EMADOC-1829012207-24322
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Omforro

International non-proprietary name: midazolam

Procedure No. EMEA/H/C/005657/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

ABBREVIATION	DEFINITION
ACRD	Acute central respiratory depression
AESI	Adverse event of special interest
AUC	Area under curve
CI	Confidence interval
CL	Clearance
Cmax	Peak concentration
CP	Comparative phase
CRO	Contract Research Organisation
CV	Coefficient of variation
DBP	diastolic blood pressure
EU	European Union
F	Bioavailability
FDA	US Food and Drug Administration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IN	Intranasal
IM	Intramuscular
IV	Intravenous
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLQ/LLOQ	Lower limit of quantification
MDZ	Midazolam
OC	Other concern
PBPK	Physiologically-based PK
PD	Pharmacodynamic
PK	Pharmacokinetic
PopPK	Population PK
PT	Physical therapy
QC	Quality control
SAEs	Serious adverse events
SBP	systolic blood pressure
SD	Standard deviation
SmPC	Summary of product characteristics
SOC	Standard of care
T1/2	Half-life
TDP	Test dose phase
TEAEs	Treatment emergent adverse events
Tmax	Time to reach the maximum concentration
ULOQ	Upper limit of quantification
Vz	Volume of distribution
WHO	World Health Organization

1. Rapporteur Recommendation

Based on the review of the data on quality , he generic/hybrid application for Omforro in the treatment of:

"Omforro is indicated in:
- *Conscious sedation before and during diagnostic or therapeutic procedures with or without local anesthesia.*
- *Premedication before induction of anesthesia.*

Omforro is indicated in adults and children from 2 years old"

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the list of questions (see section 5.).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the list of questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality aspects

1. A nitrosamine risk evaluation is missing for the drug substance (ASMF AP) and should be provided.
2. The control of drug substance performed by the drug product manufacturer, including information about reference standards, is missing and should be provided.
3. The applicant needs to address the nasal spray device used in clinical studies.
4. The presented process validation data is not considered sufficient to confirm that the control strategy is adequate to the process design and the quality of the product.
5. The proposed increase is batch size, not covered by process validation, should be removed.
6. An updated nitrosamine risk evaluation should be provided for the drug product, where the identified risks are thoroughly investigated.

Clinical aspects

7. Dose recommendation for the paediatric population should be further justified.
8. The wording of the indication.

1.1. Questions to be posed to additional experts

1.2. Proposal for inspection

1.2.1. GMP inspection(s)

Not applicable.

1.2.2. GCP inspection(s)

It is unclear which bioanalytical facility is used for study MDZ-NS-22. The applicant is asked to clarify. The applicant should also state whether the bioanalytical facility have been inspected by competent authorities (e.g. WHO, FDA, European authorities) recently and submit inspection reports if available. **(OC)**

1.3. Similarity with authorised orphan medicinal products

N/A.

1.4. Derogation(s) from market exclusivity

N/A.

2. Executive summary

2.1. Problem statement

The proposed indication is:

- Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia.
- Premedication before induction of anaesthesia.

In routine healthcare, diagnostic and therapeutic procedures requiring sedation are common in all age groups. In many cases the patient requires sedation to decrease anxiety and discomfort, with or without analgesia.

Midazolam by IV administration is a well-established and well characterised benzodiazepine for use in these indications. The IN route is potentially a clinically relevant alternative to the IV route in particular situations. The benefit of being able to administer sedation without IV access is potentially useful, particularly in children.

Regulatory context

Recently, a nasal spray solution, containing midazolam 2.5 mg, 3.75 mg and 5 mg, (Nasolam, Medir Europe B.V) has been approved in several European countries through a decentralised procedure for conscious sedation, premedication and the treatment of prolonged, acute, convulsive epileptic seizures in adults and children >12 kg and aged 2 years and older.

In parallel with this Omforro application the applicant has also submitted an application for the medicinal product Tuzodi with the proposed indication "treatment of prolonged, acute, convulsive seizures in adults, adolescents, children and toddlers (from 2 years of age)". Tuzodi has the active substance concentration 25mg/ml (2.5 mg/spray), instead of the 10mg/ml strength (1 mg/spray) for Omforro. Both medicinal products share the same manufacturing process. The submitted clinical study reports discuss both therapeutic indications.

2.2. About the product

Midazolam hydrochloride is a short-acting benzodiazepine. Midazolam has an anticonvulsant effect, a hypnosedative effect, and an anxiolytic and muscle-relaxant effect. After intramuscular or intravenous

administration anterograde amnesia of short duration occurs. The mechanism of action involves the enhancement of gamma-aminobutyric acid (GABA) neurotransmission in limbic, thalamic and hypothalamic regions of the central nervous system. Effects of midazolam resolve rapidly due to fast metabolic transformation. The duration of action is short (20–40 min) and elimination half-life 1.5-3 hours.

Midazolam was first authorised in the EU (Ipnovel, Roche) in December 1982. It is approved for use in children (including neonates <32 weeks gestational age in intensive care units) and adults as a sedative and in anaesthesia, and may be given by the IV, IM or rectal route of administration.

Midazolam is widely used for conscious sedation in several procedures and settings. For conscious sedation prior to diagnostic or surgical intervention, midazolam is administered intravenously. The dose must be individualised and titrated and should not be administered by rapid or single bolus injection. The onset of sedation varies depending on the physical status of the patient, dose, and speed of administration. The dose is titrated to effect. The onset of action is about 2 minutes after the injection. Maximum effect is obtained in about 5 to 10 minutes. In adults the dose can range from 0.5 to 7.5 mg given 5-10 minutes before the beginning of the procedure and iterated as needed.

Midazolam administered intranasally provides significant potential advantages: it is rapidly absorbed as the nasopharyngeal mucosal surface is relatively large and well vascularised, it is absorbed directly into the systemic circulation bypassing the portal system and avoiding the high first-pass metabolism after oral administration (Knoester et al., 2002; Mandema et al.,1992) Consequently, the systemic bioavailability is higher with a more rapid onset of action. Additionally, the relative simplicity of intranasal midazolam delivery does not require skilled personnel, so treatment may always be possible and more acceptable than intravenous rectal and intramuscular drug administration routes for conscious sedation (Davies, 2015).

Omforro (also referred to as MDZ-1) is a nasal spray solution containing 1mg of midazolam in a bidose container. The nasal spray consists of a bi-dose device with the following features:

1. Ready-to-use
2. Administration of only 2 sprays (2 x 0.1 ml) – 1 spray per nostril
3. One hand actuation
4. Can be applied in any orientation (360° functionality).

The nasal spray device provides a technological innovation, which was the basis for the access to the European centralised procedure (Optional Scope following Article 3(2), eligibility request accepted by the European Medicines Agency).

2.3. The development programme/compliance with CHMP guidance/scientific advice

To support the Article 10(3) marketing authorisation application of Omforro, the clinical development program included:

- a clinical PK study (MDZ-NS-22) to assess pharmacokinetics, pharmacodynamics, safety and local tolerance of single doses of midazolam nasal spray (MDZ) with respect to the reference product (Ipnovel).
- a population pharmacokinetic/pharmacodynamic (popPK/PD) model that was developed based on the data collected in MDZ-NS-22 study to derive PK/PD properties of midazolam by describing the observed response in terms of sedation in healthy volunteers.

- a physiologically based pharmacokinetic (PBPK) model that was developed based on both literature data and data collected in MDZ-NS-22 study, and predictions were performed for sedation posology in adults, paediatrics and special populations (i.e. renal impaired population, hepatic impaired population, elderly population, and obese population).

Scientific advice

The applicant received scientific advice on the development of midazolam for treatment of prolonged, acute, convulsive seizures from the CHMP on 15 October 2020 (EMEA/H/SA/4544/1/2020/SME/III). The scientific advice pertained to the following non-clinical and clinical aspects:

- Non-clinical data package and intranasal local tolerance study;
- Pharmacokinetic studies and efficacy and safety data package.

The applicant received follow-up scientific advice on the development of midazolam for the treatment of seizures from the CHMP on 15/09/2022 (EMA/SA/0000095512). The scientific advice pertained to the following clinical, non-clinical and quality aspects:

- Proposed approach to product stability testing, need for sub-visible particle testing
- Need for additional non-clinical study to evaluate pharmacokinetic and local adverse events of the proposed formulation
- Acceptability of clinical PK study design and adequacy of such study along with a PoPPK study and published clinical efficacy and safety studies to support a MAA

Co-Rapporteur's comment on section 2.3.:

I*n principle, a development strategy built on a pivotal PK-bridge is regarded acceptable.*

2.4. General comments on compliance with GMP, GLP, GCP

Based on the review of quality data, CHMP did not identify the need for a GMP inspection.

It is unclear which bioanalytical facility is used for study MDZ-NS-22. Thus, it is unclear whether the site is GCP compliant.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

- Article 10(3) of Directive 2001/83/EC, as amended– relating to applications for hybrid medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Ipnovel, 15/3 mg/ml, solution for injection
- Marketing authorisation holder: Cheplapharm Arzneimittel GmbH
- Date of authorisation: 1994-11-15
- Marketing authorisation granted by:
    - Member State (EEA): Germany MRP/DCP

- Marketing authorisation number: 41119.01.00

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Ipnovel, 15/3 mg/ml, solution for injection
- Marketing authorisation holder: Cheplapharm Arzneimittel GmbH
- Date of authorisation: 1994-11-15
- Marketing authorisation granted by:
    - Member State (EEA): Germany MRP/DCP
- Marketing authorisation number: 41119.01.00

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- N/A

2.5.2. Orphan designation

N/A.

2.5.3. Similarity with orphan medicinal products

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

2.5.4. Derogation(s) from orphan market exclusivity

N/A.

2.5.5. Information on paediatric requirements

N/A

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The information about the drug substance, midazolam hydrochloride, has been provided in form of an ASMF from the holder. The assessment of the ASMF is provided in separate ASMF assessment report with a confidential annex on the Restricted Part.

Midazolam is described in the Ph. Eur., but there is no monograph for drug substance midazolam hydrochloride.

Regulatory Pharma Net S.r.l. applies for the product Omforro nasal spray solution, 1 mg/spray, as a hybrid of Ipnovel solution for injection.

The product is available in a glass container sealed with a chlorobutyl rubber plunger, contained in a polypropylene actuator. The drug-device combination product is able to release two sprays of 100 µl, corresponding to 1 mg of midazolam (as midazolam hydrochloride) per spray.

Omforro is indicated in adults and children from 2 years old.

Other ingredients are: sodium chloride, hydrochloric acid and water for injections.

3.1.2. Active Substance

3.1.2.1. General Information

The chemical name of midazolam hydrochloride is 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine hydrochloride corresponding to the molecular formula $C_{18}H_{13}ClFN_3$*HCl. It has a relative molecular mass of 362.2 g/mol and the following structure:

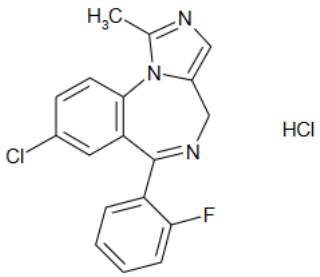


Figure 1: Midazolam hydrochloride, active substance structure

The chemical structure of midazolam hydrochloride was elucidated by a combination of infrared spectroscopy (IR), mass spectrometry (MS), and nuclear magnetic resonance spectroscopy (NMR). The solid state properties of the active substance were measured by differential scanning calorimetry (DSC) and X-ray powder diffractometer (XRPD).

The midazolam hydrochloride is a hygroscopic, pale yellow crystalline powder, soluble in water at pH less than 4, soluble in methanol (1:30) and 0.1 M HCl (1:100).

Midazolam hydrochloride has a non-chiral molecular structure.

Current production of midazolam hydrochloride is consistent from the point of view of the polymorphic form: the IR spectra, the DSC thermograms and the X-ray diffraction patterns are perfectly superimposable.

3.1.2.2. Manufacture, process controls and characterisation

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and are in general considered satisfactory. However, a few clarifications are requested.

The manufacturing process of midazolam hydrochloride is a linear synthetic pathway consisting of 7 transforming steps and two salification steps using a well-defined starting material with acceptable specification.

Detailed information regarding control of materials, control of critical steps and intermediates, process validation/evaluation and manufacturing process development is assessed in the restricted part of the ASMF.

The synthesis scheme of midazolam HCl has been provided. Solvents used are listed separately with an indication which solvents are used in the last step.

The brief description of the process states some of the reagents and solvents used. The total information on the synthesis, reagent and solvents is considered acceptable. No catalysts are used.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

A few issues regarding potential and actual impurities are raised:

- It is recommended to either include specific solvents in the drug substance specification due to their presence in the final manufacturing step, or to conduct spike and purge studies to demonstrate their absence or to control them at specific limits in their raw material.
- The all-specified impurities listed in EP monograph for midazolam should be discussed. It should be confirmed that specified impurities E, G and H reported in the EP monograph of midazolam base cannot be formed as synthesis's impurities or degradation's impurities in midazolam HCl API. The possible formation of impurities D, I and J reported in the EP monograph of midazolam base should be discussed considering the synthesis and possible degradation of the API.
- The API specification does not include a control for potential degradation impurity "Midazolam open product". To ensure product quality and safety, the open product impurity should be included in the specification, with a limit set based on the outcome of an in-silico evaluation of its mutagenic potential.
- To justify the omission of testing for specific solvents in the final API, it is necessary to provide purge factors and purge ratios.
- A detailed description of the genotoxicity assessment methodology, including in-silico screening results, to classify potential genotoxic impurities into Classes 1-5 should be provided.
- Discuss the risk of nitrosamine impurities in the drug substance and include this information in the ASMF applicant's Part.

