28 January 2021
EMA/160756/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Byfavo

International non-proprietary name: remimazolam

Procedure No. EMEA/H/C/005246/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

(c)GMP	(current)Good Manufacturing Practices
AET	Analytical Evaluation Threshold
API	Active Pharmaceutical ingredient
AR	Assessment report
ASMF	Active Substance Master File
BHT	Butylated hydroxytoluene
BIS	Bispectral index score
CAS	Chemical Abstracts Service
CES	Carboxylesterase
CES-1A	Carboxylesterase-1A
CFU	Colony Forming Unit
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Maximum Plasma Concentration
CPP	Critical process parameters
CTD	Common Technical Document
CYP	Cytochrome P450
DP	Drug product
DS	Drug substance
DSC	Differential scanning calorimetry
EC	European Commission
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
ETO	Ethylene oxide
EU	European Union
FDA	US Food and Drug Administration
FT-IR	Fourier Transform Infrared Spectroscopy
GABAA	Gamma Amino Butyric Acid Type A
GC	Gas chromatography
GC/MS	Gas chromatography/Mass spectrometry
GMP	Good manufacturing practices

HDPE	High density polyethylene
HPLC	High-Performance Liquid Chromatography
i.v.	Intravenous
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled Plasma Mass Spectrometry
ICP-OES	Inductively coupled to optical emission spectrophotometer
INN	International non-proprietary name
IPC	In-process control
IR	Infrared
JP	Japanese Pharmacopea
keo	rate constant describing the delay between plasma concentrations and effect
KF	Karl Fischer Titration
LC-MS	Liquid chromatography mass spectrometry
LDPE	Low-density polyethylene
LoC	loss of consciousness
LOD	Limit of detection
LOD	Loss on drying
LOQ	Limit of quantification
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MIA	Manufacturing/Import authorisation
MO	Major objection
MOAA/S	Modified Observer's Assessment of Alertness/ Sedation
MS	Mass spectra or Mass spectrometry
MW	Molecular weight
NLT	Not lower than
NMR	Nuclear magnetic resonance
NMT	Not more than
NOAELs	No-observed-adverse-effect levels
OC	Other concern
ONO	Ono Pharmaceuticals Limited
PAHs	Polycyclic Aromatic Hydrocarbons
PD	Pharmacodynamic(s)

PDE	Permitted Daily Exposure
Ph.Eur.	European Pharmacopea
PK	Pharmacokinetic(s)
PopPK	population pharmacokinetics
ppm	Parts per million
QC	Quality Control
QP	Qualified Person
QTc	Corrected QT-Interval
RH	Relative humidity
RRT	Relative retention time
SmPC	Summary of Product Characteristics
t½	Half Life
t½α	Half-Life in the First Compartment or Distribution Half-Life
TAMC	Total Aerobic Microbial Count
TDS-GC/MS	Thermodesorption-GC/MS
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of Toxicological Concern
TYMC	Total Yeast and Mold Count
USA	United States of America
USAN	United States Adopted Name
USP	United States Pharmacopea
UV	Ultraviolet
UV-Vis	Ultraviolet-Visible
Vc	volume of distribution at t=0 (bolus only), Vc=Dose/C0
Vss	volume of distribution at steady state of distribution, Vss=CL · MRT
Vz	volume of distribution during terminal disposition, Vz = Dose/(AUC · λz)
WFI	Water for injection
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant PAION Netherlands B.V. submitted on 20 November 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Byfavo, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 November 2018. The eligibility to the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 was based on justification of claim as a new active substance.

The applicant applied for the following indication: Remimazolam is indicated in adults for procedural sedation.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 17 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0364/2019) on the agreement of a paediatric investigation plan (PIP) in accordance with Article 17(1) of said Regulation; the granting of a deferral in accordance with Article 21 of said Regulation and the granting of a product-specific waiver for one or more subsets of the paediatric population in accordance with Article 14 of said Regulation and concluded in accordance with Article 11(1)(a) of said Regulation, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population, and Article 11(1)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for the paediatric patients.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance remimazolam contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: Selma Arapovic Dzakula

The application was received by the EMA on	20 November 2019
The procedure started on	2 January 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	6 April 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 March 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	8 April 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 April 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	17 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	1 October 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 October 2020

The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	26 November 2020
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	4 December 2020
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	10 December 2020
The applicant submitted the responses to the CHMP consolidated 2nd List of Questions on	23 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	15 January 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Byfavo on	28 January 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

In present day healthcare programmes, procedures requiring sedation are common. Routine screening and diagnostic procedures are especially frequent in adults, together with therapeutic healthcare technologies. Many of these require sedation to decrease anxiety and discomfort, with or without strong analgesia.

2.1.2. Epidemiology

In EU, according to available data, colonoscopies and bronchoscopies are listed among the top 10 surgical operations and procedures in the EU. Immediately after cataract surgery, the second most common type of surgical operations and procedures is colonoscopy with or without a biopsy (ICD-9-CM codes 45.22–45.25, 45.42 and 45.43). Bronchoscopies are also within the top 10.

Among the most frequently performed procedures requiring sedation in adults are upper gastrointestinal (GI) endoscopies and colonoscopies. In the EU, colonoscopies were performed on between 0.2% to >1% of the population, depending upon the country (Eurostat 2018), and about two-thirds of the United States (US) population aged 50 to 75 years underwent a colorectal screening (Joseph 2010). It has been estimated that 40 million short diagnostic and therapeutic procedures requiring sedation are performed in the US annually (FDA 2012), and this number is likely to be higher in the EU where the population is larger.

2.1.3. Biologic features

Procedural sedation is used in a wide range of medicinal endoscopic procedures, imaging techniques and small surgeries in order to sedate patients.

2.1.4. Clinical presentation

Although upper GI endoscopy, colonoscopy and flexible bronchoscopy can be performed with and without sedation, these procedures were associated with improved patient's tolerance, e.g. satisfaction and willingness to repeat the examination, when sedation is administered. However, more complex procedures cannot be conducted or are rarely conducted without sedation (Dumonceau 2010; Khan 2016). Without procedural sedation patients can suffer from pain, discomfort and anxiety, resulting in lack of cooperation during procedure, with potentially more difficult or prolonged procedures and decreased procedural success rates (Gross 2002; Early 2018).

Importance of co-morbidities: any co-morbid condition could be present. Hence, an ideal sedative for procedural sedation should cause predictable and well-controllable levels of sedation, rapid onset and recovery with low risk of respiratory depression, of cardiovascular effects, or of other adverse reactions.

2.1.5. Management

Currently, either propofol or a benzodiazepine, sometimes in combination with an opioid to provide analgesia, is primarily used to obtain sedation for painful medical procedures of limited duration. Among the benzodiazepines, midazolam is the most commonly utilised agent. Propofol is an intravenous (i.v.) sedative/hypnotic agent with excellent sedative properties (Sacchetti 2007). A second advantage is its extremely short half-life (Dunn 2007, Frank 2006) which allows rapid recovery from sedation. A disadvantage of propofol or of fospropofol (Garnock-Jones 2010, Silvestri 2009), its pro drug, is its potential for respiratory depression and thus hypoxia (Miller 2005), accordingly requiring constant monitoring of patient's vital signs and respiration rate. Consequently, a second physician or a nurse capable of providing general anaesthesia must be present to monitor the patient while the primary physician performs the procedure. In addition, propofol has a rather narrow therapeutic index which raises concerns with regards to involuntary overdosing or small increments needed to cause deeper sedation.

Benzodiazepines are widely used sedative agents with a lower likelihood for respiratory depression than propofol, thus these drugs require staff trained in resuscitation but not necessarily in providing general anaesthesia. Their main disadvantage is their long half-life, e.g. even midazolam, the shortest acting benzodiazepine has a half-life of approximately one to three hours (Bahn 2005).

About the product

Remimazolam (also referred to as CNS7056 or ONO-2745) is a new benzodiazepine that is being developed as an ultra-short-acting intravenous (i.v.) agent for use in procedural sedation (e.g., for colonoscopies or bronchoscopies).

Type of Application and aspects on development

Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for solution for injection containing 20 mg of remimazolam as active substance.

Each vial contains remimazolam besylate equivalent to 20 mg remimazolam. After reconstitution each mL contains 2.5 mg remimazolam.

Other ingredients are: lactose monohydrate, dextran 40 for injection, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

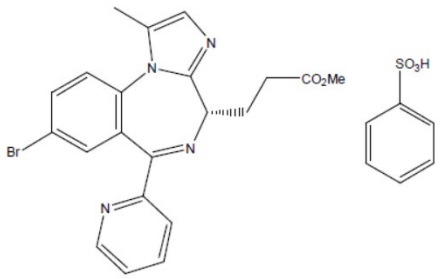
The product is available in a type 1 glass vial with a stopper (bromobutyl rubber) and seal (aluminium) with a blue polypropylene flip-off cap as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of remimazolam besylate is methyl 3-[(4S)-8-bromo-1-methyl-6-pyridin-2-yl-4H-imidazo[1,2-a][1,4]benzodiazepin-4-yl] propanoate benzenesulfonic acid or 4H imidazo[1,2-a][1,4]benzodiazepine-4-propanoic acid, 8-bromo-1-methyl-6-(2-pyridinyl)-(4S)-methyl ester, benzenesulfonate (1:1), corresponding to the molecular formula $C_{27}H_{25}BrN_4O_5S$. It has a molecular weight of 597.48 g/mol and the following structure:

Figure 1: Active substance structure



The active substance is an off-white to pale-yellow solid powder which is slightly hygroscopic, practically insoluble or very slightly soluble in aqueous media with pH ≥5.0 and sparingly soluble at acidic pH values.

The chemical structure of remimazolam besylate was elucidated by a combination of mass spectrometry, elemental analysis, infrared spectroscopy, nuclear magnetic resonance spectroscopy (^{1}H and ^{13}NMR), X-ray powder and single crystal X-ray crystallography.

The solid-state properties of the active substance were measured by polarised light microscopy, differential scanning calorimetry (DSC) including melting point, infrared spectroscopy, Fourier transform-Raman spectroscopy and X-ray powder diffraction for determination of solid state forms (by using a proprietary screening technology), determination of the solubility profile, determination of hygroscopicity (by Dynamic Vapor Sorption), and pH.

Remimazolam exhibits stereoisomerism due to the presence of one chiral centre. The chiral centre is derived from one of the starting materials. Inversion of the stereogenic centre is not plausible in the proposed synthetic process and the active substance is consistently synthesised as the S-enantiomer (an additional chiral centre is introduced during the course of the synthesis from another starting material but is not maintained in the active substance). The enantiomeric purity of the active substance is controlled routinely by chiral HPLC in the specifications.

Remimazolam besylate exhibits polymorphism and two polymorphic forms have been identified. The final crystallisation step of the active substance synthesis process is designed to consistently deliver the thermodynamically most stable polymorph.

Remimazolam besylate is sensitive to hydrolysis. To a lesser extent the active substance is sensitive to oxidation and light.

Manufacture, characterisation and process controls

Remimazolam besylate is manufactured by one manufacturing site, with a number of other sites involved in testing of the active substance.

Remimazolam besylate is synthesised in three main steps using well defined starting materials with acceptable specifications.

Routine reprocessing is not undertaken for the manufacture of remimazolam besylate and reprocessing of intermediates or the final active substance will only be performed in accordance with the principles outlined in ICH Q7. No aseptic or sterilisation process is performed in the manufacture of remimazolam besylate.

The starting materials have been defined in accordance with the scientific advice received from EMA. The applicant has committed to provide additional confirmation of capability of analytical methods to control impurities in starting materials.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The applicant has committed to provide additional confirmation of the capability of analytical methods to control impurities in intermediates.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were discussed with regards to their origin and characterised.

Following the initial assessment, the CHMP considered as Major Objection (MO) that the approach in respect to the evaluation and control of potential genotoxic/mutagenic impurities provided was insufficient. During the procedure, this was adequately addressed by the applicant and potential and actual impurities are now well discussed with regards to their origin and characterised. A risk-based assessment together with a control strategy has been provided for each potential genotoxic impurity. The control of potential impurities is adequately addressed in line with ICH Q3C.

Changes made to the manufacturing process of the active substance used in non-clinical and clinical studies as well as for registration stability batches and validation batches on production scale have been provided in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered comparable with that produced by the proposed commercial process.

The active substance is packaged in double bags, which comply with the EC directive 2002/72/EC and Commission Regulation (EU) 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR, XRPD), achiral assay (HPLC), assay (titration, chiral purity (HPLC), related substances (HPLC, GC-MS), water content (KF), residue on ignition (Ph. Eur.), completeness of solution, residual solvents (GC), microbiological purity (Ph. Eur.), and bacterial endotoxins (Ph. Eur.).

Several process-related impurities have been listed as specified impurities in the active substance specification. The specification limits for those impurities that are above the qualification threshold of ICH Q3A have been qualified through toxicological studies. The toxicological qualification, assessed in the non-clinical AR, is considered acceptable.

Genotoxic impurities have been evaluated using a combination of a purge factor approach, in-silico toxicity predictions and *in vitro* and *in vivo* assessments. A TTC-based acceptable intake was determined for each potential genotoxic impurity. Potential genotoxic impurities were classified according to ICH M7. Predicted levels of potential genotoxic impurities in the active substance are >100 times lower than the TTC.

An overall risk assessment on elemental impurities contamination in the active substance from the raw materials and the process equipment used in the manufacturing of remimazolam besylate was conducted in line with ICH Q3D. Class 1 and 2A elemental impurities as well as selected class 3 elements have been considered. Results for all elements in several validation batches were below the 30% ICH limit and hence no further control of elemental impurities in the active substance is required.

The solvents used in steps 2 and 3 of the remimazolam besylate synthesis are controlled in the active substance specification. The solvents used in Step 1 are controlled at the level of the isolated intermediate, except for one solvent which was not detected in a number of batches and therefore not included in the intermediate specification. The specification limits are in line with ICH Q3C requirements and supported by data from several validation batches.

A risk evaluation concerning the presence of nitrosamine impurities was provided, which concluded that no risk of the presence of nitrosamines was identified for remimazolam besylate active substance, or finished product.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data, including data from commercial scale batches, of the active substance are provided. The results are within the specification and consistent from batch to batch.

Stability

5°C was selected to test long term storage.

Stability data from several batches of active substance, all from the proposed manufacturer and stored in a container closure system representative of the commercial container closure system for up to 48 months under long term conditions (5 ºC), for up to 48 months at 25ºC/60% RH, and for up to six months at 40°C/75% RH (both 25°C/60% RH and 40ºC/75% RH were selected as accelerated conditions) according to the ICH guidelines were provided. The analytical methods used were the same as for release and were stability indicating. No changes or trends indicating degradation were observed for all samples either at long-term or accelerated conditions.

In addition, photostability testing following ICH guideline Q1B was performed. Light protection during storage is required.

Results of stress conditions were also provided.

Stability data has also been provided for the isolated intermediatesto support the stepwise validation of the manufacturing process and holding times.

A post-approval stability protocol has been provided, which was considered adequate regarding the parameters tested. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months in the proposed container at the proposed temperature conditions.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is described as a sterile, white to off-white lyophilised powder, reconstituted before use with sodium chloride 9 mg/mL (0.9%) solution for injection. The vial delivers a final concentration of 2.5 mg/mL of remimazolam.

The active substance remimazolam besylate is an ultra-short-acting benzodiazepine indicated for procedural sedation and therefore the aim was to develop a formulation as a solution for IV administration which enables modulation of dosage.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The choice of the sterilisation method is adequately justified and in line with the *Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container*.

Sufficient data was provided on process development. The differences between the different stages of the manufacturing process from lab scale to validation/commercial scale are described in sufficient detail to understand the changes introduced throughout clinical development.

Three validation batches of finished product were manufactured at commercial scale using active substance batches manufactured according to the commercial process.

Studies were conducted to determine the process holding time and temperature.

The studies used to investigate the compatibility between the active substance and the excipients selected for the formulation of the finished product were acceptable. The compatibility and stability studies conducted after reconstitution with NaCl 0.9% were acceptable.

The control of microbial limits at drug product release and stability is acceptable.

The formulation used during pivotal clinical studies is the same as that intended for marketing.

The selection of the container closure system was satisfactorily justified and based on data from stability studies data as well as data from extractables/leachables studies.

The primary packaging is a type 1 glass vial with a stopper (bromobutyl rubber) and seal (aluminium) with a blue polypropylene flip-off cap. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of several main steps and the process is considered a non-standard manufacturing process.

The manufacturing process has been validated on three commercial scale batches of finished product. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The identified critical steps are considered acceptable.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (powder, and reconstituted solution (Ph. Eur.)), time to reconstitution, osmolality following reconstitution (Ph. Eur.), extractable volume following reconstitution (Ph. Eur.), identification (UV, HPLC), visible particulates (Ph. Eur.), sub-visible particulates (Ph. Eur.), pH following reconstitution (Ph. Eur.), remimazolam vial content (HPLC), uniformity of dosage units (Ph. Eur.), degradation products (HPLC), moisture content (Karl Fischer Titration), sterility (Ph. Eur.) and bacterial endotoxins.

The specification is in line with ICH Q6A. The proposed limits for impurities are acceptable according to ICH Q3B.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed as requested by the CHMP as Major Objection, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided including several validation/stability batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from several batches of finished product stored for up to 48 months under long term stability conditions of 25ºC/60% RH and 6 months under accelerated stability conditions of 40ºC/75% RH according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

The analytical procedures used are stability indicating. No significant changes were observed.

Photostability studies were conducted according to ICH Guideline on Photostability Testing of New Drug Substances and Products.

The stability of the reconstituted product (after addition of 8.2 mL of 0.9% NaCl) was tested up to 24 hours and the results presented. Reconstituted vials were stored at 25°C/60% RH in inverted and upright position. Based on the available data the claimed holding time of 24 hours under controlled room

temperature at 20ºC to 25ºC after reconstitution is agreed. However, the reconstituted product should be directly administered, and the following text is included in section 6.3 of the SmPC:

In-use stability after reconstitution

Chemical and physical in use stability has been demonstrated for 24 hours under controlled room temperature at 20°C to 25°C.

From a microbiological point of view the solutions should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Based on available stability data, the proposed shelf-life of 36 months as stated in the SmPC (section 6.3) is acceptable. Except from the protection from light, the medicinal product does not require any other special storage recommendations.

Adventitious agents

The only material of animal origin is lactose monohydrate which is of bovine origin. Lactose monohydrate is derived from bovine milk in compliance with the EU guideline (EMEA/410/01) and with the requirements of the current European Pharmacopoeia. Lactose monohydrate is certified free from the risk of TSE/BSE.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The CHMP initially raised one major objection in relation to the active substance and one major objection in relation to the finished product. The first major objection concerned the approach in respect to the evaluation and control of potential genotoxic/mutagenic impurities in the active substance, which was considered insufficient. This major objection was adequately addressed by the applicant. The second major objection concerned the need to provide a risk assessment concerning the presence of nitrosamine impurities in the finished product. The major objection was addressed in a satisfactory way by the applicant.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These points are put forward and agreed as recommendations for future quality development (please see below).

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation, which should be implemented within agreed timelines:

1. Applicant to confirm that several potential impurities can be controlled as unspecified impurities by the appropriate analytical method applied for control of the starting material.
2. Applicant to confirm that several potential impurities, can be controlled as unspecified impurities by the appropriate analytical method applied for control of the starting material.
3. Applicant to confirm that one impurity can be controlled as unspecified impurity by the appropriate analytical method applied for control of one intermediate.
4. Applicant to confirm that the two impurities can be controlled as unspecified impurities by the appropriate analytical method applied for control of one intermediate.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant has submitted a full battery of non-clinical studies in support of this application.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Remimazolam is a short-acting intravenous benzodiazepine sedative/anesthetic. It acts as an agonist on the benzodiazepine site of the GABA-A receptor. In the human body, remimazolam is rapidly metabolised to an inactive metabolite by tissue esterase and is not metabolised by cytochrome-dependent hepatic pathways. GABA is the main inhibitory neurotransmitter in the central nervous system. Pharmacology studies were performed in rodents, micropigs, sheep and monkeys. Remimazolam showed sedative activity in all animal species studied, with a rapid onset and a short duration of sedation.

Receptor binding and specificity of remimazolam was characterised *in vitro*. High binding affinity of remimazolam for the benzodiazepine site of the GABAA receptor was found and it was exceeding that of its metabolite, CNS7054 by more than 300 times in brain tissue of human, pig and rat.

A substantial number of *in vivo* studies in rodents, micropigs, sheep, and Cynomolgus monkeys were performed in order to assess pharmacological properties of remimazolam, to measure possible effects on respiratory and cardiovascular systems and to identify possible pharmacodynamics interactions with drugs relevant in the clinical setting aspired for remimazolam.

Intravenous injection of 20-30 mg/kg remimazolam caused a loss of righting reflex in mice and rats. Neither the principal metabolite, CNS7054, nor the R-enantiomer of remimazolam induced LRR at doses up to 100 mg/kg and 30 mg/kg, respectively.

Secondary pharmacodynamic studies

The amnestic effect of remimazolam in comparison with that of propofol was investigated in a step-through passive avoidance apparatus in rats (n = 10/group), where the latency to enter the dark compartment was used as the index of evaluation. The latency was shortened in a dose-dependent manner by remimazolam and propofol; significant differences were recognised with doses from 0.5 mg/kg remimazolam and from 2 mg/kg propofol.

An additional radioligand study (presented in primary PD) extended these results to 24 different abuse relevant receptors, ion channels and transporters including the GABAA1 receptor. No significant responses (>50% binding at 10 µM) were observed in any primary assay except for the α1, β2, γ2 GABA-A receptor (62.1 % binding at 10 µM remimazolam).

Safety pharmacology programme

Safety pharmacology endpoints were evaluated in rats, rabbits and minipigs, and in young adult (2- to 4-year old) cynomolgus monkeys. Also, two *in vitro* experiments were done: one to explore the effect on hERG-current in cell culture, second to explore the effect of remimazolam on the action potential of isolated guinea pig papillary muscle.

In studies on guinea-pig papillary muscle, remimazolam at concentrations of 10 and 30 µM produced no significant changes compared with the vehicle control group. At 100 and 300 µM, the 30% and 50% action potential duration (APD30 and APD50) were decreased. In addition, an increase in the resting membrane potential and a prolongation of the 90% action potential duration (APD90) were observed at 300 µM. From these experiments it was concluded that remimazolam inhibited calcium channels at 100 µM or higher and the inwardly and delayed rectifying potassium channels at 300 µM. Regarding the myocardial action potential, a no-effect concentration of 30 µM was identified for remimazolam.

No abnormal changes were observed in the ECG during or for 60 minutes after infusion of remimazolam (12-100 µg/kg/min for 15 min) in miniature-pigs. Following infusion of remimazolam over 6 h in the monkey study, slight QT prolongations compared to pre-dosing values were identified at 18, 30, and 60 mg/kg (7.6, 8.2, and 10.0%, respectively) at 1 hour or 3 hours after the start of dosing. After the end of dosing, increases by 4.4 to 6.0 % compared to pre-dosing values were observed at 60 mg/kg. Lower remimazolam exposure levels failed to affect QTc and body temperature in Cynomolgus monkeys.

Pharmacodynamic drug interactions

In rats, the sedative effect of remimazolam was synergistically enhanced by fentanyl and remifentanil, as well as by sedative agents acting at sites other than the benzodiazepine site of the GABAA receptor (propofol, dexmedetomidine, thiamylal, and hydroxyzine). There was no such synergism with agents with the same mechanism of action (midazolam) or with atropine. The effective sedative dose of remimazolam decreased by 93% when administered with ketamine. Similar results were obtained with sevoflurane. Likewise, co-administration with remifentanil led to a reduction of the sedative dose of remimazolam by 92% in monkeys.

2.3.3. Pharmacokinetics

The oral bioavailability of remimazolam was studied in female New Zealand White rabbits and nasal bioavailablilty in rats and minipigs. A poor bioavailability (< 10%) was observed for both alternative routes of administration. Remimazolam has a low oral, intranasal and intraperitoneal bioavailability in animal species tested. This is of no relevance as i.v. administration is the intended route of drug delivery.

Specific studies conducted with ^{14}C-remimazolam showed minimal accumulation in any tissues. Plasma protein binding of remimazolam ranged from 70.1% to 71.0%, 76.0% to 77.2% and 91.6% to 92.1%, in rat, monkey and human serum, respectively, and from 85.5% to 86.5%, 75.9% to 78.7% and 88.6% to 90.1% in rabbit, miniature pig and human plasma, respectively.

Uptake of remimazolam by human hepatocytes was not saturated up to 1000 µg/mL and can therefore be considered to be mainly by passive diffusion.

In *in vitro* protein binding drug interaction studies with the possible concomitant drugs propofol, isoflurane, sevoflurane, thiamylal, remifentanil, rocuronium, and succinylcholine performed by ultrafiltration method at their respective maximum concentrations in clinical practice drug-drug interaction via displacement of protein binding by concomitant drugs in clinical practice were found to be negligible.

The protein binding of ^{14}C-CNS7054 over the concentration range of 0.5-50 µg/mL to rat, monkey and human serum protein was 75.4%, 86.5% and 91.9%, respectively. Protein binding of CNS7054 determined by rapid equilibrium dialysis ranged from 80% to 87%, 49% to 50% and 79% to 87% in rabbit, minipig and human plasma, respectively.

Placenta penetration of remimazolam and/or its derivatives was very limited and did not lead to a sustained exposure of the fetus. Remimazolam and/or its derivatives easily accessed breast milk; the concentrations determined in milk were linked to maternal plasma concentrations.

The main route of metabolism of remimazolam is via tissue carboxylesterases (CES, primarily type 1A) to generate CNS7054, followed by hydroxylation and glucuronidation. Conversion to the main metabolite CNS7054 is mediated by carboxylesterases type 1A. Cytochrome P450 enzymes do not meaningfully contribute to the elimination of remimazolam indicating low susceptibility to cytochrome P450-mediated drug-drug interactions.

Studies with radiolabelled drug showed that the main route of excretion is fecal via bile in rats and urinary via the kidney in monkeys. Terminal half-life is short, indicating fast metabolism and elimination. This leads to fast recovery from sedation after the end of infusion.

Remimazolam and CNS7054 caused no relevant inhibition of cytochrome P450 iso-enzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4. There were no inducing effects on CYP1A2, 2B6, and 3A4. Remimazolam was not a relevant substrate of OATP1B1, OATP1B3, BCRP, and MDR1. CNS7054 was found to be a substrate of MDR1 and BCRP, but not of MRP2-4. Both, remimazolam and CNS7054, caused no or no relevant inhibition of a panel of human drug transporters (OAT1, OAT3, OATP1B1, OATP1B3, OCT2, MATE1, MATE2-K, BCRP, BSEP, and MDR1) These results together show a very low potential of remimazolam for interactions, neither as a victim nor as a perpetrator.

Remifentanil did not influence the hydrolysis of remimazolam by human liver S9 fractions, dismissing the possibility of an interaction by competition for liver carboxylesterases.

The characteristics of the concentration-dependent inhibition of trandolaprilate and CNS7054 formation were similar for each of the tested inhibitors (diltiazem, atorvastatin, benzil and ethyl paraoxon).

Diltiazem appeared to be a more potent inhibitor than atorvastatin. Utilizing the FDA Draft Guidance In vitro metabolism- and transporter-mediated drug-drug interaction studies (2017) basic model, the risk of clinically relevant drug-drug interaction due to inhibition of CES1-mediated metabolism of remimazolam by atorvastatin and diltiazem was considered negligible. However, as these results do not reassure the lack of clinical significant pharmacokinetic interactions with therapeutic drugs known to be potent hCES1 inhibitors, the applicant has developed and performed a new pharmacokinetic interaction study, as requested, which confirmed that the influence on the exposure to remimazolam of other CES1 substrates by interaction with or competition for CES1 is negligible.

2.3.4. Toxicology

All pivotal toxicity studies on remimazolam have been conducted in compliance with international GLP-standards and followed currently accepted study designs. The investigations were performed in accordance with study protocols and laboratory standard operating procedures and met the requirements of ICH guidelines.

Single and/or repeated dose toxicity studies have been conducted in rats, mice, minipigs, and Cynomolgus monkeys, reproduction toxicity studies were performed in rats and rabbits, and the local tolerance was tested in rats, rabbits, pigs/minipigs, and monkeys.

All pivotal non-clinical studies performed so far have used different formulations:

1. Early studies conducted by Paion used remimazolam drug substance dissolved in various solvents
2. Later studies conducted by Paion used the contemporary Paion drug product (containing lactose, later lactose/dextran dissolved in saline.

In pivotal toxicity studies, different batches of the different manufacturers were used with impurity profiles comparable to that of the intended marketed product.

Single dose toxicity

Single dose toxicity studies have been conducted in rodents and Cynomolgus monkeys. Remimazolam has been administered by intravenous bolus and intravenous infusion in studies conducted in CD-1 mouse and Cynomolgus monkey, respectively. Moreover, single dose toxicity studies with oral administration of remimazolam have been conducted in SD rat and NZW rabbits.

In a dose-range finding phase, 125 mg/kg was identified as the maximum tolerated dose, which was administered as a single dose to male and female CD-1 mice, followed by a 14-day observation period. Clinical signs observed were considered to be associated with the sedative action of remimazolam. Body weight gain was reduced, but recovery was evident during the second week of the observation period. Food consumption was slightly reduced, with evidence of recovery towards the end of the observation period. No abnormal findings were recorded at necropsy.

A single dose of remimazolam was administered intravenously by continuous infusion over 6 hours to male Cynomolgus monkeys at dose levels of 6, 18, 60, and 150 mg/kg. Clinical signs consistent with the sedative properties of remimazolam (ataxic gait, incomplete eyelid opening, decrease in spontaneous activity, sitting position) were observed dose dependently in all groups. Additional symptoms at doses of 60 and 150 mg/kg were somnolence, lateral position and coma. In the high dose group, single symptoms were observed up to 9 hours after the end of the infusion. No abnormalities were observed on day 2 after dosing.

In histopathology, thickening of the intima, fibrosis and inflammation of the vascular wall, brown pigment in the vascular wall, and thrombus formation were observed at the injection site in dosed groups; however, there was no clear dependence on dose level or drug concentration.

These changes had been observed in a study using catheterisation. Thrombus was more severe at the end of the catheter than at the proximal side (marked versus slight). Both the frequencies and degrees of inflammation of the vascular wall followed a similar pattern. Therefore, it was considered that no clear relationship to remimazolam was observed, but that these changes were due to damage to the intima related to the test article.

In a further single-infusion study, remimazolam was administered as a 24-hour single intravenous continuous dose to male and female Cynomolgus monkeys at dose levels of 30, 60, and 120 mg/kg. After

observation for 14 days, necropsy and histopathology were conducted. Changes in general condition consistent with the sedative effect of the test compound were seen at all dose levels. The symptoms recovered later than 2 hours after completion of injections. Body weight, food consumption, urinalysis, haematology, blood biochemistry, necropsy and organ weight revealed no toxicological changes due to remimazolam administration. No substance dependent gross lesions were detected. Histopathology revealed mild intimal thickening at the injection site (post-cava) in animals of all groups including the control. This change was not associated with necrosis of the vascular wall, vasculitis, orhrombus and there was no obvious difference from the changes related to the physical stimulus of the catheter also observed in the control group. Nonetheless, thickening of the vascular intima was observed in the 120 mg/kg group at a high grade and frequency, so that an effect of the test article at the concentration used in this dose group (2.5 mg/mL, versus 1.25 mg/mL at the low dose level) could not be excluded. It was concluded that the NOAEL for local toxicity was 60 mg/kg/day (formulation concentration: 1.25 mg/mL), due to a possible aggravation of the local irritation reaction by the test item at the concentration of 2.5 mg/mL (used at the dose of 120 mg/kg/day).

Taking into consideration the lack of abnormalities during a 2-week observation period after single administration at higher dose levels, in the previous study, remimazolam (besylate salt, BS) was administered once intravenously by continuous infusion for 4 hours to male cynomolgus monkeys at dose levels of 3.2, 4.0, 4.8, and 6.4 mg/kg (0.8, 1.0, 1.2, and 1.6 mg/mL, respectively). Gross pathology was conducted on the day following dosing and histopathology of the injection sites was then conducted without setting a 2-week observation period.

In histopathology, deposition of fibrinoid material on the intimal surface, necrosis of the vascular intima, very slight inflammation of the vascular wall, and slight thrombus were observed at the injection site in the 4.8 mg/kg (1.2 mg/mL) group and above. Therefore, the proposed NOAEL for the local findings at the injection site was 4.0 mg/kg/day (1.0 mg/mL).

In summary, no systemic toxicological changes were observed when remimazolam was administered to monkeys by intravenous continuous infusion (up to 24 hours).

Repeat dose toxicity

Repeat-dose toxicity studies with intravenous administration of remimazolam were conducted in rats, minipigs and cynomolgus monkeys. Moreover, studies with intranasal administration of remimazolam were conducted in rats.

Subchronic toxicity studies in Sprague-Dawley rat

Subchronic toxicity studies have been conducted in CD rats with administration of remimazolam by intravenous bolus up to 4 weeks duration. Moreover, the potential toxicity of 7 impurities identified in and structurally related to the remimazolam drug substance has been assessed in a 2-weeks subchronic toxicity study by repeated intravenous infusion in CD Rats.

The administration of remimazolam to rats at 10 to 30 mg/kg/day for 28 days resulted in clinical signs associated with the sedative nature of the compound. No other findings were observed during the in-life portion of the study. Terminal investigations revealed foamy macrophages in the spleen and a local irritant effect at the site of administration.

Due to exacerbation of the incidence of splenic foamy macrophages at 20 mg/kg/day and above, a finding considered to be non-adverse as it was not considered to affect splenic function and was found to be recoverable following a 2 week recovery period, the no observable systemic effect level is considered to be 10 mg/kg/day of remimazolam when administered intravenously to rats for 28 days. Local effects at the injection site (increased perivascular inflammation and increased proliferation of the intimal lining of

local blood vessels) were more pronounced in animals treated with remimazolam, especially in the high dose group (versus control groups). At the end of the recovery period, the increase in blood vessel intimal proliferation was not completely recovered in the high dose group. Therefore, a local toxicity no adverse effect level could not be determined due to the injection site findings at all dose levels.

Subchronic toxicity studies in Cynomolgus monkey

Repeated dose toxicity studies, up to 4 weeks duration, have been conducted in cynomolgus monkeys with administration of remimazolam by intravenous bolus and by intravenous infusion.

The repeat dose toxicity of remimazolam dosed by the intravenous route, as a bolus injection, at 5, 10 and 20 mg/kg/day once daily for 4 weeks has been conducted, including a 2-week recovery period.

No signs of toxicological significance that could be considered attributable to treatment with the test substance were noted during the course of this study.

Signs commonly seen in both sexes at all dose levels included are considered to be directly related to the pharmacological (sedative) effect of the test substance. The findings observed with regards to the ECG data were considered to be due to the substantial decrease in heart rate in remimazolam treated animals. The prolongation of PR and RR observed were considered to be associated with decreased heart rate due to the sedated nature of the animals and not to be of toxicological relevance.

The changes in the kidney were present in the vehicle control group but did show a slight increase in animals dosed at 10 mg/kg/day and above. The changes appeared to be reduced in severity after the 2-week recovery period, but reversibility was not complete. The increase in liver cytoplasmic rarefaction noted in some treated females suggests a metabolic response in the liver related to glycogen storage. Changes at the injection site indicated irritation above that expected with an intravenous dosing, but this appeared to be related to the vehicle and showed no clear increase with the addition of the test substance. There was evidence of recovery, but the changes were not completely reversible after the 2-week recovery period.

Based on the results of this study, the NOEL would be considered to be 5 mg/kg/day of remimazolam when dosed intravenously to primates for 28 days.

Potential local adverse effects at the injection sites were additionally investigated in a repeat dose study with intravenously administration of remimazolam by continuous infusion for 4 days. Midazolam was the comparative control article. The proximal side at the injection sites as been evaluated following single and 4-day repeated dosing. The degrees of change at the remimazolam 6.4 mg/kg injection sites were similar to those at the midazolam 2.16 mg/kg injection sites. No effects on the remimazolam (1.6 or 3.2 mg/kg) injection sites were noted with single dosing or 4-day repeated dosing.

Subchronic toxicity studies have been conducted with longer infusion periods (up to 12h).

In a repeated-dose toxicity remimazolam was infused at doses of 6.75, 9.0, 11.25 and 22.5 mg/kg over 9 hours per day for two weeks. The clinical findings noted were mainly caused by sedative and anesthetic effects as drug efficacy. The changes at 6.75 and 9 mg/kg recovered by 2 hours after the end of dosing, while findings at 11.25 and 22.5 mg/kg recovered by the start of dosing on the following day. Local adverse effects were not dose-dependent and were seen around the tip of the indwelling catheter.

Moreover, a repeated-dose toxicity with continuous 12 h intravenous infusion of remimazolam at doses of 12, 30, and 60 mg/kg for a treatment period of four weeks has also been conducted. The expected sedative effects due to pharmacological activity of remimazolam were noted. Gross findings and histopathological lesions at the injection sites were not dose related and showed the same frequencies and degrees in the test article groups as in the control animals. These findings were considered as reactive lesions due to physical irritation from the implanted catheter.

The evaluation of toxicokinetics parameters in repeat dose studies with intravenous infusion of remimazolam demonstrate that the mean C_{max} and $AUC_{0\text{-}24h}$ of plasma remimazolam and the metabolite CNS7054 increased approximately dose proportionally. There were no effects of repeated injection and no sex differences.

Subchronic toxicity studies in Goettingen minipigs

Goettingen minipigs were considered an alternative non-rodent species for toxicological assessment of remimazolam. In the four-week intravenous infusion study conducted in minipigs, dose-related sedative effects were noted in all animals treated with remimazolam. Maximum sedative effects reached a plateau 5 min after start of infusion, persisted after the end of infusion showing a dose-depentent duration. No signs of toxicity were observed. The NOAEL was established at the highest dose tested, 120 mg/kg, which also constituted the maximum feasible dose. Additionally, it was demonstrated that the technical infusion procedure resulted in local reactions not related to the test substance.

Repeat dose toxicity studies using intranasal administration of remimazolam to rats

The local tolerability of intranasal delivery, the pharmacokinetics and bioavailability after intranasal administration, and the reversibility of any effects after a 14-day recovery, have been assessed in a four days repeated dose toxicity study following intranasal administration of Remimazolam to male Sprague-Dawley Rats. Male Sprague-Dawley rats were treated intranasally with 1, 2 or 4 mg remimazolam/animal/day corresponding to 4, 8 or 16 mg/kg/day, or intravenously with 2 mg/kg/day over 4 days. Remimazolam administered via the intranasal route resulted in mild levels of sedation but was not as efficacious as the same dose administered intravenously.

The intranasal administration of remimazolam was well tolerated in the rats, animals showed good recovery after each dosing session.

In summary, the intranasal administration of remimazolam did not lead to any signs of local or systemic toxicity. The low bioavailability after intranasal administration is demonstrated by the results of the toxicokinetic data in line with the lack of clinical symptoms.

Genotoxicity

Remimazolam showed no mutagenic potential in the bacterial reverse mutation assay.

In the mouse lymphoma assay, the frequency of gene mutations only increased in conjunction with high cytotoxicity (decrease of relative total growth to values around 20 % or less), regardless of treatment method. The mouse lymphoma assay revealed a significant increase in the total mutation frequency (T-MF) in short-term treatment with S9 mix, but no concentration-dependent increase was noted in both the initial and the confirmatory assays. In the same study, a significant concentration-dependent increase in the TMF in short-term treatment without S9 mix was noted. Concentration-dependency, however, was observed only in the initial experiment, not in the confirmatory study. Significant increases in the TMF in 24hour continuous treatment (without S9 mix) were noted in both assays. Concentration-dependency was lacking.

