

Efficacy of remimazolam versus midazolam for procedural sedation: post hoc integrated analyses of three phase 3 clinical trials



Authors

Van-Anh Dao¹, Frank Schippers^{*.2}, Thomas Stöhr^{*.1}

Institutions

- 1 PAION Deutschland GmbH, Aachen, Germany
- 2 Creative Clinical Research GmbH, Berlin, Germany

submitted 8.6.2021

accepted after revision 20.10.2021

Bibliography

Endosc Int Open 2022; 10: E378–E385

DOI 10.1055/a-1743-1936

ISSN 2364-3722

© 2022. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Corresponding author

Van-Anh Dao, PAION Deutschland GmbH, Heussstr. 25,
Aachen, Germany
Fax: +49 2414453100
van-anh.dao@gmx.de

ABSTRACT

Background and study aims Remimazolam is an ultra-short acting, fast onset/fast offset benzodiazepine for intravenous use in procedural sedation, general anesthesia, and Intensive Care Unit sedation. The aim of this work was to compare the efficacy of remimazolam versus midazolam

dosed according to medical practice (real-world midazolam) and midazolam dosed according to US prescribing information (on-label midazolam) for procedural sedation.

Patients and methods This post hoc analysis was performed using integrated data from three randomized, placebo, and active (midazolam) controlled, phase 3 clinical trials in patients undergoing colonoscopy and bronchoscopy. Statistical comparisons between treatment groups, without adjustment for potential confounding factors, were exploratory and observational in nature.

Results The mean $\pm$ SD dose of midazolam in the real-world midazolam group was 6.2 ± 3.1 mg, compared with 3.5 ± 1.5 mg in the on-label midazolam group. remimazolam showed significantly shorter time from first dose to start of procedure (median 3 minutes) compared to on-label midazolam (median 8 minutes). Recovery time from end of procedure to fully alert was significantly shorter for remimazolam (median 6 minutes) than real-world midazolam (median 14 minutes), enabling earlier transfer of patients from the procedure room to the recovery area with a lower requirement for patient monitoring. The onset and recovery times with remimazolam showed significantly less inter-patient variability than with on-label midazolam and real-world midazolam, respectively. Patients treated with remimazolam received significantly less fentanyl for analgesia ($78.2 \pm 28.4 \mu\text{g}$) than did those treated with real-world midazolam ($113.6 \pm 60.1 \mu\text{g}$) and on-label midazolam ($92.5 \pm 40.0 \mu\text{g}$).

Conclusions Remimazolam offers advantages over midazolam in terms of faster recovery and less fentanyl requirement, which may facilitate increased procedural throughput in clinical practice.

Introduction

Remimazolam is a new fast onset/fast offset benzodiazepine being developed for intravenous use in procedural sedation, general anesthesia, and Intensive Care Unit sedation. It is designed as a methyl ester molecule that can be rapidly metabo-

lized by carboxylesterase-1A to a pharmacologically inactive metabolite (CNS7054). Unlike other benzodiazepines, the metabolism of remimazolam is independent of cytochrome P450 enzymes. This mechanism of inactivation results in a faster and more predictable recovery from sedation with remimazolam than with other benzodiazepines such as midazolam [1, 2]. Remimazolam has a distribution half-life ($t_{1/2\alpha}$) of 0.5 to 2 minutes and terminal elimination half-life ($t_{1/2\beta}$) of 7 to 11 minutes

* These authors contributed equally.

[3], considerably shorter than those for midazolam (4 to 18 minutes and 1.7 to 2.4 hours, respectively [4]).

The clinical development program for remimazolam for procedural sedation included three phase 3 clinical trials. Individual reports from these trials have been published previously. Trials CNS7056–006 [5] and CNS7056–008 [6] were randomized, placebo and active (midazolam) controlled large-scale trials with identical design except for the procedure: trial CNS7056–006 was conducted in patients undergoing colonoscopy and trial CNS7056–008 in bronchoscopy. Both trials were conducted in patients with American Society of Anesthesiologists Physical Status (ASA-PS) class I to III. The third phase 3 trial, CNS7056–015 [7], was primarily a safety trial in frail patients with ASA-PS class III or IV. Except for the different patient population, trial CNS7056–015 had similar design as the other two phase 3 trials and was conducted in colonoscopy procedures.

