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APPLICATION NUMBER:

212295Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	212295
Link to EDR	\\CDSESUB1\evsprod\NDA212295\212295.enx
Submission Date	04/05/2019
Submission Type	505(b)(1) *Standard Review*
Brand Name	BYFAVO
Generic Name	Remimazolam
Dosage Form and Strength	Solution for Injection
Route of Administration	IV injection
Division Director:	Mehul Mehta. Ph.D.
OCP Division:	Division of Neuropsychiatric Pharmacology (DNP)
OND Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Dosage and Administration	An initial dose of remimazolam administered intravenously (IV) as a 5 mg (2 mL) push injection over a 1-minute time period. As needed, supplemental doses of 2.5 mg (1 mL) of remimazolam may be administered IV over a 15-seconds. At least 2 minutes must have elapsed prior to the administration of any supplemental dose
Proposed Indication	The induction and maintenance of procedural sedation in adults
Applicant	Cosmo Technologies Ltd
Associated IND	*102486*
OCP Review Team	*Deep Kwatra, Ph.D., (DNP Clinpharm Reviewer)* *Tao Liu, Ph.D., (DPM Reviewer)* *Atul Bhattaram, Ph.D., (DPM Team Lead)* *Yun Xu, Ph.D., (DNP Clinpharm Team Lead)*
OCP Final Signatory	*Mehul Mehta (DNP Clinpharm Division Director)*

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1. EXECUTIVE SUMMARY

1.1 Recommendations

From the Clinical Pharmacology perspective, NDA 212295, submitted on April 5, 2019 is acceptable and no approvability issues have been identified during the review of the NDA. Overall, adequate information has been provided characterizing the clinical pharmacology aspects of Remimazolam including to guide dosing in special populations. Labeling negotiation with the Applicant were still ongoing when this review was being documented in DARRTS.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Two pivotal Phase 3 studies support the efficacy of BYFAVO. **Study CNS7056-006 is a** Phase III, double-blind, placebo and midazolam-controlled trial assessing efficacy and safety of initial bolus dose and subsequent top-ups RMZ for procedural sedation. The total number of subjects in this study were 458 undergoing colonoscopy. **Study CNS7056-008 is a** Phase III, randomized, double-blind, placebo and midazolam-controlled trial assessing efficacy and safety of initial bolus dose and subsequent top-ups RMZ for procedural sedation. The total number of subjects in this study were 431 undergoing bronchoscopy.
General dosing instructions	The following are the dosage and administration recommendations for Byfavo. • An initial dose of remimazolam administered intravenously (IV) as a 5 mg (2 mL) push injection over a 1-minute time period • As needed, supplemental doses of 2.5 mg (1 mL) of remimazolam may be administered IV over a 15-seconds • At least 2 minutes must have elapsed prior to the administration of any supplemental dose
Dosing in patient subgroups (intrinsic and extrinsic factors)	**Renal Impairment:** No dosing adjustment needed **Hepatic Impairment:** Depending on the overall status of the patient, lower frequency of supplemental doses may be needed to achieve the level of sedation required for the procedure. All patients should be monitored for sedation-related cardiorespiratory complications.
Labeling	BYFAVO is indicated for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less.
Bridge between the to-be-marketed and clinical trial formulations	All pivotal studies submitted in this NDA were performed using the final to be marketed formulation.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Conventus Biomedical Solutions, Inc. as the authorized representative and U.S. Agent for Cosmo Technologies, Ltd. (Cosmo), of Dublin, submitted a 505(b)(1) NDA 212295 to support use of BYFAVO (remimazolam) for injection. BYFAVO (Remimazolam, also referred to as CNS7056 in the PAION development program and ONO-2745 in the previous Japanese development program) is a new ultra-short-acting benzodiazepine that is intended for intravenous (IV) repeat bolus administration for the induction and maintenance of procedural sedation in adults. Remimazolam was originally developed as an improved version of midazolam, building on the experience gained with the short-acting opiate ester, remifentanil. Conventus conducted several in vitro and in vivo studies to support the clinical pharmacology program based on recommendations provided during drug development for NDA 212295, under the IND 102486.

The clinical pharmacology package summarizes data from 11 completed Phase 1 clinical studies submitted with the original NDA. This includes 9 PK, PK/PD and cardiac function studies in healthy volunteers, 1 study in subjects with renal impairment (CNS7056-012), 1 study in subject with hepatic impairment (ONO-2745IVU007), and an abuse liability study in otherwise healthy recreational CNS depressant users (CNS7056-014, reviewed in detail by Control Substance Staff). The Pharmacokinetic studies included single ascending-dose (SAD) study (CNS7056-001); multiple ascending-dose (MAD) study (CNS7056-002); 1 IV infusion study (CNS7056-017); 2 SAD and IV infusion studies in Japanese subjects (ONO-2745-01 and ONO-2745-02); 1 oral bioavailability and 1 intranasal bioavailability study (CNS7056-016 and CNS7056-019 respectively); 2 studies to evaluate QT prolongation potential of remimazolam (CNS7056-017, the IV infusion study and CNS7056-005); 1 study to measure the effect of ethanol on orally administered remimazolam PK/PD (Study CNS7056-020). The NDA package also contained 11 Phase 2 and 3 studies, only 5 of which were in procedural sedation and two of which were pivotal Phase 3 studies (CNS7056-006 and CNS7056-008). Other supportive studies for procedural sedation were Phase 3 Study CNS7056-015, which was primarily a safety study and Phase 2 studies CNS7056-004 (with fentanyl) and CNS7056-003 (without fentanyl). As noted above, 6 clinical studies have also been performed, to evaluate IV remimazolam as an agent for general surgical anesthesia or ICU sedation. In those studies, remimazolam was administered as a continuous infusion. A population PK (PopPK) analysis was conducted on pooled data from 11 studies and submitted to the NDA. The goal of the analysis was to evaluate the effect of age, sex, race, American Society of Anesthesiologists (ASA) class, BMI, eGFR, and creatinine clearance (CrCL) on CL; the effect of concomitant medications that inhibit carboxylesterase 1 (CES-1) on CL; the effects of age, sex, race, ASA class and BMI on Vss. This review will focus on the 11 PK/PD studies, the PopPK analysis.

All the clinical pharmacology claims the sponsor has submitted and will be populated within the label are being derived from the Phase-I and II studies conducted by the sponsor. The efficacy and safety information are being derived from the pivotal Phase-III studies.

The key clinical pharmacology findings are:

When remimazolam is administered intravenously from 0.01 to 0.5 mg/kg, total exposure (AUC0-∞) suggested a close dose-proportional relationship. Volume of distribution (Vz) was 0.76 to 0.98 L/kg. Plasma protein binding was >91%, primarily to human serum albumin. Remimazolam has a terminal elimination half-life of 37 to 53 minutes and the mean distribution half-life is between 0.5 and 2 minutes.

The main route of metabolism of remimazolam is via conversion to primary inactive metabolite CNS7054, which is then subject to hydroxylation and glucuronidation. Conversion to CNS7054 is mediated by tissue carboxylesterases with no meaningful contribution by cytochrome P450 enzymes. The t1/2 of this metabolite was 2.4 to 3.8 hours. A very small fraction of remimazolam is excreted unchanged in urine, and 50% to 60% of the dose is excreted in urine as the metabolite CNS7054.

Remimazolam and the metabolite CNS7054 caused no clinically relevant inhibition of cytochrome P450 isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4. There were no inducing effects on CYP1A2, 2B6, and 3A4. No relevant inhibition of human drug transporters (OAT3, OCT2, OATP1B1, OATP1B3, OAT1, BCRP) was seen with remimazolam or CNS 7054. Remimazolam was not a relevant substrate of a panel of human drug transporters (OATP1B1, OATP1B3, BCRP). These results together show a very low potential for pharmacokinetic drug interactions.

In a thorough QT study, the largest mean placebo-adjusted change-from-baseline QTc (upper bound of 2-sided 90% confidence interval) was 6.7 (9.5) ms and 10.7 (13.4) ms, respectively, after treatment with 10 mg or 20 mg IV remimazolam. Remimazolam treatment is associated with increases in heart rate. The largest mean placebo-adjusted change-from-baseline HR (upper bound of 2-sided 90% CI) was 12.3 (14.2) bpm and 15.2 (17.1) bpm, respectively, after treatment with 10 mg and 20 mg remimazolam.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The following are the dosage and administration recommendations for Byfavo.

- An initial dose of remimazolam administered intravenously (IV) as a 5 mg (2 mL) push injection over a 1-minute time period.
- As needed, supplemental doses of 2.5 mg (1 mL) of remimazolam may be administered IV over a 15-seconds.
- At least 2 minutes must have elapsed prior to the administration of any supplemental dose

2.2.2 Therapeutic individualization

The pharmacokinetics of remimazolam were not altered in patients with mild to end stage renal disease not requiring dialysis. In a dedicated renal impairment study, remimazolam PK parameters (e.g. AUC and C_{max}) were not significantly different in subjects with varying degrees of renal function (from normal to severely impaired). Increased exposure to an inactive metabolite CNS7054 was observed with increasing

degree of renal impairment. No Therapeutic individualization is needed in patients with renal impairment for remimazolam.

The C_{max} values of total remimazolam were slightly lower in subjects with hepatic impairment than in healthy subjects. Prolonged $t_{1/2}$ of remimazolam were observed with increasing severity of hepatic impairment. The $t_{1/2}$ of remimazolam in healthy subjects and subjects with moderate and severe hepatic impairment are 42.9, 59.2 and 105 minutes, respectively. Sedation lasted longer and recovery took longer for subjects with hepatic impairment compared to healthy subjects. Since the C_{max} was not altered in a clinically meaningful way in hepatic impairment reducing the dose may lead to decreased C_{max} and hence decrease in efficacy, especially in terms of onset of action. Thus, dose reduction for hepatically impaired subjects is not suggested. Since the product is titrated to dose and subsequent top-up doses are administered in practice as needed, clinicians would be advised that a lower frequency of top-ups may be needed in patients with impaired liver function. For the suggested labeling language refer to section 2.4 of this review.

Based on population PK analysis, age, gender, race, and weight had no clinically relevant effect on remimazolam pharmacokinetics.

2.3 Outstanding Issues

Currently there are no outstanding issues from a clinical pharmacology perspective. The Labeling issues regarding QT prolongation and hepatic impairment were communicated to the sponsor in the Mid-Cycle communication and the labeling language is yet to be negotiated at the time of finalizing of this review.

2.4 Summary of Labeling Recommendations

The following labeling comments are proposed by this reviewer. Deletion is shown by ~~Strike-through text~~ and addition is shown by underline text.

Reviewer Comments:

8.5 Geriatric Use

Of the total number of subjects treated with TRADENAME in clinical studies for procedural sedation, there were 649 subjects <65 years of age, 221 subjects >65 years of age, 171 subjects between 65-74 years of age and 50 subjects >75 years of age.

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, (b) (4) greater sensitivity (a faster onset of loss of consciousness and a longer duration of sedation) of some older individuals (b) (4)

Supplemental doses of TRADENAME should be administered slowly to achieve the level of sedation required for the procedure, and all patients should be monitored for (b) (4) cardiorespiratory complications.

8.6 Hepatic Impairment

In patients with severe hepatic impairment, the dose of TRADENAME should be carefully titrated to effect. Depending on the overall status of the patient, lower frequency of supplemental doses may be needed to achieve the level of sedation required for the procedure. All patients should be monitored for sedation-related cardiorespiratory complications. *[see Clinical Pharmacology (12.3)].*

12.2 Pharmacodynamics

Dose finding studies (b) (4) the IV dosing recommendation of the initial 5 mg bolus, followed by 2.5 mg top-up doses. Median time to peak sedation in the following Phase 3 trials was 3.0 – 3.5 minutes (b) (4) median time to Fully Alert following the last dose of TRADENAME of 11.0 – 14.0 minutes.

Cardiac Electrophysiology ~~Effects on Electrocardiogram~~

In a thorough QT study (b) (4) 57 healthy volunteers were given an iv push of 10 mg or 20 mg TRADENAME, intravenous midazolam (2.5 mg or 7.5 mg) or placebo, or a single tablet of moxifloxacin 400 mg given orally. (b) (4) The largest mean placebo-adjusted change-from-baseline QTc (upper bound of 2-sided 90% confidence interval) was 6.7 (9.5) ms, 10.7 (13.4) ms, 4.5 (7.3) ms, and 8.1 (10.8) ms, respectively, after treatment with 10 mg or 20 mg TRADENAME, or 2.5 mg or 7.5 mg midazolam.

TRADENAME treatment is associated with increases in heart rate. The largest mean placebo-adjusted change-from-baseline HR (upper bound of 2-sided 90% CI) was 12.3 (14.2) bpm and 15.2 (17.1) bpm, respectively, after treatment with 10 mg and 20 mg TRADENAME.

(b) (4)

(b) (4)

12.3 Pharmacokinetics

Absorption

TRADENAME is administered intravenously. TRADENAME overall maximum plasma concentration (Cmax) after i.v. administration of 0.01 to 0.5 mg/kg was 189 to 6,960 ng/ml, and overall area under the concentration versus time curve from time 0 to infinity (AUC0-∞) was 12.1 to 452 ng·h/ml; TRADENAME cumulative dose versus TRADENAME total exposure (AUC0-∞) suggested a close to dose-proportional relationship. Metabolite Cmax was achieved approximately 20-30 minutes post dose. Metabolite AUC0-∞ was 231 to 7,090 ng·h/ml.

Metabolism

The main route of metabolism of TRADENAME is via conversion to primary inactive metabolite CNS7054, which is then subject to hydroxylation and glucuronidation. Conversion to CNS7054 is mediated by tissue carboxylesterases (primarily type 1A), with no meaningful contribution by cytochrome P450 enzymes. The t1/2 of the metabolite was 2.4 to 3.8 hours.

Special Populations

Hepatic Impairment: A Phase I open label, single dose trial evaluated the PK and safety of TRADENAME given as an i.v. bolus of 0.1 mg/kg over one minute in subjects with hepatic impairment (8 moderately hepatically impaired subjects and 3 severely hepatically-impaired subjects) and 9 matched healthy subjects.

The Cmax values of total TRADENAME were (b) (4) in subjects with hepatic impairment than in healthy subjects. Larger Vz and Vss, and prolonged t1/2, of TRADENAME were observed with increasing severity of hepatic impairment. Sedation lasted longer and recovery took longer for subjects with hepatic impairment compared to healthy subjects.

In patients with severe hepatic impairment, the dose of TRADENAME should be carefully titrated to effect. Depending on the overall status of the patient, (b) (4) less frequency of supplemental doses may be needed to achieve the level of sedation required for the procedure; (b) (4). All patients should be monitored for sedation-related cardiorespiratory complications.

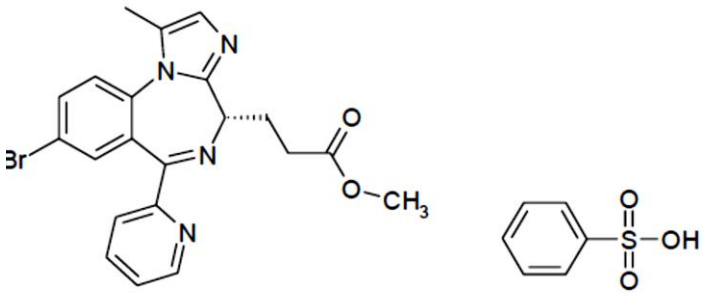
Renal Impairment: The pharmacokinetics of TRADENAME were not altered in patients with mild to end stage renal disease not requiring dialysis. In a (b) (4) renal impairment study (b) (4) TRADENAME PK parameters (e.g. AUC and Cmax) were not (b) (4) different in subjects with varying degrees of renal function (from normal to severely impaired). (b) (4) Increased exposure to (b) (4) inactive metabolite CNS7054 was observed with increasing degree of renal impairment.

Drug-drug Interactions:

TRADENAME and the metabolite CNS 7054 caused no relevant inhibition of cytochrome P450 isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4. There were no inducing effects on CYP1A2, 2B6, and 3A4. TRADENAME was not a relevant substrate of a panel of human drug transporters (OATP1B1, OATP1B3, BCRP).
No relevant inhibition of human drug transporters (OAT3, OCT2, OATP1B1, OATP1B3, OAT1, BCRP) was seen with TRADENAME or CNS 7054. Remifentanil did not influence the hydrolysis of TRADENAME by human liver S9 fractions, (b) (4) the possibility of an interaction by competition for liver carboxylesterases.
These results together show a very low potential of TRADENAME for pharmacokinetic drug interactions.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Table 2: Physical-Chemical Properties of [redacted]	
Proprietary Name of Drug Product:	BYFAVO ™
Non-proprietary Name of Drug Product:	Remimazolam for Injection
Non-proprietary Name of Drug Substance:	Remimazolam
Strengths:	12-ml vial containing [redacted] mg of remimazolam besylate; when reconstituted with 8.2 mL of sterile saline solution, the concentration obtained is 2.5 mg/mL of remimazolam (as free base)
Chemical Name	4H-imidazol[1,2-a][1,4]benzodiazepine-4-propionic acid, 8-bromo-1-methyl-6-(2-pyridinyl)-(4S)-methyl ester, benzenesulfonate (1:1)
Structure	

Formulation:

The proposed Remimazolam for Injection 20 mg drug product is a sterile, white to off-white lyophilized powder filled in single-use clear, 12 mL [redacted] glass vials fitted with [redacted] rubber stoppers and capped with aluminum seals with [redacted] flip-off caps. The vial contains [redacted] mg of remimazolam besylate, which when reconstituted with 8.2 mL of sterile saline solution, the concentration obtained is 2.5 mg/mL of remimazolam (as free base)

Table 3: Composition of Remimazolam for Injection 20 mg

USP = United States Pharmacopeia 1. Contains [redacted] overage; 2. [redacted]

Component	Quantity per Vial	Percentage (W/W)	Function	Quality Standard
Remimazolam besylate (Remimazolam base)	(b) (4) mg[1] mg)	(b) (4) %	Active ingredient	In-house
Lactose monohydrate	(b) (4) mg	%	Bulking agent / stabilizer	USP
Dextran 40	82. (b) (4) mg	%	(b) (4)	USP
(b) (4)				USP
HCl/NaOH	(b) (4)	-	pH adjustment	USP

3.1.1 Key Studies Submitted in NDA

Clinical Pharmacology Studies*:*

The core clinical development program includes 11 phase 1 studies (described in Table 4) and 11 Phase 2 and 3 studies. The PK/PD studies included single ascending-dose (SAD) study (CNS7056-001); multiple ascending-dose (MAD) study (CNS7056-002); 1 IV infusion study (CNS7056-017); 2 SAD and IV infusion studies in Japanese subjects (ONO-2745-01 and ONO-2745-02 respectively); 1 oral bioavailability and 1 intranasal bioavailability study (CNS7056-016 and CNS7056-019); 2 studies to evaluate QT prolongation potential of remimazolam (CNS7056-017: the IV infusion study and CNS7056-005); 1 study to measure the effect of ethanol or orally administered remimazolam PK/PD (Study CNS7056-020) 1 study in subjects with renal (CNS7056-012) and 1 study in subject with hepatic impairment (ONO-2745IVU007) and an abuse liability study in otherwise healthy recreational CNS depressant users (CNS7056-014).

