ORIGINAL ARTICLE

A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy

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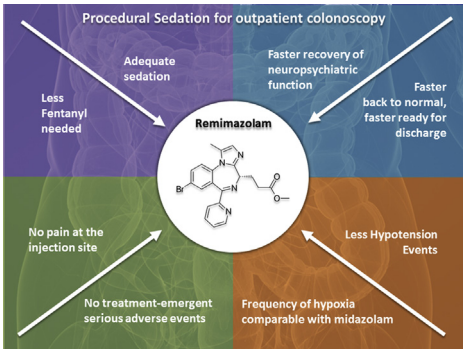
GRAPHICAL ABSTRACT



Background and Aims: Remimazolam is an ultrashort-acting benzodiazepine.

Methods: We performed a randomized double-blind comparison of remimazolam to placebo for outpatient colonoscopy. This study design was a requirement of the U.S. Food and Drug Administration. An additional group was randomized to open-label midazolam administered according to its package insert instructions (the randomization ratio for remimazolam:placebo:midazolam was 30:6:10). Study medications were administered under the supervision of the endoscopist, without any involvement of an anesthesia specialist. Patients were given 50 to 75 μg of fentanyl before receiving study medications. Patients who failed to achieve adequate sedation in any arm were rescued with midazolam dosed at the investigator's discretion. The primary endpoint was a composite that required 3 criteria be met: completion of the colonoscopy, no need for rescue medication, and ≤5 doses of remimazolam or placebo in any 15-minute interval (≤3 doses of midazolam in any 12-minute interval in the open-label midazolam arm).

Results: There were 461 randomized patients in 12 U.S. sites. The primary endpoint was met for remimazolam, placebo, and midazolam in 91.3%, 1.7%, and 25.2% of patients, respectively ($P < .0001$ for remimazolam vs placebo). Patients administered remimazolam received less fentanyl, had faster recovery of neuropsychiatric function, were ready for discharge earlier, and felt back to normal sooner than patients with both placebo and midazolam. Hypotension was less frequent with remimazolam, and hypoxia occurred in 1% of patients with remimazolam or midazolam. There were no treatment-emergent serious adverse events.

Conclusion: Remimazolam can be administered safely under the supervision of endoscopists for outpatient colonoscopy, and it allows faster recovery of neuropsychiatric function compared with placebo (midazolam rescue) and midazolam. (Clinical trial registration number: NCT02290873.) (Gastrointest Endosc 2018;■:1-11.)

(footnotes appear on last page of article)

Endoscopic sedation is generally based on either midazolam or propofol, with the percentage of cases in the United States using propofol significantly increasing over the past 2 decades.[1,2] Midazolam usually is given with an opioid.[1] Advantages of midazolam include excellent amnesia, easy titration, and widespread acceptance of administration by endoscopists. Disadvantages of midazolam include greater cumulative effects because of a long-acting metabolite that causes slow recovery of neuropsychiatric function relative to propofol.[3,4]

Propofol can be administered in combination with an opioid and/or benzodiazepine and can be titrated to moderate sedation.[5] Propofol has a rapid onset and offset of action, and there is a widespread perception that its advantages are maximized when administered as a single agent, which usually results in deep sedation and has led to restrictions that frequently confine its administration to anesthesia specialists. The increasing use of propofol for endoscopic sedation is associated with improved patient satisfaction,[6] but is not cost effective with regard to safety endpoints[7] and has been associated with high rates of aspiration pneumonia.[8,9]

Remimazolam is an ultrashort-acting benzodiazepine in development for procedural sedation.[10] Like midazolam, remimazolam acts on GABA receptors to induce sedation. Unlike midazolam, remimazolam is metabolized by tissue esterases. Remimazolam differs from all other benzodiazepines by its carboxylic ester linkage, enabling its rapid breakdown to inactive metabolites only. The mean terminal elimination half-life of remimazolam is 0.75 hours, and that of midazolam is 4.3 hours.[11,12] In phase II trials, remimazolam provided adequate procedural sedation for endoscopy, and faster recovery than midazolam.[13,14]

We describe a prospective, randomized, parallel group study comparing remimazolam to placebo (blindly). The comparison to placebo was required by the U.S. Food and Drug Administration (FDA), which sought data on the performance of fentanyl plus remimazolam compared with fentanyl alone. To provide information on the relative performance of remimazolam and midazolam, we included an open-label arm of midazolam. However, the FDA required that midazolam be administered according to its package insert. Thus, neither the placebo arm nor the midazolam arm reflect usual clinical practice. The study was initiated at 13 sites in the United States (with 12 contributing patients), in patients with American Society of Anesthesiologists Physical Status Classification System risk class of I to III. All patients received an initial dose of 75 μg of fentanyl (plus repeated 25 μg top-up doses to a total of up to 200 μg) during the first 80% of the study, which we lowered to 50 μg for the last 20% of the study. All sedation was given under the supervision of the endoscopist.

METHODS

Overall design

This study was a prospective, randomized, placebo and active controlled, multicenter, parallel group study comparing remimazolam to placebo in a double-blind manner, with an open-label midazolam arm. The composite primary and secondary endpoints for the sedation level are summarized in Table 1. The blinded comparison of remimazolam to placebo was requested by the FDA. Patients were undergoing diagnostic or therapeutic colonoscopy. Four hundred sixty-one patients were randomized into 1 of 3 groups: remimazolam, placebo, or open label midazolam in a ratio of 30:6:10.

Figure 1 shows the flow of the study design. Supplementary Table 1 (available online at www.giejournal.org) shows the procedures performed at each visit. All participating sites obtained institutional review board approval for participation. Patients were recruited between April 2015 and April 2016. The trial was registered at ClinicalTrials.gov with registration number NCT02290873.

On the day of colonoscopy, all patients received up to 1000 mL of 0.9% sodium chloride solution as an intravenous drip starting before the procedure. All patients received fentanyl before the assigned study sedative medication. For the first 80% of the study, patients received an initial dose of 75 μg of fentanyl (or a suitably reduced dose for elderly and debilitated patients). For the last 20% of the study, the initial fentanyl dose was reduced to a maximum of 50 μg. This change was made at the request of the Data Safety Monitoring Board because of the number of patients in the placebo and/or remimazolam group in the pre-amended portion of the study had transiently reached Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale (Table 2) scores of 0, which could be regarded a safety issue, although no safety signal was associated with low MOAA/S scores.

Supplemental oxygen at a rate of 4 L/minute was administered to all patients before any medication and until the patient was fully alert (defined as 3 consecutive MOAA/S scores of 5). Patients were randomized to receive an initial single intravenous dose of remimazolam 5.0 mg or an equal volume of placebo over 1 minute in a blinded manner, and colonoscopy was initiated when adequate sedation (MOAA/S score $\leq$3) was achieved. Sedation was maintained by injection of further top-up doses of remimazolam 2.5 mg (1 mL) or an equal volume of placebo not more than 2 minutes apart after assessment of the sedative effect. For the maintenance phase of sedation, adequate sedation was predefined as a MOAA/S score of $\leq$4 in all study arms. The overall number of remimazolam and/or placebo doses was limited to 5 doses in any 15 minute window. If 5 doses (including the initial bolus) within any 15-minute window were not sufficient to obtain or

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