In all three trials, patients randomized to midazolam received a midazolam dose according to the US prescribing information and those who could not be successfully sedated with their randomized treatment (i.e. remimazolam, placebo or on-label midazolam) received rescue midazolam dosed at the investigator's discretion. As a result, each randomized treatment group in these trials consists of patients who were successfully treated with the randomized sedative and those who received rescue midazolam. Thus, when analyzed by treatment group, data such as analgesic fentanyl use, onset time, and recovery time were confounded by the mixture of data generated in subjects solely on randomized drug versus those on rescue midazolam. Acknowledging the shortcoming of the conventional analyses by treatment groups as randomized, we extracted and integrated data from the three randomized treatment groups to create three new comparative groups with the aim of comparing remimazolam with midazolam dosed strictly according to the US prescribing information (on-label midazolam) and midazolam dosed according to medical practice (real-world midazolam).

Patients and methods

Trial design

The design of trials CNS7056–006, CNS7056–008 and CNS7056–015 has been described in detail in previous publications [5–7].

In all three trials, patients were randomized to three treatment arms: double-blind remimazolam or matching placebo, or open-label midazolam. All subjects were administered fentanyl for analgesia. Immediately after analgesic pre-treatment with fentanyl, subjects randomized to remimazolam or placebo received an initial dose of 5.0 mg remimazolam or equivalent volume of placebo over 1 minute, respectively. Supplemental doses of 2.5 mg each at least 2 minutes apart were used as needed for sedation induction or maintenance. In patients with ASA-PS III or IV, a lower initial dose of 2.5 mg and a lower supplemental dose of 1.25 mg could be administered at the investigator's discretion. Subjects randomized to midazolam received midazolam dosed strictly according to the US prescribing information, i.e. an initial dose of 1.75 mg (1.0 mg for pa-

tients ≥ 60 years old or debilitated/chronically ill) over 2 minutes. Supplemental doses of 1.0 mg each (0.5 mg for patients ≥ 60 years old or debilitated/chronically ill) over 2 minutes with at least 2 minutes between doses were used as needed.

In case of inadequate sedation, patients in all three treatment arms could receive midazolam as the only allowed rescue sedative in these trials. The investigators were free to dose rescue midazolam at their discretion, which was not necessarily in accordance with the US prescribing information. In fact, almost all patients initially randomized to placebo received rescue midazolam; therefore, this group represents more typical midazolam dosing in current medical practice.

All trials were conducted in the United States in accordance with the declaration of Helsinki and the International Conference on Harmonisation E6 Guidelines on Good Clinical Practice. The trial protocols and related documents were reviewed and approved by local institutional review boards, and all subjects gave their informed consent in writing before any trial procedures were performed. All trials were registered at clinicaltrials.gov, CNS7056–006 as NCT02290873, CNS7056–008 as NCT02296892, and CNS7056–015 as NCT02532647.

Trial endpoints

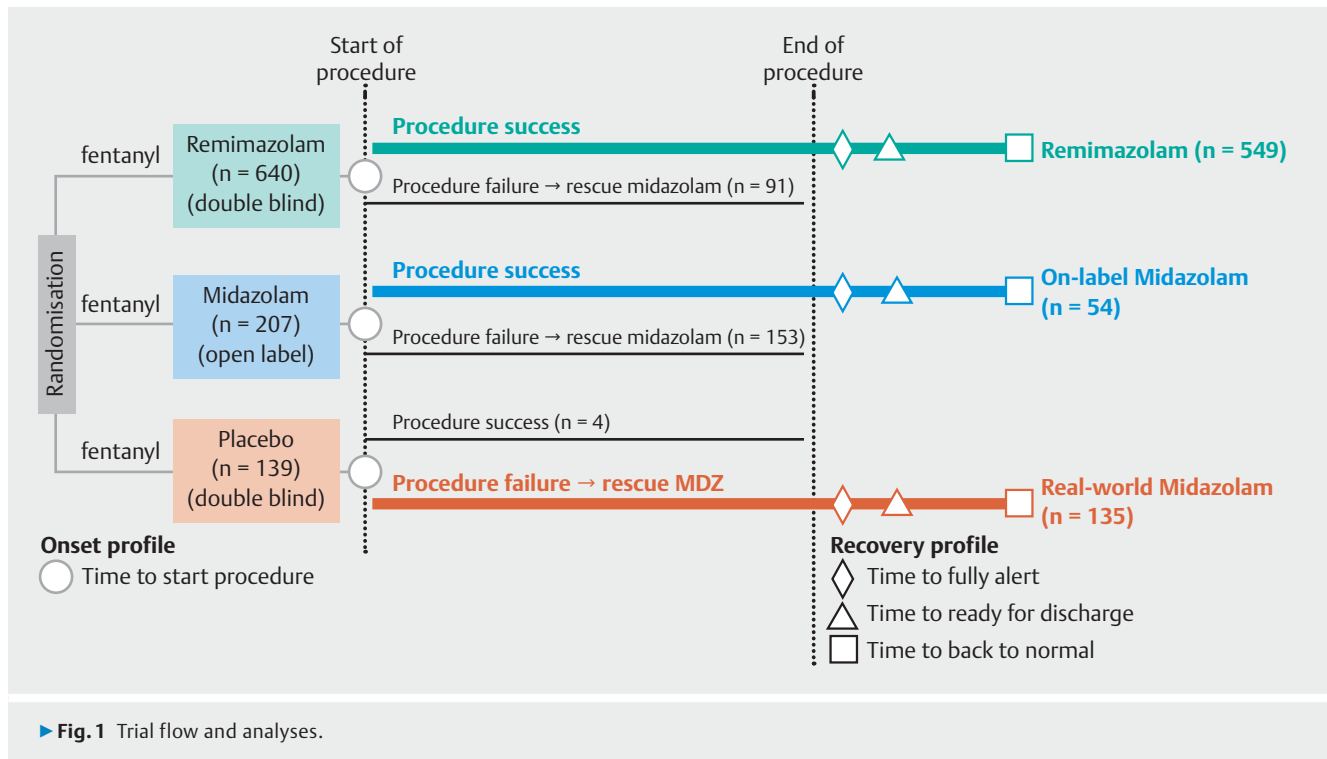
The primary efficacy endpoint in all trials was success of the procedure, designed to evaluate the sedative potency of remimazolam and defined as a composite endpoint with three components: completion of the procedure, no requirement for a rescue sedative medication, and no requirement for more than five doses of study medication (remimazolam or placebo) within any 15-minute window (for midazolam, no more than three doses within any 12-minute window).

