16.1.9 Documentation of Statistical Methods

Paion UK Ltd., Statistical Analysis Plan, Final Version 1.0, dated 09-Jun-2017

Paion UK Ltd., Statistical Analysis Plan Tables Figures, Listing TOCs, Final Version 1.0, dated 09-Jun-2017

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STATISTICAL ANALYSIS PLAN

Title:	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
Compound:	Remimazolam
Phase:	III
Sponsor:	PAION UK Ltd
Author:	[redacted]
Date:	09 June 2017
Version:	Final 1.0

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STATISTICAL ANALYSIS PLAN APPROVALS

[redacted]

Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	Definition
χ^2	chi-squared
AE	Adverse event
AESI	Adverse event of special interest
ANOVA	Analysis of variance
ASA-PS	American Society of Anesthesiologists-Physical Status
ATC	Anatomical Therapeutic Class
AUC	Area under the curve
BP	Blood pressure
bpm	Beats per minute
BMI	Body mass index
CMH	Cochran-Mantel-Haenszel
CNS 7056B	CNS 7056 besylate
cm	Centimeter(s)
CM	Concomitant medication
CRF	Case report form
CS	Clinically significant
CSR	Clinical study report
CTA	Clinical Trial Agreement
ECG	Electrocardiogram
EMA	European Medicines Agency
ET	Early termination

Abbreviation	Definition
FDA	Food and Drug Administration
GCP	Good clinical practice
h	Hour(s)
[redacted]	[redacted]
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
ITT	Intent-to-treat
IWRS	Interactive web response system
kg	Kilogram(s)
LOCF	Last observation carried forward
LS	Least squares
max	maximum
µg	Microgram
mg	Milligram
min	Minute(s)
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
MOAA/S	Modified Observer's Assessment of Alertness and Sedation
MON	Month
NDA	New Drug Application
NRS	Numeric rating scale
PP	Per protocol

Abbreviation	Definition
QTc	Corrected QT interval
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System organ class
SpO_2	Peripheral blood oxygen saturation (measured by pulse oximetry)
TEAE	Treatment-emergent adverse event
TRTM	Month of start of study treatment
TRTY	Year of start of study treatment
USA	United States of America
[redacted]	[redacted]
yr	Year
YYYY	Year
WHO-DD	World Health Organization – Drug Dictionary

1 OVERVIEW

This document presents a detailed statistical analysis plan for the available data from Paion's protocol CNS7056-008, Amendment 5.0, dated 3 March 2016 (A Phase III Study Evaluating the Efficacy and Safety of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in Patients Undergoing Bronchoscopy).

Reference materials for this statistical plan include Protocol CNS7056-008 version 1.0 Amendment 5.0, dated 03-Mar-2016 and the accompanying SDTM and ADaM specification documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this statistical analysis plan (SAP) unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials [1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association [2] and the Royal Statistical Society [3], for statistical practice.

All planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analysis not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 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 to assess data from an additional open-label midazolam group in combination with fentanyl as determined by sedation success.

2.2 Secondary Objectives

Secondary objectives include assessing time to event endpoints (as described in detail under Section 2.3.1.2 Secondary Efficacy Endpoints).

2.3 Safety and Efficacy Endpoints

2.3.1 Efficacy Endpoints

2.3.1.1 Primary Efficacy Endpoints

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 in the blinded arms (remimazolam/placebo) or no requirement for more than 3 doses within any 12 minute window in the open-label midazolam arm.

2.3.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

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 end of bronchoscopy procedure (bronchoscope out).
4. The **time to ready for discharge** after the last injection of study drug.

5. 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)).

6. The **times to fully alert** (time to first of three consecutive MOAA/S scores of 5) after the last injection of study drug).

7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]
12. [redacted]
13. [redacted]
14. [redacted]

2.3.2 Safety Endpoints

Safety endpoints include:

1. Adverse events (AEs)

2. Clinical laboratory test results

3. Vital signs (supine heart rate, systolic and diastolic blood pressure (BP), calculated mean arterial pressure, respiration rate, temperature)

4. Pulse oximetry measurements (presented by patient for pre-defined time points, and as oxygen saturation over time (AUC))

5. Electrocardiogram (ECG) findings

6. Physical examination findings

7. [redacted]
8. [redacted]

9. [redacted]

10. The safety of multiple doses (initial dose and additional top-up doses) of remimazolam including oxygen saturation and no need for mechanical ventilation following administration of a standard dose of fentanyl.

2.3.3 [redacted]

[redacted]

3 OVERALL STUDY DESIGN AND PLAN

This study is a prospective, randomized, placebo and active controlled, multi-center, parallel group study comparing remimazolam to placebo in a double-blind manner, with an additional open-label midazolam arm, in patients undergoing bronchoscopy. 420 patients will be randomized into one of three possible study groups: placebo (n=60), midazolam (n=60), and remimazolam (n=300).

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 (first of three consecutive MOAA/S scores of 5).

Blinded arms:

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 (MOAA/S ≤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.

Open-label arm:

In the open-label midazolam arm, healthy adults <60 years 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 midazolam 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 years, 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.

3.1 Study Population

This is a study in patients undergoing a bronchoscopy for diagnostic or therapeutic purposes (e.g. biopsies, lavage, brushings, and foreign body extraction). 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.

3.2 Method of Assigning Patients to Treatment Groups

Before dosing, patients will be randomly assigned in a 30:6:6 ratio 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.

Randomization will be stratified by age group. The aim is to have at least 100 patients on remimazolam aged ≥ 65 years (at least 30 of these aged ≥ 75 years or older) across the three late stage clinical trials (CNS7056-006, CNS7056-008, and CNS7056-015). The CNS7056-008 study will be included as part of an integrated analysis plan where age group will be assessed as above.

On Study Day 1, after confirming that a patient still meets entry criteria, study personnel will inform the pharmacist that the patient qualifies for randomization. The unblinded pharmacist will call the central interactive web response system (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.

