

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212295Orig1s000**

**SUMMARY REVIEW**



**Food and Drug Administration**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**Division of Anesthesiology, Addiction Medicine, and Pain Medicine**  
 10903 New Hampshire Ave.  
 Silver Spring, MD 20993-0002

Division Director Summary and  
 Cross-Discipline Team Leader Review

<b>Date</b>	July 2, 2020
<b>From</b>	Martha A. Van Clief, MD, Team Leader Rigoberto Roca, MD, Division Director
<b>NDA Number</b>	212295
<b>Applicant</b>	Cosmo Technologies, Ltd., Dublin, Ireland (U.S. Agent - Conventus Biomedical Solutions, Inc.)
<b>Date of Submission</b>	April 5, 2019
<b>PDUFA Goal Date</b>	July 3, 2020
<b>Proprietary Name</b>	Byfavo
<b>Established or Proper Name</b>	Remimazolam
<b>Dosage Form/Strength</b>	Solution for intravenous administration, 2.5 mg/mL
<b>Applicant Proposed Indication/Population</b>	For the induction and maintenance of procedural sedation in adults.
<b>Applicant Proposed Dosing Regimen</b>	<p>Adult Patients:</p> <ul style="list-style-type: none"> <li>Administer an initial dose of Byfavo intravenously as a 5 mg (2 mL) push injection over a 1-minute time period.</li> <li>If necessary, administer supplemental doses of 2.5 mg (1 mL) Byfavo over a 15-second time period.</li> <li>At least 2 minutes must have elapsed prior to the administration of any supplemental dose.</li> </ul> <p>Debilitated Patients (ASA III-IV, at the discretion of the physician):</p> <ul style="list-style-type: none"> <li>Based on the general condition of the patient, administer 2.5 to 5 mg (1 or 2 mL) of Byfavo over 1-minute time period.</li> </ul> <p>If necessary, administer supplemental doses of 1.25 to 2.5 mg (0.5 or 1 mL) Byfavo as a push injection over a 15 second time period.</p>
<b>Regulatory Action</b>	Approval
<b>Recommended Indication</b>	For the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less.
<b>Recommended Dosing Regimen</b>	Adult Patients:

	<ul style="list-style-type: none"> <li>• Administer an initial dose of Byfavo intravenously as a 5 mg (2 mL) push injection over a 1-minute time period.</li> <li>• If necessary, administer supplemental doses of 2.5 mg (1 mL) Byfavo over a 15-second time period.</li> <li>• At least 2 minutes must have elapsed prior to the administration of any supplemental dose.</li> </ul> <p>Debilitated Patients (ASA III-IV, at the discretion of the physician):</p> <ul style="list-style-type: none"> <li>• Based on the general condition of the patient, administer 2.5 to 5 mg (1 or 2 mL) of Byfavo over 1-minute time period.</li> </ul> <p>If necessary, administer supplemental doses of 1.25 to 2.5 mg (0.5 or 1 mL) Byfavo as a push injection over a 15 second time period.</p>
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	<b>Names of discipline reviewers</b>
Medical Officer Review	Renee Petit-Scott, MD, Martha A. Van Clief, MD
Statistical Review	James Travis, PhD.; Jinglin Zhong, PhD, Mark Rothmann, PhD
Pharmacology Toxicology Review	Katie Sokolowski, PhD; Newton Wu, PhD; Dan Mellon, PhD, Tim McGovern, PhD
OPQ Review	DS: Joe Leginus, PhD; DP: Valerie Amspacher, PhD;  Microbiology: Vikas Moolchandani, PhD; Manufacturing: Wendy Tan, PhD, ATL: Valerie Amspacher; Branch Chief: Julia Pinto
Microbiology Review	Wendy Tan, PhD
Clinical Pharmacology Review	Deep Kwatra, PhD; Yun Xu, PhD
CSS	Katherine Bonson
OSI	John Lee, Philip Kronstein
QT/IRT	Christine Garnett, PharmD
DPMH	Catherine Roca, MD; Miriam Dinatale, MD
OSE/DEPI	Mingfeng Zhang; Monique Falconer
OSE/DMEPA	Cameron Johnson, PharmD; Otto Townsend, PharmD
OSE/DRISK	Somya Dunn; Selena Ready

OND=Office of New Drugs  
 OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 CDTL=Cross-Discipline Team Leader  
 OSE= Office of Surveillance and Epidemiology  
 DEPI= Division of Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRISK=Division of Risk Management

## 1. Benefit-Risk Assessment Framework

### Benefit-Risk Integrated Assessment

Remimazolam (RMZ) is a novel benzodiazepine developed for the induction and maintenance of procedural sedation in adults. It is structurally similar to midazolam, but has a pharmacokinetic profile suggesting it is faster acting with a shorter distribution half-life. Like other benzodiazepines, the sedative properties can be reversed with flumazenil administration, the benzodiazepine reversal agent. Procedural sedation can encompass a wide variety of diagnostic and therapeutic procedures, including colonoscopy, bronchoscopy, and upper endoscopy, those evaluated in the Applicant's clinical development program. Procedural sedation in the United States can be achieved using intravenous medications such as midazolam, dexmedetomidine, propofol, or ketamine. These medications can be administered as monotherapy isolation or in combination, such as, the administration of ketamine and propofol to achieve appropriate sedation. If the procedure is painful, an opioid analgesic is commonly administered with the sedative agent. The choice of sedative agent typically depends on the following four factors: patient health status, procedure performed, location of procedure performed, and anticipated adverse outcomes. In general, the goals of sedation are adequate depth of sedation for the procedure performed and hemodynamic stability.

Remimazolam appears to provide adequate sedation for successful completion of diagnostic and therapeutic procedures lasting 30 minutes or less. The two adequate and well-controlled efficacy studies conducted by the Applicant, CNS7056-006 in patients undergoing colonoscopy and CNS7056-008 in patients undergoing bronchoscopy, demonstrated a statistically significant difference in procedure success rates between the remimazolam and saline placebo treatment groups. The results of the secondary efficacy endpoints support the primary analysis findings, and provide additional information regarding clinically meaningful times, such as time to fully alert and time to ready for discharge. An additional Phase 3 study, CNS7056-015 in American Society of Anesthesiologists Physical Status (ASA-PS) class III and IV patients undergoing colonoscopy, was designed as a safety study, so statistical testing was not conducted; however, the procedure success rates supported the colonoscopy and bronchoscopy studies. The evaluation of remimazolam administration in patients undergoing colonoscopy and bronchoscopy, in combination with a Phase 2 evaluation in patients undergoing upper endoscopy, provides adequate efficacy and safety information to support the proposed broad procedural sedation indication. However, because the majority of procedures evaluated were completed in 30 minutes or less and because procedure success rates appeared to decrease with longer procedures (i.e., those lasting more than 30 minutes), the final drug product label will include a recommended procedure duration of 30 minutes or less.

There are two main benefits of remimazolam when administered for procedural sedation. First, it is fast-acting with a short half-life, suggesting procedures can be initiated quickly and complete recovery appears rapid. The second main benefit of remimazolam over other non-

benzodiazepine medications for procedural sedation is the ability to reverse the sedative effects with flumazenil. This offers a degree of safety over medications such as propofol or ketamine, in which no reversal agent is available, and supports the Applicant's preference to allow non-anesthesia providers to administer remimazolam.

During procedural sedation, the Phase 3 studies permitted concomitant administration of fentanyl, up to 200 µg. The initial fentanyl premedication bolus was decreased from 75 µg to 50 µg based on the large proportion of patients in the remimazolam treatment groups under moderate to deep sedation, defined as a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score of 0 or 1, early in the course of the procedure. It also appears that increasing doses of fentanyl were correlated with decreased procedure success, increased procedure duration, and an increase incidence in reported adverse events in Study CNS7056-006 and Study CNS7056-008. This information will be included in the final drug product labeling.

The safety concerns associated with administration of remimazolam during procedural sedation do not appear to differ significantly from those associated with currently approved benzodiazepines administered for procedural sedation. Those safety concerns include prolonged sedation, changes in measured vital sign parameters, particularly respiratory parameters, and adverse events related to abuse, dependence, and withdrawal. Administration of remimazolam, in general, results in a lower incidence of prolonged sedation compared to patients treated with midazolam, either at the discretion of the investigator (in the case of the placebo treatment group) or according to the drug label recommendations (in the case of the midazolam treatment group). In Study CNS7056-008 (bronchoscopy), the mean dose of remimazolam was higher than that administered in the other Phase 3 studies and the remimazolam treatment group had a higher incidence of prolonged sedation compared to the placebo or midazolam treatment groups; however, the incidence in all treatment groups was low. The incidence of vital sign-related adverse events was lower in the remimazolam treatment groups in all three Phase 3 studies compared to either the placebo or midazolam treatment groups.

The totality of the clinical data supports a favorable benefit:risk profile for the administration of remimazolam for procedural sedation for procedures lasting 30 minutes or less. The level of training of the administering provider should comply with the ASA practice guidelines for moderate to deep procedural sedation.

From the clinical pharmacology perspective, 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. Remimazolam is administered to effect and top ups are dosed as needed. Therefore, labeling language suggesting potential increase in recovery times for hepatic impaired subjects and need of less frequent top ups will be included into the label.

From a nonclinical pharmacology/toxicology perspective, the reproductive and developmental toxicity studies for remimazolam and Dextran 40 were technically inadequate. However, the indication is for planned procedural sedation where women of childbearing potential can be

adequately screened for pregnancy prior to the procedure, the NDA may be approved at the discretion of the clinical team and with the appropriate labeling. Nonclinical pharmacology/toxicology is also recommending postmarketing requirements (PMR) to characterize the reproductive and developmental toxicity of remimazolam and Dextran 40.