Coinciding, the relative cell survival and the relative suspension growth showed a concentration-dependent decrease. As cytotoxicity of remimazolam showed a strong correlation with T-MF ($r=0.883$), the increase in T-MF was considered a nonspecific effect caused by cytotoxicity. Remimazolam did not induce micronuclei in the rat. In the comet assay, there was no increase of %Tail DNA up to the maximum dose. Thus, remimazolam showed neither evidence of micronucleus-inducing potential nor of inducing DNA damage *in vivo*.

In light of the above, remimazolam was considered to have no genotoxic properties.

Carcinogenicity

Remimazolam was not investigated in a carcinogenicity study. As the chemical structure of the test compound does not show evidence of a structure-activity relationship suggesting carcinogenic risk or any relationship to known carcinogens, and as there is no indication of genotoxicity, cytotoxicity, or effects enhancing tissue proliferation in repeat dose toxicity studies, and remimazolam and principal metabolite are not retained in tissue for longer, there is no cause of concern justifying the need of specific carcinogenicity studies.

Reproduction Toxicity

Remimazolam has been assessed in a complete reproductive and developmental toxicological programme.

The potential safety concerns of remimazolam on fertility and early embryonic development to implantation were examined in a Segment I study in Sprague Dawley rats following i.v. administration to F0 generation animals. A slight but statistically significant increase in pre-implantation loss was observed in low and high dose females. However, values for pre-implantation loss were within or below the laboratory´s historical background values, and this finding was not considered of toxicological relevance. In addition, a slight reduction of sperm motility was noted in the high dosed males. However, the NOEL established for male and female fertility correspond to the highest dose tested, 30 mg/kg/day. Furthermore, no adverse effects have been identified on male fertility parameters assessed in rabbits within the scope of the extended fertility/mating study, and in minipigs following daily exposure over 4 weeks in the context of a subchronic repeat dose toxicity study.

The influence of remimazolam on embryo-fetal development was investigated in female Sprague Dawley rats at dose levels of 3, 10, or 30 mg/kg/day remimazolam, from the 6th to the 17th day of pregnancy. Intravenous treatment with remimazolam caused the expected dose-dependent pharmacodynamic effects (starting at the lower dose level 3 mg/kg/d). No remimazolam-related increase was noted in the incidence of malformations, variations, or retardations at any dose level tested, not even at materno-toxic dose levels. Thus, the NOEL for the dams was below 3 mg remimazolam/kg bw/day. The NOEL for the fetal organism was above 30 mg remimazolam/kg/day.

In addition, potential effects on embryo-fetal development were also investigated in female Himalayan rabbits at dose levels of 1.25, 2.5 and 5.0 mg/kg/day remimazolam, from the 6th to the 20th day of pregnancy. Intravenous treatment with remimazolam caused the expected dose-dependent pharmacodynamic effects (starting at the lower dose level 1.25 mg/kg/d).The prenatal fetal development was not affected with respect to the number of corpora lutea, implantation sites, resorptions, number of live fetuses, the values calculated for the pre- and post-implantation loss and the sex distribution of fetuses. The fetal and placental weights were slightly reduced in the high dose group. The NOEL was below 1.25 mg/kg/day remimazolam for the dams and 2.5 mg/kg/day remimazolam for the fetuses.

Furthermore, an extended fertility/mating study has been conducted in New Zealand White rabbits, using a loading iv-bolus dose followed by iv-infusion in order to mimic the clinical setting of induction and maintenance of anaesthesia. No safety concerns have been identified in fertility, embryo-fetal development, and postnatal development following birth up to day 35 post-partum, after exposure of the female from prior to mating until weaning. Therefore, the NOAELs proposed for the different phases of the study correspond to the highest dose level at which the endpoints were tested: i) mating performance and fertility: 30 mg/kg/day; ii) maintenance of pregnancy, development of the conceptus and parturition: 20 mg/kg/day; iii) maternal maintenance of litter during lactation, kit survival, development and growth: 20 mg/kg/day; and iv) kit behaviour, (all behaviour except that assessed by the tactile test): 20 mg/kg/day.

The effects of remimazolam on pre- and postnatal development, including maternal function and the development of F1 and F2 offspring, were investigated in rats by intravenous administration at doses of 3, 10 and 30 mg/kg/day. The treatment period was from day 6 of gestation to day 20 of lactation. The dams were observed for delivery and nursing behaviour and necropsied on day 21 of lactation. F1 offspring were observed for physical development, reflexes, behaviour and sexual maturity and mated at 10-12 weeks of age to evaluate their fertility and development of F2 generation. No safety concerns have been identified in dams, including maternal function, when treated from day 6 of gestation to day 20 of lactation. Moreover, no toxicological effects of remimazolam on pre- and postnatal development of F1 and F2 offsprings were noted. Therefore, the highest dose tested, 30 mg/kg/day, was considered to be the NOAEL of remimazolam for general toxicity and for reproductive function of dams. The same dose of 30 mg/kg/day was considered to be the NOAEL for development of the subsequent generation (F1).

Local Tolerance

Remimazolam has been found to aggravate lesions in response to local injury at the administration site of intravenous infusion. Such vulnerability was found to depend on whether a drug is administered as a continuous infusion or an intravenous bolus, on drug concentration, and on vessel calibre. In summary, the following conclusions and recommendations can be made based on analysis of the available data:

i.v continuous infusion:

- Regardless of vessel size, remimazolam can be safely administered at a final concentration of 1 mg/ml entering the blood vessel.
- Vessels of a larger diameter ($\geqslant$ 1.5 mm) allow safe administration of remimazolam at concentrations of up to 2.0 mg/mL.
- Co-infusion of saline at a rate of 1 mL/kg/h, which is standard medical practice, with remimazolam reconstituted to 2 mg/mL and infused at 1 - 2 mg/kg/h as recommended for general anaesthesia, results in local concentrations falling short of those associated with thrombophlebitic lesions even when small veins are used. As the susceptibility to such lesions is governed by the vessel size, the use of veins of larger calibres (forearm or central) adds a further layer of safety.
- In summary, a 2 mg/mL remimazolam reconstituted concentration is recommended for continuous infusion provided that:
    - a parallel infusion of saline is in place, diluting the concentration of remimazolam to around 1 mg/mL. OR
    - veins of a larger calibre are used.

i.v bolus:

- It can be predicted that volumes administered by bolus injection in vessels typically used in humans will almost instantaneously be diluted by blood flow, resulting in tolerable local concentrations. Damage observed in rat tails in a physical dependence study can be explained by serial venipunctures of small veins of a particularly vulnerable organ and a drug concentration more than twice that used in human bolus studies – 6 mg/mL vs 2.5 mg/mL.
- In summary, remimazolam can be safely administered as an intravenous bolus at concentrations of up to 5 mg/mL.

Other toxicity

There were no findings indicating an influence of remimazolam on the immune system.

The applicant investigated a number of impurities and degradants in genotoxicity studies and in the 4-weeks toxicity study in Cynomolgus monkeys. None of the studies revealed toxicological findings. As an exception, an impurity induced by exposure to light was found to cause lethality in rats. However, a quantitative appraisal shows that this hazard can be dismissed at the specified level with significant confidence.

No metabolites of remimazolam unique to humans were found with regard to the animal species used in the toxicity studies. Therefore, specific toxicity studies with individual metabolites other than CNS7054 have not been conducted, as the metabolites were adequately investigated within the context of studies on remimazolam. CNS7054 was found to be safe in a variety of safety and toxicity studies including a 4-week toxicity study in Cynomolgus monkeys, in which a batch spiked with various impurities including CNS7054 was used.

Based on studies in rats and monkeys, remimazolam was shown to share with other benzodiazepines the potential to induce self-administration and physical dependence. These results were expected given the known pharmacodynamics of remimazolam.

The safety and tolerability of dextran as an excipient was assessed in a general toxicity study and a study on possible effects in rats with impaired kidney function. A series of toxicity studies in rabbits has been published and the applicant considered them in their assessment, offering supportive evidence in a second species. The 28 days subchronic toxicity study in rats was enhanced by histopathological investigation of the major organs of dextran-related changes (i.e. foamy/microvacuolated cells) to verify comparable systemic effects in animals of the main toxicity study and the repeat toxicokinetic study. A dedicated study in a rat cisplatin model of renal impairment showed that 7 days of repeated treatment with up to 2000 mg/kg of dextran 40 did neither exacerbate the degree of cisplatin-induced kidney injury nor did it influence the course of recovery from renal damage (). Thus, rat studies support the notion that dextran 40 at doses of up to 2 g/kg poses no risk of renal injury to healthy and renally impaired animals. This is in agreement with the rabbit studies. In rabbits, dextran was infused at dose levels of 2, 4, and 8 g/kg, repeated daily for one month, three months, or six months. Results of these higher doses were consistent with those of the rat study presented above.

According to the applicant, "as the intake of dextran 40, that is associated with using remimazolam at its recommended MDD, amounts to 4 g (80 mg/kg in a 50 kg person), this NOAEL constitutes a safety margin of 7.5 (600/80), which is acceptable, also in view of the benign changes used in identification of the NOAEL. Of note, margins will increase with body weight."

2.3.5. Ecotoxicity/environmental risk assessment

An ERA was submitted by the applicant in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2*), 2006.

The distribution coefficients were calculated by the software from the shift in the pK_a measured by potentiometric method. The applicant enclosed study report to confirm that pKa and Log P/D measurements in the ERA report were experimentally determined. The octanol water partition coefficient at pH 7,4 (log D) was reported to be 2,52 and was ranging from 2,4 to 2,52 in the pH range of 5 to 9. All log D were below the limit of 4,5 so no further PBT assessment was conducted.

With refined F_{pen}, $PEC_{SURFACE\ WATER}$ calculated with formula above is 0,00045 µg/L, which is below the action limit of 0,01 µg/L. The applicant refined F_{pen} value based on treatment regime, as if remimazolam is intended for single dose administration only and is expected to be used once a year.

Table 1: Summary of main study results

Substance (INN/Invented Name): remimazolam			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	2.52	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.52	not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		not P
Toxicity	NOEC or CMR		T/not T
PBT-statement:	The compound is not considered as PBT or vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, default or refined (e.g. prevalence, literature)	0.00045	µg/L	below 0.01 threshold (N)
Other concerns (e.g. chemical class)			N

2.3.6. Discussion on non-clinical aspects

Remimazolam was designed to be a sedative/anaesthetic drug with a short duration of action due to its breakdown by carboxylesterases to an inactive metabolite (CNS7054). It acts as an agonist on the benzodiazepine site of the $GABA_A$ receptor but may offer more predictable action and quicker recovery than midazolam due to a faster systemic clearance.

These properties of remimazolam were confirmed in early non-clinical pharmacodynamic and pharmacokinetic studies. These studies also showed that remimazolam is active in a number of different species with the exception of dogs where there was an excitatory rather than a sedative effect.

In monkey safety study at 18 mg/kg and greater, prolongation of QTc was observed. In addition, remimazolam had an effect on intra-abdominal temperature. The normal temperature range in cynomolgus macaques (Macaca fascicularis) is 98.6 to 103.1 °F (37.0 to 39.5°C). So the changes seen in this study are in the physiological fluctuation range (from cca 38 - cca 36.5°C) of the body temperature

of the monkey and cannot be connected to the QTc prolongation or remimazolam. A clear conclusion on the cause for this effect cannot be drawn.

Regarding higher doses which showed some effects on cardiovascular safety, in *in vitro* studies remimazolam decreased the hERG tail current in a concentration-dependent manner. However, the estimated IC25 and IC50 values for remimazolam inhibition of hERG tail current were 62 and 207 μM, respectively, concentrations well above those required to activate GABAA receptors *in vitro* (0.36-1.38 μM) or free plasma levels reached in clinical studies.

In monkey safety study, prolongation of QTc was observed at dose 18 mg/kg and higher. According to PK data, when remimazolam is administered as single i/v dose to monkeys at a dose 18 mg/kg, Cmax reaches 1608.51 ng/ml. Protein Binding was determined to be 69-71% in rat, 76-79% in minipig and monkey, 86- 87% and 89-92% in human plasma.

According to human PK data (data from PK AR), Cmax for 0.1 mg/kg; equals 7 mg for a standard bodyweight of 70 kg; administered in the multiple ascending dose study CNS7056-002 for the indication of procedural sedation, is 560 ng/ml. In the ascending-dose study in subjects undergoing colonoscopy (CNS7056-002), Cmax was 464 ng/mL and AUCinf 325 ng·h/mL at the initial dose of 0.075 mg/kg (5.25 mg for a 70 kg subject).

From these presented data, a safety margin for cardiovascular effects can be set to approximately 2.8 to 3.5 based on Cmax for remimazolam.

The applicant did not provide a critical review of possible CNS relevant effects but provided a modest review on respiratory effects. Since remimazolam is a benzodiazepine, the target pharmacodynamics organ/system is CNS. Taking into account overall pharmacological and toxicological profile, it is concluded that it shares class effects with other benzodiazepines when it comes to CNS safety. No further questions were raised on this topic. Respiratory effects are discussed by the applicant and a similar conclusion is drawn. Remimazolam shares with other benzodiazepines some potential to cause respiratory depression as a class effect.

The intended route of administration is via intravenous bolus or continuous infusion in humans. Nonclinical studies mirrored these modes of administration.

Pharmacokinetics and toxicokinetics of remimazolam and its main metabolite, CNS7054, were studied in different species and for different administration pathways. Intravenous, a route intended for clinical use was investigated in rat, rabbit, miniature pig, sheep and monkey. In all animal species studied, following intravenous administration a short or very short initial phase half-life and high volume of distribution were observed, indicative of extensive tissue distribution and fast elimination. Compartmental analysis performed after bolus administration in miniature pigs, dogs and sheep, indicated a PK profile described by two or three compartments. After administration by infusion, the PK profile was characterised by early attainment of a steady state.

Diltiazem appeared to be a more potent inhibitor than atorvastatin. Utilizing the FDA Draft Guidance In vitro metabolism- and transporter-mediated drug-drug interaction studies (2017) basic model, the risk of clinically relevant drug-drug interaction due to inhibition of CES1-mediated metabolism of remimazolam by atorvastatin and diltiazem was considered negligible. However, these results do not reassure the lack of clinically significant pharmacokinetic interactions with therapeutic drugs known to be potent hCES1 inhibitors. A new pharmacokinetic interaction study was requested with a panel of hCES1 inhibitors, including (but not limited to) simvastatin, troglitazone, fenofibrate, nitrendipine, telmisartan, nelfinavir and loperamide (Curr Med Chem. 2018;25(14):1627-1649). A study was performed and confirmed that the influence on the exposure to remimazolam of other CES1 substrates by interaction with or competition for CES1 is negligible as had been generally concluded for CES1 substrates with CES1 as a point of interaction in the review by Bohnert et al., 2016. (Bohnert T, Patel A, Templeton I, et al;

International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) Victim Drug-Drug Interactions Working Group. Evaluation of a New Molecular Entity as a Victim of Metabolic Drug-Drug Interactions-an Industry Perspective. Drug Metab Dispos. 2016 Aug;44(8):1399-423.)

Remimazolam shows a pharmacokinetic profile characterised by a short half-life caused by rapid conversion to CNS7054, especially in rodents. These pharmacokinetic properties are optimal for its use as intravenously administered anesthetic, as titration of the effect without sizable delays should be possible.

The short half-life of remimazolam supports fast recovery from anaesthesia or sedation.

The interaction potential of remimazolam is low.

Depending on the administration route, and at least in one species, C_{max} and/or AUC of remimazolam and its metabolite were equal or higher than those observed in humans.

The acute toxicity of remimazolam was assessed in single dose intravenous (bolus) administration study in mice and single dose intravenous (infusion) studies in cynomolgus monkeys. The major findings observed in rats and monkeys were sedative effects due to the pharmacological activity of remimazolam. A dose-dependent duration of sedative effects after the end of remimazolam infusion was noted. Aditional systemic adverse effects have not been identified. However, local adverse effects at the injection site have been noted in monkeys dosed by intavenous infusion and dedicated local tolerance studies have been conducted to address the potential local toxicity of remimazolam.

In addition, studies with oral administration of remimazolam have also been conducted. No safety concerns have been identified in the in SD rat and NZW rabbits orally dosed with remimazolam. As remimazolam is intended for intravenous use in procedural sedation, studies using the oral route of administration are less relevant to establish the safety profile of remimazolam.

Vehicle is used in numerous nonclinical studies but is not continued to the final product for which this MA is sought. There is no explicit explanation in the nonclinical part of dossier why the formulation changed during the development of the product. Some local effects and effects found in histopathological examination of rat kidneys are attributed to this vehicle.

Most findings observed in toxicological repeat-dose studies can be explained by exaggerated pharmacological action of the test compound. Singular histopathological findings and marginal changes of laboratory parameters observed in repeat-dose studies, which were reversible, or not strictly dose-dependent, do not indicate specific toxicological issues.

Remimazolam, at higher concentrations in the dosing solution, was found to be able to aggravate the inflammatory reaction at the injection site, which is known to be associated with the procedure of intravenous administration. Where tested as a comparator, midazolam produced comparable effects. It is concluded that the primary lesions are due to a mechanical irritation of the vessel wall during the puncture procedure, rather than a specific local toxic effect of the test compound. General toxicity and special studies indicate that the local irritating effect can be increased by higher concentrations of remimazolam [above 1.0-2.0 mg/mL (infusion); above 5-8 mg/mL (bolus)].

Toxicokinetic findings indicate no accumulation of drug substance and dose-linearity. Possible gender differences are noted in minipig (infusion study) where a lower exposure is achieved in females compared to males but this finding has no significance for this MAA and toxicological evaluation since exposure in both sexes is still sufficient. Sufficiently high exposure is achieved in bolus administration in monkeys but not in rats. Similar exposure is achieved in bolus administration with 20 mg/kg in monkeys and in infusion study with 120 mg/kg in minipigs and 50 mg/kg in monkeys which is indicative of higher exposure with smaller doses but faster administration. Combined infusion and bolus studies can be regarded as sufficient for exploration of toxicity of remimazolam.

Since TK data from rat studies, taken all together, are inconclusive, and PK/TK/reproductive toxicity data for rabbits are not adequate, assessor is of the opinion that this part of the non-clinical package should be treated as insufficient data. Combined with lack of exposed pregnancies in humans, labelling in the SmPC was changed to option 4 described in EMEA/CHMP/203927/2005 Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling.

Since remimazolam is to be administered during procedures performed in hospital setting and under healthcare professional monitoring, there is no safety issue with dependence potential finding at this time point.

The mutagenic potential of remimazolam was investigated in 3 Ames tests (one of which was a non-GLP assay), 2 mouse lymphoma assays, and 2 *in vivo* micronucleus assays in rat bone marrow cells. In studies (Ames test), (Mouse lymphoma assay), (Rat micronucleus test), (Rat micronucleus – comet combination assay), a remimazolam batch spiked with eight synthetic impurities/degradants and the principal metabolite CNS7054 was used. Study yielded negative results, but in study it was concluded that there is a possibility of chromosomal aberrations. The applicant provided an acceptable explanation for the observed effect. The applicant provided an adequate elaboration on adequacy of rat as a species for *in vivo* genotoxicity studies since the choice of species was initially questioned due to specific PK properties. It is agreed that the presented clinical signs of pharmacological activity of remimazolam are indicative of tissue distribution, including bone marrow, sufficient for any genotoxic changes to develop. For the study, the applicant acknowledged that the impurity concentrations tested did not reach those recommended in the ICH S2 (R1) guideline and conducted a SAR analysis using a total of five different *in silico* systems. The common outcome was that none of the tested impurities raised alerts for Ames mutagenicity and hence all of them fall into class 5 ("treat as non-mutagenic impurity") of the classification system enacted in the ICH M7(R1) Guideline.

In terms of assessment of reproductive and developmental safety of psychotropic agents such as remimazolam is limited by the achievement of sufficient over-exposures imposed by the pharmacological effects on behaviour and state of consciousness, leading to further secondary effects on food consumption and maternal care. Notwithstanding, no safety concerns have been identified in the three segments of reproductive and developmental set of studies conducted with remimazolam.

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia, demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. The clinical significance of these nonclinical findings in not known. A programme of juvenile toxicity studies was initiated in minipigs with remimazolam to address this concern (see EMA decision P/0364/2019). A pilot study in juvenile minipigs was conducted by PAION during Feb-April (2020). Results of this study indicated that juvenile minipigs do not represent a suitable model for neurotoxicological experiments with remimazolam due to insufficient sedation/anaesthesia level achieved. In summary, five piglets were treated either on PND14 (±1D) or PND28 (±1D) at dose rates indicated in the below Table 2. In none of the animals, a suitable state of sedation/anaesthesia could be induced. The animals still displayed movements (paddling behaviour) and other activity and reactions despite the infusion of remimazolam at per body weight dose rates up to 50-fold higher than typical for human sedation (1 mg/kg/h). The applicant had to conclude that the level and nature of effects noted in piglets on all study days indicate that the juvenile minipig is an inept model for testing possible risks of remimazolam when used for juvenile human sedation/anaesthesia.

However, the study is not conclusive as juvenile minipigs do not represent a suitable model for neurotoxicological assessment of remimazolam due to insufficient sedation/anaesthesia level achieved. Therefore, the applicant is planning to evaluate the neurotoxicity of remimazolam during the period of rapid brain development by prolonged treatment (over several hours) of juvenile rats (PND7) under

development to young adults. Potential cognitive deficiencies related to the use of remimazolam during the period of rapid brain development will be addressed using standardised methods such as the Morris Water Maze test and an open field test.

As a result of the repeat-dose toxicity studies, the No Observed Effect Levels or No Observed Adverse Effect Levels given in the following table were established:

Table 2: Established No Observed Effect Levels or No Observed Adverse Effect Levels

Study	**NOEL/NOAEL mg/kg**
Rat, bolus	20
Cynomolgus monkey, bolus	5
Cynomolgus monkey, infusion	22.5
	30
Minipig, infusion	120

C_{max} values in Cynomolgus monkeys reached the corresponding human values and those in minipigs exceeded them up to 4.8-fold (at NOAEL levels) considering unbound remimazolam plasma concentrations. The corresponding AUC-values achieved in toxicity studies in monkeys were up to 4.9-fold and in minipigs up to 15.1-fold higher than in humans.

The main metabolite of remimazolam, CNS7054, showed no relevant pharmacological activity. Compared to remimazolam, its sedative potency was about 400-fold lower *in vitro* (binding assays) and at least 200-fold lower *in vivo* (studies in rats, mice and Cynomolgus monkeys). No concerns were identified in dedicated safety studies including cardiac excitability, drug transporting and metabolizing proteins, phototoxicity, haemocompatibility, and preliminary toxicity studies in rats and Cynomolgus monkeys (laboratory findings and general condition).

Studies on the toxicity of dextran conducted in healthy and renally impaired rats indicated a safe use of the dextran-containing formulation at dextran exposures of at least 7.5 times that associated with the administration of remimazolam at its maximal TDI of 1 g. As presented by the applicant, the rat study data are consistent with published results of a series of dextran 40 toxicity studies performed in rabbits.

The applicant has submitted an Environment Risk Assessment for remimazolam in the indication of procedural sedation. All log D were below the limit of 4,5 so no further PBT assessment was conducted. Refined F_{pen}, $PEC_{SURFACE\ WATER}$ is below the action limit of 0,01 µg/L. The applicant is currently conducting Tier A environmental fate and effect studies covering other indications with higher doses, so that potential hazards for environment are going to be investigated and detected in ongoing studies.

2.3.7. Conclusion on the non-clinical aspects

The nonclinical pharmacologic, pharmacokinetic, and toxicologic profile of remimazolam has been satisfactorily characterised by the applicant and supports the clinical use of remimazolam in the approved indication.

2.4. Clinical aspects

2.4.1. Introduction

The clinical PK, PD, bioavailability, cardiovascular risk and abuse liability of remimazolam have been assessed in single dose, multiple bolus doses as well as continuous infusion Phase I trials in healthy volunteers and in hepatic and renal impairment patients in a total of 12 clinical trials involving 440 subjects (357 on remimazolam).

The safety, efficacy, and pharmacokinetics (PK) of remimazolam have been investigated in 23 completed clinical trials, including 22 trials in which remimazolam was administered i.v. The 22 trials with i.v. remimazolam were:

12 Phase 1 trials:

- 8 PK/PD, and cardiac function trials in healthy volunteers;
- 1 trial in subjects with renal and 1 trial in subject with hepatic impairment;
- 1 abuse liability trial in otherwise healthy recreational CNS depressant users.
- 1 trial assessing PK, PD, safety and tolerability after oral RMZ administration with ethanol

11 Phase 2-3 trials:

- 5 in procedural sedation;
- 5 in general anaesthesia;
- 1 in intensive care unit (ICU) sedation.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

2.4.2. Pharmacokinetics

The PK and PD of remimazolam were evaluated in healthy volunteers using weight-based ascending-dose IV boluses ranging from 0.01 to 0.5 mg/kg (CNS7056-001, ONO-2745-01). Multiple bolus administration was investigated in healthy patients undergoing colonoscopy (CNS7056-002). Two trials evaluated the PK/PD of remimazolam administration in the special populations of patients with hepatic impairment (ONO-2745-IVU007) and renal impairment (CNS7056-012). In these trials, the following main PK properties of remimazolam were demonstrated:

- The decline of remimazolam concentrations following bolus dose can be described by a three compartment model characterised by mean distribution half-life ($t_{1/2\alpha}$) of 0.5 to 2 minutes (CNS7056-001, ONO-2745-01), elimination half-life ($t_{1/2\beta}$) of 7 to 11 minutes and terminal half-life ($t_{1/2\gamma}$) of 38 to 52 minutes (ONO-2745-01)
- $t_{1/2}$ is prolonged with increasing severity of hepatic impairment, but is not affected by renal impairment (ONO-2745-IVU007, CNS7056-012)
- C_{max} and AUC increase proportional with dose (CNS7056-001, ONO-2745-01)
- Rapid clearance from plasma; clearance is high (54 to 75 L/h) and not related to body weight
- Fast tissue distribution and elimination

- Rapid and extensive formation of the inactive metabolite CNS7054 by CES1 enzyme, the most relevant enzyme in the metabolism of remimazolam.
- In healthy subjects at least 80% (ONO 2745-01) and after pretreatment with laxative 50 to 60% (CNS7056-002) of the remimazolam dose is excreted in urine as CNS7054 within 24h. Unchanged RMZ is excreted in urine only to a negligible extent of 0.1%.

Several plausible explanations for the observed difference between the studies were provided. Apart from CNS7056-002 being a multiple dose study where urinary excretion might not be complete after 24 hours, this was also a study in colonoscopy patients. Those patients received laxative prior to procedure which might have affected reabsorption from the GI tract and subsequently secretion in the urine. As a support to the claim that more than 80% of remimazolam is excreted in urine as inactive metabolite CNS7054 in healthy subjects, an additional reference (Sheng et al., 2020) was provided. In this study, after single intravenous administration to Chinese healthy volunteers, 70.8 to 89.1% of remimazolam dose was excreted as metabolite CNS7054.

Data from single IV administration in Japanese and Chinese healthy volunteers show that around 80% of remimazolam dose is excreted in urine in the form of inactive metabolite, CNS7054.

In colonoscopy patients administered top-up doses of remimazolam who received laxative prior to procedure, 50-60% of the dose was excreted in urine as CNS7054.

Metabolite profiling done in hepatocytes, HLMs, and human plasma and urine samples does not suggest any other metabolite than CNS7054 that would account for more than 1% of drug-related material.

No mass balance study was performed with remimazolam which would have provided confirmatory evidence of the fraction metabolised to CNS7054. However, available data show that this fraction should be around 80% in healthy subjects and that hydrolysis of remimazolam to CNS7054 seems to be the major and only relevant metabolic pathway

Furthermore:

- No significant difference in PK between healthy adults and healthy elderly subjects at the tested dose of 0.1 mg/kg was observed (ONO-2745-01)
- Total exposure to remimazolam was larger in patients with severe hepatic impairment than in healthy subjects and patients with moderate hepatic impairment. Modest dose adjustment (titration to effect) is expected only in severe hepatic impairment (ONO-2745-IVU007). Limited number (n=3) of subjects with severe hepatic impairment was evaluated in the hepatic impairment study. In those subjects, unbound remimazolam Cmax was similar to values observed in healthy subjects and subjects with moderate hepatic impairment suggesting that no adjustment of the initial dose or subsequent top-up doses is required. In subjects with severe HI, mean unbound AUCinf increased approximately 2-fold compared to healthy subjects and half-life increased accordingly. Due to increased remimazolam half-life in severe hepatic impairment, lower frequency of top-up doses might be needed. The recommendation (included in the updated Product Information) for dosing of severely HI subjects is a more careful timing of the top-up doses.
- The concentration-time profile and PK after a single IV dose of 1.5 mg remimazolam did not show relevant differences in ESRD subjects compared to subjects with normal renal function. No dose adjustment is required in renal impairment, including ESRD (CNS7056-012).

  Remimazolam is highly bound to plasma proteins (>90%). In study CNS7056-012 the possible effect of renal impairment on the unbound plasma concentrations was not evaluated. The

potential increase in unbound concentrations in renally impaired subjects was not considered clinically significant.

Population PK analysis pooled data from 11 clinical trials. The PK/PD model developed describes concentration-time data across patients and sedation scores over time in colonoscopy patients.

- PK of remimazolam was well described using a three-compartment model.
- Gender was found a significant covariate on CL and race on CL and Vss. The clearance was 10% higher in females than males. The Vss was 16% lower in African Americans than in Caucasians or Asians, and the CL was 13% lower. However, even if the effect was statistically significant it was not considered clinically relevant. Based on the results of the pop PK analysis, gender, race, ASA class, weight and age did not have clinically relevant effect on the remimazolam PK. Pop PK analysis further indicate that gender and race are not significant factors to explain inter-subject variability of remimazolam PK.
- The Population PK analysis also demonstrated that body weight and BMI were not a significant factor contributing to inter-subject variability in systemic exposure, hence remimazolam is recommended for fixed dosing. Since there is no evidence that dosing by body size will lead to decreased variability in systemic exposure compared to using fixed doses, weight-dependent dosing used in early clinical studies was switched to weight-independent dosing in the Phase 3 clinical programme and the same posology is proposed in the product information.

The choice of doses was confirmed using the pop PK/PD model by simulating several scenarios with different doses of remimazolam and fentanyl to confirm proposed posology in Phase 3 studies. Although the rationale for sedative use is to titrate to effect, the applicability of the recommended body-weight independent fixed doses also to patients at the extreme (low and high) body weights was further evaluated with simulations. Simulations with the proposed dosing regimen of initial 5 mg bolus dose of remimazolam were done to confirm that the same fixed dose would also be adequate for the patients at the extreme (low and high) body weights. The simulated weight range was 35-170 kg. Each virtual subject received one single 1-minute infusion of 5 mg remimazolam. Venous plasma concentrations of remimazolam were predicted at 3 and 5 minutes after start of infusion. Simulations of remimazolam concentrations at 3 minutes (expected maximal concentrations) after start of infusion suggest that more than 50% of patients of body weight lower than 70 kg, could reach levels above the concentration associated with loss of consciousness (500 ng/mL). It suggests that lower doses might be sufficient to reach desired level of sedation for patients with lower body weight. A change in the SmPC was introduced to recommend lower initial bolus dose (2.5 mg) in patients ≥65 years of age, with ASA-PS III-IV and/or body weight <50 kg. Further clarification on the chosen cut-off of 50 kg was provided by the applicant, based on the 3 min and 5 min simulation data for plasma concentrations after I.V. administration of a 2.5 mg bolus. The provided simulations show that 50 kg body weight cut-off provides a good balance between the risk of potential oversedation and the need to administer a top up dose during the initiation of the procedure. This is adequately reflected in the dosing recommendations in the SmPC.

Pharmacokinetic interaction studies

Effect of concomitant administration of CES1 inhibitors (lovastatin, simvastatin, clopidogrel, telmisartan, all pooled together, n=22) on remimazolam PK was assessed as a covariate in the PopPK model. No effect of this covariate on CL was shown.

From the *in vitro* study and analysis of clinical data from patients that concomitantly administered simvastatin, there was no evidence for a clinically meaningful impact of simvastatin, as a potent CES-1 inhibitor on remimazolam.

Considering currently available data from *in vitro* DDI studies, the potential for clinically relevant interactions via CES-1 (for remimazolam both as a victim and a perpetrator) seems low.

Possible effect of CES1 polymorphisms on remimazolam metabolism and its clinical relevance was not investigated, but comprehensive discussion was provided. According to the literature presented (Her and Zhu, 2019), a non-synonymous mutation (nsSNP) G143E, that causes complete loss of function of CES1, is the only clinically significant CES1 variant identified to date, associated with impact on PK of several CES1 substrates (methylphenidate, clopidogrel, enalapril, oseltamivir, dabigatran etexilate and sacubitril). Overall, there is no clinical data to confirm whether a genetic polymorphism such as G143E would have a clinically relevant effect on remimazolam exposure. Considering that individual dose titration will be put in place and specific antidote available, this information will not be requested.

The interaction potential of remimazolam and its metabolite CNS7054 has been tested in a number of *in vitro* studies. Remimazolam and CNS7054 caused no relevant competitive nor time-dependent inhibition of cytochrome P450 iso-enzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4. There were no inducing effects on CYP1A2, 2B6, and 3A4. Remimazolam was not a relevant substrate of OATP1B1, OATP1B3, BCRP, and MDR1. CNS7054 was found to be a substrate of MDR1 and BCRP, but not of MRP2-4.

Both remimazolam and CNS7054 caused no or no relevant inhibition of a panel of human drug transporters (OAT1, OAT3, OATP1B1, OATP1B3, OCT2, MATE1, MATE2-K, BCRP, BSEP, and MDR1).

A justification for not evaluating the potential for remimazolam and its metabolite to cause inhibition of UGTs was provided and is considered satisfactory.

These results together show a very low potential of remimazolam for interactions, neither as a victim nor as a perpetrator. Nevertheless, in the context of a possible future extension of indication (such as general anaesthesia) the DDI potential will be re-evaluated.

2.4.3. Pharmacodynamics

The clinical PK, PD, bioavailability, cardiovascular risk and abuse liability of remimazolam have been assessed in single dose, multiple bolus doses as well as continuous infusion Phase I trials in healthy volunteers and in hepatic and renal impairment patients in a total of 12 clinical trials involving 440 subjects (357 on remimazolam).

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- 1 trial assessing PK, PD, safety and tolerability after oral RMZ administration with ethanol

11 Phase 2-3 trials:

- 5 in procedural sedation;
- 5 in general anaesthesia;
- 1 in intensive care unit (ICU) sedation.

One additional Phase I trial investigated the interaction of oral remimazolam with alcohol.

The pharmacological rational for the use of Byfavo is adequately supported by bibliography and by already approved medications.

Mechanism of action

The mechanism of action of Byfavo (remimazolam) is by binding to $GABA_A$ receptor and acting as its agonist, enhancing its function. This mechanism of action is shared by the members of the pharmacological group of benzodiazepines and is widely known. Similarly, to other benzodiazepines, no specific selectivity among GABAA receptor subunits was identified and no evidence of off-target activities of remimazolam or its metabolite has been identified in non-clinical or clinical studies.

Remimazolam is an agonist at the benzodiazepine site of the $GABA_A$ receptor. It shares its sedative and other pharmacological properties with other members of this class like midazolam. It is a chirally pure molecule (S enantiomer) and is isolated as the besylate salt. Unlike other benzodiazepines remimazolam is an ester which is rapidly broken down by liver carboxyesterases to its pharmacologically inactive metabolite CNS7054.

Primary and Secondary pharmacology

Equi-effectiveness of 0.075 mg/kg of remimazolam and midazolam were deduced from the results of the phase I trial CNS7056-001 and refers to their maximal effect (i.e. Emax) but not to the duration of sedation (area under the time-effect curve) which was much longer for midazolam than for remimazolam.

While there is a phase I trial demonstrating equi-potency of midazolam and remimazolam with respect to peak sedation, there is no such comparison available for amnesia. However, equi-effectiveness demonstrated in the phase III clinical trials and that under conditions of clinically acceptable sedation the recall of the procedure was also comparable.

The applicant presented data analysis that indicates that there is no statistically significant difference in the recall of the procedure between all treatment groups. This indicates that remimazolam in the tested dosing regimen has the same amnestic properties as midazolam dosed at the investigator's discretion (randomised placebo group), as well as label-dosed midazolam.

The ability to prevent recall of any procedure-related episode was reported by the applicant to be in approximately 75% of all patients, independent of the treatment administered, further supported by an overall very high sedation satisfaction rating. The 592 remimazolam-treated patients scored on average 9.5 points on a 10-point scale (0= completely dissatisfied, 10=completely satisfied) versus an average of 9.3 points from 118 placebo-treated patients and 9.5 points from the 166 midazolam-treated patients. This difference is not statistically significant (p=0.2060 for placebo and p=1.0000 for midazolam).

Although listed prospectively as a secondary endpoint in the trial protocols and the statistical analyses plans, no formal statistical hypothesis with regards to recall was tested by any of the trials.

Therefore, all of the aforementioned statistical results were produced through post-hoc analyses.

Primary Pharmacology

To characterise the primary pharmacology of remimazolam 5 trials were performed with 3 different administration protocols: Single Bolus Intravenous Administration (CNS7056-001 and ONO-2745-01), Multiple Bolus IV Administrations (CNS7056-002) and Continuous IV Infusion (ONO-2745-02 and CNS7056-017). The primary PD clinical endpoint used in these trials was the assessment of sedation/loss of consciousness (LoC) according to the MOAA/S score (Modified Observer's Assessment Of Alertness/

Sedation) although some of the studies either cross-referenced with the BIS (bispectral index) in PK/PD simulations.

Modified Observer's Assessment of Alertness/ Sedation (MOAA/S) scores were used as the primary PD endpoint in bolus trials. This is in line with the objectives in clinical practice and considered to be a good sedation marker. This parameter (or variations of it) is routinely used in clinical practice to assess the level of sedation during medical procedures. The score ranges from 0 (loss of consciousness) to 5 (fully alert), and scores in-between indicating mild (4), moderate (2-3) and deep (1) sedation.

Additionally, there is a trend for the average BIS to decrease with the MOAA/S scores. However, there is also large variability which partially results from the hysteresis effect i.e. remimazolam changes the state of consciousness which is directly represented by the MOAA/S score while the change in the BIS are a consequence of this changed state of consciousness and appear with a temporal delay. Analysis of the slopes of the curve obtained in the Logistic regression analysis of BIS against MOAA/S indicates a good correlation between the two pharmacodynamics endpoints and the range is compatible with the BIS target range for propofol anaesthesia. There was also a clear dose-response relationship between the bolus dose of remimazolam (0.05-0.5 mg/kg; ONO-2745-01) and the minimal BIS value (Emax).

BIS was established as a valid endpoint to assess remimazolam-induced sedation in context of procedural sedation and general anaesthesia and that this endpoint responded with good sensitivity and specificity to remimazolam.

At dose levels above 0.05 mg/kg, the probability for a consistent MOAA/S <4 was >80%. This was also the lowest dose at which loss of consciousness was observed in healthy volunteers. The duration of unconsciousness ranged from a single time-point only at the lower doses to a median duration of 15 min at the highest dose tested (i.e. 0.5 mg/kg).

At equi-effective doses the median duration of unconsciousness was longer for midazolam (4 min at 0.075 mg/kg) as compared to remimazolam (a single time point only at 0.075 mg/kg). In elderly subjects there was a slightly increased sensitivity as evidenced by a higher proportion of subjects losing consciousness at a dose of 0.1 mg/kg (100% vs ~50% in non-elderly) and a slightly prolonged duration of unconsciousness (mean of 3.8 min vs 0.6 min in non-elderly).

Recovery of consciousness lasted 9.5 min following remimazolam and was considerably shorter than that with midazolam (90 min) at an equi-effective dose. Recovery from consciousness was not different between <65 years old subjects and elderly (mean 22 min at a dose of 0.1 mg/kg for both groups).