The active substance packaging complies with EC 10/2011 as amended.

3.1.2.3. Specification (s)

The active substance specification used by the drug product manufacturer has not been provided. Information about analytical methods, method validations and reference standards are also missing.

The Ph.Eur. impurities A, B and C characterised for midazolam and also present in midazolam hydrochloride are specified at the same limits as the Ph.Eur.

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

The current method for residual solvent has not been able to demonstrate sufficient specificity for certain solvent due to inadequate resolution. Therefore, the method must be improved or replaced.

Batch analysis data (n=3 in production scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch. However, the impurity levels for one batch should be provided in figures for transparency.

3.1.2.4. Stability

Stability data from several production scale batches of active substance from the proposed manufacturer(s) stored in the intended commercial package under long term conditions and for up to 6 months under accelerated conditions according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed. Results on stress conditions, thermal stress, acidic/ alkaline hydrolysis and oxidative stress, were also provided.

The following parameters were tested: description, solubility, colour, water content, assay by volumetric analysis, on dry basis, assay by HPLC, on anhydrous and solvent free basis, related substances by TLC, "carboxy" and related substances by HPLC. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications, except for one batch (see below). Related substances are reported within their limits in the stability studies, with no increasing trend for specified, unspecified or total impurities. Assay is stable during the stability studies.

An OOS for KF value was discovered for one batch. The OOS has been investigated and the packaging was optimised starting from 2018 with introduction of two desiccant packets between the liners and between the outer liner and the foil over-wrap according to current packaging description.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period, without storage condition restrictions, in the proposed container. Nevertheless, no re-test period can be accepted until the issues regarding specification and analytical methods raised have been satisfactorily resolved.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and pharmaceutical development

Omforro is an integral drug-device combination product intended for the administration of a solution containing the active substance midazolam in the nasal cavities. Omforro is able to release two sprays of 100 µl, corresponding to 1 mg of midazolam per spray. The composition of the finished product is presented.

Information about the quantitative composition as a concentration (i.e., amount per unit volume or weight) has been requested, as well as amount per container and per spray.

The pharmaceutical development has only been briefly described. It can be noted that the Swiss product referred to in the development section contains a preservative, whereas the applied product is preservative-free. Additional development data is requested, including information about quality target product profile (QTPP) and identified critical quality attributes (CQAs) of the drug product.

As the product is intended for children, a justification of the suitability of the available formulation for the paediatric population should be provided.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. None of the excipients is novel or of human or animal origin.

The list of excipients is included.

The pH of the solution was set based on the pH-dependent solubility of midazolam hydrochloride as well as antimicrobial properties.

No bioequivalence studies have been performed. Information should be provided regarding the test and reference product batches included in pivotal clinical studies. The nasal spray device used for clinical studies should be stated and potential influence on the results of the clinical trials should be discussed, with a special focus on particle size distribution.

The applicant has discussed the pharmaceutical study requirements listed in EMEA/CHMP/QWP/49313/2005 and draft guideline EMA/CHMP/20607/2024, including minimum fill justification, extractables and leachables, performance after temperature cycling, droplet size distribution, 360° usability and drop test study. However, no data has been provided to support the conclusions. With regard to particle / droplet size distribution, full characterisation of the product should be provided. Based on the provided summary of the 360° robustness study, it has not been demonstrated that the device can deliver two uniform sprays independent on orientation.

According to the provided documentation, the applicant considers the product to be for single use, although it contains two sprays. The expected and worst-case time between the first and second spray has not been discussed, and no maximum time is prescribed in the proposed SmPC. A question has been raised by the clinical assessor on the SmPC regarding repeated administration, with reference to midazolam IV that is titrated to effect in these indications. As the robustness testing is performed to simulate use, the applicant is asked to cover also the expected maximum time between administration of the first and second spray, to evaluate if this time has any impact on dose delivery.

The manufacturing process consists of the preparation of a solution that is filtered and filled into vials that are stoppered and then assembled with the device through a semi-automatic filling machine. The provided information regarding manufacturing process development is brief and additional development data is requested.

The only primary packaging components that come into direct contact with the product during manufacturing and storage of the drug product are the glass vial and the plunger. The glass vial is a type I clear vial; reference is made to Ph. Eur. 3.2.1. The plunger is a chlorobutyl polymer with siliconisation, PH 701/55/C black, reference is made to Ph. Eur. 3.2.9. For the primary packaging material insufficient data has been presented.

The other packaging components have a functional role and consist of the container holder and the actuator assembly. The actuator assembly, that is supplied already assembled by the manufacturer, is composed of an actuator, a finger flange, a spray pin, a cannula, a spring, a centre piece and a

bottom. The device has been classified as a class I medical device. An acceptable declaration of conformity has been provided from the drug product manufacturer, referring to Regulation 2017/745.

The main problem in the overall assessment of the product results from the fact that, according to conventional understanding, the batch size rather represents laboratory than production scale size. In addition, it appears that the information on the finished product presented in this section largely represents a review rather than a conclusive development.

3.1.3.2. Manufacture of the product and process controls

The manufacturing method is based on standard process for solutions and consists of four main steps: Bulk manufacturing, filling, assembly and packaging (Figure 2). The process is considered to be a non-standard manufacturing process due to the low concentration of active substance.

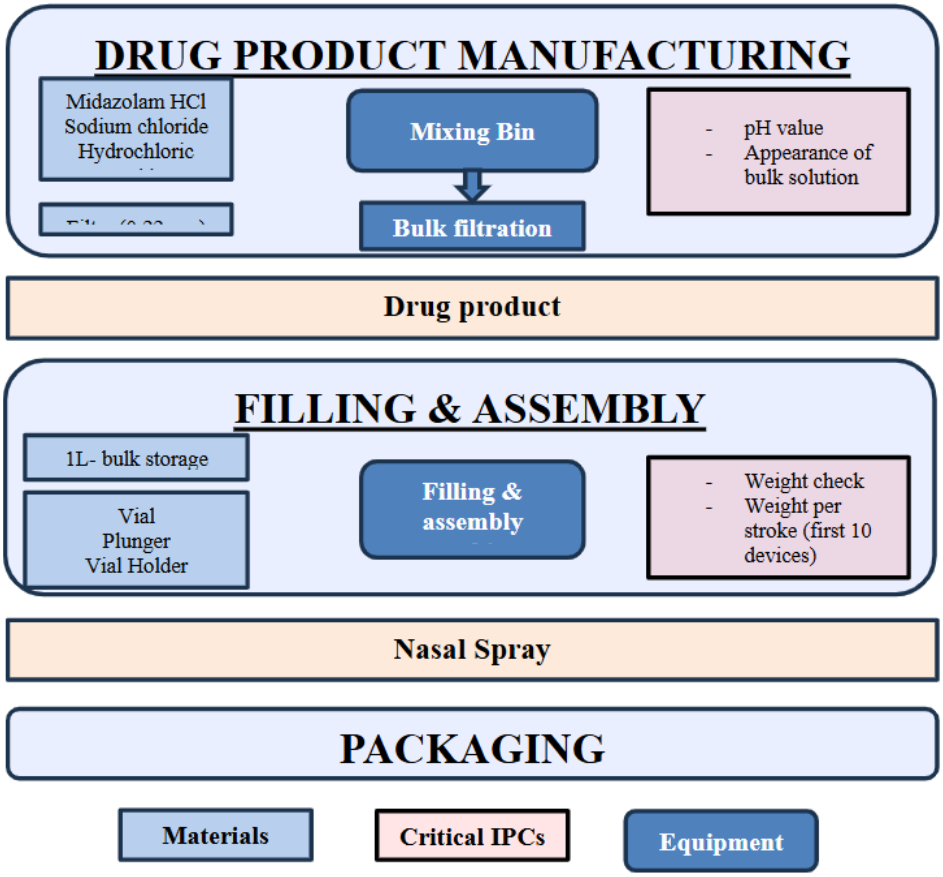


Figure 2: Finished product manufacturing process

The manufacturing process has not been described in sufficient detail; additional information has been requested. A list of control points and critical quality attributes is presented, including test methods and acceptance criteria. The process controls suggested by the applicant are not sufficient to control the critical steps during manufacture. A holding time of 60 days has been proposed for the bulk solution filled into glass flasks. The holding time is not accepted as no supporting data has been presented.

The manufacturing process is considered non-standard due to the low concentration of active substance. There is an unexplained reduction in the number of filled vials from a batch size that is already considered insufficient, this raises major doubts about the validation of the process. No data

has been provided demonstrating homogeneity during filling. It has not yet been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. This point is raised as a major objection.

The applicant claims that a scale-up of the commercial batch size can be performed without risk, based on available data and a risk analysis (not provided). This is not agreed as the manufacturing process is considered non-standard.

The previous production only served to supply a few hospitals in Switzerland with a so-called magistral prescription. It will not be possible to manufacture the nasal spray for marketing throughout Europe on the premises using the equipment described. Even the semi-automatic, manual production planned in some cases does not meet the standard of industrial-scale production. Based on this presumption, it is important to point out that the assessment was strictly focused on the smaller batch size, but having in mind future upscale of the process.

3.1.3.3. Product specification (s)

In general, the finished product release and shelf-life specifications include appropriate tests for this kind of dosage form, taking into account the Ph.Eur. monograph on nasal preparations, the requirements for the drug product preparation and the guideline ICH Q6A for Drug Products. The scope of the release specification and the testing parameters described are largely in accordance with the requirements laid down in the respective Guidelines (Guideline on Pharmaceutical Quality of Inhalation and Nasal Products, EMEA/CHMP/QWP/49313/2005 & Draft-Guideline on the pharmaceutical quality of inhalation and nasal medicinal products, EMA/CHMP/20607/2024).

There are a number of questions on the specification that should be resolved. For example, appearance of the full delivery device should be given, acceptance criteria for pH should be justified based on development data, two complementary methods should be used for the identification of the drug substance, a test for osmolarity should be added to the drug product specification and acceptance criteria for droplet size distribution should be based on the observed ranges of variation in batches that showed acceptable performance in vivo, as well as the intended use of the product.

The potential impurities in the drug product are those reported for the drug substance. There are inconsistencies between the proposed specification and the characterisation of impurities section.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach. The potential elemental impurities have been investigated in the drug products midazolam Bidose Nasal 1 mg/spray (Omforro (MDZ-1)) and midazolam Bidose Nasal 2.5 mg/spray (Tuzodi (MDZ-2.5)). The applicant concludes that the study confirms that the elemental impurities in MDZ-2.5, considered worst-case, are within safe limits over a storage period of two years, supporting the product's safety for its intended use. However, no risk analysis or analytical data has been provided to support this conclusion. A more detailed summary of the elemental impurities risk assessment has been requested.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). Nitrosamine risk factors have been identified, without further actions. An updated nitrosamine risk evaluation should be provided, where the identified risks are thoroughly investigated. This point is identified as a major objection.

The analytical in-house methods have been described, but additional data is requested. The provided summary of validations of in-house methods is not sufficiently detailed to allow for an assessment. It has not been demonstrated that the methods are stability indicating. Several sites are listed as batch control sites in dossier section P.3.1. This leads to a request for clarification what kind of release tests are performed at the single batch control sites and whether all the sites named use the identical analytical methods.

Additional information regarding the reference standards used for assay and impurities testing is requested.

There are questions on the proposed commercial batch size in other report sections.

3.1.3.4. Stability of the product

The claimed shelf-life is 24 months. The proposed storage conditions are unclear as different information is provided in different dossier parts. Photostability data is requested for the finished product.

Stability data from the three process validation batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH), up to 12 months under intermediate conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The matrixing design fulfils requirements of ICH Q1D.

The batches of Omforro are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing. The stability studies are being carried out either on the vial and the plunger or on the drug-device combination product, because some tests depend on the medicinal product contained in the vial and are not related to the device or its functionality.

The analytical methods used were the same as for release.

All presented analytical results fulfil acceptance criteria, with one exception: After 3 months at accelerated conditions, pH was out of specification (OOS) for one batch. It can be noted that pH is reported on all other occasions for all batches, thus at the lower acceptance limit. The applicant is asked to present the conclusions from the pH OOS root cause investigation, including corrective and preventive actions. Proposed pH acceptance criteria during manufacturing (IPC) and in the finished product specification should be discussed and justified based on development and stability data.

For one the assay value at 24 months shows a significantly lower value that does not correlate with an increase of impurities and it does not follow a general trend compared to the intermediate stability results for the same batch or compared to all other batches respectively.

Based on the provided data it is indicated that the final formulation remains stable over the proposed shelf life. However, there are a few issues to be resolved prior to final conclusions on the overall stability and shelf life of the finished product.

There is a question in the pharmaceutical development section regarding the maximum time between the first and second spray from one device. The applicant is asked to present in-use stability data to support the maximum time under the conditions of use as stated in the SmPC, unless otherwise justified.

The proposed shelf-life of 24 months and storage condition "Do not refrigerate or freeze" as stated in the SmPC (section 6.3) are not yet acceptable as there are open questions regarding the control of the drug product.

3.1.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Drug substance

The information about the drug substance, midazolam hydrochloride, has been provided in form of an ASMF. The assessment of the ASMF is provided in separate ASMF assessment report with a confidential annex on the restricted part.

