clinical Pharmacodynamics

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Remimazolam is rapidly metabolized to an inactive metabolite by tissue esterases
- When administered as a 1-min infusion, it produced rapid onset and dose-dependent sedation at doses of 0.05 mg/kg and higher
- Its pharmacokinetics when administered as a 1-min infusion was characterized by relatively high elimination clearance, a small steady-state volume of distribution, and a short elimination half-life

What This Article Tells Us That Is New

- Twenty adult male volunteers receiving remimazolam as continuous intravenous infusion at 5 mg/min for 5 min, then 3 mg/min for 15 min, and 1 mg/min for 15 min lost consciousness 5 ± 1 (mean ± SD) min after starting the infusion and were fully alert 19 ± 7 min after stopping it
- Remizolam produced moderate hemodynamic effects and no clinically significant effect on cardiac repolarization
- The disposition of remimazolam was characterized by a multicompartmental pharmacokinetic model with small distribution volumes and a high elimination clearance with small interindividual variability; its context-sensitive half time after a 4-h infusion was predicted to be 7 ± 2 min

ABSTRACT

Background: Remimazolam (CNS 7056) is a new ultra–short-acting benzodiazepine for intravenous sedation and anesthesia. Its pharmacokinetics and pharmacodynamics have been reported for bolus administration. This study aimed to investigate the pharmacokinetics and pharmacodynamics of remimazolam after continuous infusion.

Methods: Twenty healthy male volunteers (20 to 38 yr, 64 to 99 kg) received remimazolam as continuous intravenous infusion of 5 mg/min for 5 min, 3 mg/min for the next 15 min, and 1 mg/min for further 15 min. Pharmacokinetics of remimazolam and its metabolite were determined from arterial plasma concentrations. Sedation was assessed using the Modified Observer's Assessment of Alertness and Sedation scale. Pharmacokinetic-pharmacodynamic modeling was performed by population analysis. Hemodynamics and the electrocardiogram were also investigated.

Results: Pharmacokinetics was best described by a three-compartment model for remimazolam and a two-compartment model with transit compartment for the metabolite. Remimazolam showed a high clearance (1.15 ± 0.12 l/min, mean ± SD), a small steady-state volume of distribution (35.4 ± 4.2 l) and a short terminal half-life (70 ± 10 min). The simulated context-sensitive halftime after an infusion of 4 h was 6.8 ± 2.4 min. Loss of consciousness was observed 5 ± 1 min after start, and full alertness was regained 19 ± 7 min after stop of infusion. Pharmacodynamics of Modified Observer's Assessment of Alertness and Sedation score was best described by a sigmoid probability model with effect site compartment. The half-maximum effect site concentration for a Modified Observer's Assessment of Alertness and Sedation score less than or equal to 1 was 695 ± 239 ng/ml. The equilibration half-time between central and effect compartment was 2.7 ± 0.6 min. Mean arterial blood pressure decreased by 24 ± 6%, and heart rate increased by 28 ± 15%. Spontaneous breathing was maintained throughout the study. There was no significant prolongation of the QT interval of the electrocardiogram observed.

Conclusions: Remimazolam was characterized by a pharmacokinetic–pharmacodynamic profile with fast onset, fast recovery, and moderate hemodynamic side effects.

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Remimazolam (CNS 7056, PAION UK Ltd., United Kingdom) is a new benzodiazepine for intravenous use that is being developed as an ultra–short-acting agent for procedural sedation, and for induction and maintenance of general anesthesia.[1–5] Remimazolam is an ester-based drug that is rapidly hydrolyzed in the body by tissue carboxylesterases to an inactive metabolite, CNS 7054.[6] A phase I study in volunteers, in which remimazolam was administered as intravenous bolus injection, revealed a relatively

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high clearance, a small steady-state volume of distribution, and a short elimination half-life.[7] Remimazolam produced deep sedation with fast onset and recovery. The pharmacokinetic and pharmacodynamic data of this previous phase I study were used to develop a recirculatory pharmacokinetic model and pharmacodynamic models relating the estimated remimazolam effect site concentrations to the Bispectral Index (BIS) of the electroencephalogram (EEG) and to the Modified Observer's Assessment of Alertness and Sedation score as clinical measures of sedation.[8] The pharmacokinetic–pharmacodynamic models obtained from this study had, however, some limitations. First, remimazolam was administered as a bolus injection over 1 min. However, for other drugs it was observed that pharmacokinetics models based on data from bolus administrations may be less appropriate compared with an administration of the drug as a continuous infusion.[9] Further, the pharmacokinetic analysis was based on a combination of arterial and venous samples, whereas arterial measurements are generally preferable for pharmacokinetic–pharmacodynamic modeling.[10] Although the published recirculatory model is of great interest from a scientific point of view, a three-compartment mammillary model would be necessary for model-based dosing regimens like target-controlled infusion. Lastly, the BIS index was originally developed for propofol, and it has been reported that the correlation between depth of sedation and the BIS index was weaker for the benzodiazepine agonist midazolam.[11]

The present study was therefore conducted in order to develop linear mammillary compartment models of remimazolam and its metabolite CNS 7054 based on arterial plasma concentrations after longer lasting continuous intravenous infusion. For the purpose of pharmacodynamic modeling, the sedative effect was assessed by the Modified Observer's Assessment of Alertness and Sedation scores and by the Narcotrend index of the EEG. The spontaneous EEG was further recorded continuously from multiple electrode positions to identify other suitable EEG variables for the assessment of remimazolam-induced sedation. Because an effect of remimazolam on cardiac repolarization was not fully analyzed in previous trials, the QT interval of the electrocardiogram was also assessed using a 12-lead Holter electrocardiogram recording.

This part of the study presents the pharmacokinetics and clinical pharmacodynamics including the Modified Observer's Assessment of Alertness and Sedation scores, whereas the pharmacodynamics with respect to the EEG is reported in Part II.

Materials and Methods

This was a prospective, open-label, randomized, two-arm, single-center, crossover phase 1 clinical trial which was performed in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki. The trial was approved by the local ethics committee (ethics committee of the medical faculty of the Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany) on May 12, 2017 (reference No. AZ113_17). The trial was registered to the EudraCT database (No. 2017-000455-12). Consolidated Standards of Reporting Trials guidelines were followed, and the study was clinically monitored by the Center for Clinical Studies, Erlangen, Germany. The trial took place at the Department of Anesthesiology of the University Hospital Erlangen, Germany between July and October 2017.

Subjects

After written informed consent, 25 volunteers were enrolled. It was the aim of the present phase I study to characterize the basic pharmacokinetics and pharmacodynamics of remimazolam after continuous infusion. To limit potential sources of interindividual variability like age, weight, and sex, the study was conducted in a relatively homogenous population with the following inclusion criteria: healthy male volunteers with an age between 18 and 40 yr, a body weight between 60 and 100 kg, a body mass index between 20 and 30 kg/m^2, and an American Society of Anesthesiologists Physical Status classification of 1. Subjects with hypersensitivity to benzodiazepines or flumazenil, with clinically relevant cardiovascular, hematologic, gastrointestinal, hepatic, renal, endocrine, pulmonary, neurologic, psychiatric, allergic, or skin disorder were excluded. Further exclusion criteria were any kind of cardiovascular disorder known to increase the possibility of QT prolongation, an abnormal 12-lead electrocardiogram including Fridericia's corrected QT interval at or above 450 ms, QRS interval at or above 110 ms, PR more than 200 ms, second- or third-degree atrioventricular block or any rhythm other than sinus rhythm. Exclusion criteria were also a resting heart rate (HR) below 50 bpm or at or above 90 bpm, a resting systolic arterial blood pressure below 90 mmHg or at or above 140 mmHg, or a resting diastolic arterial blood pressure below 50 mmHg or at or above 90 mmHg. Further exclusion criteria were intake of medications with a pronounced effect on the central nervous system (CNS) such as neuroleptics, antidepressants, hypnotics, anxiolytics, or antiepileptics within three months before the trial, and intake of any medication within one week before the trial. Subjects with a history of drug or alcohol abuse within two years before the trial or with use of tobacco or e-cigarettes within six months before the trial were excluded. Further exclusion criteria were participation in an investigational drug or medical device trial within two months before the present trial, as well as blood donation of more than 300 ml within one month before this trial.

Protocol

Each subject passed four visit days. Informed consent, assessment of medical history, physical examination, routine electrocardiogram, and routine laboratory assessments were performed at visit 1. Visit 2 and visit 3 served as remimazolam visit and control visit in which the volunteers received either remimazolam or sterile sodium chloride 0.9% infusion, respectively. The sequence of the remimazolam visit and the control visit was randomized using sealed envelopes

containing the individual visit sequence for each subject. These envelopes were prepared by an independent statistician before the study started, using a computer-generated randomization list. For each subject, the envelope with the individual visit sequence was opened by the investigator after enrollment. Visit 3 was performed one to ten days after visit 2. Visit 4, which was performed within five days after visit 3, was a close-out visit with physical examination, routine electrocardiogram, and routine laboratory assessments.