Table 4: Summary of Clinical Pharmacology Studies of Remimazolam Submitted to NDA 212295

Study No.	Population	Total number of subjects	Number of Subjects Randomized to BYFAVO	Brief Description	Route and Doses	Site
CNS7056-001	Healthy adult volunteers	81	54	Double-blind, placebo- & midazolam-controlled study assessing PK, PD & safety of single ascending dose of RMZ	0.01 to 0.30 mg/kg IV	USA
ONO-2745-01	Healthy (young adult and elderly) volunteers	42	35	Double-blind, parallel group study assessing PK, PD, safety & tolerability of single ascending dose of RMZ	0.05 to 0.5 mg/kg IV	Japan

ONO-2745-02	Healthy adult male volunteers	10	8	Double-blind, placebo-controlled, parallel group study assessing PK, PD, safety & tolerability of a single continuous IV infusion of RMZ	1 mg/kg/hr IV	Japan
ONO-2745IVU007	Healthy & chronic hepatic impairment subjects	20	20	Open-label study assessing PK, PD & safety of single IV dose RMZ in healthy subjects vs those with chronic hepatic impairment	0.1 mg/kg IV	USA
CNS7056-012	Subjects with normal renal function & with ESRD not requiring dialysis	23	23	Open-label study assessing PK and safety in subjects with ESRD not requiring dialysis vs those with normal renal function	1.5 mg IV	Hungary
CNS7056-002	Healthy adult volunteers	51	51	Part A – flumazenil reversal Part B – multiple ascending dose in healthy volunteers undergoing colonoscopy	Part A: 0.25 Part B: 0.04 to 0.10 mg/kg	USA
CNS7056-017	Healthy adult volunteers	20	20	PK, PD modelling of hypnotic effect and impact on corrected QT interval	5 mg/min (5 min) 3 mg/min (15 min) 1 mg/min (15 min) Stop at 35 min (Total=85 mg)	Germany
CNS7056-016	Healthy adult volunteers	14	14	Oral bioavailability of single dose RMZ	0.14 mg/kg oral; 0.025 mg/kg IV	USA
CNS7056-019	Healthy adult volunteers	12	12	Safety, PK, PD and bioavailability of intranasal powder & solution RMZ compared to IV control	4 mg IV, 10, 20 and 40 mg intranasal powder 10, 20 and 40 mg	USA

					intranasal solution	
CNS7056-005	Healthy adult volunteers	57	57	Double-blind, placebo and midazolam controlled, cross-over study assessing effect of single-doses IV RMZ on QTc intervals	10.0 and 20.0 mg IV	USA
CNS7056-014	Recreational depressant users	83	40	Double-blind, placebo and midazolam controlled cross-over study assessing abuse potential of RMZ	5.0 and 10.0 mg IV	USA
CNS7056-020	Healthy female volunteers	32	32	A study assessing PK, PD, safety and tolerability after oral RMZ administration with ethanol	Part1: 60, 140, 240, 360 and 480 mg orally, Part 2: 360 mg plus 5%, 15% and 40% EtOH	USA

Clinical Studies:

The NDA package also contained 11 Phase 2 and 3 studies, only 5 of which were in procedural sedation and two of which were pivotal Phase 3 studies.

Phase 3 Study (with commercial scale formulation):

- **Study CNS7056-006** Phase III, Double-blind, placebo and midazolam-controlled trial Assessing efficacy and safety of initial bolus dose and subsequent top-ups RMZ for procedural sedation. The total number of subjects in this study were 458 undergoing Colonoscopy.
- **Study CNS7056-008** Phase III, Randomized, Double-blind, placebo and midazolam-controlled trial Assessing efficacy and safety of initial bolus dose and subsequent top-ups RMZ for procedural sedation. The total number of subjects in this study were 431 Undergoing Bronchoscopy.

3.1.2 Regulatory Background

Remimazolam is a new molecular entity (NME) and no remimazolam products have been previously approved by the FDA.

During the midcycle communication T-con held with the sponsor on Nov 22nd, 2019, the sponsor was informed that (b) (4)

[redacted] (b) (4) [redacted]. We intend to include a description of the drug effect on HR and QTcF from the TQT study, CNS7056-005, in labeling, if the drug is approved. The final labeling language is still being discussed and has not been finalized." The Sponsor stated that they intend to provide written explanation [redacted] (b) (4) [redacted]. The written response was received on Dec 19th and was reviewed by the QT-IRT [redacted] (b) (4). The details of the IR response and QT-IRTs recommendations are presented later in the review.

In the same meeting the sponsor was also informed regarding the hepatic impairment labeling that "Although we do agree with the observed increase in exposure (AUC) and elongated half-life for remimazolam in subjects with severe hepatic impairment, [redacted] (b) (4) [redacted]. We may recommend additional monitoring in the label [redacted] (b) (4) The final labeling language is still being discussed and has not been finalized." To which the sponsor acknowledged our comments and they clarified [redacted] (b) (4) [redacted] This point is considered during internal labeling deliberations.

For this NDA, a Pre-NDA meeting was held on July 12th, 2018. A Type-C guidance meeting was held on 11-16-2017 and two End of Phase 2 (SOP-2) meetings were held on 10/17/2013 & 08/14/2014 respectively under IND 102486. All pivotal phase 3 safety and efficacy studies conducted and submitted in this NDA were performed using the TBM formulation.

3.2 General Pharmacology and Pharmacokinetic Characteristics

BYFAVO (Remimazolam) is a fast-acting, ultra-short-duration sedative intended for the induction and maintenance of procedural sedation. It is a chirally pure molecule (S enantiomer) and is isolated as the besylate salt. Remimazolam is a benzodiazepine that was originally developed to have equivalent sedative effects to agents such as midazolam but was designed as an ester-based drug to be rapidly hydrolyzed in the body to an inactive metabolite and, consequently, to have a shorter and more predictable duration of action than current agents. Remimazolam binds to brain benzodiazepine sites (gamma amino butyric acid type A [GABAA] receptors) with high affinity, while its carboxylic acid metabolite (CNS7054, primary non-active metabolite) has a 300 times lower affinity for the receptor. No evidence of off-target activities of Remimazolam or its metabolite have been observed. Remimazolam enhanced GABA currents in cells stably transfected with subtypes of the GABAA receptor. Remimazolam, like other benzodiazepines in clinical use, does not show clear selectivity between subtypes of the GABAA receptor. Confirmation of an effect on central GABAA receptors was revealed by a dose-dependent inhibition of substantia nigra pars reticulata neuronal firing, with a rapid recovery to baseline firing rates.

The proposed remimazolam product is indicated for the induction and maintenance of procedural sedation in adults. The clinical efficacy studies, CNS7056-006 and CNS7056-008 in subjects undergoing procedural sedation involving colonoscopy and bronchoscopy respectively along with three other supportive studies for procedural sedation and the eleven clinical pharmacology studies described in section 3.3.3 and section 4.2 form the basis to support the dosing for this NDA along with some information being derived from population PK analysis conducted by the sponsor.

For final assessment of the safety and efficacy findings, see Clinical review by Dr. Renee Petit-Scott (Clinical Reviewer). For detailed information on the Population PK analysis conducted by the sponsor, refer to the pharmacometrics review conducted by Dr. Tao Liu and Dr. Atul Bhattaram in the Appendix section of this review.

Summary of Population PK

Multiple population PK and population PK/PD modelling analyses were performed during the remimazolam development program for both bolus dosing (for procedural sedation) and continuous infusion dosing (for general anesthesia). Initially, PK models utilized a physiologic recirculation model (W-06-13, W-03-09, W-03-10). These models assumed that a significant portion of the metabolism occurred in the lung. Later in vitro data suggested that the rate of metabolism in the lung is much slower than the liver (AE-7176-G) therefore, these models are not relevant for predicting exposure of remimazolam. Several early pop PK models showed that covariates such as race, body weight, and body mass index (BMI) are not important predictors of the variability in the PK of remimazolam (W-09-14, WM-06-11, W-03-10). This observation led to the decision to use fixed-dose (mg) rather than weight-adjusted (mg/kg) bolus dosing for subsequent clinical studies procedural sedation.
Many of the other PK models reported were conducted to either describe simplistic models from data in individual studies (WM-06-11, Y12CA009) or to evaluate potential mechanisms of the high concentrations seen in patients in the intensive care unit (ICU) receiving continuous infusions of remimazolam (Y14CA003, W-09-14W-04-14A, W-04-14b). After completion of the Phase 3 studies in procedural sedation, data from 11 clinical trials were pooled for more comprehensive popPK analyses. Pop PK modeling included all subjects who received an active remimazolam dose with available dosing information and remimazolam plasma levels before administration of flumazenil: 126 healthy subjects, 193 patients undergoing procedural sedation, and 40 patients undergoing induction and maintenance of anesthesia for surgery; 359 subjects total. The goal was to evaluate the effect of age, sex, race, American Society of Anesthesiologists (ASA) class, body mass index (BMI), estimated glomerular filtration rate (eGFR), and creatinine clearance (CrCL) on CL; the effect of concomitant medications that inhibit carboxylesterase 1 (CES-1) on CL; the effects of age, sex, race, ASA class and BMI on volume of distribution at steady-state (Vss).

The final population PK model was a 3-compartment model with a CL of 1.18 L/min and a Vss of 41.5 L in a 70 kg subject. Analyses indicated that:

- CL was 9.7% higher in females than males.
- CL was 13.0% lower in African Americans than in Caucasians or Asians. The Vss was 16% lower in African Americans than in Caucasians or Asians.

- Other parameters assessed, such as age, ASA class, BMI, eGFR, and creatinine clearance had no effect on the PK of remimazolam.

General PK Characteristics:

Absorption:

BYFAVO is being developed for IV administration but oral administration of remimazolam was evaluated in Study CNS7056-016 where 14 subjects received a single dose of remimazolam (0.14 mg/kg orally and 0.025 mg/kg IV) under fasting conditions, with 48-hour washout period between each dose. Mean peak (C_{max}) and total (AUC_{0-t}) remimazolam systemic exposure were considerably lower after oral treatment than after IV treatment. The absolute bioavailability of oral remimazolam was 1.2% based on dose-normalized C_{max} (90% CI: 0.008 - 0.017) and 2.2% based on dose-normalized AUC_{0-t} (90% CI: 0.015 - 0.032). The median t_{max} of the metabolite, CNS7054, was 0.5 hours for both treatments, indicating that remimazolam was rapidly metabolized to CNS7054.

Table 5: Statistical Analysis of Relative Bioavailability of Oral and Intravenous Formulations of Remimazolam

Analyte	PK Parameter (Units)	Geometric LS Mean		LS Mean Ratio (Test/Reference)	
		Oral	IV	Estimate	90% CI
Remimazolam	C_{max} (ng/mL)	4.29	65.19	0.66	(0.044, 0.098)
	AUC_{0-T} (ng·h/mL)	2.46	19.91	0.123	(0.084, 0.182)
CNS 7054	C_{max} (ng/mL)	829.91	115.55	7.182	(6.626, 7.785)
	AUC_{0-T} (ng·h/mL)	1881.59	292.46	6.343	(5.775, 7.167)

Based on dose-normalized parameters, C_{max} and AUC_{0-t} for the metabolite, CNS7054, were respectively 1.3 and 1.2-fold higher after oral treatment than after IV administration. For both oral and IV treatment, mean peak (C_{max}) and total (AUC_{0-t} and AUC_{inf}) systemic exposure to metabolite CNS7054 was considerably higher than exposure to the parent compound. The mean $t_{½}$ of CNS7054 was 1.9 hours after IV treatment and 2.5 hours after oral treatment

Distribution:

Following a single bolus dose of remimazolam, the volume of distribution (Vz) was 0.76 to 0.98 L/kg. In study CNS7056-002, when remimazolam was administered as a bolus IV loading dose (0.04-0.1 mg/kg) followed by supplemental doses to maintain sedation during colonoscopy (CNS7056-002), the mean volume of distribution (Vss) for remimazolam ranged from 52-71 L (Table 17).

In vitro studies indicate that at concentrations ranging from 1 to 10 µg/mL, the distribution of remimazolam in blood cells in humans ranged from 7.5 to 11.7% (Study report AE-7175-G). Protein

binding of ^{14}C-labeled remimazolam was found to be >91% at concentrations ranging from 1-10 µg/mL in human serum, primarily to human serum albumin (Study Report AE-6097-G). It was not affected by the addition of clinically relevant concentrations of various concomitant drugs such as propofol, isoflurane, sevoflurane, thiamylal, remifentanil, rocuronium, or succinylcholine (Study Report AE-6503-G). Thus, drug-drug interaction via displacement of protein binding by concomitant drugs in clinical practice is considered negligible.

Metabolism:

When administered IV, remimazolam is metabolized by tissue carboxylesterase (CES) (primarily type 1A) which produce a primary inactive metabolite (CNS7054) along with six others that make up less than 0.5% each of the balance of metabolism products in plasma or urine. A study on structures of metabolites in human plasma and urine (Y10AE019) was conducted and complementary information on plasma metabolites is available from a publication on a different remimazolam product authored by Zhou et al. in 2017. The metabolites and proposed metabolic pathways for remimazolam are provided in Figure 1. It is evident that experimental animals and humans share the principal metabolite, CNS7054, and all metabolites found in the circulation, though CNS7054 is the primary and only relevant metabolite of remimazolam. No clear metabolite peak apart from that of CNS7054 was observed, irrespective of cell concentrations and incubation times in either human studies in cryopreserved hepatocytes or studies in human plasma. Appearance of these further metabolites in human urine due their greater hydrophilicity and rapid renal excretion is predictable.

Figure 1: Proposed Metabolic Pathways of Byfavo.

Excretion:

Remimazolam is metabolized quickly in the liver and very little of the parent drug is recovered from plasma or urine following IV administration. In healthy subjects, at least 80% of the administered remimazolam is excreted as CNS7054. In subjects undergoing colonoscopy, after pretreatment with 2 L of resuspended HalfLytely and 2 tablets (5 mg) bisacodyl, approximately 50-60% of the administered dose is recovered as the main metabolite, CNS7054, in urine. Mean $t_{1/2}$ following single IV doses of remimazolam ranged from 24-53 minutes. Remimazolam is rapidly cleared from plasma; clearance is high (61 - 78 L/h) and not related to body weight.

Remimazolam $T_{1/2}$ is not affected by renal impairment. The $T_{1/2}$ was prolonged with increasing severity of hepatic impairment. For example, the $T_{1/2}$ of unbound remimazolam in healthy subjects and subjects with moderate and severe hepatic impairment are 42.9, 59.2 and 105 minutes, respectively.

Dose-proportionality of Remimazolam:

Dose proportionality was analyzed in numerous single and multiple dose studies for remimazolam. In Study CNS7056-001, single bolus IV injections of remimazolam of 0.01, 0.025, 0.05, 0.075, 0.1, 0.15, 0.2, 0.25, 0.3 mg/kg were administered (infused over 1 minute). Across this 30-fold increase in dose (0.01 mg/kg to 0.30 mg/kg), C_{max} increased by approximately 28-fold (50.83 to 1401.07 ng/mL), AUC_{0-t} increased by approximately 28-fold (215.14 to 5956.76 ng*hr/mL), and AUC_{0-inf} increased by approximately 37-fold (230.76 to 6338.59 hr*ng/mL). Distribution and clearance did not depend on dose; CL was 0.853 and 0.878 L/hr/kg at 0.01 and 0.30 mg/kg, respectively, and Vd was 0.757 and 0.894 L/kg.

Similar patterns were observed in other studies. For example, in Study ONO-2745-01, the C_{max} and AUC_{inf} increased in proportion to dose in the dose range of 0.05 to 0.5 mg/kg. The 95% confidence interval (CI) for the slope (β) of the regression line was in the range of 0.70 to 1.30. The differences in T_{max} and $T_{1/2}$ among the doses were not significant.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

No biological biomarker was assessed in this NDA. In both the pivotal Phase 3 studies the primary efficacy endpoint was success of the procedure, defined as the completion of the colonoscopy procedure with no requirement for a rescue sedative medication and no requirement for more than 5 doses of study medication (remimazolam or placebo) within any 15-minute window. For subjects randomized to midazolam only, the latter part of the definition was no requirement for more than 3 doses of midazolam within any 12-minute window. This primary endpoint analysis was performed in the intent-to-treat (ITT) population, defined as all randomized subjects. Several secondary assessments were also performed in both studies. For multiple initial clinical pharmacology studies, PD endpoints included:

- Sedation incidence rates: Incidence rates of the loss of consciousness (LoC) and loss of eyelid/corneal reflexes
- Distribution of Modified observer's assessment of alertness and sedation (MOAA/S) score over time
- Time to LoC
- Time to loss and return of
    - response to acoustic stimulus.
    - eyelid reflex.
    - corneal reflex.
- Time to return to orientation relating to person, time and location
- Change in QTc and other ECG parameters over time

Clinical Pharmacology information provided within the package supports dosing of BYFAVO with regards to patients' age (elderly), renal and hepatic function, as well as co-administration with other concomitant medications.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

An initial single intravenous dose over one minute of remimazolam 5.0 mg and maintenance doses of further top-up doses of remimazolam 2.5 mg (not earlier than two minutes apart after assessment of the sedative effect) appears to be efficacious in the pivotal clinical trials CNS7056-006 and CNS7056-008. For final assessment of the safety and efficacy findings, see Clinical review by Dr. Renee Petit-Scott (Clinical Reviewer). Population PK analysis showed that Age, gender, race, and weight had no clinically relevant effect on remimazolam pharmacokinetics

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

The effect of intrinsic factors (i.e., age, gender, body weight and BMI) on the PK of remimazolam were studied in multiple individual studies. Additionally, several early popPK models showed that covariates such as race, body weight, and body mass index (BMI) are not important predictors of the variability in the PK of remimazolam (Study reports W-09-14, WM-06-11, W-03-10). This observation led to the decision to use fixed-dose (mg) rather than weight-adjusted (mg/kg) bolus dosing for subsequent clinical studies procedural sedation.

After completion of the Phase 3 studies in procedural sedation, data from 11 clinical trials were pooled for more comprehensive popPK analyses: Studies ONO-2745-01, ONO-2745-02, ONO-2745-03, ONO-2745-IVU007, CNS7056-001, CNS7056-002, CNS7056-004, CNS7056-006, CNS7056-008, CNS7056-015, and CNS7056-017. (NPS2981-RPT001_01) with the goal to evaluate the effect of age, sex, race, American Society of Anesthesiologists (ASA) class, body mass index (BMI), estimated glomerular filtration rate (eGFR), and creatinine clearance (CrCL) on CL; the effect of concomitant medications that inhibit carboxylesterase 1 (CES-1) on CL; the effects of age, sex, race, ASA class and BMI on volume of distribution at steady-state (Vss).

Gender

As noted, population PK modelling (Study Report NPS2147-RPT001) to support remimazolam bolus dosing for procedural sedation found that CL was 11% higher in females than males.

In the time-to-event modelling analysis (Study Report N-12-15) evaluating the PK/PD of remimazolam administered as a continuous infusion for the induction and maintenance of general anesthesia, females required a slightly (5%) higher infusion rate to produce adequate sedation and had a slightly faster (~3-5 min) time to extubation than males.

In both cases, these effects are all small in magnitude and not considered clinically relevant.

Age

Phase 1 Study ONO-2745-01, conducted in Japan, evaluated the PK and PD of a single IV bolus dose of remimazolam 0.1 mg/kg (infused over 1 minute) in healthy young adult males (age 20-45 years) versus healthy elderly males (age 65-74 years). No difference in the PK of remimazolam between healthy young adult and elderly male subjects was observed. The PD effects between adult and elderly males was generally similar except that remimazolam 0.1 mg/kg induced deeper sedation in healthy elderly male subjects than in healthy adult male subjects, with the duration of loss of consciousness comparable to that in healthy adult male subjects at 0.3 mg/kg.

