26 January 2023
EMA/79576/2023
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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Administrative information

Name of the medicinal product	Byfavo
MAH:	PAION Deutschland GmbH Heussstrasse 25 Brand 52078 Aachen GERMANY
Active substance:	remimazolam besilate
International Non-proprietary Name/Common Name:	remimazolam
Pharmaco-therapeutic group (ATC Code):	hypnotics and sedatives, benzodiazepine derivatives (N05CD14)
Therapeutic indication(s):	Intravenous induction and maintenance of general anesthesia (GA) in adults
Pharmaceutical form(s):	Powder for concentrate for solution for injection/infusion (powder for concentrate)
Strength(s):	50 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	10 vials

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List of abbreviations

ABAP	2,2'-azobis(2-amidinopropane) dihydrochloride
ASA-PS	American Society of Anesthesiologists Physical Status
BDRM	Blind Data Review Meetings
BHT	Butylated hydroxytoluene
BIS	Bispectral index
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Human Medicinal Products
CTD	Common Technical Document
EC	European Commission
EEA	Economic European Area
EMA	European Medicines Agency
EU	European Union
FA	Final analysis
FAS	Full Analysis Set
FPFV	First patient first visit
GA	General anaesthesia
GABAA	γ-Aminobutyric acid type A
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
HPLC	High Performance Liquid Chromatography
ICH	International Conference of Harmonization
ICU	Intensive care unit
IT	Interim analysis
ITT	Intent to treat
IMP	Investigational medicinal product
KSE	Key secondary endpoint
LOC	Loss of consciousness
LOQ	Limit of quantification
LPLV	Last Patient Last Visit
LRR	Loss of Righting Reflex
MIA	Manufacturing / Importers Authorisation

NCI / NCT	Narcotrend Index
NDEA	N- nitrosodiethylamine
NDMA	Nitrosodimethylamine
NIM	Non-inferiority margin
NMT	Not more than
OC	Other concern
RAAUC	Reverse Adjusted Area Under the Curve
PACU	Post-anaesthesia care unit
PEP	Primary efficacy endpoint
Ph.Eur.	European Pharmacopeia
PIP	Paediatric Investigation Plan
PL	Package Leaflet
PDCO	Paediatric Committee
PPS	Per Protocol Set
QP	Qualified Person
RMZ	Remimazolam
SHC	Stanford Health Care
SmPC	Summary of Product Characteristics
TIVA	Total Intravenous Anaesthesia
TK	Toxicokinetic
TOI	Time of interest
TSE/BSE	Transmissible Spongiform Encephalopathy/Bovine Spongiform Encephalopathy
USA	United States of America
UK	United Kingdom
UV	Ultraviolet

1 Background information on the procedure

1.1 Submission of the dossier

On 31 December 2021 PAION Netherlands B.V. applied for an extension of the marketing authorisation to introduce a new pharmaceutical form associated with a new strength: 50 mg powder for concentrate for solution for injection/infusion (powder for concentrate).
The new presentation is indicated to include the intravenous (IV) induction and maintenance of general anesthesia (GA) in adults for Byfavo 50 mg, based on the final results from two pivotal trials:

- Study ONO-2745-05, a phase IIb/III, single-blind, randomised, parallel-group study assessing safety and efficacy in induction and maintenance of anaesthesia in ASA I/II patients (general surgery);
- study CNS-7056-022, a phase III, randomized, propofol controlled, parallel group, confirmatory single-blind efficacy and safety trial during induction and maintenance of anaesthesia in ASA III/IV patients.

A new combined version of the summary of product characteristics (SmPC), labelling and Package Leaflet (PL) solely for the 50 mg strength and the GA indication is provided accordingly.

Version 1.1 of the RMP has also been submitted.

As part of the application, the MAH also requested an extension of the market protection by one additional year.An application for the transfer of Marketing Authorisation (MA) from Paion Netherlands B.V. to PAION Deutschland GmbH was submitted on 1 September 2022 (and completed on 21 September 2022; EC decision: 7 October 2022).

1.2 Legal basis

The legal basis for this application refers to:

Article 7.2(b) EC No 1234/2008 to extend Byfavo marketing authorization for an additional strength/pharmaceutical form, including a new therapeutic indication. This new indication does not fall within any orphan designation.

1.3 Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0427/2021 on the agreement of a Paediatric Investigation Plan (PIP).

At the time of submission of the application, the PIP P/0427/2021 of 29 October 2021, was complete.

The Paediatric Committee (PDCO) issued an opinion on compliance for the PIP: EMEA-C1-001880-PIP02-19-M03.

1.4 Information relating to orphan market exclusivity

Not applicable

1.4.1 Similarity

Not applicable

1.4.2 Derogation(s) from market exclusivity

Not applicable

1.5 Additional Marketing protection

The MAH requested consideration of one year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

This request was withdrawn during the procedure.

1.6 Scientific advice

Scientific advice was sought from EMA prior to initiate a pivotal Phase III trial for remimazolam (RMZ) in the indication of general anaesthesia (GA) in adults:

1. **Procedure No.: EMEA/H/SA/2825/1/2014/SME/III**

   SA on the development programme for remimazolam (RMZ) for the indication of GA, prior to the initiation of a Phase III study;

2. **Procedure No.: EMEA/H/SA/2825/1/FU/1/2015/SME/III**

   Follow-up (FU) discussion on the previously finalized SA procedure EMEA/H/SA/2825/1/2014/SME/III on the development programme for remimazolam for the indication of GA;

In February 2016 the Phase III trial for which SA was obtained, in 2014 and 2015, as above noted, was terminated early due to the complex trial design and recruitment problems.

3. **Procedure No.: EMEA/H/SA/2825/1/FU/2/2017/SME/II**

   Scientific advice on the design of a new pivotal Phase III trial to complete the clinical development in Europe and enable filing a marketing authorisation application (MAA) for remimazolam in GA

1.7 Steps taken for the assessment of the product

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

- Rapporteur: Bruno Sepodes (PT)
- Co-Rapporteur: Selma Arapovic Dzakula (HR)

The application was received by the EMA on	31 December 2021
The procedure started on	20 January 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	29 April 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	3 May 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 April 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP on	5 May 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	19 May 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	9 September 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	18 October 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 October 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	10 November 2022
The MAH submitted the responses to the CHMP List of Outstanding Issues on	22 December 2022
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	18 January 2023
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	26 January 2023

2 Scientific discussion

2.1 Problem statement

Minimising patient discomfort via producing a calming or unconscious effect and thereby facilitating the conduct of diagnostic and therapeutic procedures is the objective of procedural sedation and general anaesthesia.

2.1.1 Disease or condition

General anaesthesia (GA) differs from procedural sedation by the depth of sedation/hypnosis, duration and often the ability of the subject to breathe independently or to require ventilatory support, and is usually required for major surgery. This can be accomplished through different methods, including inhalation anaesthesia or total intravenous anaesthesia (TIVA). For the latter, a strong very short acting hypnotic (e.g., propofol, midazolam, or remimazolam) is usually combined with a strong analgesic (e.g. remifentanil).

2.1.2 Epidemiology and risk factors, screening tools/prevention

Due to the different methods and combinations of anaesthesia that may be employed for the same condition, it is difficult to find exact figures applied across all possible indications. In general, major surgeries will require general anaesthesia, thus a reasonable surrogate of the number of subjects undergoing general anaesthesia may be the number of major surgical procedures performed per year.

In 2009, an estimated 48 million surgical procedures were performed in the United States of America (USA) according to the Stanford Health Care (SHC). Eurostat does not provide cumulative data across all possible surgeries performed in the European Economic Area (EEA) in 2018; however, it does indicate that the most frequent surgeries per 100,000 population occurred for cataract in 267-1656, Caesarean section in 141-581, transluminal coronary angioplasty in 119-410, cholecystectomy in 52-294, and inguinal hernia repair in 60-277 in the EEA countries plus Switzerland, North Macedonia and Serbia (Eurostat 2020), with an estimated European Union (EU) population size at the time of approximately 448 million people.

Currently, inhalation anaesthesia is a popular method of general anaesthesia, with TIVA accounting for a more limited percentage, due to often higher cost and technical requirements, as reflected in the United Kingdom (UK) guidance on general anaesthesia (Al-Rifai 2016). However, these numbers vary from country to country and may depend upon available resources, anaesthesiologist experience, national guidelines, and even patient preference (some subjects dislike the anaesthesia mask during induction). Recently, the Covid-19 pandemic may have resulted in some increase in the use of TIVA, due to possible lower risk of coughing and shorter time of recovery (Stewart 2020).

2.1.3 Biologic features, aetiology and pathogenesis

Subjects undergoing surgical procedures can range from healthy (ASA-PS I) to severely morbid (ASA-PS III–IV) male or female subjects, of any race or ethnic origin, aged 18 years and above. In younger age groups the requirement for surgery will be more driven by trauma, diseases such as appendicitis, or need for caesarean section while with advancing age vascular diseases, cancer, degenerative joint conditions and cataracts will contribute more to the requirement for surgery.

2.1.4 Clinical presentation, diagnosis and stage/prognosis

General Anaesthesia is a satellite condition to major surgery.

Important co-morbidities

Any co-morbid condition could be present. Hence, an ideal anaesthetic agent should cause predictable and well-controllable levels of anaesthesia, rapid onset and recovery, with low risk of respiratory depression, of cardiovascular effects or of other adverse reactions.

ASA-PS (American Society Of Anesthesiologists Physical Status) Classification

The ASA PS Classification System has been in use for over 60 years (please refer to the Table 1). The purpose of the system is to assess and communicate patient's pre-anaesthesia medical co-morbidities. The classification system alone does not predict the perioperative risks, but used with other factors (e.g. type of surgery, frailty, level of deconditioning), it can be helpful in predicting perioperative risks.

Table 1: ASA-PS (American Society Of Anesthesiologists Physical Status) Classification

ASA PS Classification	Definition	Adult Examples, Including, but not Limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Current smoker, social alcohol drinker, pregnancy, obesity (30<BMI<40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Recent (<3 months) MI, CVA, TIA or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

2.1.5 Management

In Europe, the currently authorised medications for use in "induction and maintenance of general anaesthesia" include propofol as the most commonly used agent, followed by volatile gases (inhalation vapours, or halogenated anaesthetics, e.g. sevoflurane, desflurane, isoflurane), mostly used in conjunction with IV anaesthetics and not so frequently for induction of anaesthesia.

Risks associated with the inhalation anaesthetics include malignant hyperthermia, long QT syndrome, severe post-operative nausea and vomiting, potential cerebral oedema, and myasthenia gravis. Propofol based TIVA is associated with the possible risks of injection site pain, anaphylactic reactions to the soy

components in the lipid emulsion, and severe hypotension combined with a bradycardia effect. Other benzodiazepines, in particular midazolam, have also been used for TIVA but have become less popular, due to their longer duration of action resulting in delayed recovery, and possibly higher risk of post-operative delirium. The latter is a multifactorial condition which can occur after any form of anaesthesia.

2.2 About the product

Remimazolam (also referred to as CNS7056 or ONO-2745) is a benzodiazepine (BDZ) that has been approved as an ultra-short-acting intravenous (IV) agent for use in procedural sedation.

The current application indication is for "intravenous induction and maintenance of general anaesthesia in adults".

2.3 Type of Application and aspects on development

The MAH submitted an application under article 7.2(b) EC No 1234/2008 to extend Byfavo marketing authorization for an additional strength/pharmaceutical form, including a new therapeutic indication.

2.4 Quality aspects

2.4.1 Introduction

This line extension concerns the addition of a new strength and pharmaceutical form (50 mg powder for concentrate for solution for injection/infusion) to the existing strength/pharmaceutical form (20 mg powder for solution for injection) in order to support the proposed extension of indication to "intravenous induction and maintenance of general anaesthesia in adults".

The finished product is presented as a powder for concentrate for solution for injection/infusion containing remimazolam besylate equivalent to 50 mg remimazolam as active substance.

After reconstitution each mL of concentrate contains 5 mg remimazolam. Dilution is required to reach final concentration of 1-2 mg/mL.

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 green polypropylene flip-off cap as described in section 6.5 of the SmPC.

2.4.2 Active Substance

The active substance documentation is identical to that previously approved for the authorised strength and is acceptable. Physico-chemical properties of the active substance that are relevant for the new strengths have been adequately addressed in the pharmaceutical development of the finished product.

2.4.3 Finished Medicinal Product

2.4.3.1 Description of the product and Pharmaceutical Development

The finished product is a sterile, white to off-white lyophilised powder. The product requires reconstitution before use with sodium chloride 9 mg/mL (0.9%) solution for injection.

The finished product is packaged into 12 mL type I clear glass vials fitted with bromobutyl rubber stoppers and capped with aluminum seals with polypropylene flip-off caps.

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 pharmaceutical development has been sufficiently described. Formulation development resulted in a reproducible finished product.

The development of the manufacturing process has been described in sufficient detail. The choice of the sterilisation method is justified, as previously discussed in the initial marketing authorisation.

The compatibility and stability studies conducted after reconstitution with NaCl 0.9% are provided. The results from the compatibility studies of finished product conducted after reconstitution with reconstitution diluents stated in SmPC are also provided.

The applied primary packaging systems are standard for injectable formulations. The packaging materials are described in sufficient detail and are considered suitable for the finished product. Appropriate specifications and quality control information for the proposed container closure systems are provided. Compliance of primary packaging materials with the current EU regulations (EU regulation 10/2011) is confirmed.

2.4.3.2 Manufacture of the product and process controls

The details of the manufacturing sites responsible for the production of Byfavo 50 mg Powder for solution for intravenous injection or infusion were provided, as well as valid manufacturing authorisations and/or GMP certificates.

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

The commercial batch sizes are properly identified. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The identified critical steps are considered acceptable. Details regarding the holding time during manufacturing of the drug product are provided for the finished product manufacturing process.

Sterilization conditions for the parts of primary packaging (vials, stoppers) are described.

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 validation data provided for Byfavo 50 mg Powder for solution for intravenous injection or infusion show a good reproducibility with all presented data matching the specifications and in compliance with results obtained from finished product release testing.

2.4.3.3 Product specification, analytical procedures, batch analysis

The finished product release and shelf-life/stability 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 finished product specification is considered acceptable as it is in line with relevant Ph.Eur. monographs and scientific guidelines as well as batch analysis.

A limit for bacterial endotoxins is in line with Ph.Eur. 5.1.10 monograph and, thus acceptable.

According to ICH Q3B, identification and qualification threshold is 0.2% (based on the maximum daily dose of 1 g as worst case). Therefore, stricter limits for a named impurity and individual unidentified impurities are acceptable. Considering that the named impurity is the main metabolite of remimazolam, proposed limits are regarded as qualified.

Satisfactory details have been provided for the pharmacopoeial and non-pharmacopoeial analytical methods The validation data of the analytical methods provided are in accordance with the requirements of the relevant ICH guidelines and can therefore be accepted.

Batch analyses confirm compliance with the proposed finished product specifications.

A risk-based approach to assess the potential presence of elemental impurities in the finished product is presented in line with the ICH Q3D Guideline for Elemental Impurities.

In terms of a robust risk evaluation, a detailed examination of the manufacturing process in terms of risk of formation and contamination of N-nitrosamines in active substance and finished product is provided from the finished product manufacturer. The potential presence of nitrosamines in Remimazolam 50 mg Powder for solution for intravenous injection or infusion was evaluated in accordance with the CHMP guidelines. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

For reference standards used for the analysis of finished product, cross-references to active substance section 3.2.S.5 is made. This is acceptable.

2.4.3.4 Stability of the product

Stability data from multiple finished product batches stored up to 24 months, 36 months, and 66 months at long term stability conditions of 25ºC/60%RH and up to 6 months at accelerated stability conditions of 40ºC/75%RH, according to the ICH guidelines, were provided. These batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in line with the finished product shelf life specification. The analytical procedures used are stability indicating. The results complied with specifications.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results from photo-stability testing demonstrate that the vials must be protected from light during long term storage using suitable secondary packaging material such as a sealed cardboard carton.

An in-use stability study of the product after dilution of with 10 mL sterile 0.9 % sodium chloride solution was also performed. All results of the tested physicochemical parameters were within the specifications. Based on the presented results, the reconstituted product is physically and chemically stable for 24 hours at 25°C/60%RH (appearance, pH, assay, sub-visible particles and impurities are within specified limits). A statement in section 6.3 of the SmPC is according CPMP/QWP/159/96 corr is provided.

Commitment that one production batch per year of finished product will be placed on long term stability (25ºC/60% RH) is provided. Confirmation of compliance with CPMP/QWP/072/96 regarding start of shelf-life of the finished dosage form is provided.

Based on available stability data, the proposed shelf-life of 4 years 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.

2.4.3.5 Post approval change management protocol(s)

Not applicable.

2.4.3.6 Adventitious agents

There is no risk of Transmissible Spongiform Encephalopathy (TSE) / Bovine Spongiform Encephalopathy (BSE) from the raw materials used in manufacturing of Remimazolam 50 mg Powder for solution for intravenous injection or infusion.

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.

2.4.3.7 GMO

Not applicable.

2.4.4 Discussion on chemical, and pharmaceutical aspects

This line extension concerns the addition of a new strength and pharmaceutical form (50 mg powder for concentrate for solution for injection/infusion) to the existing strength/pharmaceutical form (20 mg powder for solution for injection) in order to support the proposed extension of indication to "intravenous induction and maintenance of general anaesthesia".

There are no changes to the active substance. Information on development, manufacture and control of the 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.

2.4.5 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.

2.4.6 Recommendations for future quality development

Not applicable.

2.5 Non-clinical aspects

2.5.1 Introduction

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. The non-clinical profile of remimazolam was comprehensively characterised and assessed during initial Marketing Authorisation Application (MAA).

The following studies were added for the submission of the general anaesthesia (GA) indication:

- Receptor binding study of remimazolam and CNS7054 to peripheral benzodiazepine receptor
- Investigation of the PK of remimazolam in milk of lactating sheep following continuous infusion
- Investigation of the oral BA of remimazolam in suckling lambs
- Investigation of the PK, stability of metabolism and tissue distribution following 3 day long infusion in pig animal model of poly-trauma
- 78890 study investigating buccal BA of remimazolam in minipigs
- Feasibility studies performed in juvenile minipigs (78736) and juvenile rats (38415)

The evaluation of the above studies did not identify any particular concerns.

2.5.2 Ecotoxicity/environmental risk assessment

An environmental Phase I and II risk assessment has been conducted to evaluate the risk to the environment arising from use of remimazolam besilate 50 mg (powder for concentrate for solution for injection/infusion), for i.v. induction and maintenance of GA in adults.

In the final ERA report, only the current version *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* EMEA/CHMP/SWP/4447/00 corr 2, 2006 and Questions and answers document on the Guideline EMA/CHMP/SWP/44609/2010 Rev.1, 2016 were followed for the Environmental Risk Assessment.

Relevant endpoints, methods used and results obtained were discussed and the main study results are summarised in the Table 2. Some issues of concern were raised during the procedure.

Table 2: Summary of main study results

Substance (INN/Invented Name): Remimazolam (free base)			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD method	2.4-2.52 (pH 5,7,9)	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.4-2.52 (pH 5,7,9)´	not B

	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	PECsurface water	0.0347µg/L			> 0.01 threshold Y
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Koc= 62.9 (sewage sludge) Koc= 74.8 (sewage sludge) Koc=56.2 (sandy silt loam) Koc= 261 (loamy sand) Koc= 50.6 (clay)			
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	**Study pending**			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	13230	µg/L	*Raphidocelis subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	23520	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	7350	µg/L	*Pimephales* *Promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	132300	µg/L	
Phase IIa Effect studies					
Sediment dwelling organism	OECD 218	EC10	470	mg/ Kg	Chironomus riparius; o.c.

					1.9%, no o.c. correlation

The log D values experimentally determined for remimazolam in the environmental pH range of 5 to 9 were 2.4 (pH 5) to 2.52 (pH 7 and 9). These are significantly lower than the trigger value of 4.5 for a PBT assessment and not close to the trigger value of 3 for performing a bioaccumulation study (EMEA/CHMP/SWP/44609/2010 Rev. 1,2016). In the ERA report pKa and Log P/D measurements were experimentally determined by UV and potentiometric methods. A report of the study Pka and LogP study on CNS7056 confirms. All the results demonstrate unanimously log Dow values for remimazolam are considerably below 4.5 and are acceptable.

Fpen was refined and is in line with the Questions and answers document (EMA/CHMP/SWP/44609/2010 Rev. 1, 2016) "Refinement based on treatment regime" that is easily done for products intended for single use, taking the worst-case treatment regime and worst-case number of treatment repetitions into consideration.

The Predicted Environmental Concentration (PEC) in surface water ($PEC_{surface\ water}$) calculated in Phase I exceeded the trigger value of 0.01µg/L and a Phase II environmental fate and effects analysis was undertaken.

Data from the OECD TG106 was presented and the adsorption coefficient Koc was estimated to range between 50.6 to 261 L/Kg using the method OECD 106. These Koc values are well below the action limit (10 000 L/Kg) and suggests that remimazolam has a low adsorption to sludge. No terrestrial studies are triggered.

The MAH claimed that remimazolam is not considered to be readily biodegradable, but the biodegradability test (OECD 301) was not conducted. This test can be waived if the OECD 308 test is performed, according to EMA/CHMP/SWP/44609/2010, Rev. 1, 2016, where indicated that a water/sediment study (OECD 308) is needed for substances that are not readily biodegradable. Ultimately, as outlined in a letter of commitment, the MAH agreed to provide remimazolam transformation in water-sediment systems according to OECD 308 test and the study report as post-approval commitment. Furthermore, the MAH committed to submit an amended ERA report as post-approval commitment, by the end of 2023.

In order to perform a phase II Tier A, a review of the ecotoxicological data were provided. The effects of remimazolam besilate on sludge microorganisms, algae, daphnia and fish were studied in accordance with OECD test guidelines and GLP. The reported NOEC values are considered valid.

The predicted no effect concentration (PNEC) values derived from the laboratory studies were compared to predicted environmental concentration (PEC) values. The risk ratios (PEC/PNEC) presented for different environmental compartments are well below the action limit. Therefore, the potential risk of remimazolam besilate to the environment is considered low.

Conclusion on ERA

An updated Environmental Risk Assessment (ERA) for remimazolam was provided in accordance with the principles of the CHMP guideline of Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use EMEA/CHMP/SWP/4447/00 corr 2, 2006 and Questions and answers document on the Guideline EMA/CHMP/SWP/44609/2010 Rev.1., 2016, which is endorsed.

The applicant commits to provide a report on the OECD 308 study currently being conducted with remimazolam and an updated overall ERA report by the end of 2023. A letter of commitment was provided by the MAH as requested.

2.5.3 Discussion on non-clinical aspects

The following was concluded during the original MAA and remains unchanged during this procedure:

- 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.
- A substantial number of studies in variety of animal models were performed in order to assess non-clinical properties of remimazolam and assessed as part of IMAA. Remimazolam showed sedative activity in all animal species studied, with a rapid onset and a short duration of sedation. The sedation was reversible with flumazenil. Remimazolam produced amnesia in a passive avoidance study in rats at dose levels similar to midazolam.
- The safety profile of remimazolam is consistent with other members of the benzodiazepine class of drugs, (i.e. cardiorespiratory depressant effects at supratherapeutic doses).
- Pharmacodynamic interaction studies demonstrated synergism between remimazolam and narcotics with activity at sites other than the benzodiazepine site of the GABAA receptor while there was no such synergism with sedatives having the same mechanism of action as remimazolam.
- Non clinical interactions studies indicate a very low potential of remimazolam for interactions, neither as a victim nor as a perpetrator.

The non-clinical studies submitted in support of this extension application do not impact the overall non-clinical profile assessment.

The MAH submitted a letter of commitment to confirm provision of remimazolam transformation in water-sediment systems according to OECD 308 test and the study report as post-approval commitment. Furthermore, the MAH confirmed these data will be included in a revised ERA report, to be also submitted as a post-approval commitment, by end of 2023.

2.5.4 Conclusion on the non-clinical aspects

The CHMP consider that the application for remimazolam 50 mg powder for concentrate for solution for injection/infusion is approvable from the overall non-clinical perspective.

2.6 Clinical aspects

2.6.1 Introduction

GCP aspects

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

- **Tabular overview of clinical studies (see Tables below)**

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Healthy Subjects or Diagnosis of Patients/ Human Specimens	Duration of Treatment	Study Status; Type of Report
Safety and efficacy	CNS7056-010	5.3.5.4	Assessing efficacy, PK and safety of two induction infusion doses of RMZ	Randomized single- blind, propofol- controlled trial	RMZ: Induction 6 or 12 mg/kg/h IV maintenance 1-3 mg/kg/h IV Propofol: Induction 2.0 to 2.5 mg/kg/min, IV maintenance 3-12 mg/kg/h, IV Sevoflurane : 0.8 to 2.5 MAC (maintenance only)	90	Patients undergoing cardiac surgery	Treatment during procedure - general anesthesia; Optional ICU sedation up to 24 hours	Complete, Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Healthy Subjects or Diagnosis of Patients/ Human Specimens	Duration of Treatment	Study Status; Type of Report
Safety and efficacy	CNS7056-022	5.3.5.1	Assessing efficacy and safety of RMZ for induction and maintenance of GA during elective surgery	Randomized single-blind, propofol-controlled trial	RMZ: Induction: 6 mg/min; IV Maintenance: 0.7-2.5 mg/min; IV Propofol: Induction: 30 mg/kg/h IV Maintenance: 4-10 mg/kg/h; IV	409	Patients undergoing elective surgery	Treatment during procedure – general anesthesia	Complete, Full
Safety, efficacy , PK	CNS7056-011	5.3.5.4	Assessing efficacy, PK and safety of two induction infusion doses of RMZ	Single-blind, propofol-controlled trial	RMZ: Induction 6 or 12 mg/kg/h Maintenance 1-3 mg/kg/h; IV Propofol: Induction 1 or 2.5 mg/kg/min Maintenance 3-9 mg/kg/h; IV	23	Patients undergoing cardiac surgery	Up to 24 hours	Complete, Abbreviated

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Healthy Subjects or Diagnosis of Patients/ Human Specimens	Duration of Treatment	Study Status; Type of Report
Safety, efficacy , PK	ONO-2745-03	5.3.5.4	Assessing efficacy, PK and safety of ascending infusion doses of RMZ	Open-label, dose-finding trial	RMZ: Part A: Induction 6, 12, 21, or 30 mg/kg/h Part B: Induction + maintenance (IV) 12 + (0.8-2.0) mg/kg/h; Part C: Induction (IV) 4, 8, or 12 mg/kg/h; Part D: Induction + maintenance (IV) 4 + (0.4-1.0) mg/kg/h;	85	Surgical Patients undergoing GA	For the induction and maintenance of anesthesia during the procedure	Complete, Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Treated	Healthy Subjects or Diagnosis of Patients/ Human Specimens	Duration of Treatment	Study Status; Type of Report
Safety, efficacy , PK	ONO-2745-05	5.3.5.4	Assessing efficacy, PK and safety of two induction infusion doses of RMZ	Single-blind, propofol-controlled trial	RMZ: Induction 6 or 12 mg/kg/h Maintenance 1-2 mg/kg/h; IV Propofol: Induction 2.0 or 2.5 mg/kg/h Maintenance 4-10 mg/kg/h; IV	375	Surgical patients undergoing GA	For the induction and maintenance of anesthesia during the procedure	Complete, Full
Safety, efficacy , PK	ONO-2745-06	5.3.5.4	Assessing efficacy, PK and safety of two induction infusion doses of RMZ	Randomized double-blind trial	RMZ: Induction 6 or 12 mg/kg/h Maintenance: 1-2 mg/kg/h	62	ASA III/IV Surgical patient undergoing GA	1 day	Complete, Full

Abbreviations: IV = intravenous; PK = pharmacokinetic; PD = pharmacodynamic; GA = general anesthesia; GI = Gastrointestinal, RMZ = remimazolam; MDZ = midazolam; ICU = Intensive Care Unit; MAC = maximum alveolar concentration; ASA = American Society of Anesthesiology

2.6.2 Clinical pharmacology

2.6.2.1 Pharmacokinetics

The main conclusions from previously submitted PK studies are:

- Due to its high clearance, short half-life and inactive primary metabolite, RMZ hypnotic effect is very predictable and allows for a considerable level of control over the depth of anaesthesia;
- RMZ anaesthetic effects wear off fast and with little variability;
- C_{max} and AUC increase proportional with the dose;
- Population PK analysis demonstrated that body weight and BMI were not a significant factor contributing to inter-subject variability in systemic exposure. There is no evidence that dosing by body size will lead to decreased variability in systemic exposure compared to using fixed doses. Hence, RMZ can be dosed independently of body weight;
- RMZ sedative effects can be effectively reversed by flumazenil. Due to similar elimination half-lives of the two drugs there is low probability for re-sedation;
- The PK profile is not affected by *age*, *sex*, *race*, *body weight*, *renal impairment*, or *mild*-to-*moderate hepatic impairment*;
- RMZ is metabolized by abundant liver carboxyesterase. There is a low potential for its PK to be influenced by other drugs;
- RMZ and its primary metabolite do not induce or inhibit any tested CYP enzymes and are not substrates or inhibitors of tested human drug transporters at clinically relevant concentrations; likewise, studies did not reveal a relevant inhibitory potential regarding esterase substrates including hepatic carboxyesterase. Thus, there is a low potential to affect the PK of other drugs.

New PK information in the present application: (study CNS7056-022)

As part of the clinical development program of remimazolam for injection 50 mg/vial, the safety and efficacy of RMZ for GA have been investigated in the pivotal Phase III trial CNS7056-022.

In this study venous blood samples for PK analysis of remimazolam were obtained from a limited number of consenting patients at selected sites during induction, maintenance and after end of the infusion.

A prolonged sedation was reported for 31 patients (11% of the study population).

Using a population PK model and an exposure-response (ER) time-to-event (TTE) analysis approach, it was evaluated whether a difference between these delayed wake-up patients and the other patients (*i.e.*, patients for which this AE was not reported) could be identified.

The formal covariate analysis performed for each TTE endpoint indicated that:

- *Younger people* are predicted to reach each endpoint earlier.
- *Females* are predicted to wake up earlier for the Awakening as reported by the investigator and MOAA/S based recovery endpoints, but not for the Aldrete score and Extubation endpoints.
- Subjects who received an *opioid and/or (es)ketamine* prior to awakening and within 1h before to 1h after end of remimazolam infusion, tend to reach awakening as reported by the PI endpoint earlier.
- *Body weight* and *serotonin antagonist use* prior to reaching each endpoint did not significantly influence the time to event for any of the investigated recovery endpoints.
- When informing the final model for each endpoint with the information of whether a subject was identified as a delayed wake-up patient or not, the model fit improved significantly. Thus, a difference in individual PK parameters and covariate effects do not fully explain the differences in time-to-event between the delayed and normal wake-up groups.

It was concluded that the difference between the delayed wake-up *versus* normal wake-up patients could not be fully explained by a difference in individual PK parameters, *i.e.*, drug exposure and the evaluated covariate effects could only partially explain some of the differences in *time-to-event* between the delayed and normal wake-up groups. Within the current procedure, the MAH has described three studies as part of the planned approach to further explain the differences observed between delayed and normal wake up patients:

- The **first study,** currently ongoing, is a Phase I clinical trial to assess the PD and PK interaction of remimazolam and remifentanil. The objective is to quantify the remimazolam exposure-response relationship with and without remifentanil based on various PD endpoints in order to develop PK-PD models describing the relationship between *effect-site concentrations* of remimazolam with and without remifentanil and various *PD endpoints*, corresponding to mild, moderate, and deep sedation.
- A **second study**, also ongoing, is developing a PK/PD model for remimazolam using *all up to now available data* (including the data collected in the Phase III EU trial in general anesthesia, CNS7056-022 as well as the data from the Phase I PK/PD interaction trial described in the paragraph above).
- A **third study** is planned to provide a clinical validation of a possible remimazolam *Target Controlled Infusion* (TCI) *system* in general anaesthesia, to be developed using the PK-PD model obtained as described in the paragraph above.

It was agreed that the PK-PD models to be developed may help obtaining a better understanding of the relevant factors in the process of recovery, by identifying significant covariates in the PK and PD of remimazolam, thus contributing to explain the observed differences between delayed and normal wake up patients receiving remimazolam in their recovery from GA.

Drug interactions

In the initial MAA, the potential for remimazolam to cause clinically relevant DDIs was also evaluated for the GA setting where higher induction dose of 12 mg/kg/h was used. In study CNS7056-010, the highest individual RMZ concentration observed was 12.6 µg/ml. Due to higher remimazolam concentrations

observed in the GA setting compared to the procedural sedation setting, at the point of initial MAA, a need for re-evaluation of DDI potential with respect to inhibition of CYP2C8, CYP1A2 and OATP1B1 was deemed necessary when applying for a new indication.

Within this line extension application, in study CNS7056-010, the observed mean C_{max} at 6 mg/kg induction dose was 3.09 µg/ml, and mean C_{max} at 12 mg/kg induction dose was 4.95 µg/ml. The latter will be used for calculations as a worst-case scenario.

The cut-off values (according to EMA Guideline on Investigation of drug Interactions CHMP/EWP/560/95/Rev.1) used in the interpretation of presented DDI data, to predict potential for in vivo interactions, are presented below:

Cmax=4.95 µg/ml, MW=439.31 g/mol (remimazolam free base) (<=> 11.27 µM); fu=10%; Cmax,u=1.13 µM

50xCmax,u=56.5 µM

In vitro remimazolam inhibited:

- CYP2C8 with IC_{50} of 29.2 µM and CYP1A2 with IC_{50} of 63.6 µM. If assumed that Ki can be estimated by using equation $IC_{50}/2$, Ki values for both tested scenarios (14.6 and 31.8 µM, respectively) would be below the calculated cut-off, suggesting that potential for in vivo interactions cannot be excluded.
- OATP1B1 with IC_{50} of 10 µM. IC_{50} is well below the calculated cut-off and potential for in vivo interactions cannot be excluded.

The MAH stated that higher concentrations are achieved only in the very short induction phase and that remimazolam is rapidly metabolized; thus, there is no potential for clinically relevant interactions.

Other calculations were done using the remimazolam concentrations achieved in the maintenance phase.

During the maintenance phase, remimazolam concentrations were around 1 mg/L.

C_{max}=1 µg/ml, MW=439.31 g/mol (remimazolam free base) (<=> 2.28 µM); f_u=10%; $C_{max,u}$=0.23 µM

50x$C_{max,u}$=11.5 µM

If remimazolam concentrations are used from the maintenance phase, it can be agreed there is no potential for in vivo inhibition of CYP2C8 and CYP1A2 by RMZ. However, IC_{50} for OATP1B1 inhibition is still below the cut-off and the potential for in vivo inhibition of OATP1B1 by remimazolam could not be excluded.

The MAH provided a comprehensive discussion with regards to potential inhibition of OATP1B1 by remimazolam. Given that the cut-off value obtained by in vitro testing of OATP1B1 inhibition is borderline for its potential transition into a significant in vivo interaction, and given the specificities of the clinical setting of GA, which is of limited duration, it is considered unlikely that remimazolam would cause a clinically relevant interaction with OATP1B1 substrates. Therefore, it can be agreed that no specific warning is needed in the SmPC on this matter.

Body weight

Population PK analysis demonstrated that body weight and BMI were not a significant factor contributing to inter-subject variability in systemic exposure. There was no evidence that dosing by body size will lead to decreased variability in systemic exposure compared to using body weight independent dosing.

2.6.2.2 Pharmacodynamics

Remimazolam binds to brain benzodiazepine sites (gamma amino butyric acid type A [$GABA_A$] receptors) with high affinity, while its carboxylic acid metabolite (CNS7054) has a 300 times lower affinity for the receptor.

No new information is being submitted regarding RMZ mechanism of action.

Primary and Secondary pharmacology

No new PD studies were submitted within this application for intravenous induction and maintenance of GA.

Cardiovascular Risk Assessment

The effect of remimazolam on QTc was assessed in two trials (CNS7056-005, CNS7056-017) and in a meta-analysis where demonstrated that RMZ has no direct effects on QTc interval.

Abuse Liability assessment and Effect with Alcohol

The abuse potential of single doses of IV remimazolam was assessed in healthy recreational central nervous system depressant users in trial CNS7056-014. Overall, it was concluded that IV remimazolam presents a *significant abuse potential compared to placebo*, and *comparable to or lower than that of midazolam*.

2.6.3 Discussion on clinical pharmacology

The clinical pharmacology is basically the same for both PS and GA indications and there are no new clinical pharmacology trials included in this application for GA.

However, some sections were updated with the PK results of the European pivotal GA Phase III clinical trial (CNS7056-022) and new analyses of existing data to support various aspects of the GA indication. This includes data from a new PK/PD model and results from an integrated analysis of all GA trials.

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

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.

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

The proposed dosing for the **induction** of general anaesthesia is:

1. 6 mg/min until loss of consciousness
2. up to 12 mg/min if a fast induction is required

Most adult patients are likely to require 10-40 mg Byfavo.

The proposed dose for **maintenance** of general anaesthesia is:

- 1 mg/min initially
- option to increase up to 2.5 mg/min and to decrease down to 0.1 mg/min.

As outlined in section 4.2 of the SmPC, for maintenance of anaesthesia, during the ongoing infusion additional boluses of 6 mg over one minute can be given according to clinical requirements. A maximum of three (3) boluses not less than 5 min apart can be administered within 60 min. Towards the end of surgery (e.g. 15 min before the end) the dose of remimazolam may be titrated down to facilitate more rapid recovery from the anaesthetic effects.

To assess the impact of body weight on the required induction dose, the MAH provided additional analyses of cumulative dose administered in patient subgroups across GA trials. Population PK analysis demonstrated that body weight and BMI were not a significant factor contributing to inter-subject variability in systemic exposure, hence remimazolam is recommended for body weight independent dosing. There is no evidence that dosing by body size will lead to decreased variability in systemic exposure compared to using body weight independent dosing. A trend is observed for a slight increase in cumulative dose administered with increasing body weight.

It is agreed for the SmPC wording to refer to dosing independent of body weight, as the patients will be closely monitored and the dose titrated according to the patient's response, as detailed in section 4.2.

In general, the pharmacodynamics of remimazolam falls within the expected profile of a very short-acting BZD intended for procedural sedation or general anesthesia and no critical issues have been identified.

2.6.4 Conclusions on clinical pharmacology

Body weight effects

It is agreed for the SmPC wording to refer to dosing independent of body weight, as the patients will be closely monitored (see section 4.2) and the dose titrated according to the patient's response.

Posology

Remimazolam dosing should be individually titrated to an effective dose which provides the desired level of sedation and minimises adverse reactions (see SmPC section 4.2).

In the pivotal CNS7056-022 study, a maximum of 3 boluses (not less than 5 min apart) were allowed to be administered within 60 minutes. This information has been included in SmPC section 4.2.

No dose adjustment is required in any grade of renal impairment and in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, as the clinical effects may be more pronounced and last longer than in healthy subjects, no dose adjustments are also required but careful attention should be paid to the timing of titration doses and remimazolam titrated accordingly to effect in these patients (see SmPC section 4.4)

2.6.5 Clinical efficacy

The efficacy of remimazolam for induction and maintenance of general anaesthesia (GA) was evaluated in a total of six clinical trials (Table 3). Four of these evaluated efficacy of RMZ versus an active control. These trials were conducted in Europe and Japan; the MAH discussed and agreed with EMA and PMDA key aspects of the trial design during remimazolam development.

