

STUDY PROTOCOL

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

PROTOCOL NUMBER: CNS7056-008

IND NUMBER: 102,486

VERSION Protocol Amendment 5.0

Previous Protocols

Protocol Amendment 4.1, 10 November 2015

Protocol Amendment 4.0, 28 October 2015

Protocol Amendment 3.0, 20 July 2015

Protocol Amendment 2.0, 08 May 2015

Protocol Amendment 1.0, 17 March 2015

Version 1.0, 10 November 2014

DATE OF ISSUE: 03 March 2016

SPONSORED BY: PAION UK LIMITED
UNIT D1
BROOKMOUNT COURT
KIRKWOOD ROAD
CAMBRIDGE
CB4 2OH, UK

24-hour SAE FAX Line: [REDACTED]

Email: P [REDACTED]

Non-SAE Questions for the Medical Monitor: Dr. [REDACTED]

Cell phone: [REDACTED]

Email: [REDACTED]

Information contained in this protocol is confidential in nature and may not be used, divulged, published or otherwise disclosed to others except to the extent necessary to obtain approval of the Institutional Review Board or Ethics Committee or as required by law. Persons to whom this information is disclosed should be informed that this information is confidential and may not be further disclosed without the express permission of PAION.

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[REDACTED]

[REDACTED]
Date [REDACTED]

[REDACTED]
[REDACTED]

03 March 2016

Version Amendment 5.0

INSTITUTIONS AND LABORATORIES INVOLVED IN THE STUDY

Contract Research Organization

[REDACTED]

Safety

[REDACTED]

[REDACTED]

Study Drug Packaging

[REDACTED]

Safety Laboratory

[REDACTED]

2 INVESTIGATOR STATEMENT OF COMPLIANCE AND SIGNATURE PAGE

I confirm that I have read this study protocol Study Number CNS7056-008, Amendment 5.0 as of March 3rd, 2016 including appendices and agree to the performance of the study according to this protocol. I will perform the study in accordance with the procedures described in the protocol and potential later amendments, and will try to contribute to the study in such a way that the targeted time schedule will be fulfilled.

By my professional education and experience I am licensed to practice medicine and qualified to execute this clinical study in patients.

I will provide training and all necessary information including copies of the study protocol and the Investigator's Brochure (IB) to the staff involved in the performance of the study. I will keep them informed about the general status of the study as communicated to me by PAION including the development and report of any new information learned about the Investigational Product which may influence willingness of the participants to participate/continue to participate in the study, and will verify that all tasks are fulfilled thoroughly and in a timely manner.

I will perform the study according to the ICH-GCP Guidelines, the Declaration of Helsinki, national laws and regulations, and according to accepted moral, ethical and scientific standards within clinical research.

I confirm that my facilities (equipment, laboratory, etc) are adequate to conduct the study according to the requirements of the study protocol.

A patient will not be enrolled in the study without first providing his/her written informed consent. Only the versions of the "Patient Information Sheet/ Informed Consent Form" and "Condensed Patient Information Sheet/ Informed Consent Form" reviewed by PAION and subsequently approved by the central Institutional Review Board (IRB) will be used.

I, or one of the sub-investigators delegated by me, will review each case report form (CRF) prior to forwarding to PAION appointed monitors/ and confirm the correctness of entries by signature.

I agree to regular monitoring visits and to audits/inspections by PAION-appointed monitors/ and/or by local, national, and foreign authorities. I will provide original data (eg, medical records, ECGs) to the monitors and/or auditors/inspectors to allow Source Data Verification. I, sub-investigators or study coordinators (eg, study nurses) delegated by me will cooperate in data clarification procedures.

All patients' data will be treated as confidential; patient data will only be transferred in pseudonymous ways. All research data will be the property of PAION.

Principal Investigator

Printed Name: _____

Position: _____

Professional
Address: _____

Date/Signature: _____

Version: Amendment 5.0

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4 PROTOCOL SYNOPSIS

Protocol Title	Phase 3 Study to Evaluate the Efficacy and Safety of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in Patients Undergoing Bronchoscopy
Protocol Number	CNS7056-008
Sponsor	PAION UK Limited Unit D1, Brookmount Court Kirkwood Road CAMBRIDGE CB4 2QH United Kingdom
Study Sites & Country	Approximately 30 sites in the USA
Principal Investigator	[REDACTED]
Investigational Product	Remimazolam (CNS 7056)
Phase	3
Indication	Conscious sedation in patients undergoing bronchoscopy
Design	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 in patients undergoing bronchoscopy.
Primary Endpoint/Objective	<p>This is a confirmatory study to assess the efficacy and safety of remimazolam in inducing and maintaining suitable sedation levels for patients undergoing bronchoscopy.</p> <p><u>Primary efficacy endpoint:</u></p> <p>To assess the success of the procedure, as measured by:</p> <ul style="list-style-type: none"> ▪ Completion of the bronchoscopy procedure, AND ▪ No requirement for a rescue sedative medication, AND ▪ No requirement for more than 5 doses of study medication within any 15 minute window
Secondary Endpoints/Objectives	<p>The following evaluations will be made:</p> <ol style="list-style-type: none"> 1. The time to start of procedure after administration of the first dose of study medication. [REDACTED] 3. The times to ready for discharge after the end of bronchoscopy procedure (bronchoscope out) and after the last injection of study drug (defined as ability to walk unassisted). 4. The times to fully alert (first of three Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores of 5 after the end of bronchoscopy procedure (bronchoscope out) and after the last injection of study drug). [REDACTED]

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Investigational Product Formulation																	
Analgesic Medication	Fentanyl will be administered as an analgesic pretreatment at a dose of 25-50 µg, immediately prior to administration of the initial dose of the study medication. (with suitable dose reductions at the investigator’s discretion for elderly and debilitated patients) Top-up doses of fentanyl of 25 µg are allowed q 5-10 minutes until analgesia is adequate or the maximum dose of 200 µg per procedure has been given. An opiate antagonist (eg naloxone) should be immediately available at the site. Topical anesthesia will be administered to all the patients prior to bronchoscopy by spraying the nostril (if nasal route is used), nasopharynx and oropharynx with 3 mL of 2% lidocaine. In addition, lidocaine 2% gel may be applied to the nasal passages for ease in inserting the bronchoscope if the nasal route is used.																
Rescue Medication	<p>After determination of treatment failure, only midazolam may be administered as rescue sedation, according to local practice, in order to perform the bronchoscopy. Other sedatives are not allowed in this study.</p> <p>The benzodiazepine reversal agent flumazenil should be immediately available at the site for use according to standard medical practice.</p> <p>In situations where the investigator considers the use of reversal agents as necessary, naloxone should be considered in cases where the initial dose of flumazenil has not provided the anticipated effect.</p>																
Investigational and Reference Product	In order to maintain the study blind, drug preparation will be performed by an unblinded pharmacist at each site, and the final material will be provided to the investigational staff in a blinded manner.																
Study Treatment Plan	<p>If the fluid status allows, patients will receive a up to 1000 mL 0.9% NaCl solution bolus prior to fentanyl administration followed by a normal saline infusion during the procedure at a rate of 50 mL/hr. The administration of supplemental oxygen 4 L/min will begin shortly before the procedure and will continue until the patient is fully alert. Immediately prior to the first dose of study medication, the patients will receive 25-50 µg of fentanyl (with suitable dose reductions at the investigator’s discretion for elderly and debilitated patients).</p> <p>Patients will be randomized to manually receive in a blinded fashion an initial single intravenous (iv) dose over one minute of remimazolam or placebo or over 2 minutes of midazolam in the open-label arm at the following dose levels:</p> <table><tr><th>Study Drug</th><th>Initial Dose</th><th>Top-up</th><th>n</th></tr><tr><td>Remimazolam</td><td>5.0 mg</td><td>2.5 mg</td><td>300</td></tr><tr><td>Placebo</td><td>-</td><td>-</td><td>60</td></tr><tr><td>Midazolam</td><td>1.75 mg* 1.0 mg§</td><td>1.0 mg* 0.5mg§</td><td>60</td></tr></table> <p><i>*Healthy adults <60 yrs; §adults ≥60 yrs, debilitated or chronically ill patients.</i></p> <p><u>Sedation initiation:</u></p> <ul style="list-style-type: none">▪ <u>Remimazolam or placebo group:</u> After the initial dose, further doses may be applied at least two minutes apart, until adequate sedation is achieved▪ <u>Midazolam group:</u> After the initial dose, further doses may be applied at least two	Study Drug	Initial Dose	Top-up	n	Remimazolam	5.0 mg	2.5 mg	300	Placebo	-	-	60	Midazolam	1.75 mg* 1.0 mg§	1.0 mg* 0.5mg§	60
Study Drug	Initial Dose	Top-up	n														
Remimazolam	5.0 mg	2.5 mg	300														
Placebo	-	-	60														
Midazolam	1.75 mg* 1.0 mg§	1.0 mg* 0.5mg§	60														

	<p>minutes apart, until adequate sedation is achieved.</p> <p>When adequate sedation for scope insertion has been achieved ($MOAA/S \leq 3$) a flexible bronchoscope will be inserted after prior nasopharyngeal 2% lidocaine spray and the procedure will be performed according to the usual clinical practice.</p> <p><u>Sedation maintenance:</u></p> <p><u>Remimazolam or placebo group:</u> Subsequent doses of study drug will be administered over 15 seconds, at least two minutes apart, to maintain the sedation ($MOAA/S \leq 4$) as needed. The total number of doses of study drug throughout the procedure is not limited, as long as no more than 5 doses are administered within any 15 minute window.</p> <p><u>Midazolam group:</u> Subsequent doses will be administered over two minutes, at least two minutes apart, to maintain the sedation ($MOAA/S \leq 4$) as needed. The total number of doses of midazolam throughout the procedure is not limited, as long as no more than 3 doses are administered within any 12 minute window.</p> <p>If adequate sedation cannot be achieved at the beginning or maintained throughout the bronchoscopy using the initial dose plus the maximum allowed number of top-ups within any 15 minute window (12 minutes for midazolam), this will be defined as treatment failure. After such determination, rescue medication (<i>ie</i> midazolam) will be administered in such cases according to local practice in order to start or finalize the bronchoscopy.</p> <ul style="list-style-type: none"> Patients will be continuously monitored for early signs of hypoventilation, airway obstruction, or apnea, and interventions must be conducted early enough in order to maintain homeostasis and vital signs as close as normal for the patient as possible. Flumazenil as a reversal agent for benzodiazepines and naloxone for opioids will be immediately available for injection, if required.
Bronchoscopy	<p>The bronchoscopy procedure will be performed using a flexible device according to standard practice at the site. All findings from bronchoscopy will be documented, but will not be defined as Adverse Events (AEs).</p>
Assessment of Efficacy	<ul style="list-style-type: none"> The primary efficacy endpoint will be the successful completion of the procedure. Efficacy will also be evaluated by time ready to discharge, time to fully alert,
Assessment of Safety	<ul style="list-style-type: none"> Physical examination. Venous blood samples will be collected for routine safety evaluation of biochemistry and hematology. Vital signs (body temperature, heart rate, systolic and diastolic blood pressure and respiratory rate) will be measured throughout the study. Oxygen saturation will be measured throughout the study.

	<ul style="list-style-type: none"> ▪ 12-lead ECGs will be performed when clinically indicated (<i>eg</i> arrhythmia) and before, during and after the procedure. 3-lead ECG will be continuously monitored during the procedure until the patient is fully alert. ▪ AEs will be monitored by the investigator and study personnel and asked about or evaluated using non leading questions throughout the study. ▪ [REDACTED] ▪ Concomitant medications will be documented to evaluate possible drug interactions and also any AEs or pharmacodynamic data that could be associated with periprocedural medications. [REDACTED] ▪ AEs with a focus on respiratory and cardiovascular parameters will be documented and analyzed separately and will include the following: <ul style="list-style-type: none"> ▪ Hypoxia ▪ Bradycardia ▪ Hypotension ▪ Hypertension ▪ Respiratory depression ▪ Prolonged sedation ▪ [REDACTED] <ul style="list-style-type: none"> ▪ [REDACTED] ▪ [REDACTED] ▪ [REDACTED] ▪ [REDACTED] <ul style="list-style-type: none"> ▪ [REDACTED] ▪ [REDACTED] ▪ [REDACTED]
[REDACTED]	[REDACTED]
Statistics	<p><u>Efficacy and safety analysis:</u></p> <p>For the primary efficacy analysis the following hypothesis will be tested:</p> $H_0: \pi_{Remi} \leq \pi_{PLA} \text{ vs. } H_1: \pi_{Remi} > \pi_{PLA},$ <p>where π_{Remi} and π_{PLA} denote the success rates for remimazolam and placebo, respectively. The primary efficacy analysis will be the comparison of these success rates between the remimazolam and placebo groups, using the Cochran-Mantel-Haenszel test to account for the actual fentanyl, benzodiazepine and opioid use in the final analysis.</p> <p><u>Secondary efficacy analyses:</u></p> <ul style="list-style-type: none"> ▪ Descriptive testing will be performed on the secondary efficacy parameters. ▪ Pairwise comparisons for these endpoints will be performed between the midazolam vs remimazolam groups and between the placebo vs. remimazolam groups, in contrast to the primary endpoint, where the midazolam group serves as an internal validation of the sedation assessment only. ▪ [REDACTED]

	<ul style="list-style-type: none">▪ Descriptive <i>p</i>-values will be presented as appropriate. <p><u>Safety analysis:</u></p> <ul style="list-style-type: none">▪ Safety variables will be summarized for the overall population and for each treatment group by descriptive statistics according to their measurement scales.▪ For AEs with a respiratory and cardiovascular focus and interventions undertaken to prevent or treat such AEs, nominal <i>p</i>-values derived by the χ^2-test will be used for treatment group comparisons. <p><u>Interim analysis:</u></p> <p>No interim analysis will be performed.</p>
Version and Date	Protocol Amendment 5.0; Date 03 March 2016

5 TABLE OF CONTENTS

1	Amended Protocol Approval Signature Page	2
2	Investigator Statement of Compliance and Signature Page.....	4
3	[REDACTED]	
4	Protocol Synopsis	7
5	Table of Contents	13
6	List of Abbreviations and Definitions of Terms	18
7	Introduction.....	20
7.1	Background and Rationale	20
7.2	Study Population	20
7.3	Investigational Medicinal Product	21
7.4	Treatment of Possible Overdose	21
7.5	[REDACTED]	
7.6	Clinical Experience	22
7.6.1	First-in-man Study (CNS7056-001).....	22
7.6.2	Phase Ib Study (CNS7056-002).....	23
7.6.3	Phase IIa Study (CNS7056-003).....	24
7.6.4	Phase IIb Study (CNS7056-004).....	24
7.6.5	[REDACTED]	
7.7	Summary of Potential Risks and Benefits.....	26
8	Ethics	28
9	Objectives	29
9.1	Primary Objective	29
9.2	Secondary Objectives.....	29
10	Study Design.....	30
10.1	Overall Design	30
10.2	Duration of Study Participation	31
11	Study Population: Selection and Withdrawal of Patients	33
11.1	Inclusion Criteria.....	33
11.2	Exclusion Criteria	33
11.3	Removal of Patients from Therapy or Assessment/Stop of Recruitment	34
11.4	Data Monitoring Committee	34
12	Study Procedures	36
12.1	Screening Visit: Procedures and Assessments (up to 21 days prior to procedure day).....	36
12.2	Day 1 of Bronchoscopy - Procedures and Assessments	36
12.3	Follow-up on Day 2	43
12.4	Follow-up Telephone Interview Assessments (Day 4 [+3/-1 Days])	43
12.5	Patient Completion/Discontinuation	43

