21 July 2022
EMA/677145/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nulibry

International non-proprietary name: fosdenopterin

Procedure No. EMEA/H/C/005378/0000

Note

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

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List of abbreviations

Abbreviation	Definition
ADA	Anti-drug antibody
AE	adverse event
AED	antiepileptic drugs
API	active pharmaceutical ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ATE	Average treatment effect
BOC	tert-Butyloxycarbonyl
Bayley	Bayley Scales of Infant Development, Third Edition
CDC	Centers for Disease Control and Prevention
CFU	Colony Forming Units
CI	confidence interval
CL	total clearance
CL_r	renal clearance
C_{max}	maximum concentration
CNS	central nervous system
cPMP	cyclic pyranopterin monophosphate
CSR	clinical study report
CQA	Critical quality attribute
CYP	cytochromes P450
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
DoE	Design of Experiments
DMC	Data Monitoring Committee
DSC	Differential Scanning Calorimetry
ECG	electrocardiogram
EEG	electroencephalogram
EFD	embryo foetal development
eIND	emergency Investigational New Drug
ExAC	Exome Aggregation Consortium
FAS	Full Analysis Set
FDA	Food and Drug Administration
FMOC-Cl	fluorenylmethoxycarbonyl chloride
HPLC/UV	high-performance liquid chromatography using ultraviolet detection
GA	gestational age
GMAS	Genotype-Matched Analysis Set
GMFCS-ER	Gross Motor Function Classification System, Expanded and Revised
GMFM-88	Gross Motor Function Measure - 88
GTP	guanosine 5′ -triphosphate
HPLC-DAD	high-performance liquid chromatography-diode array detection
IND	Investigational New Drug Application
ISE	Integrated Summary of Efficacy
IP	Intraperitoneal
IPC	In-process control

Abbreviation	Definition
IR	Infrared
ISOD	isolated sulfite oxidase deficiency
IV	intravenous (ly)
LC/MS/MS	liquid chromatography/tandem mass spectrometry
LLOQ	lower limit of quantitation
LoQ	List of questions
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation holder
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MoCD	molybdenum cofactor deficiency
MoCo	molybdenum cofactor
MPT	molybdopterin
MRI	magnetic resonance imaging
MS	Mass Spectrometry
NCE	New chemical entity
ND	Not detected
NLT	Not less than
NMT	Not more than
NOAEL	No-observed-adverse-effect-level
NOEL	No-observed-effect-level
NOR	Normal acceptable range
ODD	Orphan Drug Designation
OS	overall survival
OVAT	One variable at a time
PAR	Proven acceptable range
PD	pharmacodynamic
PDE	Permitted Daily Exposure
PEDI	Pediatric Evaluation of Disability Index
PFAS	Prospective Full Analysis Set
Ph.Eur.	European Pharmacopoeia
PK	pharmacokinetic
PPND	pre- and postnatal development
PPQ	Process performance qualification
QbD	Quality by design
QD	Once daily
QP	Qualified Person
QWBA	Quantitative whole body autoradiography
rcPMP	recombinant Escherichia coli-derived cyclic pyranopterin monophosphate
RH	Relative Humidity
RRT	Relative retention time
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	system organ class
SOX	sulfite oxidase

Abbreviation	Definition
SPC	Summary of Product Characteristics
SRC	Safety Review Committee
SSC	S-sulfocysteine
TEAE	treatment-emergent adverse event
THF	Tetrahydrofuran
UK	United Kingdom
US	United States
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
V_d	volume of distribution
WHO	World Health Organization
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Comharsa Life Sciences Ltd submitted on 4 November 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Nulibry, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2019.

Cyclic pyranopterin monophosphate (cPMP), was designated as an orphan medicinal product EU/3/10/777 on 20 September 2010 in the following condition:

'Treatment of molybdenum cofactor deficiency type A.'

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Nulibry as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/nulibry

The applicant applied for the following indication:

'NULIBRY is indicated for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A.'

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0132/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0132/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0132/2022.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request(s) for consideration

1.5.1. Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation.

1.5.2. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.3. New active Substance status

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

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 May 2014	EMEA/H/SA/2782/1/2014/PA/PED/III	Fernando de Andrés Trelles, Mario Miguel Rosa
24 September 2015	EMEA/H/SA/2782/1/FU/1/2015/PA/PED/II	Fernando de Andrés Trelles, Karl-Heinz Huemer

The Protocol assistance pertained to the following non-clinical and clinical aspects:

- Adequacy of the proposed nonclinical package to support MAA.
- The dosing strategy to define the optimal therapeutic dose to be used in Study ALXN1101-MCD-202 (in neonate subjects with a diagnosis of MoCD Type A, 1-28 days of age). Proposal not to conduct a thorough QT/QTc study. Design of study ALXN1101-MCD-202, including patient population, primary and secondary endpoints, duration, absence of a control arm, definition of the evaluable cohort, sample size and statistical analyses.

  Acceptability to collect data in subjects with MoCD Type A who are older than 28 days of age in a separate study, ALXN1101 MCD-203. Acceptability to initiate ALXN1101 treatment in subjects with a clinical diagnosis consistent with MoCD Type A prior to getting confirmation of genetic diagnosis.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	4 November 2021
Accelerated Assessment procedure was agreed-upon by CHMP on	14 October 2021
The procedure started on	25 November 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	26 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 February 2022
The CHMP Co-Rapporteur's Critique Assessment Report was circulated to all CHMP and PRAC members on	2 February 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	14 April 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	20 April 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 May 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	16 June 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on (TT reverted to standard)	23 June 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 June 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 July 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Nulibry on	21 July 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	21 July 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Following the CHMP assessment of all data provided, the agreed therapeutic indication is:

'NULIBRY is indicated for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A.'

Molybdenum cofactor deficiency (MoCD) type A is an ultra-rare, rapidly progressive, chronic, and mostly fatal, autosomal recessive inborn error of metabolism.

Two-thirds of MoCD patients have Type A due to mutations in the MOCS1 gene localized on chromosome 6p21.3 which leads to a complete lack of MOCS1A/B enzyme activity with no formation of cyclic pyranopterin monophosphate (cPMP).

2.1.2. Epidemiology and risk factors, screening tools/prevention

Incidence estimates have progressively changed with an improved understanding of the disease. Initial estimates predicted that it occurs in less than one in 100,000 to 200,000 newborns worldwide. To date, more than 100 cases of MoCD have been reported in the literature, representing numerous ethnic groups with higher prevalence in areas of high consanguinity. MoCD, is thought to be underdiagnosed. The most recent estimation based on the Hardy-Weinberg equation and allelic frequencies of represented variants was within the range of one in 341,690 to 411,187.

The most recent estimates of MoCD type A in the EU are based on 20 publications and reporting cases of any types of MoCD; 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.

2.1.3. Biologic features, Aetiology and pathogenesis

MoCD Type A is one of three known types of MoCD (Type A, Type B, or Type C), which is classified based upon the affected gene, with mutations in *MOCS1*, *MOCS2*/*MOCS3* (Molybdenum Cofactor Synthesis gene 1, 2/3), and *GPHN* (Gephyrin gene), respectively.

In patients with MoCD Type A, mutations in the *MOCS1* gene lead to deficient MOCS1A/B dependent synthesis of the intermediate substrate cyclic pyranopterin monophosphate (cPMP). The majority of patients with MoCD Type A reported to date carry mutations that lead to a complete lack of MOCS1A/B enzyme activity with no formation of cPMP. In the absence of cPMP, molybdenum cofactor (MoCo) cannot be synthesized, resulting in all molybdenum-dependent enzyme activity being undetectable, most importantly sulfite oxidase (SOX). Deficient SOX activity leads to the accumulation of toxic levels of sulfites and the secondary metabolite S-sulfocysteine (SSC). Xanthine oxidase (or xanthine dehydrogenase), aldehyde oxidase, and mitochondrial amidoxime-reducing components are also MoCo dependent and inactivated when this cofactor is absent but are not believed to contribute to the pathophysiology of MoCD. The same phenotype of neurologic insult from elevated sulfite levels is found in MoCD Types A, B, and C and in isolated sulfite oxidase deficiency (ISOD); thus, implicating sulfite neurotoxicity as the primary mechanism of disease.

Sulfite toxicity due to MoCD can result in significant, irreversible structural damage to the brain.

2.1.4. Clinical presentation, diagnosis and prognosis

MOCD typically exhibits an acute onset in neonates or in early infancy however, later onset cases have also been reported. The different types of MoCD are indistinguishable clinically and biochemically, and the diagnosis of the specific type of MoCD is confirmed by genetic testing, which may take several days to weeks to complete. Laboratory findings in MoCD Type A, as well as the other two types of MoCD, include elevated levels of urinary and plasma SSC, xanthine, and hypoxanthine; a positive urine sulfite test; and a decrease in urinary and serum uric acid.

Characteristics of the disease include intractable seizures, burst suppression or multifocal epileptic electroencephalogram (EEG), abnormal magnetic resonance imaging (MRI) findings, metabolic acidosis, exaggerated startle reactions, axial hypotonia, limb hypertonia, gross destruction of the brain, failure to thrive, poor or halted feeding response, and high-pitch crying. Language, visual, and motor impairment with varying degrees of severity are observed. In the neonatal period, brain MRI and, to a lesser extent, ultrasound imaging patterns, include symmetrical pallidal or subthalamic lesions, cerebral infarction, subcortical multicystic lesions, progressive cortical and subcortical atrophy, and diffuse white matter abnormalities.

These characteristics collectively precede rapidly progressive neurodegeneration. In the absence of treatment, patients usually die within the first years of life. Median survival is reported to be 36 months.

2.1.5. Management

There is no approved treatment for MoCD Type A in the EU. 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 SSC that lead to significant developmental disabilities. Although AEDs are available for the treatment of seizures, chronic epilepsy refractory to AED therapy does occur in patients with MoCD Type A.

2.2. About the product

Fosdenopterin is a substrate replacement therapy and consists of synthetic cPMP (cPMP hydrobromide dihydrate). By replacing cPMP and permitting the two remaining MoCo synthesis steps to proceed, the activity of MoCo-dependent enzymes is restored.

The restoration of activity from the MoCo-dependent enzyme SOX leads to the clearance of neurotoxic sulfites and is accompanied by a reduction of plasma and urine levels of the secondary metabolite SSC. Given the neurotoxic potential of sulfites and SSC, adherence to fosdenopterin therapy maintains clearance of sulfites and SSC, with inhibition of the underlying neuropathology.

Fosdenopterin is for intravenous (IV) use only. For patients less than 1 year of age who are term neonates (gestational age ≥37 weeks), the recommended starting dose is 0.55 mg/kg/day administered as an IV infusion once daily. For patients less than 1 year of age who are preterm neonates (gestational age <37 weeks), the recommended starting dose is 0.40 mg/kg/day administered as an IV infusion once daily. Dosage should be titrated to the target dose of 0.90 mg/kg/day over a period of 3 months, as shown in Table 1.

For patients 1 year of age or older, the recommended dose is 0.90 mg/kg/day administered as an IV infusion once daily.

Table 1. Starting Dose and Titration Schedule of fosdenopterin for Patients Less Than One Year of Age by Gestational Age

Titration Schedule	Preterm Neonate (GA <37 weeks) mg/kg/day	Term Neonate (GA ≥37 weeks) mg/kg/day
Initial Dose	0.40	0.55
Dose at Month 1	0.70	0.75
Dose at Month 3	0.90	0.90

Abbreviations: GA = gestational age

2.3. Type of Application and aspects on development

Accelerated assessment

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on:

- The unmet need in the indicated patient population.
- The safety and efficacy of fosdenopterin is supported by data from 14 treated patients and 37 natural history controls. Although this patient number is very limited, this could be acceptable for such a rare disease.
- The efficacy will be assessed in a totality of evidence approach. The presented benefit concerning overall survival seems to be supported by positive effects on growth, motor function and disease biomarkers. Therefore, it can be concluded that the clinical data package is robust enough to support an MAA.
- In addition, these beneficial effects would constitute a major advantage for patients suffering from MoCD type A, with prolonged survival and possibly an increase in their health-related quality of life.
- With respect to the quality and non-clinical part of the dossiers, the data packages are considered robust enough to support an MAA.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as among others, major objections were raised regarding the comprehensiveness of the data. A Marketing Authorisation under exceptional circumstances was proposed by the CHMP during the assessment, after having consulted the applicant, and the applicant submitted a revised outline of the non-interventional study and proposed SOB(s) for Nulibry, which required more time to solve than possible within the accelerated assessment timetable.

Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation based on

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence;

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as powder for solution for injection containing 9.5 mg of fosdenopterin, as active substance. The product contains fosdenopterin hydrobromide dihydrate.

Other ingredients are: ascorbic acid (E300), mannitol (E421), sucrose, hydrochloric acid (E507) and sodium hydroxide (E524).

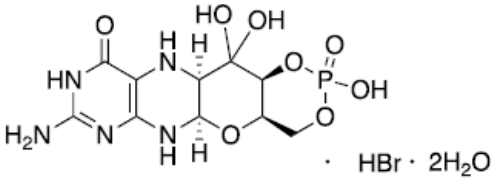
The product is available in 10 ml type I clear glass vial with an aluminium seal and butyl rubber stopper.

2.4.2. Active substance

General information

The chemical name of fosdenopterin monohydrobromide dihydrate is (4a*R*,5a*R*,11a*R*,12a*S*)-8-Amino-2,12,12-trihydroxy-4,4a,5a,6,9,10,11,11a,12,12a-decahydro-2H-1,3,5-trioxa-6,7,9,11-tetraaza-2λ^5-phosphatetracene- 2,10-dione (hydrobromide dihydrate) corresponding to the molecular formula $C_{10}H_{19}BrN_5O_{10}P$. It has a molecular mass of 480.16 g/mol and the following structure:

Figure 1: active substance structure



The chemical structure of active substance was elucidated by a combination of ^1H and ^{13}C nuclear magnetic resonance (NMR), Fourier-Transform infrared (FT-IR) spectroscopy, mass spectrometry (MS), ultraviolet visible (UV-VIS) spectroscopy and bromide content. The solid state properties of the active substance were measured by single crystal and powder X-ray diffraction (SCXRD, PXRD), dynamic vapor sorption (DVS), and differential scanning calorimetry (DSC).

2D ^1H-^1H Nuclear Overhauser Effect Spectroscopy (NOESY) and chiral high performance liquid chromatography (HPLC) were used to confirm the stereochemical form.

The active substance is a white to pale yellow to orange/red/brown crystalline solid. It is hygroscopic: Dynamic Vapor Sorption (DVS) shows absorption of water at a level of up to 35-38% w/w when exposed to relative humidity (RH) above 80%. Storage and handling conditions are established to limit water exposure. Its solubility in water is pH dependent: it is poorly soluble (<1 mg/mL) at pH 1 – 4 but is soluble (> 5 mg/mL) when the pH is > 6.8. Fosdenopterin hydrobromide, dihydrate is practically insoluble in several organic polar solvents.

Fosdenopterin exhibits stereoisomerism due to the presence of four chiral centres. Chirality is introduced from D-galactose, which is one of the designated Regulatory Starting Materials. D-galactose is tested for specific optical rotation. Although enantiomeric purity of the active substance is not routinely tested, the absence of enantiomers is ensured by upstream testing.

High through-put polymorph screening performed with multiple solvents resulted in 2 crystalline forms of the active substance (A and B). B was assigned to the target salt of fosdenopterin, while A was assigned to the dihydrobromide salt of fosdenopterin. The potential for presence or formation of polymorphs is low. The proposed commercial manufacturing process selectively provided the desired form B. No evidence of other polymorphs or transitions of the active substance as manufactured and stored according to the specified conditions has been found and the XRPD profiles were consistent throughout the development program.

Manufacture, characterisation and process controls

Fosdenopterin hydrobromide dihydrate is synthesized by a single manufacturer in five main steps using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Reprocessing of non-conforming material may be performed by repeating the required steps of the proposed synthesis process. Recovery of solvents and reworking are not included in the dossier.
The quality of the starting materials was assessed as suitable, in accordance with the general concepts presented in the relevant EMA guidelines. Information on knowledge of fate and purge of isomer impurities has been provided and a chiral control strategy developed. For all intermediates, limits for specified impurities, unspecified and total impurity content are considered acceptable and sufficiently supported by spike, fate and purge studies.
Sufficient details on the manufacturing process development have been provided.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of Quality by Design (QbD) such as risk assessment and design of experiment (DOE) studies. A design space is not claimed for the routine manufacturing process, where Normal Operating Ranges (NORs) are used. Based on a risk assessment evaluation, the critical quality attributes of the active substance were identified: assay, impurities, bromide content, residual solvents and residual acetamide. The criticality assessment was used as a guide to design process parameter mapping studies. A summary of all material quality attributes and process parameters that may have an impact on product quality were presented, together with their rationales. Risk ranking assessment of reaction process parameters with the identification of process parameters was provided. PARs were established based on the studies performed (OVAT, DoE). All the manufacturing steps have defined PARs that control volume charge of reagents, solvents, temperature, agitation and similar parameters. Steps representing higher risk have been identified, and process mapping has been performed. No critical process parameters were identified in the manufacturing process. This is based on the studies which demonstrate that product profiles at critical ranges are comparable to those observed at the nominal, centre-point conditions.

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

The known and potential impurities of the active substance have been presented and discussed regarding the stage of the manufacturing process where they are potentially formed including the impurities from the starting materials, solvents, and reagents. The control strategies are described along with the discussion about the fate and purge of impurities. A computational toxicology assessment has been performed for starting materials, intermediates, reagents, by-products and degradants of materials using (Q)SAR methodologies. The evaluated impurities have been classified with respect to the carcinogenic and mutagenic potential according to the 5 classes as defined in ICH M7. Potential genotoxic impurities are identified and controlled in the active substance or in

intermediates. The specification limits for all these impurities are set based on the compound specific PDEs.

A risk assessment for potential sources of nitrosamine impurities in fosdenopterin active substance was performed.

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

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Clinical and nonclinical active substance batches were manufactured at a development site, after which the process was transferred to the proposed commercial manufacturing site.

A free-base zwitterion form of active substance was used in early clinical studies, whereas the proposed commercial manufacturing process results in a hydrobromide dihydrate salt. Both molecular structures have been compared using multiple spectral techniques. The results demonstrate that the active substance used in the early clinical trials and active substance fosdenopterin (hydrobromide dihydrate) have the same therapeutic moiety and the only difference is the salt form. Minor modifications were implemented to the synthetic process throughout development; however, the basic chemical sequence and main reagents are common to both the development and proposed commercial manufacturers' routes.

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

Specification

The active substance specification includes tests for description (visual), colour and appearance of solution (Ph. Eur.), identification (IR, Ph. Eur., UPLC), assay (UPLC), impurities (UPLC), solid form identity (PXRD), bromide content (IC), ,residual solvents (HS-GC), sulfated ash (gravimetric, Ph. Eur.), elemental impurities (ICP-MS, Ph. Eur.), bacterial endotoxins (Ph. Eur.), microbial quality (Ph. Eur.),

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The absence of a test for enantiomeric or diastereoisomeric impurity content is justified based on the stereochemistry control strategy at the level of the intermediates, as described above.

Specifications have been set for assay and impurities (UPLC), solid form identity (PXRD), bromide content (IC), residual solvents (HS-GC), elemental impurities (ICP-MS), The active substance specification lists controls for several solvents, including: solvents used in the final fosdenopterin-forming and isolation step, solvents introduced in, but not subject to final control in upstream steps and materials that may be formed as a by-product or side-product.

The analytical methods used have been adequately described and, non-compendial methods, appropriately validated in accordance with the ICH guidelines.

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

Batch analysis data for 6 commercial scale batches of the active substance manufactured at the proposed commercial manufacturing site are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from five commercial scale batches of active substance from the proposed commercial manufacturer stored in the intended commercial package for up to 24 months under long term conditions according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch.

Results on stress conditions (forced degradation study on solution state active substance applying acid, base and oxidation stress, and on solid state active substance, applying heat and light stress) were also provide on one batch.

The following parameters were tested: description, assay, impurities, water content, identification, PXRD, microbiological quality, endotoxins. The analytical methods used were the same as for release (with two exceptions which were justified) and were stability indicating.

All tested parameters for the active substance stored at were within the specifications. The stability of polymorphic form during storage was confirmed.

In the solid-state, the active substance was not observed to be sensitive to light. Stress testing under conditions of acid, base, oxidation, heat, and light demonstrated the stability indicating nature of the methods and the intrinsic stability of the molecule. The data presented demonstrate that the active substance is sensitive to degradation across a range of pH levels and under oxidative conditions. The active substance is sensitive to heat stress conditions with darkening of the solid material observed. There was a concomitant increase in total impurities level and assay levels were observed to decrease.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months in the proposed container.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

Nulibry 9.5 mg powder for solution for injection is a sterile, white to pale yellow lyophilized powder for intravenous use. The finished product is packaged in 10 mL Type 1 clear glass vials, with an aluminium seal and butyl rubber stopper.

The finished product is to be reconstituted with 5.0 mL of sterile water for injections to provide a solution containing 1.9 mg/mL fosdenopterin and a pH range of 5–7. An overfill of 0.23 mL (5.23 mL target fill volume) is used to assure removal of 5.0 mL for administration.

The finished product is dosed with a conventional disposable syringe and an infusion tubing set (which are not part of the commercial presentation).

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

Compatibility between the active substance and excipients was demonstrated in formulation development studies, as well as stability studies.

The pharmaceutical development of the finished product contains QbD elements. The goal of the formulation development, as also described in the QTTP, was to design a stable sterile, single-dose finished product for administration by intravenous injection suitable for paediatric and adult use, with

acceptable pH and osmolality. The finished product should be stable during storage in the primary container closure, with a shelf life of at least 24 months, and during in-use period.

The CQAs identified were appearance (before reconstitution), reconstitution time, colour, clarity and completeness of solution (after reconstitution), particulate matter of reconstituted solution, pH, content uniformity, osmolality, container content, sterility, bacterial endotoxins, moisture content, identity, assay, degradants, assay of ascorbic acid.

Active substance degrades in solution forming an identified oxidation product. Therefore, ascorbic acid is included in the formulation as an antioxidant. As this product is indicated for paediatric population, the applicant was requested during the procedure to provide evidence of compliance with Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev.2), which was received and considered acceptable.

Mannitol and sucrose are included in the formulation as bulking agents for lyophilization, and to bring the osmolality of the finished product into the physiochemical range.

Manufacturing process development focused on determining conditions to minimize degradation of the active substance and produce a stable lyophilized product. Based on product knowledge derived from product characterization, formulation and process development, scale-up, and clinical manufacturing experience, a failure mode effect analysis was performed to systematically identify product CQAs and evaluate the impact of process parameters on the CQAs and process performance.

The finished product is manufactured by a non-standard process consisting of mixing, sterile filtration, aseptic filling, lyophilization, stoppering, sealing, and inspection of vials for defects.

The critical process parameters have been adequately identified.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed target setpoints and PARs.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product.

QbD studies were performed to confirm that the proven acceptable ranges for freezing rate and primary dry temperature of the lyophilization cycle are appropriate for the intended use.

The four formulations used during clinical studies were all lyophilized formulations, very similar or the same as the proposed commercial formulation. For administration via intravenous (IV) injection, the formulation changes made during clinical development are not expected to have any impact on the pharmacokinetic profile of fosdenopterin and from that perspective, the formulations are essentially considered equivalent. The basic manufacturing process was the same for clinical, registration, and commercial finished product.

The primary packaging is a 10 mL Type 1 clear glass vial, with an aluminum seal and butyl rubber stopper. The material complies with Ph.Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. In-use studies demonstrated compatibility with the administration devices (see below under ‘Stability of the Product’).

Although only minimal direct contact with the rubber stoppers is expected as the finished product is a lyophilised powder, the extractables and leachables studies have been performed. In addition, the simulated leachable study was performed included tubing systems used for administration.

Manufacture of the product and process controls

The manufacturing process consists of four main steps. The process is considered to be a non-standard manufacturing process.

All critical steps of the manufacturing process are adequately controlled. The in-process controls are adequate for this type of manufacturing process and lyophilized formulation.

Validation data include filter validation and manufacturing process validation. The applicant has initiated a concurrent validation program, for which the validation protocol was provided. Currently, validation results for two production size batch are available. This concurrent approach was accepted taking into account the benefit/risk profile, the orphan drug designation and consequent limited commercial demand requiring low volumes and infrequent manufacture. The CHMP recommended and the applicant committed to provide results of the third PPQ batch and full validation program as soon as they are available. Potential sorption of finished product solution components to the pre-filter and sterilising filter are sufficiently discussed and found acceptable.

Product specification

The finished product release specifications, include appropriate tests for this kind of dosage form: powder for solution for injection, namely: appearance before reconstitution (visual), reconstitution time (visual), degree of coloration of the reconstituted solution (visual), completeness of solution (visual), clarity and degree of opalescence (visual), particulate matter (of the solution, visual, Ph. Eur.), pH (Ph. Eur.), water content (USP), identity (UHPLC by retention time, DAD UHPLC by UV spectra), assay (UHPLC), assay of ascorbic acid (UHPLC), degradation products (UPLC), content uniformity (UHPLC), osmolality (Ph. Eur.), container content (reconstituted, Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), container closure integrity (USP). Release and shelf-life limits for degradants and shelf-life limit for assay have been tightened as requested.

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

The acceptance criteria are in accordance with compendial requirements and relevant guidelines and are therefore acceptable. Impurities which are controlled with limits above the qualification limit have been toxicologically qualified.

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

A risk assessment concerning the potential 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 "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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

Batch analysis results are provided for 17 batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 24 months under long term conditions (-20 ± 5 °C) and for up to 6 months under accelerated conditions (5 ± 3 °C) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition to this, 12 months data from one commercial scale process performance qualification batch stored for up to 24 months under long term conditions (-20 ± 5 °C) were provided, as well as supportive stability data from six batches and two commercial scale batches of finished product stored for up to 36 months under long term conditions (-20 ± 5 °C) and accelerated conditions (5 ± 3 °C) according to the ICH guidelines.

The supportive batches were manufactured with active substance from a different manufacturing site than the proposed commercial manufacturing site, and were tested with different test methodology for assay, ascorbic acid, and degradation products, though the methods were comparable to the proposed methods used for the to be marketed product.

Samples were tested for appearance before reconstitution, reconstitution time, appearance of reconstituted solution, pH, clarity and degree of opalescence, color of solution, water content, assay and degradation products, particulate matter, ascorbic acid, sterility (or container closure integrity by oxygen headspace analysis) and endotoxins. The analytical procedures used are stability indicating. These results did not show any significant trends and remained within acceptance criteria during the tested period.

In addition, samples of a batch of finished product were subjected to acid, base, oxidative, heat, and light irradiation stress. The stability indicating properties of the method are demonstrated by the reduction of peak area of the analyte peak, the presence of degradants, and the peak purity of the analyte peak.

An ICH Q1C compliant photostability study was conducted in which a slight increase of one specified degradant was observed in the exposed vials, compared to the vials in secondary packaging, and to the control vials; however, the result remained within limits. Therefore, storage in the outer carton in order to protect from light is proposed and can be accepted.

The in-use shelf life of the product after reconstitution is 4h at room temperature or refrigerated conditions (2-8 °C). In-use data from the three registration batches stored up to 24 months at -20 ± 5 °C followed by 4 hours at room temperature after reconstitution, and from three supportive batches stored up to 24 months at -20 ± 5 °C followed by 4h at 2-8 °C support this in-use period, as stated in the SmPC (section 6.3).

Based on available stability data, the proposed shelf-life of 2 years and storage conditions "Store in a freezer at -25 °C to -10 °C", "Keep the vial in the outer carton in order to protect from light", as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

Adventitious agents

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

2.4.4. Discussion on chemical, and pharmaceutical aspects

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

At the time of the CHMP opinion, there was one minor quality issues having no impact on the Benefit/Risk ratio of the product, which pertains to the fact that the applicant, applying a concurrent validation approach, still has to run the third process performance qualification batch for the finished product, in order to conclude on the outcome of the process performance qualification. This point is put forward and agreed as recommendation for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

-to provide results of the third PPQ batch and full validation program for the finished product.

2.5. Non-clinical aspects

2.5.1. Introduction

MoCo forms the active site of four apo-enzymes: sulphite oxidase (SOX), xanthine oxidase (or xanthine dehydrogenase), aldehyde oxidase, and mitochondrial amidoxime reducing component. SOX catalyses the terminal step in the degradation of cysteine. Patients with MoCD Type A have impaired MoCo production at the GTP to cPMP conversion step in cofactor synthesis, leading to accumulation of the neurotoxic SSC. Fosdenopterin is a synthetically produced cPMP indicated for substrate replacement in MoCD Type A patients. By replacing cPMP with fosdenopterin, MoCo-synthesis and clearance of the neurotoxic sulfites and SSC are to be restored.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The MoCo-synthesis is considered highly conserved between species, and cPMP is considered identical between species. Initial cPMP substrate replacement therapy for MoCD Type A was by using *E.coli*-

derived cPMP (rcPMP). Fosdenopterin (free base) is a synthetically derived cPMP with identical core structures to rcPMP, expected to be functionally identical and undergo the same metabolism and disposition as endogenous cPMP. The intended route of administration is intravenous.

In vitro data have shown similar dose-related biological activity of fosdenopterin and rcPMP, with regard to conversion to MPT and MoCo.

In vivo studies were conducted in a mouse model of MoCD (MOCS1$^{-/-}$ mice), with phenotypes having similar characteristics and biochemical anomalies as human MoCD Type A. Untreated, the mice showed severe symptoms including slowed body weight gain, dehydration, limb paralysis and dramatically shortened life span (death 8 to 16 days) compared with wild-type (+/+) or heterozygous (+/-) littermates.

Different routes of administration were applied, but not the intended intravenous (IV) route. In most studies, intrahepatic (IH) treatment with either rcPMP or fosdenopterin was initiated from PND1, with repeated dosing 3 times per week. The intrahepatic route of administration was then changed to intraperitoneal (IP) (IH/IP), subcutaneous (SC) (IH/SC) or oral (IH/PO) route in adult animals. The pharmacodynamic effects were achieved by all routes. The lack of data from the intended route of administration is considered acceptable based on the limited volume feasible for IV administration to mice.

Treatment with fosdenopterin 3 times per week from PND1 (IH/IP or IH/SC) prevented early death, and the mice appeared alert and agile, and exhibited increased body weights, decreased plasma and brain S-sulfocysteine (SSC) levels and restored liver SOX and xanthine oxidase activities compared to vehicle-treated control animals. The effects were dose-related and similar to that observed for rcPMP. Extended life span, higher weight gain and normal behaviour were also seen following oral dosing of 500 µg 3 times per week from PND27-70, but without normalising effect on plasma SSC.

2.5.2.2. Secondary pharmacodynamic studies

There were no significant findings noted for fosdenopterin in a secondary pharmacodynamic (PD) screening assay comprising 87 receptors, enzymes, ion channels and transporters.

2.5.2.3. Safety pharmacology programme

Cardiovascular parameters were evaluated in an hERG-assay in vitro, a cardiovascular safety study in dogs, and in a CNS study in rats, all GLP-compliant. Further, potential effects on a number of ion channels, including hERG, were evaluated in a non-GLP automated screening assay. No fosdenopterin-related effects were observed in vitro or on cardiovascular, CNS or respiratory parameters in vivo. Due to low maximum dose levels, margins at no-observed-effect-level (NOEL) are low to non-existing. Safety pharmacology parameters were also integrated as part of the repeat-dose toxicity studies. No effects were seen on respiratory, ECG or CNS parameters in the 39-week toxicity study in dogs or CNS or respiration in the 13- and 26-week toxicity in rats.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies have not been conducted.

2.5.3. Pharmacokinetics

The main route of administration in animal studies was IV (slow bolus or infusion), in line with the intended clinical route of administration. In juvenile animal studies, SC administration was used from PND 7-20 in rats and LD5-25 in dogs. The pharmacokinetics (PK) of fosdenopterin was evaluated in dogs after a single parenteral (intravenous [IV] or subcutaneous [SC]) dose, and toxicokinetics (TK) of fosdenopterin was evaluated in juvenile and adult rats and dogs following repeated daily dosing for up to 39 weeks. In addition, single-dose PK properties for fosdenopterin in two different vehicles were assessed in rats following IV dosing.

Concentrations of fosdenopterin in animal plasma were determined using validated LC-MS/MS methods. Overall, the results for the validation show that the assays are sensitive, selective, accurate and reproducible.

Absorption

There were no apparent sex-related differences in PK parameters in juvenile dogs receiving a single IV or SC dose of fosdenopterin at 5 mg/kg. The time to maximum plasma concentration (Tmax) occurred at 0.25 hours after the IV dose (the first blood collection time point), and at 1 hour after the SC dose. Mean Cmax was higher in animals receiving the IV dose than the SC dose. The terminal half-life was 1.12 and 1.18 hours in animals receiving the IV and SC doses, respectively. AUCs were similar following IV and SC dosing. The absolute bioavailability after SC dosing was approximately 97%.

Following repeated dosing to rats and dogs, systemic exposures to fosdenopterin generally increased in a dose-proportional manner with increasing dose. There were no apparent sex-related differences in PK parameters. Half-lives were short (generally below 1h), with no quantifiable concentrations beyond 4h after dosing in rats and beyond 6 hours in dogs.

For most studies, maximum feasible doses were limited by low solubility and maximum dose volume. An updated vehicle (vehicle 2) was applied in a 13-week toxicity study in juvenile rats to enable higher solubility and thereby higher maximum feasible dose. Single-dose PK properties, including mean plasma concentrations, were similar for the two different vehicles at comparable doses in a non-GLP study in male rats.

Distribution

In a quantitative whole-body autoradiography (QWBA) study in pigmented and non-pigmented rats administered [14C]-fosdenopterin, test article-derived radioactivity was widely distributed. Radioactivity was no longer measurable in the majority of tissues (≥75%) by 24 hours post-dose. Tissues with the highest observed levels of radioactivity included the kidneys, epiphyseal line, oesophagus, liver, and skin in both rat strains. In addition, radioactivity concentrations were relatively very high in urine but undetectable in bile. Low levels of radioactivity did cross the blood:brain barrier for a brief interval at 0.5 hours post-dose in both rat strains, indicate limited penetration into CNS tissues protected by the blood-brain barrier. There were no qualitative differences in tissue distribution patterns between pigmented and non-pigmented rats.

The in vitro studies to assess protein binding and blood cell partitioning were affected by stability issues for fosdenopterin, and different concentrations of ascorbic acid and different incubation periods were applied to increase stability. At 5 mM ascorbic acid and 5 minutes of incubation, fosdenopterin exhibited low plasma protein binding in all species tested (approximately 21-24% in mouse, 7-17% in rat, 23-34% in dog and 6-12% in human). In the non-acidified blood system, the distribution of fosdenopterin to red blood cells was approximately 30% in mouse blood, 26% in rat blood, 20% in human blood and 6% in dog blood. Little to no distribution of fosdenopterin into red blood cells were seen following addition of ascorbic acid.