These findings are consistent with the results of the two more extensive population PK/PD analyses which also showed no effect of age on remimazolam PK but found a small PD effect related to increased age (i.e., that elderly patients may have a faster onset of LoC and a longer duration of sedation than younger patients with infusion and bolus dosing, respectively) which appears to be not clinically relevant.

Race

PK Analysis (Y13CA010) evaluated the effect of race on remimazolam PK. This analysis included PK data from 30 Japanese and 54 non-Japanese subjects received single doses of remimazolam of 0.05, 0.1, 0.2 and 0.3 mg/kg. Plasma remimazolam concentrations for Japanese subjects <65 years old were taken from Study ONO-2745-01 and plasma concentrations for non-Japanese subjects (18-54 years old) were taken from Study CNS7056-001. C_{max} and AUC_{inf} values were higher in the non-Japanese subjects than in the Japanese subjects, except for AUC_{inf} at a dose of 0.1 mg/kg. However, based on the ranges of the PK parameter distribution and the changes in the plasma ONO-2745 concentrations in Japanese and Non-Japanese subjects, the PK of Japanese and Non-Japanese subjects were generally considered to be similar.

The final population PK model was a 3-compartment model with a CL of 1.18 L/min and a Vss of 41.5 L in a 70 kg subject. In this population PK analysis, CL of remimazolam was found to be 13.0% lower and the Vss was 16% lower - in African Americans than in Caucasians or Asians.

Table 6: Pharmacokinetic parameters (C_{max}, AUC_{inf}) of remimazolam after intravenous injection of remimazolam to Japanese and Non-Japanese healthy subjects at doses of 0.05 to 0.3 mg/kg

Parameter	Dose (mg/Kg)	Japanese Mean (SD)	Non-Japanese Mean (SD)	Japanese/Non-Japanese GMR (90% confidence interval)
AUC_{inf} (ng*h/mL)	0.05	49.6(2.7)	57.3(8.4)	0.87(0.76-1.00)
	0.1	120(9)	107(7)	1.11(1.03-1.20)
	0.2	199(34)	224(44)	0.90(0.73-1.10)
	0.3	255(23)	339(98)	0.78(0.61-0.99)
C_{max} (ng/mL)	0.05	654(138)	721(85)	0.90(0.74-1.08)
	0.1	1620(210)	1880(260)	0.86(0.74-1.00)
	0.2	3260(550)	3560(940)	0.93(0.72-1.22)
	0.3	4190(520)	6100(740)	0.69(0.60-0.79)

In the population PK/PD analyses race was not found to be a significant factor affecting remimazolam PK/PD with bolus dosing for procedural sedation or infusion dosing for general anesthesia.

Body Weight

Multiple PopPK and PK/PD analyses were conducted to show that body weight and BMI are not significant factors affecting the PK or PD of remimazolam. This was a key factor in switching from weight-based dosing to fixed dosing in the later Pivotal studies.

Renal Impairment

The PK/PD effects of remimazolam in subjects with renal impairment were demonstrated in Study CNS7056-012. In this open-label PK and safety study, a single dose of 1.5 mg remimazolam was administered to 6 subjects with end-stage renal disease (ESRD; estimated glomerular filtration rate [eGFR] of 15 to 30 mL/min/1.73m2), 5 subjects with ESRD (eGFR of <15 mL/min/1.73 m2), and 12 subjects with normal renal function (10 subjects with eGFR ≥90mL/min/1.73 m2 and 2 subjects with eGFR of 80 to 90 mL/min/1.73 m2).

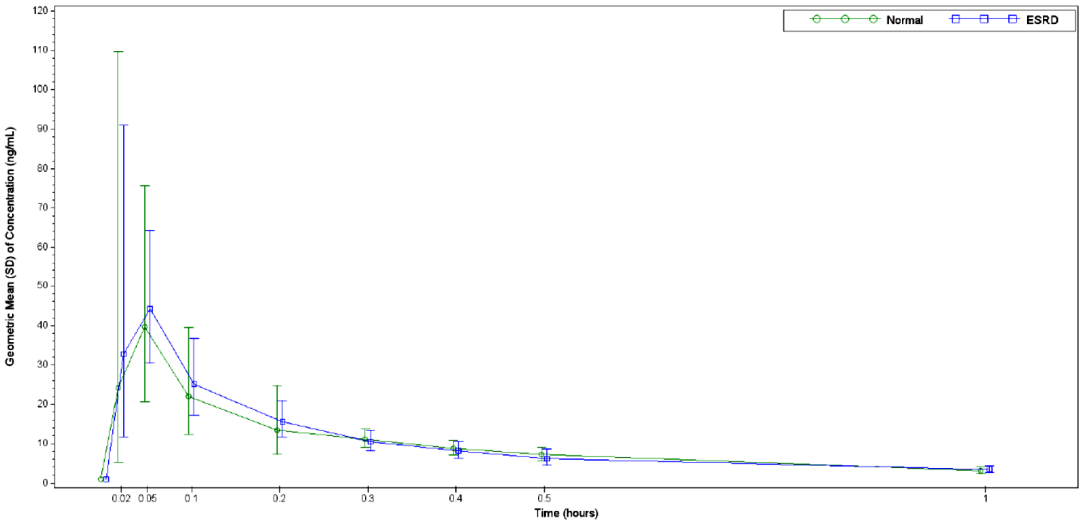
Pharmacokinetics: The concentration-time profile and PK after a single IV dose of 1.5 mg remimazolam did not show relevant differences in ESRD subjects compared to subjects with normal renal function. For example, for ESRD subjects and subjects with normal renal function, CL was 118.4 vs 111.4 L/h, C_{max} was 56.5 vs 53.0 ng/mL, T_{max} was 0.03 vs 0.04 hours, and $AUC_{0\text{-}inf}$ was 12.7 vs 13.5 (h*ng/mL) (geometric means).

Table 7: Summary Statistics of Pharmacokinetic Parameters for Remimazolam in Plasma. Study Report CNS7056-012

		Normal	ESRD
	n	**10**	**8**
CL (L/h)	Mean (SD)	112.2 (13.9)	123.0 (36.7)
	GM (CV%)	**111.4 (12.4)**	**118.4 (29.8)**
	Median (Min-Max)	113.5 (83.1-133.1)	106.9 (76.9-180.8)
C_{max} (ng/mL)	Mean (SD)	60.1 (35.4)	57.7 (12.2)
	GM (CV%)	**53.0 (58.9)**	**56.5 (21.1)**
	Median (Min-Max)	54.4 (23.6-149.5)	57.0 (36.6-74.5)
T_{max} (h)	Mean (SD)	0.04 (0.02)	0.04 (0.02)
	GM (CV%)	0.04 (40.3)	0.03 (46.0)
	Median (Min-Max)	**0.05 (0.02-0.05)**	**0.05 (0.02-0.05)**
AUC_{0-inf} (h*ng/mL)	Mean (SD)	13.6 (1.9)	13.1 (3.7)
	GM (CV%)	**13.5 (14.0)**	**12.7 (28.4)**
	Median (Min-Max)	13.2 (11.3-18.0)	14.1 (8.3-19.5)
AUC_{0-t} (h*ng/mL)	Mean (SD)	11.7 (2.0)	11.5 (3.4)
	GM (CV%)	**11.5 (16.8)**	**11.1 (29.7)**
	Median (Min-Max)	11.2 (9.7-16.6)	11.9 (7.1-17.3)
$t_{1/2}$ (h)	Mean (SD)	0.40 (0.05)	0.40 (0.23)
	GM (CV%)	**0.40 (12.8)**	**0.35 (58.3)**
	Median (Min-Max)	0.41 (0.32-0.47)	0.33 (0.20-0.77)
λ_z (1/h)	Mean (SD)	1.75 (0.24)	2.26 (1.10)
	GM (CV%)	**1.74 (13.6)**	**1.99 (48.9)**
	Median (Min-Max)	1.71 (1.48-2.16)	2.15 (0.89-3.53)
V_z (L)	Mean (SD)	65.4 (13.1)	63.1 (24.7)
	GM (CV%)	**64.1 (20.0)**	**59.4 (39.1)**
	Median (Min-Max)	68.6 (43.8-84.7)	56.2 (40.0-113.2)

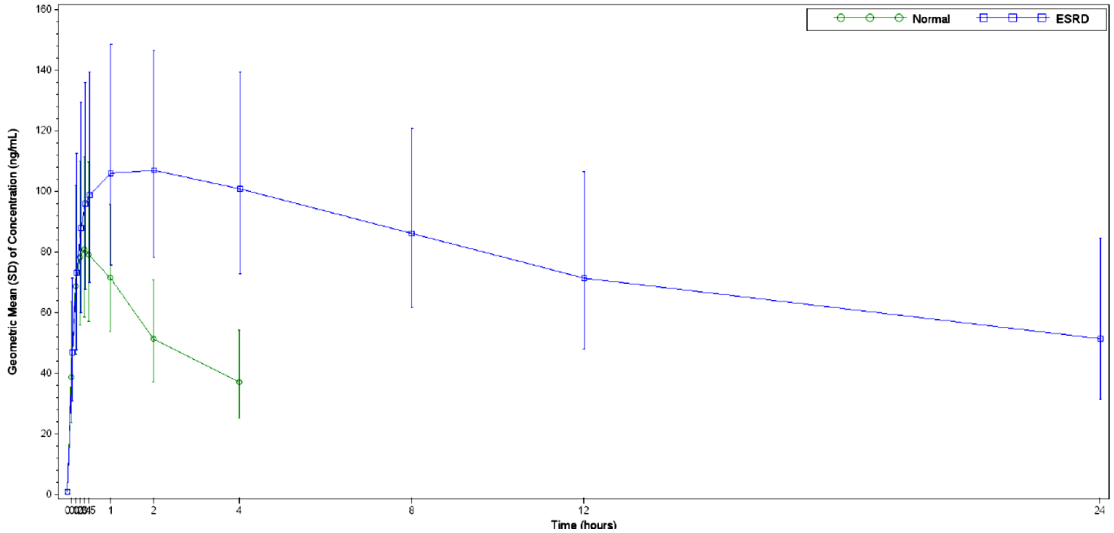
Based on these results, impairment of renal function is not expected to influence the PK characteristics of remimazolam and therefore no dose adjustment is considered necessary for patients with renal impairment.

Figure 2: Geometric Mean (SD) Plasma Concentration-Time Profiles of Remimazolam (Linear Scale). Study Report CNS7056-012



The exposure to the metabolite CNS7054 was increased and its elimination was delayed in ESRD subjects compared to subjects with normal renal function. Accumulation of CNS7054 can be expected in cases of repeated bolus administration or in continuous infusion settings, such as general anesthesia and ICU sedation. Due to its inactivity, this accumulation is not considered clinically relevant.

Figure 3: Geometric Mean (SD) Plasma Concentration-Time Profiles of CNS 7054 (Linear Scale). Study Report CNS7056-012



Based on these results no dose adjustment is required in renal impairment, including ESRD patients.

Hepatic Impairment

The PK/PD effects of remimazolam in subjects with hepatic impairment were evaluated in study ONO-2745IVU007. In this open label, single-dose IV administration study, 8 patients with moderate hepatic impairment (score of 7 to 9 on the Child Pugh scale) and 9 healthy matched subjects as well as 3 patients with severe hepatic impairment (score of 10 to 15 on the Child Pugh scale) received remimazolam as a

single IV bolus at 0.1 mg/kg infused over 1 minute. No patients with mild hepatic impairment were enrolled in the study.

Pharmacokinetics: The summary statistics of PK parameters of unbound remimazolam after IV administration to healthy subjects and subjects with hepatic impairment are summarized in Table 8. The C_{max} values of unbound remimazolam were similar among all subjects. Larger V_z and V_{ss} of remimazolam were observed with increasing severity of hepatic impairment. These data suggest that the unbound ratio of remimazolam in plasma increased in subjects with hepatic impairment and the volume of distribution of remimazolam increased accordingly. The $T_{1/2}$ was prolonged with increasing severity of hepatic impairment. For example, the $T_{1/2}$ of unbound remimazolam in healthy subjects and subjects with moderate and severe hepatic impairment are 42.9, 59.2 and 105 minutes, respectively. This can be explained by the decreasing hepatic blood flow shown in the subjects with hepatic impairment.

Table 8: Summary Statistics of PK Parameters of Unbound Remimazolam After IV Administration to Healthy Subjects and Subjects with Hepatic Impairment in Study ONO-2745IVU007 (Mean ± SD)

PK Parameter	Healthy Subjects N=8	Moderate Hepatic Impairment N=8	Severe Hepatic Impairment N=3
Cmax (ng/mL)	356 ± 97.6	280 ± 79.9	323 ± 61.0
Tmax* (min)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
AUC_{last} (ng*h/mL)	16.4 ± 4.71	17.5 ± 3.85	26.2 ± 3.76
AUC_{inf} (ng*h/mL)	16.6 ± 4.78	17.9 ± 4.02	29.6 ± 2.85
λ_z (1/min)	0.0188 ± 0.00804 0	0.0121 ± 0.00214	0.00693 ± 0.00168
$T_{1/2}$ (min)	42.9 ± 17.5	59.2 ± 11.7	105 ± 29.7
CL (L/min/kg)	0.109 ± 0.0363	0.0989 ± 0.0299	0.0567 ± 0.00548
V_z (L/kg)	6.17 ± 1.58	8.24 ± 1.92	8.73 ± 3.30
V_{ss} (L/kg)	2.40 ± 0.705	3.58 ± 1.61	5.15 ± 2.33

* Median (Min - Max)
Profile of Subject ONO-2745IVU007 (b) (6) was excluded from analyses
Source: Study ONO-2745IVU007 CSR Table 11 and Appendix 16.2.6

Geometric mean ratios of C_{max} and AUC_{inf} in subjects with moderate hepatic impairment to that in corresponding healthy subjects were calculated for total and unbound remimazolam, and total CNS7054. For total remimazolam, the geometric mean ratio (90% CI) of C_{max} was 0.59 (0.46 - 0.76), and AUC_{inf} was 0.82 (0.66 - 1.03). For unbound remimazolam, the geometric mean ratio of C_{max} was 0.78 (0.60 - 1.01), and AUC_{inf} was 1.09 (0.85 - 1.40). For total CNS7054, the geometric mean ratio of C_{max} was 0.65 (0.51 - 0.82), and AUC_{inf} was 0.91 (0.58 - 1.42).

Pharmacodynamics: LoC occurred in 7 (77.8%) of the healthy control subjects, 6 (75%) patients in the moderate hepatic impaired group, and all 3 (100%) patients in the severe hepatic impaired group following administration of 0.1mg/kg of remimazolam. There were similar durations of LoC for subjects in all three groups. There were, however, slower recovery times for patients in the hepatically impaired groups compared to the healthy control subjects. The average duration of LoC and recovery time was

3.2 minutes and 12.1 minutes, respectively for subjects in the moderate hepatically impaired group. These times were 2.0 minutes and 16.7 minutes, respectively, for the subjects in the severe hepatically impaired group. Healthy control subjects had a LoC of 1.6 minutes and a recovery time of 8.0 minutes.

(b) (4)

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Reviewers comments: Hepatic impairment did not result in any significant changes in the Cmax of remimazolam or the time to loss of consciousness. The major changes in PK and PD attributed to hepatic impairment were an increase in Half Life and increased recovery time with increased hepatic impairment.

(b) (4)

This was communicated to the sponsor in the Mid-Cycle communication T-com meeting with the sponsor they were informed regarding the hepatic impairment labeling that "Although we do agree with the observed increase in exposure (AUC) and elongated half-life for remimazolam in subjects with severe hepatic impairment, (b) (4) *We may recommend additional monitoring in the label* (b) (4) *in this patient population. The final labeling language is still being discussed and has not been finalized." To which the sponsor acknowledged our comments* (b) (4)

Since the drug is as such administered to effect and top ups are dosed as needed, labeling language suggesting potential increase in recovery times for hepatic impaired subjects and need of less frequent top ups would be included into the label. The labeling language is still being deliberated and the labeling negotiations still need to take place at the time of this review.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug interaction does not apply to this product since it is administered intravenously.

Pharmacokinetic Drug Interactions:

In Vitro Studies:

When administered IV, remimazolam is metabolized by tissue carboxylesterase (CES) (primarily type 1A) which produce a primary inactive metabolite (CNS7054) along with six others that make up less than 0.5% each of the balance of metabolism products in plasma or urine. *In vitro* experiments showed no clinically relevant metabolic interactions between remimazolam and the carboxylesterase substrates esmolol and landiolol (Study AE-7165-G) and the CES1 inhibitors atorvastatin and diltiazem (Study ADM-17-1714). Remifentanil did not influence the hydrolysis of remimazolam by human liver S9 fractions, dismissing the possibility of an interaction by competition for liver carboxylesterases.

The inhibitory effects of remimazolam on cytochrome P450 (CYP)-dependent drug-metabolizing isoenzyme activities were examined using human liver microsomes (Study Y13AG002). The potential inhibitory effects of remimazolam and CNS7054 on seven cytochrome P450 isoenzymes (CYP1A2,

CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP2B6 and CYP2C8) were examined. Neither compound showed significant inhibition of any of the isoenzymes. The IC_{50} of remimazolam for inhibition of CYP2C9, CYP2C19, CYP2D6, and CYP3A4 was higher than 100 µM, and so was the IC_{50} of CYP2B6. The values for CYP2C8 and CYP1A2 were 29.2 and 63.6 µM, respectively. The IC50 of the metabolite CNS7054 on the enzyme activity of CYP isoforms was 578 µM for CYP2C8 and higher than 600 µM for CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

Consistent results were obtained in human CYP over-expressing liver microsomes (Study Y05AE037). Inhibition of metabolism of fluorescent substrates of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 by remimazolam and CNS7054 (3 to 30 µg/mL) was less than 50% even at the highest concentration; therefore, the IC_{50} was > 30 µg/mL (equivalent to >68.3 µM for remimazolam and >70.5 µM for CNS7054) for all the CYP isoforms.

A possible induction of specific P450 isoforms (CYP1A2, 2B6, and 3A4) by remimazolam was studied in human hepatocytes and compared with the effects of prototypical inducers (Study 8235276). All prototype inducers demonstrated appropriate induction of the respective enzyme activities. The conclusion of this study was that remimazolam did not show any notable induction of human CYP1A2, 2B6, and 3A4 under the study conditions. In a further study on the same topic, the ability of CNS7054 to induce CYP1A2, CYP2B6, or CYP3A4 enzyme activities was investigated (Study 8281401). The fold induction values of CYP1A2, CYP2B6, and CYP3A4 enzyme activities were ≤1.77, ≤1.19 and ≤1.86, respectively. It was concluded that the test article (up to 500 µM) did not show induction of the enzyme activities studied.

Several in vitro studies (Studies 8281404; 8281402, 8281403, Y10AE006, Y10AG018, Paion-01-17Aug2017) were performed to identify possible interactions of remimazolam with drug transporters including the guidance-conforming standard battery. Remimazolam showed some in vitro inhibition capacity towards OCT2, OAT3, OATP1B1 and OATP1B3, but not OAT1 or BCRP. The IC_{50} values of remimazolam were estimated to be >100 µM for OAT3, about 100 µM for OCT2 and OATP1B3, and about 10 µM for OATP1B1. Since human Cmax (unbound) is < 1 µM, the probability for in vivo inhibition is negligible even for OATP1B1. The metabolite CNS7054 caused inhibition of OAT3, OATP1B1, and OATP1B3, but not OAT1, OCT2, or BCRP. The IC_{50} values were estimated to be >50 µM for OAT3 and approximately 500 µM for OATP1B1 and OATP1B3. With a human C_{max} (unbound) of 3.6 µM, the probability for in vivo inhibition is negligible even for OATP1B1.