12.6	Replacement of Patients	44
12.7	Prior and Concomitant Therapy	44
12.8	Rescue Sedative Medication	45
12.9	Clinical Trial Material and Co-medication	45
12.9.1	Identity, Supply and Storage of Clinical Trial Material	45
12.9.1.1	Remimazolam	45
12.9.1.2	Midazolam	46
12.9.1.3	Placebo	46
12.9.1.4	Flumazenil	46
12.9.1.5	Fentanyl	46
12.9.1.6	Naloxone	46
12.9.2	Dispensing, Accountability, and Destruction	46
12.9.2.1	Recording of Receipt, Dispensing and Return/Destruction	46
12.9.3	Dispensing	47
12.9.3.1	[REDACTED]	
12.9.3.2	Flumazenil Dispensing	47
12.9.3.3	Fentanyl Dispensing	47
12.9.3.4	Naloxone Dispensing	47
12.9.3.5	Accountability	47
12.9.4	Destruction	48
12.9.5	Blinding and Labeling	48
12.9.6	Randomization and Unblinding	48
12.9.7	Assessment of Compliance	49
12.9.8	Study Patient Numbering	49
13	Description of Assessments	50
13.1	Efficacy Evaluations	50
13.1.1	Modified Observer's Assessment of Alertness and Sedation	50
13.1.2	[REDACTED]	
13.1.3	[REDACTED]	
13.1.4	[REDACTED]	
13.1.5	Process to Determine Time Ready for Discharge	51
13.1.6	Readiness-for-Discharge Score	51
13.1.7	Pharmacokinetic Procedures	51
13.1.8	[REDACTED]	
13.2	Safety Procedures	52
13.2.1	Clinical Laboratory Tests	52
13.2.2	Physical Examinations	53
13.2.3	Vital Signs	53
13.2.4	Electrocardiograms [REDACTED]	
	[REDACTED] Adverse Events	55
13.2.6.1	Definitions	55
13.2.6.2	Assessment of Adverse Events	56
13.2.6.3	Collection and Recording of Adverse Events	58

13.2.6.4	Reporting of Adverse Events	59
13.2.6.5	Treatment and Follow-up of Adverse Events	60
13.2.6.6	
13.2.6.7	Adverse Events Related to Effects Seen with Medications Known to be Associated with Abuse	60
13.2.6.8	Pregnancy	61
13.2.6.9	Special Procedures for Managing SAEs and Unblinding	61
14	Study Management	62
14.1	Regulatory Guidelines.....	62
14.2	Institutional Review Board	62
14.3	Informed Consent.....	62
14.4	Discontinuation of the Study by the Sponsor.....	62
14.5	Changes to the Protocol	62
14.6	Deviations from the Protocol	63
14.7	Selection of Investigators and Study Sites	63
14.8	Data Collection	63
14.9	Study Monitoring	64
14.10	Inspections	64
14.11	Audits	64
14.12	Retention of Records.....	65
14.13	Disclosure and Confidentiality.....	65
14.14	Use of Information and Publication.....	65
15	Statistical Methods.....	66
15.1	Randomization and Blinding	66
15.2	Statistical Analysis.....	66
15.3	Analysis Populations.....	66
15.4	Disposition	67
15.5	Patient Characteristics.....	67
15.6	Efficacy Analysis	68
15.6.1	Primary Analysis.....	68
15.6.2	Secondary Analysis	69
15.7	Safety Analysis	71
15.7.1	Adverse Events.....	71
15.7.2	Clinical Laboratory Tests	71
15.7.3	Vital Signs and Pulse Oximetry	71
15.7.4	Electrocardiograms	72
15.7.5	Physical Examinations	72
15.7.6	Visual Analogue Scale	72
15.8	Interim Analysis.....	73
15.9	Sample Size and Power.....	73
16	Finance and Insurance	74
16.1	Financial Contract.....	74
16.2	Insurance	74

17	References.....	75
18	Appendices	78

CONTACT INFORMATION FOR INVESTIGATIVE SITES

Project Leader

[REDACTED]

Medical Advisor/Medical Monitor

[REDACTED]

Sponsor



[REDACTED]

Clinical Trial Leader

[REDACTED]

6 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ASA-PS	American Society of Anesthesiologists-Physical Status
AST	Aspartate aminotransferase
BP	Blood pressure
bpm	Beats per minute
BMI	Body mass index
BUN	Blood urea nitrogen
°C	Celsius
CDA	Confidentiality Disclosure Agreement
CFR	Code of Federal Regulations
CNS 7056B	CNS 7056 besylate
Cl	Clearance
cm	Centimeter(s)
CPK	Creatine phosphokinase
CRF	Case report form
CS	Clinically significant
DMP	Data Management Plan
ECG	Electrocardiogram
EEG	Electroencephalogram
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GI	Gastrointestinal
hr	Hour(s)
HCG	Human chorionic gonadotropin
hERG	Human Ether-a-Go-go Related Gene
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug Application
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
<i>iv</i>	Intravenous(ly)
IWRS	Interactive web response system
kg	Kilogram(s)
LDH	Lactate dehydrogenase
LRR	Loss of righting reflex
min	Minute(s)
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
µg	Microgram
mg	Milligram
mL	Milliliter(s)
mmHg	Millimeters of mercury
MOAA/S	Modified Observer's Assessment of Alertness and Sedation
NaCl	Sodium Chloride (0.9% NaCl solution)
NDA	New Drug Application
PD	Pharmacodynamic(s)
Ph Eur	European Pharmacopeia
PI	Principal investigator
PID	Patient identification (number)
PP	Per protocol
PRN	pro re nata (as needed)
QTc	Corrected QT interval
RBC	Red blood cells
rpm	Revolutions per minute
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SpO ₂	Peripheral blood oxygen saturation (measured by pulse oximetry)
TEAE	Treatment-emergent adverse event
t _{1/2}	Mean terminal half-life
USA	United States of America
	
Vd	Volume of distribution
Vss	Volume of distribution at steady state
WBC	White blood cells
WHO-UMC	World Health Organisation - Uppsala Monitoring Centre

7 INTRODUCTION

7.1 Background and Rationale

Patients undergoing uncomfortable medical procedures of limited duration generally require some form of sedation and/or analgesia in order to minimize their discomfort and thereby aid in the performance of the procedure. Currently, either a benzodiazepine (sometimes in combination with a narcotic) or propofol is primarily used to obtain sedation for such procedures¹⁻⁵. Among benzodiazepines, midazolam is the most commonly used agent. While both propofol and benzodiazepines have documented effectiveness for use in these procedures, each agent has disadvantages^{6,7}.

Propofol is an intravenous (*iv*) sedative/hypnotic agent with excellent sedative properties⁸. A second advantage is its extremely short half-life ($t_{1/2}$),^{9,10} which allows rapid recovery from sedation.

A disadvantage of propofol or of fospropofol^{12,13,14}, its pro drug, is due to its potential for respiratory depression and thus hypoxia¹¹, thus requiring constant monitoring of patient's vital signs and respiration rate. Consequently, a second physician or a nurse must be present to monitor the patient while the primary physician performs the procedure.

Benzodiazepines are widely used sedative agents¹⁵ with a lower likelihood for respiratory depression than propofol, thus these drugs require less intensive vital sign monitoring than in case of propofol.

Their main disadvantage is their long half life, *eg* even midazolam, the shortest acting benzodiazepine has a half-life of approximately one to three hours¹⁷.

Remimazolam, with a considerably shorter half-life than even midazolam should combine the better safety profile of benzodiazepines over propofol with a rapid recovery and an early restoration of normal cognitive function¹⁶.

For information regarding the concomitant use of fentanyl during bronchoscopy procedures, as well as regarding flumazenil, naloxone or midazolam, please refer to the full prescribing information for each product^{17, 26-28}.

7.2 Study Population

This is a study in patients undergoing flexible bronchoscopy. A total of 420 patients will be randomized, of which 300 will receive remimazolam, 60 will receive placebo (0.9% NaCl) in a blinded fashion and 60 patients will receive midazolam open label.

Randomization will be stratified by age group. The aim is to have 100 patients on remimazolam aged ≥ 65 years (at least 30 of these aged ≥ 75 years) across the three late stage clinical trials (CNS7056-006, CNS7056-008, and CNS7056-015).

7.3 Investigational Medicinal Product

Remimazolam^{18,19} belongs to the class of benzodiazepines. It is an ester-based drug that is rapidly hydrolyzed in the body by esterases to an inactive carboxylic acid metabolite (CNS 7054)²⁰.

[REDACTED]

[REDACTED]

7.4 Treatment of Possible Overdose

Flumazenil is a benzodiazepine antagonist used to reverse the effects of overdoses of benzodiazepines.

Results from preclinical work have shown that treatment with flumazenil reverses loss of righting reflex (LRR) induced by remimazolam in rats²¹. In addition, during the dog maximum tolerated dose (MTD) study, flumazenil was administered to a dog suffering from paradoxical excitation following administration of remimazolam, and the animal recovered within minutes²².

The efficacy of flumazenil as an antidote to remimazolam in humans has been shown in part A of the phase Ib study (CNS7056-002)²³, in which flumazenil or placebo have been applied to subjects after administration of 0.25 mg/kg of remimazolam. While the median time to fully alert was 16.8 minutes after the administration of placebo, the time was shortened to 1.8 minutes after the administration of flumazenil.

These data indicate that flumazenil is likely to be a suitable antidote to remimazolam in the case of accidental overdose and should be able to reverse the effects of remimazolam. Flumazenil will be immediately available on-site for use at the investigator's discretion. In situations where the investigator considers the use of reversal agents as necessary, naloxone should be considered in cases where the initial dose of flumazenil has not provided the anticipated effect. Naloxone will also be available on-site for immediate use.

Skilled personnel not participating in the procedure will provide for continuous monitoring of respiratory and cardiac function, i.e., pulse oximetry. Additionally, supervision by a person trained in Advanced Cardiac Life Support will be ensured to stay with the patient until the patient has recovered consciousness and has normal cardiovascular and respiratory function. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management will be ensured.

7.5 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.6 Clinical Experience

7.6.1 First-in-man Study (CNS7056-001)

In the first-in-man, double-blind, placebo- and midazolam-controlled Phase I study, 81 subjects received a bolus dose of 0.01 to 0.3 mg/kg of remimazolam, a dose of 0.075 mg/kg of midazolam, or placebo^{24, 25}.

Remimazolam demonstrated the expected rapid onset and a quicker offset of sedation as compared to midazolam. Onset of sedation was within one to two minutes following bolus administration at sedative doses starting from 0.05 mg/kg. Depth and duration of sedation appeared to be sufficient at doses of 0.075 to 0.20 mg/kg to allow for a short-term procedure such as upper gastrointestinal (GI) endoscopy. Recovery from adequate sedation ($\text{MOAA/S} \leq 4$) was rapid (about ten minutes) compared with midazolam (about 40 minutes). Higher doses of remimazolam (up to 0.30 mg/kg) appeared to safely induce loss of consciousness.

There were minimal changes in oxygen saturation, even at doses that led to loss of consciousness. Airway patency was maintained throughout the study with no requirement for mechanical intervention. Vital signs remained stable throughout; there were no reports of hyper- or hypotension. The most commonly reported related adverse events (AEs) were headache (five events in four out of 54 subjects [9.3%] receiving remimazolam, and one event in one of 18 subjects receiving midazolam [5.6%]) followed by bradycardia/sinus bradycardia (two events in two out of 54 subjects receiving remimazolam [3.7%], and four events in three out of nine subjects receiving placebo [33.3%]). There was no pain on injection. No serious AE (SAE) was reported.

Remimazolam was rapidly cleared from plasma with a clearance that was approximately three-fold greater than that observed for midazolam. The average percent dose cleared from plasma per cohort was 80 to 90% in one hour for remimazolam and 50% in one hour for midazolam. The elimination rate of the inactive metabolite CNS7054 was largely unchanged in the dose range studied, with linear PK.

7.6.2 Phase Ib Study (CNS7056-002)

This phase I dose-finding study evaluated the potential of flumazenil as an antidote to remimazolam (Part A), and the safety, pharmacokinetics and pharmacodynamics of multiple doses of remimazolam in volunteers undergoing colonoscopy (part B), in combination with a standard dose of fentanyl.

The efficacy of reversal of sedation with flumazenil (0.5 mg three minutes after administration of remimazolam) was tested in six subjects who were sedated with a single dose of 0.25 mg/kg remimazolam (part A). The subjects ($n=6$) were randomized to receive either flumazenil or placebo at Day 1 and to receive the alternate treatment on Day 2. The median time to fully alert after administration of remimazolam and flumazenil or placebo was 1.3 minutes versus 16 minutes, respectively. Therefore, flumazenil in the tested dose has been demonstrated to be a potent antidote to remimazolam. No re-sedation has been observed.

In part B of the study, remimazolam in combination with a standard dose of fentanyl, has been studied to provide suitable sedation levels during a colonoscopy procedure. In this study, sedation was to be maintained for 30 minutes. The subjects received three initial doses of remimazolam (0.04, 0.075, or 0.10 mg/kg, in Cohorts of $n=15$ each), five or ten minutes after administration of 50 μg of fentanyl for analgesia. In order to maintain adequate sedation for 30 minutes, up to six top-up doses of 0.04 mg/kg remimazolam each could have been administered.

Remimazolam demonstrated a rapid onset and rapid offset of sedation for all doses tested. The sedation success rate (defined as MOAA/S ≤ 4 on three consecutive measurements and completion of the procedure and no requirement for alternative sedative or ventilation) combined for the top two cohorts were found to be 83%. No dose dependency was found for time to fully alert, time to recovery and time to ready for discharge.

Remimazolam demonstrated hemodynamic stability: no dose-dependent drops in systolic or diastolic blood pressure and oxygen-saturation have been observed. Only two patients needed airway interventions (chin lift, supplemental oxygen) although the patients were on room air. There was no need for ventilation at all. No serious or severe adverse events occurred; the rate of moderate adverse events was low.

7.6.3 Phase IIa Study (CNS7056-003)

The Phase IIa study was a randomized, controlled, double-blind, dose-finding study evaluating the efficacy and safety of remimazolam in patients undergoing diagnostic upper gastrointestinal (GI) endoscopy. One hundred and two patients were randomly assigned (1:1:1:1) to receive either midazolam at a single dose of 0.075 mg/kg, or a single injection of remimazolam at a dose of 0.1 mg/kg, 0.15 mg/kg, or 0.2 mg/kg. Midazolam (1-2 mg) was planned as rescue medication in the event that the single dose of study medication was insufficient to achieve the level of sedation needed for the upper GI endoscopy. The endoscopy procedure has been performed according to the study site practice.