**Benefit-Risk Dimensions**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>• Many diagnostic and therapeutic procedures require moderate to deep sedation for successful completion and may be performed at ambulatory surgery centers.</li> <li>• Many diagnostic and therapeutic procedures are short in duration.</li> <li>• A majority of the population may undergo a diagnostic or therapeutic procedure in their life-time.</li> </ul>	<p>The goals of adequate procedural sedation include patient comfort, rapid onset and recovery, and procedure success.</p> <p>Commonly performed procedures in the U.S. include cataract extraction with intraocular lens insertion, tissue biopsy, GI endoscopy and colonoscopy, and drainage or injection of a joint.</p> <p>Most of these diagnostic and therapeutic procedures may last 30 minutes or less.</p>
<b>Current Treatment Options</b>	<ul style="list-style-type: none"> <li>• Intravenous sedative agents currently available for the induction and maintenance of procedural sedation include the following:               <ul style="list-style-type: none"> <li>○ Benzodiazepine medications</li> <li>○ Opioid analgesics, including remifentanyl</li> <li>○ Ketamine</li> <li>○ Propofol</li> <li>○ Dexmedetomidine</li> </ul> </li> <li>• Inhaled nitrous oxide is also used for procedural sedation, particularly</li> </ul>	<p>Currently available IV sedative medications include benzodiazepines, opioid analgesics, ketamine, propofol, and dexmedetomidine; however, benzodiazepines and opioid analgesics are the only sedatives that can be safely administered by non-anesthesia providers.</p> <p>Approval of remimazolam will provide</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>in the dental setting, but is generally reserved for anxiolysis during procedures causing minimal pain.</p> <ul style="list-style-type: none"> <li>• When sedation is not successful, administration of general anesthesia is an option if the administering provider has the required level of training.</li> </ul>	<p>clinicians with an additional medication for the induction and maintenance of procedural sedation. If remimazolam is approved for administration by a healthcare practitioner with proper training in conscious sedation administration and monitoring, then the procedure will need to be delayed or canceled until an anesthesia provides is available to administer a general anesthetic.</p>
<b>Benefit</b>	<ul style="list-style-type: none"> <li>• Remimazolam appears to have a short onset of action and distribution half-life, making it an ideal sedative in the ambulatory setting, where the goal is often efficiency with rapid patient turnaround. The times to fully alert and to discharge were shorter in patients treated with remimazolam when compared to patients treated with placebo after colonoscopy and bronchoscopy.</li> <li>• The sedative effects of remimazolam are reversible with flumazenil. In the clinical studies that evaluated flumazenil administration, re-sedation was not observed. This is a clear benefit over other, non-benzodiazepine medications, and even longer-acting benzodiazepines, in which more than one dose of flumazenil may be required.</li> <li>• Renal impairment does not appear to affect the efficacy or safety profile of remimazolam.</li> <li>• Patient body mass index (BMI) does not appear to impact the efficacy or safety profile of remimazolam, and given the obesity epidemic in the U.S., this is a clear advantage over other lipophilic sedatives.</li> <li>• Remimazolam can be safely administered with fentanyl in doses up to 200 µg, carefully titrated and depending on the clinical scenario, and</li> </ul>	<p>Clear advantages of remimazolam include short onset of action and distribution half-life, reversibility of the sedative effects with flumazenil, and stable PK in patients with renal impairment and increased BMI. Like other benzodiazepine medications, RMZ can be safely administered with opioid analgesics, assuming appropriate monitoring and availability of opioid antagonist medications.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	comorbidities and age of the patient.	
<b>Risk and Risk Management</b>	<ul style="list-style-type: none"> <li>• As with all sedative and anesthetic agents, the most concerning adverse events are those associated with changes in measured hemodynamic parameters, particularly respiratory parameters. There did not appear to be clinically meaningful differences in rates of respiratory depression, hypoxia, or respiratory rate decreased in the RMZ treatment group compared to the placebo or midazolam treatment groups in the Phase 3 studies. In general, the incidence of vital sign-related adverse events was lower in the RMZ treatment groups in all three Phase 3 studies compared to either the placebo or midazolam treatment groups.</li> <li>• The administering provider must be trained in monitoring, detection, and treatment of hemodynamic changes, including cardiac arrest, hypoventilation, airway obstruction, and apnea.</li> <li>• Concomitant fentanyl administration appeared to increase the duration of the procedure and occurrence of adverse events and decrease the procedure success rate. This information will be described in the drug product labeling along with prevention and mitigation strategies.</li> <li>• There was a low number of procedures evaluated which lasted longer than 30 minutes, and of those that did in Study CNS7056-008, the procedure success decreased with increasing duration of the procedure. This suggests that RMZ may be best suited for procedures of relatively short duration; i.e., 30 minutes or less.</li> <li>• RMZ like all benzodiazepines, carries the potential for recreational use and abuse. Because it is administered only in a healthcare facility and</li> </ul>	<p>Risks associated with administration of remimazolam do not appear significantly different from the known risks associated with administration of other benzodiazepine medications. The Phase 3 studies did not evaluate, in a blinded manner, the safety profile of remimazolam compared to midazolam; however, the placebo treatment group did receive midazolam rescue administered at the discretion of the investigator and consistent with clinical practice. Therefore, some data are available to inform the general safety profile of remimazolam.</p> <p>The incidence of clinically relevant vital sign changes and adverse events was not significantly different between treatment groups.</p> <p>Because administration of remimazolam can cause respiratory depression, hypoventilation, airway obstruction, and apnea, administering providers and facilities must adhere to the ASA practice guidelines for moderate to deep sedation, to include resuscitative medications and equipment. Additionally, administering</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>not prescribed for outpatient use, this risk most likely affects healthcare providers and facility staff.</p> <ul style="list-style-type: none"> <li>• Bolus dosing, in combination with the recommended procedure duration of 30 minutes or less, is a significant limitation to the widespread use of RMZ for procedural sedation. Specifically, procedures which require the administering provider to perform additional patient-care tasks, such as the administration of additional medications, supportive airway maneuvers or ventilation, or the suctioning of oral secretions, make bolus dosing challenging.</li> <li>• Hepatic impairment prolongs the half-life and increase in recovery times of RMZ, requiring careful titration of top-up doses.</li> <li>• The thorough QT study (CNS7056-005), demonstrated drug effect on heart rate and QTcF.</li> <li>• From a nonclinical pharmacology/toxicology perspective, there are technically inadequate reproductive and developmental toxicity studies for remimazolam and Dextran 40.</li> </ul>	<p>providers must be appropriately trained in Advanced Cardiac Life Support (ACLS) and be able to perform basic airway interventions in the event of hypoventilation or apnea. Concomitant fentanyl administration up to total doses of 200 µg appears safe, however, careful titration and continuous assessment of depth of sedation is recommended. The abuse potential via IV administration appears similar to that of midazolam.</p> <p>Limitations to widespread use of remimazolam for procedural sedation include the need for bolus dosing and procedure duration of 30 minutes or less. It seems likely that remimazolam will be most used in gastroenterology clinics for patients undergoing upper endoscopy and colonoscopy.</p> <p>From the Clinical Pharmacology perspective product labeling will include language regarding hepatic impairment and results of the TQT study (CNS7056-005).</p> <p>From the non-clinical pharmacology/toxicology perspective although the reproductive and developmental toxicity studies for remimazolam and Dextran 40 are technically inadequate, the intended use of remimazolam is</p>

NDA 212295  
Byfavo (Remimazolam) for injection  
Cosmo Technologies, Ltd.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		for planned procedural sedation where women of childbearing potential will be adequately screened for pregnancy prior to the procedure. Nonclinical pharmacology/toxicology is also recommending postmarketing requirements (PMR).

## 2. Background

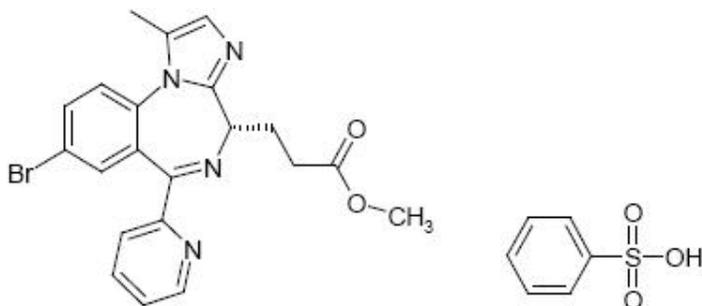
This document will serve as the Cross-Discipline Team Leader (CDTL) review of this new drug application (NDA), as well as the Division Director Summary (DD) review, and Office Director (OD) memo for the decision on the regulatory action.

The Applicant, Cosmo Technologies, Ltd. of Dublin, Ireland, has submitted a new drug application (NDA) for remimazolam. This is a 505(b)(2) submission.

This document will also capture the final outcomes of any items that were still under discussion at the time of Dr. Petit-Scott's review was finalized.

As noted in Dr. Petit-Scott's review, remimazolam (RMZ), is a new benzodiazepine developed for the induction and maintenance of procedural sedation. The Applicant describes the drug product as an ultra-short-acting intravenous (IV) benzodiazepine based on its rapid onset of action and short distribution half-life. It is structurally related to midazolam and the sedative properties of remimazolam can be reversed with IV administration of flumazenil.

### Remimazolam Besylate Salt



RMZ is an ester-based drug (see figure above) that is hydrolyzed by carboxylesterase-1 (CES-1) primarily in the liver to the inactive carboxylic acid metabolite, CNS7054. remimazolam appears to have a shorter time to onset and a shorter half-life compared to the other benzodiazepine mediations commonly administered for procedural sedation. The Applicant states that these properties make remimazolam easy to titrate for procedural sedation and offer significant advantages over existing procedural sedation medications.

The dosing regimen evaluated in the clinical studies was an initial IV bolus of 2.5 mg to 5 mg over one minute, followed by additional top-up bolus injections of 1.25 mg to 2.5 mg over 15 seconds, no sooner than two minutes apart. Lower doses may be

needed for ASA III and IV patients. The Applicant has indicated that there does not appear to be clinically relevant accumulation or prolonged duration of action after multiple administrations for procedural sedation, therefore, a maximum recommended dose has not been proposed. The regulatory history and interactions are well-summarized in Dr. Petit-Scott’s review.

