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RESEARCH**

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
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Division/Office	ON / DAAP
Reviewer Name(s)	Renee Petit-Scott, M.D.
Review Completion Date	February 20, 2020
Established/Proper Name	Remimazolam
(Proposed) Trade Name	Byfavo
Applicant	Cosmo Technologies, Ltd. (Dublin, Ireland)
Dosage Form(s)	Solution
Applicant Proposed Dosing Regimen(s)	<p><u>Adult Patients:</u></p> <ul style="list-style-type: none"> • Administer an initial dose of Byfavo intravenously as a 5 mg (2 mL) push injection over a 1-minute time period. • If necessary, administer supplemental doses of 2.5 mg (1 mL) Byfavo over a 15-second time period. At least 2 minutes must have elapsed prior to the administration of any supplemental dose. <p><u>Debilitated Patients (ASA III-IV, at the discretion of the physician):</u></p> <ul style="list-style-type: none"> • 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. • 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.
Applicant Proposed Indication(s)/Population(s)	For the induction and maintenance of procedural sedation in adults.
Recommendation on Regulatory Action	Approval.
Recommended Indication(s)/Population(s) (if applicable)	For the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less.

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document

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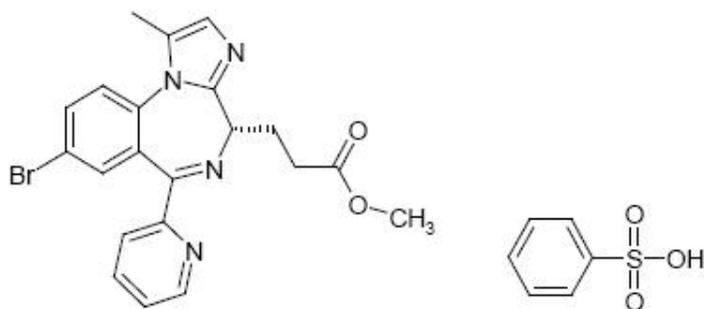
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Remimazolam, referred to as RMZ, CNS7056, or ONO-2745, is a new benzodiazepine developed for the induction and maintenance of procedural sedation. The Applicant has described 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 (refer to Figure 1) and the sedative properties of RMZ can be reversed with IV administration of flumazenil. The clinical development program conducted by the Applicant evaluated bolus dosing for procedural sedation and continuous IV infusion for maintenance of general anesthesia and ICU sedation (studies conducted outside the U.S. and not discussed in detail in this clinical review).

Figure 1. Remimazolam Besylate Salt



Source: Clinical Overview, p. 6 (PDF), Applicant's submission, NDA 212295.

RMZ is an ester-based drug that is hydrolyzed by carboxylesterase-1 (CES-1) primarily in the liver to the inactive carboxylic acid metabolite, CNS7054. RMZ appears to have a shorter time to onset and a shorter half-life compared to the other benzodiazepine medications commonly administered for procedural sedation. The Applicant states that these properties make RMZ 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 debilitated/chronically ill or elderly 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.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical development program conducted by the Applicant has demonstrated statistically significant and clinically meaningful differences in procedure success rates between RMZ and saline placebo when administered for sedation. The Phase 3 studies conducted by the Applicant evaluated RMZ-induced procedural sedation during diagnostic and therapeutic procedures that are representative of the most commonly performed procedures in adult patients. Specifically, colonoscopy and bronchoscopy are procedures commonly performed in an ambulatory setting, and while colonoscopy is not considered an overly painful procedure and can generally be performed under mild to moderate sedation, bronchoscopy is very stimulating and generally requires topical local anesthesia in addition to moderate to deep sedation. Evaluation of these two procedures, in addition to the evaluation in patients undergoing upper endoscopy in a Phase 2 study, has provided adequate evidence of efficacy to support an indication of induction and maintenance of procedural sedation. However, because the majority of procedures evaluated were completed in 30 minutes or less and because the procedure success rate decreased for procedures lasting longer than 30 minutes, the indication will include a recommended procedure duration.

The results of the Phase 3 studies supported the Applicant's claim that RMZ appears to be fast-acting and have a short duration of action, both considered beneficial characteristics of IV sedative agents. Times to fully alert and discharge were the secondary endpoints most clinically relevant and patients in the RMZ treatment group appeared to have shorter times to both compared to patients in the placebo treatment group. Other secondary endpoints, such as time to procedure start and time to peak sedation, are less informative based on the study design and use of midazolam rescue. Specifically, the placebo treatment group did not receive an IV sedative agent until several doses of placebo failed to induce adequate sedation. Therefore, several more minutes passed in this treatment group than in the RMZ treatment group prior to adequate sedation. This resulted in the times to procedure start and times to peak sedation being falsely prolonged in the placebo treatment group, thereby making the RMZ times appear significantly shorter.

Concomitant administration of fentanyl was permitted during the Phase 3 studies, with initial bolus doses ranging from 50 µg to 75 µg and total doses limited to 200 µg. The statistical reviewer, Dr. James Travis, conducted statistical analyses on the impact of fentanyl dosing on the reported efficacy results for the RMZ treatment group. Results from his analyses indicated that there was a relationship between increasing doses of fentanyl and decreased procedure success and increased procedure duration in studies CNS7056-006 and CNS7056-008. These results are not entirely surprising, however, given that more challenging procedures can require more analgesia, be less successful, and last longer.

Additionally, concomitant fentanyl administration appeared to impact the depth of sedation. There was a large proportion of patients in the RMZ treatment group who were under deep

sedation within a short period of time after RMZ administration. Because higher initial fentanyl doses were thought to play, protocol amendments reduced the initial bolus dose, which ultimately decreased the proportion of patients under deep sedation. Relevant concomitant fentanyl dosing information will be included in the drug product label.

In summary, the adequate and well-controlled studies conducted by the Applicant evaluated the sedative effect of RMZ during procedures representative of those most commonly performed in the U.S. The results of those studies support the proposed indication of induction and maintenance of procedural sedation for procedures lasting 30 minute or less. Bolus dosing was evaluated in the Phase 3 studies and will be described in the drug product label. Because not all procedures are amenable bolus dosing of sedative agents, the proposed dosing regimen will likely be a limitation to widespread use of RMZ during procedural sedation.

1.3. Benefit-Risk Assessment

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. As summarized in Section 2.2, Analysis of Current Treatment Options, 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 or in combination, and 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.

RMZ 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, did demonstrate a statistically significant difference in procedure success rates between the RMZ 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 primarily a safety study, so statistical testing was not conducted; however, the procedure success rates supported the findings of the other two studies. The evaluation of RMZ 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.

In addition to providing adequate sedation for procedures of relatively short duration, there are two main benefits of RMZ when administered for procedural sedation. First, it appears to be relatively fast-acting with a short half-life, suggesting procedures can be initiated quickly and

complete recovery appears rapid. Because the Phase 3 studies were designed with an open-label midazolam group, direct efficacy comparisons between RMZ and midazolam cannot be made; however, the placebo treatment group received midazolam rescue, such that times to fully alert and discharge were evaluated, and there were clinically significant differences between the RMZ and placebo treatment groups. Review of times to procedure start and peak sedation was not entirely informative given the time delay to midazolam rescue administration in the placebo treatment group. The second main benefit of RMZ over other non-benzodiazepine medications 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 RMZ.

As is commonly the case 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 RMZ 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. While not entirely surprising and also observed to varying degrees in the placebo and midazolam treatment groups, this information will be included in the final drug product labeling.

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

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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 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.

In summary, the totality of the data supports a favorable benefit:risk profile for the administration of RMZ for procedural sedation for procedures lasting 30 minutes or less. The efficacy data demonstrated a statistically significant difference in procedure success compared to saline placebo and evaluation of select secondary efficacy endpoints suggest additional benefits may be observed with administration of RMZ. The data suggest that the safety profile of RMZ is similar to 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.

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Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Many diagnostic and therapeutic procedures require moderate to deep sedation for successful completion, and can be performed at ambulatory surgery centers. • For painful procedures in which spontaneous ventilation is either desired or not problematic for successful completion of the procedure, avoidance of general anesthesia is possible with adequate sedation and analgesia. • Avoidance of general anesthesia decreases the associated adverse reactions, including but not limited to nausea, vomiting, and sore throat. • In cases of failed procedural sedation, administration of general anesthesia, with or without a secured airway, is most times employed for successful completion of the procedure. 	<p>While exposure to sedative agents may be low in the general population, patients undergoing diagnostic and therapeutic procedures have a high likelihood of receiving a sedative.</p> <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>
Current Treatment Options	<ul style="list-style-type: none"> • Intravenous sedative agents currently available for the induction and maintenance of procedural sedation include the following: <ul style="list-style-type: none"> - Benzodiazepine medications - Opioid analgesics, including remifentanyl - Ketamine - Propofol - Dexmedetomidine • Inhaled nitrous oxide is also used for procedural sedation, particularly in the dental setting, but is generally reserved for 	<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 clinicians with an additional medication for the induction and maintenance of procedural sedation, and while a final</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>anxiolysis during procedures causing minimal pain.</p> <ul style="list-style-type: none"> As previously mentioned, when sedation is not successful, administration of general anesthesia is an option if the administering provider has the required level of training. 	<p>determination has not been made, it is unlikely an anesthesia provider will be required for administration of RMZ. The absence of an anesthesia provider, however, will limit the ability to convert to general anesthesia, in the event RMZ does not induce or maintain adequate sedation, which may then result in delay or cancelation of procedures until such a provider becomes available.</p>
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> RMZ 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 rapid patient turnover. The times to fully alert and to discharge were shorter in patients treated with RMZ when compared to patients treated with placebo after colonoscopy and bronchoscopy. The sedative effects of RMZ 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. Renal impairment does not appear to affect the efficacy or safety profile of RMZ. Patient body mass index (BMI) does not appear to impact the efficacy or safety profile of RMZ, and given the obesity 	<p>Because the dosing of RMZ and midazolam is different, blinding during the Phase 3 studies would have been challenging, and the Applicant did not evaluate the safety and efficacy of RMZ compared to midazolam during procedural sedation. The data does suggest, however, that the time to onset and time to recovery from RMZ-induced sedation is shorter than what is commonly observed after midazolam-induced sedation. (b) (4)</p> <p>Clear advantages of RMZ include 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</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>epidemic in the U.S., this is a clear advantage over other lipophilic sedatives.</p> <ul style="list-style-type: none"> • RMZ can be safely administered with fentanyl in doses up to 200 µg, carefully titrated and depending on the clinical scenario, and comorbidities and age of the patient. 	<p>appropriate monitoring and availability of opioid antagonist medications.</p>
<p>Risk and Risk Management</p>	<ul style="list-style-type: none"> • 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. • The administering provider must be trained in monitoring, detection, and treatment of hemodynamic changes, including cardiac arrest, hypoventilation, airway obstruction, and apnea. A final determination had not been made at the time of completion of this clinical review, but it is unlikely an anesthesia provider will be required for administration of RMZ. • Concomitant fentanyl administration appeared to increase 	<p>Risks associated with administration of RMZ do not appear significantly different from the known risks associated with administration of other benzodiazepine medications. As mentioned, the Phase 3 studies did not evaluate, in a blinded manner, the safety profile of RMZ 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 RMZ.</p> <p>The incidence of clinically relevant vital sign changes and adverse events was not significantly different between treatment groups. There did appear to a higher incidence of hypertension in patients treated with RMZ, however, the majority of patients did not require treatment.</p> <p>Because administration of RMZ can cause respiratory</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>the duration of the procedure and occurrence of adverse events and decrease the procedure success rate. While this finding is not entirely unexpected clinically, it will be described in the drug product labeling along with prevention and mitigation strategies.</p> <ul style="list-style-type: none"> • 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. • RMZ like all benzodiazepines, carries the potential for recreational use and abuse. Because it is administered only in a healthcare facility and not prescribed for outpatient use, this risk most likely affects healthcare providers and facility staff. The Applicant conducted abuse potential studies and the results indicate the following: <ul style="list-style-type: none"> - Drug liking and the abuse potential of IV RMZ is similar to that of midazolam - RMZ has a low oral bioavailability, suggesting this route of abuse is unlikely - Intranasal administration, snorting, is painful and unlikely to be a commonly abused route of administration - When RMZ is co-administered with ethanol, the 	<p>depression, hypoventilation, airway obstruction, and apnea, administering providers and facilities must adhere to the ASA practice guidelines for moderate to deep sedation. Resuscitative medications, including flumazenil, and equipment must be immediately available when RMZ is administered. Additionally, administering 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, including chin lift, jaw thrust, insertion of oral and nasal airways, and supportive ventilation.</p> <p>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. Oral and nasal routes of abuse appear less likely based on limited desired response and irritation of the nasal mucosa. Concomitant administration with ethanol does appear to enhance the effects of RMZ.</p> <p>Limitations to widespread use of RMZ for procedural sedation include the need for bolus dosing and procedure duration of 30 minutes or less. It seems</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>observed sedation was enhanced compared to RMZ alone. Co-administration of oral RMZ and ethanol did not appear to result in predictable or reliable sedation, such that date-rape sexual assaults are not anticipated with this combination and route of administration.</p> <ul style="list-style-type: none"> • Hepatic impairment prolongs the half-life of RMZ, requiring careful titration of top-up doses. • 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. 	<p>likely that RMZ will be most used in gastroenterology clinics for patients undergoing upper endoscopy and colonoscopy.</p> <p>In conclusion, the Applicant’s clinical development program has provided adequate safety and efficacy data to support approval of remimazolam for the induction and maintenance of procedural sedation. Because this application received a clock extension based on additional reproductive and developmental toxicology data submitted in January and February 2020, the pharmacology-toxicology review team had not made a determination on the acceptability of the nonclinical assessment and the final regulatory recommendation.</p>

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input type="checkbox"/>	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	<input type="checkbox"/> Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	<input type="checkbox"/> Patient reported outcome (PRO)	
	<input type="checkbox"/> Observer reported outcome (ObsRO)	
	<input type="checkbox"/> Clinician reported outcome (ClinRO)	
	<input type="checkbox"/> Performance outcome (PerfO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
	<input type="checkbox"/> Input informed from participation in meetings with patient stakeholders	

	<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/>	Other: (Please specify)	
X		Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Sedation during a variety of diagnostic and therapeutic procedures provides comfort and pain relief for the patient and facilitates successful and efficient completion. Sedation also adds a layer to safety to procedures for three reasons. First, there is a dedicated nurse or anesthesia provider administering the sedation and monitoring breathing and the hemodynamic status of the patient. Second, sedated patients are less responsive during stimulating procedures and, therefore, less likely to suddenly move causing malposition of a biopsy forceps or scalpel. And third, sedation generally allows procedures to be completed more quickly, such that the time the patient is undergoing the procedure is less; i.e., MRI or CT imaging in sedated patients can be significantly shorter (compared to non-sedated patients) thereby reducing patient exposure to harmful radiation.

There are a wide variety of diagnostic and therapeutic procedures that require sedation. As indicated by the Applicant in the Clinical Information Amendment – Responses to Filing Review Issues Identified and MCC Agenda, dated 19 Nov. 2019, the most commonly performed procedures in the U.S. in 2018 included cataract extraction with intraocular lens insertion, tissue biopsy, colonoscopy ± biopsy, and drainage or injection of a joint. Sedative medications administered during such procedures are generally at the discretion of the administering provider or supervising physician, and are titrated to clinical effect.

Depths of sedation include minimal, moderate, and deep sedation followed by general anesthesia. The American Society of Anesthesiologists has practice guidelines for respiratory and hemodynamic monitoring and the required level of training of the administering provider or supervising physician. Minimal sedation, defined as anxiolysis, does not require constant hemodynamic monitoring, but level of consciousness should be assessed throughout the

sedation period. Moderate sedation, formerly known as conscious sedation, requires constant monitoring of level of consciousness, ventilation and oxygenation, hemodynamic monitoring, and availability of a designated person to monitor the patient throughout the procedure, which should not be the clinician performing the procedure. Deep sedation, defined purposeful response to a repeated painful stimulus, requires the same level of monitoring as required during administration of moderate sedation, and in addition, the administering provider must be able to provide assistance for maintenance of a patent airway, as spontaneous ventilation may be impaired. RMZ appears to induce and maintain moderate to deep sedation, by bolus dose administration, for procedures lasting 30 minutes or less.

2.2. Analysis of Current Treatment Options

Procedural sedation can be achieved via a variety of medications, administered as monotherapy or in combination, administered via a variety of dosing regimens, either bolus dosing or continuous intravenous (IV) infusion. The determination of which medication(s) to use for induction and maintenance of procedural sedation is at the discretion of the administering provider, but generally involves consideration of the following four factors.

- Patient health status –underlying medical conditions and body habitus influence the choice of sedative agent probably more than any other factor
- Procedure performed – technical difficulty and risk of the procedure, and the impact of patient movement during the procedure
- Location of procedure performed – the medical facility, and the location within the medical facility, where the procedure is being performed and availability of immediate assistance in an emergent situation
- Anticipated adverse outcomes – anticipating adverse outcomes and complications will influence the choice of sedative agent

Cosmo Technologies is seeking approval of remimazolam for the induction and maintenance of procedural sedation in adults. The following table summarizes the medications currently available for procedural sedation in adult patients.

Table 1. Summary of Medications Administered for Procedural Sedation

Product Name	Relevant Indication	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
Midazolam	Procedural sedation	IV, IM, PO	Rapid onset/offset of action	Well-tolerated; titrated to clinical effect
Dexmedetomidine	Procedural sedation	IV - continuous infusion	Rapid onset/offset of action; minimal respiratory depression	Bradycardia; cardiac Arrhythmias; hypotension
Propofol	Procedural	IV – bolus	Rapid onset/offset	Burning sensation with

Product Name	Relevant Indication	Route of Administration	Efficacy Information	Important Safety and Tolerability Issues
	sedation	dosing or continuous infusion	of action; reduced incidence of post-operative nausea and vomiting	administration; respiratory depression and apnea common
Ketamine	Sole anesthetic for diagnostic and surgical procedures	IV - bolus dosing or continuous infusion	Analgesic properties; cardiovascular and respiratory stability; airway reflexes mostly maintained	Dysphoric adverse reactions; salivation; nystagmus

IV: intravenous; IM: intramuscular; PO: oral

Source: Reviewer.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

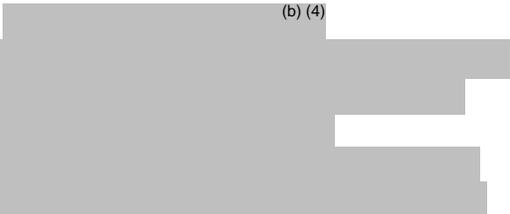
Remimazolam has not been marketed anywhere in the world. Benzodiazepines have a long history of clinical use for anxiolysis, amnesia, muscle relaxation, and procedural sedation.

3.2. Summary of Pre-submission/Submission Regulatory Activity

Remimazolam was originally developed at GlaxoSmithKline as faster-acting version of midazolam, based on information gained during the development of remifentanyl, an IV opioid with 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.

Table 2. 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	Clinical issues discussed included the following: <ul style="list-style-type: none"> Evaluated procedures must be generalizable to support

Meeting / Communication / Date	Event / Key Clinical Issues
	<p>a broad procedural sedation indication</p> <ul style="list-style-type: none"> • Phase 2b study in patients undergoing colonoscopy (b) (4)  • Non-GI procedures (i.e., bronchoscopy) should be considered for evaluation given the likelihood of broad post-market use •  (b) (4) •  •  • Required subject-exposures for adequate safety database • Clarification regarding the information needed to support dosing in patients with hepatic and renal impairment • Acceptability of proposed pediatric deferral (b) (4) • The impact of RMZ and concomitant opioid dosing on ventilatory drive needs to be evaluated • A thorough QT evaluation is needed • The abuse potential of RMZ needs to be evaluated • The proposal  (b) (4)
December 16, 2013 / Initial Pediatric Study Plan submitted	Written feedback in the form of a tracked-changes document was sent to the Sponsor.
Advice Letter regarding EOP2 meeting / Jan. 12, 2014	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).
Agreed iPSP submitted / June 17, 2014 Initial agreement / July 18, 2014	No additional advice provided.

Meeting / Communication / Date	Event / Key Clinical Issues
<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"> • Advice for evaluated procedures and need for blinded control in the Phase 3 studies • Open-label midazolam [REDACTED] (b) (4) • Studies in colonoscopy and bronchoscopy may not provide supportive data for broad procedural sedation indication • Inclusion of adequate number of ASA-PS III and IV patients • Clarification of permitted rescue medication and fentanyl dosing • 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) • Proposed midazolam dosing exceeded label recommendations • Normal saline as placebo control • Per ICH guidelines, 1500 subject exposures required for safety database • Inclusion of foreign safety data • IV fluid administration clarification • Recommended vital sign monitoring • Adverse event definitions and grading clarification • Stopping criteria clarification <p>Recommendations for SAP included the following:</p> <ul style="list-style-type: none"> • ITT population should include all patients randomized • Hierarchical testing is appropriate for multiple secondary efficacy endpoints
<p>Advice Letter / Jan. 26, 2015</p>	<p>Advice provided regarding proposed clinical and nonclinical abuse potential studies, per recommendations from the Controlled Substance Staff.</p>
<p>Advice Letter / April 6, 2015</p>	<p>Clinical issues included the following:</p> <ul style="list-style-type: none"> • Evaluated procedures must be of adequate intensity and duration to support a broad procedural sedation indication • An open-label study in ASA-PS IV patients will not provide adequate safety information • An adequate number of patients ≥ 60 years of age is required

Meeting / Communication / Date	Event / Key Clinical Issues
	<ul style="list-style-type: none"> • Clarification of rescue medication and the meaning of “any 15-minute window” • Open-label midazolam [REDACTED] (b) (4) • RMZ administration via continuous IV infusion is recommended, as bolus dosing has clinical limitations • Ventilatory drive needs to be evaluated with concomitant opioid administration • Adequate safety follow-up for all discontinued patients • Laboratory assessments required prior to facility discharge <p>Recommendations regarding vital sign monitoring:</p> <ul style="list-style-type: none"> • Capture all changes in continuously monitored vital signs, regardless of meeting the criteria of adverse events • Include mean arterial pressure monitoring • Record vital signs prior and following each dose of fentanyl <p>Recommendations regarding adverse events:</p> <ul style="list-style-type: none"> • Clarify adverse event definitions and causality relationships • Clarify hypertension, hypotension, and hypoxia definitions • Incorporate adverse event stopping criteria into the Phase 3 protocols
Advice Letter / June 8, 2015	<p>Clinical issues included the following:</p> <ul style="list-style-type: none"> • Recommended safety-based subject stopping criteria • Clarification of which adverse events and their relatedness to study drug will be forwarded to the DMC chair • Nadirs of continuously monitored vital signs must be captured, regardless if they meet the criteria of an adverse event • Clarification of exclusion criteria
Written Response, Type C Meeting / Nov. 21, 2016 and Type C Meeting, Guidance / Nov. 16, 2017	<p>Clinical and nonclinical abuse potential program for RMZ discussed.</p>
Type B Meeting, Pre-NDA / July 12, 2018	<p>Clinical issues discussed included the following:</p> <ul style="list-style-type: none"> • Phase 3 studies appear to provide adequate efficacy data to support NDA filing • Pooled efficacy and safety analyses are not appropriate

Meeting / Communication / Date	Event / Key Clinical Issues
	<p>for different patient populations and procedures performed</p> <ul style="list-style-type: none"> • Safety database appears adequate for NDA filing • Rationale for applicability of foreign data to U.S. population appears acceptable • Patient narratives and CRFs for all patients who died or discontinued due to an adverse event, regardless of causality, is acceptable • (b) (4) will not be permitted in labeling
NDA submitted / April 5, 2019	NDA received
NDA 212295 filed / June 17, 2019	<p>Clinical issues identified included the following:</p> <ul style="list-style-type: none"> • Acceptability of safety data pooling in the ISS • Duration of procedures evaluated and implications in final labeling language • Level of training required for administering provider • Lack of maximum dose provided
Mid-Cycle Communication Meeting / Nov. 22, 2019	<p>Clinical issues discussed included the following:</p> <ul style="list-style-type: none"> • The indicated procedures for remimazolam sedation based on duration • The inconvenience of bolus dosing, particularly for longer procedures • Level of training required for administering provider.
Late Cycle Communication Meeting / Feb. 27, 2020	<p>Clinical issues discussed included the following:</p> <ul style="list-style-type: none"> • Recommended procedural sedation duration of 30 minutes or less based on Phase 3 study data • Required airway training for administering provider.

3.3. Foreign Regulatory Actions and Marketing History

Remimazolam is not marketed anywhere in the world. Several clinical studies were conducted outside the U.S. and there are no known foreign regulatory actions.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

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-

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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, and voluntary action indicated, 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.

4.2. Product Quality

The Office of Product Quality has not identified any issues that would prevent approval.

4.3. Clinical Microbiology

RMZ is not an antimicrobial agent, therefore, clinical microbiology information was not submitted in the NDA.

4.4. Nonclinical Pharmacology/Toxicology

The pharmacology-toxicology review team recommended a three-month clock extension for this application based on additional reproductive and developmental toxicology data submitted in January and February 2020. There was concern that results from the rat studies were inadequate to fully characterize the toxicology profile of the parent compound and major metabolite due to rapid metabolism, resulting in limited exposure margins. Therefore, a safe human exposure limit had not been established. The late-cycle submissions, received in

January and February 2020, included additional information regarding the calculation of exposure margins. Specifically, the Applicant stated that when using the free drug concentration, versus, protein-bound concentration, the exposure margins are acceptable. The team is currently reviewing this issue, but appears to agree with the Applicant.

There were two additional pharmacology-toxicology review issues. First, the adequacy of the embryo-fetal development studies and the lack of an assessment of learning/behavior/memory development and reproductive parameters, such as fertility. And second, the adequacy of the safety qualification for the dextran 40 excipient. If the Applicant chooses to rely on information in the published literature to support the safety profile of dextran 40, this application may then be approved under the 505(b)(2) regulatory pathway. These discussions were on-going at the time of completion of this clinical review.

From a clinical perspective, the reproductive and developmental toxicology data are needed for approval of this product and to support labeling based on the potential administration of RMZ to pregnant patients undergoing diagnostic or therapeutic procedures. Because the pharmacokinetic and pharmacodynamic profile of RMZ indicates that it has a shorter time to onset and a faster recovery, there is a possibility that it may be used more commonly than other benzodiazepines in pregnant patients. Therefore, I agreed with the clock extension and will support the final recommendation of the pharmacology-toxicology review team. For additional information regarding the pharmacology-toxicology team's conclusions, refer to the review completed by Dr. Katie Sokolowski.

4.5. Clinical Pharmacology

When administered IV, RMZ is metabolized by tissue carboxylesterase (CES, primarily type 1A) to produce the primary inactive metabolite CNS7054 (also referred to as ONO-IN-252). Metabolism is rapid and very little of the parent drug is recovered from plasma or urine following IV administration. As determined in Study ONO-2745-01 conducted in healthy volunteers, at least 80% of administered RMZ is excreted as CNS7054. RMZ has a mean distribution half-life ($t_{1/2\alpha}$) between 0.5 and 2 minutes and is rapidly cleared from plasma (clearance rate 54-75 L/h).

Study CNS7056-012 demonstrated that measured PK parameters for RMZ are not affected by renal impairment, but the results from Study ONO-2745IVU007 demonstrated that half-life, exposure, and recovery from sedation are all prolonged with increasing severity of hepatic impairment. Specifically, the half-life of RMZ in healthy subjects was 42.9 minutes, compared to 59.2 and 105 minutes in patients with moderate and severe hepatic impairment, respectively. The clinical pharmacology review team, however, does not recommend dose adjustment based on the time to onset of action; i.e., a lower dose may adversely impact

efficacy. Additional monitoring may be recommended in patients with liver impairment, but final drug labeling language has not been determined.

Data from 11 clinical trials conducted by the Applicant were pooled for population pharmacokinetic analyses. The final population PK model was a three-compartment model and the results of the analyses indicated the following:

- Clearance was 9.7% higher in females,
- Clearance was 13% lower and the volume of distribution at steady state was 16% lower in African Americans compared to Caucasians or Asians
- Age, ASA-PS classification, body mass index (BMI), estimated glomerular filtration rate, and creatinine clearance had no effect on the PK of RMZ. Furthermore, results from several population PK models and analyses demonstrated that body weight and BMI do not significantly impact the reported PK of RMZ; therefore, the decision was made to switch from the weight-adjusted dosing used in early clinical studies to fixed dosing bolus dosing for the Phase 3 studies evaluating procedural sedation. Additionally, the pharmacodynamic response, observed sedation, was not significantly altered with increasing body weight.

Mechanism of Action

RMZ binds to gamma amino butyric acid Type A (GABA_A) receptors located within the central nervous system. It does not appear to preferentially bind one subtype more than others. The metabolite, CNS7054, has an approximately 300-fold lower affinity for the receptor such that it likely does not contribute to the sedative properties to a clinically relevant degree. The Applicant states that there does not appear to be any other pharmacological action of either RMZ or the metabolite.

The resulting sedation after RMZ administration is reportedly observed within one to two minutes of administration, with depth and duration of sedation being dose-dependent. The recovery from sedation appears quicker than that observed after administration of midazolam, the other benzodiazepine most commonly administered for induction and maintenance of procedural sedation. The Applicant evaluated the reversal of RMZ-induced sedation after administration of flumazenil. In Study CNS7056-002 (Part A), patients received a single RMZ 0.25 mg/kg bolus and time to fully alert was measured. In patients who received flumazenil, time to fully alert was observed within 1.8 minutes compared to 16.8 minutes after placebo administration. Re-sedation was not observed.

5. Sources of Clinical Data and Review Strategy

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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. The following table summarizes the studies used to support the proposed indication for RMZ. The Phase 3 studies will be primarily discussed in this clinical review.

5.1. Table of Clinical Studies

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Table 3. 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
Phase 3 Clinical Studies						
CNS7056-006 (NCT 02290873)	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.
CNS7056-008 (NCT 02296892)	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.
CNS7056-015 (NCT 02532647)	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			
Phase 2 Clinical Studies						
CNS7056-003 (NCT 00869440)	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: - MOAA/S \leq 4 on 3 consecutive measurements - completion of the endoscopy procedure - no requirement for rescue sedative - no manual or mechanical ventilation	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.
CNS7056-004 (NCT 01145222)	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: - MOAA/S \leq 4 on 3 consecutive measurements - completion of the endoscopy procedure - no requirement for rescue sedative - no manual or mechanical ventilation	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.

5.2. Review Strategy

The Applicant's clinical development program, with emphasis on the Phase 3 studies conducted in patients undergoing procedural sedation, was reviewed for this 505(b)(1) marketing application. The Applicant is not relying on information from other drug products or published literature.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Phase III Study Evaluating the Efficacy and Safety of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in Patients Undergoing Colonoscopy (Study CNS7056-006)

6.1.1. Study Design

Overview and Objective

This was a prospective, double-blind, randomized, placebo-controlled, multi-center, study comparing RMZ to placebo (placebo) in patients undergoing a colonoscopy for diagnostic or therapeutic reasons. Because the additional midazolam arm was open-label, the study is not considered active-controlled.

The study objectives were as follows:

- Primary objective – to establish the superiority of RMZ compared to placebo in inducing and maintaining suitable sedation levels for patients undergoing colonoscopy and in comparison to an open-label arm with midazolam in combination with fentanyl as determined by sedation success
- Secondary objectives –
 - time to start of procedure after administration of the first dose of study medication
 - time to peak sedation after administration of the first dose of study medication, assessed using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score, as follows:
 - 5 - Responds readily to name spoken in normal tone (alert)
 - 4 - Lethargic response to name spoken in normal tone
 - 3 - Responds only after name is called loudly and/or repeatedly
 - 2 - Responds only after mild prodding or shaking
 - 1 - Responds only after painful trapezius squeeze
 - 0 - Does not respond to painful trapezius squeeze

- times to ready for discharge after the end of colonoscopy procedure (colonoscope out) and after the last injection of study drug (defined as ability to walk unassisted)
- times to fully alert (time to first of 3 consecutive MOAA/S scores of 5 after the end of colonoscopy procedure [colonoscope out] and after the last injection of study drug)
- MOAA/S scores by time point
- recall of the procedure by the Brice questionnaire administered when full alertness was regained and on Day 4
- changes to the patient's cognitive function assessed by the Hopkins Verbal Learning Test - Revised (HVLRT™) administered before study medication administration and after the fully alert criteria had been achieved
- 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
- ready to discharge score 30, 60 and 90 minutes post injection of the initial dose
- drowsiness visual analogue scale (VAS) to assess for signs of re-sedation
- requirement for flumazenil during the procedure.
- patient's self-evaluation of "back-to-normal" after the procedure.
- pain on injection at application of study medication.
- population pharmacokinetics in a subgroup of patients (a minimum of 50 patients below 65 years of age, and 15 patients aged 65-74).

Trial Design

This study was a prospective, double-blind, randomized, placebo and active controlled, multi-center, parallel group study comparing remimazolam to placebo, with an additional open-label arm for midazolam. Patients in all treatment groups were administered fentanyl 75 µg (or 50 µg per Protocol Amendment 4) for analgesia immediately prior to administration of study drug. Reduced dosing was used for elderly or debilitated/chronically ill patients. Supplemental doses of fentanyl 25 µg could be administered for analgesia, to a maximum dose of 200 µg. Investigators assessed the analgesic effect of fentanyl over 5 to 10 minutes. Investigators were to administer fentanyl for analgesia only. If additional sedation was needed, supplemental doses of study medication or midazolam were administered.

RMZ or Placebo (Study Drug Treatments) Dose Administration

An initial dose of 2 mL blinded study medication was administered manually by IV injection over one minute. Supplemental doses of 1 mL of study medication were administered by slow IV injection (over approximately 15 seconds), at least 2 minutes apart, if initial sedation was insufficient, defined as a score of greater than three on the MOAA/S. If sedation was still inadequate to begin the procedure after the initial dose and a maximum of four additional

doses of study medication within a 15-minute period, the patient was considered a treatment failure and midazolam rescue sedative medication was administered at the discretion of the investigator.

If sedation was sufficient to allow the colonoscopy to begin, subsequent doses of 1 mL could be administered to maintain an adequate sedation level ($MOAA/S \leq 4$). If the $MOAA/S$ was ≥ 4 , additional 1 mL doses, over 15 seconds, could be administered, at least 2 minutes apart, to maintain or again reach an adequate sedation level. Two or more additional minutes was allowed to fully evaluate the sedative effect. The overall number of double-blinded study medication doses was not limited as long as not more than five doses were administered in any 15-minute window. During the procedure, patients were considered treatment failures if adequate sedation ($MOAA/S \leq 4$) could not be maintained despite five doses of RMZ or placebo within any 15-minute period. Midazolam rescue sedative medication was then administered at the discretion of the investigator, to allow for completion of the procedure.

Midazolam Open-Label Treatment Arm

Midazolam was the only rescue sedative medication permitted during the study. An initial dose was administered by IV injection over 2 minutes. Healthy adults < 60 years of age received an initial dose of 1.75 mg. For adults ≥ 60 years, or debilitated/chronically ill, the initial dose was 1 mg. If there was insufficient sedation to begin the procedure after the initial dose of midazolam ($MOAA/S > 3$), a supplemental dose could be administered over at least 2 minutes and after at least 2 minutes since the end of the last administered dose and after $MOAA/S$ assessment. Healthy adults < 60 years of age received doses of 1 mg. In the case of adults ≥ 60 years of age, or debilitated/chronically ill, the dose was 0.5 mg. If initial sedation was still insufficient, 1 further supplementary dose of midazolam could be given, at least 2 minutes apart. In the case of healthy adults < 60 years, the dose was 1 mL containing 1.0 mg. In the case of adults ≥ 60 years, or debilitated/chronically ill patients, the dose was 0.5 mL containing 0.5 mg.

If there was still inadequate sedation to begin the procedure after the initial dose and a maximum of two additional doses within a 12-minute period, the patient was considered a treatment failure and received midazolam rescue sedative medication at the discretion of the investigator to start the procedure. If sedation from open-label midazolam was sufficient to allow colonoscopy to begin, subsequent doses could be administered to maintain an adequate sedation level ($MOAA/S \leq 4$). If the $MOAA/S$ was ≥ 4 , additional doses could be administered, at least two minutes apart, to maintain, or again reach, an adequate sedation level. The number of midazolam doses was limited such that not more than three doses were administered in any 12-minute window. If more than three doses within any 12-minute window was needed to obtain or maintain adequate sedation for the colonoscopy, the patient was considered a treatment failure. For healthy adults < 60 years of age, the dose of midazolam was 1.0 mg and for adults ≥ 60 years, or debilitated/chronically ill, the dose was 0.5

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mg. Supplemental midazolam doses were administered over at least two minutes, and at least two minutes were permitted to evaluate the sedative effect.

The schedule of assessments for this study is summarized in the following table.

Table 4. Schedule of Study Assessments

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	Day -21 to Day -1	Day 0	Day 1	Day 4 (+3/-1 days)
	Screening	Preparation	Treatment Day	Follow-up
Informed Consent	X	Bowel preparation as local standard	See next schedule (Table 5)	
Eligibility criteria/medical and medication history/demographics	X			
Physical examination ^a	X			X
ASA-PS Score assessment	X			
Clinical Laboratory Samples ^b	X			X
Serum human chorionic gonadotrophin (females) ^c	X			
Urinary Drugs of Abuse screen	X			
Blood ethanol screen	X			
Hemodynamics ^d	X			X
Height and BMI	X			
Weight	X			
Supine respiratory rate				X
Body temperature	X			X
12-lead ECG	X			
Bowel preparation				
Fast ^e				
Fentanyl administration				
Administration of study medication				
3-lead ECG telemetry				
Pulse oximetry monitoring/recording				
Respiratory rate recordings				
MOAA/S scale score monitoring/recording				
Pain VAS				
HTLV-R				
Brice questionnaire				X
Airway management				
Assessment of	X	X		

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	Day -21 to Day -1	Day 0	Day 1	Day 4 (+3/-1 days)
	Screening	Preparation	Treatment Day	Follow-up
adverse events				
Assessment of concomitant medication	X			X

Abbreviations: ASA-PS = American Society of Anesthesiologists – physical status; BMI = body mass index; ECG = electrocardiogram; HTLV-R = Hopkins Verbal Learning Test – Revised; MOAA/S = Modified Observer's Assessment of Alertness/Sedation; VAS = visual analog scale

Note: Dosing day procedures are described in Table 5.

^a Screening physical examination included rectal examination, and American Society of Anesthesiologists – physical status score.

^b Hematology, serum chemistry.

^c For women of non-child-bearing potential a serum test for follicle stimulating hormone was performed.

^d Supine heart rate and systolic and diastolic blood pressure.

^e Fast to begin from midnight of the day before dosing (no food).

Source: Study CNS7056-006 Report Body, pp. 47-48 (PDF), Applicant's submission, NDA 212295.

Assessments performed on study day 1 are summarized in the following table.

Table 5. Study Day 1 Assessments

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Dosing Day (Day 1)																		
Procedures	Pre-dose				Dosing of study medication ^a	Post-dose												
	within 3 hr	within 30 min.	within 15 min.	1min. pre-dose		1 min.	1.5 min.	2 min.	2.5 min.	3 min.	5 min.	10 min.	Every 5 minutes until fully alert					
Review inclusion & exclusion criteria	x																	
Medical & medication histories	x																	
Adverse events	x																	
Concomitant medication	x																	
Physical examination	x (B)																	
Weight	x (B)																	
Body temperature	x (B)	x									x (post pro-cedure)			x (at fully alert)		x (at discharge)		
Clinical laboratory tests	x (B)															x (at discharge)		
3 lead ECG			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx		
3 lead ECG documentation in eCRF ^a			x	x				x			x	x	x	x	x	x		
12-lead ECG	x (B)										x		x ^f		x ^f	x ^f		
Urine pregnancy test	x																	
Urine drug-of-abuse test	x																	
Ethanol saliva test	x																	
Randomization	x																	
HVLT-R TM	Learnin g	(within 45 min)																
Hemodynamic parameters (HR, BP) ^{e,h}	x	x	x (B)	x				x			x	x	x	x	x	x		
Normal saline		xx	xx	xx	xx up to 1,000 mL administered, if fluid status allowed	xx	xx	xx	xx	xx	xx	xx	xx	until end of colonoscopy procedure				

Dosing Day (Day 1)																			
Procedures	Pre-dose				Dosing of study medication ^a	Post-dose													
	within 3 hr	within 30 min.	within 15 min.	1min. pre-dose		1 min.	1.5 min.	2 min.	2.5 min.	3 min.	5 min.	10 min.	Every 5 minutes until fully alert						
MOAA/S ^b			x (B)			x	x	x	x	every minute until fully alert, then every 5 min until ready for discharge, then every 10 min until actual discharge									
Respiratory rate ^b			x (B)	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx		
RR (document in eCRF)			x (B)	x				x			x	x	x	x	x	x			
SpO ₂ ^c (pulse oximetry)			x (B)	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx			
SpO ₂ ^{e,h} (documentation in eCRF)			x (B)	x				x			x	x	x	x	x	x			
Airway management assessment			x																
Supplemental oxygen (nasal prongs)			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx			
Fentanyl					x	Supplemental doses q 5-10 min until adequate analgesia or 200 µg maximum dose													
Pain on injection	Learn-ing				x or as soon as possible														
Drowsiness VAS ^d				x			x				x	x	15	25	35	45	60		

Abbreviations: ASA-PS = American Society of Anesthesiologists – physical status; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; eCRF = electronic case report form; HR = heart rate; HVLV-R = Hopkins Verbal Learning Test – Revised; MOAA/S = Modified Observer's Assessment of Alertness/Sedation; SpO₂ = peripheral capillary oxygen saturation VAS = visual analog scale

Key: (B) = Baseline values; x = Single action; xx = Continuous action.