Group	**Trial medication**	**Initial dose + Top up dose**
Group 1 (N = 60)	Placebo	Volume to match group 2
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 years; §adults ≥60 years, debilitated or chronically ill patients.*		

3.3 Treatment Blinding

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 and [redacted] unblinded monitor until the study is completed. This exemption also applies to the data monitoring committee (DMC) members. The pharmacist and staff will not participate in other study procedures. Patients will be blinded to treatment.

3.4 Schedule of Assessments

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) following the bronchoscopy.

Screening (Day -21 to Day 1): 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. 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).Following completion of the bronchoscopy procedure, the patients will be discharged at the discretion of the investigator and complete the assessments after reaching fully alert status. Assessment of "time back to normal" in the patient's subjective view will be collected via telephone contact by study nurse on Day 2.

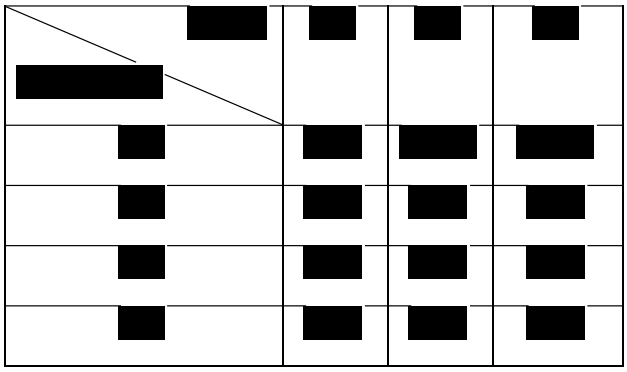
Follow-up (Day 4 [+3/-1 days]): The site will telephone the patient for safety assessments. Study participation is considered complete after all Day 4 assessments have been performed and all AEs have been followed-up until they resolve or become stable, or until they can be explained by another known 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 (e.g.clinically laboratory tests, 12 lead ECG, left to the discretion of the investigator).

3.5 Sample Size Calculation

[redacted]

[redacted]



[redacted]

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

4 ANALYSIS AND REPORTING

4.1 Software and general statistical methods

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.3 or higher) for Windows. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics.

For continuous variables, summary statistics including number of patients with data, mean, standard deviation (SD), median, minimum and maximum will be provided. For categorical variables, the number of patients and percentage for each category will be presented.

A blinded data review will be performed before the database is locked and the study groups are unblinded.

Study medication is defined as any of fentanyl or remimazolam, placebo or midazolam administered for the initial dosing or top-up doses.

Randomized study medication is defined as the Investigational Medicinal Product IMP (remimazolam, placebo or midazolam). The start of the initial dose of randomized study drug infusion will be considered Time 0 (t=0).

4.2 Interim Analyses and Data Monitoring

No interim analyses are planned for this study.

4.3 Final Analysis

All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the last study visit and end of study assessments, all relevant study data have been processed and integrated into the analysis data base, and the clinical database has been locked and the randomization code has been unblinded. In addition, no database may be locked, randomization code unblinded, or analyses completed until this SAP has been approved.

All statistics and study results will be made available to Paion after database lock and before completion of the final CSR.

5 ANALYSIS POPULATIONS

Eight analysis populations are defined:

- The Safety Population will consist of all randomized patients who receive any amount of study drug and will be analyzed as treated.
- [redacted]
- 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 randomised study medication. These will be analysed as randomized.
- 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 deviations

Protocol deviations to be considered are defined in the Protocol Deviation Guidance Plan.

Membership in the analysis populations will be determined before unblinding at the blinded data review meeting.

[redacted]

6 GENERAL ISSUES FOR STATISTICAL ANALYSIS

6.1 General Statistical Methodology

6.1.1 Adjustments for Multiple Comparisons

No adjustment for multiple testing is required for the primary endpoint as only one pairwise comparison will be performed between the remimazolam and placebo groups. Analyses of the remimazolam and placebo groups for all secondary parameters will be considered to be descriptive only as it is likely that most of the patients in the placebo group will have taken midazolam as rescue sedative medication. Therefore, these analyses will need to be interpreted with caution.

Comparison between the remimazolam and midazolam groups will be descriptive only, a 95% confidence interval of the difference will be presented but no further analysis will be performed.

6.1.2 Methods for Dropouts or Missing Data

[redacted]

Incomplete dates and times for AEs and concomitant medications will be imputed as described in section 6.1.5.5 below.

Time to event variables will be censored as described in section 6.2 below if the event did not occur.

6.1.3 Pooling of Centers

The study will include data from all centers.

Centers who recruit fewer than 20 patients will be pooled into one “Other” center.

6.1.4 Analysis Visit Windows

Analyses of all variables for this study will use the nominal visit or time point as collected in the case report form (CRF) and/or database.

6.1.5 Data Handling Conventions

6.1.5.1 Baseline Definitions

For all analyses, the baseline value is defined as the value recorded ‘Within 5 hrs’ or ‘Within 15 minutes’ before first dosing of study medication as shown in Appendix B Schedule of Assessments of the protocol. The most recent pre-dose value will be taken as baseline. Where a value is missing, the next previous value will be used.

The date/time of the first dose (t=0) for the efficacy analyses is defined as the start date/time of first administration of randomized study medication.

Change from baseline will be defined as the Value – Baseline.

6.1.5.2 Start Date, End Date of Study Treatment, and Study Day

The **start date of study treatment** is defined as the first date when study medication was taken (Day 1).

The **study day** for all assessments will be calculated using the start date of study treatment as the origin (Day 1):

study day = (date of assessment) – (start date of study treatment) + 1

For assessments/events with a date preceding the start date of study treatment, the following formula will be applied:

study day = (date of assessment) – (start date of study treatment)

6.1.5.3 Early Termination (ET) Visit

Patients who discontinue from the study after randomization and before the Day 4 visit should be scheduled for an ET visit during which all assessments listed for the Day 4 visit will be performed.