The secondary efficacy endpoints in all trials were time-to-event assessments, designed to evaluate the onset and recovery profile of remimazolam. In all trials, the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) was used to assess the sedation level over time. The main onset endpoint was time to start of procedure after the first dose of study medication. There were three recovery endpoints: time to fully alert (i.e., first of three consecutive MOAA/S scores of 5) after end of procedure (scope out), time to ready for discharge (i.e., being able to walk unassisted) after end of procedure, and time to back to normal (as self-evaluated by the patient) after end of procedure.

The neurocognitive test, Hopkins Verbal Learning Test-Revised [8], was used to assess subjects' learning and memory during the recovery from sedation. It was performed within 45 minutes prior to dosing and 5 minutes after the patient had reached the fully alert criterion.

Post hoc analyses

Outcomes of procedure success rates in individual trials have been reported in previous publications [5–7]. In total, there were 640 subjects randomized to remimazolam, 207 to midazolam, and 139 to placebo, of which, the primary endpoint was met in 549 (85.8%), 54 (26.1%), and four subjects (2.9%), respectively. The post hoc analyses comprised three groups: the remimazolam group with 549 subjects who were random-



ized to remimazolam and successfully treated with remimazolam (depicted as the green line in ► Fig. 1), the on-label midazolam group with 54 subjects who were randomized to midazolam and successfully treated with midazolam dosed strictly according to the US prescribing information (depicted as the blue line in ► Fig. 1), and the real-world midazolam group with 135 subjects who were randomized to placebo and received rescue midazolam dosed at the investigator's discretion (depicted as the orange line in ► Fig. 1).

The aim of the post hoc analyses was to compare remimazolam to on-label midazolam and real-world midazolam with respect to onset profile (time to start of procedure), recovery profile (time to fully alert, time to ready for discharge, and time to back to normal), cognitive function after recovery, and the use of analgesic fentanyl. In the remimazolam and on-label midazolam groups, time to start of procedure was calculated from the time of the first dose of sedative medication, reflecting the onset profile of remimazolam and midazolam when dosed strictly according to the US prescribing information, respectively. In the real-world midazolam group, time to start of procedure was calculated from the first dose of rescue midazolam, reflecting the onset profile of midazolam when dosed at the investigator's discretion, i.e. reflecting the common medical practice. Furthermore, we evaluated total sedation time, defined as time from the first dose administration to the time the patient became fully alert. A figure was created to illustrate a visual comparison of total sedation time between groups based on median time to start of procedure from first dose, duration of procedure (from scope in to scope out), and time to fully alert from end of procedure (scope out).