Metabolism

In vitro studies provided by the applicant indicate that fosdenopterin is stable in hepatocytes from mouse, rat, dog and human over the 240-min of incubation (studies XT134092 and XT134093). Compound Z is the only metabolite formed in all species tested, including humans. Compound Z was observed following incubation with intact and denaturated hepatocytes, indicating generation via a non-enzymatic degradation process.

In vivo studies to address metabolism have not been conducted. The applicant justifies this by lack of metabolites in vitro, and by fosdenopterin being a synthetic replacement for the endogenous molecule (cPMP) expected to be eliminated and excreted in an identical manner to that of the endogenous molecule, namely, enzymatic conversion of cPMP to MPT and subsequent formation of MoCo, or spontaneous oxidation of cPMP to Compound Z in aqueous fluids and subsequent excretion primarily in urine.

Excretion

Excretion studies have not been conducted.

Pharmacokinetic drug interactions

See below under the clinical section for assessment of potential interactions.

2.5.4. Toxicology

Toxicity studies include single-dose toxicity in adult rats, repeat-dose toxicity studies in juvenile and adult rats and dogs, genotoxicity, in vitro haemolysis, and phototoxicity. In addition, in vitro genotoxicity studies have been conducted with synthetic intermediates and impurities. All pivotal toxicity studies are considered GLP-compliant.

Most in vivo studies were conducted with 0.5 mg/mL formulation (Vehicle 1: L-Ascorbic Acid (2 mg/mL), Mannitol (45 mg/mL), and Sterile WFI). A 10 mg/mL formulation (Vehicle 2: L-Ascorbic Acid (4.6 mg/mL), Mannitol (32.5 mg/mL), Sterile WFI, pH adjusted to 7.0 ±0.1), was developed at a later stage to increase solubility and was used in 7-day and 13-week rat studies. Both vehicles were well tolerated.

2.5.4.1. Single dose toxicity

No conventional single-dose toxicity studies have been conducted. As part of a three-phase exploratory study in rats, acute IV bolus doses of fosdenopterin in vehicle 2 were well tolerated and comparable to fosdenopterin in vehicle 1.

2.5.4.2. Repeat dose toxicity

2-week studies were conducted in standard-aged rats and dogs administered fosdenopterin via daily 2-hour IV infusion. In these studies, no-observed-adverse-effect-level (NOAEL) was determined to 10 mg/kg/day, the highest administered dose level.

Long-term studies were conducted in juvenile rats (26-week study, dosing from PND7) and juvenile dogs (39-week study, dosing from LD5). Dosing was initiated by the SC route. In rats, dosing was switched to IV bolus injection from PND21. In dogs, the SC route was either replaced or supplemented by IV bolus injections from LD26. Maximum feasible doses in the 26-week rat study and the 39-week

dog study studies were 5 mg/kg in rats and 10 mg/kg, respectively, limited by low solubility and maximum dose volume.

No target organ for toxicity was seen in these studies, and no effects were seen on sexual maturation, behavioural performance, or bone parameters. In dogs, slight and non-adverse increased neutrophil counts and a mild increase in APTT were observed in males at 10 mg/kg/day, correlated with mild increases in serum globulin concentration, serum ALP and lipase activities. These findings were without histopathological correlates and were considered non-adverse. NOAELs for fosdenopterin were 5 mg/kg/day (rats) and 10 mg/kg/day (dogs), the highest dose levels evaluated.

As a follow-up, a 13-week study in juvenile rats was conducted with an alternative vehicle, leading to a higher level of solubility and allowing dosing up to 100 mg/kg/day from PND7. Fosdenopterin was well tolerated, with no test article-related ante- or post-mortem findings and no effects on sexual maturation, behavioural performance, or bone measurement. NOAEL was determined to 100 mg/kg/day.

Safety margins based on worst-case exposures in patients identified to date have been presented, indicating low margins to NOAEL in dogs, and higher margins to NOAEL in the 13-week toxicity study in rats.

2.5.4.3. Genotoxicity

Fosdenopterin was without genotoxic potential in vitro and in vivo in the standard battery of tests indicated in ICH S2(R1). TK data were not collected in the in vivo bone marrow micronucleus test. However, based on exposure data from the 13-week study in juvenile animals, exposure levels sufficiently above human levels are expected.

2.5.4.4. Carcinogenicity

No studies have been conducted to assess the carcinogenic potential of fosdenopterin. MoCD Type A is a rapidly progressive disease without treatment options, leading to rapidly progressing neurodegeneration and death within the early years of life due to lack of cPMP. Fosdenopterin is a synthetic replacement for an endogenous molecule (cPMP) with identical core structures to rcPMP. Fosdenopterin has not shown any genotoxic potential and was devoid of preneoplastic properties in long-term toxicity studies with animals dosed throughout the juvenile stages.

2.5.4.5. Reproductive and developmental toxicity

No reproductive or developmental toxicology studies have been performed with fosdenopterin.

2.5.4.6. Toxicokinetic data

TK data are addressed in section 2.5.3 Pharmacokinetics and in section 2.5.4.2 Repeat dose toxicity.

2.5.4.7. Local Tolerance

Potential injection sites reactions were examined in repeat-dose toxicology studies conducted in rats and dogs. No fosdenopterin-related effects were noted following SC or IV administrations.

2.5.4.8. Other toxicity studies

No studies on antigenicity, immunotoxicity, dependence, or metabolites have been conducted.

Impurities in drug substance

There are three specified potential related substance impurities in the fosdenopterin drug substance specifications above the threshold for qualification (0.15%). The impurities are toxicologically qualified by genotoxicity and general toxicity studies, in accordance with the ICH Q3A (R2) guideline.

Impurities in drug product:

The impurity is toxicologically qualified by genotoxicity and general toxicity studies, following the ICH Q3B (R2) guideline.

Phototoxicity

Fosdenopterin is widely distributed following IV dosing, with significant distribution to skin and eye. In vitro and in vivo data have shown that fosdenopterin is phototoxic, resulting in skin reactions and ophthalmological findings in animals at all dose levels.

2.5.5. Ecotoxicity/environmental risk assessment

Table 2. Summary of main study results

Substance (INN/Invented Name): Fosdenopterin hydrobromide (HBr)			
CAS-number (if available): 2301083-34-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Fosdenopterin: pH 5: -2.5 pH 7: -3.0 pH 9: -2.9 Mass balance: pH 5: -2.7 pH 7: -3.4 pH 9: -3.4	Potential PBT: No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined by prevalence	0.00002	µg/L	< 0.01 threshold

Fosdenopterin $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Considering the above data, fosdenopterin is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Primary pharmacology

In vivo studies were conducted in a mouse model of MoCD (MOCS1$^{-/-}$ mice), with phenotypes having similar characteristics and biochemical anomalies as human MoCD Type A patients. When applying parenteral administration to this animal model, plasma SSC is considered a biomarker for disease and disease progression (based on survival, growth and behaviour). Plasma SSC was, however, normalised at lower dose levels and following fewer doses than brain SSC and liver SOX, and is thus considered a less sensitive biomarker for central and hepatic pharmacodynamic effects. Plasma fosdenopterin levels were BLQ within 24h and were thus not correlated with the PD markers.

Extended life span, higher weight gain and normal behaviour was also seen following oral dosing of 500 µg 3 times per week from PND27-70, but there was no documented normalising effect on plasma SSC. This apparent lack of correlation between disease progression and plasma SSC following oral dosing has not been further discussed. In the study report, however, suboptimal dosing to achieve full correction of the metabolic defects has been suggested.

Safety pharmacology

According to ICH S7B, in vitro studies should be GLP-compliant, and the test substance concentrations for in vitro studies should span a broad range, covering and exceeding the anticipated maximal therapeutic plasma concentration. In the GLP-compliant hERG-assay (study 793428), fosdenopterin was only tested at 2 µM, which is significantly below the expected human concentration (free fraction). In an automated screening assay for a number of ion channels (study 190129.PSN), there were no effects of fosdenopterin on the hERG current at concentrations up to 300 µM. Although not GLP compliant, the experiment was performed in accordance with procedures published in peer-reviewed journals and with the Standard Operating Procedures of Charles River Laboratories. Further, fosdenopterin was without QT prolonging effects in GLP-compliant dog studies (studies 2087-001 and 2087-006), and was negative in a clinical thorough QT study (study ORGN001-102). Taken together, fosdenopterin is not considered to have a proarrhythmic potential.

Pharmacodynamic drug interaction

Pharmacodynamic drug interaction studies have not been conducted. No off-target effects have been detected for fosdenopterin in a screening assay comprising 87 receptors, enzymes, ion channels and transporters. Further, no alerts from the provided non-clinical documentation indicate any concern with potential interaction. Thus, the lack of dedicated non-clinical drug interaction studies is considered acceptable.

Pharmacokinetics

Metabolism

In vitro studies provided by the applicant indicate that fosdenopterin is stable in hepatocytes from mouse, rat, dog and human over the 240-min of incubation (studies XT134092 and XT134093), with Compound Z being the only metabolite formed in all species tested. In contrast to this, the briefing document accompanying the CHMP protocol assistance (EMA/CHMP/SAWP/290139/2014) refers to an earlier in vitro study where 5 metabolites were observed in hepatocytes from mouse, rat, dog and human (study HU-0025-DV-HC). M1 (1.8%), M2 (2.2%) and M3 (0.5%) were oxidative metabolites, while M4 (3.9%, glucosylation) and M5 (7.7%, glucuronidation and sulfonation) were phase 2 metabolites. The applicant has clarified that the 5 metabolites observed in HU-0025-DV-HC were due to the instability of fosdenopterin in an initial formulation. Ascorbic acid was included in later formulations and is included in the final product as an antioxidant to improve its stability. In the presence of ascorbic acid, fosdenopterin is stable in hepatocytes from multiple species including human with Compound Z identified as the only metabolite formed.

In vivo studies to address metabolism have not been conducted. This is considered acceptable since no metabolites are detected in vitro, and since fosdenopterin is a synthetic replacement for the endogenous molecule (cPMP) expected to be eliminated and excreted in an identical manner to that of the endogenous molecule.

Excretion

Excretion studies have not been conducted. Fosdenopterin is expected to be eliminated and excreted in an identical manner to that of the endogenous molecule, namely, enzymatic conversion of cPMP to MPT and subsequent formation of MoCo, or spontaneous oxidation of cPMP to Compound Z in aqueous fluids and subsequent excretion primarily in urine. Excretion via urine is supported by tissue distribution studies in rats, where the majority of [14C]-fosdenopterin-derived radioactivity was detected in urine within 24 hours after dosing, and no radioactivity was detected in bile. The lack of excretion studies is considered acceptable.

Toxicology

General toxicity

The MoCo-synthesis is considered highly conserved between species, and cPMP is considered identical between species. Thus, rat and dog are considered relevant species for toxicity studies.

Since physical and chemical analysis indicates that batches are comparable in all tested chemical attributes, lack of non-clinical bridging studies is considered acceptable.

Long-term studies were conducted in juvenile rats (26-week study, dosing from PND7) and juvenile dogs (39-week study, dosing from LD5). Dosing from PND 7 in rats and LD5 in dogs are considered acceptable, in view of the intended paediatric patient population.

Carcinogenicity

MoCD Type A is a rapidly progressive disease without treatment options, leading to rapidly progressing neurodegeneration and death within early years of life due to lack of cPMP. Fosdenopterin is a synthetic replacement for an endogenous molecule (cPMP) with identical core structures to rcPMP. Fosdenopterin has not shown any genotoxic potential and was devoid of preneoplastic properties in long-term toxicity studies with animals dosed throughout the juvenile stages. Considering the above, and in line with 3Rs, carcinogenicity studies are not considered needed for fosdenopterin. A two-year carcinogenicity study in mice is however planned as a post-marketing requirement from FDA. The results from this study will be submitted when finalised.

Reproduction toxicity

No reproductive or developmental toxicology studies have been performed with fosdenopterin. Given the nature of the product, the patient population with reduced life expectancy, physical development, and the lack of available alternative therapies, lack of reproductive toxicity studies preapproval is acceptable. The lack of studies is adequately reflected in the proposed Summary of Product Characteristics (SmPC).

Since fosdenopterin is a synthetic replacement for endogenous cPMP, and no fosdenopterin-related changes were noted on tissues reproductive tract organs/tissues in long-term toxicity studies in rats or dogs, fertility studies are not considered required post-approval.

Clinical efficacy data indicate significantly extended life expectancy with cPMP replacement therapy. Thus, post-approval embryo foetal development (EFD) and pre- and postnatal development (PPND) studies may be needed. Although Nulibry is a replacement therapy for the mother, the foetus may most likely express normal levels of cPMP. If fosdenopterin crosses the placenta, excessive exposure to

cPMP may be a potential concern for the developing foetus. If future data do indicate that the patients will be reproductively capable, conventional studies on reproduction toxicity will be conducted in mice and rabbits, in line with the US FDA post-marketing commitment.

Lack of studies on antigenicity, immunotoxicity, dependence, or with metabolites is considered acceptable for fosdenopterin.

Phototoxicity

Fosdenopterin is phototoxic in vitro and in vivo. Adequate risk minimisation measures are included in the proposed product information.

Environmental risk assessment

$PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L, and is not a PBT substance as log Kow does not exceed 4.5. Therefore, fosdenopterin is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The MoCo synthesis pathway is highly conserved, and cPMP is considered identical between species. Fosdenopterin (free base) is a synthetically derived cPMP with identical core structures to rcPMP, expected to be functionally identical and undergo the same metabolism and disposition as endogenous cPMP.

Overall, primary pharmacodynamic studies support that fosdenopterin can replace endogenous cPMP in a knock-out mouse model of MoCD ($MOCS1^{-/-}$), showing phenotypes with similar characteristics and biochemical anomalies as human MoCD Type A. In these animals, fosdenopterin treatment from PND1 prevented early death. The mice appeared alert and agile, exhibited increased body weights, decreased plasma and brain S-sulfocysteine (SSC) levels and restored liver SOX and xanthine oxidase activities.

No fosdenopterin-related effects were seen on cardiovascular, CNS or respiratory parameters in conventional studies of safety pharmacology, or in safety pharmacology parameters integrated in repeat-dose toxicity studies in juvenile animals.

Pharmacokinetic data from rats and dogs administered parenteral fosdenopterin (SC/IV or IV) indicate dose-proportional systemic exposures without any substantial accumulation, and no apparent sex-related differences in PK parameters. Half-lives were short (generally below 1h), with no quantifiable concentrations beyond 4h after dosing in rats and beyond 6 hours in dogs. In vivo studies of metabolism and excretion have not been conducted, this is justified by the applicant by lack of metabolites in vitro, and by fosdenopterin being a synthetic replacement for the endogenous molecule (cPMP) expected to be eliminated and excreted in an identical manner to that of the endogenous molecule.

Overall, the toxicology programme revealed no major concerns. Long-term studies were conducted in juvenile rats (13- and 26-week study, dosing from PND7) and juvenile dogs (39-week study, dosing from LD5). Maximum feasible doses in the 26-week rat study and the 39-week dog study studies were 5 mg/kg in rats and 10 mg/kg, respectively, limited by low solubility and maximum dose volume. As a follow-up, a 13-week study in juvenile rats was conducted with an alternative vehicle, leading to a higher level of solubility and allowing dosing up to 100 mg/kg/day. No target organ for toxicity was seen in these studies, and no effects were seen on sexual maturation, behavioural performance, or bone parameters. PK data from paediatric patients have not been presented, but safety margins are expected to be moderate to low. Fosdenopterin was negative in a standard battery of genotoxicity studies. Studies on carcinogenicity and reproduction toxicity have not been conducted. Fosdenopterin has shown phototoxic potential, this is adequately reflected in the SmPC.

In conclusion, Nulibry may be granted a marketing authorisation from a non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3. Tabular overview of clinical studies

Study ID Location(s) Study Dates[a] Status	Objectives	Phase Study Design	Drug Product	Dosing Regimen[b] and Treatment Duration	Study Population	Number of Patients
MCD-101 US 06/2013 – 10/2013 Complete	Safety, PK, Dose-finding	Phase 1 Randomized, Blinded, Placebo-controlled, Single-dose, Sequential cohort, Dose-escalation	fosdenopterin	fosdenopterin IV Cohort 1: 0.10 mg/kg Cohort 2: 0.32 mg/kg Cohort 3: 0.90 mg/kg Single dose, Day 1	Healthy Volunteers	Total: 24 fosdenopterin: 18 Placebo: 6
MCD-502 AF, MENA, EU, US, CA 09/2013 – 12/2015 Complete	Natural History	Retrospective and Prospective Natural History Study, Multinational, Multicenter	Not applicable	Not applicable	Paediatric patients with MoCD Type A, B, C, unknown, and isolated SOX deficiency	Total: 65 Type A=37 Type B=16 Other=12 Prospective subset: Type A=14 Type B=7 Other=3
MCD-501 AU, EU, UK, US 11/2012 – 10/2014 Complete	Safety, Efficacy	Retrospective, Noninterventional, Observational, Multinational, Multicenter	rcPMP	rcPMP IV Patients had previously received rcPMP treatment in accordance with named-patient treatment plans	Paediatric patients with MoCD Type A, B, and unknown	Total: 15 Type A=10 Type B=4 Unknown=1
MCD-503[d] AS, EU Started 11/2019 – 9/2020 Complete	Safety, Efficacy, Follow-up	Retrospective, Noninterventional, Observational, Multinational, Multicenter	Not applicable	Not applicable	Patients from MCD-501 and MCD-502 who were alive at study completion	Total: 6

MCD-201 AU, MENA, EU, UK, US Started 04/2014 Ongoing	Efficacy, Safety, PK, PD	Phase 2 Multicenter, Multinational, Open-Label	fosdenopterin	fosdenopterin IV starting dose same as current rcPMP IV dose After 2 months, dose escalated monthly by ⩽ 240 µg/kg/day until: Month 6, not tolerable, or exposure (AUC) exceeds 5490 µg/kg/day Maximum dose 1200 µg/kg/day Daily administration until commercially available or development is stopped	Paediatric patients with MoCD Type A	Type A=8[e]
MCD-202 AS, MENA, EU, UK, US Started 06/2016 Ongoing	Efficacy, Safety, PK, PD	Phase 2/3 Multicenter, Multinational, Open-Label	fosdenopterin	fosdenopterin IV Preterm (GA <37 weeks) Day 1: 525 µg/kg/day Term (GA ⩾37 weeks) Day 1: 700 µg/kg/day Incremental dose increases at Day 28, and Month 3, to maximum of 1200 µg/kg/day, not tolerable or exposure (AUC) exceeds 5490 µg/kg/day Maximum dose 1200 µg/kg/day[g] Daily administration until commercially available or development is stopped	Neonates, infants, and children up to 17 years of age with confirmed or suspected MoCD Type A	Total: 5 Type A=3 Unknown/ type B=2

Abbreviations: -- =no data; AF=Africa; AUC=area under the concentration × time curve; AS=Asia(n); AU=Australia; B=Black or African American; cPMP=cyclic pyranopterin monophosphate; EU=European Union; F=female; GA=gestational age; ID=identification; IV=intravenous; M=Male; MENA=Middle East, North Africa; MoCD=molybdenum cofactor deficiency; NA=North America; O=other; PD=pharmacodynamic; PK=pharmacokinetic; rcPMP=recombinant *Escherichia coli*-derived cPMP; SOX=sulfate oxidase; UK=United Kingdom; US=United States; W=white.

a Date of first to last signed informed consent date.

b Doses listed for the clinical studies are presented as the hydrobromide dihydrate.

d Additional survival data were collected in this study from patients in Studies MCD-501 and MCD-502 who were alive at study completion; these survival data are included in the integrated efficacy analyses and in the Study MCD-503 clinical study report.

e Demographic information was not collected in Study MCD-503; however, as the participants were patients previously enrolled in Studies MCD-501 and MCD-502, the demographics of the patients were known.

g As of Protocol Amendment 3, the dose escalation plan was changed to include a maximum dose of 1200 µg/kg/day to simplify the dosing and titration schedule. Prior to Protocol Amendment 3, the maximum dose was 1300 µg/kg/day.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Biopharmaceutics, bioavailability, or bioequivalence studies were not conducted with Nulibry. This approach has been agreed upon in a pre-submission meeting held with the Rapporteur in June 2021, considering that fosdenopterin is a synthetic analogue of endogenous cPMP. To support the application, one human ascending dose study (Study MCD-101) in healthy volunteers was submitted. Sparse PK sampling from two patients in Study MCD-202 were combined with those of patients in Study MCD-201 (n=8) and were included in the popPK model.

Bioanalytical methods

In general, the analytical methods are well validated. The levels of intracellularly produced cPMP are lower than the lower limit of quantitation (LLOQ) of 5 ng/ml and thus the sensitivity of the analytical assay is considered to be sufficient.

During validation LCMSC 669, maximal long term storage conditions were established to 190 days. The applicant has provided compliance between validated and long-term storage conditions for samples used for bioanalysis in Project RBWK and Project RMCB. The final reports of long term-stability for Project RBWK and Project RMCB have been provided.

Absorption

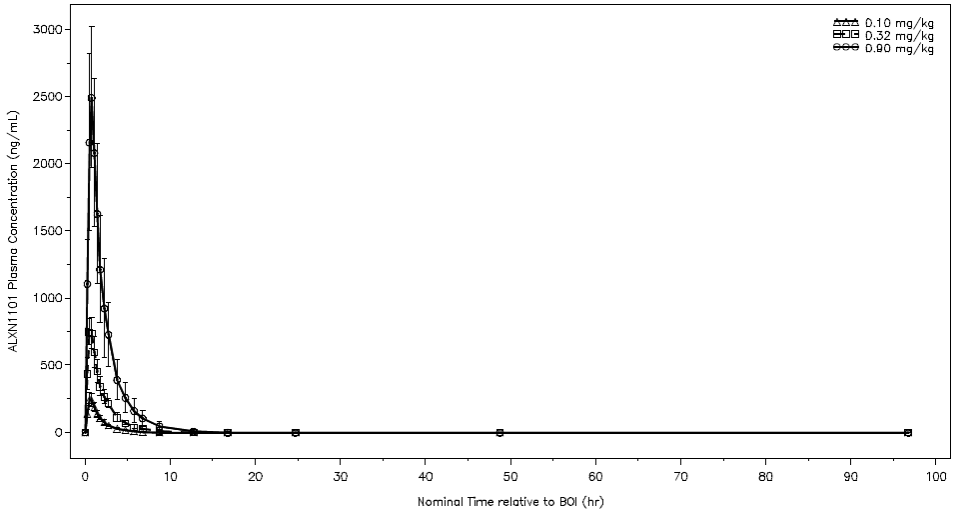
Fosdenopterin exhibited approximate dose proportionality in pharmacokinetics, with C_{max} being reached between 0.5 and 1 hr.

Study MCD-101 was a first-in-human, randomized, blinded, placebo-controlled, single-dose, sequential cohort dose-escalation study in healthy adult volunteers to evaluate the safety, tolerability and PK of single IV doses of fosdenopterin (infusion over 45 min).

The following dose levels were evaluated: Cohort 1, 100 µg/kg, Cohort 2, 320 µg/kg, Cohort 3, 900 µg/kg. Plasma fosdenopterin concentrations were assayed at dense sampling time points for all subjects post beginning of infusion (BOI) until 96.75 hours after dosing. Urine was collected from time 0 to 6 hours post start of dosing post BOI for exploratory analyses of fosdenopterin (ALXN1101) or its metabolites.

PK results are presented in Figure 2 and Table 4.

Figure 2: Mean (SD) Fosdenopterin Concentration-Time Profiles (Study MCD-101).



BOI = Beginning of Infusion
Source: Listing 16.2.6–1.1
Program Name: Figure 14.2–2.1 – Mean (SD) ALXN1101 Plasma Concentrations on Linear Scales – PK Population.sas Date: 2014–04–16T14:14:25

Table 4. Arithmetic Mean (SD) PK Parameters (Non-compartmental Analysis Performed in Study MCD-101) in Healthy Adult Volunteers.

Parameter	100 µg/kg (n=6)	320 µg/kg (n=6)	900 µg/kg (n=6)
C_{max} (ng/mL)	285 (56.5)	873 (98.7)	2800 (567)
t_{max} (h)[1]	0.500 (0.500-0.900)	0.510 (0.500-0.920)	0.875 (0.500-1.08)
Half-life (h)	1.22 (0.162)	1.67 (0.433)	1.64 (0.300)
$AUC_{0\text{-last}}$ (ng*h/mL)	508 (73.7)	1760 (205)	5930 (1820)
$AUC_{0\text{-inf}}$ (ng*h/mL)	523 (74.8)	1790 (213)	5960 (1820)
CL (mL/h/kg)	195 (29.5)	181 (19.5)	167 (66.0)
CL_r (mL/h/kg)	84.0 (10.7)	81.7 (13.5)	79.1 (30.5)
V_d (mL/kg)	341 (73.1)	436 (118)	375 (75.5)

AUC = area under the plasma concentration-time curve; CL = total clearance; CLr = renal clearance;
C_{max} = maximum observed plasma concentration; PK = pharmacokinetic; SD = standard deviation;
t_{max} = time to maximum observed plasma concentration
[1]median (range)
Source: Table 14.2-2-1 (MCD-101 CSR)

Distribution

Estimated volume of distribution (Vd) ranged from 341 to 436 mL/kg.

Elimination

The mean clearance (CL) ranged from 167 mL/hr/kg to 195 mL/hr/kg. with renal clearance accounting for about 45% of total body clearance. However, considering the $t_{1/2}$ of up to 2 hrs and urine collection of up to 6 hrs (post BOI), there were concerns that renal excretion could be underestimated. The applicant has clarified that although urine was collected only up to 2 hrs, the extrapolated AUC was lower than 10% and that underestimation of renal excretion is in a range of approximately 5 to 6%, which is not clinically relevant.

Fosdenopterin is not a substrate for CYP enzymes. Fosdenopterin is predominantly metabolized through non-enzymatic degradation processes to an inactive oxidation product of endogenous cPMP.

Time dependency

Considering $t_{1/2}$ of up to 2 hrs and daily administration, no accumulation is expected upon once daily dosing.

Special populations

Studies have not been conducted to evaluate the pharmacokinetics of fosdenopterin in specific patient populations, identified by race, age, or the presence of renal or hepatic impairment. Therefore, the effect of renal and hepatic impairment on the pharmacokinetics of fosdenopterin is unknown. Renal elimination of fosdenopterin is estimated to be 45% and although it is expected that moderate and severe renal impairment could lead to increased plasma concentrations of fosdenopterin, based on the wide therapeutic index of fosdenopterin, such an increase is not expected to have clinical consequences.

Drug-drug interaction potential

Fosdenopterin does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 isozymes when tested in vitro in human liver microsomes. There was little or no direct time-dependent or metabolism-dependent inhibition of these isozymes.

Fosdenopterin did not demonstrate induction of CYP1A2, CYP2B6, or CYP3A4.

Fosdenopterin does not inhibit efflux or uptake transporters. Inhibition of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1 (20 µM), OAT3, MATE1, and MATE2-K (20 µM) was reported as < 10% at 200 µM, while cPMP demonstrated slight inhibition of MATE2-K (25%) and OAT1 (33%) at 200 µM. These effects are not clinically relevant.

Fosdenopterin is not a substrate of P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, or MATE2-K, and is possibly a weak substrate for MATE1.

Overall, the potential for drug-drug interactions (DDI) is unlikely. Thus no in vivo DDI studies are deemed necessary.

Pharmacokinetics in the target population

Sparse PK samples from two patients in Study MCD-202 were combined with those of patients in Study MCD-201 (n=8) and were included in the popPK model. Pharmacokinetics in the target, paediatric population has not yet been adequately estimated. The final model was the two-compartment model in which the power term for scaling of systemic parameters was estimated to lead to the best objective function. In addition, a maturation function was included in the model to adjust clearance for organ maturation. The maturation function was based on a renal maturation model developed by Rhodin et al. The model in which the power term for scaling systemic parameters was estimated, and the renal maturation factor was applied to 100% of clearance yielded the smallest objective function. This, however, is not in line with the estimated renal excretion of 45% from healthy adult data.

Another limitation of the model is the small sample size of paediatric patients. Of 10 subjects, only two subjects started treatment at birth, limiting the evaluation of the effects of maturational change during the period when it is likely to be changing most rapidly. The target population is likely to be newly-diagnosed subjects in the first days-to-weeks of life.

Furthermore, the sampling regimen typically included a sample at end-infusion and one approximately four hours later. The marked decrease in the second sample suggested that samples 1-2 hours post-

infusion might have provided more insight into the distribution phase (and, thereby, better estimation of area-under-the-curve).

The applicant's final pop PK model did not converge because the limited PK data did not support such an over-parameterized model incorporating IIV for all PK parameters with a full variance-covariance matrix. With only 10 subjects, it is noted that a model is fitted with 9 parameters. As a result of the failed model convergence also no standard error on the model parameters were presented. Four IIV (eta) parameters were estimated, which values ranging from 14 to 79%, which appears reasonable. However, those values were highly correlated.

Body weight is a significant covariate on all four clearance and distribution volume parameters with the same allometric exponent value estimated to be 0.38. It is known from allometric theory that the scaling factor for the volume of distribution parameter differs from the scaling factor for clearance parameters. Therefore, the implementation of body weight in this model does not have a biological basis. In cases of very limited data and potential for extrapolation, fixing the allometric exponents to 0.75 for CL and 1 for V parameters is preferred. This could have resolved the instability of the model.

The standard goodness-of-fit plots appear to capture the data, which is not surprising with a model with 9 parameters (and 10 subjects included). VPCs support the conclusion that despite high variability, many deficiencies of the model and limits of available data, the model is able to capture the bigger trends of the concentration-time curve. Given the limitations of the available data (only n=10), no update of the popPK modelling was requested at this stage.

Simulated exposures are presented also below, according to dosing regimens (Table 5), one for full-term neonates, the other for neonates born prematurely (applying a cut-off of 37 gestational weeks). For subjects enrolling at ≥12 months of age, the starting dose is 0.9 mg/kg daily.

Table 5. Proposed Titration Schedule for Infants < 12 Months (mg/kg, once daily)

	Status at Birth	
Month of Treatment	**Premature**	**Full-Term**
Initial Dosage	0.4	0.55
Month 1	0.7	0.75
Month 3	0.9	0.9

These doses are reported in units of base; all other dosing references in this document refer to units of salt.

Simulations were performed for subjects born at full-term and at 34 weeks, applying these doses at birth, 1 month, 3 months, 12 months, 2 years, and 4 years; fosdenopterin was infused at a rate of 3.75 mg/min in units of salt (2.85 mg/min in units of base). At birth, concentrations were higher at term compared to prematures and differed minimally between males and females (Table 6, Table 7,

Figure **3**). By age 3 months, differences between groups were minimal. Cmax increased with age, the increase slowing at age 2 years.

Table 6. Values for Cmax (i.e. Cend of infusion in ng/mL) for the Proposed Dosing Regimens

		Age (months)					
Maturity	**Sex**	**0**	**1**	**3**	**12**	**24**	**48**
Full Term	Male	1722	2783	4093	5134	5940	6729
	Female	1683	2676	3890	4923	5789	6645
Premature	Male	968	2083	3635	—	—	—
	Female	941	2042	3466	—	—	—

Concentration profiles were not estimated for premature children after 3 months of age.

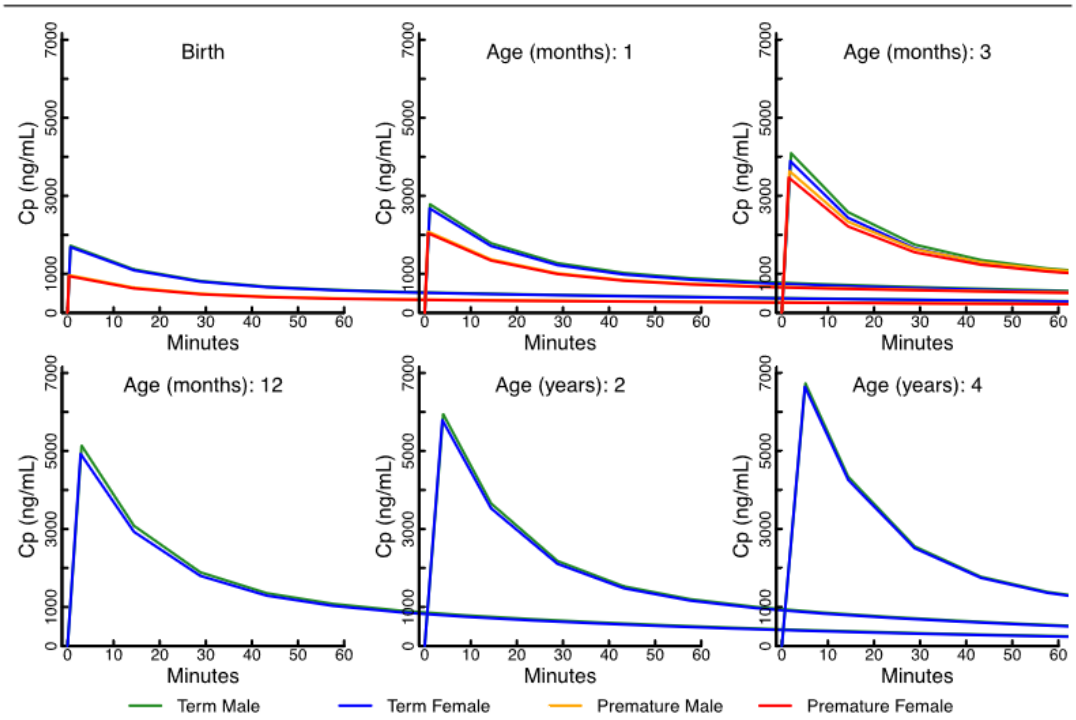
Table 7. Values for AUC (ng/mL • hours) for the Proposed Dosing Regimens

		Age (months)					
Maturity	**Sex**	**0**	**1**	**3**	**12**	**24**	**48**
Full Term	Male	3270	4339	4856	4125	4529	5167
	Female	3197	4167	4600	3936	4396	5088
Premature	Male	2651	4349	5147	—	—	—
	Female	2575	4260	4895	—	—	—

Concentration profiles were not estimated for premature children after 3 months of age.

Figure 3. Fosdenopterin concentration profiles at Successive Ages in Children Born Prematurely and at Full-term.