6.1.5.4 Unscheduled Visits

Data (such as laboratory tests and vital signs) collected at unscheduled visits will not be included in the analyses by scheduled visits, but may be used for baseline and for safety shift tables from baseline to most extreme value.

6.1.5.5 Incomplete Date and Time Imputation for Adverse Events and Concomitant Medications

For partial AE/concomitant medication (CM) start dates the imputation rules are described in the following table.

Partial start date		**Date imputation**
YYYY missing		No imputation
YYYY ≠ TRTY	MON missing	Imputed date = 01JANYYYY

Partial start date		**Date imputation**
YYYY ≠ TRTY	MON not missing, DAY missing	Imputed date = 01MONYYYY
YYYY = TRTY	MON missing	Imputed date = start date of study treatment
YYYY = TRTY	MON < TRTM, DAY missing	Imputed date = 01MONYYYY
YYYY = TRTY	MON ≥ TRTM, DAY missing	Imputed date = max (01MONYYYY, start date of study treatment)

YYYY=Year of AE/CM start date, MON=Month of AE/ CM start date, DAY=day of AE/ CM start date, TRTY=Year of start date of study treatment, TRTM=Month of start date of study treatment

For partial AE (or CM) end dates the imputation rules are defined as the following:

- If month or year of an AE (or medication) end date is missing, the AE (or medication) end date is set to the date of study completion/early termination.

- If day of an AE (or medication) end date is missing, but month and year of the AE (or medication) end date are not missing, the AE (or medication) end date is set to minimum of (end date of study treatment, last day of the month).

If an imputed AE (or CM) end date is earlier than the AE (or CM) start date, the AE (or CM) start date will be used as the imputed AE (or CM) end date.

After applying the rules above the following rules will be used to determine whether an AE is 'treatment emergent' or not and whether a medication is 'concomitant' or 'prior':

- If the start date is missing and the end date is either missing or on or after the start date of study treatment, then the AE (or medication) is considered to be treatment emergent (or concomitant).

- If the start time is missing and the start date is either on the same day as the start of study treatment or has been imputed as the same day as the start of study treatment, then the AE (or medication) is considered to be treatment emergent (or concomitant)

- If the start date is missing and the end date is before the start date of study treatment, then the AE (or medication) is considered to be not treatment emergent (or prior).

- If the start date is not missing and the end date is missing, then the medication is considered to be concomitant while the treatment emergent status is determined by the start date.

- If the start time in seconds is missing, then the seconds is replaced by a half-minute or 50 seconds.

6.1.6 By Patient Data Listings

All data available will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs, but will be included in the data listings.

6.2 Derived and Computed Variables

The following derived and computed variables have been initially identified as important for the analysis of the primary and secondary target variables. It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files. In all cases, incomplete dates will be completed for the analysis using a conservative/worst case solution.

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes, or Equation(s)
SUCCESS	Overall Success of the Bronchoscopy Procedure	1 = Yes 0 = No	SUCCESS = 1 if and only if all the following criteria are met: • Completion of the bronchoscopy procedure • No requirement for an alternative sedative medication • No requirement for more than 5 doses of study medication (these 5 doses may include the initial dose) within any rolling 15 minute window in the double-blind arms or no requirement for more than 3 doses within any rolling 12 minute window in the open midazolam arm. Otherwise SUCCESS = 0 The criterion of no more than 5 doses for a 15 minute window means that if any dose has a further 4 doses within the following 900 seconds inclusive, then SUCCESS = 0. The criterion for 3 doses within 12 minutes is defined similarly.
T2START	Time to start of procedure		T2START=1 + (start time of procedure) - (first dose of randomized study medication start time) in minutes For patients who do not start a procedure, this time will be censored at the time of dropout.
CENSOR2TS	Censor indicator for time to start of procedure	1 = Yes 0 = No	If T2START was censored, CENSOR2TS = 1, else CENSOR2TS = 0.

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes, or Equation(s)
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
T2FAP	Time to Fully Alert after the end of the procedure		T2FAP = 1 + (time fully alert achieved) – (end time of procedure) in minutes, if patient reaches fully alert. Fully alert is defined as the first of three consecutive MOAA/S measurements of 5 after the end of the procedure. If a patient withdraws early, and/or does not reach Fully Alert at the end of the study, the patient's T2FAP will be censored using a patient's last MOAA/S assessment date.
CENSORAP	Censor Indicator for Fully Alert after the end of the procedure	1 = Yes 0 = No	If T2FAP was censored: CENSORAP=1; Else CENSORAP=0.
T2FAD	Time to Fully Alert from the end of the last dose of study drug or rescue sedative drug		T2FAD = 1+ (time fully alert achieved) – (end time of last dose of randomized study medication or rescue sedative medication) in minutes, if patient reaches fully alert. Fully Alert is defined as the first of three consecutive MOAA/S measurements of 5 after the start time of the last dose of study or rescue drug. If a patient withdraws early, and/or does not reach Fully Alert at the end of the study, the patient's T2FAD will be censored using a patient's last MOAA/S assessment.
CENSORAD	Censor Indicator for Fully Alert from the end of the last dose of study drug	1 = Yes 0 = No	If T2FAD was censored: CENSORAD=1; Else CENSORAD=0.