Table 3: Clinical trials evaluating efficacy of remimazolam in GA

Trial ID	Phase	Type of Procedure	ASA class	Control
ONO-2745-03	2	Mixed surgeries		None

Trial ID	Phase	Type of Procedure	ASA class	Control
CNS7056-010	2	Cardiac surgeries	All permitted	Propofol/Sevoflurane
CNS7056-011*	3	Cardiac surgeries	All permitted	Propofol
CNS7056-022	3	Mixed surgeries	ASA III/IV	Propofol
ONO-2745-05	2b/3	Mixed surgeries	ASA I/II	Propofol
ONO-2745-06	3	Mixed surgeries	ASA III/IV	None

* study stopped when less than 10% of the planned sample size was enrolled (n enrolled = 23, n planned = 530)

Four controlled studies were prospective, randomised, single-blind studies with propofol as comparator, though sevoflurane was also used in study CNS7056-010, in the time interval between end of intubation and prior to extracorporeal circulation. These studies compared remimazolam with propofol during induction and maintenance of anaesthesia. In addition, in study CNS7056-010 and CNS7056-011 remimazolam or propofol use could be extended until 24 hours after the end of surgery, whilst the patient was in the intensive care unit (ICU).

CNS7056-011, CNS7056-022 and ONO-2745-05 were all non-inferiority studies using propofol as a comparator. CNS7056-022 and ONO-2745-05 were the two pivotal studies for this line extension application, the former conducted in Europe, the latter in Japan.

2.6.5.1 Dose response study(ies)

Two Phase II trials, dose-finding, were conducted:

- **ONO-2745-03**: a dose finding trial conducted in adult patients in Japan, in four parts. Parts A and C investigated various doses of remimazolam for induction of GA in non-elderly and elderly patients, respectively. For maintenance of general anaesthesia these patients were switched to sevoflurane. Parts B and D confirmed the induction dose in non-elderly and elderly patients and anaesthesia was maintained with a starting dose of remimazolam identified in a phase I trial (ONO-2745-02). GA was performed to support mixed surgeries. No comparator arm was included.

  Results: 75 of the 85 enrolled subjects were included in the per protocol set (PPS) (Part A, 25; Part B, 25; Part C, 18; Part D, 7) and 85 subjects in the full analysis set (FAS) (Part A, 25; Part B, 30; Part C, 20; Part D, 10) which was used for the primary efficacy analysis. All remimazolam-treated subjects achieved loss of consciousness and completed tracheal intubation. All subjects in part B and part D completed surgery without any requirement for rescue sedative medication.
  During the induction phase, loss of consciousness (LoC) was associated with a decrease in the Bispectral index (BIS) to approximately 60 or less at 2 minutes after LoC. There were no apparent differences between the four induction doses in terms of BIS.
  The BIS value (mean) during anaesthesia maintenance was 51.2 to 77.0 in Part B (non-elderly), and 44.8 to 71.0 in Part D (elderly). After the end of remimazolam administration, the BIS value (mean) increased to approximately 80, which generally indicates light sedation as the subjects were awakening from the state of unconsciousness.
  All recovery times were slightly longer in non-elderly as compared to elderly patients. Eye opening occurred at a mean of 14/11 minutes and extubation at a mean of 16/14 minutes after the end of remimazolam administration in non-elderly and elderly patients, respectively. The mean time from end of study drug administration to being able to state date of birth was 21/18 minutes, and to being ready to be discharged was 26/19 minutes, in non-elderly and elderly patients, respectively.

When interpreting these results it should be noted that somewhat higher doses were used during maintenance in non-elderly as compared to elderly patients (1 mg/kg/h starting dose rate was adjusted to 0.8 to 2.0 mg/kg/h in non-elderly and to 0.4 to 1.0 mg/kg/h in elderly subjects). In the vast majority of patients, the systolic blood pressure remained at or above 80mm Hg for the entire treatment phase.

- **CNS7056-010:** a monocentric trial conducted in Germany, which investigated remimazolam (6 mg/kg/h and 12 mg/kg/h induction doses) versus propofol in the induction and maintenance of GA during cardiac surgery. All patients randomized to propofol received sevoflurane after intubation and prior to extracorporeal circulation. Not many data have been provided via this study, besides the fact it supported the choice of the lower studied dose: time to loss of consciousness was shorter for the higher dose (1.4 min) as compared to the lower dose (2.0 min), while haemodynamic stability was better for the lower dose (i.e. 35.3% cardiostability at 6 mg/kg/h vs. 17.9% cardiostability at 12 mg/kg/h). Since haemodynamic stability is an important feature of remimazolam, the lower dose has been selected as the default induction dose. Since 12 mg/kg/h (considered largely equivalent to 12 mg/min) was also safe and efficacious, 12 mg/min is proposed as an upper limit for the induction dose to be used in situations in which a fast induction could be needed.

2.6.5.2 Main study(ies)

Two pivotal Phase III trials (**ONO-2745-05** and **CNS7056-022**) have been noted for the indication being sought in this line extension application.

CNS7056-022

A phase III study comparing the safety and efficacy of remimazolam during GA in ASA III/IV patients

Methods

CNS7056-022 was a phase III confirmatory efficacy and safety study comparing remimazolam with propofol for IV anaesthesia during elective surgery in ASA III/IV patients. The study was planned to randomise 452 patients in total: 339 to remimazolam, 113 to propofol. An interim analysis was planned after 243 randomised patients.

Study participants

Key inclusion criteria:

An individual had to meet all of the following criteria:

• Male or female ASA III / IV patients, at least 18 years old, scheduled for an elective surgical procedure of a minimum duration of approximately 90 minutes under GA and planned to be extubated immediately post-operatively;

• Total intravenous GA with the requirement for mechanical ventilation via endotracheal tube and necessary invasive BP monitoring either due to severity of illness, severity of concomitant diseases, type of surgery or decisions of the anaesthesia staff.

• Patients scheduled to stay in the hospital long enough after the surgical procedure to perform all trial follow-up procedures (~1 day);

• For female patients of childbearing potential: Negative results of 2 pregnancy tests, the first test taken at the start of Screening and the second test taken shortly before the administration of the IMP as well as consent to use highly effective birth control from the last menstrual cycle prior to the start of the IMP until the end of the trial follow-up procedures.

Key exclusion criteria:

An individual who met any of the following criteria was excluded from participation in this trial:

• Patients scheduled for spinal anaesthesia, epidural anaesthesia (central neuraxial anaesthesia) or regional anaesthesia. The placement of a peridural catheter with a test dose application of a local anaesthetic drug (up to 5 mL) to verify correct positioning to achieve post-operative analgesia and the regional administration of local anaesthetic for post-operative analgesia after wound closure (after the last skin suture) was accepted;

• Patients undergoing transplant surgery, cardiac surgery, or intracranial neurosurgery, patients which had to be in prone position for surgery, emergency surgery, or any surgical procedure with the need for or scheduled for post-operative ventilator support;

• Patients undergoing surgical procedures that required keeping the BP at a high level, e.g. surgical procedures in beach chair position;

• Patients with severe hypertension, i.e., one baseline result of systolic BP 200 mmHg or more and/or diastolic BP of 120 mmHg or more. Baseline was defined as the time after signature of ICF and beforearrival in the OR suite;

• Patients with total bilirubin of ≥3.0 mg/dL or ≥3 times increase in aspartate aminotransferase or alanine aminotransferase as per the reference range, in laboratory tests which had to be checked within the 7 days prior to start of IMP, or any other laboratory results that made the patient unsuitable for the trial;

• Patients with end-stage renal disease requiring scheduled dialysis.

Treatments

The dosing of remimazolam and propofol during the first 20 minutes of the GA is detailed in the Table 4:

Table 4: IMP doses used during the first 20 minutes of induction in CNS7056-022

Time (minutes)	Remimazolam	Propofol
00:00 to 03:00	6.0 mg/minute	30 mg/kg/hour
03:00 to 10:00	2.5 mg/minute	10 mg/kg/hour
10:00 to 20:00	1.5 mg/minute	8 mg/kg/hour
20:00	1.0 mg/minute	6 mg/kg/hour

t = 00:00 was the start of the administration of IMP. Investigators were free to dose slightly below or above the induction schedule if the NCI was outside the intended range between ≥27 and ≤60

The MAH excluded the first two patients in each study site because these patients were not randomised. This will not mimic the real life approach, where clinicians may perform differently in the first anesthetised patients than when they are acquainted with the product. Therefore, analysis of these patients was requested to:

a) As intent to treat where all patients assigned to remimazolam or propofol be analysed together, independently from having been randomised or not;

b) All non-randomised first two patients in each study site, to be compared to those randomised, to understand whether the learning curve for remimazolam was different from what clinicians are accustomed to.

The MAH performed the requested analyses:

a) Regarding the ITT analysis, it is reassuring that the results show a similar trend which is statistically significant as compared to the primary analysis of the study;

b) The MAH concludes there was a learning effect after the first patient, who became stable afterwards, due to the easiness of remimazolam use. The CHMP reasoning differs: the first patient was knowledgeably on propofol; all the others were either:

1) Using an unknown product (second patient)

2) They had a higher chance of being using an unknown product. Therefore they had to be much more cautious. This is in line with what is expected in the conduct of a trial, and apparently did not interfere with global study results.

Objectives

Study **CNS7056-022** was a confirmatory trial to establish:

1. The primary objective of non-inferior efficacy of remimazolam;

2. The key secondary objective of superior haemodynamic stability associated with the use of remimazolam compared with propofol for induction and maintenance of GA during elective surgery in patients in ASA classes III and IV. Further endpoints of efficacy and safety were investigated in an exploratory manner.

Outcomes / endpoints

Primary endpoint

- The percentage of time of NCI ≤60 during maintenance phase of GA, defined as time between the first skin incision and the completion of the last skin suture

Key Secondary Endpoint (KSE) – safety endpoint

- Superiority of remimazolam over propofol in terms of the KSE, i.e. haemodynamic instability, was defined as critical decrease(s) in mean arterial blood pressure (MAP) between start of IMP and 15 minutes after the first skin incision.

This was assessed using the total number of critical hypotensive events per patient and comparing the mean number of events of haemodynamic instability per patient between the 2 treatment groups.

Each event from the following categories was counted and events were summed up per patient:

- Incidence of MAP dropping below 65 mmHg for at least 1 minute duration
- Incidence of a MAP decrease of more than 20% below the calculated (mean) baseline MAP value for at least 1 minute duration
- Incidence of a MAP decrease of more than 30% below the calculated (mean) baseline MAP value for at least 1 minute duration
- Number of norepinephrine boluses (0.01 mg) required or, if an infusion was used to maintain MAP equal to or above 65 mmHg, then each time interval of 2 minutes duration of continuous norepinephrine infusion was counted as one event.

Secondary endpoints

- Time from start of IMP administration to LoC (i.e., MOAA/S = 0)
- The incidence of the occurrence of intra-operative awakening (explicit awareness)
- Percentage of time of NCI ≤60 and ≥27 during the maintenance phase

- Percentage of patients who were administered rescue sedative medication as defined per protocol
- Time from the end of IMP administration to response to verbal command (MOAA/S ≥4)
- Time from stop of IMP administration to extubation
- Time from the end of IMP administration to orientation to time, place, person and situation

Although the secondary outcomes include % of time of NCT in the desired range and in the undesirable range, the cut-off values are set lower than was proposed during Scientific Advice. Desired range was defined as NCI ≤60 and ≥27 (instead of between 60 and 40, per SA) and the undesirable range was defined as NCI <27 (instead of below 40, per SA). The Applicant provided an in-depth answer to CHMP's request for additional analyses with the secondary outcomes defined per Scientific Advice (EMA/CHMP/SAWP/14117/2018), i.e. NCI between 60 and 40, together with reasons for not following the mentioned scientific advice, namely the lower boundary of 27 instead of 40, which is in line with present GA literature. The provided reasons are acceptable, and the additional analyses (namely with use of the safety set population) show similar results in remimazolam and propofol arms, which is reassuring.

Sample size

It was planned to randomly assign 452 patients in total: 339 to remimazolam, 113 to propofol. In addition, the first two patients of each site were enrolled in the trial, but not included in the randomisation scheme. It was expected this process would result in a maximum total sample size of around 512 treated patients (452 randomised patients and approximately 60 non-randomised patients).

The sample size calculation for the primary endpoint (non-inferiority of remimazolam compared to propofol) is based on the following assumptions: for a one-sided type I error rate of 0.025 and a target power of 90%, the assumption of a non-inferiority margin of 10% lead to sample sizes of 84 patients with an allocation ratio of 3:1 (63:21).

The sample size calculation for the key secondary endpoint (superiority of remimazolam compared to propofol based on combined hemodynamic effect) is based on the following assumptions: for a two-sided type I error rate of 0.05 and a target power of 90%, the assumption to detect a difference of 18.60 hemodynamic events per subject (according to the composite key secondary endpoint) leads to a sample size of 324 patients with an allocation ratio of 3:1 (243:81 = 324).

A 10% dropout rate is expected and therefore the sample size for the PEP is set to 93 subjects, while the sample size for the KSE is set to 356 (3:1 = 267:89) (which includes the before mentioned sample size for the PEP of 93 subjects).

The trial was prematurely terminated due to a global health crisis caused by the COVID-19 pandemic, which led to postponement of elective surgeries and a substantial impairment of on-site monitoring due to access restrictions to hospitals. At the time of the premature termination, a total of 425 patients were enrolled by 23 sites. Of these 425 patients, 409 were exposed to the IMP, either after assignment to treatment by randomisation (365 patients) or based on pre-planned assignment (44 patients). The numbers of patients in the safety set (SAF), full analysis set (FAS), per protocol set 1 (PP1; relevant for the primary efficacy endpoint; PEP) and in the per protocol set 2 (PP2; relevant for the key secondary endpoint; KSE) are provided in the Table 5**.**

Table 5: Number of patients analyses

Numbers of patients analysed		Remimazolam n (%)	Propofol n (%)	Total n (%)
Interim Analysis (IA)	FAS	191 (100.0)	63 (100.0)	254 (100.0)
	PP1	165 (86.4)	60 (95.2)	225 (88.6)
	PP2	133 (69.6)	52 (82.5)	185 (72.8)
Final Analysis (FA)	SAF	291 (107.8)	118 124.2)	409 (112.1)
	FAS	270 (100.0)	95 (100.0)	365 (100.0)
	PP1	235 (87.0)	92 (96.4)	327 (89.6)
	PP2	193 (71.5)	82 (86.3)	275 (75.3)

Randomisation and blinding (masking)

A computer-generated randomisation schedule was prepared before the start of the trial, using an imbalanced randomisation scheme of 3:1 for remimazolam to propofol, stratified by the ASA status of the patient, ASA III and ASA IV. Screened patients are randomly allocated to one of the two treatment groups.

Two patients per site are enrolled in the trial, without being randomised, so that site personnel can familiarise themselves with trial procedures and with remimazolam. They are pre-assigned to either propofol (patient 1) or remimazolam (patient 2) and their complete data is collected. Randomisation starts with patient 3 of each site and occurs as shortly before the start of IMP as possible, i.e. Day 1 preferably. In exceptional cases and for organisational reasons, randomisation can be done late on Day -1.

The study was not blinded for investigators, but it was blinded for the patient and the statistician.

Statistical methods

This was a confirmatory trial to a) establish the primary objective of non-inferior efficacy of remimazolam compared with propofol for induction and maintenance of general anaesthesia (GA) during elective surgery and b) establish the key secondary objective of superior haemodynamic stability associated with the use of remimazolam compared with propofol for induction and maintenance of GA during elective surgery.

The FAS was defined as those patients who were randomised and who received the trial drug for ≥1 minute. Patients pre-assigned to either propofol (patient 1 at each site) or remimazolam (patient 2 at each site) were not included in the FAS. The FAS was used for the sensitivity analysis of the primary endpoint, for the primary analysis of secondary efficacy endpoints and the key secondary (safety) endpoint.

The SAF was defined as all patients who received any amount of the trial drug. The SAF was used for all safety analyses except for the KSE. All patients were treated according to their assigned treatment. PK Set (PKS): Patients randomised to remimazolam were included in the PKS if they had at least 1 plasma concentration >lowest level of quantification (LLOQ), 4 analysable PK samples (Cmax and 3 subsequent points), a pre-dose plasma concentration ≤5% of Cmax, and had no major protocol deviations that may have impacted reliability of PK data.

The PP1 consisted of all patients in the FAS who had no major protocol deviations preventing the accurate and sufficient evaluation of the PEP. The PP1 was used for the primary analysis of the primary endpoint.

The PP2 consisted of all patients in the FAS who had no major protocol deviations preventing the accurate and sufficient evaluation of the KSE. The PP2 was used for the sensitivity analysis of the key secondary endpoint.

Analysis of the primary efficacy endpoint

The main analysis of the PEP (non-inferiority) was conducted on the PP1 Set at the IA using NCT data after imputations of missing NCI values for time periods of up to 300 seconds with linear regression using one value before and after missing values. Missing NCI values for time periods of over 300 seconds were not imputed.

The clinical equivalence (non-inferiority) of remimazolam compared with propofol in terms of the PEP (% of time of NCI ≤60) was assessed using a non-inferiority test that was a one-sided two sample t-test that compared the differences to a non-zero quantity M (non-inferiority margin of 10%).

The null and alternative hypotheses were, when the higher values were better:

- H0: (μ T- μ C) ≤ - M
- H1: (μT-μC) > - M

This percentage of time with NCI ≤60 was compared between subjects who received remimazolam or propofol using a one-sided two sample t-test at a significance level of 0.025. Results were presented along with the lower bound of a 97.5% CI. As a sensitivity analysis, an ANCOVA model including patient's ASA physical status (ASA III or ASA IV) and treatment as covariates was performed.

Analysis of the key secondary endpoint

The main analysis of the KSE (superiority) was conducted on the FAS population using MAP results from invasive blood pressure monitoring by FloTrac® after imputation of missing MAP results for time periods up to 180 seconds with linear regression using one value before and after missing values. Missing MAP results for time periods of over 180 seconds were not imputed.

Superiority of remimazolam over propofol in terms of the KSE, i.e. haemodynamic instability, was defined as critical decrease(s) in MAP between start of IMP and 15 minutes after the first skin incision.

This was assessed using the total number of pre-defined critical hypotensive events per patient and comparing the mean number of events of haemodynamic instability per patient between the 2 treatment groups.

The KSE was compared in subjects who received remimazolam or propofol. It was planned to use a 2-sided z-test. The KSE was tested at a 2-sided significance level of 0.05, using the O'Brien-Fleming spending function to determine the test boundaries for the 2 sequential tests (at the IA with 243 patients and at the FA). The 2-sided type I error rate was 0.0193 at the IA and 0.0307 at the FA. Results were presented along with a 98.07% CI at the IA and with a 96.93% CI and p-value at the FA. As a sensitivity analysis, an ANCOVA model including patient's ASA physical status (ASA III or ASA IV) and treatment as covariates were calculated at the IA and at the FA.

The KSE was analysed using the following hypotheses:

- H0: μRemimazolam = μPropofol and
- H1: μRemimazolam < μPropofol

where μ described the mean number of haemodynamic events (hypotension) per patient.

During the statistical analysis of the KSE, it was found that the endpoint variable was not normally distributed. Hence, the z-test was replaced with a Wilcoxon rank-sum test. Moreover, due to the

intercomponent correlation of the components of the composite KSE, the endpoint had to be factored using the Common Factor Analysis (CFA) in order to be based on the most important factors from the statistical and medical perspective. For the analysis of the non-normally distributed factored endpoint, the z-test was replaced by the more appropriate Wilcoxon rank-sum test.

The statistical considerations regarding the post-hoc change of analysis for the key secondary outcome (haemodynamic instability) is presented in the Results section.

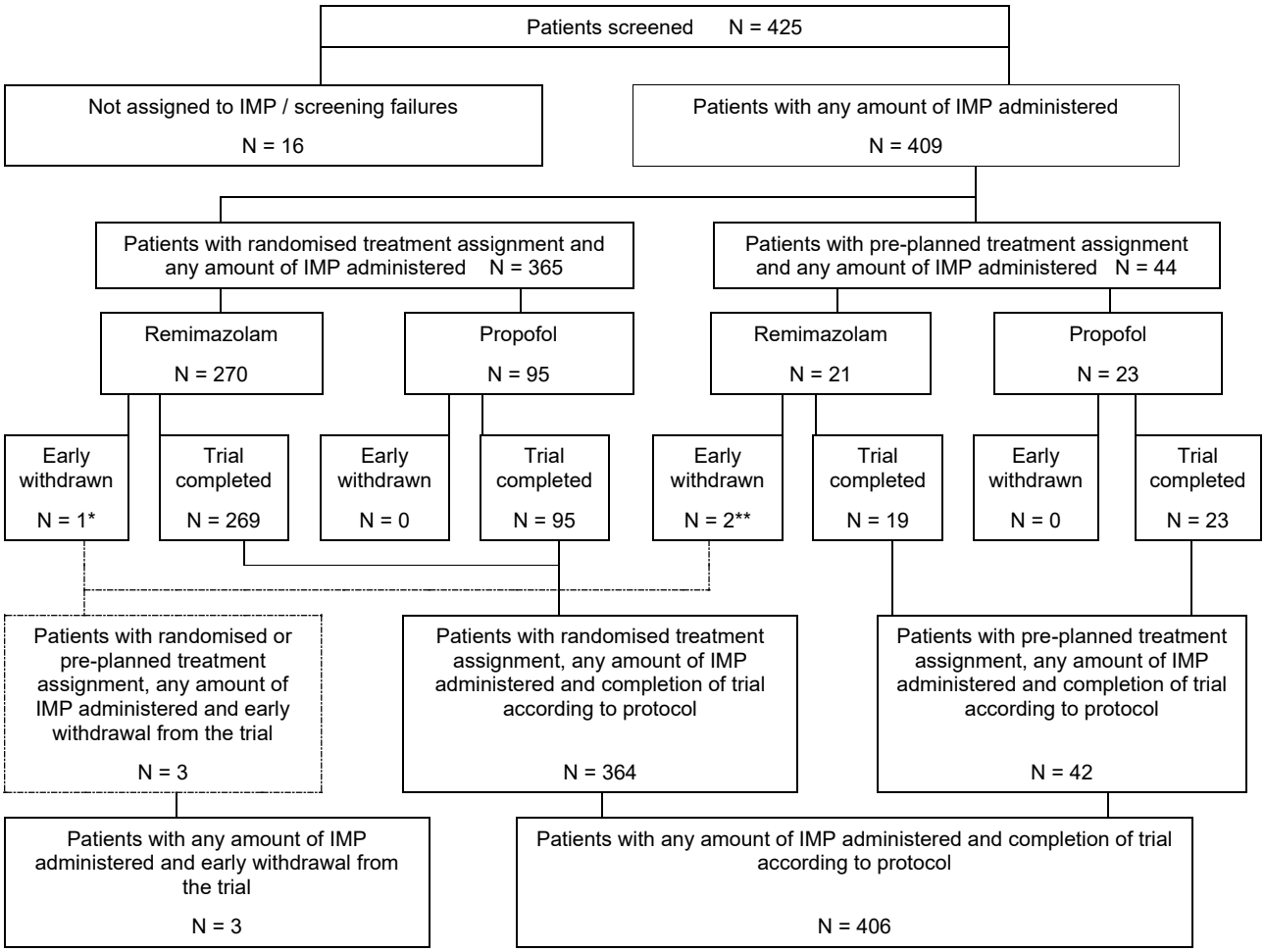
Stopping rules at the interim analysis

The stopping rules at the IA comprised the following options:

1. PEP non-inferiority shown, KSE superiority not shown: Continue to the planned number of trial patients
2. PEP non-inferiority shown, KSE superiority shown: Continue to the planned number of trial patients with open label remimazolam only
3. PEP non-inferiority not shown, KSE regardless of result: Stop trial

Results

Figure 1: Participants flow



Source: Section , Table 14.1.1, Appendix 16.2.1, Listing 16.2.1, Appendix 16.2.2, Listing 16.2.2, Appendix 16.2.3, Listing 16.2.3 and Appendix 16.2.5, Listing 16.2.10.2

Abbreviations: IMP = investigational medicinal product; N = number of patients

* Reason for early withdrawal: physician decision

** Reason for early withdrawal: protocol deviation (N=1), surgery was cancelled after completed GA induction (N=1)

In total, 425 patients were assigned to remimazolam or propofol either by randomisation or by fixed assignment, depending on whether they were the first or second trial patient of a trial site.

Of 425 patients with assignment to remimazolam or propofol at a total of 23 trial sites, 16 patients were not exposed to IMP due to reasons emerging between assignment and planned start of IMP, e.g. surgery cancelled/postponed. Among the remaining 409 patients, 365 patients had been assigned to remimazolam or propofol by randomisation, while 44 patients were among the first two patients of each individual site, hence were assigned to propofol or remimazolam depending on whether they were the first or the second patient of this site.

The trial was completed, according to the protocol, by 364 patients on remimazolam or propofol based on randomised assignment, and by 42 patients on remimazolam or propofol as consequence of pre-planned assignment. Early withdrawal after any exposure to IMP occurred in three patients.

Recruitment

The first patient's first visit (FPFV) was performed on 22 July 2018 and the last patient's last visit (LPLV) was performed on 18 March 2020. The trial was prematurely terminated on 02 April 2020, due to the global COVID-19 pandemic. A total of 23 sites in Europe contributed patients to the trial. The trial sites were in Belgium (three sites), Switzerland (four sites), Germany (six sites), France (two sites), The Netherlands (two sites), Italy (three sites) and the UK (three sites).

Conduct of the study

During Blind Data Review Meetings (BDRMs) prior to the IA and the FA, and before statistical tables by actual treatment group were produced, protocol deviations were reviewed in order to define the analysis populations.

Among all protocol deviations that had the potential to interfere with the evaluation of the PEP and the KSE, inappropriate use of rescue sedative medication was assessed as particularly important. It was defined as the use of:

- Sedatives/hypnotics other than the allocated IMP (remimazolam or propofol) or ketamine at an analgesic dose, without prior administration of the IMP dose to the maximum allowed by the protocol;
- Higher doses of IMP than the allowed by the protocol without prior increase of the IMP dose to the maximum allowed by the protocol.

Patients were included into the FAS following the definition provided in the protocol and the SAP with only one exception: one patient was excluded from the FAS despite the fact that the IMP was administered over at least one minute, because desflurane and IMP were started together inadvertently, due to the desflurane container remaining open from the preceding GA in the same room. The local trial team detected this error only after a few minutes of application of the IMP (together with desflurane).

The PP1 and PP2 were identified as part of the preparation of the IA and FA taking into account all protocol deviations that prevented an appropriate evaluation of the PEP and the KSE. The most frequent protocol deviations causing exclusion from the PP1 at both analysis time points were inappropriate use of rescue sedative medication (IA: 10 [3.9%] patients; FA: 16 [4.4%] patients) and incorrect use of post-operative analgesia (IA: 8 [3.1%] patients, FA: 8 [2.2%] patients). The most frequent protocol deviations causing exclusion from the PP2 at both analysis time points were remifentanil dosed too high during the time of interest (TOI) (IA: 54 [21.3%] patients; FA: 69 [18.9%] patients) and FloTrac® started after first IMP dose (IA: 10 [3.9%] patients, FA: 14 [3.8%] patients).

PP1 and especially PP2 analyses are expected to significantly deviate from the real treatment response since over 1/4 of the patients end up being removed from the analysis, and the behaviour of those removed is likely different from the one in the per protocol analyses.

Protocol deviations leading to exclusion from the PP1 and PP2 sets are provided in the Table 6:

Table 6: Reasons for exclusion fromPP1 and PP2

Reasons for Exclusion	Interim Analysis, FAS			Final Analysis, FAS		
	Remi-mazolam N = 191	Propofol N = 63	Total N = 254	Remi-mazolam N = 270	Propofol N = 95	Total N = 365
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Exclusion from PP1						
Exclusion for any reason(s)	26 (13.6)	3 (4.8)	29 (11.4)	35 (13.0)	3 (3.2)	38 (10.4)
○ Inappropriate use of rescue sedative	10 (5.2)	0	10 (3.9)	16 (5.9)	0	16 (4.4)
○ Incorrect use of post-operative analgesia	5 (2.6)	3 (4.8)	8 (3.2)	5 (1.9)	3 (3.2)	8 (2.2)
○ IMP reconstituted incorrectly	4 (2.1)	0	4 (1.6)	4 (1.5)	0	4 (1.1)
○ Remifentanil high dose in TOI	3 (1.6)	0	3 (1.2)	4 (1.5)	0	4 (1.1)
○ Other sedatives used*	2 (1.1)	0	2 (0.8)	2 (0.7)	0	2 (0.5)
○ Benzodiazepine used	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (0.3)
○ CNS suppressant drug used	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (0.3)
○ Opioid used	1 (0.5)	0	1 (0.4)	2 (0.7)	0	2 (0.5)
○ Remifentanil bolus administered	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (0.3)
○ Body weight measured prior to Screening	n.a.	n.a.	n.a.	1 (0.4)	0	1 (0.3)
○ Exclusion criterion no. 5**	n.a.	n.a.	n.a.	1 (0.4)	0	1 (0.3)
○ IMP and remifentanil confused	n.a.	n.a.	n.a.	1 (0.4)	0	1 (0.3)
○ IMP and remifentanil stop times differ	n.a.	n.a.	n.a.	1 (0.4)	0	1 (0.3)
Exclusion from PP2						
Exclusion for any reason(s)	58 (30.4)	11 (17.5)	69 (27.2)	77 (28.5)	13 (13.7)	90 (24.7)
○ Remifentanil high dose in TOI	44 (23.0)	10 (15.9)	54 (21.3)	57 (21.1)	12 (12.6)	69 (18.9)
○ FloTrac® started after first IMP dose	6 (3.1)	4 (6.3)	10 (3.9)	10 (3.7)	4 (4.2)	14 (3.8)
○ Inappropriate use of rescue sedative	5 (2.6)	0	5 (2.0)	9 (3.3)	0	9 (2.5)
○ IMP reconstituted incorrectly	3 (1.6)	0	3 (1.2)	3 (1.1)	0	3 (0.8)
○ FloTrac® file outside of validated transfer process	2 (1.1)	0	2 (0.8)	2 (0.7)	0	2 (0.5)
○ Incorrect use of post-operative analgesia	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (0.3)
○ Benzodiazepine used	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (0.3)
○ CNS suppressant drug used	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (0.3)
○ FloTrac® recording not done	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (0.3)
○ FloTrac® stopped before 15 min after FSI	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (0.3)
○ Norepinephrine used although MAP >65	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (0.3)
○ Opioid used	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (0.3)
○ Vasopressor other than norepinephrine	1 (0.5)	0	1 (0.4)	1 (0.4)	0	1 (0.39
○ Body weight measured prior to Screening	n.a.	n.a.	n.a.	1 (0.4)	0	1 (0.3)
○ Exclusion criterion no. 5	n.a.	n.a.	n.a.	1 (0.4)	0	1 (0.3)

Source: Section , Table 14.1.2 (IA) and Table 14.1.2, Appendix 16.2.2, Listing 16.2.2

Abbreviations: ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; CNS = central nervous system; FAS = Full Analysis Set; FSI = first skin incision; IMP = investigational medicinal product; MAP = mean arterial pressure; min = minutes; N = number of patients; n = number of observations; n.a. = not applicable; PP = per protocol; PP1 = Per Protocol Set 1; PP2 = Per Protocol Set 2; TOI = time of interest

Multiple reasons could apply to the same patient

* : local anaesthetic was given before stop of IMP (N=1); : Local anaesthetic was administered to the patient through a transversus abdominis plane (TAP) bloc, 20 min before the end of the IMP (N=1)

** Total bilirubin of ≥3.0 mg/dL or ≥3 times increase in ASAT or ALAT

No particular concerns arise from these exclusions, with the exception of remifentanil high dose as a reason for exclusion from PP2 (at interim analysis: 23% in remimazolam and 15.9% in propofol; at final analysis: 21.1% in remimazolam and 12.6% in propofol) was raised as a concern. The MAH found no apparent explanation for the observed difference (remifentanil high dose as a reason for exclusion from PP2 was observed with a notably higher frequency for remimazolam arm compared to propofol arm). However, the MAH provided several arguments which could have contributed to the observed difference in frequencies. This argumentation is considered acceptable and it can be agreed that a key reason for the difference does not emerge from the presented data.

Protocol amendments

One protocol amendment for Germany only and three global protocol amendments occurred. Protocol amendment for Germany only and the first global protocol amendment occurred before FPFV and therefore did not impact the study results.

The second and third global protocol amendments include many minor changes. A clarification on the impact of amendments was requested and duly provided by the MAH.

Baseline data

At their individual trial start and based on the FAS, patients in the remimazolam group were 68.3 ± 10.83 (mean ± standard deviation) years old and patients in the propofol group were 68.3 ± 10.21 years old. The majority of patients in both groups were male (remimazolam: 72.2%, propofol: 73.7%). The mean BMI was 27.8 ± 5.30 kg/m2 in the remimazolam group and 27.0 ± 5.29 kg/m2 in the propofol group. The ASA class was specified as ASA III for 95.6% of the patients in the remimazolam group and 93.7% of the patients in the propofol group. All other patients were assessed as ASA IV.

Across the GA studies conducted, the average BMI was similar across the remimazolam and propofol groups (see Table 7). In 2014, the global age-standardised mean BMI was 24·2 kg/m^2 (24·0–24·4 {95% credible interval}) in men, and 24·4 kg/m^2 (24·2–24·6 {95% credible interval}) in women. Therefore, the mean BMI observed across the GA studies was slightly higher than the global average.

Table 7: Mean BMI in Group C

	Remimazolam (n = 783)	**Propofol (n = 226)**
Mean BMI (SD)	25.22 (4.612)	25.98 (4.965)

Across all propofol controlled studies the BMI was comparable across the remimazolam and propofol groups). Across the Japanese studies the means of BMI ranged from 22.70 – 23.25 within the remimazolam group. This is largely similar to the mean BMI in Japan.

Looking at the mean BMI across all GA studies, there is a clear trend for lower BMI in patients in Japanese studies in comparison to patients in European studies. In European studies the means of the BMI ranged from 26.25 – 27.74 within the remimazolam group. This is consistent with the average BMI seen in many major European countries e.g., Germany (26.3) and the UK (27.3), but slightly higher than the average BMI in Italy (26.0), Netherlands (25.4) and Belgium (25.5), all countries which contributed to the European GA development program.

Across the two pivotal studies ONO-2745-05 and CNS7056-022 the difference in BMI across Japanese patients and European patients was consistent with the average BMI across these territories, as outlined by the 2014 Global status report on noncommunicable diseases. In addition, as the question highlights, a higher BMI is expected in ASA III/IV patients. As ONO-2745-05 included ASA I/II patients and CNS7056-022 included ASA III/IV patients a higher BMI is expected to be seen in the latter.

It can therefore be concluded that the BMI of the patients included in the GA development program is representative of the population within the EU. In addition, as remimazolam will generally be administered by body weight independent dosing, extremes in BMI are unlikely to have any significant impact on the dose administered. It can also be accepted that, as par as the EU population is concerned, observed differences between the studied population and the broad EU population may not have clinical relevance for most GA aspects.

Medical History

Any past medical history was reported by 215 (79.6%) patients in the remimazolam group and by 80 (84.2%) patients in the propofol group. The highest by-patient frequency emerged for the SOC surgical and medical procedures (53.7% of the patients in the remimazolam group and 51.6% of the patients in the propofol group). The SOC with the second highest by-patient frequency was neoplasms (18.1% of the patients in the remimazolam group and 16.8% of the patients in the propofol group). The PTs most often reported were myocardial infarction (6.3% of the patients in the remimazolam group and 11.6% of the patients in the propofol group) and appendicectomy (6.3% of the patients in the remimazolam group and 5.3% of the patients in the propofol group).

Current Medical Conditions

Any current medical condition was reported by all (100.0%) patients in both treatment groups. The highest by-patient frequency was found for the SOC vascular disorders (75.9% of the patients in the remimazolam group and 78.9% of the patients in the propofol group). The SOC with the second highest by-patient frequency was metabolism and nutrition disorders (52.6% of the patients in the remimazolam group and 46.3% of the patients in the propofol group). The PTs reported most often were hypertension (67.4% of the patients in the remimazolam group and 69.5% of patients in the propofol group) and type 2 diabetes mellitus (15.6% of the patients in the remimazolam group and 9.5% of the patients in the propofol group).

Prior and Concomitant Medication

In both treatment groups and based on the SAF, prior medication was most frequently from the ATC classes cardiovascular system (84.2% of the patients in the remimazolam group, 84.7% of the patients in the propofol group), blood and blood forming organs (70.4% of the patients in the remimazolam group and 69.5% of the patients in the propofol group), and alimentary tract and metabolism (62.2% of the patients in the remimazolam group and 63.6% of the patients in the propofol group). Benzodiazepine derivates were reported as prior medication for one (0.3%) patient in the remimazolam group and four (3.4%) patients in the propofol group.

In both treatment groups and based on the SAF, concomitant medication was most often from the classes nervous system (97.3% of the patients in the remimazolam group and 97.5% of the patients in the propofol group), alimentary tract and metabolism (75.6% of the patients in the remimazolam group and 68.6% of the patients in the propofol group), and anti-infectives for systemic use (72.5% of the patients in the remimazolam group and 68.6% of the patients in the propofol group.

The documentation of either type 2 DM or DM in the patients' medical history was at the discretion of the investigator. Therefore, even though patients within the group type 2 DM only includes those patients who suffer with type 2 DM, the DM group includes patients who suffer with any type of diabetes, including type 2 DM. At this moment it is not possible to further discriminate DM patients and understand which might be at higher risk of AEs.

In the trial CNS7056-022, patients with regular use of central nervous system depressant drugs were excluded. However, subgroup analyses on patients with or without reported non-single use of

benzodiazepines, opioids, antidepressants, antiepileptics and/or hypnotics and sedatives revealed differences between the subgroups in terms of the effect of remimazolam.

The MAH provided data on patients on chronic treatment with CNS depressants, in spite of the exclusion criteria stringency on chronic BZD use. Although the sample was very low (40 pts) compared to those with no CNS depressant (251 pts) - and therefore a significant statistical difference was not to be expected - there was a clear numerically difference among the patients treated with CNS depressants, in:

a) decreased duration of remimazolam sedative effect (NCI ≤60);

b) increased absolute dose of remimazolam per procedure;

c) increased dose per hour;

d) increased need for rescue sedation.

Given that all aspects studied point towards a significant risk of decreased efficacy in patients concomitantly treated with CNS depressants, the MAH included a specific warning in the SmPC and refer not only to chronic use of BZDs but to "CNS depressants", as requested by CHMP. It should be clear for the HCP that acute concomitant use of CNS depressants may increase sedation but, on the other hand, chronic concomitant use of CNS depressants may decrease remimazolam sedation. Therefore, in Section 4.4 of SmPC, the heading was revised from "Chronic benzodiazepine use" to "Chronic CNS depressants use" and the text below included: patients who receive chronic benzodiazepine therapy (e.g., for insomnia or anxiety disorders) may develop tolerance to the sedative/hypnotic effects of remimazolam. Hence, a larger cumulative dose of remimazolam may be required to achieve the desired level of anaesthesia. A similar effect may also be observed with other CNS depressants. It is recommended to follow the titration regimen in section 4.2 and titrate up based on the patient's response, until the desired depth of anaesthesia is achieved (see section 4.5).

