Non-interventional Post Authorisation Safety Study (PASS) of Patients with Molybdenum Cofactor Deficiency (MoCD) Type A Treated with NULIBRY (fosdenopterin)

Product (active substance):	NULIBRY (fosdenopterin) 9.5 mg Powder for solution for injection
Sponsor	Sentynl Therapeutics, Inc
Marketing Authorisation Holder:	TMC Pharma (EU) Limited
Version and date:	1.3 - 07 May 2024

Amy Tanti EU QPPV

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Post Authorisation Safety Study Information

Title	**A Non-interventional Post Authorisation Safety Study (PASS) of Patients with MoCD Type A Treated with NULIBRY (fosdenopterin)**
Protocol version identifier	Version 1.3
Date of last version of protocol	07 May 2024
EU PAS register number	Study will be registered prior to start of data collection
Active Substance	Fosdenopterin
Medicinal Product	NULIBRY
Product Reference	H0005378
Procedure number	Not applicable
Sponsor	Sentynl
Marketing authorisation holder(s)	TMC Pharma (EU) Limited TMC Pharma Services Limited
Joint PASS	Not applicable
Country(-ies) of study	European Union (EU) United Kingdom (UK)

Sponsor	Sentynl
Sponsor contact person	Eileen Banaga, VP, Regulatory Affairs and Quality
Investigator	Sciensus
Investigator contact person	Mathieu Loiseau Head of Rare Clinical Operations
Marketing authorisation holder(s)	TMC Pharma (EU) Limited TMC Pharma Services Limited
MAH contact person	Vincenzo Cannizzaro, Senior Director - Regulatory Services

1. Table of Contents

List of abbreviations

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
AED	Anti-Epileptic Drug
AESI	Adverse Event of Special Interest
cPMP	cyclic Pyranopterin MonoPhosphate
CNS	Central Nervous System
CRF	Case Report Form
EC	Ethics Committee
EMA	European Medicines Agency
FDA	Food and Drug Administration
GERD	Gastro-Esophageal Reflux Disease
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Infusion Diary
GA	Gestational Age
GTP	Guanosine TriPhosphate
GVP	Good Pharmacovigilance Practices
HCP	Health Care Professional
EU	European Union
NI	Non-Interventional
MAUEC	Marketing Authorisation Under Exceptional Circumstance
MAH	Marketing Authorisation Holder

Abbreviation or special term	**Explanation**
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicine and Healthcare products Regulatory Agency
MoCD	Molybdenum Cofactor Deficiency
MoCo	Molybdenum Cofactor
ODD	Orphan Drug Designation
PASS	Post-Authorisation Safety Study
PSUR	Periodic Safety Update Report
PT	Preferred Term
RMP	Risk Management Plan
SAE	Serious Adverse Event
SOC	System Organ Class
SOX	Sulphite Oxidase
SSC	S-sulfocysteine
UK	United Kingdom
US	United States

Responsible parties

Sentynl responsible Parties

Role	**Name, Title**
Regulatory Affairs and Quality	Eileen Banaga, VP, Regulatory Affairs and Quality
Medical Affairs	Jennifer Reese, PharmD, SVP, Medical Affairs
Medical	Liza Squires, MD, Medical Representative

TMC Pharma

Role	**Name, Title**
QPPV	Amy Tanti, QPPV
Regulatory Affairs	Vincenzo Cannizzaro, Senior Director, Regulatory Services

Sciensus

Role	**Name, Title**
Investigator/Clinical Operations	Mathieu Loiseau – Head of Rare Clinical Operations

2. Abstract

Title	**A Non-interventional Post Authorisation Safety Study (PASS) of Patients with MoCD Type A Treated with NULIBRY (fosdenopterin)** Version 1.3 – 07 May 2024 Main Author: Sentynl/Sciensus
Rationale and Background	Background: Inherited metabolic disorders are a heterogeneous group of conditions known cumulatively to affect approximately one in 800 neonates. Molybdenum cofactor deficiency (MoCD) is an ultra-rare subgroup of these inherited conditions characterized by disruption of the metabolic pathway for production of molybdenum cofactor with an unknown incidence. Two-thirds of MoCD patients have Type A, which is due to a mutation in the *MOCS1* gene localised on chromosome 6p21.3 which leads to a complete lack of MOCS1A/B enzyme activity with no formation of cyclic Pyranopterin MonoPhosphate (cPMP) (Reiss and Hahnewald, 2011). Current treatment options are symptom driven to provide relief from clinical manifestations of the disease (e.g., antiepileptic drugs (AEDs) for seizures) and supportive care, such as placement of a feeding tube. These symptomatic treatments have no impact on the continued neurologic injury related to elevated levels of S-sulfocysteine (SSC) that lead to the significant developmental disabilities. Although AEDs are available for treatment of seizures, chronic epilepsy refractory to AED therapy does occur in patients with MoCD Type A (Giza et al., 2009; Laxer et al., 2014). Once neural cell death occurs in the brain, the damage is unable to be reversed by cPMP. Therefore, it is critical to intervene as soon as possible by initiating treatment immediately after birth, even prior to genetic confirmation of MoCD Type A to maximise the potential for a positive clinical outcome in patients who present with clinical and laboratory manifestations of the disease. Treatment with fosdenopterin fills this unmet need. If fosdenopterin is started before widespread sulphite-induced neuronal injury and structural brain damage occurs, the child's survival, growth and development have been shown to improve relative to an untreated control group.

	In the United States (US), fosdenopterin (NULIBRY) is approved by the Food and Drug Administration (FDA) and is the only treatment approved for MoCD Type A; it is indicated to reduce the risk of mortality in patients with MoCD Type A. Fosdenopterin is the only treatment approved in the EU and indicated for the treatment of patients with MoCD Type A. A regulatory filing is expected to the UK's Medicine and Healthcare products Regulatory Agency (MHRA) as part of the European Commission Decision Reliance Procedure. Product Patients with MoCD Type A have mutations in the *MOCS1* gene, leading to deficient MOCS1A/B dependent synthesis of the intermediate substrate, cPMP. Treatment with NULIBRY provides an exogenous source of cPMP, which is converted to molybdopterin. Molybdopterin is then converted to molybdenum cofactor, which is needed for the activation of molybdenum-dependent enzymes, including sulphite oxidase (SOX), an enzyme that reduces levels of neurotoxic sulphites. Rationale: MoCD is an ultra-rare, rapidly progressive, chronic, and mostly lethal disease, and typically exhibits an acute onset in neonates or in early infancy. Systematic quantitative natural-history data are based on conclusions from two natural history studies (clinical trial.gov identifier NCT01735188, Spiegel et al., JIMD, 2022). Long term safety for neonates, infants and children has been collected in clinical trials with NULIBRY (clinical trial.gov identifiers NCT02047461 and NCT01640717). Due to the rarity of the disease and the small size of study population, currently there is limited long term safety and efficacy data available, in particular for adolescents and adults. Thus, there is a need to gather long-term safety data from all patients receiving or who have received NULIBRY to consolidate the safety profile and gain further information in the post-marketing period. This Post Authorisation Safety Study (PASS), as an additional pharmacovigilance activity of the Risk Management Plan (RMP), will evaluate the frequency and relative risk of safety concerns and adverse events of special interest (AESIs) following NULIBRY administration in the real-world setting. As NULIBRY will be prescribed in the usual way and in accordance with the terms of marketing authorisation, and because enrolled patients will not undergo additional procedures, the PASS is considered as non-interventional. The aim is to evaluate the long-term safety and efficacy of NULIBRY as used in routine practice in patients with MoCD Type A.