There was some pharmacodynamic differences between remimazolam and midazolam in the non-clinical model, mainly the lower threshold dose for inducing amnesia for midazolam (0.2 mg/kg) as compared to remimazolam (0.5 mg/kg). The absence of translation to clinical setting regarding those differences was justified by some PK and PD translation differences and further supported by a meta-analysis of results from nine trials with 587 participants comparing iv midazolam for procedural sedation to iv diazepam that revealed that those who received midazolam presented a similar percentage of patients not recalling the procedure (80%) when compared to remimazolam in trial CNS7056-002.

The sedative effect of remimazolam was shown to be rapidly reversed by administration of flumazenil, a benzodiazepine antagonist, with no re-sedation observed after the reversal of sedation with flumazenil.

On study ONO-2745-01, remimazolam 0.1 mg/kg induced loss of conscious in 5 of the 5 healthy elderly male Japanese subjects compared to only 1 of the 5 healthy adult male subjects at 0.1 mg/kg. Additionally, the mean duration of loss of consciousness after administration of remimazolam 0.1 mg/kg was 3.8 minutes in healthy elderly male subjects, which was comparable to that at 0.3 mg/kg in healthy adult male subjects (3.6 minutes). A modelling study additionally indicated a slower (~20%) recovery from sedation in elderly compared to non-elderly. However, analysis of phase III trials CNS7056-006,

CNS7056-008 and CNS7056-015 did not reveal a clinically significant age effect and that no difference in the pharmacokinetics between elderly and young subjects. Additionaly, results from a modelling and simulation approach was used to describe the pharmacokinetics (PK) and pharmacodynamics (PD) of remimazolam from 11 clinical trials suggest that there appears to be a PD effect related to increased age that is small and unlikely to be clinically relevant in most elderly patients. Also, the PD effect described on the duration of sedation was a slightly (2-3 min) longer recovery in elderly patients. When simulating the depth of sedation with different dosing regimens (fentanyl/remimazolam dose combinations) the percentage of subjects in the elderly group with adequate or too deep a sedation was 4-6% higher while it was 4-6% lower for no or too light sedation.

An advice in the SmPC was included regarding standard vs. non-standard dosing. The standard dosing is expected to be suitable for a healthy elderly patient. Non-standard dosing has a lower initial bolus and lower top-up doses and is to be used after the HCP has considered a few key factors such as overall health status (i.e. ASA class) and body weight. A non-standard dose can be considered by the health care professional for an underweight elderly patient with an ASA class of III or IV.

Guidance for administration of a top-up only in a titration-to-effect manner, in case additional sedation justified/needed by clinical observation considerably reduces the risk of increased sedation. Additionally, the update of the SmPC with further advice regarding standard vs. non-standard dosing might further reduce the risk of increased sedation with initial dosing.

Regarding a proper use of flumazenil in an elderly population, including dosing and possibility of re-sedation, data was presented from from the phase III procedural sedation clinical trials CNS7056-006 (colonoscopy), CNS7056-008 (bronchoscopy), and CNS7056-015 (colonoscopy in ASA- PS III-IV patients), useful for assessing potential differences between elderly and non-elderly in clinical practice. Although the requirement for flumazenil was assessed as a secondary objective in these phase III trials, not a single patient in the remimazolam treatment arms required flumazenil so there are no clinical data on flumazenil in remimazolam treated elderly or non-elderly in these trials.

The PK/PD analysis of the single ascending bolus dose trials indicates a plasma target concentration of 189 ng/mL for moderate sedation (MOAA/S=3). Simulations using the PK/PD model for bolus dosing predict an effect site concentration of 190 ng/mL for the highest probability of being in the targeted MOAA/S range of 2-4 for colonoscopies and bronchoscopies. While the effect site compartment in PK/PD modelling is a virtual compartment used to predict the PD of a drug, the most plausible physiological correlate for an anesthetic drug for the effect site compartment is the brain.

The target plasma and effect site concentration for induction of moderate sedation in subjects undergoing an unpleasant or painful procedure or examination (e.g. colonoscopy) was found to be around 200 ng/mL.

Secondary Pharmacology

The effect of remimazolam on cardiac conduction and QT interval was investigated in two Phase 1 clinical trials (CNS7056-005 and CNS7056-017). In addition, a meta-analysis of all ECGs generated in the other clinical trials was performed to assess potential effects of remimazolam.

In the thorough QT clinical trial CNS7056-005 a bolus injection was used, whereas in the PK/PD trial CNS7056-017, which also examined the QT interval, an infusion was used to eliminate bias of rapid and transient increases in heart rate.

Remimazolam's potential effect on the ECG was initially evaluated in a thorough QT-trial (CNS7056-005). Overall, the results from CNS7056-005 show that remimazolam has no direct effect on QTc or other ECG intervals such as PR, ST or QRS. The timepoint analysis of the tQT trial showed an increase in QTcI shortly after bolus dosing that slightly exceeded the threshold of regulatory concern.

In order to clearly determine the contribution of the QT-RR hysteresis effect to the small QTc effect noted only in the first few minutes after the remimazolam dosing, a second follow-up trial was designed by the applicant to assess the ECG effects of remimazolam using an infusion protocol intended to produce stable plasma concentrations of remimazolam (CNS7056-017), trial that the applicant stated "it complied with standards of thorough QT trials (CNS7056-017)". This trial was designed to measure the QT interval under conditions of stable heart rate at the same plasma concentrations as the Cmax of the therapeutic and supratherapeutic dose in CNS7056-005. No remimazolam-induced change in QTcI was observed under these conditions.

Use of a positive control in the thorough study CNS7056-005 for evaluation of influence in the QT interval was performed but not for the follow-up trial CNS7056-017. The two trials used the same ECG measurement methodology by a centralised ECG core lab blinded to treatment assignment, as well as the same statistical methodology. Applicant data and literature references were presented regarding the effect of meal in QT interval as potential positive controls, in comparison of the effect of moxifloxacin. The applicant then stated that both CNS7056-005 and CNS7056-017 demonstrated the small HR increase and QTc decrease expected following a meal. The extent of these changes was found by the applicant to be remarkably similar indicating a similar sensitivity to meal-induced ECG changes in both trials.

Pharmacodynamic interactions with other medicinal products or substances

No dedicated pharmacodynamic interactions study was performed in the clinical development of remimazolam, although in study CNS7056-008 (a phase 3 bronchoscopy trial) patients with long term use of opioids or benzodiazepines were enrolled.

The CNS7056-020 trial assessed the effect of remimazolam when administered orally with and without various concentrations of ethanol. The results of this trial demonstrate that due to the sheer amount of remimazolam and alcohol (18 vials of remimazolam (360 mg) and 150 mL of 40% alcohol) needed to produce significant sedation in a single female subject (1 of 10), together with the remarkably bitter taste of remimazolam and the adverse reactions caused by the combination (emesis, cardiovascular) do not suggest any potential for the remimazolam−alcohol combination to incapacitate a victim.

Although it appears that no clinically relevant PD drug-drug interaction occurred in Phase 2/3 trials in which other medicines where administered, there is not enough data to exclude the possibility of synergism in sedation and even respiratory/cardiovascular depression.

Genetic differences in PD response

At the time of MAA assessment, only one clinical trial assessing the effect of GABRA1 polymorphisms on the sensitivity to a benzodiazepine (midazolam) was published. The hypothesis of the study was based on results from *in vitro* and animal studies suggesting that mutations in GABA subunits can reduce benzodiazepine sensitivity. The differences between polymorphisms in the total dose of midazolam and the lowest BIS, although statistically significant, are of little clinical relevance and no conclusion can be made regarding their effects in the clinical outcome of remimazolam.

Relationship between plasma concentration and effect

The relationship between plasma concentration of remimazolam and effect was well established both in direct measurements and PK/PD modeling. The plasma concentration of remimazolam correlates well with the primary endpoint (MOAA/S).

For induction of medical procedures e.g. colonoscopies or bronchoscopies often a MOAA/S of 3 represents an adequate level of sedation. The Figure 2 below shows the probability for a MOAA/S <4 in dependence of dose. At dose levels above 0.05 mg/kg, the probability for a MOAA/S <4 in both trials was >80%. The dose 0.05 mg/kg was also the lowest dose at which loss of consciousness was observed in healthy

volunteers. The duration of unconsciousness ranged from a single time-point only at the lower doses to a median duration of 15 min at the highest dose tested (i.e. 0.5 mg/kg).

The PK/PD analysis of the single ascending bolus dose trials indicates a plasma target concentration of 189 ng/mL for moderate sedation (MOAA/S=3). Simulations using the PK/PD model for bolus dosing predict an effect site concentration of 190 ng/mL for the highest probability of being in the targeted MOAA/S range of 2-4 for colonoscopies and bronchoscopies.

A population pharmacodynamic model with respect to the MOAA/S score as clinical measure of sedation was successfully developed using sigmoid probability functions. The pharmacodynamic model for MOAA/S score revealed a relatively fast onset of sedation with a time to peak of about 3 min and a fast recovery with a context-sensitive half-time of about 10 min. There were no effects of age and weight on the pharmacodynamics with respect to MOAA/S score.

A paper by Schuttler and colleagues (Schuttler et al, 2020) performed the pharmacodynamic modeling of the Modified Observer's Assessment of Alertness and Sedation scores which was investigated with a logistic regression model and with a sigmoid model (Hill equation) for the cumulative probabilities. Although these two models are both characterised by con- centration-effect curves with a sigmoid shape, the logistic regression model showed a worse quality of fit. This may be explained by the different behaviour of the two models at baseline when no drug was present. In this case, the probability to achieve a Modified Observer's Assessment of Alertness and Sedation score at or below 4 equals zero for the sigmoid model but not for the logistic regression model. However, because all subjects in this study were alert (Modified Observer's Assessment of Alertness and Sedation score = 5) at baseline, the sigmoid model was more appropriate. The use of the sigmoid model by the applicant was therefore appropriate.

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology is very thorough and supported by 12 Phase 1 trials, either PK, PD, PK/PD or related to cardiovascular effects. The PK/PD studies were very thorough and were complemented with PK/PD modelling relating remimazolam concentrations in several types of administration with PD markers of sedation.

BIS was established as a valid endpoint to assess remimazolam-induced sedation in context of procedural sedation and general anaesthesia and this endpoint responded with good sensitivity and specificity to remimazolam with similar trends in profile compared to MOAA/S.

Although remimazolam acts by a well-known mechanism (agonism of GABA receptor), it is however a new active substance and there is still an uncertainty regarding the particular subunits it acts on. While there appears to have a similarity in terms of doses necessary for induction of sedation between remimazolam and midazolam, there appears to be a discrepancy in the doses necessary to induce amnesia, evidenced in non-clinical development, which was adequately discussed and equipotency was established in Phase 3 trials. Amnestic effect was added as an additional pharmacodynamic effect to section 5.1 of the SmPC.

Remimazolam administration can be associated with a transient increase in heart rate (10-20 beats per minute) starting as early as 30 seconds after the start of dosing (corresponding to the time of maximum concentration of remimazolam) before resolving within about 30 minutes after the end of administration. This increase in heart rate coincides with a decrease in blood pressure and it may confound QT correction for heart rate translating into a small prolongation in QTcF in the first few minutes following dosing. Section 4.4 of the Summary of Product Characteristics was updated to include this warning.

Given its pharmacological characteristics it is plausible that remimazolam will have limited PD interactions with other medicinal products and substances other than the ones acting also in the Central Nervous

System as CNS depressants and/or sedatives. The SmPC was updated with more specific recommendations for dosing guidelines in case of opioid co-administration.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of remimazolam has been characterised sufficiently.

2.5. Clinical efficacy

The Summary of studies submitted in support of this application is presented in Table 3 below. Colonoscopy and bronchoscopy were chosen as model procedures to reflect different levels of invasiveness, duration of stimulus, and to enrol a representative population likely to be treated with remimazolam post marketing. The Phase III trials were designed in alignment with the FDA to enable a claim for a broad indication covering all therapeutic and diagnostic procedures where sedation is required.

Table 3: Overview of remimazolam clinical development programme for procedural sedation

Design feature	CNS7056-003	CNS7056-004	CNS7056-006	CNS7056-008	CNS7056-015
Efficacy objectives	Dose-finding trial to assess the safety and efficacy of remimazolam administered as a single 1-min i.v. injection, at 3 dose levels, compared to midazolam	Assess the feasibility of safely maintaining suitable sedation levels with various dosages of remimazolam, in combination with fentanyl, for subjects undergoing a colonoscopy, compared to midazolam in combination with fentanyl	PRIMARY: To demonstrate remimazolam is superior to placebo with respect to successful completion of colonoscopy (CNS7056-006) or bronchoscopy (CNS7056-008) EXPLORATORY: To compare remimazolam with midazolam		Compare remimazolam to placebo, with an additional open-label arm for midazolam, in ASA-PS grade III/IV subjects undergoing colonoscopy
Control	Double-blind active-control (midazolam)	Double-blind active-control (midazolam)	Double-blind placebo-control Open-label active-control (midazolam)		Double-blind placebo-control Open-label active-control (midazolam)
Randomisation	1:1:1:1 to 3 doses of remimazolam and midazolam	1:1:1:1 to 4 doses of remimazolam and midazolam	30:6:10 to remimazolam: placebo: midazolam	30:6:6 to remimazolam: placebo: midazolam	2:1:2 to remimazolam: placebo: midazolam
Dose levels	Remimazolam: 0.10 mg/kg 0.15 mg/kg 0.20 mg/kg Midazolam: 0.075 mg/kg	Remimazolam: 5 mg over 1 min initial dose 3 mg top-up dose 7 mg over 1 min initial dose 2 mg top-up dose 8 mg over 1 min initial dose 3 mg top-up dose Midazolam: 2.5 mg over 1 min initial dose 1.0 mg over 15 sec top-up dose	Remimazolam: 5 mg over 1 min initial dose; 2.5 mg supplemental dose(s) Placebo: Matching volumes of placebo Midazolam: 1.75 mg over 2 min initial dose; 1.0 mg supplemental dos e(s) (or 1.0 mg initial dose/0.5 mg supplemental dose for subjects ≥60 years of age, debilitated, or chronically ill)		Remimazolam: 2.5 to 5 mg over 1 min initial dose 1.25 to 2.5 mg over 15 sec top-up dose Placebo: Matching volumes of placebo Midazolam 1.0 mg over 2 min initial dose 0.5 mg over 2 min top-up dose
Analgesia	Not specified	Fentanyl: 100 µg pretreatment (at the investigator's discretion) 25 µg top-up doses (at least 5 min apart until adequate analgesia or a maximum dose of 200 µg)	Fentanyl[a]: 50 µg pretreatment (or less for elderly/disabled subjects at the investigator's discretion) 25 µg supplemental doses (every 5-10 min until adequate analgesia or a maximum dose of 200 µg)	Fentanyl[a]: 25-50 µg pretreatment (or less for elderly/disabled subjects at the investigator's discretion) 25 µg supplemental doses (every 5-10 min until adequate analgesia or a maximum dose of 200 µg)	Fentanyl[a]: 25-50 µg pretreatment (or less for elderly/disabled subjects at the investigator's discretion) 25 µg top-up doses (every 5-10 min until adequate analgesia or a maximum dose of 200 µg)

Design feature	CNS7056-003	CNS7056-004	CNS7056-006	CNS7056-008	CNS7056-015
Population	ASA-PS I-II subjects undergoing diagnostic upper endoscopy	ASA-PS I-III subjects undergoing diagnostic or therapeutic colonoscopy	ASA-PS I-III subjects undergoing diagnostic or therapeutic colonoscopy	ASA-PS I-III subjects undergoing diagnostic or therapeutic bronchoscopy	ASA-PS Class III (severe systemic disease)/IV (severe systemic disease constant threat to life) undergoing diagnostic or therapeutic colonoscopy
Subjects **Sites** **Countries**	100 subjects planned/ 100 ITT population 7 sites USA	160 subjects planned/ 160 ITT population 9 sites USA	460 subjects planned/ 461 ITT Population 13 sites USA	420 subjects planned/ 446 ITT Population 15 sites USA	75 subjects planned/ 79 ITT population 4 sites USA
Duration	Screening: up to 14 days Treatment: 1 day Follow-up: 4 days (± 1 day)	Screening: up to 14 days Treatment: 1 day Follow-up: 4 days (1 to 7 days)	Screening: up to 21 days Treatment: 1 day Follow-up: 4 days (3 to 7 days)		Screening: up to 21 days Treatment: 1 day Follow-up: 4 days (4 to 7 days)

Abbreviations: ASA-PS = American Society of Anesthesiologists, ITT = intent-to-treat

a Fentanyl pretreatment dose was modified from 75 µg (or less for elderly/disabled subjects) with Protocol Amendment 4 for CNS7056-006 and Protocol Amendment 5 for CNS7056-008.

Source: ISE Table 2 and Table 3

2.5.1. Dose response studies

The first dose finding study, CNS7056-003, was a phase II efficacy trial.

Dose-response study 1: CNS7056-003 "A Phase 2a, Randomized, Controlled, Double-Blind, Dose-Finding Study Evaluating the Safety and Pharmacodynamics of CNS 7056 in Patients Undergoing Diagnostic Upper GI Endoscopy"

For the induction and maintenance of procedural sedation in adults, the proposed dose/administration route is remimazolam administered IV at an initial bolus dose of 5.0 mg (infused over 1 minute) with supplemental doses of 2.5 mg (as an IV push injection over 15 seconds) to induce or maintain adequate sedation. In debilitated patients (American Society of Anesthesiologists [ASA] Score III-IV), a lower initial dose in the range of 2.5 to 5 mg with supplemental doses of 1.25 to 2.5 mg can be utilised at the discretion of the physician.

Methods

Objectives

The primary objective was to assess the safety and efficacy of CNS 7056 (remimazolam) administered as a single 1-minute intravenous (IV) injection, at 3 dose levels, compared to midazolam.

Overall design

This was a Phase IIa, multi-centre, randomised, double-blind, parallel-group, dose-finding study assessing the safety and efficacy of 3 dose levels of CNS 7056 compared with midazolam in patients undergoing diagnostic upper gastrointestinal (GI) endoscopy.

On the day of procedure, patients were randomly assigned to 1 of 4 treatment groups: CNS 7056 0.10 mg/kg, 0.15 mg/kg, or 0.20 mg/kg; or midazolam 0.075 mg/kg, delivered as a single IV injection over 1 minute. The endoscopy was to be started when Modified Observer's Assessment of Alertness/Sedation (MOAA/S) ≤ 3 had been reached, but no earlier than 90 seconds after the start of study drug injection). Rescue with sedative medication (midazolam 1-2 mg) was permitted at the discretion of the administering physician.

Primary endpoint

The primary efficacy variable was success of the endoscopy procedure (a composite endpoint consisting of the following):

- MOAA/S $\leq$ 4 on 3 consecutive measurements
- Completion of the endoscopy procedure
- No requirement for rescue sedative medication
- No manual or mechanical ventilation

Secondary endpoints

- Time to fully alert (time to first of 3 consecutive MOAA/S scores of 5 beginning at or after the end of the endoscopy procedure, which was clarified to mean time to first of 3 consecutive MOAA/S scores of 5 following study drug administration in patients who underwent the endoscopy procedure)
- Time to ready for discharge (time to first of 3 consecutive Aldrete scores $\geq$ 9)
- No requirement for rescue sedative medication

Number of subjects (planned and analysed)

Planned: 100 patients (25 patients in each treatment group)

Analysed: 100 patients (Safety population); 100 patients (intent-to-treat [ITT] population); 49 patients (modified intent-to-treat [mITT] population)

Results

A total of 100 subjects were enrolled and included in the ITT analysis, 25 subjects in each treatment group. There were 46 males and 54 females with a median age of 41.0 years (range: 18–65 years). The race of all subjects was 95% White and 5% Black, the ethnicity was 46% Hispanic, and the average BMI was 25.9 kg/m2.

Efficacy

The main primary and secondary results are summarised below.

Table 4: Main Efficacy Results (Study 003)

Endpoint	RMZ 0.10 mg/kg (N=25)	RMZ 0.15 mg/kg (N=25)	RMZ 0.20 mg/kg (N=25)	MDZ 0.075 mg/kg (N=25)
Endoscopy success rate[a] (ITT)	8 (32.0%)	14 (56.0%)	16 (64.0%)	11 (44.0%)
Time to fully alert from last dose [min] (mITT)				
Mean (SD)	N=23 11.0 (10.04)	N=24 13.4 (6.51)	N=23 12.1 (5.26)	N=25 17.2 (16.71)
Median (min, max)	7.0 (1, 45)	11.0 (5, 30)	11.0 (5, 25)	9.0 (1, 55)
p (vs. midazolam)[b]	0.0487	0.2208	0.1086	
p (all doses)[b]				0.0485
Time to discharge from end of procedure [min] (mITT)				
Mean (SD)	N=20 14.0 (9.96)	N=22 12.8 (5.96)	N=22 11.8 (4.96)	N=24 17.2 (12.81)
Median (min, max)	12.5 (4, 40)	12.5 (4, 25)	10.5 (4, 25)	15.0 (4, 50)
p (vs. midazolam)[b]	0.2525	0.1048	0.0492	
p (all doses)[b]				0.0510
Requirement for rescue sedative medication [n/N] (ITT)	17/25 (68.0)	11/25 (44.0)	9/25 (36.0)	14/25 (56.0)
p (vs. midazolam)[c]	0.3821	0.3961	0.1560	
p (all doses)[c]				0.1175

a Success was defined as ALL of the following: i) MOAA/S ≤4 on 3 consecutive measurements, AND ii) Completion of the colonoscopy procedure, AND iii) No requirement for sedative rescue medication, AND iv) No manual or mechanical ventilation.

b From an ANOVA model with treatment as the main effect.

c $\chi 2$ test (or Fisher's exact test) for overall and pairwise comparisons of treatments.

Source: CNS7056-003 Table 14.2.1.1, Table 14.2.2.2, Table 14.2.3.2, and Table 14.2.4.1.

Although a dose-response relationship was observed for the endoscopy success rate and the proportion of subjects requiring rescue sedative medication, the single-dose application was considered inappropriate to ensure adequate sedation for endoscopic procedures. Trial CNS7056-004 therefore explored three different initial bolus / top-up regimens with remimazolam.

Dose-response study 2: CNS7056-004 "A Phase 2b Study Evaluating the Safety and Efficacy of Multiple Doses of CNS 7056 compared to Midazolam in Patients Undergoing Colonoscopy"

Methods

Objectives

Primary objective: To assess the feasibility of safely maintaining suitable sedation levels with various dosages of CNS7056, in combination with fentanyl, for patients undergoing a colonoscopy, compared to midazolam in combination with fentanyl.

Secondary objectives:

1. To assess the safety of multiple doses of CNS7056, following administration of fentanyl.
2. To assess the mean time to fully alert (time to first of 3 consecutive MOAA/S scores of 5 after the last injection of double-blind study medication).
3. To assess the time to peak sedation.
4. To assess the mean time to ready for discharge (first of 3 consecutive Aldrete Scores of ≥ 9)
   a) after the last injection of double-blind study medication,
   b) after the end of the colonoscopy.
5. To assess changes to the patient's recall by the HVLT-R administered before clinical trial material (CTM) administration and after the fully alert criteria have been achieved.
6. To assess the recall of the procedure by the Brice questionnaire when full alertness is regained.
7. To assess the PK of CNS7056 in a subgroup of patients by population PK during multiple administrations of fixed doses, compared to midazolam.

Treatments and overall design

Study 004 was a double blind, randomised, controlled, multicentre, parallel dose-response phase 2b study evaluating safety and efficacy of remimazolam compared to midazolam in patients undergoing colonoscopy.

Patients were randomly assigned to 1 of 4 possible study groups (1:1:1:1) to receive an initial single IV dose of either CNS7056 (8.0 mg, 7.0 mg or 5.0 mg) or midazolam (2.5 mg) at one of the following dose levels:

Table 5: Study 004 Treatments (source: CSR)

Study drug	Initial dose	Top-up dose	Maximum number of top-up doses	
			Sedation for start of colonoscopy procedure	Total[a]
CNS 7056	8.0 mg	3.0 mg	2	6
CNS 7056	7.0 mg	2.0 mg	2	6
CNS 7056	5.0 mg	3.0 mg	2	6
midazolam	2.5 mg	1.0 mg	2	6

a Top-up doses for sedation for start of the procedure and for sedation during the procedure.

Possible top-up doses:

1. If adequate sedation (MOAA/S ≥ 3) for the start of the colonoscopy procedure could not be achieved with the initial dose, up to a maximum of 2 top-up doses of study medication (CNS7056 3.0 mg for the 8.0 mg and 5.0 mg initial doses, CNS7056 2.0 mg for the 7.0 mg initial dose, or midazolam 1 mg) administered as IV boluses over approximately 15 seconds were allowed no less than 2 minutes apart and only if MOAA/S was ≥ 4.
2. To maintain the patient at an adequate sedation level for the duration of the procedure (MOAA/S ≤ 4, measured every minute), subsequent doses of study medication were administered at least 2 minutes apart up to a maximum total dose of 6 doses; ie, if 2 additional doses were used for achieving the sedation level for insertion of the colonoscope, only 4 more additional doses could be administered for maintaining the sedation during the procedure.

Pre-treatment and rescue analgesia: All patients received fentanyl 100 µg immediately prior to the administration of study medication after a fluid load of at least 500 mL (patients received normal saline 500-1000 mL drip starting prior to the procedure). If additional pain relief was required, as indicated by hypertension, tachycardia, or movement while sedated (MOAA/S ≤ 4), fentanyl top-up doses of 25 µg were allowed at least 5 minutes apart (up to a total of 200 µg).

Rescue sedation: According to the protocol, alternative sedatives could be other benzodiazepines as e.g. midazolam, or propofol, or other sedative agents (at the discretion of the investigator).

Outcomes/endpoints

Primary efficacy endpoint (composite):

- MOAA/S ≤ 4 on 3 consecutive measurements taken every minute, AND
- completion of the procedure (including if alternative sedative medication was used), AND
- no requirement for an alternative sedative, AND
- no manual or mechanical ventilation.

Secondary efficacy endpoints:

1) MOAA/S scores by time point. 2) Aldrete scores by time point. 3) Time to fully alert (time to first of three MOAA/S scores of 5 after the last injection of double-blind study medication). 4) Time to peak sedation (time of the first lowest MOAA/S score) after the start of first injection of study drug. 5) Time to ready for discharge (time to first of 3 consecutive Aldrete scores ≥ 9): after the start of the last injection of double-blind study medication; after the end of colonoscopy. 6) Necessity of alternative sedative medication. 7) Recall of the procedure by Brice-questionnaire(s) administered when patient reaches fully alert. 8) Brice questionnaire at each time point. 9) HVLT-R™ score.

Safety endpoints: The type of individual (e.g. anesthesiologist/nurse anesthesiologist or person trained in Advanced Cardiac Life Support [ACLS]) responsible for monitoring the patient, incidence of treatment-emergent adverse events (TEAEs) and Adverse Events of Special Interest (AESI), physical examination findings, vital signs (supine heart rate, systolic and diastolic blood pressure [BP], and respiration rate), electrocardiograms (ECGs), pulse oximetry measurements, clinical laboratory test results, rate of oxygen flow, exhaled carbon dioxide concentrations where available, preventive interventions to avoid an Adverse Event of Special Interest (AESI) and pain on injection intensity rating.

PK endpoint (in a subgroup of patients).

Sample size

The sample size was determined based on results of previous studies and was expected to provide sufficient data to examine dose levels of CNS7056 for sedation during colonoscopy. Since sample size was not statistically calculated, power was not determined, and no inferential statistical conclusions could be determined from the outcome of this study. A total of 160 patients was planned to be enrolled in this study.

Results

Baseline data

The applicant presented tabulated baseline characteristics for each group and average numbers. The average age of patients was approximately 55 years across all treatment groups, and 55% of patients were female. Patients were predominantly white (86%), and not of Hispanic or Latino ethnicity (78%). The overall mean BMI was 27.0 kg/m^2. Majority of patients had ASA I (44.1%) or ASA II score (53.4%).

Outcomes and estimation

All patients were successfully sedated (MOAA/S ≤ 4 on 3 consecutive measurements), and all of the patients except for 1 CNS7056 5.0/3.0 mg patient completed the colonoscopy procedure. Fewer patients required rescue sedative medication in the CNS7056 treatment groups (3, 2, and 1 in the 8.0/3.0, 7.0/2.0, and 5.0/3.0 groups, respectively), compared to 10 patients (25%) in the midazolam group. These differences were statistically significant (p=0.007, Fisher's exact test). Fisher's exact test documented the 7.0/2.0 and 5.0/3.0 treatment groups to be statistically superior to midazolam (p=0.007 and 0.025 respectively). The 8.0/3.0 group was not statistically superior to midazolam (p=0.066). No patients required manual or mechanical ventilation.

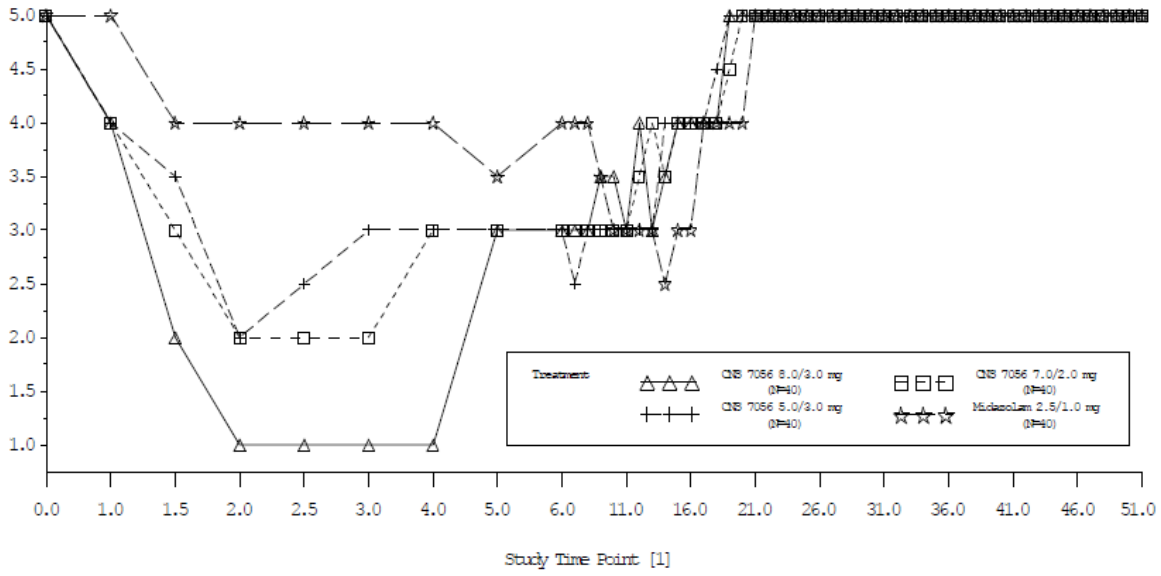
Table 6: Primary Efficacy Results – Success of Colonoscopy Procedure (Study 004, ITT population)

	CNS 7056 8.0/3.0 mg (N = 40)	CNS 7056 7.0/2.0 mg (N = 40)	CNS 7056 5.0/3.0 mg (N = 40)	Midazolam 2.5/1.0 mg (N = 40)
Did patient achieve success of colonoscopy? – n (%)				
Yes	37 (92.5%)	38 (95.0%)	39 (97.5%)	30 (75.0%)
No	3 (7.5%)	2 (5.0%)	1 (2.5%)	10 (25.0%)
MOAA/S ≤ 4 on 3 consecutive measurements - n (%)				
Yes	40 (100%)	40 (100%)	40 (100%)	40 (100%)
No	0	0	0	0
Completion of colonoscopy procedure - n (%)				
Yes	40 (100%)	40 (100%)	39 (97.5%)	40 (100%)
No	0	0	1 (2.5%)	0
Requirement for rescue sedative - n (%)				
Yes	3 (7.5%)	2 (5.0%)	1 (2.5%)	10 (25.0%)
No	37 (92.5%)	38 (95.0%)	39 (97.5%)	30 (75.0%)
Manual or mechanical ventilation required – n (%)				
Yes	0	0	0	0
No	40 (100%)	40 (100%)	40 (100%)	40 (100%)

Source of data: Section 14.2, Table 14.2.1.1

Secondary efficacy results (most important)

Figure 2: MOAA/S Score against study time point (Study 004, ITT population)



[1] 0=PRE-DOSE WITHIN 15 MIN OF DOSING, 1-51 refers to n minutes post dose, where n=(1 to 51).

Source: Listings 16.2.6.1

As shown in Figure 2 above, for the ITT population the CNS7056 treatments led to quicker (1.5 to 2.0 minutes) and deeper sedation compared to midazolam treatment. The deepest sedation with CNS7056 was observed after approximately 2 minutes, with the highest loading dose (8.0 mg) giving the deepest sedation (MOAA/S 1), compared with a MOAA/S of 2 in the other CNS7056 treatment groups. The onset of sedation appeared to be slower with midazolam, and the depth shallower, as the peak depth of MOAA/S 2.5 was not reached until approximately 15 minutes.

Table 7: Time to event Secondary Endpoints (Study 004, ITT population)

Time to Event (min)	Remimazolam 8.0/3.0 mg (N=40)	Remimazolam 7.0/2.0 mg (N=40)	Remimazolam 5.0/3.0 mg (N=40)	Midazolam 2.5/1.0 mg (N=40)
Start of procedure (mean)	2.23	3.03	2.65	4.80
Peak sedation from first dose				
Mean (SD)	2.7 (2.71)	4.0 (5.03)	4.4 (5.29)	6.4 (4.81)
p-value	<0.001	0.023	0.050	0.005
Fully alert from last dose				
Mean (SD)	13.6 (7.48)	11.3 (5.69)	13.3 (7.21)	15.2 (7.43)
Median (min, max)	11.0 (3, 31)	10 (1, 25)	12.0 (5, 34)	15.0 (4, 31)
p-value	0.323	0.014	0.226	0.106
Ready for discharge from last dose				
Mean (SD)	14.6 (8.52)	12.4 (6.72)	11.3 (4.86)	15.3 (8.13)
Median (min, max)	11.5 (3, 36)	10.0 (3, 30)	10.0 (6, 28)	14.0 (4, 35)
p-value	0.652	0.078	0.016	0.056
Ready for discharge after end of colonoscopy				
Mean (SD)	5.0 (6.29)	4.6 (4.58)	3.8 (4.16)	5.5 (6.59)
Median (min, max)	5.0 (0, 26)	5.0 (0, 20)	5.0 (0, 16)	5.0 (0, 28)
p-value	0.680	0.475	0.170	0.569

Abbreviations: ITT = Intent-to-Treat; max = maximum; min = minimum; SD = standard deviation

All p-values are based on an ANOVA model with treatment as the main effect; the p-values listed in the CNS 7056 columns are for pairwise comparisons between each CNS 7056 group and the Midazolam group; the p-value in Midazolam column is for the overall comparison.

Source: CNS7056-004 In-text Table 11.4, Table 11.5, Table 11.6.

Between the two top-up doses of 2 mg and 3 mg, the 2 mg dose resulted in more subjects who recalled the procedure. Brice Questionnaire results showed that 92.5%, 70.0%, 90.0%, and 87.5% of subjects treated with 8.0/3.0 mg, 7.0/2.0 mg, 5.0/3.0 mg remimazolam, and 2.5/1.0 mg midazolam, respectively, could not remember anything about the procedure at 10 min after fully alert. This indicated that the 2 mg top-up dose was slightly inferior compared to the 3 mg top-up doses. Implementing a simple calculation as risk mitigation for dosing errors, the top-up dose was set at 50% of the initial dose (i.e. 2.5 mg) in the Phase III trials.

Additionally, an important aspect of study drug administration in this field, and particularly with a short acting agent, is the number of top-up doses that are required in order to (a) start the procedure, and (b) complete the procedure overall. The number of top-ups to start the procedure was lower in the CNS7056 groups (mean of 0.10, 0.30 and 0.18 for the 8.0/3.0, 7.0/2.0 and 5.0/3.0 groups, respectively) compared to the midazolam group (0.93). This would usually translate to a shorter time to the start of procedure, which can be seen from the mean time to procedure start from administration of the first dose of study drug (2.23, 3.03, and 2.65 minutes for the CNS7056 8.0/3.0, 7.0/2.0 and 5.0/3.0 groups, respectively) compared 4.80 minutes for the midazolam group. Overall, the number of top-ups required throughout the whole procedure, including sedation induction, was generally lower for the CNS7056 groups (mean of 1.43, 2.35, and 1.98 for the 8.0/3.0, 7.0/2.0, and 5.0/3.0 groups, respectively) compared to the midazolam group (2.48).

2.5.2. Main studies

Main study 1: CNS7056-006 "A Phase 3 Study Evaluating the Efficacy and Safety of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in Patients Undergoing Colonoscopy"

Methods

Study Participants

Inclusion criteria

a) Male and female, aged ≥18, scheduled to undergo a diagnostic or therapeutic colonoscopy (therapeutic procedures may include: haemostasis, resection, ablation decompression, foreign body extraction)

b) American Society of Anesthesiologists Score I through III

c) Body mass index (BMI) ≤ 40 kg/m^2

d) For female patients with child-bearing potential: negative result of pregnancy test as well as use of birth control during the study period

Exclusion criteria

a) Patients with a known sensitivity to benzodiazepines, flumazenil, opioids, naloxone, or a medical condition such that these agents are contraindicated

b) Chronic use of benzodiazepines for any indication (eg. insomnia, anxiety, spasticity)

c) Female patients with a positive serum HCG pregnancy test at screening or baseline

d) Lactating female patients

e) Patients with positive drugs of abuse screen or a positive serum ethanol at baseline

f) Patient with a history of drug or ethanol abuse within the past 2 years

g) Patients in receipt of any investigational drug within 30 days or less than seven half-lives (whichever is longer) before the start of study or scheduled to receive one during the study period.

Location/setting: 13 centres in the USA.

- **Treatments and overall design**

The study is a Phase 3 prospective, multicentre, randomised, double-blind placebo and open-label midazolam study in patients undergoing a colonoscopy for diagnostic or therapeutic reasons.

Patients were randomised into one of three groups: remimazolam (double-blind); placebo (double-blind) and midazolam (open-label). All patients received fentanyl to provide analgesia and 0.9% NaCl solution up to 1,000 mL drip starting prior to the procedure, if their fluid status allowed. For rescue sedation, only midazolam was allowed.

After pre-treatment with fentanyl, subjects received an initial dose of 5.0 mg remimazolam or matching placebo over 1 min or 1.75 mg midazolam over 2 min (or 1.0 mg midazolam for adults ≥60 years of age or debilitated or chronically ill). For the remimazolam and placebo arms, supplemental doses of 2.5 mg at least 2 min apart were allowed until adequate sedation (MOAA/S score ≤3) was achieved and as necessary to maintain sedation (MOAA/S ≤4). For midazolam, supplemental doses of 1.0 mg over 2 min with 2 min between doses (or 0.5 mg for the elderly) were allowed to achieve and maintain adequate sedation.

The number of supplemental doses of study drug throughout the procedure was not limited; however, more than 5 doses (including the initial dose) within any 15-min period for remimazolam/placebo or more than 3 doses (including the initial dose) within any 12-min period for midazolam were considered treatment failure. In these cases, subjects received sedative rescue medication (i.e., midazolam dosed at the investigator's discretion) to complete the procedure.

Fentanyl was administered for pain control. Fentanyl was originally administered at a dose of 75 µg immediately before administration of the initial dose of the study medication. The dose was reduced to 50 µg in Protocol Amendment 4. Suitable dose reductions for elderly and debilitated subjects, and supplemental doses of 25 µg fentanyl every 5-10 min were allowed until adequate analgesia was achieved or a maximum dose of 200 µg per procedure had been reached.