^a Study medication: Loading dose of randomized study drug start defines t=0, supplemental doses as per protocol.

^b Colonoscopy started at sufficient sedation (MOAA/S ≤3), duration as necessary (MOAA/S ≤4), at the discretion of the investigator.

^c 90 minute value only if patient was still sedated.

^d If possible by patient.

^e Documented by running a strip.

^f After first dose, 5 minutes after dosing and every 10 minutes until the end of the procedure if possible, and also 5 minutes after the end of the procedure.

^g In addition to the times specified above, blood pressure, heart rate and peripheral capillary oxygen saturation were recorded immediately prior to, and 2 minutes after each additional dose of fentanyl

^h Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate and peripheral capillary oxygen saturation) were recorded when an adverse event with a respiratory or cardiovascular focus was observed.

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Source: Study CNS7056-006 Report Body, pp. 48-49 (PDF), Applicant's submission, NDA 212295.

Eligibility Criteria

Pertinent inclusion criteria included the following:

- adult patients ≥ 18 years of age
- ASA physical status III or less
- BMI ≤ 40 kg/m²
- non-pregnant, non-lactating females

Pertinent exclusion criteria included the following:

- known sensitivity to benzodiazepines, flumazenil, opioids, naloxone, or a medical condition such that the use of these medications is contraindicated
- chronic benzodiazepine or opioid use for any indication
- positive drug or ethanol screening at baseline, or history of abuse within past two years

Study Endpoints

The primary efficacy endpoint was the successful completion of the colonoscopy, defined as follows:

- completion of the colonoscopy procedure, AND
- no requirement for a rescue sedative medication (midazolam), AND
- no requirement for more than five doses of study medication (RMZ or placebo) within any 15-minute window, or no requirement for more than three doses of midazolam within any 12-minute window in the open-label arm

Key secondary efficacy endpoints included the following:

- time to start of procedure
- time to peak sedation
- ready for discharge time
 - from end of colonoscopy
 - from last dose of sedative medication administration
- time to fully alert
 - from end of colonoscopy
 - from last dose of sedative medication administration

Additional efficacy evaluations included MOAA/S by time point, procedure recall on day of procedure and Day 4, changes in cognitive function, readiness for discharge score at 30, 60, 90 minutes post-injection of initial dose, drowsiness VAS, flumazenil administration, and patient assessment of "back-to-normal".

Safety assessments included the following:

- Physical exam
- Laboratory assessments (hematology and chemistry)
- Vital signs (heart rate, blood pressure, respiratory rate, oxygen saturation, and temperature)
- 12-lead ECG at screening, within three hours pre-dose, after the first dose, five minutes after the start of initial dosing and every 10 minutes until the end of the procedure and five minutes after the end of the procedure, and when indicated
- 3-lead ECG was monitored continuously during the procedure until fully alert
- Adverse events
 - with emphasis on cardiorespiratory events (hypoxia, bradycardia, hypotension, hypertension, respiratory depression) and prolonged sedation
 - vital signs considered adverse events were defined as follows:
 - Bradycardia – HR < 40 bpm or a decrease of 20% or more from baseline for 30 seconds
 - Hypertension – increase in systolic blood pressure (SBP) to ≥ 180 mmHg or in diastolic blood pressure (DBP) to ≥ 100 mmHg or an increase in either SBP or DBP 20% or more from baseline or medical intervention required
 - Hypotension – decrease in SBP ≤ 80 mmHg or in DBP ≤ 40 mmHg or a fall in SBP or DBP 20% or more from baseline or medical intervention required
 - Respiratory rate decreased – < 8 breaths per minute
 - Hypoxia – oxygen saturation < 90% for one minute or longer or any decrease requiring medical intervention
 - prolonged sedation (MOAA/S ≤ 4 for 60 minutes or longer after the last dose of study drug administration) including the need for flumazenil
 - with emphasis on effects associated with abuse (euphoria-related terms, impaired attention, cognition, mood, psychomotor events)
- Interventions
 - Airway interventions
 - IV fluid and medication administration
- Pain on injection of study medication

Statistical Analysis Plan

Analysis Populations

Five analysis populations were defined:

1. Safety Population consisted of all patients randomized and who received any amount of study drug.

2. Intent-to-Treat (ITT) Population included all patients who were randomized.
3. Modified ITT Population included all patients in the ITT Population who received at least one complete dose of study drug.
4. Per Protocol (PP) Population included all patients from the ITT population who received randomized treatment according to the assignment and schedule, *and* did not have any major protocol deviations.
5. Safety Nellcor Population consisted of all patients in the Safety Population who had usable Nellcor data and were analyzed as treated. Note, these populations were defined after completion of the main study SAP.
 - Nellcor data consisted of vital sign data captured during continuous monitoring of heart rate, respiratory rate, and oxygen saturation. The usable data captured for these three vital signs were defined as three separate populations.
 - The usable data required recordings from the time of first dose of any study drug (including fentanyl, RMZ, placebo, or midazolam) administration until fully alert. Usable data were defined as follows:
 - no significant delay between the start of study drug administration and the start of Nellcor measurement (significant delay considered ≥ 2 minutes)
 - at least 90% of the observation time has valid Nellcor data for each parameter (values outside the acceptability ranges were considered missing)
 - The captured Nellcor data was analyzed for any episodes of bradycardia or hypoxia regardless of whether they were included as adverse events
 - Usable Nellcor data was defined as having no significant delay (> 2 minutes) between the start of study drug administration and the start of the Nellcor measurement and $\geq 90\%$ of the observation time had valid data for every parameter.

The primary efficacy analysis evaluated the success rates of RMZ-treated patients with pbo-treated patients, using the Cochran-Mantel-Haenszel test to account for the actual fentanyl use in the final analysis. Descriptive testing was performed on the secondary efficacy endpoints. Additional analyses were performed to assess the effect of fentanyl administration on procedural success.

Protocol Amendments

A total of four protocol amendments were implemented during conduct of this study. They are briefly described below.

Amendment 1 (March 5, 2015) – allowed principal investigators to reduce the fentanyl dose for

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elderly and debilitated/chronically ill patients. 12-lead ECG monitoring was implemented, per FDA request.

Amendment 2 (April 24, 2015) – stratification of elderly patients, documentation of all bradycardia, determination of heart rate and pulse oximetry low values, calculation of mean arterial pressure, and regular Data Monitoring Committee (DMC) meetings. Adverse event relationship to study drug was modified to include additional categories of certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable.

Amendment 3 (July 10, 2015) – the determination of respiratory rate low, use of continuous heart rate, respiratory rate, and oxygen saturation monitoring by Nellcor, non-adverse event episodes of bradycardia and hypoxia, additional stopping criteria, serious adverse events to be reported to the DMC, and clarification of vital sign documentation.

Amendment 4 (February 29, 2016) – removed a planned PK assessment in patients ≥ 75 years of age. After a DMC meeting, the initial fentanyl dose was reduced to 50 μg in elderly or debilitated/chronically ill patients. Clarification for fentanyl dosing for analgesia and sedative administration for sedation.

6.1.2. Study Results

Compliance with Good Clinical Practices

The following statement was included on the title page of the study.

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

I have no concerns regarding the validity of this statement.

Financial Disclosure

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.

Patient Disposition

A total to 461 patients were randomized in a 30:6:10 ratio, with 458 (99%) patients receiving

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treatment. Three randomized patients discontinued on the day of treatment due to Nellcor monitoring error, additional procedure added, and protocol violation that included use of prohibited medication. Patient disposition in this study is summarized in the following table.

Table 6. Patient Disposition (Safety Population)

Number of Patients	Remimazolam N=296 n (%)	Placebo N=60 n (%)	Midazolam N=102 n (%)	TOTAL N=458 n (%)
Informed Consent Given	296 (100.0%)	60 (100.0%)	102 (100.0%)	458 (100.0%)
Randomized	296 (100.0%)	60 (100.0%)	102 (100.0%)	458 (100.0%)
Treated (Fentanyl or IMP)	296 (100.0%)	60 (100.0%)	102 (100.0%)	458 (100.0%)
Completed Study Treatment Period	296 (100.0%)	59 (98.3%)	101 (99.0%)	456 (99.6%)
Completed Follow-up Visit	296 (100.0%)	59 (98.3%)	101 (99.0%)	456 (99.6%)
Early Termination (Withdrawals)	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)
Reasons for Withdrawals:				
Withdrawal by Patient	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)

Source: [Section 14.1, Table 14.1.2.1](#).

IMP = investigational medicinal product; N = number of patients; n = number of observations

Source: Study CNS7056-006 Report Body, p. 72 (PDF), Applicant's submission, NDA 211295.

Two patients discontinued the study prior to completion of all follow-up evaluations. The blind was not broken for any patient treated in this study.

Protocol Violations/Deviations

The following table provides a summary of the protocol deviations that resulted in exclusion of the patient data from the PP data set.

Table 7. Protocol Deviations (Safety Population)

Severity	Category	Remimazolam	Placebo	Midazolam	TOTAL
		N=296 n (%)	N=60 n (%)	N=102 n (%)	N=458 n (%)
Major	Deviation	68 (23.0%)	16 (26.7%)	25 (24.5%)	109 (23.8%)
	Clinical Procedures: Endoscopy	7 (2.4%)	4 (6.7%)	6 (5.9%)	17 (3.7%)
	Con Med And Therapies	3 (1.0%)	0 (0.0%)	1 (1.0%)	4 (0.9%)
	IMP/Dosing: IMP Incorrect Dosing	62 (20.9%)	13 (21.7%)	22 (21.6%)	97 (21.2%)
	IMP/Dosing: Rescue Medication	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (0.2%)
	Other	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Scales/Questionnaires: General	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (0.2%)
	Minor	Deviation	240 (81.1%)	49 (81.7%)	80 (78.4%)

Source: Study CNS7056-006 Report Body, p. 73 (PDF), Applicant's submission, NDA 212295.

Major protocol deviations were reported for approximately 24% of all treated patients. The most frequently reported protocol deviation was incorrect dosing of study drug, which was reported in 21% of treated patients, and included administration of top-up doses with adequate sedation (MOAA/S of ≤ 3), failure to administer top-up doses when sedation was inadequate (MOAA/S of 5), incorrect administration time, inadequate time between dosing, and incorrect doses. Protocol deviations that occurred in more than one patient included deviations in the colonoscopy procedure and administration of concomitant medication. Minor protocol deviations included ECG monitoring deviations, general assessment scale and questionnaire administration, vital sign deviation, and study drug dosing deviations.

Demographic and Baseline Characteristics

Demographic information for the study population is presented in in the following table.

Table 8. Demographic Characteristics (Safety Population)

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		Remimazolam	Placebo	Midazolam	TOTAL
		N=296	N=60	N=102	N=458
		n (%)	n (%)	n (%)	n (%)
Age	N	296	60	102	458
[years]	Mean	54.4	56.0	55.6	54.9
	SD	10.12	9.51	10.15	10.05
	Minimum	19	24	20	19
	Median	55.0	56.0	57.0	55.5
	Maximum	80	92	74	92
Age Group	<65	254 (85.8%)	53 (88.3%)	88 (86.3%)	395 (86.2%)
[years]	≥65	42 (14.2%)	7 (11.7%)	14 (13.7%)	63 (13.8%)
Gender	Male	147 (49.7%)	25 (41.7%)	46 (45.1%)	218 (47.6%)
	Female	149 (50.3%)	35 (58.3%)	56 (54.9%)	240 (52.4%)
Race	American Indian or Alaska Native	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Asian	18 (6.1%)	3 (5.0%)	10 (9.8%)	31 (6.8%)
	Black or African American	52 (17.6%)	14 (23.3%)	14 (13.7%)	80 (17.5%)
	Native Hawaiian or Other Pacific Islander	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	White	220 (74.3%)	43 (71.7%)	76 (74.5%)	339 (74.0%)
	Other	3 (1.0%)	0 (0.0%)	1 (1.0%)	4 (0.9%)
	Multiple	1 (0.3%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
Ethnicity	Hispanic or Latino	46 (15.5%)	10 (16.7%)	17 (16.7%)	73 (15.9%)
	Not Hispanic or Latino	250 (84.5%)	50 (83.3%)	85 (83.3%)	385 (84.1%)
Height	N	296	60	102	458
[cm]	Mean	170.1	167.8	169.5	169.6
	SD	10.36	10.24	11.15	10.53
	Minimum	144	147	143	143
	Median	170.0	166.0	170.0	170.0
	Maximum	193	193	200	200
Weight	N	296	60	102	458
[kg]	Mean	83.2	84.6	81.9	83.1
	SD	17.39	19.90	16.24	17.47
	Minimum	40	49	52	40
	Median	83.7	80.8	81.8	82.1
	Maximum	128	144	126	144
BMI	N	296	60	102	458
[kg/m²]	Mean	28.9	30.0	28.8	29.0
	SD	4.72	5.31	4.75	4.81
	Minimum	17	19	17	17
	Median	29.1	29.0	28.2	28.7
	Maximum	40	40	39	40

BMI = body mass index; N = number of patients; n = number of observations; SD = standard deviation
 Source: Study CNS7056-006 Report Body, p. 77-78 (PDF), Applicant's submission, NDA 212295.

The following table summarizes the American Society of Anesthesiologists physical status (ASA-PS) for each treatment group.

Table 9. ASA-PS Classification

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ASA-PS	Remimazolam	Placebo	Midazolam	TOTAL
	N=296	N=60	N=102	N=458
	n (%)	n (%)	n (%)	n (%)
I Healthy Person	95 (32.1%)	11 (18.3%)	37 (36.3%)	143 (31.2%)
II Mild Systemic Disease	179 (60.5%)	45 (75.0%)	61 (59.8%)	285 (62.2%)
III Severe Systemic Disease	22 (7.4%)	4 (6.7%)	4 (3.9%)	30 (6.6%)

Source: Study CNS7056-006 Report Body, p. 77-78 (PDF), Applicant's submission, NDA 212295.

Other Baseline Characteristics

In general, the medical and surgical histories reported for patients in all three treatment groups were similar. There did appear to be a larger percentage of patients in the placebo treatment group compared to the RMZ treatment group who had a past medical history in the psychiatry SOC and included alcohol abuse, alcoholism, anxiety, depression, and insomnia. Otherwise, there did not appear to be clinically relevant differences in neurological or psychiatric histories that could have contributed to the reported efficacy results.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was 100% for patients who received the initial dose of study medication. As previously discussed, midazolam was the only rescue medication permitted during the study. If patients required additional sedatives, they were considered treatment failures.

Efficacy Results – Primary Endpoint

Unless otherwise specified, all efficacy analyses were performed on the ITT population.

The primary efficacy endpoint was success of the colonoscopy, which was defined as completion of the procedure without the need for rescue sedative medication, and no more than five doses of RMZ or placebo in a 15-minute window or no more than three doses of midazolam in a 12-minute window. The following table summarizes the results.

Table 10. Primary Efficacy Endpoint Results (Study CNS7056-006)

Number of Patients	Remimazolam	Placebo	Midazolam	Total
	N=298 n (%)	N=60 n (%)	N=103 n (%)	N=461 n (%)
Success	272 (91.3%)	1 (1.7%)	26 (25.2%)	299 (64.9%)
Failure ^a	26 (8.7%)	59 (98.3%)	77 (74.8%)	162 (35.1%)
Reasons for failure:				
Rescue sedative medication taken	10 (3.4%)	57 (95.0%)	66 (64.1%)	133 (28.9%)
Too many doses within the predefined time window	18 (6.0%)	44 (73.3%)	56 (54.4%)	118 (25.6%)
Procedure not completed	7 (2.3%)	1 (1.7%)	2 (1.9%)	10 (2.2%)

Comparison	Difference in Rates	95% Confidence Interval		P-Value
		Lower	Upper	
Remimazolam vs Placebo	0.8961	0.8505	0.9416	<0.0001
Remimazolam vs Midazolam	0.6603	0.5705	0.7501	

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^a More than 1 reason for treatment failure could be reported per patient.

Note: Wald asymptotic confidence limits are presented. *P*-value calculated from a Cochran-Mantel-Haenszel test accounting for fentanyl strata.

Source: Study CNS7056-006 Report Body, p. 80 (PDF), Applicant's submission, NDA 212295.

There was a higher percentage of patients treated with RMZ who successfully completed the procedure compared to those treated with saline placebo. These results were statistically significant and clinically meaningful. Of the RMZ treatment failures, more did so based on too many doses of study drug in the predefined time window, 15 minutes. In contrast, placebo-treated patients failed based on the need for rescue medication. There was a higher percentage of RMZ-treated patients who did not complete the procedure compared to patients in either the placebo and midazolam treatment groups.

Regarding total RMZ dose, the following table, from the Applicant's clinical study report, indicates that the majority of patients (approximately 67%) were able to complete the colonoscopy with three or less doses of RMZ, including the initial bolus dose. This is in contrast to the placebo group, in which 95% required five or more doses.

Table 11. Total Number of Study Medication Doses (Safety Population)

Parameter	Sample Characteristics or Category	Remimazolam N=296	Placebo N=60	Midazolam N=102	Total N=458
Number of	1	27 (9.1%)	0 (0.0%)	1 (1.0%)	28 (6.1%)
Doses of	2	95 (32.1%)	0 (0.0%)	4 (3.9%)	99 (21.6%)
IMP	3	76 (25.7%)	0 (0.0%)	17 (16.7%)	93 (20.3%)
	4	30 (10.1%)	0 (0.0%)	67 (65.7%)	97 (21.2%)
	5	30 (10.1%)	1 (1.7%)	7 (6.9%)	38 (8.3%)
	6	30 (10.1%)	57 (95.0%)	4 (3.9%)	91 (19.9%)
	7	7 (2.4%)	1 (1.7%)	0 (0.0%)	8 (1.7%)
	8	1 (0.3%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
	10	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)

Source: Study CNS7056-006 Report Body, p. 125 (PDF), Applicant's submission, NDA 212295.

The Applicant conducted comparative analyses for procedural success between the RMZ and midazolam treatment groups. As discussed previously, the midazolam was administered in an unblinded, open-label fashion (b) (4)

It is worth noting, however, that while the comparison between RMZ and midazolam did reach statistical significance, the dose of midazolam is low and not reflective of what is administered in clinical practice, and the midazolam was

administered open-label, making interpretation of the results challenging.

Sensitivity analyses were conducted to determine a possible effect on sedation of fentanyl dosing. The following table was adapted from the Applicant's data and provided by Dr. James Travis, statistical reviewer.

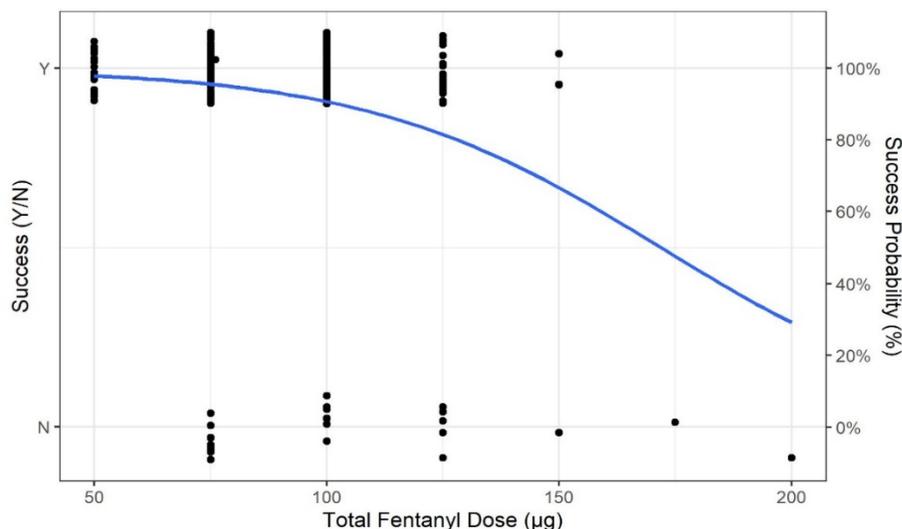
Table 12. Procedural Success by Fentanyl Dose (Study CNS7056-006)

Fentanyl Stratum	RMZ, n/N (%)	Placebo, n/N (%)	Difference in Rates (95% CI)	p-Value
< 100 µg	139/148 (94%)	0/9 (0%)	93.9% (90.1, 97.8)	<0.0001
100-150 µg	133/146 (91%)	1/43 (2%)	88.8% (82.3, 95.2)	<0.0001
> 150 µg	0/2 (0%)	0/8 (0.0%)	NA	NA

Source: Adapted from Study CNS7056-006 Report Body, Table 16, p. 81 (PDF), Applicant's submission, NDA 212295, and statistical reviewer's analysis.

Graphically, the correlation between increased fentanyl dose and procedural success for RMZ-treated patients is presented in the figure below.

Figure 2. Procedural Success Versus Total Fentanyl Dose, Remimazolam Treatment Group (Study CNS7056-006)



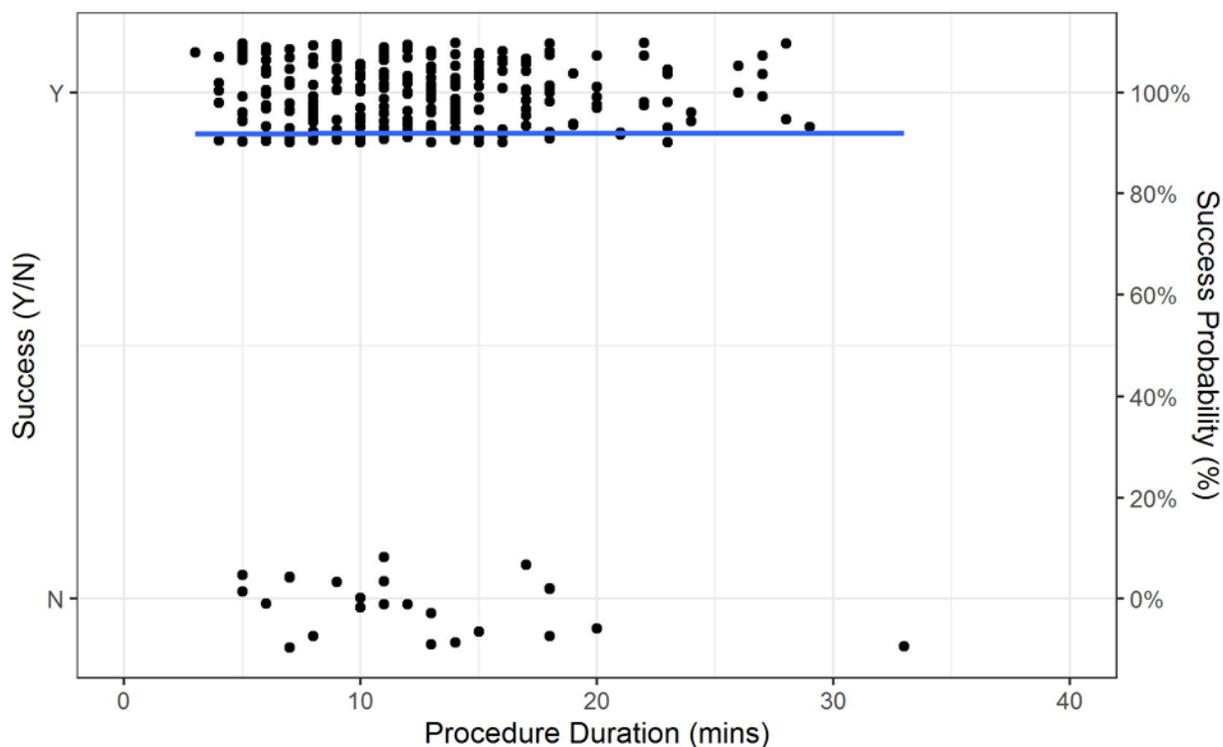
Source: Statistical Reviewer's analysis.

It appears that as the dose of fentanyl increased, procedural success decreased slightly in the RMZ treatment group and increased slightly in the placebo treatment group. The graphical representation of the relationship between fentanyl dosing and procedural success in placebo-treated patients is a relatively flat line; however, in general, placebo-treated patients received higher doses of fentanyl during the procedure compared to RMZ-treated patients. Specifically, approximately 52% of placebo-treated patients received 125 µg to 200 µg of fentanyl during

the procedure compared to only 10% of RMZ-treated patients. Additionally, the mean dose of fentanyl administered in the placebo treatment group was 121.25 µg compared to 88.85 µg in the RMZ treatment group.

An additional consideration when evaluating the data presented by the Applicant for the procedural success endpoint, is the impact of the duration of the procedure on success. Specifically, whether longer procedures reported different procedural success rates. The following figure, created by Dr. James Travis, does not indicate a correlation between procedure duration and success in the RMZ treatment group. It is again worth noting, however, that the majority of colonoscopies were completed in 20 minutes or less, such that there is limited efficacy information available for longer procedures.

Figure 3. Procedural Success with Increasing Procedure Duration, RMZ Group (Study CNS7056-006)



Source: Statistical Reviewer.

The following table summarizes the results from logistic regression analysis, conducted by Dr. James Travis. These results indicate that longer procedures did not result in lower rates of procedural success.

Table 13. Logistic Regression Analysis – Procedure Success vs. Procedure Duration, RMZ Treatment Group (Study CNS7056-006)

Clinical Review
 Petit-Scott, M.D.

	Estimate	Standard Error	p-value
Intercept	2.42	0.55	
Procedure Duration	0.00003	0.04	0.993

Source: Statistical reviewer.

In response to the Mid-Cycle Communication Meeting, the Applicant submitted additional information to clarify the proportion of patients who underwent procedures 20 minutes or longer and 30 minutes or longer, and the procedure success for longer procedures. Because 30 minutes is likely the more clinically meaningful duration of commonly performed procedures in the U.S., the Applicant’s findings using 30 minutes as the cut-off are presented in the table below.

Table 14. Distribution of Patients Undergoing Procedures < 30 minutes and ≥ 30 minutes (Study CNS7056-006)

Treatment Group	Procedure Duration			
	< 30 minutes		≥ 30 minutes	
	N	%	N	%
Remimazolam	297	99.7%	1	< 1%
Placebo	58	97%	2	3%
Midazolam	100	97%	3	3%

Source: Adapted from Clinical Information Amendment – Responses to Filing Review Issues Identified and MCC Agenda, dated November 19, 2019, p. 19 (PDF), Applicant’s submission, NDA 212295.

The table above clearly indicates that the majority of colonoscopies conducted in this study were completed within 30 minutes. In response to the Mid-Cycle Communication Meeting correspondence, the Applicant provided a table for the most frequently completed procedures in the U.S. (from Definitive Healthcare’s platform on commercial claims analytics) and stated the following:

“...a colonoscopy is generally expected to take about 20 minutes on average, comprised of 10-12 minutes to insert the scope along the entire colon and a recommended minimum of 6 minutes for the withdrawal.”

“Removal of a lesion or a particularly difficult anatomy may make the procedure last longer, however rarely longer than 30 minutes. The remaining procedures on the list are usually performed within 20 minutes, if not even shorter, e.g., biopsies, drainage or injections and venipunctures.”

“Transferring the data from Definite Healthcare into ‘benchmarks’ for a representative expected average duration for the majority of procedures, an expected average between 20 and 30 minutes appears appropriate.”

Based on this, it appears the Applicant would agree that RMZ should only be indicated for procedures of similar duration as those evaluated during the Phase 3 clinical studies. While there is some data available from the Applicant's clinical development program regarding RMZ administered for ICU sedation and induction and general anesthesia, the procedural sedation indication will be based on information from studies conducted in representative models.

Data Quality and Integrity

There were no concerns identified regarding data quality or integrity with this study.

Efficacy Results – Key Secondary and Other Relevant Endpoints

Results of the key secondary efficacy endpoints for the ITT population are presented unless otherwise specified.

Time to start of procedure

The median times to start of procedure are summarized in the following table.

Table 15. Time to Start of Procedure from First Dose of Study Drug (minutes) (Study CNS7056-006)

	Remimazolam N=298	Placebo N=60	Midazolam N=103
Number of Patients in Analysis	296	60	102
Median	4.0	19.5	19.0
95% CI: Lower limit	-	18.0	17.0
95% CI: Upper limit	-	21.0	20.0
25 th Percentile	3.0	17.0	12.0
95% CI: Lower limit	-	17.0	9.0
95% CI: Upper limit	-	18.0	15.0
75 th Percentile	6.0	23.0	21.0
95% CI: Lower limit	5.0	21.0	20.0
95% CI: Upper limit	6.0	25.0	22.0

Comparison	Hazard Ratio	95% CI		P-Value
		Lower	Upper	
Remimazolam vs Placebo	6.133	4.416	8.517	<0.0001
Remimazolam vs Midazolam	4.771	3.676	6.192	

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N = number of patients; CI = confidence interval; HR = hazard ratio

Note: Statistics taken from Kaplan-Meier analysis. Patients who did not reach the endpoint are excluded from the analysis. Wald confidence limits from Cox's proportional hazard model are presented. *P*-value calculated from logrank test.

Source: Study CNS7056-006 Report Body, p. 83 (PDF), Applicant's submission, NDA 212295.

The median time to start of procedure for the RMZ-treated patients was statistically, and clinically, significantly shorter than that observed for placebo-treated patients. Sensitivity analyses evaluating a potential impact of fentanyl dosing on the reported efficacy for RMZ-treated patients suggested that higher doses of fentanyl, > 150 µg, resulted in longer times to start of procedure (23.5 minutes versus 4 minutes). There were, however, only two patients who required this dose of fentanyl (175 µg and 200 µg) and both were considered treatment failures. There were no meaningful differences noted with higher doses of fentanyl in patients in the placebo and midazolam treatment groups.

Time to peak sedation

The median time to peak sedation was analyzed using Kaplan-Meier analysis, where peak sedation was defined as the first lowest MOAA/S score reported for each patient before any top-up doses were administered. The results, summarized in the following table, include only times for the RMZ treatment group. All patients in the placebo treatment group and all but six in the midazolam treatment group were censored at the time of their last MOAA/S assessment because they did not achieve an MOAA/S score of three or less; therefore, the time to peak sedation could not be calculated.

Table 16. Time to Peak Sedation from First Dose of Study Drug (minutes) (Study CNS7056-006)

	Remimazolam	Placebo	Midazolam
	N=298	N=60	N=103
Number of Patients in Analysis	296	60	102
Median	3.0	-	-
95% CI: Lower limit	-	-	-
95% CI: Upper limit	-	-	-
25 th Percentile	2.0	-	-
95% CI: Lower limit	-	-	6.0
95% CI: Upper limit	-	-	-
75 th Percentile	5.0	-	-
95% CI: Lower limit	4.0	-	-
95% CI: Upper limit	-	-	-

Comparison	Hazard Ratio	95% CI		P-Value
		Lower	Upper	
Remimazolam vs Placebo	13958980	0.000	-	<0.0001
Remimazolam vs Midazolam	21.139	9.315	47.969	

N = number of patients; CI = confidence interval; HR = hazard ratio

Note: Statistics taken from Kaplan-Meier analysis. Patients who did not reach the endpoint are censored at last MOAA/S. Wald confidence limits from Cox's proportional hazard model are presented. P-value calculated from logrank test.

Source: Study CNS7056-006 Report Body, p. 85 (PDF), Applicant's submission, NDA 212295.

Sensitivity analyses for fentanyl dosing in RMZ-treated patients did not impact the reported efficacy results. As previously discussed, only two patients in the RMZ treatment group received doses of fentanyl > 150 µg, and both were considered treatment failures.

Time to ready for discharge

Time to ready for discharge was defined as the ability to walk unassisted and was analyzed using Kaplan-Meier from the from last dose of study or rescue drug administration and from the end of the colonoscopy procedure. Patients who withdrew or otherwise did not have data were censored using their last assessment. Time to ready for discharge after last dose of study or rescue drug is summarized in the following table.

Table 17. Time to Ready for Discharge After Last Dose Study/Rescue Drug (Study CNS7056-006)

	Remimazolam	Placebo	Midazolam
	N=298	N=60	N=103
Number of Patients in Analysis	296	60	102
Median	51.0	60.5	57.0
95% CI: Lower limit	49.0	55.0	53.0
95% CI: Upper limit	54.0	67.0	61.0
25 th Percentile	39.5	50.0	48.0
95% CI: Lower limit	35.0	46.0	44.0
95% CI: Upper limit	42.0	55.0	50.0
75 th Percentile	60.0	71.0	66.0
95% CI: Lower limit	58.0	67.0	63.0
95% CI: Upper limit	61.0	89.0	71.0

Comparison	Hazard Ratio	95% CI		P-Value
		Lower	Upper	
Remimazolam vs Placebo	2.416	1.781	3.278	<0.0001
Remimazolam vs Midazolam	1.712	1.355	2.164	

N = number of patients; CI = confidence interval; HR = hazard ratio

Note: Statistics taken from Kaplan-Meier analysis. Patients who did not reach the endpoint are censored at last MOAA/S. Wald confidence limits from Cox's proportional hazard model are presented. P-value calculated from logrank test.

Source: Study CNS7056-006 Report Body, p. 89 (PDF), Applicant's submission, NDA 212295.

There was a statistically significant difference in time to ready for discharge between the RMZ and placebo treatment groups. This difference is likely clinically significant as well. While 9.5 minutes may not seem to be a long period of time, the cumulative time saved as 9.5 minutes per patient, per procedure would significantly impact the efficiency of a busy gastroenterology center and even a hospital-based practice.

The time to ready for discharge was also evaluated from the end of the colonoscopy procedure. The time difference between the RMZ and placebo treatment groups were less impressive (i.e., 44 minutes versus 49 minutes), but still reached statistical significance. The faster time to ready for discharge is also clinically significant for a busy GI center or hospital-based practice.

Sensitivity analyses for fentanyl dosing in RMZ-treated patients for time to ready for discharge after last dose of study/rescue medication did demonstrate an increase in the observed time with increasing doses of fentanyl. Specifically, for patients treated with fentanyl 100 µg, 100 µg to 150 µg, and > 150 µg the times to ready for discharge were 48, 53, and 55.5 minutes

respectively. There were, however, only two patients in the RMZ treatment group who received > 150 µg of fentanyl. Similar increases were observed in patients treated with placebo (49, 61, and 66 minutes, respectively). The midazolam treatment group demonstrated inconsistent times to ready for discharge based on fentanyl dosing (53, 61, and 59 minutes, respectively). The same analyses performed for RMZ-treated patients for time to ready for discharge at the end of the colonoscopy procedure did not demonstrate a meaningful difference relative to the fentanyl dose administered.

Regarding the use of rescue sedative medication, sensitivity analyses demonstrated that there was no meaningful difference in time to ready for discharge from last dose of study/rescue medication in patients who received rescue medication compared to those who did not (50 minutes versus 51 minutes) in all three treatment groups. For discharge readiness times from the end of the colonoscopy procedure, there were observed differences. Specifically, for those patients who required rescue sedative medication, the time to ready for discharge was *shorter* than those patients who did not receive rescue sedative medication (i.e., 39.5 minutes versus 44.5 minutes) in the RMZ treatment group. The number of patients who received rescue sedative medication was low (10 of 298 treated patients); however, it is interesting the patients who received more sedative medication, RMZ plus midazolam rescue, had a shorter time from end of colonoscopy to ready for discharge. Similar results were observed in the midazolam treatment group. There was no difference in median time to ready for discharge from the end of the colonoscopy procedure in patients treated with placebo.

Time to fully alert

Time to fully alert from last injection of study drug or rescue and from the end of the colonoscopy procedure was defined as the time to the first of three consecutive MOAA/S scores of 5 and was analyzed using the Kaplan-Meier. As shown in the following table, the median time to fully alert after last dose of study or rescue drug was statistically, and clinically, significantly shorter in patients treated with RMZ versus placebo. Specifically, the median time to fully alert for placebo-treated patients was double that of RMZ-treated patients.

Table 18. Time to Fully Alert from Last Dose of Study / Rescue Drug Administration (minutes)
(Study CNS7056-006)

	Remimazolam	Placebo	Midazolam
	N=298	N=60	N=103
Number of Patients in Analysis	296	60	102
Median	14.0	28.0	24.0
95% CI: Lower limit	13.0	24.0	22.0
95% CI: Upper limit	14.0	32.0	26.0
25 th Percentile	11.0	21.0	18.0
95% CI: Lower limit	10.0	17.0	16.0
95% CI: Upper limit	11.0	24.0	20.0
75 th Percentile	17.0	41.0	32.0
95% CI: Lower limit	16.0	33.0	28.0
95% CI: Upper limit	18.0	50.0	35.0

Comparison	Hazard Ratio	95% CI		P-Value
		Lower	Upper	
Remimazolam vs Placebo	4.702	3.371	6.560	<0.0001
Remimazolam vs Midazolam	3.304	2.568	4.251	

Source: Study CNS7056-006 Report Body, p. 93 (PDF), Applicant's submission, NDA 212295.

Sensitivity analyses for fentanyl dosing in the RMZ treatment group demonstrated that with increasing fentanyl dose, the time to fully alert after last dose of study/rescue drug increased. Specifically, for < 100 µg, 100 µg to 150 µg, and > 150 µg fentanyl doses, the times to fully alert were 13, 15, and 18.5 minutes respectively. This is in contrast to placebo-treated patients, in which the time to fully alert after the last dose of study/rescue drug decreased with increasing doses of fentanyl (33, 29, and 22 minutes, respectively) and for midazolam-treated patients in which fentanyl administration did not appear to have an impact on the time to fully alert after the last dose of study/rescue medication (23, 23.5, and 24 minutes, respectively).

For the time to fully alert from the end of the colonoscopy procedure, there was a statistically, and clinically, significant difference in patients treated with RMZ versus those treated with placebo. Specifically, the time to fully alert for RMZ-treated patients was 6 minutes compared to 15 minutes for placebo-treated patients. The time to fully alert increased in RMZ-treated patients with increasing fentanyl doses. Specifically, for patients treated with fentanyl 100 µg, 100 to 150 µg, and > 150 µg, the times to fully alert were 5, 7, and 14.5 minutes, respectively. This is in contrast to patients treated with either placebo or midazolam, where the times to fully alert from the end of the colonoscopy procedure decreased with increasing doses of

fentanyl.

Administration of rescue sedative medication did not appear to significantly impact the times to fully alert from last dose of study/rescue medication and from the end of the colonoscopy procedure for any treatment group, nor were there were any consistent trends observed.

MOAA/S Scores by Time Point

All patients in all three treatment groups had MOAA/S score of five, 15 minutes prior to the procedure. Within one minute of administration, six patients (2%) in the RMZ treatment group had a score of 0, which represents no response to painful trapezius squeeze. Lack of response to painful stimuli as a measure of anesthetic depth suggests that there were patients who very quickly experienced deep sedation after administration of RMZ. Additionally, there were 18 patients (6%) who experienced MOAA/S scores of two or less within one minute of RMZ administration. This is in contrast to no patients in either the placebo or midazolam treatment groups experiencing this depth of sedation or general anesthesia within a short amount of time from administration.

Dose Response and Durability of Response

There was a single dose of RMZ administered in this Phase 3 study, therefore a dose-response was not evaluated.

A pharmacokinetic property of RMZ that the Applicant states is a clear advantage over other commonly administered benzodiazepines for procedural sedation is its rapid. The majority of patients required three or more doses of RMZ to maintain adequate sedation for colonoscopies ranging from 33 to 4 minutes in duration. During this study, it did not appear that the number of doses of RMZ was positively correlated with the time to recovery from sedation, measured via time to fully alert and time to discharge.

Additional Analyses Conducted on the Individual Trial

The Applicant did provide additional efficacy and safety information based on procedure duration in response to the Mid-Cycle Meeting Communication. That information has been incorporated into appropriate sections of this review.

Data Monitoring Committee Meetings and Outcomes

The DMC held regular meetings to evaluate the safety data during the study. During the second review meeting, the DMC noted the high number of protocol deviations. The Applicant noted that most deviations were related to study procedure timing, and the clinical site with the most deviations was put on hold until a Corrective Action Prevention Action plan was implemented. Additionally, the DMC noted a higher incidence of cardiovascular-related adverse events

compared to other procedural studies. The Applicant indicated this increase may be due to the vital sign monitoring and reporting. The DMC discussed the certainly related to study drug serious adverse event of hypoxia reported during Study CNS7056-008, which was felt to be due to administration of a higher than permitted top-up dose of fentanyl. During an ad hoc meeting, the DMC discussed the increased incidence of patients under deep sedation (MOAA/S score of 0 or 1) in the RMZ treatment group in Study CNS7056-006, particularly within a short time after RMZ initial bolus dose. The Applicant suggested reducing the initial fentanyl dose to a maximum of 50 µg, or a suitable dose for the elderly or debilitated/chronically ill, and keeping the RMZ dose the same. The DMC agreed with this plan.

6.2. A Phase III Study Evaluating the Efficacy and Safety of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in Patients Undergoing Bronchoscopy (CNS7056-008)

6.2.1. Study Design

Overview and Objective

The overview and objectives for this study are identical to those from Study CNS7056-006, and will only be described in detail where differences are noted.

This was a prospective, double-blind, randomized, placebo-controlled, multi-center, study comparing RMZ to placebo (pbo) in patients undergoing flexible bronchoscopy for either diagnostic or therapeutic purposes. Because the additional midazolam arm was open-label, the study is not considered active-controlled.