Research question and Objectives	Research question: The NI-PASS is to further characterise the long-term safety and efficacy data on NULIBRY use, including patients with late-onset MoCD Type A, patients 1 year of age and older who initiate treatment without dose titration, and medication errors and administration complications in the home setting, as well as pregnancy and lactation (if reported). The primary objective of this NI-PASS is to gather data to characterise and assess the long-term safety in patients with MoCD Type A who are prescribed and treated according to routine clinical practice. The secondary objective of this NI-PASS is to assess the effectiveness of NULIBRY in all treated patients. Treatment with NULIBRY requires specific storage, dosing, and administration, which may increase the possibility of medication errors in the home setting. There is a need to assess the risk of medication errors in the home setting in a post-approval framework. An infusion diary will be available with the drug product for the patient/caregiver to complete and monitor dates and doses administered, adverse events (AEs), medication errors and administration complications. Objectives: • Primary objective is the active collection of long-term safety data • Secondary objective is the collection of effectiveness data of all treated patients. No specific hypotheses will be tested during the NI-PASS. This NI-PASS is considered as an additional pharmacovigilance activity of the RMP.
Non-interventional PASS Design	This is a multicentre, non-interventional post-authorisation safety study (NI-PASS) of patients with MoCD Type A treated in a routine clinical setting with NULIBRY. Patients meeting entry criteria will be enrolled. All patients/caregivers who consent to take part in the study will be followed to capture information on safety, effectiveness, and patient characteristics that are routinely recorded data from clinical practice. Information will be collected from patients/caregivers and their physicians if part of routine clinical assessment. Evaluations of the effectiveness of NULIBRY to be collected from patients and their physicians will include survival status, growth parameters and feeding method status. These evaluations will be collected with clinical assessments beginning with the enrolment visit, and at regularly scheduled visits that are part of routine clinical assessment (**Error! Reference source not found.**).

Non-interventional PASS Population	Male and female patients, diagnosed with MoCD Type A and who have been prescribed and treated with NULIBRY in accordance with routine clinical practice and meeting the inclusion and exclusion criteria will be part of the NI-PASS. Due to the life-threatening nature of the disease, and because the NI-PASS will consider patients being treated and who previously received NULIBRY, patients of any age will be considered for NI-PASS inclusion. All patients must meet the following inclusion and exclusion criteria: Inclusion criteria • Patients with documented genetic diagnosis of MoCD Type A. • Patients treated with NULIBRY. • Patients or legal guardian/legally authorised representatives depending on local regulations who have voluntarily provided written informed consent to participating in the NI- PASS. Exclusion criteria • None.

Non-interventional PASS Variables	Variables:
	
	Data collected from all patients genetically confirmed with MoCD Type A, who received at least one administration of NULIBRY and who are consented to participate, will be used for analysis of safety and effectiveness.
	
	The NI-PASS will collect information that is routinely recorded data from standard clinical practice. Accordingly, data entry will take into account standard procedures for patients´ visits and routine communication for the home treatment.
	
	The following variables will be collected at baseline/enrolment visit and in accordance with local standard practice.
	
	Patient Characteristics
	
	• Age (age group)
	• Sex
	• Growth parameters:
	  o Weight
	  o Height
	  o Head circumference
	• Dose
	• Age at onset of symptoms as determined by presentation of first symptoms
	• Region
	• Age at treatment initiation with NULIBRY
	• Prior and concomitant medications
	• Relevant medical history including (if available) events prior to treatment; prior medications; concurrent diagnoses such as epilepsy, static encephalopathy, Gastro-Esophageal Reflux Disease (GERD), vision problems; and imaging results (excluding actual images)
	• Any results from past assessments or tests which are of relevance according to the investigator judgement and may impact the safety reporting.
	
	Safety
	
	• AEs and serious AEs (SAEs), including special situations
	• AESIs (photosensitivity)
	• Use during pregnancy/lactation (if reported)
	• Medication errors and administration complications, including device related complications, in the home setting
	• NULIBRY treatment discontinuation or withdrawal, the reasons and outcome
	
	Effectiveness:
	
	• Survival
	  o Documentation of date and cause of death
	• Growth parameters (taken from patient characteristics)
	• Feeding method status

	○ Oral feeding or feeding through nasogastric or percutaneous endoscopic gastrostomy tube Use of ID will be evaluated by the investigators by monitoring data entry and completion by the caregivers.
Non-interventional PASS Data Sources	Patient Source Data: Patient source data will include patient medical records and infusion diary. Data will be collected prospectively, and survival will be assessed annually by contact with the caregiver or Health Care Professional (HCP) until the time of patient death, consent withdrawn or until sponsor decision to stop the NI-PASS (with consultation of the PRAC). Data may be collected from patients records retrospectively (e.g., medical history) depending on their relevance for this NI-PASS and impact on the safety evaluation. The Infusion Diary (ID) is intended to function as a communication tool between the physician, the patient, and the caregiver to monitor safety, medication errors, and administration complications in the home setting.
Non-interventional PASS Study Size	Because MoCD Type A is an ultra-rare disease, , there is no possibility to define a sample size for this NI-PASS. All confirmed MoCD Type A patients who consented (or consent obtained from legally authorised representative) and fulfilling the eligibility criteria will be enrolled in the NI-PASS.

Data Analysis	Statistical Analysis: NI-PASS will be analysed in a descriptive manner and results are intended to evaluate long-term safety and efficacy in a real-world setting. Primary safety endpoint: Frequency of AEs, AESIs, SAEs and NULIBRY discontinuation is to be summarised over the duration of the follow-up. All AEs will be coded using the MedDRA version 25.1 or higher. The AE, AESI and SAE data will be categorised by system organ class (SOC) and preferred term (PT). In addition, the SAE data will be stratified by severity (mild, moderate, and severe) and by relationship to study procedure (unrelated versus all related categories [Unlikely, Possible, Probable, and Definite]). All causes of deaths will be categorised by SOC and PT. Secondary Effectiveness endpoint: • Survival: date of contact, survival status (alive or deceased) and timing of any death • Growth: height, weight, head circumference, changes from birth in head circumference • Feeding method will be summarised and presented over time Infusion Diary Effectiveness: The NI-PASS will request feedback from patients and treating physicians regarding the use of the infusion diary (ID).
Non-interventional PASS Milestones	• Submission of the NI-PASS Protocol: 6 months after European Commission Decision. • Start date of the NI-PASS: 6 months after protocol endorsement. • Annual reports on the progress of the database and available data will be submitted in the annual re-assessments in the context of the marketing authorisation under exceptional circumstances (MAUEC); structured and thorough assessments of the data collected will be provided according to the protocol. Summary information reports will be communicated as part of the Periodic Safety Update Reports (PSURs) and will include information on patient count data to evaluate the success of recruitment.

3. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1.0	31 January 2023	Not applicable	Not applicable	Initial version of the NI-PASS protocol submitted to PRAC
1.1	5 June 2023	Throughout the study protocol	Update n°1	Based on final comments received from PRAC as of 14 April 2023.
1.2	15 August 2023	Throughout the study protocol	Update n°2	Based on comments received from PRAC Rapporteur request for a revised PASS protocol. Marketing authorisation holder changed from Zydus France S.A.S. to TMC Pharma.
1.3	07 May 2024	Throughout the study protocol	Update n°3	Administrative changes to clarify the entities and their responsibilities. Changes are considered to be non-substantial.

4. Milestones

Milestones	Planned date
Protocol Submission	31 January 2023
Protocol endorsement by EMA	31 August 2023
Registration in the EU PAS register	No later than 6 months after EMA protocol endorsement and before start of data collection
Start of data collection*	Within 6 months after EC decision (expected September 2023)
Annual interim report	Submission with annual reassessment every September from 2025 throughout the NI-PASS Cumulative interim report planned after a study duration of five years

*Start of data collection: the date from which information on the first patient is first recorded in the database

NULIBRY must be given daily throughout the patient's life, therefore end of data collection will be confirmed by the European Medicines Agency (EMA) once sufficient data is collected to address objectives of this NI-PASS. End date will be the date from which the analytical data set is completely available. After a study duration of five years, all study data captured until this time will be included in an interim report to check the amount of data that have been gathered.

Timing of the interim reports will be driven by dates of protocol endorsement by the EMA, contracting with institutions, a minimum time of data accrual and the needed documentation of data extraction, analysis, and reporting.

Annual reports will contain information on safety and efficacy which will be considered as part of the annual reassessment.

5. Rationale and background

Background:

Inherited metabolic disorders are a heterogeneous group of conditions known cumulatively to affect approximately one in 800 neonates.