During the remimazolam visit, the subjects received remimazolam (2 mg/ml in sterile sodium chloride 0.9%) as continuous intravenous infusion through a venous cannula in the dominant forearm with an infusion rate of 5 mg/min in the first 5 min, 3 mg/min in the following 15 min, and 1 mg/min in the last 15 min. Thus, each subject received 85 mg remimazolam in 35 min. The infusion rates were based on the results of a previous study[7] and aimed to produce a moderate to deep sedation. Furthermore, the infusion rates were selected to provide concentration plateaus which matched the therapeutic and supratherapeutic ranges from a previous QT trial. In parallel to remimazolam, an infusion of sterile saline solution 0.9% was administered from approximately 30 min before start of remimazolam administration until approximately 240 min thereafter at a rate of 100 to 150 ml/h.

During the control visit the subjects received only a sterile saline solution 0.9% at a rate of 100 to 150 ml/h for about 4 h.

During the remimazolam visit, the following assessments were performed: arterial blood sampling for pharmacokinetic analyses, assessment of sedation, continuous EEG monitoring and recording, continuous electrocardiogram recording, hemodynamic monitoring, and assessment of side effects and adverse events.

During the control visit, the following assessments were performed: continuous electrocardiogram recording, hemodynamic monitoring, and assessment of side effects and adverse events.

Blood Sampling

Approximately 30 min before the start of remimazolam infusion, an arterial catheter was placed in the distal radial artery of the nondominant arm. Pharmacokinetic blood samples of 4 ml each were drawn into plastic tubes containing ethylenediaminetetraacetic acid (Vacutainer K3 EDTA, Becton Dickinson, Germany). A blank sample was taken before the start of remimazolam infusion. Further samples were taken 1, 3, 5, 7, 10, 15, 20, 25, 30, 35, 36, 37, 39, 42, 45, 50, 55, 65, 80, 95, 125, 155, 185, 215, 275 and 395 min after the start of remimazolam infusion. After each sample, the arterial catheter was flushed with 2 ml of saline solution. The samples were kept on ice water and were centrifuged within 40 min after collection at approximately 2,000*g* for 10 min at approximately 4°C in a cooled centrifuge. The plasma was separated within 15 min into polypropylene tubes (Nunc cryogenic vial cryo tubes, Thermo Fisher Scientific, USA) and stored at −70°C. The samples were analyzed within two months after collection.

Drug Assay

Plasma concentrations of remimazolam and CNS 7054 were measured by Aptuit Srl (Italy) using high-performance liquid chromatography (HPLC) with tandem mass spectrometric detection. Deuterium labeled d_4-remimazolam and d_4-CNS 7054 were used as internal standards. The compounds were extracted from 50 µl plasma by protein precipitation.

The HPLC system (Waters Acquity UPLC) used a 50 × 3 mm BETASIL Phenyl-Hexyl 5-µm column. Gradient elution with two mobile phases (phase A: water plus 0.01% formic acid, phase B: acetonitrile) was performed at a flow rate of 1.2 ml/min and room temperature. The approximate elution times were 0.6 min for CNS 7054 and 0.8 min for remimazolam, respectively. Tandem mass spectrometry was performed using a Biosystems/MDS SCIEX API-4000 instrument with a TurboIonSpray interface at 650°C. Nominal mass transitions from precursor ion to product ion were 439.1 to 407.2 for remimazolam, and 425.1 to 362.9 for CNS 7054, respectively. The method was validated over the range of 2 to 2,000 ng/ml for remimazolam and 20 to 20,000 ng/ml for CNS 7054, respectively, using a sample volume of 50 µL. Quality control samples were prepared in human plasma at 6, 200 and 1,500 ng/ml for remimazolam, and at 60, 2,000 and 15,000 ng/ml for CNS 7054, respectively. Inter- and intraassay coefficients of variation were at or below 6.6% for remimazolam and at or below 5.1% for CNS 7054, respectively. Accuracy was 105 ± 6% (range: 86 to 121%) for remimazolam and 106 ± 5% (range: 89 to 121%) for CNS 7054, respectively.

Assessment of Sedation

Sedation was assessed using the Modified Observer's Assessment of Alertness and Sedation scale (table 1).[12] The Modified Observer's Assessment of Alertness and Sedation score was assessed every 2 min, starting immediately before remimazolam infusion until three subsequent Modified Observer's Assessment of Alertness and Sedation scores of 5 (alert) were recorded after stop of remimazolam administration. The time to loss of consciousness was defined as the time to the first Modified Observer's Assessment of Alertness and Sedation score less than 2. The time to return of full alertness was defined as the time to the first of the three subsequent Modified Observer's Assessment of Alertness and Sedation scores of 5 after stop of remimazolam administration.

The eyelid reflex and the corneal reflex were further tested using a cotton swab every 2 min, once a Modified Observer's Assessment of Alertness and Sedation score at or below 3 and at or below 2 had been reached, respectively. These tests were performed until recovery of the reflexes.

When after stop of remimazolam infusion, the Modified Observer's Assessment of Alertness and Sedation score had recovered to a value of 1, the subject was asked every 2 min to state his name (orientation to person), the date of the

Table 1. Modified Observer's Assessment of Alertness and Sedation 2, 3, 2M Scale

Responsiveness	Score
Subject responds readily to name spoken in normal tone	5
Lethargic response of subject to name spoken in normal tone	4
Subject responds only after name is called loudly and/or repeatedly	3
Subject responds only after mild prodding of shaking	2
Subject responds only after painful trapezius squeeze	1
Subject does not respond to painful trapezius squeeze	0

day (orientation to time), and the location (orientation to location). These questions were repeated until the subject answered correctly.

Pharmacokinetic–pharmacodynamic Modeling

The pharmacokinetic–pharmacodynamic modeling is described in full detail in paragraph S1 of the Supplemental Digital Content (http://links.lww.com/ALN/C147). In brief, pharmacokinetics of the parent drug remimazolam and its metabolite CNS 7054 were modeled using linear mammillary two- or three-compartment models linked by a transit compartment to account for the formation of the metabolite (fig. 1). Pharmacokinetic models were parametrized using the elimination clearance, intercompartmental clearances (Q_2, Q_3), and volumes of distributions (V_1,V_2,V_3). Because the Modified Observer's Assessment of Alertness and Sedation scale is not an interval ratio scale but an ordinal scale, probability models were used for pharmacodynamic modeling. We tested two types of models: an ordinal logistic regression model and a sigmoid probability model. An effect compartment was assumed as site of action. Pharmacokinetic and pharmacodynamic modeling was performed by population analysis with nonlinear mixed effect modeling using the software NONMEM 7.4.1 (ICON plc, Ireland). Interindividual parameter variability was modeled using log-normal distributions.

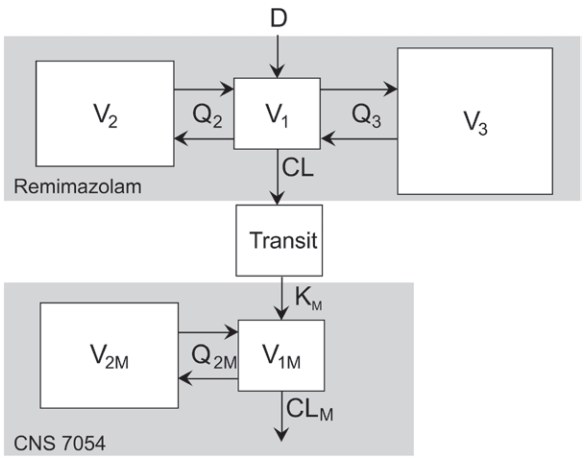

Fig. 1. Combined pharmacokinetic model, consisting of a three-compartment model for the parent drug remimazolam, a two-compartment model for the metabolite CNS 7054, and a transit compartment for the formation of the metabolite. It is assumed that 100% of the eliminated amount of remimazolam enters the transit compartment. $V_{1,\ 1M}$, central volumes of distribution; $V_{2,\ 3,\ 2M}$, peripheral volumes of distribution; CL, CL_M, elimination clearances; $Q_{2,\ 3,\ 2M}$, intercompartmental clearances; K_M, transit rate constant; D, dose.

EEG Monitoring and Recording

Continuous EEG monitoring was performed using the Narcotrend-Compact M monitor (MT MonitorTechnik, Germany) with three electrodes placed on the subject's forehead. Narcotrend monitoring started 30 min before start of remimazolam infusion and was continued until 90 min after stop of remimazolam infusion.

The raw EEG signals obtained from a multi-channel EEG device (Natus-Nicolet V32, Natus Europe, Germany) were recorded continuously from electrodes positioned according to the international 10 to 20 system at F3, F4, C3, C4, O1, and O2, with Cz as common reference. The multichannel EEG was recorded from 30 min before start of remimazolam infusion until 90 min after stop of infusion.

The monitoring, recording, and analysis of the EEG are reported in full detail in Part II of this study.

Electrocardiogram Recording and Analysis

For offline electrocardiogram analysis, a continuous 12-lead Holter electrocardiogram was recorded on a flash card using an H-12+ electrocardiogram continuous 12-lead digital recorder (Mortara Instrument, USA). During the remimazolam visit, the electrocardiogram recording was started approximately 60 min before start of remimazolam administration (time point zero) and was terminated after the last blood sample had been drawn. During control visit, the Holter electrocardiogram was recorded from approximately 60 min before the time corresponding to time point zero for approximately 390 min thereafter. Additionally, a five-lead routine electrocardiogram was continuously recorded for online cardiovascular monitoring during both remimazolam and control visit within the same time periods as the 12-lead Holter electrocardiogram.