The study objectives were as follows:

- Primary objective – to establish the superiority of RMZ compared to pbo in inducing and maintaining suitable sedation levels for patients undergoing bronchoscopy and in comparison to an open-label arm with midazolam in combination with fentanyl as determined by sedation success
- Secondary objectives –
 - time to start of procedure after administration of the first dose of study medication
 - time to peak sedation after administration of the first dose of study medication
 - times to ready for discharge (after the end of the bronchoscopy procedure and after the last injection of study drug)
 - times to fully alert (after the end of the bronchoscopy procedure and after the last injection of study drug)
 - MOAA/S scores by time point
 - recall of the procedure by the Brice questionnaire (administered when full alertness was regained and on Day 4)

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- changes to the patient’s cognitive function (assessed by the HVL-R™)
- safety of multiple doses of remimazolam, including oxygen saturation and no need for mechanical ventilation
- ready to discharge scores
- drowsiness VAS to assess for signs of re-sedation
- requirement for flumazenil
- patient’s self-evaluation of “back-to-normal” after the procedure
- pain on injection
- population pharmacokinetics in a subgroup of patients

Trial Design

Patients in all treatment groups were administered fentanyl 75 µg (decreased to 25 to 50 µg with Protocol Amendment 5) for analgesia immediately prior to administration of study drug. Of note, the majority of patients (363 total) in the study were treated under Protocol Amendment 5. Reduced dosing was used for elderly or debilitated/chronically ill patients. Supplemental doses of fentanyl 25 µg could be administered for analgesia, to a maximum dose of 200 µg. Investigators assessed the analgesic effect of fentanyl over 5 to 10 minutes. Investigators were to administer fentanyl for analgesia only. If additional sedation was needed, supplemental doses of study medication or midazolam were administered. Topical anesthesia was administered to all patients prior to bronchoscopy by spraying the nostril (if nasal route was used), nasopharynx, and oropharynx with 3 mL of 2% lidocaine. In addition, lidocaine 2% gel could be applied to the nasal passages for ease in inserting the bronchoscope if the nasal route was used.

RMZ or Placebo Dose Administration

An initial dose of remimazolam 5 mg or an equal volume of placebo was administered manually in a blinded fashion by IV injection over one minute. The bronchoscopy was started when adequate sedation (MOAA/S ≤ 3) was achieved. Sedation could be maintained by injection of additional RMZ or placebo doses, RMZ 2.5 mg or placebo in the same volume, no sooner than two minutes after assessment of the sedative effect. The number of RMZ or placebo doses was not limited as long as no more than five were administered in any 15-minute window. If five doses within 15 minutes did not obtain adequate sedation for the bronchoscopy, this patient was defined as a treatment failure.

Midazolam Open-Label Treatment Arm

Midazolam was administered according to the approved drug labeling. Healthy adults < 60 years of age received 1.75 mg of midazolam as an initial dose over two minutes. Adult patients ≥ 60 years of age, or debilitated/chronically ill patients received 1 mg as an initial dose over two minutes. Sedation could be maintained by further doses of 1 mg in healthy adults < 60 years of age or 0.5 mg in adults ≥ 60 years of age, or debilitated/chronically ill. The subsequent doses

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were administered over at least two minutes. At least two or more additional minutes were allowed to fully evaluate the sedative effect. The overall number of midazolam doses was not limited as long as not more than three doses were administered in any 12-minute window. If adequate sedation was not achieved with three doses within any 12-minute window, the patient was considered a treatment failure.

The schedule of assessments performed during this study are summarized in the following table.

Table 19. Schedule of Study Assessments

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	Day -21 to Day 1	Day 1	Day 4 Phone Call ^e (+3/-1 days)
	Screening	Treatment Day	Follow-up
Informed consent	X	See next schedule	
Eligibility criteria/medical and history/demographics	X		
Physical examination ^a	X		
Clinical laboratory samples ^b	X		
Urine HCG (females)	X		
Drugs of abuse screen	X		
Blood ethanol screen	X		
Hemodynamics ^c	X		
Height and BMI	X		
Weight	X		
Supine RR			
Body temperature	X		
Supine 12-lead ECG	X		
Fast ^d			
Fentanyl administration			
Administration of trial medication			
3-lead ECG telemetry			
Pulse oximetry monitoring/recording	X		
Respiratory rate recordings	X		
MOAA/S scale score monitoring/recording			
Pain VAS			
HTLV-R			
Brice questionnaire			
Airway management			
Assessment of adverse events and concomitant medication	X		X

Abbreviations: BMI = body mass index; ECG = electrocardiogram; HCG = human chorionic gonadotropin; HTLV-R = Hopkins Verbal Learning Test - Revised™; VAS = visual analogue scale

Note: Dosing day procedures described in the table on the next page.

- a Screening physical examination will include ASA-PS score
- b Biochemistry, hematology
- c Supine heart rate and systolic and diastolic blood pressure
- d Fast to begin from midnight of the day before dosing (no food or water)
- e In case there has been any indication for the onset of a new adverse event since discharge, patients should come back to the site immediately (preferably the same day) to perform further assessments (eg, clinically laboratory tests, 12-lead electrocardiogram, left to the discretion of the investigator)

Source: Study CNS7056-008 Report Body, p. 59 (PDF), Applicant's submission, NDA (b) (4)

The following table summarizes the assessments performed on study day 1.

Table 20. Study Day 1 Assessments

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Airway management assessment			x																
Supplemental O ₂			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Fentanyl (25-50 µg)					x	Supplemental doses of 25 µg every 5-10 min until adequate analgesia or 200 µg maximum dose													
Pain on injection	Learning				x (or as soon as possible)														
Drowsiness VAS ^d				x				x			x	x	15		25	35	45		60
Readiness for discharge score ^e													30		60				90

Abbreviations: BP = blood pressure; ECG = electrocardiogram; eCRF = electronic case report form; hr = hour; HR = heart rate; min = minute; HVLt-R™ = Hopkins Verbal Learning Test - Revised™; MOAA/S = Modified Observer's Assessment of Alertness and Sedation; NaCl = sodium chloride; SpO₂ = peripheral blood oxygen saturation (measured by pulse oximetry); VAS = visual analogue scale

^a Bronchoscopy started at sufficient sedation (MOAA/S ≤3), duration as necessary (MOAA/S ≤4), at the discretion of the investigator

^b Trial medication: Loading dose of randomized trial medication start defined t₀, supplemental doses as per protocol

^c See also [Day 1 – Further Assessments](#)

^d If patient was capable, was not awoken on purpose

^e 30, 60, and 90 minutes postdose t = 0

^f Running a strip to document presence or absence of arrhythmias

^g After first dose, 5 minutes after dosing and every 10 minutes until the end of the procedure if possible, and also five minutes after the end of the procedure and at discharge

^h In addition to times specified above, blood pressure, heart rate, and peripheral blood oxygen saturation (measured by pulse oximetry) was recorded immediately prior to and two minutes after each additional dose of fentanyl

ⁱ Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate, and peripheral blood oxygen saturation) was recorded when an AE with a respiratory or cardiovascular focus had been observed

(B) Baseline values, x single action, xx continuous action

Source: Study CNS7056-008 Report Body, pp. 60-62 (PDF), Applicant's submission, NDA 212295.

Eligibility Criteria

Pertinent inclusion criteria included the following:

- adult patients ≥ 18 years of age
- ASA physical status three or less
- BMI ≤ 45 kg/m²
- oxygen saturation ≥ 90% on ≤ 2 L/minute oxygen
- non-pregnant, non-lactating females

Pertinent exclusion criteria included the following:

- known sensitivity to benzodiazepines, flumazenil, opioids, naloxone, or a medical condition such that the use of these medications is contraindicated
- bronchoscopy in unit other than bronchoscopy unit
- patients on mechanical ventilation or with tracheal stenosis
- planned rigid bronchoscopy
- use of unstable (changes of > 50% of the previous dose within 30 days prior) doses of benzodiazepines or opioids for any indication (*Note: this is in contrast to the eligibility criteria employed during the conduct of Study CNS7056-006, in which patients taking any dose of benzodiazepine or opioid were excluded from participation)
- positive drug or ethanol screening at baseline, or history of abuse within past two years

Study Endpoints

The primary efficacy endpoint was the success of sedation of the bronchoscopy, defined as follows:

- completion of the bronchoscopy procedure and
- no requirement for a rescue sedative medication and
- no requirement for more than 5 doses of trial medication within any 15-minute window in the blinded arms (RMZ/placebo) or no requirement for more than three doses within any 12-minute window in the open-label midazolam arm

Secondary efficacy endpoints included the following:

- time to start of procedure
- time to peak sedation
- time to ready for discharge at the end of bronchoscopy
 - from end of bronchoscopy
 - from last dose of sedative medication administration
- time to fully alert
 - from end of bronchoscopy
 - from last dose of sedative medication administration

Additional efficacy evaluations included MOAA/S by time point, procedure recall on day of procedure and study day 4, changes in cognitive function, readiness for discharge score at 30, 60, 90 minutes post-injection of initial dose, drowsiness VAS, flumazenil administration, and patient assessment of “back-to-normal”.

Safety assessments included the following:

- Physical exam
- Laboratory assessments (hematology and chemistry)
- Vital signs (temperature, heart rate, blood pressure, respiratory rate)
- Pulse oximetry, pain on injection rating, and airway interventions
- 12-lead ECG at screening, after the first dose, five minutes after the start of initial dosing and every 10 minutes until the end of the procedure and five minutes after the end of the procedure, at discharge, and when indicated
- 3-lead ECG was monitored continuously during the procedure until fully alert
- Adverse events
 - with emphasis on cardiorespiratory events (hypoxia, bradycardia, hypotension, hypertension, respiratory depression) and prolonged sedation
 - vital signs considered adverse events were defined as follows:
 - bradycardia – HR < 40 bpm or a decrease of 20% or more from baseline for 30 seconds

- hypertension – increase in systolic blood pressure (SBP) to ≥ 180 mmHg or in diastolic blood pressure (DBP) to ≥ 100 mmHg or an increase in either SBP or DBP 20% or more from baseline or medical intervention required
- hypotension – decrease in SBP ≤ 80 mmHg or in DBP ≤ 40 mmHg or a fall in SBP or DBP 20% or more from baseline or medical intervention required
- respiratory rate decreased – < 8 breaths per minute
- hypoxia – oxygen saturation $< 90\%$ for ≥ 1 minute or any decrease requiring medical intervention
 - prolonged sedation (MOAA/S ≤ 4 for 60 minutes or longer after the last dose of study drug administration) including the need for flumazenil
 - with emphasis on adverse events associated with medications of abuse
- Interventions
 - airway interventions
 - IV fluid and medication administration
- Pain on injection of study medication

Statistical Analysis Plan

Analysis Populations

Eight analysis populations were defined:

- Safety population consisted of all randomized patients who received any study drug.
- Secondary Nellcor safety populations consisted of all patients in the safety population who had usable Nellcor data (defined as $\geq 90\%$ of readable Nellcor data per parameter within observation period).
 - Secondary Nellcor respiratory rate safety population.
 - Secondary Nellcor heart rate population.
 - Secondary Nellcor pulse oximetry population.
- Intent-to-treat (ITT) analysis set included all patients who were randomized.
- Modified intent-to-treat (mITT) analysis set included all patients included in the ITT population who received at least one complete dose of randomized study drug.
- The per-protocol (PP) analysis set included all patients from the ITT analysis set who received study drug according to their randomization and the planned treatment schedule and who did not have any major protocol deviations.
- The PK population consisted of all patients aged ≥ 75 years at selected sites who had PK samples collected

All safety analyses were based on the actual treatment administered. Analyses of the Nellcor data were conducted on patients in the respective population. All other safety analyses were

conducted on patients in the safety population and were based on actual treatment administered.

All efficacy analyses were conducted on patients in the ITT, mITT, and PP populations, with the mITT and PP populations planned to confirm the results of the ITT population. The analyses were based on randomization treatment assignment, not actual treatment administered. The primary efficacy analysis was the comparison of procedural success rates (using the composite endpoint) between the RMZ and placebo groups, using the CMH test to account for fentanyl dose strata, which included < 100 µg, 100 to 150 µg, and > 150 µg. Descriptive testing was performed on the secondary efficacy endpoints.

Additional sensitivity analyses were performed to assess the impact of opioid and midazolam administration on procedural success in all treatment groups.

Protocol Amendments

There were five protocol amendments implemented during conduct of this study. They are briefly summarized below.

Amendment 1 (March 17, 2015)

- fentanyl 75 µg pretreatment with top-up doses of 25 µg were allowed, maximum dose 200 µg (further dose reduction permitted in elderly or debilitated/chronically ill patients)
- 12-lead ECG during procedure
- AE definitions and eligibility criteria clarified or changed

Amendment 2 (May 13, 2015)

- Documentation of all bradycardic events, determination of heart rate and pulse oximetry nadirs, calculation of mean arterial pressure, regular DMC meetings

Amendment 3 (July 20, 2015)

- Recording nadirs for heart rate, respiratory rate, and pulse oximetry
- Non-AE episodes of bradycardia and hypoxia
- Additional subject stopping criteria
- Clarification of SAEs to be forwarded to DMC
- Vital sign clarification
- Clarification of inconsistencies

Amendment 4 (October 28, 2015)

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- Removal of BMI entry restriction, adjustment for definition of chronic use of benzodiazepines and opioids, expanded time-window for pre-dose assessments and change in study day 4 assessments from a visit to a follow-up phone call
- Amendment 4.1 (November 10, 2015) – inclusion of subgroup analysis for benzodiazepine and opioid use

Amendment 5 (March 3, 2016) (changes based on DMC recommendations made after meeting on January 21, 2016)

- Reduction of initial fentanyl dose to 25 to 50 µg or as needed for elderly or debilitated/chronically ill
- Addition of PK sampling in patients ≥ 75 years of age at selected sites
- Midazolam treatment group enrollment decreased from 100 to 60 patients
- BMI ≤ 45 kg/m² reinstated

6.2.2. Study Results

Compliance with Good Clinical Practices

The following statement was included on the title page of the study.

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

I have no concerns regarding the validity of this statement.

Financial Disclosure

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, and was the recipient of significant payments of other sorts.

Patient Disposition

A total of 446 patients were randomized in this study and 431 were treated. Patient disposition is summarized in the following table.

Table 21. Patient Disposition (Safety Population)

	Remimazolam N = 303 n (%)	Placebo N = 59 n (%)	Midazolam N = 69 n (%)	Total N = 431 n (%)
Informed consent given	303 (100.0)	59 (100.0)	69 (100.0)	431 (100.0)
Randomized	303 (100.0)	59 (100.0)	69 (100.0)	431 (100.0)
Treated (fentanyl or IMP)	303 (100.0)	59 (100.0)	69 (100.0)	431 (100.0)
Completed trial treatment period	303 (100.0)	59 (100.0)	69 (100.0)	431 (100.0)
Completed follow-up visit	298 (98.3)	59 (100.0)	68 (98.6)	425 (98.6)
ET (withdrawals):	5 (1.7)	0 (0.0)	1 (1.4)	6 (1.4)
Reason for ET:				
Lost to follow up	5 (1.7)	0 (0.0)	1 (1.4)	6 (1.4)

Source: Section 14.1, Tables 14.1.2.1

Abbreviations: ET = early termination; IMP = investigational medicinal product; N = number of patients; n = number of observations

Note: percentages were based on the number of patients randomized.

Source: Study CNS7056-008 Report Body, p. 94 (PDF), Applicant's submission, NDA 212295.

Six patients, five in the RMZ treatment group and one in the midazolam treatment group, were lost to follow-up.

Protocol Violations/Deviations

Major protocol deviations were reported for approximately 49% of treated patients and included the following:

- Study drug administration despite adequate sedation (18%)
- Oxygen supplementation discontinued prior to fully alert (16%)
- Procedure initiated without adequate sedation (10%)
- Fentanyl administered less than the 5 to 10-minute interval (9%)
- RMZ or placebo dosing interval too short (4%)
- Fentanyl administered with SpO₂ < 90% (3%)

The Applicant reported that additional protocol deviations were noted after clinical database lock and unblinding. These deviations included IV fluid used from study site supply and RMZ and fentanyl vials and syringes were lost. These were considered minor and did not appear to result in patient safety concerns.

Demographic and Baseline Characteristics

Demographic and other baseline characteristics are summarized in the following table.

Table 22. Demographic Characteristics (Safety Population)

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Parameter	Sample Characteristics or Category	Remimazolam N=303 n (%)	Placebo N=59 n (%)	Midazolam N=69 n (%)	Total N=431 n (%)
Age [years]	N	303	59	69	431
	Mean	62.7	60.8	61.5	62.3
	SD	12.09	12.08	14.03	12.41
	Minimum	22	30	26	22
	Median	64.0	63.0	64.0	64.0
	Maximum	95	78	85	95
Age group [years]	<65	154 (50.8)	32 (54.2)	36 (52.2)	222 (51.5)
	≥65	149 (49.2)	27 (45.8)	33 (47.8)	209 (48.5)
Gender	Male	139 (45.9)	24 (40.7)	35 (50.7)	198 (45.9)
	Female	164 (54.1)	35 (59.3)	34 (49.3)	233 (54.1)
Ethnicity	Hispanic or Latino	8 (2.6)	0 (0.0)	0 (0.0)	8 (1.9)
	Not Hispanic or Latino	295 (97.4)	59 (100.0)	69 (100.0)	423 (98.1)
Race	American Indian or Alaska Native	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
	Asian	3 (1.0)	1 (1.7)	1 (1.4)	5 (1.2)
	Black or African American	33 (10.9)	10 (16.9)	19 (27.5)	62 (14.4)
	White	263 (86.8)	46 (78.0)	49 (71.0)	358 (83.1)
	Other	3 (1.0)	2 (3.4)	0 (0.0)	5 (1.2)
Height [cm]	N	303	59	69	431
	Mean	168.6	167.1	170.0	168.6
	SD	9.50	10.00	9.87	9.64
	Minimum	142	147	151	142
	Median	169.0	165.0	169.0	168.0
	Maximum	189	188	191	191
Weight [kg]	N	303	59	69	431
	Mean	80.9	77.7	83.0	80.8
	SD	20.21	21.17	22.10	20.66
	Minimum	41	32	43	32
	Median	81.6	77.2	84.4	81.6
	Maximum	155	127	183	183

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BMI [kg/m ²]	N	303	59	69	431
	Mean	28.4	27.9	28.0	28.3
	SD	6.39	7.09	5.79	6.39
	Minimum	16	14	16	14
	Median	28.3	26.2	27.9	28.1
	Maximum	45	44	41	45

Source: Section 14.1, Table 14.1.3.1

Abbreviations: BMI = body mass index; N = number of patients; n = number of observations; SD = standard deviation

Source: Study CNS7056-008, p. 101-2 (PDF), Applicant's submission, NDA 212295.

Overall, there did not appear to be clinically relevant differences in the treatment groups. The majority of patients were less than 65 years of age, white, not Hispanic or Latino, and female.

The following table summarizes the ASA-PS for each treatment group.

Table 23. ASA-PS Classification

ASA-PS Status	Remimazolam N=303 n (%)	Placebo N=59 n (%)	Midazolam N=69 n (%)	Total N=431 n (%)
I Healthy person	10 (3.3)	2 (3.4)	3 (4.3)	15 (3.5)
II Mild systemic disease	185 (61.1)	29 (49.2)	40 (58.0)	254 (58.9)
III Severe systemic disease	108 (35.6)	28 (47.5)	26 (37.7)	162 (37.6)

Source: Section 14.1, Table 14.1.3.3

Abbreviations: ASA-PS = American Society of Anesthesiologists - Physical Status; N = number of patients; n = number of observations

Source: Study CNS7056-008 Report Body, p. 102 (PDF), Applicant's submission, NDA 212295.

Other Baseline Characteristics

The most common pre-existing medical conditions were hypertension, GERD, and chronic obstructive pulmonary disease. There did appear to be a larger percentage of patients in the placebo treatment group compared to the RMZ treatment group who had a past medical history in the psychiatry SOC and included alcoholism, anxiety, anxiety disorder, depression, insomnia, and nicotine dependence. Otherwise, there did not appear to be clinically relevant differences in neurological or psychiatric histories that could have contributed to the reported efficacy results.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was 100% for patients who received the initial dose of study medication. As previously discussed, midazolam was the only rescue medication permitted during the study. If patients required additional sedatives, they were considered treatment failures.

Efficacy Results – Primary Endpoint

Unless otherwise specified, all efficacy analyses were performed on the ITT population. The analyses on the mITT and PP populations confirmed the results of the ITT population.

The primary efficacy endpoint was the success of the bronchoscopy procedure, which was defined as completion of the procedure without the need for rescue sedative medication, and no more than five doses of RMZ or placebo in a 15-minute window or no more than three doses of midazolam in a 12-minute window. The following table summarizes the results.

Table 24. Primary Efficacy Endpoint Results (Study CNS7056-008)

Patient Outcome	Remimazolam N=310 n (%)	Placebo N=63 n (%)	Midazolam N=73 n (%)	Total N=446 n (%)
Success	250 (80.6)	3 (4.8)	24 (32.9)	277 (62.1)
Failure	60 (19.4)	60 (95.2)	49 (67.1)	169 (37.9)
Reasons for failure:				
Rescue sedative medication taken	49 (15.8)	57 (90.5)	39 (53.4)	145 (32.5)
Too many doses within the predefined time window	14 (4.5)	10 (15.9)	10 (13.7)	34 (7.6)
Procedure not completed	9 (2.9)	3 (4.8)	5 (6.8)	17 (3.8)

Source: Section 14.2, Table 14.2.1.1

Abbreviations: N = number of patients; n = number of observations

Source: Study CNS7056-008 Report Body, p. 104 (PDF), Applicant’s submission, NDA 212295.

There was a higher percentage of patients treated with RMZ who successfully completed the procedure compared to patients treated with saline placebo. These results were statistically significant and clinically meaningful. The majority of patients in all treatment groups did not successfully complete the procedure due to the need for rescue sedative medication. This is in contrast to the results from Study CNS7056-006, in which a larger proportion of RMZ-treated patients failed to reach the primary efficacy endpoint due to too many doses of RMZ in a predefined time window. There was a very low number of patients who failed on this endpoint due to the inability to complete the procedure. The following table summarizes the comparison of the procedure success rates between RMZ and placebo, and RMZ and midazolam.

Table 25. Procedure Success Treatment Group Comparisons (Study CNS7056-008)

Comparison	Differences in Rates	95% Confidence Interval		P-Value
		Lower limit	Upper limit	
Remimazolam versus placebo	0.7588	0.6903	0.8274	<0.0001
Remimazolam versus midazolam	0.4777	0.3613	0.5941	

Source: Section 14.2, Table 14.2.1.2.1

Note: Wald asymptotic confidence limits are presented. The P-value was calculated from a Cochran-Mantel-Haenszel test accounting for fentanyl strata.

Source: Study CNS7065-008 Report Body, p. 105 (PDF), Applicant's submission, NDA 212295.

There was a statistically significant difference in the proportion of patients treated with RMZ who met the primary efficacy endpoint compared to those treated with saline placebo. The Applicant conducted comparative analyses for procedural success between the RMZ and midazolam treatment groups. As discussed previously, the midazolam was administered in an unblinded, open-label fashion (b) (4)

Regarding total RMZ dose, the following table, from the Applicant's clinical study report, indicates that the majority of patients (approximately 67%) were able to complete the colonoscopy with four or less doses of RMZ, including the initial bolus dose. This is in contrast to the placebo group, in which 96% required five or six doses of study medication.

Table 26. Total Number of Study Medication Doses (Safety Population)

Parameter	Sample Characteristic	Remimazolam N=303	Placebo N=59	Midazolam N=69	Total N=431
Number of trial medication doses	1	45 (14.9%)	0 (0.0%)	0 (0.0%)	45 (10.4%)
	2	64 (21.1%)	0 (0.0%)	7 (10.1%)	71 (16.5%)
	3	52 (17.2%)	2 (3.4%)	33 (47.8%)	87 (20.2%)
	4	42 (13.9%)	0 (0.0%)	13 (18.8%)	55 (12.8%)
	5	57 (18.8%)	45 (76.3%)	6 (8.7%)	108 (25.1%)
	6	24 (7.9%)	12 (20.3%)	5 (7.2%)	41 (9.5%)
	7	6 (2.0%)	0 (0.0%)	3 (4.3%)	9 (2.1%)
	8	7 (2.3%)	0 (0.0%)	1 (1.4%)	8 (1.9%)
	9	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	10	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	11	4 (1.3%)	0 (0.0%)	1 (1.4%)	5 (1.2%)

Source: Study CNS7056-008 Report Body, p. 130 (PDF), Applicant's submission, NDA 212295.

Sensitivity analyses were conducted to determine a possible effect based on fentanyl dosing. The following table was adapted from the Applicant’s data and provided by Dr. James Travis, statistical reviewer.

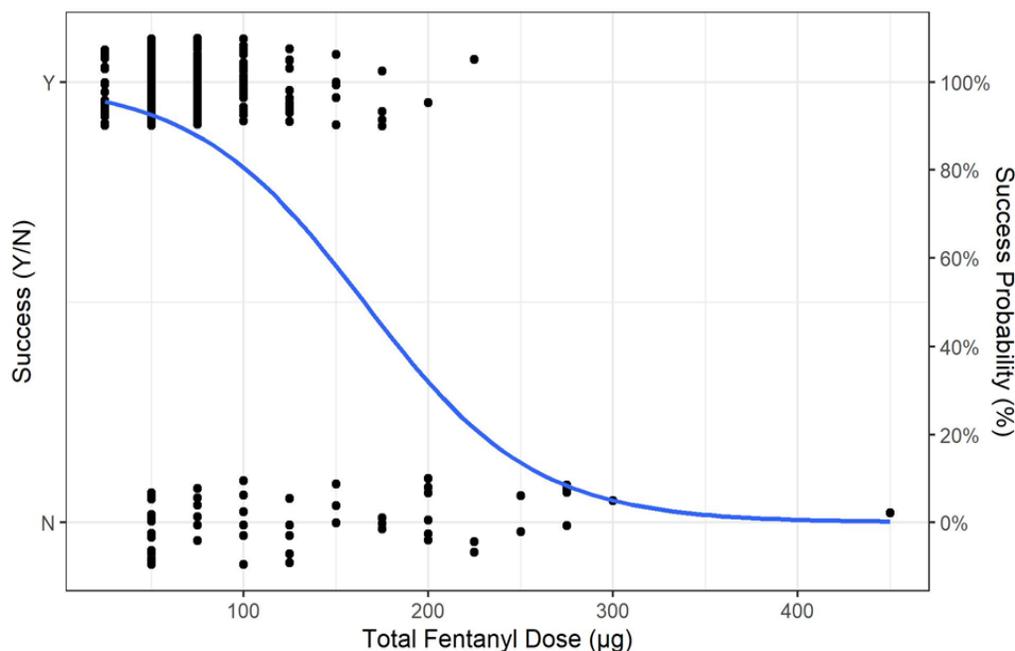
Table 27. Procedural Success by Fentanyl Stratum (Study CNS7056-008)

Fentanyl Stratum	RMZ, n/N (%)	Placebo, n/N, (%)	Difference in Rates (95% CI)	p-value
< 100 µg	195/215 (91%)	1/27 (4%)	87% (78.9, 95.1)	<0.0001
100 to 150 µg	49/63 (78%)	2/18 (11%)	67% (48.9, 84.4)	<0.0001
> 150 µg	6/25 (24%)	0/15 (0%)	24% (7.3, 40.7)	0.0421

Source: Adapted from Study CNS7056-008 Tables, Table 14.2.1.3.1, p. 200 (PDF), Applicant’s submission, NDA 212295, and statistical reviewer’s analysis.

Graphically, the correlation between fentanyl dose and procedural success in RMZ-treated patients is presented below.

Figure 4. Procedural Success Versus Total Fentanyl Dose, Remimazolam Treatment Group (Study CNS7056-008)



Source: Statistical Reviewer’s analysis.

It appears that as the dose of fentanyl increased, procedural success decreased in the RMZ treatment group and increased in the placebo treatment group. Additionally, the p value for the statistical analysis for procedure success between the RMZ and placebo treatment groups in the > 150 µg fentanyl stratum was 0.0421, which while significant, is not overwhelmingly so.

The same analysis conducted on the PP population did not reach statistical significance, as summarized in the following table.

Table 28. Procedural Success by Fentanyl Dose – Per Protocol Population (Study CNS7056-008)

Parameter	Category	Comparison	Differences in Rates	95% Confidence Interval		P-Value
				Lower Limit	Upper Limit	
Fentanyl strata	<100 µg	Remimazolam v Placebo	0.9070	0.8569	0.9571	<.0001
		Remimazolam v Midazolam	0.4903	0.2868	0.6938	
	100-150 µg	Remimazolam v Placebo	0.7273	0.4931	0.9614	<.0001
		Remimazolam v Midazolam	0.3182	-0.1131	0.7495	
	>150 µg	Remimazolam v Placebo	0.3333	-0.2001	0.8668	0.4142
		Remimazolam v Midazolam	0.3333	-0.2001	0.8668	

Source: Study CNS7056-008, Table 14.2.1.3.3, p. 204 (PDF of 14 Tables), Applicant's submission, NDA 212295.

As will be discussed in Section 7, Integrated Review of Effectiveness, there are confounding variables impacting the interpretation of these results, such as procedural difficulty. For more challenging and stimulating procedures, such as bronchoscopy, it is not uncommon for longer procedures to require more sedation and/or analgesia; however, this would be the case for both the RMZ and placebo treatment groups, such that statistical significance would not be expected to change. It is surprising that increasing doses of fentanyl appeared to have impacted the efficacy of RMZ more so than placebo.

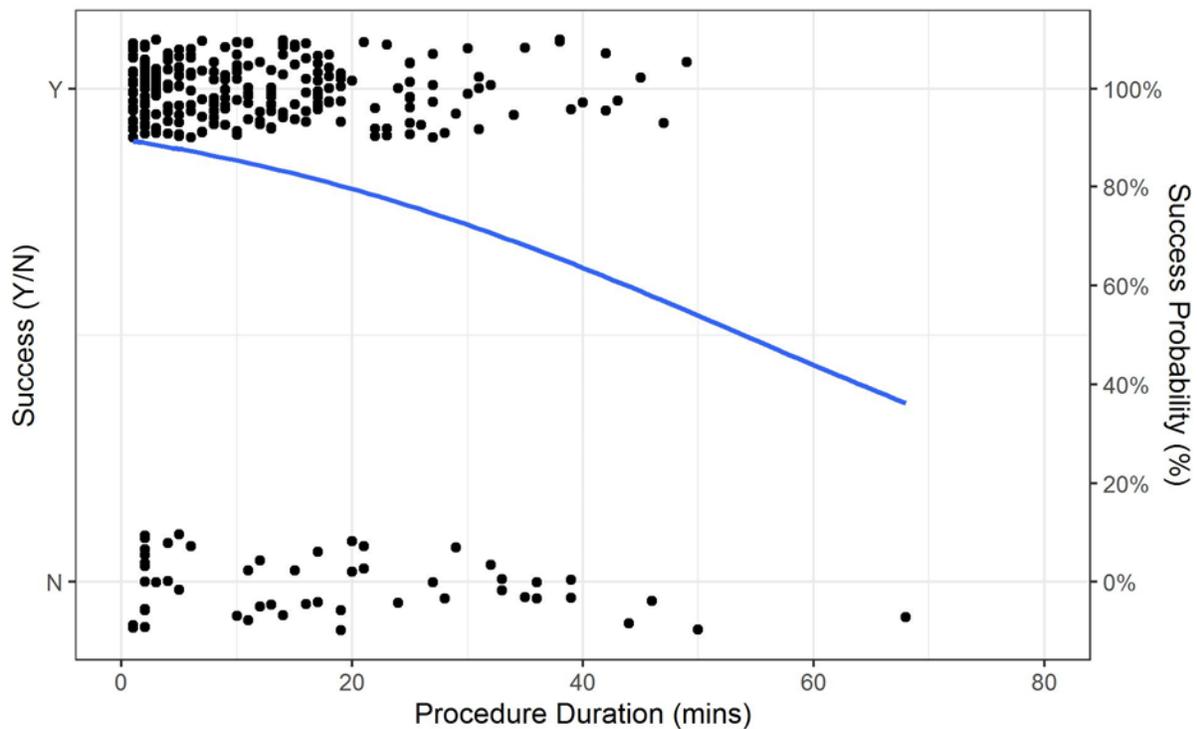
The graphical representation of the relationship between fentanyl dosing and procedural success in placebo-treated patients is a relatively flat line; however, in general, placebo-treated patients received higher doses of fentanyl during the procedure compared to RMZ-treated patients. Specifically, the mean dose of fentanyl administered in the placebo treatment group was 119 µg compared to 81.8 µg in the RMZ treatment group.

Different than the study population evaluated in Study CNS7056-006, patients on stable chronic doses of benzodiazepines and opioids were permitted to participate in this study. Unstable doses were defined as dose changes of more than 50% of the previous dose within 30 days prior to day of procedure. Sensitivity analyses were conducted for patients treated with chronic opioids and/or chronic benzodiazepine medications. The reported results indicate that the statistically significant difference in procedure success was maintained between the RMZ and placebo treatment groups for those patients receiving chronic opioid analgesics or benzodiazepines.

An additional consideration when evaluating the data presented by the Applicant for the procedural success endpoint, is the impact of the duration of the procedure on success. Specifically, whether longer procedures reported different procedural success rates. I noted during the Mid-Cycle Communication Meeting correspondence that the procedure success appeared to decrease with increasing duration. Specifically, it appeared that approximately 30%

of patients treated with RMZ who underwent a bronchoscopy lasting 20 minutes or longer were treatment failures, in contrast to approximately 13% of patients undergoing bronchoscopy lasting less than 20 minutes. The following figure, created by Dr. James Travis, suggests a negative correlation between procedure duration and success in the RMZ treatment group, such that longer procedures were less successful. It is again worth noting, however, that the majority of bronchoscopic procedures were completed in 20 minutes or less, such that there is limited efficacy information available for longer procedures.

Figure 5. Procedural Success with Increasing Procedure Duration, RMZ Treatment Group (Study CNS7056-008)



Source: Statistical Reviewer.

The following table summarizes the results from logistic regression analysis, conducted by Dr. James Travis. These results indicate that longer procedures did not result in lower rates of procedural success.

Table 29. Logistic Regression Analysis – Procedure Success vs. Procedure Duration, RMZ Treatment Group (Study CNS7056-008)

	Estimate	Standard Error	p-value
Intercept	2.17	0.250	
Procedure Duration	-0.04	0.012	<0.001

Source: Statistical reviewer.

In response to the Mid-Cycle Communication Meeting, the Applicant submitted additional information to clarify the proportion of patients who underwent procedures 20 minutes or longer and 30 minutes or longer, and the procedure success for longer procedures. Because 30 minutes is likely the more clinically meaningful duration of commonly performed procedures in the U.S., the Applicant’s findings using 30 minutes as the cut-off are presented in the table below.

Table 30. Distribution of Patients Undergoing Procedures < 30 minutes and ≥ 30 minutes (Study CNS7056-008)

Treatment Group	Procedure Duration			
	< 30 minutes		≥ 30 minutes	
	N	%	N	%
Remimazolam	280	90%	30	10%
Placebo	58	92%	5	8%
Midazolam	69	95%	4	5%

Source: Adapted from Clinical Information Amendment – Responses to Filing Review Issues Identified and MCC Agenda, dated November 19, 2019, p. 19 (PDF), Applicant’s submission, NDA 212295.

The table above clearly indicates that the majority of bronchoscopic procedures conducted in this study were completed within 30 minutes. As discussed in Section 6.1.2, Study Results for Study CNS7056-006, the Applicant provided information suggesting that the duration of evaluated procedures in the RMZ clinical development program were consistent with the average duration of commonly performed procedures in the U.S.

Data Quality and Integrity

There were no concerns identified regarding data quality or integrity with this study.

Efficacy Results – Key Secondary and Other Relevant Endpoints

Time to start of procedure

The median times to start of the procedure are summarized in the following table.

Table 31. Time to Start of Procedure from First Dose of Study Drug (minutes) (Study CNS7056-008)

		Remimazolam (N=310)	Placebo (N=63)	Midazolam (N=73)
Number of Patients in Analysis		300	60	68
Median		4.1	17.0	15.5
	95% CI: Lower Limit	4.0	16.0	13.8
	95% CI: Upper Limit	4.8	17.5	16.7
25th Percentile		3.0	15.3	11.9
	95% CI: Lower Limit	3.0	14.8	7.6
	95% CI: Upper Limit	3.3	16.0	13.0
75th Percentile		6.6	18.6	20.0
	95% CI: Lower Limit	6.0	17.5	17.8
	95% CI: Upper Limit	7.8	21.0	23.0

Source: Study CNS7056-008, 14 Tables, p. 269 (PDF), Applicant's submission, NDA 212295.

The results of the comparisons of the time to start of procedure using the log-rank test are presented in the following table.

Table 32. Log-Rank Results for Time to Start of Procedure (Study CNS7056-008)

Comparison	Hazard Ratio	95% Confidence Interval		P-Value
		Lower Limit	Upper Limit	
Remimazolam v Placebo	2.936	2.202	3.914	<.0001
Remimazolam v Midazolam	2.869	2.183	3.772	

Source: Study CNS7056-008, 14 Tables, p. 275 (PDF), Applicant's submission, NDA 212295.

The median time to start of procedure for the RMZ-treated patients was statistically, and clinically, significantly shorter than that observed for placebo-treated patients. Sensitivity analyses evaluating a potential impact of fentanyl dosing on the reported efficacy for RMZ-treated patients suggested that higher doses of fentanyl, > 150 µg, resulted in longer median times to start of procedure (9 minutes versus 4.1 minutes); however, the comparison between RMZ-treated and placebo-treated patients was still statistically significant. There was a smaller proportion of patients who required this dose of fentanyl, so definitive conclusions are challenging, and, clinically, it is not surprising that higher doses of fentanyl correlate with a longer median time to start of a procedure. This may indicate the induction of sedation is more challenging in some patients for a variety of reasons. may indicate a patient requires more sedation and analgesia. In the midazolam treatment group, it appeared an increasing dose of fentanyl also correlated with increased time to start of the procedure. For the placebo treatment group, there was no consistent trend observed with increasing doses of fentanyl administration and median time to start of procedure.

Additional sensitivity analyses for chronic opioid use did not identify a clinically significant increase in median time to start of procedure in RMZ-treated patients and the statistical significance between the RMZ and placebo treatment groups was maintained. Chronic benzodiazepine use did appear to increase the median time to start of procedure in RMZ-treated patients, 6.6 minutes versus 4 minutes; however, the statistical significance between treatment groups was maintained.

Time to peak sedation

The median time to peak sedation from the first dose of RMZ prior to any top-up dose was 3.5 minutes, which is shorter than that observed for the midazolam treatment group. Only one patient in the placebo treatment group reached peak sedation levels after the initial dose of placebo. The results of sensitivity analyses for fentanyl dose, chronic opioid, and chronic benzodiazepine use were similar to those of the main analysis.

Time to ready for discharge

Time to ready for discharge was defined as the ability to walk unassisted after the end of the bronchoscopy procedure (bronchoscope out) is summarized in the following table.

Table 33. Time to Ready for Discharge After Bronchoscope Out (Study CNS7056-008)

	Remimazolam (N=310)	Placebo (N=63)	Midazolam (N=73)
Number of Patients in Analysis	302	60	68
Median	60.0	81.0	66.0
95% CI: Lower Limit	57.0	70.0	62.0
95% CI: Upper Limit	63.0	100.0	72.0
25th Percentile	45.0	55.0	55.0
95% CI: Lower Limit	43.0	52.0	45.0
95% CI: Upper Limit	47.0	67.0	62.0
75th Percentile	78.0	125.0	102.0
95% CI: Lower Limit	72.0	100.0	80.0
95% CI: Upper Limit	83.0	139.0	134.0

Source: Study CNS7056-008, 14 Tables, p. 346 (PDF), Applicant's submission, NDA 212295.

The median time to ready for discharge was statistically and clinically significantly shorter in RMZ-treated patients compared to placebo-treated patients, but was similar in midazolam-treated patients. Sensitivity analyses for fentanyl dosing in RMZ-treated patients for time to ready for discharge after bronchoscope out did demonstrate an increase in the observed time with increasing doses of fentanyl. Specifically, for patients treated with fentanyl 100 µg, 100 µg to 150 µg, and > 150 µg the times to ready for discharge were 57, 63.5, and 84 minutes respectively. There were, however, only 24 patients in the RMZ treatment group who received

> 150 µg of fentanyl. Similar increases were observed in patients treated with midazolam (63.5, 68, and 86 minutes, respectively). The placebo treatment group demonstrated inconsistent times to ready for discharge based on fentanyl dosing (100, 71.5, and 87 minutes, respectively).

The time to ready for discharge after last dose of study drug administration was statistically significantly shorter in patients treated with RMZ (64.8 minutes) compared to patients treated with placebo (93 minutes). Patients treated with midazolam had slightly longer times to ready for discharge after last dose of study drug (70 minutes) compared to RMZ-treated patients. Sensitivity analyses indicated that all treatment groups had an increased median time to ready for discharge in the > 150 µg fentanyl stratum.

Results for patients receiving chronic benzodiazepines or opioid analgesics did not appear significantly different from the results of the main analysis for time to ready for discharge after bronchoscope out and after last dose of study drug.

Time to fully alert

Time to fully alert from last injection of study drug or rescue and from the end of the bronchoscopy procedure was defined as the time to the first of three consecutive MOAA/S scores of 5. As shown in the following table, the median time to fully alert after bronchoscope out was statistically, and clinically, significantly shorter in patients treated with RMZ versus placebo. Specifically, the median time to fully alert for placebo-treated patients was double that of RMZ-treated patients.