Molybdenum cofactor deficiency (MoCD) is an ultra-rare subgroup of these inherited conditions characterized by disruption of the metabolic pathway for production of molybdenum cofactor with an unknown incidence. Molybdenum cofactor is essential for functioning of the enzymes sulphite oxidase (SOX), xanthine oxidoreductase, and aldehyde oxidase activity. There are three types of MoCD and two-thirds of MoCD patients have Type A, which is due to a mutation in the *MOCS1* gene localised on chromosome 6p21.3 which leads to a complete lack of MOCS1A/B enzyme activity with no formation of cPMP (Reiss and Hahnewald, 2011). In MoCD Type A, the first of 4 synthetic steps in the formation of molybdenum cofactor is interrupted, and guanosine triphosphate (GTP) cannot be converted into cyclic pyranopterin monophosphate (cPMP).

Initial estimates predicted that it occurs in less than one in 100,000 to 200,000 newborns worldwide. This incidence range was established by assuming similarity between MoCD and other rare monogenic diseases that at the time were better characterised. To date more than 100 cases of MoCD have been reported in the literature, representing numerous ethnic groups with significant prevalence in areas of high consanguinity (Bayram et al., 2013; Hinderhofer et al., 2017; Johnson et al., 1980; Mendel, 2013; Reiss and Johnson, 2003). MoCD is therefore thought to be underdiagnosed with the actual number of affected individuals likely to be higher (Atwal and Scaglia, 2016). While the initial incidence assumption helped to establish MoCD as a rare genetic disease, global reports and an improved understanding of the disease suggest a correction to the incidence should be performed. This is supported by the growing belief that the original incidence estimate is most likely representative of sulphite intoxication diseases as a whole. Work done recently by researchers in Germany and presented at the Society for the Study of Inborn Errors of Metabolism in 2018 and 2019 endeavoured to address this issue (Mayr et al., 2019; Mayr et al., 2018b). With the recent availability of variant databases assembled from large and multi-ethnic populations, such as the Exome Aggregation Consortium (Lek et al., 2016), a systematic and potentially powerful tool for investigating the incidence of rare genetic diseases now exists. While not without limitations, disease incidence for high penetrance and recessive disorder estimations are made possible by traditional calculations utilising the Hardy-Weinberg equation and allelic frequencies of represented variants (Schrodi et al., 2015). Utilising a conservative and less conservative variant dataset with associated pathogenicity scores, the researchers calculated that MoCD Type A incidence is within the range of one in 341,690 to 411,187.

It is important to note that the different types of MoCD are indistinguishable clinically and biochemically and that the diagnosis of the specific subtype of MoCD is confirmed by genetic testing, which may take several days to weeks to complete. Diagnosis of MoCD Type A is based on clinical presentation (e.g., seizures, exaggerated startle response, high-pitched cry, intracranial hemorrhage, axial hypotonia, limb hypertonia, feeding difficulties, elevated urinary sulfite and/or S-sulfocysteine (SSC), or low or absent uric acid in the urine or blood) and is then confirmed by genetic testing. Affected individuals with MoCD Type A usually present as neonates with intractable seizures, burst suppression or multifocal epileptic encephalogram, exaggerated startle reactions, axial hypotonia, limb hypertonia and feeding difficulties. Neuronal injury is severe and rapidly progressive as a result of accumulation of toxic concentrations of sulphite in the brain. The prognosis for patients with MoCD Type A is poor. Death commonly occurs in the neonatal period and patients who survive that period may develop a severe static encephalopathy and developmental delay due to central nervous system (CNS) injury, including subcortical cystic cavitation, hydrocephalus, diffuse cortical atrophy, and basal ganglia injury.

Current treatment options are symptom driven to provide relief from clinical manifestations of the disease (e.g., antiepileptic drugs (AEDs) for seizures) and supportive care, such as placement of a feeding tube. These symptomatic treatments have no impact on the continued neurologic injury related to elevated levels of S-sulfocysteine (SSC) that lead to the significant developmental disabilities. Administration of a diet with restrictions on the sulfur-containing amino acids cysteine, methionine, and taurine has been attempted in the related disorder of SOX deficiency. Although AEDs are available for treatment of seizures, chronic epilepsy refractory to AED therapy does occur in patients with MoCD Type A (Giza et al., 2009; Laxer et al., 2014). Once neural cell death occurs in the brain, the damage is unable to be reversed by cPMP. In the absence of treatment, patients usually die within the first years of life and patients who survive this period usually develop encephalopathy and developmental delay, but survival with this condition has never been quantified (Mechler et al., 2015).

Therefore, it is critical to intervene as soon as possible by initiating therapy immediately after birth, even prior to genetic confirmation of MoCD Type A to maximise the potential for a positive clinical outcome in patients who present with clinical and laboratory manifestations of the disease. Treatment with fosdenopterin fills this unmet need. If fosdenopterin is started before widespread sulphite-induced neuronal injury and structural brain damage occurs, the child's survival, growth and development have been shown to improve relative to an untreated control group (see Module 2.7.3, Section 3.3).

In the United States (US), fosdenopterin (NULIBRY) is approved by the Food and Drug Administration (FDA) and is the only treatment approved for MoCD Type A; it is indicated to reduce the risk of mortality in patients with MoCD Type A. In Europe, fosdenopterin is the only treatment approved for the treatment of patients with Molybdenum Cofactor Deficiency (MoCD) Type A. A regulatory filing is expected to the UK's Medicine and Healthcare products Regulatory Agency (MHRA) as part of the European Commission Decision Reliance Procedure.

Product

Patients with MoCD Type A have mutations in the *MOCS1* gene, leading to deficient MOCS1A/B dependent synthesis of the intermediate substrate, cPMP. Treatment with NULIBRY provides an exogenous source of cPMP, which is converted to molybdopterin.

Molybdopterin is then converted to molybdenum cofactor, which is needed for the activation of molybdenum-dependent enzymes, including sulphite oxidase (SOX), an enzyme that reduces levels of neurotoxic sulphites.

NULIBRY is provided as a powder for solution and each vial contains 12.5 mg fosdenopterin hydrobromide dihydrate equivalent to 9.5 mg fosdenopterin.

In patients less than one year of age, the recommended dose of NULIBRY is titrated based on gestational age (GA).

For patients less than 1 year of age who are preterm neonates (GA < 37 weeks), the recommended starting dose of NULIBRY is 0.40 mg/kg/day administered intravenously once daily. The dose is to be titrated to the target dose of 0.90 mg/kg/day over a period of 3 months.

For patients less than 1 year of age who are term neonates (GA ≥ 37 weeks), the recommended starting dose of NULIBRY is 0.55 mg/kg/day administered intravenously once daily. The dose is to be titrated to the target dose of 0.90 mg/kg/day over a period of 3 months.

For patients 1 year of age or older and adults, the recommended dose of NULIBRY is 0.90 mg/kg (based on actual body weight) administered intravenously once daily.

NULIBRY is a treatment intended for lifetime use.

Rationale:

MoCD as ultra-rare, rapidly progressive, chronic, and mostly lethal disease, and typically exhibits an acute onset in neonates or in early infancy. Conclusions from natural history studies confirmed the poor prognosis and early death in patients with MoCD Type A (clinical trial.gov identifier NCT01735188, Spiegel et al., JIMD, 2022).

Long term safety for neonates, infants and children has been collected in clinical trials with NULIBRY (clinical trial.gov identifiers NCT02047461 and NCT01640717). Due to the rarity of the disease and the small size of study population, currently there is limited long term safety and efficacy data available, in particular for adolescents and adults.

Thus, there is a need to gather long-term safety data from all patients receiving or who have received NULIBRY to consolidate the safety profile and gain further information in the post-marketing period.

This PASS, as an additional pharmacovigilance activity of the RMP, will evaluate the frequency and relative risk of safety concerns and AESIs, as defined in the approved EU RMP, following NULIBRY administration in the real-world setting. As NULIBRY will be prescribed in the usual way and in accordance with the terms of marketing authorisation and because enrolled patients will not undergo additional procedures, the PASS is considered as non-interventional.