Descriptive statistics were used to summarize data (n, mean, standard deviation [SD], median, minimum, and maximum) for each comparative group. Exploratory pair-wise comparisons between groups were performed using the Student's *t* test for the time-to-event endpoints. Exploratory difference in variance of time-to-event endpoints was compared between groups using the F-test. The analysis of variance (ANOVA) was used to analyses results of the Hopkins Verbal Learning Test-Revised. $P < 0.05$ was considered significant.

Results

Patient population

Demographic characteristics were generally comparable between the three groups (► Table 1). Patients in this post hoc analysis represent a rather elderly population with means of 57.4 to 59.2 years of age, ranging from 19 to 95 years. There were slightly more patients over 65 years of age in the remimazolam group (33.2%) than in the real-world midazolam group (29.5%) and the on-label midazolam group (25.5%). Slight differences in the female/male distribution between treatment groups were noted. Body mass index was comparable between groups, with means of 28.6 to 29.2 kg/m², ranging from 13.8 to 59.8 kg/m². There were more patients in the real-world midazolam group with ASA-PS III or IV (35.6%) than in the remimazolam group (24.6%) and on-label midazolam group (21.9%).

Onset time

Time to start of procedure from first dose of study medication was significantly shorter in the remimazolam group (median 3 minutes) than the on-label midazolam group (median 8 min-

► **Table 1** Patient demographic characteristics.

Analysis group	Remimazolam (n = 549)	Real-world midazolam (n = 132)	On-label midazolam (n = 55)
Age (years)			
▪ Mean (SD)	59.2 (11.7)	58.7 (10.9)	57.4 (11.8)
▪ Median	59.0	59.0	54.0
▪ Min, Max	19, 95	24, 92	30, 83
Age [n (%)]			
▪ <65 Years	367 (66.8)	93 (70.5)	41 (74.5)
▪ ≥65 Years	182 (33.2)	39 (29.5)	14 (25.5)
Sex [n (%)]			
▪ Male	271 (49.4)	60 (45.5)	31 (56.4)
▪ Female	278 (50.6)	72 (54.5)	24 (43.6)
BMI (kg/m²)			
▪ Mean (SD)	28.6 (5.7)	29.2 (6.9)	28.8 (6.6)
▪ Median	28.4	28.1	27.9
▪ Min, Max	16.3, 55.3	13.8, 59.8	16.7, 54.6
ASA-PS classification [n (%)]			
▪ I	99 (18.0)	13 (9.8)	15 (27.3)
▪ II	315 (57.4)	72 (54.5)	28 (50.9)
▪ III	121 (22.0)	40 (30.3)	9 (16.4)
▪ IV	14 (2.6)	7 (5.3)	3 (5.5)

SD, standard deviation; BMI, body mass index; ASA-PC, American Society of Anesthesiologists Physical Status.

utes, $P < 0.0001$), but similar between remimazolam and real-world midazolam (median 3 minutes, $P = 0.674$) (► **Fig. 2**).

The box plots indicate that the inter-patient variability in the time to start of procedure was lower for remimazolam and real-world midazolam than on-label midazolam. The difference in variance of data for time to start of procedure between remimazolam and on-label midazolam was significant ($P < 0.0001$). The variance of time to start of procedure was not significantly different between remimazolam and real-world midazolam ($P = 0.0834$).

Recovery time

All recovery time-to-event endpoints were significantly shorter for remimazolam than for real-world midazolam: median time to fully alert was 6 vs 14 minutes, $P < 0.0001$; median time to ready for discharge was 49 vs 60 minutes, $p < 0.0001$; and median time to back to normal was 4.1 vs 7.5 hours, $P = 0.0008$ (► **Fig. 2**). There was no significant difference between remimazolam and on-label midazolam in terms of time to fully alert ($P = 0.1578$), time to ready for discharge ($p = 0.3815$), or time to back to normal ($P = 0.0718$).