The primary objective, success of the procedure, defined as MOAA/S ≤ 4 on three consecutive measurements AND completion of the procedure AND no requirement for alternative sedative or ventilation, dose-dependently increased from 32% (remimazolam 0.10 mg/kg) and 56% (remimazolam 0.15 mg/kg) to 64% (remimazolam 0.20 mg/kg) compared to 44% for midazolam (0.075 mg/kg). A rapid recovery was observed in all patients. No dose dependency was seen in the mean time to fully alert for all remimazolam groups, and a slightly longer and more variable duration for midazolam-treated patients.

Vital signs remained stable under treatment with any dose of remimazolam and Midazolam and no clinically relevant changes in ECG were observed. The rate of adverse events under treatment with remimazolam was comparable to the rate of Midazolam and did not show any dose-dependency. No dose dependent drop of oxygen-saturation has been observed. No ventilation was necessary at any of the patients. No serious adverse events occurred.

7.6.4 Phase IIb Study (CNS7056-004)

The Phase IIb study was a randomized, controlled, double-blind, dose-finding study evaluating the efficacy and safety of remimazolam in patients undergoing standard colonoscopy. One hundred and sixty patients were randomly assigned (1:1:1:1) to receive either midazolam at a single dose 2.5 mg and 1.0 mg top-ups, or an initial injection of remimazolam at a dose of 8.0 mg plus 3.0 mg top-ups, 7.0 mg plus 2.0 mg top-ups or 5.0 mg plus 3.0 mg top-ups. The colonoscopy procedure has been performed according to the study site's practice.

The primary objective, sedation success rate (see Section 7.6.3 for definition) was superior for remimazolam over midazolam with a success rate of 92.5% for remimazolam 8.0 mg, 95% for 7.0 mg remimazolam and 97.5% for 5.0 mg remimazolam (and their respective top-up doses) versus midazolam with a 75% success rate. A rapid recovery was observed in all patients. No dose dependency was seen in the mean time to fully alert for all remimazolam groups, and a slightly longer duration for midazolam-treated patients. Vital signs remained stable under treatment with any dose of remimazolam and midazolam and no clinically relevant changes in ECG were observed. Analysis of QT intervals using both a Bazett's and a Fridericia correction showed statistically significant differences between the treatment groups favoring the remimazolam groups at 5 minutes: the point nearest the C_{max} for remimazolam.

The rate of adverse events under treatment with remimazolam was comparable to the rate of midazolam and did not show any dose-dependency. No dose dependent drop of oxygen-saturation has been observed. No ventilation was necessary at any of the patients. No serious adverse events occurred. The data also indicated that a low initial dose of 5.0 mg of remimazolam and top-up doses of 2.5 mg are appropriate in colonoscopy to initiate and maintain an adequate sedation level.

7.6.5

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.7

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

8 ETHICS

This study will be conducted in compliance with the principles of the Declaration of Helsinki and its amendments, the International Conference on Harmonization (ICH) principles of Good Clinical Practice (GCP) (including archiving of essential study documents), and the applicable regulations of the country in which the study is conducted.

A properly constituted, accredited Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must review and approve the protocol, the patient information, and the patient informed consent document, and recruitment materials before the start of the study. The study will be conducted in compliance with all US IRB requirements.

It is the responsibility of the investigator to ensure that written informed consent is obtained from the patient before any activity or procedure is undertaken that is not part of routine care.

9 OBJECTIVES

9.1 Primary Objective

The objective is to establish the superiority of remimazolam compared to placebo in inducing and maintaining suitable sedation levels for patients undergoing bronchoscopy and in comparison to an additional open-label midazolam group in combination with fentanyl as determined by sedation success.

9.2 Secondary Objectives

The data will be evaluated to assess:

1. The time to start of procedure after administration of the first dose of study medication.
2. [REDACTED]
3. The times to ready for discharge after the end of bronchoscopy procedure (bronchoscope out) and after the last injection of study drug (defined as ability to walk unassisted).
4. The times to fully alert (time to first of three consecutive Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores of 5 after the end of bronchoscopy procedure (bronchoscope out) and after the last injection of study drug).
5. [REDACTED]
6. [REDACTED]
7. [REDACTED]
8. [REDACTED]
9. [REDACTED]
10. [REDACTED]
11. [REDACTED]
12. [REDACTED]
13. [REDACTED]
14. [REDACTED]

10 STUDY DESIGN

10.1 Overall Design

This study will be performed as a prospective, double-blind, randomized, multi-center, parallel group study assessing the efficacy and safety of remimazolam in patients undergoing bronchoscopy in comparison to placebo. An open-label midazolam group has been included as a validation measure for the tools to determine sedation as well as a comparator for safety. 420 patients will be randomized, of which 300 patients belong to the remimazolam group, 60 to the placebo and 60 patients to the midazolam group.

Bronchoscopy may be performed for diagnostic but as well as for therapeutic reasons, such as biopsies, lavage, brushings, and foreign body extraction for example. It is, however, limited to procedures usually performed in the bronchoscopy suite, but not the ICU (for detail see inclusion/exclusion criteria in Section 11). Subjects should follow fasting instructions as provided by the site.

All patients will receive 0.9% NaCl solution up to 1000 mL drip starting prior to the procedure, if their fluid status allows. All patients will receive 25-50 µg of fentanyl immediately prior to the administration of study medication (with suitable dose reductions at the investigator's discretion for elderly and debilitated patients). All infused fluid volumes will be recorded throughout the procedure. The administration of supplemental oxygen will be started shortly before the procedure and will be continued at a rate of 4 L/min until the patient is fully alert (three consecutive MOAA/S scores of 5).

Patients will be randomized to manually receive an initial single intravenous (*iv*) dose over one minute of remimazolam 5.0 mg or an equal volume of placebo in a blinded manner and bronchoscopy will start when adequate sedation ($\text{MOAA/S} \leq 3$) has been achieved.

Sedation may be maintained by injection of further doses of remimazolam 2.5 mg or placebo in the same volume not earlier than two minutes apart after assessment of the sedative effect. The overall number of remimazolam/placebo doses is not limited as long as not more than 5 doses are administered in any 15 minute window. Should **five doses within 15 minutes** not be sufficient to obtain adequate sedation for the bronchoscopy, this is defined as a treatment failure.

In the open-label midazolam arm, healthy adults <60 will receive 1.75 mg of midazolam as an initial dose over two minutes. Adults ≥ 60 years, debilitated or chronically ill patients will receive 1.0 mg as an initial dose over two minutes. Sedation can be maintained by further doses of 1.0 mg in healthy adults <60 years; in the case of adults ≥ 60 yrs, debilitated or chronically ill patients, the dose will be 0.5 mg. These subsequent doses should always be titrated slowly and administered over at least two minutes. At least two additional or more minutes should be allowed to fully evaluate the sedative effect. The overall number of midazolam doses is not limited as long as not more than three doses are administered in any 12 minute window. Should **three doses within any 12 minute** window not be sufficient to obtain adequate sedation for the bronchoscopy, this is to be considered a treatment failure.

After determination of treatment failure, midazolam is defined as the only rescue sedative medication in such cases in order to perform or finalize the bronchoscopy.

If the pain is not adequately controlled by the initial dose of 25-50 µg fentanyl (with suitable dose reductions at the investigator's discretion for elderly and debilitated patients), further top up doses of fentanyl of 25 µg q 5-10 minutes are allowed until adequate analgesia is achieved or the maximum dose of 200 µg per procedure has been reached. It is of note, that fentanyl is strictly to be applied for pain control only.

The flexible bronchoscope will be inserted and the procedure will be performed according to the usual clinical practice.

If the investigator does not proceed with the bronchoscopy or does not complete the bronchoscopy (*eg* for technical reasons), the reason will be documented.

The primary efficacy endpoint is to assess the success of sedation of the bronchoscopy procedure. This composite endpoint will be determined for remimazolam and placebo by the following criteria:

- Completion of the bronchoscopy procedure, AND
- No requirement for a rescue sedative medication, AND
- No requirement for more than **5 doses** of study medication **within any 15 minute window**.

With regard to the last point, in the case of midazolam a requirement for more than **3 doses** **doses within any 12 minute window** defines a treatment failure.

Skilled personnel not participating in the procedure will provide for continuous monitoring of respiratory and cardiac function, ie, pulse oximetry. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and personnel trained in their use and skilled in airway management will be ensured. A benzodiazepine reversal agent (flumazenil) as well as an opioid antagonist (naloxone) will be immediately available for use. See Appendix A for an overdose treatment protocol.

Individuals trained in Advanced Cardiac Life Support will be present in the vicinity of the patient until he/she has recovered consciousness and has normal cardiovascular and respiratory function.

10.2 Duration of Study Participation

The maximum study duration for any patient will be up to 28 days. The patients will be screened within 21 days prior to the bronchoscopy. A follow-up phone call will be performed on Day 4 (+3/-1 days) after the bronchoscopy has taken part (see Appendix B).

Screening (up to 21 days prior to procedure day):

Patients will sign informed consent and undergo procedures to determine eligibility.

Day of bronchoscopy (Day 1):

After the completion of screening procedures patients will be randomly assigned to the remimazolam, placebo or midazolam group. Patients will receive their assigned treatment with 25-50 µg fentanyl (with suitable dose reductions at the investigator's discretion for elderly and debilitated patients) and the bronchoscopy will be performed according to the study procedures. Following completion of the bronchoscopy procedure, the patients will be discharged at the discretion of the investigator and completing the assessments after reaching fully alert status. Assessment of "time back to normal" in the patient's subjective view (via telephone contact by study nurse on Day 2).

Follow-up (Day 4 [+3/-1 days]):

The site will telephone the patient for safety assessments. Study participation is considered complete after all Day 4 assessments have been performed and all Adverse Events have been followed-up until they resolve or become stable, or until they can be explained by another known cause(s).

In case there has been any indication for the onset of a new AE since discharge, patients should come back to the site immediately (preferably the same day) to perform further assessments (eg clinically laboratory tests, 12 lead ECG, left to the discretion of the investigator).

11 STUDY POPULATION: SELECTION AND WITHDRAWAL OF PATIENTS

A screening log of potential study candidates and an enrollment log of enrolled patients will be maintained by IWRS. No protected health information under the Health Insurance Portability and Accountability Act (HIPAA) regulations will be collected on the screening log.

11.1 Inclusion Criteria

A patient can be included into the study if he/she meets all of the following inclusion criteria:

- Male and female patients, aged ≥ 18 , scheduled to undergo a diagnostic or therapeutic flexible bronchoscopy in the bronchoscopy suite (therapeutic bronchoscopies may include lavage, biopsies, brushings, and foreign body extraction, for example).
- American Society of Anesthesiologists Physical Status Score 1 through 3³³.
- BMI ≤ 45 .
- SpO₂ $\geq 90\%$ in ambient air or with no more than 2L/min of O₂ support.
- For all female patients, negative result of urine pregnancy test. Additionally, for women of child-bearing potential only, use of birth control during the study period (from the time of consent until all specified observations are completed).
- Patient voluntarily signs and dates an ICF that is approved by an IRB prior to the conduct of any study procedure, including screening procedures.
- Patient is willing and able to comply with study requirements and available for a Follow-up phone call on Day 4 (+3/-1 days) after the bronchoscopy.

11.2 Exclusion Criteria

A patient will not be included if he/she meets one or more of the following exclusion criteria:

- Patients with a known sensitivity to benzodiazepines, flumazenil, opioids, naloxone, or a medical condition such that these agents are contraindicated.
- Bronchoscopy outside the bronchoscopy unit (*eg* ICU).
- Patients on mechanical ventilation.
- Tracheal stenosis.
- Planned Laser bronchoscopy, rigid scope bronchoscopy.
- Use of unstable doses of benzodiazepines and opioids for any indication *eg*, insomnia, anxiety, spasticity. An unstable dose means dose changes of more than 50% of the previous dose within 30 days prior to day of procedure.
- Female patients with a positive pregnancy test at screening or baseline and lactating female patients.

- Patients with positive drugs of abuse screen (unless explained by concomitant medication) or a positive ethanol test at baseline.
- Patient with a history of drug or ethanol abuse within the past 2 years.
- Patients in receipt of any investigational drug or use of investigational device within 30 days or less than seven half-lives (whichever is longer) before the start of the study, or scheduled to receive one during the study period.
- Participation in any previous clinical trial with remimazolam.
- Patients with an inability to communicate well in English with the investigator, or deemed unsuitable according to the investigator (in each case providing a reason).

11.3 Removal of Patients from Therapy or Assessment/Stop of Recruitment

All patients are free to withdraw from participation in this study at any time, for any reason, and without prejudice.

The investigator may terminate a patient from the study at any time for lack of therapeutic effect that is intolerable to the patient, or otherwise considered unacceptable; for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, or administrative reasons; or in the investigator's opinion, to protect the patient's best interest.

Irrespective of the investigator's discretion, a subject will be immediately discontinued from the study for the following reasons:

- Need for endotracheal intubation
- Use of catecholamines

If a patient is withdrawn before completing the study, the reason for withdrawal will be entered on the appropriate CRF page. Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

Patients who withdraw from the study after randomization will not be replaced.

On the study level: the clinical investigation can be terminated due to either administrative or safety reasons. A regular review of aggregate study data will be performed by the Data Monitoring Committee (DMC). Based on their review, the DMC may recommend to continue, impose a temporary halt or stop the study.

11.4 Data Monitoring Committee

A DMC will be formed, to monitor the study data at regular intervals, and will comprise of three independent physicians and a statistician, all of whom have no involvement with the conduct of this clinical trial. The DMC will operate according to a specific charter.

[REDACTED]

[REDACTED]

12 STUDY PROCEDURES

12.1 Screening Visit: Procedures and Assessments (up to 21 days prior to procedure day)

The Screening Visit will take place within the 21 days prior to dosing; Day -21 to Day 1.

During the Screening Visit, study procedures will be explained in detail by the investigator, informed consent will be obtained and the following evaluations will be performed (see Appendix B).

- Assign a screening number
- Review inclusion/exclusion criteria
- ASA Score³³
- Record medical and medication history
- Record last participation/receipt of investigational product or use of investigational device
- Demographics: ethnicity (Hispanic/Latino, not Hispanic/Latino), race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American, biracial), gender, age (yrs)
- Complete physical examination (except rectal, breast or genitalia exams unless medically indicated); plus height, weight, and BMI
- Assess hemodynamics, after resting supine for more than five minutes (supine heart rate, systolic and diastolic blood pressure), record respiratory rate
- Take body temperature
- Perform supine single 12-lead ECG
- Perform clinical laboratory tests (serum chemistry, hematology)
- Perform urine drugs-of-abuse test (positive result will exclude from the study unless result can be explained by concomitant medication)
- Perform oral saliva test for ethanol (by presentation of a positive result the patient will be excluded from the study)
- Perform urine pregnancy test (HCG) for female patients
- Pulse oximetry

12.2 Day 1 of Bronchoscopy - Procedures and Assessments

The patient's eligibility will be reconfirmed by a review of inclusion/exclusion criteria and the following procedures and assessments will be completed.

