EU Risk Management Plan

For

NULIBRY (fosdenopterin) 9.5 mg

Powder for solution for injection

Data Lock Point: 31 October 2021

RMP Version Number	0.7
Data Lock Point for this RMP	31 October 2021
Date of Final Sign Off	19 July 2022
Rationale for Submitting an Updated RMP	*Not applicable – This is an initial marketing authorisation application*
Summary of Significant Changes in this RMP	*Not applicable – This is an initial marketing authorisation application*
Other RMP Versions under Evaluation	*Not applicable*
Details of the Currently Approved RMP	*Not applicable – This is an initial marketing authorisation application*

EEA QPPV: Caroline DUMAS, MD, M.Sc.

QPPV Signature:

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LIST OF ABBREVIATIONS

AEDs	Antiepileptic Drugs
AEs	Adverse Events
AUC	Area Under the plasma Concentration-Time Curve
BCCRP	Breast Cancer Resistance Protein
CHMP	Committee for Medicinal Products for Human Use
CL	Total Body Clearance
C_{max}	Maximum Plasma Concentration
cPMP	Cyclic Pyranopterin Monophosphate
CTA	Clinical Trial Agreement
CVADs	Central Venous Access Devices
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GA	Gestational Age
GCS	Glasgow Coma Scale
HBV	Hepatitis B virus
HCP	Healthcare professional
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Infusion Diary
IFU	Instructions For Use
IND	Investigational New Drug
IV	Intravenous
LD	Lactation Day
LLN	Lower Limit of Normal
MAA	Marketing Authorisation Application
mARC	mitochondrial Amidoxime Reducing Component
mGCS	Modified Glasgow Coma Scale
MoCD	Molybdenum cofactor deficiency
MoCo	Molybdenum cofactor
MPE	Mean Phototoxic Effect
MTD	Maximum Tolerated Dose
NOAEL	No Observed Adverse Effect Level
ODD	Orphan Drug Designation
OECD	Organisation for Economic Cooperation and Development
OS	Overall Survival
P-gp	P-glycoprotein
PIF	Photo Irritancy Factor

PL	Package Leaflet
PND	Post-Natal Day
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Reports
PT	Preferred Term
QTcF	Fridericia's corrected QT interval
QWBA	Quantitative Whole-Body Assay
rcPMP	Recombinant form of cPMP
RMP	Risk Management Plan
SAEs	Serious Adverse Events
SC	Subcutaneous
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOX	Sulphite Oxidase
SSC	S-sulfocysteine
t½	Terminal Elimination Half-Life
TEAE	Treatment Emergent Adverse Events
t_{max}	Time To Maximum Observed Plasma Concentration
UK	United Kingdom
ULN	Upper Limit of Normal
UPLC	Ultra-Performance Liquid Chromatography
US	United States
USP	United States Pharmacopeia
UVR	Ultraviolet Radiation
UV-VIS	Ultraviolet-Visible
Vd	Volume of Distribution
WFI	Water For Injection

PART I: PRODUCT OVERVIEW

Table 1. Product Overview

Active substance (INN or common name)	Fosdenopterin
Pharmacotherapeutic group (ATC Code)	Various alimentary tract and metabolism products (A16AX19)
Marketing Authorisation Applicant	**Comharsa Life Sciences Limited** 10 Earlsfort Terrace Dublin 2 D02 T380 Ireland
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	NULIBRY
Marketing authorisation procedure	Centralised
Brief description of the product	*Chemical class:* Cyclic pyranopterin monophosphate (cPMP)
	Summary of mechanism: Patients with molybdenum cofactor deficiency (MoCD) Type A have mutations in the MOCS1 gene, leading to deficient MOCS1A/B dependent synthesis of the intermediate substrate, cPMP. Substrate replacement therapy with NULIBRY provides an exogenous source of cPMP, which is converted to molybdopterin. Molybdopterin is then converted to molybdenum cofactor, which is needed for the activation of molybdenum-dependent enzymes, including sulphite oxidase (SOX), an enzyme that reduces levels of neurotoxic sulphites.
	Important information about its composition: No relevant information.
Hyperlink to the Product Information	Summary of Product Characteristics (SmPC)
Indication in the EEA	*Current:* NULIBRY is indicated for the treatment of patients with MoCD Type A.
	Proposed: Not applicable – This is an initial marketing authorisation application.
Dosage in the EEA	*Current:* In patients less than one year of age, the recommended dose of NULIBRY is titrated based on gestational age (GA). For patients less than 1 year of age who are preterm neonates (GA < 37 weeks), the recommended starting dose of NULIBRY is 0.40 mg/kg/day administered intravenously once daily. The dose is to be titrated to the target dose of 0.90 mg/kg/day over a period of 3 months. For patients less than 1 year of age who are term neonates (GA ≥ 37 weeks), the recommended starting dose of NULIBRY is 0.55 mg/kg/day administered intravenously once daily. The dose is to be titrated to the target dose of 0.90 mg/kg/day over a period of 3 months (as described in SmPC, Section 4.2).

	For patients 1 year of age or older and adults, the recommended dose of NULIBRY is 0.90 mg/kg (based on actual body weight) administered intravenously once daily. NULIBRY is a chronic substrate replacement therapy intended for long-term use.
	Proposed: Not Applicable – This is an initial marketing authorisation application.
Pharmaceutical form and strengths	*Current:* • *Pharmaceutical form:* Powder for solution for injection (powder for injection). • *Strength:* 9.5 mg powder for solution for injection (each vial contains 12.5 mg fosdenopterin hydrobromide dihydrate equivalent to 9.5 mg fosdenopterin)
	Proposed: Not Applicable – This is an initial marketing authorisation application.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

There is no reference product available on the market.

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

II.1 Indication

NULIBRY is indicated for the treatment of patients with MoCD Type A.

II.2 Incidence

Two-thirds of MoCD patients have Type A, which is due to a mutation in the MOCS1 gene localized on chromosome 6p21.3 which leads to a complete lack of MOCS1A/B enzyme activity with no formation of cPMP (Reiss and Hahnewald, 2011).

Inherited metabolic disorders are a heterogeneous group of conditions known cumulatively to affect approximately one in 800 neonates. MoCD is an ultra-rare subgroup of these inherited conditions with an unknown incidence. Initial estimates predicted that it occurs in less than one in 100,000 to 200,000 new-borns worldwide. This incidence range was established by assuming similarity between MoCD and other rare monogenic diseases that at the time were better characterised. To date more than 100 cases of MoCD have been reported in the literature, representing numerous ethnic groups with significant prevalence in areas of high consanguinity (Bayram et al., 2013; Hinderhofer et al., 2017; Johnson et al., 1980; Mendel, 2013; Reiss and Johnson, 2003). MoCD is therefore thought to be underdiagnosed with the actual number of affected individuals likely to be higher (Atwal and Scaglia, 2016). While the initial incidence assumption helped to establish MoCD as a rare genetic disease, global reports and an improved understanding of the disease suggest a correction to the incidence should be performed. This is supported by the growing belief that the original incidence estimate is most likely representative of sulphite intoxication diseases as a whole. Work done recently by researchers in Germany and presented at the Society for the Study of Inborn Errors of Metabolism in 2018 and 2019 endeavoured to address this issue (Mayr et al., 2019; Mayr et al., 2018b). With the recent availability of variant databases assembled from large and multi-ethnic populations, such as the Exome Aggregation Consortium (Lek et al., 2016), a systematic and potentially powerful tool for investigating the incidence of rare genetic diseases now exists. While not without limitations, disease incidence for high penetrance and recessive disorder estimations are made possible by traditional calculations utilising the Hardy-Weinberg equation and allelic frequencies of represented variants (Schrodi et al., 2015). Utilising a conservative and less conservative variant dataset with associated pathogenicity scores, the researchers calculated that MoCD Type A incidence is within the range of one in 341,690 to 411,187.

II.2 Prevalence

From the information available at the time of the original European Union (EU) orphan drug designation (ODD) application in March 2010, the prevalence was estimated to be under 200 patients worldwide, well below the orphan drug threshold of 5 in 10,000 persons in the European Community. The literature review, search, and identification of published MoCD cases done in 2010 for the initial ODD application identified a total of 128 cases of MoCD between 1977 and 2009, including 59 MoCD in Europe (13 in the United Kingdom [UK]).

For the initial ODD, the prevalence of MoCD was estimated to be less than 0.01 per 10,000 inhabitants in 2010. The prevalence of MoCD Type A was reassessed based on PubMed and Embase literature searches between 2010 and 2020 and following the same methodology. A total of 20 publications, reporting cases of any types of MoCD in the EU, were identified; among those a total of 53 MoCD Type A cases were reported leading to an estimated prevalence of MoCD Type A of 0.005 per 10,000 inhabitants.

II.3 Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

To date, more than 100 cases of MoCD have been reported in the literature, representing numerous ethnic groups with significant prevalence in areas of high consanguinity (Bayram et al., 2013; Hinderhofer et al., 2017; Johnson et al., 1980; Mendel, 2013; Reiss and Johnson, 2003). Nearly half of patients with MoCD present with symptoms within the first day of life, and approximately three-quarters exhibit symptoms leading to diagnosis within the first month Mechler et al., 2015) Signs and symptoms are progressive, and in the absence of treatment, patients usually die in early childhood due to neurologic degeneration (Reiss and Hahnewald, 2011).

II.4 The main existing treatment options

Current treatment options are symptom driven to provide relief from clinical manifestations of the disease (e.g., antiepileptic drugs [AEDs] for seizures) and supportive care, such as placement of a feeding tube. These symptomatic treatments have no impact on the continued neurologic injury related to elevated levels of S-sulfocysteine (SSC) that lead to the significant developmental disabilities. Although AEDs are available for treatment of seizures, chronic epilepsy refractory to AED therapy does occur in patients with MoCD Type A (Giza et al., 2009; Laxer et al., 2014). Once widespread neural cell death occurs in the brain, the damage is unable to be reversed by cPMP. Therefore, it is critical to intervene as soon as possible by initiating substrate replacement therapy immediately after birth, even prior to genetic confirmation of MoCD Type A to maximise the potential for a positive clinical outcome in patients who present with clinical and laboratory manifestations of the disease. Substrate replacement therapy with fosdenopterin fills this unmet need. If fosdenopterin is started before sulphite-induced neuronal injury and structural brain damage occurs, the child's survival, growth and development have been shown to improve relative to an untreated control group (see Module 2.7.3, Section 3.3).