The 12-lead Holter electrocardiogram data were analyzed offline by a blinded team at ERT Ltd. (United Kingdom), following the International Conference on Harmonisation Guideline E14.[13] Details of the electrocardiogram analysis are given in paragraph S2 of the Supplemental Digital Content (http://links.lww.com/ALN/C147). In brief, digital electrocardiogram signals of 10 s duration each were extracted at the following time points: 45, 30, and 15 min before and 5, 10, 15, 20, 30, 40, 65, 110, 120, 180, 240 and 360 min after start of remimazolam infusion. On-screen measurements of the RR, PR, QRS, and QT interval durations

were performed, and the individually heart-rate–corrected QT interval (QTcI) was determined as primary endpoint of the electrocardiogram analysis. The net effect of remimazolam on QTcI was assessed as the control-corrected change from baseline at each time point (*i.e.,* the change from baseline during the remimazolam visit minus the corresponding change from baseline during the control visit). The effect of remimazolam on the QTcI interval was considered significant if the upper bound of the two-sided 90% CI of the control-corrected change from baseline exceeded 10 ms.

Hemodynamic Monitoring

During the remimazolam visit, systolic arterial blood pressure, diastolic arterial blood pressure, and mean arterial blood pressure were continuously monitored *via* the arterial catheter. Heart rate was continuously monitored using the routine five-lead electrocardiogram. Oxygen saturation (Spo_2) was continuously monitored by peripheral arterial pulse oximetry. Hemodynamics were monitored using a Draeger Infinity M540 machine (Dräger Medical GmbH, Germany). Values were recorded before remimazolam administration and approximately every 3 min thereafter until the last blood sample had been drawn. If Spo_2 levels fell below 93%, oxygen was administered through a nasal cannula. Airway patency was checked and, if appropriate, the lower jaw was manually elevated. At Spo_2 levels below 90%, assisted ventilation *via* a face mask was performed until Spo_2 levels returned to values at or above 93%.

During the control visit, systolic arterial blood pressure, diastolic arterial blood pressure, mean arterial blood pressure, and HR were intermittently monitored approximately every 15 min from approximately 60 min before time point zero for approximately 390 min thereafter, using a blood pressure cuff on the upper arm and the five-lead electrocardiogram, respectively. The Spo_2 was continuously monitored from approximately 60 min before time point zero for approximately 390 min thereafter, but no values were recorded unless a cardiovascular or respiratory adverse event occurred.

Routine Laboratory Assessments, Adverse Events

Routine laboratory assessments of hematologic, clinical chemistry, and coagulation parameters were performed at visit 1 and at the end of study visit 4. The number, nature, severity, duration, and outcome of adverse events were recorded from visit 1 until visit 4.

Simulations

Various simulations were performed to illustrate the pharmacokinetic and pharmacodynamic profile of remimazolam and its metabolite. The time to maximum concentration of CNS 7054 and the time to maximum remimazolam effect site concentration after a bolus dose of remimazolam were simulated using the individual pharmacokinetic and pharmacodynamic parameters. Using the typical parameters of the final pharmacokinetic and pharmacodynamic models of remimazolam, we determined the context-sensitive decrement times (*i.e.,* the times for a defined decrease [25%, 50%, and 75%] of the plasma and of the effect site concentration after continuous target controlled infusion of variable length).[14] To compare the pharmacokinetic profiles of remimazolam and midazolam, context-sensitive half-time was also simulated for midazolam, using the typical parameters from a previous study.[15] The infusion rates for a target-controlled infusion with remimazolam, propofol, and remifentanil were simulated using the typical parameters from the final pharmacokinetic model of remimazolam and from previous studies on propofol[16] and remifentanil,[17] assuming a body weight of 75 kg, an age of 25 yr, and a lean body mass of 60 kg.

Statistics

Data are presented as median with range or as mean ± SD if not stated otherwise. To capture patterns in the data, smoother lines were added in the figures using locally weighted scatterplot smoothing. The evaluation and selection of pharmacokinetic–pharmacodynamic models was based on the objective function (OFV). Model selection was primarily based on the Bayes information criterion defined as BIC = OFV + Ln(Nobs) • Npar, where Nobs is the number of observations and Npar is the number of parameters to be estimated. The model with the lowest Bayes information criterion was selected as best model. The difference in the OFV between two models was further tested for significance by the chi-square test with the degree of freedom being equal to the difference in the number of model parameters. $P < 0.05$ was considered as statistical significant.

Results

Twenty-five subjects were screened for this study. Three subjects who provided informed consent were not eligible because of abnormal laboratory values at screening. Two subjects were further excluded, one subject because of a vasovagal syncope during arterial cannulation and one subject because of a positive urine drug screening test on the treatment day. The remaining 20 subjects received remimazolam as scheduled and completed the study successfully. The demographic data are summarized in table 2.

Table 2. Demographics of the Study Population

Sex (male/female)	20/0
Age, yr	25 ± 4 (20–38)
Weight, kg	77 ± 10 (64–99)
Height, cm	179 ± 8 (169–197)
Body mass index, kg/m^2	24 ± 2 (21–29)

Sex is reported as number of male and female subjects, and all other data are reported as mean ± SD (range).

Pharmacokinetics of Remimazolam

All blood samples were drawn as scheduled. One remimazolam plasma concentration at 395 min after start of infusion was below the limit of quantification of 2 ng/ml. This sample was removed from the dataset for pharmacokinetic analysis. Thus, 519 concentration measurements were used for pharmacokinetic modeling of remimazolam. The individual time courses of the remimazolam plasma concentrations are shown in figure 2. The maximum remimazolam plasma concentration during infusion was 2,088 ± 196 ng/ml measured at 5 (3 to 20) min. The remimazolam plasma concentration at the end of infusion (t = 35 min) was 1,032 ± 148 ng/ml.

A three-compartment model was identified as best structural model. Covariate analysis revealed only for the central volume of distribution V_1 an influence of body weight (BW), whereas age did not show any effect on pharmacokinetics of remimazolam. The best fit was achieved when V_1 was scaled proportional to weight: $V_{1,i} = V_{1,TV} \cdot (BW/75)$. Table 3 summarizes the parameter estimates of the final pharmacokinetic model. Remimazolam showed a high clearance of 1.15 ± 0.12 l/min with a small interindividual coefficient of variation of 11%, and small volumes of distribution (Vss = 35.4 ± 4.2 l). The rapid distribution, slow distribution, and elimination half-lives of remimazolam were 1.3 ± 0.3, 18.1 ± 2.5, and 70 ± 10 min, respectively. The simulations revealed short context-sensitive decrement times for remimazolam (fig. 3). After an infusion of 4 h, the context-sensitive halftime was 6.8 ± 2.4 min. More detailed results of the pharmacokinetic modeling of remimazolam are given in paragraph S3 of the Supplemental Digital Content (http://links.lww.com/ALN/C147).

Pharmacokinetics of CNS 7054

In each subject, the first plasma concentration of CNS 7054 (taken 1 min after start of infusion) was below the limit of quantification of 20 ng/ml. These samples were removed from the dataset for pharmacokinetic analysis. Thus, 500 concentration measurements were used for pharmacokinetic modeling of CNS 7054. The individual time courses of the CNS 7054 plasma concentrations are shown in figure 4. A maximum CNS 7054 plasma concentration of 5,340 ± 687 ng/ml was measured 52 ± 9 min after start of infusion. A combined three- and two-compartment model with a transit compartment was used for pharmacokinetic modeling of CNS 7054 (fig. 1). The pharmacokinetic parameters of the parent drug remimazolam were fixed to the individual estimates of the best pharmacokinetic model. During development of the pharmacokinetic model, it was found that the model was significantly improved if one assumed an additional lag-time for the formation of CNS 7054. Based on the covariate analysis, a proportional increase of V_{2M} and Q_{2M} with body weight was included in the final pharmacokinetic model of CNS 7054:

$$V_{2M,i} = V_{2M,TV} \cdot (BW / 75)$$

$$Q_{2M,i} = Q_{2M,TV} \cdot (BW / 75)$$

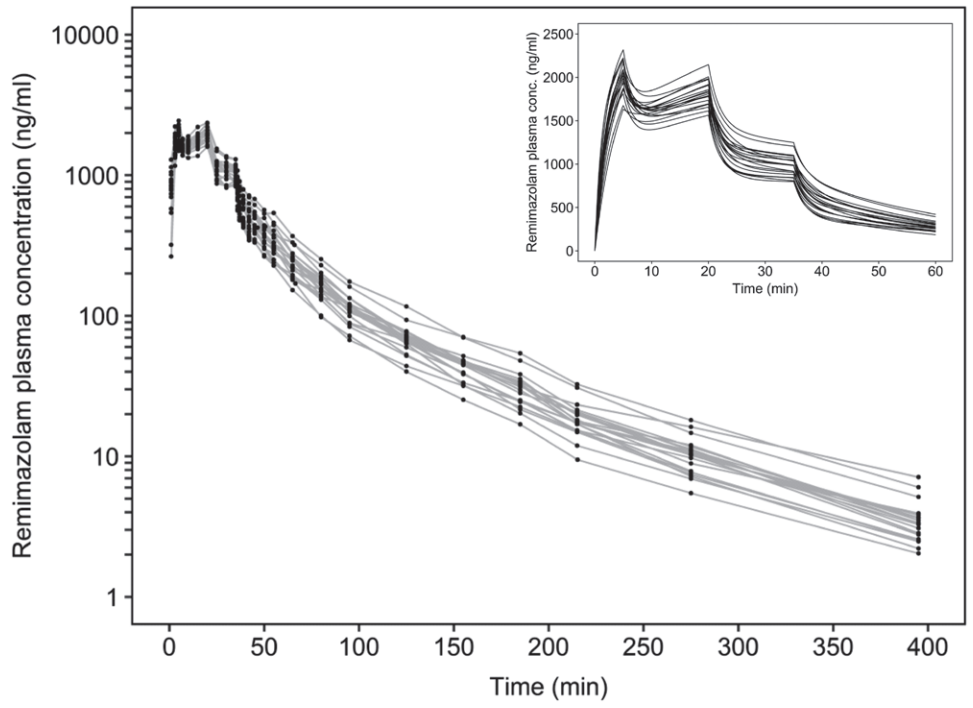

Fig. 2. Measured plasma concentrations of remimazolam. The *small inset plot* shows the predicted plasma concentrations during the first hour. Each *line* represents the data of one subject.