Within five hours prior to the initial administration of trial medication:

- Review inclusion and exclusion criteria and verify that the patient continues to meet all study entry criteria.
- Update medical history (including adverse reactions experienced and concomitant medications taken, if applicable, since Screening).

- Baseline physical examination (symptom-directed exam).
- Weight will be measured while patient is without shoes or heavy coat.
- Record vital signs (supine heart rate, systolic and diastolic BP, and temperature).
- Collect blood samples for clinical laboratory tests (hematology, serum chemistry).
- Collect a urine sample for the pregnancy test from female patients.
- Collect a urine sample for the drug screen.
- Perform ethanol saliva test.
- Perform a 12-lead ECG.

If randomization is at the same day as screening, the above mentioned assessments do not need to be repeated.

For all patients applicable:

- Adverse events and concomitant medications will be assessed.
- Assign a randomization number to each eligible patient.

[REDACTED]

[REDACTED]

- [REDACTED]

Within **30 minutes** prior to initial administration of trial medication:

- Hemodynamic parameters (supine heart rate and systolic and diastolic blood pressure) as well as body temperature will be measured at pre-defined intervals and documented using an electronic recording device, body temperature will be determined.
- Administration of 0.9% NaCl solution will start, if the fluid status of the patient allows and in absence of contraindications *eg* renal failure, and should continue until the end of bronchoscopy.

Within **15 minutes** prior to initial administration of trial medication:

- Baseline MOAA/S score will be recorded.
- Continuous 3 lead ECG recording will commence and continue until fully alert.
- Baseline SpO₂ measurement will be recorded and continuous SpO₂ monitoring by pulse oximetry will commence.
- Baseline respiratory rate measurement will be recorded and continuous RR monitoring by a medical device will commence.

- Administration of supplemental oxygen will be started at a rate of 4 L/min by nasal prongs (if standard) and will continue until the patient is fully alert. Oxygen may be increased if needed, according to oxygen saturation monitoring.
- Airway management assessment should be performed. (Immediate availability of oxygen, resuscitative drugs, age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, presence of skilled personnel for the maintenance of a patient airway and support of ventilation).
- Baseline hemodynamic parameters (supine heart rate and systolic and diastolic blood pressure) will be measured immediately before dosing of fentanyl.
- Topical airway anesthesia will be undertaken with 3 mL of 2% Lidocaine, administered either as a spray to upper airways or administered via nebulizer.

Approximately **one minute** prior to initial administration of fentanyl and trial medication for sedation initiation:

- In case of nasal route, topical lidocaine 2% gel will be inserted into nostrils (or as standard) and patient will be asked to ‘sniff’ the lidocaine into the nose.
- Hemodynamic parameters (supine heart rate and systolic and diastolic blood pressure) will be measured and documented in the eCRF at defined time points.
- [REDACTED]
- Respiratory rate will be recorded

DOSING OF FENTANYL, DOUBLE BLIND STUDY MEDICATION, AND OPEN-LABEL MIDAZOLAM

Preparation:

Up to 1000mL normal saline will be administered if the fluid status of the patient allows. In all subjects the details of fluid administration information will be documented including: the date and time of fluid initiation and end of infusion, volume infused at the time of sedation initiation, measurement of additional fluid and time administered during the procedure, as well as total volume infused.

The dose and time of administration of all medication, as well as all MOAA/S scores, will be documented.

After start of administration of the randomized study medication (t=0) MOAA/S scores will be recorded at 1, 1.5, 2, 2.5 and 3 minutes and further in 1-minute intervals until fully alert (fully alert is defined as the first of three consecutive MOAA/S measurements of 5).

Dosing of fentanyl:

Immediately before administration of study sedative medication, 25-50 µg fentanyl or a suitably reduced dose for elderly or debilitated patients will be administered *iv* slowly over 1-2 minutes for analgesia.

All patients receiving fentanyl will require close monitoring of respiratory rate and continuous oxygen saturation monitoring. Neither initial nor subsequent doses should be administered to patients who have a respiratory rate of less than 8 breaths per minute or an oxygen saturation of less than 90%.

Supplementary doses of 25 µg of fentanyl may be given until adequate analgesia is achieved or a maximum dose of 200 µg is reached. Five to ten minutes should be allowed to assess the analgesic effect. Such subsequent doses should ONLY be administered if the patient's pain is not adequately controlled. If depth of sedation is insufficient, ONLY the dose of the sedative should be adjusted.

The dose and time of administration of any medication will be documented. Patients should be observed closely for signs of adverse events and possible respiratory distress. Naloxone should be close at hand for emergency administration (see Appendix A)

Immediately after the dosing of fentanyl and depending on the allocated study arm, the following dose instructions for study sedative medication (blinded study arm **or** open label midazolam) have to be followed:

Dosing of double blind study medication (remimazolam or placebo):

Initiation of sedation (remimazolam or placebo):

The initial dose of 2 mL double-blinded study medication will be administered manually by *iv* injection over one minute with watch control.

MOAA/S scores will be recorded at 1, 1.5, 2, 2.5 and 3 minutes and further in 1-minute intervals, after start of blinded study drug dosing (t=0) until fully alert. At least two additional minutes should be allowed to evaluate fully the sedative effect. If there is sufficient sedation (MOAA/S ≤3) the procedure can start.

If there is insufficient sedation (MOAA/S 4 or 5) to begin the procedure after the initial dose of blinded study medication, a supplementary dose of 1 mL of blinded study medication may be administered by slow *iv* injection (over approximately 15 seconds) at least two minutes after the end of the first dose and after MOAA/S assessment.

If initial sedation is still insufficient, further supplementary doses of 1 mL of blinded study medication may be administered by slow *iv* injection (over approximately 15 seconds), at least two minutes apart.

If there is still insufficient sedation to begin the procedure after the initial dose and a maximum of four additional doses within a 15 minute period, "treatment failure" is recorded and the patient

should receive midazolam rescue medication at the discretion of the investigator to start the procedure.

Maintenance of sedation (remimazolam or placebo):

If sedation from blinded study medication is sufficient to allow colonoscopy to begin, subsequent doses of 1mL double blind study medication can be administered to maintain the patient at an adequate sedation level ($\text{MOAA/S} \leq 4$).

If the MOAA/S is ≥ 4 additional doses (as manual bolus injections over 15 seconds) of 1mL remimazolam or placebo can be administered, at least two minutes apart, to maintain or again reach an adequate sedation level. Two or more additional minutes should be allowed to evaluate fully the sedative effect.

During the procedure “treatment failure” is recorded if adequate sedation ($\text{MOAA/S} \leq 4$) cannot be maintained by blinded study medication despite five doses within any 15 minute period. The patient should then receive midazolam rescue sedative medication at the discretion of the investigator to allow for completion of the procedure or for scope removal. Only midazolam may be used as rescue sedative medication

Dosing of open label midazolam:

Initiation of sedation (midazolam):

The initial midazolam dose will be administered manually by *iv* injection over two minutes with watch control. In healthy adults <60 yrs, the initial dose will be 1.75 mL solution containing 1.75 mg. In the case of adults ≥ 60 yrs, or debilitated or chronically ill patients, the dose will be 1mL solution containing 1.0 mg.

MOAA/S scores will be recorded at 1, 1.5, 2, 2.5 and 3 minutes and further in one minute intervals, after start of the open label midazolam dosing ($t=0$) until fully alert. At least two additional minutes should be allowed to evaluate fully the sedative effect. If there is sufficient sedation ($\text{MOAA/S} \leq 3$) the procedure can start.

If there is insufficient sedation to begin the procedure after the initial dose of midazolam (MOAA/S 4 or 5), a supplementary dose of midazolam may be administered by *iv* injection over at least two minutes under watch control, at least two minutes after the end of the last dose and after MOAA/S assessment. In the case of healthy adults <60 yrs, the dose will be 1 mL containing 1.0 mg. In the case of adults ≥ 60 yrs, or debilitated or chronically ill patients, the dose will be 0.5 mL containing 0.5mg.

If initial sedation is still insufficient, one further supplementary dose of midazolam may be given, at least two minutes apart.

If there is still insufficient sedation to begin the procedure after the initial dose and a maximum of two further doses within a 12 minute period, “treatment failure” is recorded and the patient

should receive midazolam rescue medication at the discretion of the investigator to start the procedure.

Maintenance of sedation (midazolam):

If sedation from open label midazolam study medication is sufficient to allow colonoscopy to begin, subsequent doses can be administered to maintain the patient at an adequate sedation level ($\text{MOAA/S} \leq 4$).

If the MOAA/S is ≥ 4 additional doses (as manual injections over two minutes) of midazolam can be administered, at least two minutes apart, to maintain or again reach an adequate sedation level.

For healthy adults < 60 yrs, the dose of midazolam will be 1.0 mg (1mL); in the case of adults ≥ 60 yrs, debilitated or chronically ill patients, the dose will be 0.5 mg (0.5mL). These subsequent doses should always be administered as manual injections over at least two minutes, and two or more additional minutes should be allowed to evaluate fully the sedative effect.

During the procedure “treatment failure” is recorded if adequate sedation ($\text{MOAA/S} \leq 4$) cannot be maintained by midazolam study medication, despite three doses within any 12 minute period. The patient should then receive midazolam rescue sedative medication at the discretion of the investigator to allow for completion of the procedure or for scope removal. Only midazolam may be used as rescue sedative medication.

Sedation and analgesia reversal:

The benzodiazepine reversal agent flumazenil should be immediately available for use at the site (see Appendix A).

The opioid antagonist naloxone should be immediately available for use at the site (see Appendix A).

Start of bronchoscopy:

The scope will be inserted when sufficient sedation is achieved ($\text{MOAA/S} \leq 3$).

Post-dose assessments Day 1:

All safety and PK post-dose assessments (where appropriate) will be performed based on the start time of the initial infusion of study medication:

- Hemodynamic parameters: Systolic and diastolic blood pressure will be recorded at 2, 5, 10 and every five minutes thereafter for the duration of the procedure until the patient is fully alert and clinically stable. Heart rate will be monitored and recorded continuously using an electronic device (Nellcor, Covidien) and documented in the CRF at 2, 5, 10 and every 5 minutes thereafter for the duration of the procedure until the patient is fully alert

and clinically stable. The heart rate nadir will be determined and will also be recorded in the eCRF. In addition, these parameters will be recorded immediately prior to, and two minutes after each administration of fentanyl.

- Respiratory rate will be recorded and monitored continuously using an electronic device (Nellcor, Covidien) until fully alert. Values will be documented in the eCRF at 2, 5, 10 and every five minutes thereafter for the duration of the procedure until the patient is fully alert and clinically stable. The respiratory rate nadir will be determined and will also be recorded in the eCRF.
- SpO₂ will be monitored and recorded continuously from 15 minutes pre-dose, and values will be documented in the eCRF at 2, 5, 10, and every five minutes thereafter for the duration of the procedure until the patient is fully alert and clinically stable. The SpO₂ nadir will be determined and will also be recorded in the eCRF. In addition, SpO₂ will be recorded immediately prior to, and two minutes after each administration of fentanyl.
- Single 12-lead ECGs will be performed one minute after the first dose, five minutes after initial dosing, and every 10 minutes until the end of the procedure if possible, and also 5 minutes after the end of procedure and at discharge or if clinically warranted, *eg* in case of arrhythmias. 3 lead ECG recording will be performed continually throughout the procedure with documentation of presence or absence of any arrhythmias 2 minutes post t = 0 and every 5 minutes until fully alert. Any patients with evidence of QT prolongation should be monitored until the ECGs return to baseline.
- MOAA/S scores will be recorded post t=0 at 1, 1.5, 2, 2.5 and 3 minutes and at 1-minute intervals thereafter until fully alert (fully alert is defined as the first of three consecutive MOAA/S measurements of 5). After fully alert, MOAA/S scores will be recorded every 5 minutes until ready for discharge (see below), and after ready for discharge every 10 minutes (up to 90 minutes) until actual discharge of patient. Following completion of the procedure and fully alert, patients will be allowed clear liquids and a meal at the discretion of the investigator.
- The time ready for discharge must be determined.
- Actual times of discharge from (a) the bronchoscopy suite, and (b) the recovery room after the last injection of study medication and after the end of the bronchoscopy will be recorded.
- At 30, 60 and 90 minutes post t=0, a ready-for-discharge score will be determined.
- [REDACTED]
- [REDACTED]
- Adverse events will be assessed.
- Any airway management procedures will be recorded.
- Concomitant medications will be reviewed.
- Blood samples for clinical laboratory tests (hematology, serum chemistry) will be collected at least 3 hrs after the procedure.

- Body temperature will be determined 5 minutes after end of procedure, at fully alert and at discharge.
- [REDACTED]
- [REDACTED]

In order to capture the potential time differences between the **main clock** (used for assessment of time = 0) and the **Nellcor device clock**, both times shall be recorded simultaneously at some point within 30 minutes prior to the start of the procedure.

Pharmacokinetic determinations:

For patients ≥ 75 years at selected sites, venous blood samples (approximately 4 mL each) for plasma concentration analysis of remimazolam, will be collected in samples obtained at five accurately recorded time points during and after the procedure. The first three during the procedure should be no closer than two minutes after the end of a dose, with the first sample taken after the initial dose. The two samples after the anticipated last dose should be (a) between 5 and 15 minutes later and (b) at least 20 minutes post dose, but no later than about 2 hours.

12.3 Follow-up on Day 2

Assessment of “time back to normal” in the patient’s subjective view (via telephone contact by study nurse on Day 2).

12.4 Follow-up Telephone Interview Assessments (Day 4 [+3/-1 Days])

The following assessments will be undertaken via telephone interview at the Follow-Up Contact:

- [REDACTED]
- Record any concomitant medications and AEs reported since Day 1.

In case there has been any indication for the onset of a new AE since discharge, patients should come back to the site immediately (preferably the same day) to perform further assessments (eg clinically laboratory tests, 12 lead ECG, left to the discretion of the investigator).

12.5 Patient Completion/Discontinuation

A patient is considered to have completed the study once all Follow-up call assessments have been completed or the patient withdraws from the study prematurely.

While patients are encouraged to complete all study evaluations, they may withdraw from the study at any time and for any reason. Every effort will be made to determine why any patient

withdraws from the study prematurely. This information will be recorded. If a patient withdraws prematurely after dosing, patients will be monitored until they are stable for discharge. All data normally collected at the End of Study Visit should be recorded at the time of premature discontinuation, or at the scheduled End of Study Visit. Patients' participation may be terminated prior to completing the study for any of the following reasons:

1. Adverse event
2. Protocol violation
3. Loss to follow-up
4. Patient's own request (withdrawal of consent)
5. Endotracheal intubation
6. Use of catecholamines
7. Other

If a patient is not reachable for the Follow-up call or is discontinued from the study, an attempt will be made to determine the reason(s). If the patient is unreachable by telephone, a registered letter will be sent to the patient requesting that he/she contact the clinic.

All patients with an ongoing SAE at the End of Study call (scheduled or premature) must be followed until the event is resolved (with or without sequelae) or deemed stable.

12.6 Replacement of Patients

Patients who withdraw from the study before randomization will be replaced to ensure the planned number of patients can be randomized.