In the United States (US), fosdenopterin (NULIBRY) is approved by the Food and Drug Administration (FDA) and is the only treatment approved for MoCD Type A; it is indicated to reduce the risk of mortality in patients with MoCD Type A. Outside of the US, there is no approved treatment for this serious and life-threatening disease. Fosdenopterin is the only treatment under clinical investigation in the EU that addresses the underlying substrate deficiency in patients with MoCD Type A.

II.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

MoCD is an ultra-rare, rapidly progressive, chronic, and mostly lethal, autosomal recessive inborn error of metabolism that typically exhibits an acute onset in neonates or in early infancy. Systematic quantitative natural-history data are not available. Shortly after birth, patients with MoCD usually present signs and symptoms such as intractable seizures, exaggerated startle reactions, axial hypotonia, limb hypertonia, gross destruction of the brain, failure to thrive, poor or halted feeding response, high pitch crying, metabolic acidosis, burst suppression or multifocal

epileptic electroencephalogram, and abnormal magnetic resonance imaging findings (Johnson et al., 2001; Mechler et al., 2015; van der Knaap and Valk, 2005).

These characteristics collectively precede rapidly progressive neurodegeneration. In the absence of treatment, patients usually die within the first years of life and patients who survive this period usually develop encephalopathy and developmental delay, but survival with this condition has never been quantified (Mechler et al., 2015).

MoCD can be classified based upon the affected gene, with mutations in *MOCS1, MOCS2/MOCS3*, and *GPHN*, classified as either Type A, B or C, respectively. It is important to note that the different types of MoCD are indistinguishable clinically and biochemically and that the diagnosis of the specific subtype of MoCD is confirmed by genetic testing, which may take several days to weeks to complete. For patients with MoCD Type A, mutations in the *MOCS1* gene, which are localised on chromosome 6p21.2, lead to deficient MOCS1A/B-dependent synthesis of the intermediate substrate cPMP (Shalata et al., 1998). In the absence of cPMP, molybdenum cofactor (MoCo) cannot be synthesized, with all molybdenum-dependent enzyme activity undetectable, most importantly SOX. This leads to the accumulation of toxic levels of sulphites and the secondary metabolite SSC resulting from deficient SOX activity. Xanthine oxidase (or xanthine dehydrogenase), aldehyde oxidase, and mitochondrial amidoxime-reducing component are also MoCo dependent and inactivated when this cofactor is absent.

The prognosis for patients with MoCD Type A is poor. Elevated levels of sulphite in the brain with formation of SSC lead to severe, rapidly progressive, and largely irreversible neuronal injury resulting in significant irreversible structural damage in the brain, including dilated ventricles, hydrocephalus, brain hypodensity, and brain atrophy (Johnson et al., 2001; Kumar et al., 2017; Reiss, 2016). The central nervous system injury has also been shown to occur *in utero*. Prenatal ultrasound in an infant who was subsequently found to have MoCD Type A showed diffuse brain damage (Carmi-Nawi et al., 2011). The neurological injury leads to the clinical manifestations of the disease, including seizures, feeding difficulties, axial hypotonia with limb hypertonia, impairment in growth, and significantly delayed cognitive and motor development. Death commonly occurs in the neonatal period; however, there have been reported cases of a less severe phenotype, later disease onset, and longer-term survival (Mayr et al., 2018a) (Study MCD-502).

The poor prognosis and early death in patients with MoCD Type A were confirmed based on results of the natural history study, Study ALX-MCD-502 (MCD-502). In this study, which included 37 patients with MoCD Type A, the survival probability at 1 year of age was 0.75 with a median overall survival (OS) of 46.7 months (3.9 years) (ISE Table 1.6.1.1.1). Among the 33 patients with onset of the signs and symptoms of the disease within 28 days of birth, the survival probability at 1 year of age was 0.72 with a median OS of 47.8 months (4.0 years) (ISE Table 1.6.1.1.2). This study also confirmed the morbidity of the disease. Overall, 92% of the patients had experienced seizures, 89% were unable to sit independently at any time, and 62% were not able to feed orally (ISE, Table 1.3.1.1.1, Table 1.11.1.1.1, and Table 1.8.1.1.1). Other sequelae of MoCD Type A reported in >50% of the 37 patients included hypertonicity (86%), developmental delays (84%), hypotonia (70%), microcephaly (62%), dysmorphic features (59%), myoclonus (54%), and spastic tetraplegia (51%) (CSR MCD-502, Table 14.1.3.2.1). “Clinically significant medical events” (including significant infections, respiratory events, and exacerbations of seizures) were reported as disease observations during the prospective data collection period in Study MCD-502 (CSR MCD-502, Listing 16.2.6.12.1). The most frequently reported events were infections, primarily reports of lower respiratory tract infections (pneumonia, bronchitis) and urinary tract infections.

II.6 Important co-morbidities

MoCD an autosomal recessive disease, characterised by a rapidly progressive severe neurological damage with nearly half of patients with MoCD presenting the symptoms within the first day of life, and approximately three-quarters exhibit symptoms leading to diagnosis within the first month. Patients who overcome it present seizures, poor feeding, show a severe mental disability, prostration in bed, poor growth and very poor quality of life (Martínez et al., 2020).

Considering that MoCD is a very serious pathology that usually causes death in the immediate neonatal period, the diagnosis of co-morbidities apart from symptoms linked to the progressive neurodegeneration can be challenging. Lens dislocation is often reported but only in children surviving the neonatal period (Mechler et al., 2015) with a detection after 4-5 years of age (Scelsa et al., 2019). Other ocular abnormalities associated with MoCD include spherophakia, iris coloboma, nystagmus, enophthalmos, and cerebral blindness (van der Knaap and Valk, 2005). Isolated, slight elevations of fibrinogen have also been reported, as an indirect sign of inflammatory cascade activation (Scelsa et al., 2019). MoCD patients also present clinical findings including facial dysmorphism, microcephaly, hypotonia, and renal stones (Zaki et al., 2016).

PART II: MODULE SII-NONCLINICAL PART OF THE SAFETY SPECIFICATION

All nonclinical pharmacology, pharmacokinetic, and toxicology studies described here were conducted by or for Alexion Pharmaceuticals, Inc. (Alexion), or Origin Biosciences, Inc. (Origin). All definitive safety pharmacology and toxicology studies conducted with fosdenopterin in support of clinical development and registration were conducted in either the US or Canada in compliance with US FDA or Organisation for Economic Cooperation and Development (OECD) Good Laboratory Practice (GLP) regulations.

The nonclinical development programme for fosdenopterin was discussed with the European Medicines Agency (EMA) during the development of the product as part of an EMA protocol assistance held in 2014.

Pharmacology Programme: A series of *in vitro* and *in vivo* studies representing the Core Battery of safety pharmacology studies described in the (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline) and (ICH Harmonised Tripartite Guideline S7B) was conducted to investigate the effects of fosdenopterin on vital physiological functions. I*n vitro* and *in vivo* cardiovascular assessments were conducted as stand-alone studies. In line with (ICH Harmonised Tripartite Guideline M3(R2)) to reduce animal use, central nervous system (CNS) and respiratory assessments were incorporated into the repeat-dose toxicity studies conducted in rats and dogs. Pharmacodynamic (PD) drug interaction studies with fosdenopterin have not been conducted.

Toxicology Programme: The fosdenopterin toxicology programme is consistent with the guidance provided in the (ICH Harmonised Tripartite Guideline M3(R2))and is in accordance with clinical development of fosdenopterin as a life-saving treatment of patients with MoCD Type A.

In order to expedite availability of fosdenopterin to patients in critical need of immediate therapy, no reproductive and developmental toxicity studies were conducted with fosdenopterin. A carcinogenicity study in a single rodent species will be conducted post-approval.

Table 2: Key safety findings from nonclinical studies and relevance to human usage

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
Safety Pharmacology		
The core battery of safety pharmacology studies conducted with fosdenopterin, included *in vitro* assessment of fosdenopterin at key cardiac ion channels and *in vivo* studies of fosdenopterin-related effects on the central nervous, cardiovascular, and respiratory systems at dose up to 100 mg/kg in rats and 10 mg/kg in dogs. The safety pharmacology investigations did not indicate any undesirable pharmacodynamics effects of fosdenopterin on physiological functions in relation to exposure in the therapeutic range and above. No functional changes in vital organs or systems which are likely to be of importance in clinical testing of fosdenopterin were identified (Module 2.6.2, Section 4).	*Relevance to Human Usage*: No	None
Toxicology		
Single-Dose and Repeat-Dose Toxicity Studies		
Single-Dose Toxicity Study: Single intravenous (IV) (bolus) doses of fosdenopterin were administered in an exploratory study conducted in male rats to determine a maximum tolerated dose (MTD) of fosdenopterin formulated in two vehicles. In this study, fosdenopterin was well tolerated when administered acutely at doses ≤100 mg/kg (Module 2.6.6, Section 2.1). *Repeat-Dose Toxicity Studies:* Definitive general toxicology studies were conducted in standard-aged rats (approximately 6 weeks of age at receipt) and dogs (approximately 5.5 to 6.5 months of age at receipt) administered fosdenopterin via 2-hour IV infusion once daily for 14 consecutive days. In these studies, the no observed adverse effect level (NOAEL) for fosdenopterin was 10 mg/kg/day, the highest dose level evaluated, in both species. Steady-state systemic exposure (combined-sex area under the plasma concentration-time curve (AUC)) to fosdenopterin at the NOAEL was 4,580 ng*h/mL in rats (maximum plasma concentration (C_{max}) of 2950 ng/mL) and 14,300 ng*h/mL in dogs (C_{max} of 7050 ng/mL) (Module 2.6.6, Section 3).	*Relevance to Human Usage*: No	None

Table 2: Key safety findings from nonclinical studies and relevance to human usage