Numbers analysed

Analysis population (see Table 8)

Table 8: Analysis population

Analysis	Population	Remimazolam n (%)	Propofol n (%)	Total n (%)
Interim Analysis	FAS	191 (100.0)	63 (100.0)	254 (100.0)
	PP1	165 (86.4)	60 (95.2)	225 (88.6)
	PP2	133 (69.6)	52 (82.5)	185 (72.8)
Final Analysis	SAF*	291 (107.8)	118 (124.2)	409 (112.1)
	FAS	270 (100.0)	95 (100.0)	365 (100.0)
	PP1	235 (87.0)	92 (96.8)	327 (89.6)
	PP2	193 (71.5)	82 (86.3)	275 (75.3)
	PK Set	77 (28.5)	0 (0.0)	77 (21.1)

Source: Section 14.1, Table 14.1.1 (IA) and Table 14.1.1

Abbreviations: FAS = Full Analysis Set; n = number of patients per category; PK = pharmacokinetics; PP1 = Per Protocol Set 1; PP2 = Per Protocol Set 2; SAF = Safety Set

* The difference between the SAF and the FAS in the number of included patients resulted from patients on fixed treatment assignment (first 2 patients of each site) being by definition part of the SAF but not of the FAS. The IA did not include any analyses based on the SAF.

Outcomes and estimation

The PEP analysis was conducted on the per protocol set of the interim analysis. The mean difference between the treatment groups was -4.24 with a lower boundary of the 97.5% CI of -7.48. This lower boundary did not exceed the pre-defined threshold of -10. The corresponding p-value did not exceed the threshold of 0.025. Hence, the results indicated an efficacy of remimazolam that was non-inferior to propofol in terms of the PEP.

Interim analysis

Primary efficacy endpoint

To account for missing NCI results during the maintenance phase of the GA, several methods were applied as per the SAP. The mean percentage of time with NCI ≤60 between first skin incision and last skin suture was 94.62% ± 19.337% in the PP1 remimazolam group (n = 165) and 98.86% ± 5.153% in the PP1 propofol group (n = 60). See Table 9.

Table 9: Primary Efficacy Endpoint, Confirmatory Analysis (IA, PP1)

Percentage of GA Maintenance Time with NCI ≤60 (%)	Remimazolam N = 165	Propofol N = 60
Imputation of missing NCI values by linear regression		
Mean ± SD	94.62 ± 19.337	98.86 ± 5.153
Median (Minimum; Maximum)	100.0 (0; 100)	100.0 (61.9; 100)
Mean difference between treatment groups	-4.24; 97.5% CI: -7.48; I	
t-test	p = 0.0003	

Source: Section 14.2, Table 14.2.1.1.IA
Abbreviations: CI = confidence interval; I = infinite; IA = interim analysis; N = number of patients; NCI = Narcotrend® index; PP1 = Per Protocol Set 1; SD = standard deviation
Note: GA maintenance time was defined as the time from first skin incision to last skin suture (time of interest)

The mean difference between the treatment groups was -4.24 with a lower boundary of the 97.5% CI of -7.48. This lower boundary did not exceed the pre-defined threshold of -10. The corresponding p = 0.0003 did not exceed the threshold of 0.025. Hence, the results indicated an efficacy of remimazolam that was non-inferior to propofol in terms of the PEP. Exploratory sensitivity analyses showed that the pre-defined threshold of -10 for the lower boundary of the CI was met by analyses based on the PP1 and the FAS without imputations. The analysis based on the FAS and imputations based on linear regression yielded a mean difference between the treatment groups of -6.66 with a lower boundary of the 97.5% CI of -10.1 (see Table 10).

Table 10: Primary Efficacy Endpoint, Exploratory Sensitivity Analyses (IA)

Percentage of GA Maintenance Time with NCI ≤60 (%)	Remimazolam	Propofol	Mean Difference Lower bound of 97.5% CI	t-test p value
PP1, N	165	60		
a. Imputations worst case (all missing NCI values replaced with 61)				
Mean ± SD	85.02 ± 21.518	90.94 ± 10.346	-5.92 (-10.1; I)	0.0290
b. Without any imputations and skipping all time points with missing NCI values				
Mean ± SD	94.68 ± 19.401	98.86 ± 5.191	-4.18 (-7.44; I)	0.0003
FAS, N	191	63		
c. Imputation of NCI values by linear regression				
Mean ± SD	92.26 ± 22.239	98.92 ± 5.033	-6.66 (-10.1; I)	0.0273
d. Imputations worst case (all missing NCI values replaced with 61)				
Mean ± SD	81.90 ± 23.798	90.68 ± 10.292	-8.78 (-13.0; I)	0.2858
e. Without any imputations and skipping all time points with missing NCI values				
Mean ± SD	92.31 ± 22.395	98.91 ± 5.070	-6.61 (-10.0; I)	0.0263

Source: Section 14.2, Table 14.2.1.2.IA, Table 14.2.1.3.IA, Table 14.2.1.4.IA, Table 14.2.1.5.IA, Table 14.2.1.6.IA

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; IA = interim analysis; N = number of patients; NCI = Narcotrend® index; PP1 = Per Protocol Set 1; SD = standard deviation

Note: GA maintenance time was defined as the time from first skin incision to last skin suture (time of interest)

Key Secondary Endpoint

To account for missing MAP results during the TOI of the KSE, several methods of calculation were applied. The results for the KSE at the IA indicated a tendency for smaller numbers and lower variance of critical hypotensive events under remimazolam. According to the statistical planning, a difference between the treatment groups was not shown: The actual p-value of 0.1002 exceeded the pre-defined type 1 error at 0.0193. Therefore, recruitment of patients and randomized assignment to propofol or remimazolam was continued in line with the group sequential design (see Table 11).

Table 11: Key Secondary Endpoint, Confirmatory Analysis as Defined by the Protocol (IA, FAS)

Number of Critical Hypotensive Events Per Patient*	Remimazolam N = 191	Propofol N = 63
Mean ± SD	60.47 ± 37.926	70.71 ± 44.355
Median (Minimum; Maximum)	56.0 (0.0; 190.0)	64.0 (0.0; 230.0)
2-sided z-test	p = 0.1002	

Source: Section 14.2, Table 14.2.2.1.1.IA

Abbreviations: FAS = Full Analysis Set; IA = interim analysis; KSE = Key Secondary Endpoint; IMP = investigational medicinal product; N = number of patients; SD = standard deviation

* The time of interest for the KSE was defined as the time from start of IMP to 15 minutes after the first skin incision

The results for the KSE at the IA after transformation and based on the CFA are **as follows**:

Table 12: Key Secondary Endpoint, Confirmatory Analysis after Common Factor Analysis (IA, FAS)

Factored Critical Hypotensive Events*	Remimazolam N = 191	Propofol N = 63
Mean ± SD	-0.06 ± 0.580	0.17 ± 0.692
Median (Minimum; Maximum)	-0.09 (-0.88; 1.87)	0.10 (-0.87; 2.62)
Wilcoxon rank-sum test	p = 0.0247	

Source: Appendix 16.1.9, KSE Confirmatory Analyses, Table 14.2.2.1.1 (IAFAS)
Abbreviations: FAS = Full Analysis Set; IA = interim analysis; IMP = investigational medicinal product; KSE = key secondary endpoint; N = number of patients; SD = standard deviation
* The time of interest for the KSE was defined as the time from start of IMP to 15 minutes after the first skin incision

Final Analysis

Primary Efficacy Endpoint

Summary statistics on the TOI for the PEP (i.e. the duration of the maintenance phase of the GA defined as time from the first skin incision to the last skin suture) yielded no differences between the treatment groups (see Table 13).

Table 13: Duration of Time of Interest (TOI) for the Primary Efficacy Endpoint (FA)

	Remimazolam	Propofol
FAS, N	270	95
Time of Interest (first skin incision to last skin suture), minutes		
Mean ± SD	165.96 ± 90.642	153.75 ± 74.549
Median (Minimum; Maximum)	145.0 (23; 528)	141.0 (28; 361)
Mann-Whitney p-value	0.4918	
PP1, N	235	92
Time of Interest (first skin incision to last skin suture), minutes		
Mean ± SD	158.90 ± 87.690	151.48 ± 74.333
Median (Minimum; Maximum)	138.0 (23; 528)	132.0 (28; 361)
Mann-Whitney p-value	0.7509	

Source: Section 14.3, Table 14.3.11.4 and Table 14.3.11.5
Abbreviations: FA = final analysis; FAS = Full Analysis Set; PP1 = Per Protocol Set 1; N = number of patients; SD = standard deviation

At the FA, the mean percentage of time with NCI ≤60 was 95.48 ± 16.924 in the PP1 remimazolam group (n = 235) and 99.07 ± 4.231 in the PP1 propofol group (n = 92). A mean difference of -3.59 with a lower bound of the 97.5% CI of -5.93 resulted. Hence, the FA results supported the results from the IA. All FA results based on the primary analysis method (PP1, imputations by linear regression) and the sensitivity analyses methods.

Analyses of covariance did not indicate any impact on the results based on the ASA class or the type of surgery. Summary statistics on the amount of remifentanil used during the TOI for the PEP did not show a clinically relevant difference between the treatment groups.

Key Secondary Endpoint

The mean duration of the TOI (i.e. start of IMP until 15 min after skin incision) by treatment group was calculated prior to the analysis of the KSE (see Table 14).

Table 14: Duration of Time of Interest for the Key Secondary Endpoint (FA, FAS)

Time of Interest for the KSE (Start of IMP Until 15 Minutes after the First Skin Incision), Minutes	Remimazolam N = 270	Propofol N = 95
Mean ± SD	66.39 ± 19.160	67.18 ± 18.687
Median (Minimum; Maximum)	62.2 (35.0; 135.0)	62.2 (38.2; 124.0)
Mann-Whitney p-value	0.5649	

Source: Section 14.3, Table 14.3.11.1
Abbreviations: FA = final analysis; FAS = Full Analysis Set; IMP = investigational medicinal product; N = number of patients; SD = standard deviation; TOI = time of interest

There was no difference between the two treatment groups of the FAS in terms of the TOI for the KSE. Therefore, adjustment to duration of the TOI for the KSE as outlined in SAP was not required. The same applied to the PP2.

The FA of the KSE as described in the protocol yielded mean numbers of events of 61.92 ± 38.115 in the FAS remimazolam group and 71.03 ± 41.123 in the FAS propofol group. A 2-sided z test yielded a p-value of 0.0585.

The results for the KSE after the CFA are **shown below**:

Table 15: Key Secondary Endpoint, Confirmatory Analysis after Common Factor Analysis (FA, FAS)

Factored Critical Hypotensive Events*	Remimazolam N = 270	Propofol N = 95
Mean ± SD	-0.04 ± 0.529	0.13 ± 0.584
Median (Minimum; Maximum)	-0.08 (-0.87; 2.30)	0.02 (-0.87; 2.07)
Wilcoxon rank-sum test	p = 0.0151	

Source: Appendix 16.1.9, KSE Confirmatory Analyses, Table 14.2.3.1.1
Abbreviations: FA = final analysis; FAS = Full Analysis Set; IMP = investigational medicinal product; KSE = key secondary endpoint; N = number of patients; SD = standard deviation
* The time of interest for the KSE was defined as the time from start of IMP to 15 minutes after the first skin incision

The actual p-value = 0.0151 was below the pre-defined type 1 error at 0.0307 for the FA, so that the null hypothesis was rejected at the FA. Superiority of remimazolam over propofol regarding haemodynamic stability in terms of the KSE was proven.

Results of exploratory sensitivity analyses are presented **below.**

Table 16: Key Secondary Endpoint, Exploratory Sensitivity Analyses after Common Factor Analysis (FA)

Factored Critical Hypotensive Events	Remimazolam	Propofol	Wilcoxon rank-sum test p-value
FAS, N	270	95	
Without any imputations and skipping all time points with missing MAP values			
Mean ± SD	-0.04 ± 0.538	0.12 ± 0.585	0.0184
PP2, N	193	82	
Imputation of MAP values by linear regression			
Mean ± SD	-0.06 ± 0.446	0.13 ± 0.485	0.0037
Without any imputations and skipping all time points with missing MAP values			
Mean ± SD	-0.05 ± 0.465	0.13 ± 0.502	0.0050

Source: Appendix 16.1.9, KSE Confirmatory Analyses, Table 14.2.3.1.3 (FAS), Table 14.2.3.1.1 (PP2), Table 14.2.3.1.3 (PP2)
Abbreviations: FA = final analysis; FAS = Full Analysis Set; MAP = mean arterial pressure; N = number of patients; PP2 = Per Protocol Set 2; SD = standard deviation

Secondary efficacy endpoint

Results for the secondary efficacy endpoints referring to NCI, rescue sedative medication and other sedatives are provided in the Table 17:

Table 17: Results for the secondary efficacy endpoints referring to NCI, rescue sedative medication and other sedatives

	Remimazolam	Propofol	p-value
	Mean ± SD (n)	**Mean ± SD (n)**	
Percentage of time with NCI ≤60 and ≥27 during maintenance			
FAS	68.4 ± 31.16 (270)	78.0 ± 27.88 (95)	0.0082
PP1	70.1 ± 30.58 (235)	78.1 ± 28.22 (92)	0.0312
Percentage of time with NCI <27 during maintenance			
FAS	24.4 ± 29.28 (270)	21.1 ± 28.12 (95)	0.3331
PP1	25.3 ± 29.52 (235)	21.0 ± 28.46 (92)	0.2239
	n / N (%)	**n / N (%)**	
Patients with NCI ≤60 and ≥27 during ≥90% of maintenance			
FAS	94 / 270 (34.8)	54 / 95 (56.8)	0.0002
PP1	88 / 235 (37.5)	53 / 92 (57.6)	0.0010
Patients with rescue sedative medication during maintenance			
FAS	27 / 270 (10.0)	1 / 95 (1.1)	0.0009
PP1	11 / 235 (4.7)	1 / 92 (1.1)	0.0828
Patients with any other sedative medication during maintenance			
FAS	7 / 270 (2.6)	0	0.0388
PP1	5 / 235 (2.1)	0	0.0679

Abbreviations: FAS = Full Analysis Set; n = number of patients included in calculation; N = number of patients in treatment group; NCI = Narcotrend® index; PP1 = Per Protocol Set 1; SD = standard deviation

For the time-to-event endpoints, the **following** numbers resulted:

Table 18: Time-to-event endpoints

Time to event analyses (FAS)	Remimazolam Minutes Median (95%CI), n	Propofol Minutes Median (95%CI), n	Log-rank test p-value
Time from Start of IMP administration to			
Loss of consciousness, MOAA/S = 0	2.5 (2.5; 2.8), 268	3.0 (3.0; 3.2), 95	0.3523
Loss of palpebral reflex	2.8 (2.7; 3.0), 269	3.1 (3.0; 3.5), 95	0.1324
First NCI ≤60	3.2 (2.9; 3.5), 269	3.3 (3.1; 3.5), 95	0.0553
Time from Stop of IMP administration to			
End of extubation	12.0 (11; 13), 263	11.0 (10; 12), 95	0.0076
Response to verbal command, MOAA/S ≥4	15.0 (13; 17), 257	12.0 (10; 13), 95	<0.0001
Orientation to time, place, person and situation	54.0 (47; 61), 270	30.0 (27; 33), 95	<0.0001
Modified Aldrete Score ≥9	53.0 (44; 58), 260	37.0 (28; 45), 94	0.1205

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; MOAA/S = modified observer assessment of alertness / sedation; n = number of patients included in calculation; N = Number of patients in treatment group; NCI = Narcotrend® index; SD = standard deviation

NCI ≤60 and ≥27 During Maintenance

The percentage of time with NCI ≤60 and ≥27 during the maintenance (first skin incision to last skin suture) was higher in the propofol group than in the remimazolam group based on the FAS. This difference was smaller in the PP1.

For the time with NCI ≤60 and ≥27 During Maintenance (FAS) see Table 19.

Table 19: Time with NCI ≤60 and ≥27 During Maintenance (FAS)

Time with NCI ≤60 and ≥27 During Maintenance (%)	Remimazolam N = 270	Propofol N = 95
Mean ± SD	68.38 ± 31.159	78.00 ± 27.876
Median (Minimum; Maximum)	77.6 (0; 100)	92.2 (0; 100)
Difference in means (95% CI)	-9.63 (-16.7; -2.51)	
2-sided t test	p = 0.0082	

Source: Section 14.2, Table 14.2.3.1.1
Abbreviations: CI = confidence interval; FAS = Full Analysis Set; N = number of patients; NCI = Narcotrend® index; SD = standard deviation
Notes:
Maintenance was defined as the time from the first skin incision to the last skin suture.
Missing NCI values were imputed based on linear regression

For the Time with NCI ≤60 and ≥27 During Maintenance (PP1) see Table 20.

Table 20: Time with NCI ≤60 and ≥27 During Maintenance (PP1)

Time with NCI ≤60 and ≥27 during maintenance (%)	Remimazolam N = 235	Propofol N = 92
Mean ± SD	70.14 ± 30.584	78.11 ± 28.215
Median (Minimum; Maximum)	79.7 (0; 100)	92.2 (0; 100)
Difference in means (95% CI)	-7.97 (-15.2; -0.72)	
2-sided t test	p = 0.0312	

Source: Section 14.2, Table 14.2.3.1.2
Abbreviations: CI = confidence interval; N = number of patients; NCI = Narcotrend® index; PP1 = Per Protocol Set 1; SD = standard deviation
Notes:
Maintenance was defined as the time from the first skin incision to the last skin suture.
Missing NCI values were imputed based on linear regression

Percentage of Time with NCI <27 During Maintenance

The mean percentage of time of the GA with NCI <27 during maintenance (first skin incision to last skin suture) indicated no substantial differences between the treatment groups for the FAS and for the PP1.

Table 21: NCI <27 During Maintenance (FAS)

	Remimazolam N = 270	Propofol N = 95
Percentage of time with NCI <27 during maintenance		
Mean ± SD	24.44 ± 29.282	21.09 ± 28.120
Median (Minimum; Maximum)	11.8 (0; 100)	6.9 (0; 100)
Difference in means (95% CI)	3.35 (-3.45; 10.15)	
2-sided t test	p = 0.3331	

Source: Section 14.2, Table 14.2.3.2.1
Abbreviations: CI = confidence interval; FAS = Full Analysis Set; N = number of patients; NCI = Narcotrend® index; SD = standard deviation
Notes:
Maintenance was defined as the time from the first skin incision to the last skin suture.
Missing NCI values were imputed based on linear regression

Table 22: NCI <27 During Maintenance (PP1)

Time with NCI <27 during maintenance (%)	Remimazolam N = 235	Propofol N = 92
Mean ± SD	25.34 ± 29.524	20.96 ± 28.460
Median (Minimum; Maximum)	13.1 (0; 100)	6.8 (0; 100)
Difference in means (95% CI)	4.38 (-2.69; 11.45)	
2-sided t test	p = 0.2239	

Source: Section 14.2, Table 14.2.3.2.2
Abbreviations: CI = confidence interval; N = number of patients; NCI = Narcotrend® index; PP1 = Per Protocol Set 1; SD = standard deviation
Notes:
Maintenance was defined as the time from the first skin incision to the last skin suture.
Missing NCI values were imputed based on linear regression

NCI ≤60 and ≥27 During 90% of Maintenance

The percentage of patients with NCI ≤60 and ≥27 during 90% of maintenance (first skin incision to last skin suture) was higher in the propofol group than in the remimazolam group. The difference between the treatment groups was similar for the FAS and the PP1.

Rescue Sedative Medication

Including Use of Rescue Sedative Medication Not Per Protocol During PEP TOI The proportion of patients receiving rescue sedative medication between the first skin incision and last skin suture, i.e. TOI for the PEP, was higher in the remimazolam group than in the propofol group based on the FAS, i.e. including use of rescue sedative medication that did not follow the protocol definitions (see Tables below)

Table 23: Rescue Sedative Medication Between First Skin Incision and Last Skin Suture (FAS)

	Remimazolam N = 270 n (%)	Propofol N = 95 n (%)
Patients who received rescue sedative medication	27 (10.0)	1 (1.1)
Patients who did not receive rescue sedative medication	243 (90.0)	94 (99.0)
95% binomial CI (0.89; 0.94)	p = 0.0009	

Source: Section 14.2, Table 14.2.3.4.1.b
Abbreviations: CI= confidence interval; FAS = Full Analysis Set; N = number of patients; n = number of patients in category

Table 24: Rescue Sedative Medication Between First Skin Incision and Last Skin Suture (PP1)

	Remimazolam N = 235 n (%)	Propofol N = 92 n (%)
Patients who received rescue sedative medication	11 (4.7)	1 (1.1)
Patients who did not receive rescue sedative medication	224 (95.3)	91 (98.9)
95% binomial CI (0.93; 0.98)	p = 0.0828	

Source: Section 14.2, Table 14.2.3.4.2.b
Abbreviations: CI = confidence interval; N = number of patients; n = number of patients in category; PP1 = Per Protocol Set 1

Use of Rescue Sedative Medication During Other Time Intervals

Results were in line with the results for the time interval relevant for the PEP. Analyses of the use of rescue sedative medication between start of IMP and last skin suture yielded results that were similar to those for the TOI of the PEP and the KSE.

Other Sedative Medication

The proportion of patients receiving sedative medication that did not meet the definition of rescue sedative medication between the first skin incision and the last skin suture (TOI for the PEP), regardless of the reason, was higher in the remimazolam group than in the propofol group based on the FAS.

Any Other Sedative Medication Between First Skin Incision and Last Skin Suture, Regardless of Reason (FAS) is noted in the Table 25.

Table 25: Patients who received other sedative medications

	Remimazolam N = 270 n (%)	Propofol N = 95 n (%)
Patients who received any other sedative medication	7 (2.6)	0 (0.0)
Patients who did not receive and other sedative medication	263 (97.4)	95 (100.0)
95% binomial CI (0.96; 0.99)	p = 0.0388	

Source: Section 14.2, Table 14.2.3.5.1.b
Abbreviations: CI = confidence interval; FAS = Full Analysis Set; N = number of patients; n = number of patients in category

Intra-operative Awakening and Explicit Awareness

A series of signs were reported by the investigators as potential signs of intra-operative awakening for 50 (18.5%) patients in the remimazolam group and 7 (7.4%) patients in the propofol group.

Explicit awareness during the GA was detected for none of the patients in both treatment groups during a review of the answers provided to the Brice questionnaire by an expert who was blinded regarding treatment group assignment.

Onset of Effect

The time to loss of consciousness, time to loss of palpebral reflex and to first NCI ≤60 were measured from the start time of the IMP and were analysed using the Kaplan Meier method. Missing data for the time of loss of consciousness and/or time of loss of palpebral reflex in a small number of patients resulted in censoring at the first skin incision, as defined in the SAP.

Time to Loss of Consciousness

The median time from start of IMP to loss of consciousness was similar in both treatment groups of the FAS (see Table 26).

Table 26: Time from Start of IMP to Loss of Consciousness (FAS)

Time from start of IMP to loss of consciousness (minutes)	**Remimazolam N = 270**	**Propofol N = 95**
n	268	95
Median (95% CI)	2.5 (2.5; 2.8)	3.0 (3.0; 3.2)
1st quartile; 3rd quartile	2.0; 3.3	2.5; 3.7
2-sided Log Rank Test	p = 0.3523	

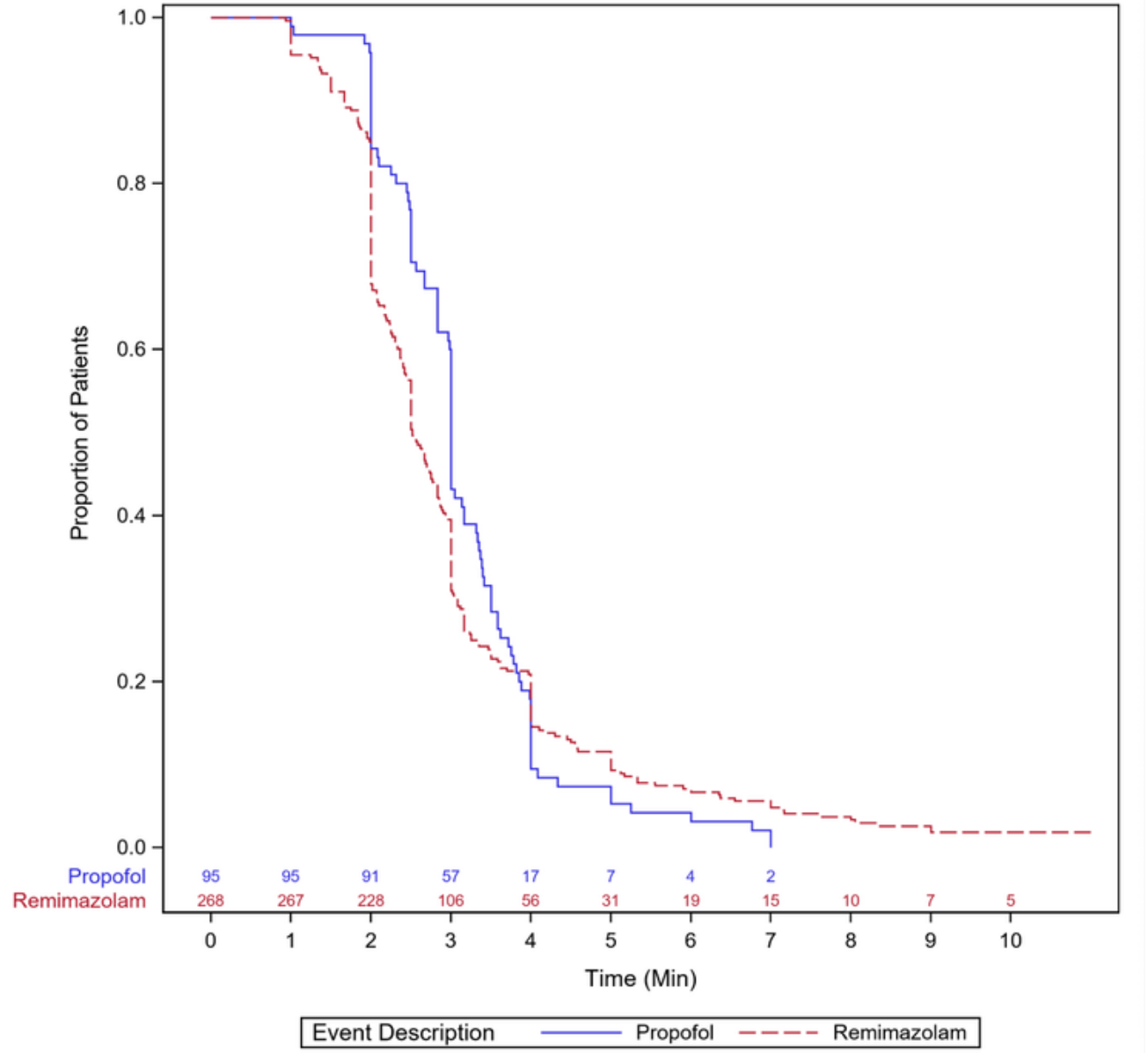
Source: Section 14.2, Table 14.2.3.9.1

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; N = number of patients in treatment group; n = number of patients in analysis; IMP = investigational medicinal product

One patient was excluded from this analysis as desflurane was started together with IMP by error.

One patient was excluded from this analysis as loss of consciousness was recorded as occurring earlier than start of IMP.

Figure 2: Time from Start of IMP to Loss of Consciousness (FAS)



Results based on the PP1 were similar to those based on the FAS.

Time to first NCI ≤60

The median time from start of IMP to first NCI ≤60 did not differ between the treatment groups (see Table 27).

Table 27:Time from Start of IMP to First NCI ≤60 (FAS)

Time from start of IMP to first NCI ≤60 (minutes)	Remimazolam N = 270	Propofol N = 95
n	269	95
Median (95% CI)	3.2 (2.9; 3.5)	3.3 (3.1; 3.5)
1st quartile; 3rd quartile	2.2; 4.9	2.8; 3.9
2-sided Log Rank Test	p = 0.0553	

Source: Section 14.2, Table 14.2.3.7.1

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; IMP = investigational medicinal product; N = number of patients; n = number of patients in analysis; NCI = Narcotrend® index

One patient was excluded from this analysis as desflurane was started together with IMP by error.

Offset of Effect

For the parameters representing the offset of the effect of the IMP, censoring rules were defined in the SAP. In addition to these rules, availability of data, the use of rescue sedative medication or other sedative medication and the use of flumazenil were taken into account.

Time to Extubation

The median time from stop of IMP to end of extubation differed by 1 minute between the remimazolam group and the propofol group, which translated into a p-value below 0.05 based on testing by a 2-sided log rank test. No clinical relevance was assigned (see Table 28).

Table 28: Time from Stop of IMP to End of Extubation (FAS)

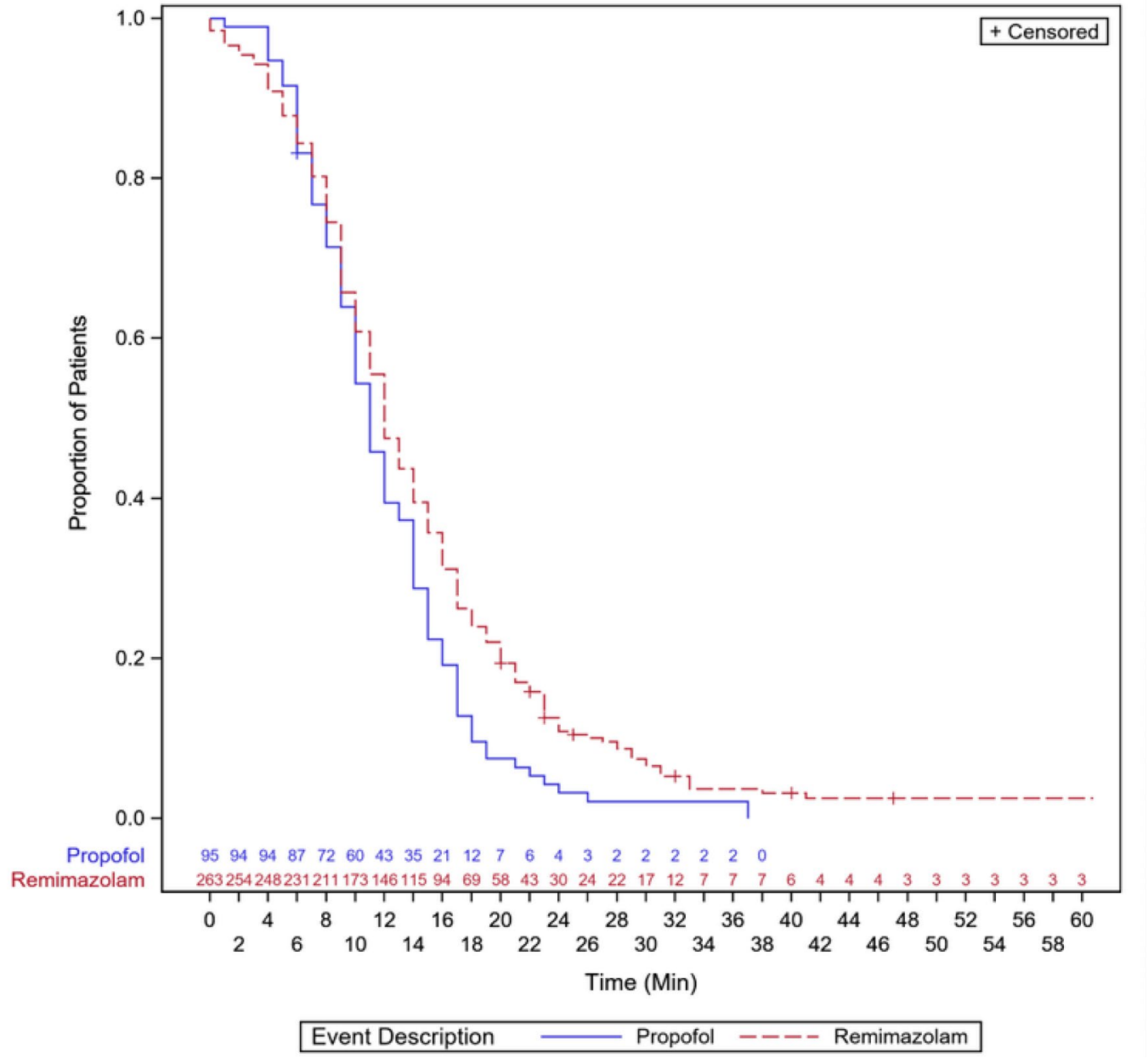
Time from stop of IMP to end of extubation (minutes)	Remimazolam N = 270	Propofol N = 95
N	263	95
Median (95% CI)	12.0 (11; 13)	11.0 (10; 12)
1st quartile, 3rd quartile	8; 18	8; 15
2-sided Log Rank Test	p = 0.0076	

Source: Section 14.2, Table 14.2.3.11.1

Abbreviations: CI = confidence interval, FAS = Full Analysis Set; IMP = investigational medicinal product; N = number of patients in treatment group; n = number of patients in analysis

Patients were excluded from this analysis if rescue sedative medication or any sedative/hypnotic drug other than IMP was in effect at time of stop of IMP.

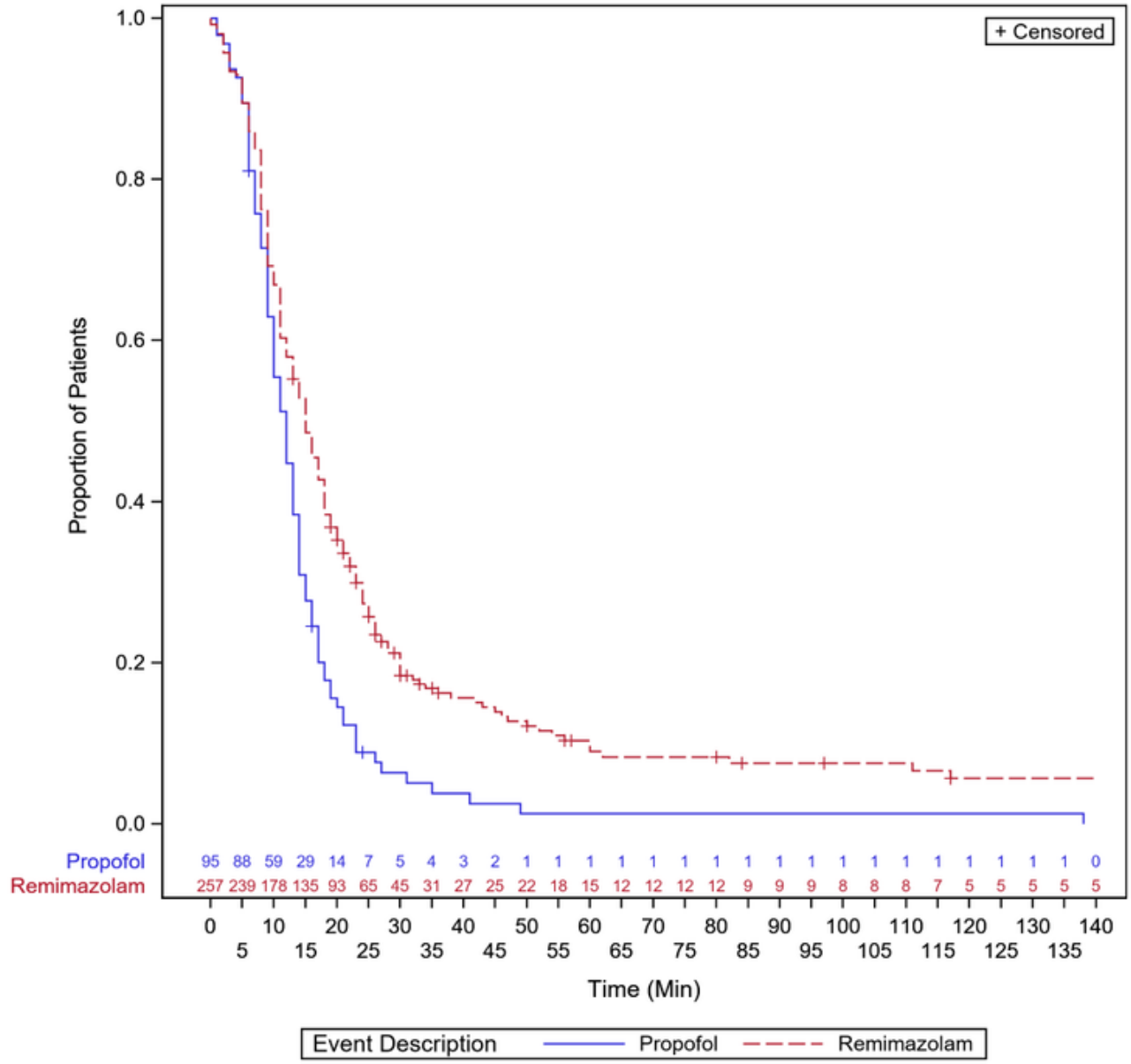
Figure 3: Time from Stop of IMP to Extubation (FAS)



Time to Response to Verbal Command

The median time from stop of IMP to response to verbal command differed by 3 minutes between the remimazolam group and the propofol group, which translated into a p-value below 0.05 based on testing by a 2-sided log rank test. No clinical relevance was assigned (see below).

Figure 4: Time from Stop of IMP to Response to Verbal Command (FAS)



Time to Orientation

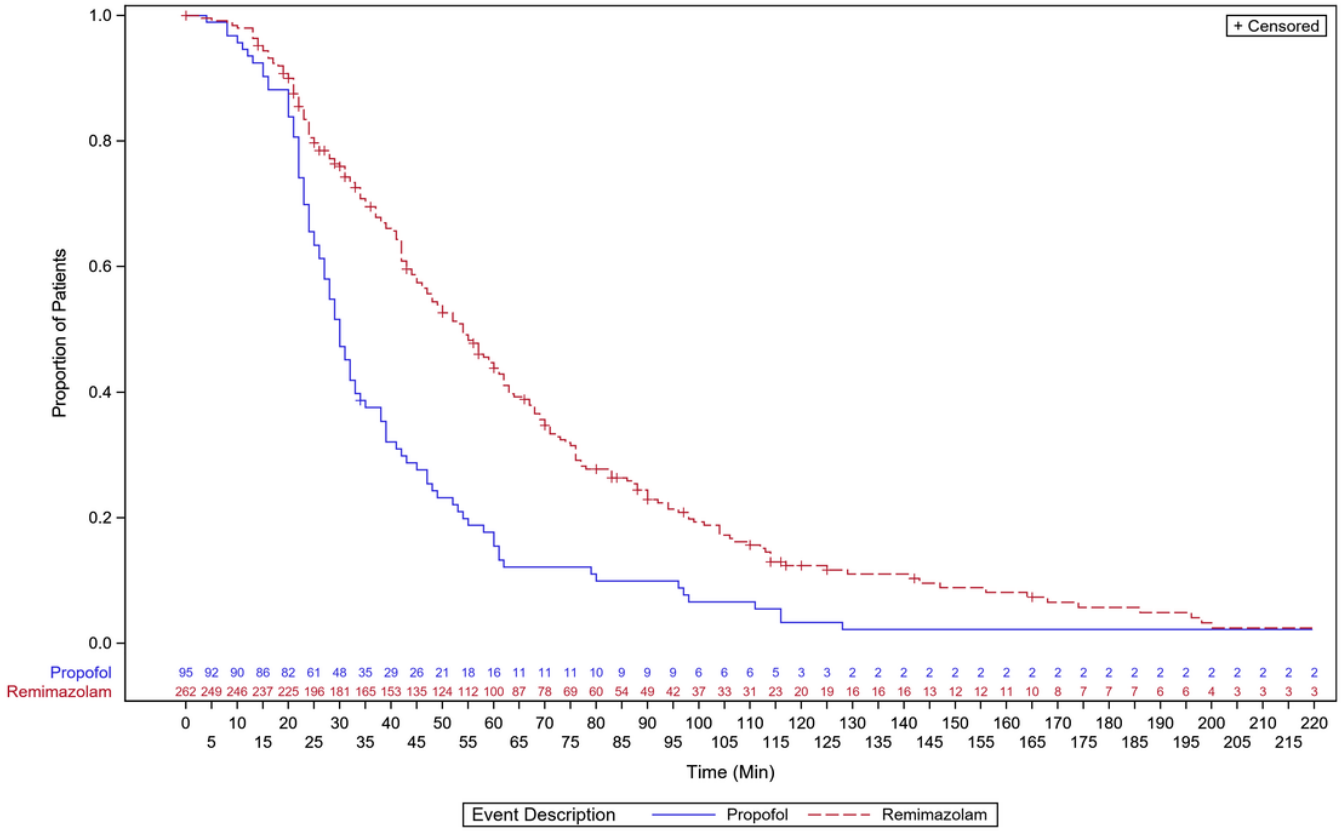
The median time from stop of IMP to orientation to time, place, person and situation was longer in the remimazolam group (see Table 29).