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes, or Equation(s)
T2RDB	Time to Ready for Discharge from the end of bronchoscopy procedure		T2RDB = 1 + (time ready for discharge) – (end time of bronchoscopy procedure) in minutes, if patient is ready for discharge. Ready for discharge is defined as ready to walk unassisted. If a patient withdraws early, and/or does not reach Ready for Discharge at the end of the study, the patient's T2RDB will be censored using the patient's last assessment.
CENSORDB	Censor Indicator for Ready for Discharge from the end of bronchoscopy procedure	1 = Yes 0 = No	If T2RDB was censored: CENSORDB = 1; Else CENSORDB = 0.
T2RDD	Time to Ready for Discharge from the end of the last dose of study drug.		T2RDD = 1 + (time ready for discharge) – (end time of last dose of randomized study medication or rescue sedative medication) in minutes, if patient is ready for discharge. Ready for discharge is defined as ready to walk unassisted. If a patient withdraws early, and/or does not reach Ready for Discharge at the end of the study, the patient's T2RDD will be censored using the patient's last assessment.
CENSORDD	Censor Indicator for Ready for Discharge from the end of the last dose of study drug.	1 = Yes 0 = No	If T2RDD was censored: CENSORDB = 1; Else CENSORDB = 0.
[redacted]	[redacted]		[redacted]

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes, or Equation(s)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
HRNADC	Lowest post-dose value of Heart Rate		Lowest recorded post-dose value of Heart Rate in CRF on treatment day
RRNADC	Lowest post-dose value of Respiratory Rate		Lowest recorded post-dose value of Respiratory Rate in CRF on treatment day

Variable Name	Description	Valid Values (Ranges)	Computation Methods, Notes, or Equation(s)
OXYNADC	Lowest post-dose value of SpO2		Lowest recorded post-dose value of SPO2 in CRF on treatment day
RRPEAK	Peak post-dose value of Respiratory Rate		Highest recorded post-dose value of Respiratory Rate in CRF on treatment day.
HRNADN	Lowest post-dose value of Heart Rate		Lowest value of Heart Rate from Nellcor data on treatment day in the interval between the first dose of study medication and the time when the patient becomes fully alert
RRNADN	Lowest post-dose value of Respiratory Rate		Lowest value of Respiratory Rate from Nellcor data on treatment day in the interval between the first dose and the time when the patient becomes fully alert
OXYNADN	Lowest post-dose value of SpO2		Lowest value of SpO2 from Nellcor data on treatment day in the interval between the first dose and the time when the patient becomes fully alert
RRPEAKN	Peak post-dose value of Respiratory Rate		Highest value of Respiratory Rate from Nellcor data on treatment day in the interval between the first dose and the time when the patient becomes fully alert
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

7 STUDY PATIENTS AND DEMOGRAPHICS

7.1 Disposition of Patients and Withdrawals

The number of patients included in each analysis set (Safety, each Safety [Nellcor], ITT, mITT, PP) will be presented by treatment group and overall.

The number and percentage of patients who completed the study treatment period, who discontinued the study prior to the end of treatment and the reason for discontinuation, along with the number who completed the Follow-up Visit will be presented for each treatment group and overall, using the safety population.

All disposition summaries will also be presented by study center.

7.2 Protocol Deviations

A list of protocol deviations that could affect the primary objective will be identified by the Clinical and Medical Monitors. This list will be finalized prior to database lock and unblinding of the study. The incidence of each protocol deviation will be presented for the ITT population.

7.3 Demographics and Baseline Characteristics

Demographics variables and baseline characteristics will be summarized for the safety population overall and by treatment group.

Demographic variables will include age, sex, race, ethnicity, height, weight, and body mass index (BMI). Baseline patient characteristics will include ASA status, physical examination findings, medical history, vital signs, clinical laboratory test results, and 12-lead ECG. Baseline patient characteristics will include prior medications.

7.4 Medical History

The number and percentage of patients with at least one medical history item in each System Organ Class (SOC) and preferred term will be presented overall and by treatment group, using the safety population.

8 EFFICACY ANALYSIS

8.1 Primary Efficacy

8.1.1 Primary Efficacy Endpoint

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. For midazolam only: no requirement of more than 3 doses within any 12 minute window. (See section 6.2 for definition of how doses within a window are defined.)

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.

8.1.2 Primary Analysis

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

Comparison of remimazolam and placebo

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

$$H0: \pi_{Remi} \leq \pi_{PLA} \text{ vs. } H1: \pi_{Remi} > \pi_{PLA},$$

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 [redacted]

[redacted]

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.*Comparison of remimazolam and midazolam*

A 95% confidence interval of the comparison of success rates between midazolam and remimazolam will be presented but there will be no significance testing.

8.1.3 [redacted]

- [redacted]
- [redacted]
- [redacted]

8.2 Secondary Efficacy

The following secondary efficacy variables will be presented with descriptive statistics by treatment group:

1. The **time to start of procedure** after administration of the first dose of randomized study medication.
2. [redacted]
3. The **time to ready for discharge** (defined as ability to walk unassisted) after the end of bronchoscopy procedure (bronchoscope out).
4. The **time to ready for discharge** (defined as ability to walk unassisted) after the last injection of study drug.
5. The **time to fully alert** (time to first of three consecutive MOAA/S scores of 5) after the end of bronchoscopy procedure (bronchoscope out)).
6. The **time to fully alert** (time to first of three consecutive MOAAA/S scores of 5) after the last injection of study drug).

7. [redacted]
8. [redacted]
9. [redacted]
10. [redacted]
11. [redacted]
12. [redacted]
13. [redacted]
14. [redacted]

All secondary efficacy variables will be compared between the three treatment groups. For the key secondary variables (variables 1-6), only the pairwise comparison between placebo and remimazolam will be used for exploratory efficacy significance testing. The time to event variables (variables 1-6, 13 above) will be analyzed by the logrank test. Kaplan-Meier graphs will also be fitted for each treatment group. Patients who do not reach fully alert will be censored at the time of their last MOAA/S assessment. Patients who do not reach ready for discharge criteria will be censored at the time of their last assessment. Median time to event with the corresponding 95% confidence interval will be presented. Additional quartiles (25% and 75%) and confidence intervals will be presented. A Cox's proportional hazard model including age group (<65, ≥65) will be fitted separately to the remimazolam and placebo, and the remimazolam and midazolam groups and the 95% confidence interval of the hazard ratio will be presented

[redacted]

For the Readiness for Discharge score (variable 10) a value of 100 (= immediate readiness for discharge) will be used if the patient has already been discharged at the defined timepoint of analysis.