6. Research questions and objectives

Research question:

The NI-PASS is to further characterise the long-term safety and efficacy on NULIBRY, including in patients with late-onset MoCD Type A, patients 1 year of age and older who initiate treatment without dose titration, medication errors and administration complications in the home setting, as well as pregnancy and lactation (if reported).

The primary objective of this NI-PASS is to gather data to characterise and assess the long-term safety in patients with MoCD Type A who are prescribed and treated according to routine clinical practice.

The secondary objective of this NI-PASS is to assess the effectiveness data in all patients treated with NULIBRY.

Treatment with NULIBRY requires specific storage, dosing, and administration, which may increase the possibility of medication errors in the home setting. There is a need to assess the risk of medication errors in the home setting in a post-approval framework. An infusion diary (ID) will be available with the drug product for the patient/caregiver to complete and monitor dates and doses administered, AEs, medication errors and administration complications.

Objectives:

- Primary objective is the active collection of long-term safety data of all treated patients
- Secondary objective is the collection of effectiveness data of all treated patients

No specific hypotheses will be tested during the NI-PASS.

7. Research Method

7.1 Study design

This is a multicentre, non-interventional post-authorisation safety study (NI-PASS). The purpose of this study is to describe contemporary, real-world presentation, and clinical outcomes in patients with MoCD Type A.

The prescription of NULIBRY is separated from the decision to include the patients in the study, therefore patients will receive their treatment in routine clinical setting without any change in their management (routine clinical care or treatments). Diagnostic or monitoring procedures are only those ordinarily applied to the therapeutic strategy. There are no dose regimens or medical procedures defined within this protocol. Every medical decision and course of treatment with NULIBRY will reflect exclusively the decision of the investigator in a routine clinical situation. The concept of this NI-PASS and its documentation procedure will not affect the routine treatment situation.

Patients meeting entry criteria will be enrolled. All patients or legally authorised representatives who consent to take part in the study will be followed to capture information on safety, effectiveness, and patient characteristics that are routinely recorded from clinical practice. Eligible patients will be identified and followed prospectively.

Safety data will be gathered from two sources:

- Primary safety data will be obtained from the Infusion Diary (ID) based on the patient and/or caregiver inputs
- Secondary data will be provided from by the investigators who will report any safety events that may have arisen in the patient as discussed in a routine patient visit

Information from the ID will be reconciled with HCP charts during data abstraction. Investigators will discuss with the patient and/or caregiver any safety events mentioned in the ID. Any safety events, whether reported in the ID or by the HCP, will additionally be reported to relevant health authorities by the MAH according to local PV regulations, including timelines of reporting upon awareness of an adverse event.

Information to evaluate the effectiveness of NULIBRY will be collected into a single clinical database for each enrolled patient, whether from the ID from patients/caregivers or by investigators as part of their medical records created in routine clinical practice.

As MoCD Type A is an ultra-rare disease, enrolment is not capped, and all eligible patients will be enrolled. There is no defined period for the enrolment period, and each included patient will be evaluated and followed-up for an undefined period, until death, withdrawal of consent to participate, or the end of the study, whichever comes first. There will be no visits imposed by this NI-PASS protocol, all visits will be conducted in accordance with the standard of care which depends on local routine practices and may differ from one site to another.

Patients who are not available for data collection for more than 12 months will have a follow-up for survival. The site will have three attempts to contact the patient by the time this 12-month is reached. The physician and/or caregiver will be contacted if the patient is lost to follow-up. They may search regional death registries for vital health statistics of lost to follow-up patients as per routine practice.

Patients lost to follow-up will be followed-up only for vital status until the end of the study or the patient's death, or consent withdrawal, whichever occurs earlier. The date of follow-up will be noted for censoring purposes. All follow-up attempts will be done in compliance with local legal regulations.

Evaluations of the effectiveness of NULIBRY to be collected from patients and their physicians will include survival status, growth parameters and feeding method status. These evaluations will be collected with clinical assessments beginning with the enrolment visit, at regularly scheduled visits, depending on local standard of care and HCP practices.

All visits shall be scheduled according to clinical practice. At each visit patients will undergo procedures as per standard of care.

7.2 Rationale for study design

This NI-PASS used an observational design as it will not interfere with patient's treatment as prescribed and directed by the investigator.

The schedule of data collection (Table 1) is also in agreement and will not interfere with the standard schedule of routine office visits for MoCD Type A patients.

No additional treatments or diagnostic or monitoring procedures will be utilized for this study.

To incorporate data from a wide range of countries, initial recruitment will start in the European Union and UK, countries may be included as soon as sites are identified, selected for submission, approved as per local regulatory requirements and ready for patient recruitment.

7.3 Collection of data

Before collecting any data, all potential patients or legally authorised representatives will sign an informed Consent Form (ICF). Patients will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient beforehand.

Refer to 0 for additional details on patient's consent.

Refer to data collection schedule provided in Table 1 for more information.

7.3.1 Enrolment assessment

Enrolment data will include the following questions related to medical history:

- Demographics information including age and sex, height, weight, geographic region
- Date and results of molecular testing confirming MoCD Type A
- Date of initial diagnosis with age at onset of symptoms
- Age at treatment initiation with NULIBRY
- Current NULIBRY dose
- Prior and Concomitant medications
- Medical history data prior to enrolment: events prior to treatment; concurrent diagnoses such as epilepsy, static encephalopathy, GERD, vision problems; and imaging results (excluding actual images), etc.

7.3.2 Baseline & follow-up assessments

Baseline and follow-up data will encompass:

- Growth parameters:
  - Weight
  - Height
  - Head circumference
- Current NULIBRY dose
- Concomitant medications
- Feeding patterns
- Vital status with date and cause of death

ID will aim to collect dates and doses administered, unexpected events such as AEs, AESI, SAEs and medication errors.

7.3.3 Safety assessments

Safety will be assessed by the documentation and collection of AEs, AESI, SAEs, use of NULIBRY during pregnancy and/or lactation.

Any medication errors and administration complications reported in the home setting and NULIBRY treatment discontinuation or withdrawal will also be recorded as part of safety assessments.

7.3.4 Survival status after treatment discontinuation

Investigators will make every effort to continue the observation of patients after treatment discontinuation and collect information about the date and cause of death if applicable. These observations may be conducted over the phone or during routine follow-up visits. All follow-up attempts will be done in compliance with local legal regulations.

Table 1: Data collection

Assessment	Enrolment*	Prospective Collection		
		Baseline	Approximately every 6 months**	After Treatment discontinuation
Informed Consent by patient/legally authorised representative	x			
Review of Inclusion Criteria	x			
Demographics information and onset of disease	x			
Medical History	x			
Change in comorbidities since last visit			x	
Growth parameters		x	x	
Feeding patterns		x	x	
Dose administered	x	x	x	
Previous and Concomitant Medications (including AED)	x	x	x	
Adverse events	x	x	x	
Documentation of age and cause of death		Throughout study period and through an annual telephone contact after Month 12 visit		x
Infusion diary	x	x	x	

*Enrolment and baseline assessments may be combined as one single visit

**Frequency of follow-up visits are reported as an approximation and expected to occur every 6 months. Frequency may be different based on local routine practices. Survival status is expected to be assessed at least annually.

8. Setting

8.1 Selection of study population

Male and female patients who have been diagnosed with MoCD Type A and have been prescribed and treated with NULIBRY will be approached for formal consent to participate in the study.

Due to the life-threatening nature of the disease, and because NI-PASS will consider patients being treated and who previously received NULIBRY, patients of any age will be considered for NI-PASS inclusion.

The following will be completed:

- Obtain signed informed consent from patients or legally authorised representatives
- Review and confirm screening inclusion/exclusion criteria

Patients for whom consent is obtained (directly or with the legally authorised representatives) will be enrolled and will be identified by their unique patient ID number.

8.2 Eligibility criteria

All patients must meet the following inclusion/exclusion criteria:

Inclusion criteria

- Patients with documented genetic diagnosis of MoCD Type A.
- Patients treated with NULIBRY.
- Patients or legal guardian depending on local regulations who has voluntarily provided written informed consent to participating in the NI-PASS.

Exclusion criteria

- None.