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
To assess the safety and use of fosdenopterin in the paediatric population, several repeat-dose toxicity studies were performed in rats and dogs juvenile at initiation of treatments. As MoCD type A patients are mostly new-borns, dosing in juvenile animals was initiated as soon as practical, and animals were treated until adulthood and up to 26 weeks and 9 months in rats and dogs, respectively, to assess the potential adverse effects of fosdenopterin. In rats, the route of fosdenopterin administration was switched from subcutaneous (SC) to IV injection (bolus; lateral tail vein) beginning on post-natal day (PND) 21. In dogs, daily SC dosing was either replaced by or supplemented with IV injection (bolus; peripheral vein) beginning on lactation day (LD) 26 (Module 2.6.6, Section 3). Special assessments incorporated into the design of these studies included sexual maturation, behavioural performance, and bone measurements. In addition, each study included assessment of recovery from fosdenopterin-related findings after a 4-week treatment-free period. In both studies, the high-dose levels evaluated (5 mg/kg/day in rats and 10 mg/kg/day in dogs) were justified as a maximum practical dose based on solubility limitations imposed by the test article (fosdenopterin) and dose volume limitations defined by the age/size of the animals and the route(s) of administration employed (Module 2.6.6, Section 3). In these chronic toxicity studies, no evidence of target organ toxicity was noted in either species at any dose level evaluated. The NOAELs for fosdenopterin were 5 mg/kg/day (rats) and 10 mg/kg/day (dogs), the highest dose levels evaluated. Steady-state systemic exposure (combined-sex AUC) to fosdenopterin at the NOAEL in these studies was 7,630 ng*h/mL in rats (C_{max} of 16900 ng/mL) and 29,700 ng*h/mL in dogs (C_{max} of 15600 ng/mL) at the end of the treatment period (Module 2.6.6, Section 3). A study was also conducted in rats to explore the feasibility and tolerability of an alternative vehicle, which would allow administration of a 100 mg/kg/day maximum daily dose by IV (bolus) injection. As fosdenopterin formulated in this alternative vehicle was found to be well-tolerated by rats when administered once daily for seven consecutive days (Study 1727-016), a 13-week sub chronic toxicity study (9000563) was conducted in rats with this alternative formulation. As in the chronic 26-week rat toxicity study, dosing was initiated in juvenile animals on PND 7 using the SC route of administration; treatment continued for 13 weeks, with a switch to IV (bolus) dosing beginning on PND 21. The study design included recovery assessments and evaluation of sexual maturation, behavioural performance, and bone measurements. As in the 26-week study conducted in rats, no test article-related ante- or post-mortem findings were noted in this study when fosdenopterin was administered daily to rats at dosages up to 100 mg/kg/day for 13 weeks. The NOAEL for fosdenopterin in this study was		

Table 2: Key safety findings from nonclinical studies and relevance to human usage

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
established at 100 mg/kg/day. Systemic exposure (C_{max} and AUC_{0-t}) to fosdenopterin at the NOAEL on PND 97 was 173,000 ng/mL and 140,000 ng*h/mL, respectively, in males and 189,000 ng/mL and 127,000 ng*h/mL, respectively, in females (Module 2.6.6, Section 3).		
Genotoxicity		
The genotoxicity studies conducted with fosdenopterin, in line with Option 1 battery of ICH Harmonized Tripartite Guideline S2(R1) , included *in vitro* bacterial reverse mutation assays, *in vitro* chromosome aberration assays conducted in human peripheral blood lymphocytes, and *in vivo* (rat) bone marrow micronucleus assays. Each study was conducted in duplicate. In the first set of studies, fosdenopterin concentrations/dosages evaluated did not meet the maximum dose levels recommended in the ICH S2(R1) guideline. In the second set of studies, the *in vitro* assays were conducted at concentrations up to and including the ICH-stipulated maximum dose levels of 5000 µg/plate (bacterial mutation assay) and 1 mM (mammalian cytogenetics assay), and the *in vivo* study was conducted at doses up to and including the maximum feasible dose (200 mg/kg/day with a volume of administration of 20 mL/kg). In the bacterial reverse mutation assays, fosdenopterin was negative (non-mutagenic) in both assays. In the *in vitro* chromosome aberration assays, fosdenopterin was negative (non-clastogenic) in both assays (Module 2.6.6, Section 4.1). In the *in vivo* (rat) bone marrow micronucleus assays, IV administration of fosdenopterin was not toxic to the bone marrow and did not result in any substantial increases in the incidence of micronucleated immature erythrocytes (Module 2.6.6, Section 4.5 and Module 2.6.6, Section 4.6). Taken together, the results of this genotoxicity testing battery indicate that fosdenopterin does not pose a genotoxic hazard to humans.	*Relevance to Human Usage:* No	None
Carcinogenicity		

Table 2: Key safety findings from nonclinical studies and relevance to human usage

Type of Non-Clinical Study	**Relevance to Human Usage**	**Safety Concern**
In accordance with the EMA protocol assistance held with the Committee for Medicinal Products for Human Use (CHMP), carcinogenicity studies can be performed post-approval. Because MoCD Type A is a rare and life-threatening disorder, flexibility in conducting carcinogenicity studies with fosdenopterin hydrobromide is warranted. Therefore, the Applicant plans to perform a 104-week carcinogenicity study in CD-1 mice post-approval (Module 2.6.6, Section 5).	*Relevance to Human Usage:* N/A	None
Reproductive and Developmental Toxicity		
Reproductive and developmental toxicity studies have not been conducted in support of fosdenopterin registration in EU. Per the ICH Harmonized Tripartite Guideline M3(R2): "Reproduction toxicity studies should be conducted as is appropriate for the population that is to be exposed". Origin's global clinical development programme comprises of pre-pubescent patients with MoCD Type A who are currently receiving fosdenopterin treatment. None of these patients will be of reproductive age or clinical condition to experience puberty at the planned time of Marketing Authorisation Application (MAA) submission. Also, in sub-chronic and chronic toxicology studies conducted in animals exposed to fosdenopterin beginning on PND 7 (rats) or LD 5 or 6 (dogs), daily parenteral administration of fosdenopterin for up to 26 (rats) or 39 (dogs) weeks resulted in no test article-related macroscopic, organ weight or microscopic findings in reproductive tract organs/tissues of either species at either the terminal or recovery necropsy intervals. These findings suggest that long-term exposure to fosdenopterin beginning prior to sexual maturity and continuing into adulthood is unlikely to have an adverse effect on fertility in either males or females.	*Relevance to Human Usage:* Yes Although the findings from chronic and sub-chronic studies suggest that long-term exposure to fosdenopterin beginning prior to sexual maturity and continuing into adulthood is unlikely to have an adverse effect on fertility in either males or females, the potential adverse effects of fosdenopterin on the developing embryo/foetus remain unknown. Given the nature of the product (substrate replacement therapy) and the patient population/indication, it is Applicant's view that pregnancy and lactation will be an unlikely event in the targeted population group. However, considering the expected extended life expectancy with the NULIBRY treatment, "Use during Pregnancy and Lactation" is considered as missing information.	Yes *Use during Pregnancy and Lactation*: Missing Information

Table 2: Key safety findings from nonclinical studies and relevance to human usage

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
Other Toxicology Studies		
Phototoxicity		
Fosdenopterin has been characterized by ultraviolet-visible (UV-VIS) spectrometry for several batches. As fosdenopterin contains a pyrimidone chromophore, it is expected to absorb between 200 nm and 400 nm. The UV spectra were acquired concomitantly to ultra-performance liquid chromatography (UPLC) data acquisition using a variable wavelength or photo diode array UV/visible detector, scanning from 200 to 400 nm. Fosdenopterin profile consists of three absorbance maxima at 220 nm, 254 nm, and 291 nm and has no absorbance above 400 nm. Extinction coefficients were not determined. The absorptions are consistent with structure and literature description (Clinch et al., 2013). In addition, in the quantitative whole-body assay (QWBA) conducted in rats, fosdenopterin was found to be highly distributed in skin (Module 2.6.4, Section 4.1). The following 2 nonclinical studies were conducted with fosdenopterin to evaluate phototoxic potential: ***Study 20181580-Neutral Red Uptake Phototoxicity Assay of ORGN001 in BALB/c 3T3 Mouse Fibroblasts:*** Results of this study, expressed as Photo Irritancy Factor (PIF) and Mean Phototoxic Effect (MPE) of >5.043 and >5.503 (PIF) and 0.326 and 0.380 (MPE) demonstrated phototoxic potential, and as OECD 432-recommended cell survival, OD540 criteria, and promethazine cytotoxicity and phototoxicity criteria were met, the definitive assays were considered valid (Module 2.6.6, Section 8.2). In conclusion, fosdenopterin (≤100 µg/mL) demonstrated phototoxic potential. The PIF and MPE criteria for a phototoxic response are >5 and >0.15, respectively. ***Study 20202895-Repeat-Dose Phototoxicity Study to Determine the Effects of Intravenous Administration of ORGN001 on Eyes and Skin in Pigmented Rats:*** Under the conditions of this study, IV (bolus) administration of fosdenopterin at dosages of 25, 50 and 100 mg/kg/day to pigmented rats for three consecutive days followed by ultraviolet radiation (UVR) exposure resulted in dose-dependent cutaneous skin reactions (erythema, oedema, flaking, and eschar) and fosdenopterin -related ophthalmic and histopathologic changes indicative of phototoxicity.	*Relevance to Human Usage:* No The Applicant has performed an in-depth analysis of adverse events occurring in the SOC of Skin disorder. There was no definitive evidence that any patient treated to date has experienced a photosensitive reaction. The Applicant is of the opinion that '*potential for photosensitivity*' is not an important risk and can be managed through routine pharmacovigilance activities.	None

Table 2: Key safety findings from nonclinical studies and relevance to human usage

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
Microscopic findings in the eye (anterior chamber, ciliary body, cornea, and lens) at fosdenopterin dosages ≥50 mg/kg/day with UVR exposure were considered related to phototoxicity. No histologic changes were detected in the bulbar conjunctiva, iris, vitreous chamber, choroid, sclera, or optic nerve (Module 2.6.6, Section 8.2). Fosdenopterin demonstrated phototoxic potential in both *in vitro* and *in vivo* nonclinical studies.		

Conclusions from the nonclinical development programme

Safety concerns based on nonclinical findings that have relevance for human usage are presented in Table 3.

Table 3: Summary of safety concerns from nonclinical development

Summary of safety concerns from nonclinical development	
Missing Information	Use during Pregnancy and Lactation

Overall, the nonclinical *in vitro* and *in vivo* pharmacology studies support the use of fosdenopterin as cPMP substrate replacement therapy as a treatment of the severe phenotype exhibited by patients with MoCD Type A.