Table 34. Time to Fully Alert from Bronchoscope Out (minutes) (Study CNS7056-008)

	Remimazolam (N=310)	Placebo (N=63)	Midazolam (N=73)
Number of Patients in Analysis	302	60	68
Median	6.0	13.6	12.0
95% CI: Lower Limit	5.2	8.1	5.0
95% CI: Upper Limit	7.1	24.0	15.0
25th Percentile	3.8	7.2	2.6
95% CI: Lower Limit	3.0	5.0	2.0
95% CI: Upper Limit	4.0	8.1	4.0
75th Percentile	19.1	34.1	23.8
95% CI: Lower Limit	14.0	24.0	15.0
95% CI: Upper Limit	22.0	45.7	35.1

Comparison	Hazard Ratio	95% Confidence Interval		P-Value
		Lower Limit	Upper Limit	
Remimazolam v Placebo	1.725	1.296	2.297	0.0001
Remimazolam v Midazolam	1.127	0.863	1.471	

Source: Study CNS7056-008, 14 Tables, pp. 472 and 475, Applicant's submission, NDA 212295.

Results of the sensitivity analysis for fentanyl dose suggest that increasing doses of fentanyl delayed the time to fully alert in all treatment groups, but the delay was greatest in the RMZ treatment group.

The results from analysis of time to fully alert after last dose of study drug or rescue medication are similar to those from bronchoscope out. The RMZ-treated patients had the shortest time to fully alert. Results of the sensitivity analysis for fentanyl dose suggest that increasing doses of fentanyl delayed the time to fully alert in all treatment groups, but the delay was greatest in the RMZ treatment group for patients who received > 150 µg fentanyl.

Results for patients receiving chronic benzodiazepines or opioid analgesics did not appear significantly different from the results of the main analysis for time to fully alert after bronchoscope out and after last dose of study drug or rescue medication.

MOAA/S Scores by Time Point

All patients in all three treatment groups had MOAA/S score of five, 15 minutes prior to the procedure. Within one minute of administration, three patients (1%) in the RMZ treatment group had a score of 0, which represents no response to painful trapezius squeeze. Lack of response to painful stimuli as a measure of anesthetic depth suggests that there were patients who very quickly experienced deep sedation after administration of RMZ. Additionally, there were 10 patients (3%) who experienced MOAA/S scores of two or less within one minute of RMZ administration. This is in contrast to no patients in either the placebo or midazolam treatment groups experiencing this depth of sedation within this short amount of time from administration.

Dose Response and Durability of Response

There was a single dose of RMZ administered in this Phase 3 study, therefore a dose-response was not evaluated.

A pharmacokinetic property of RMZ that the Applicant states is a clear advantage over other commonly administered benzodiazepines for procedural sedation is its rapid metabolism by tissue carboxylase to an inactive metabolite resulting in fast-on and fast-off sedation. The majority of patients required three or more doses of RMZ to maintain adequate sedation for

successful completion of the bronchoscopy procedure. During this study, it did not appear that the number of doses of RMZ was positively correlated with the time to recovery from sedation, measured via time to fully alert and time to discharge.

Additional Analyses Conducted on the Individual Trial

The Applicant did provide additional efficacy and safety information based on procedure duration in response to the Mid-Cycle Meeting Communication. That information has been incorporated into appropriate sections of this review.

Data Monitoring Committee Meetings and Outcomes

The DMC held regular meetings to evaluate the safety data during the study. Similar discussions to those conducted during review of Study CNS7056-006, occurred during review of this study (refer to Section 6.1.2, Study Results, for additional information). No new issues were discussed that would adversely impact the benefit:risk of the on-going study or the approval of RMZ for use during bronchoscopic procedures.

6.3. A Study Evaluating the Safety and Efficacy of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in ASA III and IV Patients Undergoing Colonoscopy (CNS7056-015)

6.3.1. Study Design

Overview and Objective

This was a prospective, double-blind, randomized, placebo-controlled, multi-center, study comparing RMZ to placebo in ASA class III and IV patients undergoing a colonoscopy for diagnostic or therapeutic reasons. The study was designed to evaluate the safety of RMZ. Because the additional midazolam arm was open-label, the study is not considered active-controlled.

The study objectives were as follows:

- Primary objective - 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
- Secondary objectives –
 - Procedural success, defined as:
 - completion of the colonoscopy procedure, AND
 - no requirement for a rescue sedative medication, AND
 - no requirement of more than 5 doses of study medication within any 15-minute window (for midazolam: 3 doses within any 12-minute window)

- to assess the time
 - to start of procedure
 - to peak sedation
 - to fully alert
- to assess
 - MOAA/S scores by time point
 - recall of procedure using the Brice questionnaire
 - drowsiness visual analog scale for re-sedation
 - requirement for flumazenil
 - pain on injection
 - population PK
 - investigator's satisfaction
 - effect of study drug or midazolam in combination with fentanyl on ventilatory drive
 - amount of study drug administered

Trial Design

This study was a prospective, double-blind, randomized, placebo and active controlled, multi-center, parallel group study comparing remimazolam to placebo, with an additional open-label arm for midazolam. Patients in all treatment groups were administered fentanyl 50 µg (or less for patient comorbid conditions if necessary; 75 µg was administered prior to Protocol Amendment 1) for analgesia immediately prior to administration of study drug. Supplemental doses of fentanyl 25 µg could be administered for analgesia, to a maximum dose of 200 µg. Investigators assessed the analgesic effect of fentanyl over 5 to 10 minutes. Investigators were to administer fentanyl for analgesia only. If additional sedation was needed, supplemental doses of study medication or midazolam were administered.

RMZ or Placebo (Study Drug Treatments) Dose Administration

An initial dose of 1 to 2 mL blinded study medication was administered manually by IV injection over one minute. Supplemental doses of 0.5 to 1 mL of study medication were administered by slow IV injection (over approximately 15 seconds), at least 2 minutes apart, if initial sedation was insufficient, defined as a score of greater than three on the MOAA/S. If sedation was still inadequate to begin the procedure after the initial dose and a maximum of four additional doses of study medication within a 15-minute period, the patient was considered a treatment failure and midazolam rescue sedative medication was administered at the discretion of the investigator.

If sedation was sufficient ($\text{MOAA/S} \leq 3$) to allow the colonoscopy to begin, subsequent doses of 1 mL could be administered to maintain an adequate sedation level ($\text{MOAA/S} \leq 4$). If the MOAA/S was ≥ 4 , additional 0.5 to 1 mL doses, over 15 seconds, could be administered, at least

2 minutes apart, to maintain or again reach an adequate sedation level. Two or more additional minutes was allowed to fully evaluate the sedative effect. The overall number of double-blinded study medication doses was not limited as long as not more than five doses were administered in any 15-minute window. During the procedure, patients were considered treatment failures if adequate sedation ($\text{MOAA/S} \leq 4$) could not be maintained despite five doses of RMZ or pbo within any 15-minute period. Midazolam rescue sedative medication was then administered at the discretion of the investigator, to allow for completion of the procedure.

Midazolam Open-Label Treatment Arm

Midazolam was the only rescue sedative medication permitted during the study. An initial dose was administered by IV injection over 2 minutes. An initial dose of 1 mg was administered manually over 2 minutes. If there was insufficient sedation to begin the procedure after the initial dose of midazolam ($\text{MOAA/S} > 3$), a supplemental dose of 0.5 mg could be administered over at least 2 minutes and after at least 2 minutes since the end of the last administered dose and after MOAA/S assessment. If initial sedation was still insufficient, an additional dose of midazolam 0.5 mg could be given, at least 2 minutes apart.

If there was still inadequate sedation to begin the procedure after the initial dose and a maximum of two additional doses within a 12-minute period, the patient was considered a treatment failure and received midazolam rescue sedative medication at the discretion of the investigator to start the procedure. If sedation from open-label midazolam was sufficient to allow colonoscopy to begin, subsequent doses could be administered to maintain an adequate sedation level ($\text{MOAA/S} \leq 4$). If the MOAA/S was ≥ 4 , additional doses could be administered, at least two minutes apart, to maintain, or again reach, an adequate sedation level. The number of midazolam doses was limited such that not more than three doses were administered in any 12-minute window. If more than three doses within any 12-minute window was needed to obtain or maintain adequate sedation for the colonoscopy, the patient was considered a treatment failure. Supplemental midazolam 0.5 mg doses were administered over at least two minutes, and at least two minutes were permitted to evaluate the sedative effect.

The schedule of assessments for this study is summarized in the following table.

Table 35. Schedule of Study Assessments

NDA 212295

Byfavo (Remimazolam) for injection

Cosmo Technologies, Ltd.

	Day -21 to Day -1	Day 0	Day 1	Day 1 (≥6h post-procedure) (+1 day)	Day 4 (+3 days)		
	Screening	Preparation	Treatment Day	Follow-up	Follow-up (phone call)		
Informed Consent	X	Bowel preparation as local standard	See next schedule (Table 5)				
Eligibility criteria/medical and medication history/demographics	X						
Physical examination ^a	X						
ASA Score assessment	X						
Clinical laboratory samples ^b	X				X		
Urine HCG (females)	X						
Oral saliva ethanol screen	X						
Haemodynamics ^c	X				X		
Height	X						
Weight	X						
Supine respiratory rate					X		
Body temperature	X				X		
12-lead ECG	X						
Bowel preparation							
Fast ^d							
Fentanyl administration							
Administration of trial medication							
3-lead ECG telemetry							
Pulse oximetry monitoring/recording							
pCO ₂ (capnography) monitoring/recording							
Respiratory rate monitoring/recording							
MOAA/S scale score monitoring/recording							
Pain VAS							
Investigator's satisfaction questionnaire							
Brice questionnaire						X	
Airway management							
Assessment of adverse events	X					X	X
Assessment of concomitant medication	X					X	

ASA = American Society of Anesthesiologists; HCG = human chorionic gonadotropin; ECG = electrocardiogram; pCO₂ = partial pressure of carbon dioxide; MOAA/S = Modified Observer's Assessment of Alertness and Sedation; VAS = visual analogue scale

^a Screening physical examination included rectal examination, and ASA score.

^b Haematology, serum chemistry.

^c Supine heart rate and systolic and diastolic blood pressure.

^d Fasting was to begin from midnight of the day before dosing (no food).

Source: Study CNS7065-015 Report Body, p. 48 (PDF), Applicant's submission, NDA 212295.

The following table summarizes the assessments performed on study day 1.

Table 36. Study Day 1 Assessments

Clinical Review
Petit-Scott, M.D.

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

Dosing Day (Day 1)																		
Procedures	Pre-dose				Dosing of trial medication ^a	Post-dose												
	within 3 hr	within 30 min	within 15 min	1min pre-dose		1 min	1.5 min	2 min	2.5 min	3 min	5 min	10 min	Every 5 minutes until fully alert					
Review inclusion & exclusion criteria	x																	
Medical & medication histories	x																	
Adverse Events	x																	
Concomitant medication	x																	
Physical examination	x (B)																	
Weight	x (B)																	
Body temperature	x (B)	x										X (post procedure)			X (at fully alert)		X (at discharge)	
Clinical laboratory tests	x (B)																X (at discharge)	
3-lead ECG			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
3-lead ECG documentation in CRF ^d			x	x				x				x	x	x	x	x	x	
12-lead ECG ^b	x (B)					x						x	Every 10 minutes until end of procedure *					
Urine pregnancy test	x																	
Ethanol saliva test	x																	
Randomisation	x																	
Haemodynamic parameters (HR ¹ , BP) ^{e, f, g}	x	x	x (B)	x				x				x	x	x	x	x	x	
Normal saline		xx	xx	xx	xx up to 1000 mL administered, if fluid status allowed	xx	xx	xx	xx	xx	xx	xx	xx	xx	until end of colonoscopy procedure			
MOAA/S ^b			x (B)			x	x	x	x	x	every minute until fully alert, then every 5 min until discharge							
Respiratory rate ^g			x (B)	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
RR (document in CRF)			x (B)	x				x				x	x	x	x	x	x	
SpO ₂ (pulse oximetry)			x (B)	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
SpO ₂ ^{h, i} (documentation in CRF)			x (B)	x				x				x	x	x	x	x	x	

Dosing Day (Day 1)																		
Procedures	Pre-dose				Dosing of trial medication ¹	Post-dose												
	within 3 hr	within 30 min	within 15 min	1min pre-dose		1 min	1.5 min	2 min	2.5 min	3 min	5 min	10 min	Every 5 minutes until fully alert					
pCO ₂ (capnography)			x (B)	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
pCO ₂ (documentation in CRF)			x (B)	x				x				x	x	x	x	x	x	
Airway management assessment			x															
Supplemental oxygen optional (nasal prongs)			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	
Fentanyl					x	Supplemental doses q 5-10 min until adequate analgesia or 200 µg maximum dose												
Pain on injection	Learning				x or as soon as possible													
Drowsiness VAS ⁵				x				x			x	x	15		25	35	45	60
Investigator's satisfaction questionnaire																		x (at discharge)

B = baseline values; BP = blood pressure; CRF = case report form; ECG = electrocardiogram; HR = heart rate; MOAA/S = Modified Observer's Assessment of Alertness/Sedation scale; pCO₂ = partial pressure of carbon dioxide; RR = respiratory rate; SpO₂ = peripheral blood oxygen saturation; VAS = visual analogue scale; x = Single action; Xx = Continuous action

¹ Trial medication: Loading dose of randomised trial drug start defined t=0, supplemental doses as per protocol.

² Colonoscopy started at sufficient sedation (MOAA/S ≤3), duration as necessary (MOAA/S ≤4), at the discretion of the investigator.

³ If possible by patient.

⁴ Documented by running a strip.

⁵ After first dose, 5 minutes after dosing and every 10 minutes until the end of the procedure if possible, and also 5 minutes after the end of the procedure.

⁶ In addition to the times specified above, blood pressure, heart rate and SpO₂ were recorded immediately prior to, and 2 minutes after each additional dose of fentanyl

⁷ Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate and peripheral capillary oxygen saturation) were recorded when an AE with a respiratory or cardiovascular focus had been observed. Additionally a set of vital signs was recorded and documented in the CRF at the onset time of AEs, if feasible or available

⁸ 12-lead ECG also in the case of a clinical event, eg, arrhythmias, where repeated ECG recordings were warranted

⁹ Heart rate was also monitored and recorded continuously by using an electronic device

Source: Study CNS7056-015 Report Body, p. 50 (PDF), Applicant's submission, NDA 212295.

Eligibility Criteria

Pertinent inclusion criteria included the following:

- adult patients ≥ 18 years of age
- ASA physical status III or IV
- non-pregnant females

Pertinent exclusion criteria included the following (*Note: there was no exclusion based on acute or chronic use of benzodiazepines or opioids in this study. This in contrast to the eligibility criteria for the other Phase 3 studies, CNS7056-006 and CNS7056-008):

- known sensitivity to benzodiazepines, flumazenil, opioids, naloxone, or a medical condition such that the use of these medications is contraindicated
- patients acutely intoxicated with alcohol or drugs of abuse at baseline

Study Endpoints

The primary efficacy endpoint was success of the colonoscopy procedure, defined as follows:

- completion of the colonoscopy procedure, AND
- no requirement for a rescue sedative medication (midazolam), AND

- no requirement for more than five doses of study medication (RMZ or pbo) within any 15-minute window, or no requirement for more than three doses of midazolam within any 12-minute window in the open-label arm

Additional efficacy endpoints were as follows:

- amount of fentanyl administered
- time to:
 - start of procedure
 - peak sedation
 - fully alert (after end of colonoscopy procedure and after the last injection of study drug)
- MOAA/S by time point
- recall of the procedure using the Brice questionnaire
- drowsiness visual analog scale
- requirement for flumazenil administration
- investigator satisfaction

Safety assessments included the following:

- Physical exam
- Laboratory assessments
- Vital signs (heart rate, blood pressure, respiratory rate, oxygen saturation, and temperature)
- 12-lead ECG at screening, within three hours pre-dose, after the first dose, five minutes after the start of initial dosing and every 10 minutes until the end of the procedure and five minutes after the end of the procedure, and when indicated
- 3-lead ECG was monitored continuously during the procedure until fully alert
- Adverse events
 - with emphasis on cardiorespiratory events and those associated with drugs of abuse
 - vital signs considered adverse events were defined as follows:
 - bradycardia – HR < 40 bpm or a decrease of 20% or more from baseline for ≥ 30 seconds
 - hypertension – increase in systolic blood pressure (SBP) to ≥ 180 mmHg or in diastolic blood pressure (DBP) to ≥ 100 mmHg or an increase in either SBP or DBP 20% or more from baseline or medical intervention required
 - hypotension – decrease in SBP ≤ 80 mmHg or in DBP ≤ 40 mmHg or a fall in SBP or DBP 20% or more from baseline or medical intervention required
 - respiratory rate decreased – < 8 breaths per minute

- oxygen saturation < 90% for ≥ 1 minute or any decrease requiring medical intervention
 - prolonged sedation (MOAA/S ≤ 4 for 60 minutes or longer after the last dose of study drug administration) including the need for flumazenil
 - with emphasis on adverse events associated with medications of abuse
- Interventions
 - airway interventions
 - IV fluid and medication administration

Statistical Analysis Plan

Analysis Populations

Eight analysis populations were defined:

1. Safety population consisted of all randomized patients who received any study drug.
2. Secondary Nellcor respiratory rate safety population. The three secondary safety populations consisted of all patients in the safety Population who had usable Nellcor data (defined as ≥ 90% of readable Nellcor data per parameter within observation period).
3. Secondary Nellcor heart rate population.
4. Secondary Nellcor pulse oximetry population.
5. Overall Nellcor population consisted all patients in the safety population who had usable Nellcor data for any of the three outcome variables
6. Intent-to-treat (ITT) analysis set included all patients who were randomized.
7. Modified intent-to-treat (mITT) analysis set included all patients included in the ITT population who received at least one complete dose of randomized study drug.
8. The per-protocol (PP) analysis set included all patients from the ITT analysis set who received study drug according to their randomization and the planned treatment schedule and who did not have any major protocol deviations.

All safety analyses were based on the actual treatment administered. Analyses of the Nellcor data were conducted on patients in the respective population. All other safety analyses were conducted on patients in the safety population and were based on actual treatment administered.

All efficacy analyses were conducted on patients in the ITT and mITT populations, and were based on randomization treatment assignment, not actual treatment administered. The primary efficacy analysis was the comparison of procedural success rates (using the composite endpoint) between the RMZ and placebo groups. The success of the procedure was summarized by subgroups of fentanyl use, defined as < 100 µg, 100 to 150 µg, and 150 to 200 µg. The success of the procedure was also summarized by subgroups of ASA status, III or IV. Descriptive testing was performed on the secondary efficacy endpoints.

Additional sensitivity analyses were performed to assess the impact of opioid and midazolam administration on procedural success in all treatment groups.

Protocol Amendments

There was one amendment dated March 3, 2016, which reduced the initial fentanyl dose from 75 µg to 50 µg, or a suitable reduced dose in elderly or debilitated/chronically ill patients, as recommended by the DMC.

6.3.2. Study Results

Compliance with Good Clinical Practice

The following statement was included on the title page of the study.

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

I have no concerns regarding the validity of this statement.

Financial Disclosure

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, and was the recipient of significant payments of other sorts.

Patient Disposition

A total of 79 patients were randomized in a 2:2:1 ratio to RMZ, midazolam, or placebo treatment. Two patients did not receive treatment and are not included in the safety population. The following table summarizes patient disposition in this study.

Table 37. Patient Disposition (Safety Population)

Number of Patients	Remimazolam	Placebo	Midazolam	TOTAL
	N=31 n (%)	N=16 n (%)	N=30 n (%)	N=77 n (%)
Informed Consent Given	31 (100)	16 (100)	30 (100)	77 (100)
Randomised	31 (100)	16 (100)	30 (100)	77 (100)
Treated (fentanyl or IMP)	31 (100)	16 (100)	30 (100)	77 (100)
Completed Trial Treatment Period	31 (100)	16 (100)	30 (100)	77 (100)
Completed Follow-Up Visit	31 (100)	16 (100)	30 (100)	77 (100)
Early Termination	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: [Section 14.1, Tables 14.1.2.1](#)

IMP = investigational medicinal product; N = number of patients; n = number of observations

Note: percentages are based on the number of patients randomised.

Source: Study CNS7056-015 Report Body, p. 71 (PDF), Applicant's submission, NDA 212295.

All patients in the safety population received treatment and completed the study follow-up visit.

Protocol Violations/Deviations

The following table provides a summary of the protocol deviations that resulted in exclusion of the patient data from the PP data set.

Table 38. Protocol Deviations (Safety Population)

Severity	Category	Remimazolam	Placebo	Midazolam	TOTAL	
		N=31 n (%)	N=16 n (%)	N=30 n (%)	N=77 n (%)	
Major	Deviation	13 (41.9)	4 (25.0)	4 (13.3)	21 (27.3)	
	Clinical Procedures: Endoscopy	1 (3.2)	2 (12.5)	0 (0.0)	3 (3.9)	
	IMP/Dosing: IMP Incorrect Dosing	13 (41.9)	2 (12.5)	4 (13.3)	19 (24.7)	
	IMP/Dosing: Rescue Sedative Medication	0 (0.0)	0 (0.0)	1 (3.3)	1 (1.3)	
	IMP/Dosing: Unblinding information distribution	1 (3.2)	1 (6.3)	0 (0.0)	2 (2.6)	
	Minor	Deviation	14 (45.2)	16 (100)	27 (90.0)	57 (74.0)
		IMP/Dosing: IMP Incorrect Dosing	14 (45.2)	16 (100)	27 (90.0)	57 (74.0)
Scales/Questionnaires: Time to Fully Alert		1 (3.2)	1 (6.3)	0 (0.0)	2 (2.6)	
Selection Criteria: Protocol Inclusion/ Exclusion Criteria		1 (3.2)	1 (6.3)	1 (3.3)	3 (3.9)	

Source: [Section 14.1, Tables 14.1.3.9](#)

IMP = investigational medicinal product; N = number of patients; n = number of observations

Note: Patient 3005 also had a major protocol violation (fulfilling exclusion criteria #1), but was excluded from the Safety population, and is therefore not included in this table.

Source: Study CNS7056-015 Report Body, p. 73 (PDF), Applicant's submission, NDA 212295.

Major protocol deviations were reported for 21 patients. The most frequently reported deviation, 19 of 21 patients, was incorrect dosing of study drug medication. This was observed more in the RMZ treatment group than in the placebo or midazolam treatment groups. The dosing errors included administration of top-up doses when sedation was adequate, dosing window too short, and inadequate dose administration time. One patient received propofol as rescue sedation. There three major protocol deviations related to starting procedure prior to adequate sedation.

Demographic and Baseline Characteristics

Demographic information for the study population is summarized in the following table.

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

Parameter	Sample Characteristics or Category	Remimazolam	Placebo	Midazolam	TOTAL
		N=31 n (%)	N=16 n (%)	N=30 n (%)	N=77 n (%)
Age (years)	N	31	16	30	77
	Mean	63.1	63.0	61.5	62.5
	Std. Deviation	8.65	8.37	10.60	9.32
	Minimum	47	49	42	42
	Lower quartile	57.0	55.5	53.0	56.0
	Median	64.0	63.0	62.5	63.0
	Upper quartile	69.0	68.0	69.0	69.0
	Maximum	84	79	81	84
Age group	Age <65 years	18 (58.1)	9 (56.3)	19 (63.3)	46 (59.7)
	Age ≥65 years	13 (41.9)	7 (43.8)	11 (36.7)	31 (40.3)
Gender	Male	17 (54.8)	12 (75.0)	14 (46.7)	43 (55.8)
	Female	14 (45.2)	4 (25.0)	16 (53.3)	34 (44.2)
Ethnicity	Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Not Hispanic or Latino	31 (100)	16 (100)	30 (100)	77 (100)
Race	American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	0 (0.0)	0 (0.0)	1 (3.3)	1 (1.3)
	Black or African American	6 (19.4)	3 (18.8)	10 (33.3)	19 (24.7)
	Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	White	25 (80.6)	13 (81.3)	19 (63.3)	57 (74.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Height (cm)	N	31	16	30	77
	Mean	171.1	171.8	168.4	170.2
	Std. Deviation	10.07	7.72	10.32	9.72
	Minimum	147	158	152	147
	Lower quartile	163.0	166.0	162.0	163.0
	Median	172.0	172.0	168.0	170.0
	Upper quartile	180.0	178.0	172.0	180.0
	Maximum	185	183	195	195

Weight (kg)	N	31	16	30	77
	Mean	91.0	94.0	87.9	90.4
	Std. Deviation	28.14	26.11	23.91	25.90
	Minimum	58	59	57	57
	Lower quartile	72.2	81.4	70.5	72.0
	Median	82.0	88.4	80.1	84.0
	Upper quartile	112.7	100.1	98.0	99.5
	Maximum	170	167	155	170
BMI (kg/m ²)	N	31	16	30	77
	Mean	30.9	30.8	30.8	30.8
	Std. Deviation	8.28	5.53	6.75	7.11
	Minimum	22	23	23	22
	Lower quartile	24.1	27.4	25.4	25.4
	Median	28.6	28.9	30.3	28.9
	Upper quartile	35.7	35.1	33.8	33.9
	Maximum	55	40	53	55

Source: [Section 14.1, Tables 14.1.3.1](#)

BMI = body mass index; N = number of patients; n = number of observations; Std. = standard

Source: Study CNS7056-015 Report Body, pp. 77-78, Applicant's submission, NDA 212295.

The overall mean patient age was 62 years and was similar across all treatment groups. The majority of treated patients were less than 65 years of age, male, white, and not Hispanic or Latino. Mean BMI was similar in all treatment groups.

The following table summarizes the ASA-PS for each treatment group.

Table 39. ASA-PS Classification

ASA Status	Remimazolam N=31 n (%)	Placebo N=16 n (%)	Midazolam N=30 n (%)	TOTAL N=77 n (%)
I Healthy person	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
II Mild systemic disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
III Severe systemic disease	16 (51.6)	9 (56.3)	15 (50.0)	40 (51.9)
IV Severe systemic disease that is constant threat to life	15 (48.4)	7 (43.8)	15 (50.0)	37 (48.1)
V A moribund person who is not expected to survive without the operation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
VI Declared brain-dead person whose organs are being removed for donor purposes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: [Section 14.1, Tables 14.1.3.3](#)

ASA-PS = American Society of Anesthesiologists – Physical Status; N = number of patients; n = number of observations

Source: Study CNS7056-015 Report Body, p. 78, Applicant’s submission, NDA 212295.

Consistent with the objectives of this study, all treated patients were of ASA-PS III or IV. An blinded, independent physician not participating in the study confirmed the ASA-PS of each patient. There was a differing assessment between the investigator and blinded reviewer for six patients, which required the medical monitor to initiate a discussion to reach agreement on the ASA-PS. Four patients had been assigned an ASA-PS III by the investigator and ASA-PS IV by the reviewer. All four patients were ultimately assigned ASA-PS IV. Two patients had been assigned ASA-PS IV by the investigator and ASA-PS III by the reviewer. One patient was assigned ASA-PS IV, and the other patient was assigned ASA-PS III. There appeared to be even numbers of both ASA-PS classifications in the study and evenly distributed across the RMZ and midazolam treatment groups. The placebo group had a higher proportion of ASA-PS III patients (56.3%) than ASA-PS IV patients (43.8%).

Other Baseline Characteristics

The most frequently reported medical histories in this study were in the vascular, surgical and medical procedures, metabolism and nutrition disorders, GI disorders, and respiratory, thoracic, and mediastinal disorders system-organ-classes.

For ASA-PS classification III patients, the most commonly administered concomitant medications in the RMZ treatment group included those in the Anatomical Therapeutic Chemical (ATC) drug classes of drugs for constipation, sedatives/hypnotics, and lipid modifying agents. The sedatives/hypnotics class included midazolam rescue medication. There was a single patient taking clonazepam daily for prevention of panic disorder. There were two

patients taking opioid analgesics prior to the study. One patient was taking tramadol for arthritis and another was taking oxycodone and norco for lumbar degenerative disk disease.

For ASA-PS classification IV patients, the most commonly administered concomitant medications in the RMZ treatment group included those in the ATC drug classes of antithrombotic agents, drugs for constipation, blood glucose lowering drugs (except insulin), and lipid-modifying agents. There were three patients taking a gabapentinoid. One patient was taking three anxiolytics (hydroxyzine, Ativan, and clonazepam) in addition to Neurontin and norco for pain and rheumatoid arthritis. One patient was taking phenobarbital and clonazepam for seizure prophylaxis.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was 100% for patients who received the initial dose of study medication. As previously discussed, midazolam was the only rescue medication permitted during the study. If patients required additional sedatives, they were considered treatment failures.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was success of the colonoscopy, which was defined as completion of the procedure without the need for rescue sedative medication, and no more than five doses of RMZ or placebo in a 15-minute window or no more than three doses of midazolam in a 12-minute window. The following table summarizes the results.

Table 40. Primary Efficacy Endpoint Results (Study CNS7056-015)

Number of Patients	Remimazolam	Placebo	Midazolam	TOTAL
	N=32 n (%)	N=16 n (%)	N=31 n (%)	N=79 n (%)
Success	27 (84.4)	0 (0.0)	4 (12.9)	31 (39.2)
Failure	5 (15.6)	16 (100.0)	27 (87.1)	48 (60.8)
Reasons for failure:				
Rescue sedative medication taken	3 (9.4)	16 (100.0)	24 (77.4)	43 (54.4)
Too many doses within the pre-defined time window	3 (9.4)	14 (87.5)	26 (83.9)	43 (54.4)
Procedure not completed	1 (3.1)	0 (0.0)	1 (3.2)	2 (2.5)

Source: [Section 14.2, Table 14.2.1.1.1](#)

N = number of patients; n = number of observations

Source: Study CNS7056-015 Report Body, p. 79 (PDF), Applicant's submission, NDA 212295.

While this study was not powered for efficacy, the reported results are consistent with the results from Study CNS7056-006 and Study CNS7065-008. The reasons for failure to complete

the procedure in the RMZ treatment group included rescue sedative medication and too many doses of study drug administered.

Regarding total RMZ dose, the following table, from the Applicant's clinical study report, indicates that the majority of patients (approximately 84%) were able to complete the colonoscopy with four or less doses of RMZ, including the initial bolus dose. This is in contrast to the placebo group, in which 100% required five or more doses.

Table 41. Total Number of Study Medication Doses (Safety Population)

Parameter		Remimazolam	Placebo	Midazolam	Total
		N=31 n (%)	N=16 n (%)	N=30 n (%)	N=77 n (%)
Number of Doses of IMP	1	6 (19.4)	0 (0.0)	0 (0.0)	6 (7.8)
	2	11 (35.5)	0 (0.0)	2 (6.7)	13 (16.9)
	3	5 (16.1)	0 (0.0)	1 (3.3)	6 (7.8)
	4	4 (12.9)	0 (0.0)	25 (83.3)	29 (37.7)
	5	0 (0.0)	1 (6.3)	0 (0.0)	1 (1.3)
	6	4 (12.9)	15 (93.8)	1 (3.3)	20 (26.0)
	8	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.3)
	11	0 (0.0)	0 (0.0)	1 (3.3)	1 (1.3)

Source: Study CNS7056-015 Report Body, p. 102 (PDF), Applicant's submission, NDA 212295.

Sensitivity analyses were conducted to determine a possible effect on sedation of fentanyl dosing. The following tables summarize the success rates by fentanyl strata for all treatment groups.

Table 42. Procedural Success by Fentanyl dose (Study CNS7056-015)

Subgroup Fentanyl Strata: < 100 [µg]				
Sample Characteristics or Category	Remimazolam (N=32)	Placebo (N=16)	Midazolam (N=31)	Total (N=79)
Number of Patients in Analysis	29 (100.0)	12 (100.0)	27 (100.0)	68 (100.0)
Success	25 (86.2)	0 (0.0)	4 (14.8)	29 (42.6)
Failure	4 (13.8)	12 (100.0)	23 (85.2)	39 (57.4)

Subgroup Fentanyl Strata: 100-150 [µg]				
Sample Characteristics or Category	Remimazolam (N=32)	Placebo (N=16)	Midazolam (N=31)	Total (N=79)
Number of Patients in Analysis	2 (100.0)	4 (100.0)	2 (100.0)	8 (100.0)
Success	2 (100.0)	0 (0.0)	0 (0.0)	2 (25.0)
Failure	0 (0.0)	4 (100.0)	2 (100.0)	6 (75.0)

Source: Study CNS7-56-015, 14 Tables, pp. 93-94 (PDF), Applicant's submission, NDA 212295.

The number of patients in the 100-150 µg fentanyl stratum is low, but it does not appear that increasing doses of fentanyl impacted reported procedural success. This is in contrast to the results from the other Phase 3 studies, CNS7056-006 and CNS7056-008, in which increased doses of fentanyl correlated with decreased procedural success. Analysis of the mean difference in fentanyl dose between treatment groups indicated that patients in the RMZ group received 7.51 µg less fentanyl than patients treated in the placebo group and 6.99 µg less fentanyl than patients in the midazolam group.

Procedural success by ASA-PS was also analyzed and the results are summarized in the following table.

Table 43. Procedural Success by ASA-PS (Study CNS7056-015)

Subgroup ASA-PS Score: III Severe Systemic Disease				
Sample Characteristics or Category	Remimazolam (N=32)	Placebo (N=16)	Midazolam (N=31)	Total (N=79)
Number of Patients in Analysis	17 (100.0)	9 (100.0)	16 (100.0)	42 (100.0)
Success	13 (76.5)	0 (0.0)	1 (6.3)	14 (33.3)
Failure	4 (23.5)	9 (100.0)	15 (93.8)	28 (66.7)
Reason for Failure:				
Rescue sedative Medication taken	2 (11.8)	9 (100.0)	13 (81.3)	24 (57.1)
Too many doses within the predefined time window	2 (11.8)	9 (100.0)	14 (87.5)	25 (59.5)
Procedure not completed	1 (5.9)	0 (0.0)	1 (6.3)	2 (4.8)

Subgroup ASA-PS Score: IV Severe Systemic Disease that is a Constant Threat to Life				
Sample Characteristics or Category	Remimazolam (N=32)	Placebo (N=16)	Midazolam (N=31)	Total (N=79)
Number of Patients in Analysis	15 (100.0)	7 (100.0)	15 (100.0)	37 (100.0)
Success	14 (93.3)	0 (0.0)	3 (20.0)	17 (45.9)
Failure	1 (6.7)	7 (100.0)	12 (80.0)	20 (54.1)
Reason for Failure:				
Rescue sedative Medication taken	1 (6.7)	7 (100.0)	11 (73.3)	19 (51.4)
Too many doses within the predefined time window	1 (6.7)	5 (71.4)	12 (80.0)	18 (48.6)
Procedure not completed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Study CNS7-56-015, 14 Tables, pp. 96-97 (PDF), Applicant's submission, NDA 212295.

Interestingly, it appears that for both RMZ and midazolam treatment groups, the procedural success rate was higher in patients with ASA-PS IV versus those with ASA-PS III.

Additional subgroup analyses performed in Study CNS7056-008 indicated a negative correlation with procedure duration and procedure success. A formal analysis was not conducted, however, it does not appear that procedures which took more time were associated with a lower success rate. In fact, it appears that procedures completed between 10 and 31 minutes

were 92% successful, while those completed between 6 and 9 minutes were only 84% successful in the RMZ treatment group.

Data Quality and Integrity

In general, there were no concerns identified regarding data quality or integrity with this study. There were four patients, however, who were recruited to replace the following four patients after randomization:

- two patients were randomized but were withdrawn (these patients were included in the ITT analysis set but were excluded from all other analysis populations)
 - Patient (b) (6) in the remimazolam group due to eligibility criteria violation
 - Patient (b) (6) in the midazolam group due to pretreatment serious adverse event
- two patients whose treatment was erroneously unblinded (Patient (b) (6) in the remimazolam group and Patient (b) (6) in the placebo group). These patients were excluded from all efficacy analyses.

Efficacy Results – Additional Efficacy Endpoints

The results for the additional endpoints were in general clinically significant. Specifically, the median time to start of procedure was 5 minutes (95% CI: 4, 5) in the RMZ group, compared to 18.3 minutes (95% CI: 17, 20) in the placebo group and 19 minutes (95% CI not calculated) in the midazolam group. The median time to peak sedation was 3 minutes in the RMZ group (95% CI: 3, 6), but could not be calculated in the placebo and midazolam groups because the majority of patients were censored at the time of their last MOAA/S assessment or the time of first top-up dose (i.e., they did not reach a MOAA/S score of three before the first top-up dose).

The median time to fully alert from the end of the colonoscopy was three minutes (95% CI: 2, 4) in the RMZ group, compared to 5.3 minutes (95% CI: 4, 12) in the placebo group, and 7 minutes (95% CI: 4, 12) in the midazolam group. The median time to fully alert after the last dose of study or rescue medication was 11 minutes (95% CI: 8.8, 12) in the RMZ group, compared to 18 minutes (95% CI: 14, 25) placebo group and 18.8 minutes the midazolam group (95% CI: 15, 26). Review of MOAA/S scores by time point indicated that 1.5 minutes after administration of study drug, nine patients (29%) in the RMZ group were adequately sedated to begin the procedure, MOAA/S score ≤ 3 . None of the patients in the placebo or midazolam groups had achieved a score of ≤ 3 . One patient in the midazolam group had a MOAA/S score of four.

The median duration of the procedure in the RMZ group was eight minutes after administration of study drug, compared to 20 minutes in the placebo group and 18.6 minutes in the midazolam. Twenty one of thirty two patients in the RMZ group had an MOAA/S score of ≤ 3 , compared to one of sixteen patients in the placebo group and two of thirty one patients in the

midazolam group. Regarding recall of the procedure, in general the results were similar between the RMZ and placebo groups. Patients in the midazolam group tended to recall less on the day of the procedure and the day four follow-up visit. Results of the drowsiness visual analog scale supported the Applicant's claim that RMZ-treated patients were drowsy for a short period of time post-dose. No patient required reversal of sedation with flumazenil and the majority of investigators in all treatment groups were satisfied with the level of sedation; however, the mean satisfaction number was lower in the placebo group compared to the RMZ and midazolam groups.

Fentanyl Administration

Fentanyl dosing in this study was low for both ASA-PS III and IV patients in the RMZ treatment groups compared to the doses administered in either of the other Phase 3 studies. Refer to the following table for fentanyl dosing strata for this study.

Table 44. Fentanyl Dose (ITT Population)

Sample Characteristics or Category	Remimazolam N=32	Placebo N=16	Midazolam N=31	TOTAL N=79
Total Dose of Fentanyl (µg)				
N	31	16	30	77
Mean	59.7	67.2	66.7	64.0
Std. Deviation	15.38	21.83	31.03	23.82
Minimum	50	50	50	50
Median	50.0	50.0	50.0	50.0
Maximum	100	100	200	200
95% CI: Lower bound	54.04	55.55	55.08	58.55
95% CI: Upper bound	65.32	78.82	78.25	69.37
Fentanyl strata				
Missing	1 (3.1)	0 (0.0)	1 (3.2)	2 (2.5)
<100 µg	29 (90.6)	12 (75.0)	27 (87.1)	68 (86.1)
100 – 150 µg	2 (6.3)	4 (25.0)	2 (6.5)	8 (10.1)
>150 – 200 µg	0 (0.0)	0 (0.0)	1 (3.2)	1 (1.3)
>200 µg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Study CNS7056-015 Report Body, p. 81 (PDF), Applicant's submission, NDA 212295.

It does not appear that the administered fentanyl dose impacted the reported efficacy findings. Specifically, of the procedural successes, there were only two patients in the RMZ treatment group who received fentanyl 100 µg and both were procedural successes. The highest dose of fentanyl administered in this study was for a patient in the midazolam treatment group, who was a treatment failure. The majority of patients in the study received low-dose fentanyl, 50 µg

or 75 µg. An additional consideration for fentanyl dosing, as will be discussed in the safety portion of this review, is the impact on respiratory depression and hypoxia. In general, there was a low incidence of respiratory depression and hypoxia during this study, likely due to the overall low fentanyl dosing in the majority of treated patients.

Dose Response and Durability of Response

There was a single dose of RMZ administered in this Phase 3 study, therefore a dose-response was not evaluated.

A pharmacokinetic property of RMZ that the Applicant states is a clear advantage over other commonly administered benzodiazepines for procedural sedation is its rapid metabolism by tissue carboxylase to an inactive metabolite resulting in fast-on and fast-off sedation. The majority of patients required three or more doses of RMZ to maintain adequate sedation for successful completion of the colonoscopy procedure. During this study, it did not appear that the number of doses of RMZ was positively correlated with the time to recovery from sedation, measured via time to fully alert and time to discharge.

Additional Analyses Conducted on the Individual Trial

Patients of ASA-PS IV classification in the RMZ treatment group had reportedly higher procedural success rates than patients of ASA-PS III classification. Possible explanations for these findings included prior concomitant medication administration and fentanyl dosing during the procedure. In general, there was low number of patients in both ASA-PS classes who had prior medication use that could have impacted the reported efficacy results. Specifically, there were three ASA-PS III patients who were taking either an opioid analgesic or an anxiolytic medication. Of the three, two were procedural successes and one was failure. Interestingly, the patient who was taking three anxiolytic medications, Neurontin, and two different opioid analgesics prior the procedure was a treatment failure. The other two patients taking either Neurontin or gabapentin were procedural successes. One patient was taking phenobarbital and clonazepam for history of seizures and was a procedural success. It does not appear that prior medication use impacted the reported efficacy findings.