Remimazolam was originally developed at GlaxoSmithKline as a faster-acting version of midazolam, based on information gained during the development of remifentanyl, an IV opioid with a rapid onset of action. The clinical development program was later sponsored by Paion UK, Ltd. Paion’s Japanese licensed partner, Ono Pharm., conducted some studies in patients receiving general anesthesia and ICU sedation, indications not currently sought in this marketing application. In December 2017, ownership was transferred to Cosmo Technologies, Ltd. (Cosmo), Ireland. Conventus Biomedical Solutions, Inc. (Conventus) has been appointed by Cosmo to be the U.S. representative for IND 102486 and NDA 212295.

Summary of Key Pre-submission and Submission Regulatory Activities

Meeting / Communication / Date	Event / Key Clinical Issues
IND 102486 opened / June 22, 2008	Phase 1 single ascending dose study allowed to proceed on Nov. 10, 2008.
End of Phase 2 Meeting (EOP2) / Oct. 17, 2013	<p>Clinical issues discussed included the following:</p> <ul style="list-style-type: none"> <li>• Evaluated procedures must be generalizable to support a broad procedural sedation indication</li> <li>• Phase 2b study in patients undergoing colonoscopy (b) (4)</li> </ul> <div style="background-color: #cccccc; width: 100%; height: 40px; margin-bottom: 10px;"></div> <ul style="list-style-type: none"> <li>• Non-GI procedures (i.e., bronchoscopy) should be considered for evaluation given the likelihood of broad post-market use</li> <li>• (b) (4)</li> <li>•</li> <li>•</li> <li>• Required subject-exposures for adequate safety database</li> </ul>

Meeting / Communication / Date	Event / Key Clinical Issues
	<ul style="list-style-type: none"> <li>• Clarification regarding the information needed to support dosing in patients with hepatic and renal impairment</li> <li>• Acceptability of proposed pediatric deferral (b) (4)</li> <li>• The impact of RMZ and concomitant opioid dosing on ventilatory drive needs to be evaluated</li> <li>• A thorough QT evaluation is needed</li> <li>• The abuse potential of RMZ needs to be evaluated</li> <li>• The proposal (b) (4)</li> </ul>
<p>Advice Letter regarding EOP2 meeting / Jan. 12, 2014</p>	<p>Clarification regarding the required number of subject-exposures for an adequate safety database, procedures evaluated, proposed indication, and fentanyl dosing during the colonoscopy study (i.e., fentanyl 125 µg likely too high for this procedure).</p>
<p>Written Response, Type C Meeting / Aug. 29, 2014 and Follow-up Advice Letter / Oct. 9, 2014</p>	<p>Clinical issues discussed included the following:</p> <ul style="list-style-type: none"> <li>• Advice for evaluated procedures and need for blinded control in the Phase 3 studies</li> <li>• Open-label midazolam (b) (4)</li> <li>• Studies in colonoscopy and bronchoscopy may not provide supportive data for broad procedural sedation indication</li> <li>• Inclusion of adequate number of ASA-PS III and IV patients</li> <li>• Clarification of permitted rescue medication and fentanyl dosing</li> <li>• Clarification of primary efficacy endpoint criterion of no more than five doses of study drug in any 15-minute window (i.e., includes sliding 15-minute windows)</li> <li>• Proposed midazolam dosing exceeded label recommendations</li> <li>• Normal saline as placebo control</li> <li>• Per ICH guidelines, 1500 subject exposures required for safety database</li> <li>• Inclusion of foreign safety data</li> </ul>

Meeting / Communication / Date	Event / Key Clinical Issues
	<ul style="list-style-type: none"> <li>• IV fluid administration clarification</li> <li>• Recommended vital sign monitoring</li> <li>• Adverse event definitions and grading clarification</li> <li>• Stopping criteria clarification</li> </ul> <p>Recommendations for SAP included the following:</p> <ul style="list-style-type: none"> <li>• ITT population should include all patients randomized</li> <li>• Hierarchical testing is appropriate for multiple secondary efficacy endpoints</li> </ul>
<p>Advice Letter / April 6, 2015</p>	<p>Clinical issues included the following:</p> <ul style="list-style-type: none"> <li>• Evaluated procedures must be of adequate intensity and duration to support a broad procedural sedation indication</li> <li>• An open-label study in ASA-PS IV patients will not provide adequate safety information</li> <li>• An adequate number of patients <math>\geq 60</math> years of age is required</li> <li>• Clarification of rescue medication and the meaning of “any 15-minute window”</li> <li>• Open-label midazolam (b) (4)</li> <li>• RMZ administration via continuous IV infusion is recommended, as bolus dosing has clinical limitations</li> <li>• Ventilatory drive needs to be evaluated with concomitant opioid administration</li> <li>• Adequate safety follow-up for all discontinued patients</li> <li>• Laboratory assessments required prior to facility discharge</li> </ul> <p>Recommendations regarding vital sign monitoring:</p> <ul style="list-style-type: none"> <li>• Capture all changes in continuously monitored vital signs, regardless of meeting the criteria of adverse events</li> <li>• Include mean arterial pressure monitoring</li> <li>• Record vital signs prior and following each dose of fentanyl</li> </ul> <p>Recommendations regarding adverse events:</p> <ul style="list-style-type: none"> <li>• Clarify adverse event definitions and causality relationships</li> <li>• Clarify hypertension, hypotension, and hypoxia definitions</li> <li>• Incorporate adverse event stopping criteria into the Phase 3 protocols</li> </ul>

Meeting / Communication / Date	Event / Key Clinical Issues
Advice Letter / June 8, 2015	Clinical issues included the following: <ul style="list-style-type: none"> <li>• Recommended safety-based subject stopping criteria</li> <li>• Clarification of which adverse events and their relatedness to study drug will be forwarded to the DMC chair</li> <li>• Nadirs of continuously monitored vital signs must be captured, regardless if they meet the criteria of an adverse event</li> <li>• Clarification of exclusion criteria</li> </ul>
Type B Meeting, Pre-NDA / July 12, 2018	Clinical issues discussed included the following: <ul style="list-style-type: none"> <li>• Phase 3 studies appear to provide adequate efficacy data to support NDA filing</li> <li>• Pooled efficacy and safety analyses are not appropriate for different patient populations and procedures performed</li> <li>• Safety database appears adequate for NDA filing</li> <li>• Rationale for applicability of foreign data to U.S. population appears acceptable</li> <li>• Patient narratives and CRFs for all patients who died or discontinued due to an adverse event, regardless of causality, is acceptable</li> <li>• (b) (4) will not be permitted in labeling</li> </ul>
NDA submitted / April 5, 2019	NDA received
NDA 212295 filed / June 17, 2019	Clinical issues identified included the following: <ul style="list-style-type: none"> <li>• Acceptability of safety data pooling in the ISS</li> <li>• Duration of procedures evaluated and implications in final labeling language</li> <li>• Level of training required for administering provider</li> <li>• Lack of maximum dose provided</li> </ul>
Mid-Cycle Communication Meeting / Nov. 22, 2019	Clinical issues discussed included the following: <ul style="list-style-type: none"> <li>• The indicated procedures for remimazolam sedation based on duration</li> <li>• The inconvenience of bolus dosing, particularly for longer procedures</li> <li>• Level of training required for administering provider.</li> </ul>
Late Cycle Communication Meeting / Feb. 27, 2020	Clinical issues discussed included the following: <ul style="list-style-type: none"> <li>• Recommended procedural sedation duration of 30 minutes or less based on Phase 3 study data</li> <li>• Required airway training for administering provider.</li> </ul>

### 3. Product Quality

The following is adapted from the Office of Product Quality (OPQ) Quality Assessment Review:

**The drug substance review team concluded the following:**

Remimazolam besylate is a benzodiazepine derivative with a single chiral center, synthesized as the S enantiomer. It is isolated as the besylate salt (1:1).

Reference is made to DMF (b) (4) for information on the remimazolam besylate drug substance. DMF (b) (4) has been recently reviewed and found to be Adequate. A copy of the Letter of Authorization to allow the Agency to refer to this DMF has been provided in the NDA. Limited information for the drug substance has been provided in NDA 212295 and is summarized below.

A retest date of (b) (4) months after manufacture is granted for remimazolam besylate drug substance when stored at (b) (4) °C. This is supported by acceptable stability data provided in DMF (b) (4).

**The drug product review team concluded the following:**

The regulatory analytical procedures are appropriate for the intended use, including method validation.

Impurities are adequately controlled according to ICH Q3B guidance.

The drug product specification is adequate to assure the identity, strength, quality, purity, and potency of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy. Batch analysis is provided and meets specifications.

We agree with the sponsor's proposed shelf-life of 36-months when stored at controlled room temperature between 20-25°C, excursions permitted between 15-30°C, and protected from light.

**The manufacturing review team concluded the following:**

The proposed commercial batch size of (b) (4) is similar to validation batch size, hence there is no scale up. There are sufficient development studies conducted to support the proposed commercial manufacturing, the identified risks associated with the manufacturing processes are adequately mitigated, and the manufacturing processes are clearly

defined and adequately controlled. Some minor deficiencies were resolved via IR process.

The drug substance manufacturing facility has experience manufacturing the API with chemical synthesis process and has acceptable GMP compliance, and the recent GMP inspection was conducted on May 2016. The drug product manufacturing facility was last inspected for SVL in 2/6/2018. There are no current compliance issues with this firm and the facility is approvable based on district recommendation.

**The microbiology review team concluded the following:**

(b) (4)

The specifications provided meet regulatory expectations. (b) (4)  
(b) (4)  
(b) (4)  
The applicant confirms that the USP compendial methodology is suitable for use during routine commercial production for release testing.

**Recommendation and Conclusion on Approvability (verbatim from the Quality Review Assessment):**

Based on a review of the submitted information and responses to IR's approval of this application is recommended.

The Division concurs with the conclusion of the OPQ team.