Table 3. Parameter Estimates for the Final Pharmacokinetic Model of Remimazolam

	Population Fit		Bootstrap (866 Successful Runs)	
Parameter	**Estimate**	**RSE**	**Median**	**95% CI**
CL, l/min	1.14	2.5%	1.15	1.09, 1.20
Q_2, l/min	1.04	4.9%	1.04	0.94, 1.14
Q_3, l/min	0.19	7.3%	0.19	0.16, 0.22
V_1, l/75 kg	4.7	5.9%	4.8	4.2, 5.4
V_2, l	14.5	4.2%	14.5	13.3, 15.8
V_3, l	15.5	6.4%	15.6	13.5, 17.4
ω^2_{CL}	0.012	32%	0.011	0.005, 0.020
ω^2_{Q2}	0.040	33%	0.036	0.013, 0.068
ω^2_{Q3}	0.052	92%	0.046	0.002, 0.14
ω^2_{V1}	0.061	29%	0.057	0.024, 0.092
ω^2_{V2}	0.021	65%	0.019	0.002, 0.045
ω^2_{V3}	0.051	56%	0.050	0.014, 0.10
σ^2	0.0079	17%	0.0077	0.0057, 0.011

CL, elimination clearance; $Q_{2,3}$, intercompartmental clearances; RSE, relative standard error; V_1, central volume of distribution; $V_{2,3}$, peripheral volumes of distribution; ω^2, interindividual variance; σ^2, intraindividual variance.

Table 4 summarizes the parameter estimates of the final pharmacokinetic model. When compared with the parent drug, CNS 7054 showed a low clearance of 0.078 ± 0.017 L/min. The distribution and elimination half-lives of CNS 7054 were 1.8 ± 0.5 and 116 ± 22 min, respectively. The simulated time to the maximum concentration of CNS 7054 after a bolus dose of remimazolam was 33 ± 8 min. More detailed results of pharmacokinetic modeling of the metabolite are given in paragraph S4 of the Supplemental Digital Content (http://links.lww.com/ALN/C147).

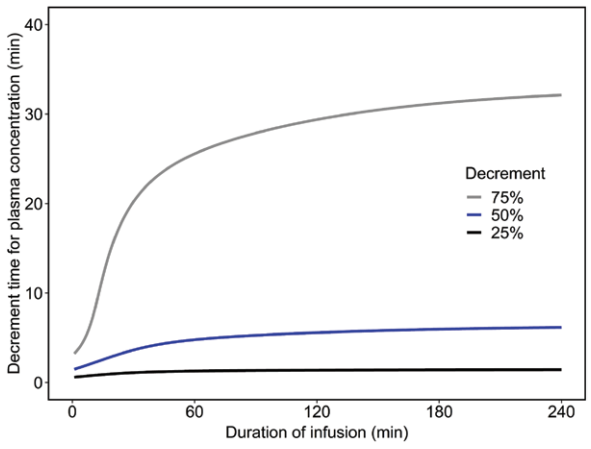

Fig. 3. Time required for a 25%, 50%, and 75% decrease of remimazolam plasma concentration after continuous infusion of variable length (context-sensitive decrement times). Simulations were performed using the final pharmacokinetic model with the typical parameter estimates for a body weight of 75 kg.

Pharmacodynamics: Sedation

The Modified Observer's Assessment of Alertness and Sedation score was assessed in all volunteers as scheduled. One assessment could not be performed because of clinical circumstances. Thus, 604 Modified Observer's Assessment of Alertness and Sedation score values were used for pharmacodynamic modeling. The time courses of the Modified Observer's Assessment of Alertness and Sedation scores are shown in figure 5. There was a rapid decrease of the Modified Observer's Assessment of Alertness and Sedation score from baseline (Modified Observer's Assessment of Alertness and Sedation score = 5 in all subjects) to values less than 2 (*i.e.*, loss of consciousness) within 5 ± 1 (range: 4 to 8) min after start of remimazolam infusion. During the remimazolam infusion, the Modified Observer's Assessment of Alertness and Sedation score stayed between 0 and 2. All subjects lost the eyelid reflex within 6 (4 to 14) min after start of remimazolam infusion. Loss of corneal reflex occurred in 11 subjects within 12 (4 to 26) min after start of remimazolam infusion. The recovery after stop of remimazolam administration was fast. The subjects were orientated to person, location, and time 19 ± 6 (10 to 34) min after stop of infusion. Full alertness (Modified Observer's Assessment of Alertness and Sedation score of 5) was regained 19 ± 7 (range: 7 to 33) min after stop of infusion. Eyelid and corneal reflex were regained 12 (1 to 29) min and 5 (−19 to 11) min after stop of remimazolam administration, respectively.

Pharmacodynamic Modeling of Modified Observer's Assessment of Alertness and Sedation Score

For modeling of the Modified Observer's Assessment of Alertness and Sedation scores, a logistic regression model and a model with sigmoid probability functions were investigated. The model with sigmoid probability functions was selected as best basic pharmacodynamic model. Covariate analysis revealed no significant effects. The final pharmacodynamic model was therefore as following:

$$P(MOAA/S \le m) = \frac{C_E^{\gamma}}{C_E^{\gamma} + EC_{50,m}^{\gamma}} \quad m = 0,1,2,3,4$$

where P(MOAA/S ≤ m) is the probability for a Modified Observer's Assessment of Alertness and Sedation score ≤ m, C_E is the effect site concentration, $EC_{50,m}$ is the effect site concentrations for a 50% probability of Modified Observer's Assessment of Alertness and Sedation ≤ m, and γ defines the steepness of the probability functions. The $EC_{50,m}$ were parametrized in an incremental manner: $EC_{50,4} = \theta_1$, $EC_{50,3} = EC_{50,4} + \theta_2$, $EC_{50,2} = EC_{50,3} + \theta_3$, $EC_{50,1} = EC_{50,2} + \theta_4$, $EC_{50,0} = EC_{50,1} + \theta_5$, with $\theta_{2,3,4,5} \ge 0$. Table 5 summarizes the parameter estimates together with the results of the bootstrap analysis. The corresponding values of the $EC_{50,i}$ in the population are given in table 6. The equilibration half-time between central and effect compartment was 2.7 ± 0.6 min. The simulated time to maximum effect site concentration after a bolus dose of

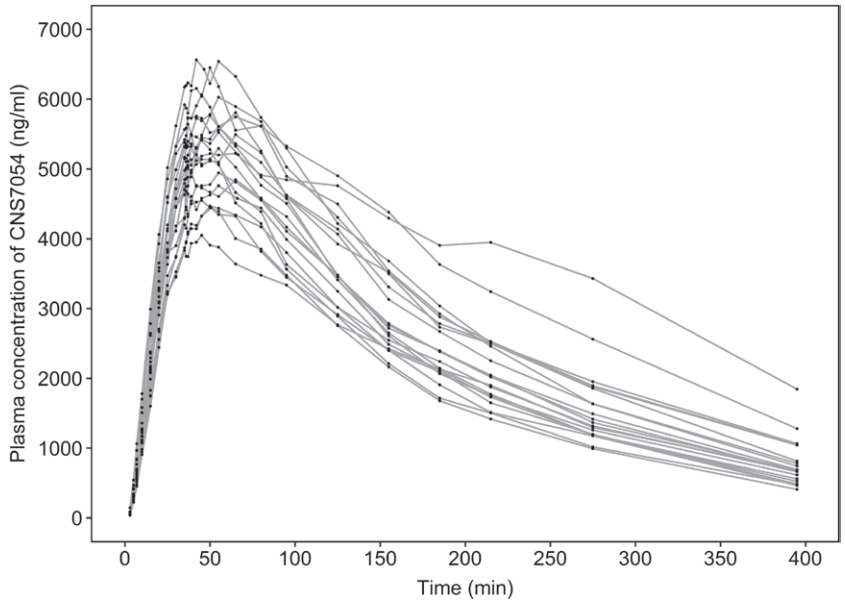

Fig. 4. Measured plasma concentrations of the metabolite CNS 7054. Each *gray line* represents the data of one subject.