Table 29: Time from Stop of IMP to Orientation (FAS)

Time from stop of IMP to orientation (minutes)	Remimazolam N = 270	Propofol N = 95
n	262	95
Median (95% CI)	54.0 (47; 61)	30.0 (27; 33)
1st quartile; 3rd quartile	31; 88	22; 48
2-sided Log Rank Test	p <0.0001	

Source: Section 14.2, Table 14.2.3.12.1
Abbreviations: CI = confidence interval; FAS = Full Analysis Set; IMP = investigational medicinal product; N = number of patients in treatment group; n = number of patients in analysis
Patients were excluded from this analysis if rescue sedative medication or any sedative/hypnotic drug other than IMP was in effect at time of stop of IMP.

Figure 5: Time from Stop of IMP to Orientation (FAS)



Time to Modified Aldrete Score ≥9

The time from stop of IMP to a modified Aldrete Score of ≥9 did not differ between the treatment groups (see below).

Table 30

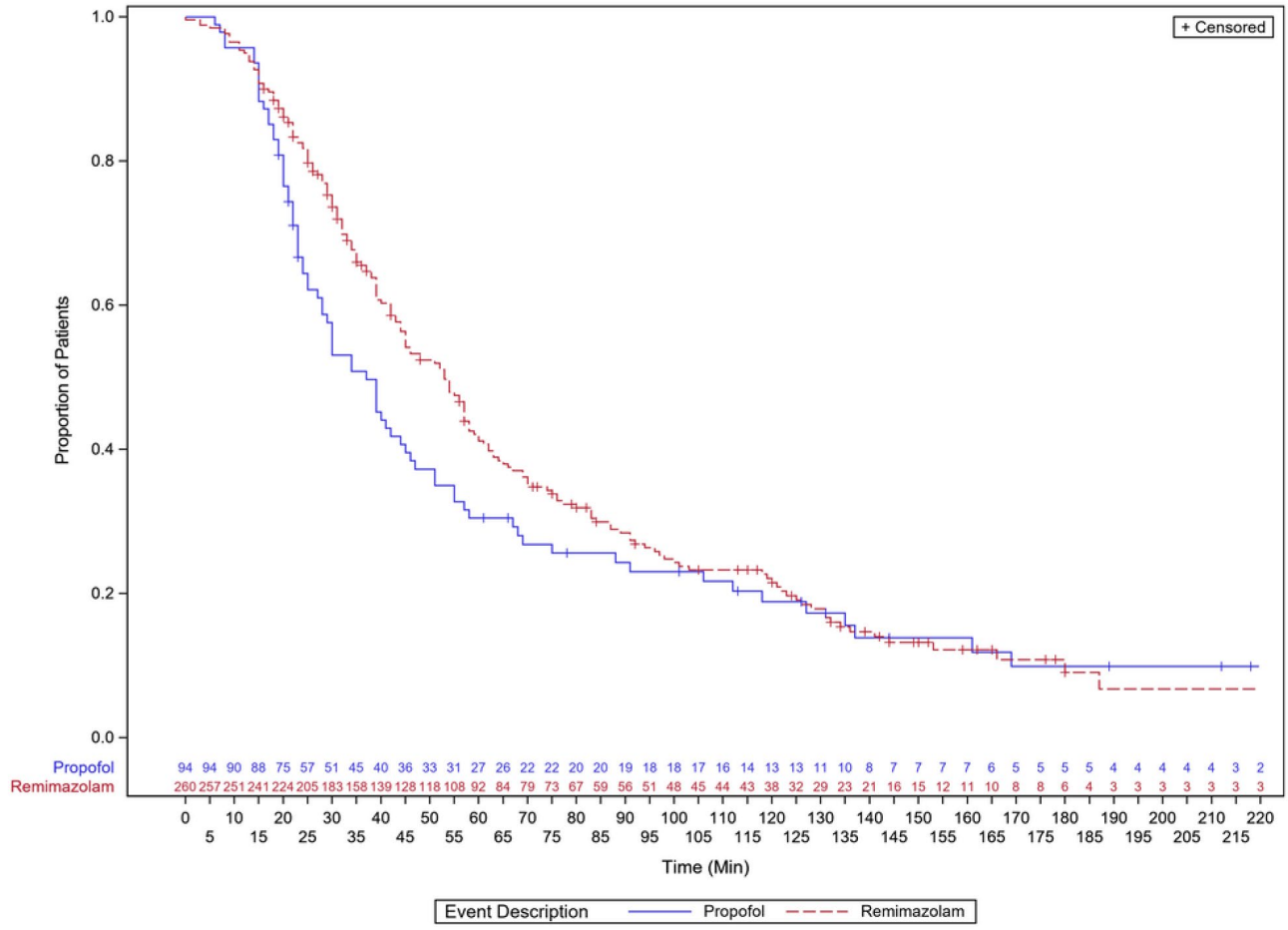
Time from stop of IMP to Modified Aldrete Score ≥9 (minutes)	Remimazolam N = 270	Propofol N = 95
n	260	94
Median (95% C)	53.0 (44.0 – 58.0)	37.0 (28.0 – 45.0)
1st quartile; 3rd quartile	30, 98	21, 88
2-sided Log Rank Test	p = 0.1205	

Source: Section 14.2, Table 14.2.3.13.1

Abbreviations: CI = confidence interval; FAS = Full Analysis Set; IMP = investigational medicinal product; N = number of patients in treatment group; n = number of patients of analysis

Patients were excluded from this analysis if rescue sedative medication or any sedative/hypnotic drug other than IMP was in effect at the time of stop of IMP.

Figure 6



Satisfaction with IMP

Overall satisfaction with the IMP was to be assessed on a scale between 1 and 10 where 1 equalled ''very dissatisfied with IMP' and 10 equalled 'very satisfied with IMP'. The proportion of assessments from 8 to 10 inclusively was similar in both treatment groups.

All Haemodynamic Events During General Anaesthesia

Between the start of the study drug and the last skin suture, event type 1 (i.e. a drop of MAP below 65 mmHg) was of similar frequency in both groups. Event type 4 (use of norepinephrine) was less frequent in the remimazolam group than in the propofol group during the time from start of the study drug to the last skin suture. These results were in line with general expectations as investigators

counteracted or mitigated the risk for event type 1 whenever possible by using norepinephrine or other vasopressors or by other therapeutic measures. More numbers are provided in the Table 31.

Table 31: Event Types 1 and 4 from Start of Study Drug to Last Skin Suture

Parameter	**Remimazolam** **N = 270**	**Propofol** **N = 95**	**p-value**
Event Type 1 All events of MAP < 65 mm			
Mean ± Standard Deviation Median (Minimum; Maximum)	12.27 ± 16.479 8 (0, 161)	14.44 ± 22.278 8 (0; 201)	0.0889[a]
Patients with zero events, n (%)	35 (13.0)	5 (5.3)	0.0388[b]
Event Type 4 All norepinephrine events			
Mean ± Standard Deviation Median (Minimum; Maximum)	51.45 ± 51.099 43.5 (0; 218)	71.18 ± 51.615 62 (0; 189)	0.0002[a]
Patients with 0 norepinephrine events, n (%)	36 (13.3%)	5 (5.3%)	0.0322[b]

a Mann Whitney-Wilcoxon test

b Chi square test

Ancillary results

Further analyses were conducted by the MAH to address the CHMP concern about haemodynamic stability.

Summary of the main efficacy results

The following table summarise the efficacy results from study CNS7056-022.

Table 32: Summary of efficacy for trial CNS7056-022

Title: Phase III confirmatory efficacy and safety trial of remimazolam (CNS7056) compared with propofol for intravenous anaesthesia during elective surgery		
Study identifier	Protocol Number: **CNS7056-022** EudraCT Number **2018-000174-29**	
Design	A parallel propofol partly blinded (patient, stats) multicentre controlled trial to investigate the use of remimazolam vs. propofol as an intravenous anaesthetic to provide GA for the purpose of elective surgery in patients with ASA classes III to IV. The first two patients in each centre were allocated to 1st propofol and 2nd remimazolam. All other were randomly allocated.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Use for GA induction / maintenance. The maximum trial duration for any patient was up to 30 days. not applicable not applicable

Title: Phase III confirmatory efficacy and safety trial of remimazolam (CNS7056) compared with propofol for intravenous anaesthesia during elective surgery			
Study identifier	Protocol Number: **CNS7056-022** EudraCT Number **2018-000174-29**		
Hypothesis	Non-inferiority		
Treatments groups	Remimazolam (RMZ)		The dosing scheme for induction with remimazolam was: • From t* = 00:00 to 03:00 6.0 mg remimazolam/min • From t = 03:00 to 10:00 2.5 mg remimazolam/min • From t = 10:00 to 20:00 1.5 mg remimazolam/min • From t = 20:00 on 1.0 mg remimazolam/min *: where t = time in minutes: seconds; t = 00:00 was the start of the administration of IMP number randomized: 165
	Propofol PPF		The dosing scheme for induction with propofol was: • From t* = 00:00 to 03:00 30 mg propofol/kg/h • From t = 03:00 to 10:00 10 mg propofol/kg/h • From t = 10:00 to 20:00 8 mg propofol/kg/h • From t = 20:00 on 6 mg propofol/kg/h *: where t = time in minutes:seconds; t = 00:00 was the start of the administration of IMP number randomized: 60
Endpoints and definitions	**Primary endpoint**	Percentage of time with Narcotrend Index ≤60 during the maintenance phase (%NCI≤60)	Percentage of time with Narcotrend Index below 60 during the maintenance phase The main analysis of the PEP (non-inferiority) was conducted on the Per Protocol 1 Set (PP1) at the Interim Analysis using Narcotrend data after imputations of missing NCI values for time periods of up to 300 seconds with linear regression using one value before and after missing values. Missing NCI values for time periods of over 300 seconds were not imputed.
	Secondary endpoint	Percentage of time with NCI ≤60 and ≥27 during maintenance (%NCI 27-60)	Percentage of time with NCI between ≤60 and ≥27 during maintenance phase The main analysis was conducted on the FAS population using MAP results from invasive blood pressure monitoring by FloTrac® after imputation of missing MAP results for time periods up to 180 seconds with linear regression using one value before and after missing values. Missing MAP results for time periods of over 180 seconds were not imputed.
	Secondary endpoint	Percentage of time with NCI <27 during maintenance (%NCI <27)	Percentage of time with NCI below 27 during maintenance phase The main analysis was conducted on the FAS population using MAP results from invasive blood pressure monitoring by FloTrac® after imputation of missing MAP results for time periods up to 180 seconds with linear regression using one value before and after missing values. Missing MAP results for time periods of over 180 seconds were not imputed.

Title: Phase III confirmatory efficacy and safety trial of remimazolam (CNS7056) compared with propofol for intravenous anaesthesia during elective surgery			
Study identifier	Protocol Number: **CNS7056-022** EudraCT Number **2018-000174-29**		
	Secondary endpoint	Patients with rescue sedative medication during maintenance (Rescue sedation)	Number of patients who had to be given rescue medication during maintenance phase to keep the level of anaesthesia
	Secondary endpoint	Patients with any other sedative medication during maintenance (Other sedation)	Number of patients who had sedative medication other than rescue during maintenance phase
	Secondary endpoint	Time to orientation (Time to Orientation)	The time between end of administration of the IMP and orientation to time, place, person and situation
Database lock	05 October 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Per protocol at time of Interim analysis PP1 consisted of all patients in the FAS who had no major protocol deviations preventing the accurate and sufficient evaluation of the PEP.		
Descriptive statistics and estimate variability	**Treatment group**	**RMZ**	**PPF**
	Number of subject PP1	165	60
	(%NCI≤60) Mean	94.6	98.9
	SD	19.34	5.15
	(%NCI 27-60) Mean	68.4	78.0
	SD	31.16	27.88
	(%NCI <27) Mean	24.4	21.1
	SD	29.28	28.12
	Number of subject FAS	270	95
	(Rescue sedation) %	10	1.1
	(Other sedation) %	2.6	0
	(Time to Orientation) Minutes (95%CI)	54.0 (47; 61)	30.0 (27; 33)
Effect estimate per comparison	**Primary endpoint (%NCI≤60)**	**Comparison groups**	RMZ - PPF
		Difference in means	-4.24
		(97.5% CI)	(-7.48, I)

Title: Phase III confirmatory efficacy and safety trial of remimazolam (CNS7056) compared with propofol for intravenous anaesthesia during elective surgery			
Study identifier	Protocol Number: **CNS7056-022** EudraCT Number **2018-000174-29**		
		P-value one-sided two sample t-test	0.0003
	Secondary endpoint (%NCI 27-60)	**Comparison groups**	RMZ - PPF
		Difference in means	-9.63
		(95% CI)	(-16.7; -2.51)
		2-sided t test	p = 0.0082
	Secondary endpoint (%NCI <27)	**Comparison groups**	RMZ - PPF
		Difference in means	3.35
		(95% CI)	(-16.7; -2.51)
		2-sided t test	p = 0.3331
	Secondary endpoint (Rescue sedation)	**Comparison groups**	RMZ - PPF
		Difference in groups	8.9
		95% binomial CI	(0.89; 0.94)
		P-value	p = 0.0009
	Secondary endpoint (Other sedation)	**Comparison groups**	RMZ - PPF
		Difference in groups	2.6
		95% binomial CI	(0.96; 0.99)
		P-value	p = 0.0388
	Secondary endpoint (Time to Orientation)	**Comparison groups**	RMZ - PPF
		Median difference	24
		(95% CI)	
		2-sided Log Rank Test	p <0.0001

ONO-2745-05

A Phase IIb/III study comparing remimazolam with propofol in patients undergoing surgery with GA Trial Design

Methods

ONO-2745-05 was a randomized, parallel-group, confirmatory non-inferiority study of remimazolam compared with propofol in surgical patients, ASA class I or II undergoing GA. Patients were allocated to one of three treatment groups; two remimazolam groups or one propofol control group. The remimazolam groups differed in terms of the dose to be administered for induction (6 mg/kg/h or 12 mg/kg/h). Subjects were blinded (single-blind) to treatment allocation and investigators were blinded (double-blind) to the dose of remimazolam for induction.

Study Participants

A total of 325 surgical patients undergoing GA were planned to be enrolled, 260 in the remimazolam groups (130 per group) and 65 patients in the propofol group.

Inclusion criteria

- Age (at the time of consent): 20 years or older;
- Sex: Male or female;
- Body weight: 100 kg or less;
- Patients scheduled to receive artificial respiratory management with (oral or nasal) endotracheal intubation;

- Patients scheduled to be hospitalized for at least three days from the day prior to the surgery to the day after the surgery;
- American Society of Anaesthesiologists (ASA) physical status Class I or II;
- Women of childbearing potential had to have negative pregnancy testing (serum or urine) results from the date of consent until the first administration of the investigational product and had to agree to use contraception during the study period (from the time of consent through the completion of all protocol-specified observations);

Exclusion criteria

- Patients scheduled to receive local anesthesia (spinal subarachnoid anesthesia, epidural anesthesia, or peripheral nerve block) between entry into the operating room on Day 1 of investigational product administration and the end of endotracheal intubation (with the exception of a test dose administered [≤3 mL] at the insertion of an epidural catheter);
- Patients scheduled to undergo hepatectomy or liver transplant during the surgery;
- Patients scheduled to use a heart-lung machine during the surgery (e.g., cardiotomy);
- Patients who had uncontrolled hypertension (e.g., systolic blood pressure ≥160 mmHg on antihypertensive medication);
- Patients who had total bilirubin ≥3.0 mg/dL, or aspartate aminotransferase (AST)/glutamicoxaloacetic transaminase (GOT) ≥2.5 times the upper limit of normal for the institution (ULN) (or ≥100 IU/L), or alanine aminotransferase (ALT)/glutamic-pyruvate transaminase (GPT) ≥2.5 times the ULN (or ≥100 IU/L) based on general laboratory tests between 7 days prior to the start of the investigational product administration and entry into the operating room;
- Patients who had serum creatinine ≥2.0 mg/dL based on general laboratory tests between 7 days prior to the start of the investigational product administration and entry into the operating room;
- Patients who were undergoing emergency surgery;
- Patients who had planned surgeries with durations <1 hour;
- Patients who were anticipated to require prolonged endotracheal intubation for respiratory management after the surgery, thereby precluding prompt extubation;
- Patients who had developed tolerance to benzodiazepines;
- Patients who had a history of hypersensitivity to benzodiazepines, propofol, remifentanil hydrochloride, fentanyl citrate, rocuronium bromide, sugammadex sodium, flumazenil, or other anesthetics;
- Patients who had acute narrow-angle glaucoma;
- Patients who had myasthenia gravis or myasthenic syndrome;
- Patients who were in shock or were in a coma;
- Patients who had acute alcohol poisoning;
- Patients who had epilepsy and were on long-term benzodiazepine therapy;
- Patients who had an implanted rate-responsive cardiac pacemaker with a bioelectrical impedance sensor;

- Patients who had organic brain abnormalities or other disorders that would preclude appropriate measurement of the Bispectral Index (BIS) value;
- Patients who had received benzodiazepines, for whom the period between the end of administration of benzodiazepines and the start of administration of investigational product was less than 5 times the half-life of benzodiazepines (or half-life of active metabolite if any);
- Patients who anticipated having massive haemorrhage (e.g., ≥15% of circulating blood) during the surgery;
- Patients who had a history of serious allergies;
- Patients who had a concurrent or past history of dependence on drugs or alcohol;
- Breastfeeding women;
- Patients who received any unapproved drugs (e.g., investigational drugs, unapproved combined formulations of drugs, unapproved dosage forms) within the past 120 days at the start of investigational product administration. This did not include approved drugs used as comparators or basal medication in a clinical study;
- Patients who were assessed as incapable of providing consent for certain reasons such as concurrent dementia;
- Patients who previously received drugs containing the same active ingredient as ONO-2745 (remimazolam);
- Other patients assessed by the investigator or sub-investigator as ineligible for entry into this study;

Treatments

Table 33: Doses used in the ONO-2745-05

Group	Trial medication	Induction dose	Maintenance dose
Group 1	Propofol	2.0–2.5 mg/kg	4–10 mg/kg/h
Group 2	Remimazolam	6 mg/kg/h	1 mg/kg/h (up to 2 mg/kg/h)
Group 3	Remimazolam	12 mg/kg/h	1 mg/kg/h (up to 2 mg/kg/h)

For induction of anaesthesia patients randomized to remimazolam received 6 or 12 mg/kg/h by continuous IV infusion until loss of consciousness. After loss of consciousness, the dose was reduced to 1 mg/kg/h. During maintenance, the infusion rate was adjusted as appropriate (maximum allowed dose, 2 mg/kg/h) based on monitoring of the general condition and BIS values of individual subjects until the end of the surgery.

In the propofol group, the drug was administered as a slow bolus at a dose of 0.2-0.25 mL/kg (2.0–2.5 mg/kg of propofol) for induction of anaesthesia. After loss of consciousness, continuous IV infusion at a dose of 0.4–1 mL/kg/h (4–10 mg/kg/h of propofol) was started, after which the infusion rate was adjusted as appropriate based on monitoring of the general condition and BIS values of individual subjects until the end of the surgery.

Propofol was used as per local SmPC.

Design

This was a multicentre (49 sites, all in Japan), randomized, parallel-group comparison study with three treatment groups (two ONO-2745 groups and one propofol control group, in surgical patients undergoing GA). Enrolment was centralized. The allocation to either ONO-2745 or propofol was not rater-blinded, but subjects were blinded (single-blind), while the allocation to either of the two ONO-2745 groups (i.e., the 6 mg/kg/h group and the 12 mg/kg/h group) for induction of anesthesia was double-blinded.

Duration: 1 day for the treatment period and 1 day for the follow-up period

Dose

- ONO-2745 groups (i.e. RMZ)

  Remimazolam was administered at a dose of 6 or 12 mg/kg/h by continuous intravenous infusion until loss of consciousness. After loss of consciousness, continuous intravenous infusion of the investigational product at a dose of 1 mg/kg/h was started, after which the infusion rate was adjusted as appropriate (maximum allowed dose, 2 mg/kg/h) based on monitoring of the general condition of individual subjects until the end of the surgery.

  - Propofol group

  Propofol was administered as a slow bolus at a dose of 0.2–0.25 mL/kg (2.0–2.5 mg/kg of propofol). After loss of consciousness, continuous intravenous infusion of the investigational product at a typical dose of 0.4–1 mL/kg/h (4–10 mg/kg/h of propofol) was started, after which the infusion rate was adjusted as appropriate based on monitoring of the general condition of individual subjects until the end of the surgery.

Objectives

To evaluate the efficacy and safety of remimazolam in induction and maintenance of GA in surgical patients undergoing general anesthesia compared to propofol.

To verify the non-inferiority of remimazolam to propofol in terms of "functional capability as a general anaesthetic" on the basis of a composite of three primary efficacy variables, which comprise "intraoperative awakening or recall," "requirement of rescue sedation with other sedatives" and "body movement."

Outcomes/endpoints

Primary endpoint

The primary endpoint was the "functional capability as a general anesthetic," as assessed on the basis of a composite of three variables specified below. In individual subjects, the investigational product was assessed as "effective" if all three variables were absent or "ineffective" if at least one of these three variables was present.

- Intraoperative awakening or recall;
- Requirement of rescue sedation with other sedatives;
- Body movement;

To assess non-inferiority, the lower limit of the confidence interval for the difference (1) between the remimazolam 12 mg/kg/h group and the propofol group, and (2) between the remimazolam 6 mg/kg/h group and the propofol group, was assessed against the pre- defined lower margin of −10%. Non-

inferiority was to be determined if the lower limit of the confidence interval for the difference was greater than −10%.

The primary endpoint was clinically based, and therefore different from the other pivotal study.

Secondary endpoints

1) Time to loss of consciousness from the start of investigational product administration

2) Intraoperative awakening or recall

3) Requirement of rescue sedation with other sedatives

4) Body movement

5) BIS value at each time point of evaluation

6) Time to awakening from the end of investigational product administration

7) Time to extubation from the end of investigational product administration

8) Time to stating date of birth from the end of investigational product administration

9) Time to decision to exit the operating room from the end of investigational product administration

10) Controllability of anaesthetic depth

Safety

- Adverse events
- Adverse reactions
- General laboratory tests (i.e., haematology, biochemistry, urinalysis)
- Vital signs (i.e., blood pressure and heart rate [supine], respiratory rate, body temperature [deep body temperature], percutaneous arterial oxygen saturation [SpO2])
- Electrocardiograms (resting 12-lead ECGs, monitored ECGs)
- Proportion of time points where systolic blood pressure was maintained within a range of ≥80 and <150 mmHg among all time points of evaluation
- Number of times vasopressor drugs were used
- Observation of the investigational product administration site
- Agitation

Pharmacokinetics: plasma concentrations of remimazolam and its metabolite ONO-IN-252

Sample size

- 325 subjects in total (260 subjects in RMZ groups [130 per group], 65 subjects in the propofol group);
- Numbers of subjects aged 65 years or older were to be ≥40 for each of the RMZ groups and ≥20 for the propofol group.

Rationale for the sample size

Assuming an efficacy rate of 96% for each of RMZ groups and the propofol group, with a non-inferiority margin of 10%, a one-sided significance level of 2.5%, and 90% power, the sample size was calculated to observe a greater than -10% lower limit for the 95% confidence interval of the intergroup difference between each of the two RMZ groups (i.e., the 6 mg/kg/h group and the 12 mg/kg/h group) and the propofol group. Confidence intervals were to be calculated using the Wilson method.

On the basis of the above, and randomization of subjects to each of the RMZ groups or the propofol group being at a ratio of 2:1, the required sample size was calculated to be 118 subjects for each of the RMZ groups and 59 subjects for the propofol group. To allow for approximately 10% discontinuations or dropouts, the sample size was set to 130 subjects for each of the RMZ groups and 65 subjects for the propofol group. In addition, to evaluate the efficacy and safety of RMZ in a patient population that includes elderly subjects, given that elderly individuals are generally more likely to suffer sedative effects and adverse reactions such as decreased blood pressure and respiratory depression compared with non-elderly individuals in this study, the numbers of subjects aged ≥65 years had to be at least 36 for each of the RMZ groups and ≥18 for the propofol group. To allow for approximately 10% discontinuations or dropouts, the numbers of subjects aged ≥65 years to be enrolled in the study were set to ≥40 for each of the RMZ group and ≥20 for the propofol group.

Randomisation and blinding (masking)

The investigator or sub-investigator confirmed the eligibility of each subject who provided consent.

The investigator, sub-investigator or clinical research coordinator then contacted the Patient Registration Center and requested enrolment of the subject.

The Patient Registration Center randomized eligible subjects to one of the RMZ groups (6 or 12 mg/kg/h group) or the propofol group using a dynamic allocation method. The Center then notified the investigator or sub-investigator, the sponsor, and the unblinded monitor appointed by the sponsor of the randomization results, i.e., either the drug number, for subjects allocated to RMZ groups (e.g., "ONO-2745, No. X"), or the allocation of the subject to the propofol group.

Subjects meeting all inclusion criteria, and not meeting any exclusion criteria, were randomized by dynamic allocation using a minimization method and utilizing the following adjustment factors:

1. Age (20 to <65 years vs. ≥65 years);
2. ASA Class (I vs. II);
3. Any planned use of local anesthesia during the surgery (spinal subarachnoid anesthesia, epidural anesthesia or peripheral nerve block) (Yes vs. No);
4. Study site.

Blinding (masking)

The participants in this study were blinded, while the anaesthesiologists in charge of general anaesthesia were not blinded.

Statistical methods

Analysis sets

The primary analysis set for efficacy evaluations was the Full Analysis Set (FAS). The Per Protocol Set (PPS) was used as the secondary analysis set.

The analysis set for safety evaluations was the Safety Set (SAF). However, safety information was reported for all subjects treated with the investigational product.

Analysis of efficacy

Primary endpoint

The rate of efficacy in terms of the primary endpoint was calculated for each treatment group. For each of the RMZ groups, the two-sided 95% confidence interval for the difference from the propofol group was calculated. To assess non-inferiority, the lower limit of the confidence interval for the difference (1) between the RMZ 12 mg/kg/h group and the propofol group, and (2) between the RMZ 6 mg/kg/h group and the propofol group, was assessed against the predefined lower margin of −10%. Non-inferiority was to be determined if the lower limit of the confidence interval for the difference was greater than −10%. If the first comparison of "(1)" failed to demonstrate non-inferiority, the second comparison of "(2)" was not to be performed.

Secondary endpoints

1) For each of the efficacy endpoints; 2) to 4), the rate of efficacy in each treatment group was calculated.

In addition, for differences between each of the RMZ groups and the propofol group and differences between the 12 mg/kg/h group and the 6 mg/kg/h group, two-sided 95%confidence intervals were calculated and compared using a chi-square test.

2) For the efficacy endpoints 1), 6), 7), 8), and 9), summary statistics for each treatment group were calculated. In addition, for differences between each of the RMZ groups and the propofol group and differences between the 12 mg/kg/h group and the 6 mg/kg/h group, two-sided 95% confidence intervals were calculated and compared using a t-test.

3) For efficacy endpoint 5), summary statistics for each treatment group were calculated at each time point of evaluation.

4) For efficacy endpoint 10), frequency distribution for each treatment group was calculated.

Results

Participants flow

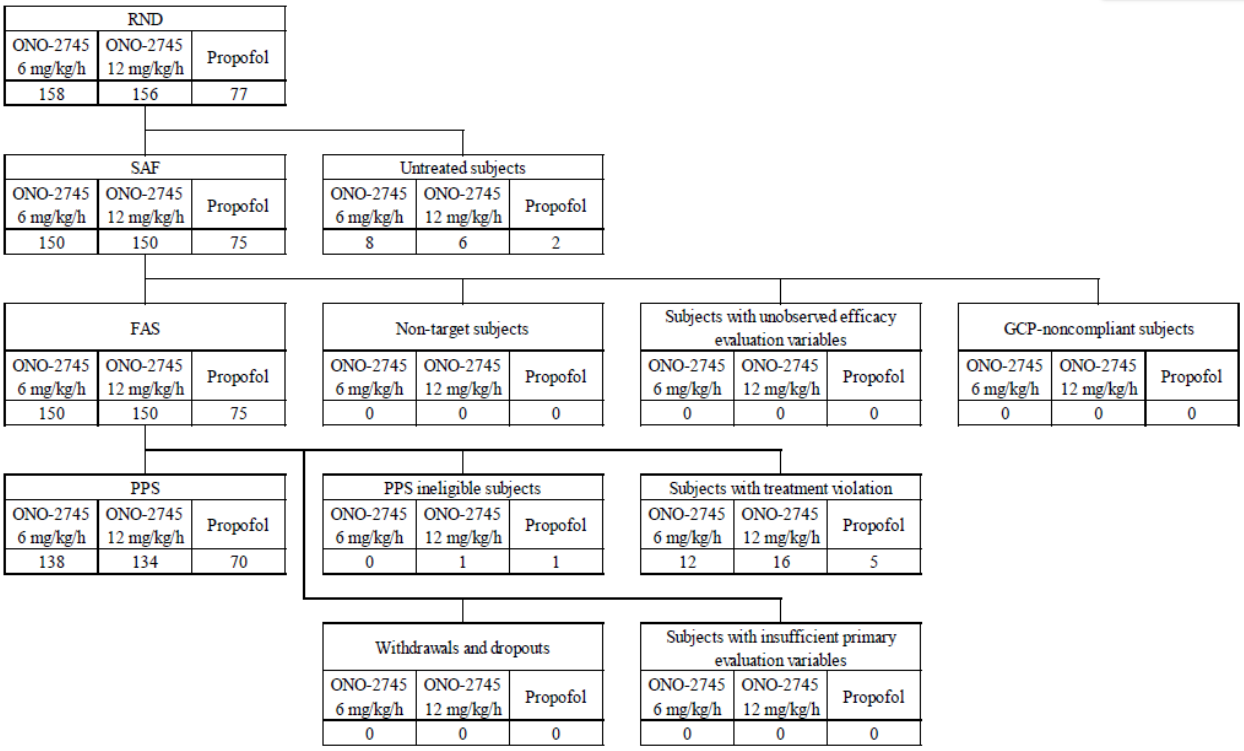
A total of 391 patients were enrolled. 375 patients were included as part of Full Analysis Set (FAS) which was the primary analysis set used for efficacy endpoints.

The number (%) of subjects for whom the investigational product was assessed as "effective" in the remimazolam 6 mg/kg/h group (n=150), remimazolam 12 mg/kg/h group (n=150) and propofol group (n=75) was 150 subjects (100%), 150 subjects (100%) and 75 subjects (100%), respectively.

Table 34: Patients who met the primary endpoint in ONO-2745-05

Treatment Group	Remimazolam		Propofol
	6mg/kg/h	12mg/kg/h	
Number of patients (FAS)	150	150	75
Number of patients meeting the primary endpoint (%)	150 (100.0)	150 (100.0)	75 (100.0)

Figure 7: Participant flow (source: translation of Study ONO-2745-05 CSR)



For the reason for exclusion from each analysis set, subjects may have more than one reason for exclusion.

Figure 8: Reasons for discontinuations or dropping out from the study

Analysis set: RND

Treatment Group			ONO-2745				Propofol	
			6		12			
Subject Classification			No.of Discontinuations	Percentage of Discontinuations and Dropouts (%)	No.of Discontinuations	Percentage of Discontinuations and Dropouts (%)	No.of Discontinuations	Percentage of Discontinuations and Dropouts (%)
Number of Subjects			158		156		77	
Reason for discontinuing or dropping out	Discontinuations and dropouts		8	(5.1)	6	(3.8)	2	(2.6)
	The subject or person acting as guardian requested that the study be discontinued.	Because of adverse events	0	(0.0)	0	(0.0)	0	(0.0)
		Requested study discontinuation for another reason	5	(3.2)	4	(2.6)	2	(2.6)
	The subject was found not to meet the inclusion criteria.		0	(0.0)	0	(0.0)	0	(0.0)
	The subject was found to meet the exclusion criteria.		1	(0.6)	1	(0.6)	0	(0.0)
	Continuation in the study was compromised by adverse events.		0	(0.0)	0	(0.0)	0	(0.0)
	The investigator deemed continuation in the study unsuitable for another reason.		2	(1.3)	1	(0.6)	0	(0.0)

Recruitment

Study initiation date: 9 November 2012 (Date of informed consent for the first subject)

Study completion date: 2 March 2013 (Date of completion of observation for the last subject)

Conduct of the study

Changes to the study

The protocol was amended only once (on 09 Oct 2012) and the modification included descriptions for dosage and administration of propofol.

No changes were made to assessment variables or to major analytical plans for this study.

Protocol deviations

The investigational product was not administered to 16 subjects (i.e., eight subjects in the RMZ 6 mg/kg/h group, six subjects in the ONO- 2745 12 mg/kg/h group and two subjects in the propofol group).

Two subjects were found meeting at least one of the exclusion criteria (i.e., one subject in the RMZ 6 mg/kg/h group, one subject in the RMZ 12 mg/kg/h group and zero subjects in the propofol group).

The specific exclusion criterion violated was "Exclusion criterion 5)" in one subject and "Exclusion criterion 27)" in the other remaining subject.

There were no subjects with no efficacy endpoints observations or no data on the primary endpoint.

A total of 33 subjects had treatment violations (i.e., 12 subjects in the RMZ 6 mg/kg/h group, 16 subjects in the RMZ 12 mg/kg/h group and five subjects in the propofol group). These 33 subjects were excluded from the PPS and included in the FAS and SAF, in accordance with stipulations of the protocol.

Baseline data

Figure 9: Baseline characteristics

Analysis set: SAF

Parameter	Treatment Group	ONO-2745		Propofol
		6	12	
All Subjects		150	150	75
Gender	Male	80 (53.3)	76 (50.7)	42 (56.0)
	Female	70 (46.7)	74 (49.3)	33 (44.0)
Age (years)	<=49	41 (27.3)	55 (36.7)	25 (33.3)
	50 - 59	29 (19.3)	21 (14.0)	13 (17.3)
	60 - 69	42 (28.0)	39 (26.0)	15 (20.0)
	70 - 79	36 (24.0)	30 (20.0)	16 (21.3)
	>=80	2 (1.3)	5 (3.3)	6 (8.0)
	<=64	92 (61.3)	93 (62.0)	47 (62.7)
	>=65	58 (38.7)	57 (38.0)	28 (37.3)
	Mean ± standard deviation	57.7 ± 14.7	56.2 ± 16.0	56.3 ± 17.6
	Median	61.0	59.0	59.0
	Minimum - maximum	20 - 81	20 - 86	21 - 88
Height (cm)	<150.0	14 (9.3)	11 (7.3)	6 (8.0)
	150.0 -< 160.0	45 (30.0)	56 (37.3)	26 (34.7)
	160.0 -< 170.0	63 (42.0)	49 (32.7)	30 (40.0)
	>=170.0	28 (18.7)	34 (22.7)	13 (17.3)
	Mean ± standard deviation	161.15 ± 8.97	161.69 ± 8.89	161.34 ± 8.33
	Median	162.00	160.60	161.00
	Minimum - maximum	133.4 - 181.5	142.1 - 182.0	134.1 - 179.1
Body weight (kg)	<40.0	1 (0.7)	2 (1.3)	1 (1.3)
	40.0 -< 50.0	14 (9.3)	28 (18.7)	8 (10.7)
	50.0 -< 60.0	58 (38.7)	41 (27.3)	33 (44.0)
	60.0 -< 70.0	49 (32.7)	47 (31.3)	17 (22.7)
	70.0 -< 80.0	23 (15.3)	24 (16.0)	13 (17.3)
	>=80.0	5 (3.3)	8 (5.3)	3 (4.0)
	Mean ± standard deviation	61.12 ± 10.03	60.50 ± 11.57	60.77 ± 10.83
	Median	60.00	60.70	59.00
	Minimum - maximum	36.3 - 98.0	35.5 - 94.2	37.7 - 96.7
BMI (kg/m^2)	<18.5	8 (5.3)	8 (5.3)	4 (5.3)
	18.5 -< 25.0	100 (66.7)	104 (69.3)	50 (66.7)
	25.0 -< 30.0	40 (26.7)	36 (24.0)	19 (25.3)
	30.0 -< 35.0	2 (1.3)	2 (1.3)	2 (2.7)
	35.0 -< 40.0			
	>=40.0			
	Mean ± standard deviation	23.49 ± 2.99	23.00 ± 3.10	23.28 ± 3.36
	Median	23.60	22.93	22.60
	Minimum - maximum	14.4 - 31.6	16.0 - 33.5	17.6 - 33.1
ASA Class	I	72 (48.0)	74 (49.3)	37 (49.3)
	II	78 (52.0)	76 (50.7)	38 (50.7)

Parentheses contain percentages.

Analysis set: SAF

Parameter	Treatment Group	ONO-2745		Propofol
		6	12	
All Subjects		150	150	75
Surgical site (Includes multiple instances)	Head	1 (0.7)		1 (1.3)
	Neck	5 (3.3)	4 (2.7)	2 (2.7)
	Chest	12 (8.0)	14 (9.3)	5 (6.7)
	Upper abdomen	7 (4.7)	5 (3.3)	3 (4.0)
	Lower abdomen	33 (22.0)	40 (26.7)	13 (17.3)
	Flank		1 (0.7)	
	Back	3 (2.0)	5 (3.3)	3 (4.0)
	Limb	27 (18.0)	30 (20.0)	18 (24.0)
	Ear and nose	20 (13.3)	19 (12.7)	8 (10.7)
	Endocrine organ	15 (10.0)	11 (7.3)	10 (13.3)
	Eye	2 (1.3)	1 (0.7)	1 (1.3)
	Oral cavity	7 (4.7)	7 (4.7)	5 (6.7)
	Other	18 (12.0)	13 (8.7)	7 (9.3)
Duration of surgery (minutes)	<60	13 (8.7)	22 (14.7)	14 (18.7)
	60 -< 240	111 (74.0)	111 (74.0)	55 (73.3)
	240 -<480	25 (16.7)	17 (11.3)	6 (8.0)
	>=480	1 (0.7)		
	Mean ± standard deviation	155.5 ± 96.5	143.7 ± 79.4	123.4 ± 73.0
	Median	125.5	131.0	112.0
	Minimum - maximum	15 - 554	15 - 405	17 - 360
Alcohol consumption	Does not drink	81 (54.0)	75 (50.0)	33 (44.0)
	Several times per month	21 (14.0)	23 (15.3)	14 (18.7)
	3-4 times per week	6 (4.0)	15 (10.0)	10 (13.3)
	Generally everyday	42 (28.0)	37 (24.7)	18 (24.0)
Tobacco use	Does not smoke	76 (50.7)	80 (53.3)	38 (50.7)
	Smoked previously	51 (34.0)	45 (30.0)	25 (33.3)
	<5 cigarettes per day	1 (0.7)	1 (0.7)	
	≥5 to <20 cigarettes per day	13 (8.7)	11 (7.3)	10 (13.3)
	≥20 cigarettes per day	9 (6.0)	13 (8.7)	2 (2.7)
Medical history	No	119 (79.3)	111 (74.0)	59 (78.7)
	Yes	31 (20.7)	39 (26.0)	16 (21.3)
Complications	No	27 (18.0)	32 (21.3)	15 (20.0)
	Yes	123 (82.0)	118 (78.7)	60 (80.0)

Parentheses contain percentages.