[redacted]

As a measure of discharge readiness, the proportion of the readiness for discharge score at 30, 60 and 90 minutes after t=0 will be compared across the treatment groups.

9 SAFETY AND TOLERABILITY ANALYSIS

All safety analyses will be performed on the Safety Population, apart from the analyses of the Nellcor data which will use the Safety (Nellcor) populations.

All safety variables will be summarized descriptively. No statistical inference will be applied to the safety variables.

Safety variables that will be analyzed as safety endpoints include

- AEs, including adverse events with focus on respiratory and cardiovascular parameters and prolonged sedation (see Appendix A) and AEs potentially related to abuse (see Appendix D)
- Concomitant medication
- Clinical laboratory test results
- Vital signs (supine heart rate, systolic, diastolic and mean BP, respiration rate, temperature)
- Pulse oximetry measurements
- 12-lead and 3-lead ECG findings
- Physical examination finding
- [redacted]

9.1 Adverse Events

Treatment-emergent AEs (TEAEs) are defined as AEs reported at or after the start time of initial fentanyl administration or IMP, whatever is earlier, 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). Pretreatment 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 maximum severity and strongest relationship to study drug will also be provided.

Summaries of serious adverse events (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.

At each level of summarization (SOC or preferred term) a patient will be counted only once at the most severe or most related category. Patients with missing severity or relationship will be counted in the most severe and related category.

In addition, tachycardia (defined as heart rate recorded as >100 bpm, or an increase of 20% or more in the heart rate from baseline) will be analyzed.

9.1.1 [redacted]

The number and percentage of patients with AEs with a respiratory or cardiovascular focus will be displayed for each treatment group by system organ class (SOC) and preferred term, and also by standardised MedDRA query (SMQ) and preferred term. The preferred terms relating to these are shown in Appendix A.

The related AEs with a respiratory or cardiovascular focus will be displayed for each treatment group by system organ class and preferred term.

The AEs with a respiratory or cardiovascular focus will be summarized split by time of onset (Day 1, after Day 1).The vital signs observed when a patient experienced a respiratory-cardiovascular AE will be summarized. The frequency of vital signs falling outside the normal range (as defined in the AE definitions above) will be given.

Interventions taken to prevent or treat these AEs are collected in the CRF. The number of patients requiring intervention and the type of interventions will be summarized.

9.1.5.1 [redacted]

[redacted]

9.1.2 [redacted]

[redacted]

9.2 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.

9.3 Vital Signs, 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 (SpO_2) will be presented by patient for pre-defined time points, and as the area under the oxygen desaturation curve (AUC_{Desat}) over time from 1 minute before the first dose of randomized study drug to fully alert (AUC_{alert}) and from 1 minute pre-dose to 20 minutes post dose (AUC_{20min}). Desaturation is defined as an SpO_2 below 90%.

Descriptive statistics 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 SpO_2 findings that were considered AEs by the Investigator will be presented by treatment in the AE summaries. The number of heart rate and SpO_2 findings (defined as being under the threshold value) that were not considered AEs as they did not meet the duration criteria will be presented by treatment, along with the duration.

The nadirs of heart rate, respiratory rate, and SpO_2, after the first dose of randomized study drug of the data recorded in the CRF on the treatment day will be calculated and summarized by treatment group.

9.3.1 Continuous Monitoring

The data from the Nellcor device used to perform continuous monitoring of heart rate, respiratory rate and SpO_2 (taken every second) during the procedure will be downloaded for analysis. All analyses of the Nellcor data will use the Safety (Nellcor) Populations.

The observational period will be from the first dose of any study medication (Fentanyl or IMP) until fully alert on the treatment day. Baseline will be defined as the pre-treatment values recorded in the CRF.

The nadirs and the peak for respiratory rate in the observational period will be identified and summarized by treatment group. If a “0” occurs then these values will be treated as missing data. Similarly, nadirs of heart rate and SpO_2 will be identified and summarized by treatment group.

All episodes of hypoxia (SpO2 <90%), bradycardia (heart rate <40 bpm), HR decreased (a drop in heart rate of 20% or more from baseline), respiratory depression (<8 breaths per minute) and respiratory increase (increase to >25 breaths per minute) in the observational period will be identified from the continuously recorded data. In addition, tachycardia (heart

rate >100 bpm or increase of heart rate of 20% or more from baseline) will be analyzed. The number of patients reporting each type of AE and the duration will be summarized.

Further, those episodes of hypoxia, bradycardia or HR decreased which last long enough to match the protocol definitions of an AE above will be identified. The number of patients reporting episodes with a duration matching the AE definition and the number of patients with episodes with a duration that does not match the AE definition will be summarized, along with a summary of the durations of the episodes. Subgroup analyses of those AEs will be done as described in section 9.1.1 above.

The sites were asked whether they agreed that AEs identified in this way were actually AEs and whether they had been clinically observed and recorded in the CRF. The number of patients reporting each type of episode will be summarized by whether the investigator agreed.

9.3.2 Continuous Monitoring – Exploratory Analyses

Further, exploratory analyses of the data collected with the Nellcor device may also be done after the main analyses of this study, and if so, those analyses will be described in a separate Exploratory SAP.

9.4 Electrocardiograms

9.4.1 12-Lead ECG

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, RR interval, QRS interval, QT interval, and QT_C interval [corrected using the Bazett and Fridericia formulae]), descriptive statistics will be given for the values themselves as well as for change from baseline, by treatment group at each time point.

9.4.2 3-Lead ECG

The number and percentage of patients with normal and abnormal 3 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.

All episodes of bradycardia or other arrhythmias, captured in continuous 3-lead ECG recording, and any interventions that were instituted, will be documented and analyzed regardless of whether or not the event had been reported as an adverse event.