Weights at each age are the 50t



h percentile from CDC Growth Charts for full-terms and Fenton Growth Charts for prematures

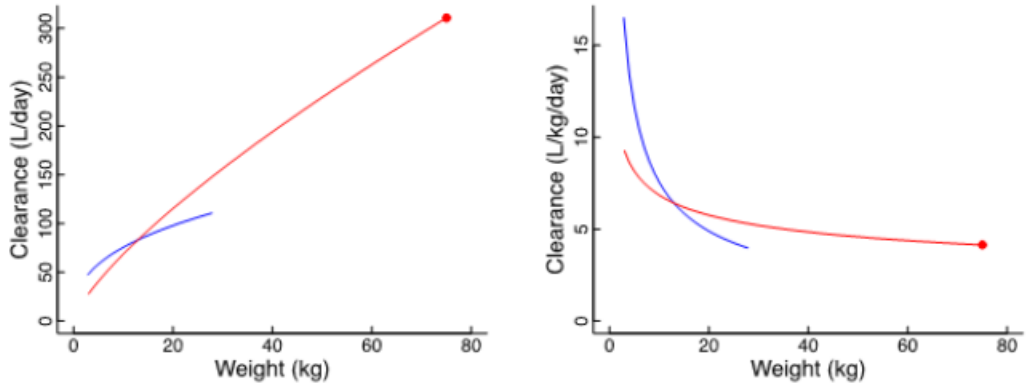
During the PK development the human, ascending dose study was performed. Single doses of 0.1, 0.32 and 0.9 mg/kg were well tolerated and no maximum tolerated dose study was set. The applicant was asked to justify further whether the maintenance dose taken is optimal, bearing in mind that exogenous supplementation provides less than 5% natural concentration in healthy subjects. The applicant explained that the estimates of the therapeutic doses were obtained from non-clinical data on the restoration of molybdenum cofactor (MoCo)-dependent enzyme activity in situations of MoCo deficiency. Based on the non-clinical data, the extrapolation to clinical dosing was performed, aiming the 50% of the activity restoration followed starting dose and the full restoration at the target dose. However, some non-clinical data suggested that the higher doses may have a more significant effect.

Nevertheless, the doses investigated in clinical studies were associated with clinical benefits and an acceptable safety profile. In addition, even if higher efficacy could be expected at the higher doses, the

dose-response studies may be challenging to conduct, bearing in mind the number of patients with MoCD.

The PK parameters were assessed in healthy adults. The data from the patients are scarce. The applicant was asked to discuss the possibility of changes in the PK of fosdenopterin in long–term perspective in children. In their response, the applicant stated that the limitations related to blood volume and other logistics made it impossible to do the extensive PK analysis in the target population. Instead, the PK in the (much younger) target population was assessed using a sparse PK dataset, and PK was analyzed using population PK methods. The PK parameters obtained with the two methods in the two populations were internally consistent as evidenced by the overlap in adult clearance values extrapolated to the paediatric weight range with the paediatric values obtained in the clinical studies (see Figure 4).

Figure 4. Clearance Values for Paediatric Subjects and Adults



Blue line represents pediatric subjects, ignoring the Rhodin factor
Red line represents the allometric extrapolation of the adult value. The red circle represents the value for a 75 kg subject.

In addition, the applicant presented indirect evidence regarding the PK of fosdenopterin, based mainly on the SSC levels. The biochemical efficacy of the fosdenopterin and clinical efficacy did not change over time, and therefore it can be concluded that the risk of PK changes is low.

2.6.2.2. Pharmacodynamics

No dedicated PD studies were conducted. Pharmacodynamic endpoints were included in the studies MCD-501, MCD-201 and MCD-202 (Table 8).

Mechanism of action

Due to a genetic deficiency in the MOCS1 gene, patients with MoCD Type A are unable to produce the precursor substrate cPMP, leading to an absence of molybdenum cofactor (MoCo). This results in a deficiency in MoCo-dependent enzymes, of which sulphite oxidase is the most problematic due to the accumulation of sulphites that are neurotoxic.

Fosdenopterin is a first-in-class cPMP hydrobromide dihydrate which treats MoCD Type A by replacing cPMP and permitting the two remaining MoCo synthesis steps to proceed, with activation of MoCo-dependent enzymes. The restoration of activity from the MoCo-dependent enzyme sulphite oxidase (SOX) leads to the clearance of neurotoxic sulfites and is accompanied by a reduction in the secondary metabolites such as S-Sulfocysteine (SSC).

Primary and Secondary pharmacology

Treatment with cPMP led to a rapid reduction in levels of the MoCD-associated urinary biomarkers of SSC and xanthine normalized to creatinine and an increase in urinary uric acid normalized to creatinine; these improvements were maintained over long term treatment with cPMP. In the untreated control group, normalized urinary SSC and xanthine levels remained elevated over time and levels of normalized urinary uric acid remained low.

Table 8. Summary of First Value, Last Visit and Changes to Last Visit for Urinary Biomarker Levels (Full Analysis Set and Genotype-Matched Analysis Set)(Data cut off 31 Oct 2021).

Parameter (µmol/mmol) Visit Statistic	cPMP-Treated Patients (FAS and GMAS)				Untreated Controls	
	MCD-501 only (N=4)	MCD-201 (N=8)	MCD-202 (N=3)	Total (N=15)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
S-Sulfocysteine/Creatinine[a]						
Baseline, First Value, n	4	8	3	15	22	10
Mean (SD)	343.9 (459.53)	92.5 (113.14)	126.6 (60.08)	166.3 (254.22)	136.3 (87.21)	167.9 (90.45)
Median	138.5	60.2	94.1	89.8	114.3	156.5
Min, Max	67, 1031	12, 364	90, 196	12, 1031	2, 345	62, 345
Last Visit, n	4	8	3	15	22	10
Mean (SD)	15.6 (6.52)	6.2 (3.13)	5.6 (1.78)	8.6 (5.8)	156.6 (100.70)	175.0 (102.35)
Median	17.2	6.0	4.8	7.0	156.5	169.2
Min, Max	7, 21	3, 11	4, 8	3, 21	11, 345	11, 345
Change to Last Visit, n	4	8	3	15	18	9
Mean (SD)	-328.3 (460.74)	-86.3 (114)	-121 (61.13)	-157.7 (253.06)	24.8 (104.61)	7.9 (102.90)
Median	-124.5	-51.6	-86.5	-82.5	2.7	-10.4
Min, Max	-1017, -47	-361, -8	-192, -85	-1017, -8	-175, 317	-175, 153
Xanthine /Creatinine[a]						
Baseline, First Value, n	4	8	3	15	23	13
Mean (SD)	270.4 (51.62)	244.9 (214.60)	195.3 (13.01)	241.8 (155.96)	315.8 (205.83)	327.3 (194.44)
Median	286.0	205.6	199.7	205.4	308.0	277.0
Min, Max	196, 313	26, 577	181, 205	26, 577	0, 764	0, 678
Last Visit, n	4	8	3	15	23	13
Mean (SD)	34.6 (44.61)	10.8 (3.41)	14.8 (3.39)	17.9 (23.33)	338.2 (233.17)	364.5 (201.64)
Median	17.3	10.8	16.2	11.4	277.0	338.8
Min, Max	4, 100	6, 16	11, 17	4, 100	6, 937	6, 678
Change to Last Visit, n	4	8	3	15	18	10
Mean (SD)	-235.8 (96.10)	-234.1 (217.01)	-180.5 (14.79)	-223.9 (161.43)	28.6 (150.65)	48.4 (171.77)
Median	-268.7	-191.8	-188.8	-189.2	6.2	9.6
Min, Max	-310, -96	-570, -16	-189, -163	-570, -16	-242, 409	-242, 409

Uric Acid/Creatinine[a]						
Baseline, First Value, n	4	8	3	15	20	12
Mean (SD)	381.1 (396.39)	365.7 (305.79)	660.8 (398.25)	428.8 (342.83)	99.1 (165.11)	53.0 (60.00)
Median	353.3	366.5	794.6	537.4	56.7	16.0
Min, Max	11, 807	18, 714	213, 975	11, 975	7, 750	7, 168
Last Visit, n	4	8	3	15	20	12
Mean (SD)	565.4 (350.17)	464.3. (156.43)	540.0 (104.18)	506.4 (205.69)	45.0 (39.28)	37.7 (43.03)
Median	556.0	482.4	595.1	528.6	33.6	15.0
Min, Max	239, 911	224, 691	420, 605	224, 911	4, 115	4, 115
Change to Last Visit, n	4	8	3	15	16	8
Mean (SD)	184.3 (740.86)	98.6 (319.65)	-120.7 (299.35)	77.6 (439.81)	-67.7 (188.42)	-22.9 (67.57)
Median	176.9	88.6	-189.5	-23.2	-8.5	-4.7
Min, Max	-517, 900	-314, 590	-380, 207	-517, 900	-735, 67	-165, 67

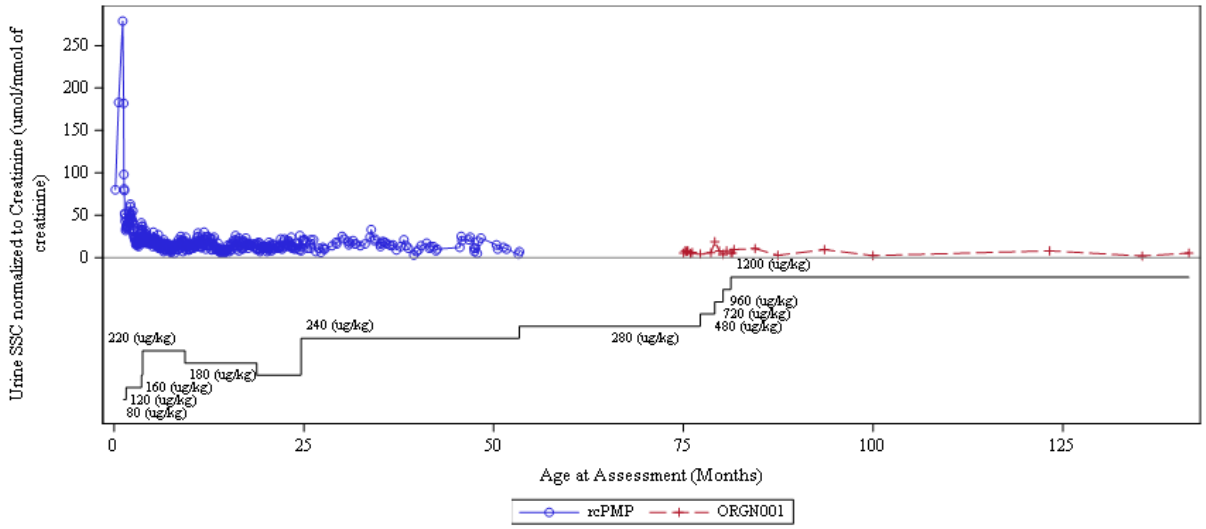
Abbreviations: cPMP=cyclic pyranopterin monophosphate; FAS=Full Analysis Set; GMAS=Genotype-Matched Analysis Set; Max= maximum; Min=minimum; NA = not applicable; SD=standard deviation. Note: The six patients that were treated with rcPMP on Study MCD-501 and went on to enroll in Study MCD-201 are only presented in the MCD-201 column. a Pathological values of biomarkers: S-sulfocysteine (> 50 µmol/mmol creatinine), xanthine (> 70 µmol/mmol creatinine), uric acid (< 100 µmol/mmol creatinine) (Blau, 2014).

Exposure-response analysis (PK/PD)

Study MCD-501 included the largest dataset of pre-treatment biomarker data; however, no exposure data was obtained in this study. Exposure data was available from study MCD-201, allowing the conduct of an exposure-response analysis, albeit not including pre-treatment (concentration = 0) data or data at drug doses ≤ 240 µg/kg/day and with the limitation that SSC and fosdenopterin were often not obtained on the same day.

The time course of urine SSC levels from pre-treatment to substrate replacement therapy with rcPMP followed later by fosdenopterin administration after enrolment into the MCD-201 study is shown for one such patient in Figure 5. Lastly, Study MCD-202 has enrolled three patients with confirmed MoCD Type A, one of whom contributed an entire dataset of PK and PD data.

Figure 5: Urine SSC Levels Over Time in one patient Enrolled in Study MCD-501 and MCD-201



ISE = integrated summary of effectiveness; SSC = S-sulfocysteine

Two types of exposure-response analyses were conducted; analyses were based on observed values and modelled values. The first is presented here.

Analyses were conducted for each matrix (plasma, urine). For each subject, Cmax (end-infusion) values for each sampling session were identified. The corresponding values for each biomarker were identified. "Corresponding" was defined as follows:

1. A sample was obtained on the same calendar day.

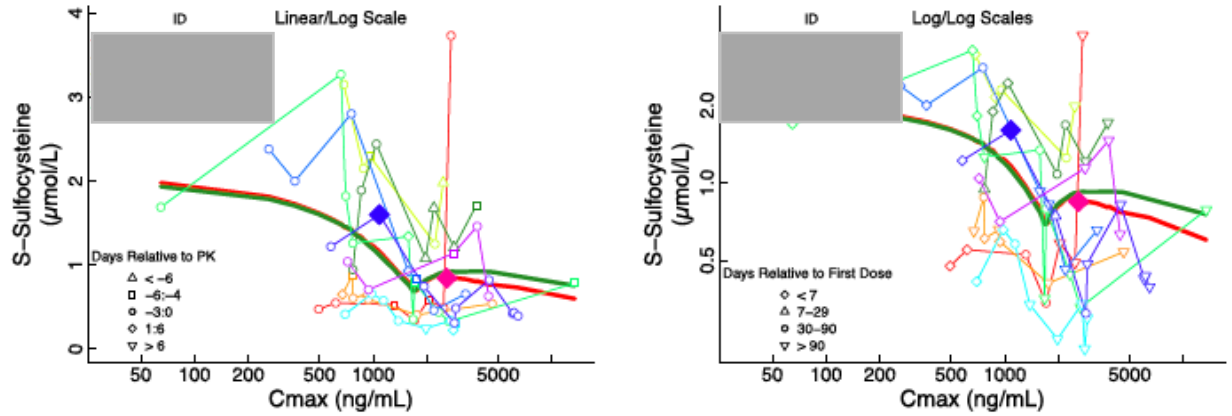
2. If no biomarker sample was obtained on the calendar day of the pharmacokinetic sample, the sample obtained in closest proximity (before or after; but never before the first dose of fosdenopterin) was identified.

3. If no biomarker sample was obtained within 10 calendar days of the pharmacokinetic sample, the Cmax value was not included in this analysis.

Results Exposure-response for biomarkers in study MCD-201 and MCD-202 based on observed Cmax values.

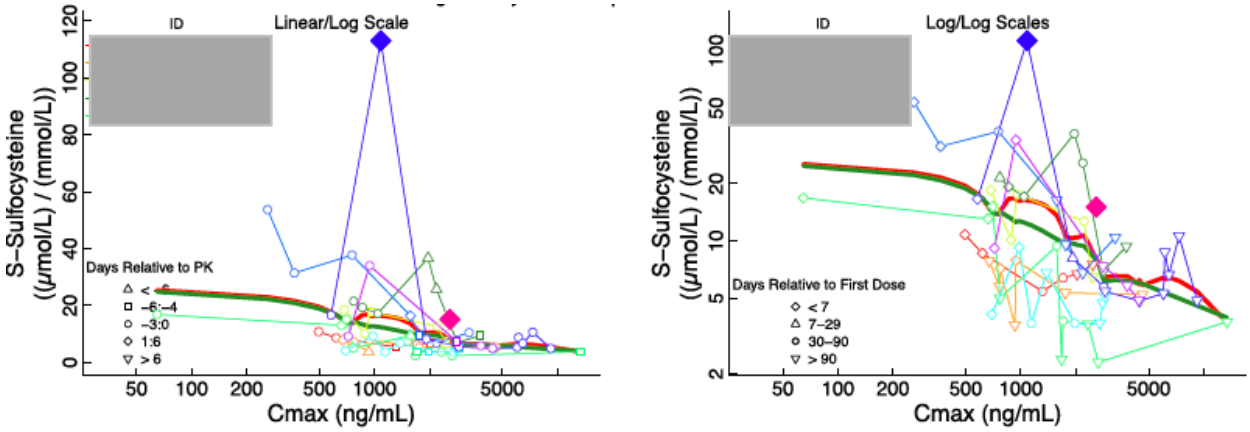
Higher exposure to fosdenopterin was associated with a lower value of plasma S-sulfocysteine, as can be observed for the composite of all subjects in Figure 6. Higher exposure to fosdenopterin was associated with a lower value of urine S-sulfocysteine (Figure 7).

Figure 6: Study MCD-201, Study MCD-202: Exposure-Response for Plasma S-Sulfocysteine.



Color-coded thin lines connect values for each subject; the larger filled symbol marks a sample obtained within the few hours following the first dose in two subjects. Thick lines are smoothers (Supersmoother); green excludes two subjects. Symbols indicate the interval between the pharmacokinetic and biomarker samples (left) or when, relative to the first dose, the pharmacokinetic sample was obtained (right).

Figure 7: Study MCD-201 and MCD-202: Exposure-Response for Urine S-Sulfocysteine (Normalized by Urine Creatinine).

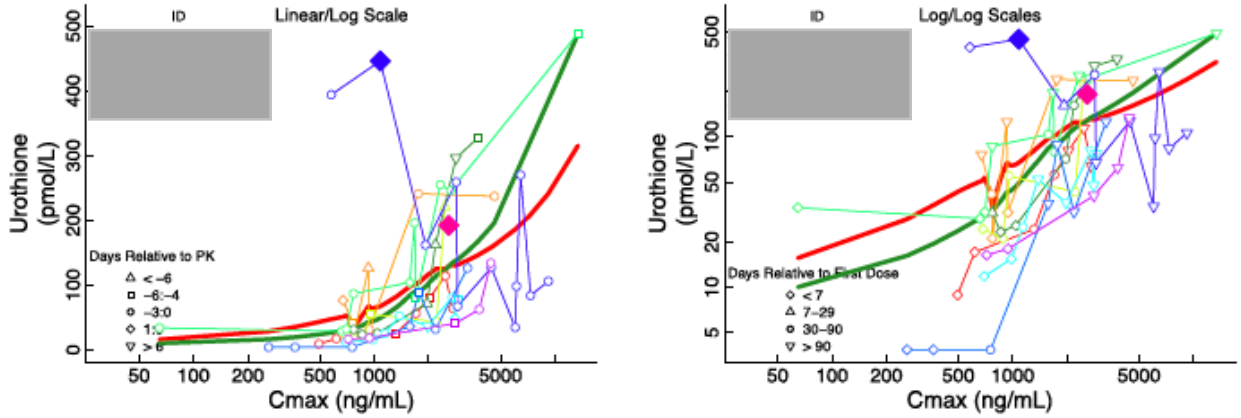


Color-coded thin lines connect values for each subject; the larger filled symbol marks a sample obtained within the few hours following the first dose in two subjects. Thick lines are smoothers (Supersmoother); green excludes two subjects. Symbols indicate the interval between the pharmacokinetic and biomarker samples (left) or when, relative to the first dose, the pharmacokinetic sample was obtained (right).

There was a slight positive trend in the relationship between plasma uric acid and fosdenopterin Cmax. There was no relationship between urine uric acid and fosdenopterin Cmax.

There was no relationship between xanthine and fosdenopterin Cmax. There was a strong positive relationship between urothione and fosdenopterin Cmax (Figure 8).

Figure 8: Study MCD-201, Study MCD-202: Exposure-Response for Plasma Urothione



Color-coded thin lines connect values for each subject; the larger filled symbol marks a sample obtained within the few hours following the first dose in two subjects. Thick lines are smoothers (Supersmoother); green excludes two subjects. Symbols indicate the interval between the pharmacokinetic and biomarker samples (left) or when, relative to the first dose, the pharmacokinetic sample was obtained (right).

2.6.3. Discussion on clinical pharmacology

Biopharmaceutics, bioavailability, or bioequivalence studies were not conducted with Nulibry. This approach has been agreed upon in a pre-submission meeting held with the Rapporteur, considering that fosdenopterin is a synthetic analogue of endogenous cPMP.

To support the application, one human ascending dose study (Study MCD-101) in healthy volunteers was submitted. Sparse PK sampling from two patients in Study MCD-202 as combined with those in Study MCD-201 (n=8) and included in the popPK model. VPCs support the conclusion that despite high variability, many deficiencies of the model and limits of available data, the model is able to capture the bigger trends of the concentration-time curve. Given the limitations of the available data (only n=10), no update of the popPK modelling was requested at this stage. The PK parameters obtained in healthy adults and patients were consistent.

The effect of renal and hepatic impairment on the pharmacokinetics of fosdenopterin is unknown. Renal elimination of fosdenopterin is estimated to be 45%. Although it is expected that moderate and severe renal impairment could lead to increased plasma concentrations of fosdenopterin, based on the wide therapeutic index of fosdenopterin, such an increase is not expected to have clinical consequences.

The potential for drug-drug interactions is low.

No dedicated PD studies were conducted. Plasma and urine biomarkers were collected in studies MCD-501, MCD-201 and MCD-202.

Study MCD-501 was a retrospective study in patients with MoCD Type A treated with rcPMP under a named-patient program. Study MCD-201 and MCD-202 are two ongoing prospective studies in paediatric patients with MoCD Type A treated with fosdenopterin. Patients in study MCD-201 were pre-treated with rcPMP in study MCD-501 and the named patient program.

The mechanism of action of fosdenopterin is well established. Due to mutations in the MOCS1 gene, patients are unable to synthesize cPMP, a substrate necessary for molybdenum cofactor production. Without MoCo, MoCo dependent enzymes, such as sulphite oxidase and xanthine oxidase, do not function. The accumulation of sulphites and secondary metabolite SSC is neurotoxic, giving rise to the

clinical phenotype. The main goal of treatment with fosdenopterin is restoring MoCo synthesis and facilitating the restoration of sulphite oxidase activity, thereby preventing neuronal damage.

MoCD type A is associated with decreased uric acid and urine SSC and xanthine levels. In addition, urothione, a degradation product of MoCo is typically very low. Since these biochemical markers are direct reflections of MoCo absence and SOX and xanthine oxidase deficiency, these markers are considered appropriate to investigate the pharmacodynamic effect of fosdenopterin.

Patients in study MCD-201 were pre-treated in study MCD-501, thus, MCD-201 baseline values reflect rcPMP treatment. After the switch to fosdenopterin, plasma and urinary SSC remained low and relatively stable throughout the study, indicating therapeutic equivalence between rcPMP and fosdenopterin.

Although some patients showed transient increases in plasma SSC during the study, the reason is unknown; in general, all patients were within the normal range for SSC most of the time. The PD effect of fosdenopterin was demonstrated in the treatment-naïve patients enrolled in study MCD-202, for whom rapid (within days) decreases in serum SSC were observed after initiation of treatment.

Normalization of plasma and urinary xanthine levels were observed in cPMP treated patients. Some control patients in study MCD-502 had a very low urinary xanthine level, which is not usually observed in MoCD type A patients. However, the complete clinical picture and the genetic diagnosis confirmed MoCD type A.

Plasma and urinary uric acid levels changed minimally over time and showed a large variation. Uric acid levels at baseline were high in the treated patients compared to the natural history controls, which might explain why no clear increase was visible upon treatment initiation. In the first days of life, when most baseline values were obtained in treated patients, uric acid can be normal due to maternal transmission.

Plasma urothione tended to increase over time in study MCD-201, consistent with the dose-escalation regimen. The applicant reports that the one treatment naïve patient in study MCD-202 showed a decrease in urothione plasma levels upon the treatment, coinciding with the clearance of maternal circulating urothione.

The applicant has not discussed potential immunogenicity, formation of anti-drug antibodies (ADAs) and the effects on safety and efficacy. Since fosdenopterin is a small molecule, it is assumed that immunogenicity will be low.

No off-target effects are expected since fosdenopterin is a substrate replacement therapy.

PD interactions with concomitant medications are not considered likely.

The pharmacodynamic effect of fosdenopterin is not expected to be affected by genotype. In addition, the PD response in one late onset patient included in study MCD-202, resembled that of the early-onset patients.

In studies MCD-201 and MCD-202, dose escalations were instated, based on preclinical studies in juvenile mice which showed that the fosdenopterin dose that normalizes plasma SSC might not be sufficient to fully restore liver SO activity and that higher doses might be needed to achieve an optimal clinical outcome. This is in concurrence with the PK/PD data, which show that low doses of fosdenopterin were generally sufficient to restore biochemical markers, and no large additional effect was seen with increased dose.

Exposure-response analysis showed that higher fosdenopterin exposure was associated with lower plasma and urine SSC levels. No relationship was found between plasma and urinary xanthine levels. There was a slightly positive trend for plasma uric acid but not for urine uric acid. There was a strong

positive effect of higher fosdenopterin exposure on plasma urothione. This data has several limitations since exposure, and PD parameters were only collected routinely in studies MCD-201 and MCD-202 and PK and PD samples were often not obtained on the same day. This issue could have been overcome by adequate performance of the population pharmacokinetic model as observed concentrations/ exposures could be extrapolated to the time/day of PD sample collection.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology package is limited, which is acceptable considering the nature of fosdenopterin. Although pharmacokinetic data in the paediatric population is scarce, it is consistent with the healthy adult population.

The PD effect of fosdenopterin is considered to be sufficiently demonstrated and supports the mechanism of action of fosdenopterin. In addition, exposure-response analysis indicated that higher fosdenopterin exposure was associated with lower plasma and urine levels.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

No dedicated dose-response studies were conducted. Therefore, the proposed dose is primarily based on pre-clinical studies, PK data and in part on the ongoing clinical studies. The justification of the dose used in the clinical studies and the proposed SmPC is briefly discussed here.

The proposed dosing schedule for fosdenopterin in the SmPC is:

For patients less than 1 year of age who are preterm neonates (gestational age < 37 weeks), the recommended starting dose of fosdenopterin 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, as shown in Table 9.

For patients less than 1 year of age who are term neonates (gestational age $\geqslant$ 37 weeks), the recommended starting dose of fosdenopterin 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, as shown in Table 9.

Table 9. Starting dose and titration schedule of Nulibry for patients less than one year of age by gestational age

Titration schedule	Preterm neonate (gestational age less than 37 weeks)	Term neonate (gestational age 37 weeks and above)
Initial dose	0.40 mg/kg once daily	0.55 mg/kg once daily
Dose at month 1	0.70 mg/kg once daily	0.75 mg/kg once daily
Dose at month 3	0.90 mg/kg once daily	0.90 mg/kg once daily

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

The proposed regimen considers the patient's age at initiation of treatment and gestational age (GA). Throughout the MAA submission documents, the fosdenopterin doses referenced are based on the salt form of the compound (i.e., fosdenopterin hydrobromide [HBr]). The proposed labelling will include dosing for fosdenopterin free base. Table 10 provides fosdenopterin HBr dose levels as referred to throughout the MAA and the corresponding dose levels for the free base both in µg/kg; the table also includes the conversion to mg/kg.

Table 10. Fosdenopterin HBr Doses Administered in Clinical Trial and Equivalent Doses for the Free Base with Proposed Label Dosing in µg/kg and mL/kg.

Dose of Fosdenopterin HBr (µg/kg)	Equivalent Fosdenopterin in Free Base Form (µg/kg)	Origin's Proposed Label Dosing for Fosdenopterin (FB) (µg/kg)[1, 2]	Origin's Proposed Label Dosing for Fosdenopterin (FB) (mg/kg)[2]
240	182	-	-
480	363	-	-
525	397	400	0.40
700	530	550	0.55
720	545	-	-
900	681	700	0.70
960	726	-	-
1000	756	750	0.75
1200	908	900	0.90
1300	983	-	-

Abbreviations: - = no proposed dose; HBr = hydrobromide; FB = free base
1 Proposed doses are rounded to the nearest 50 µg of fosdenopterin in free base form to minimize potential dosing/medication errors
2 Proposed doses include values dependent on patient's gestational age at the time of birth

In the clinical studies, a dose titration scheme was used for most patients who received rcPMP and for all patients who received fosdenopterin. The dosing regimen in patients treated with rcPMP was guided by clinical improvement and SSC and thiosulfate urine levels. Additionally, data from a study in juvenile mice showed that fosdenopterin reduced plasma SSC levels and restored liver SO activity in a dose-dependent manner. The effect of plasma SSC reduction plateaued at 1.1 mg/kg/day. However, the effect of liver SO activity restoration only reached a plateau at a higher dose of 4.4 mg/kg/day. This study indicated that the fosdenopterin dose that normalizes plasma SSC might not be sufficient to fully restore liver SO activity and that higher doses may need to be explored to achieve an optimal clinical outcome. Based on the above observations, an intra-patient dose escalation scheme was implemented in study MCD-201. Patients started fosdenopterin IV infusions at the same dose level as their current dose of rcPMP administered at a rate of 1.5 mL/minute. After 2 months of treatment with fosdenopterin, dosing with fosdenopterin increased every month by no more than 240 µg/kg/day if the patient's clinical, PK, and safety assessments were permitted, including the absence of signs and symptoms of drug-related toxicity.

The maximum dose of fosdenopterin in Study MCD-201 was 1200 µg/kg/day, and in Study MCD-202 was 1300 µg/kg/day prior to a November 2019 protocol amendment (thereafter, the maximum dose was 1200 µg/kg/day to simplify the dosing and titration schedule).

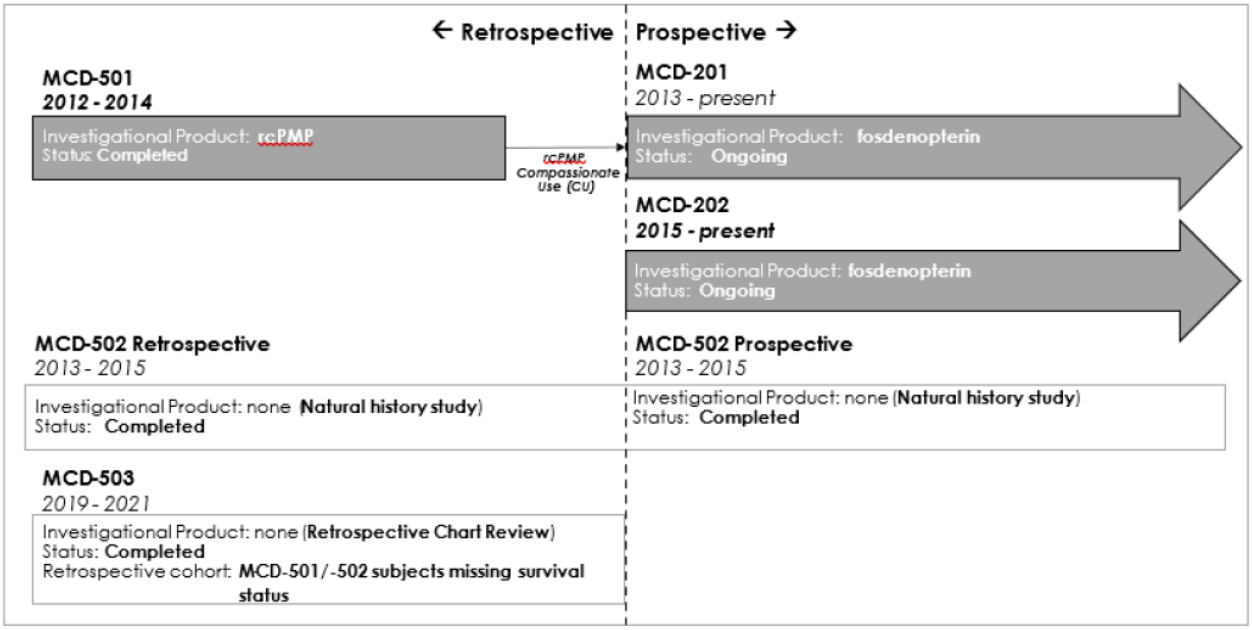
2.6.5.2. Main study(ies)

The claimed indication for fosdenopterin is "treatment of MOCD type A".

The applicant conducted 5 clinical studies (Figure 9) to support the proposed indication. The studies were conducted with recombinant cPMP (rcPMP, in study MCD-501) and fosdenopterin (cPMP, in study MCD-201 and MCD-202), which are considered to have identical active moieties (see quality AR). Two studies (study MCD-502 and 503) were aimed at collecting retrospective data to form a natural history comparator cohort for the integrated efficacy analysis.

Since the pivotal evidence comes from the integrated efficacy analysis from studies MCD-501, MCD-MCD-201, MCD-202 and natural history studies MCD-502 and MCD-503, the methodology of these studies will be described hereunder main studies. In the result section, the integrated efficacy data will be presented instead of the individual results of the studies.

Figure 9: Overview of clinical studies



Integrated efficacy analysis.

Methods

Study MCD-501 was a retrospective, observational, noninterventional data collection study for patients with MoCD type A who have been previously treated with recombinant cPMP in a named patient program.

Study MCD-201 is an ongoing, Phase 2, multicenter, multinational, open-label study designed to evaluate the safety and efficacy of fosdenopterin administered infants and children with MoCD Type A pre-treated with rcPMP. The study also includes intrapatient dose escalation to determine the safe starting dose for future studies. The initial treatment period was 6 months, after which an extension period followed in which patients were continued to be treated and followed.

Study MCD-202 is an ongoing prospective, multicenter, multinational, open-label study designed to evaluate the efficacy and safety of fosdenopterin in patients with MoCD Type A. The main study period

consisted of a 12-month treatment period, after which patients were followed up for 36 months in a long term extension part. After 36 months, patients continued to be followed every 6 months.

Study MCD-502 was a multinational, multicenter, natural history study of patients with MoCD or isolated SOX deficiency. Complete medical history through the time of enrolment was collected retrospectively for all patients.

Study MCD-503 was a follow-up data collection study where a single study coordination center managed multiple sites; data from secondary data sources were collected and provided to support evidence generation for global marketing applications. The aim was to collect survival data, and neuroimaging data for patients enrolled in studies MCD-502 and MCD-501.

Study Participants

Study MCD-501 included male and female patients of any age with MoCD Type A, suspected Type A, or Type B who previously received rcPMP only by IV route of administration and for whom parents or legal guardians voluntarily provided written informed consent.

Study MCD-201

Main Inclusion Criteria

- Male or female patients with a genetically confirmed diagnosis of MoCD Type A (*MOCS1* mutations).
- Currently treated with rcPMP infusions through named patient use with rcPMP.

Study MCD-202

Main Inclusion Criteria

- Male or female neonatal (1 to 28 days of age, inclusive, at the time of fosdenopterin administration, with day 1 of age corresponding to the day of birth), infant (29 days to < 2 years of age) or child patients (2 to 5 years of age [inclusive]) with MoCD Type A, previously untreated with fosdenopterin or treated with fosdenopterin through the compassionate use.
- In neonates, diagnosis of MoCD Type A, based on:
    - Prenatal genetic diagnosis, or
    - Onset of clinical and/or laboratory signs and symptoms consistent with MoCD Type A (e.g., seizures, exaggerated startle response, high-pitched cry, axial hypotonia, limb hypertonia, feeding difficulties, elevated urinary sulfite and/or SSC, elevated xanthine in urine or blood, or low or absent uric acid in the urine or blood) within the first 28 days after birth
- In infants or children, diagnosis of MoCD Type A, based on:
    - Confirmed genetic diagnosis (genetic confirmation of the diagnosis of MoCD Type A may have been obtained after initiation of fosdenopterin therapy in certain cases), biochemical profile, and clinical presentation consistent with MoCD Type A.