PART II: MODULE SIII-CLINICAL TRIAL EXPOSURE

The clinical development of cPMP for the treatment of patients with MoCD Type A was initiated in 2009 by Colbourne Pharmaceuticals (previously known as Orphatec Pharmaceuticals GmbH). Colbourne had developed a recombinant form of cPMP (rcPMP) of *Escherichia coli* strain. *E. coli*-derived rcPMP was shown to be structurally identical to endogenous cPMP (Santamaria-Araujo et al., 2004; Santamaria-Araujo et al., 2012).

The Colbourne product and programme were acquired by Alexion in 2011 who then developed a chemical synthetic process for cPMP. The core molecular structures of rcPMP and fosdenopterin (NULIBRY) have been compared using multiple spectral techniques as well as *in-vitro* efficacy assays, and it has been established that rcPMP and NULIBRY have identical core structures (Modules 3.2.S.3.1 and 3.2.S.2.6). In addition to demonstrating that both cPMP molecules have identical core structures, their biologic comparability has been demonstrated in *in vitro* and *in vivo* pharmacodynamic studies in animals and humans.

Leveraging the nonclinical data, Alexion initiated 4 global clinical studies as detailed below, and a natural history study. However, in July 2017, Alexion stopped recruitment in Study ALXN1101-MCD-202 (MCD-202). Subsequently, Origin acquired all assets in relation to fosdenopterin from Alexion, and effective 26 September 2018, resumed clinical trial agreement (CTA) and investigational new drug (IND) sponsorship for these global studies. Origin's acquisition of the programme has allowed for re-initiation of recruitment in Study MCD-202 and the continuation of the development of fosdenopterin as a substrate replacement therapy for the life-saving treatment of patients with MoCD Type A. Origin also assumed sponsorship of study ALXN1101-MCD-201 (MCD-201) from Alexion.

Below is an overview of the four clinical studies to evaluate safety:

- Study ALXN1101-MCD-101 (MCD-101), a completed first-in-human Phase 1, single dose, dose-escalation, placebo-controlled study conducted in healthy adult volunteers.
- Study MCD-501, a completed retrospective study in patients with MoCD Types A and B (or unknown type) treated under named-patient use with rcPMP.
- Study MCD-201, an ongoing prospective study of NULIBRY designed to transition paediatric patients with MoCD Type A who were receiving rcPMP under named-patient use to receive NULIBRY; the MAA data cut-off for this analysis is 31 October 2020.
- Study MCD-202, an ongoing prospective study of NULIBRY administered in treatment naïve neonates, infants, and children up to 17 (inclusive) years of age with suspected or confirmed MoCD Type A; the MAA data cut-off for this analysis is 31 October 2020.

Exposure Data

A total of 15 neonatal and paediatric patients with MoCD Type A were treated across the three studies MCD-501, MCD-201, and MCD-202:

- Six of the 15 patients received both rcPMP in Study MCD-501 and NULIBRY in Study MCD-201,
- Four patients received only rcPMP in Study MCD-501,

- Two patients received rcPMP outside of a clinical study (named-patient use) (who did not contribute to study MCD-501) and then received NULIBRY in Study MCD-201, and
- Three patients received NULIBRY in Study MCD-202.

As of the data cut-off date for this MAA submission, 10 of the 15 patients remained on treatment with NULIBRY, including eight patients in Study MCD201 and two patients in Study MCD202. Four patients received only rcPMP in study MCD-501 and did not continue onto study MCD201. Two patients with MoCD Type A in Study MCD501 had died and two other patients were reported as no longer receiving rcPMP.

In addition to these there were two additional patients in Study MCD-202 who received NULIBRY treatment, but had to discontinue the treatment after few days (respectively 10 days and 17 days) of treatment due to being confirmed as not having a diagnosis of MoCD Type A. These two patients are not presented in Table 4 as this table represents details of only patients with MoCD Type A.

Across the 15 treated patients, age at first dose was ≤ 14 days for 11 of the 15 patients with six patients initiating treatment at 1 day of age. The maximum time to initiate cPMP treatment across all 15 patients was 1015 days (CSR MCD-202, Listing 16.2.4.1). An overview of the extent of exposure to cPMP, including information for each of the 15 patients by dose level of rcPMP and of NULIBRY is provided in Table 4. Note that during the time between the last reported treatment with rcPMP collected in Study MCD-501 and initiation of treatment with NULIBRY in Study MCD-201, there is a gap in documentation of dosing for the six patients who were included in both studies. A summary of the duration of the gap between Study MCD-501 informed consent (last dose date) and the first dose administration date in Study MCD-201, which ranged from 1 to 2.3 years, is provided in Module 2.7.3, Table 13. Based on the data collected for patients in Study MCD-201 as part of the prior medication history, no gap in dosing between rcPMP and NULIBRY was confirmed for four of these six patients who were included in both studies (CSR MCD-201, Listing 16.2.4.7.1). Origin has also conducted a review of shipping records available for named patient use and other relevant available data, including biomarker levels upon exit in Study MCD-501 and baseline in Study MCD-201. This information is consistent with the patients receiving continued treatment with rcPMP during this period.

Overall patient-years of exposure to cPMP, from the first dose of rcPMP to the last dose of NULIBRY as of the MAA data cut-off across the 15 treated patients was substantial at 83.0 patient years (ISE Table 1.5.1.1.1). Median total time on cPMP was 1960 days (5.4 years) and ranged from 6 days to 4896 days (13.4 years). Among the 10 patients who received rcPMP in Study MCD-501, median time on treatment was 559 days (1.5 years) and ranged from 6 days to 1610 days (4.4 years). Among the 11 patients who received NULIBRY, median time on treatment as of the data cut-off was 2316.0 days (6.3 years) and ranged from 9.0 days to 2762 days (7.6 years); total patient years of exposure to NULIBRY was 55.9 years. (ISE Table 1.5.1.1.1)

Most patients in Study MCD-501 and all patients who received NULIBRY had the dose of cPMP titrated over the course of treatment. Due to the named patient treatment plans, a variety of doses and titration schemes were employed across the patients in Study MCD-501. In Study MCD-201, the initial dose of NULIBRY was matched to the patient's dose of rcPMP upon entering the study. After the first 2 months of treatment with NULIBRY, the dose was increased every month through Month 5 by no more than 240 µg/kg/day if the patient's clinical, pharmacokinetic, and safety assessments permitted, including the absence of signs and symptoms of drug-related

toxicity. The maximum dose administered in this study was 1200 µg/kg/day. Similar to Study MCD-201, Study MCD-202 also used a dose titration scheme-here the initial dose was based on GA. For term neonates (≥ 37 weeks GA), the initial NULIBRY dose was 700 µg/kg/day and for preterm neonates (< 37 weeks GA), 525 µg/kg/day. Thereafter, the dose was to be incrementally increased on Day 28 and at Months 3, 6, and 9 if the patient's clinical, pharmacokinetic, pharmacodynamic, and safety assessments permitted, including the absence of signs and symptoms of drug-related toxicity. Initially, the dose in Study MCD-202 could be increased to up to 1300 µg/kg/day. However, as of Protocol Amendment 3, in order to simplify the dosing and titration schedule, the dose escalation plan was changed to include a maximum dose of 1200 µg/kg/day. In both studies, the patient's data were reviewed by a Safety Review Committee in conjunction with a Data Monitoring Committee prior to each dose escalation to ensure the safety of treatment.

Overall, seven of the 11 patients who received NULIBRY were escalated to a maximum dose per protocol (1200 or 1300 µg/kg/day). Three patients in Study MCD 201 were escalated to a maximum dose of 960 µg/kg/day; one was maintained at that dose level based on pharmacokinetic assessments and two were dose reduced to a final dose of 240 µg/kg/day and 480 µg/kg/day, respectively, based on parent request for ease of administration and not due to safety issues (CSR MCD 201, Section 12.1).

Table 4: Duration of Treatment (Days) on rcPMP or NULIBRY by Dose Received for patients with MoCD Type A

		Dose Received (µg/kg)																
		rcPMP						NULIBRY										
Study		**80**	**120**	**160**	**180**	**220**	**240**	**240**	**280**	**480**	**525**	**700**	**720**	**800**	**960**	**1000**	**1200**	**1300**	**Total**
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[d]	-	-	-	-	-	-	-	-	-	-	-	668[c]
MCD-201		-	-	-	-	-	-	62	-	25	-	-	28	-	32	-	2190	-	2337
MCD-501		-	-	-	-	-	12[e]	-	-	-	-	-	-	-	-	-	-	-	13[d]
MCD-501		-	-	-	-	2[b]	265	-	-	-	-	-	-	-	-	-	-	-	267
MCD-201		-	-	-	-	-	-	60	-	29	-	-	30	-	28	-	2615	-	2762
MCD-501		12	21	55	-	-	363	-	-	-	-	-	-	-	-	-	-	-	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	1327	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

[an] Actual dose reported as 248 µg/kg.

[b] Based on last recorded dose date of 23 June 2021.

[b] Actual dose reported as 216 µg/kg.

[c] Actual dose reported as 240 µg/kg for 80 days and 247 µg/kg for 283 days.

[d] Actual dose calculated as 246 µg/kg. This patient also received 3 days of rcPMP at a dose of 480 µg/kg; this exposure is included in the total column.

[e] This patient also received 1 day of rcPMP at a dose of 25 µg/kg; this exposure is included in the total column.

[f] rcPMP exposure unknown.

[g] Includes 4 additional days of dosing at 25 and 480 µg/kg (see Footnotes d and e).

Source: CSR MCD-501 Listing 16.2.3.2, 90-Day Safety Update CSR MCD-201 Listing 16.2.5.1.1, 90-Day Safety Update CSR MCD-202, Listing 16.2.5.1.1

Demographic Characteristics

Demographic characteristics are summarized by study and across all 15 patients with MoCD Type A treated with cPMP in Table 5.

The gender distribution among the 15 patients with MoCD Type A who received cPMP was balanced (46.7% male and 53.3% female); 11 of 15 patients (73.3%) were white and 13 of 15 patients (86.7%) were not of Hispanic or Latino ethnicity. Median GA was 39.0 weeks and ranged from 35 to 41 weeks. Median age at genetic diagnosis was 4.0 days across the 15 patients and included six patients with a prenatal diagnosis. All patients (except one) had onset of MoCD signs and symptoms within the first month after birth; median time to onset of signs and symptoms was 1.0 day. For the subject signs and symptoms were presented at 12 months of age. The most commonly reported presenting signs and symptoms were seizures (66.7%), feeding difficulties (60.0%) and high-pitched cry (46.7%).