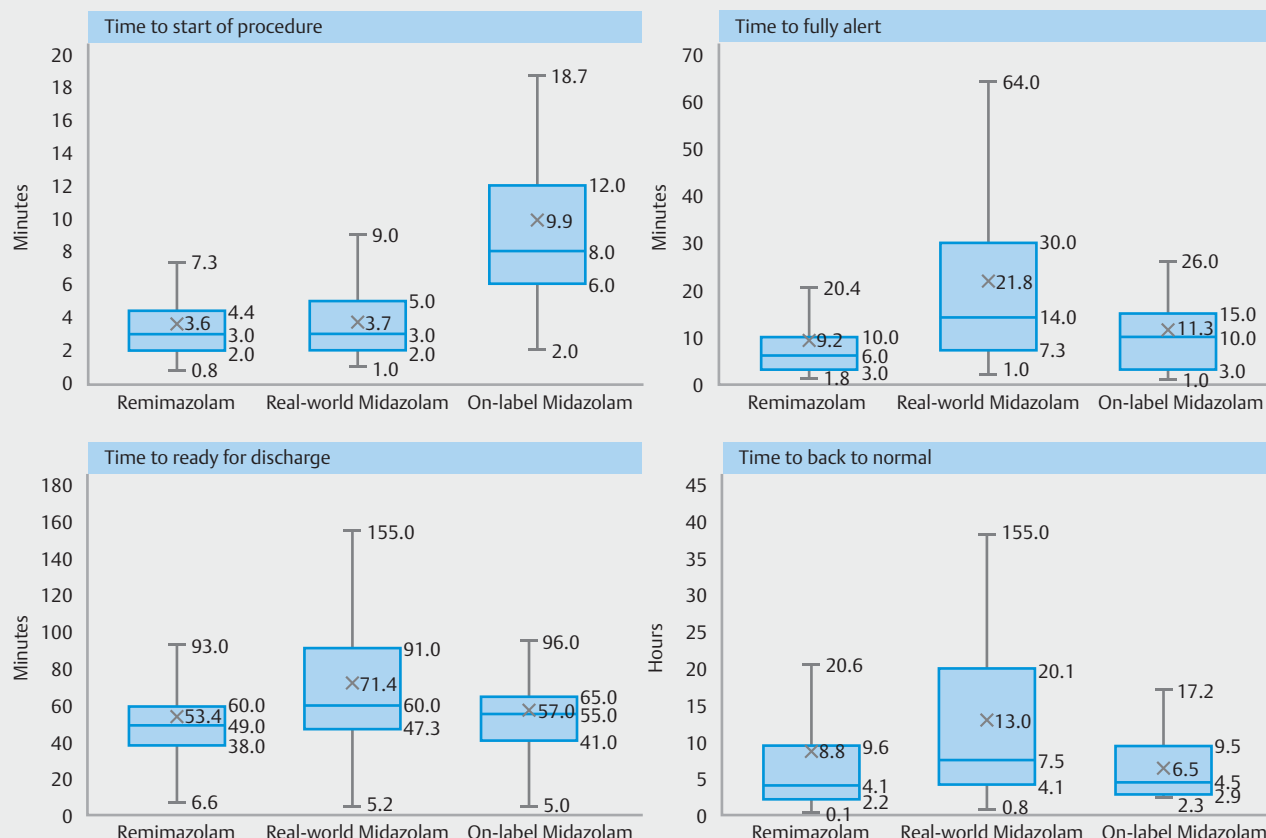
The data variance was significantly lower in the remimazolam group than in the real-world midazolam group for time to

fully alert ($P < 0.0001$) and time to ready for discharge ($P = 0.0003$), but not time to back to normal ($P = 0.0611$). The variance in recovery times comparing remimazolam and on-label midazolam showed no statistical significance (time to fully alert: $P = 0.3737$, time to ready for discharge: $P = 0.3851$, and time to back to normal: $P = 0.4541$).

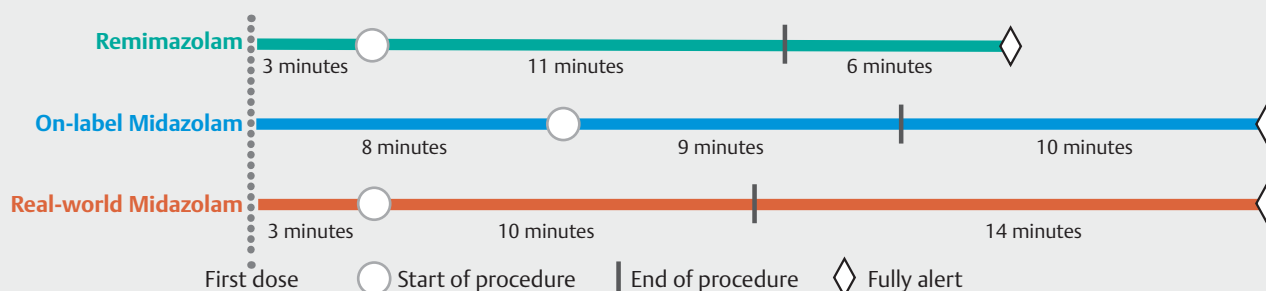
Total sedation time

The on-label midazolam and real-world midazolam groups had similar total sedation time (median 27 minutes), which was significantly longer than with remimazolam (20 minutes); $P = 0.0007$ and $P < 0.0001$, respectively. With on-label midazolam, the patient had to wait for a longer time (8 minutes) to attain adequate sedation to initiate the procedure. With real-world midazolam, the procedure could quickly commence within 3 minutes of administration but the patient stayed sedated for 14 minutes after the procedure ended (► **Fig. 3**). With its fast onset and recovery profile (3 minutes and 6 minutes, respectively), remimazolam shortened the total sedation time compared to both on-label midazolam and real-world midazolam.