Study MCD-502

Both living and deceased patients of any age were considered for study inclusion.

Main Inclusion criteria:

- Documented clinical and biochemical diagnosis or genetic diagnosis of MoCD or isolated SOX deficiency. Biochemical criteria were either 1) high urine, serum, or plasma levels of SSC or 2) a positive urine sulfite dipstick in at least 2 samples.

Treatments

Study MCD-501: this study was a noninterventional study. Patients had previously received rcPMP treatment following the named-patient treatment plans.

Study MCD-201

During the 6-month initial treatment period, patients began daily IV infusions of fosdenopterin on Study Day 1; the Day 1 dose was matched to their current rcPMP dose. Patients received their first dose of fosdenopterin approximately 24 hours after their last treatment with rcPMP. No further treatments with rcPMP were allowed during the study.

The study drug was received in the hospital on Days 1 to 7. After hospitalization, patients continued to receive daily infusions of fosdenopterin at home.

If the starting dose of fosdenopterin was not tolerated or exposure results exceeded the no observed adverse effect level (NOAEL) AUC of 5490 ng•hr/mL, the dose was to be reduced by 25% (if not tolerated) or to a level that was expected to result in exposure below the NOAEL AUC. After the first 2 months of treatment with fosdenopterin, dose-escalation occurred monthly, with the exception of unscheduled dose adjustments, until either (1) Day 180, (2) the patient reached a dose that was not tolerated, (3) the patient's exposure exceeded that of the NOAEL AUC of 5490 ng•hr/mL, or (4) the patient's exposure following dose escalation was predicted to exceed that of the NOAEL of 5490 ng•hr/mL, whichever came first, upon recommendation by the SRC/DMC. Dosing with fosdenopterin increased every month by no more than 240 µg/kg/day. Pharmacodynamic and safety laboratory assessments were repeated 7 days after dose escalation.

During the extension period, patients continued to receive uninterrupted daily dosing of fosdenopterin at their final tolerated dose based on the dose-escalation period. All doses were administered by IV infusion at a rate of 1.5 mL/minute.

Study MCD-202

Daily IV infusions of fosdenopterin began on Day 1 at either 700 µg/kg (term neonates, infants, and children) or 525 µg/kg (preterm neonates) at an infusion rate of 1.5 mL/min. The dose of fosdenopterin was then escalated to a maximum of 1300 µg/kg.

Dosing began as soon as possible after birth for neonate patients and was based on a patient's GA. Day 1 dosing for term (≥ 37 weeks GA) and preterm (< 37 weeks GA) neonates began with fosdenopterin IV infusions of 700 and 525 µg/kg/day, respectively. For all patients, the first dose adjustment was scheduled to occur at Day 28 with incremental increases up to 1300 µg/kg/day by Month 9. However, dosing may have been escalated on or before Day 28, based on the investigator and SRC/DMC review of all available data.

If the patient's Day 1 AUC was greater than the upper limit of the target AUC range (5490 ng•hr/mL), a dose decrease was recommended by the percentage that the individual AUC was greater than the midpoint of the target AUC range (4750 ng•hr/mL). If the patient's Day 1 AUC was less than the lower bound of the 95% confidence interval (CI) of the lower limit of the target AUC range (4000 ng•hr/mL), a dose increase was recommended by the percentage that the individual AUC was less than the midpoint of the target AUC range (4750 ng•hr/mL).

Study MCD-502 and MCD-503

This study was limited to data collection; no investigational medicinal product or any other exploratory therapy was administered.

Objectives

Study MCD-501

The primary objective of this retrospective observational study was to assess the safety and efficacy of prior administration of intravenous (IV) rcPMP in patients with a genetically confirmed diagnosis of MoCD Type A or who were suspected to have a diagnosis of MoCD Type A based on signs and symptoms at the time of rcPMP treatment initiation.

Study MCD-201

The primary objective of this clinical study was to evaluate the safety of fosdenopterin over the first 6 months of treatment.

The secondary objectives of this clinical study were to:

- Characterize the PK of increasing doses of fosdenopterin
- Evaluate the effect of fosdenopterin on urine and blood SSC levels
- Evaluate the effect of fosdenopterin on neurologic, motor, and cognitive functions
- Evaluate the effect of fosdenopterin on CNS structure
- Evaluate the long-term safety of fosdenopterin

The exploratory objective of this clinical study was to describe the effect of fosdenopterin on MoCD-associated urine and blood biomarker levels, including, but not limited to, uric acid and xanthine.

Study MCD-202

The primary objective of this clinical study was to evaluate the safety and efficacy of fosdenopterin in neonate, infant, and pediatric patients with MoCD Type A who were either treatment-naïve or who had received compassionate use fosdenopterin.

The secondary objectives of this clinical study were the following:

- To evaluate the effect of fosdenopterin on MoCD Type A-associated urine and blood biomarker concentrations.
- To evaluate the effect of fosdenopterin on growth and development using age-appropriate assessments
- To evaluate the effect of fosdenopterin on paediatric measures of functional ability and activities of daily living
- To characterize the PK of fosdenopterin and the impact on pharmacodynamic (PD) biomarkers

The exploratory objectives of this study were the following:

- To identify clinical measures that may be useful for characterizing MoCD Type A
- To further characterize changes in MoCD Type A-associated urine and blood biomarker concentrations

Study MCD-502

The primary objective of the study was to characterize the natural history of MoCD Type A, the most common subtype of MoCD, in terms of survival.

The secondary objectives of the study were as follows:

- To evaluate levels of the biochemical markers SSC, uric acid, and xanthine in blood and urine over time in patients with MoCD and isolated SOX deficiency
- To quantitate the natural history of MoCD Type A, Type B, Type C, unspecified type, and isolated SOX deficiency in terms of changes in head circumference, seizure frequency, and neurocognitive outcomes
- To evaluate changes in central nervous system morphology, as measured by brain magnetic resonance imaging (MRI), in patients with MoCD and isolated SOX deficiency
- To correlate biochemical marker levels with changes in head circumference, seizure frequency, neurocognitive outcomes, and MRI findings
- To quantitate the natural history of MoCD Type B, Type C, unspecified type, and isolated SOX deficiency in terms of survival

Outcomes/endpoints

An overview of the measures of efficacy in the clinical studies is presented in Table 11. A short description of some endpoints is included below.

Efficacy endpoints included the following:

- Change from baseline in urine and blood SSC levels
- Change from baseline in clinical findings from neurological examination
- Change from baseline in age-appropriate motor and cognitive assessments (Bayley Scales of Infant and Toddler Development Third Edition [Bayley-III]. The Bayley-III was administered to assess changes in gross motor, fine motor, language, and cognitive development. The Bayley-III was administered to children 3 years of age and under and to patients with severe developmental delay for whom the WPPSI-IV was not an appropriate assessment.
- Gross Motor Function Classification System-Expanded and Revised [GMFCS-E&R]. The GMFCS-E&R is a 5-level classification system that describes the gross motor function of children and youth (up to 18 years of age) on the basis of their self-initiated movement with particular emphasis on sitting, walking, and wheeled mobility for children with impaired motor skills. Children with motor functions similar to those classified in Level I can generally walk without restrictions but tend to be limited in some of the more advanced motor skills. Children with motor function classified as Level V have very little voluntary control of movement, no means of independent mobility, even with assistive technology, are generally transported by their caregivers directly or in a wheelchair, and require assistance for all activities of daily living.
- Wechsler Preschool and Primary Scale of Intelligence– Fourth Edition [WPPSI-IV]). The WPPSI-IV is an intelligence measure designed for children ages 2 years and 6 months to 7 years and 7 months that comprises 15 subtests from which composite and age equivalent scores are derived. For patients with severe developmental delay, the WPPSI-IV may not have been an appropriate assessment, and therefore, the Bayley-III may have been administered instead.

- Change from baseline in seizure frequency. At Screening, the patient's parent or legal guardian was asked to recall the frequency of seizures over the prior month and the patient's history of seizure medication, including the start and stop dates, dose, and frequency of each seizure medication. If the patient did have seizures, the patient's parent or legal guardian was given a paper diary to record the frequency of seizures and any changes in seizure medication for the entire duration of the study. Data from the diary were reported at each study visit.
- Change from baseline in neuroimaging. MRI performed at the time points shown in Table 11 if the patient's clinical condition allowed. An MRI at Month 12 and beyond was optional if the patient's clinical status had not changed since the MRI at Month 6. Additional scans may have been requested as needed.
- Changes in growth parameters (body weight, body length, head circumference)
- Change from baseline in feeding patterns

Table 11. Assessment of Measures of Efficacy Across Studies

Study:	**MCD-502[a] Natural History**		**MCD-501[a]**	**MCD-201**	**MCD-202**
Treatment:	**None**		**rcPMP**	**Nulibry**	**Nulibry**
Data Collection:	**Retrospective**	**Prospective**	**Retrospective**	**Prospective**	**Prospective**
Biomarkers:					
Urine Biomarkers:	SSC, UA, Xanthine, Creatinine	SSC, UA, Xanthine, Creatinine	SSC, UA, Xanthine, Creatinine	SSC, UA, Xanthine, Creatinine, Urothione	SSC, UA, Xanthine, Creatinine, Urothione
Blood Biomarkers:	SSC, UA, Xanthine	SSC, UA, Xanthine	None	SSC, UA, Xanthine	SSC, UA, Xanthine
Laboratory Type:	Local	Central	Local	Central	Central
Assessments conducted:	Records collected as available.	At enrollment, weekly from birth to 1 month of age, monthly until 3 months of age, and then every 3 months.	Records collected as available.	Screen/BL, Days: 1, 4[b], 7, 14[2], 28, 57, 67, 87, 97, 117, 127, 147, 157, 180. Mos: 9, 12, 18, 24, 30, 36, 48, 60, 78, every 12 months thereafter, and Safety FUP 1st day of dose adjustment and 7-day FUP following dose adjustment	Screen/BL, Days: 1, 2[b], 3[b], 4, 5[b], 6[b], 7, 14, 28, 56. Mos: 3, 4[b], 5[b], 6, 9, 12, 18, 24, 30, 36, and Safety FUP/ET[c] 1st day of dose adjustment and 7-day FUP following dose adjustment
Growth:	Weight, Length/ Height, Head Circumference	Weight, Length/Height, Head Circumference	Weight, Length/Height, Head Circumference	Weight, Length/Height, Head Circumference	Weight, Length/Height, Head Circumference
Assessments conducted:	All data from birth to 1 month of age, then at intervals not shorter than 1 month through enrollment	At enrollment and then weekly from birth to 1 month of age, monthly until 3 months of age, and then every 3 months.	All available data with suggested time points of BL, Days: 7, 8-14, Mos: 1, 3, and then every 3 months	Screen/BL, Days: 7, 14, 28, 60, 90, 120, 150, 180, Mos: 9, 12, 24, 36, 48, 60, 66, 78, and every 12 months thereafter	Screen/BL, D1, daily through D14. Days: 21, 28, 56. Mos: 3, 4, 5, 6, 9, 12, 18, 24, 30, 36, and Safety FUP/ET[c]
Feeding Status:					
Patterns Captured:	Predominant and All	Predominant and All	Predominant and All	Current	Current
Type Captured:	Oral; Nasogastric; Gastronomy tube; Other	Oral; Nasogastric; Gastronomy tube; Other	Nasogastric; Percutaneous endoscopic; Oral suck; Oral feeding; Other	Oral; Nasogastric; Gastrostomy tube; Other	Oral; Nasogastric; Gastrostomy tube; Other

Assessments conducted:	All data from birth to 1 month of age, then at intervals not shorter than 3 months through enrollment	Weekly from birth to 1 month of age, monthly until 3 months of age, and then every 3 months	All available data with suggested time points of BL, D7, M3 and then every 3 months	Screen/BL, Mos: 6, 12, 24, 36, 48, 60, 66, 78, and every 12 months thereafter, and Safety FUP	Screen/BL, Days: 1, 5, 7, 14, 28, 56. Mos: 3, 4, 5, 6, 12, 18, 24, 30, 36, and Safety FUP/ET[c]
Developmental Assessments:					
GMFCS-ER	Records collected as available.	Baseline and at Months 6 and 12 as available	Records collected as available.	Screen, Days: 28, 90, 180, Mos: 12, 24, 36, 48, 60, 66, 78, and every 12 months thereafter, Safety FUP	M: 12, 24, 36, and Safety FUP/ET[c]
Bayley	Records collected as available.	At 3 months of age, and every 6 months as available	Records collected as available.	BL, Days: 28, Mos: 3, 6, 12, 24, 36, 48, 60, 66, 78, and every 12 months thereafter	Days: 28. Mos: 3, 6, 9, 12, 18, 24, 30, 36, and Safety FUP/ET[c]
WPPSI	Records collected as available.	At 3 years of age and at the end of the 1 year prospective evaluation as available	Records collected as available.	Screen, Mos: 6, 12, 24, 36, 48, 60, 66, 78, every 12 months thereafter, and when appropriate.	Days: 28. Mos: 3, 6, 9, 12, 18, 24, 30, 36, and Safety FUP/ET[c] if applicable
Denver	Records collected as available.	Baseline and every 3 months thereafter as available	Records collected as available.	Not assessed	Not assessed
GMFM-88	Not assessed	Not assessed	Not assessed	Not assessed	Day: 28. Mos: 3, 6, 9, 12, 18, 24, 30, 36, and Safety FUP/ET[c]
Ability to Sit Unassisted	As Measured by The Denver Developmental Screening Test: Sit - No Support The Denver does not specify for 30 seconds As Measured by Bayley Item #26: Sits	As Measured by Bayley Item #26: Sits without support for 30 seconds As Measured by The Denver Developmental Screening Test: Sit- No Support The Denver does not specify for 30 seconds	As Measured by The Denver Developmental Screening Test: Sit - No Support The Denver does not specify for 30 seconds As Measured by Bayley: item #26: Sits	As Measured by Bayley Item #26: Sits without support for 30 seconds	As Measured by Bayley Item #26: Sits without support for 30 seconds As Measured by the Gross Motor Function Measure-88: Item 24: Sitting on Mat: Maintains, arms free, 3 seconds

	without support for 30 seconds Neurologic exam includes the following question: Is the patient able to sit without support for 30 seconds or longer and at what age did the patient achieve this milestone?		without support for 30 seconds		
PEDI	Not assessed	Not assessed	Not assessed	Not assessed	Mos: 6, 12, 24, 36, and Safety FUP/ET[c]
Neuroimaging:					
Types of Neuroimaging:	MRI CT Scan Ultrasound	MRI CT Scan Ultrasound	MRI CT Scan Ultrasound	MRI CT Scan	MRI Ultrasound
Results collected:	Normal Abnormal	Normal Abnormal	Normal Abnormal Indeterminate	Normal Abnormal, Not Clinically Significant Abnormal, Clinically Significant	Normal Abnormal, Not Clinically Significant Abnormal, Clinically Significant
Assessments conducted:	Records collected as available.	BL, Mos 6 and 12 (if clinical condition allowed)	Records collected as available.	Screen/BL, Mos 6, 12, 24, 36, 60, 66, 78, and every 12 months thereafter Neuroimaging is optionalif the patient's clinical status has not changed	MRI Screen/BL, Mos 24, 36, and if clinical conditions allow Additional scans may be requested if clinically indicated.
				since the Month 6 assessment.	Ultrasound Screen/BL, Day 3, 21 (neonates only)
Seizure Activity:					
Seizure type captured?	Yes	Yes	Yes	No	No

Seizure counts collected?	No	Yes	Yes	Yes	Yes
Collection method:	Chart review	Daily Diary	Chart review	Daily Diary	Daily Diary
Anti-epileptic drugs?	General question on seizure CRF plus Con med page	General question on seizure CRF plus Con med page	Captured on specific CRF	General question on seizure CRF plus Con med page	General question on seizure CRF plus Con med page
Assessments conducted:	Retrospective collection from birth totime of enrollment.	Assessed continuously during 12-month observation period.	Retrospective data collection included all available data with suggested time points asfollows – BL, Days 1-14, Mos: 1, 2, 3 and every 3 months.	During screening period, daily through Days 7, 14, 28, then monthly	During screening period, daily through Days 7, 14, 21, 28, then monthly and the 1st day of dose adjustment and 7-day FUP following dose adjustment
Neurological Examinations:					
Parameters examined:	Spontaneous Movement, Truncal Tone, Appendicular Tone, Deep Tendon Reflexes, Primitive Reflexes, Dystonic, Opisthotonic, Clonus, Ambulation, Communication	Spontaneous Movement, Truncal Tone, Appendicular Tone, Deep Tendon Reflexes, Primitive Reflexes, Dystonic, Opisthotonic, Clonus, Ambulation, Communication	Spontaneous Movement, Truncal Tone, Appendicular Tone, Deep Tendon Reflexes, Primitive Reflexes	Spontaneous Movement, Truncal Tone, Appendicular Tone, Deep Tendon Reflexes, PrimitiveReflexes, Dystonic, Opisthotonic, Clonus, Ambulation, Communication	Spontaneous Movement, Truncal Tone, Appendicular Tone, Deep Tendon Reflexes, Primitive Reflexes, Dystonic, Opisthotonic, Clonus
Assessments conducted:	Retrospective data collection included all data from birth to 1 month of age. Data from 1 month to time of enrollment collected at intervals not shorter than 1 month.	At enrollment and then weekly from birth to 1 month of age, monthly until 3 months of age, and then every 3 months.	Retrospective data collection included all available data with suggested time points asfollows – BL, Days 7, 14, and Mos 1, 2, and 3 and then every 3 months.	Screen/BL, Days: 1, 4, 7, 14, 28, 60, 90, 120, 150, 180, and Mos: 9, 12, 18, 24, 30, 36, 42 48, 54, 60, 66, 72 and every 6 months thereafter, 78 and every 12months thereafter, the firstday of any dose adjustment, the 7-day FUP following any unscheduled dose adjustment, any Safety FUP	Screen/BL and Days: 1, 4, 7, 14, 28. Mos: 3, 4, 5, 6, 9, 12, 18, 24, 30, 36, Safety FUP/ET[c], and the 1st day of any dose adjustment and 7-day FUP following dose adjustment,

Abbreviations: BL=baseline; Bayley=The Bayley Scales of Infant Development, Third Edition; CRF=case report form; CT=computerized tomography; ET=end of

treatment; FUP=follow-up; GMFCS-ER=Gross Motor Function Classification System, Expanded and Revised; Mos=month; MRI=magnetic resonance imaging; PEDI=Pediatric Evaluation of Disability Inventory; rcPMP=recombinant sourced cyclic pyranopterin monophosphate; Screen=screening; SSC=S-sulfocysteine; UA=uric acid.
a Study MCD-502 also collected available data on homocysteine, methionine, taurine, hypoxanthine, sulfite, and thiosulfate in urine and homocysteine, methionine, taurine, and hypoxanthine in plasma. Study MCD-501 also collected available data on sulfite and thiosulfate in urine.
b Assessments on these days were conducted in urine only.

Sample size

Study MCD-501

Because this was a noninterventional, observational study in which data were retrospectively collected, the sample size was dictated by the number of patients exposed to IV rcPMP treatment as of the cut-off date of 31 Dec 2013.

Study MCD-201

There was no predefined sample size. At least 4 patients with MoCD Type A were planned for enrolment in this study. Patient enrolment was determined through named patient use with rcPMP, and the actual sample size depended on the number of eligible patients currently treated with rcPMP.

Study MCD-202

There was no minimum or maximum number of patients for this study. The final sample size and determination of study success relative to efficacy depended on the overall survival (OS) rate as each successive patient reached study completion.

Study MCD-502

There was no predefined sample size, however, an enrolment of at least 30 patients was foreseen.

Randomisation and blinding (masking)

Study MCD-501, MCD-201 and MCD-202 were open-label non-controlled trials. Therefore there was no randomization and blinding.

Statistical methods

Analysis of the individual studies was exploratory in nature. Pivotal efficacy evidence is derived from the integrated efficacy analysis, of which the methods are described here for the most important efficacy parameters.

For the purposes of summarizing efficacy data, three analysis populations were constructed:

- Full Analysis Set (FAS): All patients with MoCD Type A. This population includes all treated and untreated MoCD Type A patients.
- Prospective Full Analysis Set (PFAS): All patients with MoCD Type A were followed prospectively in Studies MCD-502, MCD-201, and MCD-202. This population is a subset of the FAS.
- Genotype-Matched Analysis Set (GMAS): All patients with MoCD Type A included in the m:n matching (where m is the number of treated patients and n is the number of natural history controls in a given match).

The FAS serves as the primary analysis set for conducting the efficacy analyses, while the PFAS and GMAS are considered as supportive analysis populations.

Efficacy Analyses

Overall Survival

The first efficacy outcome measure is Overall Survival (OS). OS is defined as the interval in months from the date of birth to the date of death or date last known alive (patients still on study will be censored at the data cut-off, and patients alive at the last contact date will be censored as well), whichever occurs first. Patients in MCD-503 will be censored at the data cut-off date if it is found that they are alive after this date. This analysis will be done using the FAS population.

Genotype-Matched Overall Survival Analysis

Unadjusted Analysis

Overall survival will be analysed using the GMAS population using Kaplan-Meier methods. Survival curves of treated and natural history controls will be provided, as well as curves by symptom onset and treatment initiation subgroups. Cox proportional hazards models will also be fitted using the GMAS. No form of adjustment for genotype-matching will be used.

Adjusted Analysis by Matched ID

Overall survival will be analysed using the GMAS population using Kaplan-Meier methods, stratified by matched ID. The stratified log-rank test will be used to compare median survival between treated and natural history controls while controlling for the genotype-matched IDs. Additional analyses following the Kaplan-Meier methods will be performed. A Cox proportional hazards model will also be fitted to assess the treatment effect on overall survival.

Inversely Weighted Analysis

The average treatment effect (ATE) will be estimated based on the GMAS population via the Cox proportional hazards model that accounts for the clustering within strata (matched IDs) and incorporates the appropriate set of weights. These ATE weights will be defined post-matching to determine the effect of treatment on the hazard of the occurrence of death in the GMAS. The ATE weights are described in the statistical analysis plan (SAP).

Analysis of Biomarkers

Biomarkers to be analysed include MoCD-associated urine and plasma biomarker levels consisting of S-sulfocysteine (SSC), xanthine, and uric acid. Levels of biochemical markers that are measured in urine will be normalized to urine creatinine levels. The actual values over time will be presented via summary tabulations and graphical representations. The analysis of biomarkers will be presented using the FAS and the GMAS.

Feeding Patterns

Feeding patterns will be analysed via the frequency and percentages of each feeding method at the last visit where feeding pattern was recorded. In addition, feeding methods will also be tabulated dichotomously using the last recorded feeding pattern categorized as Oral versus Non- Oral. The age (in months) at the last feeding assessment will be summarized using descriptive statistics.

The dichotomous analysis will be performed using a logistic regression, with oral feeding (yes/no) as the dependent variable, and treatment status (yes/no), an indicator for the MoCD symptom onset subgroup, age (months) at last feeding assessment, and gender as independent variables. Odds ratios and 95% confidence intervals will be provided. The analysis of feeding patterns will be performed on the FAS and the GMAS population. A conditional logistic regression model will be fitted to investigate the relationship between feeding patterns and treatment status.

Genotype Matching

In an effort to ensure comparability between treated patients and natural history controls, a matching algorithm was applied. Treated patients were matched with one or multiple controls from the natural history study based on genotype.

The following approach was used to determine matching:

- Treated patients are matched with patients in the natural history study who have the same homozygous mutation. If a treated patient has more than one control in the natural history study with the same homozygous mutation, the treated patient is matched to each in a one-to-many fashion.
- Treated patients who do not have an exact natural history homozygous matches are matched upon mutations with a similar anticipated impact on protein function (frameshift, missense, etc.). If a treated patient does not have an exact natural history homozygous match but does have more than one match with a mutation with a similar anticipated impact on protein function, the treated patient is matched to each in a one- to-many fashion.

The protein products of MOCS1, MOCS1A and MOCS1B, contain sites and regions with highly conserved amino acids across all cellular life, from single-celled bacteria to humans (Hänzelmann, 2004). Only a small group of proteins are currently known to have this high level of conservation, with nearly all being intimately connected to sustaining life. In discussions with researchers who provided much of the published data on protein structure, the sponsor matched treated patients to natural history control patients based on the mutations' known impact on either MOCS1A or MOCS1B. Details on the matching criteria used for patients who were not an exact genotype match are provided in Comparative Case Reports.

The matching criteria utilizing the genotype that was conducted is appropriate and informs on the efficacy of fosdenopterin. This is based on the fact that key baseline characteristics of the patients are comparable, thus supporting the matching algorithm across treated and untreated patients:

- Most of the patients with MoCD Type A presented with symptoms within the first 28 days of life and many within the first 1 to 2 days of life.
- Common presenting symptoms included intractable seizures, high-pitch cry, feeding difficulties, and exaggerated startle reactions.
- The high degree of regional overlap in study centres across the natural history and treatment studies, and in the matched pairs, including the US, UK, the Netherlands, Israel, Tunisia, Germany, and Turkey, suggests access to similar standards of care across studies in the development program.
- All but one of the treated patients had at least one matched control born within 5 years, suggesting similar access to healthcare advances, including supportive care. One patient (Studies MCD-501/MCD-201) was a homozygous match with another patient.
- 9 of the 15 treated patients have at least one gender-matched control.
- 9 of the 15 treated patients have at least one genotype-matched control; five of the 15 are matched based on mutations with a similar anticipated impact on protein function.

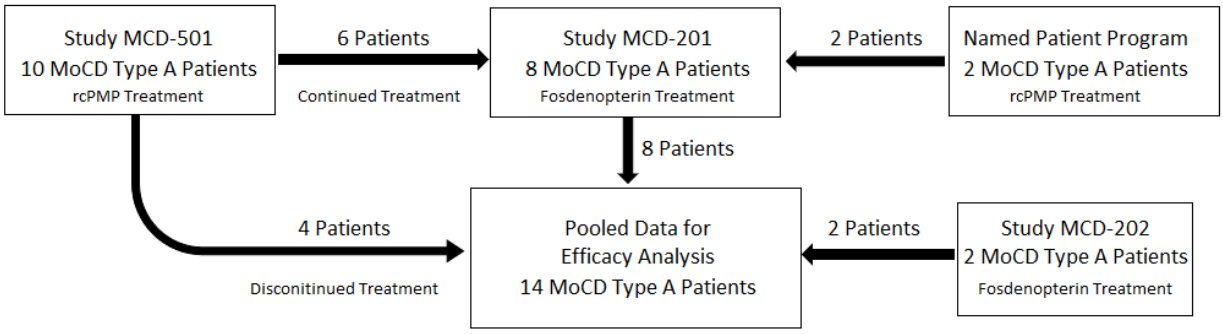
Results

Participant flow

Table 12 summarizes the disposition status of the 52 patients included in the integrated efficacy analyses; all 52 patients had a confirmed diagnosis of MoCD Type A. Overall, 15 patients who received cPMP were included in the treated patient group, and 37 patients from the natural history study were included in the untreated control group.

As of the MAA data cut-off for the initial submission, nine of the 14 (64.3%) treated patients were ongoing on fosdenopterin, including eight patients in Study MCD-201 and one patient in Study MCD-202. Overall, five of the 14 treated patients discontinued treatment. One treated patient from Study MCD-202 was discontinued from the study after 9 days (and 9 doses of fosdenopterin) per physician decision related to the poor neurologic prognosis of the patient. Of the remaining four discontinued patients, who all participated in Study MCD-501, two died, and two were reported as off treatment due to poor prognosis. In the D90 update period, one additional MoCD type A patient was enrolled in study MCD-202, bringing the total to n=15 cPMP treated patients.

Figure 10: flow of cPMP treated patients



The FAS includes all 52 patients, 15 treated and 37 untreated controls. The PFAS includes 24 patients overall: 10 patients with prospective data collected during treatment with fosdenopterin in Studies MCD-201 and MCD-202 and 14 patients from the natural history Study MCD-502 who had prospective data collected. The 15 treated patients were matched based on the genetic mutation to 19 untreated control patients; these 33 patients comprise the GMAS. Of note, due to the enrolment of 1 patient in study MCD-202 during the D90 update period, this patient is included in the FAS/PFAS and GMAS, but data was not included in all endpoint analyses.

Table 12. Patient Disposition and Summary of Integrated Analysis Sets (Data cut-off 31 October 2021).

Disposition Category	**cPMP Treated Patients**				**Untreated Controls**
	MCD-501 only (N=4) n (%)	**MCD-201 (N=8) n (%)**	**MCD-202 only (N=3) n (%)**	**Total (N=15) n (%)**	**MCD-502 (N=37) n (%)**
Number of Patients Included	4	8	3	15	37
Number of Patients Ongoing as of Data Cut-off	0	8 (100)	2 (50.0)	10 (64.3)	0

Number of Patients Off Treatment	4 (100)	0	1 (50.0)	5 (35.7)	37 (100)
Number of Patients with Follow-up Information fromStudy MCD-503[a]	0	NA	NA	0	6 (16.2)
Full Analysis Set	4 (100)	8 (100)	3 (100)	15 (100)	37 (100)
Prospective Full Analysis Set	0	8 (100)	3 (100)	11 (71.4)	14 (37.8)
Genotype-Matched Analysis Set	4 (100)	8 (100)	3 (100)	15 (100)	19 (51.4)

Recruitment

Study MCD-501

Informed consent was acquired between 01 Nov 2012 and 07 Oct 2014. Fifteen patients enrolled in the study: 10 patients with MoCD Type A, 4 patients with MoCD Type B, and 1 patient with unknown MoCD type. This study was conducted at 13 centers, located in Australia, Germany, Netherlands, Turkey, the United Kingdom, and the United States, that had previously treated pediatric patients with rcPMP.

Study MCD-201

The first patient was enrolled on 02 April 2014, and the study is ongoing. In total, 8 patients have been enrolled, with 7 patients having completed through Month 54, and the 8th patient having completed through Month 6. Three patients have completed through Month 72, and 1 patient has completed study visits through Month 78. The study was conducted at 5 study centres in 5 countries (Australia, Tunisia, the Netherlands, United Kingdom, and United States).

Study MCD-202

The first patient enrolled on 20 Jun 2016 and the study is ongoing. Five patients were screened for the study. Four patients were enrolled and received treatment with fosdenopterin. One patient was diagnosed with MoCD type B and discontinued. The study was conducted at 2 study centres, 1 in Israel and 1 in the United Kingdom, as of the data cut-off date of 31 October 2020. One additional patient was screened at a different site but did not meet screening criteria and did not receive study drug.

Study MCD-502

Informed consent was acquired between 24 Sep 2013 and 11 Dec 2015. Seventy patients were screened for this study, of whom 65 were enrolled at 27 sites in 14 countries. Of the 65 enrolled patients, 37 patients were diagnosed with MoCD Type A. Of the patients with confirmed MoCD Type A, 17 (46%) patients were enrolled in the living cohort, of whom 14 (38%) patients enrolled in the 12-month prospective data collection period. Thirteen (35%) patients with MoCD Type A completed the prospective data collection period; 1 patient died before the end of the data collection period.

Conduct of the study

For study MCD-202, MCD-202 and MCD-502, there were multiple amendments to the protocol. The majority were clarifications and administrative changes. There were also changes in endpoint hierarchy and endpoints added to the protocols.

There were 11 protocol deviations in study MCD-501. Since this was a retrospective study, the majority was due to data extraction from the medical records after the date of informed consent.

In study MCD-201 there were 3 critical protocol deviations. Two were related to privacy and informed consent, and one was due to an incorrect dose administered on one day.

In study MCD-202, no critical protocol deviations were recorded. One important deviation concerned the missing of a follow-up visit one day after dose escalation.

In study MCD-502, the protocol deviations were mainly related to the informed consent process or visits that were not completed outside the specified window.

Baseline data

Demographics and baseline characteristics are presented for the integrated analysis population. Patient demographics were generally balanced between the cPMP-treated and untreated populations (Table 13).

Table 13. Patient Demographics (Full Analysis Set and Genotype-Matched Analysis Set, patients with MoCD type A, data cut-off 31 October 2021)

Parameter Statistic	cPMP-Treated Patients (FAS and GMAS)				Untreated Controls	
	MCD-501 only (N=4)	MCD-201 (N=8)	MCD-202 (N=3)	Total (N=15)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Gender, n (%)						
Male	3 (75.0)	3 (37.5)	1 (33.3)	7 (50.0)	28 (75.7)	13 (68.4)
Female	1 (25.0)	5 (62.5)	2 (66.7)	8 (53.3)	9 (24.3)	6 (31.6)
Race, n (%)						
White	4 (100)	5 (62.5)	2 (66.7)	11 (73.3)	21 (56.8)	12 (63.2)
Asian	0	3 (37.5)	1 (50.0)	4 (28.6)	10 (27.0)	4 (21.1)
Black or African American	0	0	0	0	0	0
Other	0	0	0	0	6 (16.2)	3 (15.8)
Ethnicity, n (%)						
Hispanic or Latino	1 (25.0)	0	0	1 (6.7)	2 (5.4)	0
Not Hispanic or Latino	3 (75.0)	8 (100)	2 (66.7)	13 (86.7)	31 (83.8)	15 (78.9)
Not Reported/Unknown	0	0	1 (33.3)	1 (6.7)	4 (10.8)	4 (17.6)
Gestational Age						
n	4	8	3	15	30	16
Mean (SD)	37.4 (1.78)	38.8 (1.52)	38.1 (1.85)	38.3 (1.65)	39.0 (1.19)	39.0 (0.90)
Median	37.7	39.0	38.0	39.0	39.0	39.0

Min, Max	35, 39	36, 41	36.3, 40	35, 41	36, 41	37, 40.3

Abbreviations: cPMP=cyclic pyranopterin monophosphate; FAS=Full Analysis Set; GMAS=Genotype- Matched Analysis Set; NA=not applicable; rcPMP=recombinant Escherichia coli-derived cPMP; SD=standard deviation. Note: The six patients that were treated with rcPMP on Study MCD-501 and went on to enroll in Study MCD-201 are only presented in the MCD-201 column.

Table 14 summarizes the patient baseline disease characteristics for the FAS and GMAS.

Median age at onset of first MoCD signs or symptoms was similar in the treated patients (1 day of age) and the untreated controls (2 days of age); however, the maximum time to onset was shorter for treated patients (maximum of 3 weeks of age) compared with untreated controls (maximum of 2.5 years of age). The median age at genetic diagnosis in the treated patient group was 3 days and ranged from -181 to 59 days, including four patients diagnosed in utero. In the untreated control patients, the median age at diagnosis was longer at 269 days (8.8 months) and ranged from 4 days to 40.3 years.

In the FAS, the majority of patients had onset of first MoCD signs and symptoms within 28 days of birth (treated, 93.3%; untreated, 89.2%).