Table 5: Demographic Characteristics by Study and Overall (Safety Set-Patients with MoCD Type A)

Variable	MCD-501 (N=10)	MCD-201 (N=8)	MCD-202 (N=3)	All Patients* (N=15)
Gender, n (%)				
Male	5 (50.0)	3 (37.5)	1 (33.3)	7 (46.7)
Female	5 (50.0)	5 (62.5)	2 (66.7)	8 (53.3)
Race, n (%)				
White	7 (70.0)	5 (62.5)	2 (66.7)	11 (73.3)
Asian	3 (30.0)	3 (37.5)	1 (33.3)	4 (26.7)
Ethnicity, n (%)				
Not Hispanic or Latino	9 (90.0)	8 (100.0)	2 (66.7)	13 (86.7)
Hispanic or Latino	1 (10.0)	0	0	1 (6.7)
Not Reported	0	0	1 (33.3)	1 (6.7)
Gestational Age (weeks)				
n	10	8	3	15
Mean (SD)	38.2 (1.83)	38.8 (1.52)	38.1 (1.85)	38.3 (1.65)
Median	38.7	39.0	38.0	39.0
Min, Max	35, 41	36, 41	36.3, 40	35, 41

Abbreviations: max=maximum; min=minimum; MoCD=molybdenum cofactor deficiency; SD=standard deviation.
* Six of the 10 patients in Study MCD-501 were also treated with NULIBRY in Study MCD-201; these patients are not double-counted in the All Patients column.
Source: CSR MCD-501 Table 14.1.1.0 and ISE Table 1.2.1.1.1

A comprehensive evaluation of the safety of treatment with cPMP, including rcPMP and NULIBRY, was conducted across the clinical studies. Due to the prospective and retrospective nature of the safety information collected, as well as variable safety reporting specifications required by the different protocols, safety data across studies were not pooled.

PART II: MODULE SIV-POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The exclusion criteria that are related to ongoing or recent conditions or treatments that may impact the safety and efficacy assessment of NULIBRY from study MCD-201 and MCD-202 are listed below and not discussed further:

- Current or planned treatment with another investigational drug or device, with the exception of rcPMP treatment, through Day -1
- Diagnosis other than MoCD Type A (may be determined after the initiation of study drug)
- Condition that is considered by the treating physician to be a contraindication to therapy, including evidence of abnormalities on brain imaging not attributable to MoCD Type A, or that might otherwise interfere with the patient's participation in the study, pose any additional risk for the patient, or confound patient assessments.

The following exclusion criterion from pivotal study MCD-501 is not discussed further since this was a retrospective, observational, noninterventional study for patients with MoCD who have been previously treated with cPMP:

- Patient's parent(s) or legal guardian(s) are unable to understand the nature and scope of the study.

The following exclusion criteria from pivotal study MCD-502 are not discussed further since this was a natural history program:

- Patient has participated in Study ALX-MCD-501.
- If patient has received treatment with cPMP, only data up to date and time immediately prior to first administration of cPMP will be collected.

The remaining exclusion criteria from the pivotal studies are presented below in Table 6 and may be grouped together.

Table 6. Remaining exclusion criteria in pivotal clinical studies within the development programme

Exclusion criterion	**Study MCD-202: Antenatal and/or postnatal brain imaging prior to initiation of treatment with ORGN001 that indicates cortical or subcortical cystic encephalomalacia, clinically significant intracranial haemorrhage, or other abnormalities on brain imaging determined by the treating physician to be clinically significant.**
Reason for exclusion	Cortical or subcortical cystic encephalomalacia and significant intracranial haemorrhage are conditions in which neonates experience brain injury, softening or loss of brain tissue either by asphyxia (oxygen deprivation during or around the time of birth) or other reasons. These conditions/characteristics coincide with the characteristics of MoCD Type A. The presence of these conditions in any neonate questions the confirmation of MoCD Type A, which is the targeted indication for NULIBRY. Elevated levels of sulphite in the brain with formation of SSC lead to severe, rapidly progressive, and largely irreversible neuronal injury resulting in significant irreversible

	structural damage in the brain, including dilated ventricles, hydrocephalus, brain hypodensity, and brain atrophy (Johnson et al., 2001; Kumar et al., 2017; Reiss, 2016). The central nervous system injury has also been shown to occur *in utero*. Prenatal ultrasound at 35 weeks gestation in an infant who was subsequently found to have MoCD Type A showed diffuse brain damage with multiple subcortical cavities, ventriculomegaly, dysgenesis of the corpus callosum, and a hypoplastic cerebellum with an enlarged cisterna magna (Carmi-Nawi et al., 2011).
Is it considered to be included as missing information?	No
Rationale	This was a general risk consideration in experimental treatment/setting. Post approval NULIBRY will be indicated for patients with MoCD Type A (SmPC, Section 4.1). In real-life situations, patients with the beforementioned conditions/characteristics may be candidates for treatment. Clinicians will need to determine whether the benefit of treatment outweighs risks for an individual patient. This is not considered as a missing information.

Exclusion criterion	**Study MCD-202: Modified Glasgow Coma Scale (mGCS) for Infants and Children score of less than 7 for more than 24 hours (does not apply to children less than 1 day in age).**
Reason for exclusion	The Glasgow Coma Scale (GCS) is a clinical tool designed to assess coma and impaired consciousness. A modified GCS score of 12 in infants or children suggests a severe head injury, a score of 8 suggests need for intubation and ventilation, and a score of 6 suggests need for intracranial pressure monitoring.
Is it considered to be included as missing information?	No
Rationale	This was a general risk consideration in experimental treatment/setting. Patients with a mGCS of less than 7 for more than 24 hours have a high risk of mortality[1]. Although children do better than adults with a comparable injury, the high baseline risk of subsequent disability with persistent neurologic sequelae is a factor that would interfere for a proper assessment of the study treatment. The exclusion of this population is not considered as missing information.

[1] https://www.msdmanuals.com/professional/injuries-poisoning/traumatic-brain-injury-tbi/traumatic-brain-injury-tbi#v1111428

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes.

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions due to rarity of MoCD Type A.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 7. Exposure of special populations included or not in clinical trial development programme.

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme. There are no available data on NULIBRY use in pregnant women to evaluate for a drug associated risk of major birth defects, miscarriage, or adverse maternal or foetal outcomes. As per the proposed SmPC section 4.6, NULIBRY is not recommended during pregnancy and in women of childbearing potential not using contraception. However, considering the expected extended life expectancy with the NULIBRY treatment "Use during Pregnancy and Lactation" is considered as a missing information.
Breastfeeding women	Not included in the clinical development programme. There are no human or animal data to assess the presence of NULIBRY or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production for the mother. As per the proposed SmPC section 4.6, a risk to new-borns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue from NULIBRY therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. However, considering the expected extended life expectancy with the NULIBRY treatment "Use during Pregnancy and Lactation" is considered as a missing information.
Patients with relevant comorbidities	
Patients with hepatic and renal impairment	Due to the rarity of the disease and the small size of study population, subgroup safety analyses were not conducted based on intrinsic and extrinsic factors. The effect of renal and hepatic impairment on the pharmacokinetics of fosdenopterin are unknown.
Patients with cardiovascular impairment	No data available with use of fosdenopterin in patients with cardiovascular impairment.
Immunocompromised patients	Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Subjects were not excluded due to severity of disease.
Population with relevant different ethnic origin	See Part II SIII Table 5 providing demographic data.
Subpopulations carrying relevant genetic polymorphisms	Relevant genetic polymorphisms not applicable.
Other	Not applicable

PART II: MODULE SV-POST-AUTHORISATION EXPERIENCE

In February 2021, NULIBRY received marketing approval in the US as a treatment for MoCD Type A with the indication to reduce the risk of mortality in patients with MoCD Type A, and Origin started marketing of NULIBRY as of March 2021.

SV.1 Method used to calculate exposure

The post-authorisation exposure was estimated based on NULIBRY vials shipped/distributed to hospitals.

SV.2 Exposure

As of data cut-off date of 31 October 2021, (estimation) constituted the exposed post-approval population.

PART II: MODULE SVI-ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

NULIBRY will be available as prescription-only medication. Also, based on the mechanism of action, drug abuse is not anticipated with NULIBRY (Module 2.7.4, Section 5.5). There is no potential for misuse of NULIBRY for illegal purposes.

PART II: MODULE SVII-IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks not considered important for inclusion in the list of safety concerns (presented below) are based on nonclinical data and on data from two open-label, single-arm studies (MCD-201 (n=8) and MCD-202 (n=3), in patients with a confirmed diagnosis of MoCD Type A (8 of the 11 patients were previously treated with cPMP). In these studies, patients received a daily IV administration of NULIBRY.

Table 8. Risks not considered important for inclusion in the list of safety concerns in the RMP

Part A: Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)
None
Part B: Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated
None
Part C: Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers
Potential for photosensitivity
Part D: Known risks that do not impact the risk-benefit profile
Complications associated with device
Part E: Other reasons for considering the risks not important
None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Safety Concern	Justification for risk-benefit impact
Important Potential Risk: ***Medication Errors in the Home Setting***	Treatment with NULIBRY is to be initiated in the hospital setting. Home administration of NULIBRY can be performed by the caregiver if deemed appropriate by the HCP. Treatment with NULIBRY requires specific storage, dosing and administration which may increase the possibility of medication errors in the home setting. Therefore, "*Medication errors in the home setting'* is considered as an important potential risk The proposed SmPC (sections 4.2, 6.4 and 6.6) describes the dosing and method of administration, storage conditions and special precautions for disposal and handling of NULIBRY including special instructions for home administration. The healthcare provider (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. The caregiver/patient must read and follow carefully the detailed 'Instructions for the user' provided in the carton on the preparation, administration, storage, and disposal of NULIBRY (more details in Part V.2). *Risk-benefit impact:* NULIBRY is intended for IV use and must be given daily throughout the patient's life. The Applicant believes the benefit of administering this life-saving treatment at home outweighs the potential risks of medication errors in the home setting. NULIBRY has a wide safety margin and no adverse events related to dosing have been reported thus far in clinical trials or in the global post-marketing setting. Furthermore, mitigation steps have been taken in the SmPC, Package Leaflet (PL), the IFU and Infusion Diary (ID). Therefore, there is no significant impact on the risk-benefit balance of NULIBRY which remains positive.
Missing Information: ***Use During Pregnancy and Lactation***	Although the findings from nonclinical chronic and sub-chronic studies suggest that long-term exposure to fosdenopterin beginning prior to sexual maturity and continuing into adulthood is unlikely to have an adverse effect on fertility in either males or females, the potential adverse effects of fosdenopterin on the developing embryo/foetus remains unknown. Currently there are no available data on NULIBRY in pregnant or lactating women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or foetal outcomes. However, the patients in the clinical development program are now growing. Although these patients are at an age of reproductive potential, due to their clinical condition, in reality, they are not considered of reproductive potential. Considering the expected extended life expectancy of the target population with the NULIBRY treatment, "*Use during Pregnancy and Lactation*" is considered as a missing information. The proposed SmPC (section 4.6) states that there is not or limited amount of data from the use of fosdenopterin in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Fosdenopterin is not recommended during pregnancy and in women of childbearing potential not using contraception. *Risk-benefit impact:* Given the life-threatening nature of the disease, the need for long-term treatment with the product (as a substrate replacement therapy), and the patient population/indication, it is Applicant's view that pregnancy and lactation will be an unlikely event in the targeted population group. Despite this, the Applicant considers "*Use during Pregnancy and Lactation*" as a missing information due to the lack of data in such population.