No inhibition of MDR1(P-glycoprotein) by remimazolam was identified, as decreases of the corrected flux ratio of ^{3}H-digoxin in the presence of remimazolam (tested up to 50 µmol/L) were less than 50 % and not concentration-dependent. CNS7054 yielded comparable results: No decreases of the corrected flux ratio of ^{3}H-digoxin in the presence of CNS7054 (tested up to 30 µmol/L), and no concentration-dependent changes were observed. Thus, neither remimazolam nor CNS7054 is not an inhibitor of MDR1. Additional studies with further transporters such as human BSEP, BCRP, MDR1, MRP2, MRP3 and MRP4 efflux (ABC), and with human MATE1 and MATE2K uptake transporters were carried out *in vitro.* Remimazolam, but not CNS7054, was an inhibitor of BSEP, MATE1 and MATE2-K, causing inhibitions of 63, 30, and 33 % at 100 µM, respectively, which are unlikely to translate into the clinical situation.

Remimazolam was not a relevant substrate of a panel of human drug transporters (OATP1B1, OATP1B3, BCRP, MDR1). CNS7054 was found to be a likely substrate for BCRP and MDR1. These results together show a very low potential of remimazolam for drug-drug interactions based ADME considerations.

Clinical Studies:

No formal clinical drug-drug PK or PD interaction studies have been performed with IV remimazolam. The effects of alcohol on the PK and PD of orally administered remimazolam were assessed in Study CNS7056-020. The study consisted of 2 parts. Part 1 was an open-label, single-ascending dose trial conducted in 21 healthy female volunteers to identify the minimally biologically active dose of remimazolam (i.e., lowest dose with effects on memory and consciousness) as well as the PK, safety, and tolerability of a single oral dose of remimazolam of 60, 140, 240, 360 or 480 mg. Part 2 was a double-blind, double-dummy, single dose, crossover trial conducted in 11 female subjects to evaluate the effects of varying concentrations of ethanol on the safety and tolerability, PK, and PD of a single oral dose of remimazolam (360 mg).

Part 1 Pharmacokinetic Results: After oral administration of 60 to 480 mg remimazolam, plasma levels of remimazolam reached median T_{max} at between 0.23 to 0.48 hours, independent of dose. As dose increased from 60 to 480 mg, remimazolam C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ all increased with dose. For the 8-fold increase in dose, geometric mean C_{max} increased 5.8-fold, geometric mean $AUC_{0\text{-}last}$ increased 11.1-fold, while $AUC_{0\text{-}inf}$ increased 5.9-fold. Disappearance of parent drug from plasma was very rapid, with a geometric mean $t_{1/2}$ of 0.53 to 0.66 hours, independent of dose.

Part 1 Pharmacodynamic Results: The PD effects of remimazolam in the population tested were modest. At oral doses of 60 to 480 mg, a minimally biologically active dose of remimazolam was not identified based on protocol-specified MOAA/S and AE criteria. Most PD assessments did not show conclusive results or trends, except for Alertness/Drowsiness VAS, which suggested a modest increase in drowsiness with increasing doses of remimazolam up to 240 mg, with a plateau at higher doses.

Part 2 Pharmacokinetic Results: Remimazolam: After oral administration of 360 mg remimazolam (as a drinkable solution) with 0%, 5%, 15% and 40% of co-administered alcohol, median T_{max} occurred rapidly, ranging from 0.23 to 0.49 hours, and was independent of the amount of co-administered alcohol. Disappearance of remimazolam from plasma was rapid, with a geometric mean $t_{1/2}$ of 0.54 to 0.62 hour, independent of alcohol dose. As the amount of added alcohol increased from 0% to 40%, remimazolam C_{max}, AUC_{last}, and AUC_{inf} all increased: mean C_{max} (76.3 to 135 ng/mL); mean AUC_{last} (85.2 to 163 ng·h/mL) and mean AUC_{inf} (90.3 to 168 ng·h/mL).

Table 9: Summary of Remimazolam Plasma Pharmacokinetic Parameters: Part 1 CNS7056-020

Parameter	Statistic	Remimazolam				
		60 mg (N=3)	140 mg (N=3)	240 mg (N=5)	360 mg (N=5)	480 mg (N=5)
T_{max} (h)	n	3	3	5	5	5
	Median	0.23	0.48	0.23	0.48	0.48
	Min, Max	0.23, 0.73	0.23, 0.72	0.23, 0.75	0.23, 1.03	0.23, 0.73
C_{max} (ng/mL)	n	3	3	5	5	5
	Geometric Mean	15.0	36.4	45.7	54.0	87.0
	Arithmetic Mean	16.2	36.9	58.1	60.9	92.9
	SD	7.9	7.1	50	30	30
$AUC_{0\text{-last}}$ (h*ng/mL)	n	3	3	5	5	5
	Geometric Mean	9.83	31.1	36.7	53.9	109
	Arithmetic Mean	11.1	31.5	43.8	61.0	118
	SD	6.5	6.2	30	30	60
$AUC_{0\text{-inf}}$ (h*ng/mL)	n	1	2	5	5	5
	Geometric Mean	19.5	35.2	39.5	57.3	115
	Arithmetic Mean	19.5	35.7	46.5	64.3	124
	SD		8.1	40	30	60
$t_{1/2}$ (h)	n	1	2	5	5	5
	Geometric Mean	0.33	0.37	0.53	0.56	0.66
	Arithmetic Mean	0.33	0.37	0.55	0.59	0.69
	SD		0.01	0.17	0.21	0.25
CL/F (L/h)	n	1	2	5	5	5
	Geometric Mean	3071	3971	6068	6282	4144
	Arithmetic Mean	3071	4024	6724	7270	4428
	SD		916	2619	4826	1686
V_Z/F (L)	n	1	2	5	5	5
	Geometric Mean	1479	2106	4626	5076	3951
	Arithmetic Mean	1479	2140	5202	6180	4448
	SD		543	2537	4056	2250

Abbreviations: max = maximum; min = minimum; N = number of subjects in sample; n = number of subjects in subsample; PK = pharmacokinetic; SD = standard deviation

From the analyses, it is evident that addition of alcohol to the oral administration of remimazolam modestly increased the systemic exposure to remimazolam. Addition of alcohol to the oral dose of remimazolam had much less of an effect on systemic exposure to metabolite CNS7054 than it did on remimazolam.

Part 2 Pharmacodynamic Results: Oral remimazolam alone (360 mg) had a mild but significant effect on all PD measures as compared to alcohol alone (40%) that had no effect on any PD measure (although sometimes a difference versus pre-dose was seen, but the lack of a real placebo control precludes any conclusion). When remimazolam and alcohol were administered together, the effects were slightly stronger than with remimazolam alone, although mostly not in an alcohol dose-dependent manner. The concentration of alcohol did not, however, have a major impact on the change in PD effects of remimazolam in the presence of alcohol.

Table 10: Summary of Remimazolam Plasma Pharmacokinetic Parameters: Part 2 CNS7056-020

Parameter	Statistic	Treatment[1]			
		A	B	C	D
		(N=11)	(N=11)	(N=11)	(N=8)
T_{max} (h)	n	11	11	11	8
	Median	0.48	0.48	0.23	0.49
	Min, Max	0.23, 0.98	0.22, 0.75	0.22, 0.97	0.18, 0.97
C_{max} (ng/mL)	n	11	11	11	8
	Geometric Mean	76.3	92.5	121	135
	Arithmetic Mean	87.3	109	131	180
	SD	50	70	60	189
$AUC_{0\text{-last}}$ (h*ng/mL)	n	11	11	11	8
	Geometric Mean	85.2	97.1	138	163
	Arithmetic Mean	93	104	146	185
	SD	40	40	50	113
$AUC_{0\text{-inf}}$ (h*ng/mL)	n	11	11	10	8
	Geometric Mean	90.3	101	144	168
	Arithmetic Mean	97.6	108	152	190
	SD	40	40	50	113
$t_{1/2}$ (h)	n	11	11	10	8
	Geometric Mean	0.59	0.62	0.55	0.54
	Arithmetic Mean	0.61	0.65	0.56	0.55
	SD	0.15	0.18	0.12	0.1
CL/F (L/h)	n	11	11	10	8
	Geometric Mean	3985	3532	2488	2141
	Arithmetic Mean	4325	3773	2625	2366
	SD	1896	1531	933	1031
V_Z/F (L)	n	11	11	10	8
	Geometric Mean	3393	3184	1984	1663
	Arithmetic Mean	3692	3548	2207	1796
	SD	1668	1826	1086	756

[1]A: Remimazolam 360 mg, B: Remimazolam 360 mg + 5% v/v alcohol, C: Remimazolam 360 mg + 15% v/v alcohol, D: Remimazolam 360 mg + 40% v/v alcohol

Abbreviations: max = maximum; min = minimum; N = number of subjects in sample; n = number of subjects in subsample; PK= pharmacokinetics; SD = standard deviation

Potential Pharmacodynamic Drug-Drug Interactions:

The sedative effect of remimazolam can be accentuated by any concomitantly administered medication that depresses the CNS such as sedative-hypnotics and narcotics, (e.g., other benzodiazepines, [fos-]propofol, and opioids, such as morphine and fentanyl).

Risks from Concomitant Use with Opioids:

Concomitant use of benzodiazepines, including remimazolam, with opioids can result in profound sedation, respiratory depression, coma, and death. Remimazolam should be used for sedation only in the presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway, and supporting ventilation. Remimazolam should be used in a setting with the immediate availability of oxygen, resuscitative drugs, and appropriate equipment for bag/valve/mask ventilation. The immediate availability of specific reversal agent (flumazenil) is highly recommended.

In the placebo-controlled studies in procedural sedation, remimazolam was administered in combination with fentanyl. Higher cumulative doses of fentanyl were associated with increased rates of the most common adverse events and Important Identified Risks in all treatment groups. Higher initial doses of fentanyl (>50 µg) were associated with an increased frequency of an MOAA/S score of 0 or 1.

Other noted Clinical drug interactions:

Subjects receiving concomitant antihypertensive medications appeared to have a higher incidence of all TEAEs and TEAEs that were Vascular disorders (including hypotension and hypertension) and Respiratory, thoracic, and mediastinal disorders (including hypoxia and tachypnea) on both remimazolam and placebo. The incidences were similar on placebo but were not consistently different between subjects with and without antihypertensive medication.

Subjects on remimazolam receiving concomitant sedative/hypnotic medications appeared to have a higher incidence of all TEAEs and TEAEs that were Vascular disorders (including hypotension and hypertension); Respiratory, thoracic, and mediastinal disorders (including hypoxia and tachypnea); and Investigations (including respiratory rate increased, respiratory rate decreased, and blood pressure diastolic decreased). The effect could not be compared to placebo because only 5 subjects randomized to placebo were not taking concomitant sedatives/hypnotics.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The quantification of remimazolam and its inactive metabolite, CNS7054, in both plasma and urine - and of midazolam (active control in clinical studies) - in plasma was carried out via high performance liquid chromatography (HPLC) analyses with tandem mass spectrometry (MS/MS) detection.

The initially developed method (ZNA17619.002), covering a low concentration range, was used for the start of analysis of samples from Phase 1 and Phase 2 clinical studies. However, when a significant number of plasma concentrations were found to be outside of the linear range for remimazolam, analysis was continued using a high-range assay (ZNA17619.009). The method was revalidated at a high concentration range (VPT1548). A more sensitive method was further developed for the needs of various Phase 1 studies (oral and nasal bioavailability) as well as a pharmacokinetic (PK) study in subjects with end-stage renal disease), due to the low plasma concentration of remimazolam in those studies (VPT3108). This method was revalidated (VPT5956/2017) for study CNS7056-020 (which evaluated oral dosing) in which the ratio of the primary metabolite CNS7054 to remimazolam was unexpectedly high due to the complete absorption but extremely low bioavailability (1-2%) as a result of first pass metabolism. In the VPT5956/2017 method, the precipitating agent was switched from methanol to isopropyl alcohol. In all studies conducted by ONO, the GB10005V method was used for quantifying total remimazolam and CNS7054 concentrations in human plasma; in a subset of studies, plasma-free concentrations were quantified using the GB12046V method.

Bio-analytical Validation:

Table 11 and Table 12 provide the analytical performance (ranges, linearity, precision, and accuracy values) for the methods used in different clinical studies for remimazolam in plasma and urine, respectively. Table 13 and Table 14 show the analytical performance of the methods for metabolite CNS7054 in plasma and urine, respectively.

Table 11: Bioanalytical Methods for Remimazolam in Plasma, by Study

Method	Clinical Studies	LLOQ (ng/mL)	Linear range (ng/mL)	Linearity (Correlation Coefficient)	Precision (%)	Accuracy (%)
ZNA17619.002/ BAM-065-02	CNS7056-001 and -004	0.2	0.2-100	≥0.997	1.46-8.63 within-run, 4.54-8.94 between-run	93.7-109 within-run[a], 91.7-107 between-run[a]
ZNA17619.009/ BAM-094-01	CNS7056-001, -002, and -004	1.0	1.0-1000	≥0.997	0.881-4.75 within-run, 1.59-5.10 between-run	84.7-108 within-run[a], 85.2-105 between-run[a]
VPT1548	CNS7056-005, -006, -008, -010, -011, -014, and -015	20	20-20 000	>0.9985	≤8.1 within-run, ≤8.0 between-run	81.3-102.0[a]
VPT3108	CNS7056-012, -016, -017, and -019	2.0	2.0-2000	>0.9963	≤6.6 within-run	99.7-113.6[a]
VPT5956	CNS7056-020	2.0	2.0-2000	>0.9977	≤10.5 within-run, ≤7.6 between-run	81.5-107.1[a]
GB10005V	ONO-2745-01, -02, -03, -04, -05, -06, and ONO2745IVU007	1.00	1.00-1000	≥0.9972	0.7-4.9 (2.2-4.8 at LLOQ) within-run, 3.8-4.9 (5.0 at LLOQ) day-to-day	-12.4 to 6.4 (-9.8 to -2.2 at LLOQ) within-run[b], -9.9 to 0.3 (-5.2 at LLOQ) day-to-day[b]
GB12046V	Unbound ONO-2745: ONO2745IVU007 and ONO-2745-04	0.100	0.100-1000	≥0.9978	0.5-5.7 (4.3-7.9 at LLOQ) within-run, 1.7-4.4 (-5.8 at LLOQ) day-to-day	-4.7 to 12.2 (1.6-5.8 at LLOQ) within-run[b], -2.8 to 7.5 (3.3 at LLOQ) day-to-day[b]

Table 12: Bioanalytical Methods for Remimazolam in Urine, by Study

Method	Clinical Studies	LLOQ (ng/mL)	Linear range (ng/mL)	Linearity (Correlation Coefficient)	Precision (%)	Accuracy (%)
ZNA28446.002/ BAM-123-01	CNS7056-002	1.0	1.0-1000	≥0.99	≤15%	≤15%
GB10006V	ONO-2745-01	50.0	50.0-5000	≥0.9982	1.1-5.4 (0.8-5.0 at LLOQ) within-run, 2.1-3.6 (4.8 at LLOQ) day-to-day	13.8 to -3.8 (12.9 to -6.4 at LLOQ) within-run, -11.6 to -5.0 (-8.6 at LLOQ) day-to-day

Abbreviation: LLOQ = lower limit of quantification

Table 13: Bioanalytical Methods for Metabolite CNS7054 in Plasma, by Study

Method	Clinical Studies	LLOQ (ng/mL)	Linear range (ng/mL)	Linearity (Correlation Coefficient)	Precision (%)	Accuracy (%)
ZNA17619.002/ BAM-065-02	CNS7056-001 and -004	1.0	1.0-1000	≥0.995	2.08-6.81 within-run, 3.53-13.9 between-run	86.6-112 within-run[a], 87.5-110 between-run[a]
ZNA17619.009/ BAM-094-01	CNS7056-001, -002, and -004	1.0	1.0-1000	≥0.997	1.20-8.61 within-run, 2.12-13.0 between-run	86.6-113 within-run[a], 88.1-104 between-run[a]
VPT1548	CNS7056-005, -006, -008, -010, -011, -014, and -015	100	100-100 000	>0.9982	≤5.6 within-run, ≤3.4 between-run	91.3-106.6[a]
VPT3108	CNS7056-012, -016, -017, and -019	20	20-20 000	>0.9964	≤5.1 within-run	85.2-107.7[a]
VPT5956	CNS7056-020	20	20-20 000	≥0.9983	≤7.6 within-run, ≤4.1 between-runs	92.3 to 108.5[a]
GB10005V	ONO-2745-01, -02, -03, -04, -05, -06, and ONO2745IVU007	1.0	1.0-1000	≥0.9972	1.2-4.3 (2.6-6.8 at LLOQ) within-run, 2.1-4.5 (8.6 at LLOQ) day-to-day	-5.9-7.6 (-12.6-2.6 at LLOQ) within-run[b], -4.6-6.9 (-4.4 at LLOQ) day-to-day[b]

Abbreviation: LLOQ = lower limit of quantification
[a] % Accuracy= (Mean Conc. Determined * 100)\ (Conc. Expected)
[b] % Accuracy= [(mean quantitative value - spiked concentration) / spiked concentration] ×100

Table 14: Bioanalytical Methods for Metabolite CNS7054 in Urine, by Study

Method	Clinical Studies	LLOQ (ng/mL)	Linear range (ng/mL)	Linearity (Correlation Coefficient)	Precision (%)	Accuracy (%)[b]
ZNA28446.002/ BAM-123-01	CNS7056-002	10.0	10.0-10 000	≥0.99	≤15%	≤15%
GB10006V	ONO-2745-01	500	500-50 000	≥0.9981	0.8-3.2 (2.3-4.2 at LLOQ) within-run, 1.7-2.5 (3.4 at LLOQ) day-to-day	-12.3 to -3.5 (-7.8 to -7.0 at LLOQ) within-run, -11.6 to -4.5 (-7.5 at LLOQ) day-to-day

Abbreviation: LLOQ = lower limit of quantification
[b] % Accuracy= [(mean quantitative value - spiked concentration) / spiked concentration] ×100

4.2 Clinical PK and/or PD Assessments

Summary of Study CNS7056-001.

A Phase 1, double-blind, active-controlled study employed ascending dose bolus IV injections (administered over 1 minute) of remimazolam of 0.01, 0.025, 0.05, 0.075, 0.1, 0.15, 0.2, 0.25, 0.3 mg/kg or midazolam 0.075 mg/kg in 54 healthy adult subjects.

This was a first-in-human (FIH), Phase 1, double-blind, single-dose escalation study of CNS 7056 to determine its safety, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy adults. Up to ten single ascending dose cohorts were planned from 0.01 mg/kg to 0.35 mg/kg. The dose was increased in conservative increments only after a thorough analysis of the safety data from each preceding cohort. During drug administration, an anesthesiologist was present, and oxygen and the benzodiazepine reversal agent flumazenil was immediately available. Arterial and/or venous blood samples for analyses of PK parameters of midazolam, CNS 7056, and CNS 7054 were collected within 10 minutes pre-dose and at 1, 2, 3, 4, 6, 8, 10, 12, 15, 20, 30, 45, 60 minutes and 2, 3, 4, 6, 8- and 12-hours post-dose. These sampling times were considered sufficient to determine the PK parameters.