9.5 Physical Examinations

The number and percentage of patients with normal and abnormal physical examination findings will be displayed for each body system and treatment group at each time point.

Additionally, patients with normal physical examination findings at baseline and abnormal physical examination findings at each time point will also be summarized by treatment group.

9.6 [redacted]

[redacted]

9.7 Prior and Concomitant Medications

9.7.1 Prior and Concomitant Medications

Prior and concomitant medication analyses will be provided for the safety population. Data on sedation rescue medication (which should only be midazolam) will be collected and presented separately from concomitant therapy as described in section 9.7.2.

All prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD) Version March 2015. Prior medications are defined as any medications taken prior to the start date of study treatment (whether stopped or continued after the start date of study treatment). Concomitant medications are defined as those used between the start date of study medication and the date of study completion or early termination. A medication could be flagged both as prior and concomitant if it was started prior to the patient's start date and continued on or after the start date of study medication.

Prior and concomitant medications will be summarized by treatment group in separate tables. Medications will be presented in alphabetical order, by Anatomical Therapeutic Class (ATC) (ATC Level 4) and preferred term. Tables will also show the overall number and percentage of patients receiving at least one medication. At each level of summarization (ATC class or preferred term) patients will be counted only once.

9.7.2 Rescue Sedative Medications

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. The patient should also receive flumazenil as a reversal medication in case of remimazolam or midazolam overdose, or naloxone as a fentanyl antagonist. The number and percentage of patients receiving it will be summarized for all patients in the safety population by treatment group. A patient reporting rescue medication more than once will be counted once when calculating the number and percentage of patients.

9.8 [redacted]

The number of patients where the number of doses of double-blind IMP was more than 5 within any 15 minute window or more than 3 doses within any 12 minute window in the midazolam arm will be considered a treatment failure, and will be calculated and summarized by treatment group.

10 [redacted]

[redacted]

11 REFERENCES

1. US Department of Health and Human Services. International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Rockville, MD: September 16, 1998. Federal Register;63(179):49583-49598..
2. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm
3. The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.

12 ATTACHMENTS

The table shells will be attached in a separate document.

[redacted]

APPENDIX A: Details of AEs with a Respiratory or Cardiovascular Focus

LOW OXYGEN SATURATION/RESPIRATORY DEPRESSION

SMQ: *Acute Central Respiratory Depression*

Acute central respiratory depression (SMQ) [20000116]

Name	Code	Level	Scope
Acute respiratory failure	10001053	PT	Narrow
Apnoea	10002974	PT	Narrow
Apnoea neonatal	10002976	PT	Narrow
Apnoeic attack	10002977	PT	Narrow
Bradypnoea	10006102	PT	Narrow
Breath holding	10006322	PT	Narrow
Breath sounds abnormal	10064780	PT	Narrow
Breath sounds absent	10062285	PT	Narrow
Central-alveolar hypoventilation	10007982	PT	Narrow
Hypopnoea	10021079	PT	Narrow
Hypoventilation	10021133	PT	Narrow
Hypoventilation neonatal	10021134	PT	Narrow
Neonatal respiratory arrest	10028968	PT	Narrow
Neonatal respiratory depression	10028970	PT	Narrow
Neonatal respiratory failure	10028975	PT	Narrow
Postoperative respiratory failure	10072651	PT	Narrow
Respiratory arrest	10038669	PT	Narrow
Respiratory depression	10038678	PT	Narrow

Acute central respiratory depression (SMQ) [20000116]

Respiratory depth decreased	10038681	PT	Narrow
Respiratory failure	10038695	PT	Narrow
Respiratory paralysis	10038708	PT	Narrow
Respiratory rate decreased	10038710	PT	Narrow
Alveolar oxygen partial pressure abnormal	10068420	PT	Broad
Alveolar oxygen partial pressure decreased	10068419	PT	Broad
Anoxia	10002660	PT	Broad
Apnoea test abnormal	10074913	PT	Broad
Asphyxia	10003497	PT	Broad
Bilevel positive airway pressure	10064530	PT	Broad
Blood gases abnormal	10005539	PT	Broad
Blood pH abnormal	10005705	PT	Broad
Blood pH decreased	10005706	PT	Broad
Capnogram abnormal	10067661	PT	Broad
Carbon dioxide abnormal	10064156	PT	Broad
Carbon dioxide increased	10007225	PT	Broad
Cardiac arrest	10007515	PT	Broad
Cardiac arrest neonatal	10007516	PT	Broad
Cardiopulmonary failure	10051093	PT	Broad
Cardio-respiratory arrest	10007617	PT	Broad
Cardio-respiratory arrest neonatal	10007618	PT	Broad
Cardio-respiratory distress	10049874	PT	Broad
Cheyne-Stokes respiration	10008501	PT	Broad
Continuous positive airway pressure	10052934	PT	Broad
Cyanosis	10011703	PT	Broad

Acute central respiratory depression (SMQ) [20000116]

Cyanosis central	10011704	PT	Broad
Death neonatal	10011912	PT	Broad
Dependence on respirator	10057482	PT	Broad
Dyspnoea	10013968	PT	Broad
End-tidal CO2 abnormal	10067663	PT	Broad
End-tidal CO2 decreased	10067665	PT	Broad
Hyperbaric oxygen therapy	10057480	PT	Broad
Hypercapnia	10020591	PT	Broad
Hypercapnic coma	10072597	PT	Broad
Hypoxia	10021143	PT	Broad
Intermittent positive pressure breathing	10052959	PT	Broad
Life support	10024447	PT	Broad
Mechanical ventilation	10067221	PT	Broad
Mechanical ventilation complication	10066821	PT	Broad
Neonatal anoxia	10028921	PT	Broad
Neonatal asphyxia	10028923	PT	Broad
Neonatal hypoxia	10050081	PT	Broad
Neonatal respiratory acidosis	10028966	PT	Broad
Neonatal respiratory distress syndrome prophylaxis	10054933	PT	Broad
Oxygen saturation abnormal	10033317	PT	Broad
Oxygen saturation decreased	10033318	PT	Broad
Oxygen saturation immeasurable	10051197	PT	Broad
Oxygen supplementation	10050322	PT	Broad
PaO2/FIO2 ratio decreased	10065413	PT	Broad
PCO2 abnormal	10058982	PT	Broad