The most common presenting signs and symptoms of MoCD in both the treated patients and untreated control patients with similar incidence across these groups were seizures (treated, 71.4%; untreated, 91.9%), feeding difficulties (treated, 64.3%; untreated, 83.8%), high-pitch cry (treated, 50.0%; untreated, 43.2%), and exaggerated startle response (treated, 35.7%; untreated, 32.4%). Seizures were reported in utero or during the neonatal period in the majority of patients (treated, 78.6%; untreated, 70.3%). A higher proportion of patients in the untreated control group had late onset seizures (21.6%) compared with the treated patient group (7.1%).

Baseline disease characteristics for the untreated population were similar in the GMAS and FAS. As well, the baseline disease characteristics for the PFAS were consistent with those observed in the FAS.

Table 14. Baseline Disease Characteristics (Full Analysis Set and Genotype- Matched Analysis Set, data cut-off 31 October 2021)

	cPMP-Treated Patients (FAS and GMAS)				Untreated Controls	
ParameterStatistic	MCD-501 only (N=4)	MCD-201 (N=8)	MCD-202 only (N=3)	Total (N=15)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Age at Genetic Diagnosis (days)						
n	4	8	3	15	30	16
Mean (SD)	-28.0 (86.29)	-29.3 (84.74)	171.7 (507.17)	11.3 (220.96)	1299.6 (2875.20)	435.0 (521.86)
Median	10.0	3.0	-105	4.0	269.0	173.5
Min, Max	-157, 25	-181, 59	-137, -757	-181, 757	4, 14708	4, 1683
Age at Onset of first MoCD symptoms (days)						
n	4	8	2[d]	14	37	19

Mean (SD)	1.8 (0.96)	1.5 (1.41)	1.0[b] (0.00)	1.5 (1.16)	55.1 (192.70)	16.6 (50.83)
Median	1.5	1.0	1.0[b]	1.0	2.0	2.0
Min, Max	1, 3	1, 5[a]	1, 1[b]	1, 5[a]	1, 927	1, 222
Age at first MoCD symptom category						
≤ 28 days	4 (100)	8 (100)	2 (100)[b]	14 (100)	33 (89.2)	17 (89.5)
28 days	0	0	0	0	4 (10.8)	2 (10.5)

Table 15. Baseline Disease Characteristics (Full Analysis Set and Genotype- Matched Analysis Set, data cut-off 31 October 2021)

	cPMP-Treated Patients (FAS and GMAS)				Untreated Controls	
ParameterStatistic	MCD-501 only (N=4)	MCD-201 (N=8)	MCD-202 only (N=3)	Total (N=14)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Patients with early seizures[c]						
No symptoms reported	0	2 (25.0)	0	2 (14.3)	3 (8.1)	1 (5.3)
First Seizure *in Utero* orDuring Neonatal Period	4 (100)	5 (62.5)	2 (100)	11 (78.6)	26 (70.3)	13 (68.4)
First Seizure Post-Neonatal Period	0	1 (12.5)	0	1 (7.1)	8 (21.6)	5 (26.3)
MoCD presenting signs and symptoms[d]						
Seizures	4 (100)	5 (62.5)	1 (33.3)	10 (71.4)	34 (91.9)	18 (94.7)
Feeding difficulties	4 (100)	4 (50.0)	1 (33.3)	9 (64.3)	31 (83.8)	17 (89.5)
High-pitched cry	3 (75.0)	4 (50.0)	0	7 (50.0)	16 (43.2)	10 (52.6)
Exaggerated startle response	2 (50.0)	3 (37.5)	0	5 (35.7)	12 (32.4)	9 (47.4)
Metabolic acidosis	2 (50.0)	2 (25.0)	0	4 (28.6)	7 (18.9)	4 (21.1)
Hypertonia	NA	3 (37.5)	0	3 (21.4)	NA	NA
Hypotonia	NA	2 (25.0)	0	2 (14.3)	NA	NA
Encephalopathy	NA	3 (37.5)	0	3 (21.4)	NA	NA
Intracranial hemorrhage	2 (50.0)	0	0	2 (14.3)	2 (5.4)	0
Other	2 (50.0)	5 (62.5)	0	7 (50.0)	11 (29.7)	5 (26.3)

Note: The six patients that were treated with rcPMP on study MCD-501 and went on to enroll in study MCD-201 are only presented in the MCD-201 column. Note: Hypertonia, hypotonia, and encephalopathy were not collected as signs/symptoms in the MCD-501 and MCD-502 studies. a The maximum of 5 days is based on a patient with a

missing day for the onset of first signs and symptoms; the missing day was imputed using the 15th of the month, and based on this patient's date of birth, the first symptoms could have occurred from 1 day to 21 days of age. b Patient was diagnosed in utero and initiated treatment with Nulibry prior to the onset of signs and symptoms; the patient is included as having onset within ≤ 28 days of birth. c Early seizures are defined as those reported either while the patient was in utero or within the first 28 days of life. d No prespecified signs and symptoms were reported for one Patient in study MCD-202.

Molybdenum cofactor deficiency family history was collected. Parental consanguinity was reported in eight of the 15 treated patients (53%) and in 25 of the 37 untreated controls (67.6%).

Eight of the treated patients had a total of 15 living siblings, of which one had confirmed MoCD Type A. Seven treated patients had a total of 10 deceased siblings, of which five had confirmed MoCD Type A status and three were suspected of having MoCD Type-A. The number of living or deceased siblings along with their MoCD Type A status, was unavailable for untreated control patients. MoCD family history was similar in the FAS and GMAS untreated population and was consistent between the FAS and PFAS.

Across the 14 treated early onset patients, age at first dose was ≤ 14 days for 11 patients, with five patients initiating treatment at 1 day of age; the maximum time to initiate treatment was 69 days. The patient enrolled during the update period started treatment at 1015 days of age.

Administered doses

An overview of the extent of exposure to cPMP for each of the 15 patients by dose level of rcPMP and of fosdenopterin is provided in Table 32.

Study MCD-201

Per protocol, four of the eight patients titrated up to 1200 µg/kg/day during the study, two patients titrated up to 960 µg/kg/day and maintained that dose for the rest of the study, and two patients had dose reductions for ease of administration. Both patients had escalated to 960 µg/kg prior to dose reduction to a final dose of 240 µg/kg/day and 480 µg/kg/day, respectively.

Study MCD-202

One patient-initiated dosing on the day of birth with 525 µg/kg of fosdenopterin and escalated to 1300 µg/kg by Month 9 as scheduled. The second patient-initiated dosing on the day of birth with 700 µg/kg of fosdenopterin, and this dose was administered daily as planned through Day 9. The late-onset patient enrolled during the update period initiated treatment with fosdenopterin at a dose of 700 µg/kg once daily (QD) at 33.4 months of age. The patient's dose was increased after two months to 1000 µg/kg and 1200 µg/kg three months after initiation.

Numbers analysed

For the integrated efficacy analysis, data from studies MCD-501, MCD-201, MCD-202 were pooled and compared to the natural history cohort. See Table 16 for the different analysis sets.

Outcomes and estimation

Overall survival

Treatment of patients with MoCD Type A with cPMP led to a statistically significant improvement in OS compared with the untreated control patient population in both the FAS and GMAS (Table 16).

As of the data cut-off date of 31 October 2020, two (13.3) of the 15 treated patients and 24 (64.9%) of 37 untreated control patients in the FAS had died. Median OS was not estimated for the treated patient group given the low number of patient deaths and was 50.7 months (4.2 years) for the untreated control group (log rank p=0.0091). The rate of death among the untreated control group was 5.5 times higher than that of the treated patient group. Consistent with these results, the survival probability at 1 year of age was 93.3% for the treated group and 75.3% for the untreated controls; at 2 and 3 years of age, survival probabilities were 85.5% and 85.5% for treated patients and 69.6% and 55.1% for untreated control patients, respectively.

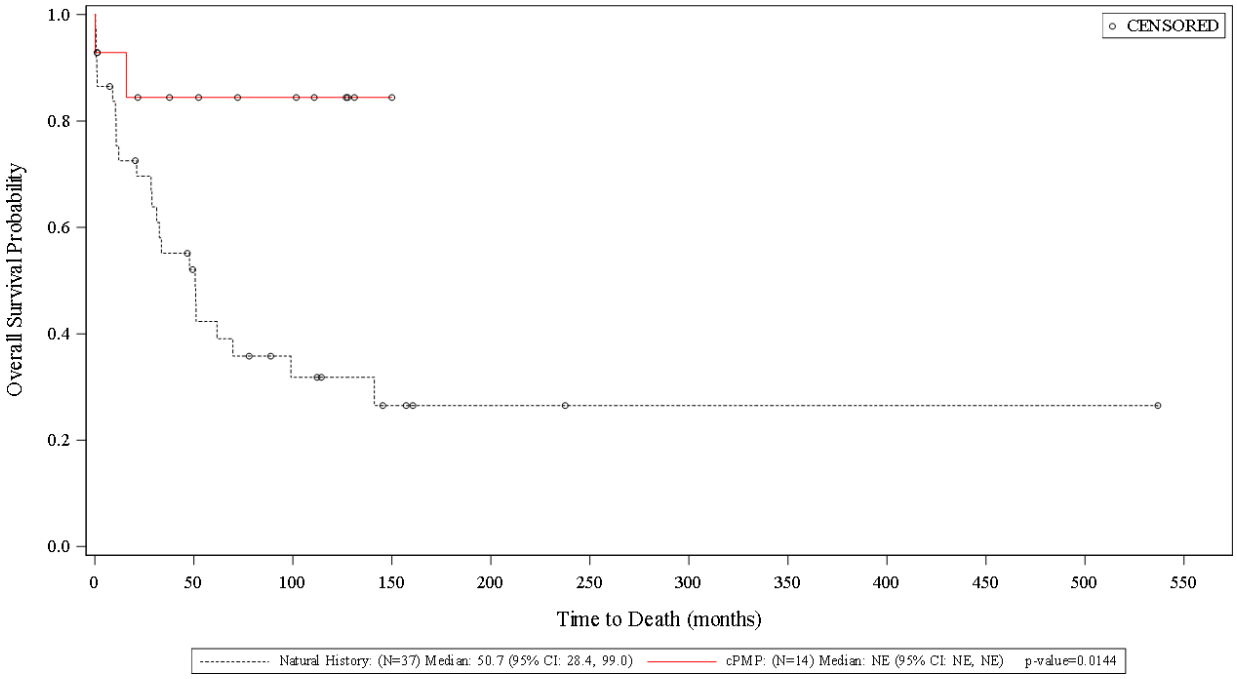
The Kaplan-Meier curves of OS for the treated and untreated patients included in the FAS are presented in Figure 11.

Table 16. Overall Survival (Full Analysis Set, data cut-off 31 Oct 2021)

	cPMP-Treated Patients				Untreated Controls
Parameter Statistic	**MCD-501 only (N=4)**	**MCD-201 (N=8)**	**MCD-202 (N=3)**	**Total (N=15)**	**MCD-502 (N=37)**
Number of patients censored, n (%)	2 (50.0)	8 (100)	3 (100)	13 (86.7)	13 (35.1)
Reason for censoring					
Data cut-off, n (%)	0	8 (100)	2 (66.7)	10 (66.7)	0
Alive at last contact	2 (50.0)	0	1 (33.3)	3 (20)	13 (35.1)
Number of deaths, n (%)	2 (50.0)	0	0	2 (13.3)	24 (64.9)
Time to Death (months)					
75th percentile (95% CI)[a]	-	-	-	NE (NE)	NE (61.7, NE)
Median (95% CI)[a]	-	-	-	NE (NE)	50.7 (28.4, 99.0)
25th percentile (95% CI)[a]	-	-	-	NE (0.2, NE)	12.1 (1.0, 31.2)
Min, Max	-	-	-	0.2, 15.9	0.3, 141.1
Log rank p-value	-	-	-	0.0091	
Cox PH Model Hazard Ratio (95% CI) [b]	-	-	-	5.5 (1.44, 21.04)	
Kaplan-Meier survival probability[c]					
6 months, (%)	-	-	-	0.9333	0.8649
1 year, (%)	-	-	-	0.9333	0.7533
2 years, (%)	-	-	-	0.8556	0.6964
3 years, (%)	-	-	-	0.8556	0.5513

Note: The six patients that were treated with rcPMP on Study MCD-501 and went on to enroll in Study MCD-201 are only presented in the MCD-201 column. aQuartile estimates from product-limit (Kaplan-Meier) method, with associated log-log confidence intervals. b Cox proportional hazards model regressing survival status on an indicator variable denoting treatment status. Hazard ratios are estimated to determine the effect of treatment on the hazard of the occurrence of death. The 95% CIs are based on the modified score test statistic under the Cox model. The hazard ratio represents the risk of death in the natural history patients compared to the treated patients. c Based on survival distribution function estimates from the product-limit method.

Figure 11: Kaplan-Meier Plot of Overall Survival for cPMP-Treated Patients and Untreated Controls (Full Analysis Set, data cut-off 31 Oct 2021).



Abbreviations: CI=confidence interval; cPMP=cyclic pyranopterin monophosphate; NE=not estimated.

Results in the GMAS were consistent with the FAS. As of the data cut-off date of 31 October 2021, two (13.3%) of the 15 treated patients and 14 (73.7%) of 19 untreated matched control patients in the GMAS had died. Median OS was not estimated for the treated patients and was 47.8 months (3.9 years) for the untreated matched controls (log rank p=0.0028, unadjusted). Patients in the untreated control group were 7.1 times more likely to have died than patients who received cPMP. Consistent with these results, the survival probability at 1 year of age was 93.3% for the treated group and 68.4% for the untreated controls, and at 2 years of age, survival probabilities were 85.5% and 63.2% for treated and untreated matched control patients, respectively.

Feeding patterns

Patients who received cPMP were more likely to be able to feed orally and had a longer time prior to requiring sustained non-oral feeding than patients in the unmatched control population. Data is presented for the 14 early-onset patients. The late-onset patient enrolled during the update period was able to feed orally.

In the FAS, eight of the 14 treated patients (57.1%) and 10 of the 33 untreated patients (30.3%) with data available for analysis were able to feed orally at the last recorded visit. The odds ratio indicates that treated patients were 7.8 times more likely to be feeding orally at the last assessment compared with patients in the untreated control group (Table 17).

Consistent with these results, the median time to sustained non-oral feeding was considerably longer at 75.0 months for treated patients compared with 10.5 months for untreated controls.

Results in the GMAS were consistent with the FAS. For this matched population, only four (22.2%) of 18 untreated patients with data available were able to feed orally at the last assessment. In this population, treated patients were 9.1 times more likely to be feeding orally at the last assessment than

the untreated matched controls. Results of the conditional logistic regression analysis of feeding patterns for the GMAS were consistent, indicating that treated patients were more likely to be feeding orally at the last assessment with a hazard ratio of 4.2. The median time to sustained non-oral feeding for the untreated matched control patients in the GMAS was 5.7 months compared with 75.0 months in treated patients.

Table 17. Analysis of Feeding Status at Last Assessment and Time to Sustained Non-Oral Feeding (Full Analysis Set and Genotype-Matched Analysis Set, data cut-off 31 October 2020)

Parameter Statistic	cPMP-Treated Patients (FAS and GMAS) (N=14)	Untreated Controls	
		MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Number of Patients with Last Feeding Assessment, n	14	33	18
Number of Patients Feeding Orally, n (%)	8 (57.1)	10 (30.3)	4 (22.2)
Number of Patients Not Feeding Orally n (%)	6 (42.9)	23 (69.7)	14 (77.8)
Logistic Regression[a]			
Odds Ratio (95% CI)	7.8 (1.38, 43.84)		9.1 (1.16, 72.39)
p-value	0.020		0.036
Time to Non-oral feeding (months)			
75th Percentile (95% CI)	NE (75.0, NE)	100.8 (19.2, NE)	53.6 (6.5, NE)
Median (95% CI)	75.0 (14.4, NE)	10.5 (4.9, 53.6)	5.7 (0.2, 22.5)
25th Percentile (95% CI)	14.5 (0.0, 75.0)	0.6 (0.1, 6.5)	0.2 (0.1, 1.7)
Min, Max	0.0, 75.0	0.1, 100.8	0.1, 53.6

Note: Sustained non-oral feeding is defined as the time at which the patient never subsequently returns to an oral method of feeding. A The logistic regression is fitted using oral feeding (yes/no) as the dependent variable, and treatment status, MoCD symptom onset subgroup, age at last feeding assessment, and gender as independent variables. The odds ratio represents the odds of feeding orally when being treated versus not being treated.

Growth parameters

The growth parameters investigated in this study included body weight, body length, head circumference, and BMI. Data is presented for the 14 early-onset patients.

At the last visit, mean and median z-scores for the untreated control patients were lower relative to the cPMP-treated patients for each of the growth parameters. Median z-scores at the last assessment were: -0.34 and -0.63 for weight for treated patients and untreated controls, respectively; -0.86 and -1.37, respectively, for height; and -0.70 and -1.91, respectively, for head circumference (Table 18).

The data shows that treated patients were more likely to have z- scores near or above zero, indicating that they had achieved growth that was closer to their age-matched peers than the untreated control patients.

Table 18. Summary of First Value and Last Assessment for Weight, Height and Head Circumference Z-Scores (Full Analysis Set and Genotype-Matched Analysis Set, data cut-off 31 October 2020)

Parameter Visit Statistic	cPMP-Treated Patients (FAS and GMAS)				Untreated Controls	
	MCD-501 only (N=4)	MCD-201 (N=8)	MCD-202 (N=2)	Total (N=14)	MCD-502 FAS (N=37)	MCD-502 GMAS (N=19)
Weight Z-Score						
Baseline, n	4	8	2	14	37	19
Mean (SD)	0.20 (0.588)	-0.30 (1.052)	-0.43 (0.685)	-0.18 (0.880)	-0.28 (1.364)	-0.45 (1.538)
Median	0.35	-0.19	-0.43	0.12	-0.06	-0.06
Min, Max	-0.6, 0.7	-2.2, 1.4	-0.9, 0.1	-2.2, 1.4	-3.7, 2.0	-3.7, 2.0
Last Visit, n	4	8	2	14	37	19
Mean (SD)	-0.18 (0.824)	-0.47 (1.575)	-0.13 (0.412)	-0.33 (1.237)	-0.70 (1.391)	-0.24 (1.555)
Median	-0.17	-0.40	-0.13	-0.34	-0.63	-0.25
Min, Max	-1.1, 0.7	-2.8, 2.5	-0.4, 0.2	-2.8, 2.5	-3.0, 2.8	-3.0, 2.8
Height Z-Score						
Baseline, n	3	7	2	12	33	16
Mean (SD)	1.12 (0.000)	-2.09 (3.113)	-0.14 (0.464)	-0.96 (2.724)	-0.44 (2.912)	-0.22 (3.630)
Median	1.12	-1.55	-0.14	-0.14	0.18	0.25
Min, Max	1.1, 1.1	-8.6, 0.6	-0.5, 0.2	-8.6, 1.1	-7.8, 5.4	-7.8, 5.4
Last Visit, n	3	8	2	13	33	16
Mean (SD)	-0.14 (1.259)	-1.16 (3.007)	-0.84 (0.031)	-0.88 (2.394)	-1.05 (2.381)	-0.67 (2.738)
Median	-0.12	-1.19	-0.84	-0.86	-1.37	-0.80
Min, Max	-1.4, 1.1	-7.1, 2.8	-0.9, -0.8	-7.1, 2.8	-4.6, 5.4	-4.4, 5.4
Head Circumference Z-Score						
Baseline, n	4	7	2	13	36	19
Mean (SD)	0.45 (0.645)	0.46 (1.424)	1.11 (0.967)	0.56 (1.121)	-0.79 (2.862)	-1.58 (3.380)
Median	0.47	0.86	1.11	0.52	0.07	-0.32
Min, Max	-0.4, 1.2	-1.4, 2.8	0.4, 1.8	-1.4, 2.8	-8.1, 3.5	-8.1, 3.5
Last Visit, n	4	8	2	14	36	19
Mean (SD)	-0.43 (1.217)	-0.94 (2.947)	0.98 (1.799)	-0.52 (2.393)	-2.03 (2.783)	-2.33 (3.218)
Median	-0.46	-1.70	0.98	-0.70	-1.91	-2.95
Min, Max	-1.7, 0.9	-5.1, 3.0	-0.3, 2.2	-5.1, 3.0	-7.5, 4.3	-7.5, 4.3

Note: The six patients that were treated with rcPMP on Study MCD-501 and went on to enroll in Study MCD-201 are only presented in the MCD-201 column. First value is defined as the measurement with the earliest date of collection.

Developmental Assessments

Data is presented for the 14 early-onset patients. Data from the late-onset patient enrolled during the update period is presented separately.

Gross Motor Function Classification System Results

Children who have motor functions classified in "Level I" can generally walk without restrictions, and children whose motor function has been classified at "Level V" are very limited in their ability to move

themselves around even with the use of assistive technology and typically are pushed in a wheelchair for their mobility.

Note that GMFCS-ER was only captured during the prospective Studies MCD-201 and MCD-202 and in the prospective part of Study MCD-502. Table 19 provides GMFCS-ER Level at the last available assessment for the PFAS; data were available for eight patients during treatment with fosdenopterin and for 11 of the 14 untreated controls included in the PFAS.

At baseline, 4/9 treated patients were rated as level I, 1 as level IV and 4 as level V. In the untreated control group, 1/11 was rated as level I, 1 as level II and 9/11 as level V.

At the last assessment prior to the MAA data cut-off, a higher percentage of patients receiving fosdenopterin who had data available were ambulatory (4/9, 44.4%) (i.e., assessed as a Level I on the GMFCS-ER) compared with the untreated controls (1/11, 9.1%). One additional treated patient was walking with assistance at 4 years old and was rated as a Level III on the GMFCS. The majority of the untreated control patients (9/11, 81.8%) required transportation in a wheelchair for mobility (Level V). In the treated patient group, four of the nine patients (44.4%), all of whom entered Study MCD-201 with static encephalopathy and GMFCS-ER Level V, were assessed as Level V at the last assessment. In the GMAS, all seven (100%) of the matched control patients with data available were non-ambulatory (Level V).

Table 19. Gross Motor Function Classification System Results at the Last Assessment (Prospective Full Analysis Set, data cut-off 31 October 2020)

Analysis Visit Result	cPMP-Treated Patients (N=10) n (%)	Untreated Controls (N=14) n (%)
Data Availability	9 [a]	11
Level I, II, III, and IV	5 (55.6)	2 (18.2)
Level I	4 (44.4)	1 (9.1)
Level II	0	0
Level III	1 (11.1)	0
Level IV	0	1 (9.1)
Level V	4 (44.4)	9 (81.8)

Abbreviations: cPMP=cyclic pyranopterin monophosphate.
a N=10 as no developmental data were available for one patient .

One patient was assessed on the Gross Motor Function Measure (GMFM-88) at 34.3 months of age and 35.8 months of age, with total percent scores of 78% and 70.2%, respectively. At the second assessment at 35.8 months of age, the scores remained similar. Per protocol, the Gross Motor Function Classification System – Expanded and Revised (GMFCS-ER) was not administered by the last assessment before the data cut-off; however, based on the patient's functioning level at 35.8 months of age (ability to walk independently without an assistive device and run with coordination), the patient would be rated Level I on the GMFCS-ER.

Bayley and WPPSI

Patients who received cPMP were more likely to be higher functioning at the last assessment based on age-equivalent scores than the untreated control patients.

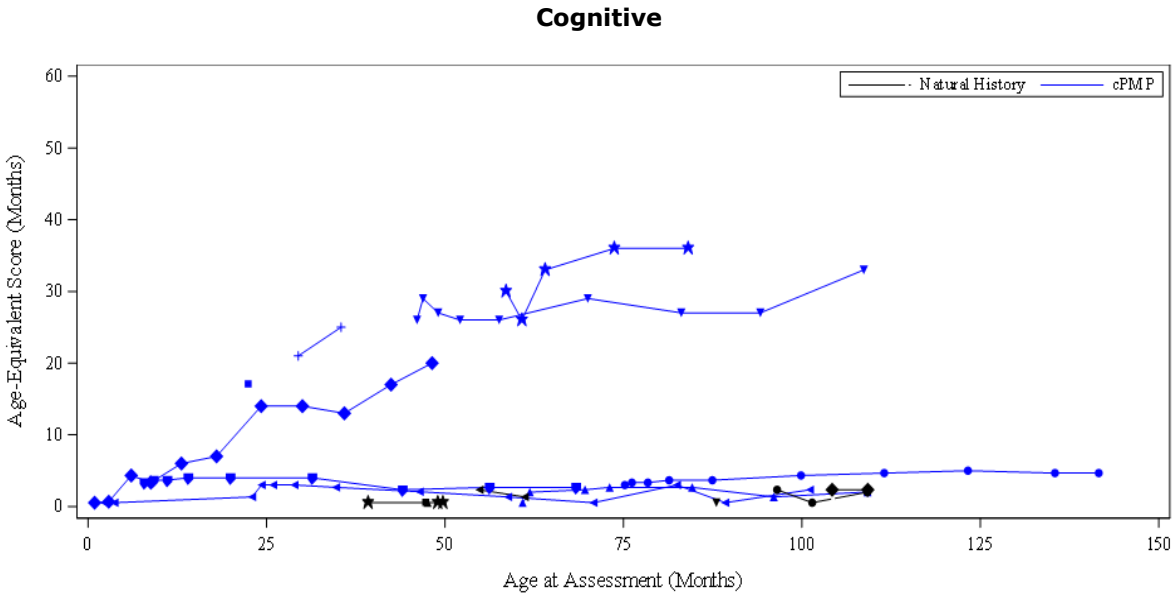
The Bayley assesses the developmental functioning of infants and children 1 month to 42 months of age and consists of the following scales: Cognitive, Language (administered only to native English

speakers in English-speaking countries), which includes Receptive and Expressive Communication subtests, and Motor, which includes Fine and Gross Motor subtests. The WPPSI measures cognitive skills in children aged 30 months to 7 years, 7 months using 14 different subtests that examine cognitive function aspects such as vocabulary, visual spatial skills, logic, processing speed, and memory.

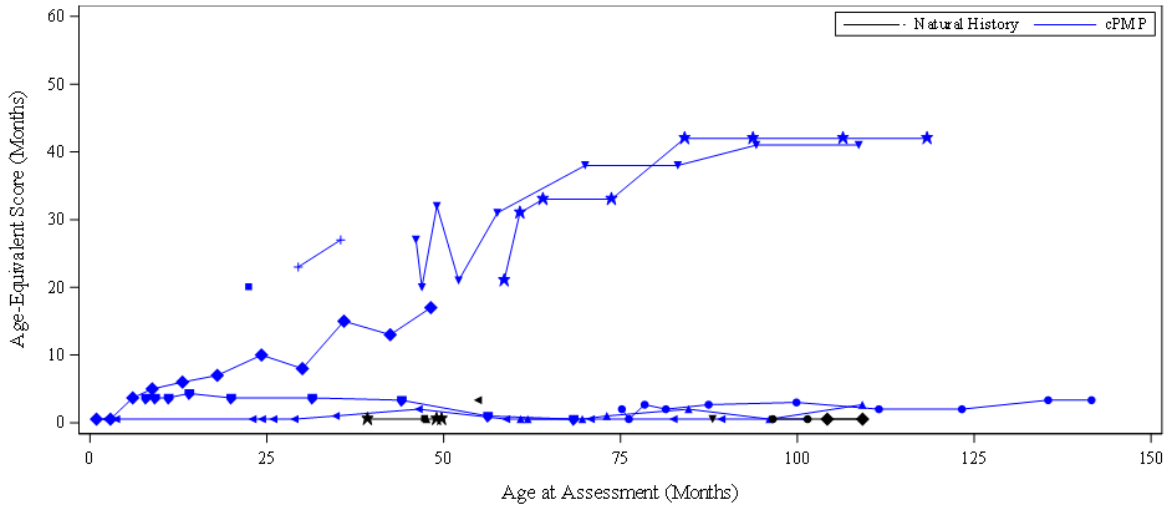
Figure 12 presents spaghetti plots of age-equivalent scores for the Bayley Cognitive, Fine and Gross Motor subtests over time that were collected prospectively for treated patients and untreated controls. The higher functioning patients in all areas received treatment with cPMP; all untreated controls were lower functioning for all Bayley assessments. All of the treated patients with lower age-equivalent scores had entered Study MCD-201 with static encephalopathy. These four patients had age-equivalent scores that generally remained stable during treatment with fosdenopterin, with some gaining new skills.

The WWPSI was only conducted for one patient from MCD-201 and one patient from MCD-202 (data not shown).

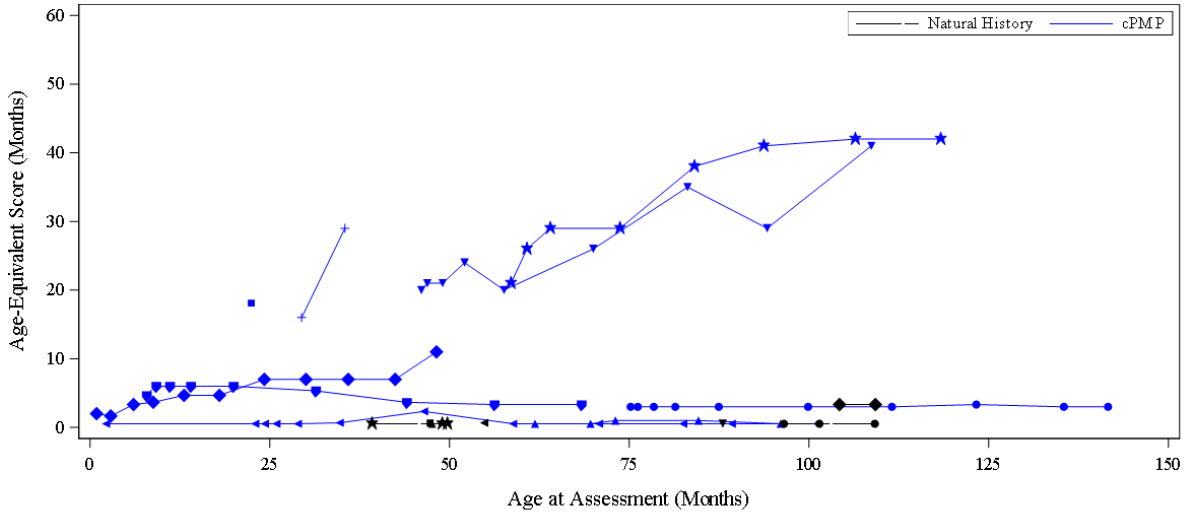
Figure 12: Spaghetti Plots of Age-Equivalent Scores in Months from the Bayley Cognitive, Fine Motor, and Gross Motor Subtests (Prospective Full Analysis Set, data cut-off 31 October 2020)



Fine Motor



Gross Motor



Abbreviations: cPMP=cyclic pyranopterin monophosphate.

A summary of the cognitive developmental assessments for baseline and last assessment (as available) for the GMAS by matched ID is presented in Table 20. The table presents all patients in the GMAS with available data, regardless of the availability of data from a matched patient.

For the treated patients, data are available from the start of fosdenopterin and are consistent with the data presented in the figures above; the four patients who entered Study MCD-201 without static encephalopathy who were higher functioning at study entry showed improvement during treatment with cPMP as did the patient who was treated with fosdenopterin in Study MCD-202.

Table 20. Summary of Cognitive Developmental Assessments by Matched ID (Genotype-Matched Analysis Set data cut-off 31 October 2020)

Matched ID	Treated/ Untreated	Age Equivalent	
		First Visit	Last Visit
1	Treated	3.0 months	4.7 months
2	Treated	30.0 months	3.8-5.8 years[a]
	Treated	0.5 months	2.0 months
3	Treated	4.0-5.0 years[a]	4.9-7.6 years[a]
4	Treated	26.0 months	33.0 months
	Untreated	2.3 months	2.0 months
5	Treated	3.3 months	2.7 months
	Untreated	0.5 months	0.5 months
6	Treated	0.5 months	20.0 months
8	Untreated	0.5 months	No other assessments
	Untreated	0.5 months	No other assessments
9	Treated	1.3 months	2.3 months
	Untreated	2.3 months	2.3 months
11	Treated	21.0 months	25.0 months

One patient, enrolled during the update period, was assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley) at 34.3 months of age and 35.8 months of age. Language scale assessments were not performed as the patient was non-English speaking.

At 34.3 months of age, the patient had age-equivalent scores of 25 months in the Cognitive subtest, 32 months in the Fine Motor subtest, and 26 months in the Gross Motor subtest.

The patient age-equivalent score on the Cognitive subtest improved to 32 months at the last available assessment at 35.8 months of age.

Unassisted Sitting

Most untreated patients with MoCD Type A are unable to sit independently at 12 months of age. An analysis of unassisted sitting in the FAS and GMAS is presented in Table 21.

Treated patients are more likely to be able to sit unassisted than the untreated controls at 12 months of age and at any time. By 12 months of age, three of the seven treated patients (42.9%) with data available were able to sit unassisted for 30 seconds compared with three of the 27 untreated control patients (11.1%). The ability to sit unassisted at any time was reported for six of the nine treated patients (66.7%) and three of the 27 untreated controls (11.1%) in the FAS for whom data are available; none of the matched control patients in the GMAS could sit unassisted at any time.

Table 21. Analysis of Unassisted Sitting (Full Analysis Set and Genotype-Matched Analysis Set, data cut-off 31 October 2020)

Parameter Result	cPMP-Treated Patients				Untreated Controls	
	MCD-501 only (N=4) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=2) n (%)	Total (N=14) n (%)	MCD-502 FAS (N=37) n (%)	MCD-502 GMAS (N=19) n (%)
Able to sit independently for 30 seconds at 12 Months?						
Number of Patients with Data	ND	6	1	7	27	13
Yes	ND	3 (50.0)	0	3 (42.9)	3 (11.1)	0
No	ND	3 (50.0)	1 (100)	4 (57.1)	24 (88.9)	13 (100)
Able to sit independently for 30 seconds at any time?						
Number of Patients with Data	ND	8	1	9	27	13
Yes	ND	5 (62.5)	1 (100)	6 (66.7)	3 (11.1)	0
No	ND	3 (37.5)	0	3 (33.3)	24 (88.9)	13 (100)

Note: Patients were only included in the analysis of unassisted sitting if they had at least one assessment on or after 9 months of age. Note: The six patients that were treated with rcPMP on Study MCD-501 and went on to enroll in Study MCD-201 are only presented in the MCD-201 column.
Note: For treated patients, results are based on the Developmental Milestones Module of the Denver Scale, or the Bayley Gross Motor Subscale Question #26. Those that do not have this question answered, but have higher Bayley gross motor subscale questions answered positively at 12 months were assumed to have been able to sit independently for 30 seconds at 12 months. For patients in MCD-502 results are based on the corresponding question from the Neurological Examination.

Seizures

A summary of seizure categories based on the most recent information collected at the time of data cut-off for the FAS and the GMAS is presented in Table 22.