Data Monitoring Committee Meetings and Outcomes

The DMC held regular meetings to evaluate the safety data during the study. The data from the three on-going Phase 3 studies was discussed during the DMC meetings. During one meeting, the adverse event of respiratory acidosis reported in 17 patients was discussed. The Applicant provided an acceptable explanation to the DMC, which subsequently did not feel had a negative impact on patient safety.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

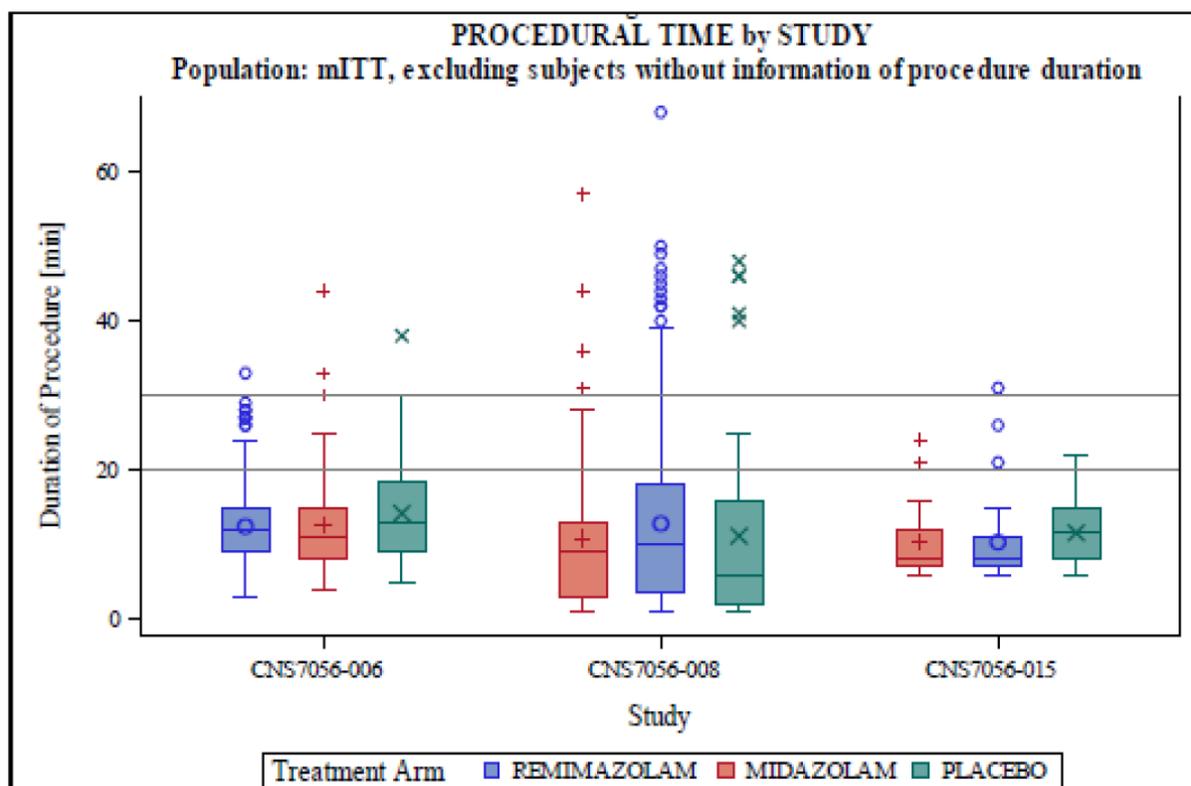
In all clinical studies in procedural sedation, the level of sedation was assessed using the Modified Observer's Assessment of Alertness and Sedation (MOAA/S), as described below:

7.1.1. Primary Endpoints

Study CNS7056-006 and Study CNS7056-008 were adequate and well-controlled studies designed to support the proposed indication and dosing of remimazolam. For Study CNS7056-015, the main objective was safety and so statistical tests were not performed for the efficacy endpoints; however, the procedure success rates were similar to the other two studies. Studies CNS7056-006 and CNS7056-008, demonstrated a statistically significant difference on the primary efficacy endpoint of procedure success compared to saline placebo. Reasons for failure included rescue sedative medication taken, too many doses within the predefined time window, and procedure not completed. The main reason for failure on the primary efficacy endpoint for the RMZ-treated patients in Study CNS7065-006 was too many doses within the predefined window, in Study CNS7056-008 was rescue sedative medication taken, and in Study CNS7056-015 was both reasons reported for failure equally. Again, the main reason for failure in Study CNS7056-008 is not surprising given the stimulating nature of the procedure. In all three studies, a low percentage of patients in all treatment groups failed due to procedure not completed; however, in Study CNS7056-006, a slightly larger proportion of RMZ-treated patients (2.3%) failed due to procedure not completed compared to placebo (1.7%) or midazolam-treated (1.9%) patients. This is likely not clinically significant.

The amount of rescue medication administered in the RMZ treatment group was lowest in Study CNS7056-006 and highest in Study CNS7056-015. This is surprising given the more stimulating nature of a bronchoscopic procedure compared to a colonoscopy; however, is supportive that RMZ provides adequate sedation for what are considered more invasive and stimulating procedures. This was an issue discussed with the Applicant throughout clinical development; i.e., a broad procedural sedation indication would need to be supported by data from studies evaluating more invasive procedures. In my view, Study CNS7056-008 clearly provides that data, albeit the procedures evaluated were of relatively short duration, as indicated in the following figure.

Table 45. Procedure Duration by Phase 3 Study



Source: Clinical Information Amendment – Responses to Filing Review Issues Identified and MCC Agenda, dated November 19, 2019, p. 18 (PDF), Applicant’s submission, NDA 212295.

This figure clearly indicates that the overwhelming majority of evaluated procedures were completed in 30 minutes or less.

In the placebo treatment group, patients failed primarily due to rescue sedative medication taken, which was strictly limited to midazolam dosed at the discretion of the investigator. A large proportion (i.e., > 73%) of placebo-treated patients in both colonoscopy studies, CNS7056-006 and CNS7056-015, were counted as failures for too many doses within the predefined time window also (patients were counted for all reasons of failure). In the bronchoscopy study, CNS7056-008, a smaller proportion of patients (i.e., 16%) failed due to too many doses within the predefined window.

7.1.2. Secondary and Other Endpoints

In general, the results of the secondary endpoint analyses support the findings of the primary analysis. Specifically, the times to start of procedure, peak sedation, ready for discharge, and fully alert were all statistically and clinically significantly shorter in patients treated with RMZ compared to those treated with placebo. The most clinically meaningful secondary endpoints

include time to start of procedure and time to ready for discharge; however, because of differences in the time to administration of sedation in the placebo treatment group, the time to start of procedure is likely longer when compared to the RMZ treatment group, and, therefore not an entirely valid comparison. Time to fully alert, which did not appear to increase with a corresponding increase in procedure duration, is clinically relevant, but can generally be reflected in time to ready for discharge. These endpoints are strongly influenced by potential safety issues, including the occurrence of adverse events that could increase time for all measured variables. Ambulatory surgery centers are acutely aware of rising healthcare costs and efficiency has become a key factor in cost calculations; therefore, any strategy which decreases patient stay and improves time to discharge, will likely be easily implemented.

The results of the analyses for MOAA/S scores by time point support the Applicant's conclusion that RMZ appears to be rapidly-acting sedative agent. In fact, there was some concern regarding the depth and time to onset of sedation after RMZ administration. Specifically, there were patients treated with RMZ in Study CNS7056-006 and Study CNS7056-008 who had MOAA/S scores of 0 within one minute of administration, which corresponds to a depth of sedation resulting in lack of response to a painful trapezius squeeze, in contrast to no patients in either the placebo or midazolam groups experiencing the same depth so quickly. This depth of sedation *may* predispose the patient to the development of adverse events related to changes in hemodynamic parameters, particularly respiratory parameters and oxygenation. This was discussed with the Applicant during the Mid-Cycle Communication Meeting. Subsequently, the Applicant provided additional safety information for patients with low MOAA/S, which suggests that the incidence of hemodynamic-related adverse events did not occur with a clinically significant increase in patients treated with RMZ. Additionally, the Applicant argued that the MOAA/S is a measure of depth of sedation (or efficacy) and has not been validated as an assessment of safety. This will be discussed in more detail in Section 8, Review of Safety, but I do not agree that the MOAA/S cannot be used to inform the safety profile of a new sedative agent such as RMZ, particularly regarding the level of training required for the administering provider.

7.1.3. Subpopulations

Subgroup efficacy analyses were conducted for gender, age, race, and ASA-PS in the Phase 3 studies. The results, by study, are as follows.

Study CNS7056-006

The procedure success rate was higher in male patients than female patients in the RMZ treatment group, 95% versus 88% respectively. The reason for the difference is not clear, but likely clinically insignificant. There was a higher procedure success rate reported for patients ≥ 65 years of age (100%) compared to patients < 65 years of age (90%) in the RMZ treatment group. The number of patients ≥ 65 years of age was lower, however (42 versus 256, respectively). Analysis of the primary efficacy endpoint by racial subgroups, including white, Clinical Review
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African American, Asian, and other, did not identify differences from the overall efficacy findings; however, the number of treated non-white patients was low. There was no trend noted in procedure success and worsening ASA-PS in the RMZ treatment group.

Study CNS7056-008

The Applicant reported that the results of subgroup analyses for patients in the RMZ treatment group were similar to those of the overall study population. There slight differences in the age subgroup analysis. Specifically, there was a higher percentage of ≥ 65 -year-old patients (84%) who were procedure success compared to < 65 -year-old patients (77%). Analysis of the primary efficacy endpoint by racial subgroups, including white, African American, Asian, and other, did not identify differences from the overall efficacy findings; however, the number of treated non-white patients was low. There did not appear to be a correlation between worsening ASA-PS and procedure success. In fact, the lowest procedure success rate was reported for ASA-PS I patients, and the highest for ASA-PS II patients.

Study CNS7056-015

As previously discussed, patients in the RMZ treatment group with ASA-PS IV had a higher procedure success rate compared to patients with ASA-PS III (93% versus 77%, respectively). Analysis of the primary efficacy endpoint by racial subgroups, including white, black, Asian, and other, did not identify differences from the overall efficacy findings; however, the number of treated non-white patients was low. In fact, there were only white and African American patients in the RMZ treatment group.

In summary, there did not appear to be any meaningful differences in the procedure success rate between any demographic subgroups.

7.1.4. Dose-Response

The Phase 3 studies evaluated a single dose of RMZ, such that a dose response could not be formally assessed. However, in the Phase 2 study, CNS7056-003, conducted in patients undergoing upper endoscopy, a RMZ dose-response was observed for the procedure success rate and the proportion of patients requiring rescue sedative medication. Doses evaluated in this study were 0.1 mg/kg, 0.15 mg/kg, and 0.2 mg/kg as a single IV injection. Top-up doses of RMZ and fentanyl premedication were not permitted.

In Study CNS7056-004, a Phase 2 study in patients undergoing colonoscopy, a dose-response was not observed after administration of initial bolus injections of RMZ 5 mg, 7 mg, or 8 mg. Patients in this study received fentanyl 100 μ g pre-procedure and top-up doses of RMZ were permitted as follows: 3 mg for the 5 mg and 8 mg initial bolus group, and 2 mg for the 7 mg initial bolus group. Procedure success rates were similar across all three dosing regimens, but highest in the 5 mg/3mg RMZ treatment group. The 7 mg/2 mg and 5 mg/3 mg treatment groups had statistically significantly higher procedure success rates compared to the midazolam

treatment group. The 8 mg/3 mg treatment group did not demonstrate statistical significance above the midazolam treatment group. RMZ 5 mg initial bolus and 2.5 mg top-up doses were chosen for the Phase 3 studies based on results from this study.

7.1.5. Onset and Duration

Results from the Phase 3 studies indicated that peak sedation after RMZ administration was within 3 to 3.5 minutes and the median time to start of procedure after first dose of study drug was between 4 to 5 minutes. The majority of patients in all three Phase 3 studies who were procedure successes required at least one top-up dose. These results support the Applicant's claim that RMZ is relatively fast and short-acting such that redosing will likely be needed for procedures of comparable duration; i.e., 30 minutes or less.

7.2. Additional Efficacy Considerations

7.2.1. Concomitant use of Chronic Opioid Analgesic or Benzodiazepine Medication

The eligibility criteria for studies CNS7056-008 and CNS7056-015 did not exclude patients receiving chronic opioid analgesic or benzodiazepine medications, defined as daily use for 90 days or more prior to the procedure. In response to an Information Request, the Applicant clarified that the proportion of patients receiving chronic opioid medications was similar across treatment groups in Study CNS7056-008, but the use of chronic benzodiazepines was higher in the RMZ and midazolam treatment groups compared to the placebo treatment group in this study. In Study CNS7056-015, a smaller proportion of patients in the RMZ treatment group were taking chronic opioids and benzodiazepines compared to patients in the midazolam treatment group.

In general, the results from Study CNS7056-008 and Study CNS7056-015 indicate that chronic administration of either opioid analgesic or benzodiazepine medications decreased the proportion of patients in the RMZ treatment groups who were procedure successes. The results of these analyses in the midazolam treatment group were inconsistent, likely due to small numbers of patients in some of the subgroups. While the impact of chronic opioid analgesic or benzodiazepine medication use on the efficacy of benzodiazepine-induced sedation is not entirely surprising, it may need to be described in RMZ drug product labeling.

Additional analyses conducted by the Applicant, at the request of the Division, determined that it did not appear that patients receiving chronic opioid analgesic or benzodiazepine medication in either Study CNS7056-008 and Study CNS7056-015 required a significantly higher mean dose of RMZ to successfully complete the procedure.

In conclusion, it appears that while the dose of RMZ needed for adequate sedation to successfully complete a procedure was not significantly higher in patients receiving chronic

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opioid analgesic or benzodiazepine medication, the proportion of patients who were procedure successes was lower compared to patients not receiving these chronic medications.

7.2.2. Considerations on Benefit in the Postmarket Setting

While it is unlikely that the final RMZ drug product label will include (b) (4) and a blinded active comparator group was not included in the Phase 3 studies, it does appear that RMZ has a shorter time to onset of action and recovery compared to other commonly administered sedative agents. Approval of RMZ would offer clinicians an alternative sedative medication for used during procedures lasting 30 minutes or less. In my clinical judgement, RMZ is most likely to be widely used during GI endoscopy procedures, primarily colonoscopy and upper endoscopy. Gastroenterologists have a strong desire to safely provide sedation to their patients in the ambulatory centers without the oversight of an anesthesia provider. The final determination regarding the required level of training of the administering provider has not been made, but RMZ may provide the depth and duration of anesthesia necessary to successfully complete diagnostic and therapeutic GI endoscopy procedures, thereby impacting a large number of patients.

Post-market surveillance reporting will provide information on the usefulness of this product during various diagnostic and therapeutic procedures lasting 30 minutes or less.

7.3. Integrated Assessment of Effectiveness

The totality of the data indicates that RMZ 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. The following table summarizes the mean, median, and maximum duration of procedures performed in the three Phase 3 studies.

Table 46. Procedure Duration, Phase 3 Studies

Treatment Arm	Mean Procedure Time (minutes)	Median Procedure Time (minutes)	Maximum Procedure Time (minutes)
<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

Treatment Arm	Mean Procedure Time (minutes)	Median Procedure Time (minutes)	Maximum Procedure Time (minutes)
<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.

The placebo treatment group is included in the table to provide information regarding standard of care midazolam administration for procedural sedation. It is worth noting, however, that midazolam rescue was administered to patients in the placebo group after they were treatment failures to the saline placebo; therefore, more time passed prior to the administration of a true sedative compared to the RMZ treatment group. This increased time prior to administration of a sedative in the placebo treatment group makes RMZ appear faster acting, thereby improving the secondary endpoints of time to start of the procedure and time to peak sedation. Efficacy comparisons between the RMZ and midazolam treatment groups will not be discussed based on the open-label administration of midazolam.

In Study CNS7056-006, there was a single procedure lasting longer than 30 minutes, and in Study CNS7056-008, only 10% of procedures lasted longer than 30 minutes. For all three studies, the mean and median procedure durations ranged from 6.5 to 13 minutes. There appeared to be more variability in procedure duration in patients undergoing bronchoscopy in Study CNS7056-008 compared to patients undergoing colonoscopy in the other two Phase 3 studies. An additional limitation to RMZ administration for procedural sedation is the proposed bolus dosing. While the Applicant has conducted studies utilizing continuous IV RMZ infusions for ICU sedation and induction and maintenance of general anesthesia, the Phase 3 studies evaluated bolusing dosing only, and will therefore be described as such in the final drug product labeling. Bolus dosing is not ideal for procedures in which the administering provider has to perform other patient care tasks, such as supporting the airway, administering other medications, or suctioning oral secretions.

The mean dose of RMZ administered to patients who successfully completed their procedures was similar across the Phase 3 studies. Specifically, the mean dose of RMZ administered was 10.5 mg, 11.4 mg, and 9 mg in Study CNS7056-006, CNS7056-008, and CNS7056-015, respectively. The mean dose of midazolam rescue was highest in Study CNS7056-015, which is somewhat surprising given the sicker ASA-PS patient make-up and the procedure performed. I would have anticipated patients undergoing bronchoscopy would have required more midazolam rescue than patients undergoing colonoscopy. Additionally, the mean fentanyl dose administered was the highest in Study CNS CNS7056-006. These results are supportive of the efficacy of RMZ when used for procedural sedation.

In all three Phase 3 studies, patients were permitted fentanyl for analgesia during the procedure. Investigators were instructed to not administer fentanyl for sedation and the

maximum dose was not to exceed 200 µg. In Study CNS7056-008, there was a large number of patients who received doses > 200 µg. Specifically, there were a total of 21 patients who received > 200 µg; four in the midazolam treatment group, six in the placebo treatment group, and 11 in the RMZ treatment group. These higher doses ranged from 225 µg to 450 µg. Increasing fentanyl dosing impacted the observed efficacy of RMZ in studies CNS7056-006 and CNS7056-008 in three ways. First, it appears that increased doses of fentanyl correlated with decreased procedure success. Specifically, in both studies, there was a statistically significant impact of increased fentanyl dose on procedure success, $p < 0.001$. While investigators should not have administered fentanyl to complement the sedation of the study drugs, clinically, it is not an unexpected observation that higher fentanyl dosing was associated with lower procedure success. Depending on the procedure performed and the underlying comorbidities of the patient, more challenging procedures are likely to require more sedation and more analgesia, which may result in a lower success rate. It is not known whether the decreased success rate was due to increased fentanyl dosing or due to a more difficult procedure, but may be a combination of both. Therefore, definitive conclusions cannot be made that increased fentanyl dosing results in decreased RMZ-induced procedural sedation.

The second way fentanyl dosing impacted the observed efficacy of RMZ is related to procedure duration. Specifically, in studies CNS7056-006 and CNS7056-008, there was a statistically significant impact of increased fentanyl dose on procedure duration, a more significant impact observed in Study CNS7056-008. Similar to the discussion regarding decreased procedure success, it is not surprising that procedures which required more fentanyl analgesia resulted in increased procedure duration. During procedures requiring sedation, if patients are uncomfortable or feeling pain, they tend to move, even when unconscious. Patient movement will usually result in a pause in the procedure and ultimately, require more time for successful completion. Therefore, it is difficult to conclude that increased fentanyl dosing alone results in increased procedure duration.

And the final consideration regarding fentanyl administration during RMZ-induced sedation is the observed depth of sedation. As discussed in Section 8.6.2, Concomitant Fentanyl Administration, there was a large proportion of patients in the RMZ treatment group who had MOAA/S scores of 0 or 1 within a short time of RMZ administration. This was in contrast to patients in the placebo treatment group. The Applicant provided additional information in response to the Mid-Cycle Communication and Meeting indicating that initial fentanyl dosing likely impacted the deep levels of sedation observed and that after implementation of protocol amendments in the Phase 3 studies that reduced initial doses from 75 µg to 50 µg, the proportion of patients with low MOAA/S decreased. The Applicant also stated, and I agree, that the proportion of patients in the placebo treatment group did experience similar depth of sedation, but at later time points, which is consistent with the pharmacokinetic profile and expected pharmacodynamic response to midazolam administration. It does appear, however, that the initial dose of fentanyl appeared to impact the depth of RMZ-induced sedation more

than placebo-induced sedation. Specifically, the fentanyl dose reduction improved the proportion of patients with MOAA/S scores in the RMZ treatment group more than in the placebo treatment group.

Regarding patients receiving chronic opioid analgesics or benzodiazepine medications, the results from studies CNS7056-008 and CNS7056-015, studies that did not exclude patients receiving these medications, indicate that chronic administration did decrease the proportion of patients in the RMZ treatment groups who were procedure successes. However, for the patients who were procedure successes, it did not appear they required a significantly higher mean dose of RMZ. In other words, it appears chronic use of an opioid analgesic or benzodiazepine may decrease the success rate, but of those who do complete the procedure, the mean dose of RMZ is not increased.

Based on the pharmacokinetic profile and pharmacodynamic response, it does appear that administration of RMZ results in rapid onset of sedation with a fast recovery. Because the placebo treatment group did not receive any real sedation for several minutes longer than patients in the RMZ treatment group, differences in time to start of procedure and to peak sedation are not informative. However, times to fully alert and to ready for discharge are clinically relevant and appear to favor RMZ over placebo. As mentioned previously, less overall time under sedation and time to discharge is beneficial to the patient and improves efficiency, particularly in ambulatory surgery centers where case completion and turn over are high priorities.

In conclusion, the clinical development program for remimazolam has consistently demonstrated superior sedation over saline placebo during procedures lasting 30 minutes or less. The results from the primary and key secondary efficacy endpoints demonstrated a statistically and clinically significant difference between remimazolam and placebo treatment groups and support approval of this marketing application with revisions to the proposed drug product label, as described in Section 9, Labeling Recommendations.

8. Review of Safety

8.1. Safety Review Approach

This application is a 505(b)(1), thus the Applicant is relying only on the safety information generated throughout remimazolam clinical development. The evaluation of the safety profile for RMZ involved a comprehensive review of adverse events known to occur after administration of other benzodiazepine medications, with particular emphasis on changes in measured vital sign parameters.

The potential safety issues of greatest concern with administration of benzodiazepine

medications, particularly when used in combination with other sedatives and/or narcotics are prolonged sedation or decreased level of consciousness, changes in measured vital sign parameters, particularly respiratory parameters (e.g., decreased ventilation, including both decreased respiratory rate and depth of respiration, and decreased oxygenation, including decreased pulse oximetry, SpO₂, or arterial oxygen content, PaO₂), and adverse events related to abuse, dependence, and withdrawal.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The Applicant conducted 23 clinical studies, 22 of which evaluated the proposed IV route of administration for RMZ and included the following:

- 11 Phase 1 studies (included patients with renal disease, recreational CNS depressant users, and patients with hepatic impairment)
- 5 Phase 2 studies
- 1 Phase 2/3 study
- 5 Phase 3 studies

The 11 Phase 2 to 3 studies were conducted in patients receiving procedural sedation (five studies, conducted in the U.S.), general anesthesia (five studies), and ICU sedation (one study). The studies evaluating RMZ when administered for procedural sedation were conducted in the U.S. and those evaluating RMZ when administered for general anesthesia or ICU sedation were conducted in Japan and Europe. The Applicant also conducted studies in patients with renal and hepatic dysfunction. There were a total of 1731 subject exposures to IV RMZ throughout clinical development. Study CNS7056-020 evaluated the PK, safety, and tolerability of oral RMZ administration with ethanol in 32 patients. A total of 969 patients received RMZ during procedural sedation.

Safety information from the 22 studies was pooled in the ISS, described in the table below.

Table 47. Integrated Pooled Safety Analysis Groups

Analysis Group	Trials Included (Number of Trials)	Treatment Groups Analyzed
Group A	<u>Controlled and uncontrolled trials in procedural sedation (6 trials)</u> CNS7056-003, CNS7056-004, CNS7056-006, CNS7056-008, CNS7056-015, and CNS7056-002 (Part B)	Total Remimazolam
Group A1	<u>Controlled trials in procedural sedation (colonoscopy and bronchoscopy) with fentanyl pretreatment (4 trials)</u> CNS7056-004, CNS7056-006, CNS7056-008, and CNS7056-015	Total Remimazolam RMZ initial doses 2.5 to 5 mg (CNS7056-015), 5 mg (CNS7056-004, CNS7056-006, and CNS7056-008) and > 5 mg (7 mg and 8 mg, only for CNS7056-004) Total Midazolam Midazolam initial doses < 1.75 mg (CNS7056-006, CNS7056-008, and CNS7056-015), 1.75 mg (CNS7056-006, CNS7056-008), and > 1.75 mg (CNS7056-004) Fentanyl treatment (in addition to all treatment groups)
Group A1A	<u>Placebo controlled trials in procedural sedation (colonoscopy and bronchoscopy) with fentanyl pretreatment (3 trials)</u> CNS7056-006, CNS7056-008, and CNS7056-015	Total Remimazolam RMZ initial doses 2.5 to 5 mg (CNS7056-015) and 5 mg (CNS7056-006 and CNS7056-008) Total Midazolam Midazolam initial doses < 1.75 mg, (CNS7056-006, CNS7056-008, and CNS7056-015) and 1.75 mg (CNS7056-006 and CNS7056-008) Placebo Fentanyl treatment (in addition to all treatment groups)

Analysis Group	Trials Included (Number of Trials)	Treatment Groups Analyzed
Group B	<u>Controlled and uncontrolled trials in general anesthesia (5 trials)</u> ONO-2745-03, ONO-2745-05, ONO-2745-06, CNS7056-010, and CNS7056-011	Total Remimazolam
Group B1	<u>Controlled trials in general anesthesia (4 trials)</u> ONO-2745-05, ONO-2745-06, CNS7056-010, and CNS7056-011	Total Remimazolam RMZ induction (LD) 6 mg/kg/h group; and (HD) 12 mg/kg/h group; (only ONO-2745-05, ONO-2745-06, and CNS7056-010) Propofol (only ONO-2745-05, CNS7056-010, and CNS7056-011)
Group C	<u>Single- and multiple-dose trials in healthy subjects not undergoing a procedural sedation or general anesthesia (10 trials)</u> ONO-2745-01, ONO-2745-02, ONO-2745IVU007 (only healthy subjects), CNS7056-001, CNS7056-002 (Part A), CNS7056-005, CNS7056-012 (only healthy subjects), CNS7056-016, CNS7056-017, and CNS7056-019	Total Remimazolam
Group D	All trials defined in Group A, B, and C, ONO-2745IVU007 (subjects with hepatic impairment), CNS7056-012 (subjects with renal impairment), CNS7056-014, and ONO-2745-04 (ICU sedation) (22 trials)	Total Remimazolam

Note: In Group B1, the "Propofol" treatment group includes subjects who received propofol and sevoflurane in CNS7056-010.
 HD = high dose; ICU = intensive care unit; LD = low dose; RMZ = remimazolam
 Source: ISS Report, p. 32-33, Applicant's submission, NDA 212295.

The safety population consisted of all subjects and patients enrolled in a clinical study who received any amount of RMZ, placebo, or midazolam. This population was used for all safety analyses. Subjects were analyzed as treated and incorrect group allocation was described. Patients pooled in Group A1A and results from the individual Phase 3 studies will be the focus of this safety review.

There were a total of 630 patients treated with RMZ in pooled Group A1A, and 99% (626 out of 630) received an initial dose of RMZ 5 mg. Four patients received an initial dose of RMZ 2.5 to < 5 mg; one in Study CNS7056-006 and three in Study CNS7056-015. The median cumulative dose of RMZ administered in Group A was 10 mg and the median cumulative dose in Group B was 181.58 mg. There were 135 patients treated with placebo and 201 treated with midazolam in Group A1A.

Patient disposition for patients treated in the pooled Group A1A is summarized in the following table.

Table 48. Patient Disposition in Controlled Studies in Procedural Sedation (Safety Population, Group A1A)

Category [n (%)]	Remimazolam			Midazolam			Placebo (N=135)
	2.5 mg to 5 mg (N=31)	5 mg (N=599)	Total (N=630)	<1.75 mg (N=113)	1.75 mg (N=88)	Total (N=201)	
Safety Population	31 (100)	599 (100)	630 (100)	113 (100)	88 (100)	201 (100)	135 (100)
Subjects who completed the trial	31 (100)	594 (99.2)	625 (99.2)	112 (99.1)	87 (98.9)	199 (99.0)	134 (99.3)
Subjects who withdrew from the trial	0	5 (0.8)	5 (0.8)	1 (0.9)	1 (1.1)	2 (1.0)	1 (0.7)
Primary reason for withdrawal from trial							
Adverse event	0	0	0	0	0	0	0
Lost to follow-up	0	5 (0.8)	5 (0.8)	1 (0.9)	0	1 (0.5)	0
Physician decision	0	0	0	0	0	0	0
Protocol deviation	0	0	0	0	0	0	0
Withdrawal by subject	0	0	0	0	1 (1.1)	1 (0.5)	1 (0.7)
Other	0	0	0	0	0	0	0

Note: Percentages are based on the Safety Population and each dose group - Group A1A.
 Source: ISS Report, p. 43 (PDF), Applicant's submission, NDA 212295.

8.2.2. Relevant characteristics of the safety population:

While the Applicant conducted studies in patients receiving general anesthesia or ICU sedation, the proposed indication is procedural sedation, thus studies evaluating RMZ administered for procedural sedation will be the focus of this safety review.

Patients in the Phase 3 studies were permitted only midazolam rescue for additional sedation and fentanyl rescue for analgesia only. If other sedative or analgesic agents were required for completion of the procedure, patients were counted as treatment failures. All Phase 3 studies were conducted in the U.S.

8.2.3. Adequacy of the safety database

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. This evaluation of the safety profile of RMZ is adequate to support a broad procedural sedation indication for two reasons. First, the procedures evaluated represent wide variability in the degree of noxious stimulation to the patient. In general, a colonoscopy procedure ± biopsy is a much less stimulating procedure than either a bronchoscopy or an upper endoscopy. The majority of patients state the most unpleasant portion of the procedure was the bowel preparation the day prior. Bronchoscopy is a very stimulating procedure, requiring local anesthetic topicalization as well as significant sedation in an attempt to blunt the gag and cough reflexes.

And second, the patient populations evaluated in the Phase 3 studies were diverse. Specifically, while two studies evaluated the same procedure, colonoscopy, the patients were of different ASA-PS such that RMZ was assessed in patients with a wide range of medical comorbidities, ranging from healthy patients to those with severe systemic disease that is a constant threat to life. Furthermore, those patients evaluated in Study CNS7056-008 represented a unique population, the majority of which had underlying pulmonary compromise or disease, including chronic obstructive pulmonary disease, asthma, pneumonia, lung nodule, and shortness of breath.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no issues regarding the data integrity or the overall quality of the submission. The information provided was organized and easy to locate.

8.3.2. Categorization of Adverse Events

The reported adverse events were categorized as treatment-emergent if they occurred after the first dose of study drug. Relatedness to study drug administration was further categorized as certain, related, probable/likely, possible, unlikely, unassessable/unclassified, and conditional/unclassified. Adverse events with a relatedness of possibly or higher were considered related to study drug administration.

Adverse events of special interest included those related to prolonged sedation or decreased level of consciousness, those associated with changes in measured vital sign parameters, particularly respiratory parameters, and those related to abuse, dependence, and withdrawal.

8.4. Safety Results

8.4.1. Deaths

In Group D and Group A1A pooled safety analyses, there were no reported patient deaths. 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 which included 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.

8.4.2. Serious Adverse Events

Serious treatment-emergent adverse events for Group A1A pooled safety analysis are summarized in the following table.

Table 49. Treatment-Emergent Serious Adverse Events by Treatment Group, System Organ Class, and Preferred Term in Group A1A Pooled Safety Analysis

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 Byfavo (Remimazolam) for injection
 Cosmo Technologies, Ltd.

System organ class Preferred term [n (%)]	Remimazolam (N=630)	Midazolam (N=201)	Placebo (N=135)
Any serious treatment-emergent adverse event	17 (2.7)	1 (0.5)	4 (3.0)
Respiratory, thoracic and mediastinal disorders	13 (2.1)	0	3 (2.2)
Pneumothorax	4 (0.6)	0	1 (0.7)
Bronchospasm	2 (0.3)	0	1 (0.7)
Hypoxia	2 (0.3)	0	1 (0.7)
Acute respiratory failure	1 (0.2)	0	0
Aspiration	1 (0.2)	0	0
Chronic obstructive pulmonary disease	1 (0.2)	0	0
Dyspnea	1 (0.2)	0	0
Organizing pneumonia	1 (0.2)	0	0
Pleural effusion	1 (0.2)	0	0
Pneumomediastinum	1 (0.2)	0	0
Respiratory failure	1 (0.2)	0	0
Hemoptysis	0	0	1 (0.7)
Cardiac disorders	3 (0.5)	0	0
Atrial fibrillation	1 (0.2)	0	0
Atrial tachycardia	1 (0.2)	0	0
Bradycardia	1 (0.2)	0	0
Infections and infestations	1 (0.2)	0	0
Lobar pneumonia	1 (0.2)	0	0
Blood and lymphatic system disorders	0	1 (0.5)	0
Anemia	0	1 (0.5)	0
Psychiatric disorders	1 (0.2)	0	0
Confusional state	1 (0.2)	0	0

Source: Summary of Clinical Safety, p. 17 (PDF), Applicant's submission, NDA 212295.

As indicated, there were 17 RMZ-treated patients in Group A1A pooled safety analyses 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. 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- (b) (6). The narrative for that patient is summarized below.

Patient CNS7056- (b) (6) was a 72-year-old ASA-PS III white male undergoing
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bronchoscopy. His relevant past medical history included depression, hypertension, coronary artery disease with stent placement, hyperlipidemia, renal cell carcinoma, benign prostate hyperplasia, and pulmonary mass. Home medications included atorvastatin, benazepril hydrochlorothiazide, carvedilol, clopidogrel, finasteride, magnesium oxide, pantoprazole, potassium chloride, sertraline, and tamsulosin. He received fentanyl 75 µg pretreatment and an additional three top-ups during the procedure (two 25 µg and one 50µg bolus). He received RMZ 5 mg within two to three minutes of the initial fentanyl dose. Two and seven minutes after the second dose of RMZ 2.5 mg, the patient experienced severe hypoxia (pulse oximetry reading 71 to 80%) and bradycardia (lowest reported heart rate in the 30-bpm range), respectively. Supplemental oxygen was administered via nasal cannula, epinephrine was administered to control biopsy-related bleeding, the bronchoscope was removed and assisted ventilation with nasal airway and bag valve mask was initiated. Vital signs improved and the procedure was completed. The serious adverse events were considered certainly related to RMZ administration; however, the investigator indicated that the fentanyl dosing during the procedure likely contributed to the decreased respiratory rate and hypoxia, clarifying that the patient never became apneic. The second dose of fentanyl was 50 µg, which was in violation of the allowable 25 µg top-ups per protocol.

This patient also experienced the nonserious adverse events of hypertension, hypotension, increased respiratory rate, and nausea, which were considered possibly related to study drug administration.

There was one serious adverse event reported in Study CNS7056-006, gastric carcinoma, but because the patient had not received RMZ prior to diagnosis, was not considered treatment-emergent. There were two serious adverse events reported in the midazolam treatment group in Study CNS7056-015, but only one, anemia, was considered treatment-emergent due to the other, angina pectoris, occurring prior to study drug administration.

While the number of serious adverse events reported in the RMZ treatment group is higher than the number reported in either the placebo or midazolam treatment groups, the overall incidence is similar between the RMZ and placebo treatment groups, 2.7% and 3% respectively. It is not clear why there was a lower incidence of serious adverse events reported in the midazolam treatment group compared to either the RMZ or placebo treatment groups in Study CNS7056-008. The mean total dose of midazolam in the midazolam and placebo treatment groups was similar, 5.76 mg versus 5.87 mg, respectively, both doses higher than that administered for rescue in the RMZ treatment group, 1.27 mg. Review of the fentanyl dosing indicates that patients in the placebo treatment group received higher mean total doses of fentanyl compared to those treated in the midazolam treatment group, 119.92 µg versus 107.03 µg, and patients in the RMZ group received the lowest total mean fentanyl dose, 81.85 µg. It may be that administration of RMZ and modest doses of fentanyl result in a similar incidence of serious adverse events in patients treated with midazolam and liberal doses of

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fentanyl.

In summary, the overall incidence of serious adverse events was low in the Group A1A pooled safety analysis and RMZ does not appear to present a clinically relevant increase in the occurrence of serious adverse events above standard of care conscious sedation. Additionally, as was discussed in Section 7, Integrated Review of Effectiveness, the mean MOAA/S scores in the RMZ treatment group were lower earlier in the course of sedation compared to either the placebo or midazolam treatment groups, suggesting that even with the potential for a deeper depth of sedation, RMZ does not appear to have a worse safety profile.

8.4.3. Discontinuations Due to Adverse Effects

The Applicant has made the distinction, in response to an Information Request, between patients who withdrew from study treatment or from the study due to an adverse event. The distinction, which appears to be based on whether patients completed all required follow-up visits and assessments, seems irrelevant, given the dosing and duration of RMZ administration.

In Group D pooled safety analysis, there were four patients in the RMZ treatment group who discontinued from the study *primarily* due to an adverse event, as described by the Applicant. The patients and brief summaries are as follows.

- Patient CNS7056- (b) (6): 26-year-old black male experienced hypotension
- Patient CNS7056- (b) (6): 62-year-old white female experienced hypoxia and hypotension
- Patient ONO-2745- (b) (6): 44-year-old Asian male experienced exacerbation of heart failure, blood pressure reduction
- Patient ONO-2745- (b) (6): 66-year-old Asian male experienced blood pressure elevation

There were an additional three patients in the Group D pooled safety analysis who discontinued RMZ treatment, but completed the study and all required follow-up. Those patients and brief summaries are as follows.

- Patient CNS7056- (b) (6): 72-year-old white male experienced the serious adverse events of hypoxia and bradycardia, as well as hypertension, hypotension, and respiratory rate increased
- Patient ONO-2745- (b) (6): 74-year-old Asian male with blood pressure reduction
- Patient CNS7056- (b) (6): 40-year-old white male experienced hemothorax

One patient in the placebo and one in the midazolam treatment group also discontinued study treatment and will not be discussed further.

There was one patient treated with RMZ, CNS7056- (b) (6) in the Group A1A pooled safety analysis, discussed above, who withdrew from study treatment due to the occurrence of
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adverse events, including two serious adverse events.

8.4.4. Significant Adverse Events

The adverse events of most concern associated with administration of RMZ for procedural sedation are those associated with changes in cardiovascular and respiratory function, prolonged sedation, and adverse events related to abuse, dependence, and withdrawal. Vital sign changes could have been reported as adverse events either from the intermittent measurements that were recorded on the eCRF, which included heart rate, blood pressure, respiratory rate, oxygen saturation, and body temperature, or they could have been reported as Nellcor adverse events, which included changes in continuous heart rate, respiratory rate, or oxygen saturation. The discussion here will focus on those events reported during intermittent vital sign measurements. The results from review of the Nellcor safety data are presented in Section 8.4.7, Vital Signs.

The criteria for a change in a vital sign to become an adverse event includes the following:

- Low oxygen saturation/hypoxia: pulse oximetry < 90% for ≥ 1 minute or any drop requiring medical intervention
- Bradycardia: < 40 beats per minute (bpm) or any drop in heart rate 20% or more from baseline that lasted ≥ 30 seconds
- Hypotension: a fall in systolic blood pressure to ≤ 80 mmHg or a fall in diastolic blood pressure to ≤ 40 mmHg, or a fall in systolic or diastolic blood pressure $\geq 20\%$ below baseline or requiring medical intervention
- Hypertension: an increase in systolic blood pressure to ≥ 180 mmHg or in diastolic blood pressure to ≥ 100 mmHg or an increase of systolic or diastolic blood pressure $\geq 20\%$ above baseline or requiring medical intervention
- Respiratory depression: < 8 breaths per minute
- Prolonged sedation: MOAA/S ≤ 4 for longer than 60 minutes after the last dose of study drug or the need to administer flumazenil at the investigator's discretion

The Applicant used Standardized MedDRA queries (SMQs) to summarize the incidence of adverse events included in the respective term. A brief summary of those adverse events by study is presented below.

Study CNS7056-006

The SMQ for hypotension included diastolic hypotension, decreased diastolic/systolic blood pressure, and presyncope, and was reported with a lower incidence in the RMZ treatment group compared to the placebo and midazolam treatment groups. Hypertension, which included hypertension, diastolic/systolic hypertension and increased diastolic/systolic blood pressure, in general was reported less frequently than hypotension during the study. RMZ-treated patients had a lower rate of reported hypertension than placebo-treated patients, but a

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higher rate than midazolam-treated patients. Bradycardia, which included bradycardia and heart rate decreased, was reported with similar frequency in the RMZ and placebo treatment groups, and a higher frequency in the midazolam treatment group. The incidence of prolonged sedation was lowest in the RMZ treatment group, and highest in the midazolam treatment group.

Adverse events grouped under the SMQ for low oxygen saturation/respiratory depression, which included the terms bradypnea, hypoxia, respiratory rate decreased, and respiratory depression, were reported the least frequently in the RMZ treatment group and the most frequently in the midazolam treatment group. The following table summarizes the results of the respiratory, cardiovascular, and prolonged sedation SMQs evaluated by the Applicant.