Patients who withdraw from the study after randomization will not be replaced. A log of screen failures and subjects who are withdrawn prior to randomization that includes the reason(s) they were not enrolled or reason(s) for their pre-randomization withdrawal will be kept.

12.7 Prior and Concomitant Therapy

Treatment with the following medications and therapies before study entry or during the study is not allowed (see also Section 11):

- Any investigational drug when taken within 30 days or less than seven half-lives (whichever is longer) before Screening.
- Use of unstable doses of benzodiazepines or opioids for any indication *eg*, insomnia, anxiety, spasticity. An unstable dose is a dose change of more than 50% of the previous dose, within 30 days prior to day of procedure.
- Use of propofol within less than 5 half-lives prior to day of procedure
- Diphenhydramine and other anti-histamines, unless they are administered on a regular dose and schedule (not PRN) for at least one week before the procedure in order to avoid any interference.

In case of nausea and vomiting, sites are allowed to administer 5HT₃-antagonists, either as prophylaxis, or to treat an adverse event.

12.8 Rescue Sedative Medication

Rescue sedative medication is defined as any medication given, over and above that of the assigned treatment arm, in order to either induce or maintain a suitable sedation level to start or continue with the procedure. Rescue sedative medication would thus be given if adequate sedation by the assigned study drug could not be induced or maintained. The patient should receive midazolam as the rescue sedative at the discretion of the investigator, to allow for completion of the procedure or scope removal. In cases where the investigator regards it necessary to use antagonizing agents, naloxone should be considered if the patient does not react as expected to flumazenil.

Sedation initiation:

Rescue sedative medication may only be applied after five doses of double-blind study drug within any 15 minute window have been given and adequate sedation to start the procedure (MOAA/S ≤ 3) has not been achieved. In the case of midazolam, rescue sedative medication may be applied if adequate sedation cannot be achieved after three doses of open label study drug within any 12 minute window.

Sedation maintenance:

Rescue sedative medication during the procedure must be applied, if adequate sedation (MOAA/S ≤ 4) cannot be maintained despite five doses of blinded study drug within any 15 minute window; or, in the case of midazolam, three doses within any 12 minute window. Any administration of rescue sedative medication will be defined as treatment failure.

12.9 Clinical Trial Material and Co-medication

12.9.1 Identity, Supply and Storage of Clinical Trial Material

All study material will be stored at the clinical site in a secure room with access restricted to pharmacy personnel.

12.9.1.1 *Remimazolam*

The chemical designation for remimazolam besylate is [REDACTED]

All doses and concentrations in this protocol are expressed as the base, remimazolam, unless stated otherwise.

Remimazolam is presented as a sterile, white-to-off-white lyophilized powder for reconstitution in a vial.

12.9.1.2 Midazolam

Midazolam (1 mg/mL) will be provided by the Sponsor as study medication. Midazolam will be stored at controlled room temperature between 20 to 25°C (68 to 77°F).

12.9.1.3 Placebo

Placebo will consist of 0.9% NaCl solution and will be provided by the Sponsor. It will be prepared by the local pharmacy in syringes in the same volumes as the other study drugs.

12.9.1.4 Flumazenil

Flumazenil will be provided by the clinical site. Flumazenil is available in multiple-use glass vials containing 5 mL or 10 mL of a 0.1 mg/mL flumazenil sterile solution for injection. Flumazenil will be stored at 25°C (77°F) with excursions permitted (15 to 30°C [59 to 86°F]).

12.9.1.5 Fentanyl

Fentanyl citrate (50 µg/mL) will be provided by the Sponsor. Fentanyl citrate (2 mL ampoules) will be stored at room temperature (15 to 30°C [59 to 86°F]), protected from freezing, light, and extreme heat.

12.9.1.6 Naloxone

Naloxone is available as a 1, 2, and 4 mg/mL sterile solution and will be provided by the clinical site. Naloxone will be stored at controlled room temperature between 15 to 30°C (59 and 86°F).

12.9.2 Dispensing, Accountability, and Destruction


12.9.2.1 *Recording of Receipt, Dispensing and Return/Destruction*

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the study medication including the date, quantity, batch or code number, and

identification of patients (patient number and initials) who received the study medication. The investigator will not supply the study medication to any persons except those named as sub-investigators on the FDA 1572, designated staff, and patients in this study. The investigator will not dispense the study drug from any sites other than those listed on the FDA 1572. Study drug(s) may not be relabeled or reassigned for use by other patients. Upon completion of the study, unused supplies of the study drug will be returned to PAION or destroyed as directed.

12.9.3 Dispensing

12.9.3.1 [REDACTED]



12.9.3.2 *Flumazenil Dispensing*

If needed, the investigator will prepare flumazenil (0.1 mg/mL) for *iv* administration. Flumazenil use as a rescue medication should be as per site practice (Appendix A).

12.9.3.3 *Fentanyl Dispensing*

The investigator will dispense 0.5 - 1.0 mL of the 0.05 mg/mL fentanyl solution for a total dose of 25-50 µg. Appropriate reductions will be used for elderly and debilitated patients, at the discretion of the investigator. Five additional syringes will be prepared, containing 0.5 mL of the 0.05 mg/mL fentanyl solution for follow-up doses of 25 µg, for use only if needed for pain control during the procedure. Further details are given in the drug handling manual.

12.9.3.4 *Naloxone Dispensing*

Naloxone, an opioid antagonist, will be immediately available in the event of fentanyl over-dosage. Naloxone use as a rescue medication should be as per site practice (Appendix A).

12.9.3.5 *Accountability*

Following dispensing, the remaining trial medication dilution will be stored in the pharmacy for subsequent analysis, according to the study manual.

A drug accountability log that documents, among other appropriate information, patient number, amount dispensed, and amount returned to the pharmacy (if any) will be maintained. Study drug returned to the pharmacy will be stored according to the study manual. The returned study drug should be marked as 'returned' and kept separate from the study drug not yet dispensed.

If institutional policy requires destruction, used IP should be destroyed per policy. There will be accountability logs in place that document amount of destructed study drug and that are witnessed by one other person.

All dispensing and accountability records will be available for Sponsor review. When the study monitor visits the participating centers, he/she will reconcile the drug accountability log with the study drug stored in the hospital or ambulatory center/bronchoscopic suite pharmacy.

12.9.4 Destruction

Upon completion of the study and after receiving Sponsor approval in writing, [REDACTED] will be responsible for destroying the remaining study drug or returning it to the sponsor's vendor.

12.9.5 Blinding and Labeling

The study will be conducted as a randomized, double-blind study with respect to remimazolam and placebo. The midazolam arm will be open-label. The identity of the blinded study drugs (remimazolam or placebo) will not be revealed to study management or to anyone at the study site except for the pharmacist, the pharmacy staff [REDACTED] unblinded monitor until the study is completed. This exemption also applies to the DMC members. The pharmacist and staff will not participate in other study procedures. Patients will be blinded to treatment.

Study-specific labeling meeting all applicable regulatory requirements can be found in the Drug Handling Manual for this study.

12.9.6 Randomization and Unblinding

Prior to dosing, patients will be randomly assigned in a 30:6:6 ratios to remimazolam, placebo or open-label midazolam. The randomization schedule will be computer-generated using a permuted block algorithm and will randomly allocate study drug to randomization numbers. The randomization numbers will be assigned sequentially as patients are entered into the study. The study site will not be stratified in the randomization schedule. Although the amount of chronic use of opioids and/or benzodiazepines will be known in advance, it is difficult to be able to stratify the randomization for amount of these drugs from a practical perspective. At Day 1 after confirming that a patient still meets entry criteria, the patient will get the next free random number in ascending order. The investigator will administer the trial medication corresponding to the random number. The doses of remimazolam or placebo will be visually indistinguishable.

Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the patient's treatment assignment. Unblinding should be discussed in advance with the medical monitor if possible. For emergency unblinding, study site personnel will call the central IWRS. If the investigator is not able to discuss treatment unblinding in advance, then he or she must notify the medical monitor as soon as possible about the unblinding incident without revealing the patient's treatment assignment. The central IWRS will capture the date and reason for the patient's treatment

unblinding. In addition, the investigator or designee must record the date and reason for study discontinuation on the appropriate CRF for that patient. In all cases that are not emergencies, the investigator must discuss the event with the medical monitor prior to unblinding the patient's treatment assignment.

12.9.7 Assessment of Compliance

Clinical trial materials will be received by pharmacy personnel at the study site, handled and stored safely and properly in a secure location. The PI or appropriate designee will administer study medication. The exact times of study medication administration will be captured in the electronic data capture system; compliance will be set to 100% if the patient received the initial dose of study medication.

If dosing is not performed per protocol, details will be recorded as a protocol deviation.

All incidents of abuse, misuse, overuse, or overdose (intentional or accidental) will be reported as AEs including case narrative. Study medication, that is lost, stolen, missing or unaccounted for will be thoroughly investigated and details related to such cases will also be narrated.

12.9.8 Study Patient Numbering

All consented patients are assigned unique patient identification (PID) numbers (screening number). The PID numbers are 6-digit numbers that identify study subjects from time of screening until time of randomization.

Before the start of the study, a computer-generated randomization schedule will be prepared by [REDACTED]. Based on the randomization schedule, patients at each study site will be randomly assigned by the central IWRS to one of the two treatment groups (Table 1) in the chronological order in which they were enrolled.

Table 1
Treatment Groups

Group	Trial medication	Initial dose + Top-up dose
Group 1 (N = 60)	Placebo	-
Group 2 (N = 300)	Remimazolam	5.0 mg + 2.5 mg
Group 3 (N = 60)	Midazolam	1.75 mg + 1.0 mg* or 1.0 mg + 0.5 mg [§]
*Healthy adults <60 yrs; [§] adults ≥60 yrs, debilitated or chronically ill patients.		

13 DESCRIPTION OF ASSESSMENTS

13.1 Efficacy Evaluations

13.1.1 Modified Observer's Assessment of Alertness and Sedation

The MOAA/S is a measure of sedation based on the clinical evaluations of the practitioner and is also an accepted and commonly used method of assessing levels of sedation (see [Appendix D](#))³⁰. This method will be used in concert to present a comprehensive assessment of the efficacy profile of remimazolam.

The MOAA/S Scores will be recorded pre-dose and then post-dose as follows: MOAA/S scores at 1, 1.5, 2, 2.5, 3 minutes after the start of trial medication injection and then, after the first 3 minutes, at 1-minute intervals until patient is Fully Alert (first of three consecutive MOAA/S scores of 5). After Fully Alert, MOAA/S scores will be recorded every 5 minutes until ready for discharge, and after ready for discharge every 10 minutes (up to 90 minutes) until actual discharge of the patient.

Time to peak sedation is defined as the time between start of the injection of the initial dose (t=0) until the lowest MOAA/S score is achieved for the first time.

Close monitoring of MOAA/S levels will be undertaken by the sponsor on a patient level during the study to ensure patient safety, and any concerns notified to the DMC. The blind will be maintained throughout.

13.1.2 [REDACTED]

[REDACTED]

13.1.3 [REDACTED]

[REDACTED]

13.1.4 [REDACTED]

[REDACTED]



13.1.5 Process to Determine Time Ready for Discharge

- The patient will be instructed that after the procedure is completed and he is fully awake again, he has to indicate by himself as soon as possible once he feels ready to get up and walk again and that he has to pass a walking test before discharge²⁹.
- Any attempts to wake the patient prematurely are not allowed.
- Prior to determine time ready to discharge, patient must be fully alert **and** meet the following criteria:
 - The patient must be free of nausea/vomiting and diaphoresis.
 - The patient must be free of dizziness in supine and in vertical position.
 - Vital signs must be within a reasonable and normal range of pre-procedure status.
- As soon as the patient indicates, that they feel ready to be discharged, the walking test will be started and patient must walk 16 ft. with a steady gait in a straight line, then turn and come back, in front of a blinded observer, *eg* the study coordinator. The patient is required to be able to walk as if they were leaving the recovery room unescorted. If the gait is still insecure, then the above must be repeated; if fulfilled, the patient is ready for discharge and time will be recorded.
- Patients will be discharged only with an accompanying person, even if they are able to walk unassisted.

13.1.6 Readiness-for-Discharge Score

Patients will be asked at 30, 60, and 90 minutes after time = 0 for their readiness-for-discharge³⁴ using the Visual Analogue Scale, where 0 denotes no readiness for discharge and 10 represents immediate readiness for discharge.



13.2 Safety Procedures

Safety will be assessed by physical examination findings, vital signs (supine heart rate, systolic, diastolic and mean arterial BP, respiration rate and temperature), ECG findings, clinical laboratory test results, and the incidence of AEs. In addition, other procedures including pulse oximetry measurements, pain on injection intensity rating, and the assessment of interventions such as airway interventions (chin lift, jaw thrust, requirement of repositioning and/or manual or mechanical ventilation), administration of additional fluids or medication or any interventions necessary due to a clinically relevant change in ECG will also be performed. Concomitant medications will be documented to evaluate possible drug interactions and also any AEs or pharmacodynamic data that could be associated with peri-procedural medications. All observations will be followed from Baseline/Screening until the Follow-up on Day 4 (+3/-1 days). Specific details on follow up of AEs can be found in Section [13.2.6.5](#).

13.2.1 Clinical Laboratory Tests

- At Screening, blood/urine/saliva will be collected for the following tests:
 - Saliva test for alcohol.
 - Urine-pregnancy test in female subjects.
 - Urine-drug screen to include amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and cannabinoids.
- At Day 1 (if not the same day as Screening) sites will test for the following:
 - Saliva test for alcohol.
 - Urine pregnancy test in female subjects.
 - Urine drug screen to include amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and cannabinoids.
- Screening (if not the same as Day 1), Day 1 at least 3 hrs after the procedure: venous blood samples will be collected for routine safety evaluations (hematology, serum chemistry):
 - Hematology and Coagulation: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential (both % and absolute), platelet count, activated Partial Thromboplastin Time (aPTT) and International Normalized Ratio (INR).
 - Serum Chemistry: AST, ALT, direct and total bilirubin, chloride, bicarbonate, calcium, magnesium, and phosphate, total protein, sodium, potassium, LDH, blood urea nitrogen (BUN), creatine phosphokinase (CPK), glucose, uric acid, albumin, creatinine, alkaline phosphatase.

Clinical laboratory tests will be performed by [REDACTED] Details of blood sampling can be found in Appendix C.

Clinical laboratory values outside the normal range:

Any value outside the normal range will be assessed by the principal investigator as to whether it is of clinical significance. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after administration of study drug or during the study, the abnormality will be recorded as an AE.

13.2.2 Physical Examinations

A complete physical examination (excluding rectal and genitourinary examination) will be performed at screening. A baseline physical examination will be performed on admission if screening and randomization is not at the same day.

13.2.3 Vital Signs

Hemodynamic parameters (heart rate and systolic and diastolic BP) will be measured using an electronic recording device after the patient has been resting supine for ≥ 5 minutes. Hemodynamics will be recorded at Screening and admission, with values recorded within five hours pre-dose, within 30 minutes pre-dose, within 15 minutes pre-dose, and 1 minute pre-dose and 2, 5, 10, and every five minutes thereafter for the duration of the procedure until the patient is fully alert and clinically stable. Continuous monitoring and recording of heart rate will take place on Day 1 from 15 minutes pre-dose until fully alert.