- **Outcomes/endpoints**

Primary efficacy endpoints:

Success of the colonoscopy procedure; a composite endpoint consisting of the following:

3. Completion of the colonoscopy procedure, **AND**
4. No requirement for an alternative sedative medication, **AND**
5. No requirement of more than 5 top-ups of study medication within any 15 min period. (For midazolam only: no requirement of more than 3 top-ups within any 12 min period).

Secondary efficacy endpoints:

1. time to start of procedure after administration of the first dose of study medication; 2. time to peak sedation after administration of the first dose of study medication (Lowest MOAA/S score after initial dose); 3. times to ready for discharge after the end of colonoscopy (colonoscope out) and after the last injection of study drug (defined as ability to walk unassisted); 4. times to fully alert (time to first of 3 consecutive MOAA/S scores of 5 after the end of colonoscopy [colonoscope out] and after the last injection of study drug); 5. MOAA/S scores by time point; 6. recall of the procedure by the Brice questionnaire administered when full alertness was regained and on Day 4; 7. changes to the patient's cognitive function assessed by the HVLT-R™ administered before study medication administration and after the fully alert criteria had been achieved; 8. ready to discharge score 30, 60 and 90 minutes post injection of the initial dose; 9. Drowsiness VAS to assess for signs of resedation; 10. requirement for flumazenil during the procedure; 11. patient's self-evaluation of "back-to-normal" after the procedure.

Safety endpoints: 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.

- **Randomisation**

Prior to dosing, patients will be randomly assigned in a 30:6:10 ratio to remimazolam, placebo, and open-label midazolam. The randomisation schedule will be computer-generated using a permuted block algorithm and will randomly allocate study drug randomisation numbers. The unblinded pharmacist will call the central IWRS and enter the requested information. The IWRS will then assign the next randomisation number in the sequence and inform the pharmacist of the study treatment assignment. Randomisation will be stratified by age group and the strata will be monitored to ensure that at least 100 remimazolam patients in the ≥ 65 yrs age group will be randomised.

- **Blinding (masking)**

The unblinded pharmacist prepared the study drug. The identity of the blinded study drugs (remimazolam and placebo) was not revealed to study management or to anyone at the study site except for the pharmacist, the pharmacy staff and Premier's unblinded monitor until after the study is completed. The pharmacist and staff will not participate in other study procedures. Patients were blinded to treatment. Midazolam arm was open label.

- **Statistical methods**

Analysis populations

- The safety population will consist of all randomised 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 randomised and will be analyzed as randomised
- 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 randomised treatment according to their randomisation and the planned treatment schedule and did not have any major protocol violations
- A second Safety Population (Safety (Nellcor)) consisted of all patients in the Safety Population who had usable Nellcor data and were analyzed as treated.

The primary efficacy analysis (success of the procedure using a composite endpoint) will be summarised descriptively.

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

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

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 to account for fentanyl use strata. The following three strata will be formed based on overall fentanyl dose:

< 100 µg; 100 - 150 µg; >150 - 200 µg

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

The only imputed data was drowsiness scores that were imputed as 100 if the patient was too drowsy to complete the assessment. There was no other imputation of missing data.

Subgroup analyses by gender, age group and ASA status were performed on the primary efficacy parameter. Subgroup analyses by gender, age group, ASA status, requirement for rescue sedative medication were performed on the time to fully alert and time to discharge.

Results

- **Participant flow**

Table 8: Subject accountability (all randomised patients)

Analysis Sets	Remimazolam N=298 n (%)	Placebo N=60 n (%)	Midazolam N=103 n (%)	TOTAL N=461 n (%)
Randomized	298 (100.0%)	60 (100.0%)	103 (100.0%)	461 (100.0%)
Safety Population[a]	296 (99.3%)	60 (100.0%)	102 (99.0%)	458 (99.3%)
Safety Population (Nellcor) - At least 1 Parameter usable[b]	216 (72.5%)	42 (70.0%)	71 (68.9%)	329 (71.4%)
Safety Population (Nellcor) - Usable Heart Rate[b1]	214 (71.8%)	40 (66.7%)	71 (68.9%)	325 (70.5%)
Safety Population (Nellcor) - Usable Respiratory Rate[b2]	116 (38.9%)	19 (31.7%)	37 (35.9%)	172 (37.3%)
Safety Population (Nellcor) - Usable Oxygen Saturation[b3]	216 (72.5%)	42 (70.0%)	71 (68.9%)	329 (71.4%)
Intention-to-treat Analysis Set[c]	298 (100.0%)	60 (100.0%)	103 (100.0%)	461 (100.0%)
Modified Intention-to-treat Analysis Set[d]	296 (99.3%)	60 (100.0%)	102 (99.0%)	458 (99.3%)
Per-Protocol Analysis Set[e]	228 (76.5%)	44 (73.3%)	77 (74.8%)	349 (75.7%)

Source: Section 14.1, Table 14.1.1.1.
N = number of patients; n = number of observations
[a] The Safety Population consists of all randomized patients who received any amount of study drug and were analyzed as treated.
[b] Safety Population (Nellcor) consists of all patients in the Safety Population who had usable Nellcor data in at least 1 parameter
[b1] Consists of all patients in the Safety Population who had usable Heart Rate data (Nellcor)
[b2] Consists of all patients in the Safety Population who had usable Respiratory Rate data (Nellcor)
[b3] Consists of all patients in the Safety Population who had usable Oxygen Saturation data (Nellcor)
[c] The Intent-to-treat analysis set includes all patients who were randomized and were analyzed as randomized.
[d] The Modified Intent-to-treat analysis set includes all patients in the ITT population who received at least 1 complete dose of study medication.
[e] The Per-Protocol analysis set includes all patients from the ITT analysis set who did not have any major protocol deviations

Three randomised patients discontinued from the study without receiving any treatment: One patient was terminated early due to a Nellcor device error; one was terminated early as the investigator added an oesophagogastroduodenoscopy procedure; Another patient terminated early due to a protocol violation, having been included despite a known sensitivity to study drug(s).

Table 9: Disposition of patients (safety population)

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

Source: Section 14.1, Table 14.1.2.1.
IMP = investigational medicinal product; N = number of patients; n = number of observations

Two patients withdrew consent and terminated the study early: 1 (1.7%) patient in the placebo group withdrew consent on Day 2, and 1 (1.0%) patient in the midazolam group withdrew consent on Day 1.

- **Baseline data**

The mean (± SD) age of patients was 54.9 (10.05) years. The majority of patients were younger than 65 years (395 [86.2%] patients). The study enrolled slightly more female patients than male (240 [52.4%] and 218 [47.6%], respectively), with a greater disparity observed in the placebo group (35 [58.3%] and 25 [41.7%], respectively) than in the other treatment groups. Overall, the majority of patients were either white (339 [74.0%] patients) or black (80 [17.5%] patients). Mean height and weight were comparable between treatment groups. The mean (± SD) BMI overall was 29.0 (4.81).

Table 10: ASA-PS Score (Safety Population)

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

Source: Section 14.1, Table 14.1.3.3
ASA = American Society of Anesthesiologists performance status; N = number of patients; n = number of observations

- **Outcomes and estimation**

Primary efficacy endpoint

Table 11: Primary Efficacy Endpoint Results – Success of Colonoscopy Procedure (Study 006, ITT population)

	Remimazolam (N=298)	Placebo (N=60)	Midazolam (N=103)	Total (N=461)
Success	272 (91.3%)	1 (1.7%)	26 (25.2%)	299 (64.9%)
Failure	26 (8.7%)	59 (98.3%)	77 (74.8%)	162 (35.1%)
Reason for failure				
Rescue sedative medication	10 (3.4%)	57 (95.0%)	66 (64.1%)	133 (28.9%)
Too many doses within the predefined time window	18 (6.0%)	44 (73.3%)	56 (54.4%)	118 (25.6%)
Procedure not completed	7 (2.3%)	1 (1.7%)	2 (1.9%)	10 (2.2%)
Comparison	**Differences in rates**	**95% Confidence Interval***		
		Lower	**Upper**	**p-value****
Remimazolam vs. Placebo	0.8961	0.8505	0.9416	<0.0001
Remimazolam vs. Midazolam	0.6603	0.5705	0.7501	

** p-value calculated from a Cochran-Mantel-Haenszel test accounting for fentanyl strata.

N = number of subjects; n = number of observations

Regarding the primary efficacy endpoint results, conducted in the ITT population, treatment success was observed in 272 (91.3%) patients in the remimazolam group, compared to 1 (1.7%) patient in the placebo group and 26 (25.2%) patients in midazolam group. The difference in treatment success rates between remimazolam and placebo is 0.8961 (95% CI: 0.8505, 0.9416); between remimazolam and midazolam 0.6603 (95% CI: 0.5705, 0.7501).

Regarding reasons for treatment failure, in the remimazolam group, 18 of the 26 treatment failures received too many doses within the predefined time window, 10 required rescue sedative medications, and 7 did not complete the procedure. The most frequently reported reason for failure in the placebo group was use of rescue sedative medication (57 out of 59 patients), and 1 patient did not complete the procedure. In the midazolam group, 66 of the 77 failures received rescue sedative medication, 56 received too many doses in the predefined time window, and 2 did not complete the procedure. For all groups, more than 1 reason for treatment failure per patient was possible.

Key secondary efficacy endpoints

Table 12: Time-to-Event Results (Study 006)

Time to event (min)	Remimazolam (N=296)	Placebo (N=60)	Midazolam (N=102)	p-value [b]
Start of procedure from first dose				
Number of subjects	296	60	102	
Median (95% CI) [a]	4.0 (-, -)	19.5 (18.0, 21.0)	19.0 (17.0, 20.0)	<0.0001
Hazard ratio (95% CI) [c]		6.13 (4.42, 8.52)	4.77 (3.68, 6.19)	
Peak sedation from first dose				
Number of subjects	296	60	102	
Median (95% CI) [a]	3.0 (-, -)	-	-	<0.0001
Hazard ratio (95% CI) [c]		NA	21.14 (9.32, 47.97)	
Ready for discharge from end of procedure				
Number of subjects	296	60	102	
Median (95% CI) [a]	44.0 (42.0, 46.0)	49.0 (44.0, 54.0)	48.0 (41.0, 51.0)	<0.0001
Hazard ratio (95% CI) [c]		2.01 (1.48, 2.72)	1.49 (1.18, 1.88)	
Ready for discharge from last dose				
Number of subjects	296	60	102	
Median (95% CI) [a]	51.0 (49.0, 54.0)	60.5 (55.0, 67.0)	57.0 (53.0, 61.0)	<0.0001
Hazard ratio (95% CI) [c]		2.42 (1.78, 3.28)	1.72 (1.36, 2.16)	
Fully alert from end of procedure				
Number of subjects	293	59	101	
Median (95% CI) [a]	6.0 (5.0, 7.0)	15.0 (13.0, 21.0)	13.0 (11.0, 16.0)	<0.0001
Hazard ratio (95% CI) [c]		3.42 (2.49, 4.71)	2.53 (1.98, 3.24)	
Fully alert from last dose				
Number of subjects	296	60	102	
Median (95% CI) [a]	14.0 (13.0, 14.0)	28.0 (24.0, 32.0)	24.0 (22.0, 26.0)	<0.0001
Hazard ratio (95% CI) [c]		4.70 (3.37, 6.56)	3.30 (2.57, 4.25)	

Abbreviations: CI = confidence interval; mITT = modified Intent-to-Treat.

a From the Kaplan-Meier analysis.

b Remimazolam vs. placebo; log-rank test stratified for fentanyl dose group (<100 µg, 100-150 µg, >150 µg.)

c Hazard ratio for remimazolam vs. placebo and midazolam. Wald confidence limits from Cox's proportional hazard model are presented.

Median time to start of procedure was 4.0 minutes in remimazolam group, 19.5 minutes (95% CI: 18.0, 21.0) in placebo group and 19.0 minutes (95% CI: 17.0, 20) in midazolam group. First and third quartiles were: 3 and 6 minutes (remimazolam); 17 and 23 minutes (placebo); 12 and 21 minutes (midazolam).

Median time to peak sedation was 3.0 minutes in remimazolam group. In placebo and midazolam group, the median time to peak sedation could not be estimated as the majority of patients were censored (for not reaching MOAA/S score of 3 at the time of their last MOAA/S assessment).

Median time to ready for discharge from the end of colonoscopy was 44.0 minutes (95% CI: 42.0, 46.0) in remimazolam group, 49.0 minutes (95% CI: 44.0, 54.0) in placebo group, and 48.0 minutes (95% CI: 41.0, 51.0) in midazolam group.

Median time to fully alert from the end of colonoscopy was 6.0 minutes (95% CI: 5.0, 7.0) in remimazolam group, 15.0 minutes (95% CI: 13.0, 21.0) in placebo group, and 13.0 minutes (95% CI: 11.0, 16.0) in midazolam group.

- **Ancillary analyses**

Sensitivity analyses

Sensitivity analysis of the primary efficacy outcome in the ITT analysis set was performed using subgroups based on the amount of fentanyl received. Results were obtained for 2 strata: patients receiving <100 µg fentanyl, and patients receiving 100-150 µg fentanyl. Analysis for patients receiving >150 µg was not possible as too few patients received doses this high. Results were similar to those seen in the primary efficacy analysis. For the comparison between the remimazolam group and the placebo group in the <100 µg fentanyl stratum, the difference in rates was 0.9392 (95% CI: 0.9007, 0.9777), and was statistically significant; in the 100-150 µg fentanyl stratum, the difference in rates was 0.8877 (95% CI: 0.8232, 0.9522), and was statistically significant. Results for the comparison between remimazolam and midazolam were comparable to those seen in the primary efficacy analysis.

Results of sensitivity analysis in the mITT and PP analysis sets were comparable to those in the ITT analysis set.

Subgroup analyses

Subgroup analysis based on gender showed treatment success in a numerically higher proportion of male patients (154 [70.3%] patients) than female patients (145 [59.9%] patients); for both genders, differences between treatment groups were similar to those seen in the overall population.

Subgroup analysis based on age groups (<65 years, ≥65 years) showed similar success rates, with success reported in 256 (64.3%) patients in the <65 years group and 43 (68.3%) patients in the ≥65 years group overall; an imbalance in the size of the subgroups was observed, with 398 patients aged <65 years, and 63 patients aged ≥65 years. In the remimazolam group, success rates were numerically higher in the patients aged ≥65 years than in those aged <65 years (100% and 89.9%, respectively); in the midazolam group however, the success rate was 28.1% in patients aged <65 years, compared to 7.1% in patients aged ≥65 years. There was no difference in success rate between age groups in the placebo group.

In subgroup analysis based on ASA-PS score, treatment success was observed overall in 104 (72.7%) patients with an ASA-PS of I, in 173 (60.5%) patients with an ASA-PS of II, and in 22 (71.0%) patients with an ASA-PS of III. In the remimazolam group, the success rate was similar in patients with ASA-PS scores of I and III (94.7% and 95.7%, respectively) but lower in patients with an ASA-PS score of II (88.9%). In contrast, amongst patients treated with midazolam, a successive decrease in the success rate was observed from ASA-PS scores of I (37.8%), to II (19.7%), to III (0.0%).

Main study 2: CNS7056-008: "A Phase 3 Study Evaluating the Efficacy and Safety of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in Patients Undergoing Bronchoscopy"

Methods

- **Study participants**

Inclusion criteria

1. Male and female, 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)
2. American Society of Anesthesiologists Physical Status Score 1 through 3
3. BMI $\leq$ 45
4. SpO2 $\geq$ 90% in ambient air or with no more than 2L/min of O2 support
5. 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
6. 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.

Exclusion criteria

1. Patients with a known sensitivity to benzodiazepines, flumazenil, opioids, naloxone, or a medical condition such that these agents are contraindicated
2. Bronchoscopy outside the bronchoscopy unit (e.g. ICU)
3. Patients on mechanical ventilation
4. Tracheal stenosis
5. Planned Laser bronchoscopy, rigid scope bronchoscopy
6. 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
7. Female patients with a positive pregnancy test at screening or baseline and lactating female patients
8. Patients with positive drugs of abuse screen (unless explained by concomitant medication) or a positive ethanol test at baseline
9. Patient with a history of drug or ethanol abuse within the past 2 years.

Location/setting: 15 centres in the USA.

- **Treatments and overall design**

This is a phase 3 prospective, double-blind, randomised, multi-centre, parallel-group trial assessing the efficacy, pharmacokinetics (PK), and safety of remimazolam compared to placebo in patients undergoing flexible bronchoscopy with an additional midazolam arm (open-label).

All patients received 0.9% NaCl solution up to 1,000 mL drip starting prior to the procedure and 75 µg (later amended to 25 to 50 µg) of fentanyl immediately prior to the administration of the trial medication (with dose reductions at the investigator's discretion for elderly and debilitated patients).

Patients were randomised to receive an initial single iv dose over one minute of remimazolam 5.0 mg or an equal volume of placebo in a blinded manner, and bronchoscopy started when adequate sedation (MOAA/S $\leq$3) was achieved.

Sedation could 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 was not limited as long as not more than five doses were administered in any 15-minute window. If five doses within 15 minutes were not sufficient to obtain adequate sedation for the bronchoscopy, this was defined as a treatment failure.

In the open-label midazolam arm, the drug was administered according to existing US label recommendation following a requirement by the FDA. Healthy adults <60 years of age received 1.75 mg of midazolam as an initial dose over two minutes. Adult patients $\geq$60 years of age, debilitated or chronically ill patients received 1.0 mg as an initial dose over two minutes. Sedation could be maintained by further doses of 1.0 mg in healthy adults <60 years; in the case of adults $\geq$60 years, debilitated, or chronically ill patients, the dose was 0.5 mg. These subsequent doses were titrated slowly and administered over at least two minutes. At least two or more additional minutes were allowed to fully evaluate the sedative effect. The overall number of midazolam doses was not limited as long as not more than three doses were administered in any 12-minute window. Should three doses within any 12-minute window not be sufficient to obtain adequate sedation for the bronchoscopy, this was considered a treatment failure.

After determination of treatment failure, midazolam was defined as the only sedative rescue medication in such cases in order to perform or finalise the bronchoscopy, irrespective of the randomised treatment.

The initial fentanyl dose was 75 µg, to be administered as an analgesic pretreatment immediately prior to administration of the initial dose of the trial medication. Top-up doses of fentanyl of 25 µg were allowed every 5-10 minutes until analgesia was adequate or the maximum dose of 200 µg per procedure had been given. The fentanyl dose for elderly and debilitated patients could be reduced at the discretion of the investigator consistent with labelling of fentanyl. Amendment 5.0 introduced a general reduction of initial fentanyl dose to 25 to 50 µg or a suitable reduced dose for elderly or debilitated patients.

- **Outcomes/endpoints**

Primary efficacy endpoints:

Success of the bronchoscopy procedure; a composite endpoint consisting of the following:

1. Completion of the bronchoscopy procedure, **AND**
2. No requirement for a rescue sedative medication, **AND**
3. 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).

Secondary efficacy endpoints: 1. time to start of procedure after administration of the first dose of study medication; 2. time to peak sedation after administration of the first dose of study medication; 3. 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. 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. MOAA/S scores by time point; 6. recall of the procedure by the Brice questionnaire administered when full alertness is regained and on Day 4; 7. changes to the patient's cognitive function by the Hopkins Verbal Learning Test - Revised (HVLT-R) administered before study medication administration and after the fully alert criteria have been achieved; 8. readiness to discharge score 30, 60 and 90 minutes post t = 0; 9. Drowsiness visual analogue scale to assess for signs of resedation; 10. requirement for flumazenil during the procedure; 11. patient's self-evaluation of "back-to-normal" after the procedure.

Further secondary endpoint: Population PK analysis

Safety endpoints: 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.

- **Randomisation**

Prior to dosing, patients were randomly assigned in a 30:6:6 ratio to remimazolam, placebo and open-label midazolam. The randomisation schedule was be computer-generated using a permuted block algorithm and randomly allocated study drug randomisation numbers. The randomisation numbers were be assigned sequentially as patients are entered into the study.

Randomisation will be stratified by age group. Study site will not be stratified in the randomisation schedule. Stratification for the amount of chronic opioids and/or benzodiazepines was not done.

At Study Day 1, after confirming that a patient still meets entry criteria, study personnel will inform the pharmacist that the subject qualifies for randomisation. The unblinded pharmacist will call the central IWRS and enter the requested information. The IWRS will then assign the next randomisation number in the sequence and inform the pharmacist of the study treatment assignment. Thereafter, the pharmacist will dispense the corresponding treatment.

- **Blinding (masking)**

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 Premier's 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.

- **Statistical methods**

Analysis populations

- The safety population will consist of all randomised 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 randomised and will be analyzed as randomised
- 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 randomised treatment according to their randomisation and the planned treatment schedule and did not have any major protocol violations.
- The secondary safety populations consisted of all patients in the safety population who had usable Nellcor data ("usable" was defined as at least 90% of readable Nellcor data per parameter available within the observation time, ie, the time from the first dose of trial medication until fully alert).

The primary efficacy analysis (success of the procedure using a composite endpoint) will be summarised descriptively for overall success and within each category for treatment group.

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

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

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 to account for fentanyl, opioid and benzodiazepine dose strata.

The following three strata were formed based on overall fentanyl dose: <100 µg; 100 to 150 µg; >150 µg (initially specified as >150 to 200 µg in the Protocol v1.0, but it was updated in the SAP to account for the change in fentanyl dose according to Amendment 5).

Comparisons between treatment groups will be performed in a descriptive manner for the secondary efficacy endpoints. For the key secondary variables (variables 1 through 6), only the pairwise comparison between placebo and remimazolam was used for exploratory efficacy significance testing.

Additional analyses

Additional sensitivity analyses will be performed to assess the influence of opioids (including fentanyl) and benzodiazepines on sedation in the three treatment groups.

Sensitivity analyses to assess the effect of the amount of fentanyl given during the study, chronic opioid dose, and chronic benzodiazepine dose (including fentanyl) and benzodiazepines will be performed on variables 1-9. They will be performed by including the doses of the medication as additional factors. For analyses the amount of fentanyl given during the study, chronic opioid dose, and chronic benzodiazepine dose will be formed. The analysis will then be changed to a stratified log rank test (variables 1-6) or a logistic regression (variable 8), while opioid (including fentanyl) and benzodiazepine strata will be added as an additional factor for the ANOVA for variables 5, 7 and 9.

Regarding subgroup analyses, the secondary efficacy endpoints were additionally analyzed by gender, age group, ASA-PS status, and rescue medication taken (yes/no).

Results

- **Participant flow**

Table 13: Subject accountability (all randomised patients)

	Remimazolam N = 310 n (%)	Placebo N = 63 n (%)	Midazolam N = 73 n (%)	Total N = 446 n (%)
Randomized patients	310 (100.0)	63 (100.0)	73 (100.0)	446 (100.0)
Safety population[a]	303 (97.7)	60 (95.2)	68 (93.2)	431 (96.6)
Safety Nellcor population - at least one parameter usable[b]	274 (88.4)	53 (84.1)	59 (80.8)	386 (86.5)
Safety Nellcor population - usable heart rate[b1]	269 (86.8)	53 (84.1)	59 (80.8)	381 (85.4)
Safety Nellcor population - usable RR[b2]	84 (27.1)	26 (41.3)	20 (27.4)	130 (29.1)
Safety Nellcor population - usable oxygen saturation[b3]	274 (88.4)	53 (84.1)	59 (80.8)	386 (86.5)
ITT population[c]	310 (100.0)	63 (100.0)	73 (100.0)	446 (100.0)
mITT population[d]	303 (97.7)	60 (95.2)	68 (93.2)	431 (96.6)
PP population[e]	154 (49.7)	35 (55.6)	33 (45.2)	222 (49.8)
PK population[f]	4 (1.3)	1 (1.6)	-	5 (1.1)

Source: Section 14.1, Table 14.1.1.1
Abbreviations: ITT = intent to treat; mITT = modified intent to treat; N = number of patients; n = number of observations; PK = pharmacokinetic(s), PP = per protocol; RR = respiratory rate
Note: Percentages were based on the total number of patients who were randomized.
[a] The safety population consisted of all randomized patients who received any amount of the trial medication and were analyzed as treated.
[b] Safety Nellcor Population consisted of all patients in the safety population who had usable Nellcor data in at least one parameter.
[b1] Consisted of all patients in the safety population who had usable heart rate data (Nellcor).
[b2] Consisted of all patients in the safety population who had usable RR data (Nellcor).
[b3] Consisted of all patients in the safety population who had usable oxygen saturation data (Nellcor).
[c] The ITT population included all patients who were randomized and were analyzed as randomized.
[d] The mITT population included all patients in the ITT population who received at least one complete dose of the trial medication.
[e] The PP population included all patients from the ITT analysis set who did not have any major protocol deviations.
[f] The numbers and percentages of the patients in the PK population were hand calculated.

15 randomised patients were excluded from the safety set (defined as all randomised patients who received any amount of trial medication): 7 patients randomised to remimazolam; 3 patients randomised to placebo and 5 patients randomised to midazolam.

Table 14: Disposition of patients (safety set)

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

Source: Section 14.1, Tables 14.1.2.1
Abbreviations: ET = early termination; IMP = investigational medicinal product; N = number of patients; n = number of observations
Note: percentages were based on the number of patients randomized.

Five patients in remimazolam and one patient in midazolam arm were lost to follow-up.

- **Baseline data**

Patients between 22 and 95 years of age were enrolled in the trial, 198 patients (45.9%) were male, and 233 patients (54.1%) were female, and the majority of patients (358 patients [83.1%]) were white. Overall, patients had a height between 142 and 191 cm and a weight between 32 and 183 kg, with a resulting BMI of between 14 and 45 kg/m^2. Patients were overall balanced across treatment groups according to medical history.

Table 15: ASA-PS Score Assessment (Safety Population)

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

Source: Section 14.1, Table 14.1.3.3
Abbreviations: ASA-PS = American Society of Anesthesiologists - Physical Status; N = number of patients; n = number of observations

- **Outcomes and estimation**

Primary efficacy endpoint

Table 16: Primary Efficacy Endpoint Results – Success of Bronchoscopy Procedure (Study 008, ITT population)

Subject Outcome	Remimazolam N=310	Placebo N=63	Midazolam N=73	Total N=446
Success	250 (80.6%)	3 (4.8%)	24 (32.9%)	277 (62.1%)
Failure	60 (19.4%)	60 (95.2%)	49 (67.1%)	169 (37.9%)
Reasons for failure				
Rescue sedative medication taken	49 (15.8%)	57 (90.5%)	39 (53.4%)	145 (32.5%)
Too many doses within the predefined time window	14 (4.5%)	10 (15.9%)	10 (13.7%)	34 (7.6%)
Procedure not completed	9 (2.9%)	3 (4.8%)	5 (6.8%)	17 (3.8%)
Comparison	**Rate Differences**	**95% Confidence Interval**		**p-value**
		Lower limit	**Upper limit**	
Remimazolam vs placebo	0.7588	0.6903	0.8274	<0.0001
Remimazolam vs midazolam	0.4777	0.3613	0.5941	

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

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

Regarding the primary efficacy endpoint results, conducted in the ITT population, treatment success was observed in 250 patients (80.6%) in remimazolam group, in 3 patients (4.8%) in placebo and 24 patients (32.9%) in midazolam groups. The difference in rates for remimazolam versus placebo was 0.7588 (95%-CI: 0.6903, 0.8274) and was statistically significant (P <0.0001). The difference in rates for remimazolam versus midazolam was 0.4777 (95%-CI: 0.3613, 0.5941).

The most common reason for treatment failure in all three treatment groups was the need for rescue sedative medications.

Main Secondary efficacy endpoints

Table 17: Time-to-Event Results (Study 008)

Time to event (min)	Remimazolam (N=303) [a]	Placebo (N=60) [a]	Midazolam (N=68) [a]	p-value [b]
Start of procedure from first dose				
Number of subjects	300	60	68	
Median (95% CI) [a]	4.1 (4.0, 4.8)	17.0 (16.0, 17.5)	15.5 (13.8, 16.7)	<0.0001
Peak sedation from first dose				
Number of subjects	303	60	68	
Median (95% CI) [a]	3.5 (3.5, 4.0)	-	7.0 (7.0, -)	<0.0001
Fully alert from end of procedure				
Number of subjects	302	60	68	
Median (95% CI) [a]	6.0 (5.2, 7.1)	13.6 (8.1, 24.0)	12.0 (5.0, 15.0)	0.0001
Fully alert from last dose				
Number of subjects	302	60	68	
Median (95% CI) [a]	11.6 (10.0, 12.8)	20.0 (15.3, 31.0)	18.0 (15.0, 20.1)	0.0001
Ready for discharge from end of procedure				
Number of subjects	302	60	68	
Median (95% CI) [a]	60.0 (57.0, 63.0)	81.0 (70.0, 100.0)	66.0 (62.0, 72.0)	0.0004
Ready for discharge from last dose				
Number of subjects	303	60	68	
Median (95% CI) [a]	64.8 (62.0, 68.5)	93.0 (75.0, 107.0)	70.0 (67.0, 87.0)	0.0002

Abbreviations: CI = confidence interval

Refer to CNS7056-008 for censoring rules.

a From the Kaplan-Meier analysis.

b Wald confidence limits from Cox's proportional hazard model are presented. p-value is calculated from log-rank test.

The median time to the start of the procedure from the first dose of randomised trial medication was shorter in remimazolam group (4.1 minutes [95%-CI: 4.0, 4.8]) than in the placebo and midazolam groups (17.0 minutes [95%-CI: 16.0, 17.5] and 15.5 minutes [95%-CI: 13.8, 16.7], respectively). In the comparison of remimazolam versus placebo, the corresponding hazard ratio was 2.936 (95%-CI: 2.202, 3.914) and was statistically significant (P <0.0001). The corresponding hazard ratio for the comparison of remimazolam versus midazolam was 2.869 (95%-CI: 2.183, 3.772).

The time to peak sedation after administration of the first dose of randomised trial medication was analysed using the first of the lowest MOAA/S scores <4 after the initial dose before any top-up. The median time to peak sedation was shorter in the remimazolam group (3.5 minutes [95%- CI: 3.5, 4.0]) than in the midazolam group (7.0 minutes [95%-CI: 7.0, -]). No data for the placebo group were available since peak sedation (MOAAS ≤3) prior to the first top-up/rescue was only reached for 1 patient (1.6%) in the placebo group compared to the majority of patients in the remimazolam group (180 patients [58.1%]) and 7 patients (9.6%) in the midazolam group.

The median time to ready for discharge after the end of the bronchoscopy was shorter in the remimazolam group (60.0 minutes [95%-CI: 57.0, 63.0]) than in the placebo group (81.0 minutes [95%-CI: 70.0, 100.0]) and slightly shorter than in the midazolam group (66.0 minutes [95%-CI: 62.0, 72.0]). The hazard ratio of the comparison of remimazolam versus placebo was 1.658 (95%-CI: 1.246, 2.206) and was statistically significant (P = 0.0004). The corresponding hazard ratio for the comparison of remimazolam versus midazolam was 1.442 (95%-CI: 1.101, 1.890).

The median time to ready for discharge after the last dose of trial or rescue sedative drug was slightly lower in the remimazolam group (64.8 minutes [95%-CI: 62.0, 68.5]) than in the midazolam group (70.0 minutes [95%-CI: 67.0, 87.0]) and lower than in the placebo group (93.0 minutes [95%-CI: 75.0, 107.0]). The hazard ratio of the comparison remimazolam versus placebo was 1.697 (95%-CI: 1.277, 2.257) and was statistically significant (P = 0.0002). The corresponding hazard ratio for the comparison remimazolam versus midazolam was 1.495 (95%-CI: 1.140, 1.959).

The time to fully alert after the end of the bronchoscopy procedure (bronchoscope out) is defined as time to first of 3 consecutive MOAA/S scores of 5. The median time to fully alert after the end of the bronchoscopy was shorter in remimazolam group (6.0 minutes [95%-CI: 5.2, 7.1]) than in the placebo and midazolam groups (13.6 minutes [95%-CI: 8.1, 24.0] and 12.0 minutes [95%-CI: 5.0, 15.0], respectively). The hazard ratio of the comparison of remimazolam versus placebo was 1.725 (95%-CI: 1.296, 2.297) and was statistically significant (P = 0.0001). Hazard ratio for the comparison of remimazolam versus midazolam was 1.127 (95%-CI: 0.863, 1.471).

The median time to fully alert after the last dose of trial or rescue sedative drug was shorter in the remimazolam group (11.6 minutes [95%-CI: 10.0, 12.8]) than in the placebo and midazolam groups (20.0 minutes [95%-CI: 15.3, 31.0] and 18.0 minutes [95%-CI: 15.0, 20.1], respectively). The corresponding hazard ratio for the comparison of remimazolam versus placebo was 1.732 (95%-CI: 1.298, 2.311) and was statistically significant (P = 0.0001). The corresponding hazard ratio for the comparison of remimazolam versus midazolam was 1.230 (95%-CI: 0.942, 1.605).

- **Ancillary analyses**

Sensitivity analyses

Sensitivity analyses of the primary efficacy outcome were performed to assess the influence of opioids (including fentanyl) and benzodiazepines on the sedation in the three treatment groups.

In all three fentanyl strata (<100 µg, 100-150 µg, and >150 µg), statistically significant differences in success rates in the comparison remimazolam versus placebo were shown (<100 µg: 0.8699 [95%-CI: 0.7888, 0.9511], P <0.0001; 100-150 µg: 0.6667 [95%-CI: 0.4889, 0.8445], P <0.0001; >150 µg: 0.2400 [95%-CI: 0.0726, 0.4074] P = 0.0421). Also, statistically significant differences were shown in analyses conducted in strata based on the patients' initial fentanyl dose (ie. 25 - <50 µg; 50 - <75 µg; ≥75 µg). In the sensitivity analysis by chronic opioid use, the differences in success rates between the remimazolam and placebo groups were also statistically significant.

Furthermore, a sensitivity analysis was conducted by chronic benzodiazepine use, which also showed statistically significant differences in rates between the remimazolam and placebo groups (yes: 0.6327 [95%-CI: 0.4977, 0.7676], P = 0.0010, no: 0.7845 [95%-CI: 0.7098, 0.8593], P <0.0001).

Results for the comparison between remimazolam and midazolam were comparable to those seen in the primary efficacy analysis, except that the difference in success rates was smaller for the initial fentanyl stratum ≥75 µg (0.0067 [95%-CI: -0.3244, 0.3377]).

Results of sensitivity analysis in the mITT and PP analysis sets were comparable to those in the ITT analysis set, except that the difference in success rates between the remimazolam and placebo groups was not statistically significant for the fentanyl stratum >150 µg in the PP population (0.3333 [95%-CI: -0.2001, 0.8668], P = 0.4142).

Sensitivity analyses were performed for several secondary outcomes. The median times to the start of the procedure were similar when analyzed in subgroups based on total fentanyl use, and chronic opioid use. The median time for the patients in the subgroup with chronic benzodiazepine use was 6.6 minutes (95%-CI: 4.4, 9.7) and was slightly higher than the median time for those patients who had no chronic benzodiazepine use (4.0 minutes [95%-CI: 4.0, 4.6]).

Regarding time to peak sedation, sensitivity analyses results were similar to those of the main analysis when analyzed in subgroups based on total fentanyl use, chronic opioid use, and chronic benzodiazepine use.

Based on the total fentanyl use, the median time to ready for discharge after bronchoscope out was slightly higher for the patients with >150 µg (5.0 minutes [95%-CI: -, -] than for the patients with <100 µg (3.5 minutes [95%-CI: 3.4, 3.8]) and those with 100-150 µg (4.0 minutes [95%-CI: 3.0, -]). The results for the analysis conducted in subgroups based on chronic opioid use, and chronic benzodiazepine use were similar to those of the main analysis.

Regarding time to fully alert after bronchoscope out, in the fentanyl stratum 100-150 µg, the median time to fully alert in the remimazolam group was 13.6 minutes (95%-CI: 8.0, 24.0), higher than in the midazolam group (12.0 minutes [95%-CI: 2.5, 23.8]) and lower than in the placebo group (15.0 minutes [95%-CI: 6.0, 35.4]). In the stratum >150 µg, the median time was higher in the remimazolam group (37.9 minutes [95%-CI: 6.0, 52.0]) than in the placebo and midazolam groups (30.0 minutes [95%-CI: 2.5, 39.8] and 18.0 minutes [95%-CI: 7.0, 32.0], respectively).

Regarding time to fully alert after the last injection of sedative drug, in the fentanyl stratum 100-150 µg, the median time to fully alert in the remimazolam group was 18.5 minutes (95%-CI: 15.0, 30.4) and was similar in the midazolam group (18.8 minutes [95%-CI: 9.0, 28.8]) and the placebo group (20.0 minutes [95%-CI: 10.3, 44.4]). In the stratum >150 µg, the median time was higher in the remimazolam group (44.2 minutes [95%-CI: 14.0, 66.0]) than in the placebo and midazolam groups (33.0 minutes [95%-CI: 18.0, 48.0] and 33.0 minutes [95%-CI: 16.0, 42.0], respectively).

Subgroup analyses

Regarding the primary outcome, results similar to those of the primary analysis were shown for the subgroups based on gender, age group, ASA-PS status, and chronic opioid use. In the subgroup of patients with chronic benzodiazepine use, a success was reported for 31 patients (63.3%) compared with a success for 219 patients (83.9%) in the subgroup with no chronic benzodiazepine use.

Regarding rime to ready for discharge after bronchoscope out, results similar to those of the main analysis were shown for the analyses by gender and age group. Patients with an ASA-PS status of I had higher median times, but these subgroup consisted only of low numbers of patients. In the subgroup of patients who did not take any rescue medication, the median values were similar in the remimazolam and midazolam groups (59.0 minutes [95%-CI: 56.0, 61.0] and 58.5 minutes [95%-CI: 50.0, 64.0]) and slightly higher in the placebo group, which only consisted of 3 patients (72.5 minutes [95%-CI: 65.0, 80.0]).

Summary of main studies

The following Table 18 and Table 19 summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18: Summary of efficacy for trial CNS7056-006

Title:"A Phase 3 Study Evaluating the Efficacy and Safety of Remimazolam (CNS 7056) Compared to Placebo and Midazolam in Patients Undergoing Colonoscopy"			
Study identifier	CNS7056-006		
Design	a Phase 3 prospective, multicentre, randomised, double-blind placebo and open-label midazolam study in patients undergoing a colonoscopy		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	28 days Screening visit up to 21 days before dosing 4 (+3/-1 days) after dosing	
Hypothesis	Superiority over placebo; exploratory over midazolam		
Treatments groups	Remimazolam	Active treatment. Initial dose/ Top-up doses allowed. Randomised: 300	
	Placebo	Inactive comparator. Initial dose/ Top-up doses allowed. Randomised: 60	
	Midazolam	Active comparator. Initial dose/ Top-up doses allowed. Randomised:	
Endpoints and definitions	Primary endpoint – composite	Success of the procedure	Completion of the colonoscopy procedure, AND No requirement for an alternative sedative medication, AND No requirement of more than 5 top-ups of study medication within any 15 min period. (For midazolam only: no requirement of more than 3 top-ups within any 12 min period)
	Secondary endpoint	Time to start	time to start of procedure after administration of the first dose of study medication
	Secondary Endpoint	Time to peak sedation	time to peak sedation after administration of the first dose of study medication (Lowest MOAA/S score after initial dose)
	Secondary Endpoint	Time to discharge	times to ready for discharge after the end of colonoscopy (colonoscope out) and after the last injection of study drug (defined as ability to walk unassisted)
	Secondary endpoint	Time to fully alert	times to fully alert (time to first of 3 consecutive MOAA/S scores of 5 after the end of colonoscopy [colonoscope out] and after the last injection of study drug)
Database lock	16 June 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT for the primary endpoint; mITT for time-to-event endpoints Time points depend on duration of procedure; secondary endpoints are time-to-event endpoints		
Descriptive statistics	Treatment group	Remimazolam	Placebo	Midazolam

and estimate variability	Number of subjects	298	60	103
	Success of procedure n (%)	272 (91.3)	1 (1.7)	26 (25.2)
	Time to start Median (95% CI) (min)	4.0 (-, -)	19.5 (18.0, 21.0)	19.0 (17.0, 20.0)
	Time to peak sedation Median (95% CI) (min)	3.0 (-, -)	-	-
	Time to discharge from end of procedure Median (95% CI) (min)	44.0 (42.0, 46.0)	49.0 (44.0, 54.0)	48.0 (41.0, 51.0)
	Time to fully alert from last dose Median (95% CI) (min)	14.0 (13.0, 14.0)	28.0 (24.0, 32.0)	24.0 (22.0, 26.0)

Effect estimate per comparison	Primary endpoint	Comparison groups	Remimazolam vs. placebo
		Difference in success rates	0.8961
		95% CI	0.8505, 0.9416
		P-value (calculated from a Cochran-Mantel-Haenszel test accounting for fentanyl strata)	<0.0001
	Secondary endpoint: Time to start of procedure	Comparison groups	Remimazolam vs. placebo
		Hazard ratio	6.13
		95% CI	4.42, 8.52
		P-value (from a log-rank test, stratified for fentanyl dose group) – for all time-to-event endpoints	<0.0001
	Secondary endpoint: Time to peak sedation	Comparison groups	Remimazolam vs.placebo
		Hazard ratio	N/A
		95% CI	N/A
		P-value	
	Secondary endpoint: Time to discharge from end of procedure	Comparison groups	Remimazolam vs. placebo
		Hazard ratio	2.01
		95% CI	1.48, 2.72
		p-value	0.0003
	Secondary endpoint:	Comparison groups	Remimazolam vs. placebo

	Time to fully alert from last dose	Hazard ratio	4.70
		95% CI	3.37, 6.56
		p-value	<0.0001
Notes	US sites only.		