Table 4. Parameter Estimates for the Final Pharmacokinetic Model of CNS 7054

	Population Fit		Bootstrap (748 Successful Runs)	
Parameter	**Estimate**	**RSE**	**Median**	**95% CI**
K_M, min^{-1}	0.024	9.4%	0.024	0.020, 0.028
CL_M, l/min	0.076	5.0%	0.076	0.069, 0.084
Q_{2M}, l/min/75 kg	0.13	12%	0.12	0.10, 0.16
V_{1M}, l	0.54	13%	0.53	0.41, 0.70
V_{2M}, l/75 kg	7.4	3.0%	7.4	6.9, 7.8
T_{Lag}, min	0.6	9.3%	0.6	0.5, 0.7
ω^2_{KM}	0.010	52%	0.009	0.0005, 0.019
ω^2_{CLM}	0.051	34%	0.047	0.020, 0.081
ω^2_{QM}	0.011	82%	0.011	0.0005, 0.029
ω^2_{V1M}	0.082	30%	0.075	0.036, 0.13
ω^2_{V2M}	0.0052	41%	0.0048	0.0015, 0.0097
ω^2_{Tlag}	0 (fixed)	-	0 (fixed)	-
σ^2_{prop}	0.0009	13%	0.0009	0.0007, 0.0011
σ_{add} (ng/mL)	13.6	15%	13.2	9.3, 18.1

CL_M, elimination clearance; K_M indicates transit rate constant; Q_{2M}, intercompartmental clearance; RSE, relative standard error; T_{Lag}, lag-time; V_{1M}, central volume of distribution; V_{2M}, peripheral volume of distribution; σ^2_{prop}, variance of the proportional intraindividual error; σ_{add}, SD of the additive intraindividual error; ω^2, interindividual variance.

remimazolam was 2.9 ± 0.4 min. The individual and typical cumulative probabilities of the different Modified Observer's Assessment of Alertness and Sedation scores are depicted in figure 6. The simulated probabilities to achieve exactly a particular Modified Observer's Assessment of Alertness and Sedation score are shown in figure 7. After an infusion of 4 h, the context-sensitive halftime of the effect site concentration was 12 ± 2 min (fig. 8). More detailed results of pharmacodynamic modeling of Modified Observer's Assessment of Alertness and Sedation score are given in paragraph S5 of the Supplemental Digital Content (http://links.lww.com/ALN/C147).

Pharmacodynamics: EEG

The EEG effects of remimazolam and the pharmacodynamic modeling are reported in Part II of this study.

Hemodynamics

Blood pressure decreased (fig. 9A) and heart rate increased (fig. 9B) during remimazolam infusion. The maximum decrease of mean arterial blood pressure compared with baseline was 24 ± 6% (range: 10 to 34%), and the maximum increase of HR was 28 ± 15% (range: 4 to 56%). The minimum value of systolic arterial blood pressure during remimazolam infusion was 96 ± 8 (range: 81 to 106) mmHg. The Spo_2 decreased during the first 5 min of remimazolam infusion (fig. 9C). In total, 28 short episodes with Spo_2 values less than 93% occurred in 15 subjects with a median duration of 0.3 (range: 0.1 to 1.1) min. In eight subjects, there were a total of nine short episodes of Spo_2 values less than 90% with a median duration of 0.5 (range: 0.4 to 1.1) min. Decrease of Spo_2 was successfully treated by oxygen administration *via* a nasal cannula with a median duration of 42 (range: 24 to 62) min, or by manual elevation of the lower jaw with a median duration of 26 (range: 0.7 to 43) min. The volunteers kept spontaneous breathing, with exception of two short episodes of mask ventilation in one subject lasting 4 and 5 s, respectively. The remimazolam plasma

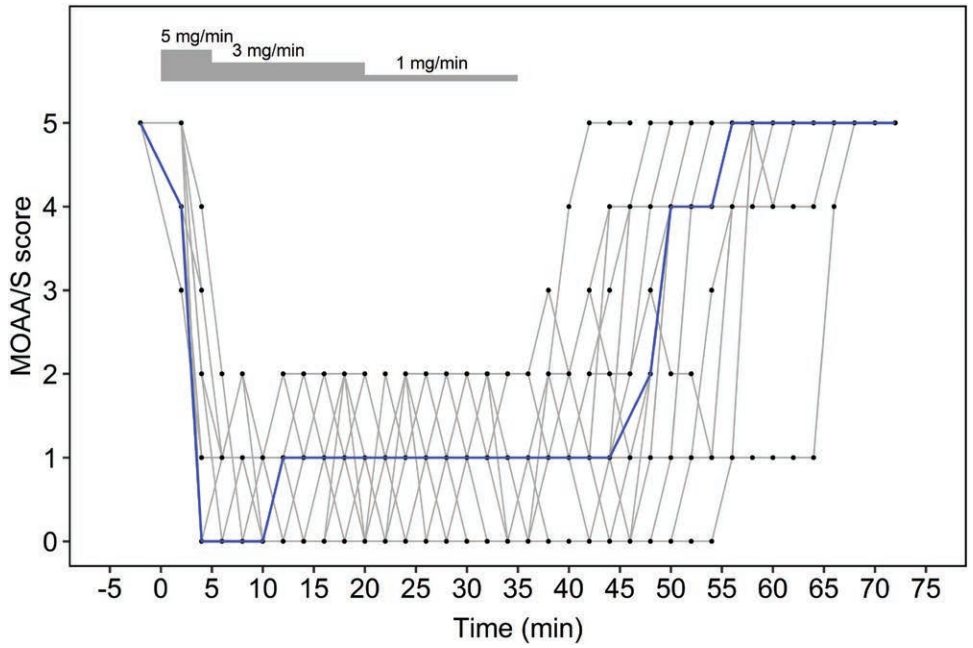

Fig. 5. Observed Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scores. Each *gray line* represents the data of one subject. The *blue line* shows the median. The *gray bars* at the top indicate the remimazolam infusion.

Table 5. Parameter Estimates for the Final Pharmacodynamic Model of Modified Observer's Assessment of Alertness and Sedation Score

	Population Fit		Bootstrap (621 Successful Runs)	
Parameter	**Estimate**	**RSE**	**Median**	**95% CI**
θ_1, ng/ml	333	7.8%	333	293, 379
θ_2, ng/ml	133	14%	128	101, 158
θ_3, ng/ml	28	40%	29	9.6, 47
θ_4, ng/ml	82	50%	81	23, 166
θ_5, ng/ml	730	33%	740	385, 1397
γ	3.6	15%	3.7	3.0, 5.4
k_{e0}, min^{-1}	0.27	11%	0.27	0.22, 0.32
ω^2_1	0.035	51%	0.034	0.004, 0.064
ω^2_2	0.087	83%	0.010	0.010, 0.26
ω^2_3	0.38	109%	0.45	0.0001, 1.6
ω^2_4	2.1	52%	2.1	0.94, 5.6
ω^2_5	1.8	47%	1.7	0.63, 4.5
ω^2_γ	0.091	115%	0.075	0.003, 0.58
ω^2_{ke0}	0.083	88%	0.079	0.010, 0.25

$\theta_{1\text{-}5}$, model parameters defining the remimazolam effect site concentrations for a 50% probability of a Modified Observer's Assessment of Alertness and Sedation score ≤ 0, 1, 2, 3, 4: $EC_{50,4} = \theta_1$, $EC_{50,3} = EC_{50,4} + \theta_2$, $EC_{50,2} = EC_{50,3} + \theta_3$, $EC_{50,1} = EC_{50,2} + \theta_4$, $EC_{50,0} = EC_{50,1} + \theta_5$. γ indicates steepness of the concentration-effect curve; k_{e0}, effect site equilibration rate constant; ω^2, interindividual variance; RSE, relative standard error.

concentrations at these time points were about 1,800 ng/ml and the Modified Observer's Assessment of Alertness and Sedation scores were 2 and 1, respectively.

Table 6. Half-maximum Effect Site Concentrations of Remimazolam

	EC_{50} (ng/ml)		
MOAA/S Score	**Median**	**Minimum**	**Maximum**
0	1,579	515	3,814
1	640	403	1,384
2	506	387	615
3	481	368	588
4	337	268	430

EC_{50} indicates remimazolam effect site concentration for a 50% probability of a Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score ≤ 0, 1, 2, 3, 4.

Electrocardiogram

The analysis of the 12-lead Holter electrocardiogram showed no clinically significant effect of remimazolam on the PR interval and on QRS duration. The largest control-corrected change of the QTcI interval from baseline was 3.7 ms (90% CI, −1.2 to 8.5 ms), which was observed 15 min after start of remimazolam infusion (fig. 10). The upper bound of the 90% CI of the control-corrected QTcI change from baseline never exceeded 10 ms, demonstrating no indication of any clinically significant effect of remimazolam on cardiac repolarization.