Respiratory rate (breaths per minute) will be manually assessed at screening and on admission. Respiratory rate during the procedure will be continuously device-monitored and recorded (Nellcor, Covidien) on Day 1 and documented once within 15 minutes pre-dose (baseline) and at approximately 2, 5, 10, and every five minutes thereafter for the duration of the procedure until the patient is fully alert and clinically stable.

Body temperature will be measured at screening, on Day 1, within 5 hours pre-dose, within 30 minutes pre-dose and 5 minutes after the procedure, at fully alert and at discharge.

A pulse oximeter for measurement of SpO₂ will be placed 15 minutes prior to start of procedure and will be monitored and recorded continuously until fully alert and documented in the eCRF at the following time points: within 15 minutes of dosing of trial medication, and immediately before administration of fentanyl (baseline) and trial medication. Post-dose measurements will be made at the following time points: 2, 5, 10, and every five minutes thereafter for the duration of the procedure until the patient is fully alert and clinically stable. Any event occurring at the same time as a significant change in SpO₂, such as a displaced sensor, will be recorded.

A set of vital signs will additionally be recorded at the onset time of adverse events, if feasible or available and documented in the eCRF (if an AE occurs outside the medical practice / hospital setting [eg during the time from screening to day 1 or after discharge until follow up when the patient is sent home] data for vital signs might be unavailable).

Systolic and diastolic BP, heart rate and SpO₂ will also be recorded immediately prior to and 2 minutes after each dose of fentanyl.

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

13.2.4 Electrocardiograms

During the procedure a 3 lead ECG recording will be used to continuously record the cardiac rhythm throughout the procedure until the patient is fully alert. Post-dose measurements will be documented at the following time points: 2, 5, 10, and every five minutes thereafter for the duration of the procedure until the patient is fully alert and clinically stable.

Single 12-lead ECGs will be performed within five hours pre-dose, 1 minute after the first dose, 5 minutes after start of initial dosing and every 10 minutes until the end of the procedure (if possible), and five minutes after end of procedure and at discharge or in case of a clinical event, eg arrhythmias, where repeated ECG recordings are warranted. The ECG will include all twelve standard leads and a Lead II rhythm strip on the bottom of the tracing. The ECG will be recorded at a paper speed of 25 mm/sec. The following ECG parameters will be collected or calculated: PR interval, RR interval QRS interval, QT interval, and QTc interval (QT corrected, using Bazett [QTcB] and Fridericia [QTcF] formulae; correction may be done by [REDACTED] Any patients with evidence of QT prolongation should be monitored until the ECGs return to baseline.

All ECGs will be evaluated by a qualified physician for the presence of abnormalities and any significant finding will be documented as an AE.

13.2.6 Adverse Events

13.2.6.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including clinically significant abnormal values from relevant tests, such as clinical safety laboratory tests, ECGs, vital signs), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug.

Diagnostic findings during the bronchoscopy procedure will not be reported as AEs, but documented as findings of the bronchoscopy in a specific section of the CRF.

Serious adverse event:

Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is a medical important event.

Adverse reaction:

Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Suspected adverse reaction:

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected suspected adverse reaction:

A suspected adverse reaction, not listed in the applicable product information (eg investigator's brochure for an unauthorized investigational product, or summary of product

characteristics/product insert for an authorized product) or the specificity or severity of which is not consistent with the applicable product information.

Suspected unexpected serious adverse reaction (SUSAR):

A suspected adverse reaction related to an investigational medicinal product (the tested investigational medicinal products and comparators) which occurs in a clinical trial, and that is both unexpected and serious.

13.2.6.2 Assessment of Adverse Events

Assessment of intensity:

There are three intensity categories:

- *Mild*: the adverse event causes minimal discomfort and does not interfere in a significant manner with the subject's normal activities.
- *Moderate*: the adverse event is sufficiently uncomfortable to produce some impairment of the subject's normal activities.
- *Severe*: the adverse event is incapacitating, preventing the subject from participating in his/her normal activities.

When changes in the intensity of an AE occur, the maximum intensity for the experience should be noted.

Assessment of causality:

Criteria for classifying AEs by causality (suspected relationship to IMP³⁵) are presented below.

Causality term	Assessment criteria*
Certain	<ul style="list-style-type: none">• Event or laboratory test abnormality, with plausible time relationship to drug intake• Cannot be explained by disease or other drugs• Response to withdrawal plausible (pharmacologically, pathologically)• Event definitive pharmacologically or phenomenologically (<i>ie</i> an objective and specific medical disorder or a recognized pharmacological phenomenon)• Re-challenge satisfactory, if necessary
Probable / Likely	<ul style="list-style-type: none">• Event or laboratory test abnormality, with reasonable time relationship to drug intake• Unlikely to be attributed to disease or other drugs• Response to withdrawal clinically reasonable• Re-challenge not required
Possible	<ul style="list-style-type: none">• Event or laboratory test abnormality, with reasonable time relationship to drug intake• Could also be explained by disease or other drugs• Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none">• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)• Disease or other drugs provide plausible explanations
Conditional/ Unclassified	<ul style="list-style-type: none">• Event or laboratory test abnormality• More data for proper assessment needed, or• Additional data under examination

Unassessable/ Unclassifiable	<ul style="list-style-type: none"> • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified
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** All points should be reasonably complied with*

Assessment of outcome:

The outcome at the time of last observation will be classified as:

- Resolved: the subject has recovered completely, and no symptoms remain.
- Resolved: with sequelae – the subject has recovered, but some symptoms remain.
- Resolving: the subject's condition is improving, but symptoms still remain.
- Not resolved: the subject's condition has not improved and the symptoms are unchanged or worsening.
- Death.

Death should only be selected as an outcome when the AE results in death. If more than one AE is possibly related to the patient's death, the outcome of death should be indicated for each such AE.

Assessment of seriousness:

For the purpose of assessing seriousness of an AE, the occurrence at any dose of any the following will be considered as qualifying the event as an SAE:

- Fatality.
- A life-threatening event.
- Hospitalization or prolongation of hospitalization.
- Persistent or significant disability/incapacity.
- A congenital abnormality or birth defect.
- An important medical event that requires immediate medical intervention to prevent the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- All AEs that require any of the following interventions will be considered SAEs:
 - Instrumentation of the airway
 - Administration of flumazenil

In-patient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of the AE, or occurred as a consequence of the event. It does not refer to pre-planned elective hospital admission for treatment of a pre-existing condition (before signing the informed consent) that has not significantly worsened, or to diagnostic procedures. It does not refer to findings during the bronchoscopy that might lead to further follow-up requiring hospitalization.

Assessment of expectedness:

The expectedness of an adverse reaction is determined by the sponsor. This should be done from the perspective of events previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product. For the study drug, the reference safety information is found in the current IB. For the comparator, the information is found in the current package insert (Summary of Product Characteristics). An unexpected suspected adverse reaction is one for which the specificity or severity is not consistent with the current version of the IB. For example, hepatic necrosis would be unexpected (of greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (of greater specificity) if the current version of the IB only listed cerebral vascular accidents.

Furthermore, adverse events listed in the investigator brochure as occurring with members of the same class of drugs, or as anticipated from the pharmacological properties of the drug, would be considered unexpected until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the angiotensin-converting enzyme (ACE) inhibitor class and angioedema would be described in the investigator brochure as a class effect, a case of angioedema observed with the drug under investigation should be considered unexpected for reporting purposes until it is included in the investigator brochure as occurring with the drug under investigation.

13.2.6.3 Collection and Recording of Adverse Events

An AE may be reported spontaneously by the patient, discovered on physical examination, or uncovered as a result of general questioning by the study staff. From signing the informed consent to admission then discharge and again at the Follow-up Visit, the patient will be asked non-leading questions such as, "How have you been since you were last asked?" All AEs will be recorded.

For all AEs, the Investigator or designee must obtain enough information to both determine the outcome of the AE and to assess whether the AE meets the criteria for classification as a SAE. All AEs will be recorded in the study subject's own words ("verbatim") as well as by the diagnostic term assigned by the PI or designee. The term will subsequently be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events should be recorded individually unless the AEs constitute a condition, disease, or syndrome. In that case, separate AEs should not be recorded for individual symptoms; rather, the condition, disease or syndrome should be recorded as one AE.

Each AE will also be described in terms of seriousness, start and stop times and dates, frequency, maximum intensity, causality (suspected relationship to trial medication), actions taken, and outcome.

All incidents of abuse, misuse, overuse, or overdose (intentional or accidental) will be reported as AEs including case narrative.

13.2.6.4 Reporting of Adverse Events

Adverse event (AE) reporting will begin upon signing of the informed consent and will continue through the Follow-up visit.

Any SAE, whether deemed IMP-related or not, must be reported to the Sponsor's local safety management organization as soon as possible after the Investigator or Coordinator has become aware of its occurrence. The Investigator/Coordinator must complete an SAE form and submit it within 24 hours of becoming aware of the event.

SAE Reporting Contact Information:

24-hour SAE Fax Line:

Email:

The Investigator must be prepared to supply the local safety management organization with the following information:

- a. Investigator's name and site number
- b. Patients number
- c. Patients initials
- d. Patients demographics
- e. Clinical event:
 1. *description*
 2. *date of onset*
 3. *severity*
 4. *treatment (including hospitalization)*
 5. *relationship to IMP (causality)*
 6. *action taken regarding IMP*
 7. *outcome*
- f. If the AE was fatal:
 1. *cause of death (whether or not the death was related to the IMP)*
 2. *autopsy findings (if available)*

Additional information about any SAE should be forwarded by the site within 24 hours of the information becoming available. Under the Sponsor's Standard Operating Procedures (SOPs), the safety management organization is responsible for immediately informing the Sponsor's Medical Monitor of the occurrence of any SAEs.

Any new SAE that occurs after the study period and is considered to be possibly related to the IMP or study participation should be handled in the same manner as that for SAEs that occur during the study.

13.2.6.5 [REDACTED]

[REDACTED]

13.2.6.6 [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

13.2.6.7 [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]

• [REDACTED]

■ [REDACTED]

13.2.6.8 Pregnancy

A pregnancy occurring in the study is not considered an AE but should be recorded as an AE on the Adverse Event Form and reported to Sponsor using the Pregnancy Form and within the same timelines as those for SAEs. The investigator must monitor the subject for the duration of the pregnancy and until three months after the child is born, and report the outcome of the pregnancy to [REDACTED].

13.2.6.9 Special Procedures for Managing SAEs and Unblinding

When a patient has a serious adverse event (SAE) that is a medical emergency requiring immediate knowledge of the patient's treatment assignment, study site personnel will call the central interactive web response system (IWRS) to obtain the treatment assignment. In all other cases, prior to unblinding, the investigator must discuss the SAE with the medical monitor. The procedure for unblinding a patient's treatment assignment is described in Section [12.9.6](#).

In addition, in the event of SUSARs, which are subject to expedited reporting, the Sponsor/CRO Pharmacovigilance will unblind the affected cases in order to fulfill reporting requirements. For such cases, unblinding will be performed according to documented procedures and the unblinded information will be kept to authorized safety personnel.

14 STUDY MANAGEMENT

14.1 Regulatory Guidelines

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (64th WMA assembly, Fortaleza, Brazil 10/2013; including amendments in effect up to the time the study was conducted) and in compliance with Good Clinical Practices (GCPs), local regulatory requirements, and U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) regulations (21 CFR 56).

14.2 Institutional Review Board

Conduct of the study must be approved by an appropriately constituted institutional review board (IRB). Approval is required for the study protocol, protocol amendments, informed consent forms (ICFs), patient information sheets, and advertising materials.

14.3 Informed Consent

For each patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the PI or designee must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patient will be informed that he/she is free to withdraw from the study at any time. The patient will receive all information that is required by federal regulations and International Conference on Harmonization (ICH) guidelines. The PI or designee will provide the Sponsor with a copy of the IRB-approved ICF prior to the start of the study.

14.4 Discontinuation of the Study by the Sponsor

The Sponsor reserves the right to discontinue the study for safety or administrative reasons at any time. Should the study be terminated and/or a site closed for whatever reason, all documentation and IMP pertaining to the study must be returned to the Sponsor. Any actions required to assess or to maintain patient safety will continue as required, in spite of termination of the study by the Sponsor.

14.5 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment or administrative letter that must be approved by the Sponsor and the Investigator before implementation. Amendments significantly affecting the safety of patients, the scope of the investigation, or the scientific quality of the study, require additional approval by the IRB and FDA. Examples of amendments requiring such approval are:

- An increase in drug dosage or duration of exposure of subjects.
- A significant change in the study design (*eg* addition or deletion of a control group).
- An increase in the number of invasive procedures to which subjects are exposed.
- Addition or deletion of a test procedure for safety monitoring.
- Change in the inclusion or exclusion criteria that may increase the risk to the subjects.
- Addition of patients to the study.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or by the Sponsor in the interests of preserving the safety of all patients. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons, the Sponsor and the monitor should be notified within 24 hours and the IRB and FDA should be informed within five working days.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval, but the IRB and FDA must be kept informed of such changes. Examples of administrative changes not requiring formal protocol amendments or IRB approval that can be treated as administrative amendments (*eg* file notes) include:

- Changes in the staff used to monitor trials (*eg* Sponsor staff or CRO staff).
- Minor changes in the packaging or labeling of study drug.

14.6 Deviations from the Protocol

The Investigator will not deviate from this protocol for any reason without prior written approval from the Sponsor/Medical Monitor, except in cases of medical emergencies. The Investigator may deviate from the protocol without prior approval only when the change is necessary to eliminate an apparent immediate hazard to a patient. In that event, the Investigator will notify the Sponsor immediately by phone, notify the IRB, and confirm notification to the Sponsor in writing within five working days after the change is implemented.

14.7 Selection of Investigators and Study Sites

The investigators and study sites will be selected by [REDACTED] and PAION UK Ltd. A pre-study site qualification visit will be performed by [REDACTED] Ltd. at all selected sites to assess the willingness and ability to perform the study in compliance with the protocol and current GCP- and regulatory guidelines.

14.8 Data Collection

An electronic data capture system will be used and provided by [REDACTED] for the clinical study. The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's

representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify errors or inconsistencies. This information will be provided to the study site by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE, and concomitant medication reporting, raw data collection forms, Airway Assistance CRF, etc.), including a record of anesthesia designed to record all observations and other pertinent data for each patient receiving IMP.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study.

14.9 Study Monitoring

All aspects of the study will be carefully monitored with respect to GCP and Standard Operating Procedures for compliance with applicable government regulations. The study monitor will be an authorized individual designated by the Sponsor. The study monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the PI.

Frequent communication between the study site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis.

14.10 Inspections

Inspections by local, regional, national, or central authorities may potentially take place at any study site. The investigator is obliged to cooperate during these inspections and make sure that study documents are available and that source data will be available for inspection. PAION or [REDACTED] might also be inspected.

14.11 Audits

Audits are routinely conducted as an overall quality check to ensure sites are adhering to the protocol and following the regulations. On-site audits may be performed at any study site and at any time (during the study or after the study is closed). Audits will take place after notification to the investigator. In the same way, audits can take place at PAION or [REDACTED].