8.3 Selection of Study sites

Patients will be enrolled in this NI-PASS from sites across the European Union and UK. The study will be extended to additional territories outside the European Union and the UK once the study is operational in the EU and the UK. Additional information about extension of the study to other territories will be included in interim reports.

8.4 Completion and Withdrawal of participants

The NI-PASS duration is defined for each patient as the date that signed written informed consent is provided through the end of the follow-up period, death, consent withdrawal, or the end of the study, whichever occurs first.

Patients will be considered as complete if they meet any of the following:

- Follow-up complete because of treatment stop or discontinuation (data collection will continue after the end of treatment with a focus on patient survival status)
- Death (due to any cause) during follow-up while still enrolled in the NI-PASS

Patients may withdraw their consent at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. In case of withdrawal, patients will have the right to be remembered and the right to be forgotten in accordance with local regulatory and data protection rules. These rights will be included in the ICF.

Patients withdrawing consent can be re-screened for the study based on their willingness and consent. They will be followed-up only for vital status until the end of the study or the patient's death, whichever occurs earlier.

Treatment will not be determined or altered by participation in this study, with patients receiving usual therapy as determined by their HCP during their care.

Patients can also be enrolled in another observational or interventional study while participating in this study. The reasons for patients not completing this NI-PASS will be recorded.

A patient may be withdrawn for the following reasons:

- The patient or legally authorised representative withdraws consent.
- The patient is lost to follow-up.
- If the patient enrols in another observational or interventional study that requires withdrawal from this NI-PASS, the patient may be re-included into this study when the patient's participation in the other study is completed.

Patient participation in this study may be discontinued without patient/legally authorised representative consent at any time at the discretion of the investigator, or a regulatory authority. The investigator will also withdraw a patient when this NI-PASS stops.

8.5 Completion or discontinuation of NI-PASS

Completion rules are not defined in agreement with EMA. However, after a study duration of five years, all study data captured until this time will be included in an interim report to check the amount of data that have been gathered.

Sponsor may terminate this NI-PASS after consultation with the PRAC.

9. Variables

Data will be collected from all patients who received at least one administration of NULIBRY from the time the ICF is signed and patient authorisation or appropriate forms per local regulations are obtained until the end of their follow-up, or end of the NI-PASS, whichever comes first.

See below for further details on data sources related to study variables. In general, primary data (dates and doses administered, problems with infusions, adverse events) will be collected prospectively by the caregivers via the ID. Additional data (demographics, medical history, growth parameters, feeding methods) will be collected at enrolment and via periodic chart abstraction, and information obtained in the ID will be additionally verified and reconciled with HCP records at least during the annal reporting process. Any safety issues identified, either from the ID (upon entry by the caregiver/patients) or the patient's records (upon chart abstraction), will be transmitted to the competent health authorities in compliance with local regulations, including timelines, for safety reporting.

9.1 Data AnalysisExposure variables

Exposure variables will be related to NULIBRY administration and derived from the ID. They are collected prospectively, and reconciled with HCP charts at the time of periodic chart abstraction:

- Dose
- Age at treatment initiation with NULIBRY
- Use during pregnancy and lactation (including dose received)
- Treatment discontinuation or withdrawal

9.2 Covariates

Covariates will be collected from patient source data (i.e., medical charts or upon enrolment by the HCP) and will include:

- Demographics data:
    - Age (age group)
    - Sex
    - Age of first recognition of MoCD-associated signs or symptoms
    - Region

- Medical history:
    - Prior and concomitant medications
    - Relevant medical history including (if available) events prior to treatment; prior medications; concurrent diagnoses such as epilepsy, static encephalopathy, GERD, vision problems; and imaging results (excluding actual images)
    - Any results from past assessments or tests which are of relevance according to the investigator judgement and may impact the safety reporting.

- Treatment initiation in patients who are one year of age or older and initiate NULIBRY without titration

- Use of ID will be evaluated by the investigators by monitoring data entry and completion by the caregivers

9.3 Primary safety outcomes

Primary safety outcomes will be derived from the ID, collected prospectively, and reconciled with clinician notes at the time of periodic chart abstraction, and include:

- Occurrence of adverse events, serious adverse events, adverse events of special interest, pregnancy/lactation
- Overall survival

9.4 Secondary efficacy outcomes

Secondary efficacy outcomes will be collected (via chart abstraction) by the HCP and include:

- Growth parameters:
    - Body weight
    - Height
    - Head circumference

- Feeding methods

10. Data sources

The data will be recorded using a CRF for data collected from routine clinical care at the HCP's office and from the infusion diary, with a unique identification for each patient.

Source may include reviews of medical records, taking into account that only existing data will be entered in the CRF.

NULIBRY dosing and administration, as well as occurrence of safety events will be collected in the ID by the patient and/or caregiver and be reconciled with investigators who will review any safety events that may have occurred. Investigators will discuss with the patient and/or caregiver safety events mentioned in the ID and report them in the CRF if not already captured.

During the study, investigators may provide unsolicited information that could constitute an AE or special situation report while seeking information for the purpose of the study. In this case, if an AE or a special situation needs to be reported, an AE form will be completed and submitted to the MAH. Pregnancy and lactation will be recorded in the CRF by the investigators as part of routine medical practice and also in the ID by the patients/caregivers if used during pregnancy or lactation.

Case Report Form (CRF):

For the CRF, data will be collected after patient's enrolment, and survival will be assessed via phone or hospital visit at least annually during the follow-up observation period, until time of patient withdrawal, death or until sponsor decision to stop the NI-PASS (with consultation from the PRAC), whichever occurs first.

Patient source data will include patient medical records and ID. When multiple data sets are available for the same visit, the most recent data set will be recorded in the CRF and used for analysis.

Vital status for lost to follow-up patients will be obtained from HCP, family, publicly available databases, or patient/caregiver reports where available and allowed per local regulations.

Medical records data will be provided by study site staff (either entered directly into the CRF by staff at the site or qualified third-party chart abstractors), utilizing patient medical notes to abstract information in order to complete electronic CRFs in the study-specific electronic database, which will be provided by the Sponsor or its qualified representative.

Infusion diary (ID):

Dates and doses administered, AEs, AESIs and SAEs as well as medication errors and administration complications in the home setting will be reported by the patient in the ID.

In the majority of cases, the ID will be provided in a password-protected, GDPR-compliant electronic format that caregivers can use to record, daily, details about treatment administration and adverse events. In the event that a caregiver prefers not to provide information electronically, a paper-based format will be supplied which will then need to be shared with the HCP for uploading or provided to the data-manager directly.

There will be two components to the ID. The first is the simple recording of date, dose, and time of administration by the caregiver. The second component seeks to identify any issues with administration and any adverse events that may have occurred. Caregivers will be asked if there were any issues related to administration and, separately, if there were any adverse events. A "yes" answer to any of these questions will trigger a request for follow-up information. Any identification of issues related to administration or adverse events will immediately be transmitted to the sponsor's pharmacovigilance department or its qualified representative, who will follow up to collect additional information as required and alert the patient's HCP as needed. Educational materials will also encourage patients/caregivers to contact their HCP on their own in case there are any issues with dosage or administration or if adverse events occur, and educational materials will include a place for emergency numbers to be entered. All adverse events will become part of the patient's CRF, including any additional information that is obtained during follow-up by the sponsor's pharmacovigilance department or its qualified representative. Adverse events will also be reconciled with HCP notes at the time of periodic chart abstraction. In addition, the sponsor's pharmacovigilance department or its qualified representative will follow all local regulations to comply with timely (upon awareness) and complete reporting of adverse events to relevant health authorities, irrespective of the data collection programme for this NI-PASS.

If requested by the patient and/or caregiver, the ID may be provided as a paper version to be completed by the patient and/or caregiver on a daily basis.