## 4. Nonclinical Pharmacology/Toxicology

The following excerpts from Dr. Katie Sokolowski, PhD, nonclinical pharmacology/toxicology reviewer.

The Applicant submitted genotoxicity studies, safety pharmacology studies, general toxicology studies in minipigs and monkeys, and developmental and reproductive toxicology studies in rat and rabbit to qualify the safety of remimazolam. Additional studies were submitted to qualify impurities and the novel excipient, Dextran 40. Extractable and leachables studies were submitted to justify the safety of the container closure system.

The Applicant adequately addressed genotoxicity, safety pharmacology, and general toxicology in appropriate animal models. See Dr. Sokolowski's nonclinical review for a detailed description.

The non-clinical pharmacology toxicology team identified issues related to developmental and reproductive toxicology. The following is adapted from Dr. Sokolowski's nonclinical review.

A full battery of developmental and reproductive toxicology (DART) studies for remimazolam in the rat and rabbit model were submitted in the NDA. The Applicant also conducted supplemental studies to characterize the effects of remimazolam on male reproductive tissues in minipigs. However, it should be noted that Agency expressed concerns with the adequacy of the planned studies during several meetings with the Applicant during development.

Female fertility was evaluated in both the rat and the rabbit. The exposures in the rat study are well below the human exposures and therefore the study is considered inadequate. However, the rabbit female fertility study is considered adequate and no further studies are necessary.

Male fertility was evaluated in rats and minipigs. There were no adverse effects on male fertility in rats up to 30 mg/kg/day (safety margins were ~0.02x and ~0.01x MRHD of 30 mg/day based on  $C_{max}$  and  $AUC_2$ , respectively). When considering systemic exposures of the free compound exposure margins in the rat male fertility study are ~0.06x and ~0.03x MRHD of 30 mg/day based on  $C_{max}$  and  $AUC$ , respectively. Due to lack of exposure to the parent compound, the male fertility assessment in rats is not adequate. In sexually mature Gottingen minipigs, a comprehensive histopathological examination of the reproductive organs was conducted as part of a 28-day repeat-dose toxicity study. These data support the conclusion that the potential for adverse effects of remimazolam on male fertility endpoints is low; however, reproductive performance has not been adequately assessed and a PMR for an adequate male fertility study is recommended.

Embryo-fetal development (EFD) was evaluated in an extended fertility study in rabbits and EFD studies in rats and rabbits. The rat EFD study did not fully characterize the effects of remimazolam on EFD. The study should be repeated testing more prolonged infusions in the rat or in a different species. The rabbit EFD study is considered adequate.

Pre- and post-natal development (PPND) was evaluated in an extended fertility study in rabbits and a standard PPND study in rats. The extended fertility study in rabbits did not evaluate learning and memory or reproductive function of the F1 kits and therefore, cannot be considered adequate to address all standard endpoints. The rat study did not test exposures comparable to the maximum recommended human dose (MRHD) of 30 mg/day over the full treatment period and the rabbit study did not evaluate all standard endpoints. Therefore, the rat PPND study does not fully characterize the effect of remimazolam on PPND and the study should be repeated testing more prolonged infusions in the rat or in a different species.

The following is adapted from Dr. Sokolowski's nonclinical review regarding her conclusion of the developmental and reproductive toxicology (DART) studies.

The developmental and reproductive toxicology (DART) studies for remimazolam do not completely characterize the effects of the drug on these endpoints. Of specific concern, data from the rat studies did not provide acceptable safety margins as the DART studies were conducted with short boluses that resulted in systemic exposures below that in humans. However, the newly released ICH S5(R3) guidance states that the "intended patient population or therapeutic indication can influence the extent of the DART testing" and provides the example of patient populations in "hospitalized settings where pregnancy can be excluded." As per the clinical team, women of childbearing potential undergoing planned procedural sedation are usually tested for pregnancy prior to administration of the sedative drug product thereby excluding pregnant women. As such the less than adequate battery of DART studies will not preclude approval of remimazolam. However, considering the clinical utility of this drug in pregnant females and given the possibility that a pregnant woman may be treated with the drug, PMRs are recommended to better characterize the effects of remimazolam on reproduction and development endpoints and to better inform labeling given the potential for inadvertent use in pregnant women, longer duration of clinical use than indicated in the labeling, and potential utility of this short acting drug in pregnant women. This will include the evaluation of remimazolam in a relevant species for 1) male fertility, 2) embryo-fetal development in a second relevant species (other than the rabbit), and 3) learning, memory, and reproductive function in the F1 offspring in a pre- and post-natal development study. The purpose of these PMRs is to support the safety of short procedural sedation indication in pregnant women and inform the label. In addition, a PMR for juvenile animal studies will be issued to further characterize the potential impact of the drug on the developing brain.

The following is adapted from Dr. Sokolowski's non-clinical review regarding the excipient Dextran 40.

Dextran 40 is listed in the Inactive Ingredient Database (IID) as being present in an FDA approved intravenous drug product (lyophilized powder for solution) with no maximum potency noted. Dextran of unknown MW is also listed in the IID as being present in an FDA-approved ophthalmic drop product. Because the dose of Dextran 40 in this drug product exceeds that of other FDA-approved IV drug products, Dextran 40 is considered a novel excipient that requires qualification. Per the excipient guidance, this generally includes repeat-dose general toxicology study in two species, standard genotoxicity battery, a fertility study, embryo-fetal development studies in two species, and a pre- and post-natal development study. The Applicant addressed the above requirements via conduct of nonclinical studies and submission of a literature-based justification.

The following is an excerpt from Dr. Sokolowski's conclusion regard reproductive and developmental toxicity with Dextran 40.

Although the existing reproductive and developmental toxicity studies with Dextran 40 are inadequate to fully qualify this new excipient, because the proposed indication is for procedural sedation and patients are tested for pregnancy prior to planned procedures, in accordance with ICH S5A(R3), the lack of adequate reproductive and developmental studies for Dextran 40 will not be considered an approval issue.

Although the existing data suggest limited concern, the lack of effects of Dextran 40 on reproduction and development will be confirmed by PMR studies testing the drug product formulation containing Dextran 40 that test exposures comparable to human exposures.

The nonclinical review team had the following labeling recommendations (adapted from Dr. Sokolowski's nonclinical review).

The package insert should include the 2016/2017 Anesthetic and Sedation Drugs Safety Labeling Change language for NMDA/GABAergic anesthetic agents and sedatives, comprehensive descriptions of the developmental and reproductive toxicity data with existing limitations, and warnings of anaphylaxis associated with Dextran 40.

The Division concurs with the nonclinical review team's conclusion regarding approvability of RMZ (adapted from Dr. Sokolowski's nonclinical review).

From a nonclinical pharmacology/toxicology perspective, although there are technically inadequate reproductive and developmental toxicity studies for remimazolam and Dextran 40, because the indication is for planned procedural sedation where women of childbearing potential will be adequately screened for

pregnancy prior to the procedure, the NDA may be approved at the discretion of the clinical team and with the recommended labeling. We also recommend the following postmarketing requirements (PMR).

1. Conduct a male fertility study testing the drug product formulation that evaluates reproductive behavior and fertility and obtains pharmacokinetic analysis in a species that provides adequate exposure to support the proposed clinical exposures for the proposed maximum duration of use based on the clinical indication.
2. Conduct an embryo-fetal development study testing the drug product formulation that results in adequate exposure to support the clinical indication in a species other than the rabbit that provides adequate exposures for the proposed clinical exposures for the proposed maximum duration of use based on the clinical indication.
3. Conduct a pre- and post-natal development study testing the drug product formulation that evaluates all standard endpoints including learning, memory, and reproductive function of the F1 offspring and obtains adequate toxicokinetic data in a species and provides adequate exposures to support the proposed clinical exposures for the proposed maximum duration of use based on the clinical indication.
4. Conduct a juvenile animal toxicology study in a rodent model to characterize the effects of remimazolam on the developing central nervous system to support clinical studies in pediatric patients under 3 years of age.
5. Conduct a juvenile animal toxicology study in a nonrodent model to characterize the effects of remimazolam on the developing central nervous system to support clinical studies in pediatric patients under 3 years of age.
6. Conduct a juvenile animal toxicology study in a rodent model to characterize the effects of remimazolam on the developing central nervous system to support a clinical indication for use in pediatric patients greater than or equal to three years of age and below 18 years age.

## 5. Clinical Pharmacology

The following ADME information is adapted from the Clinical Pharmacology Review by Deep Kwatra, PhD.

### *Absorption and Distribution*

When remimazolam is administered intravenously from 0.01 to 0.5 mg/kg, total exposure ( $AUC_{0-\infty}$ ) suggested a close dose-proportional relationship. Volume of distribution ( $V_z$ ) 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.

### *Metabolism and Excretion*

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 t<sub>1/2</sub> 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.

### *Pharmacokinetic drug interactions*

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.

### *Intrinsic Factors Affecting Elimination*

#### *Gender (Verbatim)*

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 (Adapted)*

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.

#### *Race (Adapted)*

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.

Renal Impairment (Adapted)

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.

Hepatic Impairment (Adapted)

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. Since decrease in the initial bolus dose may result in decreased Cmax and hence both increase in LoC and decreased efficacy. Remimazolam should be administered to effect with top ups administered 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 Division concurs with the plan to include language in the labeling for hepatic impaired patients.

QT Study (adapted from the consultation review of Nan Zheng from the Interdisciplinary Review Team for QT Studies dated August 2, 2019.)

A small dose- and concentration-dependent effect of remimazolam (10 mg and 20 mg IV bolus injection) on the QTc interval was detected in the TQT study. The effect of remimazolam was evaluated in study the TQT study, CNS7056-005. The highest dose that was evaluated was 20 mg, which covers the highest dose possible with a single patient-use vial (20 mg as 7 injections in approximately 15 min). The data were analyzed using central tendency as the primary analysis, which suggest that remimazolam 20 mg is associated with small QTc prolonging effect. See the table below for overall results. The findings of this analysis are further supported by the available nonclinical data, exposure-response analysis and categorical analysis.