	Given that NULIBRY will provide a life-saving treatment to patients with the ultra-rare disease of MoCD Type A, the overall benefit/risk balance of NULIBRY continues to be favourable.
Missing information: *Long term safety*	Long term safety is well established in neonates, infants and children. There is limited safety data available in adolescents and adults. The proposed SmPC (section 5.1) states that there are limited data in adolescents and adults. *Risk –benefit impact* Given the safety data available so far from the clinical trials, the pathophysiology of MoCD Type A and the known mechanism of action of NULIBRY, there is no reason to believe that the safety profile will be different in adolescents and adults compared to neonates, infants and children. Despite this, the Applicant considers "*Long term safety*" as a missing information as an approval of the NULIBRY MA application under exceptional circumstances indicates sufficient data are not available for full approval. Given that NULIBRY will provide a life-saving treatment to patients with the ultra-rare disease of MoCD Type A, the overall benefit/risk balance of NULIBRY continues to be favourable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable. This is an initial marketing authorisation application.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk: Medication Errors in the Home Setting	
Potential mechanisms	Treatment with NULIBRY is to be initiated in the hospital setting. Home administration of NULIBRY can be performed by the caregiver if deemed appropriate by the HCP. Treatment with NULIBRY requires specific storage, dosing, and administration, which may increase the possibility of medication errors in the home setting.
Evidence source(s) and strength of evidence	Treatment with NULIBRY requires specific storage, dosing, and administration, which may increase the possibility of medication errors in the home setting. Most patients (90%) in the clinical studies received NULIBRY which was administered by a caregiver in the home setting. Across the 11 patients treated with NULIBRY, total exposure was 55.9 patient-years (with median time on treatment, as of the data cut-off, of 6.3 years which ranged from 9.0 days to 7.6 years). No adverse events related to dosing were reported throughout the clinical development program (~ 55.9 patient-years of exposure to NULIBRY treatment).
Characterisation of the risk	Treatment with NULIBRY is to be initiated in the hospital setting. Home administration can be performed by the caregiver if deemed appropriate by the HCP. Treatment with NULIBRY requires specific storage, dosing and administration which may increase the possibility of a medication error in the home setting.
Risk factors and risk groups	Caregivers will need to be informed on the specific details for storage, dosing, and administration. Caregivers must fully understand the way NULIBRY should be stored, reconstituted and administered and the dose needed before they commence administration of NULIBRY in the home setting. Lack of this information is the main risk factor for medication errors in the home setting. No other particular risk factors or risk groups have been identified.

Important Potential Risk: Medication Errors in the Home Setting	
Preventability	SmPC In the proposed SmPC, section 4.2 describes in detail the dosing recommendations for NULIBRY, and both section 4.2 and section 6.6 instruct the HCP to assess if home administration of NULIBRY is appropriate and to provide the dosing volume (mL) and the number of vials needed to prepare each dose to the caregiver. Section 6.4 contains the storage instructions. PL In the proposed PL, section 3 advises the caregiver/patient that their doctor or nurse will train them in how to prepare the medicine, how to give a dose of NULIBRY and to check with their doctor if they are not sure about how to use NULIBRY in the home setting. In addition, the caregiver/patient is advised that their doctor will work out the dose to give. In section 5, the storage conditions are given for both unopened vial and reconstituted NULIBRY as well instructions not to use the medicine if any particles are present or the solution is discoloured IFU As part of the training for home administration, the caregiver/patient must read the detailed instructions for the user (IFU) provided in the carton. The IFU contains step by step instructions in nontechnical language and visuals on the preparation, administration, storage, and disposal of NULIBRY to assist the caregivers. The IFU is intended to reinforce the caregiver's training and serve as a guide. The IFU also advises the caregiver/patient that their doctor or nurse should show them the right way to prepare and give the prescribed dose of NULIBRY before administering for the first time, that the dose is based on age and body weight and that the doctor will work out the amount of NULIBRY needed for each dose in millilitres and number of vials (more details in Part V.2). Outer Carton The outer carton displays the storage conditions along with instructions for the caregiver/patient to read the package leaflet before use and that the product is for intravenous use after reconstitution. Infusion Diary The infusion diary is intended to function as a communication tool between the physician, the patient, and the caregiver to monitor safety, medication errors, and administration complications. This document will contain items outlined by the CHMP including emergency contact numbers, dates, doses administered, AEs, and medication errors and administration complications in the home setting.
Impact on the risk-benefit balance of the product	The benefits of NULIBRY include improvements in survival, biochemical markers and a positive impact on growth and development. NULIBRY has been safely administered in the home-setting throughout the development program. The proposed risk minimisation measures put in place support home administration of NULIBRY. Overall, the benefits that the patient receives from treatment with NULIBRY outweigh the potential risk patients will undergo due to medication errors in the home setting.
Public health impact	This important potential risk has very minimal impact on public health and the benefit/risk balance of NULIBRY continues to remain favourable.

SVII.3.2. Presentation of the missing information

Missing Information: Use during Pregnancy and Lactation	
Evidence source	*Non-Clinical Data:* Reproductive and developmental toxicity studies have not been conducted in support of fosdenopterin registration in EU. In sub-chronic and chronic toxicology studies conducted in animals exposed to fosdenopterin beginning on PND 7 (rats) or LD 5 or 6 (dogs), daily parenteral administration of fosdenopterin for up to 26 (rats) or 39 (dogs) weeks resulted in no test article-related macroscopic, organ weight or microscopic findings in reproductive tract organs/tissues of either species at either the terminal or recovery necropsy intervals. These findings suggest that long-term exposure to fosdenopterin beginning prior to sexual maturity and continuing into adulthood is unlikely to have an adverse effect on fertility in either males or females. *Clinical Data*: Currently there are no available data on NULIBRY's use in pregnant or lactating women to evaluate for a drug associated risk of major birth defects, miscarriage, or adverse maternal or foetal outcomes. Considering the expected extended life expectancy of the target population with the NULIBRY treatment, "*Use during Pregnancy and Lactation*" is therefore considered as a missing information.
Population in need of further characterisation	Population in need of further characterisation are pregnant and lactating women. The potential adverse effects of fosdenopterin on the developing embryo/foetus remains unknown. Given the nature of the product (substrate replacement therapy), the patient population/indication; and given that NULIBRY is not recommended during pregnancy and in women of childbearing potential not using contraception (as per the proposed SmPC section 4.6), it is Applicant's view that pregnancy and lactation will be an unlikely event. Despite this, the Applicant plans to collect further information in this set of population (if any) by use of targeted follow-up questionnaire (Annex 4). Overall, this missing information has very minimal impact on public health and the benefit/risk balance of NULIBRY continues to remain favourable.

SVII.3.3. Presentation of the missing information

Missing Information: Long term safety	
Evidence source	*Clinical Data*: Long term safety for neonates, infants and children has been established in clinical trials. Due to the rarity of the disease, currently there is limited long term safety available, in particular for adolescents and adults. Therefore, "*Long term safety*" is considered as missing information given that an approval of the NULIBRY MA application under exceptional circumstances indicates sufficient data are not available for full approval.
Population in need of further characterisation	Given the safety data available so far, the pathophysiology of MoCD Type A and the mechanism of action of NULIBRY, there is no reason to believe that the safety and benefit/risk profile will be different for older patients compared to neonates, infants, and children. Despite this, the Applicant plans to implement a non-interventional post authorisation safety study (PASS) that will allow for the active collection of long-term safety data (primary objective) as well as efficacy data (secondary objective) (Annex 3). Overall, this missing information is expected to have no impact on public health and the benefit/risk balance of NULIBRY continues to remain favourable.

PART II: MODULE SVIII-SUMMARY OF THE SAFETY CONCERNS

Table 9. Summary of 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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

Comharsa has a pharmacovigilance system in place, which fulfils the European requirements and provides adequate evidence that Comharsa has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any potential risks occurring either in the Community or in a third country.

Comharsa has put in place a Pharmacovigilance System Master File (PSMF) describing the set of activities required to fulfil the legal requirements for routine pharmacovigilance activities for the medicinal product(s) for which they are applying for in the EU.

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include (but are not limited to):

- Collection, collation, assessment, and reporting of spontaneous reports;
- Periodic literature surveillance; and
- Signal detection activities.

Routine pharmacovigilance practice includes comprehensive post-marketing surveillance assessment of spontaneously reported events with expedited reporting in compliance with worldwide regulatory requirements, and submission of Periodic Safety Update Reports (PSURs) in accordance with applicable regulatory requirements.

Periodic safety evaluation of cumulative data will also be conducted to evaluate safety signals. If a safety signal is identified, further assessment and characterisation of the safety signal will be conducted, including evaluation of individual case reports and aggregate data analysis.

New safety information will be communicated to the regulatory authorities worldwide, in accordance with local regulations. Additional activities may include product label revisions and updates with new safety information, in discussion with regulatory authorities, and informational letters to the treating physicians.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the safety concerns

- Targeted follow-up questionnaires for pregnancy and lactation, and medication errors in the home setting have been developed and will be available to collect and evaluate specific data related to these safety concerns to gain further information in the post-marketing period (Annex 4).