Study sites to be audited will be randomly selected, but may also be chosen for specific reasons, eg high number of patients recruited, research-naïve sites, a particularly high or low number of AEs or SAEs compared to other sites, monitor's reports about data quality, and noncompliance with the study protocol.

14.12 Retention of Records

It is the responsibility of the Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. The Investigator will be instructed to retain all study records required by the Sponsor as well as the regulatory documents in a secure facility with limited access for the following required period: a minimum of two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or after at least two years have elapsed since the formal discontinuation of clinical development of the IMP.

14.13 Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from his staff and the IRB. Study documents (protocols, Investigator's Brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial or to comply with regulatory requirements.

14.14 Use of Information and Publication

The information developed in this study will be used by PAION in connection with the continued development of PAION and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

Publication or other public presentation of remimazolam data resulting from this study requires prior review and written approval of PAION. Abstracts, manuscripts, and presentation materials should be provided to PAION for review at least 30 days prior to the relevant submission deadline. Neither party shall have the right to unreasonably prohibit publication unless such publishing can be shown to affect possible patent filings, applications, rights or violate the terms set forth under separate Confidentiality Disclosure Agreement (CDA) or Clinical Trial Agreement (CTA).

15 STATISTICAL METHODS

Statistical summaries will be provided for all demographic, efficacy, and safety parameters, as described in Sections 15.6 and 15.7. The data from all study sites will be combined for analysis. All data will be provided in listings. Descriptive summaries will be provided where applicable.

15.1 Randomization and Blinding

Prior to dosing, patients will be randomly assigned in a 30:6:6 ratio to remimazolam, placebo and open-label midazolam. The randomization schedule will be computer-generated using a permuted block algorithm and will randomly allocate study drug randomization numbers. The randomization numbers will be assigned sequentially as patients are entered into the study. Randomization will be stratified by age group. The aim is to have at least 100 patients on remimazolam aged ≥ 65 yrs (at least 30 of these aged ≥ 75 years or older) across the three late stage clinical trials (CNS7056-006, CNS7056-008, and CNS7056-015). Study site will not be stratified in the randomization schedule. Although the amount of chronic use of opioids and/or benzodiazepines will be known in advance, it is difficult to be able to stratify the randomization for amount of these drugs from a practical perspective. At Study Day 1, after confirming that a patient still meets entry criteria, study personnel will inform the pharmacist that the subject qualifies for randomization. The unblinded pharmacist will call the central IWRS and enter the requested information. The IWRS will then assign the next randomization number in the sequence and inform the pharmacist of the study treatment assignment. Thereafter, the pharmacist will dispense the corresponding treatment. For treatment unblinding please refer to Section 12.9.6.

15.2 Statistical Analysis

This section presents a summary of the planned statistical analyses. A Statistical Analysis Plan (SAP) describing in detail the analyses to be conducted will be written and approved prior to unblinding. All statistical analyses will be performed in SAS[®]. This study is a superiority study whose sample size was determined based on the results of previous studies.

15.3 Analysis Populations

The analysis populations include the following:

- The safety population will consist of all randomized patients who receive any amount of study drug and will be analyzed as treated.
- The intent-to-treat analysis set (ITT) will include all patients who were randomized and will be analyzed as randomized.
- The modified intent-to-treat analysis set (mITT) will include all patients included in the ITT population who received at least one complete dose of study medication.
- The per-protocol analysis set (PP) will include all patients from the ITT analysis set who:
 - received randomized treatment according to their randomization and the planned treatment schedule.
 - did not have any major protocol violations.

Membership in the analysis populations will be determined prior to unblinding.

All safety analyses will be conducted on patients in the safety population and will be based on the actual treatment administered.

All efficacy analyses will be conducted on patients in the ITT, mITT and PP populations and will be based on the treatment assigned at randomization.

15.4 Disposition

The number of patients randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated for the overall population and by treatment group. Additionally, the disposition of patients may be given by study site.

15.5 Patient Characteristics

Demographic variables will include age, sex, race, ethnicity, height, weight, and BMI. Baseline patient characteristics will include physical examination findings, medical history, vital signs, clinical laboratory test results, and 12-lead ECG. Baseline and post-baseline patient characteristics will include prior and concomitant medications, including additional sedative medications administered during the study procedure.

The number and percentage of patients taking prior and concomitant medications will be summarized by treatment group. Medications will be classified using the most current World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

The remaining patient characteristic variables will be summarized descriptively by treatment group and for the overall population. Summary statistics will consist of sample size (n), mean, median, standard deviation (SD), minimum, and maximum for continuous measurements; and numbers and percentages of patients for categorical measurements. For categorical variables, percentages will be based on the number of the patients in the analysis population.

15.6 Efficacy Analysis

15.6.1 Primary Analysis

The primary efficacy variable is success of the bronchoscopy procedure; a composite endpoint consisting of the following:

- Completion of the bronchoscopy 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, *ie* 0-15, 1-16, 2-17 minutes, *etc.* (For midazolam only: no requirement for more than 3 doses within any 12 minute window, *ie* 0-12, 1-13, 2-14 minutes, *etc.*).

Exceeding 5 doses within any sliding 15 minute window in the blinded (remimazolam or placebo) arm will be considered a treatment failure. Exceeding 3 doses within any 12 minute sliding window in the open label midazolam arm will be considered a treatment failure.

The primary efficacy analysis (success of the procedure using a composite endpoint) will be summarized descriptively for overall success and within each category for treatment group, with summaries to include the number and percentage of patients.

For the primary efficacy analysis, the following primary hypothesis will be tested:

$$H_0: \pi_{\text{Remi}} \leq \pi_{\text{PLA}} \text{ vs. } H_1: \pi_{\text{Remi}} > \pi_{\text{PLA}},$$

where π_{Remi} and π_{PLA} denote the success rates for Remimazolam and placebo, respectively. The primary efficacy analysis will be the comparison of these success rates between the remimazolam and placebo groups, using the Cochran-Mantel-Haenszel (CMH) test to account for fentanyl, opioid and benzodiazepine dose strata. Three strata will be formed based on amount of fentanyl given during the study, chronic opioid dose, and chronic benzodiazepine dose. The details of the strata will be decided at the end of the study by examination of completely blinded data.

The primary efficacy analysis will be based on the ITT, mITT and PP populations, with the mITT and PP population planned to confirm the results of the ITT population.

In the case that one of the strata contains all but 10 patients for the remimazolam or the placebo group, the other strata will be pooled if they are adjacent. If they are not adjacent, an unstratified χ^2 test will be used for the primary analysis. Similarly, if one of the strata contains all but 5 patients for either the remimazolam or the placebo group, an unstratified χ^2 test will be used for the primary analysis.



15.6.2 Secondary Analysis

Comparisons between treatment groups will be performed in a descriptive manner on the following parameters:

1. The time to start of procedure after administration of the first dose of study medication.
2. [Redacted]
3. The time to ready for discharge (defined as ability to walk unassisted) after the last injection of study drug and after the end of bronchoscopy procedure (bronchoscope out).
4. The time to fully alert (time to first of three Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores of 5 after the last injection of study drug and after the end of bronchoscopy procedure (bronchoscope out).
5. [Redacted]
6. [Redacted]
7. [Redacted]
8. [Redacted]
9. [Redacted]
10. [Redacted]
11. [Redacted]

All secondary efficacy variables will be compared between the three treatment groups. For the key secondary variables, only the pairwise comparison between midazolam and remimazolam will be used for efficacy significance testing.

Variables 1-4 will be analyzed using the logrank test. Median time to event with the corresponding 95% confidence interval will be presented. Additional quartiles (25% and 75%) and confidence intervals will be presented. All the time to event analyses will also be presented in Kaplan-Meier curves. Patients who do not reach the fully alert or ready for discharge criteria will be censored at the time of their last assessment. To account for the different sedation properties of remimazolam and midazolam, the following additional stratification factors will be added: For variables 3 and 4, the mean MOAA/S score for the last 3 minutes before last injection

of study drug or the mean MOAA/S score for the 3 minutes prior to bronchoscope out. For variables 1 and 2, such covariates will not be added as they aim at comparing the different sedation properties of remimazolam and midazolam.

For secondary efficacy variables 5, 7-9 and 11 descriptive summaries (n, mean, SD, median, minimum, and maximum), and summary graphs (mean \pm SD) against assessment times will be provided. Overall and pairwise comparisons at each time point using ANOVA models with treatment as the main effect will be conducted for descriptive purposes.

For secondary efficacy variables 6 and 10, which is binary/categorical, descriptive summaries will be provided to include the number and percentage of patients within each category for each treatment group.

Further secondary objective:

Assessment of the population PK in patients (a minimum of 15 patients \geq 75 years).

15.7 Safety Analysis

Safety variables that will be analyzed as safety endpoints include AEs, clinical laboratory test results, vital signs (supine heart rate, systolic and diastolic BP, respiration rate, temperature), pulse oximetry measurements, ECG findings, physical examination findings, and pain on injection intensity rating on a verbal score, airway interventions (chin lift, jaw thrust, requirement of repositioning and/or manual or mechanical ventilation), administration of additional fluids or medication or any interventions necessary due to a clinically relevant change in ECG. All analyses will be performed on the Safety population.

15.7.1 Adverse Events

Treatment-emergent AEs are defined as AEs reported during treatment (at or after the start time of initial fentanyl injection administration) that are not present at Baseline, or that represent an exacerbation of an event that is present at Baseline. Any AE with an unknown start date and time will be considered treatment-emergent if the event does not discontinue prior to study drug administration. The number and percentage of patients with TEAEs will be displayed for each treatment group by system organ class and preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Pre-treatment AEs (reported from signing informed consent to before administration of study treatment) will be analyzed and displayed in a similar manner to TEAEs.

Summaries in terms of severity and relationship to study drug will also be provided. Summaries of SAEs similar to those of AEs will be provided separately. By-patient listings of AEs causing discontinuation of study drug and SAEs will be produced.

15.7.2 Clinical Laboratory Tests

For qualitative clinical laboratory tests, the number and percentage of patients in each category will be displayed for each treatment group at each time point.


For all laboratory tests, a shift table will be produced summarizing changes from baseline to the end of the treatment period by treatment group.

Individual data listings of laboratory results will be presented for each patient at all study visits (scheduled and non-scheduled), including normal range limits for each laboratory test. Out-of-range results will be flagged, and determinations of whether the results were considered to be of clinical significance by the investigator will be included. Clinically significant laboratory test abnormalities that are considered AEs by the investigator will be presented in the AE summaries.

15.7.3 Vital Signs and Pulse Oximetry

Individual data listings of vital signs (supine heart rate, systolic and diastolic blood pressure, calculated mean arterial pressure, temperature, and respiration rate) will be presented for each patient at all visits (scheduled and non-scheduled). Pulse oximetry data (SpO₂) will be presented by patient for pre-defined time points, and as oxygen saturation over time (AUC).

Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be used to summarize the observed values at each time point, and the changes from baseline, for each treatment group. Graphic presentations of heart rate, blood pressure, and respiration rate may be presented by patients and as means by treatment over time. Vital sign and SpO₂ findings that were considered AEs by the Investigator will be presented by treatment in the AE summaries. In addition, the respiratory rate, heart rate and SpO₂ nadirs, as well as the duration of any bradycardia and desaturation period(s) will be presented. Instances of airway assistance will be summarized by treatment and by technique employed. Categorical summaries of endpoints of interest may be presented.




15.7.4 Electrocardiograms

The number and percentage of patients with normal and abnormal 12 lead ECG findings will be displayed for each treatment group at each time point. Additionally, patients with normal ECG findings at baseline and abnormal ECG findings at each time point will also be summarized by treatment group. For quantitative ECG variables (PR interval, QRS interval, QT interval, and QTc interval [corrected using the Bazett and Fridericia formulae]), descriptive statistics including the n, mean, SD, median, minimum, and maximum will be given for the values themselves as well as for change from baseline, by treatment group at each time point. In continuous 3 lead ECG recording, all episodes of bradycardia or other arrhythmias, and any interventions that were instituted, even if the event had not been deemed an adverse event will be displayed.

15.7.5 Physical Examinations

The number and percentage of patients with normal and abnormal ECG findings will be displayed for each treatment group at each time point. Additionally, patients with normal ECG findings at baseline and abnormal ECG findings at each time point will also be summarized by treatment group.



15.8 Interim Analysis

No interim analyses are planned.

15.9 Sample Size and Power

[REDACTED]

[REDACTED]

The midazolam group, which will not be part of the primary confirmatory analysis but is included for assay sensitivity, will be set to 60 patients.

A total of 420 patients will be randomized, 300 to receive remimazolam, 60 to receive open-label midazolam, and 60 to receive placebo.

16 FINANCE AND INSURANCE

16.1 Financial Contract

[REDACTED]

16.2 Insurance

[REDACTED]

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18 APPENDICES

Appendix A Rescue Medication Protocol

Flumazenil

For the reversal of the sedative effects of benzodiazepines flumazenil should be administered as per site practice in accordance with the label.

Naloxone

For the reversal of any opiate related effects, naloxone should be administered as per site practice in accordance with the label.