Midazolam is described in the Ph. Eur., but there is no monograph for drug substance midazolam hydrochloride. The Ph.Eur. impurities A, B and C characterised for midazolam and also present in midazolam hydrochloride are specified at the same limits as the Ph.Eur. The proposed limit for one related substance cannot be accepted.

The risk of nitrosamine impurities in the drug substance shall be discussed and information included in the ASMF applicant's Part. This issue is raised as a major objection.

Stability studies have been performed with the drug substance. A retest period has not been accepted yet as there are questions regarding the specification and analytical methods.

The active substance specification used by the drug product manufacturer has not been provided. Information about analytical methods, method validations and reference standards are also missing.

Drug product

Omforro is an integral drug-device combination product intended for the administration of a solution containing the active substance midazolam in the nasal cavities. Omforro is able to release two sprays of 100 µl, corresponding to 1 mg of midazolam per spray.

The development of the product has been described; however, questions have been raised. The choice of excipients has been justified, and their functions explained. Since the product includes posology for children, further information/discussions are required with respect to the paediatric population.

Information should be provided regarding the test and reference product batches included in pivotal clinical studies.

All excipients are well known, and their quality is compliant with Ph. Eur. standards.

In general, the product specifications cover appropriate parameters for this dosage form, but questions have been raised. There are also open questions on analytical methods, validations of analytical methods and standards used. Batch analysis data show that the finished product meets the specifications proposed.

The risk assessments on elemental impurities and nitrosamine impurities must be complemented with additional information.

The manufacturing process consists of the preparation of a solution that is filtered and filled into glass vials that are stoppered and then assembled with the device. The manufacturing process is considered non-standard due to the low concentration of active substance. It has not yet been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

A holding time of 60 days has been proposed for the bulk solution filled into glass flasks. The holding time is not accepted as no supporting data has been presented.

The container closure system consists of a type I clear glass vial and a chlorobutyl polymer plunger with siliconisation. The device has been classified as a class I medical device. An acceptable declaration of conformity has been provided.

The conditions used in the stability studies are according to the ICH stability guideline. The claimed shelf-life is 24 months. The proposed storage conditions are unclear as different information is provided in different dossier parts. No photostability data has been provided for the finished product. As there are open questions regarding the control of the drug product, shelf-life and storage conditions have not yet been assessed.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have not yet been presented in a satisfactory manner. There are major objections and several other concerns that need to be addressed before the application can be recommended for approval from a chemical and pharmaceutical perspective.

3.1.6. Recommendation(s) for future quality development

Not applicable.

3.2. Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of midazolam has been provided. Pharmacodynamic, pharmacokinetic and toxicological properties of midazolam are well known. As midazolam is a widely used, well-known active substance no additional studies have been provided and further studies are not considered necessary.

The indications sought for Omforro are the same as those for the reference product Ipnovel. The differences between Omforro and the reference product relate to the pharmaceutical form, strength and route of administration. Nasal administration of Omforro is not expected to result in higher systemic exposures than that following Ipnovel administration. There is a strong relationship between midazolam plasma concentrations and response, and Omforro, like Ipnovel, will be titrated to desired effect (e.g. sedation).

No non-clinical studies have been conducted to evaluate the local tolerance of the intranasal route of the Omforro formulation. This is considered acceptable as local tolerability was assessed in a clinical PK study through the analysis of subjective nasal symptoms evaluation and nasal examination by Ear Nose Throat specialist. Local symptoms were most commonly reported in close relation to administration and were mainly of mild-moderate severity (see further in section 3.3.6). The nasal spray formulation includes no new excipients and contains, beyond water, only small amounts of sodium chloride (0.7%) as isotonic agent and HCl (0.2%) as pH adjuster. Moreover, Omforro is not indicated for chronic administration. Overall, this is in agreement with the EMA scientific advice (EMA/SA/0000095512).

One impurity in the drug substance is specified at 0.2%, i.e. above the qualification threshold, which is discussed in section 3.1.2.3 Specifications.

3.2.1. Ecotoxicity/environmental risk assessment

The applicant has submitted an ERA document including Phase I and PBT/vPvB risk assessments. A conclusion is reached that the ERA can stop in Phase I.

Phase 1

The default the PEC_{sw} value is equal to 0.01 µg/L considering a maximum daily dose of 2 mg as outlined in SmPC section 4.2. However, as further discussed in the clinical part and LoQ, midazolam is titrated to effect in both indications, and a higher maximum daily dose may be needed. Therefore, a revision on the maximum daily dose used in the PEC_{sw} calculations may be warranted.

A refinement of the F_{PEN} value based on prevalence and treatment regime is proposed. For prevalence, the applicant has used the number of MRI scans in Germany, the country with the highest number of diagnostic procedures in EU according to the OECD database. Considering the German population (including children), it is assumed that about 12,843,345 MRI exams are performed per year. However, this measure is not considered an adequate estimate of the prevalence as the first indication, *procedural sedation,* may include a number of other potential uses such as endoscopies (colon, gastro-intestinal, respiratory, urinary), fracture and wound care, change of dressing, placements of drains and catheters, in gynaecology, paediatrics, ophthalmology (examinations and procedures e.g. eye lasering), ear-nose-throat, or dental procedures. Therefore, using the prevalence of numbers of only MRI scans in one country is not considered an appropriate measure of prevalence for the indication *procedural sedation*. In addition, no prevalence for the second indication, *premedication before anaesthesia*, has been included.

For refinement based on treatment regime, a treatment period of 1 day and a treatment repetition of 1 per year was considered. However, no source for these assumptions has been provided, nor are there support for this treatment regime in the SmPC. As outlined the ERA guideline, F_{PEN} may be refined taking the worst-case treatment period and the worst-case number of treatment repetitions per year into consideration. For an intermittent treatment regime, refinement should be based on clinical considerations and justified by a reliable and independent source.

Taken together, the phase 1 risk assessment is not considered acceptable. A revised maximum daily dose should be used in the PEC_{sw} calculations (if applicable). The PEC_{sw} may be refined based on prevalence data and/or based on treatment regime and should cover all designated indications of Omforro. A worst-case scenario must be included in the refinement and the treatment regime should be justified by a reliable and independent source. If the refined PEC_{SW} value is less than 0.01 µg/L, the risk assessment can stop in Phase 1 (**OC**). If not, a phase II risk assessment should be performed.

PBT/vPvB risk assessment

In the PBT/vPvB risk assessment, the $logK_{ow}$ values of midazolam referred to are not considered acceptable. Therefore, a new experimentally determined $logK_{ow}$ value should be presented (**OC**).

Alternative strategy for Phase 1 and PBT/vPvB risk assessments

On the other hand, it is noted that the decision trees for Article 10 medicinal products in the ERA guideline has not been taken into consideration. An optional strategy to complete the ERA would be to follow the phase 1 and the PBT/vPvB decision trees and provide relevant information (**OC**). This would be an alternative strategy to complete the ERA.

Table 1. Summary of main study results

Substance (INN/Invented Name): midazolam hydrochloride			
CAS-number (if available): 59467-96-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	No study submitted	Potential PBT (Y/N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ (default/refined)	open	µg/L	> 0.01 threshold (Y/N)

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of midazolam hydrochloride to the environment or on the PBT/vPvB assessment.

3.2.2. Discussion on non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of midazolam are well known. No new non-clinical studies have been conducted with midazolam in this application, and this is considered acceptable.

The justification for the absence of a non-clinical local tolerance study following nasal administration is agreed.

In a scientific advice (EMA/SA/0000095512) in 2019, a pharmacokinetic bridging study with the new formulation in a validated animal model was recommended. Such non-clinical bridging study has not been performed and is not considered necessary. A clinical bridging study (MDZ-NS-22) in adult healthy volunteers has been performed. In this study, subjects were administered four different single

doses of intra-nasal midazolam (1, 2, 4 and 5 mg) and 2.5 mg iv midazolam as the reference arm (see further in section 3.3.2).

A substance impurity was specified in the substance at 0.2%, while the qualification limit is 0.15%. The impurity is known for midazolam products. It is not genotoxic, and its total intake is very low, see further discussion in section 3.1.2.3. For completeness of the dossier, the non-clinical overview should include a discussion of impurities according to Directive 2001/83/EC Annex I, Part I and the Notice to applicants, Volume 2B **(OC**).

SmPC section 5.3 is identical to the reference product Ipnovel, and section 4.6 is largely in agreement with the reference product. However, some comments to section 4.6 are provided in the SmPC document.

One other concern is raised on the ERA (see above and LoQ).

3.2.3. Conclusion on non-clinical aspects

There are no concerns regarding the pharmacodynamics and pharmacokinetics part of the dossier. However, the non-clinical overview should be updated with a discussion on impurities (**OC**), and the ERA should be completed in agreement with the ERA guideline (**OC**).

3.3. Clinical aspects

Tabular overview of clinical studies

To support the application, the applicant has submitted one PK/PD study and PopPK, PBPK and PK/PD models.

Table 2. Overview of the clinical studies

Type of Study Study Identifier	Objective(s) of the Study	Study Design Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patient	Duration of Treatment	Study Status Type of Report	Location of Study Report
PK study MDZ-NS-22	The primary objective of this study was: To assess the pharmacokinetic profiles of intranasally administered midazolam and its metabolite α-hydroxymidazolam, versus the intravenous reference formulation, in male and female healthy subjects. The secondary objectives of this study were: -To evaluate the general safety, local tolerance of the test drug administered intranasally (IN), compared to intravenous (IV) reference drug administration, in male and female healthy subjects. -To evaluate the sedation level reached with the test drug compared to the reference drug. The exploratory objective of this study was: -To evaluate the first pass effect after intranasal administration.	Open, randomized, cross-over study	-MDZ-1 (10 mg/mL) 1 mg (100 µL) :one puff into a nostril -MDZ-1 (10 mg/mL) 2 mg (200 µL) : one puff per nostril -MDZ-1 (10 mg/mL) 4 mg (400 µL): four puffs into both nostrils -MDZ-2.5 (25 mg/mL) 5 mg (200 µL): one puff per nostril -Ipnovel (15 mg/3 mL solution for injection) 2.5 mg: intravenous	28	Healthy Subjects	Single dose	Completed	5.3
PK/PD and PBPK models ACS-2024-0007	Identification of posology of the nasal spray formulation (MDZ) for the following indications in selected populations (adults, children, elderly, obese, renal impaired, liver impaired subjects): 1.Conscious sedation before and during diagnostic or therapeutic procedures with or without local anesthesia. 2. Treatment of prolonged, acute, convulsive seizures	-	Ipnovel (15 mg/3 mL solution for injection) as 2.5 mg diluted in 2.5 mL infused over 2 min. MDZ-1 (10 mg/mL) 1 mg (100 µL) - the dose was reached through one Bi-Dose device, as one puff into a nostril. MDZ-1 (10 mg/mL) 2 mg (200 µL) - the dose was reached through one Bi-Dose device, as one puff per nostril. MDZ-1 (10 mg/mL) 4 mg (400 µL) - the dose was reached through two Bi-Dose devices, as four puffs into both nostrils (two puffs per nostril). MDZ-2.5 (25 mg/mL) 5 mg (200 µL) - the dose was reached through one Bi-Dose device, as one puff per nostril.	-	-	-	Completed	5.3

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Methods

Bioanalytical methods

A bioanalytical LC-MS/MS method was developed to measure midazolam and 1-OH midazolam concentrations in plasma, using midazolam-D_4 maleate and alpha-hydroxymidazolam-D_4 as internal standards. K_3EDTA was used as anticoagulant.

Pre-study validation

The validation report was not submitted.

Within-study validation

Satisfactory method performance during study sample analysis was demonstrated, including acceptable overall (mean) accuracy and precision of the Quality Control (QC) samples of all accepted runs. Appropriate run acceptance criteria were used. Incurred sample reanalysis was performed for 7.6% of the midazolam and 1-OH midazolam samples, respectively, with satisfactory results. Lower limit of quantification (LLOQ) was below 1/20 of average Cmax for midazolam.

Five (5) samples were reanalysed for pharmacokinetic reasons. Carry-over was more than 20% of the response at the LLQ for the analytes in one run. During sample storage, the freezer exceeded the alarm threshold for 3:55h. The maximum temperature reached was -11.74°C as the door was left open by mistake.

Population pharmacokinetic analysis

A population pharmacokinetic (PopPK) model was developed based on the observed plasma concentrations of midazolam and midazolam 1-OH from Study MDZ-NS-22.

PopPK modelling was performed with Monolix Suite® (Build 2023R1 or higher, Lixoft). All models were identified using SAEM estimation algorithm.

The disposition of midazolam and midazolam 1-OH was described by the 2-compartment disposition model with first-order elimination and absorption (Figure 2). Different rate and extent of absorption were estimated for the two different IN formulations (MDZ-1 and MDZ-2.5). Body weight was included as a covariate on the formation rate constant for midazolam 1-OH.