Consistent with the disease, most patients in the natural history control group had seizures that were either controlled or ongoing (present) on AED therapy. Among treated patients, seven of the 14 patients (50.0%) had seizures ongoing and two (14.3%) had seizures controlled on AEDs and in the untreated control group, 13 of 37 patients (35.1%) had seizures ongoing, and 20 patients (54.1%) had seizures controlled. Very few patients did not have seizures present at any time: two of 14 treated patients (14.3%) and three of 37 (8.1%) were untreated patients. Importantly, three of the 14 treated patients (24.1%) had seizures resolved while treated with cPMP compared with one of the 37 untreated controls (2.7%).

The incidence of seizures was similar in the GMAS, eight of the 19 untreated patients (42.1%) had seizures ongoing at the last visit, with ten patients (52.6%) having their seizures controlled and no patients' having seizures resolved.

Based on the odds ratios, there was no apparent difference between the treated patients and untreated controls for the likelihood of having seizures not present or resolved versus having seizures controlled or continuing (present) in the FAS or GMAS. Results were consistent based on the adjusted model for the GMAS.

Table 22. Seizure Status at Last Assessment (Full Analysis Set and Genotype-Matched Analysis Set)

Parameter Result	cPMP-Treated Patients (FAS and GMAS)				Untreated Controls	
	MCD-501 only (N=4) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=2) n (%)	Total (N=14) n (%)	MCD-502 FAS (N=37) n (%)	MCD-502 GMAS (N=19) n (%)
Not present	0	2 (25.0)	0	2 (14.3)	3 (8.1)	1 (5.3)
Resolved	0	2 (25.0)	1 (100)	3 (21.4)	1 (2.7)	0
Controlled	1 (25.0)	1 (12.5)	0	2 (14.3)	20 (54.1)	10 (52.6)
Present	3 (75.0)	3 (37.5)	1 (50.0)	7 (50.0)	13 (35.1)	8 (42.1)
Odds Ratio[a] (95% CI)	-	-	-	1.216 (0.337, 4.387)		1.461 (0.368, 5.808)

Note: Seizure status is derived based on the last date of contact. Note: The six patients that were treated with rcPMP on Study MCD-501 and went on to enroll in Study MCD-201 are only presented in the MCD-201 column.

[a] A proportional odds model is fitted based on the cumulative logit function, with seizure status as dependent variable and treatment status, MoCD symptom onset, and gender as independent variables. The Odds Ratio represents the odds of the treated patients to have seizure status as either Not Present or Resolved versus Controlled or Present, compared to the natural history patients.

In the FAS, 10 of the 14 treated patients (71.4%) and 31 of the 37 untreated control patients (83.8%) reported prior and/or concomitant therapy with an AED, as did 17 of the 19 matched controls (89.5%) (Table 23).

The number and types of prior and concomitant AEDs reported in the GMAS were similar to those reported in the FAS.

One patient had no past history of seizures. This patient did not experience seizures during the observation period from 32.7 months of age to 3.3 years of age and no antiepileptic drugs (AEDs) were administered. Results of an electroencephalogram performed at screening (32.7 months of age) were normal.

Table 23. Summary of Prior and Concomitant Anti-Seizure Medication Reported in Two or More Patients by WHO ATC Class (Full Analysis Set, data cut-off 31 October 2020)

WHO ATC Class	cPMP-Treated Patients (FAS and GMAS)				Untreated Controls	
	MCD-501 only (N=4) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=2) n (%)	Total (N=14) n (%)	MCD-502 FAS (N=37) n (%)	MCD-502 GMAS (N=19) n (%)
Patients with at least One Anti-Seizure Medication	4 (100.0)	4 (50.0)	2 (100.0)	10 (71.4)	31 (83.8)	17 (89.5)
Antiepileptics/ Barbiturates and Derivatives	4 (100.0)	1 (12.5)	2 (100.0)	7 (50.0)	31 (83.8)	17 (89.5)
Psycholeptics	2 (50.0)	0	0	2 (14.3)	12 (32.4)	6 (31.6)
Benzodiazepine Derivatives	0	4 (50.0)	0	4 (28.6)	0	0
Fatty Acid Derivatives	0	2 (25.0)	0	2 (14.3)	0	0
Other Antiepileptics	0	3 (37.5)	0	4 (28.6)	0	0

Note: The six patients that were treated with rcPMP on Study MCD-501 and went on to enroll in Study MCD-201 are only presented in the MCD-201 column.

Neuroimaging

A summary of first and last status reported for neuroimaging is presented for the FAS in Table 24. Note that there are differences between the studies with regard to reporting of normal and abnormal results: Studies MCD-201 and -202 reported results as 'normal', 'abnormal not clinically significant', or

'abnormal clinically significant', whereas in Studies MCD-501 and MCD-502 results were only reported as 'normal' or 'abnormal'. Detailed by-patient results for the first and last neuroimaging assessments describing the abnormalities reported for the GMAS by matched ID are summarized in Table 24 of the summary of clinical efficacy.

As expected, based on the MoCD Type A phenotype, most patients in both the treated and untreated groups had abnormal neuroimaging results. Further, the majority of patients who completed the neuroimaging assessments experienced no change in findings. One patient who received both rcPMP and fosdenopterin, had an improvement reported from abnormal, clinically significant at the first assessment in Study MCD-201 to abnormal, not clinically significant at 0.6 years later with the MRI results continuing to be reported as not clinically significant through the last assessment.

Among patients in the untreated control group, 33 (89.2%) of the 37 patients had abnormal results at the first assessment, with consistent results reported at the last assessment (35 patients, 94.6%). Results were similar for the 19 matched control patients in the GMAS, with 17 of 19 patients (89.5%) having abnormal results at the last assessment.

The neuroimaging results reported in the PFAS were similar to those reported in the FAS.

For one patient, A magnetic resonance imaging (MRI) performed at screening (32.7 months of age) was abnormal, not clinically significant, and showed abnormal basal ganglia. No other imaging assessments were performed.

Table 24. Summary of Neuroimaging Results (Full Analysis Set and Genotype-Matched Analysis Set, data cut-off 31 October 2020)

	cPMP-Treated Patients				Untreated Controls	
Analysis Visit Result	**MCD-501 only (N=4) n (%)**	**MCD-201 (N=8) n (%)**	**MCD-202 (N=2) n (%)**	**Total (N=14) n (%)**	**MCD-502 FAS (N=37) n (%)**	**MCD-502 GMAS (N=19) n (%)**
First Value						
Normal	0	1 (12.5)	1 (50.0)[a]	1 (8.3)	4 (10.8)	3 (15.8)
Indeterminate	1 (25.0)	1 (12.5)	0	2 (16.7)	0	0
Abnormal	3 (75.0)	5 (71.4)	0	8 (66.7)	33 (89.2)	16 (84.2)
Abnormal, NCS	0	0	0	0	0	0
Abnormal, CS	0	1 (14.3)	1 (50.0)	1 (8.3)	0	0
Last Value						
Normal	0	2 (25.0)	0	2 (14.3)	2 (5.4)	2 (10.5)
Indeterminate	0	0	0	0	0	0
Abnormal	4 (100)	0	0	4 (28.6)	35 (94.6)	17 (89.5)
Abnormal, NCS	0	2 (25.0)	0	2 (14.3)	0	0
Abnormal, CS	0	4 (50.0)	2 (100)	6 (42.9)	0	0

Note: The six patients that were treated with rcPMP on Study MCD-501 and went on to enroll in Study MCD-201 are only presented in the MCD-201 column.

[a] This patient had two neuroimaging assessments *in utero*, including an ultrasound that was reported as normal (as reflected in the table) and an MRI conducted ~3 weeks prior to birth that showed cerebral dysgenesis

Neurologic Examinations

Overall, cPMP-treated patients generally had better neurological functioning at the last visit compared with untreated controls.

A summary of neurological findings at baseline and last visit in the FAS and GMAS is presented in Table 25. Results for data collected prospectively for neurologic examinations are summarized in Table 26.

A lower percentage of patients (FAS analysis) who received cPMP treatment had abnormal results at the last assessment for truncal tone (50.0% treated vs 89.2% untreated), appendicular tone (57.1% treated vs 94.6% untreated), and deep tendon reflexes (64.3% treated vs 81.1% untreated).

The neurologic examination results reported in the PFAS were similar. At last visit, cPMP-treated patients had better neurological functioning compared with untreated control patients with a lower percentage of patients reporting abnormal results for spontaneous movement (60.0% treated vs 92.9% untreated), truncal tone (70.0% treated vs 92.9% untreated), appendicular tone (80.0% treated vs 100% untreated), and deep tendon reflexes (70.0% treated vs 92.9% untreated).

For one patient, Results from neurologic examinations performed at screening (32.7 months of age) were normal and remained unchanged up to the last available assessment at 3.3 years of age.

Table 25. Summary of Neurologic Examination Results at the Last Assessment (Full Analysis Set and Genotype-Matched Analysis Set, data cut-off 31 October 2020)

	cPMP-Treated Patients				Untreated Controls	
Parameter Result	**MCD-501 only (N=4) n (%)**	**MCD-201 (N=8) n (%)**	**MCD-202 (N=2) n (%)**	**Total (N=14) n (%)**	**MCD-502 FAS (N=37) n (%)**	**MCD-502 GMAS (N=19) n (%)**
Spontaneous Movement						
Normal	2 (50.0)	3 (37.5)	0	5 (35.7)	5 (13.5)	2 (10.5)
Abnormal	2 (50.0)	5 (62.5)	1 (50.0)	8 (57.1)	29 (78.4)	15 (78.9)
Not examined	0	0	1 (50.0)	1 (7.1)	0	0
Truncal Tone						
Normal	0	2 (25.0)	1 (50.0)	3 (21.4)	3 (8.1)	1 (5.3)
Abnormal	0	6 (75.0)	1 (50.0)	7 (50.0)	33 (89.2)	17 (89.5)
Not examined	0	0	0	0	0	0
Appendicular Tone						
Normal	0	0	1 (50.0)	1 (7.1)	1 (2.7)	1 (5.3)
Abnormal	0	8 (100)	0	8 (57.1)	35 (94.6)	17 (89.5)
Not examined	0	0	1 (50.0)	1 (7.1)	0	0
Deep Tendon Reflexes						
Normal	2 (50.0)	2 (25.0)	1 (50.0)	5 (35.7)	3 (8.1)	2 (10.5)
Abnormal	2 (50.0)	6 (75.0)	1 (50.0)	9 (64.3)	30 (81.1)	15 (78.9)
Not examined	0	0	0	0	0	0
Primitive Reflexes						
Normal	1 (25.0)	0	0	1 (7.1)	0	0
Abnormal	2 (50.0)	0	0	2 (14.3)	0	0
Not examined	0	1 (12.5)	0	2 (14.3)	0	0

Abbreviations: cPMP=cyclic pyranopterin monophosphate; FAS=Full Analysis Set; GMAS=Genotype-Matched Analysis Set. Note: The six patients that were treated with rcPMP on Study MCD-501 and went on to enroll in Study MCD-201 are only presented in the MCD-201 column.

Table 26. Summary of Neurologic Examination Results at the Last Assessment (Prospective Full Analysis Set, data cut-off 31 October 2020)

Parameter Result	**cPMP-Treated Patients (N=10) n (%)**	**Untreated Controls (N=14) n (%)**
Spontaneous Movement		
Normal	3 (30.0)	1 (7.1)
Abnormal	6 (60.0)	13 (92.9)
Not examined	1 (10.0)	0

Parameter Result	cPMP-Treated Patients (N=10) n (%)	Untreated Controls (N=14) n (%)
Truncal Tone		
Normal	3 (30.0)	1 (7.1)
Abnormal	7 (70.0)	13 (92.9)
Not examined	0	0
Appendicular Tone		
Normal	1 (10.0)	0
Abnormal	8 (80.0)	14 (100)
Not examined	1 (10.0)	0
Deep Tendon Reflexes		
Normal	3 (30.0)	1 (7.1)
Abnormal	7 (70.0)	13 (92.9)
Not examined	0	0
Primitive Reflexes		
Normal	0	0
Abnormal	0	0
Not examined	2 (20.0)	0

Note: The six patients that were treated with rcPMP on Study MCD-501 and went on to enroll in Study MCD-201 are only presented in the MCD-201 column.

Ancillary analyses

The following section presents key efficacy results to assess for the potential effects in subpopulations, including time of cPMP treatment initiation and gender. As all 14 treated patients had MoCD-symptom onset within 28 days of birth, no conclusions can be drawn on this aspect.

Treatment Initiation

As specified in the SAP, early treatment of cPMP is defined as treatment occurring within 14 days of birth whereas late treatment is > 14 days after birth. Most patients (11/14, 78.6%) had initiated treatment within 14 days of birth.

Overall Survival

There was no apparent difference in OS for patients who were treated early versus those who were not. As of the data cut-off date of 31 October 2020, one patient treated within 14 days of birth and one patient treated > 14 days after birth had died. Median OS was not estimated in either group.

Feeding Pattern, Growth, and Mobility

Patients who initiated treatment within 14 days of birth were more likely to be feeding orally (7/11, 63.6%) compared with those patients who initiated treatment later (0/3, 0%). Patients who initiated treatment within 14 days of birth had improved z-scores for head circumference compared with those patients who initiated treatment later (median: 0.19 vs -2.52). There was no apparent difference in median height z-scores (-0.84 vs -1.40) or weight z-scores (-0.26 vs -0.54) at the last assessment for these groups.

Data are available for GMFCS-ER and for the evaluation of unassisted sitting for nine of the 10 patients included in the prospective Studies MCD-201 and MCD-202 (no developmental data were available for one patient from Study MCD-202 due to the patient's discontinuation from the study on Day 13).

Patients who initiated treatment within 14 days of birth were more likely to be ambulatory (4/7, 57.1%) compared with those who initiated treatment later (0/2, 0%).

Similarly, patients who initiated treatment within 14 days of birth were more likely to be able to sit unassisted (6/7, 85.7%) compared with those who initiated treatment later (0/2, 0%).

Seizures and Neurologic Examination

Seizures were reported as not present, resolved, or controlled in a higher percentage of patients who initiated treatment within 14 days of birth (7/11, 63.7%) compared with patients who initiated treatment later (0/3, 0%).

Patients who initiated treatment within 14 days of birth were more likely to have normal results reported on the neurological examination compared with patients who initiated treatment later, including spontaneous movements (45.5% vs 0%), truncal tone (assessment 27.3% vs 0%), and deep tendon reflexes (45.5% vs 0%).

Gender

Overall Survival

In males, the survival probability at 1 year of age was 100% for treated patients compared with 78% in the untreated controls; median survival time was not estimated in the treated group and was 50.7 months in the untreated group. In females, the survival probability at 1 year of age was 86% for treated patients and 67% for untreated controls; median survival time was not estimated in the treated group and was 61.7 months for in the untreated group.

There was no apparent difference in OS between males and females who received cPMP with survival probabilities at 2 years of age of 83% and 86% for males and females who received treatment with cPMP. The median OS was not estimated for either males or females due to the low number of deaths.

Other Efficacy Parameters

There was no apparent difference in reduction in biomarker levels for treated patients based on gender; both groups showed rapid reductions upon initiation of treatment with cPMP in contrast to the untreated control patients where biomarker levels remained elevated.

Both males and females who received cPMP were more likely to have GMFCS-ER Level I- IV compared with the untreated control group, with no differences observed in the treated group based on gender. Among males, three of the four treated patients (75.0%) with prospective data collected were GMFCS-ER Level I-IV at the last assessment compared with two of eight untreated controls (25.0%). Similarly, for females, two of five treated patients (40.0%) with prospective data collected were GMFCS-ER Level I-IV at the last assessment compared with none of three untreated controls (0%) who were all assessed at Level V.

Treated patients of both genders were more likely to be able to sit unassisted at any time compared with untreated controls. Among males, three of four treated patients (75.0%) compared with three of 21 untreated patients (14.3%) could sit unassisted at any time. Similarly, for females, three of five treated patients (60.0%) compared with none of the six untreated patients (0%) could sit unassisted.

There was no difference in seizure status between treated patients and untreated controls and no difference in the incidence of seizures by gender for treated patients.

Patients who received cPMP were more likely to have normal neurological examination results than the untreated controls regardless of gender.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as

well as the benefit risk assessment (see later sections).

Table 27. Summary of efficacy for the integrated efficacy analysis, data cut-off 31 October 2021

Title: Integrated efficacy analysis			
Study identifier	MCD501 MCD201 MCD202 MCD502		
Design	Study MCD-501 is a retrospective study of patients with MoCD type A treated with rcPMP in the named patient program. Study MCD-201 is an ongoing, single-arm, dose-escalation study with fosdenopterin in patients pre-treated with rcPMP. Study MCD-202 is an ongoing, single-arm, dose-escalation study in treatment naïve patients with MoCD type A. Results from studies MCD-501, MCD-201 and MCD-202 are pooled and analysed in an integrated way. Study MCD-502 is a natural history study used to compare the data from the integrated efficacy analysis.		
	Duration of Studies		Study MCD-201: initial treatment phase of 6 months, followed by long term extension. Study MCD-202: initial treatment phase of 12 months, followed by long term extension. Median total time on cPMP was 1773 days (4.9 years) and ranged from 6 days to 4531 days (12.4 years)
Hypothesis	Exploratory: efficacy of fosdenopterin in treatment of MoCD type A.		
Treatments groups	cPMP treated patients		rcPMP in study MCD-501, fosdenopterin in study MCD-201 and MCD-202. N=15
	Natural history control		No treatment. N=37
Endpoints and definitions	Primary endpoint	Overall survival	Survival probability at 1 year of age.
	Secondary endpoint	Urine SSC	Change from baseline in urine SSC levels.
	Secondary endpoint	Feeding	Number of patients able to feed orally at the last visit
	Secondary endpoint	GMCFS-ER	Number of patients with ambulation without restriction (level I of the GMFCR) at the last visit
	Secondary endpoint	Seizures	Number of patients **seizure free** at the last visit
	Secondary endpoint	Sitting unassisted	Number of patients able to sit unassisted for 30 seconds at 12 months of age based on item #26 on the Bayley scale.
Database lock	30 OCT 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		

Title: Integrated efficacy analysis			
Study identifier	MCD501 MCD201 MCD202 MCD502		
Analysis population and time point description	Integrated efficacy population (FAS). Number of patients with available assessment at last visit is presented per efficacy variable (n/N).		
Descriptive statistics and estimate variability	Treatment group	cPMP treated	Natural history
	Number of subjects in group	15	37
	Overall survival	93.3%	75.3%
	Urine SSC Mean (SD)	-157.7 (253.06)	24.8 (104.61)
	Feeding n/N(%)	9/15 (60)	10/33 (30.3)
	GMCFS-ER n/N (%)	5/10 (50)	1/11 (9.1)
	Seizures n/N (%)	6/15 (40)	3/37 (8.1)
	Sitting unassisted n/N (%)	3/7 (42.9)	3/27 (11.1)
Notes	Analysis in de FAS is supported by analysis in the GMAS		

2.6.5.3. Clinical studies in special populations

Since this is an inborn disease with onset during childhood, the clinical studies were conducted in paediatric patients and not in the elderly.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

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

Since the integrated efficacy analysis is considered pivotal for this application, the pooled analysis is discussed in the main studies.

2.6.5.6. Supportive study(ies)

Not applicable

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Five clinical studies were conducted to support the proposed indication of MoCD type A.

Study MCD-501 was a retrospective data collection of patients treated with rcPMP under a named patient program. A retrospective study design has limitations that might complicate conclusions on

treatment efficacy such as the potential of selection bias. Twenty-one patients were treated in the named patient program. The exact reasons for not including patients in the clinical studies have been provided on patient level and did not raise any concerns with regards to the potential introduction of selection bias. Since study MCD-501 was the study in which most patients enrolled in study MCD-201 were pre-treated, this study also provides pre-treatment baseline values for these patients. Patients pre-treated with rcPMP were eligible to enrol in study MCD-201, an ongoing open-label single-arm trial. Study MCD-202 is an ongoing open-label single-arm phase 2/3 trial for patients not pre-treated with rcPMP.

Data collected in studies MCD-501, MCD-201 and MCD-202 were compared to a natural history cohort from study MCD-502. It was argued that a (placebo) controlled trial was not feasible in this patient population given the severity of the disease and the absence of other treatment options. This rationale is acknowledged and accepted. Since rcPMP and fosdenopterin are considered therapeutically equivalent based on the quality attributes and the consistency in pharmacodynamic effect, the pre-treatment with rcPMP is not considered an issue.

The use of a natural history comparator has limitations concerning the external and internal validity and is only acceptable in case the natural history is predictable, the expected treatment effect large and the endpoints objective. In the case of MoCD type A, these criteria are considered to be fulfilled. The majority of patients show a severe neonatal-onset form of MoCD type A, for which disease progression is rapid and predictable. Positive results were obtained in the named-patient program and case studies published in the literature. Since natural history data was retrospectively collected, there is potential for selection bias. Enrolment of study MCD-501 occurred before the natural history study, and the enrolment of study MCD-201 after the natural history study. There was a good regional overlap between treated patients and controls. Overall, it is considered unlikely that selection bias has occurred.

The eligible patient population for the clinical studies consisted of patients of all ages with a confirmed or suspected diagnosis of MoCD type A. If the diagnosis could not be genetically confirmed, treatment was discontinued. This is understood and acceptable given the mechanism of action of fosdenopterin. For study MCD-202 specifically, cohorts were specified for patients with onset of symptoms after 28 days of age. Enrolment of patients pre-symptomatically, based on a prenatal diagnosis was also possible. Study MCD-202 is the only study with fosdenopterin enrolling treatment naïve patients. Since the aimed indication is the treatment of MoCD type A, the patient population eligible for enrolment in the clinical studies is representative of the proposed indicated population.

Treatment schedules differed between the clinical studies. Study MCD-501 was a retrospective study; patients had previously received rcPMP treatment in accordance with the named-patient treatment plans. Study MCD-201 included a dose-escalation schedule to increase the dose until a dose was reached that was not tolerated or if this dose resulted in exposures above the NOAEL AUC (based on maximum observed exposure in non-clinical studies and not based on toxicological findings). The starting dose was similar to the rcPMP dose that was received in study MCD-501. Dose escalation and maximum dose were formalized in the protocol of study MCD-202. The deviations in dosing between study MCD-501 and study MCD-201 and MCD-202 should be kept in mind when interpreting the efficacy results. In all studies, after the initiation of treatment in the hospital, doses were prepared and administered by the parents/caregivers at home via a central venous line (port-a-cath), after instructions and training. This is understood given the daily infusions.

The objective of study MCD-501 was purely retrospective data collection to gather information on the treatment with rcPMP. The primary objective of study MCD-201 was to study the safety of fosdenopterin. Efficacy parameters were included as secondary endpoints. The efficacy and safety of fosdenopterin were further studied in study MCD-202. The main objective of Study MCD-502 was to

collect survival data and other parameters relevant to describing the clinical status of patients with MoCD type A. The objectives are considered appropriate.

All clinical studies consistently measured efficacy endpoints, plasma and urine biomarkers (see pharmacodynamics section), growth parameters, feeding status, and seizure activity. The prospective studies collected developmental, neuroimaging, and neurological assessments per protocol. For the retrospective studies, data collection was dependent on available records. The included efficacy endpoints are considered appropriate to assess the efficacy of fosdenopterin in the MoCD type A population. Patients present, often soon after birth, with seizures refractory to treatment. SSC-induced neuronal injury leads to abnormal motor and cognitive development in all MoCD type A patients.

An effect on seizures would be an appropriate endpoint to assess efficacy. However, as the applicant pointed out in the protocol assistance, the quantification of seizures is difficult given the diversity of presentation and the confounding introduced by alterations in seizure medications. The Bayley scale is a validated scale for assessing development in children starting from 2 months of age. Although this scale is not validated for the use in MoCD type A patients specifically, it is expected to give a good overall idea of the motor and cognitive development of patients relative to healthy peers.

The applicant has amended the primary endpoints of the prospective studies multiple times. As also suggested in the protocol assistance and follow-up advice, it is not considered appropriate for such a complex and rare disease to focus on one specific primary endpoint. The strategy of the applicant to collect data on multiple parameters indicative of the health status of a child is therefore supported. The data will be assessed in a totality of evidence approach. Although survival was not a pre-defined endpoint in the separate study protocols, it is a primary outcome of efficacy in the integrated analysis of efficacy. This is not considered an issue since it is expected that survival data was captured in a systematic way across studies.

Given the rare nature of the disease, no formal sample size calculations were done, and enrolment was dictated by the availability of patients. This is understood and acceptable, also given the descriptive nature of the analyses. Given the limited number of included patients, the applicant has decided to present the efficacy data of these studies in an integrated efficacy analysis. This approach is understood and was found acceptable in the pre-submission meeting. For the assessment of the integrated efficacy analysis, the FAS will be considered of primary importance. However, the GMAS, in which genotype-matched patients are included, will provide important supportive information and the PFAS (prospective analysis set) since not all parameters were retrospectively collected.

For MoCD type A, no clear genotype-phenotype relationship has been described. It remains unclear whether genotype is the only variable on which matching should be based, that is, whether it captures all possible confounding between treatment and outcome. For the matching to be valid, we have to assume that given the matching variable (genotype) both the prognosis and the treatment effect are independent of other variables (e.g. gender). However, given the supportive nature of the matched analysis, the need for a pragmatic approach to matching, and the lack of a known mechanism by which gender affects prognosis or treatment effect, the issue is not further pursued.

It is unclear why no missing data imputation was planned, especially for the longitudinal outcomes. However, since those outcomes are only analysed in an exploratory and graphical manner, this issue is not further pursued.

The analysis of OS is considered pivotal for the assessment. As such, emphasis should be placed on the actual treatment effect measure estimated, with respect to the handling of intercurrent events and the estimands framework as outlined in EMA/CHMP/ICH/436221/2017 reflecting on ICH E9 (R1). One intercurrent event of immediate interest here is treatment discontinuation which was observed for three patients (2/8 survivors=25% from study MCD-501 that did not enrol in study MCD-201 and 1/2,

50% from study MCD-202). For the analysis of OS, the applicant employed the treatment policy strategy (i.e. ignoring the occurrence of intercurrent events, in this case, treatment discontinuation), which is considered acceptable. In addition, worst- and best-case scenario sensitivity analyses were provided.

The main estimand for the time to non-oral feeding is based on the treatment policy estimand approach, thus ignoring intercurrent events. This approach does not properly account for the competing event of death. It is however clarified that most of the deaths occurred in the natural history study and thus the inappropriate handling of the competing events is not expected to impact the overall assessment.

Even though the above described approaches to the analysis of feeding patterns can be acceptable given the limited sample size and information available, the shortcomings associated with them imply that they can only be seen as descriptive and supportive.

Efficacy data and additional analyses

Study MCD-501 enrolled 15 patients, of which 10 patients with MoCD type A. In study MCD-201, 8 patients previously treated with rcPMP were enrolled, 6 from study MCD-501 and 2 from the named patient program. In study MCD-202, 5 patients were enrolled, of which two patients with type A is currently on treatment and included in the study. One patient with later onset of MoCD type A was included after the initial submission. One patient turned out to have MoCD type B and one patient was discontinued. The natural history study MCD-502 enrolled 65 patients, of which 37 were diagnosed with MoCD type A.

In total, 15 patients treated with (r)cPMP are included in the FAS and are compared to 37 untreated control patients with MoCD type A. All 15 patients were matched to 1 or more genotype-matched controls from study MCD-502 (GMAS). 11 patients were prospectively followed under cPMP treatment in studies MCD-201 and MCD-202 (PFAS). Ten/14 patients are ongoing on treatment at the data cut-off. Five patients discontinued treatment because of death (2 patients), poor prognosis (1 patient) or with a reason not recorded (2 patients). No pre-symptomatic patients were enrolled in the studies.

The majority of the included patient population treated with rcPMP/fosdenopterin all had symptom onset in utero or shortly after birth and thus represent the severely affected patient population classically described for MoCD type A. Supportive evidence has been submitted from two patients with late onset MoCD type A treated with fosdenopterin, a form of MoCD that presents with a more heterogeneous phenotype. A discussion has been provided that the efficacy and safety data in early onset patients can be extrapolated to the whole patient's population based on the same underlying enzymatic defect and the mechanism of action of fosdenopterin, which is agreed.

For study MCD-202, MCD-202 and MCD-502, there were multiple amendments to the protocol. The majority were clarifications and administrative changes. There were also changes in endpoint hierarchy and endpoints added to the protocols. This is not considered to have a major impact on the data since the data are analysed in an integrated way across the clinical trials. Whether endpoints are primary or secondary is considered a formal issue and will not impact the assessment. There were no protocol deviations that are considered to have impacted the results. Some deviations considered dosing errors in the hospital setting or at home, but all of these were incidental and since fosdenopterin is administered daily over a prolonged period of time this is not considered an issue.

The data cut-off is early (30 October 2020) relative to the submission date of the MAA. In the response to the LoQ, the applicant provided updated efficacy (OS, biomarkers) data which has been included in this overview.

Patient demographics were comparable between cPMP treated patients and the natural history control cohort. The genetic diagnosis was generally confirmed at a later age for the natural history patients. The median age of symptom onset is similar, with 1 day in the treated patients and 2 days in the natural history patients in the FAS. Fourteen treated patients presented with first MoCD symptoms in the first days (1-5) after birth. One late onset patient was enrolled after the initial data cut-off, with symptom onset at 12 months of age. Diagnosis was confirmed at 25 months of age. In the natural history cohort, four patients with symptom onset after 1 month of age, "late-onset" were enrolled, indicating less severe disease. This re-enforces the idea that a clear genotype-phenotype relation cannot be established, and the influence of epi-genetic factors on the efficacy of fosdenopterin cannot be ruled out. As it is considered impossible to correct for these factors – as they are unknown - this issue is not further pursued.

Most patients experience seizures in utero or in the neonatal period. This is similar between treatment patients and the natural history controls. However, baseline % of seizures and the presence of feeding difficulties differs between treated patients and controls. It is assumed that the early initiation of treatment prevented onset of seizures and feeding difficulties, explaining the difference, but this cannot be confirmed. Most patients received their first treatment in the first days of life. However, there were some exceptions with the onset of treatment at day 32, 37 and 69, which is considered relatively late.

All patients included in study MCD-501 received 240 ug/kg as the maximum dose. In study MCD-201 and MCD-202, dose-escalation to 1200 and 1300 ug/kg was possible. This maximum dose was achieved by 4 patients in MCD-201 and two patients in MCD-202.

The data were submitted as an integrated efficacy analysis across trials. All available data was also presented on a patient level. This approach is considered acceptable given the very limited number of patients included and the amount of missing data. This approach has also been agreed upon during the pre-submission meeting.

In the cPMP treated cohort, 10 patients were ongoing on treatment and were alive at the data cut-off. Two patients treated in study MCD-501 had died. Three patients who had discontinued treatment were alive at the last contact. In the natural history cohort, 24/37 patients had died. Median OS was 4.2 years for the natural history cohort and could not be estimated for the treated patients since there were not many events. There is a clear benefit of cPMP treatment on overall survival in the FAS which is supported by the sensitivity analysis in the GMAS and a worst and best-case analysis.

There was a clear benefit of treatment on oral feeding. In the natural history cohort, the median time to sustained non-oral feeding was 10.5 months compared to 65 months in the treated cohort. The applicant reports a lower percentage of patients able to feed orally at the last visit in the treated group compared to the natural history controls (both in the FAS and GMAS).

The data on weight, height and head circumference z-scores is numerically in favour of fosdenopterin, but the variation in both the natural history cohorts and treated patients is large. At one year of age, z-scores for head circumference are generally below zero in the natural history cohort. Growth is often delayed, but height and weight z-scored in the natural history cohort vary significantly. Review of the individual data shows that there is also a large variation within the cohort of treated patients for whom treatment is ongoing (n=10). Normal or near-normal head circumference was reported in 6/10 patients.

The GMFCS was used to assess gross motor function in the prospectively followed patients. Although this scale is not very sensitive to change (with 5 levels of gross motor function) and is developed for cerebral palsy, it is indicative of functional ability. Baseline motor function according was lower in the natural history cohort, but the age at which a baseline value was obtained was higher (mean: 103.5 vs

41.7 months of age in the treated patients). Treatment was initiated in the first days of life. Consequently, at the moment of the baseline measurement for this specific parameter, patients were already treated for months to years, while the natural history control patients were untreated, possibly explaining the baseline difference. It can be concluded, however that the gross motor function of cPMP treated early onset MoCD type A patients is clearly better at the last visit than the natural history controls with 4/9 patients being ambulatory without restriction versus 1/11 natural history controls for whom data was available.

Data from the Bayley scale was available for 9 cPMP treated patients prospectively followed in study MCD-201 and MCD-202. Four patients showed improvements in the score on three of the domains, the cognitive, fine motor, and gross motor domains. However, the relatively low scaled scores suggest a clear cognitive developmental delay, which is not completely prevented by fosdenopterin treatment. Furthermore, in the natural history controls for whom Bayley scores were available, very low functioning was recorded over all three domains. Given this, it is clear that at least for some patients, the cognitive and motor development clearly exceeds what can be expected based on natural history data. However, given the (substantial) developmental delay visible in most patients, it is expected that a progression will slow down until a plateau is reached which, dependent on baseline neurological damage, is below the level of their healthy peers.

The late onset patient in study MCD-202 presented with a delay in cognitive development. After 1.5 months of treatment with fosdenopterin, 7 months of progress was demonstrated in the patient's cognitive skills.

Based on the natural history, it is unlikely that children with MoCD type A achieve the motor milestone of sitting unassisted. In the cPMP treated group, data was available from 9 patients. Of these, 6 were able to sit unassisted for 30 seconds at any time during the study compared to 3/27 in the FAS and 0/13 in the GMAS natural history controls for whom data was available. The late-onset patient enrolled in study MCD-202 was able to sit unassisted.

Seizures are one of the first and most common presenting symptoms of MoCD type A. Only 3/37 patients in the FAS and 1/19 patients in the GMAS is reported to be seizure-free. In approximately half of the patients in the natural history cohort, seizures are controlled on AED therapy. In the cPMP treated patients, seizures are not resolved in 5/14 patients. Four/14 patients are not on AED's. The seizure data is difficult to interpret since seizure activity was scored by parents and not coherently presented in the listings. Therefore, it is unclear whether the number of seizures per day was stable or decreased on treatment and whether the number of seizures per day was less in the treated patients than in the natural history. In addition to the patients described above, the late-onset patient enrolled in study MCD-202 did not experience seizures at baseline or during the study.