Table 19: Summary of efficacy for trial CNS7056-008

Title:" A Phase III Study Evaluating the Efficacy and Safety of Remimazolam (CNS 7056) compared to Placebo and Midazolam in Patients Undergoing Bronchoscopy"			
Study identifier	CNS 7056-008		
Design	a Phase 3 prospective, multicentre, randomised, double-blind placebo and open-label midazolam study in patients undergoing a bronchoscopy		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28 days Screening visit up to 21 days before dosing 4 (+3/-1 days) after dosing
Hypothesis	Superiority over placebo; exploratory over midazolam		
Treatments groups	Remimazolam		Active treatment. Initial dose/ Top-up doses allowed. Randomised: 310
	Placebo		Inactive comparator. Initial dose/ Top-up doses allowed. Randomised: 63
	Midazolam		Active comparator (open label). Initial dose/ Top-up doses allowed. Randomised: 73
Endpoints and definitions	Primary endpoint – composite	Success of the procedure	Completion of the colonoscopy procedure, AND No requirement for an alternative sedative medication, AND No requirement of more than 5 top-ups of study medication within any 15 min period. (For midazolam only: no requirement of more than 3 top-ups within any 12 min period)
	Secondary endpoint	Time to start	time to start of procedure after administration of the first dose of study medication
	Secondary Endpoint	Time to peak sedation	time to peak sedation after administration of the first dose of study medication (Lowest MOAA/S score after initial dose)
	Secondary Endpoint	Time to discharge	times to ready for discharge after the end of colonoscopy (colonoscope out) and after the last injection of study drug (defined as ability to walk unassisted)
	Secondary endpoint	Time to fully alert	times to fully alert (time to first of 3 consecutive MOAA/S scores of 5 after the end of colonoscopy [colonoscope out] and after the last injection of study drug)
Database lock	20 June 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	ITT for the primary endpoint; mITT for time-to-event endpoints Time points depend on duration of procedure; secondary endpoints are time-to-event endpoints			
Descriptive statistics and estimate variability	Treatment group	Remimazolam	Placebo	Midazolam
	Number of subjects	310	63	73
	Success of procedure n (%)	250 (80.6)	3 (4.8)	24 (32.9)
	Time to start Median (95% CI) (min)	4.1 (4.0, 4.8)	17.0 (16.0, 17.5)	15.5 (13.8, 16.7)
	Time to peak sedation Median (95% CI) (min)	3.5 (3.5, 4.0)	-	7.0 (7.0, -)
	Time to discharge from end of procedure Median (95% CI) (min)	60.0 (57.0, 63.0)	81.0 (70.0, 100.0)	66.0 (62.0, 72.0)
	Time to fully alert from last dose Median (95% CI) (min)	11.6 (10.0, 12.8)	20.0 (15.3, 31.0)	18.0 (15.0, 20.1)

Effect estimate per comparison	Primary endpoint	Comparison groups	Remimazolam vs. placebo
		Difference in success rates	0.7588
		95% CI	0.6903, 0.8274
		P-value (calculated from a Cochran-Mantel-Haenszel test accounting for fentanyl strata)	<0.0001
	Secondary endpoint: Time to start of procedure	Comparison groups	Remimazolam vs. placebo
		Hazard ratio	2.94
		95% CI	2.20, 3.91
		P-value (from a log-rank test) – for all time-to-event endpoints	<0.0001
	Secondary endpoint: Time to peak sedation	Comparison groups	Remimazolam vs. placebo
		Hazard ratio	46.72
		95% CI	6.55, 333.47
		P-value	
	Secondary endpoint:	Comparison groups	Remimazolam vs. placebo
		Hazard ratio	1.66

	Time to discharge from end of procedure	95% CI	1.25, 2.21
		p-value	0.0004
	Secondary endpoint: Time to fully alert from last dose	Comparison groups	Remimazolam vs. placebo
		Hazard ratio	1.73
		95% CI	1.30, 2.31
		p-value	0.0001
Notes	US sites only.		

Analysis performed across trials (pooled analyses and meta-analysis)

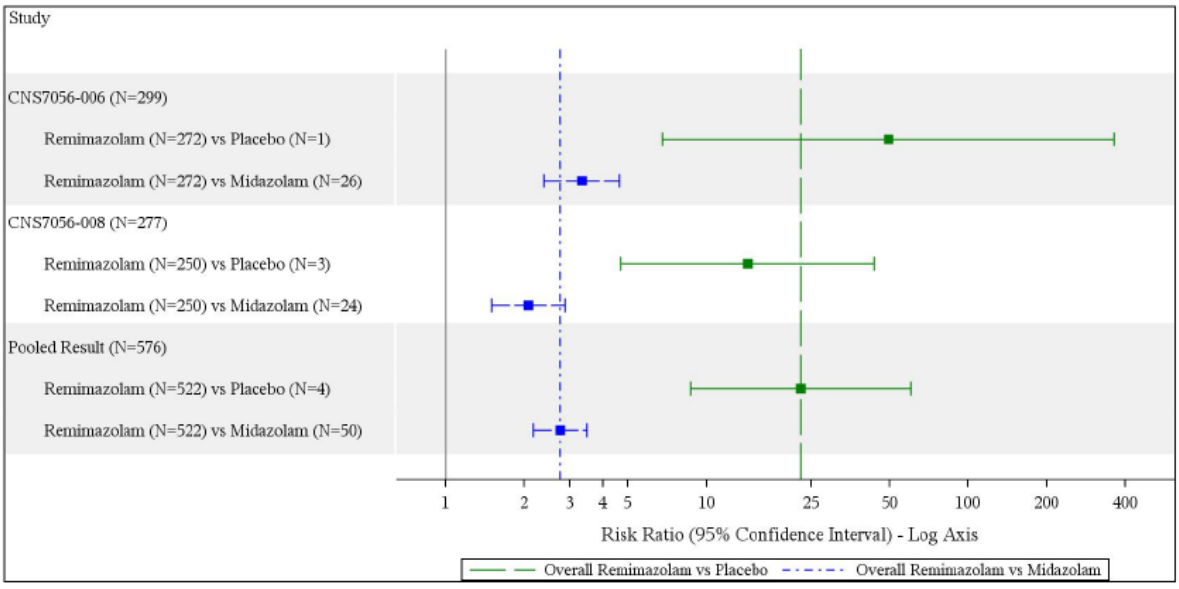
The applicant presented the integrated summary of efficacy.

The main focus was the pooled data analysis of the Phase 3 trials (analysis of two Phase 3 trials CNS7056-006 and CNS7056-008 (Group A) to compare:

- Success rate remimazolam vs placebo (before rescue midazolam).
- Success rate remimazolam vs midazolam (open label midazolam dosing per USPI).
- Onset time to event endpoints remimazolam vs midazolam (midazolam dosing per USPI).
- Recovery time to event endpoints remimazolam vs placebo (midazolam dosing per common medical practice).

Main results pooled analysis will be presented briefly below.

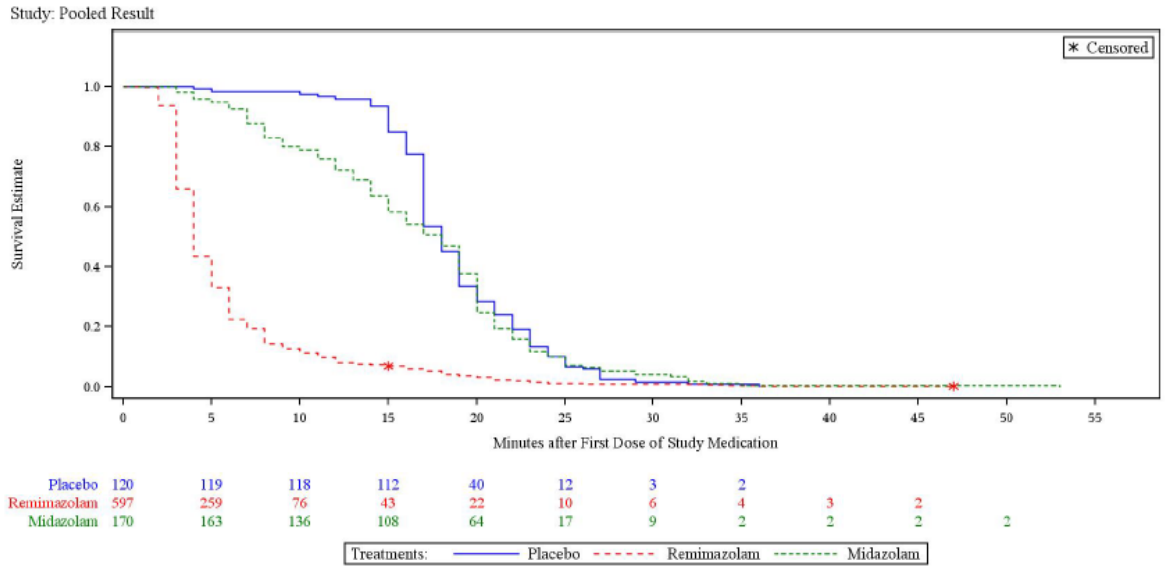
Figure 3: Forest Plot of the Risk Ratios of Success Rates in Placebo Controlled Studies in Procedural Sedation using the Cochran-Mantel-Haenszel Test (mITT Population - Group A)



Reference: Table 3.1.1.1 Note: Integrated analysis Group A includes studies CNS7056-006 and CNS7056-008.
Note: A log2 scale is used for the x-axis. Vertical lines represent 1 and the overall risk ratios, independent of study. N = Subjects with procedure success.
Dataset: ADOUTPR , Program: f_succrate, Output: f_06_01_01_succrate_A.rtf, Generated on: 08MAY2018 10:57, Page 1 of 1

Source: ISE, Figure 6.1.1

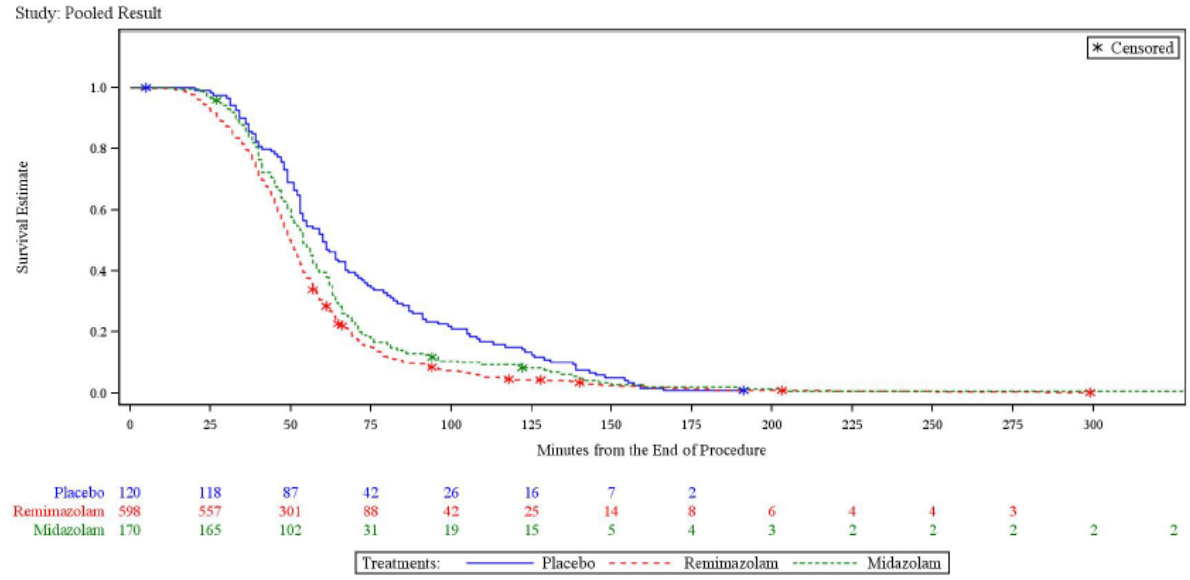
Figure 4: Kaplan-Meier Survival Plot of Time to Start of Procedure after First Dose of Study Medication in Placebo Controlled Studies in Procedural Sedation (ITT Population - Group A)



Reference: Table 3.2.1.1
Note: Integrated analysis Group A includes studies CNS7056-006 and CNS7056-008.
Numbers for each treatment represent the number of subjects at risk at the start of each 5 minute interval.
Dataset: ADTTE, Program: f_tte.sas, Output: f_06_02_01_01_tte_A_prcstart.rtf, Generated on: 08MAY2018 10:57, Page 3 of 3

Source: ISE, Figure 6.2.1.1

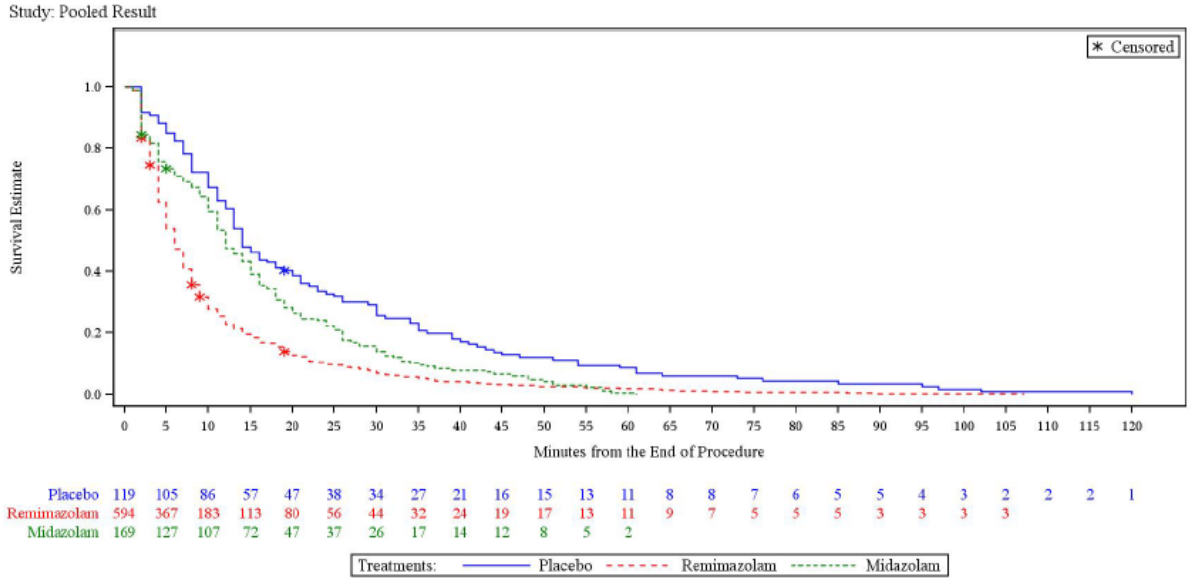
Figure 5: Kaplan-Meier Survival Plot of Time to Ready for Discharge from End of Procedure in Placebo Controlled Studies in Procedural Sedation (ITT Population - Group A)



Reference: Table 3.2.3.1
Note: Integrated analysis Group A includes studies CNS7056-006 and CNS7056-008.
Numbers for each treatment represent the number of subjects at risk at the start of each 25 minute interval.
Note: The figure is cut at 300 minutes and does not include the outlying ready for discharge from end of procedure time of 751 minutes for subject CNS7056-008-008003.
Dataset: ADTTE, Program: f_tte.sas, Output: f_06_02_03_01_tte_A_dschproc.rtf, Generated on: 08MAY2018 10:58, Page 3 of 3

Source: ISE, Figure 6.2.3.1

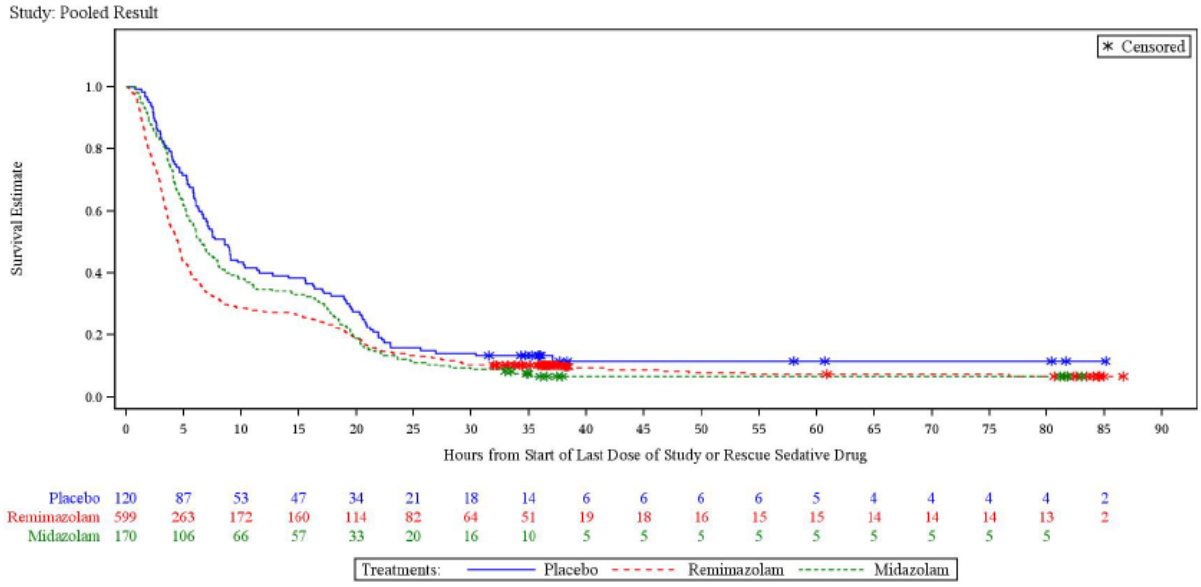
Figure 6: Kaplan-Meier Survival Plot of Time to Fully Alert from End of Procedure in Placebo Controlled Studies in Procedural Sedation (ITT Population - Group A)



Reference: Table 3.2.5.1
Note: Integrated analysis Group A includes studies CNS7056-006 and CNS7056-008.
Numbers for each treatment represent the number of subjects at risk at the start of each 5 minute interval.
Dataset: ADTTE, Program: f_tte.sas, Output: f_06_02_05_01_tte_A_alrtproc.rtf, Generated on: 08MAY2018 10:58, Page 3 of 3

Source: ISE, Figure 6.2.5.1

Figure 7: Kaplan-Meier Survival Plot of Time to Back to Normal from Start of Last Dose of Study or Rescue Sedative Drug in Placebo Controlled Studies in Procedural Sedation (ITT Population - Group A)



Reference: Table 3.2.7.1
Note: Integrated analysis Group A includes studies CNS7056-006 and CNS7056-008.
Numbers for each treatment represent the number of subjects at risk at the start of each 5 hour interval.
Dataset: ADTTE, Program: f_tte.sas, Output: f_06_02_07_01_tte_A_norm.rtf, Generated on: 08MAY2018 10:58, Page 3 of 3

Source: ISE Figure 6.2.7.1

Clinical studies in special populations

There were no dedicated clinical studies focusing on efficacy in children or elderly patients. Clinical trial CNS7056-012 examined PK parameters of remimazolam in subjects with end stage renal disease. Clinical trial ONO-2745IVU007 examined the PK and PD parameters of remimazolam in subjects with moderate and severe hepatic impairment.

The applicant summarised and discussed efficacy across age strata for patients included in the main trials in order to support that the benefit-risk among these patients is positive.

Supportive study

Supportive study 1: CNS7056-015 "A Phase 3 Study Evaluating the Safety and Efficacy of Remimazolam (CNS7056) Compared to Placebo and Midazolam in ASA III and IV Patients Undergoing Colonoscopy"

Methods

- **Study participants**

Inclusion criteria

- Male and female patients, aged ≥18, scheduled to undergo a diagnostic or therapeutic colonoscopy (therapeutic procedures may include haemostasis, resection, ablation, decompression, and foreign body extraction, for example).
- ASA grade III/IV
- For all female patients, negative result of urine or serum pregnancy test. Additionally, for women with childbearing potential only, use of birth control during the study period.
- Patient is willing and able to comply with study requirements and will be available for a Follow-up Visit on Day 1 (+ 1 day) and Follow-up Phone call (Day 4 +/- 3 days) after the colonoscopy.

Exclusion criteria

- Patients with a known sensitivity to benzodiazepines, flumazenil, opioids, naloxone, or a medical condition such that these agents are contraindicated.
- Patients clearly acutely intoxicated with alcohol or drugs of abuse at baseline.
- Patients with an inability to communicate well with the Investigator, or deemed unsuitable according to the Investigator (in each case providing a reason).

Locations/setting: 3 sites in the USA

- **Treatments and overall design**

Study 015 was a prospective, double-blind, randomised, placebo and active controlled, multicentre, parallel group phase 3 study comparing remimazolam to placebo, with an additional open-label arm for midazolam, in American Society of Anesthesiologists (ASA) grade III/IV patients undergoing a colonoscopy for diagnostic or therapeutic reasons.

Patients were randomised into one of 3 groups: remimazolam, placebo (double-blind) and midazolam (open label).

Table 20: Study 015 Treatments (source: CSR)

Trial Drug	Initial Dose	Top-up	n
Remimazolam	2.5 - 5.0 mg*	1.25 - 2.5 mg*	30
Placebo	-	-	15
Midazolam	1.0 mg	0.5 mg	30

*Dose range. Start with appropriate amount according to patient status according to the discretion of the investigator

IP formulation: Remimazolam will be presented as a lyophilised powder in a 10 mL vial, each vial containing 20 mg remimazolam, which will be reconstituted with sterile 0.9% NaCl solution to yield a 2.5 mg/mL solution for injection.

Sedation initiation:

- Remimazolam or placebo group: After the initial dose, further doses may be applied at least two minutes apart, until adequate sedation is achieved.
- Midazolam group: After the initial dose, further doses may be applied at least two minutes apart, until adequate sedation is achieved.

When adequate sedation for scope insertion has been achieved (MOAA/S ≤3) a colonoscope will be inserted and the procedure will be performed according to the usual clinical practice.

Sedation maintenance:

- Remimazolam or placebo group: Subsequent doses of study drug will be administered over 15 seconds, at least 2 minutes apart, to maintain the sedation (MOAA/S ≤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.
- Midazolam group: Subsequent doses will be administered over two minutes, at least two minutes apart, to maintain the sedation (MOAA/S ≤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.

Pre-treatment and rescue analgesia: Fentanyl will be administered as an analgesic pre-treatment at a maximum dose of 50 µg (with suitable dose reductions for debilitated patients according to the discretion of the investigator), immediately prior to administration of the initial dose of the study medication. Top-up doses of 25 µg fentanyl q 5-10 minutes are allowed until analgesia is adequate or a maximum dose of 200 µg per procedure has been given.

Rescue sedation: After determination of treatment failure, only midazolam may be administered as rescue sedation, according to local practice, in order to perform the colonoscopy.

- **Outcomes/endpoints**

Primary efficacy endpoint (composite):

- Completion of the colonoscopy procedure, AND
- No requirement for a rescue sedative medication, AND
- No requirement of more than 5 doses of trial medication within any 15-minute window. For midazolam only: no requirement of more than 3 doses within any 12-minute window.

Secondary efficacy endpoints:

1) Amount of fentanyl used. 2) The time to start of procedure after administration of the first dose of trial medication. 3) The time to peak sedation after administration of the first dose of randomised trial medication. 4) The time to fully alert (time to first of three MOAA/S scores of 5): after the end of colonoscopy procedure (colonoscope out) and after the last injection of randomised trial drug. 5) The MOAA/S scores by time point (at every time point up to 20 minutes post-dose, and thereafter as the last recorded score in each 5-minute time interval). 6) The recall of the procedure by the Brice questionnaire administered when full alertness was regained and on Day 4. 7) The drowsiness VAS 8) The requirement for flumazenil during the procedure (yes or no). 9) The investigator's satisfaction with the sedation agent (assessed using an NRS).

Safety endpoints: AEs, including AEs with focus on respiratory and cardiovascular parameters and AEs potentially related to abuse; Concomitant medication; Clinical laboratory test results; Vital signs; Pulse oximetry measurements; Transcutaneous pCO2 measurements; 12-lead and 3-lead ECG findings; Physical examination finding; Pain on injection intensity rating using VAS; Airway interventions; Administration of additional fluids or medication or any interventions necessary due to a clinically relevant change in ECG; Withdrawals due to the need for endotracheal intubation or the use of catecholamines; Administration of flumazenil.

PK endpoints (are to be described in separate PK analysis plan).

- **Randomisation**

Before dosing, patients will be randomly assigned in a 2:1:2 ratio to remimazolam, placebo, and open-label midazolam. A minimisation algorithm will be used for randomisation. This takes account of age group (< 65 years, 65-74 years, and ≥ 75 years) and ASA status (grade III or IV), and adjusts the probabilities of randomisation for each new patient based on the characteristics of that patient, to ensure that randomisation is balanced for both age and ASA status. The unblinded pharmacist will call the central interactive web response system (IWRS) and enter the requested information. The IWRS will then assign the next randomisation number in the sequence and inform the pharmacist of the study treatment assignment. Thereafter, the pharmacist will dispense the corresponding treatment.

Randomisation will be stratified by age group and ASA status. The aim is to have an approximately equal distribution between ASA status III and IV patients on remimazolam.

Study site will not be stratified in the randomisation schedule. Also, although foreseen for the primary analysis, patients will not be stratified for fentanyl use in the randomisation as the need for fentanyl dosing cannot be determined beforehand.

- **Blinding (masking)**

All patients, investigators, and study personnel involved in the conduct of the study, including data management, were to be blinded to treatment assignment in the 2 double-blind arms. The midazolam arm is open label.

In order to maintain the study blind, drug preparation for remimazolam and placebo was to be performed by an unblinded pharmacist at each site, and the final material provided to the investigational staff in a blinded manner.

DMC was involved for monitoring of safety. DMC members had access to unblinded data.

- **Statistical methods**

Analysis populations

- The ITT analysis set included all patients who were randomised and were analysed as randomised.
- The mITT analysis set included all patients included in the ITT analysis set who received at least 1 complete dose of randomised trial medication.
- The PP analysis set included all patients from the ITT analysis set who: received randomised treatment according to their randomisation and the planned treatment schedule and did not have any major protocol deviations.
- The Safety population consisted of all randomised patients who received any amount of trial drug and were analysed as treated.
- Secondary safety populations consisted of all patients in the Safety population who had usable Nellcor data and were analysed as treated.

The primary efficacy analysis (success of the procedure using the composite endpoint) will be summarised descriptively for overall success for each treatment group, with summaries to include the number and percentage of patients. No inferential statistical tests will be done.

For the continuous variables (amount of fentanyl used, Brice questionnaire, drowsiness VAS, and investigator satisfaction), pairwise comparisons at each time point using analysis of variance (ANOVA) models with treatment as the main effect will be done. Pairwise comparisons will be done between the midazolam and remimazolam group and between the placebo and remimazolam groups, and the 95% CI of the difference presented. Those CIs will be interpreted in an exploratory sense only; no formal hypotheses will be tested.

Subgroup analyses (on primary efficacy endpoint)

To investigate the effect of fentanyl on sedation, the success of the procedure will be summarised by subgroups of fentanyl use (<100 µg, 100-150 µg, >150-200 µg, >200 µg). If some of those subgroups have only few patients, then some of those categories may be combined for analysis. A decision about which subgroups will be included in the analysis will be made at the blinded data review meeting.

The success of the procedure will be summarised by subgroups of ASA status (ASA grade III and IV).

Results

- **Participant flow**

Table 21: Trial Populations (Study 015)

	Remimazolam N=32 n (%)	Placebo N=16 n (%)	Midazolam N=31 n (%)	TOTAL N=79 n (%)
Randomised Patients	32 (100)	16 (100)	31 (100)	79 (100)
Safety Population[a]	31 (96.9)	16 (100)	30 (96.8)	77 (97.5)
Safety Nellcor Population - At least one Parameter usable[b]	30 (93.8)	13 (81.3)	30 (96.8)	73 (92.4)
Safety Nellcor Population - Usable Heart Rate [b1]	29 (90.6)	13 (81.3)	29 (93.5)	71 (89.9)
Safety Nellcor Population - Usable Respiratory Rate[b2]	19 (59.4)	7 (43.8)	18 (58.1)	44 (55.7)
Safety Nellcor Population - Usable Oxygen Saturation[b3]	29 (90.6)	13 (81.3)	30 (96.8)	72 (91.1)
Intent-to-treat Analysis Set[c]	32 (100)	16 (100)	31 (100)	79 (100)
Modified Intent-to-treat Analysis Set[d]	31 (96.9)	16 (100)	30 (96.8)	77 (97.5)
Per-Protocol Analysis Set[e]	18 (56.3)	12 (75.0)	26 (83.9)	56 (70.9)

Source: Section 14.1, Tables 14.1.1.1

Table 22: Participant Disposition (Study 015, Safety population)

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

Source: Section 14.1, Tables 14.1.2.1
IMP = investigational medicinal product; N = number of patients; n = number of observations
Note: percentages are based on the number of patients randomised.

Protocol deviations led to exclusion from the PP analysis set. Major protocol deviations were reported in 21 patients (27.3%) in the Safety population. The most frequently observed major deviation was incorrect IMP dosing, observed in 19 patients (24.7%) overall; this was observed in more patients in the remimazolam group. These errors included administration of top-up doses when sedation was adequate (MOAA/S of 3 or less), inadequate windows between two doses (less than 2 minutes), and inadequate dose administration time. A complete listing of all reported protocol deviations (major and minor), by patient, is provided in the submitted dossier.

- **Baseline data**

The applicant presented tabulated baseline characteristics for each group and average numbers. The mean age was 62 years overall, and was comparable between the 3 treatment groups; the trial included more patients under the age of 65 (46 patients, 59.7%) than patients who were aged ≥65 years (31 patients, 40.3%), with no imbalance observed between treatment groups. The trial enrolled more male patients than female patients (55.8% versus 44.2% overall), with a greater imbalance observed in the

placebo groups (75.0% versus 25.0%) than in the other treatment groups; in the midazolam group, there were more female patients than male patients (53.3% versus 46.7%). Overall, the majority of patients were either white (57 patients, 74.0%) or black/African American (19 patients, 24.7%); a greater proportion of black/African American patients was observed in the midazolam group (33.3%) than in the remimazolam group (19.4%) or the placebo group (18.8%). The mean height was comparable between treatment groups. Mean weight was also comparable between groups, and was higher than might be considered normal, with a mean weight of 91.0 kg in the remimazolam group, 94.0 kg in the placebo group, and 87.9 kg in the midazolam group. The mean BMI overall was 30.8 kg/m2, with no difference observed between treatment groups.

Table 23: ASA-PS Score Assessment (Study 015, Safety population)

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

Source: Section 14.1, Tables 14.1.3.3

Details of medical and surgical history were summarised by treatment group. At the SOC level, the most frequently reported medical history was in vascular disorders (70 patients, 90.9%), surgical and medical procedures (68 patients, 88.3%), metabolism and nutrition disorders (67 patients, 87.0%), GI disorders (64 patients, 83.1%), respiratory, thoracic, and mediastinal disorders (57 patients, 74.0%), cardiac disorders (51 patients, 66.2%), musculoskeletal and connective tissue disorders (51 patients, 66.2%), and psychiatric disorders (50 patients, 64.9%).

- **Outcomes and estimation**

In the primary efficacy analysis, conducted in the ITT analysis set, the majority of patients (27 patients, 84.4%) in the remimazolam group met the criteria for successful completion of the procedure; in comparison, no patients in the placebo group (0 patients, 0.0%) and few the midazolam group (4 patients, 12.9%) completed the procedure successfully. For the 5 patients (15.6%) in the remimazolam group who failed to complete the procedure in accordance with the definition of success, the reasons for failure included the use of rescue sedative medication (3 patients, 9.4%), too many doses being used within the pre-defined time window (3 patients, 9.4%), and failure to complete the procedure (1 patient, 3.1%; this was Patient 3005 who was withdrawn without being treated).

Use of rescue sedative medication and use of rescue sedative medication were the most frequently reported reasons for failure in all 3 treatment groups, each reported in 43 patients (54.4%) overall. As might be expected, the use of rescue medication was reported in all patients in the placebo group (16 patients, 100.0%). Amongst 27 patients (87.1%) in the midazolam treatment group who failed, 24 patients (77.4%) failed due to the use of rescue medication; furthermore, 26 (83.9%) of these patients received too many doses of the IMP within the predefined window, which was also considered a reason for failure. More than 1 reason for failure was possible.

Table 24: Primary Efficacy Results – Success of the Procedure (Study 015, ITT population)

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

Source: Section 14.2, Table 14.2.1.1.1

Secondary efficacy results

The mean fentanyl dose (total) was numerically lower in the remimazolam group (59.7 µg) than in the placebo group (67.2 µg) or the midazolam group (66.7 µg). The median time to start of procedure was numerically lower in the remimazolam group than in the placebo or midazolam groups. The median time to peak sedation was 3.0 min in the remimazolam group but could not be estimated in the placebo or midazolam groups as more than half the subjects in the analysis were censored, having failed to reach a MOAA/S of 3 before the first supplemental dose of either randomised study medication or fentanyl. Both times to fully alert from the end of the colonoscopy and from the last dose of study medication or rescue sedative were shorter in the remimazolam group than in the placebo or midazolam group.

Table 25: Time to Event Secondary Efficacy Endpoints (Study 015, mITT population)

Time to event (min)	Remimazolam (N=31)	Placebo (N=16)	Midazolam (N=30)
Start of procedure from first dose			
Median (95% CI) [a]	5 (4.0, 5.0)	18.3 (17.0, 20.0)	19 (-, -)
Peak sedation from first dose			
Median (95% CI) [b]	3.0 (3.0, 3.6)	-	-
Fully alert from end of procedure			
Median (95% CI) [b]	3.0 (2.0, 4.0)	5.3 (4.0, 12.0)	7.0 (4.0, 12.0)
Fully alert from last dose			
Median (95% CI) [b]	11 (8.8, 12.0)	18 (14.0, 25.0)	18.8 (15.0, 26.0)

Abbreviations: CI = confidence interval

a Statistics taken from Kaplan-Meier analysis. Patients who did not reach the endpoint are excluded from analysis.

b Statistics taken from Kaplan-Meier analysis. Patients who did not reach the endpoint are censored at last observation.

Source: CNS7056-015 Table 14.2.3.4.1.1, Table 14.2.3.2.1.1, Table 14.2.3.3.1.1, Table 14.2.3.1.1.1

Evaluation of recall of the procedure using the Brice questionnaire showed no clinically relevant differences between treatment groups in terms of recall of the procedure, their satisfaction with the sedation, or the incidence of unwanted effects on the day after the procedure. Analysis of the investigators' assessment of satisfaction showed that mean satisfaction scores were comparable in the remimazolam group (9.1) and the midazolam group (9.4), but were numerically lower in the placebo group (7.5). All other secondary efficacy endpoints are also analysed and presented in the CSR.

- **Ancillary analyses**

Efficacy analyses included subgroup analyses according to fentanyl dose (<100 µg, 100-150 µg, >150-200 µg, >200 µg) and ASA status. Some additional analyses are mentioned in the CSP, but are regarded as not classified correctly.

Results were obtained for 2 fentanyl strata: patients receiving <100 µg fentanyl and patients receiving 100-150 µg fentanyl; an additional planned stratum for patients receiving >150-200 µg fentanyl included 1 patient (midazolam group), while a planned stratum for patients receiving>200 µg fentanyl did not include any patients. According to the CSR, a comparisons between the <100 µg fentanyl subgroup and the 100-150 µg fentanyl subgroup are difficult to interpret because of a disparity in the size of the 2 subgroups; the majority of patients (68/79 patients) received <100 µg fentanyl (29/32, 12/16 and 27/31 patients in remimazolam, placebo and midazolam group respecitely). The incidence of procedural success in this subgroup was largely comparable to that seen in the primary analysis, with success reported in 86.2% of the remimazolam group vs 0.0% and 14.8% of placebo and midazolam group respectively. Amongst 8 patients included in the 100-150 µg subgroup, 2 patients in the remimazolam group achieved success, while all 4 patients in the placebo group and 2 patients in the midazolam group failed to successfully complete the procedure.

The 27 patients in the remimazolam group who successfully completed the procedure were distributed evenly between the ASA-PS grade III subgroup (13 patients) and the ASA-PS grade IV subgroup (14 patients). Amongst 4 patients in the midazolam group who successfully completed the procedure, 3 had ASA-PS grade IV, while 1 had ASA-PS grade III. All patients in the placebo group failed to complete the procedure successfully.

Subgroup analysis showed little effect of fentanyl dose or ASA-PS on the success rate in remimazolam treated subjects.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical programme included several phase 2 and phase 3 procedures requiring sedation, with and without analgesia with fentanyl. Studies were mostly carried against placebo, with midazolam as an active comparator or rescue medication in most studies. This approach is acceptable.

The endpoint "success of the procedure" with the operational criteria was pragmatic and is considered adequate for registration purposes.

The choice of midazolam over propofol, the other possible alternative for procedural sedation / analgesia is understood, given the similarity of remimazolam to midazolam, and the approach to target the practitioner as the sedating personnel and not an anaesthetist.

Uncertainties were raised regarding the capability of the practitioner to perform both sedation and control the depth of sedation and perform the diagnostic procedure in the same timeframe as it would be performed with both practitioner and anaesthetist**.**

Also uncertain was the superiority in efficacy as compared to midazolam. Midazolam was underdosed in the trials where it was an active comparator, as the USPI (also similar to the proposed dosing of midazolam EU SmPC) recommend doses which are clearly below commonly used doses.

All 5 main trials were conducted in the US. The applicant has provided a discussion regarding extrapolation to EU population taking into consideration differences regarding standard of care in the clinical setting, the use of fentanyl and midazolam between the US and EU and procedural dissimilarities. The applicant explained who assessed the completion of the endoscopic procedure. Although the identity of the person assessing the completeness of the endoscopic procedure was not captured in the eCRF, the PI took ultimate responsibility for the correctness of all trial data. The number and relative frequency of incomplete procedures was very small (9 incompleted procedures out of 966 patients treated; i.e. 0.9%) and this is reassuring. It can be assumed that having an independent assessment would not significantly influence the results.

Phase 2 studies **CNS7056-003** and **CNS7056-004** are evaluated as dose response studies, Phase 3 studies **CNS7056-006 and CNS7056-008** are evaluated as main pivotal confirmatory studies while Phase 3 study **CNS7056-015** in ASA III/IV patients is evaluated as a supportive study.