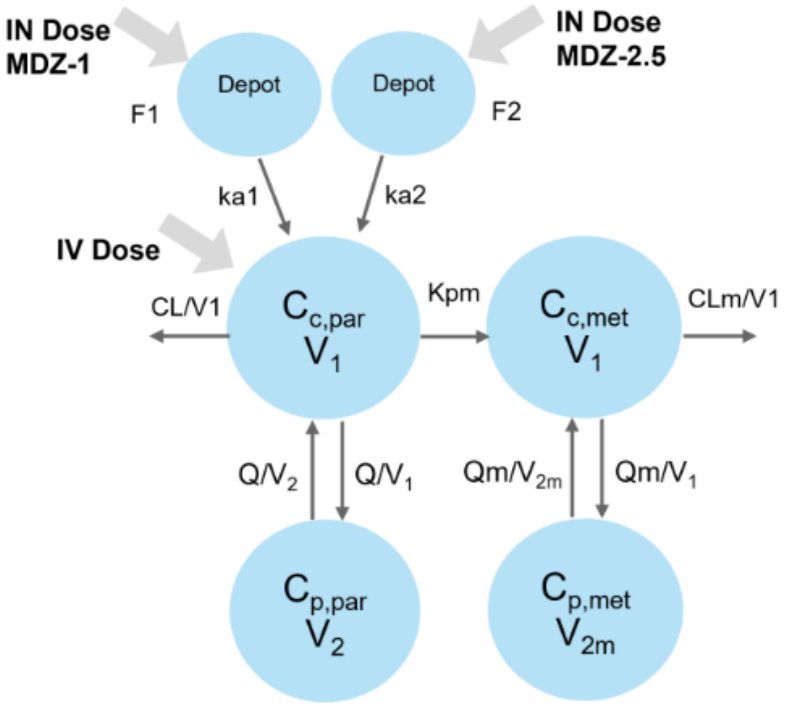


Figure 3: Population PK model scheme

The PK model parameters identified with the final model are given in Table 3.

Table 3: Midazolam PK model parameters

Parameter	Distribution	Estimate (CV%)	SE	RSE (%)
Fixed Effects				
F1_pop (-)	Logitnormal	0.95	0.02	2.1
F2_pop (-)	Logitnormal	0.99	0.00082	0.08
ka1_pop (1/h)	Lognormal	5.40	0.65	12.1
ka2_pop (1/h)	Lognormal	5.55	0.62	11.2
V1_pop (L)	Lognormal	14.37	2.67	18.6
Cl_pop (L/h)	Lognormal	19.99	1.82	9.1
Q_pop (L/h)	Lognormal	63.90	11.65	18.2
V2_pop (L)	Lognormal	30.29	2.10	6.9
Clm_pop (L/h)	Lognormal	20.59	4.92	23.9
Qm_pop (L/h)	Lognormal	4.28	0.43	10.1
V2m_pop (L)	Lognormal	10.40	2.65	25.4
Kpm_pop (1/h)	Lognormal	0.62	0.20	31.7
beta_Kpm_WEIGHT		-0.017	0.0046	27.1
Standard Deviation of the Random Effects (ω)				
omega_F1		1.64 (16.6%)	0.35	21.3
omega_F2		4.4 (17.3%)	1.28	29.2
omega_ka1		0.61 (67.2%)	0.09	14.9
omega_ka2		0.57 (62.3%)	0.08	14.2
omega_V1		0.94 (118.4%)	0.13	14.0
omega_Cl		0.45 (47.6%)	0.07	14.9
omega_Q		0.84 (101.1%)	0.19	22.3
omega_V2		0.3 (30.3%)	0.05	17.8
omega_Clm		1.18 (174.7%)	0.18	14.9
omega_Kpm		0.28 (28.3%)	0.04	15.1
Error Model Parameters				
a1		9.37	0.17	1.77
a2		0.68	0.012	1.81

RSE: Percentage of relative standard error (100%·SE/Estimate).
ω Represents the standard deviation of the interindividual variability parameter.
The parameter b is the proportional component of the residual error of the model.

VPC plots of the PK model are reported in Figure 4 and Figure 5.

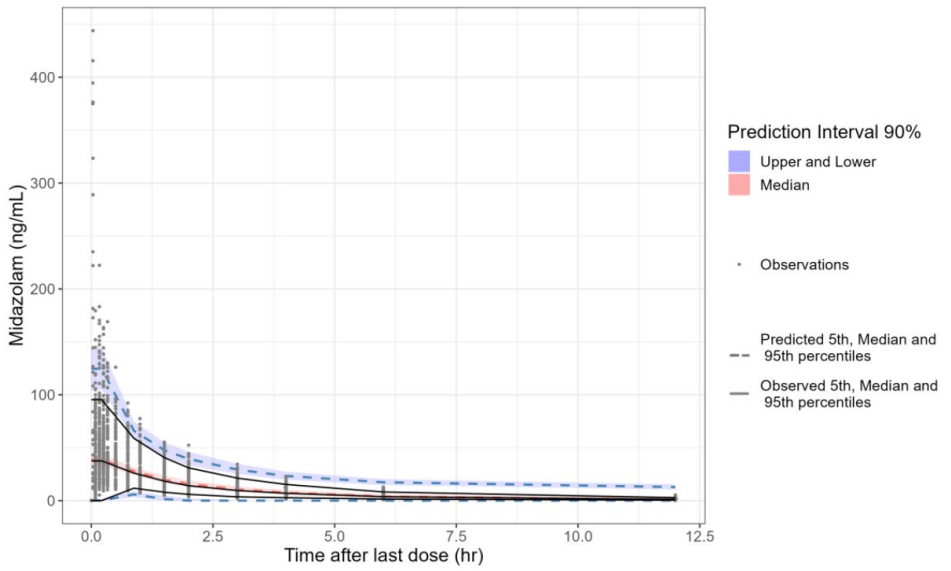


Figure 4: PK VPC plots (parent)

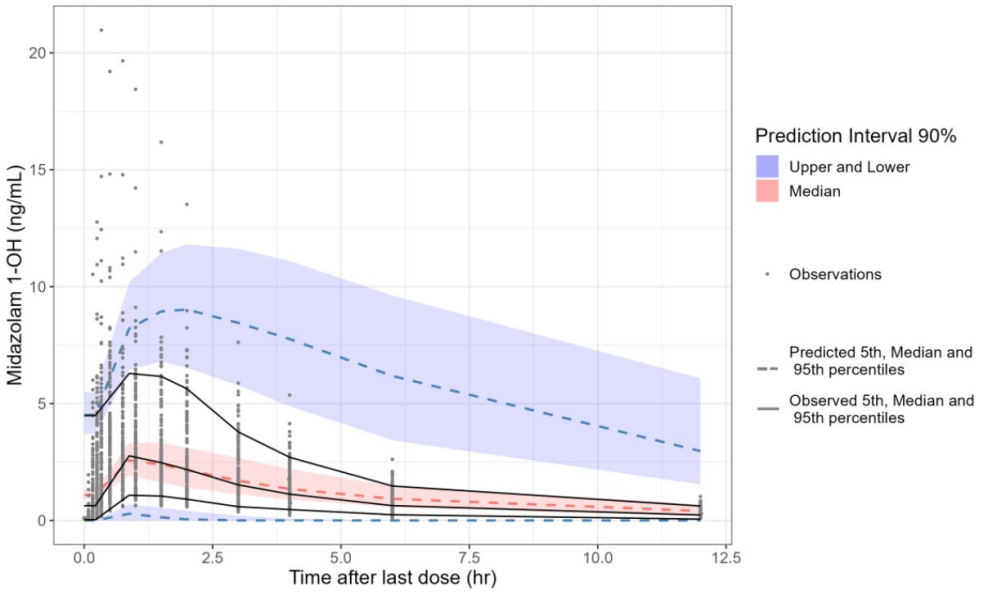


Figure 5: PK VPC plot (midazolam 1-OH)

The final PopPK model was used to simulate administration of repeated dosing of two IN doses, separated by a period of 10 minutes. This included simulations of repeated 2 mg doses shown in Figure *6*.

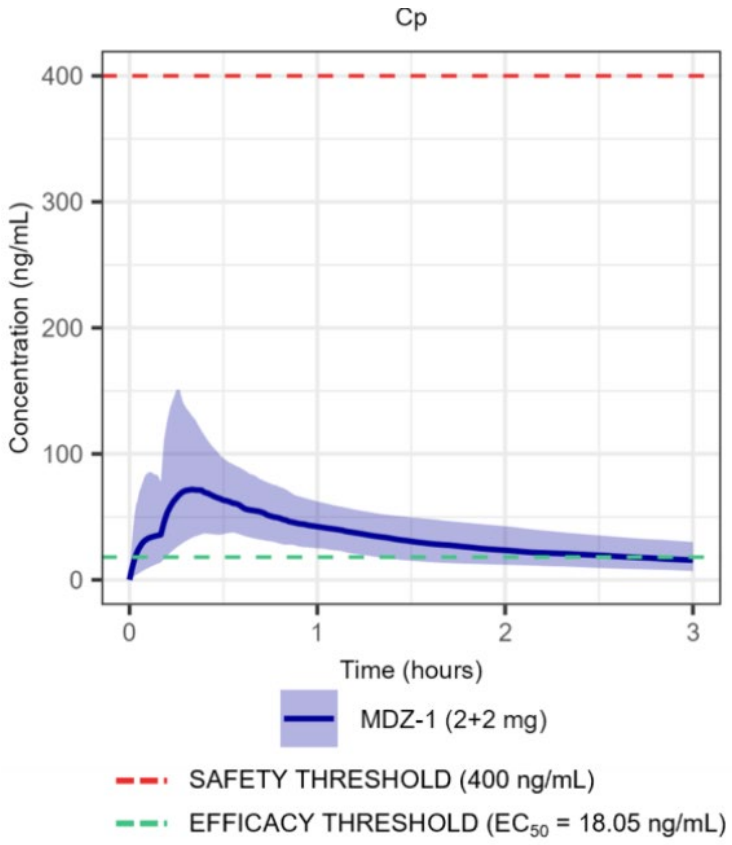


Figure 6: Simulated PK profiles (median and [10th-90th] percentile range) obtained with MDZ-1 (2+2 mg) in central compartment

Physiologically based pharmacokinetic modelling

A physiologically based pharmacokinetic (PBPK) model of midazolam was built in GastroPlus using published in vitro and in vivo experimental data and predicted data. The predicted profiles were compared to experimental data from literature and MDZ-NS-22 clinical study.

The model was used to describe PK in special populations and to validate the physiologies used. To do this, the physiology of the model was changed to that of the target population with the demographic described in the literature including paediatric subjects.

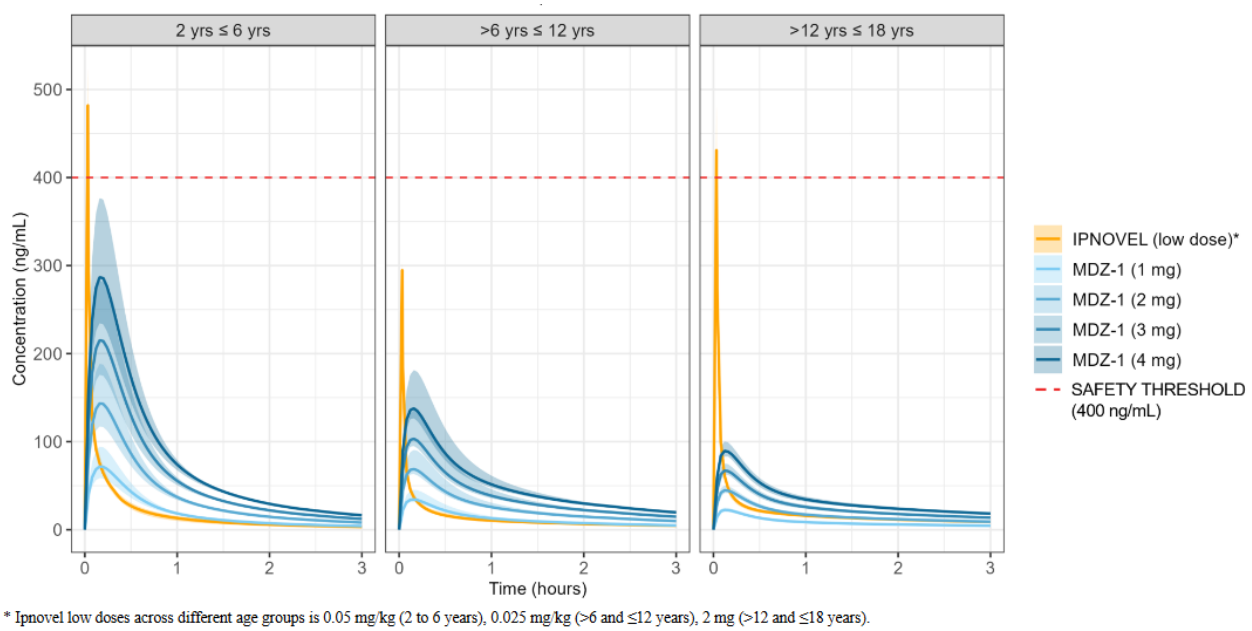
The model was deemed to be validated if the model could predict relevant pharmacokinetic parameters such Cmax, AUC and AUC∞, as well as the shape of the curves.

The PBPK predictions of the IN profiles of midazolam against published data were overall satisfactory. The PBPK predictions of the IV profiles of midazolam against published data were satisfactory. The PBPK predictions of the PO profiles of midazolam against published data were overall satisfactory.

The same model was used to predict the profiles of both IV Ipnovel and IN MDZ-1 and MDZ-2.5 from the clinical study MDZ-NS-22. The optimisation of the nasal parameters allowed a very good prediction of the observed values for all dose regimens tested.