Pharmacokinetics: Following administration of a single IV bolus dose (infused over 1 minute), remimazolam was rapidly cleared from plasma (mean clearance 0.90 L/hr/kg). The mean t½α was approximately 1.6 minutes, compared with 3.35 minutes for midazolam. Terminal half-life t½, of remimazolam was 37 to 48.5 minutes, while that of midazolam was 1.6 h. Remimazolam was converted rapidly to the inactive metabolite, CNS7054, with the elimination rate of the latter being largely unchanged within the dose ranges studied. The mean elimination half-life of the metabolite CNS7054 was found to be between 2.4 and 3.8 hours. The PK behavior of remimazolam was observed to be linear within the dose ranges studied (0.01 to 0.30 mg/kg) in this study (mean C_{max} and AUC parameters increased in proportion to dose).

Table 15: Statistical Summary of the Dose Proportionality Model

CNS 7054 Parameter	Slope	95% Confidence Interval
Cmax	1.03	0.97, 1.10
AUC0-t	0.99	0.95, 1.04

Plasma concentration profile for remimazolam and midazolam are represented in figure 4 and the summary of PK parameters is represented in Table 16.

Figure 4: Mean (±SD) CNS 7056 and Midazolam Plasma Concentration-Time Data -Log Scale

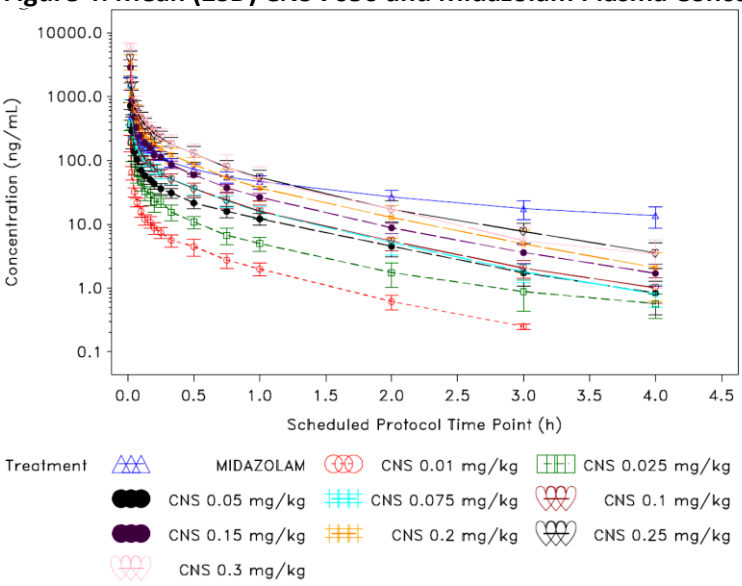


Table 16: Summary of Midazolam and Remimazolam (CNS 7056) Plasma Pharmacokinetic Parameter Data

Treatment (mg/kg)	Statistic	C_{max} (ng/mL)	T_{max}* (hr)	$t_{½}$ (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	CL (L/hr/kg)	Vd (L/kg)	AUMC (hr*hr*ng/mL)	MRT (hr)
0.075 Midazolam	N	16	16	16	16	16	16	16	16	16
	Mean	1584.039	0.020	1.613	194.526	227.842	0.343	0.781	412.680	1.738
	CV (%)	20.9276	0.01-0.02	18.2625	17.6231	21.6894	20.1746	15.8842	45.6631	24.4392
0.01 CNS	N	6	6	6	6	6	6	6	6	6
	Mean	189.204	0.020	0.617	11.767	12.064	0.853	0.757	5.401	0.438
	CV %	29.4834	0.02-0.02	15.1654	18.3189	18.2421	18.8399	22.8198	23.6451	19.6035
0.025 CNS	N	6	6	6	6	6	6	6	6	6
	Mean	369.212	0.020	0.809	29.205	29.867	0.861	0.970	17.453	0.569
	CV %	14.6002	0.02-0.03	41.0385	19.6302	19.3383	17.9623	38.0762	44.1488	43.5574
0.05 CNS	N	6	6	6	6	6	6	6	6	6
	Mean	720.609	0.020	0.744	57.151	58.106	0.883	0.931	37.673	0.627
	CV %	11.8235	0.02-0.02	16.0873	15.0329	15.4605	20.0137	12.0987	30.7743	21.3762
0.075 CNS	N	6	6	6	6	6	6	6	6	6
	Mean	1470.005	0.020	0.703	92.012	92.831	0.840	0.859	46.121	0.486
	CV %	39.1871	0.02-0.02	6.9113	20.0514	20.0745	23.3660	28.3508	26.4252	16.1574
0.1 CNS	N	6	6	6	6	6	6	6	6	6
	Mean	1882.645	0.020	0.731	106.672	107.748	0.931	0.984	50.014	0.455
	CV %	13.9382	0.02-0.03	9.8138	6.6421	6.5933	6.3910	14.1091	23.6905	22.6583
0.15 CNS	N	6	6	6	6	6	6	6	6	6
	Mean	2885.703	0.020	0.732	170.777	172.622	0.873	0.920	83.207	0.473
	CV %	31.1515	0.02-0.02	9.0897	7.3307	7.4589	7.7090	8.7261	18.8833	16.6767
0.2 CNS	N	6	6	6	6	6	6	6	6	6
	Mean	3558.109	0.020	0.707	228.538	230.806	0.894	0.902	114.941	0.475
	CV %	26.4386	0.02-0.02	11.6049	17.8879	18.1269	20.5131	15.3746	45.3203	35.5798
0.25 CNS	N	6	6	6	6	6	6	6	6	6
	Mean	4082.074	0.020	0.780	302.487	306.506	0.840	0.945	170.379	0.538
	CV %	26.3039	0.02-0.02	7.3565	16.8498	17.0565	20.9846	21.3457	29.5933	14.8391
0.3 CNS	N	6	6	5	6	5	5	5	5	5
	Mean	6095.452	0.020	0.713	340.136	362.532	0.878	0.894	175.205	0.456
	CV %	12.2021	0.02-0.02	11.1709	28.4134	26.8908	27.0961	24.1543	47.6884	22.4025

Source: Section 14, Table 14.2.2
* T_{max} is summarized by median and range
Parameter data for Subjects (b) (6) (midazolam) were excluded from the table due to incorrect processing of their blood samples in the bioanalytical laboratory.

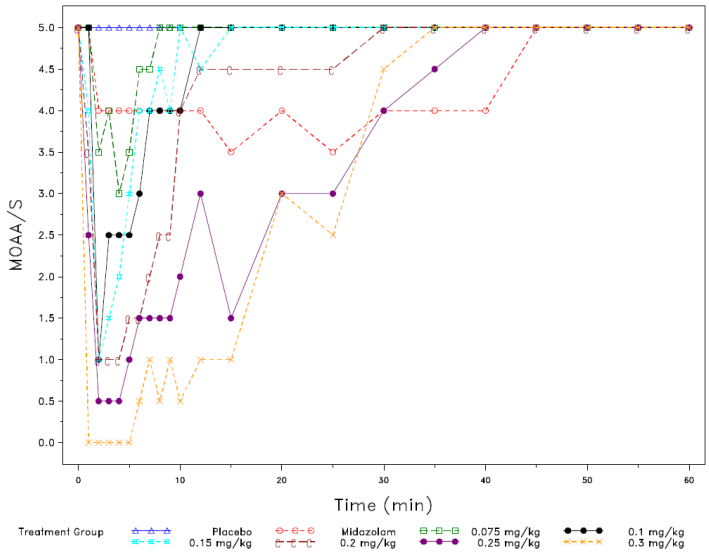
Pharmacodynamics: Sedation (defined as median MOAA/S score < 4) was observed in all subjects receiving a single bolus dose of remimazolam of 0.075 mg/kg or higher. The onset of sedation was rapid,

with sedation being observed at 1-2 minutes across all active remimazolam doses compared to an onset of sedation of 15 minutes for the dose of midazolam tested (0.075 mg/kg).

The duration of sedation with remimazolam showed dose-dependency. Duration of sedation was approximately 8 minutes at 0.075 mg/kg and approximately 40 minutes at 0.25 mg/kg. Durations of Loss of Consciousness (LOC) also increased with increasing remimazolam dose, with median MOAA/S scores of <2 for approximately 0, 1, 3, 5, 9, and 12 minutes in the 0.075, 0.1, 0.15, 0.2; 0.25, and 0.3 mg/kg remimazolam treatment groups, respectively. Mean recovery times from first MOAA/S of < 5 to Fully Alert (defined as time to the first of 3-consecutive median MOAA/S scores of 5 after dosing) also showed a dose-dependent increase across remimazolam treatment groups. Subjects treated with 0.075, 0.1, 0.15, 0.2; 0.25, and 0.3 mg/kg remimazolam were fully alert after approximately 5, 13, 12, 21, 50, and 35 minutes of sedation, respectively.

In comparison, subjects treated with 0.075 mg/kg midazolam were not as deeply sedated but were sedated for longer than those treated with CNS 7056. No median MOAA/S score in the midazolam group was below 3.5 and subjects remained at a median MOAA/S score of 3.5 or 4 for approximately 45 minutes post-dose.

Subjects in the placebo treatment group were Fully Alert throughout the study. Based on the results of this study, a dose of 0.075 mg/kg was considered appropriate for procedural sedation.



Source: Section 14, Figure 14.2.10.2

Figure 5: Median MOAA/S Scores over Time - High Dose CNS 7056 Groups and Midazolam.

Summary of Multiple Bolus IV Administration Study (CNS7056-002).

A Phase 1, two-part multiple bolus IV administration study of remimazolam.

Part A was a double-blind, placebo-controlled, crossover design evaluating the effect of flumazenil, a benzodiazepine antagonist, as a reversal agent for remimazolam in 6 healthy subjects.

Part B was an open-label, ascending-dose study evaluating the safety, PK, and PD of remimazolam in healthy subjects undergoing a colonoscopy. In Part B of this study, 45 healthy subjects were randomized to initially receive a single IV bolus (over 1 minute) dose of remimazolam 0.04, 0.075, or 0.1 mg/kg. Prior to administration of the initial dose of remimazolam, an initial 50 µg dose of fentanyl, was administered IV over 1 to 2 minutes. After the initial remimazolam dose, supplemental bolus IV doses of 0.04 mg/kg remimazolam were administered to maintain adequate sedation. One additional dose of 25 µg fentanyl was allowed if needed to maintain analgesia. The primary PD endpoint in Part B was the assessment of the success of the procedure (a composite endpoint consisting of the following: MOAA/S ≤ 4 on 3 consecutive measurements, completion of 30-minute period of sedation [including if alternative sedative medication used], no requirement for an alternative sedative, and no manual or mechanical ventilation).

Pharmacokinetics: CNS 7056 plasma PK parameters were derived via a 2-compartment model with intravascular administration using WinNonlin. Remimazolam showed extensive tissue distribution and fast elimination after IV administration and was rapidly and extensively metabolized and Overall, C_{max} for remimazolam ranged from 60.8 to 1573 ng/mL and overall $AUC_{0\text{-}inf}$ ranged from 86.7 to 560 ng*h/mL). Distribution and elimination half-lives were short; mean $t_{½\alpha}$ ranged from 6 to 7 minutes and mean $t_{½\beta}$ ranged from 56 to 73 minutes. Clearance was high (mean CL ranged from 61 to 78 L/hr), and volume of distribution was extensive (mean Vss ranged from 52 to 71 L), suggesting fast tissue distribution and elimination. Dose proportionality analysis of remimazolam cumulative dose versus CNS 7056 total exposure ($AUC_{0\text{-}inf}$) suggests a close to dose-proportional relationship. The point estimate of the slope was close to 1.0 (1.03 for $AUC_{0\text{-}inf}$), and the range of possible values for the slope provided by the 90% CI estimate (0.846, 1.209), which fell just outside of the pre-specified range (0.859, 1.141).

Table 17: Dose-independent PK parameters of remimazolam in MAD study CNS7056-002.

Treatment Group	Statistic	$t_{½}$ α (h)	$t_{½}$ β (h)	CL (L/h)	Q (L/h)	V1 (L)	V2 (L)	MRT (h)	Vss (L)
0.04 mg/kg	n	15	15	15	15	15	15	15	15
	Mean	0.110	1.03	60.9	76.1	19.5	35.4	0.929	54.9
	CV (%)	85.6	33.8	27.7	82.5	83.7	23.6	32.2	33.5
0.075 mg/kg	n	15	15	15	15	15	15	15	15
	Mean	0.103	0.925	71.8	47.4	19.0	32.8	0.713	51.8
	CV (%)	64.7	24.1	24.9	64.8	71.8	46.2	27.0	37.6
0.1 mg/kg	n	15	15	15	15	15	15	15	15
	Mean	0.116	1.21	78.4	61.0	23.9	47.3	1.03	71.2
	CV (%)	73.3	98.5	27.6	54.5	71.2	90.2	116.6	74.1

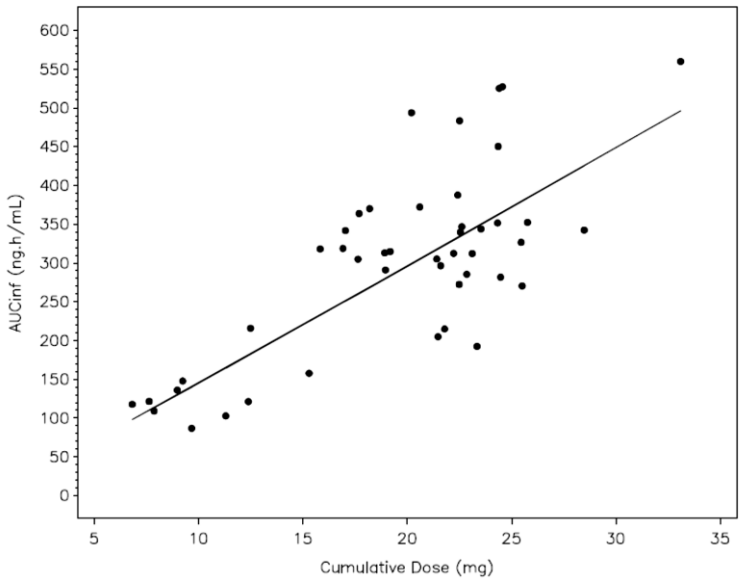


Figure 6: Scatter Plot of $AUC_{0\text{-}inf}$ versus remimazolam Cumulative Dose.

Urine CNS 7056 PK parameters were also studied and showed that very little of the remimazolam dose excreted unchanged in the urine (approximately 0.003%); it was excreted in the urine primarily as the inactive metabolite CNS7054 (50-60% within 24h).

Pharmacodynamics: Flumazenil administration (0.5 mg) in Part A decreased the Time to Fully Alert following a single IV infusion of 0.25 mg/kg CNS 7056 from approximately 21 minutes to approximately 6 minutes, (1.8 and 16.8 minutes after administration of flumazenil or placebo respectively), indicating that flumazenil was able to reverse the sedative effects of CNS 7056. No re-sedation was observed.

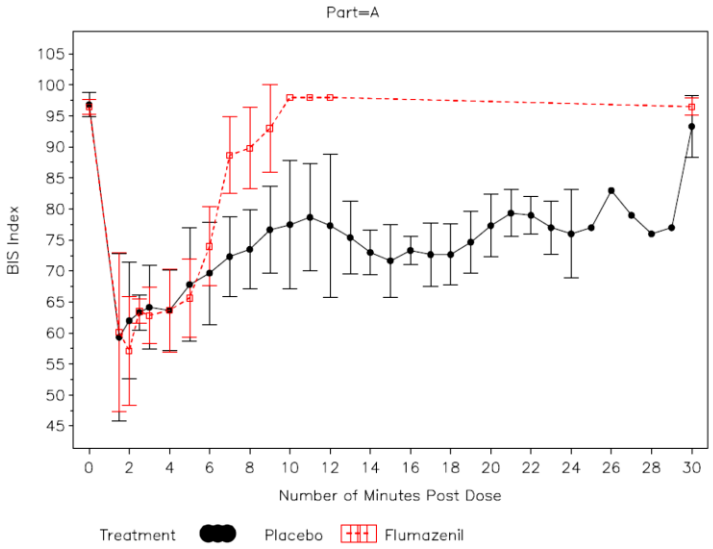


Figure 7: Mean (Standard Deviation) Bispectral Index Scores over Time, Part A;
Note: Remimazolam was administered at T = 0 and flumazenil/placebo was administered at approximately 4 minutes post remimazolam administration

In Part B, the primary PD endpoint was the assessment of the success of the procedure, a composite endpoint consisting all of the following: MOAA/S ≤ 4 on 3 consecutive measurements, completion of 30-minute period of sedation, no requirement for an alternative sedative, and no manual or mechanical ventilation. All subjects in the 0.075 mg/kg group and approximately 65% of subjects in both the 0.04 mg/kg and 0.1 mg/kg groups had successful procedures by this definition.

Part B results also showed that the recovery time following the last dose of study drug was fast, with the mean time to fully alert ranging from 6.9 - 9.8 minutes, and mean time to ready for discharge (Aldrete score) ranging from 23.0 - 24.1 minutes. The amnestic effect of remimazolam was evaluated by the subject's ability to recall the procedure, which was assessed by using the Brice Questionnaire. The results indicated that between 60% (Cohort 1) and 80% (Cohorts 2 and 3) of subjects did not recall the procedure.

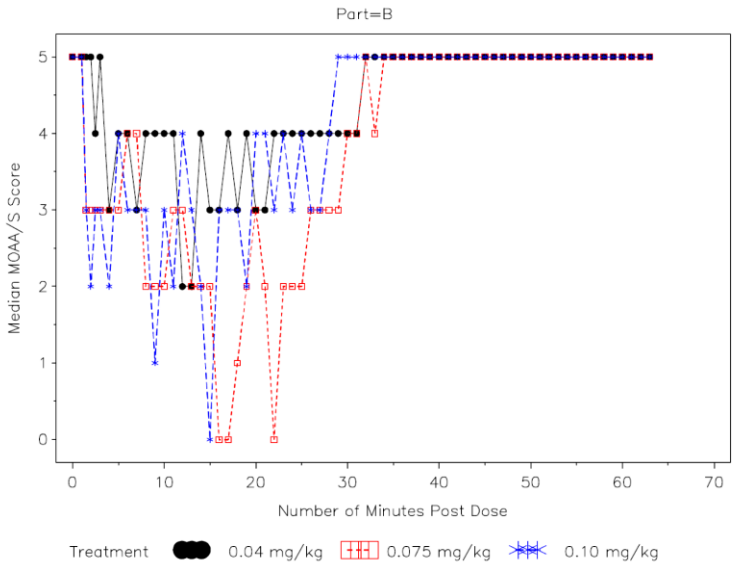


Figure 8: Median Modified Observer's Assessment of Alertness and Sedation Scores over Time, Part B

Summary of Study CNS7056-017 (IV Infusion Study).

The CNS7056-017 study involved continuous IV remimazolam administration at a rate of 5 mg/min for 5 minutes, followed by 3 mg/min for 15 minutes and 1 mg/min for another 15 minutes in 20 healthy adult males. Administration was stopped after 35 minutes, when 85 mg remimazolam had been administered.

This study was a prospective open-label randomized two-arm single-center crossover phase 1 clinical trial for pharmacokinetic/pharmacodynamic modeling of the hypnotic effect of remimazolam and its impact on corrected QT interval in healthy male volunteers. In this summary the PK and PD aspects of the study would be discussed. The QT measurements of the study is discussed in section 2.7.

Pharmacokinetics: Based on a three-compartment model, remimazolam showed a high clearance (CL=1.15±0.12 L/min, mean±standard deviation [SD]), a small central volume of distribution (V_1=4.99±1.35 L), and a short terminal half-life ($t_{1/2}$=69.5±10.0 min). V_1 showed a proportional increase with body weight (not significant). The simulated time for a 50% decrease of remimazolam (context-sensitive halftime) after an infusion of 4 hours was 6.6±2.4 minutes.