The difference in onset and recovery profile between the on-label midazolam and real-world midazolam groups can be explained by the total dose of midazolam used. The mean $\pm$ SD to-



► **Fig. 2** Box plots of time to event. Fully alert is defined as the first of three consecutive MOAA/S measurements of five after start time of the last dose of study or rescue drug. Ready for discharge was determined by a walking test. Date and time of back to normal in the patient's subjective view were recorded via telephone contact by the study nurse on Day 4 (+3/-1 days) after the procedure. Time to ready for discharge and time to back to normal were not assessed in trial CNS7056-015.



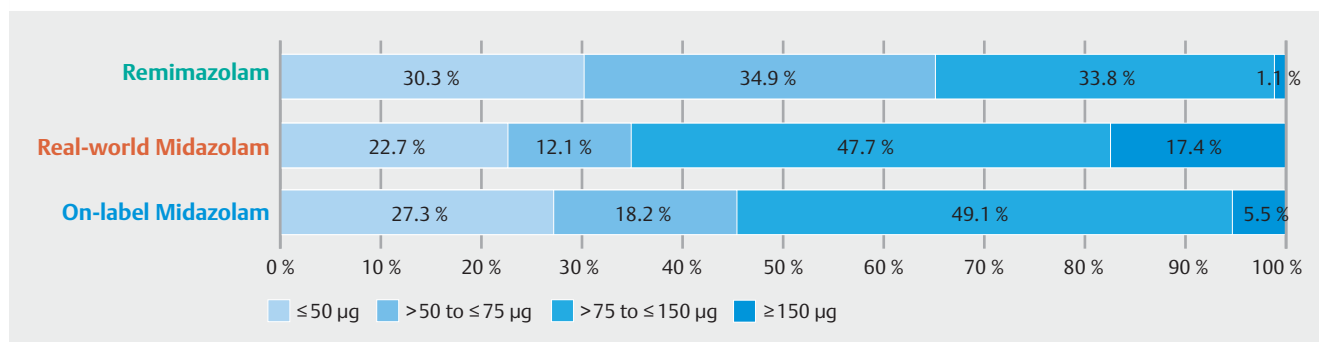
► **Fig. 3** Total sedation time comparing remimazolam, on-label midazolam, and real-world midazolam. Data presented are medians.

tal dose of midazolam per procedure in the on-label midazolam group (dosed strictly according to the US prescribing information) was 3.5 ± 1.5 mg, whereas the mean $\pm$ SD total dose of rescue midazolam required to adequately induce and maintain sedation for a procedure in the real-world midazolam group (dosed at the investigator's discretion) was much higher, 6.2 ± 3.1 mg. However, the number of midazolam doses was comparable between on-label midazolam (3.5 ± 1.4 doses) and real-

world midazolam (3.0 ± 2.1 doses). The number of remimazolam doses was similar to real-world midazolam, 3.1 ± 1.7 doses.

Cognitive function

Results of the Hopkins Verbal Learning Test-Revised show that post-treatment decline in cognitive function was more severe for patients with on-label midazolam and real-world midazolam than with remimazolam. Before treatment, the mean total recall t-score was 34.8 ± 13.6 in the remimazolam group, $33.5 \pm$



► **Fig. 4** Distribution of patients (%) by cumulative fentanyl strata.

23.7 in the on-label midazolam group, and 31.8 ± 14.1 in the real-world midazolam group. Five minutes after fully alert, the mean total recall t-score decreased to 26.9 ± 13.6 in the remimazolam group, 21.8 ± 14.1 in the on-label midazolam group, and 23.7 ± 10.4 in the real-world midazolam group. Total recall t-scores range from 20 to 80, with higher scores representing a better performance in the cognitive tests. The mean change from baseline in the total recall t-score was -7.9 ± 9.6 in the remimazolam group, smaller than in the on-label midazolam group (-10.0 ± 10.6) and the real-world midazolam group (-10.3 ± 9.6). The difference between the remimazolam group and the real-world midazolam group reached statistical significance ($p = 0.0193$), whereas the difference between the remimazolam group and the on-label midazolam group was not significant ($P = 0.1642$).