The PBPK model for each special population used either the experimentally measured CL, or the CL scaled using the PEAR Physiology within GastroPlus and each profile was evaluated against the published experimental data. In terms of predictions, all special populations modelled showed to have Cmax, AUC∞ and AUCt within 2 folds of the experimental values.

Simulated PK profiles of midazolam central compartment concentration in children grouped by age range, i.e., 2 to 6 years, >6 and ≤12 years, >12 and ≤18 years, are shown in Figure 7 (single dose) and Figure 8 (two doses).



* Ipnovel low doses across different age groups is 0.05 mg/kg (2 to 6 years), 0.025 mg/kg (>6 and ≤12 years), 2 mg (>12 and ≤18 years).

Figure 7: Simulated PK profiles (median and [10th-90th] percentile range) obtained with MDZ-1 (all QD doses) versus Ipnovel (low dose: 0.05 mg/kg in 2 to 6 years, 0.025 mg/kg in >6 and ≤12 years, 2 mg in >12 and ≤18 years)

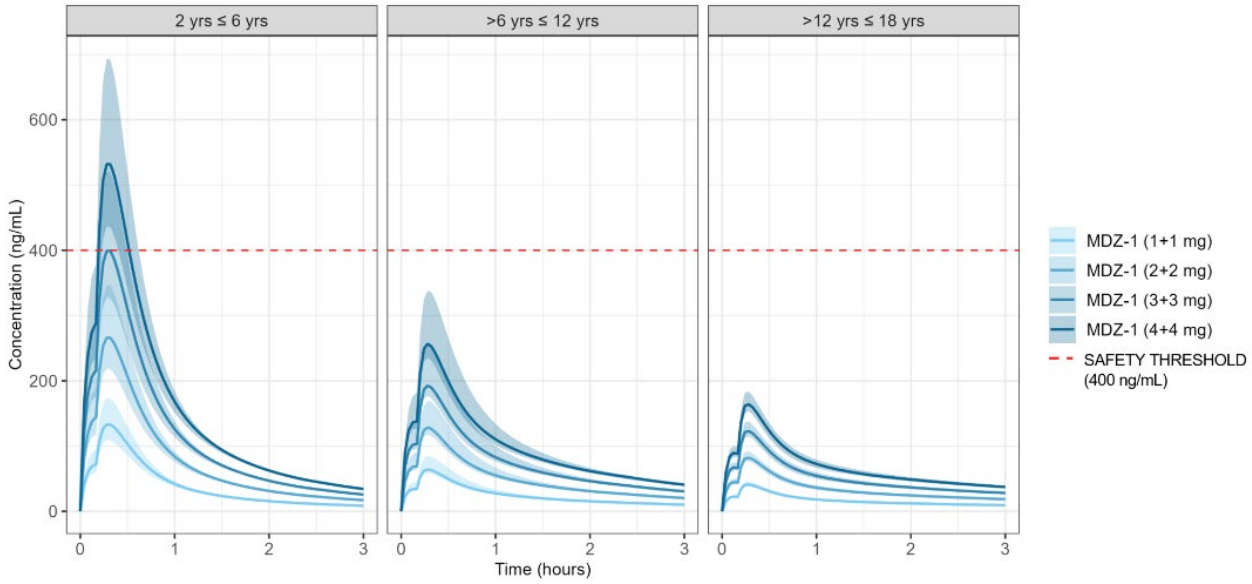


Figure 8: Simulated PK profiles (median and [10th-90th] percentile range) obtained with MDZ-1 (all BID Doses) in 2 to 6 years, >6 and ≤12 years and ≤18 years

Absorption

Study MDZ-NS-22: Open, randomized, cross-over study to assess the pharmacokinetics, safety and local tolerance of single doses of midazolam nasal spray in healthy subjects

Study design

The study was a phase I, monocentre, open label, randomised, 5-single-dose, cross-over study conducted in 28 healthy males and females, aged 18-49 years and body mass index of 18.40-27.80 kg/m^2. The healthy volunteers were randomised in 28 different sequences of the five treatments.

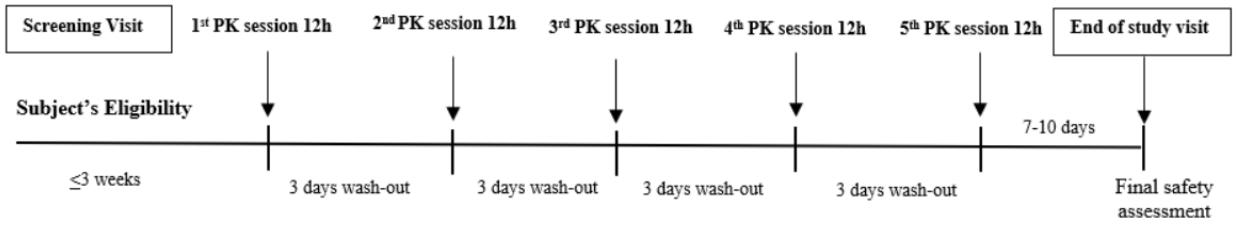


Figure 9: Study design

Four dose levels of IN midazolam were compared to a single IV 2.5 mg dose. Following treatments were administered:

- MDZ-1 (10 mg/mL) 1 mg (100 µL) as one puff into a nostril
- MDZ-1 (10 mg/mL) 2 mg (200 µL) as one puff per nostril
- MDZ-1 (10 mg/mL) 4 mg (400 µL) as four puffs into both nostrils (two puffs per nostril)
- MDZ-2.5 (25 mg/mL) 5 mg (200 µL) as one puff per nostril
- Ipnovel (15 mg/3 mL solution for injection) as 2.5 mg diluted in 2.5 mL injected over 2 min. (Reference Product).

For IN administration, blood samples were collected pre-dose and at 5, 10, 15, 20, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 12 hours post-dose. T0 for IN administration was defined as time since administration completion.

For IV administration, blood samples were collected pre-dose and at 2, 5, 10, 15, 20, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 12 hours post-dose. T0 for IV administration was defined as time since administration start.

Results

The results of midazolam PK parameters are presented in Table 4 and Figure 10.

Table 4: Midazolam mean plasma PK parameters per treatment group

Treatment	$AUC_{(0-\infty)}$ (ng*h/mL) Mean (SD)	$AUC_{(0-t)}$ (ng*h/mL) Mean (SD)	C_{max} (ng/mL) Mean (SD)	T_{max} (h) Median (Min;Max)	$T_{1/2}$ (h) Mean (SD)
MDZ-1 1 mg	44.52 (8.674)	41.90 (7.846)	25.52 (7.181)	0.17 (0.08;0.50)	3.20 (0.678)
MDZ-1 2 mg	84.72 (17.206)	79.79 (15.343)	49.49 (15.975)	0.17 (0.08;0.75)	3.13 (0.673)
MDZ-1 4 mg	157.58 (38.958)	147.97 (34.687)	85.79 (27.745)	0.25 (0.08;0.50)	3.07 (0.729)
MDZ-2.5 5 mg	219.20 (50.676)	207.23 (45.736)	119.24 (39.640)	0.17 (0.08;0.50)	3.07 (0.633)
Ipnovel 2.5 mg	106.80 (23.676)	101.01 (21.186)	179.40 (125.517)	0.03 (0.03;0.17)	3.14 (0.701)

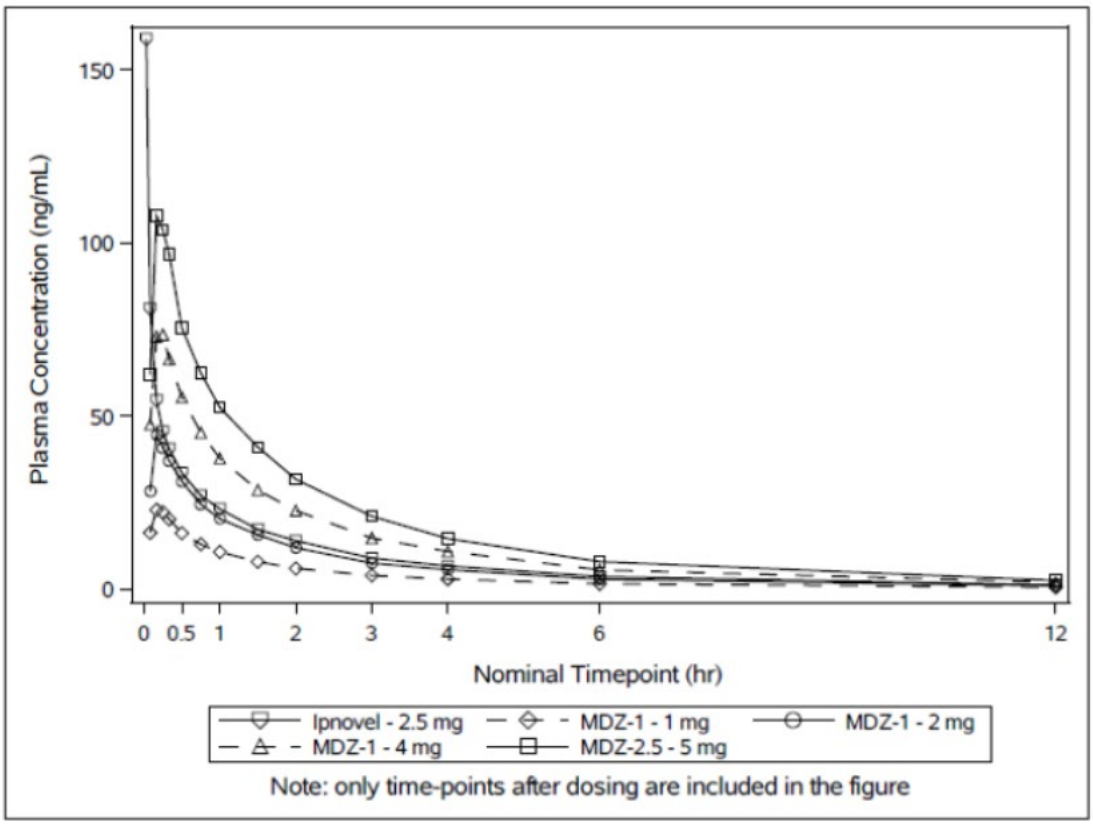


Figure 10: Mean midazolam plasma concentrations vs nominal time (all formulations)

The results of 1-OH midazolam PK parameters are presented in Table 5.

Table 5: 1-OH midazolam mean plasma PK parameters per treatment group

Treatment	$AUC_{(0-\infty)}$ (ng*h/mL) Mean (SD)	$AUC_{(0-t)}$ (ng*h/mL) Mean (SD)	Ratio (%) $AUC_{(0-t)}$ IN vs IV	C_{max} (ng/mL) Mean (SD)	Ratio (%) C_{max} IN vs IV	T_{max} (h) Median (Min;Max)	$T_{1/2}$ (h) Mean (SD)
MDZ-1 1mg	5.37 (1.790)	4.68 (1.737)	92.42	1.32 (0.578)	78.76	0.75 (0.33;2.00)	2.95 (1.052)
MDZ-1 2mg	10.92 (3.897)	9.80 (3.710)	96.76	2.66 (1.177)	79.36	0.75 (0.33;1.50)	3.25 (0.833)
MDZ-1 4mg	21.86 (7.826)	19.86 (7.217)	98.04	5.28 (2.150)	78.76	0.75 (0.25;2.00)	3.23 (0.653)
MDZ-2.5 5mg	29.80 (11.379)	27.01 (10.847)	106.67	6.97 (3.705)	83.17	0.50 (0.33;1.50)	3.36 (0.793)
Ipnovel 2.5mg	14.02 (5.508)	12.66 (5.170)	100.00	4.19 (2.015)	100.00	0.33 (0.17;1.00)	3.29 (0.903)

The bioavailability results were compared between Ipnovel 2.5 mg vs MDZ-2.5 5 mg for midazolam and 1-OH midazolam. The data are presented in Table 6 and Table 7.

Table 6: Bioavailability assessment – midazolam

Parameter	Ipnovel	MDZ-2.5 - 5 mg	Ratio LS Mean [%]	Lower bound of 90% CI [%]	Upper bound of 90% CI [%]
Max Conc (ng/mL)	136.29	113.07	82.96	65.96	104.35
AUC to Last Nonzero Conc (h*ng/mL)	99.38	202.02	203.28	184.16	224.39

Table 7: Bioavailability assessment - 1-OH midazolam]

Parameter	Ipnovel	MDZ-2.5 - 5 mg	Ratio LS Mean [%]	Lower bound of 90% CI [%]	Upper bound of 90% CI [%]
AUC Infinity Obs (h*ng/mL)	13.18	27.95	211.98	178.88	251.22

Overall, the percentage of midazolam that reached the systemic circulation (F parameter) for each test product is reported by treatment group in Table 8. The geometric means were 91.38 for MDZ-1 4 mg group, 99.44 for MDZ-1 2 mg group, 102.28 for MDZ-2.5 5 mg group and 104.19 for MDZ-1 1 mg group.

Table 8: Summary of F parameter

	MDZ-1 1 mg	MDZ-1 2 mg	MDZ-1 4 mg	MDZ-2.5 5 mg	Ipnovel 2.5 mg
N (patients)	27 (100.0%)	28 (100.0%)	27 (100.0%)	28 (100.0%)	28 (100.0%)
Mean (SD)	106.33 (20.41)	101.22 (19.03)	93.52 (20.07)	104.19 (19.75)	100.00 (0.00)
Median	106.89	102.21	93.91	103.83	100.00
Min / Max	51.58 / 145.87	64.93 / 142.31	54.70 / 132.89	55.49 / 158.93	100.00 / 100.00
CV(%)	19.20	18.80	21.46	18.95	0.00
Geometric Mean	104.19	99.44	91.38	102.28	100.00

The bioavailability of MDZ-1 and MDZ-2.5 formulations were estimated in the PopPK analysis where the bioavailability was high and similar between both formulations (MDZ-1: 95%, MDZ-2.5: 99%).