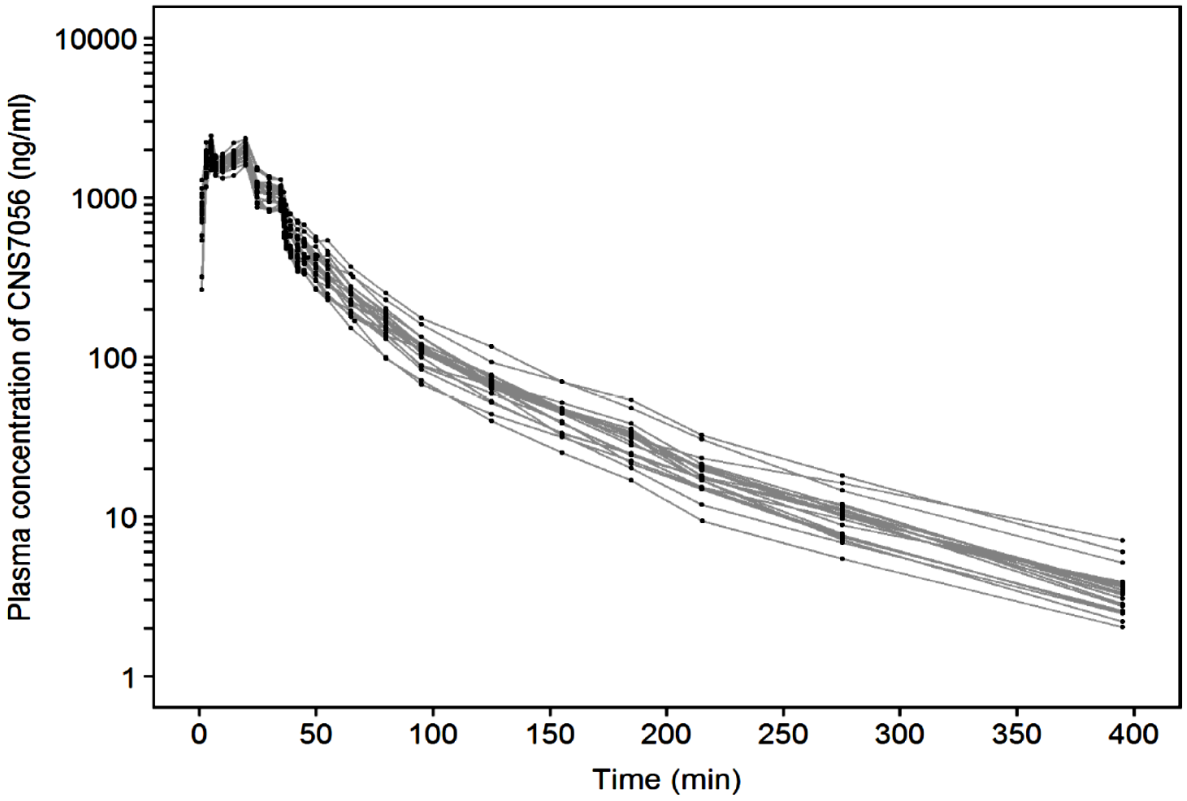


Figure 9: Measured plasma concentrations of remimazolam. The black dots show the measured concentrations. Each grey line represents the data of one volunteer.

Based on a two-compartment model with a transit compartment and lag time when compared to remimazolam, the metabolite CNS7054 showed a low clearance (CL=0.078±0.012 L/min, mean±SD), an

even smaller central volume of distribution (V_1=0.55±0.17 L), and a longer terminal half-life ($T_{1/2el}$=116±22 min). The rate constant for the transit compartment (K_m) was 0.024±0.002 1/min, and the lag time was 0.56±0.17 min. The simulated time to maximum concentration of CNS7054 after a bolus dose of remimazolam was 32.8±7.9 min.

Pharmacodynamics: All 20 subjects showed sedation, with all 20 subjects experiencing both LoC (defined as MOAA/S score < 2 at least once) and loss of eyelid reflex, but only 11 subjects (55.0%) showing loss of corneal reflex. The mean (± SD) time to LoC was 4.60 (1.14) minutes. The mean (± SD) time return to consciousness (defined as the time from the end of IMP administration until 1st of three subsequent MOAA/S scores of 5) was 23 (7) minutes.

A model with sigmoid probability functions was selected as the best model. The half maximum effect site concentrations were 1779±988 ng/ml for a MOAA/S score =0, 695±239 ng/ml for a MOAA/S score <=1, 506±66 ng/ml for a MOAA/S score <=2, 477±63 ng/ml for a MOAA/S score<=3 and 341±49 ng/ml for a MOAA/S score<=4 (Figure 10). The simulated time to peak effect after a bolus dose of remimazolam was 2.9±0.4 min. The simulated time for a 50% decrease of the effect site concentration (context-sensitive halftime) after an infusion of 4 h was 12.1±1.7 min. There were no effects of age and weight.

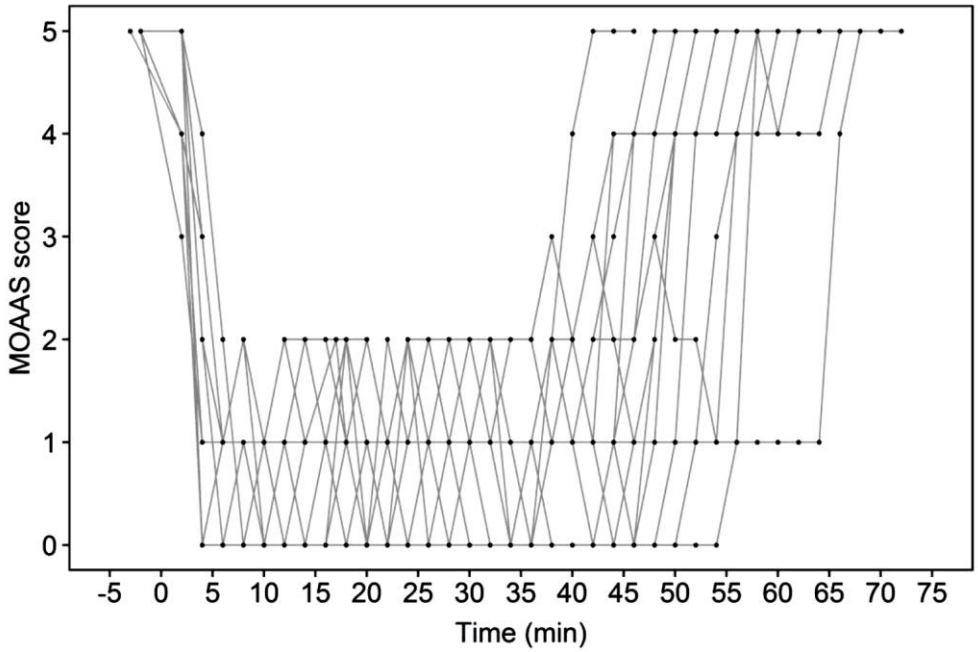


Figure 10: Observed MOAA/S scores. The black dots show the observed values. Each grey line represents the data of one volunteer.

Summary of Japanese Phase 1 Study ONO-2745-01.

The study ONO-2745-01 was a double-blind, parallel-group comparative study consisted of two parts. In Part A, 30 healthy young adult Japanese males (20-45 years) were administered single ascending IV bolus (over 1 minute) doses of remimazolam of 0.05, 0.1, 0.2, 0.3, 0.4, 0.5 mg/kg. Six healthy young adults were administered placebo. In Part B, 10 healthy elderly adult Japanese males (65-74 years) were to be administered 0.10 and 0.30 mg/kg. The 0.30 mg/kg dose was not administered as all elderly patients in the 0.10-mg dose group (5 patients) achieved LoC (i.e., objectives of the study met at this dose).

Pharmacokinetics: In healthy adult male subjects, the plasma remimazolam concentration reached C_{max} at 1.0 to 2.0 minutes after starting administration. $T_{1/2}$, V_{ss}, and CL were 39 to 53 minutes, 0.480 to 0.580 L/kg, and 0.0140 to 0.0198 L/min/kg, respectively. In healthy elderly male subjects, remimazolam reached Cmax at the end of injection. The $T_{1/2}$, V_{ss}, and CL were 47 minutes, 0.473 L/kg, and 0.0164 L/min/kg, respectively.

The results of compartmental analysis of the data from healthy adult male subjects were: T1/2α, $T_{1/2\beta}$, $T_{1/2\gamma}$ and V_1 were 0.52 to 0.87 minutes, 9.2 to 11 minutes, 38 to 52 minutes, and 0.0366 to 0.0606 L/kg, respectively. In healthy elderly male subjects, the $T_{1/2\alpha}$, $T_{1/2\beta}$, $T_{1/2\gamma}$, and V_1 were 0.67 minutes, 7.4 minutes, 45 minutes, and 0.0469 L/kg, respectively. At least 80% of the IV administered remimazolam dose was excreted in urine as inactive metabolite CNS7054. A tabular summary of PK parameters by dose are presented in more detail in Table 18.

Table 18: Pharmacokinetic parameters (C_{max}, T_{max}, AUC_{4h}, AUC_{inf}, $T_{1/2}$, CL, Vss) of remimazolam after single intravenous injection of remimazolam at 0.05 to 0.5 mg/kg over one minute to healthy adult and elderly male Japanese subjects

Part	Dose (mg/kg)	Cmax (ng/mL)	Tmax (min)	AUC4h (ng·h/mL)	AUCinf (ng·h/mL)	T1/2 (min)	CL (L/min/kg)	Vss (L/kg)
A	0.05	654 (138)	1.0 (1.0 - 2.0)	48.3 (2.8)	49.6 (2.7)	39 (8)	0.0168 (0.0009)	0.507 (0.123)
	0.1	1620 (210)	1.0 (1.0 - 1.0)	117 (8)	120 (9)	52 (13)	0.0140 (0.0011)	0.480 (0.090)
	0.2	3260 (550)	1.0 (1.0 - 1.0)	196 (32)	199 (34)	52 (9)	0.0171 (0.0025)	0.516 (0.058)
	0.3	4190 (520)	1.0 (1.0 - 1.0)	252 (23)	255 (23)	48 (8)	0.0198 (0.0017)	0.580 (0.094)
	0.4	6000 (1700)	1.0 (1.0 - 1.0)	361 (45)	365 (47)	45 (7)	0.0185 (0.0023)	0.533 (0.085)
	0.5	6960 (1210)	1.0 (1.0 - 1.0)	445 (53)	452 (55)	53 (9)	0.0187 (0.0025)	0.573 (0.080)
B	0.1	1590 (580)	1.0 (1.0 - 1.0)	103 (19)	104 (19)	47 (12)	0.0164 (0.0030)	0.473 (0.093)

Mean (standard deviation), except for Tmax. For Tmax, median (min – max)
N=5

Pharmacodynamics:

Adults: LoC (defined as MOAA/S score ≤ 1) was observed in 2 out of 5 young adults at a single bolus dose of 0.05 mg/kg and was observed in all young subjects administered 0.20 mg/kg and higher doses. Onset of sedation (defined as median MOAA/S score < 4) was fast, occurring at 1 to 2 minutes after injection for all doses tested. The mean durations of LoC at 0.2, 0.3, 0.4 and 0.5 mg/kg (doses that induced LoC in all subjects) were 3approximately 3, 4, 6, and 16 minutes, respectively, indicating a dose-dependent prolongation of the duration of LoC. The mean times to recovery of consciousness (time from the end of administration to the last point when the MOAA/S score returned from ≤ 4 to 5) were approximately 24, 25, 29, 32, 40, and 54 minutes at the remimazolam 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5 mg/kg doses, respectively, indicating dose dependent prolongation.

Elderly: LoC was observed in all elderly adults at 0.10 mg/kg (while in the younger group, LoC was observed in only one of the five subjects at 0.10 mg/kg). The mean duration of LoC was 3.8 minutes, which was comparable to that at 0.30 mg/kg in the younger subjects (3.6 minutes). The mean time to recovery of consciousness was 22.0 minutes, which was equivalent to that at the same dose in the younger subjects (24.8 minutes).

Summary of Japanese IV infusion Study ONO-2745-02.

In the ONO-2745-02 double-blind, parallel-group, comparative study, 8 healthy, adult, male subjects received continuous IV infusion of 1 mg/kg/hr remimazolam until 10 minutes after LoC (or a maximum of 1 hour).

The objective of this study was to investigate the pharmacokinetics, pharmacodynamics, safety, and tolerability of a single continuous intravenous dose of remimazolam given until loss of consciousness.

Pharmacokinetics: PK analysis using arterial plasma remimazolam concentrations in 8 healthy male subjects led to the selection of a 3-compartment model as the optimal model for simulation. Using this model, the concentration immediately before the end of infusion (C_{eoi}), $T_{1/2}$, V_{ss}, and CL of remimazolam in arterial plasma were 672 ng/mL, 57 minutes, 30.9 L, and 1.11 L/min, respectively. Those of remimazolam in venous plasma were 619 ng/mL, 59 minutes, 43.1 L, and 1.11 L/min, respectively. The AUC_{last}, AUC_{inf}, $T_{1/2}$, and CL of remimazolam in arterial blood were equivalent to those in venous blood (Table 19). The C_{eoi} and V_{ss} in arterial blood were higher and lower, respectively, than those in venous blood. The CL was estimated to be 0.0177 L/min/kg.

Table 19: Pharmacokinetic parameters of plasma ONO-2745 after continuous intravenous infusion of ONO-2745 at the infusion rate of 1 mg/kg/hr to healthy adult male subjects

	Ceoi (ng/mL)	AUClast (ng·h/mL)	AUCinf (ng·h/mL)	T1/2 (min)	CL (L/min)	Vss (L)
Arterial plasma	672 (71)	422 (157)	428 (161)	57 (5)	1.11 (0.26)	30.9 (4.1)
Venous plasma	619 (89)	420 (163)	431 (170)	59 (13)	1.11 (0.26)	43.1 (7.7)

Mean (standard deviation), N=8

Pharmacodynamics: All 8 of the 8 subjects experienced LoC at the employed remimazolam 1 mg/kg/hr dose. The time to LoC (mean ± SD) was 16.5 ± 8.6 minutes. The duration of LoC was 12.5 ± 9.0 minutes (mean ± SD). The condition in 2 of the 8 subjects changed from loss of consciousness to a sedated state during infusion: one remained sedated until the end of administration and the other lost consciousness again. The time to recovery of consciousness was 24.9 ± 19.1 minutes (mean ± SD) after the end of the infusion. As expected, the MOAA/S score decreased as the plasma remimazolam concentration increased.

Summary of Study CNS7056-019 (Intranasal Administration Study).

The CNS7056-019 study involved a cross-over study, remimazolam was administered intranasally as a non-reconstituted drug product powder (10, 20, and 40 mg), intranasally as a solution (10, 20, and 40 mg) and compared to an intranasal placebo solution, intranasal placebo powder, and 4 mg IV remimazolam (bolus dose over 1 minute).

Pharmacokinetics: After remimazolam 4 mg IV, median Tmax occurred at 0.033 hours, corresponding to a mean C_{max} of 213 ng/mL. An initial mean plasma concentration at time zero (C_0) of 417 ng/mL was estimated by back extrapolation. Mean systemic exposures, AUC_{last} and AUC_{inf}, were 55 ng·h/mL and 59 ng·h/mL, respectively.
The intranasal solution formulation remimazolam C_{max} and systemic exposure were similar to the powder formulation, except at the higher dose levels (20 and 40 mg), where the powder formulation had higher exposure. C_{max} for the solution formulation ranged from 112-209 ng/mL and that for the powder formulation ranged from 108-330 ng/mL. Compared to the 4 mg IV administration, intranasal administration achieved higher C_{max} at the 40 mg dose level and higher total systemic exposure (AUC_{last} and AUC_{inf}) at all dose levels (AUC_{inf} from 72-268 and 62-144 ng·h/mL for the powder and solution formulations, respectively). C_{max} increased in a dose-proportional manner for the intranasal powder formulation but was less than dose proportional for the intranasal solution formulation.

Table 20: Summary of Remimazolam Pharmacokinetic Parameters – Pharmacokinetic Population

Parameter (unit)	Statistic	A (N = 12)	B (N = 11)	C (N = 11)	D (N = 10)	E (N=11)	F (N = 11)	G (N = 10)
C_{max} (ng/mL)	n	12	11	11	10	11	11	10
	Mean	213	108	188	330	112	165	209
	SD	144	44	59	90	36	106	100
C_0 (ng/mL)	n	12	--	--	--	--	--	--
	Mean	417	--	--	--	--	--	--
	SD	512	--	--	--	--	--	--
T_{max} (h)	n	12	11	11	10	11	11	10
	Mean	0.040	0.212	0.190	0.23	0.132	0.146	0.150
	SD	0.022	0.078	0.075	0.10	0.044	0.037	0.077
	Median	0.033	0.167	0.167	0.175	0.167	0.167	0.167
	min, max	0.017, 0.083	0.167, 0.333	0.083, 0.333	0.083, 0.367	0.083, 0.183	0.083, 0.167	0.083, 0.333
$AUC_{0\text{-last}}$ (h*ng/mL)	n	12	11	11	10	11	11	10
	Mean	55	69	135	262	60	93	133
	SD	16	20	42	80	25	37	15
$AUC_{0\text{-inf}}$ (h*ng/mL)	n	12	11	11	10	10	11	10
	Mean	59	72	141	268	62	98	144
	SD	16	19	45	83	26	39	16
$t_{1/2}$ (h)	n	12	11	11	10	10	11	10
	Mean	0.49	0.66	0.87	0.69	0.71	0.97	1.17
	SD	0.19	0.20	0.19	0.11	0.27	0.19	0.18
F (%)	n	--	11	11	10	10	11	10
	Mean	--	49	49	48	47	34.4	26.1
	SD	--	12	18	22	23	9.8	8.7

A: Remimazolam 4 mg IV. B: Remimazolam 10 mg powder, C: Remimazolam 20 mg powder, D: Remimazolam 40 mg powder, E: Remimazolam 10 mg solution, F: Remimazolam 20 mg solution, G: Remimazolam 40 mg solution.

Remimazolam absolute bioavailability based on dose normalized $AUC_{0\text{-inf}}$ was 49%, 49%, and 48% for the 10 mg, 20 mg, and 40 mg powder treatments, respectively. Intranasal powder treatment relative C_{max} concentration based on dose-normalized C_{max} was 18% to 22% of the IV administration. The intranasal solution formulation resulted in similar absolute bioavailability at the 10 mg dose (47%), but then deceased with increasing doses to 34% at 20 mg and 26% at the 40 mg dose. Similarly, intranasal

solution relative exposure based on dose-normalized C_{max} decreased from 24% of the iv administration in the 10 mg treatment to 11% in the 40 mg treatment.

T_{max} for the powder and solution intranasal formulations ranged from 0.21-0.23 and 0.13-0.15 hours, respectively. The mean $t_{1/2}$ after IV injection was 0.49 hours and was extended for the intranasal formulations (0.66-0.87 hours and 0.71-1.17 hours for the powder and solution, respectively).

Pharmacodynamics: Intranasal administration of remimazolam as either a powder or solution increased drowsiness with the strongest effects observed at higher doses. These effects persisted longer when remimazolam was dosed as powder.

Intranasal dosing of remimazolam at all doses tested produced relaxation effects. The effect persisted longer following powder administration compared to administration as a solution.