Fentanyl use

Patients in the remimazolam group required significantly less cumulative fentanyl than did those in the real-world midazolam group (mean $\pm$ SD: 78.2 ± 28.4 vs 113.6 ± 60.1 μ g, $P < 0.001$) and the on-label midazolam group (92.5 ± 40.0 μ g, $P = 0.013$). The mean $\pm$ SD number of fentanyl doses was 1.7 ± 0.9 doses in the remimazolam group, compared with 2.7 ± 1.6 doses in the real-world midazolam group and 2.2 ± 1.3 doses in the on-label midazolam group. The majority of remimazolam patients (65.2%) needed ≤ 75 μ g total fentanyl, whereas the majority of patients in the on-label midazolam group (54.6%) and the real-world midazolam group (65.1%) required > 75 μ g of fentanyl for analgesia (► **Fig. 4**).

Discussion

Our results show that the time to start of procedure was comparable between remimazolam and real-world midazolam; however, midazolam, when dosed strictly according to the US prescribing information, required a significantly longer time to start the procedure than remimazolam, most likely due to the need to administer additional top-ups. With regard to the recovery profile, all time-to-events were significantly shorter in the remimazolam group than in the real-world midazolam. The total sedation time, from the first administration until the patient became fully alert, was shorter in the remimazolam group

than in the real-world midazolam and on-label midazolam groups, driven by the fast onset and recovery profile of remimazolam. Fully alert signifies the time when the patient can be transferred from the procedure room to the recovery area, which requires a lower level of patient monitoring. In addition, we show that the onset time and recovery times with remimazolam were significantly less variable, and thus more predictable, than those with on-label midazolam and real-world midazolam, respectively. This is likely due to the non-specific tissue esterase metabolism of remimazolam, which avoids the genetic variability of the CYP 450 enzymes involved in midazolam metabolism.

The longer onset associated with on-label midazolam resulted from the low dose recommended by the US prescribing information (1.75 mg for induction and 1.0 mg for maintenance). It is important to note that the success rate in the randomized midazolam group in the three phase 3 trial was very low (CNS7056-006: 25.2%, CNS7056-008: 32.9%, CNS7056-015: 12.9%). Of note, our previous phase 2 study investigated a higher dose of midazolam for procedural sedation in colonoscopy (2.5 mg for induction and 1.0 mg for maintenance) and reported a procedure success rate of 75.0% [9]. This is somewhat lower than the procedure success rate attained with remimazolam in our phase 3 colonoscopy trials (CNS7056-006: 91.3%, CNS7056-015: 84.4%).

Interestingly, patients treated with remimazolam required significantly less fentanyl for analgesia than those treated with both real-world midazolam and on-label midazolam. The mean cumulative dose of fentanyl in patients on remimazolam was 78.2 μ g (equivalent to one initial dose of 50 μ g and a top-up dose of 25 μ g), lower than in those on on-label midazolam (mean = 92.5 μ g, equivalent to one initial dose and 1.5 top-up doses) and midazolam dosed at the investigator's discretion (mean = 113.6 μ g, equivalent to one initial dose and 2.5 top-up doses). The combination of a sedative and an opioid is frequently used in sedation and general anesthesia, and synergism between them has been shown [10, 11]. Several preclinical and clinical studies indicate a reduction in dose as a result of the synergism between a sedative and an opioid, and the level of effect differs between combinations [12–14]. The lower requirement for fentanyl observed in the remimazolam group suggest

that remimazolam might have stronger synergism with fentanyl than does midazolam.

The aim and the strength of our post hoc analysis approach was to overcome the limitation of the conventional analyses by randomized treatment groups as in the published reports of the three phase 3 trials [5–7]. For regulatory reasons, the phase 3 clinical trial program of remimazolam employed a midazolam active comparator group dosed according to the US prescribing information, which specifies initial and top-up doses somewhat lower than typically used in clinical practice. In addition, each randomized treatment group was comprised of subjects successfully treated with the randomized sedative and those who received rescue midazolam. In this work, we extracted and integrated data from the randomized treatment groups to create three new analysis groups which more accurately reflect the efficacy of remimazolam in comparison with midazolam dosed strictly according to the US prescribing information and midazolam typically used in medical practice. In addition to the creation of the three new analysis groups, which allows for clear differentiation of real-world midazolam and on-label midazolam, some of our analysis methods deviated from the analysis plan for the three clinical trials. Time to start of procedure in the two midazolam groups was calculated from the administration of rescue midazolam and not the first dose of randomized study medication as in the original analysis. A major outcome of our current work was the analysis of variability which was not foreseen in the original analysis. Compared with the patient populations in the original reports, the patient population in our post hoc analysis showed comparable baseline characteristics, indicating that the sedative effects of both remimazolam and midazolam are likely independent of demographic factors.