- Planned: 325 subjects (260 subjects in the RMZ groups [130 per group], 65 subjects in the propofol group)
- Analysed: 391 enrolled subjects (158 subjects in the RMZ 6 mg/kg/h group, 156 subjects in the RMZ 12 mg/kg/h group, and 77 subjects in the propofol group)
- Safety Set (SAF): 375 subjects (150 subjects in the RMZ 6 mg/kg/h group, 150 subjects in the RMZ 12 mg/kg/h group, and 75 subjects in the propofol group)
- Primary analysis set = Full Analysis Set (FAS): 375 subjects (150 subjects in the RMZ 6 mg/kg/h group, 150 subjects in the RMZ 12 mg/kg/h group, and 75 subjects in the propofol group)
- Secondary analysis set = Per Protocol Set (PPS): 342 subjects (138 subjects in the RMZ 6 mg/kg/h group, 134 subjects in the RMZ 12 mg/kg/h group, and 70 subjects in the propofol group)

Outcomes and estimation

The primary efficacy endpoint was functional capability as a general anaesthetic, as assessed on the basis of a composite of 3 variables: "intraoperative awakening or recall," "requirement of rescue sedation with other sedatives" and "body movement." The absence of these 3 variables is essential in induction and maintenance of general anesthesia. In individual subjects, the investigational product was assessed as "Effective" when all 3 variables were absent or "Ineffective" when at least one of these 3 variables was present.

The rate of efficacy in terms of functional capability as a general anesthetic was 100% for all treatment groups: RMZ 6 mg/kg/h, RMZ 12 mg/kg/h, and propofol. Given the 100% rate of efficacy in all 3 treatment groups, the RMZ 12 mg/kg/h group and RMZ 6 mg/kg/h group were verified as non-inferior to the propofol group in terms of functional capability as a general anesthetic.

In terms of induction of anesthesia, continuous intravenous infusion of RMZ caused loss of consciousness in all subjects, thereby demonstrating the compound's capability to appropriately induce anesthesia. In the RMZ 6 mg/kg/h group (n=150) and RMZ 12 mg/kg/h group (n=150), mean time to loss of consciousness from the start of investigational product administration was 102.0 and 88.7 seconds, respectively, with a statistically significant shorter duration observed in the RMZ 12 mg/kg/h group compared with the RMZ 6 mg/kg/h group (p<0.0001). In the propofol group (n=75), mean time to loss of consciousness was 78.7 seconds, which was a statistically significant shorter duration compared with the RMZ 6 mg/kg/h group and ONO- 2745 12 mg/kg/h group (p<0.0001 and p=0.0149, respectively).

Table 35: Time from initiation of study drug administration to loss of consciousness

Analysis set: FAS

Parameter	Treatment Group	ONO-2745		Propofol
		6	12	
Time from initiation of study drug administration to loss of consciousness (seconds)	Number of subjects	150	150	75
	Mean ± standard deviation	102.0 ± 26.6	88.7 ± 22.7	78.7 ± 38.4
	Median	100.5	87.5	80.0
	Minimum - maximum	24 - 165	30 - 170	17 - 280
	Difference and 95% confidence interval of difference	12 vs propofol		10.0 [2.0 , 18.1]
		6 vs propofol		23.3 [14.7 , 31.9]
		12 vs 6		-13.3 [-18.9 , -7.7]
	t test[a)]	12 vs propofol		p=0.0149 *
		6 vs propofol		p<0.0001 *
		12 vs 6		p<0.0001 *

a) *: p<0.05, N.S.: p≥0.05

In the RMZ 6 mg/kg/h group (n=150) and RMZ 12 mg/kg/h group (n=150), mean (5 to 95 percentile points) dose required for loss of consciousness was 0.17 (0.10 to 0.24) and 0.29 (0.18 to 0.43) mg/kg, respectively.

In terms of maintenance of anesthesia, continuous intravenous infusion with RMZ allowed the adjustment of infusion rate based on monitoring of BIS value and general condition of individual subjects. The mean (5 to 95 percentile points) optimal infusion rate during maintenance of anesthesia in the RMZ 6 mg/kg/h group and RMZ 12 mg/kg/h group was 0.97 (0.40 to 1.58) and 0.99 (0.40 to 2.00) mg/kg/h, respectively. The BIS values (mean) during maintenance of anesthesia in the RMZ 6 mg/kg/h group, RMZ 12 mg/kg/h group and propofol group ranged between 40.0–82.0, 47.8–84.0 and 39.0–56.3, respectively.

The time (mean) from end of investigational product administration to awakening, extubation, stating date of birth, and decision to exit the operating room in the RMZ 6 mg/kg/h group were 14.9, 19.2, 24.8 and 28.7 minutes, respectively, and were 14.5, 19.2, 24.1 and 27.9 minutes, respectively, in the RMZ 12 mg/kg/h group, showing no statistically significant differences between the RMZ 6 mg/kg/h group and RMZ 12 mg/kg/h group (p=0.7294, p=0.9743, p=0.7290 and p=0.6730, respectively). Awakening was not observed after 30 minutes from the end of RMZ administration in 14 subjects in the RMZ 6 mg/kg/h group and 13 subjects in the RMZ 12 mg/kg/h group; among these 10/14 and 7/13 subjects, respectively, were given flumazenil. Of these, 1 subject in the RMZ 6 mg/kg/h group was given flumazenil twice before awakening; while the other subjects were given flumazenil once. The mean time from initial flumazenil dosing to awakening in the RMZ 6 mg/kg/h group and RMZ 12 mg/kg/h group was 1.8 minutes and 0.9 minutes, respectively. In the propofol group (n=75), the mean time to awakening, extubation, stating date of birth, and decision to exit the operating room were 10.3, 13.1, 15.6 and 19.1 minutes, respectively, which were statistically significant shorter durations compared with the RMZ 6 mg/kg/h

group and RMZ 12 mg/kg/h group (p=0.0007 and p=0.0006, p=0.0004 and p<0.0001, p<0.0001 and p<0.0001, and p<0.0001 and p<0.0001, respectively).

Table 36: Time from completion of study drug administration to opening of eyes, extubation, ability to state date of birth, and ability to leave the operating room

Analysis set: FAS

Parameter	Treatment Group	ONO-2745		Propofol
		6	12	
Time from completion of study drug administration to opening of eyes (minutes)	Number of subjects	150	150	75
	Mean ± standard deviation	14.9 ± 11.1	14.5 ± 9.8	10.3 ± 5.1
	Median	12.0	12.0	10.0
	Minimum - maximum	1 - 87	0 - 50	0 - 24
	Difference and 95% confidence interval of difference	12 vs propofol		4.2 [1.9 , 6.6]
		6 vs propofol		4.7 [2.0 , 7.3]
		12 vs 6		-0.4 [-2.8 , 2.0]
	t test[a)]	12 vs propofol		p=0.0006 *
		6 vs propofol		p=0.0007 *
		12 vs 6		p=0.7294 N.S.
Time from completion of study drug administration to extubation (minutes)	Number of subjects	150	150	75
	Mean ± standard deviation	19.2 ± 14.1	19.2 ± 10.8	13.1 ± 6.5
	Median	15.5	18.0	12.0
	Minimum - maximum	3 - 104	2 - 58	3 - 42
	Difference and 95% confidence interval of difference	12 vs propofol		6.1 [3.4 , 8.8]
		6 vs propofol		6.1 [2.8 , 9.5]
		12 vs 6		0.0 [-2.9 , 2.8]
	t test[a)]	12 vs propofol		p<0.0001 *
		6 vs propofol		p=0.0004 *
		12 vs 6		p=0.9743 N.S.
Time from completion of study drug administration to ability to state date of birth (minutes)	Number of subjects	149	149	75
	Mean ± standard deviation	24.8 ± 16.2	24.1 ± 14.8	15.6 ± 11.0
	Median	21.0	21.0	14.0
	Minimum - maximum	3 - 106	2 - 125	4 - 86
	Difference and 95% confidence interval of difference	12 vs propofol		8.5 [4.7 , 12.3]
		6 vs propofol		9.2 [5.1 , 13.3]
		12 vs 6		-0.6 [-4.2 , 2.9]
	t test[a)]	12 vs propofol		p<0.0001 *
		6 vs propofol		p<0.0001 *
		12 vs 6		p=0.7290 N.S.
Time from completion of study drug administration till subject judged able to leave operating room (minutes)	Number of subjects	150	150	75
	Mean ± standard deviation	28.7 ± 18.1	27.9 ± 15.7	19.1 ± 13.1
	Median	25.0	25.0	16.0
	Minimum - maximum	4 - 144	5 - 125	5 - 87
	Difference and 95% confidence interval of difference	12 vs propofol		8.8 [4.6 , 12.9]
		6 vs propofol		9.6 [5.0 , 14.2]
		12 vs 6		-0.8 [-4.7 , 3.0]
	t test[a)]	12 vs propofol		p<0.0001 *
		6 vs propofol		p<0.0001 *
		12 vs 6		p=0.6730 N.S.

a) *: p≤0.05, N.S.: p≥0.05

Controllability of anaesthetic depth was assessed as either "Very Good" or "Good" in all subjects except for two (1.3%) in the RMZ 6 mg/kg/h group and 5 subjects (3.3%) in the RMZ 12 mg/kg/h group.

Table 37: Summary of efficacy for trial ONO-2745The following table summarise the efficacy results from study ONO-2745-05.

Title: A multicenter, randomized, parallel-group study of ono-2745 compared with propofol in surgical patients undergoing general anesthesia		
Study identifier	Protocol Number: **ONO-2745-05**	
Design	A randomized, parallel-group, multi-centre, confirmatory non-inferiority study of remimazolam compared with propofol in surgical patients, ASA class I or II undergoing GA. Patients were allocated to 1 of 3 treatment groups; two remimazolam groups or one propofol control group. The remimazolam groups differed in terms of the dose to be administered for induction (6 mg/kg/h or 12 mg/kg/h. Subjects were therefore allocated at a 2:1 ratio to either remimazolam or propofol. Subjects were blinded (single-blind) to treatment allocation and investigators were blinded (double-blind) to the dose of remimazolam for induction. A patient registration centre was used to randomise patients using dynamic allocation.	
	Duration of main phase: **Duration of Run-in phase:** **Duration of Extension phase:**	Use for GA induction / maintenance. The maximum trial duration for any patient was up to 30 days. not applicable not applicable
Hypothesis	Non-inferiority	
Treatments groups	**Propofol** **PPF**	Propofol was administered as a slow bolus at a dose of 0.2–0.25 mL/kg (2.0– 2.5 mg/kg of propofol). After loss of consciousness (LoC), continuous intravenous infusion at a dose of 0.4– 1 mL/kg/h (4–10 mg/kg/h of propofol) was started, after which the infusion rate was adjusted as appropriate based on monitoring of the general condition of individual subjects until the end of the surgery. number randomized: 75
	Remimazolam 6 mg/Kg **RMZ**	Remimazolam was administered at a dose of 6 mg/kg/h until LoC. After LoC a dose of 1 mg/kg/h was started, after which the infusion rate was adjusted as appropriate (maximum allowed infusion rate, 2 mg/kg/h) based on monitoring of the general condition of individual subjects until the end of the surgery. number randomized:150
	Remimazolam 12 mg/Kg **RMZ**	Remimazolam was administered at a dose of 12 mg/kg/h until LoC. After LoC a dose of 1 mg/kg/h was started, after which the infusion rate was adjusted as appropriate (maximum allowed infusion rate, 2 mg/kg/h) based on monitoring of the general condition of individual subjects until the end of the surgery. number randomized:150

Title: A multicenter, randomized, parallel-group study of ono-2745 compared with propofol in surgical patients undergoing general anesthesia			
Study identifier	Protocol Number: **ONO-2745-05**		
Endpoints and definitions	**Primary endpoint**	The functional capability of remimazolam as a general anaesthetic (GA)	Assessed on the basis of a composite of 3 variables. In individual subjects, the investigational product was assessed as "Effective" if all 3 variables were absent or "Ineffective" if at least one of these 3 variables was present. 1. Intraoperative awakening or recall 2. Requirement of rescue sedation with other sedatives 3. Body movement The following two hypotheses were to be tested: 1. The ONO-2745 12 mg/kg/h group is noninferior to the propofol group. 2. The ONO-2745 6 mg/kg/h group is noninferior to the propofol group. Non-inferiority was to be concluded if the lower limit of the confidence interval for the difference was greater than -10%. If the first comparison for "1." failed to demonstrate non-inferiority, then the second comparison for "2." was not to be performed. Noninferiority was also to be declared if the efficacy rate was 100% for both treatment groups compared and thus no confidence interval could be calculated.
	Secondary endpoint	Onset characteristic – Time to LoC	Time to loss of consciousness from the start of investigational product administration
	Secondary endpoint	BIS value at each time point of evaluation	Assessed on Day 1 of investigational product administration (at entry to the operating room [prior to remifentanil administration], immediately prior to the start of investigational product administration, at loss of consciousness, 2 minutes after loss of consciousness, immediately after endotracheal intubation, during maintenance of anaesthesia [every 5 minutes], immediately prior to the end of investigational product administration, from the end of investigational product administration to the decision to exit the operating room [every 5 minutes], at discontinuation of investigational product administration)
	Secondary endpoint	Offset characteristic – Time to awakening after end of IMP	Following the end of investigational product administration, awakening in response to verbal stimuli was verified approximately every 30 seconds. The time of awakening was defined as the time when the subject first opened his/her eyes in response to verbal stimuli.
	Secondary endpoint	Offset characteristic – Time to extubation after end of IMP	Following the end of IMP administration, the appropriateness of extubation was determined according to the following criteria a. Awakening in response to verbal stimuli b. Adequate recovery of respiration c. Stable blood pressure and heart rate d. Recovery of muscle strength (e.g., head lift for 5 seconds, strong hand grip) Subjects had to fulfill all of the criteria prior to extubation
	Secondary endpoint	Offset characteristic – Time to stating date of birth after end of IMP	Following extubation, the subject was asked to state his/her date of birth approximately every 30 seconds. The time when the subject was first able to accurately state his/her date of birth was recorded.

Title: A multicenter, randomized, parallel-group study of ono-2745 compared with propofol in surgical patients undergoing general anesthesia			
Study identifier	Protocol Number: **ONO-2745-05**		
	Secondary endpoint	Offset characteristic – Time to decision to exit the operating room after end of IMP	Following extubation, the appropriateness of exiting the operating room was determined according to the following criteria for exit. a. Ability to correctly state his/her date of birth. b. Adequate recovery of respiration c. Stable blood pressure and heart rate d. Recovery of muscle strength (e.g., head lift for 5 seconds, strong hand grip) Subjects had to fulfil all of these criteria prior to exiting the operating room:
	Safety endpoint	The percentage of time points where systolic blood pressure was maintained within a range of ≥80 and <150 mmHg among all time points of evaluation was ≥90%	Non-invasive BP was recorded at the following timepoints across all treatment arms 1. Entry into the operation room 2. Immediately before study treatment 3. At LoC 4. 2 minutes after LoC 5. Immediately after intratracheal intubation 6. Every 5 minutes during maintenance period 7. Immediately before the end of study medication 8. Every 5 minutes after end of study medication to the time when subjects were assessed to be able to leave the room 9. At exiting the room 10. 24h after the end of the study medication
	Safety endpoint	Number patients requiring vasopressor drugs (%)	For the entire study period
Database lock	Not reported		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis set for efficacy evaluations was the Full Analysis Set (FAS)		
Descriptive statistics and estimate variability	**Treatment group**	RMZ 6/12	PPF
	Number of subjects	150 / 150	75
	The number of patients demonstrating functional capability of remimazolam as a GA (%)	100 / 100	100
	Onset characteristic – Time to LoC in seconds (mean)	102 / 88.7	78.7
	SD	26.6 / 22.7	38.4
	Range of BIS values at each time point of evaluation during maintenance (mean)	40.0-82.0 / 47.8-84.0	39.0-56.3

Title: A multicenter, randomized, parallel-group study of ono-2745 compared with propofol in surgical patients undergoing general anesthesia			
Study identifier	Protocol Number: **ONO-2745-05**		
	Offset characteristic – Time to awakening after end of IMP in minutes (mean)	14.9 / 14.5	10.3
	SD	11.1 / 9.8	5.1
	Offset characteristic – Time to extubation after end of IMP in minutes (mean)	24.8 / 24.1	15.6
	SD	16.2 / 14.8	11
	Offset characteristic – Time to decision to exit the operating room after end of IMP in minutes (mean)	28.7 / 27.9	19.1
	SD	18.1 / 15.7	13.1
	The percentage of time points where systolic blood pressure was maintained within a range of ≥80 and <150 mmHg among all time points of evaluation was ≥90% (%)	72.7 / 70.7	50.7
	Number patients requiring vasopressor drugs (%)	40 / 42.7	64
Effect estimate per comparison	**Primary endpoint (functional capability as a GA)**	Comparison groups	1. RMZ 12 – PPF 2. RMZ 6 - PPF
		Difference in means	1. 0 2. 0
		(95% CI)	1. - [- , -] 2. - [- , -]
	Secondary endpoint (Time to LoC)	Comparison groups	1. RMZ 12 – PPF 2. RMZ 6 - PPF
		Difference in means	1. 10 2. 23.3
		(95% CI)	1. [2.0 , 18.1] 2. [14.7 , 31.9]
		P-value (t-test)	1. 0.0149 2. <0.0001
	Secondary endpoint (Time to awakening)	**Comparison groups**	1. RMZ 12 – PPF 2. RMZ 6 - PPF
		Difference in means	1. 4.2 2. 4.7
		(95% CI)	1. [1.9 , 6.6] 2. [2.0 , 7.3]
		P-value (t-test)	1. 0.0006 2. 0.0007
	Secondary endpoint	**Comparison groups**	1. RMZ 12 – PPF 2. RMZ 6 - PPF

Title: **A multicenter, randomized, parallel-group study of ono-2745 compared with propofol in surgical patients undergoing general anesthesia**

Study identifier	Protocol Number: **ONO-2745-05**		
	(Time to extubation)	**Difference in means**	1. 6.1 2. 6.1
		(95% CI)	1. [3.4 , 8.8] 2. [2.8 , 9.5]
		P-value (t-test)	1. <0.0001 2. 0.0004
	Secondary endpoint (Time to stating date of birth)	**Comparison groups**	1. RMZ 12 – PPF 2. RMZ 6 - PPF
		Difference in means	1. 8.5 2. 9.2
		(95% CI)	1. [4.7 , 12.3] 2. [5.1 , 13.3]
		P-value (t-test)	1. <0.0001 2. <0.0001
	Secondary endpoint (Time to decision to exit the operating room)	**Comparison groups**	1. RMZ 12 – PPF 2. RMZ 6 - PPF
		Difference in means	1. 8.8 2. 9.6
		(95% CI)	1. [4.6 , 12.9] 2. [5.0 , 14.2]
		P-value (t-test)	1. <0.0001 2. <0.0001
	Safety endpoint (vasopressor use)	**Comparison groups**	1. RMZ 12 – PPF 2. RMZ 6 - PPF
		Difference in means	1. 21.3 2. 24
Notes			
Analysis description	**Secondary analysis**		

Analysis population and time point description	The secondary analysis for the primary analysis set for efficacy evaluations was the Per Protocol Set (PPS)			
Descriptive statistics and estimate variability	Treatment group	RMZ 6 mg/kg/h	RMZ 12 mg/kg/h	PPF
	Number of subject	138	134	70
	The number of patients demonstrating functional capability of remimazolam as a GA (%)	100	100	100

Effect estimate per comparison	Primary endpoint (functional capability as a GA)	Comparison groups	1. RMZ 12 – PPF 2. RMZ 6 - PPF
		Difference in means	1. 0 2. 0
		(95% CI)	1. - [- , -] 2. - [- , -]

2.6.5.3 Clinical studies in special populations

Four studies have been conducted in special populations. These are outlined in the Table 38**.**

Table 38: Clinical studies in special populations

		exposed
ONO-2745- IVU007	Moderate or severe chronic hepatic impairment	11
CNS7056-012	End Stage Renal Disease:	11
CNS7056-014	Recreational CNS Depressant Users	40
CNS7056-020	Alcohol intoxication	11

Study **ONO-2745-IVU007** included 11 patients with either moderate or severe chronic hepatic impairment, eight patients with moderate hepatic impairment and three patients with severe hepatic impairment.

Study **CNS7056-012** included 11 patients with end stage renal disease not requiring dialysis, six patients with eGFR15-30 mL/min/1.73m2 and five patients with eGFR<15 mL/min/1.73m2.

In addition to these patients, group C of the integrated analysis included 47 patients who suffered from severe renal impairment (eGFR <30 mL/min/1.73 m2).

Study **CNS7056-014** was an abuse liability study conducted in healthy adults who were non-dependent, non-treatment–seeking, recreational CNS depressant users. Commonly used recreational drugs were cannabis, benzodiazepines and opioids.

Within **CNS7056-020**, 11 healthy female volunteers were exposed to various concentrations of ethanol prior to oral administration of remimazolam.

Insufficient data

The Table 39 highlights all those subpopulations, in addition to pregnant women, where there is insufficient data across the general anaesthesia development program.

Table 39: Populations with insufficient data in group C

Population	Number of patients
African American Or Black	3 (0.4%)
Moderate Liver Dysfunction	5 (0.6%)
Severe Liver Dysfunction	0 (0.0%)
Medical History: Dementia	1 (0.1%)
Medical History: Cognitive Disorder	0 (0.0%
Neurosurgery	4 (0.5%)

Adapted from GA-IA Table 4.2.1.3. Total number of remimazolam patients was 783

Even though only three patients of African American or black origin were included in the development program, no ethnic differences in remimazolam PK or PD have been identified.

The characterisation of moderate and severe liver dysfunction was based on bilirubin, and not Child-Pugh criteria, as in in study ONO-2745-IVU007. The lack of patients observed with severe liver dysfunction is likely consistent with the assumption of lack of patients with severe hepatic impairment

according to the Child-Pugh score. Hepatic impairment is mentioned accordingly under "Special populations" in section 4.2. of the SmPC. No dose adjustment is recommended for patients with mild (Child-Pugh scores 5 and 6) or moderate (Child-Pugh scores 7 to 9) hepatic impairment. In patients with severe hepatic impairment (Child-Pugh scores 10 to 15; data from only 3 subjects in clinical trials), the clinical effects may be more pronounced and last longer than in healthy subjects. No dose adjustments are required but careful attention should be paid to the timing of titration doses and remimazolam should be carefully titrated to effect in these patients (see also SmPC section 4.4).

For the majority of studies patients were excluded if they lacked capacity to be able to provide informed consent. This explains the lack of patients with a history of dementia or cognitive disorders.

Many indications of neurosurgery under general anaesthesia include patients with an underlying organic brain defect. These patients were excluded from the non-cardiac pivotal studies to ensure that did not confound the measurement of the Bispectral Index (BIS) value. Therefore, the following text is included in SmPC section 4.2:

Other populations

The safety and efficacy of remimazolam in patients undergoing intracranial surgery and patients with pre-existing cognitive disorders have not yet been established. No data are available.

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

The analysis of efficacy across trials focused on the pivotal and all controlled trials versus propofol (groups A and B). Group C (all GA trials) was used mostly for the purpose of sensitivity analysis of the results obtained in groups A and B. For the majority of the analyses the per protocol (PP) set is shown while the analyses using the intent to treat (ITT) population set is provided in the set of tables. All remimazolam patients receiving an induction dose of either 6 mg/kg/h or 6 mg/min were pooled into the low remimazolam dose group while the ones receiving 12 mg/kg/h were assigned to the remimazolam high dose group. These two groups were considered for induction endpoints only in order to characterize efficacy of both doses for induction of GA. However, for analyses of other endpoints only the total remimazolam group was considered (i.e. low and high dose patients pooled) since the difference in dosing was only during the first few minutes of a treatment that lasted many hours.

Since the primary efficacy endpoint was different between trials and could not be pooled, an integrated efficacy endpoint was designed. This endpoint was defined as:

1) successful conduct of the surgical intervention

2) no need for rescue sedative medication (see GA-IA SAP).

Both parameters needed to be met for the patient to reach the endpoint. Success rates were compared between total remimazolam and total propofol groups with a non-inferiority approach.

Secondary endpoints that were available across the majority of trials were analysed additionally, for potential differences between remimazolam and propofol as well as between subgroups (e.g. age).

Results of Primary Endpoint

Non-inferiority of remimazolam when compared to propofol was demonstrated in the two pivotal Phase III trials (ONO-2745-05 and CNS7056-022) and in the Phase II trial CNS7056-010 using primary endpoints as defined in each trial. The remaining propofol controlled trial (CNS7056-011) was initially designed as a pivotal Phase III study, but prematurely terminated due to lack of recruitment. For this trial non-inferiority was not assessed. All individual trials confirmed non-inferiority of remimazolam to propofol, as outlined in the Table 43.

Table 40: Non-inferiority of remimazolam to propofol as assessed in individual propofol controlled trials

Trial ID/ definition of primary endpoint	Remimazolam	Propofol
CNS7056-010 n/N (%) % of patients with successful GA defined as no need for rescue medication	61/62 (98.4)	27/28 (96.4)
ONO-2745-05 n/N (%) % of patients with no intraoperative awakening/ recall, no need for rescue sedation and no body movement	300/300 (100.0)	75/75 (100.0)
	Difference and 95% CI[a] - [- , -]	
CNS7056-022 (Mean ± SD) % of time with NCI ≤60 during maintenance	94.62 ± 19.337 N=165	98.86 ± 5.153 N=60
	Mean difference -4.24; 97.5% CI: -7.48; I t-test; p = 0.0003	

[a] Wilson's method was used

2.6.5.5 Supportive study(ies)

Studies **ONO-2745-06, CNS7056-010** and **CNS7056-011** are regarded as supportive studies for this line extension application.

CNS7056-010

This was a Phase II safety, efficacy and PK study in patients undergoing cardiac surgery, including follow-up sedation, in the post anaesthesia care unit.

In terms of **trial design**, CNS7056-010 was a randomized, single-blind, active-controlled, parallel-group Phase II study to investigate the efficacy and safety of remimazolam (compared to sevoflurane/propofol) as an anaesthetic/sedative drug used in general anaesthesia in patients undergoing major elective cardiac surgery (i.e. surgery assumed to require more than two hours of maintenance of general anaesthesia and the use of extracorporeal circulation).

The study included 62 patients receiving remimazolam and 28 patients receiving propofol/sevoflurane in the pooled ITT set.

Patients were randomized at a rate of 1:1:1 to receive sevoflurane/propofol or 1 of 2 doses of remimazolam, 6 mg/kg/h or 12 mg/kg/h for the purposes of induction (see Table 41). Randomization was stratified by planned post-anaesthesia care (stratum 1: patients planned for the post-anaesthesia care unit [PACU], stratum 2: patients planned for the intensive care unit [ICU]).

Table 41: Groups and dose ranges used in CNS7056-010

Group	Trial medication	Induction dose	Maintenance dose	ICU dose
Group 1	Propofol*	2.0 to 2.5 mg/kg over 1 minute	3 – 12 mg/kg/h**	As per product label
	Sevoflurane	---	0.8 – 2.5 MAC	---
Group 2	Remimazolam*	6 mg/kg/h	1 mg/kg/h (up to 3 mg/kg/h)	0.25 – 1.0 mg/kg/h
Group 3	Remimazolam*	12 mg/kg/h	1 mg/kg/h (up to 3 mg/kg/h)	0.25 – 1.0 mg/kg/h

* The infusion speed at induction as well as during maintenance could be reduced according to the condition of the patient.

** During extracorporeal circulation and thereafter until end of surgery.

Sedation with remimazolam for ICU mechanical ventilation was limited to 24 hours after the end of the surgery.

The **primary objective** of the study was to assess the efficacy of remimazolam as general anaesthetic when given in combination with fentanyl/remifentanil to patients undergoing elective cardiac surgery.

Efficacy was measured as the proportion of patients with successful anaesthesia, i.e. patients with no use of rescue sedative medication between start of the study medication and end of the surgical procedure (completion of last skin suture).

With regards to **efficacy results,** anaesthesia was successful, i.e. no rescue sedative medication was used between the start of the study medication and the end of the surgical procedure (completion of last skin suture), in all patients except one in the remimazolam 12 mg/kg/h-induction group and one in the propofol/sevoflurane group (see Table 42).

Table 42: Number of patients that met the primary objective in CNS7056-010

	Remimazolam			Propofol / Sevoflurane
	6 mg/kg/h	12 mg/kg/h	Pooled	
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
ITT set	34/34 (100.0)	27/28 (96.4)	61/62 (98.4)	27/28 (96.4)
PP set	31/31 (100.0)	23/24 (95.8)	54/55 (98.2)	26/27 (96.3)

Source: CNS7056-010 Table 15 and Table 16

Three patients (8.8%) in the remimazolam 6 mg/kg/h group showed signs of awakening during the maintenance phase. The signs were specified as "breathing against the ventilator" and "fluctuation of blood pressure" in one patient each. In the third patient signs of awakening were not specified. In the remimazolam 12 mg/kg/h and propofol/sevoflurane groups no patient showed signs of intra-operative awakening.

The mean percentage of time with NCI ≤60 during maintenance of anaesthesia was almost 100% and comparable between the 3 treatment groups: remimazolam 6 mg/kg/h 95.8%, remimazolam 12 mg/kg/kg 93.3%, and propofol/sevoflurane 96.9%, indicating the efficacy of remimazolam for maintenance of general anaesthesia as compared to propofol.

Results of time-to-events are summarized in theTable 43. In general, all time to events were slightly shorter in the propofol/sevoflurane group than in the two remimazolam groups and the onset times were longer for remimazolam 6 mg/kg/kg than for remimazolam 12 mg/kg/h. LoC was achieved quickly (approximately 1 minute) in all three treatment groups. Time to LoC was slightly shorter for propofol than for remimazolam 6 mg/kg/h and remimazolam 12 mg/kg/kg. Intubation was completed within

approximately five minutes after start of study drug administration. Within approximately 5-6 hours after the end of the surgery, patients were ready to be discharged from PACU/ICU.

Table 43: Time to event assessments in CNS CNS7056-010

	Remimazolam 6 mg/kg/h N = 34	Remimazolam 12 mg/kg/h N = 28	Remimazolam Pooled N = 62	Propofol / Sevoflurane N = 28
Time to LoC from start of study drug (seconds)				
Median	75.0	60.5	67.5	56.0
95% CI	63.0, 82.0	54.0, 73.0	60.0, 78.0	51.0, 65.0
Time to Intubation from start of study drug (seconds)				
Median	293.0	284.5	286.5	286.5
95% CI	260.0, 328.0	253.0, 323.0	266.0, 317.0	265.0, 301.0
Time to Extubation from arrival at PACU/ICU or first occurrence of normothermia (≥36°C body temperature) (minutes)				
Median	136.5	165.0	145.5	97.0
95% CI	98.0, 163.0	111.0, 195.0	111.0, 170.0	83.0, 140.0
Time to RASS Score ≥–1 from extubation (minutes)				
Median	10.0	10.0	10.0	10.0
95% CI	5.0, 10.0	5.0, 10.0	5.0, 10.0	(-)
Time to Discharge from PACU/ICU from end of surgery (minutes)				
Median	363.0	368.0	363.0	319.5
95% CI	308.0, 427.0	335.0, 411.0	335.0, 408.0	290.0, 366.0
Time Transfer to Normal Ward from end of surgery (minutes)				
Median	1606.0	1573.0	1600.0	1622.0
95% CI	1447.0, 2517.0	1350.0, 2545.0	1478.0, 2068.0	1523.0, 2986.0
Time to Discharge from Hospital from end of surgery (days)				
Median	8.0	10.0	9.0	9.5
95% CI	8.0, 11.0	8.0, 11.0	8.0, 11.0	8.0, 11.0

Source: CNS7056-010 Table 17, Table 18, Table 21, Table 22, Table 23, Table 25, Table 26

During the course of this trial, there was a learning effect in the use of remimazolam for general anaesthesia. At later stages of the trial, the dose of remimazolam was tapered down to 0.1 mg/kg/h prior to arriving at PACU/ICU in 14 patients. In these patients, the time to extubation (median 109.0 minutes, 95% CI: 87.0, 148.0) was shorter than that in all remimazolam patients in total (median 145.5 minutes, 95% CI: 111.0, 170.0) and similar to that in the propofol/sevoflurane group (median 97.0 minutes, 95% CI: 83.0, 140.0). These results suggested that tapering by reducing the infusion rate of remimazolam towards to end of surgery can shorten recovery time to a level similar to propofol.

With regards to **hemodynamic stability,** all patients in this study were administered vasopressors. Norepinephrine was used by all patients, except for one in the remimazolam 6 mg/kg/h group, whereas epinephrine and dobutamine were used much less frequently considered. Vasopressor use is presented in the Table 44.

The median dose of norepinephrine and the median time on norepinephrine were larger in the propofol/sevoflurane group than in the remimazolam pooled group. Patients on remimazolam 6 mg/kg/h required less norepinephrine than did those on remimazolam 12 mg/kg/h.

The data on dose and duration of epinephrine and dobutamine were extremely skewed and based on a small number of subjects. Patients in the remimazolam pooled group used slightly more epinephrine than those on propofol/sevoflurane, but median duration of use was the same in both groups. The median dose of dobutamine was larger in the remimazolam pooled group than in the propofol/sevoflurane group, but the duration of use was otherwise.

Table 44: Vasopressor use (CNS7056-010)

	Remimazolam 6 mg/kg/h N = 34 Mean (SD) median n	**Remimazolam 12 mg/kg/h N = 28** Mean (SD) median n	**Remimazolam Pooled N = 62** Mean (SD) median n	**Propofol / Sevoflurane N = 28** Mean (SD) median n
Norepinephrine				
Dose (µg/kg)	8.49 (8.20) 5.574 32	12.52 (15.07) 7.913 28	10.37 (11.97) 6.841 60	15.62 (12.65) 12.181 28
Dose (ng/kg/min)	22.73 (21.95) 14.404 32	24.76 (18.59) 22.634 28	23.68 (20.31) 19.920 60	43.17 (38.78) 31.453 28
Epinephrine				
Dose (µg/kg)	1.91 (3.132) 0.250 5	10.06 (21.561) 0.183 6	6.36 (15.953) 0.208 11	0.21 (0.107) 0.176 7
Dose (ng/kg/min)	4.52 (7.279) 0.461 5	10.86 (19.596) 0.418 6	7.98 (14.972) 0.461 11	0.53 (0.183) 0.553 7
Dobutamine				
Dose (µg/kg)	396.44 (237.73) 379.01 8	1569.2 (2703.3) 644.10 7	943.7 (1878.0) 452.24 15	378.4 (292.8) 297.36 8
Dose (ng/kg/min)	992.57 (565.17) 858.47 8	1815.7 (1550.1) 1519.18 7	1376.7 (1170.6) 1246.24 15	783.8 (495.5) 614.23 8

Source: CNS7056-010 Table 40

In this trial cardio-depressive effects were assessed using two specific safety endpoints: cardiac instability and low cardiac output syndrome.

Cardiac instability was defined as all of the following:

- Fall in mean arterial blood pressure of more than 30% from baseline at induction of general anaesthesia;
- Heart rate at induction below 50 bpm over at least one minute;
- Need for vasopressive treatment, defined as >0.1 µg/kg/min noradrenalin for >3 hours in the face of normovolemia. For epinephrine and norepinephrine, the corresponding dose is >0.05 µg/kg/min.

The incidence of cardiostability (not fulfilling any of the criteria above) was higher in the pooled remimazolam group (27.4%) than in the propofol/sevoflurane group (14.3%).

Between the two remimazolam doses, the 6 mg/kg/h showed higher incidence of cardiostability (35.3%) than the 12 mg/kg/h (17.9%).

Low cardiac output syndrome was defined as at least two of the following four criteria being met during the general anaesthesia or during recovery until extubation:

- ScvO2 <60% with SAO2 98%
- Mean arterial pressure <60 mmHg
- Urine output <0.5 mL/kg/h
- Lactate >2.0 mmol/L

Remimazolam appeared to have less cardio-depressive effect than propofol/sevoflurane, despite a lower dose of norepinephrine (see Table 45). During general anaesthesia (including recovery period until extubation), proportions of patients with a low cardiac output syndrome were larger in the propofol/sevoflurane group (25%) than in the pooled remimazolam group (14.5%) as well as 6 mg/kg/h and 12 mg/kg/h induction dose groups (14.7% and 14.3% respectively). The same trend was observed when the entire observation period was split into GA only period and recovery period for both of them.

Table 45: Cardiac stability and low cardiac output syndrome

	RMZ 6 mg/kg	RMZ 12 mg/kg	RMZ all	Propofol/ Sevoflurane
Cardiostability				
All patients	N=34	N=28	N=62	N=28
Yes	12 (35.3%)	5 (17.9%)	17 (27.4%)	4 (14.3%)
No	22 (64.7%)	22 (78.6%)	44 (71.0%)	24 (85.7%)
N	34 (100%)	27 (96,4%)	61 (98.4%)	28 (100%)
Low Cardiac Output Syndrome (during GA and/or recovery until extubation)				
All patients	N=34	N=28	N=62	N=28
Yes	5 (14.7%)	4 (14.3%)	9 (14.5%)	7 (25.0%)
No	29 (85.3%)	24 (85.7%)	53 (85.5%)	21 (75.0%)
N	34 (100%)	28 (100%)	62 (100%)	28 (100%)

Source: CNS7056-010 CSR, Table 14.3-13.1 and 14.3-22.1

CNS7056-011

This was a randomized, single-blind propofol-controlled phase III study evaluating efficacy and safety of remimazolam in GA adult patients undergoing major non-emergency cardiac surgery utilizing extracorporeal circulation, including follow-up sedation, in the post-anaesthesia care unit/intensive care unit.

A total of 530 patients were planned to participate in this study. Patients were randomized at a ratio of 4:1 to receive sedation during cardiac surgery, with remimazolam or propofol, according to the schedule outlined in the Table 46.

Table 46

Group	Study medication	Induction dose	Maintenance dose
Group 1	Propofol*	1.0 to 2.5 mg/kg over 1 minute**	3 – 9 mg/kg/h**
Group 2	Remimazolam*	6 mg/kg/h	1 mg/kg/h (up to 3 mg/kg/h)

* The infusion speed at induction as well as during maintenance could be reduced according to the condition of the patient.

** If TCI (target-controlled infusion) was used for patients on propofol, the dosage was adapted to the condition of the patient using the functionalities of the TCI. For maintenance, the recommended range of the target concentration was 2 to 10 µg/mL.

Due to low acceptance of propofol only as comparator, and the complex regulatory and technical set-up of all involved study centres, the study was stopped prematurely. Patient recruitment was stopped when less than 10% of the planned sample size (n enrolled = 23, n planned = 530) was enrolled. A total of 18 patients were randomised to remimazolam and five to receive propofol.