Distribution

Based on the similar AUC metabolite/parent ratio after intravenous and intranasal administration, distribution of midazolam is expected to be comparable between IN administration and IV administration.

Elimination

Plasma half-life values of midazolam across MDZ-1 1 mg, MDZ-1 2 mg, MDZ-1 4 mg, MDZ-2.5 5 mg and Ipnovel 2.5 mg were similar and approximately equal to 3 hours. Mean total clearance (CL) of midazolam were also comparable across MDZ-1 1 mg, MDZ-1 2 mg, MDZ-1 4 mg, MDZ-2.5 5 mg and Ipnovel 2.5 mg, ranging from 23.34 to 26.95 L/h.

Dose proportionality

Linearity was shown in the dose range of 1-5 mg.

Intra and inter individual variability

The inter-subject variability in terms of CV for AUCt was ranging from 18.7% to 23.4%, and for Cmax ranging from 28.1% to 33.2%.

Special populations

A PBPK model was developed based on both literature and MDZ-NS-22 study collected data, in order to translate and predict drug exposure, thus supporting posology of special populations and paediatric populations. For details, see section Physiologically based pharmacokinetic modelling above.

3.3.1.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application. PD endpoints have been integrated at predefined time points in the open-label study design. The Stanford Sleepiness Scale (SSS) is a PRO measure validated for adult populations. The

OAA/SS scale is a validated scale aligned with the ASA continuum of depth of sedation and was rated by the blinded Investigator in this study. OAA/SS is frequently used in clinical settings/trials on procedural sedation, while SSS is usually used to measure levels of sleepiness throughout the day. With the SSS score deeper sedation levels (OAA/SS 0-3 or 4) cannot be differentiated. Like the compilation of the PK data, also the measured scores of the OAA/SS have not been provided, for the SSS only a figure on the degree of sleepiness over time has been presented (**OC**).

Deriving PK/PD correlations from PRO measures in an open-label setting as a surrogate for a quite variable clinical endpoint (sedation level) is challenging and of questionable value. In contrast, OAA/SS can rather be regarded as an established clinical endpoint for determination of the level of sedation than a PD endpoint. The boxplot distribution of $AUC_{sedation}$ presented, however, does not suggest any correlation to the administered dose.

Figure 11 suggests that the average Stanford Sleepiness Scale (SSS) pattern is similar to the concentration time profiles. The SSS rises slower for the 2 mg IN dose (*yellow curve*) compared to the 2.5 mg IV dose (*purple curve*), but the SSS levels are approximately comparable after 15 minutes. In conclusion, the presented sedation scores can be regarded supportive, however, a dose correlation based on the data presented cannot be established.

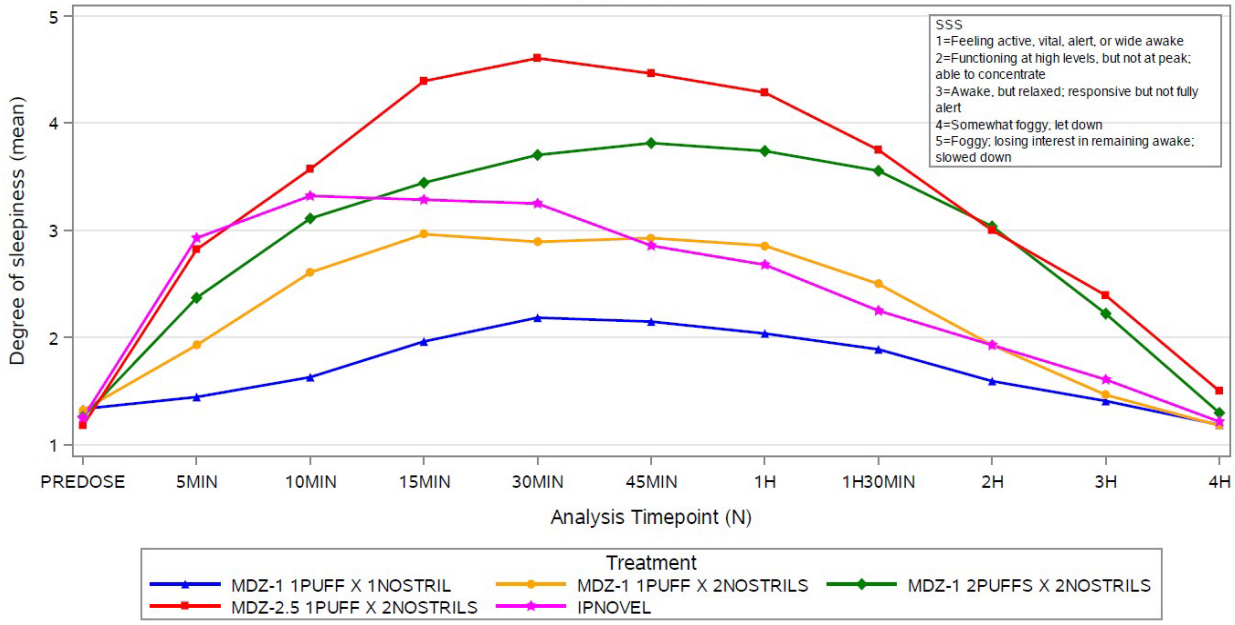


Figure 11: SSS at each timepoint per treatment group

The pharmacodynamic data were included in a PKPD model-based analysis (data not shown).

3.3.2. Discussion on clinical pharmacology

The applicant submitted a PK/PD study (MDZ-NS-22) in adults comparing IN and IV administration of midazolam and PopPK, PBPK and PK/PD models in order to bridge the efficacy and safety of Ipnovel and to justify the suggested posology for adults and children from 2 years of age. This approach is acceptable for an article 10 (3) Hybrid application. For applications according to Article 10 of Directive 2001/83/EC, reference must be made to a product which is or has been authorised in the Union. It is currently unclear whether the reference product used in the study is from EU. **(OC)**

The study design of MDZ-NS-22 is overall satisfactory. There are however some comments related to missing data (PK tables and figures and certificate of analysis) and unclarity regarding the bioanalytical

site. **(OC)** The study showed that the absolute bioavailability was high for the intranasal route, that risk of a lower bioavailability when higher volume is administered is considered low and the applied product shows dose-proportionality in range of 1-5 mg.

Given an absolute bioavailability of approximately 1 for the IN formulation, when comparing Ipnovel 2.5 mg and midazolam 2 mg IN formulation in the presented midazolam mean plasma PK parameters, AUC is about 20% lower and Cmax about 70% lower for midazolam IN formulation. The applicant did not thoroughly justify this difference in exposure when bridging to the safety and efficacy data of Ipnovel. However, based on the presented data, the concentration-time curves appear comparable after approximately 15-20 minutes which suggests that bridging efficacy and safety to the reference product could be reasonable (see also Discussion on clinical efficacy). To confirm that bridging of efficacy and safety is applicable, the applicant is asked to submit additional PK tables and figures from study MDZ-NS-22 for a more detailed comparison of the PK profiles between IN and IV midazolam. **(OC)** Further regarding the comparison of Ipnovel and midazolam IN, inter individual variability in exposure is deemed comparable. Tmax occur in average later for IN administration and the possible effect on time to onset of action is adequately reflected in the SmPC.

Studies to characterise distribution, metabolism, elimination and interactions of IN midazolam were not conducted. This is acceptable for the Hybrid application. It seems as if the AUC metabolite/parent ratio after IV and IN administration was shown to be similar and thus, the distribution, metabolism, eliminations and interactions are not considered to differ between IV and IN route. However, the applicant is asked to submit the AUC metabolite/parent ratio data. **(OC)**

The applicant did not perform any studies in special populations. A PBPK model was developed based on both literature and MDZ-NS-22 study collected data, in order to translate and predict drug exposure, thus supporting posology of special populations and paediatric populations. PBPK modelling is not sufficient to support dose recommendations in these special populations due to limitations in the model (see discussion below). However, the dose reduction in elderly, patients with renal impairment and patients with mild and moderate hepatic impairment is in agreement with the reference product and can be accepted provided that the issue regarding bridging the efficacy and safety to Ipnovel can be resolved.

Bioanalytical methods

The bioanalytical method seems adequately validated based on the submitted summary. However, the validation report was not submitted. The applicant is asked to submit the validation reports. (**OC**) The applicant is also asked to show selectivity in the presence of the concomitantly administered medications in study MDZ-NS-22 and to submit the assessment for the run that showed carry-over. (**OC**)

Five samples were reanalysed for pharmacokinetic reasons. Unless the applicant can justify the PK deviations, the applicant should submit the PK analysis using the original data. (**OC**)

Population pharmacokinetic analysis

The development programme of the proposed IN midazolam program is mainly based on a PK-bridge (PK is pivotal) which applies also to paediatric patients. Since there are no observed PK data in children, a model-based approach should be used to support dosing recommendations in paediatric patients. Adequate PopPK modelling and simulation analyses can be used to support paediatric dosing recommendations which would be supported by EMA guidance (EMEA/CHMP/EWP/147013/2004) and regulatory precedent. However, due to limitations of the PopPK model and as no PopPK simulations in paediatric patients have been provided to support the posology in paediatric patients, the proposed posology in children is currently not acceptable (**MO**). Based on previous CHMP scientific advice on the clinical development strategy (see central advice EMEA/H/SA/4544/1/2020/SME/III and follow-up

advice EMA/SA/0000095512), the applicant received the advice that PopPK-based simulations from an adequate PopPK model is needed to support a paediatric indication. The applicant has provided PBPK-based simulations but this is not sufficient for supporting paediatric dosing recommendations.

The PopPK model was developed based on the observed PK data from Study MDZ-NS-22 which included 28 adult subjects with rich PK sampling of midazolam and midazolam 1-OH from five different doses. This is considered a reasonable dataset to develop a joint parent-metabolite PopPK model. The model structure in the final model included the 2-compartment disposition model for the parent and metabolite which seems overall reasonable for descriptive purposes in adults. However, the PopPK model is pivotal for supporting a paediatric indication and the provided PopPK model has significant limitations and should be updated in order to support dose recommendations in paediatric patients as outlined below.

The PopPK model does not include body weight in a mechanistically plausible manner; The lower body weight in paediatric patients is an important variable to account for when predicting paediatric PK exposures from adults. This should be resolved by including body weight using allometric scaling with exponents fixed to literature values (0.75 for all clearance terms and 1 for all volume terms) in an updated PopPK model (**OC**).

The PopPK model does not include any age-related differences in the nasal absorption of midazolam between children and adults. The applicant should discuss differences in nasal absorption of midazolam between children and adults. The applicant should justify whether any differences in nasal absorption in children should be reflected in the PopPK model (**OC**).

Of note, the model did not include any age-related organ maturation function for the elimination of midazolam which is acceptable since it can be assumed that no clinically relevant organ maturation is on-going beyond two years of age. Furthermore, the bioavailability for IN is high where no difference in elimination and distribution is expected between IN and IV dose administration.

A simulation-based paediatric posology requires demonstration of the predictive performance using adequate VPCs. The VPCs were presented by pooling all PK data from all IN+IV doses in the same panel which is unacceptable. The VPC for the updated model should be stratified by route of administration (IN vs IV) and by dose (1, 2, 2.5, 4, 5 mg). The VPCs should have a logged y-axis. The applicant should demonstrate that the updated PopPK model has acceptable predictive performance according to the updated VPCs. If there are major model misspecifications, the model should be further refined to give acceptable description of both the central tendency and variability in the updated VPCs (**OC**).

There are several PK studies with midazolam in paediatric subjects with various routes of administration (see modelling report and also Nasolam referral). The applicant should make a selection amongst these studies and use as external validation to demonstrate that the updated popPK model is suitable for simulations in the paediatric population (**OC**).

It is unclear if the values below LLOQ were excluded or not during model development. The applicant should specify the total number of PK observations included in the PopPK model development and clarify the number of excluded PK observations including the reason for exclusion (**OC**).

PopPK simulations should be provided for the proposed IN posology in paediatric patients aged 2-18 years. The simulations should be stratified by body weight and age where body weights should be simulated down to 10 kg assuming a uniform distribution. The simulated paediatric IN simulations should be compared with the reference treatment in adults (2.5 mg IV). If deemed relevant, comparisons with paediatric IV PK data based on simulations and/or literature data may be provided as supportive evidence. The requested PK comparisons should include midazolam (the metabolite

midazolam 1-OH is considered supportive only). The following comparisons should be included for midazolam (**OC**):

- Primary PK endpoints. Compare AUC and Cmax for the proposed IN posology in paediatric patients with the corresponding observed exposures following 2.5 mg IV in Study MDZ-NS-22. The central tendency (e.g. median/mean) and variability (e.g. SD/CV) should be compared. The comparison should include plots where the exposure metrics are plotted against body weight and age according to the EMA modelling and simulation question and answers (Modelling and simulation: questions and answers | European Medicines Agency (EMA)). Based on the exposure comparison, the applicant should discuss whether the exposures in paediatric patients are comparable to adults and discuss whether potential differences in exposures are clinically relevant from an efficacy- (AUC) and safety (Cmax) perspective.
- PK-profiles. Graphically compare the simulated PK-profile vs time for the proposed IN posology in paediatric patients with the observed PK-profile following 2.5 mg IV in Study MDZ-NS-22. The plots should focus on the first 2 hours following the dose. The plots should have a logged y-axis. Based on the exposure comparison, the applicant should discuss whether the exposures in paediatric patients are comparable to adults and discuss whether potential differences in exposures are clinically relevant. From an efficacy perspective, the concentrations between ~15-45 minutes should be comparable between IN and IV. From a safety perspective, the concentrations at 2 hours for IN should not exceed the corresponding concentration following the IV dose.
- Based on the above, the applicant should discuss if a weight cut-off is needed in the indication.