Acute central respiratory depression (SMQ) [20000116]

PCO2 increased	10034183	PT	Broad
PO2 abnormal	10062087	PT	Broad
PO2 decreased	10035768	PT	Broad
Positive end-expiratory pressure	10059890	PT	Broad
Respiration abnormal	10038647	PT	Broad
Respiratory acidosis	10038661	PT	Broad
Respiratory disorder	10038683	PT	Broad
Respiratory disorder neonatal	10061484	PT	Broad
Respiratory distress	10038687	PT	Broad
Respiratory fume inhalation disorder	10061485	PT	Broad
Respiratory gas exchange disorder	10062105	PT	Broad
Respiratory therapy	10059828	PT	Broad
Sleep apnoea syndrome	10040979	PT	Broad
Venous oxygen partial pressure abnormal	10068424	PT	Broad
Venous oxygen partial pressure decreased	10068423	PT	Broad
Venous oxygen saturation abnormal	10068428	PT	Broad
Venous oxygen saturation decreased	10068427	PT	Broad
Ventilation perfusion mismatch	10069675	PT	Broad
Ventilation/perfusion scan abnormal	10047265	PT	Broad
Wean from ventilator	10056353	PT	Broad
Weaning failure	10066829	PT	Broad

BRADYCARDIA:

- Bradyarrhythmias (incl conduction defects and disorders of sinus node function, SMQ):
  Bradyarrhythmia
- Conduction defects (SMQ)**:**
  Atrial conduction time prolongation, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, atrioventricular dissociation, Bifascicular block, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Conduction disorder, Defect conduction intraventricular, Electrocardiogram PQ interval prolonged, Electrocardiogram PR prolongation, Electrocardiogram QRS complex prolonged, Electrocardiogram QT prolonged, Long QT syndrome, Sinoatrial block, Trifascicular block, heart rate decreased
- Disorders of sinus node function (SMQ):

  Sinus arrest, Sinus bradycardia, Sinus node dysfunction,

Should add: *PT Bradycardia*

HYPOTENSION:

- PTs: *Blood pressure ambulatory decreased, blood pressure decreased, blood pressure diastolic decreased, blood pressure orthostatic decreased, blood pressure systolic decreased, mean arterial pressure decreased, pulmonary arterial pressure decreased, diastolic hypotension, hypotension, orthostatic hypotension, procedural hypotension, vasoplegia syndrome, orthostatic intolerance, presyncope, syncope*

HYPERTENSION:

SMQ: *Hypertension*

Hypertension (SMQ) [20000147]

Name	Code	Level	Scope
Accelerated hypertension	10000358	PT	Narrow
Blood pressure ambulatory increased	10005732	PT	Narrow
Blood pressure diastolic increased	10005739	PT	Narrow
Blood pressure inadequately controlled	10051128	PT	Narrow
Blood pressure increased	10005750	PT	Narrow
Blood pressure management	10063926	PT	Narrow
Blood pressure orthostatic increased	10053355	PT	Narrow
Blood pressure systolic increased	10005760	PT	Narrow
Diastolic hypertension	10012758	PT	Narrow
Eclampsia	10014129	PT	Narrow
Endocrine hypertension	10057615	PT	Narrow
Essential hypertension	10015488	PT	Narrow
Gestational hypertension	10070538	PT	Narrow
HELLP syndrome	10049058	PT	Narrow
Hyperaldosteronism	10020571	PT	Narrow
Hypertension	10020772	PT	Narrow
Hypertension neonatal	10049781	PT	Narrow
Hypertensive angiopathy	10059238	PT	Narrow
Hypertensive cardiomegaly	10020801	PT	Narrow

Hypertension (SMQ) [20000147]

Hypertensive cardiomyopathy	10058222	PT	Narrow
Hypertensive cerebrovascular disease	10077000	PT	Narrow
Hypertensive crisis	10020802	PT	Narrow
Hypertensive emergency	10058179	PT	Narrow
Hypertensive encephalopathy	10020803	PT	Narrow
Hypertensive heart disease	10020823	PT	Narrow
Hypertensive nephropathy	10055171	PT	Narrow
Labile hypertension	10049079	PT	Narrow
Malignant hypertension	10025600	PT	Narrow
Malignant hypertensive heart disease	10025603	PT	Narrow
Malignant renal hypertension	10026674	PT	Narrow
Maternal hypertension affecting foetus	10026924	PT	Narrow
Mean arterial pressure increased	10026985	PT	Narrow
Metabolic syndrome	10052066	PT	Narrow
Neurogenic hypertension	10067598	PT	Narrow
Orthostatic hypertension	10065508	PT	Narrow
Page kidney	10076704	PT	Narrow
Pre-eclampsia	10036485	PT	Narrow
Prehypertension	10065918	PT	Narrow
Procedural hypertension	10062886	PT	Narrow
Renal hypertension	10038464	PT	Narrow
Renal sympathetic nerve ablation	10074864	PT	Narrow
Renovascular hypertension	10038562	PT	Narrow
Retinopathy hypertensive	10038926	PT	Narrow
Secondary aldosteronism	10039808	PT	Narrow

Hypertension (SMQ) [20000147]