Table 50. Treatment-Emergent Adverse Events with Respiratory, Cardiovascular, or Prolonged Sedation Association (Safety Population)

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Standardized MedDRA Query	Remimazolam	Placebo	Midazolam	Total
Preferred Term	N=296 n (%)	N=60 n (%)	N=102 n (%)	N=458 n (%)
Any TEAEs	211 (71.3%)	47 (78.3%)	90 (88.2%)	348 (76.0%)
Hypotension	131 (44.3%)	28 (46.7%)	68 (66.7%)	227 (49.6%)
Hypotension	115 (38.9%)	25 (41.7%)	63 (61.8%)	203 (44.3%)
Diastolic hypotension	23 (7.8%)	4 (6.7%)	9 (8.8%)	36 (7.9%)
Blood pressure diastolic decreased	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Blood pressure systolic decreased	1 (0.3%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
Presyncope	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Hypertension	95 (32.1%)	24 (40.0%)	30 (29.4%)	149 (32.5%)
Hypertension	59 (19.9%)	17 (28.3%)	18 (17.6%)	94 (20.5%)
Diastolic hypertension	29 (9.8%)	6 (10.0%)	9 (8.8%)	44 (9.6%)
Systolic hypertension	16 (5.4%)	5 (8.3%)	6 (5.9%)	27 (5.9%)
Blood pressure diastolic increased	3 (1.0%)	0 (0.0%)	1 (1.0%)	4 (0.9%)
Blood pressure systolic increased	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Bradycardia	34 (11.5%)	7 (11.7%)	16 (15.7%)	57 (12.4%)
Bradycardia	33 (11.1%)	7 (11.7%)	16 (15.7%)	56 (12.2%)
Heart rate decreased	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Prolonged sedation	28 (9.5%)	7 (11.7%)	13 (12.7%)	48 (10.5%)
Tachycardia	23 (7.8%)	7 (11.7%)	13 (12.7%)	43 (9.4%)
Dizziness	3 (1.0%)	0 (0.0%)	0 (0.0%)	3 (0.7%)
Presyncope	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Low oxygen saturation/Respiratory depression	11 (3.7%)	4 (6.7%)	7 (6.9%)	22 (4.8%)
Bradypnoea	4 (1.4%)	2 (3.3%)	3 (2.9%)	9 (2.0%)
Hypoxia	3 (1.0%)	2 (3.3%)	1 (1.0%)	6 (1.3%)
Respiratory rate decreased	3 (1.0%)	0 (0.0%)	2 (2.0%)	5 (1.1%)
Respiratory depression	1 (0.3%)	0 (0.0%)	1 (1.0%)	2 (0.4%)

Source: Section 14.3, Table 14.3.1.6.1.2

MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; n = number of observations; TEAE = treatment-emergent adverse event
 Note: The denominator for the percentages is the number of patients in each treatment. At each level of summarization, a patient is counted only once.
 MedDRA version 18.0 has been used for the reporting of adverse events.

Source: Study CNS7056-006 Report Body, p. 137-138 (PDF), Applicant's submission, NDA 212295.

There did not appear to be clinically significant relationship between ASA-PS and the incidence of respiratory or cardiovascular-related adverse events in the RMZ treatment group.

The Applicant reported significant adverse events for 18 patients in the RMZ treatment group, six patients in the midazolam treatment group, and two patients in the placebo group. The majority of these significant adverse events were reported in the investigations SOC and included changes in measured hemodynamic parameters, as previously discussed, and headache, vasovagal episodes, and changes in measured lab values in the RMZ treatment group, URI, changes in measured hemodynamic parameters, T-wave changes, itching, and common cold in the midazolam treatment group, and changes in measured lab values in the placebo treatment group.

Study CNS7056-008

The SMQ for hypertension had the highest incidence of reported adverse events in the study, and a higher percentage of patients in the RMZ treatment group (61%) reported these adverse events compared to patients in the placebo treatment group (53%) or midazolam treatment group (60%). Patients in the placebo treatment group had the highest incidence of adverse events in the SMQ for hypotension (63%) compared to those in the RMZ treatment group (42%) or in the midazolam treatment group (49%). In the SMQ for low oxygen/respiratory depression, the incidence of adverse events was similar in all treatment groups; i.e., 25% in the RMZ treatment group, 24% in the placebo treatment group, and 23% in the midazolam treatment group. The following table summarizes the results of the respiratory, cardiovascular, and prolonged sedation SMQs evaluated by the Applicant.

Table 51. Treatment-Emergent Adverse Events with Respiratory, Cardiovascular, or Prolonged Sedation Association (Safety Population)

SMQ	Preferred Term	Remimazolam (N=303)	Placebo (N=59)	Midazolam (N=69)	Total (N=431)
Any Treatment Emergent Adverse Events		257 (84.8%)	49 (83.1%)	60 (87.0%)	366 (84.9%)
Hypertension	Hypertension	184 (60.7%)	31 (52.5%)	41 (59.4%)	256 (59.4%)
	Diastolic hypertension	85 (28.1%)	9 (15.3%)	19 (27.5%)	113 (26.2%)
	Systolic hypertension	77 (25.4%)	15 (25.4%)	16 (23.2%)	108 (25.1%)
	Blood pressure diastolic increased	67 (22.1%)	13 (22.0%)	17 (24.6%)	97 (22.5%)
	Blood pressure increased	3 (1.0%)	1 (1.7%)	0 (0.0%)	4 (0.9%)
	Blood pressure systolic increased	3 (1.0%)	0 (0.0%)	0 (0.0%)	3 (0.7%)
Hypotension	Hypotension	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
	Diastolic hypotension	126 (41.6%)	37 (62.7%)	34 (49.3%)	197 (45.7%)
	Blood pressure decreased	99 (32.7%)	28 (47.5%)	23 (33.3%)	150 (34.8%)
	Blood pressure diastolic decreased	41 (13.5%)	17 (28.8%)	16 (23.2%)	74 (17.2%)
	Blood pressure systolic decreased	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Low Oxygen Saturation/Respiratory Depression	Hypoxia	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Respiratory rate decreased	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Dyspnoea	77 (25.4%)	14 (23.7%)	16 (23.2%)	107 (24.8%)
	Acute respiratory failure	66 (21.8%)	12 (20.3%)	13 (18.8%)	91 (21.1%)
	Breath sounds abnormal	7 (2.3%)	2 (3.4%)	3 (4.3%)	12 (2.8%)
		4 (1.3%)	0 (0.0%)	0 (0.0%)	4 (0.9%)
Low Oxygen Saturation/Respiratory Depression	Hypopnoea	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Oxygen saturation decreased	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Respiratory depression	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.2%)
	Respiratory distress	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (0.2%)
	Respiratory failure	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Prolongued Sedation	Pyrexia	19 (6.3%)	1 (1.7%)	3 (4.3%)	23 (5.3%)
	Tachycardia	11 (3.6%)	1 (1.7%)	1 (1.4%)	13 (3.0%)
	Somnolence	4 (1.3%)	0 (0.0%)	0 (0.0%)	4 (0.9%)
	Dizziness	1 (0.3%)	0 (0.0%)	2 (2.9%)	3 (0.7%)
	Confusional state	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
	Disorientation	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
		1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Bradycardia	Bradycardia	13 (4.3%)	4 (6.8%)	5 (7.2%)	22 (5.1%)
	Atrioventricular block first degree	11 (3.6%)	4 (6.8%)	4 (5.8%)	19 (4.4%)
	Electrocardiogram QT prolonged	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Heart rate decreased	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Sinus bradycardia	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (0.2%)
		1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)

Note: The denominator for the percentages is the number of patients in each treatment. At each level, a patient is counted only once. MedDRA version 18.0 has been used for the reporting of adverse events.

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Source: Study CNS7056-008, 14 Tables, p. 933-934 (PDF), Applicant's submission, NDA 212295.

The severe adverse events reported in this study were in the respiratory, thoracic, and mediastinal disorders, cardiac disorders, the infections and infestations, and psychiatric disorders SOCs. There were three patients with severe hypoxia, two treated with RMZ and one treated with placebo. One patient each in the RMZ treatment group had severe oropharyngeal pain, pneumothorax, chronic obstructive pulmonary disease, respiratory failure, aspiration, bradycardia, lobar pneumonia, and confusional state. There were two patients treated with RMZ and one treated with placebo who had bronchospasm.

The number of significant adverse events is higher than that reported during Study CNS7056-006 and they appear to be more severe; however, given the invasive nature of the procedure and comorbid medical conditions of evaluated patients, the results are not surprising. It does not appear that administration of RMZ for procedural sedation adversely impacts the outcomes of patients undergoing bronchoscopic procedures.

Study CNS7056-015

The SMQ for hypotension had the highest incidence of reported adverse events in the study, and a higher percentage of patients in the placebo group reported these adverse events (75%), compared to patients in the RMZ treatment group (61%) or in the midazolam treatment group (57%). Hypertension was reported less frequently overall, but the RMZ treatment group had the highest incidence (52%). Adverse events in the SMQ for low oxygen/respiratory depression were reported with the highest frequency in the midazolam treatment group (33%).

Table 52. Treatment-Emergent Adverse Events with Respiratory, Cardiovascular, or Prolonged Sedation Association (Safety Population)

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Standardised MedDRA Query Preferred Term	Remimazolam N=31 n (%)	Placebo N=16 n (%)	Midazolam N=30 n (%)	Total N=77 n (%)
Any Treatment Emergent Adverse Events	28 (90.3)	13 (81.3)	26 (86.7)	67 (87.0)
Hypotension	19 (61.3)	12 (75.0)	17 (56.7)	48 (62.3)
Hypotension	18 (58.1)	11 (68.8)	17 (56.7)	46 (59.7)
Diastolic hypotension	1 (3.2)	1 (6.3)	0 (0.0)	2 (2.6)
Hypertension	16 (51.6)	6 (37.5)	13 (43.3)	35 (45.5)
Hypertension	13 (41.9)	6 (37.5)	13 (43.3)	32 (41.6)
Diastolic hypertension	3 (9.7)	0 (0.0)	0 (0.0)	3 (3.9)
Systolic hypertension	2 (6.5)	0 (0.0)	0 (0.0)	2 (2.6)
Blood pressure diastolic increased	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.3)
Blood pressure increased	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.3)
Blood pressure systolic increased	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.3)
Low oxygen saturation/ Respiratory depression	7 (22.6)	3 (18.8)	10 (33.3)	20 (26.0)
Respiratory acidosis	6 (19.4)	2 (12.5)	8 (26.7)	16 (20.8)
Respiratory rate decreased	1 (3.2)	1 (6.3)	2 (6.7)	4 (5.2)
Bradycardia	1 (3.2)	1 (6.3)	4 (13.3)	6 (7.8)
Bradycardia	1 (3.2)	1 (6.3)	4 (13.3)	6 (7.8)
Prolonged sedation	0 (0.0)	2 (12.5)	0 (0.0)	2 (2.6)
Tachycardia	0 (0.0)	2 (12.5)	0 (0.0)	2 (2.6)

Source: [Section 14.3, Table 14.3.1.6.1.2](#)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; n = number of observations; TEAE = treatment-emergent adverse event
 Note: The denominator for the percentages is the number of patients in each treatment group. At each level of summarisation, a patient is counted only once.
 MedDRA version 18.0 was used for the reporting of adverse events.

Source: Study CNS7056-015 Report Body, p. 110 (PDF), Applicant's submission, NDA 212295.

Analysis of the overall incidence of respiratory or cardiovascular adverse events did not identify clinically significant differences between ASA-PS III or IV patients, 88% versus 87%, respectively. There were, however, potentially meaningful differences between ASA-PS groups in adverse event reporting in specific SMQs. For example, adverse events in the low oxygen saturation/respiratory depression SMQ were reported with a greater incidence in ASA-PS IV patients compared to ASA-PS III patients, 32% versus 20%, respectively. Adverse events in the hypotension, bradycardia, and hypertension SMQs had a greater incidence in the ASA-PS III patients than ASA-PS IV patients, 70% versus 54%, 15% versus 0%, and 50% versus 41%, respectively.

Additionally, the incidence of specific adverse events by ASA-PS was different between treatment groups. Specifically, for ASA-PS III patients, hypertension was reported more frequently in the RMZ treatment group (69%) than in the placebo (33%) or midazolam (40%) treatment groups, while for ASA-PS IV patients, hypertension was reported less in the RMZ treatment group (33%) than in the placebo (43%) or midazolam (47%) treatment groups. The incidence of hypotension was greater in the placebo group than the RMZ and midazolam groups in both ASA-PS III and IV patients.

Of note, there were two patients treated with RMZ during clinical development who experienced the adverse event of apnea. One occurred in a healthy volunteer who received RMZ 85 mg, the other occurred in a surgical patient who received RMZ for maintenance of general anesthesia. No episodes of apnea were reported in the procedural sedation studies.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The following table was included in the proposed package insert submitted by the Applicant. This table is (b) (4) data from studies CNS7056-006, CNS7056-008, and CNS7056-015.



Source: Package Insert, Section 6, Adverse Reactions, Applicant's submission, NDA 212295.



The following discussion will include adverse events not previously discussed, by study, with emphasis on those reported with a higher frequency in the RMZ treatment group.

Study CNS7056-006

A summary of the overall incidence of reported treatment-emergent adverse events in this study is included in the following table.

Table 54. Summary of Treatment-Emergent Adverse Events (Safety Population)

Number of Patients	Remimazolam N=296	Placebo N=60	Midazolam N=102	Total N=458
All Adverse Events	228 (77.0%)	48 (80.0%)	95 (93.1%)	371 (81.0%)
TEAEs	218 (73.6%)	47 (78.3%)	93 (91.2%)	358 (78.2%)
Serious TEAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAEs Leading to Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAEs Leading to Discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Related TEAEs	125 (42.2%)	35 (58.3%)	67 (65.7%)	227 (49.6%)

Source: Section 14.3, Table 14.3.1.1.1

N = number of patients; TEAE = treatment-related adverse event

Source: Study CNS7056-006 Report Body, p. 129 (PDF), Applicant's submission, NDA 212295.

There were no serious adverse events and no deaths reported in this study for any patient in any treatment group. The overall incidence of adverse events was lowest in the RMZ treatment group, and highest in the midazolam treatment group. Similarly, adverse events related to study drug treatment were reported with the highest incidence in the midazolam treatment group. This should be surprising given the Applicant has indicated that while the dose of midazolam administered in this group was consistent with the label dosing guidelines for patients receiving concomitant opioid medications, it is considered low for sedation during the procedures evaluated compared to the doses likely administered at the discretion of individual providers. However, in reviewing the midazolam use data during this study, it appears that the midazolam treatment group actually had the highest mean dose of midazolam, 7.1 mg, compared to that administered in the placebo treatment group, 6.84 mg, or in the RMZ treatment group, 0.31 mg.

The following table summarizes the incidence of treatment-emergent adverse events by SOC and PT.

Table 55. Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in > 1 patient (Safety Population)

System Organ Class Preferred Term	Remimazolam N=296 n (%)	Placebo N=60 n (%)	Midazolam N=102 n (%)	Total N=458
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Any TEAEs	218 (73.6%)	47 (78.3%)	93 (91.2%)	358 (78.2%)
Vascular disorders	184 (62.2%)	41 (68.3%)	83 (81.4%)	308 (67.2%)
Hypotension	115 (38.9%)	25 (41.7%)	63 (61.8%)	203 (44.3%)
Hypertension	59 (19.9%)	17 (28.3%)	18 (17.6%)	94 (20.5%)
Diastolic hypertension	29 (9.8%)	6 (10.0%)	9 (8.8%)	44 (9.6%)
Diastolic hypotension	23 (7.8%)	4 (6.7%)	9 (8.8%)	36 (7.9%)
Systolic hypertension	16 (5.4%)	5 (8.3%)	6 (5.9%)	27 (5.9%)
Cardiac disorders	53 (17.9%)	14 (23.3%)	26 (25.5%)	93 (20.3%)
Bradycardia	33 (11.1%)	7 (11.7%)	16 (15.7%)	56 (12.2%)
Tachycardia	23 (7.8%)	7 (11.7%)	13 (12.7%)	43 (9.4%)
Respiratory, thoracic and mediastinal disorders	11 (3.7%)	4 (6.7%)	6 (5.9%)	21 (4.6%)
Bradypnoea	4 (1.4%)	2 (3.3%)	3 (2.9%)	9 (2.0%)
Hypoxia	3 (1.0%)	2 (3.3%)	1 (1.0%)	6 (1.3%)
Respiratory depression	1 (0.3%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
Gastrointestinal disorders	8 (2.7%)	5 (8.3%)	3 (2.9%)	16 (3.5%)
Nausea	5 (1.7%)	4 (6.7%)	2 (2.0%)	11 (2.4%)
Vomiting	3 (1.0%)	2 (3.3%)	0 (0.0%)	5 (1.1%)
Diarrhoea	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)
Nervous system disorders	11 (3.7%)	0 (0.0%)	3 (2.9%)	14 (3.1%)
Headache	5 (1.7%)	0 (0.0%)	3 (2.9%)	8 (1.7%)
Dizziness	3 (1.0%)	0 (0.0%)	0 (0.0%)	3 (0.7%)
Presyncope	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Investigations	8 (2.7%)	1 (1.7%)	4 (3.9%)	13 (2.8%)
Respiratory rate decreased	3 (1.0%)	0 (0.0%)	2 (2.0%)	5 (1.1%)
Blood pressure diastolic increased	3 (1.0%)	0 (0.0%)	1 (1.0%)	4 (0.9%)
Blood pressure diastolic decreased	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Blood pressure systolic decreased	1 (0.3%)	0 (0.0%)	1 (1.0%)	2 (0.4%)
Blood pressure systolic increased	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.4%)
Haematocrit decreased	1 (0.3%)	1 (1.7%)	0 (0.0%)	2 (0.4%)
Haemoglobin decreased	1 (0.3%)	1 (1.7%)	0 (0.0%)	2 (0.4%)
Infections and infestations	2 (0.7%)	1 (1.7%)	1 (1.0%)	4 (0.9%)
General disorders and administration site conditions	2 (0.7%)	0 (0.0%)	1 (1.0%)	3 (0.7%)
Metabolism and nutrition disorders	2 (0.7%)	0 (0.0%)	1 (1.0%)	3 (0.7%)
Injury, poisoning and procedural complications	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)
Contusion	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)
Musculoskeletal and connective tissue disorders	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)
Back pain	0 (0.0%)	1 (1.7%)	1 (1.0%)	2 (0.4%)
Eye disorders	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.2%)
Psychiatric disorders	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Skin and subcutaneous tissue disorders	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.2%)

Source: Section 14.3, Table 14.3.1.2

N = number of patients; n = number of observations; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

Note: The denominator for the percentages is the number of patients in each treatment. At each level of summarization, a patient is counted only once.

MedDRA version 18.0 has been used for the reporting of adverse events.

Source: Study CNS7056-006 Report Body, p. 130-131 (PDF), Applicant's submission, NDA 212295.

There did not appear to be any clinically meaningful differences between the RMZ treatment group and either the placebo or midazolam treatment groups that would adversely impact the safety profile of RMZ. Of the adverse events that did not have a respiratory or cardiovascular

focus, nausea, headache, vomiting, and dizziness were the most commonly reported. Dizziness was the only adverse event reported with increased incidence in the RMZ treatment group. No other adverse events were reported in more than two patients in this study and will not be discussed further.

The majority of adverse events were mild in severity. Only two patients reported severe adverse events; one patient in the RMZ treatment group reported severe abdominal pain and one patient in the placebo group reported severe back pain, both unlikely related to study drug treatment. Moderately severe adverse events were reported in seven patients total, six in the RMZ treatment group and one in the midazolam treatment group. Three patients had moderate hypotension; two in the RMZ treatment group and one in the midazolam treatment group. Other moderate adverse events reported in one patient each in the RMZ treatment group included tachycardia, abdominal discomfort, headache, respiratory rate decreased, diastolic blood pressure increased, and systolic blood pressure increased. All other adverse events were mild in severity.

Adverse events considered related to study drug administration by the investigators were reported with the highest incidence in the midazolam treatment group. Specifically, related adverse events were reported in approximately 66% of patients in the midazolam treatment group, compared to 42% in the RMZ treatment group and 58% in the placebo treatment group. Treatment-related adverse events were reported with the highest incidence in the vascular disorders and cardiac disorders SOC. For both of these SOCs, the incidence of treatment-related events was lowest in the remimazolam group compared to the placebo or the midazolam groups. After Protocol Amendment 2, additional relatedness categories were added, including related/not related, to certain/probable-likely/possible/unlikely/conditional-unclassified/unassessable-unclassifiable.

Analysis of adverse events known to occur with medications of abuse did not identify concerns regarding RMZ administration during the procedures evaluated. Dizziness was the only treatment-emergent adverse event possibly associated with abuse potential and that was reported with a higher incidence in the RMZ treatment group compared to either the midazolam or placebo groups. There were only three patients, however, who experienced dizziness and this is not likely clinically significant.

Study CNS7056-008

A summary of the overall incidence of reported treatment-emergent adverse events in this study is included in the following table.

Table 56. Summary of Treatment-Emergent Adverse Events (Safety Population)

Number of Patients with	Remimazolam N=303 n (%)	Placebo N=59 n (%)	Midazolam N=69 n (%)	Total N=431 n (%)
All AEs	273 (90.1)	52 (88.1)	64 (92.8)	389 (90.3)
TEAEs	268 (88.4)	52 (88.1)	63 (91.3)	383 (88.9)
Serious TEAEs	17 (5.6)	4 (6.8)	0 (0.0)	21 (4.9)
TEAEs leading to withdrawal	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Related TEAEs	105 (34.7)	15 (25.4)	22 (31.9)	142 (32.9)

Source: Section 14.3, Table 14.3.1.1.1

Abbreviations: AE = adverse events; N = number of patients; n = number of observations; TEAE = treatment-emergent adverse event

Source: Study CNS7056-008 Report Body, p. 133 (PDF), Applicant's submission, NDA 212295.

There were no deaths during this study. As previously discussed, there were a total of 21 patients with serious adverse events reported in this study; 17 treated with RMZ and four treated with placebo. All serious adverse events appeared to be related to underlying disease and the procedure and unlikely related to study drug administration. It is surprising, however, that no patient treated with midazolam experienced a serious adverse event.

Similar to the safety findings reported in Study CNS7056-006, the overall incidence of adverse events was highest in the midazolam treatment group. Unlike that study, however, the mean dose of midazolam was lower in that treatment group compared to the mean dose administered in the placebo group, 5.76 mg versus 5.87 mg, respectively.

The following table summarizes the treatment-emergent adverse events reported in this study by SOC and some preferred terms.

Table 57. Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in $\geq 5\%$ of Patients in any Group (Safety Population)

System Organ Class	Preferred Term	Remimazolam N=303 n (%)		Placebo N=59 n (%)		Midazolam N=69 n (%)		Total N=431 n (%)	
		n	(%)	n	(%)	n	(%)	n	(%)
Any TEAE		268	(88.4)	52	(88.1)	63	(91.3)	383	(88.9)
Vascular disorders		235	(77.6)	47	(79.7)	56	(81.2)	338	(78.4)
	Hypotension	99	(32.7)	28	(47.5)	23	(33.3)	150	(34.8)
	Hypertension	85	(28.1)	9	(15.3)	19	(27.5)	113	(26.2)
	Diastolic hypertension	77	(25.4)	15	(25.4)	16	(23.2)	108	(25.1)
	Systolic hypertension	67	(22.1)	13	(22.0)	17	(24.6)	97	(22.5)
	Diastolic hypotension	41	(13.5)	17	(28.8)	16	(23.2)	74	(17.2)
Respiratory, thoracic, and mediastinal disorders		95	(31.4)	20	(33.9)	20	(29.0)	135	(31.3)
	Hypoxia	66	(21.8)	12	(20.3)	13	(18.8)	91	(21.1)
	Tachypnoea	7	(2.3)	6	(10.2)	4	(5.8)	17	(3.9)
Investigations		57	(18.8)	8	(13.6)	13	(18.8)	78	(18.1)
	Respiratory rate increased	43	(14.2)	6	(10.2)	10	(14.5)	59	(13.7)
Cardiac disorders		21	(6.9)	4	(6.8)	6	(8.7)	31	(7.2)
	Bradycardia	11	(3.6)	4	(6.8)	4	(5.8)	19	(4.4)
Gastrointestinal disorders		21	(6.9)	3	(5.1)	5	(7.2)	29	(6.7)
General disorders and administration site conditions		17	(5.6)	4	(6.8)	3	(4.3)	24	(5.6)
Nervous system disorders		12	(4.0)	3	(5.1)	6	(8.7)	21	(4.9)

Abbreviations: N = number of patients; n = number of observations; TEAE = treatment-emergent adverse event

Source: Section 14.3, Table 14.3.1.2

Note: The denominator for the percentages was the number of patients in each treatment group. At each level of summarization, a patient was counted only once.

MedDRA version 18.0 was used for the reporting of AEs.

Source: Study CNS7056-008 Report Body, p. 135 (PDF), Applicant's submission, NDA 212295.

The most commonly reported adverse events not in the respiratory or cardiovascular systems and not previously discussed, were nausea, pyrexia, and headache. The incidences of nausea and pyrexia were the highest in the RMZ treatment group and lowest in the midazolam treatment group, but the differences are likely not clinically significant. Headache was reported with the highest frequency in the midazolam treatment group.

The majority of patients experienced adverse events that were mild in severity. Moderately severe adverse events were reported in 35 patients treated with RMZ, 8 patients treated with placebo, and 6 patients treated with midazolam. Ten patients in the RMZ treatment group and one patient in the placebo treatment group experienced severe adverse events, discussed in Section 8.4.4, Significant Adverse Events.

Adverse events considered related to study drug administration by the investigators were reported with the highest incidence in the RMZ treatment group. Specifically, related adverse events were reported in approximately 35% of patients in the RMZ treatment group, compared to 25% in the placebo treatment group and 32% in the midazolam treatment group. The most frequently reported related adverse events were in the vascular disorders, respiratory, thoracic, and mediastinal disorders, and investigations SOCs. By PT, the most frequent treatment-related adverse events were hypotension, hypertension, and hypoxia. The presence of a concomitant illness, including congestive heart failure, hypertension, coronary artery disease, chronic obstructive pulmonary disease, preexisting mental impairment, and gastrointestinal disorder, appeared to increase the incidence of hypertension in all treatment groups, to the greatest extent in the midazolam treatment group.

Analysis of adverse events known to occur with medications of abuse did not identify concerns regarding RMZ administration during the procedures evaluated. Somnolence, dizziness, and confusional state and disorientation were the only treatment-emergent adverse events that could be possibly associated with abuse potential and they were reported in a very low number of patients in general.

Study CNS7056-015

A summary of the overall incidence of reported treatment-emergent adverse events in this study is included in the following table.

Table 58. Summary of Treatment-Emergent Adverse Events (Safety Population)

Number of Patients	Remimazolam	Placebo	Midazolam	Total
	N=31	N=16	N=30	N=77
	n (%)	n (%)	n (%)	n (%)
All Adverse Events	28 (90.3%)	13 (81.3%)	28 (93.3%)	69 (89.6%)
TEAEs	28 (90.3%)	13 (81.3%)	26 (86.7%)	67 (87.0%)
Serious TEAEs	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (1.3%)
TEAEs Leading to Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAEs Leading to Withdrawal	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (1.3%)
Related TEAEs	3 (9.7%)	2 (12.5%)	2 (6.7%)	7 (9.1%)

Source: [Section 14.3, Table 14.3.1.1.1](#)

N = number of patients; n = number of observations; TEAE = treatment emergent adverse event

Source: Study CNS7056-015 Report Body, p. 105 (PDF), Applicant's submission, NDA 212295.

There were no deaths reported in this study for any patient in any treatment group. There was one serious adverse event, anemia, reported in one patient in the midazolam treatment group, and this was felt to be unrelated to study drug administration. One patient in the midazolam treatment group discontinued from study treatment due to the adverse event of respiratory acidosis, as measured via transcutaneous CO₂ monitoring, which was considered possibly related to study drug. The patient received midazolam 1 mg, followed by three 0.5 mg top-up doses, and 5 mg rescue dose, for a total of 7.5 mg midazolam, and fentanyl 50 µg.

As summarized in the following table, the majority of reported adverse events were in the vascular disorders, respiratory, thoracic, and mediastinal disorders, cardiac disorders, and investigations SOCs.

Table 59. Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)

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

System Organ Class Preferred Term	Remimazolam N=31 n (%)	Placebo N=16 n (%)	Midazolam N=30 n (%)	Total N=77 n (%)
Any Treatment-Emergent Adverse Events	28 (90.3)	13 (81.3)	26 (86.7)	67 (87.0)
Vascular disorders	26 (83.9)	13 (81.3)	24 (80.0)	63 (81.8)
Hypotension	18 (58.1)	11 (68.8)	17 (56.7)	46 (59.7)
Hypertension	13 (41.9)	6 (37.5)	13 (43.3)	32 (41.6)
Diastolic hypertension	3 (9.7)	0 (0.0)	0 (0.0)	3 (3.9)
Diastolic hypotension	1 (3.2)	1 (6.3)	0 (0.0)	2 (2.6)
Systolic hypertension	2 (6.5)	0 (0.0)	0 (0.0)	2 (2.6)
Respiratory, thoracic, and mediastinal disorders	6 (19.4)	2 (12.5)	8 (26.7)	16 (20.8)
Respiratory acidosis	6 (19.4)	2 (12.5)	8 (26.7)	16 (20.8)
Cardiac disorders	1 (3.2)	2 (12.5)	4 (13.3)	7 (9.1)
Bradycardia	1 (3.2)	1 (6.3)	4 (13.3)	6 (7.8)
Tachycardia	0 (0.0)	2 (12.5)	0 (0.0)	2 (2.6)
Investigations	2 (6.5)	1 (6.3)	2 (6.7)	5 (6.5)
Respiratory rate decreased	1 (3.2)	1 (6.3)	2 (6.7)	4 (5.2)
Blood pressure diastolic increased	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.3)
Blood pressure increased	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.3)
Blood pressure systolic increased	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.3)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (3.3)	1 (1.3)
Anaemia	0 (0.0)	0 (0.0)	1 (3.3)	1 (1.3)
Infections and infestations	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.3)
Upper respiratory tract infection	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.3)

Source: [Section 14.3, Table 14.3.1.2](#)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; n = number of observations; TEAE = treatment-emergent adverse event
 Note: The denominator for the percentages is the number of patients in each treatment group. At each level of summarisation, a patient is counted only once.
 MedDRA version 18.0 was used for the reporting of adverse events.

Source: Study CNS7056-015 Report Body, p. 107 (PDF), Applicant's submission, NDA 212295.

Aside from a single event each of anemia and upper respiratory infection, there were no adverse events reported that were not in the respiratory or cardiovascular systems. There did not appear to be any clinically meaningful differences between treatment groups in the incidence of adverse events, with the exception of diastolic hypertension, systolic hypertension, respiratory rate decreased, blood pressure diastolic increased, blood pressure increased, and blood pressure systolic increased. With the exception of diastolic hypertension and systolic hypertension, all adverse events were reported only once.

All adverse events, except for anemia previously discussed, were mild in severity. As summarized in the following table, there were ten treatment-related adverse events reported in seven patients; four reported in three RMZ-treated patients, three reported in two placebo-treated patients, and three reported in two midazolam-treated patients.

Table 60. Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Remimazolam N=31 n (%)	Placebo N=16 n (%)	Midazolam N=30 n (%)	Total N=77 n (%)
Any related TEAEs	3 (9.7)	2 (12.5)	2 (6.7)	7 (9.1)
Vascular disorders	2 (6.5)	2 (12.5)	1 (3.3)	5 (6.5)
Hypotension	1 (3.2)	2 (12.5)	1 (3.3)	4 (5.2)
Diastolic hypertension	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.3)
Respiratory, thoracic and mediastinal disorders	1 (3.2)	0 (0.0)	2 (6.7)	3 (3.9)
Respiratory acidosis	1 (3.2)	0 (0.0)	2 (6.7)	3 (3.9)

Source: [Section 14.3, Table 14.3.1.5](#)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients; n = number of observations;
 TEAE = treatment-emergent adverse event

Note: The denominator for the percentages is the number of patients in each treatment group. At each level of summarisation, a patient is counted only once.

MedDRA version 18.0 was used for the reporting of adverse events.

Source: Study CNS7056-015 Report Body, p. 108 (PDF), Applicant's submission, NDA 212295.

The results in this table suggest that the majority of adverse events reported in this study were considered not related/unlikely by the investigators. There were no adverse events reported during this study that are known to be associated with medications of abuse.

8.4.6. Laboratory Findings

Laboratory data was captured within three hours pre-dose, prior to discharge, and at respective follow-up visits for each study.

Study CNS7056-006

In all treatment groups, a slight decrease in mean alkaline phosphatase was observed pre-dose and prior to discharge on study day 1 that returned to baseline by the day 4 follow-up. This appears to be a clinically insignificant finding. Similarly, there were decreases in mean AST and ALT from within three hours pre-dose to prior to discharge and at the study day 4 follow-up visit. The decreases were slight and consistently observed in all treatment groups. This also appears to be a clinically insignificant finding. Mean bilirubin levels decreased in all treatment groups through the study day 4 follow-up visit, the timepoint with the lowest reported levels. Mean blood urea nitrogen (BUN) levels increased in all treatment groups from three hours pre-dose to the study day 4 follow-up visit. Mean calcium levels decreased in all treatment groups from the three-hour pre-dose assessment to the prior to discharge assessment, but returned to normal by study day 4 follow-up visit. Mean magnesium levels decreased from three hours pre-dose to the study day 4 follow-up visit in all treatment groups. Mean chloride levels, creatine kinase, and creatinine increased from three hours pre-dose through the study day 4 follow-up visit. The observed changes in measured biochemistry parameters were small, generally observed in all treatment groups, and of indeterminate clinical relevance.

There was a decrease in mean hemoglobin concentration in all treatment groups from three hours pre-dose to prior to discharge, which increased close to baseline by the study day 4 follow-up visit. There was a decrease in mean platelet count in all treatment groups from three hours pre-dose to prior to discharge, and returned to baseline by the study day 4 follow-up visit. There were no changes in mean coagulation parameter values across treatment groups.

There were eight treatment-emergent adverse events related to abnormal lab values in five patients, as summarized in the following table. Four patients received RMZ and one patient received placebo.

Table 61. Abnormal Laboratory Values Reported as Treatment-Emergent Adverse Events (Safety Population)

Patient / Group	Adverse Event	Severity/ Related	Assessment	Start / Stop date	Value	Normal Range
(b) (6) Rem	Haematocrit decreased	Mild/ No	Prior to discharge	(b) (6)	0.344 L/L	0.364 – 0.489
(b) (6) Plac	Haematocrit decreased	Mild/ Possible	Prior to discharge		0.274 L/L	0.364 – 0.489
(b) (6) Rem	Haemoglobin decreased	Mild/ No	Prior to discharge		109 g/L	115 - 160
(b) (6) Plac	Haemoglobin decreased	Mild/ Possible	Prior to discharge		95 g/L	115 - 160
(b) (6) Plac	Platelet count decreased	Mild/ Possible	Prior to discharge		126×10 ⁹ /L	130 – 400
(b) (6) Rem	Blood lactate dehydrogenase increased	Mild/ No	Prior to discharge		778 U/L	120 – 246
(b) (6) Rem	Hyperglycaemia	Mild/ No	Follow-up		12.3 mmol/L	3.3 – 7.8
(b) (6) Rem	Hyperkalaemia	Mild/ Unlikely	Prior to discharge		6.0 mmol/L	3.5 – 5.1

Source: [Listing 16.2.7.1](#), [Listing 16.2.8.1.1](#), [Listing 16.2.8.1.2](#)

Plac = placebo; Rem = remimazolam

Source: Study CNS7056-006 Report Body, p. 146 (PDF), Applicant's submission, NDA 212295.

All lab-related adverse events were reported as mild in severity.

Study CNS7056-008

The Applicant has indicated that there were no meaningful changes in laboratory values from

mean baseline assessments to follow-up assessments.

There did not appear to be any consistent trends observed either within or between treatment groups in liver function tests. Specifically, AST and ALT did not significantly change from three hours pre-dose to prior to discharge. There were no meaningful changes observed in mean alkaline phosphatase levels throughout the study, either within or between treatment groups. Mean bilirubin levels increased in all treatment groups, but the increase did not appear to be clinically relevant. Mean BUN levels decreased in the RMZ treatment group. There was no consistent trend observed in the midazolam or placebo treatment groups. Mean serum calcium levels decreased in all treatment groups from three hours pre-dose to prior to discharge. Creatine kinase levels increased in the RMZ and midazolam treatment groups. There did not appear to be any clinically meaningful changes in electrolyte levels throughout the study.

There was a decrease in mean hemoglobin concentration in all treatment groups from three hours pre-dose to prior to discharge. There was a decrease in mean platelet count in all treatment groups. There were no changes in mean coagulation parameter values across treatment groups.

Abnormal laboratory values that were reported as adverse events were reported only in the RMZ treatment group and included the following:

- two patients with hyperglycemia
- one patient with hypomagnesemia
- one patient with anemia
- one patient with low bicarbonate level
- one patient with leukocytosis

Study CNS7056-015

There were no clinically meaningful changes reported in mean alkaline phosphatase in any treatment group in this study. Mean ALT decreased in all treatment groups prior to discharge, but was returning to baseline by study day 2. Mean AST decreased in the RMZ and midazolam treatment groups from three hours pre-dose to prior to discharge, but there was no change observed in the placebo group. Mean bilirubin was decreased in all treatment groups on study day 2. In all treatment groups, mean protein and albumin were reduced at discharge and were returning to baseline on study day 2. Mean creatine kinase was decreased prior to discharge in the RMZ group, but no changes were observed in the placebo or midazolam treatment groups. Of note, the measured CK levels in the midazolam group were substantially higher than those measured in the RMZ or placebo groups at all time points. There were no changes reported in mean electrolyte concentrations.

There was a decrease in mean hemoglobin concentration and platelet count in all treatment

groups from three hours pre-dose to prior to discharge, which increased close to baseline by the study day 2 follow-up visit. There were no changes in mean coagulation parameter values across treatment groups.

8.4.7. Vital Signs

Vital signs, including heart rate, blood pressure, respiratory rate, pulse oximetry, and temperature, were documented at various times pre-, intra-, and post-procedure until fully alert on the eCRF. Additionally, heart rate, respiratory rate, and pulse oximetry were continuously monitored during the evaluated procedures through fully alert and comprised the Nellcor safety populations. Criteria for clinically relevant vital sign changes are summarized in the following table.

Table 62. Criteria Used to Identify Clinically Relevant Changes in Vital Sign Parameters

Clinically Notable Vital Sign Abnormalities	Definition
Hypoxia	SpO2 <90%
Bradycardia	<40 bpm or a drop in heart rate of >20% from baseline
Hypotension	Systolic BP to ≤80 mmHg or diastolic BP to ≤40 mmHg, or a fall in systolic or diastolic BP 20% or more below baseline
Respiratory depression	<8 breaths per minute
Hypertension	Systolic BP to ≥180 mmHg or diastolic BP to ≥100 mmHg, or an increase of systolic or diastolic BP of 20% or more over baseline

BP=blood pressure; bpm = beats per minute; SpO2=arterial oxygen saturation

Source: ISS Report, p. 158 (PDF), Applicant's submission, NDA 212295.

Adverse events were documented based on both the intermittent vital sign measurements captured on the eCRF and changes observed during continuous Nellcor monitoring. The adverse events documented on the eCRF had additional duration criteria, as discussed in Section 8.4.4, Significant Adverse Events.

eCRF Vital Sign Data

Clinically relevant changes in measure vital signs for the pooled safety analysis Group A1A are summarized in the following table.

Table 63. Incidence of Clinically Relevant Changes in Measure Vital Signs (Safety Population)

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

Clinically Notable Abnormalities Criterion [n (%)]	Total Remimazolam (N=630)	Total Midazolam (N=201)	Placebo (N=135)
Hypoxia			
SpO2 measured	630 (100)	201 (100)	135 (100)
SpO2 <90%	66 (10.5)	15 (7.5)	14 (10.4)
Bradycardia			
HR measured	630 (100)	201 (100)	135 (100)
HR <40 bpm	0	0	0
Decrease in HR >20%	45 (7.1)	22 (10.9)	11 (8.1)
Any bradycardia criteria	45 (7.1)	22 (10.9)	11 (8.1)
Respiratory Depression			
Breaths per minute measured	616 (97.8)	199 (99.0)	133 (98.5)
Breaths per minute <8	14 (2.3)	12 (6.0)	5 (3.8)
Hypotension			
SBP or DBP measured	630 (100)	201 (100)	135 (100)
SBP ≤80 mmHg	7 (1.1)	6 (3.0)	3 (2.2)
DBP ≤40 mmHg	9 (1.4)	4 (2.0)	5 (3.7)
SBP ≤80 mmHg or DBP ≤40 mmHg	15 (2.4)	7 (3.5)	7 (5.2)
Decrease in SBP ≥20%	186 (29.5)	83 (41.3)	47 (34.8)
SBP ≤80 mmHg	5 (0.8)	5 (2.5)	3 (2.2)
Decrease in DBP ≥20%	195 (31.0)	95 (47.3)	61 (45.2)
DBP ≤40 mmHg	8 (1.3)	4 (2.0)	5 (3.7)
Decrease in SBP or DBP ≥20%	271 (43.0)	120 (59.7)	78 (57.8)
SBP ≤80 mmHg or DBP ≤40 mmHg	13 (2.1)	7 (3.5)	7 (5.2)
Any hypotension criteria	273 (43.3)	120 (59.7)	78 (57.8)
Hypertension			
SBP or DBP measured	630 (100)	201 (100)	135 (100)
SBP ≥180 mmHg	99 (15.7)	28 (13.9)	20 (14.8)
DBP ≥100 mmHg	123 (19.5)	33 (16.4)	25 (18.5)
SBP ≥180 mmHg or DBP ≥100 mmHg	163 (25.9)	49 (24.4)	35 (25.9)
Increase in SBP ≥20%	139 (22.1)	38 (18.9)	34 (25.2)
SBP ≥180 mmHg	45 (7.1)	17 (8.5)	13 (9.6)
Increase in DBP ≥20%	225 (35.7)	59 (29.4)	53 (39.3)
DBP ≥100 mmHg	92 (14.6)	20 (10.0)	21 (15.6)
Increase in SBP or DBP ≥20%	266 (42.2)	74 (36.8)	60 (44.4)
SBP ≥180 mmHg or DBP ≥100 mmHg	116 (18.4)	33 (16.4)	29 (21.5)
Any hypertension criteria	313 (49.7)	90 (44.8)	66 (48.9)

n = number of subjects with at least one episode; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure;
 Note: Percentages for subjects with measurements are based on the Safety Population and each dose group - Group A1A.
 Percentages for individual events are based on the number of subjects with postdose measurements.
 Note: Increase and decrease in heart rate or blood pressure are compared to baseline.
 Note: Any bradycardia, hypotension, and hypertension criteria were counted if at least one of the corresponding criteria are met.
 The baseline definition for the analyses in this table uses the last scheduled or unscheduled measurement prior to the first dose of study medication (IV remimazolam or comparator) or the initial fentanyl application (whatever was applicable first).
 Source: [Table 7.1.1.3.2](#)

Source: ISS Report, p. 160 (PDF), Applicant's submission, NDA 212295.