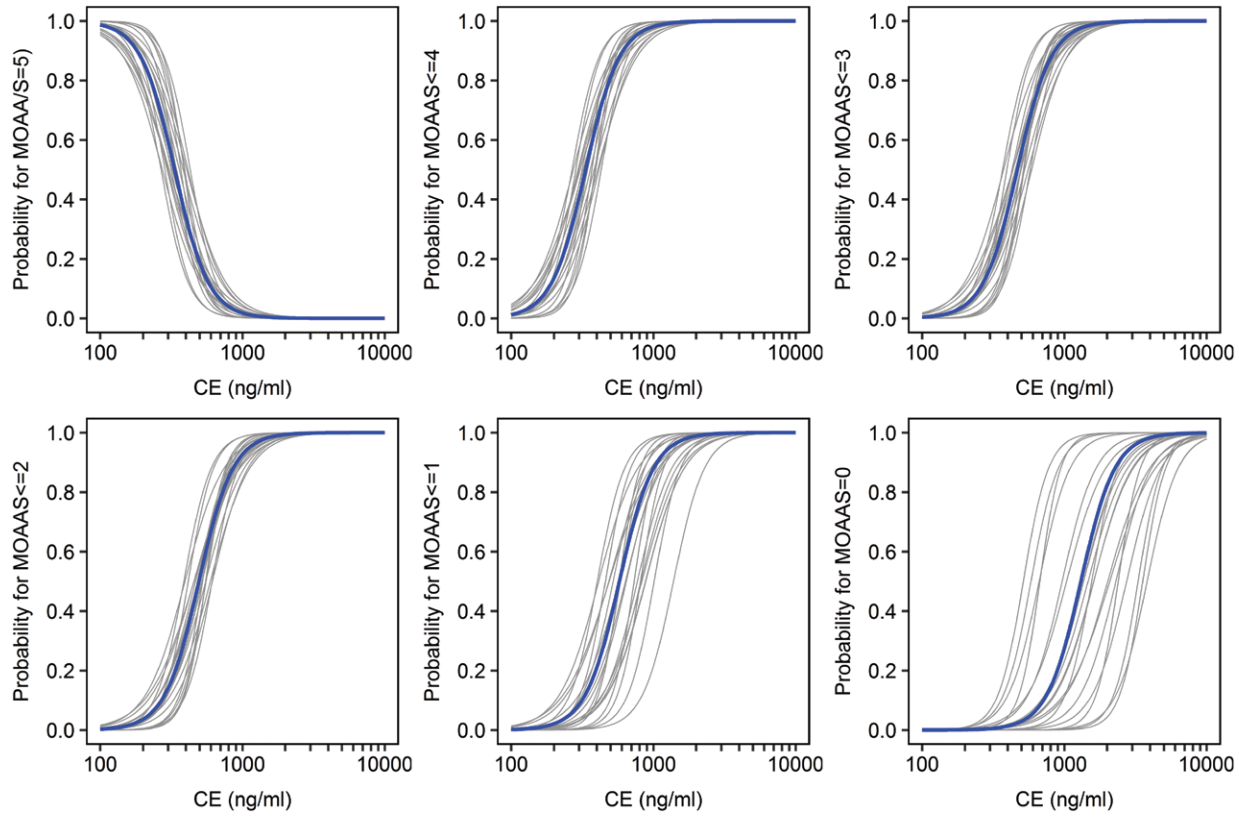

Fig. 6. Cumulative probabilities for the different Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scores, as predicted by the final pharmacodynamic model. The grey and blue lines show the predictions for the individual and typical parameter estimates, respectively. CE, effect site concentration of remimazolam.

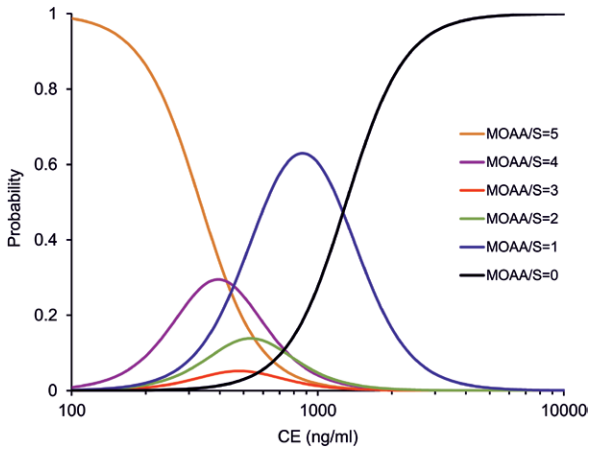

Fig. 7. Probabilities to achieve exactly a particular Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score, as predicted by the final pharmacodynamic model with the typical parameter estimates. CE, effect site concentration of remimazolam.

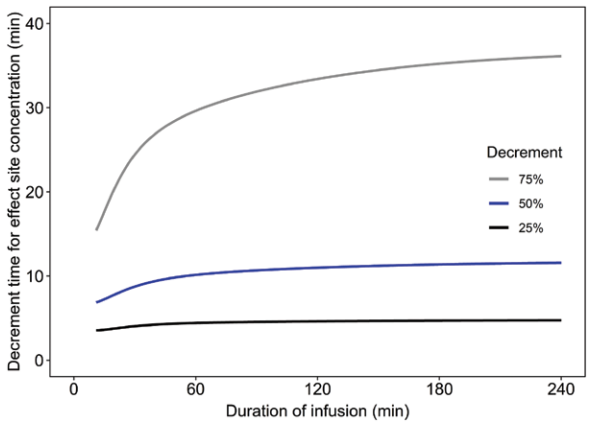

Fig. 8. Context-sensitive decrement times for the effect site concentration of Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score as predicted by the final and pharmacokinetic–pharmacodynamic model with the typical parameter estimates for a body weight of 75 kg.

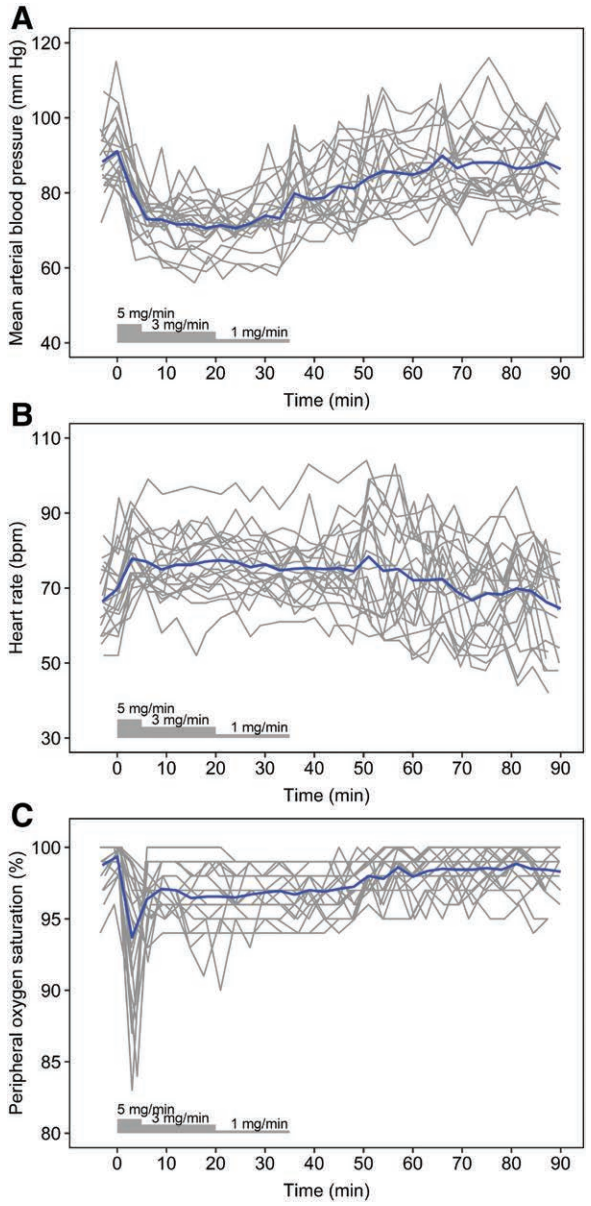

Fig. 9. Time courses of mean arterial blood pressure (*A*), heart rate (*B*), and arterial oxygen saturation (*C*). Each *gray line* represents the data of one subject, the *blue lines* show the mean values. The *gray bars* at the bottom indicate the remimazolam infusion.

Adverse Events

Besides the effects on blood pressure, heart rate, and oxygen saturation, the main adverse event was involuntary movements, which were observed in nine subjects. Psychomotor hyperactivity, cough, hiccup, sneezing, and apnea (lasting 0.9 min) were observed in one subject, respectively. All adverse events were classified as mild or moderate. No clinically significant changes or trends were found in any of the clinical laboratory parameters. Concerning vital signs, no clinically significant changes or trends were observed at the last visit compared with baseline.