III.2 Additional pharmacovigilance activities

The Applicant plans to implement the following additional pharmacovigilance activities:

- yearly updates that will provide new information concerning the safety and efficacy of Nulibry
- a post-marketing non-interventional post authorisation safety study (PASS) that will allow for the active collection of safety data and specific efficacy parameters of all treated patients (Annex 3).

III.3 Summary table of additional pharmacovigilance activities.

Table 10. Planned additional pharmacovigilance activities

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. Primary objective: • Long-term safety data Secondary objectives: • Efficacy	Important potential risk of medication errors in the home setting Missing information: • long-term safety, • use during pregnancy and lactation	Protocol submission	Within 6 months after EC Decision
			Start date:	Within 6 months after protocol endorsement
			Annual reports	Annually (with annual re-assessment)

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

There are no planned post-authorisation efficacy studies imposed as conditions of the marketing authorisation.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine risk minimisation measures

Table 11. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation measure
Medication Errors in the Home Setting	Routine risk communication: • *SmPC section 4.2, 6.4 and 6.6* • *PL section 3 and 5* • *Outer carton* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *The dosage and method of administration is 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, and administration and disposal are provided in section 6.6.* • *A statement in the SmPC in sections 4.2 and 6.6 to caregiver/patient that if deemed appropriate by the HCP NULIBRY maybe administered at home by caregiver/patient and that 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 doing this 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.* • *Storage conditions and instructions not to use the medicine if there are any particles or if the solution is discoloured in section 5 of the PL* • *Statements on the outer carton to read the package leaflet before use and intravenous use after reconstitution and the storage conditions.* Other routine risk minimisation measures beyond the Product Information: • *Legal status: NULIBRY will be available as a prescription-only medicine*
Missing information	**Routine risk minimisation measure**
Use during Pregnancy and Lactation	Routine risk communication: • *SmPC section 4.6* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *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 therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.* Other routine risk minimisation measures beyond the Product Information: • *Legal status: NULIBRY will be available as a prescription-only medicine.*

Long term safety	Routine risk communication • *SmPC section 5.1* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *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.* Other routine risk minimisation measures beyond the Product Information: • *Legal status: NULIBRY will be available as a prescription-only medicine*

V.2. Additional risk minimisation measures

Additional risk minimisation 1: Instructions for Use (IFU)

Objectives:

The objective of proposing IFU is to help caregivers/ patients completely understand various steps involved in the reconstitution and administration of NULIBRY. This IFU contains step by step instructions, contains visuals for the majority of the steps, and uses typeface and white space to emphasise critical information.

The IFU will contain statements that the doctor or nurse will show the patient/caregiver the right way to prepare and give the prescribed dose of NULIBRY before doing it for the first time; and that the doctor will work out the amount of NULIBRY needed for each dose in millilitres (mL) and the number of vials.

The IFU will help patients/caregivers to function independently with minimal support from visiting home healthcare (HHC).

This additional risk minimisation measure will focus on the following risk:

- Medication errors in the home setting

Rationale for the additional risk minimisation activity:

NULIBRY is intended for IV use and the treatment must be given daily throughout the patient's life. The treatment with NULIBRY is to be initiated in the hospital setting, however considering the life-long daily IV administration of NULIBRY, if home administration is deemed appropriate by the HCP, the administration of the product could be performed by the caregiver in the home setting. Because reconstitution and administration of NULIBRY is likely to occur by the caregiver/patient in home setting, this IFU has been proposed as an additional risk minimisation measure.

Target audience and planned distribution path:

The target audience consists of the caregivers/patients who will reconstitute and administer NULIBRY to patient in home setting.

The IFU will be part of NULIBRY's packaging along with the PL. IFUs will be distributed to caregivers/patients and should be used by HCPs when providing training to the caregiver for home administration of the product. HCPs are expected to perform training of the caregiver before starting the NULIBRY treatment in the home setting.

Administration of IV drugs in the out-patient setting typically requires coordination among the treating physician, hospital discharge planners, the patient's health insurance plan, the caregiver/patient, home administration pharmacies, and, if needed, home health agencies. Visiting HHC often plays a role in home IV administrations. HHC typically reinforces the physician training provided to the patient or caregiver on administration of the drug, provides education about side effects and goals of therapy, and visits periodically to assess the device site and provide dressing changes.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness will be assessed using both process and outcome indicators.

Process indicator:

The distribution of the IFU can be considered as a process indicator and can be documented within each scheduled PSUR for NULIBRY.

Outcome indicator:

Origin commits to collecting all medication errors (with or without adverse events) and pregnancy and lactation reports from post-market experience. Origin will perform routine pharmacovigilance activity to analyse the reported medication errors and cases of pregnancy or lactation. Origin also commits to additional PV activities in the form of a non-interventional PASS (Annex 3). All relevant data including AEs/SAEs will be presented within each PSUR.

Additional risk minimisation 2: Infusion Diary

Objectives:

The Infusion Diary (ID) is intended to function as a communication tool between the physician, the patient, and the caregiver to monitor safety, medication errors, and administration complications in the home setting. This document will contain items outlined by the CHMP including emergency contact numbers, dates, doses administered, AEs, and medication errors and administration complications in the home setting.

Rationale for the additional risk minimisation activity:

This ID captures additional information to facilitate communication between the caregiver and treating physician, and to capture certain treatment information for review by the physician; thereby to minimize medication error. This ID will capture:

1. Unexpected "events" (such as AEs),

2. Departure from "well-established use" of the drug that could be transient (eg. catheter blocking) or permanent (eg. in the event of dose adjustment (increase) a 7-day follow up should be documented).

Additionally, the ID could be used in the context of AEs reporting to enable

1. Contextualisation of the use of the drug (i.e. within the "normal conditions of use"),

2. Provide information for full assessment of the AEs

Target audience and planned distribution path:

The target audience consists of the caregivers, who will administer NULIBRY to patient in the home setting, and patients.

The infusion diary will be shipped with the drug product, as well as available online for printing.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness will be assessed using both process and outcome indicators. The non-interventional post authorisation safety study (PASS) will request feedback from treating physicians regarding the use of the ID.

Process indicator:

The regular use of the ID can be considered as a process indicator and can be documented for patients in the non-interventional PASS.

Outcome indicator:

The information captured in the ID including medication errors, administration complications, and unexpected AEs or AEs of special interest, can be reviewed by the treating physician and captured in the non-interventional PASS for an assessment of any intercurrent event.

V.3 Summary of risk minimisation measures

Table 12. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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*	Routine activities beyond adverse reactions reporting and signal detection • *Targeted follow up questionnaire on medication errors in the home setting* *Additional pharmacovigilance activities* • *NULIBRY non-interventional post authorisation safety study (PASS)*

Table 12. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	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 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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Targeted follow up questionnaire on Pregnancy and Lactation* Additional pharmacovigilance activities: • *NULIBRY non-interventional PASS*
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.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *NULIBRY non-interventional PASS*

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for NULIBRY (fosdenopterin)

This is a summary of the risk management plan (RMP) for NULIBRY. The RMP details important risks of NULIBRY, how these risks can be minimised, and how more information will be obtained about NULIBRY's risks and uncertainties (missing information).

NULIBRY's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how NULIBRY should be used.

This summary of the RMP for NULIBRY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of NULIBRY's RMP.

I. The medicine and what it is used for

NULIBRY is authorised for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A. It contains fosdenopterin as the active substance and it is given intravenously.

Further information about the evaluation of NULIBRY's benefits can be found in NULIBRY's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of NULIBRY, together with measures to minimise such risks and the proposed studies for learning more about NULIBRY's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken, as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of NULIBRY is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of NULIBRY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of NULIBRY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

List of important risks and missing information	
Important Identified Risks	None
Important Potential Risks	Medication Errors in the Home Setting
Missing Information	Use during Pregnancy and Lactation Long term safety

II.B Summary of important risks

Important Potential Risk: Medication Errors in the Home Setting	
Evidence for linking the risk to the medicine	Treatment with NULIBRY requires specific storage, dosing, and administration, which may increase the possibility of medication errors in the home setting. Most patients (90%) in the clinical studies received NULIBRY which was administered by a caregiver in the home setting. Across the 11 patients treated with NULIBRY, total exposure was 55.9 patient-years (with median time on treatment, as of the data cut-off, of 6.3 years which ranged from 9.0 days to 7.6 years). No adverse events related to dosing were reported throughout the clinical development program (~ 55.9 patient-years of exposure to NULIBRY treatment).
Risk factors and risk groups	Caregivers will need to be informed on the specific details for storage, dosing, and administration. Caregivers must fully understand the way NULIBRY should be stored, reconstituted and administered and the dose needed before they commence administration of NULIBRY in the home setting. Lack of this information is the main risk factor. No other particular risk factors or risk groups have been identified.
Risk minimisation measures	Routine risk minimisation measures: • *The dosage and method of administration is 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, and administration and disposal are provided in section 6.6A note in the SmPC section 4.2 and 6.6 to caregiver/patient that if deemed appropriate by the HCP NULIBRY maybe administered at home by caregiver/patient, 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 section 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 stating that NULIBRY can be given at home, that before doing this 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 the storage conditions.* Other routine risk minimisation measures beyond the Product Information: • *Legal status: NULIBRY will be available as a prescription-only medicine.* Additional risk minimisation measures: • *Instructions for use* • *Infusion Diary*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *NULIBRY non-interventional PASS*

Missing Information: Use during Pregnancy and Lactation	
Risk minimisation measures	Routine risk minimisation measures: • *Warning in SmPC 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 therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.* Other routine risk minimisation measures beyond the Product Information: • *Legal status: NULIBRY will be available as a prescription-only medicine.* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *NULIBRY non-interventional PASS*

Missing Information: Long term safety	
Risk minimisation measures	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.* Other routine risk minimisation measures beyond the Product Information: • *Legal status: NULIBRY will be available as a prescription-only medicine.* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *NULIBRY non-interventional PASS*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation.

NULIBRY is granted Marketing Authorisation under Exceptional Circumstances. Hence, part of the conditions to be fulfilled by the Marketing Authorisation, a specific obligation lying with additional pharmacovigilance activities in the form of a non-interventional PASS (Category 2) is deemed necessary. It is described in Annex 3 of this document.