Study **CNS7056-003** was a Phase 2a, dose-finding study evaluating the safety and efficacy of CNS 7056 (ie.remimazolam) compared to midazolam in patients undergoing diagnostic upper GI endoscopy. Patients were randomised to receive 1 of the 4 treatments: remimazolam 0.10 mg/kg, 0.15 mg/kg, or 0.20 mg/kg; or midazolam 0.075 mg/kg, delivered as a single IV injection over 1 minute. Rescue with midazolam was allowed as at the discretion of the administering physician. This is the only study in procedural sedation that was performed withought concomitant use of fentanyl for analgesia. This is also the only study where dosing of remimazolam was done according to body weight, and top-up doses of remimazolam/midazolam were not used. In phase 3 studies the applicant decided to proceed with a fixed dose of 5mg remimazolam (which is lower than the doses used in this study) plus top-up doses consisting of 2.5mg remimazolam. The dose of midazolam in this study is too high compared to EU midazolam (adults <60 y: initial dose 2-2.5 mg). In this study the dose of midazolam was 0.075 mg/kg, which corresponds to 5.25mg for an adult weighing 70kg.

Study **CNS7056-004** was a Phase 2b study evaluating the safety and efficacy of multiple doses of CNS 7056 (i.e. remimazolam) compared to midazolam in patients undergoing colonoscopy. Patients were randomised to receive 1 of the 4 treatments: remimazolam 8mg initial dose+3mg top-ups; remimazolam

7mg initial+2mg top-ups; remimazolam 5mg initial+3mg top-ups; or the comparator midazolam 2.5mg initial+1mg top-ups. As rescue medications, several drugs were allowed, which is different from other procedural sedation studies where only midazolam rescue was allowed. Fentanyl was administered for analgesia (100 µg initially with top-ups allowed).

Study **CNS7056-006** was a phase 3 study evaluating the efficacy and safety of remimazolam compared to double-blind placebo and open-label midazolam in patients undergoing colonoscopy. Participants were randomised to receive one of the following 3 treatments: remimazolam 5mg initial dose+2.5mg top-ups; matching placebo or midazolam 1.75mg initial dose+1mg top-ups (for adults ≥60 years of age/debilitated/chronically ill initial dose of midazolam was reduced to 1mg and top-up doses were reduced to 0.5mg). The number of supplemental doses of study drug was not limited; however, more than 5 doses (including the initial dose) within any 15-min period for remimazolam/placebo or more than 3 doses (including the initial dose) within any 12-min period for midazolam were considered treatment failure. In these cases, participants received rescue midazolam dosed at the investigator's discretion. Fentanyl was administered for analgesia (initially 75µg, reduced to 50µg in protocol amendment 4; top-ups were allowed). The initial dose of midazolam is slightly lower than EU midazolam. The ITT set was used for the primary efficacy analysis and consisted of all randomised patients: 298 in remimazolam; 60 in placebo and 103 in midazolam arms. The ITT set (all randomised) and safety set (received any amount of study drug) differ by 3 patients, who were excluded prior to receiving any treatment and their exclusion was unlikely to introduce bias.

Study **CNS7056-008** was a phase 3 study evaluating the efficacy and safety of remimazolam compared to double-blind placebo and open-label midazolam in patients undergoing bronchoscopy. Patients were randomised to receive remimazolam, placebo or midazolam in the same doses as in study 006. The same criteria was used for declaring treatment failure and rescue sedative was also midazolam. Fentanyl was administered for analgesia (initially 75 µg, later amended to 25 to 50 µg; top-ups were allowed). The ITT set was used for the primary efficacy analysis and consisted of all randomised patients: 310 in remimazolam, 63 in placebo and 73 in midazolam. The ITT set and safety set differ by 7, 3 and 5 patients in remimazolam, placebo and midazolam arm, respectively. Details concerning 15 patients excluded after randomisation as well as details on missing information were provided upon request and indeed protocol deviations for the ITT population stratified by treatment arm are considered balanced.

Study **CNS7056-015** was a phase 3 study evaluating the safety and efficacy of remimazolam compared to double-blind placebo and open-label midazolam in ASA III and IV patients undergoing colonoscopy.

Dosing is based on phase 2 trials. However, none of the two phase 2 trials can entirely justify the dose initially proposed for marketing, since remimazolam doses were higher than the ones intended for marketing. Even the lowest dose in phase 2 trials, 5 mg initial + 3 mg top-ups (Study 004) does not correspond totally to the dose intended for marketing (5 mg initial + 2.5 mg top-ups, reduced for elderly). The applicant has reasoned that the 5mg bolus dose and 2.5 mg top up doses have been used in phase 3 trials and show the best B-R. The modelling of the 4 mg has shown interesting results since light and moderate sedation (58%) were comparable to the 5 mg (47%) with less (possibly 7%) deep sedation and only 4% more of non-responders. The top-up dose, being slightly smaller than the phase II studied dose is not debatable. Patient population is adequately selected and represents the target colonoscopy and bronchoscopy population. Study 015 included only patients with ASA grade III/IV, ie. patients with severe systemic disease (ASA III) and patients with severe systemic disease that is a constant threat to life (ASA IV). No imbalances regarding distribution of ASA grades was observed in study 015. Imbalances in distribution of ASA grades per treatment arm were noted in studies 006 and 008. Patients allocated to placebo tended to have higher ASA grades (26.8% ASA III) than patients allocated to remimazolam (21.7%) and midazolam (17.0%).

Procedures selected for the broad indication of procedural sedation are colonoscopy and bronchoscopy (study 003 was a phase 2 trial in upper GI endoscopy but it is not considered pivotal since (too) high doses of both midazolam and remimazolam were used). According to the applicant, colonoscopies and bronchoscopies are listed among the top 10 surgical operations and procedures in the EU. This is acknowledged. Initially planned study CNS7056-007 was not conducted but substituted by the bronchoscopy trial (CNS7056-008).

Procedural sedation may be used for any procedure in which a patient's pain or anxiety is pronounced and may interfere with performance. This includes a variety of procedures of different duration, level of invasiveness and urgency. Due to its rapid onset of action and a favourable recovery profile, it can be expected that remimazolam will be of interest for procedures performed in emergency departments, such as closed reductions of dislocated joints, complicated laceration repair, diagnostic CT imaging and many other. Cardiac patients who at higher risk of sedation complications may also require procedural sedation for procedures such as left heart catheterisation or coronary stenting, electrical cardioversion and implantation of internal defibrillators, pacemakers or trans-femoral aortic valves. These patients/procedures were not evaluated during the procedural sedation programme of remimazolam.

The applicant discussed the generalisability of procedural sedation during colonoscopy and bronchoscopy to other procedures during which sedation may be required. In Studies CNS7056-006 and CNS7056-008, 577 out of 608 procedures lasted for less than 30 minutes amounting to almost 95% of all procedures. Only 31 out of 608 procedures lasted longer than (or equal to) 30 minutes amounting to 5% of all procedures. The numbers of patients with procedures lasting ≥30 minutes are very small, precluding firm conclusions on efficacy in this longer duration group. Numerically less successful procedures are observed with longer duration procedures for patients receiving remimazolam compared to shorter procedures. On the contrary, the proportion of successful procedures with midazolam stayed unchanged regardless of the duration of procedure. Proportion of successful procedures with placebo (real-life midazolam) even increased with longer procedures. However, proportion of success of procedures in procedures lasting ≥30 minutes is still higher in remimazolam compared to midazolam and placebo (real-life midazolam) groups. The frequencies of TEAEs in virtually all SOCs is higher in procedures lasting for ≥30 minutes compared to procedures lasting for less than 30 minutes. It is acknowledged that the numbers of procedures in the longer duration group are very small hampering meaningful comparisons. However, the same trend is apparent across all treatment groups (midazolam, remimazolam and placebo). The applicant's rationale of longer observation time allowing for more TEAEs to be collected is a reasonable explanation for this observation. The applicant was asked to update section 5.1 of the SmPC with information regarding main efficacy, safety and recovery data for procedures lasting less than 30 minutes compared to those lasting for ≥30 minutes in trials 006 and 008 in order to clearly informed the prescribers that in longer procedures recovery time with remimazolam was prolonged compared to midazolam.

The comparator for the 3 phase 3 studies was double-blind placebo and open-label midazolam. Initial dose of midazolam in studies **006** and **008** (1.75mg) is somewhat lower than the initial dose for indication conscious sedation for EU midazolam (2-2.5mg), while in study **003** the initial dose of midazolam is too high (0.075 mg/kg, corresponding to 5.25mg for an adult weighing 70kg). Studies **004** and **015** utilised midazolam dose in accordance with EU SmPC. Placebo as comparator is acceptable since rescue midazolam was allowed after failure of placebo. The majority of patients allocated to placebo were treated with midazolam according to investigators clinical practice.

Endpoints were similar for all 5 procedural sedation studies – primary endpoint for all studies (except study 015) was a composite endpoint evaluating the success of procedure. The main secondary endpoints were time-to-event endpoints that evaluated the onset (time to start of procedure and time to peak sedation) and recovery (time to fully alert, time to ready for discharge, time to back to normal) profile of

remimazolam. The primary outcome of study 015 was safety in ASA III/IV populations, but the efficacy outcomes were the same as for other procedural sedation studies.

The primary efficacy endpoint (success of procedure) is defined as follows:

> For Studies 003 and 004: ALL of the following: a) MOAA/S ≤4 on 3 consecutive measurements, AND b) Completion of the endoscopy procedure, AND c) No requirement for rescue sedative medication, AND d) No manual or mechanical ventilation.
>
> For Studies 006, 008 and 015: ALL of the following: a) Completion of the colonoscopy/bronchoscopy procedure, AND b) No requirement for an alternative sedative medication, AND c) No requirement of more than 5 doses of study medication within any 15 min window. (In the case of midazolam: no requirement of more than 3 doses within any 12 min window.)

These composite endpoints are in general acceptable although depending on the clinician's perspective, completing the colonoscopy/bronchoscopy might be more clinically relevant than not requiring rescue sedative.

Main secondary endpoints are clinically relevant time-to-event endpoints.

Statistical inference for study **006** and **008** was based on comparisons with placebo, while comparisons with midazolam were regarded as exploratory. The other procedural sedation studies presented only descriptive statistical analyses.

In general, no critical issues were identified during the assessment regarding study conduct and analysis. Analysis per treatment arm shows a large reduction in the incidence of deep sedation in remimazolam arm (from 24.5% to 6.4%), while the incidence of deep sedation in other two arms (midazolam and placebo), despite of small number of events, remained almost unchanged (midazolam: from 6.7% to 9.3%; placebo: from 12.5% to 11.8%). Identical results were obtained when patients with success of procedure were analysed. A reduction was also seen in remimazolam patients who received rescue midazolam (from 50% to 9.8%). However, the incidence of deep sedation was higher in those patients compared to patients treated with only remimazolam. After fentanyl dose reduction, the incidence of deep sedation seems to be of shorter duration.

Efficacy data and additional analyses

In general, during the assessment of efficacy in procedural sedation trials, only a few issues were identified. Notwithstanding, it has to be kept in mind that the midazolam arm in studies **006**, **008** and **015** was not blinded and the dosing of midazolam was not optimal as discussed earlier.

In Study **CNS7056-003**, regarding efficacy results, there seems to be a dose-response relationship. A clarification was requested regarding recommendation in section 4.2 of remimazolam SmPC about the initial and top-up doses in case of no narcotic medicinal product co-administration. Study 003 is the only procedural sedation study in which fentanyl was not used and no top-ups of remimazolam were allowed so the basis for the dosing recommendation is unclear. In fact, since the study did not foresee top-up doses, the applicant leans on the efficacy and safety of the 5mg plus 2.5 mg dose combination (i.e. top-up dose equals 50% of the initial bolus) in pivotal trials as rationale for choosing 3.5mg as top-up dose. In other words, there is no clinical data about top-ups in patients not receiving opioids. The applicant reduced the top-up dose in patients not receiving opioids from 3.5mg to 2.5mg claiming that this dose is 'similarly suited to maintain sedation, albeit when administered with a higher frequency but probably a lower risk of over-sedation'. Top-up doses of 2.5mg are used in patients receiving opioids. Reducing

top-up doses in patients not receiving opioids can be accepted based on the applicant's claims that the dose is similarly suited to maintain sedation.

An effect on the respiratory system (more desaturations and increased respiratory rate) is noted for remimazolam compared to midazolam. In Study 003 higher doses of remimazolam were used compared to doses intended for clinical use. This alone might be related to more desaturations. No rationale other than the comparatively higher dose is presented to explain the difference in hypoxia events leading to airway management between remimazolam (all dose levels) and midazolam. This is an acceptable explanation for the higher dose levels (0.15 mg/kg and 0.2 mg/kg remimazolam), but not for the lowest dose level (0.1 mg/kg remimazolam). However, both the separate healthcare professional who will be dedicated to monitoring the patient and the availability of flumazenil mitigate this risk.

Study **CNS7056-004** was not powered for inferential conclusions. Nevertheless, the results for primary and secondary efficacy endpoints suggest better efficacy of remimazolam over midazolam in the studied setting. All efficacy results are of the same direction and can suggest clinically relevant difference.

High success rates of colonoscopy procedures were observed (92.5%, 95%, 97.5% vs 75% for 8.0/3.0mg, 7.0/2.0mg, 5.0/3.0mg remimazolam vs midazolam group respectively). Significance testing of exploratory value was performed for each remimazolam dose and midazolam; remimazolam 7.0/2.0 and 5.0/3.0 treatment groups were statistically superior to midazolam (p=0.007 and 0.025 respectively). The 8.0/3.0 group was not statistically superior to midazolam (p=0.066). These results are important for contextualisation of remimazolam vs midazolam, since this is the only study where direct head-to-head comparison with double-blind midazolam was done. Requirement for rescue sedative medications was lower in remimazolam groups compared to midazolam group. Secondary efficacy endpoints indicated that remimazolam treatments led to earlier and quicker (1.5 to 2.0 min according to the applicant; around 0.5 min according to graphically presented MOAA/S scores by time point) onset of sedation compared to the midazolam treatment. It is questionable, though, is the modest shorter time of onset of sedation for remimazolam clinically significant compared to midazolam. Recovery times were favourable. High initial remimazolam doses of 8.0 mg were associated with non-desired deep level of sedation.

Mean number of top-up doses was lower for remimazolam compared to midazolam. Nevertheless, the duration of procedures was similar for all study groups (approx. 13-14 min).

The lowest remimazolam dose (5.0 mg) achieved the highest procedural sedation success rate and was also associated with the quickest recovery times. Thus, this dose was selected for the initial bolus dose in the Phase 3 trials. It can be agreed that top-up dose was set at 50% of the initial dose (i.e. 2.5 mg) in the Phase 3 trials.

In Study **CNS7056-006** treatment success was observed in 272 (91.3%) patients in the remimazolam group, compared to 1 (1.7%) patient in the placebo group and 26 (25.2%) patients in midazolam group. The difference in treatment success rates between remimazolam and placebo is 0.8961 (95% CI: 0.8505, 0.9416) and was statistically significant; between remimazolam and midazolam 0.6603 (95% CI: 0.5705, 0.7501). Primary efficacy results favour remimazolam over placebo and, to a lesser extent, over midazolam. However, success rate of midazolam was quite low, which could be partially explained by lower dose of midazolam used in this study (lower than the EU labelled dose for conscious sedation indication).

As expected, failure of reaching the primary composite outcome is driven by the need for rescue sedative medication (midazolam dosed according to clinical practice) and too many doses of treatment drug within the predefined time window. This may indicate medication error potential. The relative frequency of 'procedure not completed' is similar in all 3 treatment arms, which shows that the failure of procedure due to reasons unrelated to sedations was similar in all treatment arms, which is reassuring for validity of the composite outcome.

The key secondary outcomes (time-to-event outcomes) also favour remimazolam over placebo and midazolam.

Time to start of procedure is 15 minutes shorter in remimazolam compared to midazolam and placebo arms (difference in median times). Peak sedation is reached in 3 minutes with remimazolam and time to peak sedation could not be established for midazolam and placebo. Similarly, time to fully alert from end of procedure was 7 minutes shorter in remimazolam compared to midazolam while time to fully alert from last dose is 10 minutes shorter in remimazolam compared to midazolam arms. These results point towards a faster onset of and recovery from sedative effects of remimazolam compared to midazolam and are clinically relevant.

However, some of the time-to-event results do not seem very clinically relevant - differences in time to ready for discharge from the end of colonoscopy is 4 minutes in favour of remimazolam over midazolam and 5 minutes over placebo (with overlapping 95% CI). Similarly, time to ready for discharge from last dose is 6 minutes in favour of remimazolam over midazolam (with slightly overlapping 95% CI) and 9 minutes in favour of remimazolam over placebo (95% CI do not overlap) - these results can be viewed as having questionable clinical relevance.

Regarding MOAA/S score by timepoint, at 4 minutes post-dose 89% of patients receiving remimazolam are within target range compared to around 21% of patients receiving placebo and around 38% of patients receiving midazolam. At 19 minutes more patients receiving midazolam are within target range compared to patients receiving remimazolam or placebo, while the proportion of patients with MOAA/S score 5 is largest in remimazolam group. These data suggest a more rapid onset of action of remimazolam and a shorter duration of the colonoscopy procedure. However, the results also show a higher relative frequency of deep sedation (MOAA/S score 0, equivalent to general anaesthesia) seen at practically all timepoints for remimazolam compared to placebo and midazolam.

Results of the Drowsiness VAS endpoint also point towards faster onset of sedation for remimazolam compared to placebo and midazolam; signs of resedation were not observed. Highest mean VAS score for remimazolam (86.9) was a larger number compared to highest VAS score for placebo and midazolam (82.2 and 78.5, respectively) denoting more severe drowsiness.

Importantly from patient's perspective, time required to feeling 'back to normal' was shorter with remimazolam compared to placebo or midazolam.

In Study **CNS7056-008** treatment success was observed in 250 patients (80.6%) in remimazolam group, in 3 patients (4.8%) in placebo and 24 patients (32.9%) in midazolam groups. The difference in rates for remimazolam versus placebo was 0.7588 (95%-CI: 0.6903, 0.8274) and was statistically significant, for remimazolam versus midazolam was 0.4777 (95%-CI: 0.3613, 0.5941). Primary efficacy results favour remimazolam over placebo and, to a lesser extent, over midazolam. As expected, the superiority over placebo arises due to the need for a rescue sedative medication which is, by protocol definition, treatment failure of placebo. Success rate of midazolam is quite low in itself, which could be partially explained by lower dose of midazolam used in this study (lower than the EU labelled dose for conscious sedation indication).

The main secondary outcomes (time-to-event outcomes) also favour remimazolam.

Time to start of procedure is around 11 minutes shorter for remimazolam compared to midazolam and 13 minutes shorter compared to placebo. Peak sedation is reached in 3.5 minutes, which is 3.5 minutes quicker in remimazolam compared to midazolam (could not be evaluated for placebo). Time to fully alert from last dose is approximately 6 minutes shorter in remimazolam compared to midazolam and 8 minutes shorter compared to placebo. These reductions are clinically relevant and point towards a faster onset of and faster resolution of sedative effects of remimazolam compared to midazolam.

However, some of the time-to-event results do not seem very clinically relevant when comparing remimazolam and midazolam - the difference in time to ready for discharge from end of procedure and time to ready for discharge from last dose is 5 and 6 minutes in favour of remimazolam over midazolam (with slightly overlapping 95% CI of the median time), respectively. Time to fully alert from end of procedure is 6 minutes in favour of remimazolam over midazolam, but with overlapping 95% CI of the median time.

MOAA/S scores by time point indicate a shorter time elapsed from the injection of the sedative to beginning of the procedure with remimazolam compared to placebo and midazolam.

Data for MOAA/S score by timepoint show a higher relative frequency of deep sedation (MOAA/S score 0, equivalent to general anaesthesia) with remimazolam compared to other two treatment arms at the majority of timepoints. In remimazolam arm, MOAA/S score of 0 is first noted at 1-minute post-dose and the relative frequency of score 0 remains higher (at around 2%) in remimazolam compared to midazolam and placebo (0%) up to 19 minutes postdose. At 19 and 20 minutes (the last two observed timepoints), the relative frequency of MOAA/S score 0 is higher in midazolam arm. The tendency of remimazolam to produce deep sedation shortly after dosing (observed after 1 minute) is noted; this may pose a limitation for the use of remimazolam.

A coping strategy for clinical practice regarding unintended deep sedation observed in clinical trials was requested, with several updates to SmPC were proposed to detail or reinforce this, namely to inform clinicians about a very fast onset and offset of sedation, with information regarding how soon after the initial bolus peak sedation occurs and how long does sedation last. Time to fully alert from last dose of remimazolam (12-14 minutes) instead of time to fully alert after the end of procedure was also included.

Recall of the procedure was comparatively low and patient satisfaction with sedation was comparatively high in all three treatment groups.

Results of the Drowsiness VAS point towards faster onset of sedation for remimazolam (highest mean VAS score detected at 5 minutes postdose for remimazolam) compared to midazolam (highest mean VAS score detected at 25 minutes postdose for midazolam). Highest mean VAS score for remimazolam (85.6) was a larger number compared to highest VAS score for placebo and midazolam (81.4 and 72.1, respectively) denoting more severe drowsiness. No signs of resedation were observed.

Median time required to feeling back to normal (self-evaluated by patients) was similar in remimazolam and midazolam groups and shorter compared to placebo arm. The interquartile range were very similar for remimazolam and midazolam, denoting an absence of benefit of remimazolam from a clinical point of view regarding this outcome.

In Study **CNS7056-015** higher success rates of colonoscopy procedures were recorded for patients receiving remimazolam (84.4% vs 0% and 12.9% for placebo and midazolam group respectively). Reasons for procedure failure were common for all study groups, and for the most failures included use of rescue sedative medications and too many doses within the pre-defined time window (multiple reasons observed in most participants). Later suggests potential for medication errors.

Most of secondary efficacy endpoints are supportive of better efficacy properties of remimazolam, but it is difficult to assess clinical meaningfulness of the results. Mean fentanyl dose was numerically lower in remimazolam group. Median time to start of procedure was 13-14 min shorter in remimazolam group compared to placebo and midazolam, which seems substantial and could be meaningful for clinical practice. Median time to fully alert from the end of procedure was 2.3-4 min shorter in remimazolam group compared to placebo and midazolam. Median time to fully alert from last dose was 7-7.8 min shorter in remimazolam group (95%CI 8.8, 12.0) compared to placebo and midazolam.

MOAA/S scores by the time point are suggestive of faster onset of sedation in remimazolam group in comparison with placebo and midazolam. At 1.5 minutes after administration 29.0% patients in remimazolam group who had an MOAA/S score of ≤3, i.e. adequately sedated to begin the procedure (vs 0 and 3.3% in placebo and midazolam group respectively). The median time to procedure in remimazolam group was 8 minutes after initiating treatment compared to 18.6 minutes in midazolam and 20 minutes in placebo groups.

Drowsiness VAS is presented by the time points and the trend was positive in remimazolam group until 15 min post-dose suggesting higher level of drowsiness produced by remimazolam. There was no requirement for flumazenil during the procedure reported in any study group. Peak sedation from first dose was not comparable with placebo and midazolam groups. There was no important difference observed for recall of the procedure by the Brice questionnaire and for investigator's satisfaction with the sedation agent.

Although no inferential statistics are available for the study **015**, presented data suggest better efficacy of remimazolam over placebo and midazolam in the studied setting.

Sensitivity analysis for the primary outcome based on total fentanyl received and initial fentanyl dose showed similar results to those seen in the primary efficacy analysis for remimazolam versus placebo in studies 006 and 008. For remimazolam versus midazolam the sensitivity analysis showed similar results to those seen in primary efficacy analysis except that the difference in success rates was smaller for the initial fentanyl stratum ≥75 µg (0.0067 [95%-CI: -0.3244, 0.3377]) in study 008.

2.5.4. Conclusions on the clinical efficacy

Efficacy of remimazolam over placebo and to a lesser extent over midazolam for procedural sedation in patients undergoing colonoscopy and bronchoscopy was demonstrated. Comparison with midazolam needs to be viewed as exploratory, since it was subdosed regarding to EU practice and it was administered in an open-label fashion in all phase 3 trials.

Success of procedure was higher with remimazolam compared to placebo in the pivotal trials. These results were statistically significant and clinically relevant, supporting the marketing authorisation in the claimed indication.

Procedures in the pivotal trials were of relatively short duration; majority of them lasted less than 30 minutes. Analysis of efficacy and safety data from pivotal studies in procedural sedation has been conducted separately for 2 categories: procedures lasting for 30 minutes of less and procedures lasting for more than 30 minutes. Efficacy of remimazolam in longer duration procedures is reduced compared to shorter procedures but is still higher than efficacy with placebo in longer procedures. Recovery time with remimazolam is prolonged in longer procedures compared to shorter procedures. Also, recovery time with remimazolam in longer procedures is prolonged compared to midazolam in longer procedures. This suggests that patients undergoing procedures of short duration can be expected to have more benefit of remimazolam treatment compared to patients undergoing procedures of longer ≥30 min duration. Consequently, the results were presented in the SmPC separately for procedures shorter and longer than 30min in order to inform the prescribers of this difference.

2.6. Clinical safety

Introduction

The evaluation of the safety of remimazolam in procedural sedation was based primarily on the pooled data of 750 subjects from controlled clinical trials (CNS7056-004, CNS7056-006, CNS7056-008, and CNS7056-015). Safety in subjects with hepatic impairment was assessed in a dedicated trial (ONO-2745IVU007, 11 subjects) and safety in subjects with renal impairment was assessed in another dedicated trial (CNS7056-012, 11 subjects). As remimazolam is a benzodiazepine with abuse potential, a dedicated trial was conducted in recreational CNS depressant users (CNS7056-014, 40 subjects). Comparisons of safety profiles were conducted between the Total Remimazolam group (any dose) and the Total Midazolam group (combination of midazolam dosed according to the USPI and common medical practice) as well as the Placebo group.

Additionally, the applicant submitted the pooled ISS analyses which are comprised of safety data from the 22 trials (around 1,700 subjects) in the IV remimazolam clinical development programme. Those includes trials in general anaesthesia, ICU sedation, healthy volunteers and special populations as well. There is one additional trial concerning oral administration of remimazolam.

Table 26: Concerned ISS analyses groups*

Table: ISS Analysis Groups		
Analysis Group	**Trials Included (Number of Trials)**	**Treatment Groups Analyzed**
Group A	Controlled and uncontrolled trials in procedural sedation (6 trials) CNS7056-003, CNS7056-004, CNS7056-006, CNS7056-008, CNS7056-015, and CNS7056-002 (Part B)	Total Remimazolam
Group A1	Controlled trials in procedural sedation (colonoscopy and bronchoscopy) with fentanyl pretreatment (4 trials) CNS7056-004, CNS7056-006, CNS7056-008, and CNS7056-015	Total Remimazolam Remimazolam initial doses 2.5 to 5 mg (CNS7056-015), 5 mg (CNS7056-004, CNS7056-006, and CNS7056-008) and >5 mg (7 mg and 8 mg, only for CNS7056-004) Total Midazolam Midazolam initial doses <1.75 mg (CNS7056-006, CNS7056-008, and CNS7056-015), 1.75 mg (CNS7056-006, CNS7056-008), and >1.75 mg (CNS7056-004) Fentanyl treatment (in addition to all treatment groups)
Group A1A	Placebo-controlled trials in procedural sedation (colonoscopy and bronchoscopy) with fentanyl pretreatment (3 trials) CNS7056-006, CNS7056-008, and CNS7056-015	Total Remimazolam Remimazolam initial doses 2.5 to 5 mg (CNS7056-015) and 5 mg (CNS7056-006 and CNS7056-008) Total Midazolam Midazolam initial doses <1.75 mg, (CNS7056-006, CNS7056-008, and CNS7056-015) and 1.75 mg (CNS7056-006 and CNS7056-008) Placebo Fentanyl treatment (in addition to all treatment groups)
Group B	Controlled and uncontrolled trials in general anaesthesia (5 trials) ONO-2745-03, ONO-2745-05, ONO-2745-06, CNS7056-010, and CNS7056-011	Total Remimazolam
Group B1	Controlled trials in general anaesthesia	Total Remimazolam

Table: ISS Analysis Groups		
Analysis Group	**Trials Included (Number of Trials)**	**Treatment Groups Analyzed**
	(4 trials) ONO-2745-05, ONO-2745-06, CNS7056-010, and CNS7056-011	Remimazolam induction 6 mg/kg/h group; and 12 mg/kg/h group; (only ONO-2745-05, ONO-2745-06, and CNS7056-010) Propofol (only ONO-2745-05, CNS7056-010, and CNS7056-011)
Group C	Single- and multiple-dose trials in healthy subjects not undergoing a procedural sedation or general anaesthesia (10 trials) ONO-2745-01, ONO-2745-02, ONO-2745IVU007 (only healthy subjects), CNS7056-001, CNS7056-002 (Part A), CNS7056-005, CNS7056-012 (only healthy subjects), CNS7056-016, CNS7056-017, and CNS7056-019	Total Remimazolam
Group D	All trials defined in Group A, B, and C shown above plus ONO-2745IVU007 (subjects with hepatic impairment), CNS7056-012 (subjects with renal impairment), CNS7056-014, and ONO-2745-04 (ICU sedation) (22 trials)	Total Remimazolam

* There are ISS groups B, B1, C and D which are also described.

In the 4 controlled trials in procedural sedation, the mean/median cumulative remimazolam dose administered was 11.02/10.00 mg (range 5.00 to 30.00 mg), and the mean/median duration of treatment (from first to last bolus dose) was 10.64/9.46 min (range 1.00 to 49.50 min). The mean/median number of supplemental bolus doses was 2.3/2.0 (range 0 to 10). The mean/median cumulative fentanyl dose was 90.6/75.0 µg (range 25 to 450 µg), and the mean/median time between initial fentanyl dose and first dose of remimazolam was 2.44/2.00 min (range 0.0 to 12.0 min).

As with other benzodiazepines, the sedative effects of remimazolam can be reversed by the $GABA_A$ antagonist flumazenil, offering an additional safety measure in case of overdose and unintentional "deep" sedation. During the clinical development in procedural sedation, no remimazolam-treated subjects required reversal with flumazenil for safety reasons.

Patient exposure

A total of 1731 (100.0%) subjects received IV remimazolam in the 22 clinical trials of IV remimazolam. Of these, 870 (50.3%) of all subjects received remimazolam in any trial in procedural sedation (CNS7056-002 [Part B], CNS7056-003, CNS7056-004, CNS7056-006, CNS7056-008, and CNS7056-015) represented in ISS Group A. ISS Group A1, the main group for comparison, represents the controlled trials in procedural sedation (CNS7056-004, CNS7056-006, CNS7056-008, and CNS7056-015), in which 750 subjects received remimazolam (43.3% of subjects overall and 86.2% of all subjects exposed in context of procedural sedation), 242 subjects received midazolam, and 135 subjects received placebo. In all controlled clinical trials in procedural sedation, an opioid premedication (i.e., IV

fentanyl at 25-100 µg) was administered for its analgesic effect prior to the initial dose of remimazolam and during the procedure as needed in accordance with standard clinical practice.

Other subjects treated with remimazolam were 527 (30.5% of all subjects; ISS Group B) undergoing surgery in the trials in general anaesthesia, 223 (12.9% of all subjects; ISS Group C) healthy volunteers, and an additional 111 subjects, comprising 49 subjects in the ICU sedation trial, 11 subjects with hepatic impairment, 11 subjects with renal impairment, and 40 subjects who were recreational CNS depressant users.

Demographic characteristics

Table 27: Demographic characteristics of subjects in controlled procedural sedation setting (Safety population - ISS Group A1)

	Total Remimazolam (N = 750)	Total Midazolam (N = 242)	Placebo (N = 135)
Age (years)			
Mean (SD)	58.1 (11.62)	58.0 (11.24)	58.9 (10.87)
Median	58.0	58.0	59.0
Q1, Q3	52.0, 66.0	51.0, 65.0	52.0, 66.0
Min, Max	18, 95	20, 85	24, 92
Age [n (%)]			
18-39 years	47 (6.3)	13 (5.4)	6 (4.4)
40-64 years	484 (64.5)	166 (68.6)	88 (65.2)
65-74 years	169 (22.5)	49 (20.2)	32 (23.7)
≥75 years	50 (6.7)	14 (5.8)	9 (6.7)
Age [n (%)]			
< 65 years	531 (70.8)	179 (74.0)	94 (69.6)
≥ 65 years	219 (29.2)	63 (26.0)	41 (30.4)
Sex [n (%)]			
Male	354 (47.2)	116 (47.9)	61 (45.2)
Female	396 (52.8)	126 (52.1)	74 (54.8)
Race categories [n (%)]			
White	611 (81.5)	177 (73.1)	102 (75.6)
Black	99 (13.2)	47 (19.4)	27 (20.0)
Asian	26 (3.5)	15 (6.2)	4 (3.0)
Other	14 (1.9)	3 (1.2)	2 (1.5)
BMI (kg/m²)			
Mean (SD)	28.39 (5.53)	28.49 (5.75)	29.21 (6.84)
Median	28.18	27.98	28.13
Q1, Q3	24.47, 31.67	24.54, 31.88	24.54, 34.35
Min, Max	16.01, 55.27	16.71, 65.15	13.84, 59.81
BMI categories [n (%)]			
Underweight	21 (2.8)	4 (1.7)	3 (2.2)
Normal weight	194 (25.9)	62 (25.6)	33 (24.4)
Overweight	253 (33.7)	86 (35.5)	43 (31.9)
Obese	282 (37.6)	90 (37.2)	56 (41.5)
ASA-PS [n (%)]			
I-II	585 (78.0)	182 (75.2)	87 (64.4)
III	150 (20.0)	45 (18.6)	41 (30.4)
IV	15 (2.0)	15 (6.2)	7 (5.2)

Medical history and prior/concomitant medicinal products (Safety population - ISS Group A1)

Medical history of hypertension was the most frequent in all three groups, and it was lower in the Total Remimazolam group (47.6%) than in the Total Midazolam group (52.1%) and the Placebo group (60.7%). Other medical history records found in over 20% of subject in any group were gastrooesophageal reflux disease (Total Remimazolam: 33.5%, Total Midazolam: 33.1%, Placebo: 35.6%), hyperlipidaemia (Total Remimazolam: 21.2%, Total Midazolam: 16.5%, Placebo: 24.4%), depression (Total Remimazolam: 19.6%, Total Midazolam: 17.4%, Placebo: 27.4%), drug hypersensitivity (Total Remimazolam: 18.8%, Total Midazolam: 21.1%, Placebo: 27.4%), anxiety (Total Remimazolam: 18.1%, Total Midazolam: 16.1%, Placebo: 25.9%), COPD (Total Remimazolam: 16.4%, Total Midazolam: 14.5%, Placebo: 23.0%).

Adverse events

Table 28: Overall summary of TEAEs by Treatment group in Controlled trials in Procedural sedation with analgesia

Adverse event category [n (%)]	Total Remimazolam (N = 750)	Total Midazolam (N = 242)	Placebo (N = 135)
Any treatment-emergent adverse event	553 (73.7)	192 (79.3)	112 (83.0)
Any treatment-emergent adverse event related to study drug	245 (32.7)	97 (40.1)	52 (38.5)
Any treatment-emergent serious adverse event	17 (2.3)	1 (0.4)	4 (3.0)
Any treatment-emergent serious adverse event related to study drug	1 (0.1)	0	0
Any treatment-emergent adverse event leading to discontinuation of study drug	1 (0.1)	1 (0.4)	0
Any treatment-emergent adverse event with outcome of death	0	0	0

Note: Percentages are based on the Safety Population and each dose group - Total Remimazolam and Total Midazolam from Group A1, Placebo from Group A1A.

Note: For each category, subjects are included only once, even if they experienced multiple events in that adverse event category.

Note: Treatment-emergent adverse events are defined as adverse events that started or worsened on or after the first study medication dose or fentanyl pretreatment date/time.

Common Adverse Events

According to the applicant, the incidence of these events in remimazolam subjects was similar or lower than that observed in midazolam or placebo subjects in most cases. For any event that occurred more frequently in the Total Remimazolam group than in the Total Midazolam or Placebo groups, the difference in incidence between the groups was <5%.

Table 29: TEAEs by SOC and PT with an Incidence of ≥ 1% in any Treatment group in Controlled trials in Procedural sedation with analgesia

System organ class Preferred term [n (%)]	Total Remimazolam (N = 750)	Total Midazolam (N = 242)	Placebo (N = 135)
Vascular disorders	453 (60.4)	167 (69.0)	101 (74.8)
Hypotension	235 (31.3)	103 (42.6)	64 (47.4)
Hypertension	163 (21.7)	54 (22.3)	32 (23.7)
Diastolic hypertension	109 (14.5)	25 (10.3)	21 (15.6)
Systolic hypertension	85 (11.3)	23 (9.5)	18 (13.3)
Diastolic hypotension	65 (8.7)	25 (10.3)	22 (16.3)
Respiratory, thoracic and mediastinal disorders	113 (15.1)	35 (14.5)	26 (19.3)
Hypoxia	69 (9.2)	14 (5.8)	14 (10.4)
Tachypnoea	8 (1.1)	4 (1.7)	6 (4.4)
Oropharyngeal pain	7 (0.9)	1 (0.4)	2 (1.5)
Respiratory acidosis	6 (0.8)	8 (3.3)	2 (1.5)
Bradypnoea	4 (0.5)	3 (1.2)	2 (1.5)
Cardiac disorders	79 (10.5)	36 (14.9)	20 (14.8)
Bradycardia	49 (6.5)	24 (9.9)	12 (8.9)
Tachycardia	27 (3.6)	13 (5.4)	9 (6.7)
Investigations	73 (9.7)	21 (8.7)	10 (7.4)
Respiratory rate increased	43 (5.7)	10 (4.1)	6 (4.4)
Respiratory rate decreased	14 (1.9)	7 (2.9)	3 (2.2)
Gastrointestinal disorders	46 (6.1)	11 (4.5)	8 (5.9)
Nausea	24 (3.2)	5 (2.1)	6 (4.4)
Vomiting	15 (2.0)	4 (1.7)	3 (2.2)
Abdominal pain	8 (1.1)	0	0
Nervous system disorders	32 (4.3)	12 (5.0)	3 (2.2)
Headache	20 (2.7)	8 (3.3)	0
Dizziness	8 (1.1)	0	0
General disorders and administration site conditions	20 (2.7)	4 (1.7)	4 (3.0)
Pyrexia	11 (1.5)	1 (0.4)	1 (0.7)

Note: Adverse events are coded using MedDRA version 18.0.

Note: For each category, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.

Note: Treatment Emergent Adverse Events are defined as adverse events that started or worsened on or after the first study medication dose or fentanyl pretreatment date/time.

According to the applicant, most of subjects experienced events with a maximum severity of mild or moderate as assessed by the Investigator. Frequencies of events assessed as severe were similar across the 3 groups: 20 subjects (2.7%) in the Total Remimazolam group, in 6 subjects (2.5%) in the Total Midazolam group, and in 2 subjects (1.5%) in the Placebo group. Severe TEAEs in the Total Remimazolam group included hypertension (3 subjects), hypoxia, bradycardia, and bronchospasm (2 subjects each),

and hypotension, blood pressure decreased, hypercalcaemia, lobar pneumonia, confusional state, oropharyngeal pain, pneumothorax, chronic obstructive pulmonary disease (COPD), acute respiratory failure, aspiration, and abdominal pain (1 subject each). Severe TEAEs in the Total Midazolam group included hypertension (4 subjects), ECG QT prolonged and neck pain (1 subject each). Severe TEAEs in the Placebo group included hypoxia, bronchospasm, and back pain (1 subject each).