Discussion

The present study aimed to characterize the pharmacokinetics and pharmacodynamics of remimazolam after continuous infusion. A standard three-compartment model described the measured plasma concentrations of remimazolam appropriately. Wiltshire *et al.* reported that a three-compartment model was not appropriate, but that a recirculation model was needed.[8] However, Wiltshire *et al.* administered remimazolam as bolus injection over 1 min and in this situation the assumption of instantaneous mixing, which is essential for mammillary compartment models, may be violated. In the present study, slower continuous infusions were used, so that the initial mixing may be less important. Because of the different model structures, the results of this study and the study by Wiltshire *et al.* cannot be directly compared. However, the estimates of elimination clearance (1.14 l/min in this study *vs.* 1.11 l/min in the Wiltshire study), steady-state volume (35 l *vs.* 37 l), and terminal half-life (70 min *vs.* 55 min) were very similar. There was no effect of age found in the present study, which is in accordance with the findings in the study by Wiltshire *et al.*, who found no effect of age and body weight. With respect to body weight, a proportional scaling of the central compartment of distribution improved the model in the present study. The improvement, however, was relatively small, which means that this body weight effect was not completely evident. One has, however, to consider that the populations in both the present and the previous study were relatively homogenous, so that one cannot draw definite conclusions concerning covariate effects. A body weight effect is important only for the initial loading dose, whereas the maintenance infusion rate depends on clearance and would therefore be independent of weight in the studied range of 64 to 99 kg. Because we did not include women, we cannot rule out an influence of sex on remimazolam pharmacokinetics. However, Wiltshire *et al.* did not find any significant influence of sex on the pharmacokinetics of remimazolam.[8] In addition, it has been reported that the abundance of hepatic carboxylesterases showed no effect of sex.[18] Because remimazolam is metabolized by carboxylesterases, it is therefore unlikely that the elimination clearance of remimazolam will be different between men and women.

Showing a high clearance, small volumes, and short half-lives, remimazolam can be characterized as a well-controllable drug, particularly as the interindividual variability of clearance was also small. Concerning the administration of remimazolam as target-controlled infusion, one might argue that because of its pharmacokinetics, target-controlled infusion may not differ considerably from constant rate infusion. However, target-controlled infusion simulations showed that it would take nearly 1 h until the steady

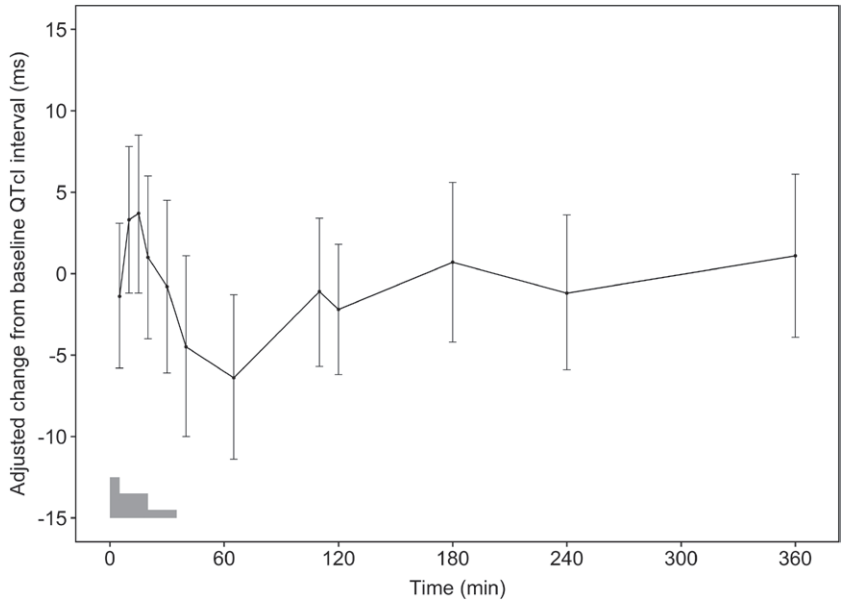

Fig. 10. Time course of the control-corrected change from baseline of the QTcI interval. Data are shown as mean and 90% CI. The *gray bars* at the bottom indicate the remimazolam infusion.

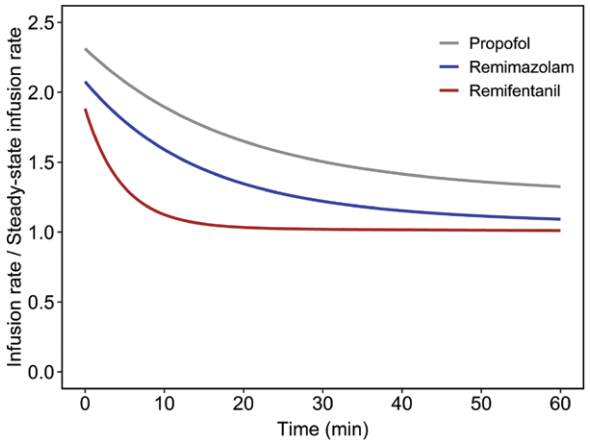

Fig. 11. Simulated infusion rates for a target-controlled infusion with a constant target concentration of propofol, remimazolam and remifentanil, respectively. For remimazolam, the final pharmacokinetic model with the typical parameter estimates for a body weight of 75 kg was used. Pharmacokinetic models from previous studies were used for propofol[16] and remifentanil,[17] assuming a body weight of 75 kg, an age of 25 yr, and a lean body mass of 60 kg. The infusion rate is expressed as ratio of the actual infusion rate and the infusion rate at steady state, as this ratio is independent of the target concentration. The initial bolus dose is not shown.

state is approximately achieved with remimazolam, whereas it takes only about 10 min for the ultra–short-acting opioid remifentanil (fig. 11). Therefore, use of target-controlled infusion might be beneficial for administration of remimazolam.

The pharmacokinetics of the metabolite CNS 7054 was modeled by a standard mammillary model with two compartments and a transit compartment to account for the formation of the metabolite. In each subject, the CNS 7054 concentration 1 min after start of infusion was below the limit of quantification, and these data were removed from the analyses. It has been reported that removing below the limit of quantification samples can lead to a significant bias of the model if their proportion is higher than 10%.[19] In the present study, however, these below the limit of quantification samples encompassed only about 4% of the total number of samples, and it affected the samples at one time point. Therefore, the impact was probably small. As the model for CNS 7054 was based on the model for remimazolam, the parameter estimates for CNS 7054 depend also on the parameter estimates for remimazolam and cannot be directly compared with the results of other studies. However, the average estimates of clearance (0.076 l/min) and time to maximum remimazolam effect site concentration after a bolus dose of remimazolam (33 min) were similar to those reported in the previous volunteer study (clearance: 0.070 l/min, time to maximum remimazolam

effect site concentration after a bolus dose of remimazolam: 20 to 30 min, respectively),[7] whereas the terminal half-life was shorter than in the previous study (116 min *vs.* 173 min).[7]

The pharmacodynamic modeling of the Modified Observer's Assessment of Alertness and Sedation scores was investigated with a logistic regression model and with a sigmoid model (Hill equation) for the cumulative probabilities. Although these two models are both characterized by concentration-effect curves with a sigmoid shape, the logistic regression model showed a worse quality of fit. This may be explained by the different behavior of the two models at baseline when no drug was present. In this case, the probability to achieve a Modified Observer's Assessment of Alertness and Sedation score at or below 4 equals zero for the sigmoid model but not for the logistic regression model. However, because all subjects in this study were alert (Modified Observer's Assessment of Alertness and Sedation score = 5) at baseline, the sigmoid model was more appropriate. Whereas the final pharmacodynamic model showed a quite good accordance of observed and predicted probability for Modified Observer's Assessment of Alertness and Sedation at or below 1, 2, 3, or 4, the probability for Modified Observer's Assessment of Alertness and Sedation score = 0 was less well predicted (fig. 11S in the Supplemental Digital Content, http://links.lww.com/ALN/C147). For effect site concentrations between 1,400 and 2,000 ng/ml, the observed probability of Modified Observer's Assessment of Alertness and Sedation score = 0 was lower than predicted. However, when assessing the Modified Observer's Assessment of Alertness and Sedation score, the discrimination between Modified Observer's Assessment of Alertness and Sedation scores of 0 and 1 was difficult as the volunteers showed some delayed repeated movements with the arm or leg after the trapezius squeeze, and it was not completely clear whether this was a response on the stimulus (*i.e.*, Modified Observer's Assessment of Alertness and Sedation score = 1) or some involuntary movement (*i.e.*, Modified Observer's Assessment of Alertness and Sedation score = 0). Therefore, some Modified Observer's Assessment of Alertness and Sedation assessments with a score value of 1 might have correctly been rated as 0. Correspondingly, the EC_{50} for a Modified Observer's Assessment of Alertness and Sedation score of 0 might be overestimated.

There was large overlap of the EC_{50} values for Modified Observer's Assessment of Alertness and Sedation scores of 2, 3, and 4 (table 6). Correspondingly, the model revealed only a small probability to achieve a Modified Observer's Assessment of Alertness and Sedation score of exactly 2 or 3 (fig. 7). For clinical practice this would imply that it might be hard to titrate a patient to moderate sedation. However, one has to consider that the observed overlap might be explained by the infusion scheme of the present study which led to a fast transition from a Modified Observer's Assessment of Alertness and Sedation score of 5 to 0 or 1, so that the intermediate levels were observed quite seldom.