The Point Estimates and the 90% Confidence Intervals of QTcF (FDA Analysis)

ECG parameter	Treatment	Time	$\Delta\Delta$ (ms)	90% CI (ms)
QTc	Remimazolam 10mg	0.5 min	6.7	(4.0, 9.5)
QTc	Remimazolam 20mg	0.5 min	10.7	(8.0, 13.4)
QTc	Midazolam 2.5mg	0.5 min	4.5	(1.8, 7.3)
QTc	Midazolam 7.5mg	0.5 min	8.1	(5.4, 10.8)

Source: QT Study Review, completed by Interdisciplinary Review Team for QT Studies, dated Aug. 2, 2019.

Remimazolam is administered as an IV bolus injection. Dose and injection/infusion rate are the most significant factors that impact the  $C_{max}$ . The proposed initial adult dose is 5 mg push injection over a 1-minute; supplement doses of 2.5 mg over a 15-seconds can be administered at least 2 min apart. The proposed product label does not have specify an upper limit of total dose.

The Division concurs with the conclusions from the IRT-QT team and the recommendation to include findings, including drug effect on heart rate and QTcF, from Study CNS7056-005.

## 6. Clinical Microbiology

Remimazolam is not a therapeutic antimicrobial therefore clinical microbiology data were neither required or submitted.

## 7. Clinical/Statistical- Efficacy

The sources of clinical data are well-summarized in Dr. Petit-Scott's review.

The safety and efficacy of intravenously administered remimazolam was evaluated in 22 clinical studies, 12 conducted in the United States, and included 1767 subject exposures, which includes 32 subjects exposed to RMZ via the oral route. There were 1731 patients exposed to IV RMZ. A brief summary of the studies by phase is as follows:

- Phase 1 – 11 studies
  - 8 studies in healthy volunteers
  - 1 study in patients with end-stage renal disease
  - 1 study in central nervous system depressant abusers
  - 1 study in patients with hepatic impairment
- Phase 2 – 5 studies
- Phase 2/3 – 1 study
- Phase 3 – 5 studies

The Phase 2 and Phase 3 studies were conducted in patients receiving procedural sedation, general anesthesia, and ICU sedation. See Appendix 1 for the clinical studies supporting NDA 212295.

The following is adapted from the statistical review by James Travis, Ph.D. The Clinical Review by Dr. Petit-Scott contains additional details.

The applicant's development program consisted of two adequate and well-controlled studies (CNS7056-006 and CNS7056-008), which were designed to evaluate the efficacy

and safety of remimazolam for procedural sedation in two different procedures (colonoscopy and bronchoscopy) and a third study in high risk patients undergoing colonoscopy for which the primary objective was to assess the safety of remimazolam. Patients were considered high risk if they were classified as ASA III or ASA IV. All three studies included an open-label midazolam treatment arm. The use of an open-label midazolam treatment arm was discussed with the Applicant during the drug development program. The Agency conveyed that the open-label design (b) (4) See the table below for a brief summary of the three studies.

**List of all studies included in the statistical analysis**

	<b>Phase and Design</b>	<b>Treatment Period</b>	<b>Follow-up Period</b>	<b># of Treated Subjects per Arm</b>	<b>Study Population</b>
CNS7056-006 NCT02290873	MC, R, DB, PG, PC, AC	Procedure duration	Day 4 (+3/-1 days)	RMZ: 296 Placebo: 60 Midazolam: 102	Patients undergoing colonoscopy
CNS7056-008 NCT02296892	MC, R, DB, PG, PC, AC	Procedure duration	Day 4 (+3/-1 days)	RMZ: 303 Placebo: 59 Midazolam: 69	Patients undergoing bronchoscopy
CNS7056-015 NCT02532647	MC, R, DB, PG, PC, AC	Procedure duration	Day 4 (+3/-1 days)	RMZ: 31 Placebo: 16 Midazolam: 30	ASA III/IV patients undergoing colonoscopy

\* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled  
 Note: Hereinafter the studies will be referenced by the last three digits of the study id number.

All three conducted studies followed the same general design, with the difference being the procedure performed (colonoscopy or bronchoscopy) and the population studied (lower risk [ASA categories I-III] or high risk [ASA categories III-IV]). In all studies, patients were screened for their study eligibility and then scheduled for treatment.

The key eligibility criteria are described below:

Inclusion:

- Male and female patients, aged ≥18, scheduled to undergo a diagnostic or therapeutic colonoscopy (therapeutic procedures may include hemostasis, resection, ablation decompression, foreign body extraction, for example). (Studies 006 and 015 only)
- Male and female patients, aged ≥18, scheduled to undergo a diagnostic or therapeutic flexible fiberoptic bronchoscopy in the bronchoscopy suite (therapeutic bronchoscopies may include lavage, biopsies, brushings, and foreign body extraction, for example). (Study 008 only)

- American Society of Anesthesiologists Score I through III. (Studies 006 and 008 only)
- ASA grade III/IV. (Study 015 only)
- Body mass index (BMI)  $\leq 40$  kg/m<sup>2</sup>. (Studies 006 and 008 only)
- For female patients with child-bearing potential, negative result of pregnancy test (serum or urine) as well as use of birth control during the study period (from the time of consent until all specified observations are completed).
- Patient voluntarily signs and dates an ICF that is approved by an IRB prior to the conduct of any study procedure.
- Patient is willing and able to comply with study requirements and return for a Follow-up Visit on Day 4 (+3/-1) after the colonoscopy/bronchoscopy.

Exclusion:

- Patients with a known sensitivity to benzodiazepines, flumazenil, opioids, naloxone, or a medical condition such that these agents are contraindicated.
- Chronic use of benzodiazepines for any indication (e.g., insomnia, anxiety, spasticity). (not 015)
- Female patients with a positive pregnancy test at screening or baseline.
- Lactating female patients.
- Patients with positive drugs of abuse screen or a positive serum ethanol at baseline.
- Patient with a history of drug or ethanol abuse within the past 2 years.
- Patients in receipt of any investigational drug within 30 days or less than seven half-lives (whichever is longer) before the start of the study or scheduled to receive one during the study period.
- Patients with an inability to communicate well in English with the investigator.

On the day of the procedure patient's eligibility criteria were reviewed, medical and medication histories were obtained, and other screening assessments were performed (physical examination, including weight, body temperature, clinical laboratory tests and 12-lead ECG). Following successful completion of these procedures, patients were randomized to receive either remimazolam, placebo, or the open-label active-comparator midazolam. The randomization ratio varied by study and is summarized in the table below

**Randomization Ratio by Study**

Study	Randomization Ratio (remimazolam: placebo: midazolam)
006	30:6:10
008	30:6:10
015	2:1:2

Source: Dr. Travis' statistical review.

Patients would then receive sedation and undergo the study procedure. Patients would be administered an initial dose of sedative. For patients in the remimazolam or placebo groups this consisted of a 5 mg dose of remimazolam or matched placebo manually by injection over one minute with watch control. Following the initial dose, top-up doses (2.5 mg of double-blinded study drug) could be administered anytime sedation was thought to be inadequate. If adequate sedation could not be achieved, then rescue sedation (midazolam) could be administered. Patients in the midazolam arm received an initial 1.75 mg bolus injected over 2 minutes with 1.0 mg supplemental doses or (1.0 mg initial dose/0.5 mg supplemental dose for patients 60 years of age and older, debilitated, or chronically ill).

To proceed with the required procedure, patients had to achieve an adequate level of sedation. Sedation was measured using the Modified Observer's Assessment of Alertness and Sedation Scale (MOAA/S). The MOAA/S scoring categories are described in the following table. Adequate sedation for initiation was defined as a MOAA/S score of 3 or less and adequate maintenance sedation was defined as MOAA/S scores of 4 or less.

**Modified Observer's Assessment of Alertness and Sedation Scale**

Response	Score
Responds readily to name spoken in normal tone	5 (alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

Source: Appendix, applicant's study report and Dr. Travis' statistical review.

Following completion of the procedure, sedation was discontinued and the times to alertness and discharge were recorded. Finally, patients completed several safety assessments 3 days after the procedure (+3/-1 days).

The primary efficacy objective for all three studies was the success rate for sedation with remimazolam compared to placebo. Success was defined as the following:

- Completion of the prescribed procedure, AND
- No requirement for a rescue sedative medication, AND
- For remimazolam & placebo: No requirement of more than 5 doses of study medication within any 15-minute window.
- For midazolam: No requirement of more than 3 doses within any 12-minute window.

The sponsor had the following secondary endpoints for studies 006 and 008:

1. The time to start of procedure after administration of the first dose of study medication.

2. The time to peak sedation after administration of the first dose of study medication.
3. The time to ready for discharge (defined as ability to walk unassisted) after the last injection of study drug and after the end of bronchoscopy procedure (bronchoscope out).
4. The time to fully alert (time to first of three Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores of 5 after the last injection of study drug and after the end of bronchoscopy procedure (bronchoscope out).
5. The MOAA/S scores by time point.
6. The recall of the procedure by the Brice questionnaire administered when full alertness is regained and on Day 4.
7. The changes to the patient's cognitive function by the Hopkins Verbal Learning Test -Revised (HVLN-R) administered before study medication administration and after the fully alert criteria have been achieved.
8. The safety of multiple doses (initial dose and additional top-up doses) of remimazolam (including oxygen saturation and no need for mechanical ventilation), following administration of a standard dose of fentanyl.
9. The readiness to discharge score 30, 60- and 90-minutes post injection of the first dose.
10. The Drowsiness visual analogue scale to assess for signs of re-sedation.
11. The requirement for flumazenil during the procedure.
12. The patient's self-evaluation of "back-to-normal" after the procedure.
13. The pain on injection at application of study medication.
14. The population PK in a subgroup of patients (a minimum of 50 patients below 65 years of age, and 15 patients aged 65-74). (Study 006 only).
15. Population PK in elderly patients ( $\geq 75$  years) at selected sites. (Study 008 only).