The applicant is discussing that because the side effect profile of fentanyl overlaps somewhat in the areas of respiratory and haemodynamic effects, the potential influence should be taken into consideration when reviewing incidences of TEAEs and vital sign changes.

Furthermore, the applicant is arguing that, as a result of regulatory requirements (FDA) regarding pre-defined changes in vital signs with focus on cardio-respiratory parameters, there may have been over-reporting and inflation of the rates of these types of events. Further analyses were performed on heart rate, respiratory rate, SpO2).

Adverse Events of Special Interest

The applicant has done standardised and customised MedDRA queries with purpose of identifying adverse reactions for the target indication of procedural sedation. Filtered TEAEs:

- Hypoxia: The proportions of subjects experiencing hypoxia were slightly lower in the Total Remimazolam than in the Total Midazolam and the Placebo treatment groups (13.1%, 14.0%, and 15.6%, respectively).
- Bradycardia: The incidence of bradycardia was slightly lower in the Total Remimazolam than in the Total Midazolam and Placebo treatment groups (7.1%, 10.7%, and 8.9%).
- Hypotension: The incidence of hypotension was lower in the Total Remimazolam treatment group than in both the Total Midazolam and Placebo treatment groups (37.3%, 49.2%, and 57.0%, respectively).
- Hypersensitivity events were reported in 4 remimazolam subjects (0.5%), 0 midazolam, and 1 (0.7%) placebo subjects.
- Drug-related hepatic disorder events were not reported in any group.
- Acute renal failure events were not reported in any group.
- Haemorrhage events were found in 8 (1.1%) remimazolam, 3 (1.2%) midazolam and 3 (2.2%) placebo subjects.

Other findings relevant to safety

Vital signs findings are integral part of common AEs and AEs of special interest, so they are not analysed separately here.

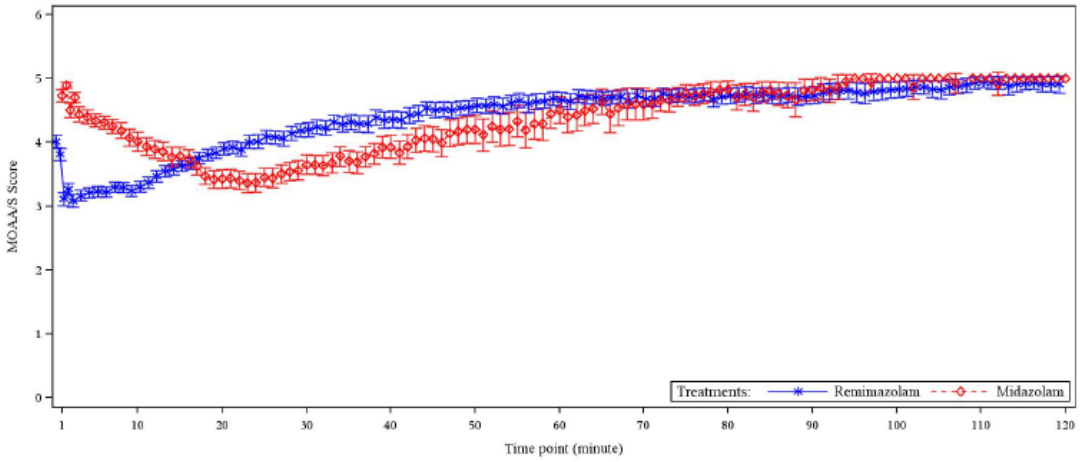
ECG findings – According to the applicant, 3 subjects in the Total Remimazolam treatment group (0.4%) had ECG shifts from normal or abnormal/not clinically significant at baseline to abnormal/clinically significant as their worst post-dose result in ISS Group A1. One subject developed nonspecific ST and T wave abnormalities immediately after her first dose of remimazolam. Another subject developed multifocal atrial tachycardia after her first dose of remimazolam. The third subject developed sinus tachycardia that was reported for every 10 minutes during the procedure and 5 minutes after the end of the procedure. These events resolved without sequalae.

Airway interventions – In the controlled trials in procedural sedation (ISS Group A1), the proportion of subjects in need of an airway intervention was higher in the Total Remimazolam treatment group (10.1%) than in the Total Midazolam (6.2%) or Placebo (8.9%) treatment groups. However, the most frequent

airway intervention was changes in oxygen flow, reported in 8.5%, 3.7%, and 5.9% in the Total Remimazolam, Total Midazolam, and Placebo groups, respectively. The numbers of "true" interventions, such as chin lifts, jaw thrusts, etc., were low and comparable between all treatment groups. Short-term manual ventilation was employed in 0.8%, 0% and 2.2% of subjects in the Total Remimazolam, Total Midazolam, and Placebo treatment groups, respectively. No subjects required emergency intubation. According to the applicant, all of these interventions can be professionally and safely handled by the respective endoscopy staff.

Deep sedation - In the controlled trials in procedural sedation (ISS Group A1), 27.7% of subjects on Remimazolam had an MOAA/S score of 0 or 1 (indicating deep sedation) at any time during sedation, compared to 15.7% of midazolam subjects and 11.9% of placebo subjects (most of whom received rescue midazolam).

Figure 8: Mean (± 95% CI) MOAA/S score by Time-point in Controlled Trials in Procedural Sedation with Analgesia (ISS Group A1 – safety population)



CI = confidence interval; MOAA/S = Modified Observer's Assessment of Alertness/Sedation
Timepoints with less than 5 subjects not shown.
Source: Figure 10.1.3.1

According to the applicant, observed incidence of MOAA/S scores of 0 or 1 however appears to be a function of the initial concomitant dose of fentanyl. For remimazolam, the incidence of MOAA/S 0 or 1 was clearly more common in subjects who received the initial fentanyl dose of 75 µg (46.5%) and was successfully reduced to 8.0% with 50 µg initial fentanyl bolus as implemented by protocol amendments in the Phase III trials CNS7056-006, CNS7056-008, and CNS7056-015. It remains somewhat speculative whether the further reduction to less than 50 µg (i.e., 25 µg) has the potential to further reduce this incidence. This dependency is less striking for both midazolam and placebo, mainly due to the rather low number of subjects in the lowest category of less than 50 µg. Vital signs and TEAEs pertaining to hypoxia, bradycardia, or hypotension did not show any correlation to the level of consciousness (MOAA/S scores), regardless of the treatment.

Table 30: Subjects with MOAA/S Score 0 or 1 (from T=0 until fully alert) in Controlled Studies in Procedural Sedation with Analgesia by Initial Fentanyl Dose Category

	Total Remimazolam	Total Midazolam	Total Placebo
Subjects with initial fentanyl dose <50 µg	N = 50	N = 17	N = 6
Subjects with MOAA/S score of 0 or 1	3 (6.0%)	4 (23.5%)	1 (16.7%)
Subjects with initial fentanyl dose 50 to ≤75 µg	N = 312	N = 91	N = 72
Subjects with MOAA/S score of 0 or 1	25 (8.0%)	6 (6.6%)	7 (9.7%)
Subjects with initial fentanyl dose ≥75 µg	N = 387	N = 133	N = 57
Subjects with MOAA/S score of 0 or 1	180 (46.5%)	28 (21.1%)	8 (14.0%)

The proportion of subjects in the Total Remimazolam treatment group with MOAA/S scores of 0 or 1 did not appear to be related to the time between the first dose of fentanyl and the first dose of remimazolam.

The applicant concludes that condition of deep sedation (MOAA/S score of 0 or 1) did not appear to be associated with any adverse effect on vital signs regardless of the treatment. In particular, there was no clear evidence that a state of deep sedation resulted in more AE, clinically notable vital sign abnormalities and airway interventions for any of the administered treatments. The higher proportion of patients experiencing deep sedation at any time during the treatment under the combination of 5 mg remimazolam and 75 µg fentanyl initial dose could be successfully mitigated by a lower initial dose of fentanyl, i.e., 50 µg. The regimen of 50 µg fentanyl with 5 mg remimazolam or midazolam dosed according to the USPI resulted in equally low proportion of subjects experiencing deep sedation.

Abuse potential - In the 22 trials in the remimazolam clinical development programme that were included in the pooled analyses, no subject experienced a TEAE in the SMQ drug abuse and dependence. In the controlled trials (Group A1), the rates of TEAEs in the customised MedDRA Abuse Potential were similar on remimazolam (1.5%) and midazolam (0.8%); these events were most commonly dizziness and somnolence. Searching the whole clinical database of 1,731 subjects exposed to remimazolam with the SMQ Drug Abuse, Dependence and Withdrawal did not reveal a single case.

Administration routes alternative to intravenous, such as oral and intranasal had no abuse potential on account of the extremely low oral bioavailability and the significant nasal pain produced by remimazolam (trials CNS7056-016 and CNS7056-019, respectively). A dedicated abuse liability trial (CNS7056-014) showed that remimazolam had an abuse potential similar to or lower than that of midazolam via i.v. injection.

Even though remimazolam will be used strictly in controlled hospital settings, there might be a risk of repeated administration of remimazolam (e.g. in patients requiring multiple diagnostic or therapeutic procedures) which might cause drug dependence. Repeated administrations were tested in a Phase 1 trial (CNS7056-019) where subjects were exposed 7 times to remimazolam (1 intravenous and 6 intranasal administrations) within 17 days. The trial did not show systematic trends in the occurrence of abuse-related events with multiple remimazolam exposure (e.g. tolerance or sensitisation) that could be indicative of any development of dependence

Withdrawal and rebound - Dependence potential has been studied in self-administration experiments in monkeys, during induction of physical dependence in rats and monkeys, and the development of tolerance in micropigs. Results indicate that remimazolam, like other benzodiazepines, has dependence-inducing potential. However, no withdrawal symptoms have been detected in clinical trials with remimazolam. In the 22 trials in the IV remimazolam clinical development programme included in

the pooled analyses, no subject experienced a TEAE in the SMQ drug withdrawal. Due to the short exposure time to remimazolam during sedation for diagnostic or therapeutic procedures, withdrawal symptoms are not expected in this clinical setting.

Pain at injection site – Injection site pain was explored by employing VAS (or verbal) scores.

Serious adverse event/deaths/other significant events

Deaths

Overall, amongst the 1731 subjects who received IV remimazolam, there was no TEAE with an outcome of death. Although no subjects died during treatment with remimazolam, 1 subject in Group B died approximately 7 months after completing treatment with remimazolam for general anaesthesia.

This subject with a history of aortic valve stenosis grade III, single vessel disease, aneurysm of ascending aorta, atrial fibrillation, systemic hypertension, hyperlipidemia, presbyakusis, status post surgery for prostate cancer, and heart insufficiency NYHA II received remimazolam as a continuous infusion. The patient experienced life-threatening acute renal failure the day after remimazolam treatment and surgery. The reaction was considered to be serious by the reporter as it was medically important and life-threatening. The patient received continuous venovenous haemodialysis as a corrective therapy for the event. The event was ongoing, and the subject died approximately 7 months after study treatment; the cause of death was unknown. A number of other concomitant medications were reported. According to the provided CIOMS report, both the Investigator and the Sponsor considered the adverse event to be not related to study medication.

Other Serious Adverse Events

Of the subjects in controlled trials in procedural sedation (Group A1), 2.3% in the Total Remimazolam group, 0.4% in the Total Midazolam group, and 3.0% in the Placebo group, experienced at least 1 SAE. In general, the incidence of SAEs was low, and it was similar between the Total Remimazolam and the Placebo groups but higher than in the Total Midazolam group.

All SAEs in procedural sedation were exclusively reported from a single trial (CNS7056-008) which was performed in the clinical setting of bronchoscopy. According to the applicant, this biased the type of reported SAEs with the vast majority (13/17) falling in the SOC Respiratory, thoracic and mediastinal disorders.

Table 31: Serious Adverse Events by Treatment Group, System Organ Class, and Preferred Term in Controlled Trials in Procedural Sedation (group A1)

System organ class Preferred term [n (%)]	Total Remimazolam (N = 750)	Total Midazolam (N = 242)	Placebo (N = 135)
Any serious treatment-emergent adverse event	17 (2.3)	1 (0.4)	4 (3.0)
Respiratory, thoracic and mediastinal disorders	13 (1.7)	0	3 (2.2)
Pneumothorax	4 (0.5)	0	1 (0.7)
Bronchospasm	2 (0.3)	0	1 (0.7)
Hypoxia	2 (0.3)	0	1 (0.7)
Acute respiratory failure	1 (0.1)	0	0
Aspiration	1 (0.1)	0	0
COPD	1 (0.1)	0	0
Dyspnea	1 (0.1)	0	0
Organizing pneumonia	1 (0.1)	0	0
Pleural effusion	1 (0.1)	0	0
Pneumomediastinum	1 (0.1)	0	0
Respiratory failure	1 (0.1)	0	0
Haemoptysis	0	0	1 (0.7)
Cardiac disorders	3 (0.4)	0	0
Atrial fibrillation	1 (0.1)	0	0
Atrial tachycardia	1 (0.1)	0	0
Bradycardia	1 (0.1)	0	0
Infections and infestations	1 (0.1)	0	0
Lobar pneumonia	1 (0.1)	0	0
Blood and lymphatic system disorders	0	1 (0.4)	0
Anaemia	0	1 (0.4)	0
Psychiatric disorders	1 (0.1)	0	0
Confusional state	1 (0.1)	0	0

Note: Adverse events are coded using MedDRA version 18.0.

Note: For each category, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.

Note: Treatment Emergent Adverse Events are defined as adverse events that started or worsened on or after the first study medication dose or fentanyl pretreatment date/time.

All of the SAEs in Group A1 subjects who received remimazolam were assessed by the Investigator as unlikely / not related to study treatment except for 2 events in 1 subject in the remimazolam group in trial CNS7056-008. The 2 events were bradycardia and hypoxia. For both events, the relationship to study treatment was assessed as "certain" and study treatment was withdrawn.

Laboratory findings

There was no evidence of a clinically important mean or median change in clinical laboratory tests associated with remimazolam.

Safety in special populations

Age

The incidences of TEAEs increased with increasing age in all treatment groups, except for events from the SOC Cardiac disorders. The increase was not always apparent in the age ⩾75 years group, however those groups had a small sample size.

Table 32: Incidence of TEAEs by Age Category in controlled trials in procedural sedation

System organ class Preferred term [n (%)]	Total Remimazolam			Total Midazolam			Placebo		
	< 65 years (N=531)	65-74 years (N=169)	≥75 years (N=50))	< 65 years (N=179)	65-74 years (N=49)	≥75 years (N=14)	< 65 years (N=94)	65-74 years (N=32)	≥75 years (N=9)
Any TEAE	360 (67.8)	146 (86.4)	47 (94.0)	138 (77.1)	41 (83.7)	13 (92.9)	77 (81.9)	29 (90.6)	6 (66.7)
Cardiac disorders	59 (11.1)	16 (9.5)	4 (8.0)	27 (15.1)	6 (12.2)	3 (21.4)	15 (16.0)	3 (9.4)	2 (22.2)
Bradycardia	39 (7.3)	10 (5.9)	0	18 (10.1)	4 (8.2)	2 (14.3)	8 (8.5)	2 (6.3)	2 (22.2)
Tachycardia	20 (3.8)	6 (3.6)	1 (2.0)	12 (6.7)	1 (2.0)	0	8 (8.5)	1 (3.1)	0
Vascular disorders	285 (53.7)	127 (75.1)	41 (82.0)	117 (65.4)	39 (79.6)	11 (78.6)	69 (73.4)	26 (81.3)	6 (66.7)
Hypotension	153 (28.8)	63 (37.3)	19 (38.0)	75 (41.9)	21 (42.9)	7 (50.0)	43 (45.7)	17 (53.1)	4 (44.4)
Hypertension	100 (18.8)	44 (26.0)	19 (38.0)	31 (17.3)	18 (36.7)	5 (35.7)	23 (24.5)	9 (28.1)	0
Diastolic hypertension	64 (12.1)	36 (21.3)	9 (18.0)	18 (10.1)	5 (10.2)	2 (14.3)	13 (13.8)	7 (21.9)	1 (11.1)
Systolic hypertension	49 (9.2)	25 (14.8)	11 (22.0)	15 (8.4)	6 (12.2)	2 (14.3)	11 (11.7)	5 (15.6)	2 (22.2)
Diastolic hypotension	35 (6.6)	24 (14.2)	6 (12.0)	18 (10.1)	3 (6.1)	4 (28.6)	14 (14.9)	6 (18.8)	2 (22.2)
Respiratory, thoracic and mediastinal disorders	51 (9.6)	44 (26.0)	18 (36.0)	19 (10.6)	11 (22.4)	5 (35.7)	17 (18.1)	7 (21.9)	2 (22.2)
Hypoxia	27 (5.1)	29 (17.2)	13 (26.0)	8 (4.5)	3 (6.1)	3 (21.4)	9 (9.6)	3 (9.4)	2 (22.2)
Tachypnoea	6 (1.1)	1 (0.6)	1 (2.0)	2 (1.1)	1 (2.0)	1 (7.1)	5 (5.3)	1 (3.1)	0
Investigations	37 (7.0)	27 (16.0)	9 (18.0)	13 (7.3)	6 (12.2)	2 (14.3)	7 (7.4)	3 (9.4)	0
Respiratory rate increased	22 (4.1)	16 (9.5)	5 (10.0)	5 (2.8)	5 (10.2)	0	3 (3.2)	3 (9.4)	0
Respiratory rate decreased	10 (1.9)	4 (2.4)	0	4 (2.2)	1 (2.0)	2 (14.3)	3 (3.2)	0	0

ASA Physical Status Classification

There appeared to be higher or comparable incidences of any TEAE and those in the SOCs Vascular disorders, Respiratory, thoracic and mediastinal disorders, and Investigations in subjects with ASA-PS >II than those with ASA-PS I-II in all treatment groups. On the other hand, Cardiac disorders were slightly more common among subjects with ASA I-II than those with ASA > II.

Table 33: Incidence of TEAEs by ASA-PS Classification in controlled trials in procedural sedation

System organ class **Preferred term** **[n (%)]**	**Total Remimazolam**		**Total Midazolam**		**Placebo**	
	ASA-PS I-II (N=585)	ASA-PS >II (N=165)	ASA-PS I-II (N=182)	ASA-PS >II (N=60)	ASA-PS I-II (N=87)	ASA-PS >II (N=48)
Any TEAE	412 (70.4)	141 (85.5)	139 (76.4)	53 (88.3)	74 (85.1)	38 (79.2)
Cardiac disorders	69 (11.8)	10 (6.1)	28 (15.4)	8 (13.3)	16 (18.4)	4 (8.3)
Bradycardia	45 (7.7)	4 (2.4)	17 (9.3)	7 (11.7)	10 (11.5)	2 (4.2)
Tachycardia	23 (3.9)	4 (2.4)	12 (6.6)	1 (1.7)	6 (6.9)	3 (6.3)
Vascular disorders	327 (55.9)	126 (76.4)	118 (64.8)	49 (81.7)	64 (73.6)	37 (77.1)
Hypotension	173 (29.6)	62 (37.6)	75 (41.2)	28 (46.7)	41 (47.1)	23 (47.9)
Hypertension	118 (20.2)	45 (27.3)	32 (17.6)	22 (36.7)	22 (25.3)	10 (20.8)
Diastolic hypertension	68 (11.6)	41 (24.8)	16 (8.8)	9 (15.0)	13 (14.9)	8 (16.7)
Systolic hypertension	51 (8.7)	34 (20.6)	17 (9.3)	6 (10.0)	11 (12.6)	7 (14.6)
Diastolic hypotension	46 (7.9)	19 (11.5)	20 (11.0)	5 (8.3)	13 (14.9)	9 (18.8)
Respiratory, thoracic and mediastinal disorders	80 (13.7)	33 (20.0)	20 (11.0)	15 (25.0)	18 (20.7)	8 (16.7)
Hypoxia	50 (8.5)	19 (11.5)	10 (5.5)	4 (6.7)	10 (11.5)	4 (8.3)
Tachypnoea	4 (0.7)	4 (2.4)	1 (0.5)	3 (5.0)	2 (2.3)	4 (8.3)
Investigations	51 (8.7)	22 (13.3)	14 (7.7)	7 (11.7)	4 (4.6)	6 (12.5)
Respiratory rate increased	27 (4.6)	16 (9.7)	6 (3.3)	4 (6.7)	3 (3.4)	3 (6.3)
Respiratory rate decreased	11 (1.9)	3 (1.8)	4 (2.2)	3 (5.0)	0	3 (6.3)

Pregnancy and breastfeeding

An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) has been suggested in several trials. There are no adequate and well controlled trials of remimazolam in pregnant women. One subject in clinical trial CNS7056-005 became pregnant with date of conception one or two days after remimazolam administration. A healthy male baby was delivered at term, and the child was developing normally at 3.5 months when the follow-up information was received.

Reproductive toxicity studies on rabbits and rats were performed and revealed no abnormalities. According to the applicant, since animal reproduction studies are not always predictive of human response, the drug should be used during pregnancy only if clearly needed. However, according to the nonclinical assessment, the non-clinical package should be treated as insufficient data and remimazolam is not recommended during pregnancy and in woman of childbearing potential not using contraception (see non-clinical AR).

Remimazolam has been shown to be excreted in breast milk in animal studies. It is not known whether remimazolam is excreted in human milk; however, midazolam is excreted in human milk. Following oral administration, remimazolam undergoes rapid and extensive first-pass metabolism, and, as a result, has very low oral bioavailability (2.2% based of systemic exposure and 1.2% based on maximum plasma concentration). The applicant advises nursing mothers to stop breast-feeding for 24 h after remimazolam administration.

Hepatic impairment

The PK/PD effects of remimazolam in subjects with hepatic impairment were evaluated in Phase I Study ONO-2745IVU007 which included 8 patients with moderate hepatic impairment (score of 7 to 9 on the Child-Pugh scale) and 9 healthy matched subjects, as well as 3 patients with severe hepatic impairment (score of 10 to 15 on the Child-Pugh scale).

The half-life (t½) was prolonged with increasing severity of hepatic impairment (mean ± SD 42.9 ± 17.5 minutes, 59.2 ± 11.7 minutes, and 105 ± 29.7 minutes in healthy, moderate, and severe hepatic impairment subjects, respectively). Total exposure to remimazolam (as indicated by AUCinf), was larger in patients with severe hepatic impairment than in healthy subjects and patients with moderate hepatic impairment (AUCinf mean ± SD were 16.6 ± 4.78, 17.9 ± 4.02, and 29.6 ± 2.85 ng/h/mL in healthy, moderate, and severe hepatic impairment, respectively). Duration of sedation and time for recovery from sedative effects were longer for patients with hepatic impairment compared to healthy control subjects. The average duration of loss of consciousness was 1.6, 3.2, and 2.0 minutes in healthy, moderate, and severe hepatic impairment, respectively. Time to recovery was 8.0, 12.1, and 16.7 minutes in healthy, moderate, and severe hepatic impairment, respectively.

According to the applicant, moderate dose adjustments in patients with severe hepatic impairment appear appropriate, whereas no dose adjustments are needed for subjects with mild or moderate hepatic impairment.

Renal impairment

The PK/PD effects of remimazolam in subjects with renal impairment were evaluated in Phase I Study CNS7056-012 which included 12 subjects with normal renal function and 11 subjects with end-stage renal disease (ESRD) not on dialysis (6 subjects with eGFR of 15 to 30 mL/min/1.73 m^2 and 5 subjects with eGFR of <15 mL/min/1.73 m^2). The concentration-time profile and PK after a single IV dose of 1.5 mg IV Remimazolam did not show relevant differences in ESRD subjects compared to subjects with normal renal function. The excretion of the main metabolite CNS7054 however was prolonged in subjects with renal

impairment; however, this metabolite is pharmacological inactive. Based on these results, no dose adjustment is suggested for renal impairment patients.

Safety related to drug-drug interactions and other interactions

Extrinsic Factors

To evaluate abuse potential, the effect of alcohol on the PK and PD of orally administered Remimazolam was evaluated in Phase I Study CNS7056 020.

Compared to remimazolam alone, the number of TEAEs increased with remimazolam + alcohol, depending on the concentration of alcohol. However, the incidence of TEAEs was comparable between Remimazolam + 40% alcohol and 40% alcohol alone, indicating that the increase in the number of TEAEs observed following the coadministration of alcohol and remimazolam was, most likely, solely dependent on the dose of co-administered alcohol. There is a potential for slightly enhanced PD effects when remimazolam and alcohol are co-administered, compared to remimazolam alone.Results of the trial led to the overall conclusion that a combination of 18 vials of the remimazolam drug product (360 mg) and 150 mL of 40% v/v alcohol did not result in a predictable and reliable level of sedation that would allow for drug-facilitated criminal assaults. Moreover, the sheer amount of remimazolam and alcohol needed to produce significant sedation, together with the remarkably bitter taste of remimazolam do not suggest any potential whatsoever for the remimazolam-alcohol combination to incapacitate a victim.

Drug Interactions

The sedative effect of remimazolam can be accentuated by any concomitantly administered medication that depresses the CNS such as sedative-hypnotics and narcotics, (e.g., other benzodiazepines, [fos-]propofol, and opioid agonists).

Risks from Concomitant Use With Opioids

Comparisons of TEAEs across fentanyl dose groups are best characterised with pooled data from three Phase III trials (CNS7056 006, CNS7056 008, and CNS7056 015; i.e. Group A1A). This is because these trials cover the whole range of fentanyl dose from <75 µg to >150 µg, whereas the other controlled trial in procedural sedation (CNS7056 004) only covers higher doses of fentanyl >100 µg. More importantly, Phase III trial protocols pre-defined certain criteria for reporting AEs with focus on respiratory and haemodynamic effects (as mentioned earlier), which are slightly different for CNS7056 004.

Table 34 presents incidences of TEAEs in SOCs Cardiac disorders, Vascular disorders, Respiratory, thoracic and mediastinal disorders, and Investigations in Group A1A. It is apparent that higher cumulative doses of fentanyl were associated with increased rates of respiratory and haemodynamic AEs in all treatment groups. The same trend was observed in the SMQ/CMQ analyses of Hypotension, Bradycardia, and Hypoxia

Table 34: Incidence of Selected TEAEs by Cumulative Fentanyl Dose Category, Treatment Group, and System Organ Class in Controlled trials in Procedural Sedation

System organ class Preferred term [n (%)]	Total Remimazolam			
	<75 µg (N=184)	75-<100 µg (N=208)	100-150 µg (N=211)	>150 µg (N=27)
Any treatment emergent adverse event	151 (82.1)	161 (77.4)	177 (83.9)	25 (92.6)
Cardiac disorders	8 (4.3)	25 (12.0)	33 (15.6)	9 (33.3)
Vascular disorders	127 (69.0)	136 (65.4)	158 (74.9)	25 (92.6)
Respiratory, thoracic and mediastinal disorders	42 (22.8)	25 (12.0)	34 (16.1)	11 (40.7)
Investigations	21 (11.4)	17 (8.2)	20 (9.5)	10 (37.0)
System organ class Preferred term [n (%)]	**Total Midazolam**			
	<75 µ (N=48)	**75-<100 µg (N=39)**	**100-150 µg (N=91)**	**>150 µg (N=23)**
Any treatment emergent adverse event	41 (85.4)	34 (87.2)	85 (93.4)	22 (95.7)
Cardiac disorders	0	5 (12.8)	24 (26.4)	7 (30.4)
Vascular disorders	38 (79.2)	29 (74.4)	75 (82.4)	21 (91.3)
Respiratory, thoracic and mediastinal disorders	8 (16.7)	4 (10.3)	14 (15.4)	8 (34.8)
Investigations	5 (10.4)	1 (2.6)	9 (9.9)	4 (17.4)
System organ class Preferred term [n (%)]	**Placebo**			
	<75 µg (N=30)	**75-<100 µg (N=17)**	**100-150 µg (N=65)**	**>150 µg (N=23)**
Any treatment emergent adverse event	23 (76.7)	13 (76.5)	53 (81.5)	23 (100)
Cardiac disorders	2 (6.7)	1 (5.9)	13 (20.0)	4 (17.4)
Vascular disorders	22 (73.3)	13 (76.5)	46 (70.8)	20 (87.0)
Respiratory, thoracic and mediastinal disorders	9 (30.0)	2 (11.8)	6 (9.2)	9 (39.1)
Investigations	1 (3.3)	2 (11.8)	3 (4.6)	4 (17.4)

Furthermore, higher initial doses of fentanyl (>50 µg) were associated with an increased frequency of an MOAA/S score of 0 or 1. It is known that concomitant use of benzodiazepines with opioids can result in profound sedation, respiratory depression, coma, and death. Our analyses showed that remimazolam is similar to midazolam with regards to these interactions. Remimazolam should therefore be used for sedation only in the same infrastructure as midazolam, i.e., under presence of personnel skilled in early detection of hypoventilation, maintaining a patent airway, and supporting ventilation. Immediate availability of oxygen, resuscitative drugs, appropriate equipment for bag/valve/mask ventilation and a specific reversal agent (flumazenil) is highly recommended. Corresponding language is incorporated into the SmPC.

Pharmacokinetic Drug Interactions

Remimazolam is metabolised via hydrolysis by tissue esterases, predominantly expressed in the liver. Because it is not a CYP substrate, exposure is not expected to be affected by drugs that induce or inhibit CYP enzymes. Remimazolam and its primary metabolite, CNS7054, do not induce or inhibit any tested CYP enzymes, and they are not substrates of - nor do they cause any relevant inhibition of - the tested human drug transporters. Thus, there is a low potential for PK drug interactions.

Clinical Drug Interactions

The clinical safety data were examined for any evidence of an interaction between remimazolam and other drugs (concomitant fentanyl [either as initial or cumulative dose]; concomitant antihypertensive drugs; sedative or hypnotic drugs; and concomitant or prior chronic use of opiates and/or benzodiazepines), and between remimazolam and concomitant conditions (hypertension, COPD, pre-existing mental impairment, and gastrointestinal impairment). The primary analyses were based on the controlled trials in procedural sedation (Group A1). The following potential interactions were noted:

- Subjects receiving concomitant antihypertensive medications appeared to have a higher incidence of all TEAEs and TEAEs that were Vascular disorders (including hypotension and hypertension) and Respiratory, thoracic, and mediastinal disorders (including hypoxia and tachypnea) on all remimazolam, midazolam and placebo. The incidences were similar across groups but were not consistently different between subjects with and without antihypertensive medication (Table 35 below).
- Subjects on remimazolam receiving concomitant sedative/hypnotic medications appeared to have a higher incidence of all TEAEs and TEAEs that were Vascular disorders (including hypotension and hypertension); Respiratory, thoracic, and mediastinal disorders (including hypoxia and tachypnea); and Investigations (including respiratory rate increased, respiratory rate decreased, and blood pressure diastolic decreased). The effect could not be compared to placebo because only 5 subjects randomised to placebo were not taking concomitant sedatives/hypnotics (Table 36 below).
- On remimazolam and midazolam, subjects with pre-existing arterial hypertension appeared to have a higher incidence of all TEAEs and TEAEs that were Vascular disorders (including hypotension and hypertension) and Respiratory, thoracic, and mediastinal disorders (including hypoxia and tachypnea) than those without arterial hypertension. On placebo, subjects with pretrial arterial hypertension appeared to have a lower incidence or similar incidence of all TEAEs and all TEAEs in the SOCs Vascular disorders and Respiratory, thoracic, and mediastinal disorders when compared to those without arterial hypertension. However, the incidences of the specific events hypotension, hypertension, hypoxia, and tachypnea had a similar pattern as that shown for subjects on remimazolam and midazolam, i.e., higher incidence among subjects with arterial hypertension (Table 37 below).

These risks can be minimised by dose individualisation and titration to desired clinical response. The low numbers of subjects in some subgroups precluded assessment of some interactions.

Table 35: TEAEs related to concomitant antihypertensive medications in controlled trials in procedural sedation

System organ class Preferred term [n (%)]	Total Remimazolam		Total Midazolam		Placebo	
	Antihypertensives (N=363)	No Antihypertensives (N = 387)	Antihypertensives (N = 127)	No Antihypertensives (N = 115)	Antihypertensives (N = 84)	No Antihypertensives (N = 51)
Any TEAEs	289 (79.6)	264 (68.2)	106 (83.5)	86 (74.8)	69 (82.1)	43 (84.3)
Vascular disorders	247 (68.0)	206 (53.2)	96 (75.6)	71 (61.7)	62 (73.8)	39 (76.5)
Hypotension	130 (35.8)	105 (27.1)	59 (46.5)	44 (38.3)	44 (52.4)	20 (39.2)
Hypertension	97 (26.7)	66 (17.1)	38 (29.9)	16 (13.9)	23 (27.4)	9 (17.6)
Respiratory, thoracic and mediastinal disorders	74 (20.4)	39 (10.1)	20 (15.7)	15 (13.0)	16 (19.0)	10 (19.6)
Hypoxia	46 (12.7)	23 (5.9)	7 (5.5)	7 (6.1)	11 (13.1)	3 (5.9)
Tachypnoea	5 (1.4)	3 (0.8)	3 (2.4)	1 (0.9)	3 (3.6)	3 (5.9)

Table 36: TEAEs related to concomitant sedative/hypnotic medications in controlled trials in procedural sedation

System organ class Preferred term [n (%)]	Total Remimazolam		Total Midazolam		Placebo	
	Sedative/ Hypnotic (N=112)	No Sedative/ Hypnotic (N=638)	Sedative/ Hypnotic (N=139)	No Sedative/ Hypnotic (N=103)	Sedative/ Hypnotic (N=130)	No Sedative/ Hypnotic (N=5)
Any TEAEs	97 (86.6)	456 (71.5)	126 (90.6)	66 (64.1)	108 (83.1)	4 (80.0)
Vascular disorders	85 (75.9)	368 (57.7)	114 (82.0)	53 (51.5)	97 (74.6)	4 (80.0)
Hypotension	42 (37.5)	193 (30.3)	75 (54.0)	28 (27.2)	63 (48.5)	1 (20.0)
Hypertension	25 (22.3)	138 (21.6)	34 (24.5)	20 (19.4)	31 (23.8)	1 (20.0)
Respiratory, thoracic and mediastinal disorders	27 (24.1)	86 (13.5)	25 (18.0)	10 (9.7)	25 (19.2)	1 (20.0)
Hypoxia	21 (18.8)	48 (7.5)	11 (7.9)	3 (2.9)	14 (10.8)	0
Tachypnoea	4 (3.6)	4 (0.6)	4 (2.9)	0	6 (4.6)	0
Investigations	19 (17.0)	54 (8.5)	11 (7.9)	10 (9.7)	10 (7.7)	0
Respiratory rate increased	14 (12.5)	29 (4.5)	6 (4.3)	4 (3.9)	6 (4.6)	0
Respiratory rate decreased	3 (2.7)	11 (1.7)	4 (2.9)	3 (2.9)	3 (2.3)	0
Blood pressure diastolic decreased	2 (1.8)	5 (0.8)	1 (0.7)	0	1 (0.8)	0

Table 37: TEAEs related to arterial hypertension in controlled trials in procedural sedation

System organ class Preferred term [n (%)]	Total Remimazolam		Total Midazolam		Placebo	
	Arterial hypertension (N=366)	No Arterial hypertension (N = 384)	Arterial hypertension (N=125)	No Arterial hypertension (N = 117)	Arterial hypertension (N=79)	No Arterial hypertension (N = 56)
Any TEAEs	296 (80.9)	257 (66.9)	104 (83.2)	88 (75.2)	64 (81.0)	48 (85.7)
Vascular disorders	252 (68.9)	201 (52.3)	92 (73.6)	75 (64.1)	58 (73.4)	43 (76.8)
Hypotension	131 (35.8)	104 (27.1)	57 (45.6)	46 (39.3)	43 (54.4)	21 (37.5)
Hypertension	97 (26.5)	66 (17.2)	35 (28.0)	19 (16.2)	21 (26.6)	11 (19.6)
Respiratory, thoracic and mediastinal disorders	74 (20.2)	39 (10.2)	20 (16.0)	15 (12.8)	15 (19.0)	11 (19.6)
Hypoxia	46 (12.6)	23 (6.0)	7 (5.6)	7 (6.0)	9 (11.4)	5 (8.9)
Tachypnoea	5 (1.4)	3 (0.8)	3 (2.4)	1 (0.9)	4 (5.1)	2 (3.6)

In all treatment groups (remimazolam, midazolam and placebo), the incidence of TEAEs was higher in patients who were also receiving antihypertensive medications compared to patients not receiving antihypertensive medications. The same was observed for patients receiving sedative/hypnotic drugs across treatment groups.

Discontinuation due to adverse events

In controlled trials in procedural sedation, 1 subject in the Total Remimazolam group (0.1%), 1 subject in Total Midazolam group (0.4%), and 0 subjects in the Placebo group had at least 1 TEAE leading to discontinuation of study treatment.

The remimazolam-treated subject was in the 5 mg dose group in Study CNS7056-008 and experienced two severe SADRs of hypoxia and bradycardia (relationship to study drug: certain) and 7 mild TEAEs of hypertension (possible [3 events]), hypotension (possible [3 events]), and respiratory rate increased (possible) with outcome of recovered/resolved. This case, with reported PTs that included hypoxia and bradycardia, was discussed in an ad-hoc meeting by the Data Monitoring Committee who assessed the event as a predictable consequence of administration of a second dose of fentanyl that was twice that allowed by the trial protocol, together with trial medication, to an individual with considerable comorbidity and who was receiving concomitant medication, including beta blockade. The applicant agrees to the causal association of these events to fentanyl.

The midazolam-treated subject was in the <1.75 mg dose group and discontinued study drug due to an AE of Grade 2 respiratory acidosis (relationship to study drug: possible; outcome: not recovered/not resolved).

Post marketing experience

NA

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Safety database

Evaluation of remimazolam's safety profile primarily concerns the target indication setting. Main comparisons are done between Total Remimazolam and Total Midazolam groups (ISS group A1). For evaluation of safety it is important to note that 95.2 to 100% of subjects in placebo group have received rescue midazolam dosed at the investigator's discretion. Main safety population of 750 adult subjects from active and placebo-controlled trials in target indication that have received remimazolam is deemed appropriate for safety profile characterisations, although the exposure was too small to capture rare adverse reactions which is important for overall conclusions. All participants were exposed to an opioid (fentanyl) premedication and during the procedures as needed (due to its analgesic properties). Proposed doses are investigated.

Safety database limitation

The applicant stated some limitations of safety database: a) In all trials, pregnant and lactating women were excluded from the study population. The former was because a risk of congenital abnormalities cannot be excluded. The latter was because it has been shown in nonclinical studies that remimazolam and its metabolite were excreted in breast milk. Therefore, remimazolam is not recommended in pregnant women, and lactating women are advised to stop breast-feeding for 24 h after receiving remimazolam. b) The clinical development programme is unlikely to detect rare adverse events due to its size. These limitations are addressed in the Risk Management Plan for remimazolam.

Availability of antagonist

As with other benzodiazepines, the sedative effects of remimazolam can be reversed by the $GABA_A$ **antagonist flumazenil**, offering an additional safety measure in case of overdose and unintentional "deep" sedation. During the clinical development in procedural sedation, no remimazolam-treated subjects required reversal with flumazenil for safety reasons.

Baseline characteristics of safety population

According to the baseline demographic characteristics, participants were adequately balanced among compared groups (remimazolam vs midazolam and placebo). There was slight imbalance regarding race, but majority of subjects were White. There was no obvious significant finding regarding medical history and prior or concomitant medications when explored by frequency of the preferred term in concerned safety population. None of the clinical trials were conducted in EU. The applicant provided thorough discussion on applicability of the data from foreign trials (trials conducted in the US and Japan). It is agreed that remimazolam can be classified as a compound not likely to be sensitive to ethnic factors according to the ICH E5(R1) guideline.

TEAEs

Generally, safety profiles of compared groups are similar.

The **most common** (>5%) events in Total Remimazolam group by PT were hypotension, hypertension, diastolic hypertension, systolic hypertension, hypoxia, diastolic hypotension, bradycardia, and respiratory rate increased.