Intranasal delivery of remimazolam as either a powder or solution produced mild to moderate nasal pain as measured by the visual analog scale (VAS) for "Pain", with 0 being no pain/discomfort and 100 being extreme pain/discomfort. When administered as an intranasal solution, the E_{max} values for the VAS scale for Pain for the 10, 20 and 40 mg remimazolam doses were 24.9, 31.7 and 46.9, respectively. When administered as an intranasal powder, the E_{max} values for the 10, 20 and 40 mg remimazolam doses were 40.9, 45.0, and 37.7, respectively. Nasal pain peaked at 5 to 15 minutes post-dose and generally subsided within 60 minutes. However, dosing with 40 mg powder resulted in mild pain persisting at 60 minutes post-dose.

A small but generally dose-dependent effect on memory, as measured by the Total Adjusted Errors in the PAL Test, was observed that was stronger for the intranasal powder as compared to the solution formulation. A possible training effect may have been seen with IV remimazolam being dosed first which made it appear that memory and reaction time (RTI) improved with repeat assessment in inexperienced subjects, when it could have been a conditioned effect and not a drug effect. In addition, there was high variability in scores for both memory effects and RTI.

RTIs were increased slightly following intranasal dosing with powder remimazolam in a dose dependent manner. RTI effects were only observed for 60 minutes following dose. Effects on RTI were not observed following intranasal remimazolam solution administration.

Summary of Study CNS7056-016 (Oral Administration Study).

The oral administration of remimazolam was evaluated in Study CNS7056-016 where 14 subjects received a single dose of remimazolam 0.14 mg/kg orally and 0.025 mg/kg IV under fasting conditions, with 48-hour washout period between each dose.

Pharmacokinetics: Mean peak (C_{max}) and total (AUC_{0-t}) remimazolam systemic exposure were considerably lower after oral treatment than after IV treatment. The absolute bioavailability of oral remimazolam was 1.2% based on dose-normalized Cmax (90% CI: 0.008 - 0.017) and 2.2% based on dose-normalized AUC0-t (90% CI: 0.015 - 0.032). AUC_{inf} was excluded from the statistical analysis, as there were not enough valid observations to perform the analysis. The median t_{max} of the metabolite, CNS7054, was 0.5 hours for both treatments, indicating that remimazolam was rapidly metabolized to CNS7054.

Table 21: Summary Statistics of Pharmacokinetic Parameters for Remimazolam in Plasma

		Treatment[1]	
Parameter (unit)	**Statistic**	**A**	**B**
C_{max} (ng/mL)	n	14	14
	Geometric mean	4.29	65.19
	%CV	35.4	113.5
	Min, max	2.3, 7.5	18.6, 434.6
T_{max} (hr)	n	14	14
	Median	0.500	0.040
	%CV	49.1	49.9
	Min, max	0.08, 0.72	0.03, 0.10
AUC_{0-t} (hr*ng/mL)	n	14	14
	Geometric mean	2.46	19.91
	%CV	48.6	46.0
	Min, max	0.4, 5.4	7.4, 51.0
AUC_{0-inf} (hr*ng/mL)	n		13
	Geometric mean		22.01
	%CV		44.6
	Min, max		8.3, 53.5
$t_{1/2}$ (hr)	n		13
	Geometric mean		0.411
	%CV		38.2
	Min, max		0.21, 0.76
CL (L/hr)	n		13
	Geometric mean		84.8
	%CV		33.3
	Min, max		36, 150
Vz (L)	n		13
	Geometric mean		50.4
	%CV		41.4
	Min, max		27, 110

CV = coefficient of variation; max = maximum; min = minimum; n = number of subjects within subset
[1] Treatment A: oral remimazolam 0.14 mg/kg; Treatment B: intravenous remimazolam 0.025 mg/kg

Based on dose-normalized parameters, C_{max} and AUC_{0-t} for the metabolite, CNS7054, were respectively 1.3 and 1.2-fold higher after oral treatment than after IV administration. For both oral and IV treatment, mean peak (C_{max}) and total (AUC_{0-t} and AUC_{inf}) systemic exposure to metabolite CNS7054 was considerably higher than exposure to the parent compound. The mean $t_{½}$ of CNS7054 was 1.9 hours after IV treatment and 2.5 hours after oral treatment.

These results indicate complete absorption of orally administered remimazolam followed by an extensive first-pass effect in the liver. The results also indicate that the oral route of administration is unlikely to reveal clinically significant plasma levels for remimazolam.

Summary of Study CNS7056-020 (Oral Administration Study with Ethanol).

The CNS7056-020 trial assessed the effect of remimazolam when administered orally with various concentrations of ethanol. The study consisted of 2 parts.

- Part 1 was an open-label, single-ascending dose trial conducted in 21 healthy female volunteers to identify the minimally biologically active dose of remimazolam (i.e., lowest dose with effects on memory and consciousness) as well as the PK, safety, and tolerability of a single oral dose of remimazolam of 60, 140, 240, 360 or 480 mg.
- Part 2 was a double-blind, double-dummy, single dose, crossover trial conducted in 11 female subjects to evaluate the effects of varying concentrations of ethanol on the safety and tolerability, PK, and PD of a single oral dose of remimazolam (360 mg).

Pharmacokinetics:

Part 1: In Part 1, after oral administration of 60 to 480 mg remimazolam, plasma levels of remimazolam reached median T_{max} at between 0.23 to 0.48 hours, independent of dose. As dose increased from 60 to 480 mg, remimazolam Cmax, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ all increased with dose. For the 8-fold increase in dose, geometric mean Cmax increased 5.8-fold, geometric mean $AUC_{0\text{-}last}$ increased 11.1-fold, while $AUC_{0\text{-}inf}$ increased 5.9-fold. Disappearance of parent drug from plasma was very rapid, with a geometric mean $t_{1/2}$ of 0.53 to 0.66 hours, independent of dose.

Part 2: In Part 2, after oral administration of 360 mg remimazolam (as a drinkable solution) with 0%, 5%, 15% and 40% of co-administered alcohol, median T_{max} occurred rapidly, ranging from 0.23 to 0.49 hours, and was independent of the amount of co-administered alcohol. Disappearance of remimazolam from plasma was rapid, with a geometric mean $t_{1/2}$ of 0.54 to 0.62 hour, independent of alcohol dose. As the amount of added alcohol increased from 0% to 40%, remimazolam C_{max}, AUC_{last}, and AUC_{inf} all increased: mean C_{max} (76.3 to 135 ng/mL); mean AUC_{last} (85.2 to 163 ng·h/mL) and mean AUC_{inf} (90.3 to 168 ng·h/mL).

Metabolite CNS7054: After oral administration of 360 mg remimazolam with 0%, 5%, 15% and 40% of added alcohol, remimazolam was rapidly and extensively metabolized to CNS7054. Formation of CNS7054 appeared to be delayed slightly by the presence of added alcohol. Median T_{max} was approximately 1 hour after administration of remimazolam with 0% or 5% added alcohol, increasing to 1.5 hours after administration of remimazolam with 15% or 40% added alcohol. Disappearance of the metabolite CNS7054 from plasma was somewhat slower than parent, with a geometric mean $t_{1/2}$ ranging from 1.82 to 2.02 hours, independent of the amount of added alcohol. As the amount of added alcohol increased from 0% to 40%, Cmax, AUClast and AUC0inf for CNS7054 all appeared to increase in relation to the amount of added alcohol, although the degree of change was much smaller compared to that of remimazolam: mean C_{max} (25.9 to 27.5 mg/L); mean AUC_{last} (82.5 to 100 mg·h/L) and mean AUC_{inf} (88.2 to 111 mg·h/L).

From the analyses, it is evident that addition of alcohol to the oral administration of remimazolam modestly increased the systemic exposure to remimazolam. Addition of alcohol to the oral dose of

remimazolam had much less of an effect on systemic exposure to metabolite CNS7054 than it did on remimazolam.

Table 22: Summary of Remimazolam Plasma Pharmacokinetic Parameters: Part 1

Parameter	Statistic	Remimazolam				
		60 mg (N=3)	140 mg (N=3)	240 mg (N=5)	360 mg (N=5)	480 mg (N=5)
T_{max} (h)	n	3	3	5	5	5
	Median	0.23	0.48	0.23	0.48	0.48
	Min, Max	0.23, 0.73	0.23, 0.72	0.23, 0.75	0.23, 1.03	0.23, 0.73
C_{max} (ng/mL)	n	3	3	5	5	5
	Geometric Mean	15.0	36.4	45.7	54.0	87.0
	Arithmetic Mean	16.2	36.9	58.1	60.9	92.9
	SD	7.9	7.1	50	30	30
$AUC_{0\text{-last}}$ (h*ng/mL)	n	3	3	5	5	5
	Geometric Mean	9.83	31.1	36.7	53.9	109
	Arithmetic Mean	11.1	31.5	43.8	61.0	118
	SD	6.5	6.2	30	30	60
$AUC_{0\text{-inf}}$ (h*ng/mL)	n	1	2	5	5	5
	Geometric Mean	19.5	35.2	39.5	57.3	115
	Arithmetic Mean	19.5	35.7	46.5	64.3	124
	SD		8.1	40	30	60
$t_{1/2}$ (h)	n	1	2	5	5	5
	Geometric Mean	0.33	0.37	0.53	0.56	0.66
	Arithmetic Mean	0.33	0.37	0.55	0.59	0.69
	SD		0.01	0.17	0.21	0.25
CL/F (L/h)	n	1	2	5	5	5
	Geometric Mean	3071	3971	6068	6282	4144
	Arithmetic Mean	3071	4024	6724	7270	4428
	SD		916	2619	4826	1686
V_Z/F (L)	n	1	2	5	5	5
	Geometric Mean	1479	2106	4626	5076	3951
	Arithmetic Mean	1479	2140	5202	6180	4448
	SD		543	2537	4056	2250

Abbreviations: max = maximum; min = minimum; N = number of subjects in sample; n = number of subjects in subsample; PK = pharmacokinetic; SD = standard deviation

Table 23: Summary of Remimazolam Plasma Pharmacokinetic Parameters: Part 2

Parameter	Statistic	Treatment[1]			
		A	B	C	D
		(N=11)	(N=11)	(N=11)	(N=8)
T_{max} (h)	n	11	11	11	8
	Median	0.48	0.48	0.23	0.49
	Min, Max	0.23, 0.98	0.22, 0.75	0.22, 0.97	0.18, 0.97
C_{max} (ng/mL)	n	11	11	11	8
	Geometric Mean	76.3	92.5	121	135
	Arithmetic Mean	87.3	109	131	180
	SD	50	70	60	189
$AUC_{0\text{-last}}$ (h*ng/mL)	n	11	11	11	8
	Geometric Mean	85.2	97.1	138	163
	Arithmetic Mean	93	104	146	185
	SD	40	40	50	113
$AUC_{0\text{-inf}}$ (h*ng/mL)	n	11	11	10	8
	Geometric Mean	90.3	101	144	168
	Arithmetic Mean	97.6	108	152	190
	SD	40	40	50	113
$t_{1/2}$ (h)	n	11	11	10	8
	Geometric Mean	0.59	0.62	0.55	0.54
	Arithmetic Mean	0.61	0.65	0.56	0.55
	SD	0.15	0.18	0.12	0.1
CL/F (L/h)	n	11	11	10	8
	Geometric Mean	3985	3532	2488	2141
	Arithmetic Mean	4325	3773	2625	2366
	SD	1896	1531	933	1031
V_Z/F (L)	n	11	11	10	8
	Geometric Mean	3393	3184	1984	1663
	Arithmetic Mean	3692	3548	2207	1796
	SD	1668	1826	1086	756

[1]A: Remimazolam 360 mg, B: Remimazolam 360 mg + 5% v/v alcohol, C: Remimazolam 360 mg + 15% v/v alcohol, D: Remimazolam 360 mg + 40% v/v alcohol

Pharmacodynamics:

Part 1: In Part 1, The PD effects of remimazolam in the population tested were modest. At oral doses of 60 to 480 mg, a minimally biologically active dose of remimazolam was not identified based on protocol-specified MOAA/S and AE criteria. Most PD assessments did not show conclusive results or trends, except for Alertness/Drowsiness VAS, which suggested a modest increase in drowsiness with increasing doses of remimazolam up to 240 mg, with a plateau at higher doses.

Part 2: In Part 2, Oral remimazolam alone (360 mg) had a mild but significant effect on all PD measures as compared to alcohol alone (40%) that had no effect on any PD measure (although sometimes a difference versus pre-dose was seen, but the lack of a real placebo control precludes any conclusion). When remimazolam and alcohol were administered together, the effects were slightly stronger than with remimazolam alone, although mostly not in an alcohol dose-dependent manner. The concentration of alcohol did not, however, have a major impact on the change in PD effects of remimazolam in the presence of alcohol.

Abuse potential studies

Study CNS7056-014 was a single-dose, randomized, double-blind, placebo- and active-controlled crossover study with a single inpatient treatment visit. The abuse potential of single doses of IV remimazolam 5 mg and 10 mg was compared with that of 2.5 mg and 5 mg IV midazolam (active control) and placebo in healthy recreational CNS depressant users.

Eligible subjects received each of the following 5 treatments (on Days 5, 7, 9, 11, and 13), administered IV over 1 minute, in a randomized, double-blind, crossover manner following an overnight fast:

- Remimazolam 5 mg
- Remimazolam 10 mg
- Midazolam 2.5 mg
- Midazolam 5 mg
- Placebo (saline injection)

Each drug administration was separated by approximately 48 hours. Serial pharmacodynamic (PD) evaluations were conducted up to 8 hours post-dose. PK and safety were also assessed.

The primary PD endpoint was the maximum effect (E_{max}) on the bipolar Drug Liking visual analogue scale (VAS). Secondary endpoints included Drug Liking VAS (minimum effect [E_{min}] and time-averaged area under the effect curve to 8 hours after study drug administration [TA_AUE]); Overall Drug Liking VAS (E_{max}/E_{min}); Take Drug Again VAS (E_{max}); Good Effects VAS (E_{max} and TA_AUE); Bad Effects VAS (E_{max} and TA_AUE); Alertness/Drowsiness VAS (E_{min} and TA_AUE); Agitation/Relaxation VAS (E_{min} and TA_AUE); Any Effects VAS (E_{max} and TA_AUE); and Paired Associates Learning (PAL) total error score (E_{max} and TA_AUE).

Pharmacodynamics: Remimazolam demonstrated an absolute abuse potential relative to placebo based on a its subjective effects on recreational drug abusers. The abuse potential of remimazolam was comparable to that of midazolam based on the primary measure, drug liking E_{max}. The Drug Liking VAS for remimazolam 5 mg and the comparable midazolam dose (2.5 mg) was 77.69 and 78.6, respectively and were 79.8 and 81.5 for remimazolam 10 mg and midazolam 5 mg, respectively (a score of 0 = "Strong disliking"; 50 = "Neither like nor dislike"; 100 = "Strong liking"). Take Drug Again E_{max} was significantly lower for 5 mg remimazolam compared to 2.5 mg midazolam; the difference was no longer statistically different for the comparison of 10 mg remimazolam vs 5 mg midazolam, indicating that any difference flattens out when the dose is increased. The duration of drug liking and of other drug effects were generally longer for midazolam compared to remimazolam (drug liking for both remimazolam and midazolam peaked at between 2- and 20-minutes post-dose and were sustained for up to approximately 4 hours post-dose). The TA_AUE of good effects were statistically significantly higher for midazolam than remimazolam and the TA_AUE of bad effects were statistically significantly higher for remimazolam than midazolam. For more details on the abuse liability of this product refer to the Control Substance Staff (CSS) review for the NDA.

Table 24: Statistical Analysis of Drug Liking Parameters of IV Midazolam and Placebo: Completer Population (N=39)

	Treatment[1]			LS Mean		LS Mean Difference (Test - Ref)	
Assessment	**Test**	**Ref**	**PD Parameter**	**Test**	**Ref**	**Estimate**	**95% CI**
Drug Liking	C	E	E_{max}	78.81	53.28	25.53	(21.29, 29.76)
			E_{min}	46.41	46.19	0.22	(-5.39, 5.83)
			TA_AUE	42.98	-5.50	48.47	(28.22, 68.73)
	D	E	E_{max}	81.59	53.28	28.32	(24.08, 32.55)
			E_{min}	44.87	46.19	-1.33	(-6.93, 4.28)
			TA_AUE	49.70	-5.50	55.20	(34.94, 75.45)

[1]C: Midazolam IV 2.5 mg, D: Midazolam IV 5 mg, E: Placebo
CI = confidence interval; E_{max} = maximum effect; E_{min} = minimum effect; IV = intravenous; LS = least squares; PD = pharmacodynamic; TA AUE = time-averaged area under the effect curve

For more details on the abuse liability of this product refer to the CSS review for the NDA.

QT prolongation potential Studies

Two studies were conducted to evaluate the effect of remimazolam on QTc Study CNS7056-005 and Study CNS7056-017. In Study CNS7056-005, a thorough QT trial following the principles of ICH guidance E14, 57 healthy subjects (approximate 1:1 ratio of males to females) were randomized using a double William's square cross-over design to a sequence of the following treatments: IV bolus placebo, 1 tablet moxifloxacin 400 mg per oral, IV bolus remimazolam 10 mg, IV bolus remimazolam 20 mg, IV bolus midazolam 2.5 mg, and IV bolus midazolam 7.5 mg. There was a minimum 3-day washout period between treatments.

The time-matched (timepoint) analysis demonstrated a very rapid increase in heart rate immediately following dosing, and these heart rate increases persisted for 5 to 10 minutes before resolving by 30 to 60 minutes after dosing. This study detected the expected QT interval prolongations with moxifloxacin, validating assay sensitivity. As shown in Table 25, a transient increase in QTc at 30 seconds and 2 minutes after dosing was observed for both remimazolam and midazolam which slightly exceeded the "regulatory threshold of concern" (two-sided 90% CI exceeding 10 ms) cited in ICH E14 guidance. Beyond the first 2 minutes, there was no evidence of any clinically significant effect of remimazolam on QTc.

Table 25: Effects of Remimazolam on QTc interval: Study CNS7056-005

	QTcI (0.5 min / 2 min)	**Lower Bound CI (0.5 min / 2 min)**	**Upper Bound CI 0.5 min / 2 min)**
Remimazolam 10mg	7.2 ms / 4.7 ms	3.2 ms / 0.7 ms	11.2 ms / 8.7 ms
Remimazolam 20mg	10.4 ms / 6.3 ms	6.5 ms / 2.3 ms	14.3 ms / 10.2 ms
Midazolam 2.5mg	5.4 ms / 4.5 ms	1.4 ms / 0.6 ms	9.4 ms / 8.5 ms
Midazolam 7.5 mg	8.2 ms / 5.9 ms	4.4 ms / 2.0 ms	12.1 ms / 9.8 ms

This initial transient effect on repolarization in the first 2 minutes after bolus dosing was hypothesized to be due to QT-RR hysteresis due to the large, rapid increase in heart rate immediately after dosing. This hypothesis was further explored in Study CNS-7056-017.

Study CNS7056-017 was an open-label, randomized, placebo-controlled, crossover Phase 1, PK/PD clinical PK/PD study in which the effect of steady state plasma concentrations of remimazolam and its metabolite CNS7054 on cardiac repolarization during continuous infusion of remimazolam was evaluated without the confounding effect of QT-RR hysteresis observed with bolus dosing. The trial employed 3 different remimazolam infusion rates: initially 5 mg/min over 5 min, followed by 3 mg/min for the next 15 min, and then 1 mg/min for another 15 min. As expected, the remimazolam plasma concentrations ranged from 1.6 to 2.0 µg/mL during the 3 mg/min infusion and from 1.0 to 1.1 µg/mL during the 1 mg/min infusion.