II.C.2 Other studies in post-authorisation development plan

Not applicable

PART VII: ANNEXES

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Annex 4–Specific adverse drug reaction follow-up forms

Targeted follow-up questionnaires for routine pharmacovigilance activities have been developed to collect and evaluate specific data during the post marketing period for following:

- Medication errors in the home setting (important potential risk)
- Use during Pregnancy and Lactation (missing information)

These specific follow-up questionnaires are provided below:

Questionnaire 1: Pregnancy and Lactation Follow-Up Questionnaire

origin

NULIBRY (fosdenopterin hydrobromide)

PREGNANCY AND LACTATION FOLLOW-UP QUESTIONNAIRE

Origin Biosciences Case ID: 202XXXXXX

Dear Doctor xxx/Ms xxx/M xxxx,

Origin is committed to providing safe and effective treatments to patients.
You reported an occurrence of pregnancy in one of your patients while on NULIBRY® treatment.

In order to properly evaluate the effects of this medicinal product on pregnancy, we would be very grateful if you may complete and return to us the below questionnaire. Your feedback is of greatest value to allow an ongoing assessment of the safety profile of NULIBRY®.
Please complete this questionnaire according to your best knowledge. In case you do not have the information for one item available, please leave the box empty or cross it out.

MATERNAL DETAILS			
Mother Initials		Date of last menstrual period prior to conception	*(dd/mm/yy)*
Age	*(in years)*	Ethnic Origin	☐ Caucasian
Date of Birth	*(dd/mm/yy)*		☐ Asian
Height	*(in cm)*		☐ Hispanic or Latino
Weight	*(in Kg)*		☐ Black
Date pregnancy confirmed	*(dd/mm/yy)*		☐ Other Specify……

OBSTETRIC HISTORY	
Number of previous pregnancies:	
Live births: Miscarriages: Elective Terminations:	Late Foetal Deaths: Ectopic Pregnancies: Molar Pregnancies:
Were there any birth defects in any previous pregnancies? *(include any defect affecting appearance, organ function, and physical and mental development)*	☐Yes ☐No If yes, please provide details _____ _____ _____

MATERNAL MEDICAL HISTORY			
Rh:	☐ Pos	☐ Neg	
Smoking:	_____ cig/day		Duration of smoking:
Alcohol:	_____ glass(es) /day		Duration of alcohol consumption:
Drug abuse:	☐ Yes	☐ No	Details:
Regular menstrual periods?	☐ Yes	☐ No	Details:
Sterility treatment?	☐ Yes	☐ No	Details:
Anterior immunisation? *(toxoplasmosis, rubella, other)*	☐ Yes	☐ No	Details:

Was there any relevant medical history? *(including high blood pressure, heart disease, thyroid disease, diabetes, psychiatric disorder, epilepsy, etc.)*	☐Yes ☐No If yes, please provide details _____ _____ _____

Pregnancy and Lactation Follow-Up Questionnaire
Version 1.0

origin

Was there any relevant family history? *(including malformations, brother/sister died young, psychomotor retardation, consanguinity, etc.)*	☐ Yes ☐ No If yes, please provide details

CURRENT PREGNANCY DETAILS			
Presumed date of conception	*(dd/mm/yy)*	**Expected date of delivery**	*(dd/mm/yy)*
Gestational age at knowledge of pregnancy	*(dd/mm/yy)*	**Multiple pregnancies**	☐ Yes ☐ No
During course of this pregnancy			
Smoking:	_____cig/day	Alcohol:	_____glass(es) /day
Drug abuse:	Type of drug:		

What type of contraception was the patient using at the time of the conception?	☐No contraception ☐Barrier ☐Birth Control Pill ☐Implant ☐Intrauterine Device ☐ Other Specify _____
Describe any relevant diagnostic test results during pregnancy (amniocentesis, ultrasound, etc.) and provide test dates?	☐ Yes ☐ No If yes, please provide details
Is there evidence of a defect from a prenatal test?	☐ Yes ☐ No If yes, please provide details
Give details of any infections/illnesses during pregnancy (flu, diabetes, hypertension, etc.) and provide dates?	☐ Yes ☐ No If yes, please provide details

DRUG EXPOSURE DURING PREGNANCY				
NULIBRY® treatment details *(add further page if required)*				
Indication:			**Batch N°:**	
Dates (treatment duration if dates unknown)		**Route**	**Total Daily Dose**	**Dosing frequency**
Start *(dd/mm/yy)*	**Stop** *(dd/mm/yy)*			

CONCOMITANT MEDICATION/VITAMIN/DIETARY SUPPLEMENT INFORMATION Did the patient take any medications/vitamins/dietary supplements during pregnancy?				
Medication/Vitamin/Supplement name	**Route/Dose**	**Indication**	**Start date**	**Stop date**

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LABOUR AND DELIVERY

Mode of delivery:	Gestational age at delivery:

Please provide method of analgesia during labour and any other medicines during labour

Brand and generic name (if known)	Indication	Dosage	Route of administration	Duration of use (from/to)

Give details of any complications during labour

Give details of any placental abnormality

OUTCOME OF THIS PREGNANCY

Live-born infant	☐	weeks from LMP*: _____
Elective termination	☐	weeks from LMP*: _____
Spontaneous abortion	☐	weeks from LMP*: _____
Late Foetal Death / Stillborn	☐	weeks from LMP*: _____
Ectopic Pregnancy	☐	
Molar Pregnancy	☐	

*LMP: Last Menstrual Period

NEONATE

Date of birth	*(dd/mm/yy)*	Length at Birth	*(in cm)*
Birth Weight	*(Kg)*	Head Circumference at Birth	*(in cm)*
Sex	☐ Male ☐ Female	APGAR scores	1 minute _____ 5 minutes _____

Was resuscitation required?	☐ Yes	☐ No	☐ Not known
Was admission into intensive care required for the neonate?	☐ Yes	☐ No	☐ Not known

Does the neonate have any congenital anomalies? ☐ Yes ☐ No If yes, please provide details

_____

_____

_____

Were there complications in the neonate other than congenital anomalies? *(e.g. signs linked to placenta insufficiency, neonatal illness, hospitalisation, need for specific therapies)* ☐ Yes ☐ No If yes, please provide details

_____

_____

_____

Was breast feeding to new born initiated? ☐ Yes ☐ No

If yes, please provide start date: _____

Length of lactation: _____ weeks/months

Pregnancy and Lactation Follow-Up Questionnaire
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Please provide any further information that you consider may be relevant *(add further page if required)*	_____ _____ _____ _____ _____

Reporting ☐Doctor ☐Pharmacist ☐other: _____ Name: _____ Address: _____ _____ Postcode: _____ Signature _____	**Contact details (email and phone)** Date: _____ *(dd/mm/yy)*

Thank you for your time to provide responses and sending the questionnaire back to Origin at email xxxx or to the following fax number xxxxxxxxx.

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Questionnaire 2 – Medication errors in the home setting Follow Up Questionnaire

NULIBRY (fosdenopterin hydrobromide)

Targeted follow-up questionnaire – Medication errors in the home setting

Origin Biosciences Case ID: 202XXXXXX

Dear Doctor xxx/Ms xxx/M xxxx,

Origin is committed to providing safe and effective treatments to patients.
You reported an occurrence of medication error in one of your patients while on NULIBRY® treatment in the home setting.

In order to properly evaluate the effects of this medicinal product due to medication error, we would be very grateful if you may complete and return to us the below questionnaire. Your feedback is of greatest value to allow an ongoing assessment of the safety profile of NULIBRY®.
Please complete this questionnaire according to your best knowledge. In case you do not have the information for one item available, please leave the box empty or cross it out.

PATIENT DETAILS			
Initials		Sex	*(M/F)*
Age (at the time of medication error)	*(in years)*	Weight	*(in Kg)*

DRUG DETAILS	
NULIBRY® treatment details *(add further page if required)*	
Prescribed dose (ml):	**Number of vials:**
Dose actually used (ml):	**Treatment date:**

DETAILS OF MEDICATION ERROR	
• **Classification of medication error:**	☐ Error did reach the patient and led to a medication error ☐ Error was noticed before medication was taken by the patient and there was no actual medication error ☐ Unknown
• **Which stage of the medication process did the medication error occur?**	☐ Prescribing ☐ Dispensing ☐ Transcription ☐ Preparation for administration ☐ Administration ☐ Unknown ☐ Other, please specify: …….... ……
• **Please provide start and stop dates of the occurrence of the medication error:**	Start date:…… Stop date:…… Cumulative dose:……. in ……..days

• **Where did the error occur**	☐ Hospital ☐ Home ☐ Other, please specify: …… ……
• **Were there any contributing factors that may have played a part in the origin or the development of the medication error?**	☐ Human factor: ☐ Healthcare professional ☐ Caregiver ☐ Organisational ☐ External factors beyond the control of the healthcare professional, caregiver or patient ☐ Unknown ☐ Other, please specify …… ……

DETAILS OF ANY ADVERSE REACTION(S) (SIDE EFFECTS) only complete this section if an adverse reaction (side effect) was experienced	
Was there an adverse drug reaction (side effect) experienced as a consequence of the medication error?	☐ Yes ☐ No ☐ Unknown Please specify…… ……
Event Start date of the adverse drug reaction (side effect)	(dd/mm/yy)
Event Stop date of the adverse drug reaction (side effect)	(dd/mm/yy)
Outcome of event	☐ Recovered ☐ Recovering ☐ Continuing ☐ Resolved with sequelae ☐ Fatal ☐ Unknown
Action taken with the medicinal product as a result of the medication error	☐ Drug Withdrawn ☐ Dose Reduced ☐ Dose not changed ☐ Unknown ☐ Other, please specify …… ……
Seriousness Criteria	☒Serious ☐ Non-serious If yes, please indicate why (tick all that apply): ☐ Patient died due to reaction ☐ Life threatening ☐ Involved or prolonged an inpatient hospitalisation ☐ Involved persistent or significant disability ☐ Congenital anomaly/birth defect ☐ Medically significant/Required intervention to prevent one of the above Please Specify …….. ……
Was the reaction related to the drug?	☐ Yes ☐ No Rationale: …… …… …… …… ……

Short narrative with (additional) relevant information (including concurrent medical conditions and test results): *Add further pages if required*

Reporting ☐Doctor ☐Pharmacist ☐Other: Name: Address: Postcode: Signature	**Contact details (email and phone)** Date: *(dd/mm/yy)*

Thank you for your time to provide responses and sending the questionnaire back to Origin at email xxxx or to the following fax number xxxxxxxxxx.

Annex 6–Details of proposed additional risk minimisation activities

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 minimization 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.