Appendix B Schedule of Assessments

All days

	Day -21 to Day 1	Day 1	Day 4 Phone Call ⁵ (+3/-1 days)
	Screening	Treatment Day	Follow-up
Informed consent	X	See next schedule	
Eligibility criteria/medical and medication history/demographics	X		
Physical examination ¹	X		
Clinical laboratory samples ²	X		
Urine HCG (females)	X		
Drugs of abuse screen	X		
Blood ethanol screen	X		
Hemodynamics ³	X		
Height and BMI	X		
Weight	X		
Supine respiratory rate			
Body temperature	X		
Supine 12-lead ECG	X		
Fast ⁴			
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			
			X
Airway management			
Assessment of adverse events and concomitant medication	X		X

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

1. Screening physical examination will include ASA-PS score.
2. Biochemistry, hematology.
3. Supine heart rate and systolic and diastolic BP.
4. Fast to begin from midnight of the day before dosing (no food or water).
5. In case there has been any indication for the onset of a new AE since discharge, patients should come back to the site immediately (preferably the same day) to perform further assessments (e.g. clinically laboratory tests, 12 lead ECG, left to the discretion of the investigator)

Day 1 – Assessments Based on Dosing Time

Procedures	Pre-dose				Dosing of trial medication ²	Post-dose												
	within 5 hr	within 30 min	within 15 min	within 1 min		1 min	1.5 min	2 min	2.5 min	3 min	5 min	10 min	Every 5 minutes until <u>fully alert</u>					
Medical & medication histories	X																	
Adverse events	X																	
Concomitant medication	X																	
Physical examination	x (B)																	
Weight	x (B)																	
Body temperature	x (B)	x											x (5min post procedure)	x (at fully alert)				x (at actual discharge)
Clinical laboratory tests	x (B)																	x (at least 3hrs after the procedure)
12-lead ECG ⁷	x (B)					x					x		x ⁷		x ⁷		x ⁷	x (at actual discharge)
3-lead ECG			xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
3-lead ECG documentation in CRF ⁶			x	x				x			x	x	x	x	x	x	x	x
Urine pregnancy test	X																	
Urine drug-of abuse test	X																	
Ethanol saliva test	X																	
Randomization	X																	
██████	████	████																

Procedures	Pre-dose				Dosing of trial medication ²	Post-dose												
	within 5 hr	within 30 min	within 15 min	within 1min		1 min	1.5 min	2 min	2.5 min	3 min	5 min	10 min	Every 5 minutes until <u>fully alert</u>					
Hemodynamic parameters (HR, BP) ^{8,9}	x	x	X (B)	X				x			x	x	x	x	x	x	x	x
0.9% NaCl infusion (up to 1,000 mL, if fluid status allows)		xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx until end of procedure						
MOAA/S ^{1,3}			x (B)			x	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, ⁹			x (B)	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
RR documentation in CRF			x (B)	x				x			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	xx
SpO ₂ documentation in CRF ^{8,9}			x (B)					x			x	x	x	x	x	x	x	x
Airway management assessment			x															
Supplemental O ₂			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 mcg q 5-10 min until adequate analgesia or 200 mcg maximum dose												
██████████	██████				██████████													
██████████				I				I			I	I	■		■	■	■	■
Readiness for discharge score ⁵													30		60			90

- NOTE:
1. Bronchoscopy starts at sufficient sedation (MOAA/S ≤3), duration as necessary (MOAA/S ≤4), at the discretion of the investigator.
 2. Trial medication: Loading dose of randomized study drug start defines t₀, supplemental doses as per protocol.
 3. See also schedules next page.
 4. If patient is capable, do not awake on purpose.
 5. 30, 60 90 min post dose t=0.
 6. Running a strip to document presence or absence of arrhythmias.
 7. After first dose, 5 mins after dosing and every 10 minutes until the end of the procedure if possible, and also 5 minutes after the end of the procedure and at discharge
 8. In addition to times specified above, blood pressure, heart rate & SpO₂ will be recorded immediately prior to, & two minutes after each additional dose of fentanyl
 9. Vital signs (heart rate, systolic & diastolic BP, respiratory rate and SpO₂) will be recorded when an AE with a respiratory or cardiovascular focus has been observed.
- (B) Baseline values, x single action, xx continuous action.

Day 1 – Further Assessments

Procedures	after fully alert							
	5 min.	10 min.	20 min.	30 min.	40 min.	50 min.	60 min.90 min.
MOAA/S	After fully alert every five minutes until ready for discharge, then every 10 min until actual discharge							
██████	█							
████		██████						
Time ready for discharge ¹	After end of procedure							

Procedures	after procedure
ECG (single)	5 min after end of procedure
Adverse Events	after procedure
Concomitant medication	after procedure
Documentation of airway management	after procedure
“Time back to normal” assessment	Day 2

Notes: ¹ Ability to walk unassisted. No attempt to prematurely awake patient. Walking 16 ft. (5 meters) on a straight line with turn back, documented by a blinded observer, or, if unable to walk, back to baseline state of mobility.

Appendix C Blood Sampling, Storage, and Shipping Instructions

Clinical Laboratory Tests

Clinical laboratory tests will be performed by [REDACTED]

- Hematology: Blood (3 mL) will be collected into a lavender-top tube.
- Biochemistry: Blood (7.5 mL) will be collected into a red/black marble-top tube.

Total Blood Sample Volume

Test	Volume/sample (mL)	Number of samples	Total volume/test (mL)
Hematology	3	3	9.0
Biochemistry	7.5	3	22.5
Total			31.5

[REDACTED]			
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]			

Appendix D Modified Observer's Assessment of Alertness and Sedation Scale

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

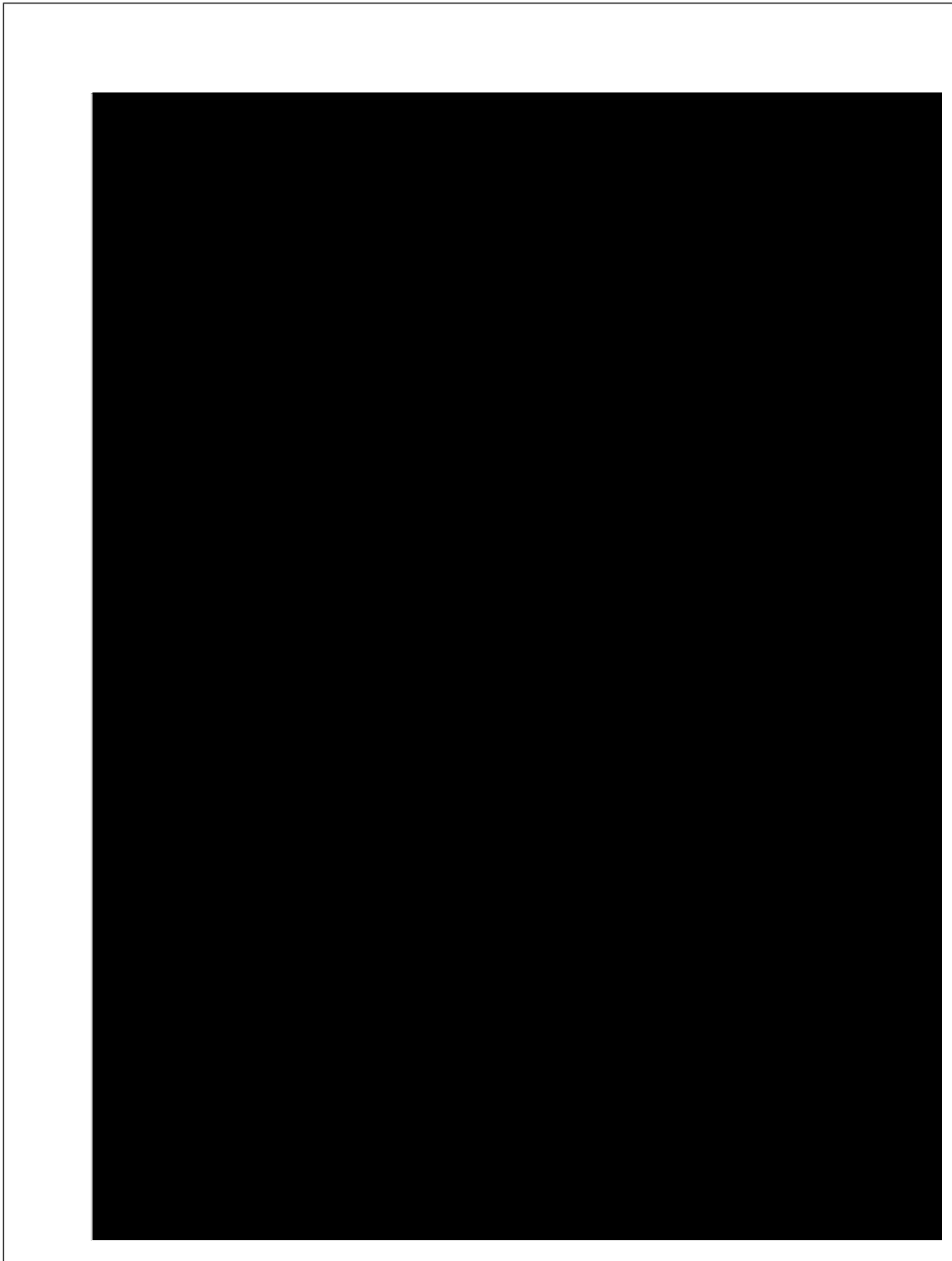
Cohen LB. Clinical trial: a dose-response study of fospropofol disodium for moderate sedation during colonoscopy. *Aliment Pharmacol Ther.* 2008 Apr 1; 27(7):597-608³⁰.

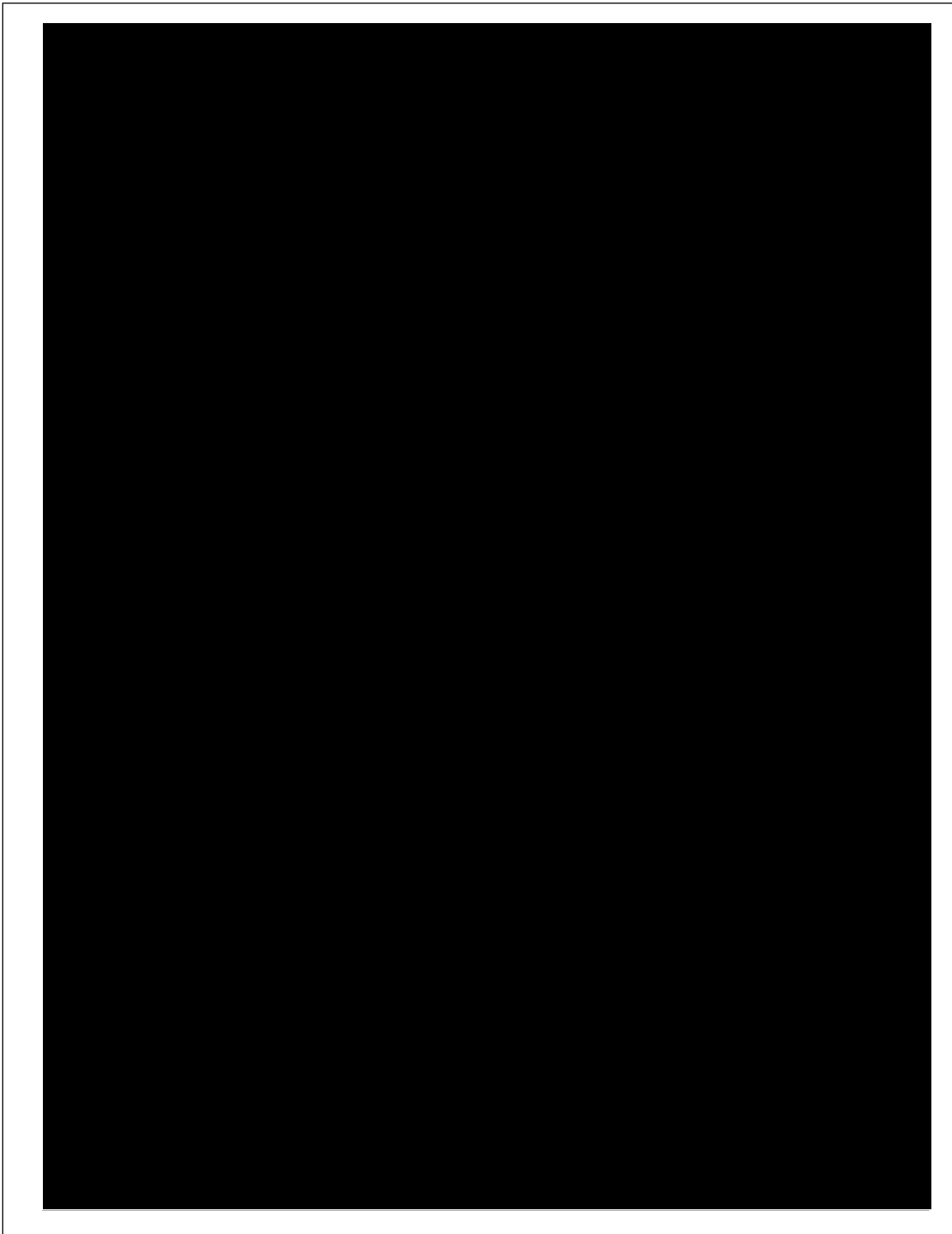
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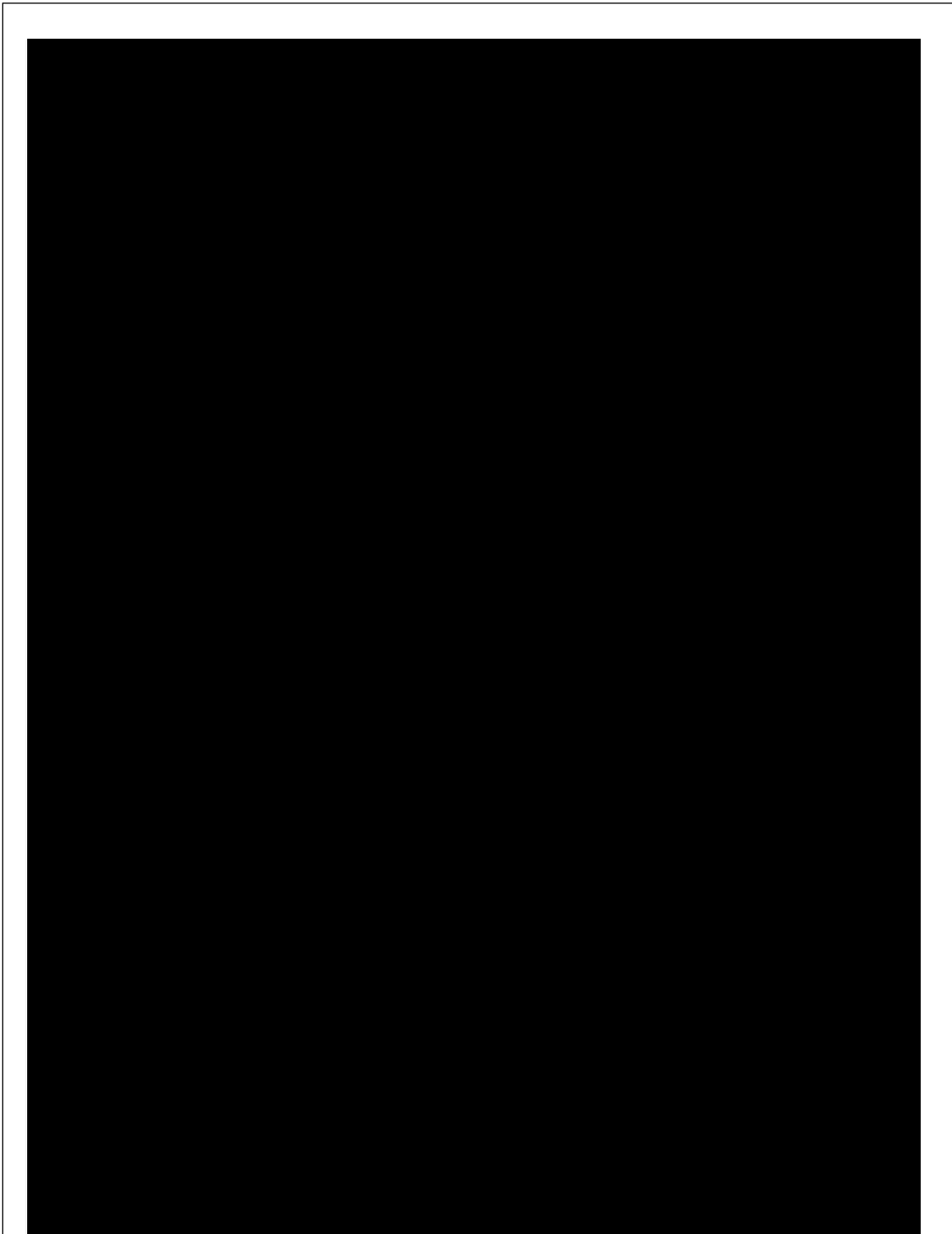
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[REDACTED]

[REDACTED]







[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]