Of the 18 patients randomised to receive remimazolam, four did not meet the primary efficacy endpoint, two failed to achieve NCI ≤60 during at least 85% of maintenance time, one required rescue sedative medication and one required both rescue sedative medication and failed to achieve NCI ≤60 during >85% of maintenance time. Among the patients who received propofol, there was one who did not meet the primary efficacy endpoint, because the NCI did not remain ≤60 during at least 85% of maintenance time, as detailed in the Table 47.

Table 47: Proportion of patients with successful sedation (miTT) in CNS7056-11

	Remimazolam (N = 18)		Propofol (N = 5)	
	n	%	n	%
Patients with sedation successful	14	77.8	4	80.0
Patients with sedation not successful	4	22.2	1	20.0

Successful sedation was defined as: NCI ≤60 during ≥85% of the maintenance time **AND** No use of rescue sedative medication;

Source: CNS7056-011 Table 7

Ultimately, as study CNS7056-011 was stopped prematurely due to poor enrolment (after randomising less than 10% of the planned sample size of 23 participants), drawing conclusions from this study would be inappropriate; it is only presented here for completeness.

ONO-2745-06*

* *The trial is briefly presented here since the value (for this particular application) of an uncontrolled small Japanese study, in light of the existence of a large phase 3 controlled confirmatory study undertaken in Europe (CNS7056-022), is limited.*

ONO-2745-06 was a small, muticenter, uncontrolled, randomized, double-blind, parallel-group, comparative, Phase 3 study conducted in Japan evaluating two doses of remimazolam (6 or 12 mg/kg/h; followed by maintenance dose of 1-2 mg/kg/h) in induction and maintenance of GA in surgical patients (ASA class III or higher) undergoing GA.

IV administration of remimazolam was continued at a dose of 6 or 12 mg/kg/h until loss of consciousness was observed. After loss of consciousness, intravenous administration was started at a dose of 1 mg/kg/h, and infusion rate adjusted as appropriate (upper limit: 2 mg/kg/h), based on monitoring of the systemic condition of the subject until the end of the surgery.

The planned number of subject was 50 (25 in each group). A total of 67 subjects were registered (33 in the 6 mg/kg/h group and 34 in the 12 mg/kg/h group); 62 subjects were included in the FAS (31 in the 6 mg/kg/h group and 31 in the 12 mg/kg/h group) and 55 in the PPS (27 in the 6 mg/kg/h group and 28 in the 12 mg/kg/h group).

The primary efficacy endpoint was remimazolam functional capability as general anesthetic (assessed on the basis of a composite of the three variables described below). The investigational product was assessed as "Effective" if all three variables were absent or "Ineffective" if at least one of these three variables was present:

- Intraoperative awakening/recall
- Requirement of rescue sedation with other sedatives
- Body movement

The secondary endpoints are listed below:

- Time from start of administration of investigational product to loss of consciousness
- Intraoperative awakening/recall
- Requirement of rescue sedation with other sedatives
- Body movement
- BIS value at each time point of evaluation
- Time from end of administration of investigational product to awakening
- Time from end of administration of investigational product to extubation
- Time from end of administration of investigational product to patient stating his/her date of
- birth
- Time between end of administration of investigational product and determination of ability to
- discharge the patient from the operating room
- Controllability of anesthesia depth

Looking at the efficacy results, 62 subjects (31 in the ONO-2745 6 mg/kg/h group and 31 in the ONO-2745 12 mg/kg/h group) were included in the FAS, which was used as the primary analysis set for efficacy.

The functional capability of remimazolam as general anesthetic was evaluated as the primary endpoint for efficacy. The rate of efficacy for the functional capability of remimazolam as general anesthetic was 100% in both the 6 and 12 mg/kg/h groups.

For induction of anesthesia, LoC by continuous intravenous administration of remimazolam was observed in all subjects, showing that remimazolam could induce anesthesia appropriately. The mean time from start of IMP administration to loss of consciousness was 97.2 and 81.7 seconds in 31 subjects in the 6 mg/kg/h group and 31 subjects in the 12 mg/kg/h group, respectively, showing there was a significant shorter mean time from start of remimazolam administration to loss of consciousness in the 12 mg/kg/h group compared with the 6 mg/kg/h group. The mean dose (5% to 95% point) of remimazolam until loss of consciousness was 0.16 (0.11 to 0.24) and 0.27 (0.17 to 0.42) mg/kg in 31 subjects in the 6 mg/kg/h group, and 31 subjects in the 12 mg/kg/h group, respectively.

For maintenance of anesthesia, continuous administration of remimazolam, with proper dose adjustments while monitoring BIS value and systemic condition, was possible. The mean optimal infusion rate (5% to 95% point) during maintenance of anesthesia with remimazolam was 0.56 (0.13 to 1.00) and 0.57 (0.10 to 1.00) mg/kg/h in the 6 mg/kg/h and 12 mg/kg/h groups, respectively.

The mean BIS value during maintenance of anesthesia was in ranges from 46.0 to 68.0 and 44.7 to 67.5 in the 6 mg/kg/h and 12 mg/kg/h groups, respectively.

The mean time from end of remimazolam administration to awakening, extubation, patient stating his/her date of birth, and determination of ability to discharge the patient from the operating room was 9.6, 12.8, 15.2, and 18.0 minutes, respectively, in the 6 mg/kg/h group and 8.6, 11.6, 17.7, and 21.6 minutes, respectively, in the mg/kg/h group, showing there were no statistically significant differences between the 6 mg/kg/h and 12 mg/kg/h groups (p=0.6307, p=0.5975, p=0.3617, and p=0.1808, respectively).

Flumazenil was administered to two subjects in the 6 mg/kg/h group who did not awaken 30 minutes after the end of remimazolam administration. The mean time from flumazenil administration to awakening was 1.0 minute, the mean time to extubation was 2.0 minutes, the mean time until the patient could state his/her date of birth was 3.0 minutes, and the mean time until determination of ability to discharge the patient from the operating room was 3.5 minutes, and no re-sedation was reported in these two subjects in the 6 mg/kg/h group.

Controllability of anesthesia depth was "very good" or "good" in all subjects.

2.6.6 Discussion on clinical efficacy

The efficacy of remimazolam for induction and maintenance of GA was evaluated in six clinical trials.

Studies **CNS7056-022** and **ONO-2745-05** were the two pivotal studies, the former conducted in Europe, the latter in Japan. Both were randomised, open-label, non-inferiority studies using propofol as comparator.

The non-inferiority margin for study CNS7056-022 was discussed during a scientific advice procedure (EMA/CHMP/SAWP/14117/2018) and the NIM of 10% was found to be acceptable.

This trial planned to randomly enrol 542 patients. However, due to the pandemic, the trial was terminated before the sample size could be reached. At the time of termination, 365 patients had been randomised (about 67% of planned sample size).

One protocol amendment for Germany only, and three global protocol amendments occurred. The protocol amendment for Germany only and the first global protocol amendment occurred before FPFV, thus they did not impact the study results. The second and third global protocol amendments included

many minor changes. However, two important exceptions were noted and required further clarification from the MAH. In the second global protocol amendment, the dosing regimen for remifentanil was changed, from remifentanil in the range of 0.2 to 0.5 µg/kg/min, for the first 15 minutes after the first skin incision, to from intubation until 15 minutes after first skin incision, remifentanil was to be dosed between ≥0.1 to ≤0.2 µg/kg/min, depending on the individual needs of the patient. In other words, the dosing was significantly reduced, and the reduction concerned the critical period (15 minutes after the first skin incision), when haemodynamic superiority to propofol was tested. One of the most common adverse reactions of remifentanil is hypotension; therefore, this protocol amendment could have influenced study results. This concern was addressed accordingly. The reduction of the remifentanil dose during the first 15 minutes after the first skin incision was done at the request of several investigators. The reduction was done via the Global Protocol Amendment (GPA) 2, when only 50 of the total participants (13.7%) had been already included. The MAH provided additional analyses, as requested, showing results for patients randomised before and after GPA 2, per treatment arm. It was reassuring to see that the results before and after GPA 2 did not differ to a clinically important extent. The MAH further explained that, although in GPA 3 changes to Section 'Analysis Populations' occured, these changes were only wording clarifications. The definitions of populations did not change and therefore there was no change in the assignment of any individual patient to the analysis populations. Regarding the protocol deviations leading to exclusions from the PP1 and PP2 sets, no particular concerns arose from these exclusions.

The primary efficacy endpoint (PEP) was the anaesthetic effect of remimazolam and propofol assessed as percent (%) of time of NCI ≤60 during the maintenance phase of the GA, defined as the time between the first skin incision and the completion of the last skin suture. The confirmatory statistical analysis of the primary endpoint was conducted on the PP1.

Secondary efficacy endpoints were designed to evaluate time to onset of action of both IMPs. **Haemodynamic instability was defined as the key secondary endpoint (KSE).** Superiority of remimazolam over propofol in terms of the KSE was defined as critical decrease(s) in mean arterial blood pressure (MAP) between start of investigational medical product and 15 minutes after the first skin incision.

One interim analysis (IA) and one final analysis (FA) were planned for study CNS7056-022. The primary efficacy endpoint (PEP) was to be analysed at IA, while the key secondary endpoint (KSE) was to be analysed at both IA and FA.

The SAP was updated several times (SAP V 2.0 was in place at the time of trial starting, but the Wilcoxon test was only present in V 7.0 KSE confirmatory analyses, and these were not pre-planned). It became apparent that relevant (superiority) analyses were implemented *a posteriori*, which might jeopardize the real effect of the product. In spite of the lack of anticipation of the sample type of patients, the MAH justified the adaptation of the SAP to allow a minimally adequate primary analysis assessment.

Primary endpoint

The mean difference between remimazolam and propofol in percentage of time spent with NCI ≤60 during the maintenance phase of the GA was -4.24, with a lower boundary of the 97.5% CI of -7.48, which is above the pre-defined threshold of 10. Therefore, non-inferiority of remimazolam to propofol was confirmed. As pointed out during scientific advice (EMA/CHMP/SAWP/14117/2018), since the dosing is adaptive and based on the target NTC score, this endpoint, by definition, will almost always be reached.

Although the MAH considered there was no significant difference from propofol in the ToI of PEP, a clinically significant difference in the variance was noted by the CHMP, with patients in the remimazolam arm requiring up to 528 minutes and propofol patients up to 361 minutes. The standard deviation was 90.6 minutes in remimazolam and 74.5 minutes in propofol. A discussion on this matter was therefore

deemed necessary to ascertain whether propofol seemed more reliable or not in induction of GA. Ultimately, it was concluded that, in spite of the increase in the meantime of interest of 12 minutes for remimazolam as compared to propofol, the median only differs in four minutes. Even in prolonged surgeries, the difference is considered as not clinically relevant. On the other hand, the induction of GA is numerically quicker with remimazolam. All aspects considered, it was agreed that the numerical difference is non-clinically significant.

"Key" secondary endpoint

Several secondary efficacy endpoints pointed towards a different direction from the primary endpoint, such as time to orientation in study CNS 7056-022, where propofol performed significantly better than remimazolam.

Onset of effect - the time to event secondary efficacy endpoints indicated a slightly quicker onset of action in remimazolam compared to propofol, although these results were difficult to interpret in the light of a higher percentage of patients with too deep anaesthesia in remimazolam arm.

Offset of effect - the secondary efficacy outcomes of time from the stop of the IMP to extubation were similar in both treatment arms. However, a difference was observed in time from stop of IMP to response to verbal command (15 min in remimazolam compared to 12 min in propofol). An even larger difference disfavouring remimazolam is observed in time from stop of IMP to orientation (54 minutes in remimazolam compared to 30 minutes in propofol). The almost doubling of time to orientation in time, place, person and situation observed with remimazolam was noted as clinically relevant and unlikely to be solely the consequence of lack of experience with the product. The prolonged disorientation is outlined in the SmPC (section 4.4, 4.8).

Similarly, time to modified Aldrete Score ≥9 was 53 minutes in remimazolam compared to 37 minutes in propofol groups with almost no overlapping in CIs (95% CI 44-58 mins for remimazolam and 28-45 mins for propofol). Since the modified Aldrete score is used to evaluate patients in post anaesthesia care, with the purpose to check whether they can be safely discharged, this information is considered to be of importance for healthcare practitioners, thus outlined in the SmPC (section 4.4, 5.1). These characteristics demand more time from the anaesthesiologist team to attend the patient after surgery.

Explicit awareness (incidence of the occurrence of intra-operative awakening) was not evident in either treatment groups during the procedures. However, unspecific, potential signs of intraoperative awakening were reported with a notably higher occurrence in remimazolam arm compared to propofol (18.5% vs 7.4%). This could partially be explained by the unfamiliarity of investigators with remimazolam resulting in closer observation of patients.

The percentage of time with NCI ≤60 and ≥27 during the maintenance (first skin incision to last skin suture) was higher in the PPF arm than in the RMZ (78% vs 68%) arm based on the FAS. This was due to a higher proportion of patients with both NCI< 27 and NCI>60, which may be related to a higher difficulty in adequately refine the level of anaesthesia.

Secondary efficacy endpoints related to NCI and rescue/other sedatives generally showed a higher percentage of time within the target NCI in propofol, as well as a higher percentage of time below target NCI in remimazolam arm. The percentage of patients in target NCI range during ≥90% of maintenance was higher in propofol compared to remimazolam arms (56.8% vs 34.8%, respectively). Consistent with these results, the use of rescue sedatives and other sedatives was higher among patients receiving remimazolam compared to patients receiving propofol. To summarise, these results indicated better secondary efficacy results with propofol. However, the familiarity of investigators with propofol compared to no prior experience with remimazolam might play an important role in these results.

Hemodynamic stability was analysed separately, as a key secondary outcome. Superiority of remimazolam over propofol was formally evaluated only in the European pivotal study. The CHMP noted that the conclusions of this analysis are hampered by post-hoc modifications of the statistical analysis plan. Therefore, no superiority of remimazolam over propofol on the account of haemodynamic stability can be claimed.

The MAH argued that based on historical data from previous remimazolam trials, a normal distribution was assumed for this endpoint and a 2-sided z-test comparing the mean number of events of haemodynamic instability per patient between the two treatment groups was chosen to demonstrate this. Study power and sample size was calculated using assumption of normal distribution for KSE. However, historical data were not graphically displayed, and normality tests were not presented, so appropriateness of the assumption of normal distribution does not appear to be adequately justified. Moreover, considering the definition of this endpoint, and the fact that the observation is count data, the assumption of normal distribution instead of Poisson or negative binomial distribution does not seem appropriate.

When the data were unblinded for the interim analysis, a non-normal asymmetric distribution was seen. Using the Pearson Chi-Square test by Maximum Likelihood Estimations, the KSE event data was found to have negative binomial distribution (NBD) for the FAS population, which, in line with the above comments, could have been expected from the start. It is agreed that, in case of non-normally distributed data, the use of z-test is not appropriate.

The MAH further argued that during IA a high correlation between the sub-events of the composite KSE endpoint was found. This should also have been expected in the planning stage considering the definition of this endpoint (e.g. it is clear that all patients who have MAP decrease of > 30% also have MAP decrease of > 20%). The MAH claimed that "*As recommended by the ICH E9, in case of a composite endpoint the high inter-component correlation of the sub-events must be taken into account*" and "*Moreover, sub-events with high correlation to each other (20% and 30% decrease) were discouraged by general guidelines*". However, such recommendation could not be found neither in ICH E9 nor in ICH E9(R1).

In addition, the composite endpoint did not seem to be validated.

Taking into account all of the above, it seemed that, in the planning stage, the MAH did not thoroughly think through all relevant aspects of this endpoint.

Thus, the MAH proposed a new method to analyse KSE: the Common Factor Analysis (CFA). The CFA is a statistical method used to describe variability among observed, correlated variables in terms of a potentially lower number of unobserved variables called factors. However, the argumentation for the choice of factors to be included in the analysis was unclear, and it was difficult to conclude how well the selected factor represents the original data.

Although it can be agreed with the MAH that an endpoint without highly correlated components would be more relevant than the initially planned one, clinical relevance of the observed difference is ultimately difficult to interpret.

In line with the discussions during the scientific advice procedure EMEA/H/SA/2825/1/FU/2/2017/SME/II, the MAH was asked to present results of the KSE that counts only events of "Incidence of MAP dropping below 65 mmHg for at least 1 min duration" and "Number of norepinephrine boluses (0.01 mg) required or, if an infusion is used to maintain MAP equal to or above 65 mmHg, then each time interval of 2 min duration of continuous norepinephrine infusion will be counted as one event." (i.e. sub-components 1 and 4 of the initially proposed KSE). The MAH provided the requested analyses and it was reassuring to see that, according to the subcomponents which are clinically most meaningful, remimazolam was associated with less events of MAP drops below 65mmHg and with less events of norepinephrine administrations compared to propofol.

Regarding investigator's overall satisfaction with IMP, it is acknowledged that that the majority of investigators found both treatments satisfactory, i.e. on the scale of 1 to 10 with 1 being the lowest and 10 the highest level of satisfaction, a score above 8 was registered for 55.2% patients in remimazolam and for 54.7% patients in propofol group. However, the lowest level of satisfaction (category 1-3) was recorded for 7.4% patients in remimazolam and 3.2% in propofol groups.

Discussion of ancillary analysis for study CNS 0756-022

Preventing organ injury is the overarching concept behind anaesthetic management during surgical interventions. While oxygen consumption is usually downregulated during phases of anaesthesia due to a downregulation of the sympathetic nerve tone, the oxygen delivery to the tissues is still dependent on the oxygen uptake through the lungs and the transport of oxygen through the vascular system.

The setting of controlled ventilation, which is most frequently applied in the context of general anaesthesia, results in limited ventilatory compensation in regards to oxygen delivery and makes the haemodynamic situation so important. The human body controls the haemodynamic situation by two main parameters – cardiac output and vessel resistance. Both parameters then determine the mean arterial pressure (see Section 2.1.1).

Scientific literature focuses on thresholds for MAP with regards to haemodynamic monitoring, simply due to the fact that non-invasive measurements of blood pressure are easily and reliably possible, whereas non-invasive measurements of more complex parameters, such as cardiac output and vessel resistance are not easily implementable, and sometimes do not exist yet.
Mean arterial pressure alone may not always be the correct guide to recognize low oxygen delivery. For example, a low cardiac output combined with a high systemic vessel resistance may produce a reasonably high mean arterial pressure although the end organs still suffer due to too little blood delivery. Hence, it is recommended to widen the view when describing the haemodynamic situations of patients in general and for the purpose of the evaluation of the effects of propofol and remimazolam in particular.

Results were therefore evaluated and presented for the above-mentioned main parameters – CO, SVR and MAP. In addition, evaluations were presented for the reversed adjusted area under the curve (RAAUC) and for the use of vasopressors.

Besides very few exceptions, all parameters in all patient populations and for all time periods of interest clearly demonstrated significant differences in favor of remimazolam. Exploring these differences along their physiological dependencies of the underlying parameters leads to substantial and clinically relevant advantages for remimazolam in both, cardiac output and MAP, which are -statistically evident- more compromised under propofol than under remimazolam and indicate that the MAP as well as the CO consistently remained above those thresholds which are associated with organ injury.

The above presented analyses are considered a robust body of evidence for a statistically significant and clinically relevant advantage of remimazolam over propofol. This advantage should be seen in the superior preservation of the haemodynamic status rather than in an "improvement" of haemodynamic stability.

It is of particular importance that these advantages were demonstrated for remimazolam *despite* the fact that significantly more vasopressors were used in the propofol group. It seems to be common sense that the significantly higher need to administer a vasopressor to preserve haemodynamic stability is a disadvantage in itself.

Clinical relevance can best be demonstrated in the evaluation of the RAAUC, namely the integration of the time periods in which patients were under the threshold of 65 mmHg. Salmasi et al have clearly demonstrated the dependency of organ injury on both dimensions, the extent of MAP decrease (in mmHg

below 65 mmHg) as well as the duration of this decrease. It is therefore a relevant difference if MAP drops further below 65 mmHg and remains for a longer time below that threshold.

Discussion

The choice of the studies mostly on cardiac surgery was chosen due to the availability of invasive haemodynamic data. However, this significantly decrease the external validity and extrapolation exercise to the other types of surgical procedures: first, on these pts a tight control of the haemodynamic parameters is performed (the justification for invasive continuous monitoring); second, there are other variables which, if not balanced among the different study arms, may influence the results. The Applicant has studied one of these very important variables – the use of vasopressors – but not the blood loss / use of erythrocyte transfusions. Also, along the discussion, the Applicant highlights the high variance of remimazolam or propofol for to extol the haemodynamic advantage of remimazolam, but the rationale should be identical. One cannot mention or deemphasise variance in remimazolam results of MAP, and emphasise variance in propofol data of SVR, especially when vasopressors are concomitantly used.

All things considered and weighing the fact that most of these procedures were cardiac surgeries, there is only one aspect which is considered clinically relevant and likely devoid of other confounders, which is the use of concomitant vasopressors. While the doses were similar between remimazolam and propofol – as would be expected, the percentage of time under vasopressors is 23% witn remimazolam and 42% with propofol. This is considered an indirect measure of haemodynamic stability. Very experienced anaesthesiologists like those who assist cardiac surgery are capable of continuously control haemodynamic status of the patient, at the cost of a higher use of vasopressor agents.

Study **ONO-2745-05**

The primary efficacy endpoint was functional capability as a general anaesthetic and was achieved by all participants (100%) in each of the treatment arms.

Regarding the mean time from initiation of study drug to loss of consciousness, propofol showed statistically significant shorter time compared to both doses of remimazolam (78.7 seconds in propofol compared to 102.0 seconds in remimazolam 6 mg/kg/h and 88.7 seconds in remimazolam 12 mg/kg/h groups).

Regarding the mean time to awakening, extubation, stating date of birth, and decision to exit the operating room, propofol showed statistically significant shorter time compared to both doses of remimazolam.

The mean (5 to 95 percentile points) optimal infusion rate during maintenance of anesthesia in the ONO-2745 6 mg/kg/h group and ONO-2745 12 mg/kg/h group was 0.97 (0.40 to 1.58) and 0.99 (0.40 to 2.00) mg/kg/h, respectively.

The time (mean) from end of IMP administration to awakening, extubation, stating date of birth, and decision to exit the operating room in the ONO-2745 6 mg/kg/h group were 14.9, 19.2, 24.8 and 28.7 minutes, respectively, and 14.5, 19.2, 24.1 and 27.9 minutes, respectively, in the ONO-2745 12 mg/kg/h group. In the propofol group (n=75), the mean time to awakening, extubation, stating date of birth, and decision to exit the operating room were 10.3, 13.1, 15.6 and 19.1 minutes, respectively, which were statistically significant shorter durations compared with both remimazolam groups.

Study **CNS7056-010**

The primary efficacy endpoint was the proportion of patients with successful anaesthesia (defined a no use of rescue of sedative medications). By that definition, anaesthesia was successful in all patients except one in the remimazolam 12 mg/kg/h-induction group and one in the propofol/sevoflurane group.

In general, time to events were shorter in the propofol/sevoflurane group than in the two remimazolam groups. No difference was observed between the treatment groups regarding time to discharge from PACU/ICU (approximately 27 hours) and time to discharge from hospital (identical 95%CI 8-11 in all treatment arms).

Haemodynamic stability was investigated in this study. All patients were administered vasopressors and cardio-depressive effects were assessed using two specific safety endpoints: cardiac instability and low cardiac output syndrome (both composite outcomes). The incidence of cardiostability was higher in the pooled remimazolam group (27.4%) than in the propofol/sevoflurane group (14.3%). Between the two remimazolam doses, the 6 mg/kg/h showed higher incidence of cardiostability (35.3%) than the 12 mg/kg/h (17.9%). During general anaesthesia (including recovery period until extubation), proportions of patients with a low cardiac output syndrome were larger in the propofol/sevoflurane group (25%) than in the pooled remimazolam group (14.5%) as well as 6 mg/kg/h and 12 mg/kg/h induction dose groups (14.7% and 14.3% respectively).

Study **ONO-2745-06**

The rate of efficacy for the functional capability of remimazolam as general anesthetic (defined as the absence of intraoperative awakening/recall and requirement of rescue sedation and body movement) was 100% in both ONO-2745 6 and 12 mg/kg/h groups.

2.6.7 Conclusions on clinical efficacy

Loss of consciousness was achieved and maintained in nearly all patients receiving remimazolam during surgical procedures. Thus, general anaesthesia was achieved (efficacy: nearly 100%). Based on the mechanism of action and the fact that the medicine was titrated to effect, this was expected.

Time to onset of action appears to be shorter in remimazolam compared to propofol (although with some conflicting results in the two pivotal studies) while time to offset is consistently shorter in propofol compared to remimazolam, as communicated in the SmPC (see section 5.1).

Haemodynamic stability results are only formally evaluated in one study (the European pivotal study) and the conclusions are hampered by post-hoc modifications of the statistical analysis plan. No superiority of remimazolam over propofol on the account of haemodynamic stability can be firmly claimed.

2.6.8 Clinical safety

2.6.8.1 Patient exposure

As detailed in the Table 48, a total of 783 patients received remimazolam across all GA studies, group C.

Of these 783 patients 529 received low dose remimazolam for induction, whilst 254 received high dose remimazolam for induction.

A total of 226 patients received propofol as comparison within group C.

The mean cumulative dose of remimazolam was 255.61 mg ranging from a minimum of 14 mg up to a maximum of 1399 mg.

The mean duration of exposure of remimazolam was 213.0 minutes, whilst the maximum exposure was 682.9 minutes.

The minimum duration of exposure was 3.9 minutes.

Table 48: Study drug exposure across all GA studies

Study drug exposure (group C)	Low-Dose Remimazolam (N =529)	High-Dose Remimazolam (N = 254)	Total Remimazolam (N = 783)	Total Propofol (N = 226)
Cumulative Dose (mg)				
Mean (SD)	269 (194)	227 (183)	256 (192)	1356 (760)
Median	219	184	210	1174
Min, Max	14, 1399	14, 998	14, 1399	40, 7133
Duration (minutes)				
Mean (SD)	221 (108)	196 (109)	213 (109)	202 (90)
Median	205	189	197	192
Min, Max	5, 667	4, 683	4, 683	40, 515

An overview of the clinical trials in general anaesthesia and the safety endpoints across these GA studies are provided in the tables below.

Table 49: Overview of clinical trials in general anaesthesia

Trial ID	Treatment Arms (number of subjects)	Dosing regimens			
		Remimazolam		Comparator	
		Induction	Maintenance	Induction	Maintenance
ONO-2745-03	Part A: n = 25 • A1 : n= 5 • A2 : n= 10 • A3 : n= 5 • A4 : n= 5 Part B : n = 30 Part C • C1 :n=10 • C2 :n=5 • C3 :n=5 Part D : n=10	*Part A:* A1 = 6 mg/kg/hr A2 = 12 mg/kg/hr A3 = 21 mg/kg/hr A4 = 30 mg/kg/hr *Part B:* 12 mg/kg/hr *Part C* C1 = 4 mg/kg/hr C2 = 8 mg/kg/hr C3 = 12 mg/kg/hr *Part D*: 4 mg/kg/hr	*Part B:* Starting rate = 1 mg/kg/hr Range = 0.8 to 2.0 mg/kg/hr *Part D:* Starting rate = 1 mg/kg/hr Range = 0.4 to 1.0 mg/kg/hr	N/A	N/A
CNS7056-010	Group 1: n=28 Group 2: n=24 Group 3: n= 28	Group 2 6 mg/kg/hr Group 3 12 mg/kg/hr	Group 2 & 3 Starting rate = 1 mg/kg/hr Maximum rate = 3 mg/kg/hr	Group 1 Propofol 2.0 to 2.5 mg/kg	Group 1 *Prior to commencing extracorporeal circulation:* Sevoflurane = 0.8 – 2.5 minimum alveolar concentration *After commencing extracorporeal circulation:* Propofol = 3 to 12 mg/kg/hr
CNS7056-011	Group 1: n=5 Group 2: n=18	Group 2 6 mg/kg/hr	Group 2 Starting rate = 1 mg/kg/hr Maximum rate = 3 mg/kg/hr	Group 1 Propofol 1.0 to 2.5 mg/kg	Group 1 Propofol 3 to 9 mg/kg/hr
CNS7056-022	Remimazolam: n= 291 Propofol: n = 118	t=0 min: 6 mg/min t=3 min: 2.5 mg/min t=10 min: 1.5mg/min t=20 min: 1 mg/min	0.7 to 2.5 mg/min	Propofol t=0 min: 30 mg/kg/hr t=3 min: 10 mg/kg/hr t=10 min: 8 mg/kg/hr t=20 min: mg/kg/hr	Propofol 4 to 10 mg/kg/hr
ONO-2745-05	Remimazolam 6 mg/kg/hr: n=150 Remimazolam 12 mg/kg/hr: n=150 Propofol: n=75	6 mg/kg/hr or 12 mg/kg/hr	Starting rate = 1 mg/kg/hr Maximum rate = 2 mg/kg/hr	Propofol 2.0 to 2.5 mg/kg	Propofol 4 to 10 mg/kg/hr
ONO-2745-06	Remimazolam 6 mg/kg/hr: n=31 Remimazolam 12 mg/kg/hr: n=31	6 mg/kg/hr or 12 mg/kg/hr	Starting rate = 1 mg/kg/hr Maximum rate = 2 mg/kg/hr	N/A	N/A

Table 50: Safety endpoints across the GA studies

	ONO-2745-03	CNS7056-010	CNS7056-011	ONO-2745~05	CNS7056-022	ONO-2745-06
Adverse Events	✓	✓	✓	✓	✓	✓
Laboratory tests	✓	✓	✓	✓	✓	✓
Physical examination	×	✓	✓	×	✓	×
12 lead & continuous ECG monitoring	12 lead & continuous ECG monitoring	12 lead & continuous ECG monitoring	12 lead ECG	12 lead & continuous ECG monitoring	12 lead & continuous ECG monitoring	12 lead & continuous ECG monitoring
Vital Signs	NIBP monitoring at pre-scheduled timepoints	Continuous monitoring via PiCCO	Continuous monitoring via PiCCO	NIBP monitoring at pre-scheduled timepoints	Continuous monitoring via FloTrac	NIBP monitoring at pre-scheduled timepoints
Monitoring for injection site reaction	Monitoring from start of IMP till day 2	×	×	Monitoring from start of IMP till day 2	Pain on injection from start of IMP till LOC	Monitoring from start of IMP till day 2
Agitation/Delirium	Observation of agitation from start of IMP till LOC	Richmond Agitation & Sedation Scale following extubation	MMSE once on the normal ward and once prior to discharge	Observation of agitation from start of IMP till LOC	Nu-DESC following arrival at PACU until fit for discharge	Observation of agitation from start of IMP till LOC
Requirement of vasopressor	✓	✓	✓	✓	✓	✓
Invasive Haemodynamic monitoring	×	✓ (PiCCO)	✓ (PiCCO)	×	✓ (FloTrac)	×
Haemodynamic assessment	×	×	The amount of norepinephrine administered between start of study medication and the completion of the last skin suture	Proportion of time points where systolic blood pressure was maintained within a range of ≥80 and <150 mmHg among all time points of evaluation	Number of haemodynamic events between start of IMP and 15 minutes after the first skin incision.	Proportion of time points where systolic blood pressure was between 80 mmHg and <150 mmHg among all time points of evaluation
Bradycardic events	×	×	×	×	Bradycardic events including requirement for glycopyrrolate/atropine	×
Reintubation	×	✓	✓	×	×	×

Pooling Strategy

To allow a broader comparison of the safety of remimazolam, data was pooled across six GA studies. Studies were pooled into two different groups: group B, which included the controlled studies, and group C, which included all GA studies (please refer to the Table 51). Pool A was used for efficacy analyses only.

All analyses are based on the safety (SAF) population, which is defined as all subjects who received at least one dose of remimazolam or active comparator and was evaluated as being treated.

Table 51: Pooling of studies for comparison of safety

Group	Studies	Treatment Groups Analyzed Safety
Group A: Pivotal Trials (N=2)	ONO-2745~05 CNS7056-022	Total remimazolam Low dose induction RMZ 6 mg/kg/h (ONO-2745-05) and 6 mg/min (CNS7056-022), High dose induction RMZ 12 mg/kg/h (ONO-2745~05) Propofol
Group B: Controlled trials (N=4)	ONO-2745-05 CNS7056-022 CNS7056-010 CNS7056-011	Total remimazolam Low dose induction RMZ • 6 mg/kg/h (ONO-2745-05, CNS7056-010, CNS7056-011) and • 6 mg/min (CNS7056-022), High dose induction RMZ • 12 mg/kg/h (ONO-2745-05, CNS7056-010), Propofol
Group C: All GA trials (N=6)	ONO-2745-05 CNS7056-022 CNS7056-010 CNS7056-011 ONO-2745-03 ONO-2745-06	Total remimazolam Low dose induction RMZ • 6 mg/kg/h (ONO-2745-05, CNS7056-010, CNS7056-011, ONO-2745-03, ONO-2745-06) and • 6mg/min (CNS7056-022), High dose induction RMZ • 12 mg/kg/h (ONO-2745-05, CNS7056-010, ONO-2745-03, ONO-2745-06), Propofol (ONO-2745-05, CNS7056-010, CNS7056-011 and CNS7056-022 only)

A safety analysis of pool A (not initially provided) was performed upon request during the course of this procedure. While there are some expected differences between group A (cardiac surgery) and the pooled group B, the AE profile is not critically different, nor any higher frequency AE in cardiac surgery deserve mention, apart from the higher percentage of patients experiencing agitation on recovery from cardiac surgery as compared to the pooled surgeries. This may in fact be related to the higher use of flumazenil in cardiac surgery and is thus justified.

Across both groups (B & C) the treatment groups for comparison include total remimazolam, low dose remimazolam (6 mg/kg/h or 6 mg/min), high dose remimazolam (12 mg/kg/h) and propofol. ONO-

2745-03, within group C, also contained induction dose levels 4, 8, 21 and 30 mg/kg/hr. Data pertaining to these 35 patients is not included in the analysis. It is important to note that low and high dose remimazolam pertains to the induction dose only, i.e. an infusion rate that was used during the first few minutes of treatment. The average cumulative dose for these two treatment groups was very similar. In general group C was used for comparison between treatment groups relating to study drug exposure, demographics and baseline characteristics and group B for TEAEs. Unless relating to induction, comparisons were made between total remimazolam and total propofol. All comparisons are based on the SAF unless specified.

The safety database (including 783 patients) is not large enough to capture rare adverse events. That is a, given the expected widespread of use of remimazolam.

2.6.8.2 Adverse events

An overall summary of TEAEs for controlled studies in general anaesthesia is presented in the Table 52. The incidence of TEAEs was largely similar across the total propofol and remimazolam groups.

Table 52: Overall Summary of Treatment-emergent Adverse Events in Controlled Trials in General Anaesthesia

	Total	Total
	Remimazolam	Propofol
	(N = 671)	(N = 226)
Any TEAE	596 (88.8%)	209 (92.5%)
Severity of TEAE		
Mild	314 (46.8%)	107 (47.3%)
Moderate	234 (34.9%)	82 (36.3%)
Severe	48 (7.2%)	20 (8.8%)
Relationship with study drug		
Not Related	239 (35.6%)	58 (25.7%)
Related	357 (53.2%)	151 (66.8%)
Any TEAE that led to IMP discontinuation	5 (0.7%)	1 (0.4%)

The incidence of mild, moderate or severe TEAEs is also similar across total remimazolam and total propofol groups.

Only one severe TEAE occurred with a frequency of $\geq$1%, pleural effusion, and predominantly in studies where cardiac surgeries were performed. These TEAEs are likely to be secondary to the patient's medical history or surgical procedure. All other severe TEAEs occurred with a low frequency, and with a similar incidence between remimazolam and propofol group.

As the incidence of TEAEs in the total remimazolam and total propofol group was generally similar, a meaningful comparison of the relationship with the study drug can be made accordingly between these two groups. The incidence of related or not related TEAEs represents the percentage proportion of any TEAE for that particular treatment group. As it can be seen in the Table 52, there were a greater number of subjects with related TEAEs in the total propofol group [151 (66.8%)] in comparison to the total remimazolam group [357 (53.2%)].

Slightly more TEAEs led to discontinuation of the study drug in the total remimazolam group [5 (0.7%)] in comparison to the total propofol group [1 (0.4%)]. These TEAEs in the total remimazolam group were post procedural haemorrhage, vascular access site occlusion, cough, haemothorax and hypotension and, in the total propofol group, the TEAE was hypotension.

Common Adverse Events

TEAEs that occurred at an incidence of ≥1% in controlled trials in general anaesthesia are presented in the Table 53. In most cases, the incidence of these events in remimazolam patients was similar, or lower, than that observed in propofol patients. For any event that occurred more frequently in the total remimazolam group than in the total propofol groups, the difference in incidence between the groups was <5%.

The most common TEAEs in the total remimazolam group (>5%) by preferred term (PT) were: hypotension (25.0%), blood pressure decreased (20.1%), nausea (14.2%), bradycardia (10.1%), vomiting (9.7%), pleural effusion (9.7%), procedural nausea (7.9%), wound complications (6.9%), hypertension (6.4%), procedural vomiting (5.5%), pyrexia (5.5%), chills (5.5%), and postoperative anaemia (5.4%).