For Study 015 the primary objective was to assess the safety of multiple doses (initial dose and additional top-up doses) of remimazolam compared to placebo and midazolam, following administration of a standard dose of fentanyl. The secondary objectives for Study 015 were:

1. To assess the success of the procedure, as measured by the success definition described above.
2. The time to start of procedure after administration of the first dose of study medication.
3. The time to peak sedation after administration of the first dose of study medication.
4. The time to fully alert (time to first of three Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores of 5 after the last injection of study drug and after the end of bronchoscopy procedure (bronchoscope out).
5. The MOAA/S scores by time point.
6. The recall of the procedure by the Brice questionnaire administered when full alertness is regained and on Day 4.

7. The Drowsiness visual analogue scale to assess for signs of re-sedation.
8. The requirement for flumazenil during the procedure.
9. The pain on injection at application of study medication.
10. To assess the population pharmacokinetics (PK) in the remimazolam arm.
11. To assess the Investigator’s satisfaction with the sedation agent.
12. To assess the effect of study drug / midazolam in combination with fentanyl on the ventilatory drive.
13. To assess the amount of study medication administered to the patient.

The patient disposition in the studies demonstrated a completion rate of at least 98% in all treatment arms.

The patient demographics for studies 006, 008, and 015 do not demonstrate any major imbalances between the populations in any of the studies. Overall, patients in study 006 (colonoscopy) were younger by approximately 8 to 9 years than patients in the other two studies. There was also a greater proportion of Hispanic or Latino patients enrolled in study 006 (colonoscopy). Otherwise, the demographics were similar between the studies.

The following table shows the distribution of ASA categories for all three studies. Studies 006 and 008 enrolled lower risk patients (ASA I-III), while study 015 enrolled only higher risk patients (ASA III-IV). The distributions are different for all three studies, with patients in study 006 (colonoscopy) generally having the lowest risk (lowest ASA score). This disparity most likely reflects the conduct of routine screening colonoscopies on otherwise healthy individuals.

**Table 1: Summary of ASA Risk Category by Study and Treatment**

Study	Treatment	ASA Category			
		ASA I	ASA II	ASA III	ASA IV
006 Colonoscopy	Remimazolam	95/296 (32.1)	179/296 (60.5)	22/296 (7.4)	0
	Placebo	11/60 (18.3)	45/60 (75.0)	4/60 (6.7)	0
	Midazolam	37/102 (36.3)	61/102 (59.8)	4/102 (3.9)	0
008 Bronchoscopy	Remimazolam	10/303 (3.3)	185/303 (61.1)	108/303 (35.6)	0
	Placebo	2/60 (3.3)	29/60 (48.3)	29/60 (48.3)	0
	Midazolam	3/68 (4.4)	40/68 (58.8)	25/68 (36.8)	0
015 Colonoscopy (High Risk)	Remimazolam	0	0	16/31 (51.6)	15/31 (48.4)
	Placebo	0	0	9/16 (56.2)	7/16 (43.8)
	Midazolam	0	0	15/30 (50.0)	15/30 (50.0)

Source: Dr. Travis’ statistical review.

The following was adapted from Dr. Travis’ statistical review.

The results of the applicant’s primary efficacy analyses are shown below for studies 006, 008 and 015 respectively. In the first two studies (006 and 008), there is a large,

statistically significant difference in the treatment success rate between the remimazolam and placebo arms. For study 015 the main objective was safety, so statistical tests were not performed for the efficacy endpoints, though the success rates were similar to the other two studies.

The reasons for treatment failure are also noted in the same tables. For patients in the placebo arm in all three studies, the main reason for treatment failure was use of rescue. This varied between 90-100% in the three studies. In studies 006 and 015, there was also a high percentage of placebo patients (study 006: 73% and study 015: 88%) who used more than the allowable number of doses within a 15-minute window. The main reason for treatment failure in the remimazolam arm varied by study between too many doses within any 15-minute window for study 006, the need for rescue medication in study 008, or the same failure rate for both in study 015.

**Primary Analysis Results – Study 006 (colonoscopy)**

	<b>Remimazolam N = 298 n (%)</b>	<b>Placebo N = 60 n (%)</b>	<b>Difference in Rates (95% CI)</b>	<b>P-Value</b>
Treatment Success	272 (91.3%)	1 (1.7%)	89.6% (85.1, 94.2)	<0.0001
Failure	26 (8.7%)	59 (98.3%)		
<b>Reasons for failure</b>				
Rescue sedative medication taken	10 (3.4%)	57 (95%)		
Too many doses within the predefined time window	18 (6.0%)	44 (73.3%)		
Procedure not completed	7 (2.3%)	1 (1.7%)		

Source: Table 15, applicant’s study report and Dr. Travis’ statistical review.

**Primary Analysis Results – Study 008 (bronchoscopy)**

	<b>Remimazolam N = 310 n (%)</b>	<b>Placebo N = 63 n (%)</b>	<b>Difference in Rates (95% CI)</b>	<b>P-Value</b>
Treatment Success	250 (80.6%)	3 (4.8%)	75.9% (69.0, 82.7)	<0.0001
Failure	60 (19.4%)	60 (95.2%)		
<b>Reasons for failure</b>				
Rescue sedative medication taken	49 (15.8%)	57 (90.5%)		
Too many doses within the predefined time window	14 (4.5%)	10 (15.9%)		

	<b>Remimazolam</b> N = 310 n (%)	<b>Placebo</b> N = 63 n (%)	<b>Difference in Rates</b> <b>(95% CI)</b>	<b>P-Value</b>
Procedure not completed	9 (2.9%)	3 (4.8%)		

Source: Table 12 & 13, applicant's study report and Dr. Travis' statistical review.

**Efficacy Analysis Results – Study 015 (ASA 3 and 4, colonoscopy)**

	<b>Remimazolam</b> N = 32 n (%)	<b>Placebo</b> N = 16 n (%)	<b>Difference in Rates</b> <b>(95% CI)</b>
Treatment Success	27 (84.4%)	0 (0.0%)	84.4% (71.8, 97.0)
Failure	5 (15.6%)	16 (100.0%)	
<b>Reasons for failure</b>			
Rescue sedative medication taken	3 (9.4%)	16 (100.0%)	
Too many doses within the predefined time window	3 (9.4%)	14 (87.5%)	
Procedure not completed	1 (3.1%)	0 (0.0%)	

Source: Table 14, applicant's study report and Dr. Travis' statistical review.

Total amounts of study and rescue medication use are summarized below for studies 006, 008, and 015 respectively. In all three studies, study drug and rescue medication usage were higher in the placebo arm than in the remimazolam arm.

**Study Drug and Rescue Use for Procedure Completers – Study 006 (colonoscopy)**

<b>Statistics</b>	<b>Remimazolam</b>	<b>Placebo</b>
<b>Study Drug (mL)*</b>		
Mean (SD)	4.21 (1.60)	7.07 (0.55)
Median	4	7
(Min, Max)	(2, 9)	(6, 11)
<b>Rescue (mg)</b>		
Mean (SD)	0.29 (2.08)	6.79 (4.26)
Median	0	6
(Min, Max)	(0, 25)	(0, 25)

Source: Dr. Travis' statistical review.

\* For Remimazolam 1mL = 2.5 mg

**Study Drug and Rescue Use for Procedure Completers – Study 008**

<b>Statistics</b>	<b>Remimazolam</b>	<b>Placebo</b>
<b>Study Drug (mL)*</b>		
Mean (SD)	4.57 (2.02)	6.03 (0.97)
Median	4	6
(Min, Max)	(2, 12)	(0 <sup>†</sup> , 7)
<b>Rescue (mg)</b>		
Mean (SD)	1.20 (3.38)	5.78 (3.75)
Median	0	5
(Min, Max)	(0, 20)	(0,17)

Source: Dr. Travis' statistical review.

\* For Remimazolam 1mL = 2.5 mg

† One patient randomized to placebo received midazolam erroneously.

**Study Drug and Rescue Use – Study 015**

<b>Statistics</b>	<b>Remimazolam</b>	<b>Placebo</b>
<b>Study Drug (mL)*</b>		
Mean (SD)	3.61 (1.48)	6.47 (0.99)
Median	3	7
(Min, Max)	(2, 7)	(3.5, 7)
<b>Rescue (mg)</b>		
Mean (SD)	2.48 (10.2)	7.22 (2.50)
Median	0	7.5
(Min, Max)	(0, 55)	(2, 10)

Source: Dr. Travis' statistical review.

\* For Remimazolam 1mL = 2.5 mg

In all three studies, patients were dosed with fentanyl immediately before administration of study drug. Additional supplemental doses of fentanyl were administered for inadequate pain control. In addition to its analgesic properties, fentanyl has a sedative effect, therefore, it was important to evaluate whether there were any differences in overall fentanyl use. Additionally, fentanyl could serve as an additional rescue medication. Summaries of fentanyl use for patients who were able to complete the procedure are shown in the table below. In all three studies, patients in the placebo group received higher doses of fentanyl than patients in the remimazolam group.

**Fentanyl Use by Study (Treated Patients)**

<b>Statistics</b>	<b>Remimazolam</b>	<b>Placebo</b>
<b>Study 006<sup>†</sup></b>		
N	296	60
Mean (SD)	88.9 (21.7)	121.2 (34.4)
Median	88	125

<b>Statistics</b>	<b>Remimazolam</b>	<b>Placebo</b>
(Min, Max)	(50, 200)	(75, 200)
<b>Study 008</b>		
N	303	60
Mean (SD)	81.8 (54.3)	119 (79.1)
Median	75	100
(Min, Max)	(25, 450)	(25, 400)
<b>Study 015</b>		
N	31	16
Mean (SD)	59.7 (15.4)	67.2 (21.8)
Median	50	50
(Min, Max)	(50, 100)	(50, 100)

Source: Dr. Travis' statistical review.