These data will then be gathered with CRF data by the data-manager appointed by the Sponsor or its qualified representative for analyses in the clinical database. The following data will be collected throughout the NI-PASS study:

Safety

- Adverse Events (AEs) and serious AEs
- AEs of special interests (AESIs, e.g., photosensitivity)
- Use during pregnancy/lactation (if reported)
- Medication errors and administration complications, including device complication, in the home setting
- NULIBRY treatment discontinuation or withdrawal, the reasons and outcome

These data will be reported daily and transmitted (if using electronic data capture) by the caregivers via the ID and reconciled with HCP notes at the time of periodic chart abstraction. Any identification of a potential AE will alert the sponsor's pharmacovigilance department and immediately trigger relevant procedures, including any necessary follow-up and timely reporting to the competent health authority by the sponsor's pharmacovigilance department and in compliance with local regulations.

Effectiveness:

- Survival
    - Documentation of date and cause of death
- Growth
    - Taken from patient characteristics
- Feeding method status
    - Oral feed or feeding through nasogastric or percutaneous endoscopic gastrostomy tube

These data will be derived from periodic chart abstraction from clinician notes (or entered prospectively at the clinician's site if preferred by the site).

The investigator is ultimately responsible for the collection and reporting of all patient data and safety data and other forms for data collection (source documents) as part of their routine clinical practice and must guarantee that their medical records are accurate, authentic/original, traceable, complete, consistent, legible, timely (contemporaneous), permanent, and available as required. All corrections of entries must be explained (reason for change) and properly described.

11. Study size

MoCD Type A is an ultra-rare disease, and in the absence of an EU and UK MoCD Type A registry, there is no possibility to determine a sample size for this NI-PASS.

From the information available at the time of the original European Union (EU) orphan drug designation (ODD) application in March 2010, the prevalence was estimated to be under 200 patients worldwide, well below the orphan drug threshold of 5 in 10,000 persons in the European Community. The prevalence of MoCD Type A was reassessed based on PubMed and Embase literature searches between 2010 and 2020. A total of 20 publications, reporting cases of any types of MoCD in the EU, were identified; among those a total of 53 MoCD Type A cases were reported leading to an estimated prevalence of MoCD Type A of 0.005 per 10,000 inhabitants.

The actual sample size will depend on the number of patients with genetically confirmed MoCD Type A to be enrolled in the study and for whom an informed consent is obtained.

12. Data Analysis

The statistical reporting of the endpoints and overall survival will be entirely descriptive, with no formal statistical testing performed. No missing data imputation will be performed.

Long-term safety will be assessed by patient frequency of all AEs, SAEs, fatal AEs, and AESIs.

12.1 Analyses variables

NI-PASS data will be analysed in a descriptive manner and results are intended to assess the long-term safety and efficacy data of NULIBRY.

Description will include for each visit:

- Use of NULIBRY during pregnancies and/or lactation,
- Medication errors and administration complications in the home setting,
- Treatment discontinuation or withdrawal.

Descriptive summaries will be provided overall and may include:

- Information on patient participation, completion status and total duration of follow-up,
- Patient characteristics at baseline with demographics details and onset of disease,
- Prior and concomitant medications, which will be listed and summarized to WHO-DD terms (for example summarized by ATC4 and PT),
- Medical history, which will be listed and summarized in each dose group according to the MedDRA terminology (SOC and PT),

- Duration of exposure,
- Treatment initiation in patients who are one year of age or older and initiate NULIBRY without titration.

A stratified analysis will be performed with the following stratifications: age at treatment initiation <1 year or ≥ 1 year of age.

12.1.1 Primary safety endpoint

Safety is the primary objective of this NI-PASS. Safety analyses will be performed for all patients who consented and received at least one dose of NULIBRY.

Long-term safety as assessed by the incidence and percentages of patients with AE, SAE including special situations, AESI, use during pregnancy/lactation, medication errors and administration complications, including device related complications, in the home setting will be summarised over the duration of the follow-up. NULIBRY treatment discontinuation or withdrawal, including the reasons and outcome will also be summarised.

All AEs will be coded using the MedDRA version 25.1 or higher.

The AE and SAE data will be categorised by SOC and PT. In addition, the SAE data will be stratified by severity (mild, moderate, and severe) and by relationship to study procedure (unrelated versus all related categories [Unlikely, Possible, Probable, and Definite]). All causes of deaths will be categorised by SOC and PT.

12.1.2 Secondary Effectiveness endpoint

The secondary objective of this NI-PASS is to evaluate the effectiveness of NULIBRY in MoCD Type A patients. Effectiveness measures, listed below, will be summarised descriptively at each visit:

- Survival: date of contact, survival status (alive or deceased) and timing of any death,
- Growth parameters: height and weight, head circumference and changes over time relative to age- and sex-matched norms,
- Feeding method will be summarised and presented over time.

Infusion Diary Effectiveness:

The regular use of the ID feedback from treating physicians and patients/caregivers regarding the use of the ID will be considered for effectiveness. Investigator and caregiver's feedback will be sought to assess if the use of ID allows patients to be to be in better, worse, or equivalent health than if they did not use an ID.

12.2 Interim analysis

The analyses for the first annual interim report will be conducted after about 1 year of data is accumulated. Then an interim analysis will be performed every year. In each interim analysis, the number of patients treated with NULIBRY will be monitored, and patient demographic and baseline characteristics will be presented.

After a study duration of five years, all study data captured until this time will be included in an interim report to check the amount of data that have been gathered and discuss if the study can be terminated. Results will be contextualized with available natural history data.

The first interim report is planned in 2025, interim reports should be provided annually, and the final report will be based on cumulative data as agreed with regulators.

13. Quality control

The Sponsor will delegate the set up and conduct of the NI-PASS to a third party. The handling of data will comply with regulatory guidelines and applicable standards from the Sponsor or its qualified representative.

There are two sources of data for this study. Primary data will be collected by the caregivers into the ID. As described in Section 10 (Data Sources), caregivers will input information daily regarding dose, administration and any issues with administration, or adverse events. In the event that any issues with administration or adverse events are identified, the sponsor's pharmacovigilance department or its qualified representative will follow-up immediately with the caregiver upon identification, and the HCP as needed, to ensure complete, accurate, and timely information is gathered related to any issues, and the sponsor's pharmacovigilance department or designee will ensure that all information is accurately entered into the CRF and transmitted to the health authorities per local regulations. All adverse events will become part of the patient's CRF, including any additional information that is obtained during follow-up by the sponsor's pharmacovigilance department or its qualified representative. Periodic monitoring by the sponsor will evaluate the extent and completeness of ID entries by the caregiver.

Secondary data will be collected via chart abstraction from HCP notes by qualified chart extractors employed either by the Sponsor or its qualified representative or, if preferred by the sites, qualified on-site staff. This method is utilised to minimize burden on the HCPs and their staff during the conduct of the study. Data from the chart abstraction process will be entered into the patient's CRF and reconciled with relevant information from the ID.

Investigators will ensure that data from CRF are reconciled with the ID, in particular any safety events reported in the ID that should be noted as an AEs, SAEs, AESIs as applicable. Monitoring activities will ensure that there are no discrepancies between the ID and the CRF and that queries are properly addressed. In the event that HCPs prefer to not use chart abstraction, then qualified site staff will be utilised to enter data directly into the patient's study CRF at the time of the patient visit and subsequently reconciled with the ID on a periodic basis.

For missing data in the ID, investigators will liaise with the patient and/or caregiver and remind them to complete the ID as much as possible.

The investigator will comply with the protocol (which will have been approved/given favourable opinion by the competent/health authority and/or ethics committee (EC), as applicable), and applicable regulatory requirements.

The investigator will retain source documents and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy.

All parties should maintain transparency and open communication in order to effectively manage the NI-PASS and proactively mitigate any risks. The sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g., GVP), and applicable laws and regulations. If a significant quality issue is identified at any time during the conduct of the NI-PASS, it must be escalated to the sponsor immediately. A significant quality issue is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients and/or the integrity of the data.

13.1 Study monitoring

Monitoring activities will be performed by a third-party. The Sponsor or its qualified representative will oversee these activities. Study specific plans will be used during the NI-PASS.

The sponsor or its qualified representative will ensure that the HCPs participating in the study (investigator) and/or any qualified chart abstractors understand all requirements of the protocol and his/her responsibilities. In addition, the sponsor or its qualified representative will be available for consultation with the investigator. The sponsor or its qualified representative is responsible for ensuring and verifying that each study site conducts the study according to the protocol, standard operating procedures, other written instructions/agreements, and applicable regulatory guidelines/requirements.