Among TEAEs with incidence ≥1% there are some observed with higher incidence in Total Remimazolam group by PT than Total Midazolam group: diastolic hypertension, systolic hypertension, hypoxia, oropharyngeal pain, respiratory rate increased, nausea, vomiting, abdominal pain, dizziness, pyrexia.

Observed TEAEs indicate remimazolam's *potential for haemodynamic and respiratory disturbances, gastrointestinal disorders, dizziness and pyrexia* as most pronounced AEs. Generally, the incidences of specific TEAEs by SOCs/PTs are not markedly different when compared to midazolam and placebo (rescue midazolam). As participants in midazolam groups have received fentanyl also, the observed TEAEs' profile is deemed attributable to remimazolam regardless of fentanyl administration.

The applicant pointed out hypoxia, bradycardia and hypotension as important identified risks. Analysis done did not revealed any specific AE with higher frequency in Total Remimazolam group compared to Total Midazolam (and Placebo) group.

There have been a significant number of cases of decreased ventilation upon remimazolam administration. In the pooled analysis, patients with MOAA/S 1 or zero have occurred in 115/630 cases (18.3%); only 9/115 have been identified as respiratory disorder. Of the 67/630 who developed RR less than 8/min, virtually all (66) have been identified as respiratory depression. It is interesting that investigators as a whole did not report the episodes as SAEs or as hypoxia AE (1/67). As such, it can be reasonably accepted that clinicians have discriminated CNS depression from respiratory depression.

The comparison of remimazolam to midazolam is not much useful, as administration of midazolam occurred in different circumstances as remimazolam, and therefore, the direct comparison of 2.3% of vital sign anomalies as compared to 6% in midazolam (and 3.8% the called placebo patients) is not possible.

Unlike the applicant's conclusion, it is shown that overshooting CNS depression does occur with remimazolam, with 18% of pts reaching MOAA/S ≤1, and almost 8% having respiratory disorders identified as SAE. It is true that only 10.6% did show respiratory rate decrease, and all have been identified as having respiratory depression or hypoxia by clinicians, with none reported as SAE. It can be admitted that all events have been adequately dealt within a CT setting, but the applicant should have elaborated more upon extrapolation to the real world.

Although number of clinically significant ECG abnormalities was low, caution is needed. Studies 005 and 017 found that remimazolam produced rapid and transient increases in heart rate immediately after dosing, but no effects on PR and QRS interval duration or ECG morphology were observed. There was also indication that remimazolam has an effect on QT-RR hysteresis but this was assessed as not significant. However, there are no data for individuals that are genetically sensitive to potential QT prolonging medication and the applicant did not conduct drug-drug interaction studies with QT prolonging medication and remimazolam. It will be necessary to monitor the effects of remimazolam on ECG abnormalities in the postmarketing period.

A need for airway intervention was observed in Total Remimazolam group and it was higher compared to Total Midazolam and Placebo (rescue midazolam) groups.

Significantly higher incidence of **undesirable deep sedation** (MOAA/S 0-1) in Total Remimazolam group compared to Total Midazolam and Placebo (rescue midazolam) groups was observed. Major

difference in level of sedation and time to achieve sedation between remimazolam and midazolam is seen during first 10 to 15 minutes post-dose. Remimazolam achieves deeper and faster sedation that is deemed clinically significant from the safety point of view. Furthermore, there seems to be interindividual variabilities regarding depth of sedation. Relevant CNS AEs were explored. While confirmed that no case of paradoxical reaction or aggressive behaviour has been observed during clinical development, newly provided data from SOCs Psychiatric disorders, Nervous system disorders, and Injury, poisoning and procedural complications can suggest that there might be some glimpse of possible paradoxical reactions. However, overall incidences of concerned AEs are too small to allow conclusions and AEs observed with higher incidences are included in the SmPC Section 4.8. Hypothetical discussion regarding paradoxical reaction or aggressive behaviour is missing. Nevertheless, according to presented data, routine post-marketing pharmacovigilance will suffice at this stage. In clinical trials, no cases of anterograde amnesia or paradoxical reactions including hyperactive or aggressive behaviour have occurred.

The applicant explored the **abuse potential** of remimazolam, and its **withdrawal and rebound effects** as benzodiazepines are associated with abuse potential, withdrawal and rebound effects. Trials and analyses done did not reveal development of dependence in the controlled clinical trials setting. Withdrawal is not expected due to the anticipated short exposure in the procedural sedation setting.

Injection site pain obtained data did not reveal differences between remimazolam and midazolam.

Local tolerance issues are known for parenteral benzodiazepines, i.e. thrombophlebitic reactions to benzodiazepines, with diazepam and midazolam as notable examples. Non-clinical data revealed the vascular lesions at higher concentrations of remimazolam which seems to reflect an effect frequently associated with benzodiazepines.

According to the applicant, all SAEs in procedural sedation were reported from the bronchoscopy trial (CNS7056-008) which biased the type of reported SAEs with the vast majority of them pertaining to **SOC Respiratory, thoracic and mediastinal disorders**. A discussion on these observations has been provided upon request. However, as the depth of sedation is a continuum ranging from minimal sedation to general anaesthesia, and the most severe end of spectrum for respiratory effects is respiratory failure, in order to be able to manage these complications, performance of sedation with remimazolam must be limited to professionals skilled in managing general anaesthesia and providing advanced life support, ie. anaesthesiologists or another dedicated ICU trained clinician. The revised SmPC wording was accepted as it addresses this issue. Firstly, it states that the administering clinician, experienced in sedation, should not be the one conducting the procedure. Secondly, a separate healthcare professional should monitor the patient throughout the procedure, which involves continuous respiratory and cardiovascular monitoring. Furthermore, these personnel must be trained in the detection and management of airway obstruction, hypoventilation and apnoea, including the maintenance of a patent airway, supportive ventilation and cardiovascular resuscitation.

Safety in special populations

Some adverse events were more frequently observed **in elderly**: AEs belonging to the *SOC Vascular disorders* (53.7% vs 75.1% vs 82.0% in groups <65 years, 65-74 years, ≥75 years respectively) and *hypoxia* (5.1% vs 17.2% vs 26.0% in groups <65 years, 65-74 years, ≥75 years respectively).

In the study 015 (**patients with ASA-PS III-IV**) treatment-emergent AEs were reported in 90.3% of patients in the remimazolam group (58 TEAEs), in 81.3% of patients in the placebo group (30 TEAEs), and in 86.7% of patients in the midazolam group (55 TEAEs). All TEAEs reported were mild in severity, with the exception of 1 episode of moderate anaemia in a patient in the midazolam group. The majority of TEAEs were not considered to be related to treatment; treatment-related TEAEs were reported in 9.7% of patients in the remimazolam group, in 12.5% of patients in the placebo group, and in 6.7% of patients in the midazolam group. The most frequently reported events at the SOC level were Vascular disorders

(81.8% overall) and Respiratory, thoracic and mediastinal disorders (20.8% overall). All of the treatment-related TEAEs reported during the course of the trial were in these 2 SOCs. There were no discontinuation due to TEAEs and there was no serious AE observed in the study 015. The most frequently reported TEAEs on the PT level were *hypotension* (59.7% overall), *hypertension* (41.6%), and *respiratory acidosis* (20.8%). **In patients aged ≥65 years**, the incidence of events grouped under the terms *hypotension* (71.0% versus 56.5%), *hypertension* (58.1% versus 37.0%), and *respiratory depression* (29.0% versus 23.9%) was greater than in younger patients (<65 years).

The observed increasing frequency of TEAEs with increasing age and ASA-PS classification was translated into a recommendation for a more cautious and individualised dosing in **patients ≥ 65 years of age and/or with ASA-PS III-IV** in the proposed SmPC. Increasing incidences with increasing age were observed for PT Hypoxia in the SOC Respiratory, Thoracic and Mediastinal Disorders and for PTs related to Hypotension and Hypertension in the SOC Vascular Disorders. The proposed PI already addresses ADRs observed in elderly.

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of remimazolam in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Byfavo during pregnancy.

Patients with **severe hepatic impairment** have longer half-life, larger total exposure and longer time to recovery with remimazolam compared to healthy subjects. These effects are more pronounced in the severe hepatic impairment groups.

No dose adjustment is proposed for patients with **renal impairment**. Based on the presented data and provided that there was also no change in the unbound exposure of remimazolam, this is acceptable.

Given the complexity of the proposed posology for this product, with differences in initial and subsequent bolus doses depending on concomitant use of opioids, patient age, ASA status and weight, details of the remimazolam dosing guidelines were presented in section 4.2 of the SmPC and instructions for use to facilitate ease of access to this important information by HCPs when using this product. Furthermore, information on the effects of concomitant use of opioids/CNS depressants/alcohol was provided to HCPs within this section of the PL, following the information on the training requirements for the practitioner responsible for administering the product and monitoring the patient, to outline that concomitant use of remimazolam and opioids/CNS depressants/alcohol may increase the sedative effects of remimazolam, which may result in profound sedation and respiratory depression, and that patients should be monitored closely during and after the procedure for signs and symptoms of respiratory depression and sedation.

Excipients (dextran and lactose)

Hypersensitivity reactions were observed during the clinical development programme. According to the the applicant, the addition of dextran 40 in combination with lactose to the remimazolam formulation allows for the acceleration of the freeze-drying cycle in the production process of the freeze-dried product. Calculations were done based on proposed use in general anaesthesia setting and according to the applicant, dexran 40 is highly unlikely to pose a hazard to human health at the exposure level investigated in the proposed indication, and the issue was further discussed upon request, with the conclusion that routine PhV measures will be sufficient for safety monitorisation. The applicant has done comprehensive assessment regarding above mentioned effects of dextran on coagulation and renal function. It is agreed that there is no obvious risk on coagulation and renal function with doses proposed in the procedural sedation setting.

Drug-drug interactions

Drug-drug interactions and the potential impact with antiepileptics and antidepressants have been elucidated during the assessment. Although some differences were suspected to be clinically relevant from the raw data, the magnitude of differences regarding antiepileptics or antidepressants were not relevant with respect to impact on O_2 saturation, use of fentanyl or time to onset and offset of sedation.

2.6.2. Conclusions on the clinical safety

Safety profile of remimazolam seems broadly comparable to the safety profile of midazolam. Observed TEAEs indicate remimazolam's potential for haemodynamic and respiratory disturbances, gastrointestinal disorders, dizziness and pyrexia. Observed AEs seem manageable, but the speed of occurrence is of concern. Based on different PD profile compared to midazolam and medication error potential, the conditions for use should include administration of remimazolam only by clinicians experienced in sedation and proper precautionary measures are needed. Significant drawback of medicinal product formulation are excipients that poses risk of anaphylactic/ anaphylactoid reactions.

The following main warning and precautions have been included in the SmPC: there should be a dedicated clinician to sedation other than the practitioner, and the CNS and respiratory depression may occur. Interactions with chronic concomitant medication and co-administration of opioids need to be taken into account.

2.7. Risk Management Plan

Safety concerns

Table 38: Summary of the safety concerns

Important identified risks	None
Important potential risks	Deep sedation associated with respiratory depression leading to hypoxia or respiratory arrest
Missing information	Use during pregnancy

Pharmacovigilance plan

No additional pharmacovigilance activities are deemed necessary.

Risk minimisation measures

Table 39: Summary table of PV and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Deep sedation associated with respiratory depression leading to hypoxia or respiratory arrest	Routine risk minimisation measures: SmPC section 4.4, SmPC section 4.8, SmPC section 4.9. PL section 2, PL section 3, PL section 4. Medicinal product subject to restricted medical prescription. Additional risk minimisation measures: none	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Use during pregnancy	Routine risk minimisation measures: SmPC section 4.6. PL section 2. Medicinal product subject to restricted medical prescription Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 23 January 2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of remimazolam with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Based on the fact that the product is reconstituted and then injected intravenously and will only be used by HCPs in a clinical setting and considering the small size of the vial and associated lack of space, the QRD group accepted the request to use minimum particulars on the 12 ml vial label.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Byfavo (remimazolam) is included in the additional monitoring list as it contains new active substance.

Therefore. the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new

safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication is: "Remimazolam is indicated in adults for procedural sedation."

Procedural sedation may be used for any unpleasant medical procedure in which a patient's pain or anxiety is pronounced and may interfere with performance. Sedatives don't have analgesic properties; therefore they are commonly used in combination with opioids. The applicant has chosen colonoscopy and bronchoscopy as model procedures in phase 3 trials.

Aim of therapy is to enable performance of the procedure.

3.1.2. Available therapies and unmet medical need

Available medicinal products for procedural sedation are the benzodiazepine midazolam and the general anaesthetic propofol in combination with opioids.

Propofol is a lipophilic intravenous general anaesthetic with a short onset of action (9 to 51 seconds) and a short half-life, which allows rapid recovery from sedation. Disadvantages of propofol include its potential for respiratory depression with loss of airway potency, common and profound hypotension and a narrow therapeutic index which can lead to involuntary overdosing. The administration of propofol requires a physician trained in the administration of general anaesthesia or management in an intensive care unit.

Among benzodiazepines, midazolam is the most commonly used agent for procedural sedation. Disadvantage of benzodiazepines is their long half-life; even midazolam as the shortest acting benzodiazepine on the market has a half-life of 1-3 hours. Other disadvantages include a possibility for respiratory depression and prolonged sedation/drowsiness. The availability of an antidote (flumazenil) is an advantage. The administration of midazolam requires the presence of a dedicated person trained in the recognition and management of expected adverse events including respiratory and cardiac resuscitation.

Overall, midazolam is a satisfactory benzodiazepine for procedural sedation and no unmet medical need has been identified. However, patients and clinicians would benefit from a benzodiazepine with a more rapid recovery and a better safety profile.

3.1.3. Main clinical studies

The main evidence of efficacy submitted comes from three randomised, controlled, Phase 3 trials in the indication of procedural sedation. Fentanyl was co-administered for analgesia in these three trials. All studies were conducted in adult patients.

Phase 3 Studies **CNS7056-006** and **CNS7056-008** are designated as pivotal, while Study **CNS7056-015** is designated as supportive.

Phase 2b trial **CNS7056-004** is designated as a dose-finding trial. However, since it is the only trial that provided head-to-head comparison with blinded midazolam, it is briefly mentioned here for contextualisation purposes.

Study **CNS7056-006** was a phase 3 study evaluating the efficacy and safety of remimazolam compared to double-blind placebo and open-label midazolam in patients undergoing colonoscopy. Participants were randomised to receive one of the following 3 treatments: remimazolam 5mg initial dose+2.5mg top-ups; matching placebo or open-label midazolam 1.75mg initial dose+1mg top-ups. Fentanyl was administered for analgesia (initially 75µg, reduced to 50µg in protocol amendment 4; top-ups were allowed). The initial dose of midazolam is slightly lower than EU midazolam. The ITT set was used for the primary efficacy analysis and consisted of all randomised patients: 298 in remimazolam; 60 in placebo and 103 in midazolam arms.

Study **CNS7056-008** was a phase 3 study evaluating the efficacy and safety of remimazolam compared to double-blind placebo and open-label midazolam in patients undergoing flexible bronchoscopy. Patients were randomised to receive remimazolam, placebo or midazolam in the same doses as in study 006. Fentanyl was administered for analgesia (initially 75 µg, later amended to 25 to 50 µg; top-ups were allowed). The ITT set was used for the primary efficacy analysis and consisted of all randomised patients: 310 in remimazolam, 63 in placebo and 73 in midazolam.

Study **CNS7056-015** was a phase 3 study evaluating primarily safety of remimazolam compared to double-blind placebo and open-label midazolam in ASA III and IV patients undergoing colonoscopy. Patients were randomised into one of three groups: remimazolam 2.5-5mg initial dose plus 1.25-2.5mg top-up doses; placebo or midazolam 1.0mg plus 0.5mg top-up doses. Fentanyl was administered for analgesia (up to 50 µg; top-ups were allowed). The ITT set included 32 patients in remimazolam, 16 in placebo and 31 in midazolam arms.

Study **CNS7056-004** was a Phase 2b dose-finding study evaluating safety and efficacy of multiple doses of remimazolam compared to midazolam in patients undergoing colonoscopy. Patients were randomised to receive 1 of the 4 treatments: remimazolam 8mg initial dose+3 mg top-ups (40 patients); remimazolam 7mg initial+2 mg top-ups (40 patients); remimazolam 5mg initial+3 mg top-ups (41 patients); or the comparator midazolam 2.5 mg initial+1 mg top-ups (41 patients). Fentanyl was administered for analgesia (100 µg initially with top-ups allowed). This is the only clinical study in procedural sedation where remimazolam and midazolam were both administered in a blinded fashion which provides head-to-head comparison data.

Rescue strategies were defined – rescue analgesia consisted of additional doses of fentanyl and rescue sedation consisted of midazolam only (except in study 004, where other sedatives could have been used as rescue).

3.2. Favourable effects

Success of procedure is the primary efficacy outcome in pivotal trials. Success of procedure is a **composite primary outcome** and responders in phase 3 trials were patients who completed the procedure, did not require alternative sedatives and with a maximum of remimazolam 5 top-ups in any 15 minutes window (for midazolam: maximum 3 top-ups within any 12 min window).

Success of procedure was observed in 91.3%, 80.6% and 84.4% in patients treated with remimazolam in studies 006, 008 and 015 respectively. This is to be compared with 1.7%, 4.8% and 0% patients treated with placebo in studies 006, 008 and 015 respectively. In open-label midazolam arm, treatment success was recorded in 25.2%, 32.9% and 12.9% patients in studies 006, 008 and 015, respectively. The non-response was mainly due to need for rescue sedative medication.

The above stated results in phase 3 trials translate into difference in treatment success rates between remimazolam and placebo of 89.6% (95% CI: 85%, 94.2%; p-value <0.0001) and 75.9% (95% CI: 69%, 82.8%; p-value <0.0001) in studies 006 and 008, respectively. The difference in treatment success rates between remimazolam and midazolam were 66% (95% CI: 57%, 75%) and 47.8% (95%CI: 36.1%, 59.4%) in trial 006 and 008, respectively. Significance levels for comparison of remimazolam and midazolam were not obtained since midazolam was open-label and these results were exploratory.

For contextualisation purposes, the results for the primary outcome success of procedure from phase 2b Study 004 (comparison of blinded remimazolam vs. blinded midazolam) can be used. Responders were defined as patients with MOAA/S≤ 4 on 3 consecutive measurements taken every minute who completed the procedure, did not require alternative sedative nor manual/mechanical ventilation. Success of procedure in Study 004 was observed in 92.5% of patients (remimazolam dose 8.0mg initial/3.0 mg top-ups); 95% (remimazolam 7.0mg/2.0mg) and 97.5% (remimazolam 5.0mg/3.0mg). This is to be compared with 75% of patients treated with midazolam. Pairwise comparison to midazolam was performed and exploratory p-values obtained: 0.066 (for remi 8.0mg/3.0mg); 0.025 (for remi 7.0/2.0mg) and 0.007 (for remi 5.0/3.0mg).

The main secondary outcomes were time-to-event outcomes aiming to describe the onset and recovery profile of remimazolam. These endpoints support the clinical relevance of the primary endpoint.

Time to peak sedation was reached in 3 minutes (95% CI -,-), 3.5 minutes (95% CI 3.5, 4.0) and 3 minutes (95% CI 3.0, 3.6) for patients treated with remimazolam in studies 006, 008 and 015, respectively. Time to peak sedation could not be established for placebo and for midazolam it was 7 minutes (95% CI: 7.0,-) in study 008 (could not be established in other two studies).

Time to fully alert from last dose of study drug was reached in 14 minutes (95% CI: 13.0, 14.0), 11.6 minutes (95% CI 10.0, 12.8) and 11 minutes (95% CI 8.8, 12.0) in patients receiving remimazolam in studies 006, 008 and 015. This is to be compared with 28 minutes (95% CI 24.0, 32.0), 20 minutes (95% CI 15.3, 31.0) and 18 minutes (95% CI 14.0, 25.0) in patients receiving placebo in studies 006, 008 and 015, respectively. In the open-label midazolam arm, this outcome was reached in 24 minutes (95% CI 22.0, 26.0), 18 minutes (95% CI 15.0, 20.1) and 18.8 minutes (95% CI 15.0, 26.0) in studies 006, 008 and 015, respectively.

From the patient's perspective, **time to feeling 'back to normal'** was 3.2 hours (95% CI 3.0, 3.5) in remimazolam group, compared to 5.8 hours (95% CI 4.0, 7.4) in placebo group and 6.1 hours (95% CI 5.0, 7.2) in midazolam group. Hazard ratio for the comparison of remimazolam vs placebo was 1.751 (92% CI 1.312, 2.337) and for the comparison of remimazolam vs midazolam 1.775 (95% CI 1.407, 2.239).

Sensitivity analysis for the primary outcome based on total fentanyl received and initial fentanyl dose showed similar results to those seen in the primary efficacy analysis for remimazolam versus placebo in studies 006 and 008. Sensitivity analysis for remimazolam versus midazolam in Study 006 obtained results similar to those seen in primary analysis.

3.3. Uncertainties and limitations about favourable effects

Midazolam was administered as an **open-label** study drug in all phase 3 studies. This may have inflated the treatment effect of remimazolam. The statistic comparisons with midazolam were exploratory.

Another issue with midazolam as a comparator in pivotal phase 3 studies 006 and 008 is the **suboptimial dose** used (ie. 1.75 mg as the initial dose; EU label midazolam states 2-2.5mg as the initial dose in procedural sedation). Top-up doses were in line with EU label midazolam (ie. 1mg). Placebo was used as a double-blind comparator in pivotal trials and statistical analysis were based on superiority over placebo.

After failure of placebo, rescue midazolam was to be used. This enabled the procedures to be completed but uncertainty was introduced since the comparator arm was effectively **no longer blinded**.

Sensitivity analysis for the primary outcome based on total fentanyl received and initial fentanyl dose for remimazolam versus midazolam showed similar results to those seen in primary efficacy analysis except that the difference in success rates was smaller for the initial fentanyl stratum ≥75 µg (0.0067 [95%-CI: -0.3244, 0.3377]) in study 008.

Median **time to ready for discharge from the end of procedure** was 5 minutes shorter in remimazolam compared to placebo (with overlapping 95% CIs) and 4 minutes shorter compared to midazolam (with overlapped 95% CIs) in Study 006. These reductions (in absolute terms: from 49 minutes in placebo and 48 minutes in midazolam to 44 minutes in remimazolam) are hardly clinically relevant. In Study 008 time was reached 6 minutes earlier for remimazolam compared to midazolam (with overlapping 95% CIs). This is not clinically relevant (in absolute terms: from 66 minutes in placebo to 60 minutes in remimazolam). On the other hand, time to discharge in remimiazolam group was 21 minutes shorter compared to placebo and this is clinically relevant.

Median **time to ready for discharge from the last dose** of study drug was 6 minutes shorter in remimazolam compared to midazolam with overlapping 95% CIs in Study 006 (reduction from 57 to 51 minute). In study 008, this outcome was also reached 6 minutes earlier in remimazolam compared to midazolam with overlapping 95% CIs (reduction from 70 to 64 minutes). These reductions are not clinically relevant. On the other hand, time to discharge from last dose in remimazolam compared to placebo was 9 and 19 minutes shorter (95% CIs do not overlap) in studies 006 and 008, respectively, and this is clinically relevant.

From the patient's perspective, **time to feeling 'back to normal'** in Study 008 was 6.7 hours (95% CI 5.7, 8.5) in remimazolam arm compared to 15.6 hours (95% CI 7.7, 20.3) in placebo and 7.4 hours (95% CI 5.2, 16.8) in midazolam arm. Hazard ratio for the comparison of remimazolam versus placebo was 1.277 (95%-CI: 0.940, 1.734) and was not statistically significant (P = 0.1165). Hazard ratio for the comparison remimazolam versus midazolam was 0.916 (95%-CI: 0.690, 1.216). These results are not statistically significant nor clinically relevant.

The final indication –procedural sedation - is broad. Due to its rapid onset of action and a favourable recovery profile, it can be expected that remimazolam will be of interest for a variety of procedures, and not just the ones studied. However, procedures in the pivotal trials were of relatively short duration; majority of them lasted. Efficacy and safety data from pivotal studies in procedural sedation has been analysed in 2 categories: procedures lasting for 30 minutes of less and procedures lasting for more than 30 minutes. This analysis suggests that patients undergoing procedures of short duration can be expected to have more benefit of remimazolam treatment compared to patients undergoing procedures of longer ≥ 30 min duration. Consequently, the results were presented in the SmPC separately for procedures shorter and longer than 30min in order to inform the prescribers of this difference.

3.4. Unfavourable effects

Overall 750 subjects received remimazolam in procedural sedation active and placebo controlled clinical trials clinical trials.

Of the 750 subjects in Total Remimazolam treatment group, 73.7% of subjects had a TEAE, and 32.7% of subjects had a TEAE related to study drug compared to 79.3% and 40.1% in Total Midazolam group respectively. 17 subjects (2.3%) in Total Remimazolam group had an **SAE** compared to 1 subject (0.4%) in Total Midazolam group.

The most common (>5%) events in Total Remimazolam group by PT were (not all listed): *hypotension* (31.3%), *hypertension* (21.7%), *hypoxia* (9.2%), *bradycardia* (6.5%), and *respiratory rate increased* (5.7%). Among TEAEs with incidence ≥1% there are some observed with higher incidence in Total Remimazolam group by PT than Total Midazolam group (not all listed): ***diastolic hypertension*** (14.5% vs 10.3%), ***systolic hypertension*** (11.3% vs 9.5%), ***hypoxia*** (9.2% vs 5.8%), ***respiratory rate increased*** (5.7% vs 4.1%), *nausea* (3.2% vs 2.1%).

Significantly higher incidence of undesirable ***deep sedation*** *(MOAA/S 0-1)* in Total Remimazolam group compared to Total Midazolam and Placebo (rescue midazolam) groups (27.7% vs 15.7% and 11.9% respectively). When analysing frequencies of MOAA/S scores 0-1 in ISS group A1, notable differences are seen from minute 1 post-dose between remimazolam and midazolam: 7.6% vs 0.9% in minute 1; 14.6% vs 1.6% in minute 2; 8.3% vs 0.8% in minute 5; 7.0% vs 1.2% in minute 7; 7.9% vs 4.2% in minute 10; 6.4% vs 4.2% in minute 12; 5.1% vs 3.8% in minute 15.

In study 006, a higher relative frequency of **deep sedation (MOAA/S score 0**, equivalent to general anaesthesia) was seen at all timepoints for remimazolam (ranging from 1.2% to 6.4%) compared to placebo (0%) and midazolam (ranging from 0% to 2%), except for the last timepoint that reported 1 patient (1%) in midazolam with score 0 compared to no patients (0%) in other treatment arms with score 0. A similar trend was observed in study 008 with a higher frequency of MOAA/S scores 0 observed with remimazolam for all except the last two timepoints.

Drowsiness was evaluated with VAS, where a larger number denotes more severe drowsiness. In study 006, the highest mean VAS score for remimazolam (86.9) was larger compared to highest VAS score for placebo and midazolam (82.2 and 78.5, respectively). Similarly, in Study 008 the highest mean VAS score for remimazolam (85.6) was larger compared to highest VAS score for placebo and midazolam (81.4 and 72.1, respectively).

Hypersensitivity events were reported in 4 remimazolam subjects (0.5%), 0 midazolam, and 1 (0.7%) placebo subjects. SMQ hypersensitivity consists of 2 cases of bronchospasm (0.3%), 1 case of anaphylactic reaction (0.1%) and 1 case of periorbital oedema (0.1%).

Some adverse events were more frequently observed **in elderly**: AEs belonging to the SOC Vascular disorders (53.7% vs 75.1% vs 82.0% in groups <65 years, 65-74 years, ≥75 years respectively) and hypoxia (5.1% vs 17.2% vs 26.0% in groups <65 years, 65-74 years, ≥75 years respectively).

Patients with **severe hepatic impairment** have longer half-life, larger total exposure and longer time to recovery with remimazolam compared to healthy subjects.

3.5. Uncertainties and limitations about unfavourable effects

Several ***uncertainties*** about unfavourable effects have been identified:

The excipients used in remimazolam drug product are **dextran** and **lactose**. Data on possible clinical scenarios with **repeated remimazolam administrations** have not been sufficiently discussed. **Local tolerance issues** are known for parenteral benzodiazepines, i.e. thrombophlebitic reactions to benzodiazepines, with diazepam and midazolam as notable examples. Non-clinical data revealed the vascular lesions at higher remimazolam concentrations.

Furthermore, some ***limitations*** have been identified:

Depth of sedation is unpredictable and there are **interindividual variabilities** in the level of sedation observed.

Rare adverse events could not be revealed during the clinical development due to the database size.

3.6. Effects Table

Table 40: Effects Table for remimazolam for procedural sedation

Effect	Short Description	Unit	Remimazolam	Midazolam	Placebo (rescue midazolam)	Uncertainties/ Strength of evidence	References
	Favourable Effects						
Success of procedure in phase 2b trial	Composite primary efficacy outcome[1]	%	92.5-97.5%	75%	n/a	Unc: phase 2 trial, exploratory Strength: midazolam was double-blind	CNS7056-004
Success of procedure in phase 3 trials	Composite primary efficacy outcome[2]	%	91.3%, 80.6% and 84.4% in 006, 008 and 015, respectively	25.2%, 32.9% and 12.9% in 006, 008 and 015, respectively	1.7%, 4.8% and 0% in 006, 008 and 015, respectively	Unc: midazolam is open-label; initial dose of midazolam (1.75mg) lower than EU midazolam SmPC (2.0-2.5mg) in studies 006 and 008 Strength: sensitivity analysis based on total fentanyl and initial fentanyl supportive of primary analysis for remi vs. placebo	CNS7056-006, CNS7056-008 and CNS7056-015
Time to peak sedation	time to peak sedation after first dose of study drug (lowest MOAA/S score after initial dose)	Minutes (95% CI)	3 (-,-), 3.5 (3.5, 4.0) and 3 minutes (3.0, 3.6) in studies 006, 008 and 015	7 minutes (95% CI: 7.0,-) in study 008	Could not be established	Unc: secondary outcome with descriptive analysis only	CNS7056-006, CNS7056-008 and CNS7056-015

Effect	Short Description	Unit	Remimazolam	Midazolam	Placebo (rescue midazolam)	Uncertainties/ Strength of evidence	References
Time to fully alert from last dose	time to first of 3 consecutive MOAA/S scores of 5 after the last injection of study drug	Minutes (95% CI)	14 (13.0, 14.0), 11.6 (10.0, 12.8) and 11 minutes (8.8, 12.0) in studies 006, 008 and 015	24 (22.0, 26.0), 18 (15.0, 20.1) and 18.8 (15.0, 26.0) in studies 006, 008 and 015	28 (24.0, 32.0), 20 (15.3, 31.0) and 18 (14.0, 25.0) in studies 006, 008 and 015	Strength: similar outcome (time to fully alert from the end of procedure) yielded similar results (same direction of results but some overlapping of 95% CI of remi and mida) Unc: 2 similar outcomes (time to discharge from end of procedure and time to discharge from last dose) yielded clinically nonrelevant results with overlapping 95% CIs when remi was compared to mida; Unc: secondary outcome with descriptive analysis only Difference between time ready for discharge vs time to fully alert may be related to anterograde amnesia	CNS7056-006, CNS7056-008 and CNS7056-015
	Unfavourable Effects						
Undesirable deep sedation	MOAA/S 0-1, (MOAA/S 0 is equivalent to general anaesthesia)	MOAA/S	27.7%	15.7%	11.9%	Differences are observed from at each measured timepoint between remi and midazolam (more deep sedation in remi); beginning from 1 minute post-dose (7.6% vs 0.9%); largest difference in minute 2: 14.6% vs 1.6% in minute 2.	ISS group A1 (ISS)
Maximum drowsiness	on VAS during the first hour post-dose; from 0 to 100 (100 = worst imaginable)	VAS	86.9 and 85.6 in studies 006 and 008	78.5 and 72.1 in studies 006 and 008	82.2 and 81.4 in studies 006 and 008	Self-Assessment by patients	CNS7056-006, CNS7056-008

Effect	Short Description	Unit	Remimazolam	Midazolam	Placebo (rescue midazolam)	Uncertainties/ Strength of evidence	References
Respiratory rate increased		%	5.7	4.1	4.4		ISS A1 group
Hypoxia		%	9.2	5.8	10.4		ISS A1 group
Hypersensitivity reactions		Number (%)	4 (0.5)	0 (0)	1 (0.7)		ISS

[1] Success of procedure in Study CNS7056-004: Responders were defined as patients with MOAA/S≤ 4 on 3 consecutive measurements taken every minute who completed the procedure, did not require alternative sedative nor manual/mechanical ventilation

[2] Success of procedure in Studies CNS7056-006, CNS7056-008 and CNS7056-015: responders were patients who completed the procedure, did not require alternative sedatives and with a maximum of remimazolam 5 top-ups in any 15 minutes window (for midazolam: maximum 3 top-ups within any 12 min window).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A consistently **higher success rate** (the composite primary endpoint) was observed with remimazolam compared to placebo and midazolam. A non-responder is a patient requiring more frequent dosing of the Investigational product, or rescue sedative. However, more frequent dosing may not be envisioned as a failure by clinicians, if adequate sedation is achieved in the end. The clinical relevance is better illustrated by secondary endpoints on onset and recovery. The vast majority of procedures in all treatment arms was finished (ie. procedure completed).

In all phase 3 trials, failing the primary outcome is driven by the need for rescue sedatives/too many doses of study drug, while the percentage of patients who failed because the procedure was not completed is 2.2%, 3.8% and 2.5% in studies 006, 008 and 015.

Results of phase 3 procedural sedation trials show a **faster onset of action** of remimazolam compared to placebo and midazolam (11-15 minutes faster than the comparators, depending on the study), and this is viewed as clinically relevant. **Peak sedation** is achieved faster with remimazolam (in 3 minutes) compared to midazolam (in 7 minutes, could be established only in 1 study). Time to peak sedation could not be established for placebo. Accordingly, a conclusion can be made of a faster onset of sedation for midazolam vs both comparators.

Regarding the recovery profile, **time to fully alert from the last dose** of study drug shorter for remimazolam compared to midazolam (6-10 minutes shorter) and compared to placebo (7-14 minutes). **Time to ready for discharge from the last dose** of study drug (evaluated in studies 006 and 008) is also shorter for remimazolam, but these results are not as robust as those seen for time to fully alert from last dose of study drug. Namely, time to discharge from last dose is 5-6 minutes shorter for remimazolam compared to midazolam, which is not very clinically relevant; however, it is 9-28 minutes shorter for

remimazolam compared to placebo. Similar results with overlapping 95% CI are seen for time to discharge from the end of procedure. According to patients themselves, **drowsiness** with remimazolam was more severe compared to midazolam. Also according to patients, **time to feeling back to normal** yielded somewhat mixed results – although shorter for remimazolam compared to mida and placebo, the difference was clinically relevant (around 3 hours difference for both remi vs. placebo and remi vs.mida) in study 006 but it wasn't clinically relevant for remi vs.mida in study 008.

Taken together, data demonstrates faster onset of action of remimazolam vs placebo and midazolam and deeper sedation achieved with remimazolam vs placebo and midazolam. Data also demonstrates a faster recovery, although the effect size is considered to be limited.

There were several **methodological flaws** that may have inflated the treatment effect. The active **comparator midazolam** was administered in an **open-label** fashion in pivotal trials and 'success' of procedure with midazolam was quite small in itself. Midazolam was also **subdosed** in the pivotal trials. On the other hand, in the only trial where midazolam was administered in a double-blinded fashion and an adequate initial dose (study 004), success of procedure with midazolam (75%) was much closer to success of procedure with remimazolam (92-97%) and also much higher that success of procedure with midazolam seen in pivotal trials (13-33%).

Placebo is used as a double-blind comparator in pivotal trials. After failure of placebo (which understandably happened in almost all placebo cases), rescue midazolam was used, which de facto led to **unblinding** of that study arm adding to uncertainty about the internal validity of the trial.

It is important to note that all comparisons with midazolam and all secondary outcomes are to be viewed as exploratory.

Procedures selected for phase 3 clinical trials for the broad indication of procedural sedation are colonoscopy and bronchoscopy. Due to its rapid onset of action and a favourable recovery profile, it can be expected that remimazolam will be of interest for a variety of procedures, and not just the common and pre-scheduled colonoscopies/bronschoscopies. Most prominent unfavourable effect is **undesirable deep sedation** (MOAA/S 0-1, level equal to general anaesthesia) achieved fast after administration of remimazolam. Undesirable deep sedation is observed in significantly higher incidence in Total Remimazolam group compared to midazolam group between minute 1 and minute 15 post-dose. The pharmacodynamics differences between remimazolam and midazolam, and interindividual variabilities are in the clinical development programme shown to be **unexpected by the clinicians**. Considering different pharmacodynamics properties of remimazolam and midazolam, an appropriate wording in SmPC was introduced.

The **CNS and ventilation depression** of RMZ has been more thoroughly discussed. RMZ patients have developed more frequently unwanted deeper sedation and respiratory SAEs that did not occur in MDZ treated patients. Significantly, clinicians did not relate the respiratory SAEs to sedation. It is shown that overshooting CNS depression does occur with remimazolam, with 18% of pts reaching MOAA/S <=1, and almost 8% having respiratory disorders identified as SAE. However, only 10.6% did show respiratory rate decrease, and all have been identified as having respiratory depression or hypoxia by clinicians, with none reported as SAE. It can be admitted that all events have been adequately dealt within a CT setting, but the applicant might have discussed further the extrapolation to the real world.

Patients ≥ 65 years of age and/or with ASA-PS III-IV

The applicant conducted dedicated study 015 which included patients with ASA-PS III-IV. Results show effectiveness of remimazolam similar to those shown in studies 006 and 008. However, the number of exposed patients is limited.

Regarding safety data obtained for the elderly patients, adverse events pertaining to the SOC Vascular disorders and hypoxia were observed more frequently in elderly, especially in ≥75 years group. Similarly, in patients with ASA-PS III-IV (study 015) observed AEs pertained to the SOC Vascular disorders and SOC Respiratory, thoracic and mediastinal disorders. Caution is needed, but adverse events seem manageable. Furthermore, it is expected that in clinical practice special care is given to ASA-PS III-IV and elderly patients and they are probably candidates for in-hospital procedures in most clinical practices in the EU.

The sedative effects of remimazolam can be reversed with the **benzodiazepine antagonist** flumazenil. Since remimazolam and flumazenil have comparable elimination half-lives, the risk of re-sedation is low in comparison with other benzodiazepines with longer t1/2 and/or pharmacologically active metabolites (e.g. midazolam).

3.7.2. Balance of benefits and risks

Success of procedure was higher with remimazolam compared to placebo in the pivotal trials. These results were statistically significant and clinically relevant. Comparison with midazolam also favoured remimazolam, although the effect is smaller. However, more frequent dosing (or a need for rescue sedatives) that led to declaring treatment failure in pivotal studies may not be envisioned as a failure by clinicians, if adequate sedation is achieved in the end.

The main benefit of remimazolam is its fast onset of action that gives the opportunity to start the procedure faster than if midazolam was used. Patients who receive remimazolam are fully alert and able to be discharged sooner than patients receiving midazolam and placebo although these results are somewhat less robust than the ones pertaining to the onset profile of remimazolam. More severe drowsiness was noted for remimazolam and the incidence of deep sedation (even the sedation level of general anaesthesia) is consistently higher for remimazolam compared to midazolam and placebo. More hypoxia was noted for remimazolam and in general the respiratory profile may be more of an issue with remimazolam compared to midazolam.

In general, all of the above can be managed by a separate clinician (not performing the procedure), trained in sedation and properly informed of the effects of remimazolam, and an antidote is available in case of overdose.

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall B/R of Byfavo is positive in the approved indication

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Byfavo is favourable in the following indication:

Remimazolam is indicated in adults for procedural sedation.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Not applicable.

Obligation to conduct post-authorisation measures

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that remimazolam is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.