Secondary hypertension	10039834	PT	Narrow
Systolic hypertension	10042957	PT	Narrow
Withdrawal hypertension	10048007	PT	Narrow
Aldosterone urine abnormal	10061625	PT	Broad
Aldosterone urine increased	10001653	PT	Broad
Angiotensin converting enzyme increased	10049530	PT	Broad
Angiotensin I increased	10002488	PT	Broad
Angiotensin II increased	10002495	PT	Broad
Blood aldosterone abnormal	10005294	PT	Broad
Blood aldosterone increased	10005296	PT	Broad
Blood catecholamines abnormal	10005412	PT	Broad
Blood catecholamines increased	10005414	PT	Broad
Blood pressure abnormal	10005728	PT	Broad
Blood pressure ambulatory abnormal	10005730	PT	Broad
Blood pressure diastolic abnormal	10005736	PT	Broad
Blood pressure fluctuation	10005746	PT	Broad
Blood pressure orthostatic abnormal	10053354	PT	Broad
Blood pressure systolic abnormal	10005757	PT	Broad
Catecholamines urine abnormal	10061747	PT	Broad
Catecholamines urine increased	10061034	PT	Broad
Diuretic therapy	10053073	PT	Broad
Ectopic aldosterone secretion	10014148	PT	Broad
Ectopic renin secretion	10014171	PT	Broad
Epinephrine abnormal	10061845	PT	Broad
Epinephrine increased	10015064	PT	Broad

Hypertension (SMQ) [20000147]

Labile blood pressure	10023533	PT	Broad
Metanephrine urine abnormal	10062193	PT	Broad
Metanephrine urine increased	10027445	PT	Broad
Non-dipping	10065226	PT	Broad
Norepinephrine abnormal	10061874	PT	Broad
Norepinephrine increased	10029752	PT	Broad
Normetanephrine urine increased	10049097	PT	Broad
Pseudoaldosteronism	10037113	PT	Broad
Renin abnormal	10038556	PT	Broad
Renin increased	10038559	PT	Broad
Renin-angiotensin system inhibition	10049415	PT	Broad
Tyramine reaction	10067895	PT	Broad

PROLONGED SEDATION

SMQ: *Anticholinergic Syndrome plus single PTs*

Anticholinergic syndrome (SMQ) [20000048]

Name	Code	Level	Scope
Anticholinergic syndrome	10002757	PT	Narrow
Ataxia	10003591	PT	Broad
Autonomic nervous system imbalance	10003840	PT	Broad
Balance disorder	10049848	PT	Broad
Coordination abnormal	10010947	PT	Broad
Depressed level of consciousness	10012373	PT	Broad
Dizziness	10013573	PT	Broad
Hyporesponsive to stimuli	10071552	PT	Broad
Loss of consciousness	10024855	PT	Broad
Presyncope	10036653	PT	Broad
Sedation	10039897	PT	Broad
Slow response to stimuli	10041045	PT	Broad
Somnolence	10041349	PT	Broad
Stupor	10042264	PT	Broad
Agitation	10001497	PT	Broad
Confusional state	10010305	PT	Broad
Delirium	10012218	PT	Broad
Disorientation	10013395	PT	Broad
Hallucination	10019063	PT	Broad

Anticholinergic syndrome (SMQ) [20000048]

Hallucination, auditory	10019070	PT	Broad
Hallucination, gustatory	10019071	PT	Broad
Hallucination, olfactory	10019072	PT	Broad
Hallucination, synaesthetic	10062824	PT	Broad
Hallucination, tactile	10019074	PT	Broad
Hallucination, visual	10019075	PT	Broad
Hallucinations, mixed	10019079	PT	Broad
Restlessness	10038743	PT	Broad
Thinking abnormal	10043431	PT	Broad
Abasia	10049460	PT	Broad
Accommodation disorder	10000389	PT	Broad
Anhidrosis	10002512	PT	Broad
Blindness transient	10005184	PT	Broad
Cycloplegia	10011719	PT	Broad
Dry eye	10013774	PT	Broad
Dry mouth	10013781	PT	Broad
Dysphagia	10013950	PT	Broad
Gait disturbance	10017577	PT	Broad
Hemifacial anhidrosis	10075470	PT	Broad
Hyperaemia	10020565	PT	Broad
Hyperpyrexia	10020741	PT	Broad
Hypohidrosis	10021013	PT	Broad
Mydriasis	10028521	PT	Broad
Pyrexia	10037660	PT	Broad
Tachycardia	10043071	PT	Broad

Anticholinergic syndrome (SMQ) [20000048]

Thirst	10043458	PT	Broad
Toxicity to various agents	10070863	PT	Broad
Urinary retention	10046555	PT	Broad
Vision blurred	10047513	PT	Broad
Visual acuity reduced	10047531	PT	Broad
Visual acuity reduced transiently	10047532	PT	Broad

Add PTs: *Sedation, Post-injection delirium sedation syndrome, Reversal of sedation*

APPENDIX B: Diseases of Interest for Drug-Disease Interaction Analysis

Disease	**Preferred Terms**
Congestive Heart Failure	Cardiac failure (SMQ)
Arterial Hypertension	Hypertension (SMQ)
Coronary artery disease	Ischaemic heart disease (SMQ), including both Myocardial infarction (SMQ) and Other ischaemic heart disease (SMQ) In addition other coronary artery diseases, not related with ischaemic heart disease include: Arteritis coronary, Coronary artery aneurysm, Coronary artery perforation, Coronary artery dilatation, Coronary artery stent removal, Chest discomfort, and Chest pain.
Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease, Bronchitis chronic, Infective exacerbation of chronic obstructive airways disease, asthma.
Pre-existing mental impairment (e.g. dementia)	Mental disability, Mental retardation, Mild mental retardation, Moderate mental retardation, Profound mental retardation, Severe mental retardation, Mental status changes postoperative, Mental disorder due to a general medical condition. Dementia (SMQ) Psychosis and psychotic disorders (SMQ)
Gastrointestinal disorder	GI non-specific inflammation and dysfunctional conditions (SMQ) and GI perforation, ulceration, haemorrhage or obstruction (SMQ)

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]