This work has some inherent weaknesses. First, midazolam use in both the on-label midazolam and the real-world midazolam groups was open label; thus, data for both groups, without adjustment for potential confounding factors, were observational in nature. Second, due to the data extraction, the three new analysis groups can no longer be regarded as randomized. Thus, all statistical comparisons between groups were purely exploratory. For the purpose of this analysis, treatment failures were removed from the on-label midazolam and the remimazolam group, thereby creating a potential bias. However, due to the overall low success rates in the on-label midazolam and the high success rate in the remimazolam group this potential bias affected predominantly on-label midazolam. Similarly, the real-world midazolam group is presumably not subjected to potential bias because only very few subjects initially randomized to placebo were excluded from this analysis. In addition, one might argue that patients might be more agitated after obvious failure of placebo, which might affect the efficacy of real-world midazolam. However, time to procedure start from rescue midazolam in the real-world midazolam group was short and comparable to time to procedure start in the remimazolam group, suggesting that prior use of placebo did not alter the characteristics of real-world midazolam.

Conclusions

In conclusion, lower-dose, on-label midazolam has similar recovery characteristics to remimazolam but a significantly longer time to produce adequate initial sedation; whereas higher dose, real-world midazolam produces similarly rapid onset of sedation to remimazolam but significantly longer recovery times. Regardless of dose, midazolam is associated with longer total sedation time and more concomitant fentanyl use for analgesia than remimazolam. Remimazolam has the potential to significantly reduce the workload of monitoring staff for procedural sedation and to facilitate increased procedural throughput in clinical practice.

Acknowledgments

The authors thank Dr. Gabriel Fox (Acacia Pharma), Dr. Adam Morley (PAION), and Dr. Axel Drews (PAION) for their critical reading of this manuscript.

Competing interests

As current or former employees of PAION, all authors may own stocks or stock options of PAION.

References

- [1] Pambianco DJ, Cash BD. New horizons for sedation: The ultrashort acting benzodiazepine remimazolam. *Tech Gastrointest Endosc* 2016; 18: 22–28
- [2] Sneyd JR, Rigby-Jones AE. remimazolam for anaesthesia or sedation. *Curr Opin Anaesthesiol* 2020; 33: 506–511
- [3] PAION. Remimazolam Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/byfavo-epar-product-information_en.pdf
- [4] Malamed SF. Sedation: A Guide to Patient Management. 6th Edition. Mosby 2016: 319–358
- [5] Rex DK, Bhandari R, Desta T et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc* 2018; 88: 427–437 e426
- [6] Pastis NJ, Yarmus LB, Schippers F et al. Safety and efficacy of remimazolam compared with placebo and midazolam for moderate sedation during bronchoscopy. *Chest* 2019; 155: 137–146
- [7] Rex DK, Bhandari R, Lorch DG et al. Safety and efficacy of remimazolam in high risk colonoscopy: A randomized trial. *Dig Liver Dis* 2021; 53: 94–101
- [8] Shapiro AM, Benedict RH, Schretlen D et al. Construct and concurrent validity of the Hopkins Verbal Learning Test-revised. *Clin Neuropsychol* 1999; 13: 348–358
- [9] Pambianco DJ, Borkett KM, Riff DS et al. A phase IIb study comparing the safety and efficacy of remimazolam and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc* 2016; 83: 984–992
- [10] Whitwam JG. Co-induction of anaesthesia: day-case surgery. *Eur J Anaesthesiol* 1995; 12: 25–34
- [11] Ben-Shlomo I, abd-el-Khalim H, Ezry J et al. midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth* 1990; 64: 45–47

- [12] Short TG, Plummer JL, Chui PT. Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. *Br J Anaesth* 1992; 69: 162–167
- [13] Liou JY, Ting CK, Teng WN et al. Adaptation of non-linear mixed amount with zero amount response surface model for analysis of concentration-dependent synergism and safety with midazolam, alfentanil, and propofol sedation. *Br J Anaesth* 2018; 120: 1209–1218
- [14] Kops M, Pesic M, Petersen KU et al. Impact of concurrent remifentanil on the sedative effects of remimazolam, midazolam and propofol in *Cynomolgus* monkeys. *Eur J Pharmacol* 2020; 890: 173639