† One patient was reported as using 76 µg, while the lowest dose increment used in the study was 25 µg.

Adapted from the statistical review by James Travis, PhD, and the clinical review of Renee Petit-Scott, MD.

The studied procedures, colonoscopy and bronchoscopy, were relatively short with a mean duration of 12.4 minutes in the colonoscopy study (006) and 12.8 minutes in the bronchoscopy study (008) for remimazolam-treated patients. Furthermore, there was only one procedure in the colonoscopy study (006) lasting longer than thirty minutes and only 10% lasting longer than thirty minutes in the bronchoscopy study (008). For all three studies, the mean and median procedures ranged from 6.5 to 13 minutes.

#### **Procedure Duration, Phase 3 Studies**

<b>Treatment Arm</b>	<b>Mean Procedure Time (minutes)</b>	<b>Median Procedure Time (minutes)</b>	<b>Maximum Procedure Time (minutes)</b>
<i>Study CNS7056-006</i>			
RMZ treatment group	12.4	12	33
Placebo treatment group	14.2	13	38
<i>Study CNS7056-008</i>			
RMZ treatment group	12.8	10	68
Placebo treatment group	11.1	6.5	48
<i>Study CNS7056-015</i>			
RMZ treatment group	10.3	8	31
Placebo treatment group	11.6	11.5	22

Source: Adapted from Applicant's data and Renee Petit-Scott's clinical review

The following conclusion is adapted from the clinical review of Renee Petit-Scott, MD.

The totality of the data indicates that remimazolam provides superior sedation over saline placebo for colonoscopy and bronchoscopy procedures lasting 30 minutes or

less. The Applicant has stated, and I agree, that these two procedures, in addition to the Phase 2 evaluation conducted in patients undergoing upper endoscopy, are representative of the invasiveness, stimulation, and duration of commonly performed procedures in the U.S. Based on this information, I do not think the proposed indication needs to be modified to include only those procedures studied, but I do recommend a time limitation based on the duration of the evaluated procedures in the Phase 3 studies.

In conclusion, the Division concurs with Dr. Petit-Scott's assessment that the Applicant has provided substantial evidence of effectiveness per 21 CFR 314.126(a)(b) to support approval. Remimazolam has been shown to be effective for its intended use in three Phase 3 trials, two in colonoscopy and one in bronchoscopy.

## 8. Safety

The following is adapted from Dr. Renee Petit-Scott's clinical review.

There were no issues regarding the data integrity or the overall quality of the submission.

There were 11 Phase 2 to 3 studies conducted in patients receiving procedural sedation (five studies, conducted in the U.S.), general anesthesia (five studies), and ICU sedation (one study). The Applicant also conducted studies in patients with renal and hepatic dysfunction. The safety population consisted of all subjects and patients enrolled in a clinical study who received any amount of RMZ, placebo, or midazolam. There were a total of 1731 subject exposures to IV RMZ throughout clinical development and a total of 969 patients received RMZ during procedural sedation.

The totality of the safety database is adequate to support the revised indication with the recommended procedure duration, 30 minutes or less. The Applicant evaluated the safety (and efficacy) of RMZ in two procedures, colonoscopy and bronchoscopy, in the Phase 3 studies, and upper endoscopy in a Phase 2 study.

There were 17 RMZ-treated patients in the pooled procedural sedation safety analysis group who experienced a serious adverse event, compared to one in the midazolam treatment group and four in the placebo treatment group. All serious treatment-emergent adverse events in the RMZ treatment group were reported during Study CNS7056-008 (bronchoscopy). Pneumothorax, bronchospasm, and hypoxia occurred in two or more patients. There were two events of respiratory failure. The Applicant has indicated that of these treatment-emergent adverse events, all were considered unlikely related to the study drug treatment with the exception of those reported for patient CNS7056-008-(b) (6). The narrative for that patient is summarized below.

There were no reported patient deaths during clinical development. There was one patient, however, who died seven months after administration of RMZ for maintenance of general anesthesia. This was a 73-year-old male with a relevant past medical history of aortic valve stenosis, coronary artery disease, thoracic aortic aneurysm, atrial fibrillation, hypertension, hyperlipidemia, prostate cancer, and congestive heart failure who received RMZ during aortic valve replacement. On post-operative day one, he experienced hemothorax and acute renal failure, both considered unrelated RMZ administration. Subsequent follow-up information is limited but it appears the patient had on-going hemodialysis and died of unknown cause(s) seven months after RMZ administration. Given the lack of a temporal relationship and the seriousness of the patient's underlying comorbidities and surgical procedure, it seems unlikely RMZ played a causal role; however, the impact of RMZ administration on hemodynamic instability and whether abnormal vital signs are potentiated during RMZ administration is unknown.

The safety concerns associated with administration of RMZ during procedural sedation do not appear to differ significantly from those associated with currently approved benzodiazepines administered for procedural sedation. Those safety concerns include prolonged sedation, changes in measured vital sign parameters, particularly respiratory parameters, and adverse events related to abuse, dependence, and withdrawal. Administration of remimazolam, in general, results in a lower incidence of prolonged sedation compared to patients treated with midazolam, either at the discretion of the investigator (in the case of the placebo treatment group) or according to the drug label recommendations (in the case of the midazolam treatment group). In Study CNS7056-008, the mean dose of RMZ was higher than that administered in the other Phase 3 studies and the RMZ treatment group had a higher incidence of prolonged sedation compared to the placebo or midazolam treatment groups; however, the incidence in all treatment groups was low.

While the Phase 3 studies did not formally evaluate a dose-response, there did appear to be an increased incidence of select adverse events in patients who received higher total doses of RMZ. Specifically, in the pooled procedural sedation safety analysis group, the incidence of hypoxia, bradycardia, and hypotension was increased in the RMZ 14.372 mg to 23.744 mg dose range group compared to the RMZ 5 mg to 14.372 mg dose range group. The number of patients in the highest dose range group, 23.744 mg to 33.116 mg, was too low to make definitive conclusions regarding the potential adverse event dose-response. In the Phase 2 study, CNS7056-004 in patients undergoing colonoscopy, the incidence of bradycardia, hypertension, and nausea increased with increasing doses of RMZ and the incidence of oxygen saturation decreased was higher in the RMZ 8 mg/3 mg and 7 mg/2 mg treatment groups compared to the RMZ 5 mg/3 mg treatment group.

There were clinically relevant changes in measured vital sign parameters, particularly respiratory parameters, observed during the Phase 3 studies; however, there did not

appear to be clinically meaningful differences in rates of respiratory depression, hypoxia, or respiratory rate decreased in the RMZ treatment group compared to the placebo or midazolam treatment groups. In general, the incidence of vital sign-related adverse events was lower in the RMZ treatment groups in all three Phase 3 studies compared to either the placebo or midazolam treatment groups. As summarized in Dr. Petit-Scott's clinical review, Section 8.4.7, Vital Signs, results from the pooled procedural sedation safety analysis group indicated that increased systolic and diastolic blood pressure were the only vital sign changes consistently reported with increased incidence in the RMZ treatment group. This finding was consistent across the individual Phase 3 studies, suggesting that elevations in blood pressure may be a RMZ drug effect and will be included in the drug product label.

There were no clinically relevant observations that RMZ administered for procedural sedation resulted in adverse events associated with abuse, dependence, or withdrawal. Dizziness was the only adverse event considered possibly related to abuse that was reported with a higher incidence in the RMZ treatment group in both Study CNS7056-006 and CNS7056-008; however, the overall incidence was so low as to not be of clinical concern.

The Division concurs with the Dr. Renee Petit-Scott's conclusion regarding the safety of RMZ.

In summary, the totality of the safety data supports a favorable benefit:risk profile for the administration of RMZ for sedation for procedures lasting 30 minutes or less. The safety data suggest that the safety profile of RMZ is similar or better than that of midazolam when administered either at the discretion of individual physicians or according to label recommendations. I, therefore, conclude that remimazolam, in combination with total fentanyl doses up to 200 µg, is a safe sedative option for adult patients undergoing diagnostic and therapeutic procedures lasting 30 minutes or less, and recommend approval. The level of training of the administering provider should comply with the ASA practice guidelines for moderate to deep procedural sedation.

## **9. Advisory Committee Meeting**

An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

## **10. Pediatrics**

The drug product has changed hands since initiation of the IND May 22, 2008. The safety and efficacy of remimazolam has not been evaluated in pediatric patients to date. An initial pediatric study plan (iPSP) was submitted on December 16, 2013, and it was agreed upon on July 18, 2014. The Applicant, Cosmo Technologies, LTD (Cosmo), submitted a draft pediatric

## 11. Other Relevant Regulatory Issues

### *Application Integrity Policy (AIP)*

There are no apparent issues related to the integrity of the data or information in this submission.

### *Exclusivity or patent issues*

There are no exclusivity or patent issues of concern.

### *Financial Disclosure (verbatim from the Clinical Review)*

Per FDA form 3454, Mr. Richard Jones, Director of Cosmo Technologies Ltd., certified that of the studies conducted by the Applicant, no clinical investigator participated in a financial arrangement whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study, had proprietary interest in this product or significant equity interest in the sponsor of the covered study, or was the recipient of significant payments of other sorts.

### *Good Clinical Practice (Verbatim from the Clinical Review)*

The applicant states the following on the title page of each of the Phase 3 studies.

This study (or trial) was performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents.

### *Office of Scientific Investigations (OSI) (Verbatim from the Clinical Review, Section 4.1)*

In consultation with the Office of Scientific Investigations, clinical study sites 002 (Principal Investigator, Bal Bhandari) and 005 (Principal Investigator, Taddese Desta) for Study CNS7056-006; sites 004 (Principal Investigator, Gregory Feldman) and 021 (Principal Investigator, Lonny Yarmus) for Study CNS7056-008; and site 001 (Principal Investigator Bal Bhandari) for Study CNS7056-015 were selected for inspection. These sites were inspected based on high patient enrollment (all sites), procedure duration (sites 004 and 005), and reported efficacy results (sites 005 and

021). Specifically, the decision to inspect site 004 for Study CNS7056-008, Dr. Feldman, was based primarily on the seemingly short duration of bronchoscopic procedures completed at this site compared to other sites.