The equilibration between plasma and effect site concentration was relatively fast with a time to peak of about 3 min. Correspondingly, the context-sensitive half-time for the

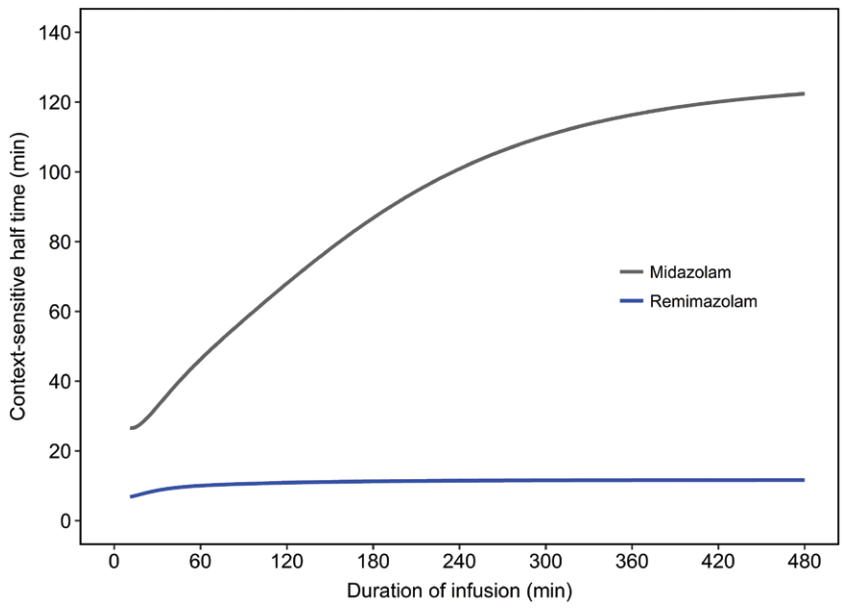

Fig. 12. Context-sensitive half times of the effect site concentration of remimazolam and midazolam. The context-sensitive half time of remimazolam was simulated using the final pharmacokinetic–pharmacodynamic model of this study. The context-sensitive half time of midazolam was simulated using the results of a previous study on midazolam.[15]

effect site concentration was also short (fig. 8), particularly when compared with midazolam, which showed a much longer context-sensitive half-time (122 min *vs.* 12 min after an infusion of 8 h, fig. 12). When compared with the results of the previous phase I study,[8] the ke0 of remimazolam was very similar (0.27 min^{-1} in the current *vs.* 0.25 min^{-1} in the previous study), whereas the EC_{50} of remimazolam tended to be lower in the previous study (938 ng/ml, 551 ng/ml, 412 ng/ml, 321 ng/ml, and 216 ng/ml for Modified Observer's Assessment of Alertness and Sedation score = 0, ≤1, ≤2, ≤3, and ≤4, respectively). This may be explained by the use of different models and by a different time resolution of the Modified Observer's Assessment of Alertness and Sedation assessments. The higher EC_{50} for Modified Observer's Assessment of Alertness and Sedation score = 0 in the present study is probably due to some uncertainty in the assessment described above. Generally, the pharmacodynamic model for Modified Observer's Assessment of Alertness and Sedation score allows to define target concentrations for specific levels of sedation which can then be realized by target-controlled infusion using the present pharmacokinetic model. However, one has to consider the relatively large interindividual variability for the deeper levels of sedation (fig. 6).

The effects of remimazolam on hemodynamics were moderate. Heart rate increased by about 20 bpm, mean arterial blood pressure decreased by about 20 mmHg, and the systolic arterial blood pressure never fell less than 80 mmHg. Therefore, these effects might be considered as clinically minor relevant. In previous studies with single doses of remimazolam, there were similar increases of heart rate but no changes of blood pressure reported.[2,7] This may be explained by the short administration of remimazolam in these studies compared with the longer lasting continuous infusion in the present study. The subjects maintained spontaneous breathing, and the decrease of Spo_2 during remimazolam infusion could be easily treated by chin lift and oxygen supply *via* a nasal cannula. This means for clinical use of remimazolam that in case of rapidly increasing concentrations during induction with high doses, temporary respiratory depression and oxygen desaturation may occur in patients breathing room air. On the other hand, even for the relatively high concentrations in the present study, only one subject stopped breathing for a very short time.

Because the QT interval of the electrocardiogram is considered a relevant endpoint in drug development,[20] this trial was also designed to evaluate the effect of remimazolam on cardiac repolarization. The infusion scheme of the present study achieved approximately steady-state plasma concentrations (fig. 2), avoiding rapid HR changes and thus minimizing the confounding influence of QT-RR hysteresis.[21] The use of QTcI further eliminated the effect of increasing HR throughout the remimazolam infusion. The upper bound of the 90% CI of the control-corrected QTcI change from baseline never approached or exceeded 10 ms. Thus, there was no signal of any clinically significant effect of remimazolam on cardiac repolarization at an exposure that is anticipated to be used in or exceeds that in procedural sedation and anesthesia.

Other treatment-related adverse events were generally moderate with respect to incidence and severity. The main adverse events were involuntary movements, whereas we did not observe headache and somnolence which were reported in the previous phase I study.[7]

There are several limitations of the present study. First, one has to consider that the study population was small and relatively homogenous, because this was a phase I study which aimed for a first characterization of remimazolam pharmacokinetics and pharmacodynamics after infusion. Therefore, we cannot draw definite conclusions concerning the effect of weight, age, and sex on remimazolam pharmacokinetics and pharmacodynamics in obese, children, and elderly subjects. The present pharmacokinetic model is, however, at least a first step toward target-controlled infusion with remimazolam in non-obese young subjects, particularly because there did not exist any compartment model of remimazolam for target-controlled infusion yet. Future studies may provide data to refine the pharmacokinetic and pharmacodynamic model of remimazolam for use in broader populations.

Second, the applied infusion scheme caused a relatively fast increase of the plasma concentration within the first 5 min after start of infusion. Correspondingly, the Modified Observer's Assessment of Alertness and Sedation score dropped relatively fast to values less than 2. Similarly, there was a fast increase of the Modified Observer's Assessment of Alertness and Sedation scores after stop of remimazolam infusion. As the Modified Observer's Assessment of Alertness and Sedation score was assessed every 2 min, Modified Observer's Assessment of Alertness and Sedation scores of 2 and 3 were observed relatively seldom, thereby limiting the results of the pharmacodynamic modeling. A further problem with the Modified Observer's Assessment of Alertness and Sedation score assessment was the correct discrimination between a score of 0 and 1 in the presence of involuntary movements.

In conclusion, remimazolam showed a high clearance, small volumes of distribution, short half-lives, and a fast onset and recovery of sedation. It is therefore a drug with good controllability. The pharmacokinetics of remimazolam after longer-lasting continuous infusion was similar to that reported after bolus administration. The hemodynamic effects were moderate, and there was no clinically significant effect of remimazolam on cardiac repolarization.

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Competing Interests

Drs. Schüttler and Fechner are scientific advisors of PAION UK Ltd., Cambridge, United Kingdom. The remaining authors declare no competing interests.

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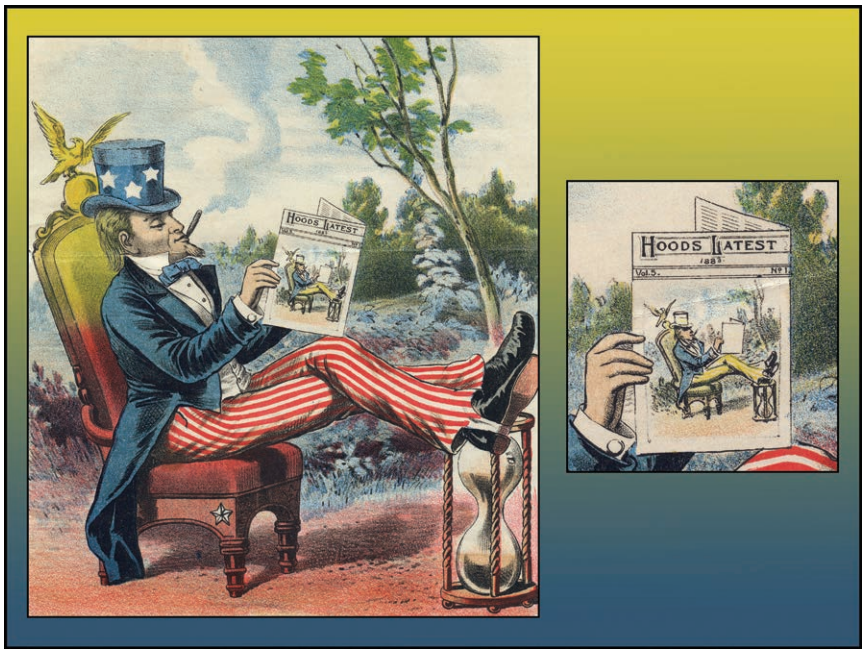
Could "Hood's Sarsaparilla" Root Out Uncle Sam's Rash of Pains?



Before the onetime sassafras-based "root beer" of today, sarsaparilla (pronounced "sass-puh-RILL-uh"; *Smilax* sp.) reigned as America's vine for flavoring beverages and remedies. Originally a Native American treatment for gastrointestinal and dermatologic complaints, sarsaparilla began to be used for "blood disorders," scurvy, scrofula, syphilis, and even leprosy. Popularizing this panacea was Vermont native Charles Ira Hood (1845 to 1922), who had moved to Lowell, Massachusetts, to apprentice as a pharmacist. After compounding his namesake sarsaparilla in 1876, Hood marketed it nationally with color lithographs of various characters reading a *Hood's Latest* advertising magazine (*left*). Here, Uncle Sam rests his legs on an hourglass—suggesting the nostrum's speedy onset—and reads the same booklet as the reader—hinting at its recurring effect. Rapid relief did not owe to the gentian, dandelion, and juniper berries that were also mixed in; rather, swift southern (New England) comfort likely came from sarsaparilla's 18% alcohol content…. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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