Table 53: TEAEs by SoC and PT with an Incidence of ≥1% in total remimazolam group in controlled trials in General Anaesthesia (Group B)

System Organ Class / Preferred Term	Total Remimazolam (N = 671)	Total Propofol (N = 226)
Blood and lymphatic system disorders	51 (7.6%)	15 (6.6%)
Anaemia	9 (1.3%)	6 (2.7%)
Blood Loss Anaemia	16 (2.4%)	4 (1.8%)
Coagulopathy	7 (1.0%)	2 (0.9%)
Leukocytosis	8 (1.2%)	2 (0.9%)
Thrombocytopenia	13 (1.9%)	6 (2.7%)
Cardiac disorders	131 (19.5%)	55 (24.3%)
Atrial Fibrillation	23 (3.4%)	11 (4.9%)
Bradycardia	68 (10.1%)	39 (17.3%)
Tachycardia	15 (2.2%)	1 (0.4%)
Gastrointestinal disorders	157 (23.4%)	40 (17.7%)
Constipation	8 (1.2%)	2 (0.9%)
Nausea	95 (14.2%)	26 (11.5%)
Vomiting	65 (9.7%)	13 (5.8%)
General disorders and administration site conditions	131 (19.5%)	53 (23.5%)
Chills	37 (5.5%)	11 (4.9%)
Oedema	11 (1.6%)	5 (2.2%)
Pain	21 (3.1%)	8 (3.5%)
Pyrexia	37 (5.5%)	10 (4.4%)
Therapeutic Product Effect Prolonged	33 (4.9%)	6 (2.7%)
Injury, poisoning and procedural complications	207 (30.8%)	72 (31.9%)
Anaemia Postoperative	36 (5.4%)	15 (6.6%)
Delayed Recovery From Anaesthesia	14 (2.1%)	2 (0.9%)
Post Procedural Haemorrhage	10 (1.5%)	2 (0.9%)
Postoperative Delirium	16 (2.4%)	3 (1.3%)
Procedural Hypertension	10 (1.5%)	3 (1.3%)

System Organ Class / Preferred Term	Total Remimazolam (N = 671)	Total Propofol (N = 226)
Procedural Hypotension	21 (3.1%)	11 (4.9%)
Procedural Nausea	53 (7.9%)	20 (8.8%)
Procedural Pain	24 (3.6%)	10 (4.4%)
Procedural Vomiting	37 (5.5%)	12 (5.3%)
Wound Complication	46 (6.9%)	11 (4.9%)
Investigations	310 (46.2%)	104 (46.0%)
Bilirubin Conjugated Increased	8 (1.2%)	0 (0.0%)
Blood Albumin Decreased	22 (3.3%)	6 (2.7%)
Blood Bilirubin Increased	16 (2.4%)	4 (1.8%)
Blood Creatine Phosphokinase Increased	30 (4.5%)	11 (4.9%)
Blood Pressure Decreased	135 (20.1%)	57 (25.2%)
Blood Pressure Increased	27 (4.0%)	3 (1.3%)
Electrocardiogram QT Prolonged	8 (1.2%)	5 (2.2%)
Glucose Urine Present	7 (1.0%)	1 (0.4%)
Haematocrit Decreased	17 (2.5%)	3 (1.3%)
Haemoglobin Decreased	22 (3.3%)	5 (2.2%)
Heart Rate Decreased	12 (1.8%)	5 (2.2%)
Heart Rate Increased	8 (1.2%)	0 (0.0%)
Lymphocyte Count Decreased	13 (1.9%)	3 (1.3%)
Mean Arterial Pressure Decreased	21 (3.1%)	7 (3.1%)
Neutrophil Count Increased	10 (1.5%)	2 (0.9%)
Oxygen Saturation Decreased	32 (4.8%)	16 (7.1%)
Protein Total Decreased	22 (3.3%)	6 (2.7%)
Protein Urine Present	16 (2.4%)	3 (1.3%)
Red Blood Cell Count Decreased	19 (2.8%)	3 (1.3%)
Urinary Occult Blood	15 (2.2%)	3 (1.3%)
Urinary Occult Blood Positive	32 (4.8%)	1 (0.4%)
Urine Ketone Body Present	8 (1.2%)	5 (2.2%)
White Blood Cell Count Increased	22 (3.3%)	4 (1.8%)
Metabolism and nutrition disorders	56 (8.3%)	21 (9.3%)
Fluid Retention	22 (3.3%)	5 (2.2%)
Hyperglycaemia	13 (1.9%)	7 (3.1%)
Hypokalaemia	8 (1.2%)	2 (0.9%)
Musculoskeletal and connective tissue disorders	29 (4.3%)	6 (2.7%)
Back Pain	20 (3.0%)	3 (1.3%)
Nervous system disorders	49 (7.3%)	14 (6.2%)
Dizziness	8 (1.2%)	2 (0.9%)
Headache	11 (1.6%)	2 (0.9%)
Psychiatric disorders	78 (11.6%)	25 (11.1%)
Agitation	33 (4.9%)	7 (3.1%)
Delirium	10 (1.5%)	4 (1.8%)
Insomnia	9 (1.3%)	1 (0.4%)
Sleep Disorder	33 (4.9%)	13 (5.8%)
Renal and urinary disorders	34 (5.1%)	12 (5.3%)

System Organ Class / Preferred Term	Total Remimazolam (N = 671)	Total Propofol (N = 226)
Haematuria	7 (1.0%)	5 (2.2%)
Oliguria	9 (1.3%)	2 (0.9%)
Respiratory, thoracic and mediastinal disorders	118 (17.6%)	54 (23.9%)
Bronchospasm	10 (1.5%)	4 (1.8%)
Cough	20 (3.0%)	3 (1.3%)
Hypoxia	22 (3.3%)	14 (6.2%)
Oropharyngeal Pain	7 (1.0%)	2 (0.9%)
Pleural Effusion	65 (9.7%)	25 (11.1%)
Pneumothorax	10 (1.5%)	2 (0.9%)
Respiratory Failure	14 (2.1%)	4 (1.8%)
Skin and subcutaneous tissue disorders	24 (3.6%)	6 (2.7%)
Erythema	10 (1.5%)	0 (0.0%)
Vascular disorders	213 (31.7%)	94 (41.6%)
Haematoma	10 (1.5%)	0 (0.0%)
Haemorrhage	7 (1.0%)	3 (1.3%)
Hypertension	43 (6.4%)	15 (6.6%)
Hypotension	168 (25.0%)	77 (34.1%)

PTs relating to haemodynamic changes were the ones most commonly observed: blood pressure decreased, hypotension and bradycardia. The incidence was lower in the total remimazolam groups in comparison to the total propofol groups: hypotension 25.0% vs 34.1%; blood pressure decreased 20.1% vs 25.5%; bradycardia 10.1% vs 17.3%, in remimazolam versus propofol groups, respectively.

Nausea (14.2% vs. 11.5%) and vomiting (9.7% vs 5.8%) were the only PTs where there was a substantially higher incidence in the remimazolam treatment groups in comparison to the propofol groups.

Within the general anaesthesia line extension, large parts of efficacy involved a comparison between treatment arms within group A. Safety comparisons were generally made between treatment arms in group B. Comparisons between the treatment arms in group A were not made, as these patients are included in group B, and it is expected that the frequencies of Treatment Emergent Adverse Events (TEAEs) is likely to be similar in group A and group B.

A comparison of the TEAEs in group A and group B is provided below.

Overview of TEAEs

Overall frequency of any TEAE and of drug related TEAEs was similar in group A and group B, but there were less mild and more moderate to severe TEAEs in group B (please see the Table 54). The difference between group A and B are the CNS7056-10 and CNS7056-11 trials, performed in cardiac surgery. Accordingly, in group B it can be expected a similar overall frequency, but more moderate or severe TEAEs, especially related to cardiac diseases.

A common TEAE within studies CNS7056-10 and CNS7056-11 was pleural effusion, a known complication of cardiac surgery (Labidi et al), which accounted for the majority of the differences in the moderate and severe TEAEs between group A and group B.

One additional case of a TEAE, leading to withdrawal of study medication was observed in group B. This was seen in CNS7056-10. One patient experienced a TEAE of hemothorax that started 90 minutes after the end of the elective surgical procedure. The TEAE was assessed as serious due to the need for immediate medical intervention. Intensity was assessed as life-threatening. The serious TEAE was assessed as not related to the study medication, permanently discontinued because of this serious TEAE, for which the subject required a re-operation with another general anaesthesia (of note: CNS7056-010 study protocol included continuation of remimazolam for sedation at Intensive Care Unit up to 24 hours, but not the use of study medication for re-surgery after the elective surgical procedure had ended). The patient recovered completely from this serious TEAE.

Table 54: Overall comparison of Treatment-Emergent Adverse Events in group A and group B

	Remimazolam (Group A)	**Remimazolam (Group B)**
	(N = 591)	(N = 671)
Any TEAE	517 (87.5%)	596 (88.8%)
Severity of TEAE		
Mild	313 (53.0%)	314 (46.8%)
Moderate	182 (30.8%)	234 (34.9%)
Severe	22 (3.7%)	48 (7.2%)
Relationship with study drug		
Not Related	197 (33.3%)	239 (35.6%)
Related	320 (54.1%)	357 (53.2%)
Any TEAE that led to IMP discontinuation	4 (0.7%)	5 (0.7%)

Source: GA-IA Table 3.3.1.1, Table 3.3.2.1.1, Table 3.3.2.1.2 and Table 3.3.5.1 group A and B

The incidence of TEAEs of the SOC (System Organ Class) GI disorders, investigations, nervous system, renal and urinary system, skin and subcutaneous tissue disorders, and vascular system disorders were similar between group A and group B.

The SOCs with a higher incidence in group B in comparison to group A were cardiac disorders, respiratory, thoracic and mediastinal disorders, blood and lymphatic system disorders, general disorders and administration site conditions, injury, poisoning and procedural complications and Metabolism and nutrition disorders, and psychiatric disorders. The difference in incidences ranged from 4.4 - 9.8%.

A higher incidence of TEAEs for the SOC cardiac disorders and respiratory, thoracic and mediastinal disorders was observed in group B in comparison to group A. Considering that the additional studies in group B are all cardiac surgeries, this is an expected finding.

A higher incidence of blood and lymphatic system disorders was observed in group B in comparison to group A. The TEAEs which were observed with a higher incidence in group B in comparison to group A were blood loss anaemia (16 [2.4%] vs 0 [0%]), coagulopathy (7 [1%] vs 0 [0%]), leukocytosis (8 [1.25%] vs 1 [0.3%]) and thrombocytopaenia (13 [1.9%] vs 3 [0.5%]) respectively. These findings are consistent with the use of extracorporeal circulatory circuits in cardiac surgery (Watel et al) and blood loss.

The higher incidence of general disorders and administration site conditions seen in group B in comparison to group A is due to higher frequencies of TEAEs chills (37 [5.5%] vs 25 [4.2%]), oedema (11 [1.6%] vs 1 [0.2%]) and therapeutic product effect prolonged (33 [4.9%] vs 21 [3.6%]) respectively. Reducing body temperature to protect the myocardium is commonly used in cardiac surgery (Saad et al) and is the likely reason contributing to a higher incidence of chills. The type of oedema was not specified. Ankle oedema secondary to cardiac impairment is more likely in patients undergoing cardiac surgery, who are likely to have a degree of cardiac impairment.

The differences between group B and group A for the SOC injury, poisoning and procedural complications conditions were due to the TEAEs postoperative anaemia (36 [5.4%] vs 3 [0.5%]), procedural nausea (53 [7.9%] vs 21 [3.6%]) and procedural vomiting (37 [5.5%] vs 12 [2.0%]). As highlighted above, it appears that a greater blood loss was observed in CNS7056-010 and CNS7056-011. This would help explain the increase in postoperative anaemia. The high incidence of nausea and vomiting is discussed further in this assessment report.

For the SOC Metabolism and nutrition disorders the PT which predominantly contributed to the higher incidence in group B in comparison to group A was fluid retention (22 [3.3%] vs 0 [0.0%], respectively). A large number of patients enrolled in studies CNS7056-10 and CNS7056-11 had a pre-existing history of heart failure; fluid retention is a known clinical sign within this population.

The difference in incidence in Musculoskeletal and connective tissue disorders between group B and group A was due to back pain (20 [3.0%] vs 0 [0.0%], respectively). Cardiac surgeries tend involve patients lying supine for prolonged periods: the long duration in a single position is the most likely cause of back pain.

For the SOC psychiatric disorders the TEAE agitation accounted for the difference between group B and group A (33 [4.9%] vs 0 [0.0%], respectively). Study CNS7056-10 accounted for the majority of patients that experienced agitation. A high incidence of flumazenil use was observed within this study: agitation is a known side effect of flumazenil and likely explains the high incidence of agitation in these patients.

In general all these differences are accountable to the special population of patients with cardiac diseases. This support's the claim, that the safety profile built based on group B is also applicable to group A.

2.6.8.3 Serious adverse event/deaths/other significant events

Deaths

There were no TEAEs with an outcome of death. Although no patients died during the observation periods of the GA studies, 1 patient in study CNS7056-022, randomised to propofol, died from a complex leakage of a major artery, approximately 1 month after completing the study. This was considered unrelated to the study treatment.

Other Serious Adverse Events

Overall, the incidence of serious TEAEs was slightly higher in the total propofol group in comparison to the total remimazolam group.

When comparing the SOC/PTs, the incidence of serious TEAEs was similar across the treatment groups. The SOC with the highest incidence of serious, TEAEs in both the total remimazolam and propofol group, was injury, poisoning and procedural complications which occurred in 2.7% of patients in both groups. Within this SOC, the PT with the highest incidence in both treatment groups was postoperative delirium, occurring in 1.0% of all total remimazolam patients and 1.3% of total propofol patients. This slightly higher incidence in the propofol group is in contrast to the incidence of non-serious postoperative delirium seen across the treatment groups, where there was a higher incidence in total remimazolam group

(2.4%) in comparison to the propofol group (1.3%). Postoperative delirium is a serious complication of GA, associated with a 30-day mortality of 7-10% (Jin, 2020). Its aetiology is multifactorial, and is most prevalent in older patients, those with existing neurocognitive disorders and those undergoing complex or emergency procedures. It is also noted that the choice of anaesthetic does not contribute to the risk of delirium.

Postoperative delirium is the only SAE PT with an incidence ≥1% in either the remimazolam or propofol group.A comparison of the frequency of **severe TEAEs** across group A and group B has also been looked at and noted as higher in group B (11%) than in group A (5%). Except for pleural effusion, which (as discussed above) is a known complication of cardiac surgery, the increase in severe TEAEs in group B cannot be attributed to a single PT and is likely to be representative of the surgery and the underlying patient characteristics.

Overview of serious TEAEs

A comparison of the frequency of serious TEAEs between group A and group B by SOC revealed an incidence approximately 2% higher in group B in comparison to group A. Where differences exist in serious TEAEs related to the SOC, these are reflective of the nature of the surgery and the patients enrolled (i.e. a higher frequency of serious SAEs for the SOCs cardiac disorders and respiratory, thoracic and mediastinal disorders in group B).

Protocol design and pharmacokinetic considerations

According to the study protocols for all studies with two remimazolam induction doses, the induction period extended for some minutes only versus a maintenance period, which often lasted for hours. Although there is a difference between the induction doses, the allowed range for the maintenance dose was identical for all these studies. Therefore, it can be concluded that the differences between the induction doses during the comparably short induction period have a minor and negligible effect on the quality of anesthesia during the maintenance period and subsequently, the duration of the maintenance period, in the case of the administration of a fast-acting drug, like remimazolam with half-lives of some minutes only and no relevant cumulative effect.

These data indicate that in trials that included a randomized allocation of patients to either the low or the high remimazolam induction dose there were no notable differences in

- the level of anaesthesia even early on during maintenance indicating that the extent of anaesthesia from the start of maintenance did not differ
- the average duration of surgery/maintenance, indicating that there were no complications prolonging the surgery time
- the maintenance dose, indicating that anaesthetic requirements were not greater in the low-dose remimazolam group
- the incidence of adverse drug reactions, indicating that neither a low nor a high dose presented a safety issue and confirming that the efficacy and safety were mainly determined by the maintenance dose rather than the induction dose.

This is supported by the known pharmacokinetic and pharmacodynamic characteristics i.e. a short alpha and beta half-life and a rapid keo which result in rapid changes of plasma and effect site concentrations following dose adaptations and a rapid corresponding change in the level of sedation/anaesthesia.

In summary, the data presented did not reveal sufficient evidence for an association between the low-dose induction dose of remimazolam and the duration of the maintenance. Moreover, all intra-study comparisons between low-dose and high-dose remimazolam induction doses revealed similar results. Since the observation made for pooled group C could not be confirmed to be methodologically superior

intra-study comparisons, these observations are considered not attributable to the remimazolam induction dose regimen.

There was a clinically significant higher frequency of nausea and particularly of vomiting in the remimazolam arm as compared to propofol. This might be of special concern in situations where Valsalva manoeuvres are to be avoided. The review and assessment of the detailed circumstances in which postoperative vomiting occurred did not reveal any relevant differences between remimazolam and propofol. Applying scientifically accepted risk factors onto those patients that experienced PONV revealed no relevant differences in distribution of those risk factors in both groups and thus confirmed the assessment from the review in detail. Moreover, the risk factors revealed a high predictive value for both groups – remimazolam and propofol- and thus, further confirmed the applicability of general risk factors for PONV also for remimazolam exposure. In particular, there was no evidence to suggest any characteristic which would foster PONV solely for remimazolam. The percentage of patients in which vomiting occurred as well as the percentage of patients in which a Valsalva manoeuvre should have been avoided are not statistically different between remimazolam and propofol, confirming the absence of a relevant difference between these two compounds with regards to a) Frequency of postoperative vomiting; b) Risk factors for PONV and c) Avoidance of Valsalva maneouvres.

2.6.8.4 Laboratory findings

Haematology

The incidence of markedly abnormal haematology was very low in all groups. Across all treatment groups there were no changes from baseline to follow-up which represented any concern.

Blood Chemistry

In general the incidence of markedly abnormal blood chemistry results was low and there were no changes from baseline to follow-up which represented any concern. A small increase in the number of patients experiencing a markedly abnormal creatinine kinase was observed across all groups at follow-up. This is a common finding with surgical procedures and not considered to be treatment related.

A substantial increase in the number of patients that experienced a markedly abnormal protein was seen at follow-up (protein <5.0 g/dL). The incidence appeared similar across the total remimazalom group and the total propofol group. However, the increase was greater in the high-dose remimazolam group and likely to be related to a dilution effect representing a fall in protein concentration due to administration of IV fluids rather than a fall in the absolute protein level.

Urinalysis

The FDA's *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* document provides severity classification for 3 urinary parameters. These are glucose, occult blood and protein. The incidence of patients experiencing markedly abnormal urinary protein and glucose was low.

It was noted that an increased number of patients experienced markedly abnormal occult blood within the urine at follow-up, predominantly in study ONO-2745-05. A deeper review of available data indicated only increased erythrocytes or positive urine occult blood testing, but not findings of casts. This made a renal cause of the haematuria unlikely and that the bladder or urethra are more likely to be the source of the bleeding. Urinary catheterisation is a common cause of post-operative haematuria. Post-operative catheterisation, to check for adequate urine production or urine retention, is considered an important element of post-operative nursing care. It is possible that such catheterisations are mentioned only in nursing notes and not registered routinely in clinical study documentation. Also, catheterisation during surgery may not have always been documented. This makes it difficult to assess how often

catheterisation may have occurred in the different studies during or after surgery. Benzodiazepines can have some muscle relaxant effects, which may reduce the ability to empty the bladder. Opiates may reduce the sensation of bladder fullness. This combination of drug effects in post-surgical subjects could result in single bladder catheterisation. Therefore, this finding was not thought to be treatment related.

As requested, the MAH elaborated further on the amount of evidence clearly relating haematuria to catheterization due to urinary retention, confirming that a signal of microscopic haematuria had arisen mainly from one trial (ONO-2745-05), but a final conclusion could not be made on the initial analysis due to limited data collected. Other studies in GA did not provide significant support for this signal.

The subsequent GA study CNS7056-022 collected additional information on microscopic haematuria in a structured way (and also data on catheterisation). These data did not show a significant difference in incidence of microscopic haematuria between treatment groups at any time. The study documented that incidence of clinically non-significant microscopic haematuria in surgery patients was approximately 23% prior to surgery and increased to 57% to 63% and 62% to 64%, on days 1 and 2, for propofol and remimazolam, respectively, after surgery, with no increase in the number of subjects with clinically significant haematuria. Approximately 80% of the study population received urinary catheterisation during surgery, with no significant difference between treatment groups. Other recent studies also did not provide evidence supporting a signal. With no evidence supporting any direct effect of remimazolam on urinary tract inflammation or crystallisation, no evidence suggesting a renal origin of haematuria, and with the hypothesis that some of the identified cases of microscopic haematuria may have resulted from surgical or early post-surgical bladder catheterisation, as part of routine anaesthesia, or post-surgical nursing case, the signal was considered refuted and closed. In conclusion, it is agreed on insufficient information to support a signal.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs

The mean arterial pressure (MAP) values and vasopressor use in remimazolam and propofol patients were explored to assess remimazolam haemodynamic stability over propofol.

Mean Arteral Pressure (MAP) following remimazolam and propofol use

A decrease in MAP < 65 mmHg is associated with an increased risk of myocardial and kidney injury (Salmasi et all, 2017). Therefore, this threshold was chosen to make comparisons between remimazolam and propofol. The haemodynamic profile of remimazolam, based on patients MAP, was assessed and compared against propofol, applying the reverse adjusted AUC method (RAAUC), a measure for duration and extent of MAP drop below the threshold of 65mmHg. Comparisons were made for extended induction, surgical intervention and recovery. Extended induction refers to the period between start of study medication and first skin incision.

Assessment of MAP AUC based on intrinsic factors

In adults (< 65) and elderly patients between 65-74 years remimazolam demonstrated statistically significant haemodynamic superiority over propofol across all 3 phases of anaesthesia. In the category, 75-84 the RAAUC was lower in the remimazolam group in comparison to the propofol group across all phases of anaesthesia. Although the difference was similar to that seen in the younger age groups, this did not reach statistical significance, probably because of the lower sample size. The oldest age group, $\geq$ 85 contained too few patients to allow any comparison of the data.

A pre-existing history of hypertension greatly increased the risk of patients developing intraoperative hypotensive events. Hypertension is not considered to be a risk factor for haemodynamic instability during the perioperative period. These findings are most likely explained by the patients anti-hypertensive medication, which continue to exert its effect during the perioperative period.

Assessment of MAP AUC based on extrinsic factors

The patient cohort receiving antihypertensive medications are generally the same as the hypertensive patients highlighted. As a consequence, a similar finding of greatly increased risk of intra-operative hypotensive events in patients who were on anti-hypertensives was observed. Remimazolam demonstrated statistically significant higher haemodynamic stability in patients receiving antihypertensive and/or beta-blockers across all phases of GA in comparison to propofol. A similar finding was also seen in patients who were not using these medications.

Findings for vasopressor use across the different age categories was similar to the RAAUC for MAP < 65 years. Vasopressor use was greater in patients < 65 years and in patients between 65-74 years who received propofol. This finding is similar in adults ≥ 75 years but, due to lower numbers, it could not be confirmed statistically. Findings of vasopressor use across ASA status was similar to those for RAAUC for MAP under 65 mmHg. Vasopressor use increased with higher ASA scores for both propofol and remimazolam.

2.6.8.5 In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6 Safety in special populations

Intrinsic Factors

Demographics

An overall review of the TEAE's was performed to determine if there was evidence of a differential response to treatment in the drug-demographic interaction subgroups; age, sex, race, ASA-PS classification, and weight/BMI.

Based on their relevance within GA, the following SMQs and CMQs were selected for comparison within subgroups:

- Cardiac disorders: bradycardia
- Vascular disorders: hypotension
- Respiratory, thoracic and mediastinal disorders: hypoxia
- Agitation & Delirium

Age

In general, the incidences of these TEAEs was higher in elderly patients (≥65 year of age) in comparison to younger ones (<65 years of age). This was consistent in both remimazolam and propofol groups, with the exception of agitation and delirium, where incidence appeared similar both in elderly and younger patients, in the total remimazolam and total propofol groups. The incidence of TEAE's in the age group ≥85 years was low, perhaps due to the small number of patients included within this age group.

The MAH has outlined the main characteristics of the efficacy and safety profile of remimazolam in different age groups and provided a benefit-risk assessment for use of this drug in the elderly, with focus on specific potential risks, such as cognitive and cardiovascular effects, and the influence on renal and hepatic function, as detailed further i.e. in different subsections of this assessment report.

Ultimately, it is agreed that, as the elderly would be more sensitive to the effects of anaesthetics, a careful assessment of the overall condition of patients ≥ 65 years is of particular relevance when deciding

upon individualised dose adjustments (see SmPC section 4.2, 4.4) and the starting dose should be considered at the lower range.

An increase in recovery times with age was observed across all evaluated recovery endpoints. Furthermore, age had more effect on the recovery time of propofol patients, compared to remimazolam.

There was no clear sign that the elderly population has a higher risk with remimazolam than with propofol. As compared to those <65 years, the increased risk in those aged 65-74 is within the expected values, as it is also the subsequent stabilisation in the patients aged 75-84 and slight decrease in the very old one (>85 years).

Sex

When comparing total remimazolam group with total propofol group the incidence of hypoxia and hypotension were similar across males and females. For bradycardia, the incidence was greater in males dosed with propofol. A similar effect was also seen in the total remimazolam group; however this difference was less substantial.

Agitation and delirium was also more prevalent in males. This effect was seen in both total remimazolam and propofol groups, however, was greater in the remimazolam group. The effect was seen in both low and high dose remimazolam groups but was more obvious in the high-dose group. The presence of post-operative agitation is multifactorial and probably not remimazolam related. Therefore, no dosing adjustments are required between sexes to prevent agitation or delirium.

BMI

The incidence of TEAEs across the BMI categories were similar when the total all remimazolam group was compared to propofol. It was also noted the risk of hypoxia increased as the BMI increased. This was consistent across both groups, though the incidence of hypoxia was slightly lower across all weight categories within the remimazolam group. The increased risk of hypoxia with higher weights is likely to be secondary to obstructive sleep apnoea, the risk of which increases with increasing weight.

Prolonged sedation was more common with remimazolam than propofol. This has occurred with older and heavier patients.

There is indeed an age effect when evaluating the recovery characteristics of remimazolam, i.e. older patients seem to take longer to recover than young subjects. This was visible in the analysis of prolonged sedation as a TEAE, as well as in the analysis of recovery endpoints such as time to orientation. Interestingly, the same effect was seen for propofol, and for some parameters the age effect of propofol was more pronounced, resulting in a similar recovery time between the two drugs in elderly. For example, the median time to orientation increased with age from 20.0 min (<65 years) to 25.0 min (>85 years) for remimazolam while for propofol the increase was from 14.0 min (<65 years) to 25.0 min (>85 years).

The incidence of prolonged sedation, as assessed by the CMQ prolonged sedation, increased to some extent with body weight (Table 55) and BMI (Table 56). The extent of increase for both, remimazolam and propofol was somewhat similar for both factors (i.e. body weight and BMI). While propofol accumulates in fat remimazolam does not. Thus, in the MAH's opinion there was no clear evidence for a special role of fat tissue (e.g. as a tissue in which drug accumulates and is slowly released after end of drug administration) in the phenomenon of prolonged sedation. The MAH concluded that there is no higher risk for obese versus high body weight patients to experience prolonged sedation.

Table 55: Incidence of CMQ Prolonged sedation by weight category (pool C)

Weight	Total remimazolam	Total propofol
<50 kg (N=72 / 13)	2 (2.8%)	0 (0%)
50-<75 kg (N=432 / 106)	21 (4.9%)	1 (0.9%)
75-<100 kg (N=228 / 84)	21 (9.2%)	6 (7.1%)
≥100 kg (N=51 / 23)	3 (5.9%)	1 (4.3%)

Table 56: Incidence of CMQ Prolonged sedation by BMI (pool C)

BMI	Total remimazolam	Total propofol
Underweight (N=29 / 6)	1 (3.4%)	0 (0%)
Normal weight (N=379 / 94)	16 (4.2%)	2 (2.1%)
Overweight (N=268 / 90)	19 (7.1%)	5 (5.6%)
Obese (N=107 / 36)	11 (10.3%)	1 (2.8%)

There seemed to exist a delay in recovery for overweight plus patients. The MAH stated that the behaviour is similar to propofol which can be agreed to, but the rationale was not clearly understood. With remimazolam there is a clear increase in the frequency of patients with prolonged sedation more related to high BMI than to the weight itself.

As detailed below, the MAH proposed several justifications for the prolonged sedation observed in obese patients, considered plausible by the CHMP.

In the MAH's view, it is unlikely a direct causal relation between the increased incidence of prolonged sedation in overweight or obese patients exist. Instead, there appears to be confounding factors which should be considered when interpreting the results:

1. Confounding effect of Japanese studies

GA trials were conducted in Japan and Europe. Across the different trials, the BMI of the study population was comparable to that of the general population in the respective countries of origin. However, as outlined in the Table 57 the BMI of Japanese subjects was generally lower than the BMI of European subjects, with a mean BMI ranging from 22.70 - 23.25 kg/m2 for Japanese subjects (remimazolam group), compared to a mean BMI of 26.25 - 27.74 kg/m2 for European subjects (remimazolam group).

The incidence of prolonged sedation in the Japanese cohort is considerably lower than in the European cohort, with only one AE related to prolonged sedation (incidence of 0.3%) being reported in a Japanese trial. Hence, a predominantly regional effect would be noted (i.e. more reporting of prolonged sedation in European as compared to Japanese clinical trials). In support of this, there was no body weight effect observed within the European study population. The mean BMI of patients with prolonged sedation was 27.35 kg/m2 (study CNS7056-010) and 25.72 kg/m2 (study CNS7056-022), compared to 26.88 kg/m2 and 27.74 kg/m2, respectively, for patients without prolonged sedation.

Therefore, it can be concluded that the on average lower body weight in Japanese trials (where also reporting of prolonged sedation was less) has a confounding effect on the interpretation of a potential correlation of body weight with an increased risk of prolonged sedation.

Table 57: Mean body weight, BMI, and incidence of prolonged sedation by study – Group C – PP

	EU		Japan		
	CNS7056-010 (N = 82)	**CNS7056-022 (N = 327)**	**ONO-2745-03 (N = 45)**	**ONO-2745-05 (N = 45)**	**ONO-2745-06 (N = 55)**
Mean BMI of total study population (kg/m^2)	26.88	27.74	22.70	23.25	22.83
Incidence of prolonged sedation AE (%)	18 (22.0%)	28 (8.6%)	0	1 (0.3%)	0
Mean body weight (kg)*	81.94	75.13	NA	98.00	NA
Mean BMI (kg/m^2)*	27.35	25.72	NA	31.64	NA

* body weight / BMI of patients with AE of prolonged sedation

2. Association between higher ASA score and age with increased incidence of prolonged sedation

ASA III/IV patients in the study population had a higher BMI than ASA I/II patients, as demonstrated in the Table 58. The mean BMI of ASA III/IV patients was 26.93 kg/m2 compared to a mean BMI of 23.55 kg/m2 in ASA I/II patients.

In general, ASA III/IV patients with prolonged sedation had comparable body weights and BMIs as those who did not experience prolonged sedation.

Patients with an age of 65 years and older had, on average, a higher body weight and BMI than those younger than 65 years. At the same time, the incidence of prolonged sedation increased with age (Table 57).

There is a known association between higher ASA class and higher age, with an increased incidence of prolonged sedation. Thus, it is likely that the higher incidence of AEs related to prolonged sedation in obese patients was a coincidental finding, as the majority of these subjects also had higher ASA class (III-IV) and older age.

Table 58: Mean Body Weight and BMI by ASA, Age and Prolonged Sedation Event – Group C - PP

			No event of prolonged sedation (N = 804)	Prolonged sedation (N = 47)	Total (N = 851)
Mean BMI (kg/m^2)	ASA group (n, Mean (SD))	ASA I-II	423, 23.50 (3.407)	3, 30.14 (1.821)	426, 23.55 (3.442)
		ASA III-IV	381, 27.01 (5.224)	44, 26.22 (3.585)	425, 26.93 (5.082)
	Age group (n, Mean (SD))	< 65 years	391, 24.87 (4.913)	8, 26.28 (4.326)	399, 24.90 (4.901)
		65-74 years	257, 25.43 (4.474)	22, 26.80 (3.915)	279, 25.54 (4.441)
		75-84 years	140, 25.66 (4.506)	16, 26.14 (3.110)	156, 25.71 (4.378)
		≥ 85 years	16, 23.78 (4.183)	1, 26.04 (n/a)	17, 23.91 (4.087)
Mean body weight (kg)	ASA group (n, Mean (SD))	ASA I-II	423, 61.83 (12.133)	3, 100.3 (6.807)	426, 62.10 (12.521)
		ASA III-IV	381, 79.63 (18.492)	44, 76.72 (14.164)	425, 79.33 (18.100)
	Age group (n, Mean (SD))	< 65 years	391, 69.25 (17.997)	8, 80.85 (17.753)	399, 69.48 (18.044)
		65-74 years	257, 71.95 (17.943)	22, 77.92 (15.848)	279, 72.42 (17.834)
		75-84 years	140, 70.53 (17.220)	16, 78.16 (13.097)	156, 71.31 (16.968)
		≥ 85 years	16, 65.75 (16.610)	1, 65.00 (n/a)	17, 65.71 (16.084)

3. Effects of obesity on remimazolam pharmacokinetics

A potential causal relationship could result from an effect of body weight or BMI on clearance. This was investigated in several PK and PK/PD models using different remimazolam datasets. Overall, there was no consistent effect of body weight or BMI on clearance. In one dataset of patients undergoing general anaesthesia there was an increased clearance with increasing body weight. Such an effect would be counterintuitive for a potential causal relationship of body weight on recovery times by a prolongation of the elimination half-life (i.e. a reduction in clearance).

4. Effects of obesity on remifentanil pharmacokinetics

While the pharmacokinetics of remimazolam are independent of body weight, as described above, this is not the case for remifentanil, a short-acting opioid administered concomitantly with

remimazolam in the pivotal phase III trials, and which acts synergistically with remimazolam. As clearance of remifentanil is significantly decreased in obese patients, consequently, the synergistic effects of remifentanil on remimazolam could be prolonged in obese patients, contributing to an apparent association of increased body weight with prolonged sedation.

Race

The vast majority of subjects were either white or Asian. Black or other ethnicity account for a very small proportion of patients, therefore it was difficult to make comparisons and draw conclusions from these groups.

Overall, the incidence of hypoxia, hypotension, bradycardia and agitation & delirium seemed to be lower in Asian patients in comparison to white patients. This difference is thought to be secondary to the different clinical trial designs rather than race differences. PAION sponsored trials conducted in Europe were largely made up of white patients. For these studies there were strict criteria based on vital signs for capturing hypoxia or hypotension as TEAEs, while this approach was not utilised for studies conducted in Japan. Therefore, no difference in dosing recommendations based on race is required for the purposes of GA.

The incidence of agitation and delirium was also greater in white patients in comparison to Asian patients. This was consistent across all remimazolam groups and propofol groups. However, this finding appeared most obvious in the high dose remimazolam group.

ASA Physical Status Classification

There was a general trend for higher incidences of hypoxia, hypotension, bradycardia and agitation & delirium, in patients with ASA-PS >II than those with ASA-PS I-II in all treatment groups. The Japanese pivotal study accounts for the majority of ASA I/II patients whilst the European pivotal study accounts for the majority of ASA III/IV patients. Therefore, within treatment groups, the differences between ASA subgroups is likely explained by the differences in trial design and reporting of AEs.

In ASA I/II patients remimazolam appears to be associated with a reduced risk of hypotension in comparison to propofol. Though this is not seen in ASA III/IV patients, it is important to note that haemodynamic stability over propofol has been demonstrated in these patients in study CNS7056-022, which accounts for the majority of patients in ASA III/IV group, where remimazolam was associated with a reduced risk of hypoxia and bradycardia.

Hepatic Impairment

The PK/PD effects of remimazolam in subjects with hepatic impairment were evaluated in the Phase I Study ONO-2745IVU007. In this open-label, single dose IV administration study, eight patients with moderate hepatic impairment (score of 7 to 9 on the Child-Pugh scale) and nine healthy matched subjects, as well as three patients with severe hepatic impairment (score of 10 to 15 on the Child-Pugh scale) received remimazolam as a single IV bolus at 0.1 mg/kg infused over 1 minute after fasting for at least 10 hours.

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.

Doses at the lower end of the dose ranges appear to be more appropriate in patients with severe hepatic impairment, where no dose adjustments are needed for subjects with mild or moderate hepatic impairment.

In controlled clinical trials in general anaesthesia, assessment of hepatic function was based on total bilirubin (TBil) and AST:

- Normal liver function (TBil ≤1.5ULN and AST ≤ULN)
- Mild liver disfunction (TBil ≤1.5 ULN and AST >ULN)
- Moderate liver disfunction (TBil >1.5-3.0 x ULN and AST any)
- Severe liver disfunction (TBil >3.0 x ULN and AST any)

There were 37 remimazolam patients with mild hepatic impairment and five with moderate hepatic impairment. Of the propofol patients there were 16 patients with mild hepatic impairment and three with moderate hepatic impairment. There were no patients with severe hepatic impairment. In the category, mild hepatic impairment, there was a reduced incidence of hypotension in the total remimazolam group (n=21, [57%]) vs the propofol group (n=12 [75%]). The incidence of the remaining special interest TEAEs was similar across the total remimazolam and propofol group. There were too few patients within the moderate hepatic impairment category to be able to draw any firm conclusions.

Ultimately, having considered all available data, it is agreed that no dose adjustment is required in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, as the clinical effects may be more pronounced and last longer than in healthy subjects, no dose adjustments are also required, but careful attention should be paid to the timing of titration doses and remimazolam titrated accordingly to the effect in these patients (see SmPC section 4.2, 4.4, 4.8, 5.2): severe impairment of hepatic function resulted in a reduced clearance and, as a consequence, a prolonged recovery from sedation was confirmed. These patients may also be more susceptible to respiratory depression.

Renal Impairment

The PK/PD effects of remimazolam in subjects with renal impairment were evaluated in Phase I Study CNS7056-012. In this open-label PK and safety study, a single IV dose of 1.5 mg remimazolam was administered to:

- 12 subjects with normal renal function (10 subjects with estimated glomerular filtration rate [eGFR] ≥90 mL/min/1.73 m^2 and 2 with eGFR of 80 to 90 mL/min/1.73 m^2)
- 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, due to its pharmacological inactivity, no changes in dosing are required.

In controlled trials in general anaesthesia, the incidence of TEAEs of interest was assessed in patients with renal impairment. These were classified as follows:

- Normal renal function – >90 mL/min/1.73 m^2
- Mild renal impairment – 60-90 mL/min/1.73 m^2
- Moderate renal impairment – 30-59 mL/min/1.73 m^2
- Severe renal impairment – <30 mL/min/1.73 m^2

In general there was an increased incidence of hypoxia, hypotension and bradycardia with decreasing renal function. This was probably more related to a decrease in the overall health condition that comes

with decreased renal function rather than a direct effect. This mirrors the findings for worsening ASA status. For agitation and delirium no trends were observed across any of the treatment groups. As outlined in SmPC section 4.2, the results from the controlled GA studies also confirm that no dose adjustment is required for renal impairment, including ESRD patients.

Co-morbid conditions

The data was analysed to determine if there were any trends in TEAEs of special interest following exposure to remimazolam and propofol in patients with the following pre-existing medical histories:

- Hypertension
- Cardiac dysfunction
- Cognitive dysfunction
- Dementia/Mild Cognitive Impairment

There were very few patients with a medical history of cognitive dysfunction and dementia. Therefore, these patients were included as a single group. However, this combined group included very low numbers; consequently, no trends for the TEAEs of special interest could be observed.

In patients with a pre-existing history of hypertension a lower incidence of hypoxia/respiratory depression, hypotension and bradycardia was observed in those who received remimazolam in comparison to patients who received propofol. In patients with a pre-existing history of cardiac dysfunction the incidence of these TEAEs of special interest was similar between the two treatment groups. However, similar to previous subgroups, the incidence of agitation and delirium was higher in the remimazolam group in comparison to the propofol group for patients with a pre-existing medical history of hypertension or cardiac dysfunction.

Cognitively impaired patients requiring hospitalisation and surgical interventions are at an increased risk of adverse outcomes, including an increased risk of delirium and of (temporary) post-operative cognitive decline. Current guidelines on anaesthesia in cognitively impaired patients conclude there is no convincing evidence that the risk of decline of cognitive function in cognitively impaired patients is tied only to anaesthesia itself, or to a particular intravenous anaesthetic drug. The guidelines do suggest that the totality of peri-operative management, including adequate pain management, optimisation of all other aspects of peri-operative care, avoidance of unnecessary post-operative sedation, and attention to medication interactions in patients more likely to have polypharmacy, and to the psychological needs to cognitively impaired subjects, all contribute to better outcomes. Recent literature reviews come to similar conclusions that there is no strong evidence linking the particular type of anaesthesia (local-regional, inhalation or total intravenous) itself to cognitive decline, but that post-operative cognitive decline is seen more frequently after coronary bypass surgery and is also more likely in elderly patients.

Belrose and Noppens in their 2019 paper concluded: *"Alzheimer's Disease or similar underlying pathology may make individuals more susceptible to the potential neurotoxic effects of the surgical stress and/or anaesthesia exposure and increase the risk of progression of cognitive impairment. Several mechanisms have been implicated including altered Amyloid-β processing or accumulation, pathological modifications to tau, neuroinflammation, calcium dysregulation, and mitochondrial dysfunction".* They quote from the guidance/recommendations developed by the fifth international perioperative neurotoxicity working group, which included over 30 experts who developed recommendations specific to postoperative brain health in individuals > 65 years of age: *"Current literature is insufficient to define a specific anaesthetic regimen to decrease risk of perioperative neurocognitive disorder; however, cautious use or avoidance of medications such as first-generation antihistamines, centrally acting anticholinergics, benzodiazepines, and meperidine is recommended. The authors also suggest avoiding relative hypotension, maintenance of normothermia, use age-adjusted minimal alveolar concentration of volatile*

anaesthetic agents, and use EEG-based depth of anaesthesia monitoring to titrate anaesthetic delivery". Benzodiazepines here should be read as longer acting benzodiazepines as those are more likely to impact memory.