The results from clinical site inspections with Principal Investigators Bhandari, Feldman, and Yarmus did not identify any objectionable conditions or practices that would justify enforcement action by the Office of Compliance.

A Form FDA 483 was issued for clinical site 005, Taddese Desta, Study CNS7056-006, for minor GCP deficiency observations, primarily for three discrepancies between the source record and the CRF for three subjects. The following were noted as minor isolated recordkeeping errors unlikely to be significant.

- MOAA/S scores of 1 (source) and 4 (CRF), initial time point
- VAS drowsiness scores of 15 (source) and 20 (CRF)
- VAS injection site pain scores of 13 (source) and 3 (CRF)

Study conduct appeared GCP-compliant, including Applicant oversight. There were no GCP deficiencies noted for short colonoscopy times. All audited NDA data were otherwise adequately verifiable against source records and CRFs.

## 12. Labeling

### Prescribing Information Clinical Recommendations

The following is reproduced from the clinical review by Dr. Renee Petit-Scott.

The proposed indication for RMZ is for the induction and maintenance of procedural sedation in adults. Based on the duration of procedures evaluated and the decreased procedural success with longer lasting procedures, the proposed indication will likely include a recommended time limitation of 30 minutes or less.

The drug product labeling had not been finalized at the time of completion of this clinical review. Sections of the label that are likely to undergo substantial edits include Section 2, 5, 6, and 14. The following is a very high-level summary of the proposed edits, suggested at the time of this clinical review.

#### Section 2

Section 2.1 will be edited to include important dosage and administration instructions. Information from Sections 2.4 and 2.5 will be moved to Section 2.1 for clarity and improved organization.

#### Section 5

Section 5.1 will need to clarify the information regarding concomitant opioid administration, risks of respiratory and cardiovascular adverse events, and mitigating strategies.

#### Section 6

Major edits to this section will include the addition of adverse reaction information from the individual Phase 3 studies, (b) (4). Because the three studies were conducted in different procedures and patient populations, I feel the information needs to be conveyed separately in the drug product label.

#### Section 14

This section will need to include relevant, not all, secondary efficacy endpoints, and the impact of fentanyl dosing on procedural success and duration.

### Prescribing Information Clinical Pharmacology and Nonclinical Pharmacology and Toxicology

Clinical Pharmacology Team labeling recommendations:

- 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.
- In a thorough QT study (CNS7056-005), 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. 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.

Nonclinical Review Team labeling recommendation:

- The package insert should include the 2016/2017 Anesthetic and Sedation Drugs Safety Labeling Change language for NMDA/GABAergic anesthetic agents and sedatives, comprehensive descriptions of the developmental and reproductive toxicity data with existing limitations, and warnings of anaphylaxis associated with Dextran 40.

## 13. Postmarketing Recommendations

### Postmarketing Requirements (PMRs)

Nonclinical Pharmacology/Toxicology PMR recommendations:

- Conduct a male fertility study testing the drug product formulation that evaluates reproductive behavior and fertility and obtains pharmacokinetic analysis in a species that provides adequate exposure to support the proposed clinical exposures for the proposed maximum duration of use based on the clinical indication.
- Conduct an embryo-fetal development study testing the drug product formulation that results in adequate exposure to support the clinical indication in a species other than the rabbit that provides adequate exposures for the proposed clinical exposures for the proposed maximum duration of use based on the clinical indication.
- Conduct a pre-and post-natal development study testing the drug product formulation that evaluates all standard endpoints including learning, memory, and reproductive function of the F1 offspring and obtains adequate toxicokinetic data in a species and provides adequate exposures to support the proposed clinical exposures for the proposed maximum duration of use based on the clinical indication.
- Conduct a juvenile animal toxicology study in a rodent model to characterize the effects of remimazolam on the developing central nervous system to support clinical studies in pediatric patients under 3 years of age.
- Conduct a juvenile animal toxicology study in a nonrodent model to characterize the effects of remimazolam on the developing central nervous system to support clinical studies in pediatric patients under 3 years of age.
- Conduct a juvenile animal toxicology study in a rodent model to characterize the effects of remimazolam on the developing central nervous system to support a clinical indication for use in pediatric patients greater than or equal to three years of age and below 18 years age.

The Pediatric Research Equity Act (PREA) applies to this NDA. Under PREA, the Applicant is required to conduct studies to assess safety, efficacy, and appropriate dosing.

The proposed procedures from the Agreed PSP from July 18, 2014 are described efficacy, safety, and PK studies stratified for gender and age within the age group. To determine appropriate dose and extrapolate dose for next younger age group. Efficacy (primary end point): completion of the procedure, without the addition of an alternative sedative.

The proposed timelines, updated by the Applicant in response to an Information Request on January 3, 2020, are as follows.

- For ages three to less than 17 years

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- Draft Protocol Submission: January 31, 2019
- Final Protocol Submission: mid-2020 = approximately July 2020
- Study Completion: +3-4 years = approximately July 2024
- Final Report Submission: +6 months = approximately January 2025
- For birth to less than three years of age
  - Draft Protocol Submission: either January 2024 or extend protocol with disclaimer to start after juvenile toxicity study
  - Final Protocol Submission: July 2024 (after completion of pediatric trial in 3 to 16-year-old children)
  - Study Completion: +3 years = approximately July 2027
  - Final Report Submission: +6 months = approximately January 2028

**Appendix 1. Clinical Studies Supporting NDA 212295**

Study Identity	Study Design	Regimen and Route	Primary Efficacy Endpoints	No. of Patients Dosed	Study Population	No. and Location of Study Sites
<b>Phase 3 Clinical Studies</b>						
<b>CNS7056-006 (NCT 02290873)</b>	Randomized, double-blind, active and saline placebo-controlled	RMZ: 5.0 mg (2.5 mg top-ups) IV MDZ: 1.75mg (1.0 mg top-ups) IV PBO: 2 mL (1 mL top-ups)	Successful completion of the colonoscopy, defined as: - completion of the procedure - no requirement for rescue sedative - no requirement for > 5 doses of study medication (RMZ or pbo) within any 15-minute window, or no requirement for > 3 doses of midazolam within any 12-minute window	RMZ: 296 MDZ: 102 PBO: 60	ASA I – III patients undergoing colonoscopy	13 sites within the U.S.
<b>CNS7056-008 (NCT 02296892)</b>	Randomized, double-blind, active and saline placebo-controlled	RMZ: 5.0 mg (2.5 mg top-ups) IV MDZ: 1.75mg (1.0 mg top-ups) IV PBO: 2 mL (1 mL top-ups)	Successful completion of procedure, defined as: - completion of the procedure - no requirement for a rescue sedative - no requirement for > 5 doses of study medication (RMZ or pbo) within any 15-minute window, or no requirement for > 3 doses of midazolam within any 12-minute window	RMZ: 303 MDZ: 69 PBO: 59	ASA I – III patients undergoing bronchoscopy	15 sites within the U.S.
<b>CNS7056-015 (NCT 02532647)</b>	Randomized, double-blind, active and saline placebo-controlled	RMZ: 2.5 to 5.0 mg (1.25 to 2.5 mg top-ups) IV MDZ: 1.0 mg (0.5 mg top-ups) IV PBO: 1- 2 mL (0.5 -	Successful completion of the colonoscopy, defined as: - completion of the procedure - no requirement for rescue sedative - no requirement for > 5 doses	RMZ: 31 MDZ: 30 PBO: 16	ASA III – IV patients undergoing colonoscopy	6 sites within U.S. (2 sites did not treat any study patients)

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Study Identity	Study Design	Regimen and Route	Primary Efficacy Endpoints	No. of Patients Dosed	Study Population	No. and Location of Study Sites
		1 mL top-ups)	of study medication (RMZ or pbo) within any 15-minute window, or no requirement for > 3 doses of midazolam within any 12-minute window			
<b>Phase 2 Clinical Studies</b>						
<b>CNS7056-003 (NCT 00869440)</b>	Randomized, double-blind, dose-finding	RMZ: 0.1 mg/kg, 0.15 mg/kg, or 0.2 mg/kg MDZ: 0.0075 mg/kg	Successful completion of the procedure, defined as: <ul style="list-style-type: none"> <li>- MOAA/S <math>\leq</math> 4 on 3 consecutive measurements</li> <li>- completion of the endoscopy procedure</li> <li>- no requirement for rescue sedative</li> <li>- no manual or mechanical ventilation</li> </ul>	RMZ 0.1 mg/kg: 23 RMZ 0.15 mg/kg: 24 RMZ 0.2 mg/kg: 25 MDZ: 25	ASA I – II patients undergoing upper endoscopy	7 sites within the U.S.
<b>CNS7056-004 (NCT 01145222)</b>	Randomized, double-blind, parallel-group	RMZ: 8 mg initial dose, 3 mg top-up; 7 mg initial dose, 2 mg top-up; 5 mg initial dose, 3 mg top-up MDZ: 2.5 mg initial dose, 1 mg top-up	Successful completion of the procedure, defined as: <ul style="list-style-type: none"> <li>- MOAA/S <math>\leq</math> 4 on 3 consecutive measurements</li> <li>- completion of the endoscopy procedure</li> <li>- no requirement for rescue sedative</li> <li>- no manual or mechanical ventilation</li> </ul>	RMZ 8/3 mg: 40 RMZ 7/2 mg: 40 RMZ 5/3 mg: 40 MDZ: 41	ASA I – III patients undergoing colonoscopy	9 sites within the U.S.

RMZ: remimazolam; MDZ: midazolam; PBO: placebo; ASA: American Society of Anesthesiologists; MOAA/S: Modified Observer’s Assessment of Alertness and Sedation.

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**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.**  
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/s/  
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