The applicant should provide PopPK simulations for repeated doses in adult and paediatric patients based on the updated PopPK model (**OC**). The applicant should justify recommendations on the minimum time between doses.

Physiologically based pharmacokinetic modelling

A PBPK model for midazolam was developed to support dose recommendations in special populations including elderly, obese, renally impaired, hepatically impaired and paediatric patients. However, PBPK modelling is not sufficient to support dose recommendations in these special populations, as outlined below.

Of note, the PBPK model gave reasonable description of the observed mean concentrations over time for IV and IN in the healthy adults in Study MDZ-NS-22. There were literature data included for all concerned special populations which were used for model validations including literature data following IN administration in a limited number of elderly and paediatric patients. A crucial aspect is how midazolam PK scales from adults to children, including how the IN absorption changes with decreasing age. There were paediatric IN data available but only in 9 patients, and although the pre-specified validation criteria were met in most cases (based on PE% as well as AUC and Cmax within two-fold), this is not a sufficient degree of qualification for supporting a paediatric posology without any paediatric PK data for the proposed product. For renally impaired, hepatically impaired and obese patients, there were no IN available which is a limitation.

Another critical aspect which has not been adequately reflected in the PBPK model is the variability aspect. For this intended PK-bridging approach, it is necessary with a model that can predict variability between individuals in a reasonable manner. The presented model validations focused on the mean- or median trend only so it is not possible to assess if the variability aspect is described well. Regardless, to predict variability in a PBPK model would require assumptions (related to which specific physiological or pharmacokinetic process that caused the variability) which may introduce uncertainty.

Taken together, the developed PBPK model is considered too uncertain to support dose recommendations in special populations without any observed PK data for the proposed product. Therefore, no updated PBPK model is requested. Reasonable simulations are needed in particular for the paediatric posology. The PK-LoQ is focused on requesting PopPK-based simulations which is considered a more reasonable approach in this case and is a more established approach for extrapolating PK in the paediatric population.

Pharmacokinetic-pharmacodynamic modelling

A PKPD model-based analysis was provided (data not shown). However, the PKPD analysis is supportive only which is in line with the Study MDZ-NS-22 protocol where PD-markers for sedation was listed as a secondary objective (PK was the primary endpoint). Thus, the PKPD analysis does not have a relevant contribution to the overall benefit-risk assessment and is not described further in the current report.

Dose justification

The dose justification is based on a PK-bridging approach which is acceptable. For the typical adult patient, the applicant supported the proposed posology by the observed PK data from Study MDZ-NS-22. The dose in special populations (elderly, obese, renally impaired, hepatically impaired and paediatric patients) were supported by PBPK simulations. PBPK modelling is not sufficient to support dose recommendations in these special populations due to limitations in the model (see discussion above).

The exposure comparison relies on PK parameters such as AUC and Cmax which were listed as primary endpoints in Study MDZ-NS-22. However, comparisons of the PK profiles (concentration vs time curves) for IN vs IV provide further important support for the benefit/risk assessment. This is motivated by a strong relationship between midazolam plasma concentrations and response (e.g. sedation). midazolam has a very fast effect on-set due to rapid CNS distribution. Literature PKPD modelling suggests a very short effect delay between midazolam plasma concentration and sedation (half-life for the effect delay has been estimated to ~10 minutes e.g. according to Barends et al 2023 Br J Anaesth) which means that it is relevant to compare plasma concentrations instead of concentrations in the effect compartment and/or PD data.

Of note, the applicant proposed efficacy and safety exposure thresholds to support the proposed dose. However, this is not acceptable since these exposure thresholds has not been verified in a clinical setting.

IN is known to have slightly slower effect on-set than IV midazolam due to the longer tmax (~10 min for 2 mg IN compared to ~2 min for 2.5 mg IV). The onset of sedation effects is known to begin within ~10 minutes following IN midazolam administration (Bouw et al 2021 Epilepsy research) which is later than for IV (within a few minutes). This is adequately handled by planning the dose 10-15 minutes prior to the procedure/anaesthesia which is adequately reflected in the proposed SmPC.

3.3.3. Discussion on clinical efficacy

Midazolam is a parenteral benzodiazepine that exhibits sedative, amnesic, anxiolytic, muscle relaxant, and anticonvulsant properties. It functions by binding to a receptor complex, thereby facilitating the action of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). Compared to other benzodiazepines, such as diazepam and lorazepam, midazolam has a faster onset of effect and a shorter duration of action.

With over 40 years of use for procedural sedation, midazolam's efficacy and safety profiles are well-established. It offers a rapid onset of action, good effectiveness, and minimal adverse effects. Administration routes include oral, intravenous, intranasal, and intramuscular.

The primary goal of premedication is to provide sedation and anxiolysis, facilitating therapeutic and diagnostic interventions. midazolam is a commonly used sedative for both surgical and non-surgical procedures, as well as for premedication before anaesthesia.

IN administration of midazolam for procedural sedation and premedication has a sound clinical rationale, particularly in situations where sedating a patient without IV access is desirable. Children are consequently a significant part of the target population for this administration route.

The characterisation of efficacy in this application relies on a pharmacokinetic bridge to IV administration, which is an acceptable approach. Although the concentration-time profiles differ between administration routes, this can be acceptable if the clinical consequences of these differences are well-described, variability in IN uptake and exposure is not excessive, and a paediatric posology can be adequately justified.

In general, there is a correlation between midazolam plasma concentrations, its active metabolite (1'-hydroxy-midazolam), and the degree of sedation at the population level. However, it is impossible to predict the level of sedation solely based on these concentrations due to high interpatient variability in midazolam pharmacokinetics.

The comparison of pharmacokinetic profiles of 2 mg IN and 2.5 mg IV midazolam (please see Clinical Pharmacology section) may support, pending the resolution of the PK issues raised in the LoOI, that based on the AUC, bridging efficacy and safety to the reference product is reasonable, in spite of an approximately 20% lower AUC with the IN administration. As expected, C_{max} is lower after IN administration compared to the IV administration and t_{max} is longer, but the concentration-time curves become comparable after approximately 15-20 minutes.

The longer latency from administration to effect is expected and not a significant clinical concern in these indications. The proposed SmPC adequately informs that the medicine should be administered 10-15 minutes before the diagnostic procedure. The coincidence of the concentration-time profile with the IV comparator thereafter provides reassurance that the recovery phase will not be unduly prolonged. Provided that the product information adequately describes the concentration-time profile after IN administration in comparison to IV administration, the pharmacokinetic differences are manageable in the clinical context of the proposed indications.

However, there are outstanding issues, primarily regarding paediatric posology and repeated dosing. The proposed indication covers adults and children from 2 years old, but there are no pharmacokinetic data submitted for children, who are part of the target population where clinical utility of the product is expected to be most notable. The justification for the proposed paediatric posology is currently insufficient (**MO**).

The proposed dose-recommendations concern a single dose only, which does not meet the usual requirements for the intended indications. While a single dose might be appropriate for premedication prior to anaesthesia, the dosing requirements for procedural sedation vary. In procedural sedation, the dose of IV midazolam is typically titrated to effect to reach the desired level and duration of sedation. Common scenarios are that the initial dose does not provide sufficient sedation to start with the procedure or that during the procedure the sedative effect declines. Presentation of clinical data on multiple dose application is not expected; however, appropriate PK simulations should be provided to support recommendations regarding repeated doses. Information regarding repeated administration should be provided in the product information, including whether it is recommended or not, and if not recommended the reason should be stated in the SmPC (**OC**).

Additionally, there is insufficient discussion on the potential impact of preexisting nasal pathology or conditions such as rhinitis on bioavailability and clinical effectiveness (**OC**). Supportive literature data on IN administration of midazolam are provided, but it should be clarified if the formulations used in the literature correspond to Omforro (**OC**).

Co-Rapporteur's comment (Rapp and CoRapp not in agreement):

*The proposed dose-recommendations concern a single dose only, which does not meet the usual requirements for the intended indications. While a single dose might be appropriate for premedication prior to anesthesia, the dosing requirements for procedural sedation vary. Common scenarios are that the initial dose does not provide sufficient sedation to start with the procedure or that during the procedure the sedative effect declines. Presentation of clinical data on multiple dose application is not expected, however, appropriate popPK simulations should be provided to enable respective repeated dosing recommendations. Without these, an overarching indication "procedural sedation" cannot be accepted (**MO**). B/R would be negative for the proposed indication, as the "single dose only" must then be reflected in the indication.*

3.3.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

3.3.5. Discussion on clinical safety

The characterisation of safety also mainly rests on pharmacokinetic bridging to IV midazolam. IV/IM/rectal midazolam is well-established in clinical practice since several decades in these indications. The added safety evaluation needed in this application primarily concerns local tolerance. The product is a simple aqueous formulation with a pH 3.2 to 3.4, which may cause irritations of the nasal mucosa. For single use or short-term application this is likely acceptable.

Regarding local tolerance, no preclinical study on local tolerability has been performed. It follows that characterisation of local tolerability rests on the observations in study MDZ-NS-22 and on literature data. Local tolerability was in MDZ-NS-22 assessed through the analysis of patient-reported nasal symptoms and nasal examination by an Ear Nose Throat (ENT) specialist. This is an appropriate study design.

The characterisation of local tolerability from study MDZ-NS-22 rests on 28 (27) subjects exposed to different doses, with a maximum dose of 5 mg (two administrations of 2.5 mg) and a maximum of 4 administrations (four administrations of 1 mg).

Throughout MDZ-NS-22 local symptoms were reported by participants on a Nasal symptom scale. Intranasal administration was generally well tolerated. Nasal congestion or stuffiness, nasal irritation or itching, runny nose and pain or discomfort were reported mostly between 5 and 30 min after application and generally of mild to moderate severity, in single subjects also severe and with a duration up to 1 hour. No alteration in the sense of smell was perceived by the subjects. Nasal examination evidenced few, mild and transient abnormalities, completely resolved within 6 hours from dosing, with comparable incidence in the different treatment groups.

The observed incidence of *Nasal congestion or stuffiness* (Table 9), *Nasal Irritation or Itching* (Table 10), *Runny Nose* (Table 11), and *Nasal Pain or Discomfort* (Table 12), should be adequately reflected in the product information, but do not raise any safety concern with an impact on the overall benefit-risk balance.

Table 9: Nasal congestion or stuffiness

No. of subjects per symptom severity and per treatment group and %	Absent	Mild	Moderate	Severe
Nasal congestion or stuffiness at pre-dose				
MDZ-1 1 mg	21 (77.78%)	6 (22.22%)	-	-
MDZ-1 2 mg	24 (85.71%)	4 (14.29%)	-	-
MDZ-1 4 mg	24 (88.89%)	3 (11.11%)	-	-
MDZ-2.5 5 mg	23 (82.14%)	5 (17.86%)	-	-
Ipnovel	23 (82.14%)	5 (17.86%)	-	-
Nasal congestion or stuffiness at time point 5 minutes				
MDZ-1 1 mg	20 (74.07%)	7 (25.93%)	-	-
MDZ-1 2 mg	12 (42.86%)	12 (42.86%)	4 (14.29%)	-
MDZ-1 4 mg	15 (55.56%)	12 (44.44%)	-	-
MDZ-2.5 5 mg	16 (57.14%)	11 (39.29%)	1 (3.57%)	-
Ipnovel	24 (85.71%)	4 (14.29%)	-	-

Table 10: Nasal irritation or itching

No. of subjects per symptom severity and per treatment group and %	Absent	Mild	Moderate	Severe
Nasal irritation or itching before dosing				
MDZ-1 1 mg	27 (100.0%)	-	-	-
MDZ-1 2 mg	27 (96.43%)	1 (3.57%)	-	-
MDZ-1 4 mg	27 (100.0%)	-	-	-
MDZ-2.5 5 mg	28 (100.0%)	-	-	-
Ipnovel	28 (100.0%)	-	-	-
Nasal irritation or itching at time point 5 minutes				
MDZ-1 1 mg	12 (44.44%)	12 (44.44%)	3 (11.11%)	-
MDZ-1 2 mg	11 (39.29%)	13 (46.43%)	2 (7.14%)	2 (7.14%)
MDZ-1 4 mg	14 (51.85%)	10 (37.04%)	2 (7.14%)	1 (3.70%)
MDZ-2.5 5 mg	13 (46.43%)	11 (39.29%)	3 (10.71%)	1 (3.57%)
Ipnovel	28 (100.0%)	-	-	-
Nasal irritation or itching at time point 30 minutes				
MDZ-1 1 mg	23 (85.19%)	3 (11.11%)	1 (3.70%)	-
MDZ-1 2 mg	24 (85.71%)	3 (10.71%)	1 (3.57%)	-
MDZ-1 4 mg	20 (74.07%)	5 (18.52%)	1 (3.70%)	1 (3.70%)
MDZ-2.5 5 mg	19 (67.86%)	8 (28.57%)	-	1 (3.57%)
Ipnovel	28 (100.0%)	-	-	-