Due to the nature of the disease, neuronal damage occurs very early in life or even in utero. It is therefore not surprising that nearly all patients had abnormal neuroimaging results. The clinical impact of these findings is unknown and cannot be easily deduced from the presented findings. It is clear though, that fosdenopterin treatment does not reverse neuronal injury once present. Patients with MoCD type A often present with axial hypotonia and limb hypertonia. Patients in the natural history cohort for whom data was available nearly all presented with abnormal truncal and appendicular tone and deep tendon reflexes. At the last recorded assessment, patients in the treated group had better neurologic examinations; both compared to the FAS and GMAS historical controls even though the patients in the treated cohort were overall older at the last visit than the controls

Efficacy parameters were compared between children treated before and after 14 days of age. Numbers are very small, 11/14 patients had initiated treatment within 14 days after birth and 3/14 after. This makes it not possible to draw firm conclusions about the impact of treatment initiation on expected benefit. However, as MoCD is a progressive disease, it can be safely assumed that early

treatment is always preferable. No clear trend could be observed with regard to survival. A positive trend of early treatment was observed on developmental parameters. Patients treated after day 14 all had seizures, not responsive to fosdenopterin treatment, which can be explained by the irreversible brain damage which has already occurred. The late onset patient from study MCD-202 was not included in this analysis.

No effect of gender was observed on treatment efficacy. This is as expected given the disease pathology and mechanism of action of fosdenopterin.

Taken together, of the 10 early onset patients treated with fosdenopterin, 5 patients clearly show a coherent overall picture of clinical benefit, which exceeds what can be expected based on natural history. These 5 patients were between 3.1 and 10.9 years of age at the data cut-off. These 5 patients are seizure-free without the need for AED's. Four out of 5 are ambulatory without restrictions. One patient has a delay in gross motor development due to hemiplegia. All 5 patients are able to feed orally and show continued neurodevelopmental progress. Three out of 5 were diagnosed prenatally. All patients showed symptoms consistent with MoCD type A within the first day-week of life, but most did not have seizures and for none of these 5 patients, static encephalopathy was present at baseline. Treatment was initiated on day 1-9 for these patients.

Seizures, static encephalopathy, or progressive brain damage on MRI were recorded at baseline for the other five patients. Despite early treatment initiation in some of these patients (two patients were treated later at respectively 37 and 69 days of age), clear overall clinical benefit is not present in these patients, although they were all still alive at data cut (with the exception of one patient in MCD-202 who discontinued treatment and for whom survival status is not known). These patients have ongoing seizures that are not well controlled on AED's and show severe motor and cognitive development delay consistent with static encephalopathy/microcephaly.

For the 4 patients treated with rcPMP in study MCD-501 who did not enrol in study MCD-201, it is difficult to conclude their benefit from treatment. Two/four patients are deceased, and 2 discontinued treatment shortly after treatment initiation. No reason was recorded for treatment discontinuation, which hampers conclusions.

Justification of the proposed dose

No dedicated dose-finding study was performed. Instead, the dose is substantiated based on pre-clinical findings, PK studies and clinical experience. Please refer to the respective sections for the assessment of the respective findings.

Overall, the justification of the proposed posology is limited. The applicant assumes additional clinical benefit on top of normalization of plasma and urine biomarkers based on pre-clinical findings (see pre-clinical AR). This implies that urine/plasma SSC levels, which show almost immediate decreases with lower doses in study MCD-501, is not the best marker to guide the optimal dose. The plateau effect on SSC levels is also visible in the E-R curves (see clinical pharmacology section). If additional benefit of the higher dose is assumed, it is questioned whether the relatively slow dose escalation (maximal dose is reached after only three months) is justified. However, this was the only dosing regimen studied. For the patients below 1 year of age, a starting dose recommendation is based on gestational age, which is acceptable based on the known differences in renal clearance between term and pre-term neonates.

For patients above one year of age, no starting dose and escalation regimen is proposed, while it can be expected that treatment initiation in late onset patients occurs past 1 year of age. Given the near completion of the renal maturation at 1 year of age and the mild safety profile of fosdenopterin, the

proposed posology is acceptable. Nevertheless, patients should be followed up in the proposed non-interventional Post authorisation safety study (PASS).

Additional efficacy data needed in the context of a MA under exceptional circumstances

Taking into account the totality of the available data, the CHMP was of the view that the data set on the clinical efficacy of Nulibry under normal conditions of use could not be considered comprehensive as due to the rarity of the studied conditions, active or placebo controlled studies of sufficient size are not feasible. In addition, the inclusion of late onset patients in the clinical data set submitted was limited. Due to these limitations it is not possible to establish robust conclusions on the efficacy of Nulibry.

The CHMP was therefore of the view that a marketing authorisation under exceptional circumstances should be granted subject to a number of specific obligations, including a non-interventional PASS in order to further characterise the long-term safety and efficacy of Nulibry.

2.6.7. Conclusions on the clinical efficacy

It can be concluded that fosdenopterin, in the proposed dose, has a beneficial effect on overall survival that exceeds survival of the natural history cohort. In part of the patients, the survival benefit was supported by a consistent overall clinical benefit compared to a natural history population, although a developmental delay compared to healthy peers is present for all patients in various degrees. The benefit consisted of conservation of the ability to feed orally, to grow, continued motor and cognitive development, prevention or stabilization of seizures, all indicative of a protective effect on the brain. As is expected for a disease with irreversible neuronal damage, early treatment before a significant injury has occurred will give the most benefit to patients. This is supported by the data that shows that benefit was limited in patients with extensive neuronal damage/static encephalopathy at baseline. Therefore, the treating physician should carefully consider the treatment of these patients based on the expected treatment benefit.

The included patient population treated with rcPMP/fosdenopterin mainly had symptom onset in utero or shortly after birth and thus represent the severely affected patient population classically described for MoCD type A. One late-onset patient was included in the studies and one patient was treated in the named patient program. It is considered that the efficacy and safety can be extrapolated to late-onset patients based on the same underlying enzymatic defect and the mechanism of action of fosdenopterin. This conclusion is supported by the data of the late-onset patients treated with fosdenopterin. Nevertheless, it is considered valuable to obtain long term efficacy data via the proposed non-interventional PASS.

Overall, the justification of the proposed posology is limited. It is uncertain whether patients are treated with the optimal dose. A higher dose was used in the phase 2/3 clinical studies based on pre-clinical findings that indicated a beneficial effect past the normalization of the urine and plasma SSC levels. Dose escalation was used as a safety precaution and was the only dose regimen used in the studies. Pre-clinical studies give some reassurance that the starting dose of fosdenopterin will lead to a meaningful restoration of liver SOX activity. Therefore, in conclusion, the proposed posology is accepted.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a MA under exceptional circumstances:

- In order to ensure adequate monitoring of safety and efficacy of Nulibry in the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Nulibry.

- Non-interventional Post authorisation safety study (PASS): In order to further characterise the long-term safety and efficacy of Nulibry, the MAH should conduct and submit the results of an observational, prospective study of patients with molybdenum cofactor deficiency (MoCD) Type A treated with Nulibry.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

In study MCD-501, 15 patients were enrolled with suspected MoCD type A who were treated on a named patient basis with rcPMP (80-240 µg/kg per day). Ten of these patients were confirmed to have MoCD type A, four were diagnosed with MoCD type B and one had an unknown diagnosis. In study MCD-201, 8 patients were treated with fosdenopterin, all had previously received rcPMP. In the ongoing study MCD-202, five treatment naïve patients have been treated with fosdenopterin thus far. Three were confirmed to have MoCD type A, and two patients were diagnosed with MoCD type B. The dose of cPMP and fosdenopterin has been gradually increased over the course of the treatment for most patients, for the duration of treatment per quantity of the dose received for patients with MoCD type A, see Table 28. Patients with MoCD type B or an unknown diagnosis were treated between 3 and 17 days before treatment was discontinued.

Table 28. Duration of treatment (days) on rcPMP or fosdenopterin by dose received for patients with MoCD Type A (data cut-off 31 OCT 2021).

Study	[redacted]	Dose Received (µg/kg)																	Total
		rcPMP						NULIBRY											
		80	120	160	180	220	240	240	280	480	525	700	720	800	960	1000	1200	1300	
MCD-501		12	62	186	287	171	892	-	-	-	-	-	-	-	-	-	-	-	1610
MCD-201		-	-	-	-	-	-	-	92	34	-	-	28	-	30	-	2454	-	2638
MCD-501		11	21	35	-	-	1033	-	-	-	-	-	-	-	-	-	-	-	1100
MCD-201		-	-	-	-	-	-	2364	-	83	-	-	57	-	91	-	-	-	2595
MCD-501		11	23	24	-	-	942	-	-	-	-	-	-	-	-	-	-	-	1000
MCD-201		-	-	-	-	-	-	57[a]	-	2092	-	-	71	-	49	-	-	-	2269[b]
MCD-501		12	22	53	-	-	1067	-	-	-	-	-	-	-	-	-	-	-	1154
MCD-201		-	-	-	-	-	-	59	-	31	-	-	32	-	2250	-	-	-	2372
MCD-501		-	-	-	-	-	665[c]	-	-	-	-	-	-	-	-	-	-	-	668[c]
MCD-201		-	-	-	-	-	-	62	-	25	-	-	28	-	32	-	2190	-	2337
MCD-501		-	-	-	-	-	12[d]	-	-	-	-	-	-	-	-	-	-	-	13[d]
MCD-501		-	-	-	-	2[e]	265	-	-	-	-	-	-	-	-	-	-	-	267
MCD-201		-	-	-	-	-	-	60	-	29	-	-	30	-	28	-	2615	-	2762
MCD-501		12	21	55	-	-	363[f]	-	-	-	-	-	-	-	-	-	-	-	451
MCD-501		-	-	-	-	-	22	-	-	-	-	-	-	-	-	-	-	-	22
MCD-501		-	-	-	-	-	6	-	-	-	-	-	-	-	-	-	-	-	6
MCD-201		-	-	-	-	-	-	59	-	33	-	-	27	-	30	-	2167	-	2316
MCD-201		-	-	-	-	-	-	119	-	30	-	-	49	-	63	-	354	-	615
MCD-202		-	-	-	-	-	-	-	-	-	2	25	-	60	-	70	110	1693	1960
MCD-202		-	-	-	-	-	-	-	-	-	-	9	-	-	-	-	-	-	9
MCD-202		-	-	-	-	-	-	-	-	-	-	55	-	-	-	39	108	-	202
Total Days of Dosing	rcPMP	58	149	353	287	173	5267												6291[h]
	NULIBRY							2780	92	2357	2	89	322	60	2573	109	9998	1693	20075
	Both																		26366

Abbreviations: ID=identity; MoCD=molybdenum cofactor deficiency; rcPMP=recombinant Escherichia coli derived cyclic pyranopterin monophosphate. a Actual dose reported as 248 µg/kg. b Based on last recorded dose date of 23 June 2021. Due to missed visits because of restrictions related to the COVID-19 pandemic, forms recording exposure were not yet received, therefore not entered into datasets, although exposure until the data cut-off date of 31 October 2021 was verbally confirmed. c Actual dose calculated as 246 µg/kg. Actual dose reported as 216 µg/kg. f Actual dose reported as 240 µg/kg for 80 days and 247 µg/kg for 283 days. g rcPMP exposure unknown; patient received named-patient use. h Includes 4 additional days of dosing at 25 and 480 µg/kg in two patients (see Footnotes c and d).

Overall patient-years of exposure to cPMP, from the first documented dose of rcPMP to the last dose of fosdenopterin as of the data cut of off 31 October 2021- across the 15 treated MoCD type A patients

was 83.0 patient years. Median total time on cPMP was 1960 days (5.4 years) and ranged from 6◦days to 4896 days (13.4 years). Among the 11 patients who received fosdenopterin, median time on treatment as of the data cut-off for this safety update was 2316.0 days (6.3 years) and ranged from 9 days to 7.6 years.

2.6.8.2. Adverse events

A summary of the overall incidence of treatment-emergent adverse events (TEAEs) is presented by study in Table 29. In study MCD-501, severity and causality were only collected for serious AEs (SAEs). Most patients in each study experienced at least one TEAE, including nine of 10 patients during treatment with rcPMP in Study MCD-501 and all 10 patients in Studies MCD-201 and MCD-202 during treatment with fosdenopterin. The majority of patients reported at least one SAE, including eight out of 10 of patients during treatment with rcPMP (Study MCD-501) and 9 out of 10 patients during treatment with fosdenopterin (Studies MCD-201 and MCD-202); for details, see section Serious adverse events, deaths, and other significant events below.

Table 29. Overall Summary of Treatment-emergent Adverse Events (Safety Set–Patients with MoCD Type A, cut-off 31 October 2021).

Patients with:	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=3) n (%)
Any TEAE	9 (90.0)	8 (100.0)	3 (100.0)
Any treatment-related TEAE[a]	NA	3 (37.5)	0
Any severe TEAE[a]	NA	5 (62.5)	2 (66.7)
Any SAE	8 (80.0)	7 (87.5)	2 (66.7)
Any treatment-related SAE	1 (10.0)	0	0
Any TEAE leading to death	2 (20.0)	0	0
Any TEAE leading to dose modification	0	0	0
Any TEAE leading to treatment discontinuation	0	0	0

Abbreviations: MoCD=molybdenum cofactor deficiency; NA=not available; SAE=serious adverse event; TEAE=treatment-emergent adverse event. a In Study MCD-501, severity and causality were collected only for SAEs. Note: Six of the 10 patients in Study MCD-501 were also treated with Nulibry in Study MCD-201.

The specific TEAEs, categorized by MedRA system organ class (SOC) and preferred term (PT) occurring in more than one patient when combining the studies MCD-501, MCD-201 and MCD-202, are shown in Table 30.

Table 30. Treatment-emergent Adverse Events Reported in >1 Patient by MedDRA SOC and Preferred Term (Safety Set - Patients with MoCD Type A, data cut-off 31 OCT 2021)

System Organ Class Preferred Term	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=2) n (%)
Patients with at least one Adverse Event	***9 (90.0)***	***8 (100.0)***	***3 (100.0)***
Infections and infestations	**8 (80.0)**	**8 (100.0)**	**2 (66.7)**
Pneumonia	3 (30.0)	3 (37.5)	1 (33.3)
Viral infection	0	5 (62.5)	1 (33.3)
Otitis media	2 (20.0)	3 (37.5)	0

System Organ Class Preferred Term	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=2) n (%)
Upper respiratory tract infection	3 (30.0)	2 (25.0)	0
Device related infection	3 (30.0)	1 (12.5)	0
Influenza	0	4 (50.0)	0
Sepsis	2 (20.0)	2 (25.0)	0
Catheter site infection	0	2 (25.0)	1 (33.3)
Gastroenteritis	1 (10.0)	1 (12.5)	1 (33.3)
Gastroenteritis viral	0	2 (25.0)	1 (33.3)
Oral candidiasis	2 (20.0)	1 (12.5)	0
Varicella	2 (20.0)	1 (12.5)	0
Bacteraemia	0	1 (12.5)	1 (33.3)
Bronchitis	1 (10.0)	1 (12.5)	1 (33.3)
Device related sepsis	2 (20.0)	0	0
Ear infection	0	2 (25.0)	0
Fungal skin infection	2 (20.0)	0	0
Lower respiratory tract infection	0	3 (37.5)	0
Nasopharyngitis	0	2 (25.0)	1 (33.3)
Otitis media acute	0	1 (12.5)	1 (33.3)
Respiratory tract infection	1 (10.0)	1 (12.5)	0
Urinary tract infection	1 (10.0)	2 (25.0)	0
Vascular device infection	0	2 (25.0)	0
Viral tonsillitis	0	1 (12.5)	1 (33.3)
Viral upper respiratory tract infection	0	2 (25.0)	0
General disorders and administration site conditions	**8 (80.0)**	**7 (87.5)**	**1 (**33.3**)**
Pyrexia	3 (30.0)	6 (75.0)	1 (33.3)
Complication associated with device	0	6 (75.0)	1 (33.3)
Catheter site discharge	0	2 (25.0)	0
Catheter site extravasation	0	2 (25.0)	0
Catheter site haemorrhage	0	1 (12.5)	1 (33.3)
Catheter site inflammation	1 (10.0)	1 (12.5)	0
Catheter site pain	0	2 (25.0)	0
Device dislocation[a]	2 (20.0)	0	0
Device leakage[a]	2 (20.0)	0	0
Medical device complication	2 (20.0)	0	0
Respiratory, thoracic and mediastinal disorders	**5 (50.0)**	**7 (87.5)**	**2 (66.7)**
Cough	1 (10.0)	4 (50.0)	1 (33.3)
Sneezing	1 (10.0)	2 (25.0)	0
Asthma	1 (10.0)	1 (12.5)	0
Epistaxis	0	2 (25.0)	0
Oropharyngeal pain	0	2 (25.0)	0

System Organ Class Preferred Term	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=2) n (%)
Rhinorrhoea	1 (10.0)	0	1 (33.3)
Skin and subcutaneous tissue disorders	**5 (50.0)**	**7 (87.5)**	**2 (66.7)**
Rash	0	3 (37.5)	0
Dermatitis	1 (10.0)	0	1 (33.3)
Eczema	2 (20.0)	0	1 (33.3)
Rash maculo-papular	0	2 (25.0)	0
Skin disorder	0	2 (25.0)	0
Gastrointestinal disorders	**4 (40.0)**	**6 (75.0)**	**2 (66.7)**
Vomiting	0	3 (37.5)	2 (66.7)
Diarrhoea	0	2 (25.0)	1 (33.3)
Abdominal pain	0	2 (25.0)	0
Constipation	1 (10.0)	1 (12.5)	0
Injury, poisoning and procedural complications	**0**	**6 (75.0)**	**1 (**33.3**)**
Contusion	0	1 (12.5)	1 (33.3)
Blood and lymphatic system disorders	**2 (20.0)**	**3 (37.5)**	**1 (**33.3**)**
Anaemia	2 (20.0)	1 (12.5)	1 (33.3)
Eye disorders	**2 (20.0)**	**3 (37.5)**	**1 (**33.3**)**
Conjunctival haemorrhage	1 (10.0)	0	1 (33.3
Eye swelling	0	2 (25.0)	0
Strabismus	1 (10.0)	1 (12.5)	0
Nervous system disorders	**1 (10.0)**	**4 (50.0)**	**1 (**33.3)
Seizure	0	2 (25.0)	1 (33.3)
Metabolism and nutrition disorders	**0**	**2 (25.0)**	**2 (66.7)**
Hypoglycaemia	0	0	2 (66.7)
Product issues	**0**	**4 (50.0)**	**0**
Device dislocation[a]	0	3 (37.5)	0
Device leakage[a]	0	2 (25.0)	1 (33.3)
Device occlusion	0	2 (25.0)	0
Psychiatric disorders	**1 (10.0)**	**3 (37.5)**	**0**
Agitation	0	2 (25.0)	0
Irritability	1 (10.0)	1 (12.5)	0
Surgical and medical procedures	**2 (20.0)**	**1 (12.5)**	**1 (**33.3**)**
Central venous catheterisation	0	1 (12.5)	1 (33.3)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; MoCD=molybdenum cofactor deficiency; SOC=system organ class
Note: Six of the 10 patients in Study MCD-501 were also treated with Nulibry in Study MCD-201.
[a] Coding was conducted using MedDRA version 17.0 in Study MCD-501 and MedDRA version 21.1 in Studies MCD-201 and MCD-202; the SOC for these preferred terms (device dislocation and device leakage) was modified between these two versions of the dictionary.

Seven of the 11 patients from studies MCD-201 and MCD-202 reported a TEAE of severe intensity. In study MCD-201 TEAEs of severe intensity were reported in four patients; all four had severe events relating to complications associated with the device used to infuse cPMP. Other severe events that were reported were mostly viral infections and respiratory failure/infection. In study MCD-202, the severe

events were apnoea, bacteraemia, pneumonia, and vomiting in one patient and seizure in the other. All severe events of both studies were assessed as unrelated to study treatment, except one report of device dislocation, which was assessed as probably related.

Device-related complications

Eight of ten patients treated with fosdenopterin experienced at least one device-related adverse event. The events reported in more than one patient included complications associated with the device (7 patients), device dislocation and catheter site infection (3 patients each), catheter site extravasation, catheter site pain, central venous catheterization, catheter site discharge, device leakage, device occlusion, bacteraemia, sepsis, and vascular device infection (2 patients each).

Skin Disorders

Overall, skin and subcutaneous tissue disorders were reported in five out of 10 patients in study MCD-501, seven out of 8 patients in study MCD-201, and one out of 2 patients in study MCD-202. The events within the skin and subcutaneous tissue disorders SOC reported in >1 patient overall were rash (three patients) and dermatitis, eczema, maculo-papular rash, and skin disorder (verbatim term: skin defect nearby port central venous line with the risk of dislocation) (two patients each). The event of skin disorder (study MCD-201) was assessed as serious and severe in intensity.

Treatment related TEAEs

In study MCD-501, causality was only collected for SAEs. One SAE reported during treatment with rcPMP was considered possibly treatment-related; this was necrotizing colitis, which resulted in the patient's death (see section *Serious adverse events, deaths, and other significant events* for details). In study MCD-201, one patient experienced a TEAE of catheter site inflammation that was moderate in severity and a TEAE of device dislocation that was severe; both AEs were assessed by the Investigator as probably related to study drug. In study MCD-202 no TEAEs were assessed as being treatment-related by the Investigator.

Phototoxicity

One notable safety concern (i.e., a potential risk of phototoxicity) was identified in the nonclinical toxicology program. In vitro and in vivo animal studies demonstrated phototoxic effects of fosdenopterin. Although there was no evidence of phototoxicity in the clinical studies, potential phototoxicity was identified late in the nonclinical program; thus, the clinical studies did not include specific monitoring procedures for phototoxicity. During clinical studies up until the cut-off date of 31 October 2021 there have been two reports of skin related AEs which are possibly related to phototoxicity. However, causality to fosdenopterin treatment cannot be established.

AEs in patients later diagnosed not to have MoCD type A

The patients in studies MCD-501 and MCD-202 who were suspected of having MoCD type A but were later diagnosed not to have MoCD type A, were treated with cPMP relatively short (range: 3-17 days). Among the five patients in study MCD-501 with MoCD Type B or with an unknown type, one patient with MoCD Type B experienced TEAEs. The reported events in this patient included tachycardia, oral candidiasis, and stridor; all events were non-serious.

In study MCD-202, one patient was enrolled based on a suspected diagnosis of MoCD Type A. All TEAEs in this patient were assessed as unrelated to study treatment. The patient was discontinued from treatment on day 17 after genetic testing failed to confirm the diagnosis of MoCD Type A.

AEs in healthy adults of study MCD-101

Overall, TEAEs, both related and unrelated to treatment, were reported at similar incidence rates between subjects treated with fosdenopterin and placebo in the clinical study MCD-101. The majority of TEAEs were mild in intensity, most resolved spontaneously, and all were resolved by the end of the study. No TEAEs led to discontinuation or death, and no severe or life-threatening TEAEs occurred during the study. There was one SAE reported in a placebo-treated subject.

2.6.8.3. Serious adverse event/deaths/other significant events

In study MCD-501 eight out of 10 patients and in in studies MCD-201 and MCD-202 nine out of 10 patients experienced at least one treatment-emergent SAE. All SAEs reported across the three studies are summarized by MedDRA SOC and the preferred term in Table 31.

The most commonly reported types of SAEs were device/catheter-related events and infections. Most SAEs were reported in only one patient. SAEs by MedDRA PT reported in more than one patient in study MCD-501 were device-related infection (three patients); and pneumonia, sepsis, device-related sepsis, pyrexia, medical device complication, and device dislocation (two patients each). In patients who received fosdenopterin, SAEs reported in more than one patient were complications associated with the device (five patients), pneumonia (three patients), and pyrexia, lower respiratory tract infection, catheter site infection, central venous catheterization, vascular device infection, viral infection, and bacteraemia (two patients each).

All but one SAE were considered by the Investigators to be unrelated to study treatment. One event reported during treatment with rcPMP in study MCD-501 was considered possibly treatment-related. The reported event was necrotizing colitis, which resulted in the patient's death. There were no treatment-related SAEs in studies MCD-201 and MCD-202. There were no hypersensitivity or acute infusion-related reactions associated with the administration of cPMP in any patient.

Table 31. Treatment-emergent Serious Adverse Events by MedDRA SOC and Preferred Term (Safety Set - Patients with MoCD Type A, data cut-off 31 october 2021)

System Organ ClassPreferred Term	**MCD-501 (N=10) n (%)**	**MCD-201 (N=8) n (%)**	**MCD-202 (N=2) n (%)**
Patients with at least one SAE	***8 (80.0)***	***7 (87.5)***	***2 (66.7)***
Infections and infestations	**6 (60.0)**	**6 (75.0)**	**1 (33.3)**
Pneumonia	2 (20.0)	2 (25.0)	1 (**33.3**)
Device related infection	3 (30.0)	1 (12.5)	0
Sepsis	2 (20.0)	1 (12.5)	0
Bacteraemia	0	1 (12.5)	1 (**33.3**)
Catheter site infection	0	2 (25.0)	0
Device related sepsis	2 (20.0)	0	0
Lower respiratory tract infection	0	2 (25.0)	0
Vascular device infection	0	2 (25.0)	0
Viral infection	0	1 (12.5)	1 (**33.3**)
Catheter site abscess	0	1 (12.5)	0
Febrile infection	1 (10.0)	0	0
Gastroenteritis	0	0	1 (**33.3**)

System Organ ClassPreferred Term	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=2) n (%)
Gastroenteritis viral	0	0	1 (**33.3**)
Infection	1 (10.0)	0	0
Otitis media	0	1 (12.5)	0
Pneumonia influenzal	0	1 (12.5)	0
Pneumonia respiratory syncytial viral	1 (10.0)	0	0
Respiratory tract infection	1 (10.0)	0	0
Rhinovirus infection	0	1 (12.5)	0
Staphylococcal infection	1 (10.0)	0	0
Staphylococcal sepsis	1 (10.0)	0	0
Upper respiratory tract infection	1 (10.0)	0	0
Urinary tract infection	0	1 (12.5)	0
Varicella	1 (10.0)	0	0
Viral tonsillitis	0	0	1 (**33.3**)
Viral upper respiratory tract infection	0	1 (12.5)	0
General disorders and administration site conditions	**5 (50.0)**	**5 (62.5)**	**1 (33.3)**
Complication associated with device	0	4 (50.0)	1 (**33.3**)
Pyrexia	2 (20.0)	2 (25.0)	0
Device dislocation[a]	2 (20.0)	0	0
Medical device complication	2 (20.0)	0	0
Catheter site discharge	0	1 (12.5)	0
Catheter site extravasation	0	1 (12.5)	0
Catheter site inflammation	0	1 (12.5)	0
Catheter site swelling	0	0	1 (**33.3**)
Device leakage[a]	1 (10.0)	0	0
Swelling	0	1 (12.5)	0
Respiratory, thoracic andmediastinal disorders	**2 (20.0)**	**1 (12.5)**	**1 (33.3)**
Apnoea	0	0	1 (**33.3**)
Pleural effusion	1 (10.0)	0	0
Pneumonia aspiration	0	1 (12.5)	0
Respiratory distress	1 (10.0)	0	0
Respiratory failure	0	1 (12.5)	0
Upper airway obstruction	0	1 (12.5)	0
Gastrointestinal disorders	**2 (20.0)**	**0**	**1 (33.3)**
Erosive oesophagitis	**0**	1 (12.5)	**0**
Necrotising colitis	1 (10.0)	0	0
Stomatitis	1 (10.0)	0	0
Vomiting	0	0	1 (**33.3**)
Metabolism and nutrition disorders	**0**	**2 (25.0)**	**0**
Dehydration	0	1 (12.5)	0

System Organ ClassPreferred Term	MCD-501 (N=10) n (%)	MCD-201 (N=8) n (%)	MCD-202 (N=2) n (%)
Diabetic ketoacidosis	0	1 (12.5)	0
Type 1 diabetes mellitus	0	1 (12.5)	0
Product issues	**0**	**1 (12.5)**	**0**
Device dislocation[a]	0	1 (12.5)	0
Device leakage[a]	0	1 (12.5)	0
Nervous system disorders	**1 (10.0)**	1 (12.5)	**1 (33.3)**
Epilepsy	0	1 (12.5)	0
Myoclonus	1 (10.0)	0	0
Seizure	0	0	1 (**33.3**)
Subdural effusion	1 (10.0)	0	0
Surgical and medical procedures	**0**	**1 (12.5)**	**1 (33.3)**
Central venous catheterisation	0	1 (12.5)	1 (**33.3**)
Psychiatric disorders	**1 (10.0)**	**0**	**0**
Irritability	1 (10.0)	0	0
Skin and subcutaneous tissuedisorders	**0**	**1 (12.5)**	**0**
Skin disorder	0	1 (12.5)	0
Vascular disorders	**0**	**1 (12.5)**	**0**
Venous thrombosis	0	1 (12.5)	0

[a] Coding was conducted using MedDRA version 17.0 in Study MCD-501 and MedDRA version 21.1 in studies MCD-201 and MCD-202; the SOC for these preferred terms (device dislocation and device leakage) was modified between these two versions of the dictionary.

Deaths

There were two deaths reported in Study MCD-501 in patients with MoCD type A and one death in a patient with MoCD Type B.

No deaths were reported during treatment with fosdenopterin in studies MCD-201 and MCD-202; nine of 10 patients in these studies were ongoing on treatment as of the data cut-off (31 October 2020).

2.6.8.4. Laboratory findings

In study MCD-501, the number of patients with haematology and chemistry data available was limited and are not shown. In the two prospective studies, MCD-201 and MCD-202 shift analyses from baseline to last visit based on the normal range were conducted for haematology and for chemistry parameters and are described briefly below.

Haematology

In study MCD-201, most patients showed no shifts in erythrocyte count, haemoglobin, haematocrit, Mean Corpuscular Volume (MCV), leukocytes, neutrophils, lymphocytes and platelets.

Shifts from normal to high values were observed for platelets in one of eight patients and for MCV in two of seven patients. Five out of eight patients in study MCD-201 had shifted from normal to low values in haemoglobin, erythrocytes, neutrophils, haematocrit, MCV, and/or leukocytes.

In study MCD-202: shifts from normal to low lymphocytes were seen in one patient, and shifts from normal to low erythrocytes, haematocrit, haemoglobin and shifts from normal to high platelets were

seen in another patient. This study noted no shifts to low or high values for MCV, leukocytes, and neutrophils.

In study MCD-501, two patients had laboratory-related abnormalities assessed as significant and reported as AEs. In addition, two patients experienced anaemia on day 5 and day 7 after initiation of rcPMP treatment, respectively. Unfortunately, no information was available in either patient record regarding the resolution of the anaemia.

Chemistry

In study MCD-201: most patients showed no shifts in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, sodium, potassium, chloride and creatinine.

Shifts from normal to high values were observed for ALT and AST in one of eight patients, for chloride in one of seven patients, and for creatinine in one of eight patients. Shifts from normal to low values were observed for ALT in one of eight patients, for AST in two of seven patients, for ALP in two of eight patients, for creatinine in one of eight patients, and chloride in one of seven patients.

In study MCD-202:

At the last assessment, one of the two patients experienced a shift in sodium from normal (136 mmol/L) to low (134 mmol/L; normal range: 136 – 145 mmol/L). No shifts to low or high values were noted for ALT, AST, ALP, bilirubin, potassium, chloride, and creatinine.

Electrocardiograms

In section 2.5.2.3. *Safety pharmacology programme*, results from the non-clinical studies on cardiovascular safety are described.

Cardiac safety has been and is observed in clinical studies MCD-101, MCD-501, MCD-201 and MCD-202 through the monitoring of electrocardiogram (ECG) abnormalities.

An analysis of ECG results from the MCD-101 study (where single ascending doses of fosdenopterin were administered to healthy adults) showed that a 10 ms prolongation of the heart-rate corrected QT interval was excluded up to ~7000 ng/mL.

In study MCD-202, ECGs were performed at screening/baseline when feasible, on Day 28; at months 3, 6, 9, 12, 24, and 36; and any safety follow-up visit or early termination visit, if applicable, or as per Safety Review Committee (SRC) recommendation. Up to the data cut-off, no clinically significant abnormal ECG findings have been reported.

In study MCD-501, One patient experienced tachycardia that was not assessed as serious. Another patient presented with an abnormal sinus rhythm, which was considered clinically significant. However, no follow-up information is available.

In study MCD-202, two patients had cardiac-related disorders reported as TEAEs, including moderate cyanosis and moderate tachycardia (Cardiac Disorders SOC) in one patient and mild heart rate increased (Investigations SOC) in another patient. None of these events were assessed as treatment-related.

In the natural history study MCD-502, cardiac abnormalities were reported as "clinically significant medical events" for nine patients with MoCD Type A, including four patients with tachycardia, two patients with data collected retrospectively and two with data collected prospectively.

The applicant conducted a blinded, randomized, single dose, crossover thorough qt study to evaluate the effects of fosdenopterin on cardiac repolarization in healthy subjects. Single IV dose was tested of 1.2 mg/kg fosdenopterin HBr dihydrate, which corresponds to 0.9 mg/kg free base, the maximum dose

proposed in the label. It is stated that in the by-time point analysis of QTcF, no clinically relevant effect was observed. LS mean ΔQTcF on fosdenopterin very closely followed the placebo pattern across post-dose time points and the largest mean ΔΔQTcF of 2.2 ms was observed at 24 hours post-dose.

Using a concentration-QTc approach, The effect on ΔΔQTcF can be predicted to -0.40 ms (90% CI: -2.45, 1.64) for fosdenopterin (6408.0 ng/mL).

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Due to the rarity of the disease and the small size of study population, subgroup safety analyses based on intrinsic factors (such as age, sex and race) have not been conducted.

2.6.8.7. Immunological events

No information has been collected in the clinical studies on the formation of antibodies directed against cPMP.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Due to the rarity of the disease and the small size of study population, subgroup safety analyses based on extrinsic factors such as concomitant medication use, diet, etc., were not conducted. To date, drug-drug interactions have not been evaluated for fosdenopterin.

Fosdenopterin is neither an inhibitor nor an inducer of cytochrome P450 (CYP) isozymes in vitro. It is considered unlikely that coadministration of fosdenopterin will affect systemic exposure of other CYP substrates. In general, the probability of drug-drug interaction with fosdenopterin is regarded as low.

2.6.8.9. Discontinuation due to adverse events

During study MCD-501, two patients with MoCD Type A died while receiving rcPMP and two other patients were reported as no longer receiving rcPMP; reasons for discontinuation were reported to be due to "abnormal imaging" or "poor neurologic prognosis". In study MCD-202, one patient was reported to have discontinued treatment due to the physician's decision; this patient received fosdenopterin for 9 days. In the healthy adult volunteer study MCD-101, no TEAEs led to discontinuation or death.

As of the data cut-off date of the D90 update report, ten of the 15 patients remained on treatment with fosdenopterin, including eight patients in study MCD-201 and two patients in study MCD-202.

2.6.8.10. Post marketing experience

Limited post-marketing data was available. As of 31 October 2021, 13 patients have received fosdenopterin under named patient use. Four patients were ongoing on treatment at the data cut-off, the reasons for discontinuations were similar as seen in the clinical studies (poor neurological prognosis and MoCD type A diagnosis not confirmed). The reported SAEs were related to complications and infections associated with the central line.