The sponsor or its qualified representative will conduct periodic study monitoring to ensure the data accuracy. Where relevant (e.g., on-site data entry), the investigator will provide direct access to study documents and data, including source documentation for monitoring, audits by the MAH or its representatives, review by the EC, and inspections by applicable regulatory authorities.

13.2 Data management

All data management activities including data capture, data storage, data cleaning, data security, and system backup processes will be undertaken under the supervision of a qualified third party.

The Sponsor or its qualified representative is responsible for verifying the CRFs throughout the study to verify completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of research.

Direct access to patient medical records and other study-related records, if needed to verify the site-level entries on the CRFs, should be granted in accordance with the local laws and regulations. The investigator or qualified designee are responsible for recording and verifying the accuracy of patient data. By entering his/her electronic signature, the investigator or qualified chart abstractor confirms that all recorded surveillance data will be verified as accurate/consistent with patient charts.

The investigator agrees to cooperate with the Sponsor or its qualified representative to ensure that any problems detected in the course of data quality assessment are resolved.

To ensure the quality of data across all patients and sites, a data management review is performed on de-identified patient data received at the Sponsor or its qualified representative. During this review, patient data is checked for consistency, omissions, and any apparent discrepancies. In addition, the data is reviewed for adherence to GVP and applicable national or regional regulations/guidelines to resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the CRF for site resolution and closed by Sponsor reviewer.

14. Limitations of the research methods

14.1 Potential selection bias

This study is subject to limitations related to study design and because patients are being selected by the investigator. Potential selection bias could also be introduced by participation of only some referral centres (e.g., only tertiary care centres may choose to participate) or HCP specialization (e.g., only some types of specialists may choose to participate). However, given the rarity of the disease, efforts will be made to ensure that every patient treated with NULIBRY can participate in the registry.

14.2 Methodological limitations

This study is subject to common limitations arising from observational studies conducted to evaluate rare diseases and the potential effects of orphan medicinal products. With respect to studies in rare disease, the low incidence and heterogeneity of the disease may limit the presentation and interpretation of results for subgroups, e.g., patients with attenuated disease and longer survival vs. patients with shorter survival, including death within the first 12 months after study enrolment. To mitigate this limitation, data will be collected regarding timing of onset of symptoms and relevant medical history (also for potential confounders at baseline), and data will be stratified by timing of initiation of treatment.

Information bias (inaccurate assessment of outcomes) is another potential methodologic limitation. This will be partially mitigated by inclusion of objective efficacy endpoints (survival, growth, and feeding methods ascertained in the HCP's office) and also, especially with respect to safety, by reconciliation of caregiver reports (collected as part of the daily ID entries) with HCP records (which will emphasize events that were important enough for the caregiver to bring to the attention of the HCP).

Given that NULIBRY is the first product obtaining marketing authorisation for the treatment of MoCD Type A, the study does not include plans for a comparator. The interim report providing data after 5 years of study duration will contextualize the results with all available natural history data that were presented as part of the marketing authorisation application and has not yet been presented as part of the marketing authorisation, when available.

As there is no end date set for this study, and because patients are expected to be followed-up for at least five years, there is a risk of patient drop-out and bias from missing data. Every effort will be made to facilitate ease-of-use of the ID for caregivers, including the identification of adverse events. However, even if caregivers cease to provide primary data, the protocol is designed to have a minimum burden on the patient's HCPs (by utilizing chart extraction), so that important adverse events and objective measures of efficacy may still be ascertained secondarily, provided the caregivers continue to provide consent to sharing medical records. Management of potential lost to follow-up patients is additionally described in section 7.1. Nevertheless, concerns that patients do not comply with ID completion, possibly invalidating the benefit of ID data, will be addressed with the HCP's oversight during reconciliation of records and by obtaining their direct feedback on the effectiveness of the diary.

15. Other aspects

The study is a post-authorisation study of safety and efficacy and will comply with Directive 2001/83/EC (the Medicinal Products Directive), Regulation (EC) No 726/2004 (as amended), Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC

- GVP Module VI - Collection, management and submission of reports of suspected adverse reactions to medicinal products

- GVP Module VIII - Post-authorisation safety studies

The study will be registered in the EU PASS Register before the study implementation commences.

16. Protection of human subjects

16.1 Patient information

All parties will ensure that organizational and technical measures are in place to maintain protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. In the event of a potential personal data breach, the study site, sponsor, or its qualified representative shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law. To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to the Sponsor or its qualified representative and other authorised parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by the Sponsor or its qualified representative. All other identifiable data transferred to the Sponsor, or its qualified representative or other authorised parties will be identified by this single, patient-specific code.

The investigator site/third-party chart abstractors will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, the Sponsor or its qualified representative will maintain high standards of confidentiality and protection of patients' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

16.2 Patient consent

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or legally authorised representative before any study-specific activity is performed.

The informed consent documents must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws. The informed consent documents used during the informed consent process must be approved by EC before use, and available for inspection.

The investigator must ensure that each patient or legally authorised representative is fully informed about the nature and objectives of the NI-PASS, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator must ensure that each patient or legally authorised representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The acquisition of informed consent from patient or legally authorised representative is to be documented in the patient's medical records, and the informed consent form is to be signed and personally dated by the patient or/legally authorised representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient or legally authorised representative.

16.3 Patient Withdrawal

Patients or legally authorised representatives may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or the Sponsor or its qualified representative for safety, behavioural, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events. If the patient withdraws from the study, and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor or its qualified representative may retain and continue to use any data collected before such withdrawal of consent.

16.4 Ethics Committee

It is the responsibility of the investigator to obtain EC approval of the NI-PASS, or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document.

A copy of the protocol proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the EC or other relevant ethical review board for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor or its qualified representative before study can be executed.

All correspondence with the EC should be retained in the Investigator File. Copies of EC approvals should be forwarded to the Sponsor or its qualified representative.

16.5 Patient confidentiality

Data protection and privacy regulations (GDPR) should be respected in collecting, forwarding, processing, and storing data from study participants.

The investigator/third-party chart abstractor must ensure that the patient's confidentiality is maintained for documents submitted to the Sponsor or its qualified representative.

Patients are to be identified by a unique patient identification number.

For SAEs reported to the Sponsor or its qualified representative, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).

Documents that are not for submission to the Sponsor or its qualified representative (e.g., signed informed consent forms, as applicable) are to be kept in confidence by the investigator, except as described below.

Investigators, institutions, and third-party chart abstractors must permit authorised representatives of the Sponsor, the MAH, or the regulatory agency(s), and the EC or other relevant ethical review board direct access to review the patient's original medical records for verification of study-related activities and data if necessary. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

17. Management and reporting of safety events and adverse drug reactions

17.1 Definitions of safety events

Adverse event:

Adverse event (AE) means any untoward medical occurrence in a patient administered a medicinal product. The event does not necessarily have a causal relationship with the product treatment or usage. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal product, whether or not it is related to the medicinal product. This includes any new event or worsening of a previous condition.

Adverse Drug Reaction:

An adverse drug reaction (ADR) is defined as an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product.

Serious adverse event:

A Serious Adverse Event (SAE) is any untoward medical occurrence in a patient administered a medicinal at any dose that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of hospitalisation (see below for circumstances that do not constitute AEs).
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions).
- Results in congenital anomaly/birth defect. Medical and scientific judgment is exercised in determining whether an event is an important medical event.

An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Hospitalisation is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance. Hospitalisation in the absence of a medical AE is not in itself an AE and is not reportable.