There did not appear to be any significant differences in clinically relevant vital sign changes in patients treated with RMZ. Because RMZ appears to be rapidly-acting, clinically relevant vital signs are likely to occur early in the course of administration and during times of moderate to deep sedation. In the pooled safety analysis Group A1A, the majority of clinically relevant changes in vital signs for all treatment groups were observed in patients under mild to moderate sedation and there did not appear to be an increased risk of developing significant changes with increased depths of sedation. In the RMZ treatment group, however, it did appear there were more relevant vital sign changes in patients with MOAA/S scores of 0 to 1 compared to scores of 5. This is in contrast to the placebo or midazolam treatment groups in which there were, in general, more clinically significant vital sign changes in patients with MOAA/S scores of 5 versus scores of 0 or 1.

The following table summarizes the proportion of patients at each depth of sedation who experienced a clinically relevant change in measured vital signs.

Table 64. Clinically Relevant Changes in Measured Vital Sign Parameters by Lowest MOAA/S Score Prior to the Event (Safety Population)

MOAA/S Score Category	Number (%) of Subjects with Clinically Notable Vital Signs	Lowest MOAA/S Score of a Subject		
		0 to 1 (N=115)	2 to 4 (N=514)	5 (N=1)
<u>Remimazolam (N=630)</u>		<u>(N=115)</u>	<u>(N=514)</u>	<u>(N=1)</u>
Hypoxia ^a	66	5 (4.3)	61 (11.9)	0
Bradycardia ^b	42	13 (11.3)	29 (5.6)	0
Respiratory depression ^c	12	3 (2.6)	9 (1.8)	0
Hypotension ^d	271	59 (51.3)	211 (41.1)	1 (100)
Hypertension ^e	294	47 (40.9)	247 (48.1)	0
<u>Midazolam (N=201)</u>		<u>(N=17)</u>	<u>(N=183)</u>	<u>(N=1)</u>
Hypoxia ^a	15	1 (5.9)	14 (7.7)	0
Bradycardia ^b	22	3 (17.6)	19 (10.4)	0
Respiratory depression ^c	12	2 (11.8)	10 (5.5)	0
Hypotension ^d	120	12 (70.6)	108 (59.0)	0
Hypertension ^e	85	7 (41.2)	77 (42.1)	1 (100)
<u>Placebo (N=135)</u>		<u>(N=16)</u>	<u>(N=119)</u>	<u>(N=3)</u>
Hypoxia ^a	14	3 (18.8)	11 (9.2)	0
Bradycardia ^b	11	1 (6.3)	10 (8.4)	0
Respiratory depression ^c	5	0	5 (4.2)	0
Hypotension ^d	78	8 (50.0)	70 (58.8)	0
Hypertension ^e	66	7 (43.8)	59 (49.6)	0

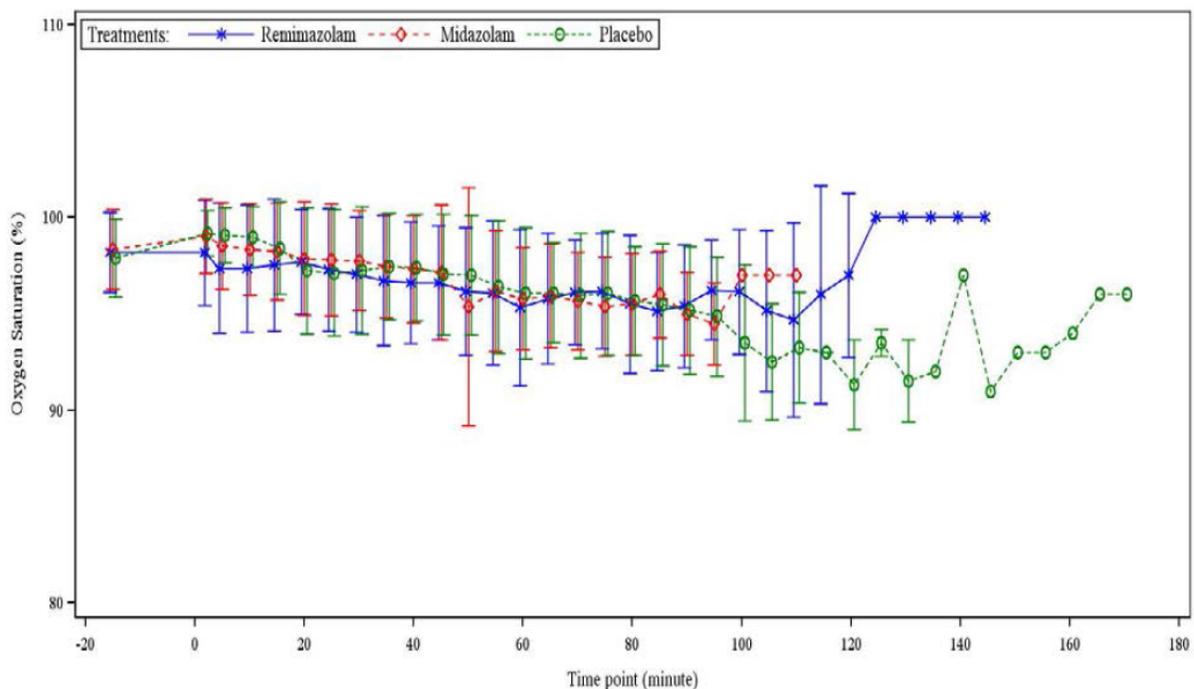
- a SpO₂ < 90%.
- b Heart rate < 40 bpm or a drop in heart rate of > 20% from baseline.
- c Respiratory rate < 8 breaths/min.
- d Systolic blood pressure ≤ 80 mmHg or diastolic blood pressure ≤ 40 mmHg, or systolic or diastolic blood pressure ≥ 20% below baseline.
- e Systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg, or systolic or diastolic blood pressure of 20% or above baseline.

Source: ISS Report, p. 211 (PDF), Applicant's submission, NDA 212295.

This information allows an assessment of whether RMZ appears to adversely impacted measured vital signs to a greater degree than placebo or midazolam treatment at the same depth of sedation. The RMZ treatment group had the lowest proportion (4.3%) of patients who experienced hypoxia with MOAA/S scores representative of deep sedation, compared to the midazolam (5.9%) or placebo (18.8%) treatment groups. This is also true for the proportion of patients who experienced bradycardia. There did appear to be a larger proportion of patients with MOAA/S scores of 0 or 1 in the RMZ treatment group with respiratory depression and hypotension compared to patients in the placebo treatment group. In considering clinically relevant vital sign changes within the RMZ treatment group at different depths of sedation, it appears that there was an increased incidence of bradycardia, respiratory depression, and hypotension as depth of sedation increased. This is in contrast to the placebo treatment group, in which there was an increased incidence of bradycardia, respiratory depression, hypotension, and hypertension in patients with MOAA/S scores of 2 to 4.

The following figure represents the line-plot of mean oxygen saturation by treatment group in the pooled safety analysis Group A1A.

Figure 6. Line-Plot of Oxygen Saturation by Treatment Group (Safety Population Group A1A)



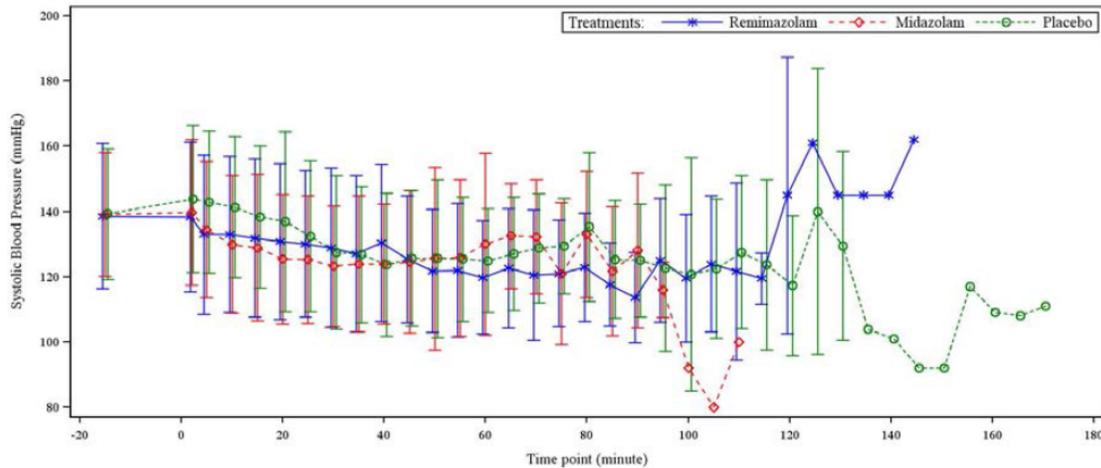
Symbols and whiskers represent the mean values with standard deviation at the corresponding timepoints. Symbols without error bars represent single observation.

Source: ISS Report, p. 169 (PDF), Applicant's submission, NDA 212295.

It does not appear there were clinically significant differences in mean oxygen saturation between the treatment groups. The mean nadir oxygen saturations across the treatment groups did not appear significantly different either, however, the box plots did appear wider for the RMZ treatment group than those for either the placebo or midazolam treatment groups, suggesting more variability in the RMZ-treated patients. The Applicant evaluated the amount of time patients in each treatment group experienced an oxygen saturation < 90%, using area under the curve 0 to 20 minutes ($AUC_{0\text{ to }20}$). The results indicate that more patients in the RMZ treatment groups had experienced an oxygen saturation < 90% for at least some period of time from 0 to 20 minutes. It appears, however, that the percentage of patients with this degree of hypoxia for this length of time was low, 0.3 to 0.6%. There was no patient in the placebo treatment groups who experienced an oxygen saturation < 90% for greater than 1% of the time from 0 to 20 minutes. The percentage of patients in each treatment group who did not experience an oxygen saturation of < 90% using $AUC_{0\text{ to alert}}$ was similar across the three treatment groups; 90%, 90%, and 93% for the RMZ, placebo, and midazolam treatment groups, respectively.

The following two figures are line-plots of systolic and diastolic blood pressure by treatment group beginning at time 0 through discharge, for pooled safety analysis Group A1A.

Figure 7. Line-Plot of Mean Systolic Blood Pressure by Treatment Group (Safety Population Group A1A)



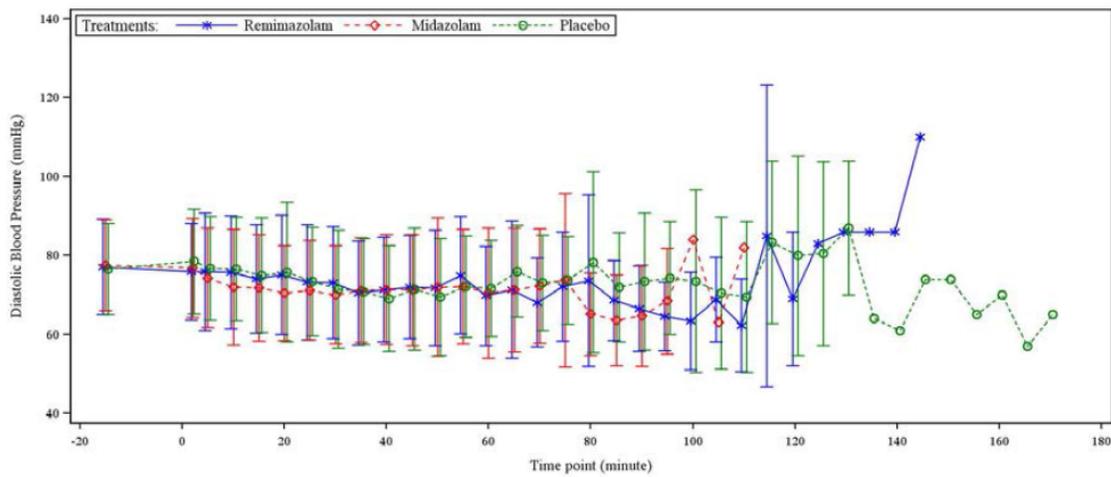
Symbols and whiskers represent the mean values with standard deviation at the corresponding timepoints. Symbols without error bars represent single observations.

Source: [Figure 7.1.4.2a](#)

Source: ISS Report, p. 164 (PDF), Applicant's submission, NDA 212295.

The above figure indicates that mean systolic blood pressure decreased through approximately 90 minutes post-dose in the RMZ treatment group and through approximately 50 minutes in the placebo and midazolam treatment groups. There did not appear to be any clinically significant differences in mean systolic blood pressure between treatment groups.

Figure 8. Line-Plot of Mean Diastolic Blood Pressure by Treatment Group (Safety Population Group A1A)



Symbols and whiskers represent the mean values with standard deviation at the corresponding timepoints. Symbols without error bars represent single observations.

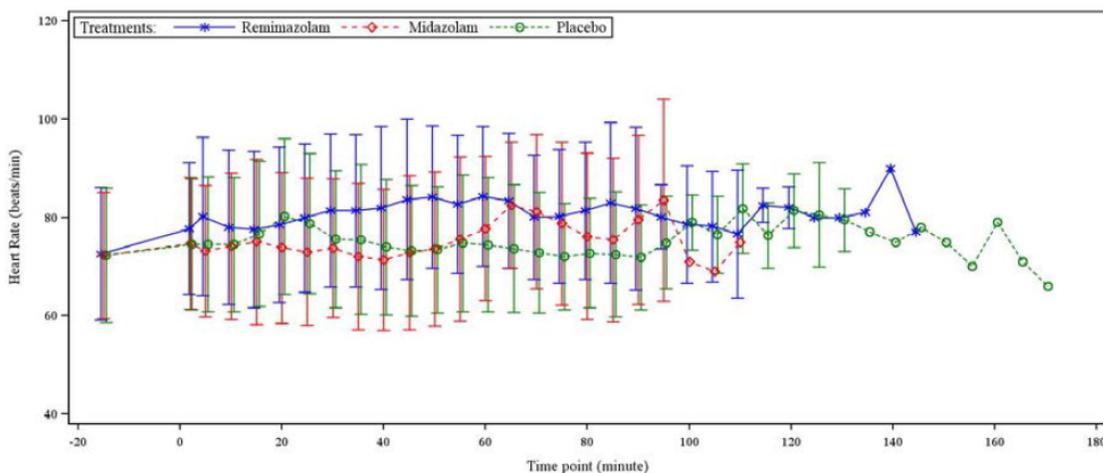
Source: [Figure 7.1.4.4a](#)

Source: ISS Report, p. 164 (PDF), Applicant's submission, NDA 212295.

This figure indicates that mean diastolic blood pressure decreased through approximately 100 minutes post-dose in the RMZ treatment group, and through approximately 60 minutes in the placebo and midazolam treatment groups. There did not appear to be any clinically significant differences in mean diastolic pressure between treatment groups.

The following figure represents the line-plot for mean heart rate for patients in the pooled safety analysis Group A1A.

Figure 9. Line-Plot of Mean Heart Rate by Treatment Group (Safety Population Group A1A)



Symbols and whiskers represent the mean values with standard deviation at the corresponding timepoints. Symbols without error bars represent single observations.

Source: [Figure 7.1.4.6a](#)

Source: ISS Report, p. 166 (PDF), Applicant's submission, NDA 212295.

The differences in mean heart rate between the RMZ treatment groups, and the placebo and midazolam treatment groups are most noticeable between approximately 25 and 65 minutes post-dose. The Applicant suggests the differences in mean heart rates are likely due to most patients in the RMZ treatment groups having completed the procedure, and being fully alert during this time, while patients in the placebo and midazolam treatment groups were still sedated. This explanation is not completely supported by the results of the secondary endpoint of time to fully alert, however. In Study CNS7056-006, median time to fully alert from the end of the procedure in the RMZ treatment group was 6 minutes, in the placebo treatment group it was 16 minutes, and in the midazolam treatment group it was 15 minutes. In Study CNS7056-008, median time to fully alert from the end of the procedure was six minutes in the RMZ treatment group, 13 minutes in the placebo treatment group, and 10 minutes in the midazolam treatment group. In Study CNS7056-015, median time to fully alert from the end of the procedure was three minutes in the RMZ treatment group, 5.3 minutes in the placebo treatment group, and seven minutes in the midazolam treatment group. Based on these results, it seems unlikely that many, if any, patients were still sedated at 65 minutes post-dose. Review of the mean nadir heart rates in pooled safety Group A1A indicates that, in general, patients in the RMZ treatment group had higher nadirs than patients in either the placebo or midazolam treatment groups.

The mean respiratory rates for the pooled safety analysis Group A1A were higher in the RMZ treatment group compared to the placebo or midazolam treatment groups. Additionally, the mean nadir respiratory rates were highest in the RMZ treatment.

In Study CNS7056-015, transcutaneous partial pressure of carbon dioxide (pCO_2) was monitored throughout the procedure until fully alert. The results indicate the pCO_2 was similar across all treatment groups from time 0 to 20 minutes post-dose. There were differences noted between the RMZ treatment group, and the placebo and midazolam treatment groups from time 0 through fully alert, with the RMZ treatment group having less than 50% the mean pCO_2 values observed in the other treatment groups. These results may be due to the shorter time patients were sedated with RMZ versus placebo or midazolam.

Nellcor Vital Sign Data

There were two Nellcor safety populations used in the clinical studies evaluating RMZ for procedural sedation. Population 1 included patients with usable Nellcor data for at least one parameter (heart rate, respiratory rate, and pulse oximetry), and Population 1 included usable data for all three parameters. Usable Nellcor data is defined in the following table.

Table 65. Definition of Usable Nellcor Data

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

Variable Name	Description	Valid Values (Acceptability Ranges)	Computation Methods, Notes, or Equation(s)
Arterial oxygen saturation (SpO2)	Oxygen saturation as exported from the Nellcor device	60% - 100% Accuracy \pm 2% for 70% to 100%, \pm 3% for 60% to 80% (according to the Nellcor manual)	The Nellcor monitoring system searches for and locks onto a signal for approximately 5 to 10 seconds. Averaging time of the Nellcor system is 6 to 7 seconds. This time can be extended up to 20, and in a subsequent step, up to 40 seconds in difficult conditions such as external interference such as light or movement. Thereafter, an alarm will be raised. The response to changes in blood oxygen saturation is 5 to 7 seconds.
Heart rate	Pulse rate as exported from the Nellcor device	20 to 200 bpm Accuracy \pm 3 digits. BPM rates below 20 will appear as a zero (0).	The Nellcor monitoring system searches for and locks onto a signal for approximately 5 to 10 seconds. Averaging time of the Nellcor system is 6 to 7 seconds. This time can be extended up to 20, and in a subsequent step, up to 40 seconds in difficult conditions such as external interference such as light or movement. Thereafter, an alarm will be raised.
Respiratory rate	Respiratory rate as exported from the Nellcor device	4 to 40 breaths/min Accuracy \pm 1 breath/min	Respiratory rate values are calculated every 5 seconds. Three or more events of irregular cardiac rhythm within 30 seconds may cause inaccurate respiratory rate values or loss of information.

See Covidien 2012a, Covidien 2012b

Source: ISS Report, p. 35 (PDF), Applicant's submission, NDA 212295.

As with administration of all sedative-hypnotics, there is concern regarding a decrease in measured vital signs, particularly respiratory rate and oxygen saturation. The tables below summarize the post-dose nadir values for the measured Nellcor parameters.

Table 66. Post-Dose Nadir Values for Nellcor Variables (Nellcor Safety Population, Study CNS7056-006)

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

Parameter	Sample Characteristics	Remimazolam	Placebo	Midazolam	Total
Heart Rate -	N	214	40	71	325
Lowest Nellcor Value (bpm)	Mean	61.5	59.3	57.5	60.4
	Std. Deviation	10.90	10.58	7.99	10.40
	Minimum	34	38	40	34
	Lower Quartile	55.0	52.0	53.0	54.0
	Median	61.0	59.0	57.0	59.0
	Upper Quartile	68.0	65.5	64.0	66.0
	Maximum	100	86	81	100
Respiratory Rate (breaths per minute) -	N	116	19	37	172
Lowest Nellcor Value	Mean	10.3	8.9	9.2	9.9
	Std. Deviation	2.43	2.61	1.99	2.42
	Minimum	5	6	5	5
	Lower Quartile	9.0	7.0	8.0	8.0
	Median	11.0	8.0	9.0	10.0
	Upper Quartile	12.0	11.0	10.0	12.0
	Maximum	19	15	14	19
Oxygen Saturation (%) -	N	216	42	71	329
Lowest Nellcor Value	Mean	93.5	88.5	93.1	92.7
	Std. Deviation	5.71	9.07	6.53	6.59
	Minimum	63	56	65	56
	Lower Quartile	91.0	87.0	91.0	90.0
	Median	95.0	91.0	95.0	95.0
	Upper Quartile	97.0	94.0	97.0	97.0
	Maximum	100	98	100	100

Source: Section 14.3, Table 14.3.7.1.1, Table 14.3.7.1.2, and Table 14.3.7.1.3.

Bpm = beats per minute; N = number of patients

Note: analysis of heart rate was conducted in the Safety Population (Nellcor – Usable Heart Rate); analysis of respiratory rate was conducted in the Safety Population (Nellcor – Usable Respiratory Rate); analysis of oxygen saturation was conducted in the Safety Population (Nellcor – Usable Oxygen Saturation).

Source: Study CNS7056-006 Report Body, p. 151 (PDF), Applicant’s submission, NDA 212295.

Table 67. Post-Dose Nadir Values for Nellcor Variables (Nellcor Safety Population, Study CNS7056-008)

Parameter	Sample Characteristics	Remimazolam (N=269)	Placebo (N=53)	Midazolam (N=59)	Total (N=381)
Heart Rate [bpm] - Lowest Nellcor Value (calculated)	N	269	53	59	381
	Mean	71.8	67.2	68.6	70.6
	Std. Deviation	12.98	10.84	12.39	12.71
	Minimum	21	43	39	21
	Lower Quartile	63.0	59.0	60.0	62.0
	Median	72.0	69.0	70.0	71.0
	Upper Quartile	80.0	76.0	77.0	79.0
	Maximum	111	89	93	111
Parameter	Sample Characteristics	Remimazolam (N=84)	Placebo (N=26)	Midazolam (N=20)	Total (N=130)
Respiration Rate [breaths\min] - Lowest Nellcor Value (calculated)	N	84	26	20	130
	Mean	11.5	10.4	10.5	11.1
	Std. Deviation	3.13	3.00	2.86	3.08
	Minimum	6	6	5	5
	Lower Quartile	9.5	9.0	8.5	9.0
	Median	11.0	10.0	10.0	11.0
	Upper Quartile	13.0	12.0	12.5	13.0
	Maximum	20	17	16	20

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

Parameter	Sample Characteristics	Remimazolam (N=274)	Placebo (N=53)	Midazolam (N=59)	Total (N=386)
Oxygen Saturation [%] - Lowest Nellcor Value (calculated)	N	274	53	59	386
	Mean	87.0	86.3	88.8	87.2
	Std. Deviation	7.89	9.14	6.77	7.93
	Minimum	58	60	68	58
	Lower Quartile	83.0	81.0	85.0	84.0
	Median	88.0	88.0	91.0	88.5
	Upper Quartile	93.0	93.0	93.0	93.0
	Maximum	100	99	100	100

Source: Study CNS7056-008, 14 Tables, pp. 1784-1786, Applicant's submission, NDA 212295.

Table 68. Post-Dose Nadir Values for Nellcor Variables (Nellcor Safety Population, Study CNS7056-015)

Parameter	Sample Characteristic	Remimazolam	Placebo	Midazolam	Total
Heart Rate (bpm)	N	29	13	29	71
	Mean	62.8	66.4	65.3	64.5
	Std. Deviation	12.84	8.29	13.27	12.26
	Minimum	36	56	45	36
	Lower quartile	54.0	60.0	55.0	56.0
	Median	64.0	67.0	66.0	64.0
	Upper quartile	70.0	72.0	72.0	71.0
	Maximum	100	83	94	100
Respiratory Rate (breaths per minute)	N	19	7	18	44
	Mean	12.1	12.0	12.3	12.2
	Std. Deviation	3.02	1.83	3.40	2.97
	Minimum	7	10	7	7
	Lower quartile	10.0	11.0	10.0	10.0
	Median	12.0	11.0	12.0	12.0
	Upper quartile	14.0	14.0	15.0	14.0
	Maximum	17	15	19	19
Oxygen Saturation (%)	N	29	13	30	72
	Mean	93.2	90.2	92.5	92.4
	Std. Deviation	5.49	9.97	7.28	7.17
	Minimum	78	59	71	59
	Lower quartile	93.0	91.0	89.0	90.0
	Median	95.0	93.0	94.0	94.0
	Upper quartile	97.0	95.0	98.0	97.0
	Maximum	99	97	100	100

Source: Section 14.3, Table 14.3.7.1.1, Table 14.3.7.1.2, and Table 14.3.7.1.3

N = number of patients; n = number of observations; Std. = standard

Source: Study CNS7056-015 Report Body, p. 127 (PDF), Applicant's submission, NDA 212295.

The data in the above tables indicates that there were small differences in mean nadir heart rate values across the three treatment groups. Studies CNS7056-006 and CNS7056-008 indicated slightly higher mean nadir heart rates and respiratory rates in the RMZ treatment group compared to the placebo or midazolam treatment groups, but this is likely not clinically significant. Furthermore, while hyperventilation is not desirable, a slight increase in respiratory rate may be beneficial in the sedated patient. In Studies CNS7056-006 and CNS7056-015, the mean nadir oxygen saturation was the highest in the RMZ treatment group compared to the placebo and midazolam treatment groups. In Study CNS7056-008, the mean nadir oxygen

saturations were much lower in all treatment groups when compared to the values in the two studies evaluating patients undergoing colonoscopy. This is not surprising given the bronchoscopic procedure performed, and the mean values were similar across all treatment groups, with the lowest mean nadir observed in the placebo group.

It is reassuring that the measured Nellcor values were not significantly different between groups in studies that evaluated sicker patients (Study CNS7056-015) and more stimulating and challenging procedures (Study CNS7056-008). The incidence of out-of-range Nellcor parameters that were reported as adverse events in the RMZ treatment group was either similar to or lower than those reported for the placebo or midazolam treatment groups in all three studies. Specifically, bradycardic or heart rate decreased events were reported with the lowest incidence in the RMZ treatment groups in Studies CNS7056-006 and CNS7056-015. In Study CNS7056-008, bradycardia was reported in a single patient in the RMZ treatment group and no patient in either the placebo or midazolam treatment groups. Respiratory depression was reported with the lowest incidence in the RMZ treatment groups in Studies CNS7056-006 and CNS7056-008. In Study CNS7056-015, respiratory depression was reported in more patients in the RMZ treatment group than the placebo treatment group but in less patients than in the midazolam treatment group. The duration of respiratory depression in Study CNS7056-008 was the shortest in the RMZ treatment group (66.4 seconds) compared to the placebo (85.1 seconds) and midazolam (126.4 seconds) treatment groups.

Hypoxia, using the Nellcor data, was reported with the highest incidence in the RMZ treatment group in Study CNS7056-006, but rates were in general low (i.e., < 2.5%) and similar between all groups. In Study CNS7056-008, the incidence of hypoxia was significantly higher in all treatment groups compared to the incidences in the other studies, which is not surprising. There were approximately 18% of RMZ-treated, 23% of placebo-treated, and 17% of midazolam-treated patients who experienced hypoxia during this study using the continuous Nellcor pulse oximetry. The difference in incidence between the three treatment groups is likely not clinically significant. Of note, the duration of hypoxic episodes in Study CNS7056-008 was the shortest in the midazolam treatment group (75.27 seconds) compared to the RMZ treatment group (143 seconds) and the placebo treatment group (155.1 seconds).

8.4.8. Electrocardiograms (ECGs)

In the Phase 3 studies, 12-lead ECGs were performed before, during, and after the procedure and when clinically indicated. Three-lead ECGs were continuously monitored throughout the procedure until fully alert. In Study CNS7056-006, a large proportion of patients in all treatment groups had insignificant abnormalities at baseline, and the proportion of abnormal results increased during the treatment period. Clinically significant ECG findings post-dose were reported for two patients, one in the RMZ and one in the midazolam treatment group. There is no additional information regarding the patient in the RMZ treatment group, and the

patient in the midazolam treatment group experienced sinus tachycardia with PVCs, right atrial enlargement, and cannot rule out anterior infarct.

In Study CNS7056-008, a large proportion of patients in all treatment groups had insignificant abnormalities at baseline. Clinically significant abnormal findings were reported for the following five patients in the RMZ treatment group during the study.

- Patient (b) (6) had premature ventricular contractions within three hours pre-dose
- Patient (b) (6) had multifocal atrial tachycardia at five minutes after dosing and at two minutes after the first one
- Patient (b) (6) had atrial fibrillation at screening and new onset atrial fibrillation within three hours pre-dose that appears to have persisted through discharge
- Patient (b) (6) had unspecified clinically significant abnormal findings immediately after the first dose, which continued through discharge. No additional information provided, patient was to follow-up with cardiologist
- Patient (b) (6) had sinus tachycardia during the procedure (timing not specified) and five minutes after the end of the procedure

Clinically significant abnormal findings were reported not reported for any patient in the placebo or midazolam treatment groups. Clinically significant abnormal three-lead ECGs were noted in one patient each in the placebo and midazolam treatment groups, and three patients in the RMZ treatment group. In the RMZ treatment group, the abnormalities included a rhythm artifact, bradycardia, and sinus tachycardia, and all events occurred after the start of study drug administration.

In Study CNS7056-015, no clinically significant abnormal 12-lead ECG findings were noted post-dose in any treatment group. Clinically insignificant ECG findings were reported in the majority of patients (86.8%) in all treatment groups within three hours pre-dose. A slight increase in the incidence of abnormal findings was reported immediately post-dose (89.3%), which returned to the pre-dose incidence by five minutes post-dose.

In general, it does not appear that administration of RMZ for procedural sedation in patients undergoing colonoscopy or bronchoscopy resulted in clinically significant ECG changes that would adversely impact the risk-benefit profile.

8.4.9. QT

The Applicant conducted two studies to evaluate the impact of RMZ administration on the QT interval and the potential for clinically significant prolongation, defined by the Agency as an increase of 10 milliseconds (msec). The results from Study CNS7056-005, designed as a thorough QT study (TQT), demonstrated an increase in the QT interval which exceeded the

regulatory threshold for concern with administration of the maximum dose, 20 mg, evaluated. Refer to the following table for those results.

Table 69. 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.

(b) (4)
Study CNS7056-017 was conducted to evaluate the effect of remimazolam on the QT interval during continuous IV infusion, in an attempt to limit the potential impact of heart rate on the reported QT interval after bolus dosing.

Upon review of both studies evaluating the QT interval, the Interdisciplinary Review Team for QT Studies (IRT-QT) provided the Division with the following comments:

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

The IRT-QT did not agree (b) (4)
The recommendation is to include study findings, including drug effect on heart rate and QTcF, from Study CNS7056-005, the study described as a TQT study. For additional information regarding the QT studies, refer to the review completed by Nan Zheng

I agree with the conclusions from the IRT-QT based on the proposed bolus dosing of RMZ post-market. The results of Study CNS7056-005 are relevant (b) (4)

8.4.10. Dose Response

In the Phase 2 studies, CNS7056-003 and CNS7056-004, in patients undergoing upper endoscopy and colonoscopy respectively, dose-responses were evaluated for both efficacy and safety. In Study CNS7056-003, maximum RMZ dosing included 0.2 mg/kg with no top-up dosing or fentanyl premedication. The majority of adverse events reported in this study did not appear dose-related; however, the incidence of decreased oxygen saturation did increase with increasing doses of RMZ (16%, 20%, and 24% for treatment groups 0.1 mg/kg, 0.15 mg/kg, and 0.2 mg/kg, respectively).

In Study CNS7056-004, maximum RMZ dosing included 8 mg initial dose with 3 mg top-up doses and fentanyl 100 µg premedication. Similar to the findings in Study CNS7056-003, the majority of adverse events did not appear dose-related; however, there was a higher incidence of bradycardia, hypertension, and nausea in the RMZ 8 mg/3 mg treatment group. 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/3mg treatment group. Based in part on these results, the Applicant selected RMZ 5 mg initial dose and 2.5 mg top-up doses for evaluation in the Phase 3 studies.

In the Phase 3 studies, the Applicant did evaluate the occurrence of three adverse events of special interest, hypoxia, bradycardia, and hypotension, in three RMZ dose range groups. Those results are summarized for the pooled safety analysis Group A1A in the following table.

Table 70. Incidence of Three Adverse Events of Interest in the Pooled Safety Group A1A by RMZ Dose Range (Safety Population, Group A1A)

Adverse events – important identified risk, [n (%)]	Remimazolam		
	5 to 14.372 mg (N=459)	14.372 to 23.744 mg (N=165)	23.744 to 33.116 mg (N=6)
Hypoxia			
Yes	67 (14.6)	26 (15.8)	2 (33.3)
No	392 (85.4)	139 (84.2)	4 (66.7)
Bradycardia			
Yes	32 (7.0)	16 (9.7)	0
No	427 (93.0)	149 (90.3)	6 (100)
Hypotension			
Yes	185 (40.3)	89 (53.9)	3 (50.0)
No	274 (59.7)	76 (46.1)	3 (50.0)

Note: Percentages are based on the Safety Population and each dose group - Group A1A.

Note: Individual cumulative doses for remimazolam were divided into 3 equally large intervals based on the minimum and maximum of cumulative dose in Group A, as follows: Minimum to I2, I2 to I3, and I3 to Maximum.

Source: ISS Report, p. 229 (PDF), Applicant's submission, NDA 212295.

The highest dose range was evaluated in only six treated patients in Group A1A, therefore, definitive conclusions regarding the safety findings are challenging. However, there did appear to be a dose-response for the occurrence of the three adverse events of interest between the other two dose range groups. Dr. James Travis, statistical reviewer, using a logistic regression model, evaluated the relationship between increasing RMZ dose and the occurrence of causally related (possibly or higher) adverse events for Study CNS7056-006 and CNS7056-008. He determined that there was not a statistically significant difference in the adverse event rates for these two studies with increasing doses of RMZ.

8.5. Safety Analyses by Demographic Subgroups

The incidence of adverse events was summarized by age, sex, and race demographic subgroups. The following table summarizes the demographic information for patients included in pooled safety analysis Group A1A.

Table 71. Demographic Information for Patients in Pooled Safety Analysis Group A1A (Safety Population)

Variable	Remimazolam			Midazolam			Placebo (N=135)
	2.5 mg to 5 mg (N=31)	5 mg (N=599)	Total (N=630)	<1.75 mg (N=113)	1.75 mg (N=88)	Total (N=201)	
Age (years)							
n	31	599	630	113	88	201	135
Mean (SD)	63.1 (8.65)	58.6 (11.90)	58.8 (11.80)	65.4 (8.49)	49.7 (9.94)	58.5 (12.00)	58.9 (10.87)
Median	64.0	58.0	58.0	64.0	51.0	59.0	59.0
Q1, Q3	57.0, 69.0	52.0, 67.0	52.0, 67.0	60.0, 72.0	45.0, 57.0	51.0, 67.0	52.0, 66.0
Min, Max	47, 84	19, 95	19, 95	42, 85	20, 72	20, 85	24, 92
Age [n (%)]							
< 65 Years	18 (58.1)	408 (68.1)	426 (67.6)	58 (51.3)	85 (96.6)	143 (71.1)	94 (69.6)
≥ 65 Years	13 (41.9)	191 (31.9)	204 (32.4)	55 (48.7)	3 (3.4)	58 (28.9)	41 (30.4)
≥ 75 Years	3 (9.7)	47 (7.8)	50 (7.9)	14 (12.4)	0	14 (7.0)	9 (6.7)
Sex [n (%)]							
Male	17 (54.8)	286 (47.7)	303 (48.1)	46 (40.7)	49 (55.7)	95 (47.3)	61 (45.2)
Female	14 (45.2)	313 (52.3)	327 (51.9)	67 (59.3)	39 (44.3)	106 (52.7)	74 (54.8)
Race categories [n (%)]							
White	25 (80.6)	483 (80.6)	508 (80.6)	84 (74.3)	60 (68.2)	144 (71.6)	102 (75.6)
Black	6 (19.4)	85 (14.2)	91 (14.4)	25 (22.1)	18 (20.5)	43 (21.4)	27 (20.0)
Asian	0	21 (3.5)	21 (3.3)	3 (2.7)	9 (10.2)	12 (6.0)	4 (3.0)
Other	0	10 (1.7)	10 (1.6)	1 (0.9)	1 (1.1)	2 (1.0)	2 (1.5)

Source: ISS Report, p. 58 (PDF), Applicant's submission, NDA 212295.

There was a slightly higher proportion of female patients in all treatment groups in the pooled safety analysis Group A1A, with the largest discrepancy observed in the placebo treatment group (55% female versus 45% male). The mean age was similar in all treatment groups. The majority of patients in all treatment groups were white and less than 65 years of age. Additional demographic groups evaluated, were weight, BMI, and ASA-PS classification. Review of the proportion of patients in each demographic group did not identify clinically relevant

differences across treatment groups, in general; however, there was smaller proportion of patients with ASA IV physical status in the RMZ treatment group (2.4%) compared to patients in either midazolam (7.5%) or placebo (5.2%) treatment groups. This difference is likely clinically insignificant, but it is worth noting that because there was a low number of ASA IV physical status patients treated in the Phase 3 studies, there is limited information regarding the safety profile of RMZ in patients with this degree of comorbid medical conditions.

Following is a discussion of the incidence of select adverse events, those in the cardiac disorders, vascular disorders, respiratory, thoracic, and mediastinal disorders, and investigations SOCs, by age, sex, and race demographic subgroups.

Age

In general, the incidence of adverse events in the above-mentioned SOCs was increased with increasing age, with the exception of the cardiac disorders SOC. The following table summarizes the incidence of select adverse events by age.

Table 72. Incidence of Select Adverse Events by Age Group (Safety Population, Group A1A)

System organ class Preferred term [n (%)]	Total Remimazolam		
	< 65 Years (N=426)	65-74 Years (N=154)	>= 75 Years (N=50)
Any treatment emergent adverse event	330 (77.5)	137 (89.0)	47 (94.0)
Cardiac disorders	57 (13.4)	14 (9.1)	4 (8.0)
Bradycardia	37 (8.7)	8 (5.2)	0
Tachycardia	20 (4.7)	6 (3.9)	1 (2.0)
Vascular disorders	281 (66.0)	124 (80.5)	41 (82.0)
Hypotension	151 (35.4)	63 (40.9)	19 (38.0)
Hypertension	98 (23.0)	41 (26.6)	19 (38.0)
Diastolic hypertension	64 (15.0)	36 (23.4)	9 (18.0)
Systolic hypertension	49 (11.5)	25 (16.2)	11 (22.0)
Diastolic hypotension	35 (8.2)	24 (15.6)	6 (12.0)
Respiratory, thoracic and mediastinal disorders	50 (11.7)	44 (28.6)	18 (36.0)
Hypoxia	27 (6.3)	29 (18.8)	13 (26.0)
Tachypnoea	6 (1.4)	1 (0.6)	1 (2.0)
Investigations	34 (8.0)	25 (16.2)	9 (18.0)
Respiratory rate increased	22 (5.2)	16 (10.4)	5 (10.0)
Respiratory rate decreased	7 (1.6)	4 (2.6)	0

Source: Adapted from Table 85, ISS Report, Applicant's submission, NDA 212295.

Patients > 75 years of age had the lowest incidence of adverse events reported in the cardiac disorders SOC, including both bradycardia and tachycardia. The incidence of hypoxia in patients

> 75 years of age was more than four times the incidence in patients < 65 years of age. Similar results were observed in the placebo and midazolam treatment groups.

Sex

In general, as summarized in the following table, the incidence of select adverse events was higher in females compared to males in all treatment groups.

Table 73. Incidence of Select Adverse Events by Sex (Safety Population, Group A1A)

System organ class Preferred term [n (%)]	Total Remimazolam		Total Midazolam		Placebo	
	Male (N=303)	Female (N=327)	Male (N=95)	Female (N=106)	Male (N=61)	Female (N=74)
Any treatment emergent adverse event	230 (75.9)	284 (86.9)	86 (90.5)	96 (90.6)	48 (78.7)	64 (86.5)
Cardiac disorders	36 (11.9)	39 (11.9)	16 (16.8)	20 (18.9)	6 (9.8)	14 (18.9)
Bradycardia	24 (7.9)	21 (6.4)	9 (9.5)	15 (14.2)	3 (4.9)	9 (12.2)
Tachycardia	12 (4.0)	15 (4.6)	6 (6.3)	7 (6.6)	4 (6.6)	5 (6.8)
Vascular disorders	196 (64.7)	250 (76.5)	75 (78.9)	88 (83.0)	42 (68.9)	59 (79.7)
Hypotension	109 (36.0)	124 (37.9)	50 (52.6)	53 (50.0)	31 (50.8)	33 (44.6)
Hypertension	74 (24.4)	84 (25.7)	22 (23.2)	28 (26.4)	16 (26.2)	16 (21.6)
Diastolic hypertension	31 (10.2)	78 (23.9)	7 (7.4)	18 (17.0)	4 (6.6)	17 (23.0)
Systolic hypertension	25 (8.3)	60 (18.3)	6 (6.3)	17 (16.0)	4 (6.6)	14 (18.9)
Diastolic hypotension	29 (9.6)	36 (11.0)	16 (16.8)	9 (8.5)	6 (9.8)	16 (21.6)
Respiratory, thoracic and mediastinal disorders	46 (15.2)	66 (20.2)	19 (20.0)	15 (14.2)	13 (21.3)	13 (17.6)
Hypoxia	29 (9.6)	40 (12.2)	9 (9.5)	5 (4.7)	7 (11.5)	7 (9.5)
Tachypnoea	3 (1.0)	5 (1.5)	3 (3.2)	1 (0.9)	1 (1.6)	5 (6.8)
Investigations	28 (9.2)	40 (12.2)	10 (10.5)	9 (8.5)	5 (8.2)	5 (6.8)
Respiratory rate increased	17 (5.6)	26 (8.0)	7 (7.4)	3 (2.8)	3 (4.9)	3 (4.1)
Respiratory rate decreased	5 (1.7)	6 (1.8)	3 (3.2)	4 (3.8)	2 (3.3)	1 (1.4)

Note: Percentages are based on the Safety Population, chronic use category, and each dose group - Group A1A.
 Note: For each category, subjects are included only once, even if they experienced multiple events in that SOC or PT.