Table 11: Runny nose

No. of subjects per symptom severity and per treatment group and %	Absent	Mild	Moderate	Severe
Runny nose before dosing				
MDZ-1 1 mg	24 (88.89%)	3 (11.11%)	-	-
MDZ-1 2 mg	27 (96.43%)	1 (3.57%)	-	-
MDZ-1 4 mg	27 (100.0%)	-	-	-
MDZ-2.5 5 mg	28 (100.0%)	-	-	-
Ipnovel	28 (100.0%)	-	-	-
Runny nose at time point 5 minutes				
MDZ-1 1 mg	17 (62.96%)	10 (37.04%)	-	-
MDZ-1 2 mg	15 (53.57%)	9 (32.14%)	4 (14.29%)	-
MDZ-1 4 mg	10 (37.04%)	15 (55.56%)	1 (3.70%)	1 (3.70%)
MDZ-2.5 5 mg	14 (50.00%)	13 (46.43%)	1 (3.57%)	-
Ipnovel	28 (100.0%)	-	-	-
Runny nose at time point 30 minutes				
MDZ-1 1 mg	26 (96.30%)	1 (3.70%)	-	-
MDZ-1 2 mg	20 (71.43%)	8 (28.57%)	-	-
MDZ-1 4 mg	21 (77.78%)	6 (22.22%)	-	-
MDZ-2.5 5 mg	21 (75.00%)	7 (25.00%)	-	-
Ipnovel	28 (100.0%)	-	-	-

Table 12: Nasal pain or discomfort

No. of subjects per symptom severity and per treatment group and %	Absent	Mild	Moderate	Severe
Nasal pain or discomfort before dosing				
MDZ-1 1 mg	27 (100.0%)	-	-	-
MDZ-1 2 mg	27 (96.43%)	1 (3.57%)	-	-
MDZ-1 4 mg	27 (100.0%)	-	-	-
MDZ-2.5 5 mg	28 (100.0%)	-	-	-
Ipnovel	28 (100.0%)	-	-	-
Nasal pain or discomfort at time point 5 minutes				
MDZ-1 1 mg	17 (62.96%)	9 (33.33%)	-	1 (3.70%)
MDZ-1 2 mg	16 (57.14%)	10 (35.71%)	2 (7.14%)	-
MDZ-1 4 mg	16 (59.26%)	9 (33.33%)	1 (3.70%)	1 (3.70%)
MDZ-2.5 5 mg	16 (57.14%)	8 (28.57%)	3 (10.71%)	1 (3.57%)
Ipnovel	28 (100.0%)	-	-	-
Nasal pain or discomfort at time point 30 minutes				
MDZ-1 1 mg	25 (92.59%)	1 (3.70%)	1 (3.70%)	-

No. of subjects per symptom severity and per treatment group and %	Absent	Mild	Moderate	Severe
MDZ-1 2 mg	25 (89.29%)	2 (7.14%)	1 (3.57%)	-
MDZ-1 4 mg	22 (81.48%)	4 (14.81%)	1 (3.70%)	-
MDZ-2.5 5 mg	20 (71.43%)	7 (25.00%)	-	1 (3.57%)
Ipnovel	28 (100.0%)	-	-	-
Nasal pain or discomfort at time point 1 hour				
MDZ-1 1 mg	27 (100.0%)	-	-	-
MDZ-1 2 mg	28 (100.0%)	-	-	-
MDZ-1 4 mg	24 (88.89%)	3 (11.11%)	-	-
MDZ-2.5 5 mg	23 (82.14%)	4 (14.29%)	1 (3.57%)	-
Ipnovel	28 (100.0%)	-	-	-

As noted regarding efficacy, the potential impact of rhinitis, nasal congestion or other potentially relevant nasal pathologies on safety of the product has not been addressed. A discussion should be provided, including also the potential impact of concomitant administration of other nasal products (**OC**).

In the literature data, 282 adults and 4632 children exposed to IN midazolam were identified. It should, however, be clarified if the literature data is based on a comparable midazolam formulation, and thereby can provide representative data on local tolerability (**OC**). An analysis of the literature data is missing with respect to the need of labelling further safety concerns in addition to what is outlined in the reference SmPC of Ipnovel. The literature using relevant formulations and doses for this application should therefore be summarised respectively. The applicant should provide a tabular summary of studies of IN administration of midazolam in the literature, indicating the formulation used, number exposed in different age categories, if local tolerance is reported, and type and incidence of local intolerance (**OC**).

Supportive literature data on IN administration of midazolam in children has been provided, but it should be clarified if the formulations used in the literature correspond to Omforro (**OC**). It is of particular importance to substantiate local tolerability in the paediatric population, considering the low pH (3.2-3.4) of the formulation. Since study data from the PK/PD study is restricted to data on adults, data from the literature on tolerability in children is important evidence. Further justification for local tolerability in children is required and the potential consequence for the SmPC should be discussed (**OC**).

A possible safety concern related to the differences in concentration-time profiles between the IN and the IV administration routes is if IN administration can result in higher exposure during the recovery phase. The PK and PD data available provide some reassurance that this is not an issue.

In summary, bridging to the safety profile of the reference product may be appropriate, pending the resolution of issues regarding the PK characterisation raised in the LoOI. No major concerns have been at this stage been identified in relation to local tolerability or differences in PK profiles.

3.3.6. Conclusions on clinical aspects

The bridging of efficacy and safety from the reference product is overall acceptable but several issues have been identified that require further clarification, mainly regarding the proposed posology. See section 5 for Proposed list of questions. Major objections have been raised.

3.4. Risk management plan

3.4.1. Safety Specification

3.4.1.1. Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 13: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Device not working in critical situation Exposure during pregnancy and breastfeeding

3.4.2. Discussion on safety specification

No important identified or potential risks have been identified by the applicant for inclusion in the summary of safety concerns. This is agreed.

The proposal to add *Device not working in critical situation* as missing information requires further justification by the applicant or else be removed from the proposed summary of safety concerns (**OC**). It should be clarified what a "critical situation" would be, in the context of the proposed indications, which are elective in their nature, and use restricted to healthcare professionals who closely monitor the patient. If this simply reflects potential medication errors, it is anticipated that this can be followed through routine pharmacovigilance without any need for further studies or characterisation.

Exposure during pregnancy and breastfeeding has not been sufficiently justified as missing information. The guidance provided in GVP Module V – Risk management systems revision 2 (28 March 2017; EMA/838713/2011 Rev 2) should be fully considered, this item be further justified, or else removed from the proposed summary of safety concerns (**OC**).

3.4.3. Conclusions on the safety specification

Having considered the data in the safety specification, it is considered that the proposal to add *Device not working in critical situation* and *Exposure during pregnancy and breastfeeding* as missing information requires further justification by the applicant, or else removed from the proposed summary of safety concerns (**OC**).

3.4.4. Pharmacovigilance plan

Please refer to the D94 PRAC Rapp RMP AR.

3.4.5. Risk minimisation measures

Please refer to the D94 PRAC Rapp RMP AR.

3.4.6. Conclusion on the RMP

The RMP could be acceptable provided an updated RMP and satisfactory responses to the <list of questions below is submitted.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

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

3.5.2. 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.

The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD)

4. Benefit/risk assessment

This application concerns a hybrid version of midazolam, nasal spray (1mg/spray), solution for the indications including conscious sedation and premedication before induction of anaesthesia in adults and children from 2 years. The reference product Ipnovel 15 mg/3 ml solution for injection is indicated for a broad indication including Conscious sedation before and during diagnostic or therapeutic procedures, with or without local anaesthesia. The two products are similar in terms of composition but differ in the pharmaceutical form, strength and route of administration.

Midazolam is a widely used drug with considerable clinical experience since many decades. There are several routes of administration (intravenous, intramuscular, buccal, rectal, intra-nasal, etc) across several indications. For conscious sedation and premedication before induction of anaesthesia, midazolam must only be used by healthcare professionals. Patients are monitored for efficacy and safety after administration.

This application is based on the results from Study MDZ-NS-22 which studied 1, 2, 4 and 5 mg single doses of intra-nasal midazolam versus a reference arm of a single intravenous dose of Ipnovel 2.5 mg in 28 adult subjects. The proposed formulation (MDZ-1) was studied for the 1, 2 and 4 mg intra-nasal doses (whereas a different intra-nasal formulation [MDZ-2.5] was used for the 5 mg dose). The study was a bioavailability study with a cross-over design with rich PK sampling. PK was the primary endpoint.

No efficacy and safety data were collected. Instead, the favourable and unfavourable effects are based on extrapolation of efficacy and safety by means of a PK-bridge with exposure comparisons between midazolam IN versus the IV reference dose (Ipnovel 2.5 mg). This is a reasonable strategy and is supported by regulatory precedent and previous scientific advice from the EMA (see central advice EMEA/H/SA/4544/1/2020/SME/III and follow-up advice EMA/SA/0000095512). midazolam has a

strong relationship between midazolam plasma concentrations and response (e.g. sedation) with very fast effect on-set due to rapid CNS distribution (i.e. virtually no effect delay) which means that it is relevant to compare midazolam plasma concentrations to draw inferences on favourable and unfavourable effects (thus, lack of efficacy and safety data in the target population could be acceptable).

Midazolam has considerable variability in the PD response/tolerability to the drug. The clinical context is, however, well suited to monitor and handle variability in response, regarding both efficacy and safety. The dose is at least in the procedural sedation indication mainly titrated and the dosing recommendation in the proposed SmPC is a standard dose which should be adapted as needed in the clinical setting. A clinically relevant adaption of the dosing regimen is to administer additional dose(s) but this has not been reflected in the proposed SmPC which is not acceptable (**OC**).

The exposure comparison relies on PK parameters such as AUC and Cmax which were listed as primary endpoints in Study MDZ-NS-22. In adults, when comparing Ipnovel 2.5 mg and midazolam 2 mg IN formulation presented midazolam mean plasma PK parameters, AUC is about 20% lower and Cmax about 70% lower for midazolam IN formulation. The Cmax is lower for IN which is expected and manageable regarding efficacy, and AUC in the later phase is comparable which is appropriate from a efficacy perspective, regarding recovery from sedation. These discrepancies in exposure could therefore be acceptable provided that the remaining issues in the list of questions are resolved.

Differences between IV and IN midazolam administration are expected. This is acceptable but the applicant is asked to provide additional results to better understand the differences between IN and IV administration, and a clearer description is needed in the SmPC section 5.2 (**SmPC comment**). Comparisons of the PK profiles (concentration vs time curves including central tendency [such as mean] and variability [such as standard deviation]) for IN vs IV provide further important support for the benefit/risk assessment and should be provided before the proposed posology in adults can be acceptable (**OC**).

IN is known to have slightly slower effect on-set compared to IV midazolam due to the longer tmax (~10 min for 2 mg IN compared to ~2 min for 2.5 mg IV). The onset of sedation effects is known to begin within ~10 minutes following IN midazolam administration (Bouw et al 2021 Epilepsy research) which is later than for IV (within a few minutes). This is handled by planning the dose 10-15 minutes prior to the procedure/anaesthesia which is adequately reflected in the proposed SmPC.

The dose in special populations (elderly, obese, renally impaired, hepatically impaired and paediatric patients) were supported by PBPK simulations (no studies in special populations). PBPK modelling is not sufficient to support dose recommendations in these special populations. However, the dose reduction in elderly, patients with renal impairment and patients with mild and moderate hepatic impairment is in agreement with the reference product and can be accepted provided that the issue regarding bridging the efficacy and safety to Ipnovel can be resolved.

Regarding paediatric patients, the proposed nasal spray (MDZ-1) was only studied in adults. While the comparison of PK profiles with the IV reference product may support bridging of efficacy and safety, the dose recommendations for paediatric patients is currently insufficiently justified (**MO**). Concerns in the pharmacokinetic list of questions including an updated PopPK model should be addressed before the proposed posology in paediatric patients can be accepted (**OC**). The extrapolation of efficacy and safety to paediatric patients from 2 years of age, and the dose recommendations for the paediatric population, should be justified.

Although general safety data on midazolam exposure can be extrapolated from the reference product, data on local tolerability relies primarily on the limited exposure of 28 adult subjects to Omforro during the MDZ-NS-22 trial. Whether supportive published data on local tolerability of other nasal midazolam

applications may be acceptable, especially for the paediatric population, still needs to be adequately justified (**OC**).

The application currently contains inadequate data. The aspects that are inadequately demonstrated are outlined in the list of questions.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information.

Co-Rapporteur's comment (Rapp and CoRapp not in agreement):

*Dose recommendations were derived from popPK and PBPK modelling. They cover a single dose only, which does not meet the usual requirements for the intended indications. While a single dose might be appropriate for premedication prior to anesthesia, the dosing requirements for procedural sedation vary. Common scenarios are that the initial dose does not provide sufficient sedation to start with the procedure or that during the procedure the sedative effect declines. Presentation of clinical data on multiple dose application is not expected, however, appropriate popPK simulations should be provided to enable respective repeated dosing recommendations. Without these, an overarching indication "procedural sedation" cannot be accepted (**MO**).*

4.1. Conclusions

The overall benefit/risk balance of Omforro is negative, given the major objections raised in the list of questions.