2.6.9. Discussion on clinical safety

Fosdenopterin is a first-in-class cPMP hydrobromide dihydrate intended to be used for (paediatric) patients with MoCD Type A, who have a genetic deficiency in the MOCS1 gene and are unable to produce cPMP.

The safety analysis for fosdenopterin is based on data from 4 clinical studies. The safety population is small, it consists of 18 healthy adult volunteers from study MCD-101 and 21 paediatric patients (of whom 15 had MoCD type A) from retrospective study MCD-501 and two prospective studies MCD-201 and MCD-202. The number of subjects is very low, which is plausible considering the rarity of the disease. Nevertheless, it is therefore challenging to fully characterise the safety of fosdenopterin. Furthermore, the retrospective nature of study MCD-501 signifies that less safety data is available for study MCD-501 compared to the other three studies. In the D90 update report, safety data was submitted with the cut-off date of 31 October 2021. Further information about the long-term safety of Nulibry will be collected via a non-interventional PASS.

As of the cut-off date for this MAA submission, 15 neonatal and paediatric patients with MoCD type A have received rcPMP and/or fosdenopterin, of whom 10 patients are currently still receiving fosdenopterin in studies MCD-201 and MCD-202. In addition, 6 paediatric patients later diagnosed as not having MoCD type A received cPMP, though this was done for a limited time. Overall exposure to cPMP, from the first documented dose of rcPMP to the last dose of fosdenopterin as of 31 October 2021 across the 15 treated patients, was 83.0 patient-years, which is quite extensive. The median total time on cPMP was 1960 days (5.4 years) and ranged from 6 to 4896 days (13.4 years).

The treated patients that were included in the clinical studies thus far were primarily early onset patients, i.e. patients who presented with symptoms in utero, or shortly after birth, corresponding to the severely affected patient population. One late-onset patient was included during the update period. As discussed in the clinical efficacy section, is it considered appropriate to extrapolate safety data from early to late onset patients.

Since both prospective and retrospective data were collected, and safety reporting specifications were quite variable in the different protocols, safety data across studies were not pooled. Instead, side-by-side comparisons of safety data obtained from studies MCD-201, MCD-202 and MCD-501 (patients with MoCD Type A) were made. This approach is acceptable.

Adverse Events

The single treatment arm studies make it difficult to disentangle whether an adverse event is due to treatment with cPMP, MoCD type A disease, its complications, or natural occurring common childhood diseases. However, given that the most reported Treatment Emergent Adverse Events (TEAES) in the three studies were in the SOC domain of 'Infections and infestations' and in the SOC domain 'General disorders and administration site conditions' (mostly pyrexia and complications associated with device), it is plausible that a substantial part of the TEAEs are attributable to the complications associated with the central line used to infuse cPMP and/or to background childhood diseases. This is reflected by the frequency of reported viral infections (0% in study MCD-501, 62.5% in study MCD-201, 33.3% in study MCD-202), pneumonia (30% in study MCD-501, 37.5% in study MCD-201, 33.3% in study MCD-202) and influenza (0% in study MCD-501, 50% in study MCD-201, 0% in study MCD-202). It is acknowledged that patients in need of long-term indwelling catheters (such as the Port-a-Cath used in these children) will often suffer from device-related complications, such as sepsis.

Children with MoCD type A have difficulties with oral feeding. This may have caused the high frequency of MedRA system organ class (SOC) gastrointestinal disorders (40% in study MCD-501, 75% in study

MCD-201, 50% in study MCD-202) that are seen in the studies. On the PT level, these were: vomiting, diarrhoea, abdominal pain and constipation.

In study MCD-501, causality to treatment was only determined for SAEs. In study MCD-202 there were no TEAEs assessed to be related to treatment and in study MCD-201 there were two TEAEs assessed to be related to treatment in one patient (device dislocation and catheter site inflammation). In all three studies many of the TEAEs were related to (the complications associated with) the device, however most were not assessed as treatment-related by the Investigator, this appears to be a matter of how the Investigator assesses the AE, 'treatment-related' or 'device-related'.

The TEAEs observed in 6 patients of the MCD-501 and MCD-202 studies who were later diagnosed not to have MoCD type A, were most likely caused by the underlying disease, rather than by cPMP treatment.

Skin disorders, phototoxicity and antibodies

One safety concern for fosdenopterin has been identified in the non-clinical toxicology program, i.e. fosdenopterin was found to have phototoxic effects in in vitro and in vivo animal studies. During the clinical studies up until the cut-off date of 31 October 2021 there have been two reports of potential skin AEs related to sun exposure, however, causality cannot be determined.

Serious adverse events and deaths

The most commonly reported types of SAEs were device-related events and infections and can be linked to either common childhood diseases and/or the complications associated with the central line used to infuse cPMP. The majority of the SAEs were assessed to be mild or moderate. There was one SAE (a case of necrotizing colitis) assessed by the Investigator as possibly related to treatment. The causality with treatment is considered uncertain. The underlying MoCD disorder and resulting seizures, hypotension and hypertension events, probably leading to poor blood flow in the intestinal tissue is likely to have instigated the necrotizing enterocolitis. One case of erosive oesophagitis and Barret's oesophagus have been detected. This was assessed as probably related to gastric reflux. This explanation is considered plausible.

Laboratory findings

There is limited haematology and chemistry data available from study MCD-501. For studies MCD-201 and MCD-202, shift analyses have been performed. Notably, 4 out of 10 patients experienced shifts from normal to low erythrocytes levels and 3 out of 10 patients had shifted from normal to low in haemoglobin level. In addition, two patients in study MCD-501 were reported to have AEs classified as anaemia. No clear relationship has been observed between the transient shifts in haemoglobin, platelets and erythrocytes and either concurrent infections or fosdenopterin dosing.

Some patients in study MCD-201 experienced transient increases in various chemistry parameters, one patient shifted from a normal creatinine value of 29 µmol/L to a high value of 71 µmol/L at last visit. One patient, had (< 3x ULN) increased ALT and AST values on the last visit. All events were mild and resolved without dose reductions.

Cardiac safety

Based on the monitoring of ECG abnormalities in the clinical studies, there is no concern for cardiac safety in relation to cPMP treatment. The results from the MCD-101 study showing that a 10 ms prolongation of the heart-rate corrected QT interval was excluded up to ~7000 ng/mL are reassuring and are in agreement with the EMA guideline CHMP/ICH/2/04 (The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs). In addition, there were no TEAEs related to ECG abnormalities in the 15 patients with MoCD Type A included in studies

MCD-501, MCD-201 or MCD-202. The cardiac abnormalities seen in 9 out of 37 patients with MoCD type A in the natural history study MCD-502 suggest that any cardiac problems seen in MoCD type A patients are likely related to the disease itself rather than to cPMP treatment. A cardiac safety report was submitted with the D90 responses based on the FDA request for a thorough QT study. A single IV dose was tested of 1.2 mg/kg fosdenopterin HBr dihydrate, corresponding to 0.9 mg/kg free base, the maximum dose proposed in the label. It is stated that no clinically relevant effect was observed in the by-time point analysis of QTcF. LS mean ΔQTcF on fosdenopterin very closely followed the placebo pattern across post-dose time points and the largest mean ΔΔQTcF of 2.2 ms was observed at 24 hours post-dose.

Using a concentration-QTc approach, the effect on ΔΔQTcF can be predicted to -0.40 ms (90% CI: -2.45, 1.64) for fosdenopterin (6408.0 ng/mL). Since the upper bound of the 90% CI does not exceed 10 ms, the conclusion that there is not clinically relevant effect on ECG parameters can be endorsed.

Subgroup analyses and in vitro biomarker tests

It is unknown whether specific subgroups would have distinct safety data after treatment with fosdenopterin. Considering the small number of MoCD type A patients, it is understandable that there were no subgroup analyses. In view of the rarity of the disease, also no in vitro biomarker tests have been developed. It is not expected that there would be patients with a different safety profile.

Additional safety data needed in the context of a MA under exceptional circumstances

Taking into account the totality of the available data, the CHMP was of the view that the data set on the clinical safety of Nulibry under normal conditions of use could not be considered comprehensive as due to the rarity of the studied conditions, active or placebo controlled studies of sufficient size are not feasible. In addition, with a safety database of 15 treated MoCD type A patients, the number of patients is very limited. Even though safety follow-up duration in the clinical data set is considered quite extensive, safety in older children has not been shown. Due to these limitations it is not possible to establish robust conclusions on the safety of Nulibry.

The CHMP was therefore of the view that a marketing authorisation under exceptional circumstances should be granted subject to a number of specific obligations, including a non-interventional PASS in order to further characterise the long-term safety and efficacy of Nulibry.

2.6.10. Conclusions on the clinical safety

Fosdenopterin seems to be a relatively safe therapy with a manageable safety profile. The most commonly reported types of (overall and serious) adverse events were related to central line complications and respiratory tract and viral infections that are also frequently observed in otherwise healthy children. Since fosdenopterin is identical to endogenous cPMP, the safety profile is expected to be mild, in line with the observations from clinical studies. Although there are no clear indications from the clinical studies that fosdenopterin is phototoxic, it cannot be ruled out. A warning in section 4.4. of the SmPC is therefore considered appropriate.

Fosdenopterin is meant as a lifelong treatment. Given the limited size of the safety database and the limited inclusion of late onset patients, the applicant has committed to instate a post-marketing non-interventional PASS in order to address long term safety including safety in late-onset patients.

The CHMP considers the following measures necessary to address the missing safety data in the context of a MA under exceptional circumstances:

- In order to ensure adequate monitoring of safety and efficacy of Nulibry in the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Nulibry.
- Non-interventional Post authorisation safety study (PASS): In order to further characterise the long-term safety and efficacy of Nulibry, the MAH should conduct and submit the results of an observational, prospective study of patients with molybdenum cofactor deficiency (MoCD) Type A treated with Nulibry.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Medication errors in the home setting
Missing information	Use during pregnancy and lactation Long term safety

2.7.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Yearly updates on any new information concerning the safety and efficacy of Nulibry	In order to ensure adequate monitoring of safety and efficacy of Nulibry in the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Nulibry	Any new information concerning the safety and efficacy of Nulibry	Annual reports	Annually (with annual re-assessment)
Nulibry non-interventional post authorisation safety study (PASS) (planned)	The objective of this non-interventional PASS is to characterise and assess the long-term safety and efficacy of Nulibry prescribed in routine practice for patients with MoCD Type A.	Important potential risk of medication errors in the home setting Missing information:	Protocol submission	Within 6 months after EC Decision
			Start date:	Within 6 months after protocol endorsement

	Primary objective: • Long-term safety data Secondary objectives: • Efficacy	• long-term safety, • use during pregnancy and lactation	Annual reports	Annually (with annual re-assessment)

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures
Medication errors in the home setting (Important potential risk)	Routine risk minimisation measures • The dosage and method of administration are described in the SmPC in section 4.2, storage instructions are provided in section 6.4 and instructions on reconstitution of the medicinal product before administration, administration and disposal are provided in section 6.6 • A statement in the SmPC section 4.2 and 6.6 that if deemed appropriate by the HCP Nulibry may be administered at home by the patient/caregiver, they must read and follow carefully the detailed instructions for the user provided in the carton on the preparation, administration, storage and disposal of Nulibry • A statement in the SmPC section 4.2 and 6.6 that the HCP should calculate and provide the volume of Nulibry in millilitres (ml) and the number of vials needed for each dose to the caregiver/patient. • A statement in the PL section 3 that Nulibry can be given at home, that before administering for the first time the doctor or nurse will train the patient/caregiver in how to prepare the medicine and give a dose of Nulibry and that the doctor will work out the dose to give. • Section 5 of the PL contains the storage conditions and instructions not to use the medicine if there are any particles or if the solution is discoloured • The outer carton contains statements to read the package leaflet before use and intravenous use after reconstitution and storage conditions. Additional risk minimisation measures: • Instructions for Use • Infusion Diary
Use during Pregnancy and Lactation (Missing Information)	Routine risk minimisation measures: • Warning in SmPC in section 4.6 that there is no or limited data from the use of fosdenopterin in pregnant women, that animal studies are insufficient with respect to reproductive toxicity and that Nulibry is not recommended during pregnancy and in women of childbearing potential not using contraception. • Warning in SmPC section 4.6 that it is unknown whether fosdenopterin/metabolites are excreted in human milk, a risk to newborns/infants cannot be excluded and a decision must be made whether to discontinue breast-feeding or to discontinue from Nulibry

Safety concern	Risk minimisation measures
	therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. • Prescription-only medicine. Additional risk minimisation measures: • None
Long term safety (Missing Information)	Routine risk minimisation measures: • A statement in SmPC section 5.1 that, due to the rarity of the disease it has not been possible to obtain complete information and that there are limited data in adolescents and adults. • Prescription-only medicine.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.7 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 26.02.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nulibry (fosdenopterin) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and as the marketing authorisation is approved under exceptional circumstances.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed therapeutic indication is treatment of patients with molybdenum cofactor deficiency (MOCD) type A.

MOCD is an ultra-rare, rapidly progressive, chronic, and mostly fatal, autosomal recessive inborn error of metabolism. Two-thirds of MoCD patients have Type A, and the remainder have type B or C, depending on the deficient gene. The different types of MoCD are indistinguishable clinically and biochemically, and the diagnosis of the specific type of MoCD is confirmed with genetic diagnostics. Due to mutations in the MOCS1 gene, patients with MoCD type A completely lack MOCS1A/B enzyme activity with no formation of cPMP. cPMP is a substrate essential for the synthesis of molybdenum cofactor (MoCo). Without MoCo, there is a deficiency in MoCo dependent enzymes such as sulphite oxidase (SOX) and xanthine oxidase. SOX deficiency leads to the accumulation of neurotoxic sulphites and s-sulphocysteine (SSC) which can result in significant, irreversible structural damage to the brain. MOCD typically exhibits an acute onset in neonates or in early infancy, although milder/late-onset forms are also reported with onset of symptoms after the first month(s) of life.

Characteristics of the disease include intractable seizures, burst suppression or multifocal epileptic electroencephalogram (EEG), abnormal magnetic resonance imaging (MRI) findings, metabolic acidosis, exaggerated startle reactions, axial hypotonia, limb hypertonia, gross destruction of the brain, failure to thrive, poor or halted feeding response, and high-pitch crying. These characteristics collectively precede rapidly progressive neurodegeneration.

3.1.2. Available therapies and unmet medical need

Given that there is no approved treatment for MoCD Type A in the EU, there is a clear unmet medical need in this patient population. 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. Patients often suffer from epilepsy which is refractory to AED therapy. The available symptomatic treatment options have no impact on the progressive neurologic injury related to elevated levels of SSC.

The most recent incidence estimates are within the range of one in 300,000-400,000. The estimated prevalence in the EU of MoCD type A is 0.005 per 10,000 inhabitants.

In the absence of treatment, patients usually die within the first years of life. The median survival of MoCD type A is approximately 3 years.

3.1.3. Main clinical studies

The applicant conducted 5 clinical studies to support the proposed indication. Three clinical studies were conducted, 1 with recombinant cPMP (rcPMP, in study MCD-501) and 2 with fosdenopterin (cPMP, in studies MCD-201 and MCD-202). rcPMP and fosdenopterin have the same active moiety (see quality section); therefore, both molecules are not expected to act differently and are considered to be therapeutically equivalent.

Two studies (study MCD-502 and MCD-503) were aimed at collecting retrospective data to form a natural history comparator cohort for the integrated efficacy analysis.

In the retrospective study MCD-501, 10 patients were enrolled and treated with rcPMP in a named patient program. Of those patients, 6 enrolled in study MCD-201 where they were switched to fosdenopterin. Two additional patients were enrolled in MCD-201 who were pre-treated with rcPMP in a named patient program. Three MoCD type A patients were enrolled in study MCD-202, for two treatment is still ongoing. These studies recorded plasma and urine biomarkers, survival, seizure activity, feeding status, developmental aspects, and neurological examinations to provide efficacy and safety data for a totality of evidence approach.

The pivotal evidence comes from the integrated efficacy analysis from study MCD-501, MCD-201, MCD-202 and natural history studies MCD-502 and MCD-503; comparing 15 cPMP treated patients with 37 natural history controls (FAS). Analysis of the FAS was supported by data of the GMAS, where the 15 treated patients were compared to 19 genotypically matched controls.

3.2. Favourable effects

cPMP treatment led to the normalization of urinary SSC levels. Mean urinary SSC at baseline was 166.3 µmol/mmol creatinine versus 8.6 µmol/mmol creatinine at the last visit in the treated patients and 136.3 µmol/mmol creatinine at baseline versus 156.6 µmol/mmol creatinine for the natural history controls.

At 1 year of age, survival probability was 93.3% in the treated patients versus 75.3% in the natural history controls (FAS). This data is supported by the data from the GMAS, in which the survival probability at 1 year of age was 93.3% for the treated group and 68.4% for the genotypically matched natural history controls.

In the FAS, nine of the 15 treated patients (60%) and 10 of the 33 untreated patients (30.3%) with data available for analysis were able to feed orally at the last recorded visit. Results in the GMAS were consistent with the FAS. For this matched population, only four (22.2%) of 18 untreated patients with data available were able to feed orally at the last assessment. The median time to sustained non-oral feeding was considerably longer at 75.0 months for treated patients compared with 10.5 months for untreated controls (FAS).

At the last visit, mean and median z-scores for the untreated control patients were numerically lower relative to the cPMP-treated patients for each of the growth parameters. Median z-scores at the last assessment were: -0.34 and -0.63 for weight for treated patients and untreated controls, respectively; -0.86 and -1.37, respectively, for height; and -0.70 and -1.91, respectively, for head circumference.

At the last assessment prior to the MAA data cut-off, a higher percentage of patients receiving fosdenopterin who had data available were ambulatory (4/9, 44.4%) (i.e., assessed as a Level I on the GMFCS-ER) compared with the untreated controls (1/11, 9.1%). In the GMAS, all seven (100%) of the matched control patients with data available were non-ambulatory (Level V).

Five of the ten prospectively followed patients showed improvements in the fine motor, gross motor and cognitive domains of the Bayley scales of infant development, whereas patients in the natural history control group consistently scored low on all three domains.

By 12 months of age, three of the seven treated patients (42.9%) with data available were able to sit unassisted for 30 seconds compared with three of the 27 untreated control patients (11.1%). The ability to sit unassisted at any time was reported for seven of the ten treated patients (70%) and three

of the 27 untreated controls (11.1%) in the FAS for whom data are available; none of the matched control patients in the GMAS could sit unassisted at any time.

At the last visit, 5/15 patients in the treated group had no seizures, compared to 4/37 control patients in the FAS. In the GMAS, 1/19 patients had no seizures ongoing at the last visit.

3.3. Uncertainties and limitations about favourable effects

The number of patients in the clinical study program is low, with 15 cPMP treated patients and 37 natural history controls; together with the open-label character of the studies, this hampers the conclusions.

In the primary analysis (FAS), treated patients are not matched to natural history controls. In the GMAS, individual matching is based on genotype. For MoCD type A, no clear genotype-phenotype relationship has been described, the true value of this matching criterion remains uncertain.

Baseline differences were observed for the occurrence of seizures, and the presence of feeding difficulties differs between treated patients and controls. Since treated patients were sometimes diagnosed prenatally and treatment was initiated early, it is unclear whether the baseline characteristics are comparable.

It is unclear whether the number of seizures per day was stable or decreased on treatment and whether the number of seizures per day was less in the treated patients than in the natural history.

No dedicated dose-finding study was performed. Instead, the dose is substantiated based on pre-clinical findings, PK studies and clinical experience. There are several uncertainties with regard to the dose-finding and the proposed posology. The applicant assumes additional clinical benefit on top of normalization of plasma and urine biomarkers based on pre-clinical findings (see pre-clinical AR). This implies that urine/plasma SSC levels, which show almost immediate decreases with lower doses in study MCD-501, are not the best marker for dosing. However, an alternative biomarker is not currently available. The plateau effect on SSC levels is also visible in the E-R curves (see clinical pharmacology section).

3.4. Unfavourable effects

Most common TEAEs throughout the three studies were device-related AEs: complications associated with the device (7 out of 15 patients), such as device dislocation and catheter site infection (3 patients each), and catheter site extravasation, catheter site pain, central venous catheterization, catheter site discharge, device leakage, device occlusion, bacteraemia, sepsis, and vascular device infection (2 patients each).

Other common TEAs were events in the Infections and Infestations domain, notably viral infections (0% in study MCD-501, 62.5% in study MCD-201, 50% in study MCD-202), pneumonia (30% in study MCD-501, 37.5% in study MCD-201, 50% in study MCD-202) and influenza (0% in study MCD-501, 50% in study MCD-201, 0% in study MCD-202).

Skin and subcutaneous tissue disorders were reported in five out of 10 patients in study MCD-501, seven out of 8 patients in Study MCD-201, and one out of 2 patients in study MCD-202. The events within the skin and subcutaneous tissue disorders SOC reported in >1 patient overall were rash (three patients) and dermatitis, eczema, maculo-papular rash and skin disorder (two patients each).

In study MCD-501 three deaths were reported. Two of them were in patients with MoCD type A. There was one death in a patient with MoCD Type B, who died more than 2 years after discontinuation of rcPMP treatment.

3.5. Uncertainties and limitations about unfavourable effects

The safety population from the clinical studies is small, 21 paediatric patients (15 with MoCD type A) and 18 healthy adult volunteers. In addition, the clinical study MCD-501 was conducted retrospectively, and less safety data is available for this study, as in the study MCD-501 causality to treatment was only assessed for SAEs. Therefore, a full characterisation of the safety assessment is challenging.

In the non-clinical toxicology program, fosdenopterin was found to have phototoxic effects. In the clinical studies, there have been no reports of phototoxicity. Nevertheless, potential phototoxicity cannot be completely ruled out.

3.6. Effects Table

Table 32. Effects Table for Fosdenopterin for the treatment of MoCD type A. (data cut-off: 30 OCT 2021).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Overall survival	Survival Probability at 1 year (FAS[2])	%	93.3	75.3	SoE: FAS: Cox PH Model Hazard Ratio (95% CI): 5.1 (1.32, 19.36). Data supported by analysis in GMAS.	Updated IEE (integrated efficacy analysis)
Urinary SSC level[4]	Mean of Baseline, First value vs last visit (FAS[2])	µmol/mmol	Baseline, First Value: 166.3 Last Visit: 8.6	Baseline, First Value: 136.3 Last Visit: 156.6	SoE: rapid decline upon treatment initiation. Supported by other PD parameters. Un: relevance of urinary SSC as biomarker for additional clinical benefit of higher doses is unclear.	Updated IEE
Time to non-oral feeding	Median (95% CI)	Months	75.0 (14.4, NE)	10.5 (4.9, 53.6)	SoE: supported by higher percentage of patients able to feed orally at last visit in the treated cohort. Un: Competing event of death inappropriately handled.	IEE
Motor function	Level I on the GMFCS-ER (ambulatory without restriction	n/N (%)	4/9 (44.4)	1/11 (9.1)	SoE: supported by other parameters measuring motor function, such as sitting unassisted and the Bayley score.	IEE
Seizures	Seizure free at last visit	n/N (%)	5/15 (35.7)	4/37 (10.8)	Un: potential baseline difference between groups.	IEE
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Device-related Complications	% of patients who experienced at least one device-related TEAE.	%	80	n/a	Although device-related complications are captured as an ADR, the events are attributed to the device used for administration and not to Fosdenopterin.	Safety Summary

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The proposed indication encompasses all patients with MoCD type A. Although limited data is available from patients with late onset MoCD type A (defined by the applicant as onset after 1.5 months of age), it is considered that efficacy and safety data can be extrapolated based on the similar underlying enzymatic defect and the mechanism of action of fosdenopterin. Data from two late-onset patients treated with fosdenopterin support the benefit and safety in these patients, however, because of the very small number of late-onset patients, the clinical efficacy in late-onset patients is uncertain. Nevertheless, since there is consistency of effect across different domains, this is not of major concern.

Clinical benefit is shown in overall survival. Survival is an important favourable effect given the short life expectancy of children with MoCD type A. Analysis of the FAS, GMAS and the best and worst-case sensitivity analyses show a consistent effect in favour of fosdenopterin. The survival data in the fosdenopterin population is therefore considered to be robust. However, it should be acknowledged that in the comparison an external, retrospectively collected natural history control has been used that inherently leads to a biased comparative estimate.

As was also stressed in the scientific advice (SA) procedures, the benefit of survival should be supported by a consistent improvement across different domains which are representative of the health status of a young child. The integrated efficacy results show positive effects of treatment on growth, feeding, seizures, cognitive and motor development. All endpoints are considered to represent aspects of the disease which are considered to have a severe impact on the quality of life. It is important to view the results in a totality of evidence approach.

The observation that consistent clinical benefit across all domains is observed in part of the patients is reassuring. Of the 15 patients treated with cPMP, 10 patients are ongoing on treatment. Of those, 5 patients show a consistent improvement across all domains. These 5 patients are seizure-free, can feed orally; the majority is ambulatory without restriction and within the normal range with regard to growth. Continued cognitive development is observed in these patients. One patient entered the trial with late onset MoCD type A and showed improvements in cognitive development upon treatment initiation. The other 4 patients entered the trial with severe neurological damage/static encephalopathy. This clearly shows that treatment with fosdenopterin is not able to reverse brain damage that has already occurred. In addition, even though the results clearly exceed what can be expected based on the natural history, treated patients, to a varying degree, show a delay in development compared to their healthy peers. The data indicate that with fosdenopterin treatment, existing functions are preserved and disease progression is halted, but the baseline condition of the patient dictates treatment outcome. This is important since it is essential to inform treating physicians and parents about the treatment benefit, which can be expected to enable an informed decision on

whether treatment should be initiated. This can be handled with appropriate warnings and presentation of the results in the SmPC.

The justification of the posology is limited. In the named patient program, patients were treated with a maximum dose of 240 µg/kg, leading to pronounced decreases in urine SSC levels. Based on preclinical studies, which showed that approximately 4-fold and 2-fold doses were necessary for a full restoration of liver SOX activity and normalization of brain SSC levels, respectively, dose escalation to 1200 µg/kg/day was instated in the following phase 2/3 studies. The mechanism behind a clinical benefit beyond the normalization of plasma SSC is not completely clear. This is of importance since the impact of underdosing is therefore difficult to establish. Although exposure-response graphical analysis shows lower plasma SSC levels also in the higher exposure range, the uncertainties regarding the Pop PK model complicate the usability of PK data to support the proposed dose. A dose escalation to a fixed maximum dose, as proposed by the applicant, is usually applicable for treatments where tolerability is an issue or where the dose is individually titrated based on a specific biomarker. For fosdenopterin, this is not the case. However, since the proposed posology is the only dosing regimen that has been studied and considering the efficacy and favourable safety profile, the proposed posology for patients below 1 year of age can be approved. A divergent dosing regimen without dose escalation is proposed for the patients initiating treatment above 1 year of age, based on the mild safety profile and near complete renal maturation after this age. Since no conclusive data is available in these patients justifying either a dose recommendation with dose escalation or without escalation, this can be accepted. Nevertheless, it is considered important to follow-up these patients in the non-interventional PASS, for which an outline has been submitted.

Although pharmacokinetic data in paediatric population is scarce, it is consistent with the healthy adult population.

The clinical studies are all open-label single-arm trials, comparing the observed efficacy to the natural history cohort from study MCD-502. This is understandable given the rare nature and the rapid progression of the disease. In addition, early named-patient use gave indications that the treatment might be effective, rendering further controlled trials unethical. Inherently, the use of an external natural history control gives rise to issues. In this case, the primary analysis compared the treated patient to the entire cohort of 37 MoCD type A patients. The control group seems more heterogeneous than the treated cohort, but there is no clear indication that the control group has a more severe or milder disease burden overall. Demographically, the treated and control group was similar. Overall, age at onset of symptoms was similar between treated and control patients. However, the baseline incidence of seizures and feeding difficulties was lower in the treated cohort. The early treatment in the fosdenopterin treated patients has likely prevented the onset of these symptoms in the natural history controls. As it is assumed that the age of onset of first symptoms is one of the main baseline prognostic factors for disease progression, the cohorts are considered comparable.

In an additional analysis, treated patients were matched to one or more genotypically matched patients (GMAS). Since the genotype-phenotype relationship for MoCD type A is not well described, the value of this analysis is unclear. Therefore, it is assessed as a supportive analysis to the primary analysis in the FAS. For most efficacy parameters, the difference between the treated and control cohort in the GMAS was more pronounced than in the FAS. This is reassuring and adds to the robustness of the results.

It is challenging to thoroughly assess safety and efficacy data in light of the very small population. The overall patient-years exposure to cPMP across the 15 treated patients, being 83.0 patient years is reasonable considering the rarity of the disease. Nevertheless, since this is a lifelong treatment, the long-term safety, especially in older children is considered as missing information. The proposed non-

interventional PASS is considered a meaningful instrument to collect as much safety and efficacy data as possible in the post-authorisation phase.

No major safety issues have surfaced in the clinical studies. Most adverse events seen were device-related events. Complications related to the central line may affect the quality of life for these children, but given the seriousness of the disease, the benefit of fosdenopterin treatment will normally outweigh the risks of the device. However, when the baseline condition of a patient is already unfavourable, the physician should take into account the burden of a central line in the decision to start treatment.

Adverse events not related to the device were principally childhood diseases. There has been no clear indication of phototoxicity in the clinical studies. However, given the limited number of patients, phototoxicity cannot be completely ruled out. The warning in the SmPC relating to phototoxicity is therefore considered appropriate.

3.7.2. Balance of benefits and risks

Fosdenopterin provides a survival benefit in treated patients with MoCD type A compared to the natural history controls. However, it should be acknowledged that an external, retrospectively collected natural history control inherently leads to a biased comparative estimate. In a part of the patients, who entered the study without extensive brain damage, the survival benefit is accompanied by preservation of the ability to grow, feed orally and continued overall development, both in motor and cognitive functioning. The disease progression determines the extent of the benefit at treatment initiation.

Fosdenopterin has a favourable safety profile. Most adverse effects that can be expected are associated with the central line needed for the daily intravenous administration of fosdenopterin. However, the number of patients is very limited and a robust conclusion on efficacy and safety cannot be drawn.

The benefit/risk balance is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

The comprehensiveness of the data package

In the D90 LoQ, the applicant was requested to discuss whether the data package can be seen as comprehensive, supporting a full MA, specifically with respect to the quality of evidence, precision of effect size, duration of effect, exposure and duration of follow-up. For the sake of completeness, the comprehensiveness will be discussed based on a total of 9 criteria.

1. Quality of evidence. The use of a single-arm open-label trial is considered sufficiently justified in this rare disease. However, using an external, retrospectively collected natural history control inherently leads to bias. Therefore, the quality of evidence is not considered to be sufficient to justify a full approval.
2. The precision of effect size. While a treatment effect has been demonstrated, based on the small sample size its precision is inevitably low'. Although the applicant has provided multiple analyses supporting the positive effect on survival, using an external, retrospectively collected natural history control inherently leads to a biased estimate in this group. The data on biomarkers is considered robust. There are some remaining uncertainties around some of the other endpoints and the magnitude of clinical efficacy in late-onset patients. However, since there is consistency of effect across different domains, this is not of major concern.

3. The endpoints are considered to be clinically meaningful. Extension of survival is considered a benefit in this disease which is fatal in the first few years of life in a significant proportion of the patients. However, since the disease burden spans many domains, from motor development to cognition, from problems feeding to seizures, effects were to be shown across these different domains. The endpoints are considered adequate to capture these effects.
4. The maintenance of efficacy is considered reasonably demonstrated. Follow-up was provided until 13.4 years after treatment initiation. However, the number of patients is very limited, and it is not considered possible to draw indisputable conclusions.
5. Safety exposure. With a safety database of 15 treated MoCD type A patients, the number of patients is very limited. It is not considered possible to draw robust conclusions on safety based on such a limited patient population.
6. The safety follow-up duration is considered quite extensive. Across the 11 patients who received fosdenopterin, the total patient-years of exposure was 55.9 years. The median duration of treatment was 6.3 years, with a maximum exposure of 7.6 years as of the data cut-off. Nevertheless, safety in older children has not been shown. Given that this is a lifelong treatment, the totality of exposure is not considered sufficient for a full approval.
7. Target population versus the study population. The applicant aims to treat the complete MoCD type A patient population, while only patients with pre/neonatal onset of disease were included in the clinical studies. Although the applicant has sufficiently discussed that efficacy and safety could be extrapolated to later-onset patients based on the mechanism of action and this argumentation was supported with data from two treated late-onset MoCD type A patients, the available supporting data is considered to be limited. Therefore, this criterium is considered moderately fulfilled.
8. Being a substrate replacement therapy, the pharmacological rationale is strong. The mechanism of action is clear. This criterium is considered fulfilled.
9. The natural history of the disease has been well described. As external comparator, a natural history cohort study has been included with 37 MoCD type A patients. The use of a natural history cohort is considered justified, although using a natural history control leads to unavoidable bias. Therefore, this criterium is considered fulfilled.

In conclusion, the CHMP does not agree with the applicant that the data can be considered comprehensive based on the insufficient quality of evidence, scarce data in late-onset patients and limited safety database. Therefore, the applicant was requested to apply for a marketing authorization under exceptional circumstances.

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was proposed by the CHMP during the assessment, after having consulted the applicant.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence. Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

3.8. Conclusions

The overall benefit/risk balance of Nulibry is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nulibry is favourable in the following indication(s):

Nulibry is indicated for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A.

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Nulibry in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational material, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational material is aimed at minimising medication errors.

The MAH shall ensure that in each Member State where Nulibry is marketed, all patients/caregivers who are expected to use Nulibry in home setting are provided with the following educational material to be disseminated through healthcare professional:

- Instructions for use
- Infusion Diary

Instructions for use:

- Important information patient/caregiver need to know before preparing and giving Nulibry;
- Instructions on the time over which the product should be administered;
- A description of the diluent for reconstitution;
- The administration time required after reconstitution;
- Step by step instructions (with visuals for the majority of the steps, and typeface and white space).

Infusion Diary:

- It should function also as a communication tool between the physician, the patient, and the caregiver to monitor safety and additional risk minimisation measures.
- This document will contain items including
    - emergency contact numbers,
    - the prescribed dose and regimen provided by the treating physician,
    - a record of the drug administration by the caregiver including dates, doses administered, adverse events, medication errors, and administration complications in the home setting.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
In order to ensure adequate monitoring of safety and efficacy of Nulibry in the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Nulibry.	Annually (with annual re-assessment)
Non-interventional Post authorisation safety study (PASS): In order to further characterise the long-term safety and efficacy of Nulibry, the MAH should conduct and submit the results of an observational, prospective study of patients with molybdenum cofactor deficiency (MoCD) Type A treated with Nulibry.	Annually (with annual re-assessment)

Conditions or restrictions with regard to the safe and effective use of the medicinal product

to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that fosdenopterin is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0132/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.