Source: [Table 4.4.2.3](#)

Source: ISS Report, p. 281 (PDF), Applicant's submission, NDA 212295.

Race

Select adverse event information is presented in the following table for white and black demographic subgroups only, because the number of Asian and other racial subgroups was too low to provide meaningful comparative analysis.

Table 74. Incidence of Select Adverse Events by Racial Subgroup (Safety Population, Group A1A)

System organ class Preferred term [n (%)]	Total Remimazolam		Total Midazolam		Placebo	
	White (N=508)	Black (N=91)	White (N=144)	Black (N=43)	White (N=102)	Black (N=27)
Any treatment emergent adverse event	423 (83.3)	68 (74.7)	129 (89.6)	40 (93.0)	84 (82.4)	23 (85.2)
Cardiac disorders	55 (10.8)	16 (17.6)	28 (19.4)	6 (14.0)	12 (11.8)	6 (22.2)
Bradycardia	35 (6.9)	6 (6.6)	19 (13.2)	4 (9.3)	8 (7.8)	3 (11.1)
Tachycardia	16 (3.1)	11 (12.1)	9 (6.3)	2 (4.7)	5 (4.9)	3 (11.1)
Vascular disorders	368 (72.4)	57 (62.6)	115 (79.9)	36 (83.7)	75 (73.5)	21 (77.8)
Hypotension	186 (36.6)	34 (37.4)	74 (51.4)	20 (46.5)	47 (46.1)	13 (48.1)
Hypertension	134 (26.4)	22 (24.2)	36 (25.0)	11 (25.6)	21 (20.6)	10 (37.0)
Diastolic hypertension	86 (16.9)	14 (15.4)	14 (9.7)	10 (23.3)	18 (17.6)	2 (7.4)
Systolic hypertension	73 (14.4)	9 (9.9)	15 (10.4)	8 (18.6)	14 (13.7)	3 (11.1)
Diastolic hypotension	57 (11.2)	2 (2.2)	21 (14.6)	3 (7.0)	16 (15.7)	5 (18.5)
Respiratory, thoracic and mediastinal disorders	98 (19.3)	9 (9.9)	26 (18.1)	8 (18.6)	19 (18.6)	6 (22.2)
Hypoxia	65 (12.8)	4 (4.4)	11 (7.6)	3 (7.0)	10 (9.8)	3 (11.1)
Tachypnoea	6 (1.2)	1 (1.1)	2 (1.4)	2 (4.7)	5 (4.9)	1 (3.7)
Investigations	58 (11.4)	9 (9.9)	13 (9.0)	5 (11.6)	9 (8.8)	0
Respiratory rate increased	33 (6.5)	9 (9.9)	6 (4.2)	4 (9.3)	5 (4.9)	0
Respiratory rate decreased	11 (2.2)	0	6 (4.2)	1 (2.3)	3 (2.9)	0

Note: Percentages are based on the Safety Population, chronic use category, and each dose group - Group A1A.
 Note: For each category, subjects are included only once, even if they experienced multiple events in that SOC or PT.

Source: Table 4.4.3.3

Source: ISS Report, p. 282 (PDF), Applicant's submission, NDA 212295.

The incidence of adverse events appears similar in white and black patients in the RMZ treatment group with the exception of tachycardia, systolic hypertension, diastolic hypotension, and hypoxia. These adverse events were reported substantially more in either white or black patients; however, the difference in the number of patients in each group makes interpretation difficult.

Review of the results from individual studies revealed some minor differences in the incidence of adverse events between demographic subgroups, but did not differ substantially from the results reported for the pooled safety analysis Group A1A. Prolonged sedation was observed more frequently in patients ≥ 65 years of age compared to those < 65 years of age in Study CNS7056-008.

8.6. Additional Safety Explorations

8.6.1. Pre-Emptive Action / Intervention

The pre-emptive actions or interventions most closely evaluated during review of this NDA are those involving the respiratory or cardiovascular systems. Specifically, the incidence of airway intervention and treatment of changes in measured hemodynamic parameters will impact the safety profile of RMZ and potentially the regulatory decision regarding its use during procedural sedation. The following table summarizes the incidence of airway intervention in the pooled safety analysis Group A1A.

Table 75. Pre-Emptive Action / Intervention in Pooled Safety Analysis Group A1A (Safety Population)

Pre-emptive Action/Intervention [n (%)]	Remimazolam			Midazolam			Placebo (N=135)
	2.5 mg to 5 mg (N=31)	5 mg (N=599)	Total (N=630)	<1.75 mg (N=113)	1.75 mg (N=88)	Total (N=201)	
Airway Interventions	0	76 (12.7)	76 (12.1)	6 (5.3)	6 (6.8)	12 (6.0)	12 (8.9)
CHANGES IN OXYGEN FLOW	0	64 (10.7)	64 (10.2)	5 (4.4)	4 (4.5)	9 (4.5)	8 (5.9)
CHIN LIFTS	0	15 (2.5)	15 (2.4)	1 (0.9)	3 (3.4)	4 (2.0)	5 (3.7)
JAW THRUSTS	0	10 (1.7)	10 (1.6)	0	1 (1.1)	1 (0.5)	3 (2.2)
MANUAL VENTILATION	0	6 (1.0)	6 (1.0)	0	0	0	3 (2.2)
6L/M MASK*	0	1 (0.2)	1 (0.2)	0	0	0	0
A REQUIREMENT FOR REPOSITIONING	0	1 (0.2)	1 (0.2)	0	0	0	0
NON-REBREATHER MASK*	0	1 (0.2)	1 (0.2)	0	0	0	0
MASK 8L PER MINUTE*	0	0	0	0	1 (1.1)	1 (0.5)	0
Other Pre-emptive Action/Intervention	0	1 (0.2)	1 (0.2)	0	1 (1.1)	1 (0.5)	1 (0.7)
ADMINISTRATIONS OF MEDICATIONS	0	1 (0.2)	1 (0.2)	0	0	0	1 (0.7)
STERNAL RUB*	0	0	0	0	1 (1.1)	1 (0.5)	0

Note: Percentages are based on the Safety Population and each dose group - Group A1A.

Note: Subjects can appear in more than one category but for each category, subjects are included only once, even if they experienced multiple events in that category.

Note: Terms marked with * were reported in the Other category.

Source: [Table 9.2.2](#)

Source: ISS Report, p. 195 (PDF), Applicant's submission, NDA 212295.

It appears that the incidence for airway interventions was consistently higher in the RMZ treatment group compared to the midazolam or placebo treatment groups. Specifically, the incidence in the RMZ treatment group was nearly double the incidence in the midazolam treatment group and approximately 26% higher than the incidence in the placebo treatment group. In all treatment groups, the most frequent airway intervention was a change in oxygen flow, followed by a chin lift. The proportion of patients who required more invasive airway interventions, including jaw thrust and manual ventilation, was highest in the placebo treatment group, followed by the RMZ treatment group. There was a single patient in the midazolam treatment group who required a jaw thrust and none who required manual ventilation. There was a single patient each in the RMZ treatment group who required high flow oxygen via face mask and non-rebreather mask, and repositioning, compared to none in the placebo treatment group. The Applicant has indicated that no patient in the pooled safety analysis Group A1A experienced the adverse event of apnea, and my review of the adverse event data did not identify any cases of apnea in either Study CNS7056-006, CNS7056-008, or CNS7056-015. Hypoxia appears to be the most common reason for initiating manual ventilation, and performing a jaw thrust, or chin lift.

These results suggest that while a larger percentage of RMZ-treated patients needed changes in oxygen flow and high flow oxygen delivery via face mask or non-rebreather mask, it is reassuring that more invasive airway interventions were needed with higher frequency in the

placebo treatment group, which essentially represents standard of care procedural sedation in the absence of propofol administration.

Regarding depth of sedation during airway interventions, the Applicant has stated that no patient treated with RMZ required airway intervention following a MOAA/S score of 0 or 1. This suggests that increasing depth of sedation with RMZ does not appear to result in an increased need for airway intervention, which is not only supportive of the safety profile of RMZ, but is also informative for determining the level of training required for the administering provider.

8.6.2. Concomitant Fentanyl Administration

Fentanyl administration was permitted during the Phase 3 studies for analgesia during the procedure. It was not meant to supplement the study drug-induced procedure sedation and was limited to a total dose of 200 µg. There were four concerns associated with concomitant fentanyl administration of identified during the Phase 3 studies. They were increased incidence of adverse events, increased incidence of deep sedation, decreased procedure success, and increased procedure duration associated with increased fentanyl dose. Each will be discussed in turn below.

Incidence of Adverse Events

As indicated in the following table, there was a positive correlation between increased fentanyl dose and incidence of adverse events in Study CNS7056-006 and Study CNS7056-008.

Table 76. Logistic Regression of Related Treatment-Emergent Adverse Event Likelihood vs. Fentanyl Dose (RMZ Treatment Group)

	Estimate	Standard Error	p-value
<i>Study CNS7056-006</i>			
Intercept	-0.917	0.564	0.104
Fentanyl dose (µg)	0.014	0.006	0.019
<i>Study CNS7056-008</i>			
Intercept	-1.864	0.347	<0.001
Fentanyl dose (µg)	0.014	0.004	<0.001

Source: Adapted from Statistical Reviewer's analysis.

The comparisons in both studies were statistically significant, but the results from Study CNS7056-008, were significant at $p < 0.001$. There too few patients in Study CNS7056-015 to perform this analysis, but there is no reason to think the results from sicker patients undergoing a colonoscopy would be different. Analyses conducted in the placebo and midazolam treatment groups demonstrated a similar association between fentanyl dose and the likelihood of experiencing a treatment-emergent adverse event in Study CNS7056-006, but not in Study

CNS7056-008. This suggests that increasing fentanyl doses, in general, are associated with increased rates of treatment-emergent adverse events in patients undergoing colonoscopy. In patients undergoing bronchoscopy, there appears to be an association in the RMZ treatment group only.

The following table summarizes the incidence of select adverse events by fentanyl dose.

Table 77. Incidence of Select Adverse Events by Cumulative Fentanyl Dose (Safety Population, Group A1A)

System organ class Preferred term [n (%)]	Total Remimazolam			
	<75 ug (N=184)	75-<100 ug (N=208)	100-150 ug (N=211)	>150 ug (N=27)
Any treatment emergent adverse event	151 (82.1)	161 (77.4)	177 (83.9)	25 (92.6)
Cardiac disorders	8 (4.3)	25 (12.0)	33 (15.6)	9 (33.3)
Bradycardia	3 (1.6)	13 (6.3)	24 (11.4)	5 (18.5)
Tachycardia	3 (1.6)	11 (5.3)	12 (5.7)	1 (3.7)
Vascular disorders	127 (69.0)	136 (65.4)	158 (74.9)	25 (92.6)
Hypotension	43 (23.4)	75 (36.1)	97 (46.0)	18 (66.7)
Hypertension	38 (20.7)	41 (19.7)	61 (28.9)	18 (66.7)
Diastolic hypertension	45 (24.5)	32 (15.4)	32 (15.2)	0
Systolic hypertension	38 (20.7)	23 (11.1)	23 (10.9)	1 (3.7)
Diastolic hypotension	20 (10.9)	18 (8.7)	27 (12.8)	0
Respiratory, thoracic and mediastinal disorders	42 (22.8)	25 (12.0)	34 (16.1)	11 (40.7)
Hypoxia	23 (12.5)	13 (6.3)	24 (11.4)	9 (33.3)
Tachypnoea	5 (2.7)	0	3 (1.4)	0
Investigations	21 (11.4)	17 (8.2)	20 (9.5)	10 (37.0)
Respiratory rate increased	12 (6.5)	10 (4.8)	12 (5.7)	9 (33.3)
Respiratory rate decreased	3 (1.6)	1 (0.5)	6 (2.8)	1 (3.7)

Source: Adapted from Table 76, ISS Report, p. 234 (PDF), Applicant's submission, NDA 212295.

It does appear that there is an increased incidence in the majority of preferred terms with increasing fentanyl dose, and that with the exception of tachycardia, systolic hypertension, and tachypnoea (sic), all adverse events were reported with the highest incidence in patients who received > 150 µg fentanyl. It is worth noting, however, that there were similar observations in the midazolam treatment group. In the placebo treatment group, however, the results were not as consistent and, in some cases, more adverse events were reported in the < 75 µg fentanyl group compared to the > 150 µg fentanyl group. Additionally, it appears that for all treatment groups, higher initial fentanyl doses did not correlate with an increased incidence of adverse events. However, as discussed below, the higher initial doses did correlate with deeper levels of sedation (MOAA/S scores of 0 or 1) and was the rationale for protocol amendments implementing an initial dose reduction.

Depth of Sedation

Clinical Review
 Petit-Scott, M.D.

The Applicant determined that there appeared to be a large proportion of patients who had deep levels of sedation (MOAA/S score of 0 or 1) in Study CNS7056-006 and presented this information to the DMC. The DMC made several recommendations and the Applicant opted to reduce the initial dose of fentanyl from 75 µg to 25-50 µg. It appears that there were only eight patients enrolled after implementation of Protocol Amendment 4 in Study CNS7056-006, so definitive conclusions regarding fentanyl dose and depth of sedation are challenging for this study in isolation. In Study CNS7056-008, however, the initial dose of fentanyl was reduced in Protocol Amendment 5, after a small proportion of patients had been treated, thus the majority received initial doses of only 25-50 µg. The results indicate that fentanyl dose reduction appeared to impact the depth of sedation in the RMZ treatment group more than either the midazolam or placebo treatment groups. Specifically, the proportion of RMZ-treated patients with MOAA/S scores of 0 or 1 decreased from approximately 25% to 6% after implementation of Protocol Amendment 5. In the midazolam treatment group, the incidence of MOAA/S scores of 0 or 1 increased with implementation of Protocol Amendment 5, 7% to 9%, and in the placebo treatment group, the incidence was similar before and after implementation of Protocol Amendment 5, 12.5% to 12%. These results suggest that RMZ may impact the depth of sedation to a greater extent than midazolam, administered either according to the package insert or at the discretion of the provider.

Procedure Success

As noted in Dr. James Travis' review and discussed previously, logistic regression analysis found a statistically significant negative effect of increasing fentanyl dose on procedure success for patients in the RMZ treatment group in both Study CNS7056-006 and Study CNS7056-008. The number of placebo-treated patients who were procedure successes is low, such that similar analyses could not be performed. Patients in the midazolam treatment group, however, demonstrated a similar relationship. Clinically, this is not be entirely surprising given that challenging procedures may require more opioid analgesia and have a lower success rate.

Procedure Duration

Also using logistic regression, there appeared to be a statistically significant effect of increasing fentanyl dose on procedure duration for both Study CNS7056-006 and Study CNS7056-008. The relationship is more pronounced in Study CNS7056-008, with a p value < 0.001. Again, clinically this may not be entirely informative or concerning in isolation. Longer procedures are likely to require more opioid analgesia; however, given the other associations with increasing fentanyl dose and RMZ administration, the findings may not be entirely explained by clinical need.

8.6.3. Remimazolam or Fentanyl Reversal

There was a single patient in the placebo treatment group in Study CNS7056-006 who received flumazenil reversal to decrease procedure time, versus because of a medical need to reverse

the procedural sedation. No patient in the pooled safety analysis Group A1A required flumazenil reversal.

There was a single patient in Study CNS7056-008 who required opioid analgesic reversal with naloxone for moderate hypoxia.

8.6.4. MOAA/S Scores to Inform the Safety Profile of Remimazolam

As previously mentioned in the efficacy portion of this review, there is concern that patients with low MOAA/S scores, specifically 0, within two minutes of administration suggests that RMZ is a rapid-acting, deep sedative, and possibly general anesthetic, agent. This concern was discussed with the Applicant during the Mid-Cycle Communication Meeting. Subsequent to the meeting, the Applicant presented additional safety information for patients treated with RMZ who had MOAA/S scores of 0. Additionally, the Applicant argued that a MOAA/S score of 0 does not represent general anesthesia because a trapezius squeeze does not represent the same level of pain as a surgical stimulus. The point was not that the trapezius squeeze is the pain equivalent of a surgical incision, but that a MOAA/S score of 0 *could* represent deep sedation to the point of general anesthesia because a more painful stimulus is not part of the MOAA/S assessment. The article by Kim *et al* (2015) provided by the Applicant to support this position could also be used to refute it with the following statement:

Given that the noxious stimulus of the MOAA/S has typically been a trapezius muscle squeeze, the method can only identify when a subject has become unresponsive to a mildly painful stimulus. The transition to deeper levels of central nervous system depression wherein a subject would be unresponsive to more noxious stimulation (e.g. skin incision, tracheal intubation) cannot be determined.

The authors go on to state that, "...respiratory complications associated with sedation practice, such as airway obstruction and apnea, are expected to be more likely when deeper levels of anesthesia are produced (i.e. 'deeper-than-intended' sedation states are used as a surrogate safety signal in these studies)."

The issue at hand is not whether general anesthesia can be assessed using the MOAA/S scale, as the Applicant contends, but whether the score can inform safety, and not just efficacy, during sedation. I would argue that while it should not be used in isolation to inform the safety profile of a sedative agent, it can clearly provide additional safety information to help guide recommendations regarding the required level of training of administering providers.

The ASA's Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia (October 23, 2019) provides the following summary table.

Table 78. ASA Continuum of Depth of Sedation

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	<i>Minimal Sedation/Anxiolysis</i>	<i>Moderate Sedation/Analgesia ("Conscious Sedation")</i>	<i>Deep Sedation/Analgesia</i>	<i>General Anesthesia</i>
<i>Responsiveness</i>	Normal response to verbal stimulation	Purposeful** response to verbal or tactile stimulation	Purposeful** response following repeated or painful stimulation	Unarousable even with painful stimulus
<i>Airway</i>	Unaffected	No intervention required	Intervention may be required	Intervention often required
<i>Spontaneous Ventilation</i>	Unaffected	Adequate	May be inadequate	Frequently inadequate
<i>Cardiovascular Function</i>	Unaffected	Usually maintained	Usually maintained	May be impaired

Source: Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia Committee of Origin: Quality Management and Departmental Administration, Oct. 23, 2019.

As indicated in this table, general anesthesia is defined as unresponsiveness to painful stimuli. While one could argue whether a trapezius squeeze is truly painful, one could not argue that the deeper the sedation, through general anesthesia, the more attentive the administering provider must be and able to provide airway and hemodynamic support if needed.

The Applicant acknowledges that the incidence of MOAA/S scores of 0 within two minutes of administration of study drug is higher in the RMZ treatment group than in the placebo or midazolam treatment groups, but states that patients in both the placebo and midazolam treatment groups have a higher incidence of lower MOAA/S scores at later time points. The following table summarizes the proportion of patients by MOAA/S score in each treatment group through 10 minutes post-dose.

Table 79. Proportion of Patients by MOAA/S Score and Timepoint (Safety Population, Group A1A)

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 Cosmo Technologies, Ltd.

Timepoint [n (%)]	MOAA/S Score Category	Remimazolam (N=630)	Midazolam (N=201)	Placebo (N=135)
Baseline	0 to 1	0	0	0
	2 to 4	0	0	0
	5	593 (100)	184 (100)	127 (100)
	Total	593 (100)	184 (100)	127 (100)
1 minute postdose	0 to 1	11 (1.9)	0	0
	2 to 4	244 (41.2)	16 (8.5)	10 (7.8)
	5	337 (56.9)	173 (91.5)	118 (92.2)
	Total	592 (100)	189 (100)	128 (100)
1.5 minutes postdose	0 to 1	23 (3.9)	0	0
	2 to 4	368 (62.2)	19 (9.9)	9 (7.1)
	5	201 (34.0)	172 (90.1)	118 (92.9)
	Total	592 (100)	191 (100)	127 (100)
2 minutes postdose	0 to 1	42 (6.8)	0	0
	2 to 4	453 (72.8)	41 (21.0)	11 (8.2)
	5	127 (20.4)	154 (79.0)	123 (91.8)
	Total	622 (100)	195 (100)	134 (100)
2.5 minutes postdose	0 to 1	41 (6.8)	0	0
	2 to 4	464 (76.9)	47 (24.6)	15 (11.6)
	5	98 (16.3)	144 (75.4)	114 (88.4)
	Total	603 (100)	191 (100)	129 (100)
3 minutes postdose	0 to 1	44 (7.1)	0	0
	2 to 4	498 (80.2)	52 (26.1)	15 (11.4)
	5	79 (12.7)	147 (73.9)	117 (88.6)
	Total	621 (100)	199 (100)	132 (100)
4 minutes postdose	0 to 1	28 (4.5)	0	0
	2 to 4	536 (86.5)	70 (35.4)	19 (14.2)
	5	56 (9.0)	128 (64.6)	115 (85.8)
	Total	620 (100)	198 (100)	134 (100)
5 minutes postdose	0 to 1	28 (4.5)	0	0
	2 to 4	546 (87.4)	78 (38.8)	20 (14.8)
	5	51 (8.2)	123 (61.2)	115 (85.2)
	Total	625 (100)	201 (100)	135 (100)
10 minutes postdose	0 to 1	34 (5.6)	2 (1.0)	0
	2 to 4	501 (82.4)	113 (56.5)	21 (15.7)
	5	73 (12.0)	85 (42.5)	113 (84.3)
	Total	608 (100)	200 (100)	134 (100)

Source: ISS Report, p. 199 (PDF), Applicant's submission, NDA 212295.

In the pooled safety analysis Group A1A, there were no patients in the placebo treatment group with an MOAA/S score of 0 through 10 minutes post-dose. In the midazolam treatment group, there were no patients with an MOAA/S score of 0 through five minutes post-dose. These results are in contrast to patients in the RMZ treatment group, in which between 1.9% and 7.1%

of patients had an MOAA/S score of 0 through 10 minutes post-dose. The following table summarizes MOAA/S scores for later timepoints.

Table 80. Proportion of Patients by MOAA/S Score and Timepoint (Safety Population, Group A1A)

Timepoint [n (%)]	MOAA/S Score Category	Remimazolam (N=630)	Midazolam (N=201)	Placebo (N=135)
15 minutes postdose	0 to 1	19 (3.5)	1 (0.5)	1 (0.7)
	2 to 4	419 (76.7)	137 (68.8)	82 (60.7)
	5	108 (19.8)	61 (30.7)	52 (38.5)
	Total	546 (100)	199 (100)	135 (100)
20 minutes postdose	0 to 1	9 (2.0)	4 (2.1)	5 (3.7)
	2 to 4	309 (70.2)	169 (87.6)	112 (83.6)
	5	122 (27.7)	20 (10.4)	17 (12.7)
	Total	440 (100)	193 (100)	134 (100)
25 minutes postdose	0 to 1	10 (2.9)	4 (2.2)	8 (6.3)
	2 to 4	204 (59.6)	160 (87.4)	109 (85.8)
	5	128 (37.4)	19 (10.4)	10 (7.9)
	Total	342 (100)	183 (100)	127 (100)
30 minutes postdose	0 to 1	2 (0.8)	5 (2.9)	7 (6.1)
	2 to 4	151 (56.8)	134 (78.4)	96 (84.2)
	5	113 (42.5)	32 (18.7)	11 (9.6)
	Total	266 (100)	171 (100)	114 (100)
40 minutes postdose	0 to 1	5 (2.5)	4 (3.0)	3 (3.1)
	2 to 4	87 (43.5)	86 (63.7)	76 (79.2)
	5	108 (54.0)	45 (33.3)	17 (17.7)
	Total	200 (100)	135 (100)	96 (100)
50 minutes postdose	0 to 1	1 (0.6)	2 (2.4)	4 (5.2)
	2 to 4	57 (36.3)	44 (53.7)	49 (63.6)
	5	99 (63.1)	36 (43.9)	24 (31.2)
	Total	157 (100)	82 (100)	77 (100)
60 minutes postdose	0 to 1	1 (0.8)	1 (1.5)	1 (1.8)
	2 to 4	33 (28.0)	23 (33.8)	29 (52.7)
	5	84 (71.2)	44 (64.7)	25 (45.5)
	Total	118 (100)	68 (100)	55 (100)
75 minutes postdose	0 to 1	0	0	0
	2 to 4	22 (26.2)	10 (23.3)	18 (48.6)
	5	62 (73.8)	33 (76.7)	19 (51.4)
	Total	84 (100)	43 (100)	37 (100)
90 minutes postdose	0 to 1	0	0	0
	2 to 4	14 (28.0)	4 (17.4)	9 (28.1)
	5	36 (72.0)	19 (82.6)	23 (71.9)
	Total	50 (100)	23 (100)	32 (100)

Source: ISS Report, p. 200 (PDF), Applicant's submission, NDA 212295.

It does appear that the proportion of patients in the placebo and midazolam treatment groups with MOAA/S scores of 0 was higher at later time points; i.e., 20 through 60 minutes post-dose, the times during which the proportion of patients in the RMZ treatment group with scores of 0 was low. The highest proportion of patients in the RMZ treatment group with MOAA/S scores of 0 was at three minutes post-dose. This is in contrast to patients in the placebo treatment group in which the highest proportion of scores of 0 was at 25 minutes post-dose and in the midazolam treatment group the highest proportion of scores of 0 was at 40 minutes post-dose.

The Applicant also stated that the total dose of midazolam administered to patients in the placebo groups was at the discretion of the investigator, consistent with clinical practice, and likely higher than that administered to patients in the midazolam treatment group, in which dosing was based on midazolam prescribing information (midazolam prescribing information, Lake Forest, IL: Akorn, Inc. 2017). Therefore, the Applicant claims that the observed depth of sedation in the placebo treatment group is representative of clinical practice. Review of the midazolam rescue data in the three Phase 3 studies, however, indicates the doses of midazolam administered to patients in the placebo and midazolam treatment groups were similar, with subtle differences suggesting the midazolam treatment group actually received more midazolam, on average. What may be true, however, is that *timing* of midazolam doses may have been different when administered at the discretion of the investigators, which may explain the larger proportion of patients overall in the placebo treatment group compared to the midazolam treatment group with MOAA/S scores of 0. Regardless, I concur with the Applicant's assertion that while RMZ administration appears to result in early deep sedation, administration of midazolam results in a similar proportion of patients under deep sedation, only at later time points.

In summary, RMZ does appear to have a relatively short time to onset of desired clinical effect, which is a potential clinical benefit, particularly in the ambulatory surgery setting. Administering providers will need to be made aware, however, that the depth of sedation appears to be greater at earlier time points when compared to patients treated midazolam rescue medication.

8.6.5. Pregnancy and Lactation

There are no adequate and well-controlled studies of RMZ in pregnant or lactating women; therefore, RMZ is not recommended for use in pregnant or lactating women. One patient treated in Study CNS7056-005, a pharmacodynamic, pharmacokinetic study in healthy volunteers, reportedly became pregnant approximately one or two days after RMZ administration. There were no pregnancy complications noted and the infant was born full-term and reportedly had no developmental delays noted at 3.5 months of age.

The Division of Pediatrics and Maternal Health has recommended the following information be included in the drug product label.

Infants exposed to remimazolam through breast milk should be monitored for sedation, respiratory depression, and feeding problems. A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk during treatment and for 5 hours (approximately 5 elimination half-lives) after remimazolam administration in order to minimize drug exposure to a breastfed infant.

I concur with their recommendation and have nothing additional to add.

8.6.6. Pediatrics and Assessment of Effects on Growth

The safety and efficacy of RMZ has not been evaluated in pediatric patients. The Applicant submitted an initial pediatric study plan on December 16, 2013, and it was agreed upon on July 18, 2014. Refer to Section 11, Postmarketing Requirements and Commitments for additional information on the planned pediatric studies.

8.6.7. Overdose, Abuse Potential, Dependence, and Withdrawal,

Overdose

Benzodiazepine overdose is characterized by sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, and changes in measured hemodynamic parameters. Nonclinical data indicate that RMZ overdose symptoms are similar to those observed after overdose of other benzodiazepine medications, including subdued behavior, prostration, unresponsiveness, drowsiness, reduction in heart rate, ataxia, abnormal breathing, abnormal gait, piloerection, and lip licking.

Treatment of RMZ overdose includes vital sign monitoring, supportive care, and treatment for clinically significant changes in measured hemodynamic parameters, with close attention to ventilation and oxygenation. Administration of flumazenil can reverse RMZ-induced sedation, with the understanding that supportive care is still required and re-sedation can occur. Additionally, there is a risk of seizures with administration of flumazenil, particularly in patients on chronic benzodiazepine treatment and those suffering a tricyclic antidepressant overdose.

Abuse Potential

The Applicant conducted three studies, CNS7056-016, CNS7056-019, and CNS7056-020, to evaluate the oral and intranasal bioavailability of remimazolam to assess the abuse potential via these alternative routes of administration. The results from these studies indicate a low likelihood that RMZ would be abused via either route. Specifically, RMZ demonstrates low oral bioavailability, suggesting that this route of abuse is not likely to result in relevant desired

effects. Sedative effects did appear enhanced in subjects who ingested RMZ with alcohol; however, the Applicant states that a combination of RMZ 360 mg with 40% alcohol did not result in predictable or reliable sedation. Regarding intranasal abuse, the Applicant indicates that large amounts of RMZ powder are necessary to produce a desired effect and that evaluated subjects complained of pain associated with snorting RMZ.

Study CNS 7056-014 was conducted to evaluate the abuse potential of IV RMZ. The results of this study suggest that RMZ has significant abuse potential, assessed via drug liking, relative to placebo and similar to midazolam in recreational CNS depressant users. Take drug again measures appeared to be higher for midazolam-treated subjects compared to RMZ-treated subjects.

There was no patient during clinical development who experienced a treatment-emergent adverse event in the standard MedDRA query (SMQ) Abuse Potential. As indicated in Table XX, there were related adverse event preferred terms that were reported with an increased incidence in RMZ-treated patients compared to placebo or midazolam-treated patients in pooled safety analysis Group A1A.

Dependence

Nonclinical data suggests that RMZ has dependence-inducing potential similar to other mediations in the benzodiazepine class.

Withdrawal

No withdrawal symptoms were reported in any of the clinical studies with RMZ. No patient experienced an adverse event in the SMQ Drug Withdrawal.

Because the proposed indication includes procedural sedation only, which involves a limited time of exposure, the results of the SMQ Abuse Potential for pooled safety analysis Group A1A are summarized in the following table.

Table 81. Incidence of Treatment-Emergent Adverse Events Associated with the SMQ Abuse Potential (Safety Population – Group A1A)

Customized MedDRA Query Preferred term [n (%)]	Remimazolam			Midazolam			Placebo (N=135)
	2.5 mg to 5 mg (N=31)	5 mg (N=599)	Total (N=630)	<1.75 mg (N=113)	1.75 mg (N=88)	Total (N=201)	
Any treatment emergent adverse event related to abuse potential	0	8 (1.3)	8 (1.3)	0	2 (2.3)	2 (1.0)	0
Drug abuse, dependence and withdrawal (SMQ)	0	0	0	0	0	0	0
Drug abuse and dependence (sub-SMQ)	0	0	0	0	0	0	0
Drug withdrawal (sub-SMQ)	0	0	0	0	0	0	0
Selected preferred terms							
Confusional state	0	1 (0.2)	1 (0.2)	0	0	0	0
Disorientation	0	1 (0.2)	1 (0.2)	0	0	0	0
Dizziness	0	5 (0.8)	5 (0.8)	0	0	0	0
Somnolence	0	1 (0.2)	1 (0.2)	0	2 (2.3)	2 (1.0)	0

Note: Percentages are based on the Safety Population and each dose group - Group A1A.

Note: AEs are coded using MedDRA version 18.0.

Note: For each category, subjects are included only once, even if they experienced multiple events in that SMQ or PT.

Note: Table only displays PTs for which at least one subject was identified. The full list of PTs that were searched can be found in the SAP.

Source: ISS Report, p. 119 (PDF), Applicant's submission, NDA 212295.

The findings in this table indicate there were no treatment-emergent adverse events reported in the standard MedDRA queries (SMQ) for drug abuse, dependence, and withdrawal; drug abuse and dependence; and drug withdrawal. There were patients who experienced selected preferred term adverse events, and while the overall incidence is low in all treatment groups, three preferred terms were reported with a higher incidence in RMZ-treated patients compared to placebo or midazolam-treated patients.

It appears unlikely that when administered for procedural sedation in an appropriate medical setting, the risk of abuse, dependence, and withdrawal is very low. Diversion, abuse, and misuse by employees with controlled substance access is a concern with this drug, but the risk does not appear to be increased above what is observed with other benzodiazepines and opioid analgesics. Refer to the review completed by Katherine Bonson, Controlled Substances Staff, for additional information.

8.7. Safety in the Postmarket Setting

8.7.1. Safety Concerns Identified Through Postmarket Experience

Remimazolam has not been marketed anywhere in the world at the time of this NDA review, therefore, no postmarketing information is available. The clinical concerns surrounding RMZ are similar to those associated with other benzodiazepine administration and relate primarily to CNS depression, hemodynamic changes, respiratory depression, and risks of abuse, dependence, and withdrawal.

8.7.2. Expectations on Safety in the Postmarket Setting

In general, it does not appear that there are adverse events associated with RMZ administration that are not observed with other benzodiazepine medications. However, because RMZ is likely to be indicated for procedures lasting less than 30 minutes, the safety profile for longer procedures is not known. Furthermore, because the Applicant did not evaluate RMZ administered via continuous infusion for procedural sedation, the safety profile for that route is not known.

8.8. Integrated Assessment of Safety

The results of the Applicant's clinical development program evaluating the administration of remimazolam for procedural sedation have demonstrated that it can be safely added to the armamentarium of sedative agents currently used for procedures in adults lasting 30 minutes or less. The safety concerns associated with administration of RMZ during procedural sedation do not appear to differ significantly from those associated with currently approved benzodiazepines, including midazolam, likely the most commonly used benzodiazepine administered for procedural sedation. Those safety concerns include prolonged sedation or decreased level of consciousness, changes in measured vital sign parameters, particularly respiratory parameters, and adverse events related to abuse, dependence, and withdrawal.

Comparator treatment groups in the Phase 3 studies included a saline placebo treatment group that defaulted to midazolam rescue administration at the discretion of the investigator, and open-label midazolam treatment group, administered according to drug label recommendations. The Applicant has stated that because the placebo treatment group received midazolam at the discretion of the investigator and consistent with clinical practice, the doses were likely higher than those administered in the midazolam treatment group, and therefore, more representative of the safety profile of midazolam as currently administered for sedation. In general, however, the mean dose of midazolam administered in both treatment groups was similar, with the exception of Study CNS7056-015, in which the placebo treatment group received substantially more midazolam as rescue medication compared to the midazolam treatment group.

Regarding the incidence of prolonged sedation, administration of remimazolam appears to result in a lower incidence 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 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. Because this was the only study to evaluate a non-GI procedure, it is possible that prolonged sedation may be more likely in patients undergoing bronchoscopy. Additionally, the total mean dose of RMZ administered during this study was higher than that administered in either of the studies evaluating patients undergoing colonoscopy, which could

have contributed to the low incidence of prolonged sedation.

It does appear that increasing doses of RMZ are associated with increased incidence of select adverse events. As previously discussed, the incidence of decreased oxygen saturation increased with increasing doses of RMZ in the supportive Phase 2 study, CNS7056-003, and the incidence of bradycardia, hypertension, and nausea increased in the supportive Phase 2 study, CNS7056-004. Additionally, 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 in the same study. In the pooled safety analysis Group A1A, 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. This information will be conveyed in the final drug product label.

All patients in the Phase 3 studies received fentanyl premedication in doses ranging from 50 µg to 75 µg, with a maximum dose of 200 µg permitted. It did appear that increasing total dose of fentanyl did increase the risk of experiencing an adverse event in the vascular disorders, cardiac disorders, respiratory, thoracic, and mediastinal disorders, and investigations SOCs. With the exception of tachycardia, systolic hypertension, and tachypnoea (sic), all adverse events in these SOCs in the pooled safety analysis Group A1A were reported with the highest incidence in patients who received > 150 µg fentanyl. It is worth noting, however, that there were similar observations in the midazolam treatment group. In the placebo treatment group the results were not as consistent and, in some cases, more adverse events were reported in the < 75 µg fentanyl group compared to the > 150 µg fentanyl group. Additionally, it appears that for all treatment groups, it was not higher *initial* fentanyl doses that correlated with an increased incidence of adverse events, but higher *total* fentanyl doses. As previously mentioned in Section 7, Integrated Review of Effectiveness, there was also a statistically significant relationship between increasing fentanyl dose and procedure success, and between increasing fentanyl dose and procedure duration in both Study CNS7056-006 and CNS7056-008. Therefore, it appears that increasing doses of fentanyl have the potential to impact both the efficacy and safety profile of RMZ, information that will be described in the final drug labeling.

There were clinically relevant changes in measured vital sign parameters observed during the Phase 3 studies. Those of most relevance involved changes in respiratory parameters such as respiratory rate and oxygen saturation. 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. As summarized in Section 8.4.7, Vital Signs, results from the pooled safety

analysis Group A1A indicated that the only vital sign changes observed more frequently in the RMZ treatment group compared to the placebo or midazolam treatment groups were increased systolic and diastolic blood pressure. 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 prescribing information.

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 compared to the placebo or midazolam treatment groups in both Study CNS7056-006 and CNS7056-008; however, the overall incidence so low that it was not of clinical concern.

There are two clear advantages of RMZ-induced procedural sedation, which improve the benefit:risk profile. First, as stated by the Applicant and supported by the data, RMZ has a short time to onset of sedation and decreased times to fully alert and to discharge. A faster acting sedative agent permits procedures to begin sooner and potentially end earlier, such that total time under sedation is less, which is clearly beneficial to the patient. In the case of radiographic procedures and studies, less total sedation time results in less exposure to harmful radiation for the patient. While comparisons between the three treatment groups are not informative, based on the open-label dosing in the midazolam treatment group and the time to determine rescue medication need in the placebo treatment group, in my clinical experience, the times to fully alert and to discharge were clinically significant. A decrease in time to discharge of even five minutes in a busy ambulatory surgery center will add significant time savings at the end of the day. Furthermore, time to ready for discharge is one of the best measures to assess how well the patient tolerated the procedure overall, including pre-, intra-, and post-procedure time periods. Complications or the occurrence of adverse events at any time can impact the time to ready for discharge.

The second advantage, over non-benzodiazepine sedatives such as dexmedetomidine and propofol, is the ability to reverse the sedative properties of RMZ with flumazenil. Study CNS7056-002, Part A, demonstrated that the mean time to fully alert, defined as time to the first of three MOAA/S scores of five was decreased with flumazenil administration from 16.8 minutes in the placebo treatment group to 1.8 minutes in the flumazenil treatment group in patients undergoing colonoscopy, and re-sedation was not observed. This is a unique and important property of RMZ that improves its safety profile. While the sedation induced by administration of other benzodiazepines can also be reversed with flumazenil, re-sedation is possible, therefore, more than one dose of flumazenil may be required.

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. Labeling Recommendations

9.1. Prescription Drug Labeling

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.

10. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not indicated at this time. If the Agency becomes aware of future safety concerns, one may become necessary.

11. Postmarketing Requirements and Commitments

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 Applicant submitted an initial pediatric study plan (iPSP) on December 16, 2013, and it was agreed upon on July 18, 2014. The Applicant has requested a deferral for all pediatric studies until after NDA approval. Proposed pediatric studies evaluating remimazolam as outlined in the Agreed iPSP are summarized in the following table.

Table 82. Proposed Pediatric Clinical Studies

Source: Agreed iPSP, p. 11 (PDF), Applicant's submission, NDA 212295.

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
 - 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

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- 16 year-old children)
- Study Completion: +3 years = approximately July 2027
- Final Report Submission: +6 months = approximately January 2028

The Division was in discussion with the Applicant regarding the pediatric program at the time of completion of this clinical review. (b) (4)



12. Appendices

12.1. References

ASA's Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia (October 23, 2019), available at, <https://www.asahq.org/standards-and-guidelines/continuum-of-depth-of-sedation-definition-of-general-anesthesia-and-levels-of-sedationanalgesia>

Kim TK; Niklewski PJ; Martin JF; Obara S; and Egan TD. Enhancing a Sedation Score to Include Truly Noxious Stimulation: the Extended Observer's Assessment of Alertness and Sedation (EOAA/S). *British Journal of Anaesthesia* 2015;115(4):569–77.

12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number):

- Study CNS7056-003
- Study CNS7056-004

Clinical Review
Petit-Scott, M.D.

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- Study CNS7056-006
- Study CNS7056-008
- Study CNS7056-015

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>37</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>0</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

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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.

/s/

RENEE L PETIT-SCOTT
06/30/2020 04:42:42 PM

MARTHA A VAN CLIEF
06/30/2020 05:43:57 PM