17.2 Collecting and recording of safety events

The primary mode by which safety issues are identified will be through the ID and subsequent follow-up with the sponsor's pharmacovigilance department or its qualified representative. Caregivers will be asked, daily, if there were any issues related to administration and, separately, if there were any adverse events. A "yes" answer to any of these questions will trigger a request for follow-up information. Any identification of issues related to administration or adverse events will immediately be transmitted to the sponsor's pharmacovigilance department or its qualified representative, who will follow-up to collect additional information as required. All adverse events will become part of the patient's CRF, including any additional information that is obtained during follow-up by the sponsor's pharmacovigilance department or its qualified representative. In addition, the sponsor's pharmacovigilance department or its qualified representative will follow all local regulations to comply with timely (upon awareness) and complete reporting of adverse events to relevant health authorities, irrespective of the data collection programme for this NI-PASS. Similarly, any AEs identified during the chart abstraction will trigger a notification to the sponsor's pharmacovigilance department or its qualified representative to ensure complete and accurate record-keeping and reporting, as required, per local regulations. In addition, all HCPs participating in the study will be encouraged to report any adverse events directly to relevant health authorities at the time of identification per country-specific regulations.

Pregnancy and lactation will be recorded in the CRF by the investigators as part of routine medical practice and reconciled with the ID. Complete information should be obtained so that, once the AE report form is transferred to the MAH, it can be assessed and processed according to MAH's SOPs, including requests for follow-up.

The above listed safety events will be collected from the patient medical records or ID and captured in the CRF:

- AEs and SAEs, including special situations
- AESIs (photosensitivity)
- Use during pregnancies/lactation (if reported)
- Medication errors and administration complications in the home setting
- NULIBRY treatment discontinuation (temporary or permanent)
- Device related complications

The table below summarises the requirements for recording safety events in the eCRF and for reporting to PV team.

Table 2: Safety requirements

Safety Events	Recorded in the eCRF	Reported to PV within 24h of awareness
Non-serious AE	All	No
SAE	All	All
AESI (Photosensitivity)*	All	All
Pregnancies/Lactation	All	All
Medication error/Complication**	All	All
Treatment discontinuation**	All	No
Device related complication ***	All	Yes

*Photosensitivity is considered as an AESI which deems to be reported. Investigators must be advised to seek medical attention immediately if the patient develops a rash or if they notice symptoms of photosensitivity reactions.

**Details on medication error and administration complications will be reported directly by the caregiver/patient in the infusion diary.

***As complications associated with device were reported in clinical trials for 11 patients with MoCD Type A, adverse drug reaction attributed to the catheter will be reported during the NI-PASS.

When an AE is reported in the CRF for a patient at a site, the investigator will be asked to complete a standard reporting form. Sufficient information should be recorded to enable the AE to be fully described and collected in the CRF.

If an AE needs to be reported, the following information should be collected in the CRF:

- A description of the AE
- Start and stop date of the AE
- Outcome of the AE
- Actions taken by the investigator
- Causal relationship to treatment, to concurrent medical conditions, to medical or surgical procedures
- Severity of the AE
- Seriousness criteria met

For events which need to be reported within 24h of awareness, Investigators will have to notify the Sponsor or its qualified representative via the dedicated safety form or via the CRF. For potential safety events reported by caregivers/patients in the ID, investigators will review them during routine follow-up visits. Additionally, the use of an electronic ID will allow the Sponsor or its qualified representative to be notified if a potential safety event has occurred at the time it is reported in the ID, and this will trigger follow-up by the Sponsor's PV department or qualified representative as described above.

17.3 Reporting Period

Serious adverse events (SAEs) will be reported to the Sponsor or its qualified representative from the time the investigator obtains the patient's or legally authorised representative signed ICF throughout the patient's participation in the study.

For each AE, the Investigator/Sponsor PV must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as an SAE.

17.4 Scenarios necessitating reporting within 24 hours

Exposure during pregnancy:

Given the nature of the product, the patient population/indication, and given that NULIBRY is not recommended during pregnancy and in women of childbearing potential not using contraception, pregnancy and lactation will be an unlikely event.

An exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed to NULIBRY or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to NULIBRY (maternal exposure)
- A male has been exposed due to treatment

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with NULIBRY this information must be submitted to the Sponsor safety or its qualified representative, irrespective of whether an adverse event has occurred. Information submitted should include the anticipated date of delivery.

Follow-up is conducted to obtain general information on the pregnancy; a pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and the Sponsor or its qualified representative is notified of the outcome. This information is provided as a follow up report.

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine foetal demise, neonatal death, or congenital anomaly (in a live born, a terminated foetus, an intrauterine foetal demise, or a neonatal death)), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion.
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to NULIBRY.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with a form to deliver to his partner. It must be documented that the patient was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE.

Medication error or complication in home setting:

Treatment with NULIBRY is to be initiated in the hospital setting. Nevertheless, home administration of NULIBRY can be performed if deemed appropriate by the HCP. Treatment with NULIBRY requires specific storage, dosing and administration which may increase the possibility of medication errors in the home setting. Therefore, medication errors in the home setting are considered as an important potential risk and should be monitored as such.

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the HCP or patient. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

The investigator must submit the following medication errors to the Sponsor or its qualified representative, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
    - An identifiable reporter.
    - A suspect product.
    - The event medication error

These events will also be captured as part of the patient's infusion diary and submitted to the Sponsor or its qualified representative.

17.5 Causality assessment

The investigator is required to assess and record the causal relationship. In the case of adverse events identified from a caregiver's input into the infusion diary, the sponsor's pharmacovigilance department or its qualified representative will be responsible for obtaining additional information about the adverse event at the time of awareness, including determining a causality assessment and, if needed, with input from the patient's HCP.

For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to NULIBRY, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilise at a level acceptable to the investigator, and the Sponsor or its qualified representative concurs with that assessment.

A NULIBRY causality assessment is the determination of whether there exists a reasonable possibility that NULIBRY caused or contributed to an AE.

If the investigator's final determination of causality is "unknown" and s/he cannot determine whether NULIBRY caused the event, the safety event must be reported within 24 hours. In that case, causality assessment will be performed by the Sponsor who will consider it as related with NULIBRY administration.

If the investigator cannot determine the aetiology of the event but s/he determines that NULIBRY did not cause the event, this should be clearly documented on the eCRF.

18. Plans for disseminating and communicating results

The protocol, study progress reports, interim reports, and final study report will be included in regulatory communications in line with the Risk Management Plan, periodic benefit-risk evaluation report, and other regulatory milestones and requirements.

Study reports will be prepared using a template following the GVP Module VIII Section B.6.3.

The progress report will include status updates (i.e., progress against milestones, number of patients receiving NULIBRY) and will report and address any challenges in the progress of the project.

In line with EMA GVP Module VIII, the research team will have independent publication rights.

The MAH will be entitled to view the results and interpretations included in the manuscript(s) and provide comments before submission of the manuscript(s) for publication.

19. Administrative and legal obligations

19.1 Protocol Amendments and Study Termination

Any substantial amendments shall be submitted to the competent regulatory authorities prior to their implementation according to GVP module VIII section VIII. C.2.1.

If the Sponsor amends the protocol, written agreement from the investigator must be obtained. The EC or other relevant ethical review board must be informed of all amendments and give approval.

The investigator must send a copy of the approval letter from the EC or other relevant ethical review board to the Sponsor or its qualified representative.

The Sponsor reserves the right to terminate the study at any time. Both the Sponsor and the investigator reserve the right to terminate the investigator's participation in the study according to the contractual agreement. The investigator is to notify the EC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to the Sponsor or its qualified representative. It is acknowledged that there is no defined end date for the study. Nevertheless, all study data captured after a duration of five years will be included in an interim report to check the amount of data that have been gathered. Sponsor may then agree with the PRAC on a hypothetical date for study termination.

A summary of the final report will be published in the EU PAS register and TMC Pharma or its qualified representative will submit the final study report to the respective regulatory authorities within 12 months after the end of data collection.

19.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. If applicable, all persons authorised to make entries and/or corrections on CRFs will be included on the Delegation of Authority Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. CRF entries may be considered source data if the CRF is the site of the original recording (i.e., there is no other written or electronic record of data).

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by qualified representatives from the Sponsor and/or applicable regulatory authorities. Elements to include:

- patient files containing completed CRF, informed consent forms, and patient identification list,
- study files containing the protocol with all amendments, and all correspondence to and from the EC or other relevant ethical review board.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the contractual agreement with the Sponsor or its qualified representative.

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