Cottrell and Hartung in their 2022 paper indicated: "*Unless and until it would be possible to classify anaesthetic neurotoxicity as a rare complication, the first-do-no-harm approach should be to: (1) add anaesthesia to surgical intervention on the physiological cost side of the cost/benefit ratio when making decisions about whether and when to proceed with surgery; (2) minimize anaesthetic depth and periods of electroencephalographic suppression; (3) limit the duration of continuous anaesthesia whenever possible; (4) consider the possibility that regional anesthesia with deep sedation may be as neurotoxic as general anaesthesia; and (5) when feasible, use regional anaesthesia with light or no sedation*".

Based on the similar duration of action of propofol and remimazolam a significant difference in outcomes of anaesthesia in cognitively impaired patients is not anticipated. There is currently no scientific evidence which suggests otherwise.

In view of the high interest of anesthesiologists in optimising treatment of cognitively impaired patients and the ageing population, it is likely that cases with unexpected cognitive decline after general anaesthesia in patients with or without pre-existing cognitive impairment will be reported as single cases. It is also likely that there will be publications looking at outcomes in patients with cognitive impairment undergoing anaesthesia with remimazolam, and all publications related to remimazolam will be monitored by the MAH on a weekly basis. Either source of information presenting evidence not in line with the current expectation, that remimazolam anaesthesia is unlikely to have significant impact on cognitive impairment, would be picked up by the MAH's signaling processes.

As detailed below, the MAH provided a thorough justification for not including the cognitively frail population as an important safety concern in the RMP, mostly based on the present special cautions which are taken *a priori* with this special population.

It is well recognized that patients with dementia or cognitive impairment who may have functioned reasonably well in their home environment, may decompensate when suddenly moved to a different location or setting as occurs with planned or acute hospitalization. Such decompensation is not dependent on the department to which a patient is admitted. Medical factors such as trauma / pain, illness, circulatory instability, hypoxia, electrolyte disturbances, polypharmacy, and sleep deprivation will increase risks of such decompensation and associated risks of e.g., wandering about while unsteady or disoriented, falls, and need for sedation or restraining.

The risk of decompensation is considered already in the decision to admit patients with dementia or cognitive impairment. These patients are generally not admitted for procedures which would not improve or maintain their quality of life, or for mild illness. As clearly indicated in guidelines, besides considering medico-legal issues with respect to decision making ability of such patients, the surgery in these patients normally will only occur if the reasons for the procedure and the expected improvement of retention of quality of life outweigh the risks of decompensation and associated problematic behaviours.

Patients do not fall during anaesthesia or in the recovery room or intensive care unit (ICU) where those will not ordinarily be mobile, and patients with known dementia will normally be closely watched, and where fixation of infusion lines or sensors will already occur with more care to avoid decompensated patients removing them too easily. Unless the patient's vital signs are unstable, in that closely monitored setting removal of infusion lines or sensors is not very probable or of particular risk to the patient. Risk of inappropriately getting out of bed and falling in hospital is also reduced by having high sides of the bed up in such patients.

After surgery, a patient with known dementia or cognitive impairment will normally only return to a ward (or be discharged to the home address if sufficient care can be provided there) if considered (and

expected to remain) stable. At that time, any remaining infusion lines would likely only be there if required to maintain fluid balance or administer medications and sensor lines will generally not be present. As in the recovery room and ICU there either would be additional attention to fixation of any lines or, if possible, IV access would be reduced to just a well fixated needle which a patient is less likely to remove. Temporary loss if such lines or IV access is not a significant risk in a stable patient.

Post-surgery pain may well require strong analgesics and both pain and analgesics, in particular opioids, will increase the risk of decompensation well past the recovery of anaesthesia period. In addition, pain, unusual noises, illness, constipation, urinary retention, and other factors may contribute to the risk of decompensation. In the general ward decompensation can increase the risk of wandering and falling.

Independent of whether decompensation occurs in a post-surgery patient with dementia or cognitive impairment or such a patient in another hospital ward, if unwanted behaviour cannot be managed by additional attention for such a patient, including e.g., allowing family members to remain with the patient longer than just visiting hours, then the hospital staff will have to weigh the risks of not sedating or restraining the patient (wandering, falling, removal if lines or remaining sensors) with the very well recognized risks of sedation or restraining (further decompensation, prolonged hospitalisation, airway infections, decubitus, etc). Such considerations will generally also include the possibility of early discharge as another way to bring such patients back into their normal environment as this may be the quickest route to recovery of the patient's behaviour to prehospitalisation status.

The focus of the anaesthesia guidelines quoted by the MAH is not only on the long-term cognitive outcome, as suggested by the assessor, but also on minimizing the impact of anaesthesia and other required interventions on the short term risks to the patient with dementia or cognitive impairment. Such risks include mental decompensation and the associated risks thereof. In as far as anaesthesia may be a contributing factor, it should be as short as possible, not deeper than needed, using short acting anaesthetics and avoiding longer acting sedatives, and avoiding or reducing opioid analgesics as much as possible. All other treatable risk factors should be optimally treated, as also indicated in the anaesthetist's guideline.

A recent publication detailing results of a cohort study in anaesthesia with remimazolam in 78 compared to 122 patients with other anaesthesia showed no significant difference in rate of delirium. Based on the PAION clinical trials and such recent publications of independent investigators, there is no reason to expect that anaesthesia with remimazolam would be such a significant risk factor for decompensation of patients with dementia or cognitive impairment that this could be recognized above the multitude of background risk factors such patients encounter due to change of environment, illness, pain, and sleep deprivation.

Although remimazolam is a benzodiazepine, due to its shorter duration of action its risk is likely to be lower than those of i.e. midazolam, closer to those of propofol, as evidenced by available trial and post-marketing data.

Ultimately, although agreed not to include the cognitively frail population as an important safety concern in the RMP (mostly based on the present special cautions which are taken *a priori* with this special population), considering that frequency and magnitude of the effect of remimazolam related events are not known in the real world, the CHMP is of the view that "Use in cognitively impaired patients" should be included in the PSUR list of safety concerns and followed up closely, with special attention to the frequency of all relevant events in the cognitively impaired population, as compared to the general population. Relevant events should include not only CNS events, such as disorientation and agitation, but also risk of falls, self-removal of IV lines, monitorization devices or the need to restrain or sedate.

Extrinsic Factors

Owing to the intended use of remimazolam as an IV agent, no analyses were conducted evaluating the effects of extrinsic factors such as food or alcohol on the safety profile of IV remimazolam.

An important extrinsic factor which could have an impact on the incidence of TEAEs is the type of surgery performed.

It was noted that, in general, the incidence of TEAEs with respect to type of surgery was similar across the total remimazolam and propofol groups. A lower incidence of hypotension was seen in patients who underwent orthopaedic or urological surgery within the total remimazolam group. Due to its beneficial effects on haemodynamic stability, a lower incidence of hypotension within remimazolam groups is to be expected.

Use in Pregnancy and Lactation

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 follow-up information was received.

Drug Abuse Potential

Drug abuse potential was examined as part of the procedural sedation summary of clinical safety. Here it was demonstrated there was no drug abuse potential associated with remimazolam. As the route of administration for the proposed indication is also IV this matter was not further explored.

2.6.8.7 Immunological events

Immunological events were not explored during the Phase 3 pivotal trials.

2.6.8.8 Safety related to drug-drug interactions and other interactions

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, volatile anaesthetics and opioid agonists).

Risks from Concomitant Use With Opioids

TEAEs of special interest in the controlled clinical trials in general anaesthesia (group B) were analysed according to the amount of concomitant remifentanil, co-administered in all clinical trials with remimazolam. For this purpose, the cumulative, time-normalised remifentanil infusion dose was calculated for each patient, and TEAEs are presented according to dose categories by quartiles.

Hypoxia increased with cumulative remifentanil dose in the propofol treatment group but not with remimazolam. The incidence of hypotension was not different in the remifentanil dose categories, but bradycardia seemed to be more frequent in the lowest remifentanil dose group. Similarly, agitation and delirium appeared to be more frequent in the lowest remifentanil dose group.

Pharmacokinetic Drug Interactions

Remimazolam is metabolized via ester cleavage by carboxylesterase-1A, 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

Clinical safety data were examined for any evidence of an interaction between remimazolam and other drugs; concomitant antihypertensive drugs, sedative or hypnotic drugs and concomitant or prior chronic use of opiates and/or benzodiazepines. The primary analyses were based on the controlled trials in general anaesthesia (Group B) and focused on the SMQs and CMQs identified as pertinent for this indication. The following potential interactions were noted:

- Subjects receiving CES1 inhibitors exhibited a higher number of TEAEs in S/CMQs hypoxia/respiratory depression, hypotension, bradycardia and agitation/delirium in the total remimazolam and the total propofol treatment groups;
- Subjects receiving anti-histamines exhibited a higher number of TEAEs in S/CMQs hypoxia/respiratory depression and bradycardia. The increase in respiratory depression TEAEs was more pronounced in the total propofol group in comparison to the total remimazolam group, while the opposite trend was seen for bradycardia;
- Subjects receiving anti-cholinergics showed an increased incidence for hypoxia, bradycardia and agitation/delirium and a decreased incidence of hypotension. These differences were similar across treatment groups.
- Subjects receiving concomitant antihypertensive medications appeared to have a higher incidence of hypoxia, hypotension, bradycardia and agitation in both treatment groups;
- Subjects receiving drugs acting on the renin-angiotensin-aldosterone system (RAAS) had increased incidences of bradycardia and agitation with no differences between treatment arms;
- Subjects receiving anti-arrhythmic drugs had increased incidences of hypoxia, bradycardia and agitation and a decreased incidence of hypotension with no differences between treatment arms;
- Subjects receiving anti-epileptic or anti-depressant drugs had increased incidences of hypoxia with no differences between treatment arms.

The analyses did not point to a special risk posed by one of the co-medications when used with remimazolam. While incidences for some of the examined S/CMQs increased by the use of comedications this increase was similar in the propofol treatment arm. The increased incidences are likely to represent the impact of the underlying disease and/or differences in the demographics between users and non-users (e.g. antihypertensives probably more frequently used by elderly).

These risks can be minimized by dose individualization and titration to desired clinical response. It is noted that the low numbers of subjects in some subgroups precluded assessment of some interactions.

The analysis of treatment emergent adverse events (TEAEs) in all subjects of propofol-controlled trials did not indicate an influence of remifentanil. Based on other evidence, however, a warning for the co-administration with opioids is mentioned in different sections of the SmPC (i.e. section 4.2, 4.4, 4.5).

An analysis of TEAEs for other potential drug-drug interaction was performed and some potential interactions identified. However, it is difficult to assess whether those are true interactions or whether certain adverse events are increased with a concomitant drug because of the underlying medical condition this concomitant drug treats, the specific adverse effect profile of the concomitant drug or a demographic effect whereby the subjects receiving a certain concomitant drug are on average older or of a worse overall physical condition. Moreover, for some of the concomitant drug classes and analysed TEAEs the numbers are too small to draw conclusions. In addition, the observation that similar trends are observed for propofol, and none of those interactions are mentioned in propofol's SmPC, indicates that anaesthesiologists are aware of increased sensitivities e.g. for patients with a cardiovascular

background history to be at a higher risk for hemodynamic adverse events such as hypotension or bradycardia.

Subjects receiving CES1 inhibitors exhibited a higher number of TEAEs in Standardised/Customised MedDRA Queries (S/CMQs) hypoxia/respiratory depression, hypotension, bradycardia and agitation/delirium in the total remimazolam and the total propofol treatment groups. CES inhibitors can theoretically interact with remimazolam on a pharmacokinetic basis but not with propofol. Since there is a similar trend for both drugs, a PK interaction can be excluded. CES inhibitors come from different pharmacological classes, hence a pharmacodynamic interaction with remimazolam and propofol is unlikely. Therefore, the MAH concluded that the increased incidence of some TEAEs in the presence of CES1 inhibitors is due to the medical condition for which those are used rather than a direct interaction with remimazolam.

Subjects receiving inhibitors of the renin-angiotensin-system (RAS inhibitors) or anti-hypertensives showed higher incidences of hypotension and bradycardia. The MAH is of the opinion that the background disease (i.e. hypertension) predisposes to hemodynamic adverse events such as hypotension (particularly when assessed as change from baseline) and bradycardia. This is agreed upon by the CHMP.

Anticholinergic drugs in general, and antimuscarinics in particular, can cause confusion and are used for the treatment of drug-induced dyskinesias. Hence, it is conceivable that adverse events from the CMQ agitation that encompasses preferred terms such as cognitive disorder, confusional state, or delirium are increased when anti-cholinergic drugs are used.

The analysis of DDIs in the submitted dossier is based on pool B of clinical trials in general anaesthesia i.e. all propofol-controlled trials. Pool B in comparison to pool A (the pivotal trials) has data from two small trials involving patients undergoing cardiac anaesthesia (studies CNS7056-010 and CNS7056-011). The patient's characteristics (e.g. medical history and concomitant medications), as well as the adverse event profiles (e.g. incidence of agitation/delirium), were different than in the pivotal trials. In order to assess the impact of these trials on the DDI analyses, the analyses were repeated for pool A.

The most striking difference is for the adverse event of special interest 'agitation'. Overall (as outlined in the Table 59) the incidences are considerable lower and, particularly for remimazolam, in pool A (pivotal trials) there is no apparent increase in the incidence of agitation with concomitant drugs. This is in contrast to the analysis of pool B where there was a bias of cardiac patients with a high incidence of agitation, and a higher likelihood for receiving concomitant medications, particularly for the treatment of cardiovascular diseases.

Table 59: TEAEs of special interest by concomitant medication (pool A)

	Hypoxia		**Hypotension**		**Bradycardia**		**Agitation**	
	RMZ	**PROP**	**RMZ**	**PROP**	**RMZ**	**PROP**	**RMZ**	**PROP**
CES1 inhibitors								
No	7%	15%	49%	73%	11%	19%	3%	2%
Yes (n=142/ 50)	19%	24%	82%	90%	20%	28%	6%	2%

	Hypoxia		Hypotension		Bradycardia		Agitation	
	RMZ	**PROP**	**RMZ**	**PROP**	**RMZ**	**PROP**	**RMZ**	**PROP**
Anti-histamines								
No	10%	13%	56%	77%	13%	21%	4%	2%
Yes (n=12/14)	17%	64%	83%	86%	25%	29%	0%	7%
Anti-cholinergics								
No	9%	17%	56%	78%	12%	22%	4%	2%
Yes (n=16/5)	38%	20%	75%	60%	31%	0%	0%	20%
Anti-hypertensives								
No	7%	10%	48%	71%	10%	18%	3%	2%
Yes (n=183/68)	16%	29%	77%	88%	19%	27%	7%	3%
RAAS acting agents								
No	9%	11%	51%	76%	9%	11%	3%	1%
Yes (n=221/76)	11%	26%	67%	80%	19%	36%	6%	4%
Anti-arrhythmics								
No	10%	17%	57%	77%	13%	22%	4%	2%
Yes (n=10/3)	30%	0%	80%	100%	30%	0%	10%	0%
Anti-epileptics								
No	9%	15%	57%	77%	13%	22%	4%	2%

	Hypoxia		Hypotension		Bradycardia		Agitation	
	RMZ	**PROP**	**RMZ**	**PROP**	**RMZ**	**PROP**	**RMZ**	**PROP**
Yes (n=20/12)	35%	50%	55%	83%	15%	8%	0%	8%

The MAH concluded there is no evidence for the adverse event of agitation (included in SmPC section 4.8 with frequency *common*) to increase with a particular co-medication.

A warning for enhanced sedation and cardiorespiratory depression when remimazolam is used together with centrally depressing drugs, including anti-histamines and anti-hypertensives, was included in section 4.5 of the SmPC.

An analysis of TEAEs for other potential DDI was performed and some potential interactions identified. In the opinion of the MAH no further warning is warranted since other potential interactions evaluated are rather due to the underlying medical condition, the specific adverse events caused by the concomitant drugs, or demographic differences. Furthermore, for all potential interactions there is a similar effect seen with propofol, and none of those interactions are mentioned in propofol's SmPC, indicating that anaesthesiologists are aware that such increased sensitivities can exist. Nevertheless, the option to conduct further analyses was considered, as requested by the CHMP. The MAH satisfactory justified why further analyses would not yield any meaningful results, especially not sufficiently robust enough as to allow for conclusions to be presented in the SmPC:

- Some subgroups have a very low number of subjects;
- It is impossible to assess as to whether a specific effect is due to the co-medication itself or the underlying medical condition;
- The average age and/or physical condition (e.g. ASA class) is likely to be higher in patients receiving certain co-medications, thereby skewing the results;
- Some of the drug classes have drugs with rather different pharmacological modes of action, hence a pharmacodynamic interaction is difficult to hypothesize;
- The proposed analyses would result in >20 individual statistical tests. The likelihood of false positive results is high with this number of individual test further precluding any meaningful conclusion.

The CHMP, having considered the above, concluded that no further warning is warranted with regards to other potential DDI. The existing analyses point to very similar potential interactions with propofol, and none of those interactions are mentioned in propofol SmPC, indicating that anaesthesiologists are aware that such increased sensitivities can exist and will be able to anticipate patients at risk. It is also considered that section 4.4 of the SmPC is updated with regards to chronic use of CNS depressant drugs.

2.6.8.9 Post marketing experience

Remimazolam has been approved for procedural sedation in adults in Europe (EEA and UK), USA and China; for GA in adults in Japan, and for both indications in Korea. The International Birth Date (IBD) is 23 January 2020 (Japan). It has been marketed in Europe (Netherland and UK), USA, China, Japan and Korea.

The data lock point (DLP) for post-marketing data included in this line extension application is the DLP of the Periodic Benefit Risk Evaluation Report (PBRER) covering the period 22 January 2021 - 22 July 2021 (EMEA/H/C/PSUSA/00010924/202107).

For procedural sedation exposure data were calculated based on the estimated use of 1 vial of 20 mg by patient in the USA, while the number of patients exposed in China was provided by the licensing partner. Up to the DLP of 22 July 2021, there have been no sales in Europe. For GA, the calculation was based on the estimated use of 4 vials of 50 mg by patient for Japan and Korea.

The estimated cumulative post-authorisation sales volumes, until 22 July 2021, was 13,484,500 mg (165,240 vials of 50 mg and 261,125 vials of 20 mg), and the estimated cumulative post-authorisation exposure was 302,435 patients; 261,125 patients in procedural sedation (mainly from China) and 41,310 patients in general anaesthesia (mainly from Japan).

The safety signals that were ongoing during the reporting interval of PBRER number 03 (covering the period 23 January 2021 – 22 July 2021) were: blood in urine, prolonged sedation, delirium and anaphylaxis (not clear whether linked to remimazolam or rather to the excipient dextran 40).

In addition, a vascular access site occlusion was evaluated. Eleven cases of vascular access site occlusion were reported, linked to the use of solvents not compatible with remimazolam. The information is included in SmPC section 4.5. Within the PSUSA for PBRER number 03 (EMEA/H/C/PSUSA/00010924/202107), concluded in February 2022, PRAC, having considered available data (i.e. from Eudravigilance, literature), agreed for "anaphylactic reaction" to be added to Byfavo 20 mg SmPC, in the tabulated list of ADRs from post-marketing experience, and "sudden, severe allergic reaction", (frequency: *unknown*) to be added to the side effects section of the PIL for Byfavo 20 mg.

Furthermore, as completed by the time of writing this AR, within the following PSUSA (EMEA/H/C/PSUSA/00010924/202201), concluded in July 2022, given data from literature and spontaneous reports, PRAC recommended to strengthen Byfavo 20 mg PI to ensure HCPs are adequately informed about the potential risk of vascular access site occlusion when remimazolam is administered with incompatible fluids (which may result in precipitation/turbidity, which may cause occlusion of vascular access site) via an update of SmPC section 6.2 (and PIL, accordingly).

The above has also been reflected in the PI for Byfavo 50 mg.

2.6.9 Conclusion on clinical safety

There are differences between remimazolam and propofol pooled groups. A higher proportion of overweight and obese participants were included in propofol group (40% and 16% vs 34% and 14% in remimazolam group). Higher proportion of participants with ASA III/IV were enrolled in propofol group (61% vs 50% in remimazolam group). Higher proportion of participants with moderate renal impairment were enrolled in propofol group (34% vs 26% in remimazolam group). Higher proportions of patients with cardiac disorder and hypertension were included in propofol group (45% and 62% vs 37% and 54% in remimazolam group). These differences in the baseline characteristics of the safety population triggered few uncertainties in the interpretation of safety data (i.e. when attempting to make a complete comparison of remimazolam and propofol safety profiles), without a major impact on the safety conclusions.

The safety database (including 783 patients) is not large enough to capture rare adverse events. Despite this limitation, the safety profiles of remimazolam and propofol are broadly comparable. Observed TEAEs indicate remimazolam potential for haemodynamic disturbances, gastrointestinal disorders, pyrexia, chills, wound complications, postoperative anaemia, postoperative delirium and agitation,

hypersensitivity. These observed adverse events seem manageable given the general anaesthesia setting.

2.7 Risk Management Plan

2.7.1 Safety concerns

- ***Summary table 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

2.7.2 Pharmacovigilance plan

The CHMP, having considered data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product and to monitor the effectiveness of the risk minimisation measures (RMMs).

2.7.3 Risk minimisation measures

The CHMP is of the opinion that the proposed (routine) RMMs are sufficient to minimise the risks of the product in the agreed indication. No additional RMMs are deemed necessary.

2.7.4 Conclusion

The CHMP concluded that Byfavo RMP version 1.3 is acceptable.

2.8 Pharmacovigilance

2.8.1 Pharmacovigilance system

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

2.8.2 Periodic Safety Update Reports submission requirements

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.

2.9 Product information

2.9.1 User consultation

Conclusion from the checklist for the review of user consultation

The PL for Byvafo 20 mg Powder for solution for injection/ infusion was successfully tested during the MAA procedure in 2019/2020. Changes in the PL for Byfavo 50 mg Powder for concentrate for solution for injection/ infusion, are introduced in sections 1, 2, 3, 4 and 6.Overall the methodology is considered satisfactory and the results meet the success criteria for all questions posed, as set out in the EC Guideline on Readability of Label and Package Leaflet of Medicinal Products for Human Use.

The focus test has successfully demonstrated the comprehensibility and usability of the PL.

2.9.2 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 a 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

Remimazolam completed clinical development in the indication for induction and maintenance of general anesthesia (GA) and had received marketing approval for this indication in January 2020 in Japan (ANEREM®) and in January 2021 in South Korea. The clinical program for this latter indication was also completed in Europe. For the induction of anaesthesia a dose of 6mg/min (used in the EU phase III trial) is given until loss of consciousness and maintenance is achieved by continuous infusion of 1 mg/min (which could be titrated down to 0.1mg/min and up to a maximum of 2.5mg/min). In the propofol-controlled trials for remimazolam in GA i.e. ONO-2745-05, CNS7056-010, CNS7056-011 and CNS7056-022 the mean cumulative dose administered was 275 mg (3.8 mg/kg). The mean duration of exposure was 218min (range: 32-683 min).

3.1.2 Available therapies and unmet medical need

Although there are several alternatives for total infusion anaesthesiology, such as gases, infusion induced and maintained general anaesthesia is limited to propofol and midazolam.

Risks associated with the inhalation anaesthetics include malignant hyperthermia, long QT syndrome, severe post-operative nausea and vomiting, potential cerebral oedema, and myasthenia gravis. Propofol based TIVA is associated with the possible risks of injection site pain, anaphylactic reactions to the soy components in the lipid emulsion, and severe hypotension combined with a bradycardia effect. Other benzodiazepines, in particular midazolam, have also been used for TIVA but have become less popular, due to their longer duration of action resulting in delayed recovery, and possibly higher risk of post-operative delirium.

3.1.3 Main clinical studies

The efficacy of remimazolam for induction and maintenance of general anaesthesia (GA) was evaluated in a total of six clinical trials.

CNS7056-022 and ONO-2745-05 were the two pivotal studies, the former conducted in Europe, the latter in Japan.

Table 60: Clinical trials evaluating efficacy of RMZ in GA

Trial ID	Phase	Type of Procedure	ASA class	Control
ONO-2745-03	2	Mixed surgeries		None
CNS7056-010	2	Cardiac surgeries	All permitted	Propofol/Sevoflurane
CNS7056-011*	3	Cardiac surgeries	All permitted	Propofol
CNS7056-022	3	Mixed surgeries	ASA III/IV	Propofol
ONO-2745-05	2b/3	Mixed surgeries	ASA I/II	Propofol
ONO-2745-06	3	Mixed surgeries	ASA III/IV	None

* study stopped when less than 10% of the planned sample size was enrolled (n enrolled = 23, n planned = 530)

3.2 Favourable effects

The main efficacy data for this line extension application have come from the European pivotal trial (study CNS7056-022) where remimazolam was non-inferior to propofol in the percentage of time with narcotrend Index ≤60 during the maintenance phase (RMZ: 94.6% of patients and PPF 98.9% of patients). Loss of consciousness was achieved and maintained in nearly all patients receiving RMZ during surgical procedures. Thus, GA was achieved (efficacy: nearly 100%). Based on the mechanism of action and the fact that the medicine was titrated to effect, this was expected. With regards to secondary endpoints (NCI between 27 and 60, NCI < 27, Need for rescue sedation), results were also non-inferior to propofol. RMZ was also superior to PPF regarding critical hypotensive events per patient (RMZ 56% versus PPF (64%) at the interim analysis. Time to onset of action appears to be shorter in RMZ compared to PPF.

In the Japanese pivotal trial, Study ONO-2745-05, the (different) primary efficacy endpoint was functional capability as a general anaesthetic, and was achieved by all participants (100%) in each of the treatment arms.

The availability of flumazenil is favourable for remimazolam.

3.3 Uncertainties and limitations about favourable effects

Study CNS 7056-022 (the European pivotal trial) planned to randomly enrol 542 patients. However, due to COVID-19 pandemic, this study was terminated before the planned sample size could be reached. At the time of study termination, 365 patients had been randomised (about 67% of the planned sample size). Furthermore, in this trial the statistical analysis of the 'key secondary outcome' (i.e. haemodynamic stability), designed to test superiority of remimazolam over propofol, was changed post hoc and the modifications introduced hampered the conclusion. Therefore, no superiority of remimazolam over propofol on the account of haemodynamic stability can be claimed.

In addition, several secondary efficacy endpoints pointed towards a different direction from the primary endpoint. However, the below was considered:

- Onset of effect - the time to event secondary efficacy endpoints indicated a slightly quicker onset of action in remimazolam compared to propofol, although these results were difficult to interpret in the light of a higher percentage of patients with too deep anaesthesia in remimazolam arm.
- Offset of effect - the secondary efficacy outcomes of time from the stop of the IMP to extubation were similar in both treatment arms. However, a difference was observed in time from stop of IMP to response to verbal command (15 min in remimazolam compared to 12 min in propofol). An even larger difference disfavouring remimazolam is observed in time from stop of IMP to orientation (54 minutes in remimazolam compared to 30 minutes in propofol). The almost doubling of time to orientation in time, place, person and situation observed with remimazolam was noted as clinically relevant and unlikely to be solely the consequence of lack of experience with the product. Similarly, time to modified Aldrete Score ≥9 was 53 minutes in remimazolam compared to 37 minutes in propofol groups with almost no overlapping in CIs (95% CI 44-58 mins for remimazolam and 28-45 mins for propofol). Since the modified Aldrete score is used to evaluate patients in post anaesthesia care, with the purpose to check whether they can be safely discharged, this information is considered to be of importance for healthcare practitioners, thus outlined in the SmPC. These characteristics demand more time from the anaesthesiologist team to attend the patient after surgery.
- Explicit awareness (incidence of the occurrence of intra-operative awakening) was not evident in either treatment groups during the procedures. However, unspecific, potential signs of intraoperative awakening were reported with a notably higher occurrence in remimazolam arm compared to propofol (18.5% vs 7.4%). This could partially be explained by the unfamiliarity of investigators with remimazolam resulting in closer observation of patients.
- The percentage of time with NCI ≤60 and ≥27 during the maintenance (first skin incision to last skin suture) was higher in the PPF arm than in the RMZ (78% vs 68%) arm based on the FAS. This was due to a higher proportion of patients with both NCI< 27 and NCI>60, which may be related to a higher difficulty in adequately refine the level of anaesthesia.

Study ONO-2745–05, which was conducted almost a decade ago in Japan, did not formally evaluate haemodynamic stability results.

3.4 Unfavourable effects

In controlled clinical trials, 88.8% of patients experienced any TEAE in the remimazolam group in comparison with 92.5% in propofol group.

The incidence of (mild, moderate or severe) TEAEs was largely similar across the total propofol and remimazolam groups.

The most common TEAEs in the total remimazolam group (>5%) by PT were: hypotension (25.0% vs 34.1% in propofol group), blood pressure decreased (20.1% vs 25.5%), nausea (14.2% vs 11.5%), bradycardia (10.1% vs 17.3%), vomiting (9.7% vs 5.8%), pleural effusion (9.7% vs 11.1%), procedural nausea (7.9% vs 8.8%), wound complications (6.9% vs 4.9%), hypertension (6.4% vs 6.6%), procedural vomiting (5.5% vs 5.3%), pyrexia (5.5% vs 4.4%), chills (5.5% vs 4.9%), and postoperative anaemia (5.4% vs 6.6%). Overall, the incidence of serious TEAEs was slightly higher in the total propofol group in comparison to the total remimazolam group.

The SOC with the highest incidence of serious TEAEs in both the total remimazolam and propofol group, was injury, poisoning and procedural complications which occurred in 2.7% of patients in both groups.

Within this SOC, the PT with the highest incidence in both treatment groups was postoperative delirium, occurring in 1.0% of all total remimazolam patients and 1.3% of total propofol patients.

Five TEAEs (0.7%) led to study drug discontinuation in comparison with one (0.4%) in the propofol group. These TEAEs in the total remimazolam group were post procedural haemorrhage, vascular access site occlusion, cough, haemothorax and hypotension and, in the total propofol group, the TEAE was hypotension. There were no TEAEs with an outcome of death.

Incidences of AESI by SMQ/CMQs in controlled clinical trials were: hypoxia (11.2% vs 18.6%), hypotension (51.3% vs 66.4%), bradycardia (14.3% vs 22.1%), hypersensitivity (2.5% vs 1.8%), agitation and delirium (10.1% vs 7.5%), injection site reaction (0.7% vs 4.9%) in remimazolam and propofol groups, respectively.

In the controlled trials incidences of SAEs were 8.6% vs 11.1% in remimazolam and propofol groups, respectively.

Postoperative delirium is the only SAE PT with an incidence ≥1% in either remimazolam or propofol group.

An overall review of the TEAE's, was performed and did no determine evidence of a differential response to treatment in the drug-demographic interaction subgroups; age, sex, race, ASA-PS classification and weight/BMI.

The list of safety concerns in the risk management plan, in comparison to the initial MAA, is unchanged.

Further details of the adverse event profile are contained in the section on clinical safety.

3.5 Uncertainties and limitations about unfavourable effects

The lack of effect or extended duration of effect of RMZ as compared to PPF might have – to some extent – been related to the low number of patients studied, which may have not been sufficient to adequately discriminate among the treatment arms. The safety database (including 783 patients) is not large enough to capture rare adverse events.

Participants with severe hepatic impairment were excluded from the clinical studies in the GA and the same holds true for patients with patent cognitive deficits.

Differences were noted in the baseline characteristics of the safety population, between remimazolam and propofol pooled groups. A higher proportion of overweight and obese participants were included in propofol group (40% and 16% vs 34% and 14% in remimazolam group). Higher proportion of participants with ASA III/IV were enrolled in propofol group (61% vs 50% in remimazolam group). Higher proportion of participants with moderate renal impairment were enrolled in propofol group (34% vs 26% in remimazolam group). Higher proportions of patients with cardiac disorder and hypertension were included in propofol group (45% and 62% vs 37% and 54% in remimazolam group). These differences triggered few uncertainties in the interpretation of safety data (i.e. when attempting to make a complete comparison of remimazolam and propofol safety profiles), without a major impact on the safety conclusions.

Although safety in the cognitively frail population is not included in the RMP as missing information (mostly based on the present special cautions which are taken *a priori* with this population), considering that frequency and magnitude of the effect of remimazolam related events are not known in the real world, "Use in cognitively impaired patients" should be included in the PSUR list of safety concerns and followed up closely.

From the post-marketing experienced with Byfavo 20 mg, it is not clear whether anaphylactic/anaphylactoid shock or reaction could be linked to remimazolam or rather to the excipient dextran 40.

3.6 Effects Table

Effects Table of RMZ as per CNS7056-022 study

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
NCI≤60	Mean % time with Narcotrend Index ≤60 during the maintenance phase	Percentage	RMZ: 94.6	PPF: 98.9	Interim analysis population; study stopped at the beginning of COVID pandemics	Study CNS7056-022 report body
NCI 27-60	Mean % time with Narcotrend Index 27-60 during the maintenance phase	Percentage	RMZ: 68.4	PPF: 78.0	Interim analysis population; study stopped at the beginning of COVID pandemics	Study CNS7056-022 report body
Critical Hypotensive Events per patient	Number of critical hypotensive events per patient	Mean number of events per patient	RMZ: 60.5	PPF: 70.7	Interim confirmatory analysis population; study stopped at the beginning of COVID pandemics 2-sided z-test p=0.1002	Study CNS7056-022 report body
Unfavourable Effects						
Rescue sedation	% patients in need for rescue sedation between first skin incision and last suture	Percentage	RMZ: 10	PPF: 1.1	Interim analysis (PP1) Study stopped at the beginning of COVID pandemics	Study CNS7056-022 report body
Time to Extubation	Median time from stop of IMP to end of extubation	minutes	RMZ: 12.0	PPF: 11.0	Final analysis set Relevance of 1 minute delay	Study CNS7056-022 report body
Time to response to verbal command	Median time from stop of IMP to response to verbal command	minutes	RMZ: 15	PPF: 12	Relevance of 3 minutes delay	Study CNS7056-022 report body
Time to Orientation	Median time from stop of IMP to orientation to time, place, person and situation	minutes	RMP: 54	PPF:30	Final analysis set 2-sided Log Rank Test p<0.0001	Study CNS7056-022 report body

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Agitation and delirium	Frequency of agitation and / or delirium in the pooled population B (controlled trials) by SMQs and CMQs	percentage	RMZ: 10.1	PPF: 7.5%	Patients with dementia excluded from studies	Summary of clinical efficacy 2.7.3

Effects Table of RMZ as per ONO-2745 study

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Efficacy as a GA	Successful conduct of the surgical intervention and no need for rescue sedative medication	Percentage	RMZ:99.2	PPF: 100	Non-inferiority confirmed between the 2 interventions	2.7.3 (General anaesthesia) Pool A
Haemodynamic stability during extended induction	The reverse adjusted AUC (RAAUC) for MAP values < 65	mmHg *min (± SD)	RMZ 55.5 (± 119.4)	PPF 99.8 (± 235.1)	P<0.001. Takes into consideration the duration and extent of drop of the MAP below the threshold of 65mm Hg	2.7.4 (General anaesthesia) Pool A
Haemodynamic stability during surgical intervention	The reverse adjusted AUC (RAAUC) for MAP values < 65	mmHg *min (± SD)	RMZ 19.7 (± 40.1)	PPF 34.4 (± 79.7)	P<0.001. Takes into consideration the duration and extent of drop of the MAP below the threshold of 65mm Hg	2.7.4 (General anaesthesia) Pool A
Haemodynamic stability during recovery	The reverse adjusted AUC (RAAUC) for MAP values < 65	mmHg *min (± SD)	RMZ 14.8 (± 37.0)	PPF 35.7 (± 107.0)	P<0.001. Takes into consideration the duration and extent of drop of the MAP below the threshold of 65mm Hg	2.7.4 (General anaesthesia) Pool A
Vasopressor use	Absolute norepinephrin e equivalent dose during extended induction, surgical intervention and recovery phase	µg (± SD)	RMZ 269.53 (±623.610)	PPF 478.76 (±746.334)	= 0.0005. Results affected by difference in duration of the procedure between the 2 treatment arms. An estimate for converting nonnorepinephrine vasopressors to norepinephrine equivalent was required for patients that received nonnorepinephrine vasopressors	Table 2.9.1.1, Pool A
Unfavourable Effects						
Rescue medication use	% patients in need for rescue sedation between first skin incision and last suture	Percentage	RMZ: 0%	PPF: 0 %	A significant difference in rescue sedative medication use from CNS7056-022	ONO-2745-05 – Clinical trial report

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Time to Extubation	Median time from stop of IMP to end of extubation	Minutes (95% CI)	RMZ:14 (13.0-15.0)	PPF: 11.3 (10.0-12.5)	P<0.0001 (Log rank test). Small difference is not of clinical relevance	2.7.3 (General Anaesthesia) Pool A
Time to eye opening	Median time from stop of IMP till eye opening	Minutes (95% CI)	RMZ:13.0 (11.6-14.1)	PPF:10.7 (9.0-12.0)	P<0.0001 (Log rank test). Response to verbal command considered surrogate eye opening	2.7.3 (General Anaesthesia) Pool A
Time to Orientation	Median time from stop of IMP till orientation	Minutes (95% CI)	RMZ:23.0 (22.0-24.0)	PPF:18.9 (16.8-21.0)	P<0.0001 (Log rank test). Small difference is not of clinical relevance	2.7.3 (General Anaesthesia) Pool A
Agitation and delirium	Frequency of agitation and / or delirium in the pooled population B (controlled trials) by SMQs and CMQs	percentage	RMZ: 10.1	PPF: 7.5	Patients with dementia excluded from studies – same as above in study CNS7056-022	2.7.4 (General Anaesthesia) Pool B

3.7 Benefit-risk assessment and discussion

3.7.1 Balance of benefits and risks

The MAH provided sufficient evidence of remimazolam non-inferiority versus propofol.

The duration of action of propofol is slightly shorter than that of remimazolam, but the effect of remimazolam can be countered almost immediately with flumazenil, while it is not possible to immediately terminate the effects of propofol.

Haemodynamic stability results were only formally evaluated in one study (European pivotal study) and the conclusions hampered by post-hoc modifications of the statistical analysis plan. Due to differences in baseline characteristics, no superiority of remimazolam over propofol on the account of haemodynamic stability can be claimed.

The safety profiles of remimazolam and propofol seems broadly comparable. Observed TEAEs indicate RMZ potential for haemodynamic disturbances, gastrointestinal disorders, pyrexia, chills, wound complications, postoperative anaemia, postoperative delirium and agitation, hypersensitivity. These observed AEs seem manageable given the general anaesthesia setting.

3.8 Conclusions

The overall benefit/risk balance of remimazolam 50 mg for intravenous induction and maintenance of general anaesthesia in adults is positive, subject to the conditions detailed in section 4 of this AR.

4 Recommendations

Based on the review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of, Byfavo 50 mg, powder for concentrate for solution for injection/infusion (powder for concentrate), is favourable in the following indication:

- Intravenous induction and maintenance of general anesthesia (GA) in adults

The CHMP therefore recommends the extension(s) of the marketing authorisation for Byfavo 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).

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (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 measure**

  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

Additional Data exclusivity/Marketing protection

Not applicable

Paediatric Data

Not applicable