A total of 20 subjects were randomized and received at least one dose of study drug. The results showed no effect of remimazolam on AV conduction as measured by the PR interval or on cardiac depolarization as measured by the QRS duration. There were no clinically relevant morphological changes

demonstrating a signal of concern. A 15 bpm but stable increase in HR was observed from 5 minutes to 65 minutes after the start of infusion.

No signal of any effect of remimazolam on cardiac repolarization was observed, based on time point, outlier, and PK/PD analyses. The largest control-corrected change from baseline for QT interval with individual correction (QTcI) was 3.7 ms (two-sided 90% upper confidence interval 8.5 ms) 15 minutes after the start of infusion. None of the remimazolam time points demonstrated an upper bound that approached or exceeded 10 ms.

(b) (4)

The data from both the studies were evaluated by the office's QT internal review team (QT-IRT). The IRT review concluded that remimazolam treatment is associated with large increase in heart rate. In the thorough QT study, the largest mean placebo-adjusted change-from-baseline HR (upper bound of 2-sided 90% CI) was 12.3 (14.2) bpm and 15.2 (17.1) bpm, after treatment with 10 mg and 20 mg remimazolam, respectively. The observation does not impact the overall conclusion that remimazolam increases the QTc interval because in a separate study (CNS7056-017) where heart rate is kept constant by using a slow IV infusion, small increases in QTc interval were detected. Furthermore, the slopes of the concentration- QTc relationship between the two studies were similar.

The following were the IRTs comments to the review team (b) (4) We recommend reporting study findings, including drug effect on HR and QTcF, from the TQT study, CNS7056-005." To get further details on the QT-IRT review refer to the review written by Dr. Nan Zheng submitted to DARRTS on 08/02/2019.

These issues raised by the QT-IRT were communicated to the sponsor in the Mid-Cycle communication meeting. During the midcycle communication T-con held with the sponsor on Nov 22nd, 2019, the sponsor was informed that (b) (4) . We intend to include a description of the drug effect on HR and QTcF from the TQT study, CNS7056-005, in labeling, if the drug is approved. The final labeling language is still being discussed and has not been finalized." (b) (4)

Reviewers Comments: We agree with the QT-IRT assessment that the study results from study CNS7056-005 should be reported in the remimazolam label. The suggested labeling language is described in section 2.4 of this review.

4.3 Population PK and/or PD Analyses

Pharmacometrics Review

Introduction

The primary objectives of this population pharmacokinetic (PopPK) analysis were to:

1. Characterize the pharmacokinetics (PK) of remimazolam in adults following intravenous (IV) administration of remimazolam.

2. Identify influential covariates, such as bodyweight, age, sex, race, American Society of Anesthesiologists (ASA) class, body mass index (BMI), estimated glomerular filtration rate (eGFR), and creatinine clearance (CrCL) on CL; the effect of concomitant medications that inhibit carboxylesterase 1 (CES-1) on CL; the effects of age, sex, race, ASA class and BMI on volume of distribution at steady-state (Vss) in patients.

Model development

Data

The PopPK analysis was based on PK data from 11 clinical studies: ONO-2745-01, ONO-2745-02, ONO-2745-03, ONO-2745-IVU007, CNS7056-001, CNS7056-002, CNS7056-004, CNS7056-006, CNS7056-008, CNS7056-015, CNS7056-017. The study design and blood sampling schedule varied among the 11 clinical studies.

A summary of the number of subjects in PopPK model is given in **Base model**

The base model was based on previously developed PopPK models. Inter-individual variability (IIV) for log-transformed PK parameters was modeled assuming a normal distribution for patient level random effects. The base structural model included 3 compartments to describe remimazolam concentrations over time. Even though previous PopPK models have shown that there is no relationship between body weight and PK parameters, the effect of body weight on all CL and V of distribution parameters was included with the allometric exponent (fixed to 0.75 for CL and intercompartmental clearances, Q2 and Q3, and 1.0 for V1 and volumes of the peripheral compartments [V2 and V3]).

Covariate analysis

A systematic covariate search was performed that led to the final model in the PK analysis. Covariate parameters, including the effect of age, sex, race, ASA class, BMI, eGFR, and CrCL on CL; the effect of concomitant medications that inhibit CES-1 on CL; the effects of age, sex, race, ASA class and BMI on Vss, were investigated in the PopPK analysis.

Table 26. Pop PK modeling included all subjects who received a remimazolam dose with available dosing information and remimazolam plasma levels before administration of flumazenil: 126 healthy subjects, 193 patients undergoing procedural sedation, and 40 patients undergoing induction and maintenance of anesthesia for surgery; 359 subjects total.

Base model

The base model was based on previously developed PopPK models. Inter-individual variability (IIV) for log-transformed PK parameters was modeled assuming a normal distribution for patient level random effects. The base structural model included 3 compartments to describe remimazolam concentrations over time. Even though previous PopPK models have shown that there is no relationship between body weight and PK parameters, the effect of body weight on all CL and V of distribution parameters was included with the allometric exponent (fixed to 0.75 for CL and intercompartmental clearances, Q2 and Q3, and 1.0 for V1 and volumes of the peripheral compartments [V2 and V3]).

Covariate analysis

A systematic covariate search was performed that led to the final model in the PK analysis. Covariate parameters, including the effect of age, sex, race, ASA class, BMI, eGFR, and CrCL on CL; the effect of concomitant medications that inhibit CES-1 on CL; the effects of age, sex, race, ASA class and BMI on Vss, were investigated in the PopPK analysis.

Table 26 Number of Subjects for Population PK Analyses

Study ID	Study	Number of Subjects	Number of Subjects Included in Analysis[a]	Number of PK Samples	Removed BLQs	Number of PK Samples Included in Analysis[d]
1	ONO-2745-01	42	35	620	49	571
2	ONO-2745-02	10	8	215	8	207
3	ONO-2745-03	85	40	136	0	127
7	ONO-2745-IVU007	9	9	150	15	135
11	CNS7056-001	81	54	1242	201	1038
12	CNS7056-002	51	45	630	239[b]	376
14	CNS7056-004	120	28	206	29	176
15	CNS7056-015	47	31	126	2[c]	122
16	CNS7056-006	356	85	388	26[b]	361
17	CNS7056-017	20	20	560	41	519
18	CNS7056-008	362	4	14	3[b]	10
TOTAL		1183	359	4287	613	3642

[a] This number includes those with quantifiable concentrations. There were prediction records for all subjects to be included in the PK/PD analysis. [b] A total of 5 quantifiable pre-dose values were removed from the dataset because the recorded time of sampling was before or equal to the recorded time of the first dose. [c] One additional record was removed for missing sample time. [d] This number does not reflect the data that was not included in modeling because the samples were considered erroneous or outliers.

(Source: Applicant's Population PK report nps2981-rpt001, Table 17)

Results

The final PopPK model was a 3-compartment model with a CL of 1.18 L/min and a Vss of 41.5 L in a 70 kg subject. Analyses indicated that:

- CL was 9.7% higher in females than males.
- CL was 13.0% lower in African Americans than in Caucasians or Asians. The Vss was 16% lower in African Americans than in Caucasians or Asians.
- Other parameters assessed, such as age, ASA class, BMI, eGFR, and creatinine clearance had no effect on the PK of remimazolam.

Final Population Pharmacokinetic Model

The parameter estimates for the final PopPK model in the analysis are listed in

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Table 277. The goodness-of-fit plots for the final covariate model for all data are shown in

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Figure 11. The final PopPK model reasonably described the observed data, and the PK parameter estimates were reasonable.

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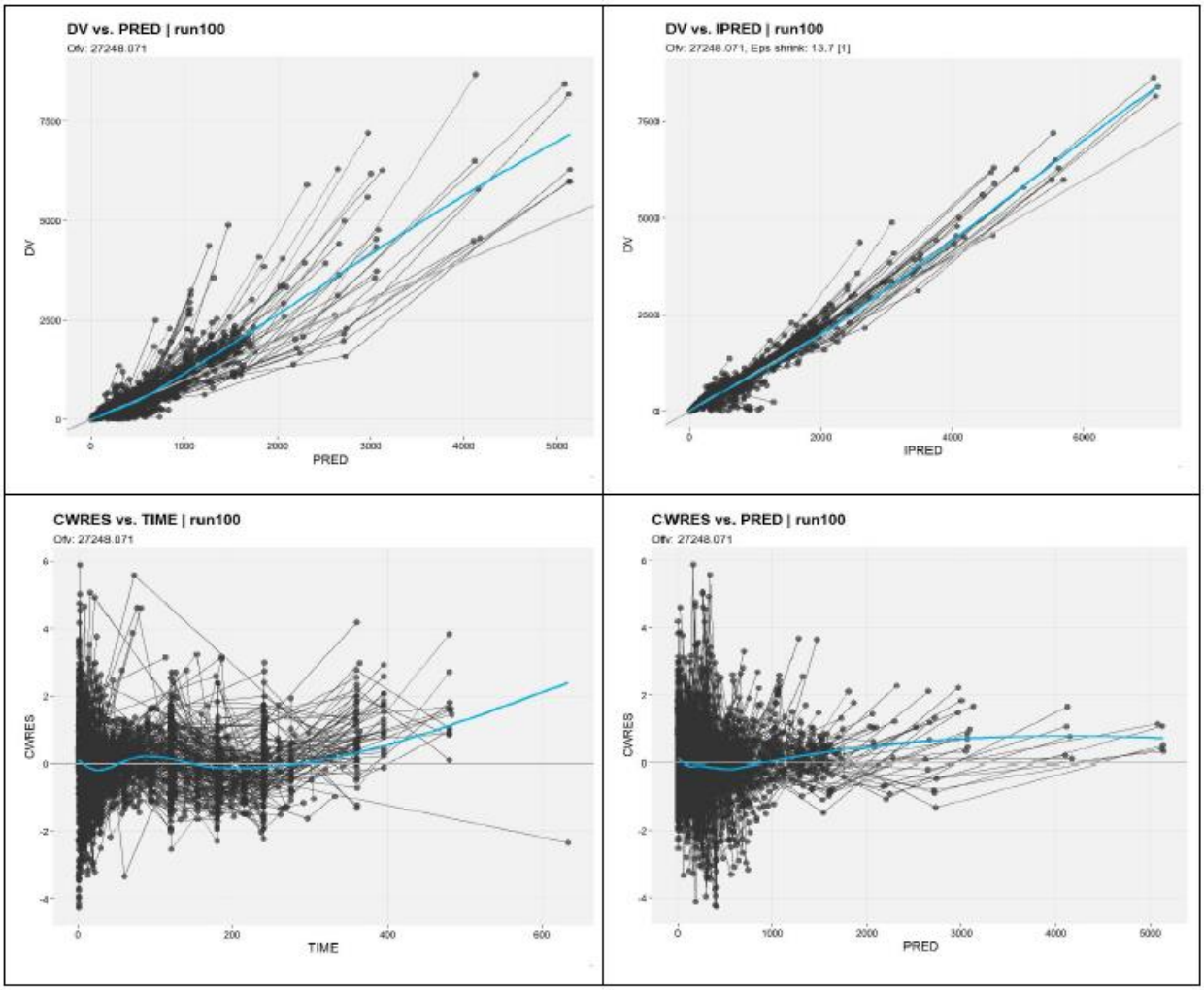
Table 27 NONMEM Estimates and Bootstrap Estimates for the Final Pop PK Model (Model #100)

Description	NONMEM Estimate (%RSE)	Bootstrap median (%RSE) [95 %CI)
CL L/min/70 kg [a]	1.18 (2%)	1.17 (1.7%) [1.14, 1.21]
V1 L/70 kg [a]	4.83 Fixed	4.83 Fixed
Q2 L/min/70 kg [a]	0.284 (2.7%)	0.279 (4.7%) [0.258, 0.309]
V2 L/70 kg [a]	18.7 (2.8%)	18.5 (3.4%) [17.3, 19.9]
Q3 L/min/70 kg [a]	1.92 (6%)	1.90 (4.8%) [1.74, 2.12]
V3 L/70 kg [a]	18 (5.3%)	17.9 (3.3%) [16.5, 19.1]
R_{MAX} (max venous:arterial ratio) [b]	1 Fixed	1 Fixed
T_{50} (min) [c]	1.63 Fixed	1.63 Fixed
RATIO2 (venous:arterial ratio after infusion) [d]	1.28 Fixed	1.28 Fixed
SEX EFFECT on CL (female:male ratio)	1.1 (2.5%)	1.10 (2.7%) [1.04, 1.16]
RACE (African Americans vs Asians and Caucasians) effect on CL	0.87 (2.9%)	0.867 (3.2%) [0.817, 0.932]
RACE (African Americans vs Asians and Caucasians) effect on Vss	0.839 (2.1%)	0.840 (3.8%) [0.787, 0.922]
CL IIV (%)	22.9 (5%)	23.0 (10.9%) [20.6, 25.3]
CL/Q3 correlation	0.51 (9.4%)	0.524 (20.3%) [0.418, 0.578]
Q3 IIV (%)	92.9 (4.8%)	94.5 (16.2%) [83.0, 112]
CL/V3 Correlation	0.55 (8%)	0.569 (15.3%) [0.500, 0.612]
Q3/V3 correlation	0.9 (1.9%)	0.900 (12.1%) [0.882, 0.902]
V3 IIV (%)	74.1 (5.2%)	73.9 (8.8%) [69.7, 79.9]
V1 IIV (%)	61.7 (11.1%)	61.6 (9.5%) [55.2, 67.6]
V2 IIV (%)	24.8 (6.4%)	24.9 (18.2%) [20.2, 29.5]
Residual error	20.7 (0.7%)	20.7 (5.7%) [19.5, 21.8]

[a] clearance and volume parameters are based on a 70kg subject
[b] maximum venous:arterial ratio, fixed to 1 based on the data
[c] T_{50} is the venous:arterial ratio at 50% of R_{MAX}
[d] Venous:arterial ratio after the infusion ends

(Source: Applicant's Population PK report nps2981-rpt001, Table 3)

Figure 11 Final PopPK Pharmacokinetic Model Goodness of Fit Plots (Model #100)



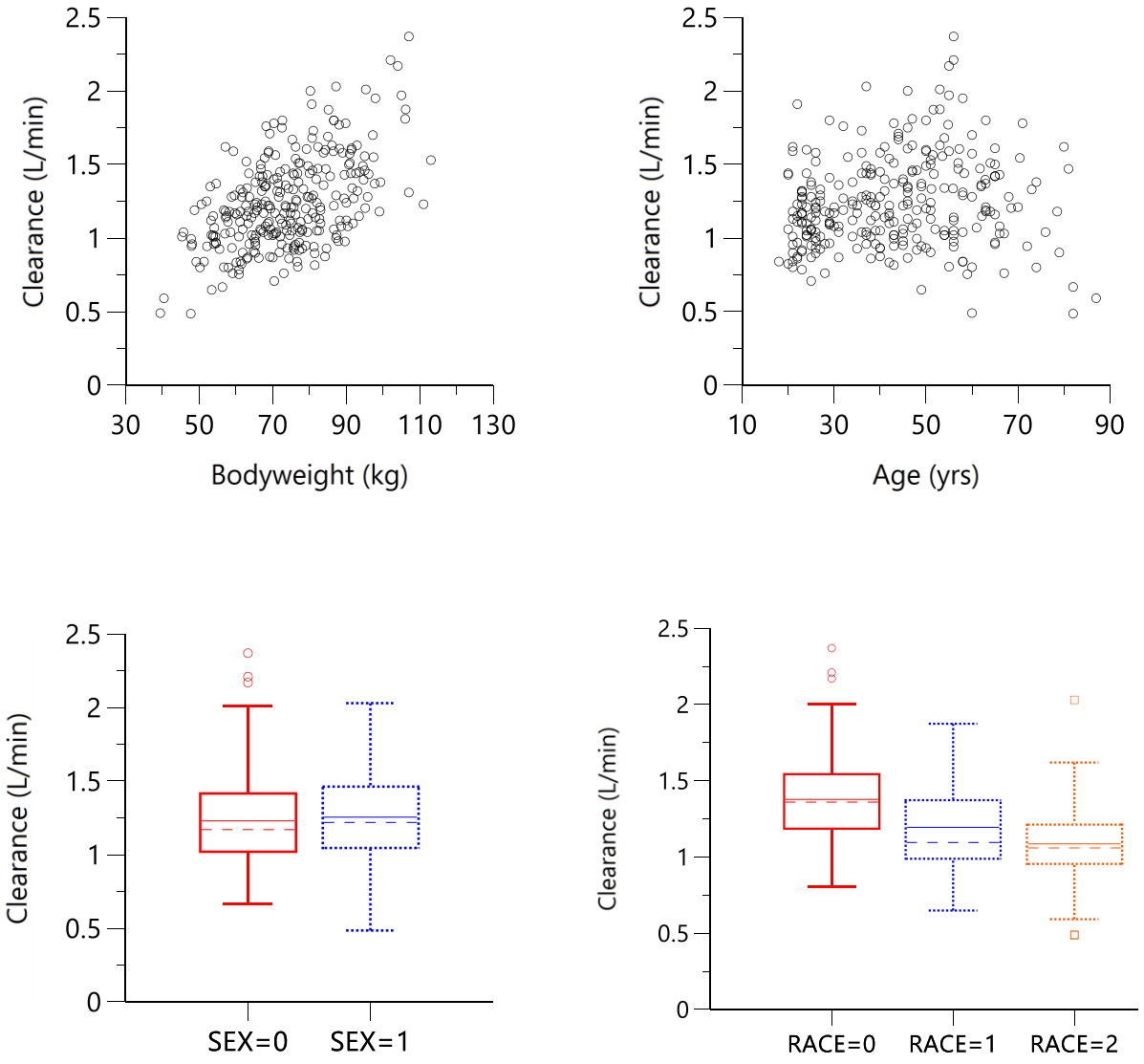
DV: dependent variable, observed remimazolam concentration (ng/mL); PRED: population predicted remimazolam concentration (ng/mL); IPRED: individual predicted remimazolam concentration (ng/mL); CWRES: conditional weighted residual error

(Source: Applicant's Population PK report nps2981-rpt001, Figure 3)

In the final PopPK model, the effect of categorical covariates including sex, race, ASA class, concomitant medications that inhibit CES-1 and the effect of continuous covariates including age, BMI, eGFR, and CrCL were evaluated. The major findings in the covariate analysis were depicted in

Figure 12 below. The effect of covariates on remimazolam PK were not clinically meaningful.

Figure 12 Covariate analysis result: Clearance vs bodyweight (top left), age (top right), gender (bottom left), and race (bottom right)



RACE = (0 = White/Caucasian, 1 = Black/African-American, 2 = Asian), and SEX = (0 = male, 1 = female)

(Reviewer's assessment based on the sponsor's final PopPK model)

Reviewer's comments: The applicant's population PK analysis is acceptable. The goodness-of-fit plots indicated that the final population PK models for remimazolam was adequate in characterizing the PK profiles. The applicant's analyses were verified by the reviewer, with no significant discordance

identified. The allometric scaling approach sufficiently described bodyweight effect on remimazolam disposition. In another PopPK analysis based on Phase 2 studies (ONO-2745-03, ONO-2745-04, ONO-2745-05, and ONO-2745-06), bodyweight was found not to be a clinically relevant covariate. Hence, the dose evaluated in the Phase 3 clinical studies was not adjusted for bodyweight.

The reviewer recommends the following labeling statement in section 12.3:

Other Specific Populations

Age, gender, race, and weight had no clinically relevant effect on remimazolam pharmacokinetics.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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TAO LIU
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VENKATESH A BHATTARAM
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YUN XU
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MEHUL U MEHTA
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